The Emergence of a New Human Superorganism After Organ Transplantation

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

The biological human being is an emergent human superorganism consisting of the human organism physiologically integrated with other organisms. The persistence of a superorganism in space and time requires communication among its organisms. This communication occurs through immune processes at the biological boundaries of these organisms. Immune processes also repair disrupted boundaries, with this repair resulting in either health or disease processes depending on how the boundaries are restored. Health, disease, and biological personal identity all emerge from the mode of arrangement of, and communication of biological information among the superorganism's parts. The study of solid organ transplantation enables the ontology of the biological human being as a superorganism by bringing together the structural and functional boundaries of different organisms in a way that communication can be better understood. By understanding that organ transplant recipients are not just non-transplanted patients with an extra part, but are newly emergent human superorganisms, we can better understand both post-transplant health and disease and target our therapies more effectively. Successful reintegration of the superorganism after disruption may be relevant to many health processes, and therefore to the goals of medicine in general.

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Dedication

This thesis is dedicated to my parents, who are my first teachers, best friends, most ardent cheerleaders, ideal role models, and greatest source of inspiration.

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List of Abbreviations

CRISPR/Cas9	clustered regularly interspaced short palindromic repeats/ clustered regularly interspaced short palindromic repeats-associated system
DNA	Deoxyribonucleic Acid
FMT	fecal microbiota transplantation
MHC	major histocompatibility complex
PAMP	pathogen-associated molecular patterns
SOT	solid organ transplantation

Preface

Medicine is largely concerned with the diagnosis, causes, and treatment of disease. Correspondingly, much of our medical knowledge relates to the basic biological processes that are involved in supporting the healthy functioning of the human body (Thagard 2011). End-stage failure of a solid organ such as the kidney, liver, heart, or lung is among the most serious diseases that can afflict the human body. Organ failure results in severe morbidity and even death. The most effective therapy for irreversible end-stage organ failure in humans is the functional replacement of the failed organ. In the case of kidney failure, long-term functional replacement of the failed kidneys is possible with the help of a machine, in a process called dialysis. However, there are no similarly effective long-term, machine-based therapies to sustain life when many of the other solid organs fail.

Besides machines, another means of replacing the function of a failed solid organ is with a better functioning organ transferred from another human being, in a process called solid organ transplantation, or SOT. SOT is one of the most significant medical advances of the past century. In SOT, a healthier organ effectively replaces the seriously diseased or failed organ. This healthier transplanted organ connects to the rest of the body, sometimes in a different location while leaving the failed organs intact in their usual location, such as in the case of a kidney transplant. In other instances, the new healthier organ is implanted in the same location as the diseased organ removed from that location, as in the case of a liver, heart, or lung transplant. In all these cases, the transplanted organ is now in an environment that is new for that organ. The human being is also in a new situation after the organ transplant, since it now contains a new organ from a different human being.

One important clinical motivation for SOT is to provide relief from serious human disease. Another clinical motivation is to prolong human life after one or more essential organs fail (Wolfe 1999). SOT has the remarkable ability to provide a significant improvement in the quality of life of patients with end-stage organ failure (Evans 1985).

Important measures of quality of life such as appetite, strength, endurance, cognition, and the ability to eat a normal diet as well as travel are vastly improved. SOT also has the demonstrated ability to extend life in patients with end-stage organ failure (Wolfe 1999). Timely SOT is truly a life-saving procedure. Transplantation is widely regarded as the treatment of choice for end-stage organ failure, because it provides a much greater amount of organ function than any machine can ever provide, and therefore leads to all these advantages.

The technology of transplantation is clearly very successful. This success is the result of a robust scientific program. Organ transplantation has also been subject to many bioethical analyses over the years. Such interest in bioethics is perfectly understandable, since the removal of organs from some human beings and placing them into other human beings can lead to significant ethical quandaries. However, the literature on the associated metaphysics of organ transplantation is sparse. I hope to fill some of this void in my dissertation. Organ transplantation lends itself well to the study of personal identity and human individuality. Some great early scientists approached the concept of biological individuality through SOT (Loeb 1930, Medawar 1961). These scientists provided insights such as the self-nonself distinction that established the paradigms according to which transplantation science and clinical SOT were developed and practiced respectively for over half a century.

Transplantation science has significantly advanced since the days of Loeb, Medawar, and Burnet (1961). The clinical practice of SOT has also developed considerably over the past fifty years, and has become so successful that any further success consists only of minor increments in areas such as drug development, surgical technique expansion, donor optimization, and donor-recipient matching. In parallel to these developments, the philosophy of biology and philosophy of immunology has significantly expanded. The philosophy of medicine is an increasingly recognized sub-discipline in both philosophy and medicine. My goal for this dissertation is to bring the philosophy of medicine, biology,

and immunology back into this much larger picture of transplantation science, because doing so might help improve post-transplant outcomes and extend the success of transplantation science into areas where its success has so far been extremely limited. Correspondingly, I hope to bring transplantation science back into the philosophical understanding of biological human individuality, through an interpretation of organisms and individuality, boundaries and emergence, and disease and health. Philosophy and medicine have much to learn from each other.

Chapter One

Biological Human Beings and Solid Organ Transplantation

My dissertation describes how transplanting organs affects the biological human being. The intersection of the human biological sciences with the science of solid organ transplantation (SOT) raises interesting philosophical issues about biological identity. Although SOT is generally a very successful therapy, SOT still faces many challenges that compel us to examine wide-ranging philosophical concepts in biology such as *organism*, *superorganism*, *individual* and *species*; *mechanism* and *emergence*; and *health* and *disease*. The science and technology of SOT continues to develop at a rapid pace. My goal is to provide alongside SOT a philosophical approach to help better understand the ontology of the biological human being. Conversely, a more philosophically informed approach to SOT might better inform where our efforts to improve post-transplant success are more likely to yield reward.

In this first chapter, I will first state my dissertation hypothesis, and then follow this with by what it means to be a human being in a biological sense. I will next discuss what it might mean to be a human being who is also a transplant recipient. Finally, I will review the current success and limitations of SOT.

1.1 Dissertation Hypothesis

My dissertation hypothesis is that the *biological human being is an emergent human superorganism consisting of the human organism and other organisms, in which health and disease processes arise from the disruption and restoration of boundaries.*

Whenever we discuss any biological concept related to a human being, what we really mean is either a concept related to the *human organism* or the *human superorganism.* Which concept we mean depends on the context in which we are using the

term *human being*. At least in the case of the human being, it is possible to demonstrate based on the principles of human biology that there is an important distinction that we should make between the organism and the superorganism. The distinction between the human organism and the human superorganism is important because this distinction bears significant medical implications, including for the success of SOT. In turn, SOT provides the unique opportunity to study the role of boundaries in emergent health and disease processes. I intend to demonstrate that health and biological personal identity emerge from the mode of arrangement of the superorganism's parts.

1.2 The Biological Human Being

I am convinced that I am a human being. It would be quite hard for anyone to convince me otherwise. There are two important aspects to this conviction about one's personal identity. First, I know that as a human being I am different from every other type of *living* being on earth. Second, I know that I am different in important respects from every other *human* being on earth. These convictions about one's own status as a biological human being, both as a human being distinct from all species of animals, plants, and microbes, i.e., as an entity distinct from every other type of living entity; and as a human being distinct from every other human being probably hold true for most people. It seems ludicrous for anyone to claim otherwise.

However, what exactly does it mean from a biological perspective when a person says that he or she is a human being? In other words, what is our biological personal identity?

There are of course other aspects to personal identity besides biological identity. I will not be discussing these other forms of personal identity since they mostly pertain to the philosophy of mind. I am using SOT to understand personal identity. Although SOT can affect the human mind, more research in SOT has been biological rather than psychosocial. The philosophy literature contains interesting thought experiments about mind or brain

transplantation when trying to analyze concepts of personal identity. However, we practice SOT in human beings based on our current state of knowledge of biological principles. We will continue to do so indefinitely. Even though we can consider brain transplantation a form of SOT, brain transplantation is not currently compatible with life. Moreover, mind copying or transfer to another human being is impossible with our currently available technology. The brain function we are most interested in, at least for transplantation purposes, is the mind. Human SOT for now remains limited to organs that are not capable of thought. Therefore, thought experiments will not form part of my argument. Until there arrives such a time that brain transplants, mind copies, and mind transfer are possible, it will be most beneficial to our understanding of biological personal identity for us to firmly remain within the confines of the extant knowledge of biology and biotechnology.

Multi-organ solid organ transplants are possible, and in fact, there are widely performed examples of such transplants, like heart-lung, kidney-pancreas, etc... However, current available technology does not permit us to replace the *entire* human being in succession of all its parts as could be done with the ship of Theseus. We may raise philosophically interesting issues by considering multi-organ transplants rather than just single-organ transplants. From a biological perspective, however, the issues raised with multi-organ transplants will be largely similar to those of single-organ transplants. Therefore, I will also be limiting my dissertation to the case of single-organ transplants. I will also focus mostly on kidney transplants since the surgical procedure involved in kidney transplants is relatively simple and more straightforward than with other organ transplants. More kidney transplants are also performed than all other transplant types combined, and so the conclusions drawn from a philosophical analysis of kidney transplants will also apply to the largest number of patients.

I will now discuss the human being as it relates to other species, and then the human being as it relates to other human beings.

Human Beings versus Other Species

Biologists use the term *Homo sapiens* to describe the modern human being, and to distinguish the modern human being from other closely related species both extant and extinct. All that the word *human* means is "an animal belonging to the genus *Homo*". Unfortunately, we cannot make direct comparisons between living specimens of modern humans and the other *very* closely related species belonging to *Homo*, and which would therefore also qualify as human, because all these other very closely related species (like *Homo neanderthalis*, *Homo erectus* and others) are now extinct. Our last close relative, *Homo floresiensis*, became extinct about 12,000 years ago. We are the last *Homo* species around (Harari 2015).

Homo sapiens is therefore the last surviving human species, having been named as such to represent the so-called "wise man". Henceforth, I will reserve the noun *human being* or the adjective *human* to refer to members of *Homo sapiens*.

With all the other *Homo* species now extinct, our closest extant living relative is the chimpanzee. The chimpanzee still possesses marked genetic similarity with the human being, but there is never any danger of confusing a human being with a chimpanzee, let alone with any other animal or plant. Is it enough then to claim, as a reasonably informed person might, that a human being is that which is composed of human-derived deoxyribonucleic acid, or DNA? DNA analysis provides enough distinction between human beings and other species. *Homo sapiens* shares up to 4% of its unique DNA with the extinct *Homo neanderthalis*. The percentage of shared DNA with other species can only be smaller. It may be reasonable to posit that DNA composition defines *Homo sapiens*, but this is not the same as positing that DNA defines the *human being*, for the simple reason that there are also non-biological aspects to the human being.

We can distinguish species from one another based on many differences. Intelligence is one such difference among species. Human beings exhibit a high degree of

intelligence when compared to the other extant species on earth, at least in their own estimation (hence the name *Homo sapiens*). One measure of this so-called higher level of intelligence in human beings is the ability of human beings to pass the mirror self-recognition test. There are a few other animal species besides human beings, such as other primates, dolphins, orcas, and the European magpie, which are also able to pass the mirror self-recognition test, however. We could then perform many other tests to prove that human beings are more intelligent than these other species. We just do not bother to perform these tests because the difference in intelligence between human beings and other animals seems so obvious.

A more robust measure of intelligence is that human beings are also willingly able, and have the unique capacity to *transform* their bodies to meet their desired needs, even at short notice, in a variety of environments. The simplest example of this capacity for transformation is the ability of human beings to create and wear clothing on their bodies. Human beings create clothing from carefully selected materials derived from plants or other animal species, e.g. cotton or wool. We always perceive clothing as being external to the body, and so no thought is ever entertained about having created a merged human-cotton or human-sheep species construct whenever a human being wears clothing. We actually expect human beings to wear clothing most of the time.

Yet even then, the ability to transform the body is not unique to human beings, nor does it always depend on intelligence. Other species can spectacularly transform their bodies as well. Transformation can be gradual as part of a natural life cycle in the case of caterpillars-butterflies, or quick as when chameleons change color when they sense danger. Some species can even transfer body parts among their members. For example, bacterial cells can transfer or exchange their genetic material with other bacterial cells through a process called *lateral gene transfer*, and yet still remain as intact cells after the process of lateral gene transfer is complete.

Human beings, however, by applying their intelligence are able to transform their bodies using one method that many other species cannot. We can selectively transfer whole body parts from one human being to another human being in the form of SOT. Over the course of the last century, we acquired the ability to remove parts from one region of the human body, and then place these parts in another region of the same body in a procedure called *autotransplantation*[1]. We also acquired the ability to safely remove body parts from one human being and place them successfully into other human beings in a procedure called *allotransplantation*. Surgical procedures for autotransplantation and allotransplantation are established, safe, and common, although there remain important limitations to their success. SOT in human beings differs significantly from lateral gene transfer in bacteria, however.

Human beings do not perform allotransplantation and allotransplantation on themselves, but only on other human beings. In addition, human beings do not exchange body parts between themselves; they just transfer them. The transaction is one-sided. Only one human being is the biological beneficiary. SOT also lacks any evolutionary benefit to human beings apart from the few human beings who have children afterwards through restored reproductive fitness. SOT situates outside the natural design of human beings. In these two respects, SOT in human beings differs substantially from lateral gene transfer in bacteria. SOT is an action borne from human intelligence. There are many differences between human beings and other species based on biology or intelligence. The ability to perform SOT is what distinguishes human beings from other species when based on *both* biology *and* intelligence.

Even if we *wanted* to transfer our membership to another species, the other species would never admit a human being to their membership. The human species is so distinct from other species despite the fact that all living organisms share an evolutionary history

[1] Two common examples of autotransplantation are skin grafting after severe burns, and implantation of a small amount of parathyroid gland tissue in the forearm after the parathyroid glands in the neck are surgically removed.

going back hundreds of millions of years (McFall-Ngai 2013). Regardless of what science fiction would have us believe, we can never transform ourselves into another member of the human species, let alone another species.

Human Beings versus Other Human Beings

Modern human beings are social animals. In other words, we commonly find human beings together, typically in close proximity. When we see two human beings next to each other, we are quite confident in our assertion that each of them is a distinct human being, aside from our assertion that they both belong to the same species. We know they both belong to the same species even if we do not study their features closely. There are no *Homo neanderthalis* with whom *Homo sapiens* can mingle with, to cause us any confusion in this regard.

The question of what exactly is a human being therefore leads directly to the question of what is it exactly that constitutes biological human individuality. Biological individuality is the next step in identification once species status has been established, for besides distinguishing the group of human beings as a species from the group that constitutes the species of chimpanzees, bonobos, eagles, sharks, fungi, and amoeba, there is also the question of what exactly distinguishes one biological human being from the next biological human being. This distinction runs much deeper than analyzing DNA composition or just looking at the silhouettes of two human beings from a distance. No one will dispute that even identical twins or conjoined twins are distinct biological human beings.

What is it that specifically makes two human beings distinct? In 2017, there were more than 7 billion human beings on earth. Yet each human being is unique and there is little doubt that the next billion humans to be born will be unique and different too. They will also be unique and different from the current 7 billion human beings on earth. We all have our own external body characteristics such as pattern of hair distribution, weight, and

height. Digital retinal and palmar blood vessel pattern images as well as ink fingerprints have withstood the test of time as unambiguous personal identifiers in the modern technological world. Even without these tests, we somehow know that each one of us is unique, which is why these tests were invented in the first place.

If we are all unique, then it should come as no surprise to us that we are not at all in a position where we can *freely* exchange body parts among ourselves when it comes to SOT, even if all the relevant ethical issues could be set aside. There are rules to follow. Biological personal identity dictates these rules.

The default answer to how we can biologically conceptualize a single specimen of a human being might again be the difference in human tissue DNA composition. DNA sequences are not identical between any two human beings, not even identical human twins. There are innumerable and immeasurable differences in DNA composition between any two human being specimens. Perhaps we could set a limit on the degree of difference in DNA composition from some accepted standard. If a biological specimen fit within this standard, then that person would qualify as a human being. We could also set some limit of similarity between two human beings to consider them different human specimens.

DNA is not a fixed entity; DNA slowly transforms over a lifetime regardless of externally visible changes to the body, yet the species identity of a human specimen is never lost. Likewise, biological personal identity is never lost. A single specimen of a human being does not transform into another human being during his or her lifetime, let alone into some other species, even as a result of some disease process. The status of a human being as a member of *Homo sapiens,* as well as a human being separate from all other human beings never changes. There is no apparent choice in this matter; one's fixed status as a distinct human being seems involuntary. An organism must exist as a member of a species (Shcherbakov 2010). No known disease process changes biological personal identity.

Each human is a member of *Homo sapiens*, and each one of us is our own unique specimen of *Homo sapiens*. In later chapters, I will show how immunity is a key process by which we maintain these two levels of biological personal identity. It follows that immunity imposes many restraints on SOT in human beings.

1.3 Addressing the Limitations of Solid Organ Transplantation

Patients with end-stage organ failure experience a significant improvement in both their quality of life (Evans 1985) and long-term survival (Wolfe 1999).

Despite the great success of SOT with treating serious diseases, there are still some serious limitations to extending SOT to more patients. The first limitation is that due to the restrictions imposed by human physiology on biological personal identity, not everyone can donate an entire organ such as a kidney or part of an organ such as a liver to anyone they choose. The second limitation is that SOT recipients still face disease after their transplant. I will briefly discuss each of these limitations of SOT in turn.

The Shortage of Transplantable Organs

There are two main reasons for why the organ supply is so limited.

The *first* reason for why organ donation and therefore SOT may not be possible is that we give paramount importance to protecting the health of the living donor. Living organ donors are very healthy and as long as we properly select such donors, they can expect to enjoy lifespans at least as long as the general population. Donors do not experience any decline in their quality of life (Clemens 2006). Living organ donors also typically do not suffer any serious specific short- or long-term adverse consequences from the removal of one of their organs. However, since living organ donors need to be very healthy and sufficiently motivated to undergo a major surgical procedure that provides no direct benefit to them, they are in short supply. As a result, many patients who require SOT simply do not have a living donor available to them.

The *second* reason is that even if a living donor is available, the potential SOT recipient can immediately *reject* the organ of their donor because they possess antibodies in their bloodstream directed against that donor. Human beings generate antibodies for a variety of biological reasons. For these two reasons, the available living donor pool represents a very small percentage of the total human population. In the case of end-stage failure of other organs besides the kidney and liver, transplanting an organ from a living donor is not even an option. There are long waiting lists for all organs, and some patients unfortunately do not survive long enough on the waiting list to receive an organ transplant.

Post-Transplant Disease

Performing more organ transplants may also not be possible because a different set of disease processes affect the SOT recipient, even if the health of the well-selected SOT recipient is likely to be significantly better overall than it was before the transplant. Many patients with end-stage organ failure are just too sick to undergo SOT, for reasons not directly related to organ failure. Additionally, almost all[2] SOT recipients are required to consume several medications on an ongoing basis to prevent rejection of their organ. Despite their overall better health after receiving a transplant, SOT recipients must manage to live with some of the side effects associated with those medications. SOT recipients are prone to developing a wide variety of opportunistic infections because we suppress the normal functioning of their immune system to prevent organ rejection. SOT recipients can reject their transplanted organ at any time despite taking medication. SOT recipients can also develop serious new diseases such as diabetes, cardiovascular disease, and cancer. We can trace many of these disease processes otherwise common in the general population back to the ongoing need of SOT recipients to consume anti-rejection medications daily. All medications have side effects, not all of which trace directly back to the medications themselves. In addition to these problems, sometimes the original disease recurs in the transplanted organ.

[2] The one exception to the need for anti-rejection medications is the case of a transplant between identical twins.

Possible Solutions to the Limitations of Solid Organ Transplantation

What solutions do we have to the serious limitations of transplantation? We have to either increase the compatible organ supply, or make the donor and recipient more compatible with each other to prevent post-transplant disease.

SOT between human beings is quite a successful procedure despite its many limitations, but because we always strive to do better, the science of transplantation is moving beyond mere intra-species organ transfer. Ambitious human beings have successfully transplanted tissues such as heart valves from pigs into human beings; the long-term results from implanted bio-prosthetic heart valves are excellent. Yet the identity of the human species demarcates so well from other species that it serves us a constant reminder that it is impossible to perform successfully organ transplants from another species into human beings, in a process called *xenotransplantation*. Organ transplants from animals reject immediately and vigorously. Xenotransplantation is presently far from being a solution to the organ shortage.

Some studies report limited success in transplanting organs from one animal species to another. One might think that it will be possible to transplant the corresponding organ from an animal species other than a human, if it is of the right size and shape, and appropriately processed to ensure it transmits no infections. There is a larger supply of organs from certain animal species other than humans and fewer ethical concerns with which to contend. Scientists have attempted xenotransplantation in human beings (Starzl 1996). However, even the short-term success of xenotransplantation is extremely limited, and the procedure remains only experimental for now. There is currently an international moratorium on human xenotransplantation. Xenotransplantation remains a major obstacle that transplantation science currently faces.

Even intra-species organ transfer has significant limitations. Overcoming some of these limitations requires a detailed selection and matching process of donor and recipient

that is full of caveats and potential pitfalls. Even if we follow the best possible matching process, it is not yet possible to perform SOT without the use of anti-rejection (i.e., immunosuppressive) medications that selectively suppress immunity in the recipient. *Transplant tolerance* is a state of the recipient in which the body does not reject the organ even without using anti-rejection medication. True transplant tolerance is such a distant goal currently that scientists considered it the "holy grail" of SOT (Suthanthiran 1996). Even if the SOT recipient consumes anti-rejection medications regularly, organ transplants still have a finite lifespan because the body ultimately rejects the organ. There are numerous papers in scientific journals that report the results from human clinical trials to prevent organ rejection and improve transplant survival. In all these trials, we administer a variety of drugs and compare their effects on outcomes, including side effects. True tolerance however is not demonstrable presently.

We can link the two sets of problems, namely a limited donor organ supply and prevalent post-transplant complications in the recipient, through the workings of the immune system.

In my dissertation, I will be following an approach to improving transplant success somewhat different from the approaches found in traditional science. I will be approaching the important limitations surrounding the long-term success of SOT through the philosophy of biology and the philosophy of medicine. I will largely focus on philosophical concepts throughout the dissertation because I believe that philosophy has an important role to play in scientific advancement. I will also be generously referencing the relevant scientific literature because I also believe that being scientifically informed can help to make one a better philosopher. When backed by a philosophical underpinning, clinical organ transplantation might progress to succeeding with xenotransplantation and transplant tolerance. I will continuously straddle the fine line between philosophy and science, although I may be compelled to veer towards one direction and away from the other depending on the specific assertion.

I will also use the transplantation experience as a unique opportunity to explain what it means for us to be biological human beings. Due to the intimate relationship between immunity and personal identity, findings from transplantation science have considerable potential to add to the philosophical literature on biological personal identity. The transplantation experience can inform us about philosophical concepts such as organism and superorganism, mechanism and emergence, and health and disease, to name just a few. Emergence in particular is informed by the transplantation experience.

1.4 Splitting the Human Being into Organism and Superorganism

My approach to addressing the limitations of organ transplantation is to explain the difference between the *human organism* and the *human superorganism*, which in turn depends on the effects of *immunity*. Understanding the difference between a human organism and a human superorganism may facilitate a better or more reliable organ supply, improve post-transplant success, and advance the metaphysics of organ transplantation through understanding the relationship of the human organism to its associated microorganisms.

I shall defend the view that whenever we discuss anything about a human being, we mean either a human organism or a human superorganism. *Human being* is therefore an ambiguous concept. The view I shall defend is as follows. The *human organism* consists of all those parts of a human being that constitute human lineage-derived cells. On the other hand, the human superorganism consists of all the human lineage-derived cells plus other species of organisms that constitute the *human microbiota*.

If we make this distinction between human organism and human superorganism, we can dispense with any biological concept of *human being* when discussing the relationship between two human beings, between a human being and other large animal or plant species, or between human beings and any other entity in an environment. *Human being* might still be helpful socially and psychologically however, so I do not propose abandoning

the term altogether. Although it is perfectly appropriate to distinguish between human beings and chimpanzees in everyday language, it may be more appropriate to describe any level of biological interaction between two human beings as an interaction between two human superorganisms but not between two human organisms.

If we strictly follow this terminology of human organism and human superorganism, it becomes readily apparent that in SOT the human donor-human recipient interaction is an interaction between two human organisms. The human organism fundamentally changes after receiving a transplant. SOT is not currently an intentional interaction between two human superorganisms because in SOT we intend to transplant only human lineage-derived cells across two human organisms, even though some contamination with other organisms might occur during the otherwise aseptic procedure. However, even if there is no contamination and the transplant occurs strictly between human organisms, the human superorganism still changes.

Obviously, in many respects we have more control over the human organism than we do over the human superorganism. However, a philosophical concept needs to be generalizable. We cannot make a general distinction between an organism and a superorganism so easily in philosophy. There are caveats and exceptions to the organism-superorganism distinction pervading the literature in the philosophy of biology. By distinguishing between the *human* organism and the *human* superorganism, I do not claim to provide a solution to every exotic example that nature provides to confound such a distinction. Instead, I will use some examples from nature in the early part of my dissertation to help put my proposed structure of the biological human being into better perspective.

The very recent phenomenon of successful human SOT provides us with new opportunities to understand the human organism-human superorganism distinction specifically, and to understand the behavior of other biological entities more generally.

Disease processes may be more predictable if we understand them as a disruption of the human organism, the human superorganism, or both. We might even be able to understand the severity of disease processes, based on whether the disease process disrupts the human organism or the human superorganism.

If we are going to extend SOT successfully into new areas such as xenotransplantation and transplant tolerance, then we must understand much more about the biological entity in which we are performing SOT in the first place. Therefore, we cannot restrict all our research in SOT to the human organism or simply extrapolate the results from xenotransplantation performed between a limited number of animal species to xenotransplantation in human beings. We need to place SOT in the human being into the much larger context of biology, transplant-related or otherwise, in the entire natural world. Understanding the human being as the human organism and the human superorganism first requires an understanding of the biological organism and biological superorganism.

In summary, there is adequate motivation to split conceptually the human being into the human organism and the human superorganism. We will better understand the conceptual distinction between the biological organism and the biological superorganism in nature. We will also understand how new health-promoting technologies such as SOT affect biological personal identity, and how biological personal identity can affect the success of SOT.

1.5 Is a Human Being with a Transplant a Different Kind of Human Being?

SOT involves combining parts of one human organism with the parts of another human organism. Our intuitive notion is that a human being who has received an SOT from another human being is still the original human being after the transplant. We do not always view the transplant recipient as some newly created human being consisting of an admixture of parts derived from two or more separate human beings. The expectation of bodily continuity is a need of the human psyche. When we successively replace planks

from the ship of Theseus and the ship still floats, the continuity of the original ship entity remains open to discussion. Even if we improperly plan or execute the replacement procedure and the ship therefore sinks at some point midway during the replacement of parts, we might still consider the sunken ship as the original ship. There is, however, an important difference between the example of the biologically inert ship having its parts replaced and the SOT recipient with a newly transplanted organ.

In human SOT, we implant a *living* body part from one human being into another *living* human being. The transplanted organ in SOT is a living organ, whether its original owner is deceased or alive. As a result, there is now a two-way interaction between the transplanted organ and its new body. With organ transplantation, we force two living entities to face each other directly. This two-way interaction between the transplanted organ and the recipient's body persists for the life of the SOT recipient. We cannot afford to ignore this interaction if our attempts at SOT are to achieve any success. Even if we remove the transplanted organ for some reason, as might be required when the organ's blood clots or the body rejects it, the effects from that organ on immunity will persist indefinitely. The immune system is activated almost immediately after the organ is connected to the rest of the body. Immunity provides the mechanism for the two-way interaction between the organ donor and the organ recipient. Since the immune system is an organ system in its own right, an organ transplant affects more than one organ system.

Transplanting an organ is conceptually not the same as implanting an inert object such as a cardiac pacemaker or a hip prosthesis into the body. These types of implants are made of inert, non-living material such as metal. Cardiac pacemakers and hip prostheses have no immune activity of their own. Biological tissues such as porcine heart valves are usually decellularized, and therefore have no immune activity of their own either. The body cannot reject inert prostheses. The transplanted solid organ on the other hand carries with it a distinctive biological identity. This biological identity carried by the human organ remains distinct from the identity of the human recipient. The biological identity the

transplanted organ continues to carry is that of the donor, who is another human being. There is always the possibility therefore that the organ will be rejected by the recipient, because the immune system is always engaged after transplantation.

An exception to this persistent possibility of rejection of a solid organ might be the peculiar situation of transplantation between identical twins, in which case rejection does not occur. The first successful SOT was performed between identical twins, so chosen to eliminate the concern about rejection. However, this phenomenon of apparent transplant tolerance does not prove genetic identity between the twins. The medical history of two identical twins can be very different over a lifetime. It is these differences in medical outcome which led to one twin being a donor and therefore healthy, and the other twin experiencing serious disease and becoming an organ recipient. We cannot perform many transplants between identical twins since very few potential SOT recipients will have an identical twin. The biological identity of a human being as separate from every other human being on earth is unequivocal. SOT is an attempt to circumvent biological personal identity. The SOT recipient therefore has an altered biological identity when the transplant is successful. Since there are ongoing immune effects from the transplant, biological identity alters even when the transplant is unsuccessful.

Biological personal identity appears resistant to sudden change, and this resistance may be the source of many clinical problems after transplantation. The biological human being is resistant to the prospect of forcibly becoming another human being, so it is conceivable that the biological challenge to identity posed by the procedures of clinical medicine also apply to the rest of the body. A transplant involves an interaction between two sets of body parts derived from two human organisms with their two distinct sets of human DNA and their associated biochemical products. A transplanted human being is therefore different from other human beings by containing some human DNA that he or she did not inherit through lineage, or generate through creating lineage as pregnancy can do

to mothers. There is some more to be said about boundaries and resistance to boundary violation outside of biology, which I will briefly mention in Chapter Seven.

Human beings do not interbreed with other species even though human DNA is not all that there is to the biological identity of a human being. Human germ cell lines segregate from other cell lines at an early stage of development, thereby keeping the identity of human DNA secure. However, human beings contain abundant non-human DNA associated with their own DNA. This non-human DNA is contained within the many microorganisms (including bacteria, viruses, and fungi) present inside various cavities and crevices of the human body. These microorganisms together constitute the *human microbiota*. The human microbiota consists of about 100 trillion bacteria that are resident in the gastrointestinal tract and several other sites. These bacteria are in a symbiotic relationship with the 10 billion-or-so human-derived cells. It does not appear intuitively correct to label these bacterial cells as part of the human being. Yet the presence of these bacterial cells is indispensable to the health of human beings.

Therefore, if health is required for persistence through time, then we must accept the presence of these bacteria and other types of organisms, by some means, as contributing to the biological identity of human beings. For this reason, the human microbiota has garnered attention from philosophers of biology interested in human identity.

SOT recipients possess, in addition to every other human being, one more living entity, a transplanted organ, which is added to the mix of human organisms and microorganisms. The transplanted organ has an origin different from the rest of the human organism in which it situates. Even though the transplanted organ is unmistakably of human origin, it expresses a different biological personal identity. In this respect, therefore, the transplanted human being is a different kind of human being worthy of philosophical treatment. I propose that the biological human being is a human

superorganism, and the transplanted human being is another kind of human superorganism because of its transplanted organ.

1.6 Structure of Dissertation

I will structure my argument for the important role of the human organism-human superorganism distinction as follows.

In Chapter Two, I first provide an overview of the meaning of species, organism, individual, and superorganism. I will discuss the methods used by philosophers of biology to distinguish one species from the next, and to distinguish among *organism, individual,* and *superorganism*. During this discussion, I will highlight some major controversies pervading the philosophy of biology. I will then describe several examples from the natural world to illustrate how, despite the attempts of philosophers and biologists to arrive at unifying criteria for defining species, organism, individual, and superorganism, the distinctions among them remain vague and blurred. These lessons from the natural world will help to illustrate that the human being, as a member of the natural world, is also subject to a "crisis" of identity when it comes to organism, individual, and superorganism, even though an evolutionary accident has permitted us to be unambiguous about the human species. The human superorganism is similar to some, but not all superorganisms found in nature. I will explain why *superorganism* may be a more appropriate term than *individual* for the biological entity in which the human organism is the largest constituent. Chapter Two provides an argument that *superorganism* is philosophically relevant in biology.

In Chapter Three, I focus on the human superorganism. I will discuss the biology of the human microbiota to show how the human superorganism consists of both human-derived cells that constitute the human organism, and abundant microorganisms that are not part of the human organism. These microorganisms are essential to the maintenance of health in the human organism and human superorganism. This discussion will serve to

confirm the distinction between the human organism and the human superorganism through an understanding of biological *boundaries*, even though we cannot physically separate the human organism from the rest of the human superorganism. The human superorganism exemplifies unity in diversity. The great species diversity among organisms closely associated with the human being further serves to muddle the biological and philosophical distinctions among species, organism, and superorganism. In describing interactions among organisms, I point out that organisms possess real boundaries and cross other real boundaries to survive. If we find organisms in association with each other in creating superorganisms, then there must be a boundary between the organisms.

I will also introduce some known associations of the microbiota with human health and disease, including how microorganisms perform their actions through their interactions with the human organism. I will make the case that to understand disease processes in the human superorganism we must know the human organism and all the other organisms associated with it. I will discuss one simple therapy, fecal transplantation, as an example of a therapy directed towards the human superorganism, and as an exception to most of our therapies that we typically direct towards either the human organism or some microorganism. In sum, Chapter Three provides the argument to defend my claim that the biological differences between the human organism and the human superorganism, contextualized to their boundaries, relate to human health and disease.

In Chapter Four, I explain that the immune system is the collection of mechanisms by which the human superorganism holds together. I discuss the immune system as consisting of the mechanisms for maintaining both the organism and the superorganism through communication across their boundaries. The immune system is the defining feature and causal mechanism of biological individuality. Transplantation violates boundaries similar to how microorganisms violate boundaries when they cause infections. The immune system and its product, the immune response, serve as the link or bridge across the boundaries among different organisms belonging to the same or different

species through the signals it provides. I discuss how our understanding of immunity and the immune system can help us elucidate the distinctions among species, organisms, and superorganisms. I will explain the similarities and differences in the immune response between the human organism and microorganisms, and the human organism with a transplanted organ. I discuss biological information, and the boundary as the location where that information can be accessed.

Even though organ transplantation is not part of routine non-human health care, understanding how the biological human organism and human superorganism fit into the natural scheme of biology will serve to contextualize the current successes and failures of SOT. In nature, the members of a species do not just interact among themselves, but they regularly interact with the members of other species despite the extensive differences that exist among them. SOT provides unique insights into the species-organism-superorganism distinction that an understanding of the human microbiota alone cannot provide.

In Chapter Five, I show how a mechanistic understanding of the two-way interaction occurring between the organism of the SOT recipient and the transplanted organ, mediated through the actions of the immune system, can be used to build a further understanding of how a new type of human superorganism *emerges* through the violation and subsequent restoration of biological boundaries. I will discuss how an understanding of emergence can help provide a medical explanation for how the human superorganism arises and sustains. We observe many different phenomena surrounding SOT, and we invoke a variety of mechanisms to explain those phenomena. Using the examples of some common post-transplant phenomena, I will explain how disease processes in the human superorganism might be different from disease processes in other types of human superorganisms. Dissolution and reconstitution of boundaries can lead to new types of emergent processes. We must approach post-transplant conditions therapeutically based on the understanding that these disease processes may be mechanistically different from non-transplant related disease processes, even if they carry the same label and similar treatment.

In Chapter Six, I explain how we can better understand the philosophical concepts of disease and health through the human organism-human superorganism distinction. I will propose a cohesive theory by which some human diseases are states of incompatibility between the human organism and the human superorganism. By understanding specific disease and health processes as emergent processes in the organism *or* superorganism, we might be able to prevent or treat them more effectively. We may also be able to understand better the reasons behind our current inability to achieve the ambitious but inspiring goals of xenotransplantation and transplant tolerance. I describe inflammation, consisting of the immune response and tissue repair, as the process for reestablishing boundaries and as the unifying process of the organism and superorganism.

In Chapter Seven, I summarize the accomplishments of my dissertation. Having drawn upon philosophy, science, and my professional experience, I advance new ways of thinking about a variety of interrelated concepts: human beings, species, organisms, individuals, superorganisms, boundaries, emergence, disease, and health. The philosophy of science and medicine has not previously addressed metaphysical issues brought forth by SOT. The human being is a type of superorganism, but medical practice directs towards the organism. Just as microorganisms trigger immune responses when violating boundaries of the human organism, organ transplants trigger immune responses because the transplant procedure also violates boundaries of the human organism. Organ rejection reflects a physiological immune response yet rejection is approached as a disease process. The immune response and its output, inflammation, reintegrate the human superorganism as new processes emerge from boundary violation and restoration. The immune response maintains the emergent superorganism. To advance post-transplant success into areas such as xenotransplantation and transplant tolerance, whose success depends heavily on stable biological personal identity, we must incorporate the human superorganism into our therapies. Health promotion requires understanding the human superorganism, since many human disease processes are actually diseases of the human superorganism.

Chapter Two

The Diversity of Life

The distinctions among species, organism, superorganism, and individual remain blurred. All this vagueness illustrates the diversity of life on earth. To understand the human being as a human organism and as a human superorganism, we must first understand how the human entity relates to other forms of life. Life is not only diverse, but it interrelates. My first major goal of the dissertation is to demonstrate that the biological human being is a superorganism consisting of multiple integrated organisms, but to get to that point I must first travel in-depth through the meanings of species, organism, and individual. Once clarity obtains for these three concepts, understanding the superorganism readily follows at the end of this chapter.

2.1 Biological Hierarchies and Relationships

The earth sustains a great diversity of life that fascinates both philosophers and biologists. Until recently, many philosophers of science found physics and chemistry more fascinating because of their longer histories and allegedly more fundamental nature than biology. The philosophy of biology became a prominent subfield of philosophy only in the last three decades of the twentieth century. Understanding the diversity of life has since become a central theme in the philosophy of biology.

It has been estimated that there are 8.7 million (± 1.3 million) eukaryotic species alone, and only 1.2 million among them have been catalogued. About 86% of species await description, including 91% species resident in the ocean (Mora 2011). Our capacity for observation determines our ability to recognize these diverse life forms. Young children readily identify and first learn the names of animal and plant species (such as *dog, elephant, apple tree,* and *ant*) that are close in their size relative to human beings. We also learn early on, more advanced concepts such as *two dogs, three elephants*, *six apple trees*,

and *a colony of ants*. Wider travel by human beings in the modern era has enabled the assembly of longer lists of previously unfamiliar life forms. The advent of the microscope has enabled human beings to extend further the compendium of life forms by allowing the visualization of animals and plants not visible to the naked human eye. Yet we often consider organisms and individuals as synonymous. In other words, the organism is the paradigmatic individual.

There is also the semantic confusion created by the term *individual organism*, which probably results from considering organisms as the paradigmatic individuals. Common species of animals and plants appear distinct from other species of animals and plants, and members within each species appear to be both distinct organisms and distinct individuals. As I will soon show, this delineation of species members is not always an easy one to make. Delineation is important to classify life forms so that we may understand them.

In lay terms, the concepts of *organism*, *species*, and *individual* all seem straightforward and uncontroversial. However, it takes just a little more thought and studying no more than a few problematic examples from nature to illustrate that the organization of the natural world is far more complicated than the dictum "every organism is an individual member of so-and-so species". I will start by discussing the prevalent literature on the concepts of *species, organism* and *individual* in turn, highlighting some of the historical and current controversies that surround each concept. I will then introduce the superorganism, and distinguish between *individual* and *superorganism*.

The reason I am following this particular sequence in explaining these concepts is that the status of the human species is unambiguous. However, biologists view concepts in terms of a taxonomic hierarchy of biological organization, ranging from individual molecules to large-scale processes. Concepts in biology are composed of simpler concepts. Obsolete theories of concepts include definitions. It is very easy to provide counterexamples to definitions, unlike concepts, quickly leading to sidetracks from the

main discussion about biological entities. Concepts are best viewed as semantic pointers[3] (Blouw 2016).

In ascending order, *organism* and *species* are both terms that fit within the hierarchy of biological organization (Stegmann 2007). The full hierarchy in ascending order consists of *atom*, *molecule*, *macromolecule*, *organelle*, *cell*, *tissue*, *organ*, *organ system*, *organism*, *population*, *species*, *community*, *ecosystem*, and *biosphere*. *Individual* is not a term included in this hierarchy. *Species* is the only member of this hierarchy that is also a member of another hierarchy of taxonomic ranks, which consists in ascending order of *species*, *genus*, *family*, *order*, *class*, *phylum*, *kingdom*, and *domain*. Among all these many levels, I will focus only on *species* and *organism*, and make sense of *individual* in the process. I will also scrupulously avoid the pervasive *individual organism* that is unfortunately an oft-used term fraught with difficulties. The longer and therefore less convenient term "single specimen of a such-and-such organism" as a descriptor is neither vague nor ambiguous, so I will use this term when needed instead.

Although controversy exists in defining the above hierarchal entities, perhaps the most difficult entity of all to conceptualize is the *individual*. It is possible that this difficulty is the reason why *individual* is not included in a biological hierarchy. An individual is far more than that "which cannot be divided". *Species* and *organism* provide the greatest theoretical and practical relevance in SOT. I will therefore discuss the concepts of species, organism and individual in-depth.

Species precedes *organism* in my discussion even though the former depends on at least a basic understanding of the latter, because fortunately the human species is a less difficult concept to grasp. *Individual* as a concept overlaps all the hierarchal entities in its descriptors, including *organism* and *species*, is the most complicated, and so I will therefore present this last. Why is *individual* so complicated? It is unproblematic to use a

[3] There is a developed literature on semantic pointers that I will not be discussing.

term such as *individual chair* or *individual book* because chairs and books are things. However, the casual use of terms like *individual atom*, *individual molecule*, *individual community*, *individual family*, *individual class*, and so on, can adequately illustrate how much confusion might be created by combining the word *individual* with a concept rather than a thing. At least the concept of *organ* is unproblematic in clinical SOT; a kidney, liver, heart, and lung are all organs. These solid organs are physical objects that we can hold in our hand. All organs possess a size and a mass, we can remove organs from the body, and we can reconnect organs in another body.

If it is possible to understand *individual* within the diversity of life even if it is not within the conventional biological hierarchy, then perhaps we can better understand all other biological concepts that actually do exist within the hierarchy. We might even better understand other terms not within the biological hierarchy, like *superorganism*.

2.2 The Meaning of Species

We find it necessary to use the term *species* because we need to describe, characterize, and then research the living world.

Among the "biological" professions, we become botanists or zoologists, small animal or large animal veterinarians, and physicians or surgeons. All these professions require a common concept of *species* for daily use. Commonly employed criteria to define a species include genetic similarity or reproductive isolation, shared lineage, similarity in appearance or habitat, mating restriction, and so on. Besides these numerous means of defining a species, there is also the question of whether *species* has some special status beyond *genus* or *grouping*. We mostly think about species in the present world. However, we also need to account for extinct species if we are to fully understand the meaning of *species*; any account based on information about only the species to which we have current access will be incomplete.

It is useful, therefore, to discuss *species* in the form of two distinct but related contexts: species taxa and species category. *Homo sapiens* (human being) and *Canis familiaris* (dog) are examples of species taxa, while the class of all species taxa is referred to as species category i.e., what is a species in general. Species taxa interest biologists, but both species taxa and species category are interesting to philosophers. I believe both species taxa and species category will be useful to a philosophical understanding of organ transplantation. I will now provide a brief review of the literature on species taxa followed by species category.

Species Taxa

Species essentialism, which is the position that a species is a natural kind with essences, dates back to Aristotle and Locke but has largely fallen out of favor. Species essentialism implies that all members of *Homo sapiens* and only members of *Homo sapiens* share a common essential property. We can then explain all other properties of *Homo sapiens* based on this essential property. It has proven impossible to find such a single property since evolution causes constant changes in the characteristics of any given species. It is much simpler to explain the differences among the members of a species by gene frequencies and evolutionary forces that affect gene frequency and expression (Sober 1980).

Genetic mutation and recombination illustrate the fragility of assigning a particular trait as the defining characteristic of a species. Moreover, parallel evolution leads to the expression of very similar traits across species. Speciation occurs across an extremely long time. Speciation is also gradual; there are no fixed or sharp demarcation points along the path of evolution and so the threshold for transitioning between species always remains vague. For example, we have no way of knowing when exactly *Homo sapiens* originated, even though we can readily identify one in the present time or from the recent past.

An alternate view to species being essences is that species are *individual*. Species are units of evolution in evolutionary biology, and are therefore individuals (Hull 1978). Individuals are thereby causally and spatiotemporally restricted. By *individual*, Hull means *particular*. Therefore, the term *individual* as used by Hull is not to be confused with the term as otherwise used in my dissertation that reflects its more common usage. If species are individuals, then it implies that the relationship between a species and an organism is one of a whole to a part, not class to a member[4] of that class. Lineage becomes everything. Similarity in traits among specimens has no role in membership of a species. Propagation of the species requires that its members contact each other. Change in gene frequencies leads to evolution. Hull's view about species was criticized based on numerous examples found in nature that exhibit asexual reproduction, and are therefore not causally restricted (Ruse 1987).

Besides Ruse's concern regarding the abundance of asexual reproduction, it may not even be necessary to define species spatiotemporally, since it is also equally possible to conceptualize *species* based on structural similarities. Species, in other words, are *sets* of organisms (Kitcher 1984). It should be possible in a practical sense to delineate a species. However, similar structural features are present across species otherwise widely disparate. Consider for example the structural similarities between bats and birds of similar size that are also capable of flight. From a distance, one might confuse the two, and it is possible that the confusion will persist for some, even upon closer external inspection of a specimen of each. Kitcher's concept allows convenience based on evolution or structure to define species, even if it dispenses with Hull's spatiotemporal component.

The Homeostatic Property Cluster theory of natural kinds of species proposes that members of a species share a set of properties that occur together at a frequency greater

[4] David Lewis (Parts of Classes, 1991) argues that membership in a set is actually a whole-part relation. There is no doubt that a common lineage is a very important feature of a species, but as I will soon show, lineage is not required for the concept of organism. When members of a species consist of multiple organisms, if we abide by Lewis' view, then whole-part relations between organism and species become very problematic.

than would be expected by chance. The Homeostatic Property Cluster theory states that mechanisms that include common environmental exposures and similar genetic material maintain homeostasis of a species and make the status of a species stable (Boyd 1999). There is no need for an essential property. Similarities between species are the result of interbreeding among species. The concept of *species* itself is theoretical; its use in biological theory determines its meaning. However, the Homeostatic Property Cluster theory does not account for variation *within* a species, just between species. Gene polymorphisms and genetic heterogeneity are required for the survival of a species. The Homeostatic Property Cluster theory does not even acknowledge such fundamental differences as male-female within a species. The Homeostatic Property Cluster theory also ignores genealogy.

In contrast to the Homeostatic Property Cluster theory, the Population Structure Theory emphasizes equally similarity and diversity within a species from the most obvious such as the sexes, to the distribution of more subtle traits. Population Structure Theory states that species identity is determined both by structures within and between populations (Ereshefsky 2005). Genealogy is a structure between populations while sexual dimorphism is a structure within a population. Population Structure Theory distinguishes from the Homeostatic Property Cluster theory by its accommodation of both genealogy and structure.

How are species taxa relevant to human beings, and to my purpose of understanding organ transplantation? Species taxa provide fixed and rigid boundaries in limiting the extent of SOT. At least based on the currently available technology, we can only transplant solid organs within the same species. Xenotransplantation is unsuccessful and even organ transplants between strains of animal species reject[5] (Marco 2006). Regardless of the epistemic status of a species taxon, based on the criterion used to define a species, either

[5] A problematic example to the inability to combine organisms of different species is grafting in horticulture, except that organisms are combined but a new organism is not created. However, I do not know of any similar accomplishment in animals.

an organism is a member of a species or it is not. Transplanting a solid organ from another species into a human requires that the organ in the donor species perform the same functions and to the same extent as the human analogue, but this is not enough. At least for *Home sapiens*, the potential for successful transplantation is the ultimate criterion of species membership.

Species Category

"Species category" refers to the concept of species. What is a species generally? Since there is no universal agreement on the concept of species itself that is independent of criteria used to define particular species, following a *pluralistic* approach to species category promises to be rewarding. We have been looking for a single unifying criterion of the species category for too long. Either we accept a pluralistic approach to species, or we need to disown the concept altogether. Vagueness in species category is the result of insufficient information available at our disposal. Since we must cope with having an insufficient amount of information at our disposal, we need a pluralistic approach to species category (Ereshefsky 1992). Due to chance alone, intelligence has proven to be a sufficient criterion for distinguishing *Homo sapiens* from every other extant species, without the need for evolutionary or structural considerations, or even experimental organ transplantation. For almost every other species found in nature however, additional criteria will be required.

There are three main criteria used in the pluralistic approach to species category. Species may be *interbreeding* species, which requires sexual reproduction; *ecological* species, where selection forces maintain lineage; and *phylogenetic* species defined by genealogy rather than by mode of reproduction (Ereshefsky 1992). Therefore, there is no single criterion to apply to all species. We can also apply these three criteria to entities other than species (Mishler 1982).

One counter-argument to the pluralistic approach is that using different criteria or different systems to define *species* just creates different groups of organisms that will be non-overlapping. We are usually unable to find or use a single overlapping criterion to identify a common, unifying definition for species category. A monistic approach to species, contrary to the pluralistic approach, implies that only one of these three approaches has to be correct; we just have not been looking hard enough.

The pluralistic approach illustrates the difficulties inherent in classifying two or more species derived from the same common ancestor. The pluralistic approach illustrates how species all relate to each other. The addition of structural similarities as proposed by Kitcher to the three criteria noted above may help to clarify species category further. Under the pluralistic approach, both spatiotemporally restricted and unrestricted categories for structure are permissible, yet remain open to criticism.

Hull criticizes the criteria used in species pluralism as being too liberal, as a case of "anything goes" (Hull 1987). Some criteria may be more important than other criteria. For example, interbreeding as a process contributes the most to evolution in biology. Yet asexual reproduction is much more common in the natural world than sexual reproduction, and so we would prohibit many organisms from forming species if we relied on the interbreeding definition alone. In response to Hull's monist criticism, pluralists propose that a species concept must be empirically testable as well as be internally consistent (Ereshefsky 1992). The interbreeding criterion is empirically testable. Finally, others criticize the approach of defining a species based on its molecular genetic sequence, on the basis that genetic similarity and the capacity to interbreed, as well as adapt to an environment do not necessarily coincide (Ferguson 2002, Wu 2004). These findings mean that we cannot define particular species such as *Homo sapiens* based on a genetic code. To put this more crudely, there is no barcode for *Homo sapiens*, or any other species for that matter. Species must be testable by experience (Mainx 1955).

Although an attempt to define species by DNA structure appears inadequate based on the limitations of molecular genetic sequences, another attempt based on genetics using small-subunit ribosomal ribonucleic acid sequences exists. Using small-subunit ribosomal ribonucleic acid in a process called *phylotyping* has been dubbed "the biggest boon to environmental microbiology since the Petri plate" (Doolittle 2010). A technique called *average nucleotide identity* compares gene sharing between organisms. A species then is "a category that circumscribes a genomically coherent group of individual isolates/strains sharing a high degree of similarity in independent features, comparatively tested under highly standardized conditions". Similarity defines as 97% identity between small-subunit ribosomal ribonucleic acid sequences, although others have used an average nucleotide identity of 95 or 99% to define identity (Doolittle 2010).

Such percentage cutoffs as these are obviously arbitrary since they create new species or subsume existing species under others, depending on the selected cutoff percentage. Yet any single organism can only be a member of one species at a time if we are to avoid ambiguity. We remain to see whether these science-based attempts by biologists to linearize species identity along a continuum, rather than treat species as a categorical variable of membership or non-membership will ever satisfy philosophers of biology.

Lineage and reproduction are especially important to the concept of *species,* in contrast to *organism*. Lineage adds more value beyond mere groupings of organisms that look similar no matter how strict are the other criteria for their collection. For an organism to be a member of a species is to imply that the organism has participated in the lineage of that species. This participation can be as being part of the progeny of members of that species, or being among the parents producing progeny. Progeny may be the product of either asexual or sexual reproduction in the species, or both. Regardless of the mode of reproduction, there is always at least some similarity and some diversity within a species.

Empirical testing is possible in the form of DNA or small-subunit ribosomal ribonucleic acid comparative analysis; whether the results of such an analysis overlap with reproductive capacity is irrelevant to parenthood when we ascertain lineage in this manner.

Unlike a philosopher perhaps, a clinician will be interested in species category only to the extent that such knowledge guides therapy. As I have discussed, species taxa are especially important in SOT because of the limits it creates on the transfer of organs. Clinical medicine currently treats species as a categorical variable. There is the human species and there are all the non-human species. Human species cannot breed with any other extant species and produce offspring. However, acknowledgement of species pluralism in clinical SOT is implicitly contained within the human species taxon. All that matters to the transplant clinician is that the physiology of the transplanted organ be compatible with human physiology. This similar physiology is how animal species are selected for xenotransplantation.

Clinicians have transplanted non-human organs only from baboons so far (Starzl 1996) because baboons are primates, and have a closer shared ancestry than other available animals of comparable size. Clinicians selected baboons over chimpanzees as donors for the initial xenotransplantation procedures because baboons have tails while chimpanzees do not, and it was felt that using baboons was less likely to raise ethical objections to xenotransplantation. Baboons are more distant from Homo sapiens than chimpanzees, since baboons are monkeys, not great apes.

Pigs are the only other animals seriously considered as a candidate for a supply of organs, because they are more readily available than baboons, and are of comparable size to human beings. Pigs also breed quickly. Genetic engineering on pigs minimizes the impact of their organs on immunity. In all attempted cases of xenotransplantation, only secondary consideration is given to lineage and the relatedness of those species to humans. Therefore, technological advances in clinical SOT have promoted species

pluralism because clinical convenience defines and tailors species suitability for organ retrieval. However, there remain insurmountable limits to technological advances in transplantation not always imposed by the differences in species anatomy and physiology. It will always be impossible to transplant organs from reptiles and fish because they are just too different physiologically to produce the same types of waste products as *Homo sapiens*, but there is no physiological reason for not transplanting organs from other mammals into *Homo sapiens*.

SOT is the ultimate categorization tool for species both anatomically and physiologically.

2.3 The Meaning of Organism

I will first discuss some of the prominent views associated with the meaning of the term *organism*.

Machine View of Organism

One common conception of an organism is that of a *machine* (Nicholson 2014). The machine conception of the organism (MCO) is a powerful conceptual tool of heuristic value that depends on ontological correspondence between organisms and machines, and dates back at least to Descartes (Nicholson 2014). Another metaphor is closely associated with a machine when used to describe an organism. The "genetic program" (Mayr 1961), is based on "coding in the DNA of the nucleus of the zygote" and has therefore been likened to a computer software program. Dawkins calls organisms "survival machines-robot vehicles blindly programmed to preserve the selfish molecules known as genes" (Nicholson 2014). The genetic program envisioned by Mayr carries a perception of stability through time to organisms that in turn entails stability to the method by which new organisms are produced.

Using the machine metaphor for the organism immediately leads to substantial difficulties, however. Parts within an organism, unlike within machines, are not independent of the whole organism, but depend upon each other for their survival. Connectedness among the parts is everything. An organism, unlike a machine, does not come together by assembling pre-created parts. Organisms and machines are both purposive systems; the difference however is that organisms are intrinsically purposive while machines are extrinsically purposive. An organism's priorities are to serve itself. Organisms are self-organizing, self-producing, self-maintaining, and self-regenerating. Organisms have no output other than themselves. Unlike in a machine, an organism's structure does not entail its function (Nicholson 2014).

As for Mayr's genetic program, DNA is an inert substance outside the cell, and neither energy nor material flows within DNA. Genes are not even the sole vehicles for information transfer from one generation to the next, since epigenetic phenomena are equally important in determining phenotype. Genes are simply repositories of information available to the organism for its use. A genetic code is not a sufficient explanation for the great fidelity seen in embryogenesis. Natural selection operates on the organism as a whole, not on its parts, and favors the survival of the whole organism. There is no designer of an organism as there would be for a machine (Nicholson 2014). For all the reasons noted, scientists and philosophers no longer consider the machine view of the organism tenable.

How is an organism not a machine when it has mechanisms? Mechanisms do not entail function of the organism if the organism does not express them. Mechanisms in an organism cannot yet be turned into algorithms for processing by a computer. Even if such a computer is created, not every function in an organism can be replicated. Organisms also create mechanisms according to their needs. Redundant mechanisms are suppressed to the point that they are undetectable, yet can be expressed when the need for them arises. In principle, machines may one day cross some threshold of computational processing

capability to count as organisms, but the organisms found in the natural world today are very different from the machines of today.

Self View of Organism

In what I call the *self* view of the *organism,* Fox Keller (2000) characterizes the organism as "a bounded physicochemical body capable not only of self-regulation or self-steering, but also, and perhaps most importantly, of self-forming. An organism is a material entity that transforms into a self-generating self by virtue of its peculiar and particular organization. In her characterization of the organism, Fox Keller uses the metaphor of the *self* five times, including in the apparent tautology of "self-generating self".

Fox-Keller's use of the *self* makes her characterization of the organism very difficult to conceptualize. What she calls peculiar and particular also requires unpacking. However, it is helpful that she indirectly describes *organism* in terms of its capability to withstand and persist through a process of self-regulation when faced with unpredictable changes in the environment and changes in its genome. Self-organization brings about persistence. Fox-Keller also characterizes the organism as "bounded", which I will show later is very helpful to my project whose starting point is that biological entities have boundaries.

Logical Empiricist View of Organism

Mainx (1955) characterized *populations of organisms* among his so-called *complex* points of view, distinguishing such complex views from more *elementary* methods such as morphology, physiology, and genetics. Mainx's much larger objective was to provide a space for biology in the logical empiricist agenda despite its emphasis on physics, the observed peculiarity of its object and biology's own methods of research and points of view required by its object. Biological statements have the features of empirical statements testable by experience, subject to verification and falsification, and just like all other scientific statements these statements lead to predictions that in turn lead to new hypotheses and experiments.

We can split "blanket statements" like organism into smaller, partial processes that are more easily testable and lead to the elimination of contradiction. The organism and its environment form a system. Organisms are capable of *self-regulation* in their environment, and possess a genome with distinct structural and functional properties. Mainx cautions against the intuition of "wholeness" of the organism needed to satisfy the emotional needs of the biologist or philosopher, and thus indirectly acknowledges that organisms can potentially be taken apart without a loss of identity.

In summary, the logical empiricist agenda cautions against making mistakes in conceptualizing organism without actually providing firm concepts beyond self-regulation and specific genomic properties.

Plasticity View of Organism

We can conceptualize an organism in terms of its *plasticity*. According to West-Eberhard (2003), plasticity in phenotype is the essential feature of an organism. Plasticity is the "ability of an organism to react to an internal or external environmental input with a change in form, state, movement, or rate of activity" (West-Eberhard 2003). This plasticity allows organisms to react to unpredictability by making compensatory changes in both their physiology and development, besides also permitting novelty and stability to occur at the same time. Initially, an organism produces novel traits or trait combinations for immediate adaptation without underlying genetic change. Later on, due to variation in the developmental plasticity of different individuals, developmental recombination occurs, producing a population of novel phenotypes and providing material for selection (West-Eberhard 2003). Repeated developmental recombination leads to variable reproductive success, which in turn leads to evolution. Thus, plasticity leads to evolution, and phenotype precedes genotype. Phenotypic novelty is therefore reorganizational rather than driven by genes (West-Eberhard 2005).

While West-Eberhard produces a distinctly counter-intuitive proposal for an organism's phenotype, by placing phenotype before genotype, she does use the term "individuals" instead of what I presume is "different specimens of the same organism" in describing development and evolution that appear to be her main interest. Plasticity defines the organism itself, which appears straightforward.

Tripartite View of Organism

According to the *tripartite* view of the organism, all organisms are living agents at some point in their existence, and are physically bounded and continuous. Organisms are distinguished from other living agents by virtue of being part of a reproductive lineage, and by being functionally autonomous. Some members of the lineage have the potential to possess an intergenerational life cycle. Reproductive lineage and a life cycle distinguish organisms from other living agents, *including organs*. The vagueness of this concept of organism captures the messiness of the biological world (Stegmann 2007). The tripartite view of organism therefore, emphasizes both reproduction and autonomy as characteristics of the organism.

Metabolic View of Organism

According to the *metabolic* system view (Godfrey-Smith 2013), organisms are systems that contain parts, the parts are diverse in their nature, and these parts all work together in maintaining the system's structure. Organisms turn over material, and to do so, they obtain resources including energy from the environment. Organisms continually use energy to resist decay. Reproduction is contingent for the organism, and so the organism can possess any kind of history. The boundaries of the organism can be vague, and the functioning of an organism's parts can be heterogeneous. The metabolism system view emphasizes cooperation among the parts of an organism. Therefore, an organism is the

"largest unit of near unanimous design" with unanimity being understood in terms of cooperation among the parts (Queller 2009, Godfrey-Smith 2013).

Degrees of organismality are possible in the metabolic view of organism, based on the degree of cooperativeness exhibited among its parts and the absence of conflict. From an anatomical perspective, it is possible to divide an organism, since it is possible for an organism to survive being cut up. However, it is likely that the cut-up parts will not be able to function as metabolic wholes to the same extent as the intact original organism functioned (Godfrey-Smith 2013). Organisms may be unicellular or multicellular, as well as prokaryotic or eukaryotic, and vary in complexity accordingly. Since the parts of a system may display autonomy, it is also possible for organisms to exist within other organisms, which is not uncommon in nature.

The metabolic view of organ implies that just as an organism can be cut up with the pieces retaining substantial metabolic function, parts can also be added to an organism without a loss of biological identity, as long as the metabolism of the new part successfully integrates with the rest of the organism.

Genotype View of Organism

Finally, defining an organism in terms of a *genotype and phenotype* has appealing simplicity. Every organism has both a genotype and a phenotype, both of which are required as part of the organism's description. The genotype is the descriptor of the genome, which is the set of physical DNA molecules inherited from the organism's parents. The phenotype is the descriptor of the *phenome,* the manifest physical properties of the organism, namely its physiology, morphology and behavior. Although describing the organism simply in terms of its genotype and phenotype provides an epistemological foundation to knowing about specific organisms, it does not help us understand the ontological status of an organism. Moreover, the organism's DNA sequence does not contain all the required information needed to specify the organism. Rather, the organism's

identity really depends on the outcome of developmental processes dependent on genotype, and the temporal sequence of environments in which the organism develops.

A Synthesized View of Organism

I will now sift through these various concepts of the organism, extracted from the various descriptions above, but now add some clinical experience. The metaphor of the organism as a machine (Nicholson 2014) is helpful when likening a physician to a mechanic. This metaphor is also at least partially helpful heuristically in the case of standard surgical procedures, where anatomy is consistent across human organisms. Although the genetic program is considered an important source of biological information, the genetic program is presently rarely a target of therapy for disease; rather, it is the downstream effects of the genetic program that interest the patient and the clinician the most. The metabolic system view (Godfrey-Smith 2013) emphasizes cooperation and leaves boundaries vague, and allows for reproduction to be optional. It describes human metabolism accurately. Degrees of organismality (Godfrey-Smith 2013) are at least conceptually possible, because there are many organisms that reside in association with the human being. Godfrey-Smith's metabolic view of the organism appears most promising as a base view, with the addition of a conceptual boundary taken from Fox-Keller.

In summary, *an organism is a bounded physical-chemical body which is or was a living agent at some point in its existence, is potentially but not necessarily capable of reproduction at some point in its living existence, and that uses energy to exchange resources with its environment in order to resist decay.*

Now I will explain my synthesized concept of organism further. For an organism to be a *bounded physical-chemical body* implies that the organism has a *boundary*, external to which the organism is not present, and internal to which it is present. For an organism such as the quaking aspen (to be discussed soon), this boundary could be very extensive, and for the human organism, this boundary could limit the extent of space occupied by cells of the

same human lineage. Two specimens of the same species count as different organisms, even if they are identical in every respect. "Same" here refers to the specimen under study. Likewise, a dead organism still counts as an organism as long as it has not undergone appreciable decay; we can still consider a single specimen of an organism preserved indefinitely in a jar of formalin an organism.

The *physical-chemical* part of the concept's articulation is self-explanatory; all organisms as we know them are subject to the laws of physics and chemistry. *Potentially* capable of reproduction[6] allows for the inclusion of animals such as the mule as organisms even when mules do not have the capacity to reproduce on their own. Potential reproduction also allows us to include organisms produced by cloning. Energy use combined with resource exchange with the environment is important for conceptualizing *organism* to encompass respiration, and also because waste products from one organism can become a valuable resource for another in the immediate vicinity. All organisms must reside in some kind of an ecosystem.

Organism therefore requires a boundary, a physical-chemical nature, life, a potential for reproduction, the consumption of energy, and an exchange of resources with the environment.

I have excluded behavior from my definition of the organism since "behavior" already encompasses existence itself and the occupation of space *per se* in an environment. Plasticity, reproduction, utilizing energy, and exchanging resources with the environment all count as behaviors. One organism can be a resource for another organism that harbors it. Behavior is therefore a redundant term. The definition excludes *genetic* lineage because an organism does not need it; both clones and products of sexual and asexual reproduction count as organisms even though they might originate from different lineages. We do not need to know the lineage of an organism to describe it as an organism. Even though

[6] Such as reproduction through cloning, for example.

organisms do have a lineage, it may be the case that we never have the means of ascertaining that lineage.

Lineage is also not required in the concept of *organism* because non-organisms may also have a lineage. Viruses straddle the boundary between life and non-life because they do not have their own metabolism, although they satisfy many other criteria for *organism*. The status of viruses as organisms is controversial. However, viruses do have a lineage. Since all organisms must have been living at some point, present or past, and we do not have the capability to create life, lineage is excluded from the definition even though it still needs to be acknowledged in some form as a descriptor to distinguish one organism from another.

Autonomy is not required for an organism either, since conceptually no organism is truly autonomous from its environment or from other organisms. There is a continuous dependence on the environment in which the organism is situated, without which the organism quickly ceases to exist. Furthermore, viruses are not autonomous.

In summary therefore, an *organism* does not require genetic lineage or autonomy. Lineage in some form is required when distinguishing among organisms but is not required for the concept of *organism*. On the other hand, an organism requires a boundary, a physical-chemical structure, life at some point, a potential for reproduction at some point in its living existence, and use of energy to exchange resources with its environment in order to resist decay. Each of these criteria is relevant to my project on biological personal identity, but I will focus most on boundaries since boundaries are especially helpful in distinguishing organisms from other organisms with which they associate.

As I will later show, organisms combine to form superorganisms, but I will first tackle the messy concept of *individual* next, to show that understanding the physiological individual provides the most direct path to arrive at a concept of superorganism.

2.4 The Meaning of Individual

Now that I have surveyed the concepts of *species* and *organism* found in the philosophy of biology, we are now ready to tackle the meaning of *individual*. I have already described *organism* as a bounded physical-chemical body which is or was a living agent at some point in its existence, is potentially but not necessarily capable of reproduction at some point in its living existence, and that uses energy to exchange resources with its environment in order to resist decay. I have also described how adding lineage helps to define a species when grouping organisms. However, the term *individual* is much broader than that of *species* or *organism*. *Individual* therefore warrants a separate discussion from either *species* or *organism*.

The word individual derives from the Latin root *individuus* that means "that which cannot be divided". If we divide an individual, then the individual would cease to exist, and all the characteristics and attributes of that individual would cease to exist as well. The concept of *individual*, however, is more nuanced than just the word "individual". Since my approach to *individual* is biological, it will be especially helpful to understand *individual* through a biological entity such as *organism*.

The organism is the paradigmatic individual, and so while it may be helpful to discuss *individual* and *organism* together, it is important to acknowledge that there are many other types of individuals. Unfortunately, the literature often uses *organism* and *individual* interchangeably, and the even more unfortunate "individual organism" appears frequently. For example, Turner calls individuality the defining attribute of the organism (Turner 2013). Yet genes, cells, and groups can all be individuals (Godfrey-Smith 2013). Even non-living objects like chairs or abstract concepts like ideas qualify as individuals. I will restrict the concept of individual to the *biological individual*, and describe the *evolutionary individual* briefly in the next section, before moving on to the concept of *physiological individual* for the rest of the dissertation.

We can subdivide the biological individual into two categories: the evolutionary individual and the physiological individual (Pradeu 2016a). Although these two categories have overlap, they are not interchangeable. Understanding both categories of biological individual provides a more complete picture of the individual and will be more compatible with how biologists practice (Pradeu 2016a). However, fully understanding both categories of *individual* is an enormous undertaking, and so philosophers of biology may prefer to "specialize" in one or the other categories of individual. The current literature skews towards describing the evolutionary individual (Pradeu 2016a). Yet combining other biological perspectives with evolution is more likely to inform the concept of biological individuality (Pradeu 2016b). My analysis in this dissertation proceeds through the physiological individual.

Wilson and Sober (1989) provide us with a more useful starting point for understanding the biological individual than provided by a study through evolution alone. They acknowledge both the evolutionary and physiological aspects of an individual. The human body is a product of biology. The human being has a start date and an end date, and works as one unit between those dates even though its parts are constantly replaced. Sometimes, parts are added[7], or parts are removed without being replaced[8]. A biological individual can be therefore considered a "functionally integrated entity whose integration is linked to the common fate of the system when faced with selective pressures of the environment" (Wilson 1989). The key phrase to take away from this definition of the individual is *functionally integrated*.

The Evolutionary Individual

I will discuss two prominent views of the evolutionary individual, those of Godfrey-Smith (2013) and Goodnight (2013).

[7] Organ transplants and blood transfusions are examples of added parts.
[8] Common examples of part removal include appendectomy (appendix) and cholecystectomy (gallbladder).

According to Godfrey-Smith (2013), an individual is *Darwinian*, which means that any *individual* is a member of a Darwinian population. In turn, a Darwinian population is a collection of entities that evolves by natural selection, or Darwinian change, which means that there is variation, heredity, and differences in reproductive success. The central criterion for an individual then becomes reproduction, even though the reproduced entities (offspring) need not be identical to the parent.

Bacteria are an example of *simple* reproducers, using their own machinery, while human beings are *collective* reproducers, who not only reproduce but also contain many different types of cells that reproduce according to their own rules. Some entities that reproduce do not even need their own machinery to do so, like viruses, are "*scaffolded* reproducers". All three types of reproducers count as individuals. By this token, genes and chromosomes are also individuals (Godfrey-Smith 2013). According to Godfrey-Smith, organisms are systems that contain parts, diverse in their nature, and these parts all work together in maintaining the system's structure. As mentioned previously (section 2.3), Godfrey-Smith prefers the metabolic view of the organism. The metabolic view of organism puts Darwinian individuals in a symbiotic relationship with an organism, and makes a human being both an organism and an individual. Although Godfrey-Smith's definition does not explicitly state this, I take it to mean that he believes that a human being is *simultaneously* both an individual and an organism.

Godfrey-Smith claims that he "does not know" of cases of multispecies Darwinian individuals that are not organisms (Godfrey-Smith 2013). In my view, Godfrey-Smith's view is helpful in recognizing that there is a conceptual difference between organism and individual, but it does not show us how to (or whether we should) distinguish an organism from an individual when analyzing a complicated biological entity such as a human being. I will be devoting an extensive discussion to the human microbiota in Chapter Three, but suffice it to say for now that Godfrey-Smith's view of the multispecies Darwinian organism may not be compatible with his own metabolic view of the organism, at least in the case of

the human individual. Non-viral microorganisms (bacteria, yeast, and parasites) associated with the human organism each have their own metabolism, which is at most only partly dependent on human metabolism, so a multi-species Darwinian individual like the human being meets the criteria for a human individual, but not criteria for a human organism. The overlap of metabolism among species is only partial.

Goodnight (2013) discusses the *individual* from the multilevel-selection evolutionary perspective. He proposes three definitions for the individual: the individual is the level at which fitness is assigned, the individual is the lowest level at which selection is acting, and the individual is the lowest level at which a response to selection can occur. I will briefly describe each of these definitions of an individual from Goodnight in turn.

According to Goodnight, the evolutionary individual may simply be an arbitrary construct of the observer. An observer chooses a convenient level of organization, such as the level of the cell or the level of the organism. The scientist designates the individual based on what specifically the scientist is studying from the available data. This is particularly true when the organisms are extinct and there is a great dependence on fossil records. Controversies arise not from the data, but from the level at which fitness has been assigned. Data may be available only at a species but not organism level, in which case "species" becomes the individual and changes become "species selection". In this case, fitness then is assigned at the group level (Goodnight 2013).

The evolutionary individual might also be the lowest level at which selection is acting, so the *individual*, therefore, is the product of selection. This could be at the level of the gene or the cell. However, searching individual genes or cells, one after the other, for any variation would be an exhausting if not impossible task to accomplish. In addition, internal processes within the organism mediate the responses to selection at the level of the organism. Processes internal to the group mediate responses at the group level. Only the germ cells matter in human heredity. When somatic cells mutate causing diseases like

cancer, they do not spread beyond the organism to the next generation because somatic cells segregate from germ cells. Segregating germ cells from somatic cells prevents evolution below the organism level (Goodnight 2013). In the case of a human organism, the specific part of reproduction accomplished by the germ cells does not require their functional integration with other organisms, but it does require a functionally integrated individual.

Goodnight's third definition of an evolutionary individual is that it is the lowest level at which a *response* to selection can occur. This third definition adds to the previous definition by taking into account as another variable the evolutionary response to the pressure of selection (Goodnight 2013).

All three of Goodnight's definitions emphasize the role of the individual in evolution. Even if the human being is both an individual and an organism, Goodnight's definitions add little to the work of Godfrey-Smith in distinguishing between them.

The Physiological Individual

Having discussed the evolutionary individual to acknowledge the literature around *individual*, I will now discuss the physiological individual to arrive at the concept of *superorganism.* When an individual is functionally integrated, it means that whatever the individual contains is "whatever works together and dies together". By this token, groups and communities also possess similar properties of functional organization, and are therefore individuals. When organisms associate with each other to create individuals, all parts of the individual share a common physiology to some extent.

Wilson and Sober use the term *superorganism* in this case of groups and communities of organisms, instead of *individual* (Wilson 1989). Genes are irrelevant to functional organization *per se*. In addition, evolution in structured populations is best understood as evolution in units of functional organization. Although the concept of

biological individual as discussed by Wilson and Sober appears firmly founded in biological principles of functional organization, and includes both evolutionary individual and the physiological individual, their concept again does not help in distinguishing individual from organism, similar to the views of Godfrey-Smith (2013) and Goodnight (2013).

Functional integration is also a part or whole of numerous other definitions of organism (Fox Keller 2000, West-Eberhard 2003, Godfrey-Smith 2013). In the case of the human being, it is important to recognize that microorganisms in the human body do not necessarily cease to function along with the human organism. Physiological individuality permits an acknowledgement of the vital role of microorganisms in human physiology, but without becoming entangled in details about the different lineages of microorganisms and the human being. Distinguishing between organism and individual requires distinguishing between the evolutionary individual and physiological individual first.

The concept of the physiological individual includes the study of the physiology of an individual right from conception to death (Pradeu 2016a). The study of embryology, anatomy, neuroscience, immunology, and many other branches of biology all play important roles in the story of physiological individuality (Pradeu 2016a). Immunology plays an especially important, perhaps central role in establishing and maintaining physiological individuality because of its pervasive role throughout the individual's space and throughout the course of the individual's life. According to Pradeu, the immune system delineates the boundaries of the organism by acting as a self-nonself discriminating mechanism, and by defining the relationship between organisms, it also delineates the boundaries of the individual.

In summary, an individual is a functionally integrated entity whose integration links to the common fate of the system when faced with selective pressures of the environment. Wilson's 1989 definition of the individual is accurate for *individual*, but must not be

confused with a definition for *organism*. Godfrey-Smith and Goodnight offer definitions for the *evolutionary individual*, and Pradeu explains the concept of *physiological individual*.

We are now making some progress in distinguishing individual from organism, through identifying the physiological individual as the result of functionally integrated organisms. This is not to say that understanding the evolutionary individual cannot be a route to understanding the distinction between individual and organism. However, the physiological individual provides a means for direct observation of phenomena that interest clinicians. As I will discuss in subsequent chapters, the *physiological individual* is the most useful type of individual to consider when understanding the impact of SOT on biological personal identity.

2.5 Why the Organism-Individual Distinction is Still Problematic

I have discussed some reasons for why arriving at an acceptable definition for species, organism, and individual can be so problematic. These difficulties are compounded by a further difficulty not yet discussed; one that will pose an especially significant challenge to distinguishing the organism from the individual. The organism-individual distinction therefore needs to be further sorted out before proceeding to the concept of superorganism. Since organ transplantation adds more complexity to the concept of superorganism, as I will later show, it becomes even more important to first understand *superorganism* in the context of the larger biological world.

Organisms in nature not only live together, but they *combine* with each other, and they *depend* on each other for their survival even when they do not physically combine with each other. Nature provides many examples of how the organism-individual distinction is conceptually blurred. These examples of organisms range from the mundane to the exotic when viewed from the human perspective. At least some of these examples have the potential to inform our understanding of the biological human being.

There are several problematic examples[9] selected across phyla and kingdoms. I will first discuss bacteria generally, as an example of a prokaryotic unicellular organism, and then a certain type of amoeba, as the representative for a eukaryotic unicellular organism. Next, I will describe a tree called the quaking aspen as a representative of plants. Following this example, I will discuss a type of termite and then the Hawaiian bobtail squid as examples among land-based and aquatic animals respectively.

Bacteria

It is not difficult to visualize organisms such as prokaryotic cells, for example bacteria, distinctively as individuals under the microscope. However, prokaryotes such as bacteria do not typically live isolated lives, but rather live in association with other organisms in competitive, parasitic, commensal, or symbiotic relationships (O'Malley 2007). Single prokaryotic cells that may be unable to accomplish tasks such as accessing sources of energy, living in difficult habitats, or reproducing when isolated are able to do so through coordination with other cells and differentiating into specialized cell types (O'Malley 2007). There are several well-described communal activities or social processes exhibited by prokaryotes. I will next briefly describe four such communal activities as described by O'Malley (2007).

The exudation of slimy substances creates biofilms that unite many bacterial cells together. The biofilm creates metabolic diversity, enabling survival of the bacterial cells in harsh antibiotic environments (Davey 2000). Chemotaxis, which is the directed movement of cells in response to chemical stimuli, is also a social process involving chemical communication among cells (Park 2003) that can lead to further interactions such as the biofilm. Quorum sensing enables bacterial cells to assess the density of their population through cell-to-cell communication similar to that seen in higher organisms (Miller 2001). Finally, genetic material transfers between bacterial cells through a process called lateral

[9] These examples are all taken from Bouchard and Huneman (2013) *From Groups to Individuals*. The MIT Press, Cambridge, MA, USA.

gene transfer (also called horizontal gene transfer). DNA can be transferred through direct cell-to-cell contact, through mediating bacteriophages, or directly though the medium of the environment. Lateral gene transfer enables antibiotic resistance and increased virulence, and promotes the stability of biofilms (Molin 2003).

Lateral gene transfer forces us to review the notion that one organism equals one genome because the "distributed genome" is an enormous global resource not contained within, yet accessible to single bacterial cells (O'Malley 2007). Since the possession of a genome is not part of my definition of the organism, the concept of organism holds up to this significant challenge posed by bacteria. In addition, autonomy is not part of my concept either, and so these common bacterial activities do not challenge the concept. Biofilms therefore count as physiological individuals. The individual, not the organism, provides autonomy as well as a large genome to enable persistence in the environment.

In summary, a bacterial community is not just a random conglomeration of cells. We can consider a bacterial community an individual with indeterminate boundaries that have some un-organism like properties while still possessing many organismal characteristics (O'Malley 2007). Since bacterial cells often live their lives in the form of biofilms, constantly communicate with each other, and transfer genetic material, bacteria do not fully qualify as either organisms or individuals.

Amoeba

A spectacular example of how individuality can change is what we observe with the group of social amoebae, or cellular slime molds. *Dictyostelium dicoideum* is an example of a so-called "social amoeba", which lives in soil, and is a eukaryote. *Dictyostelium discoideum* displays a spectacular transition between a unicellular and multicellular entity. Bacteria in the soil are its main food. For much of its natural life the organism exists in an asexual unicellular form, but in times of food scarcity the unicellular amoebae coalesce by using a mechanism of chemical signaling to form a multicellular organism called a *slug*.

This slug is a "society" of 10,000-100,000 amoebae that exhibits elements of competition, altruism, and social cheating (Strassmann 2000). The slug can move to areas where there is a more abundant food supply. Some cells in the multicellular slug become a nonviable stalk so that they may support other viable cells to form spores that can then disperse to suitable environments. The survival of the organism is thereby ensured. The organism then eventually returns to a unicellular state when conditions become favorable again.

This "life cycle" of *Dictyostelium discoideum*, with its transitions between the unicellular and multicellular states challenges the notion of *individuality in the organism.* If the species is capable of moving back-and-forth between unicellular and multicellular states, it becomes unclear which entity is the organism and which entity is the individual. If the unicellular amoeba is the organism, then the slug represents exemplary cooperation among many organisms to facilitate survival of the whole population. On the other hand, if the multicellular slug is actually the organism, then the unicellular amoeba are just physically separate parts of that multicellular organism. Therefore, which form of *Dictyostelium discoideum* is the individual and which is the organism is unclear. The concept of individuality reduces to one of timing in the life cycle. Each amoeba specimen will have its own history and lead its own life independent of all the other unicellular amoebae around, if they do not coalesce.

I propose that having a boundary is the most important requirement for an organism. Calling a population of unicellular amoebae an organism leaves it without reasonably fixed boundaries, which is an important requirement for an organism. The spatial relationship between two amoeba will be at least partially random. Therefore, I propose that when the amoeba is its unicellular state, it is *both* an organism and an individual. When the amoeba is in its multicellular state, it is an individual only. However, one could take the opposite stance and claim that the unicellular amoebae are a distributed individual and the multicellular slug is both an individual and organism, to which I respond that if we remove a particular amoeba specimen from its environment, away from all its

companions, then it is still both an individual and an organism because the amoeba can live independently.

Plants and Trees

The quaking aspen, or *Populus tremuloides*, is a huge organism. Current lay notions of the largest organism on earth are the blue whale (no particular specimen) and one giant sequoia specimen called General Sherman. However, the largest known organism might actually be a 6-million kilogram quaking aspen, *Populus tremuloides*, which is located in Utah in the southwestern United States and is more than 3 times the size of the next largest organism (Mitton 1996).

Quaking aspen can also live for over a million years (Mitton 1996). An unusual feature of the quaking aspen is its regular reproduction through a process called suckering, by which lateral roots sprout erect stems at some distance from the original stem. Suckering gives the impression to an observer situated above the ground that these new stems, called *ramets*, represent separate trees. These seemingly separate trees can be spaced 30 metres or more apart, but are in fact one genetic individual. Up to 47,000 individual stems from one clone has been described (Mitton 1996). This form of reproduction typically occurs after a major environmental disturbance such as a forest fire has occurred. Clones are either male or female, and the habitats, growth rates, and physical characteristics of these clones differ. Yet *Populus tremuloides* also reproduces by seeds, like many other trees, and is therefore quite unremarkable in this respect. Genetic variation exists within the species, and this variation is believed to be due to differences in physiology, growth, and survival among genotypes (Mitton 1996).

Populus tremuloides thus provides yet another enigma in the individual-organism distinction. The forest in this case turns out to be one organism, even though the trees appear as individuals that may be subject to different fates. The quaking aspen's great success means that the species is "doing something right" (Bouchard 2008). Continued

access to proven resources in the environment by the new stems, while being able at the same time to explore new territory for the organism may be the significant evolutionary advantages of the quaking aspen's suckering. Furthermore, seeds produced through sexual reproduction have a high mortality rate, so suckering becomes very important as a means of persistence. There may even be variation in fitness within the quaking aspen grove (Bouchard 2008). This variation also contributes to prolonged survival of the organism as a whole. Genetic lineage does not matter as much as the environmental pressure when reproduction can be both sexual and asexual.

Varying survival times of the stems of the quaking aspen would mean that head counting of trees is no measure of evolutionary success, when the identity of even a single tree is open to question. What matters is the persistence of the entire organism through time. Consequently, the fate of one visible quaking aspen stem is neither the fate of an organism nor an individual.

Perhaps the distinction between organism and individual in the case of *Populus tremuloides* becomes easier to understand if there is no soil line to hide the underground parts of the system from us. We can then view the forest as just one large organism with each stem being reduced to a simple body part, albeit with a differential level of fitness. The individual then can still be *Populus tremuloides* with all its underground parts and symbiotic soil bacteria. If we sever an individual stem of *Populus tremuloides* from its source, or "parent", that stem is capable of independent existence apart from its parent. So we can view *Populus tremuloides* as an individual consisting of conjoined organisms. Members of the genus *Populus* possess an extensive microbiome with which it exists in a symbiotic relationship (Hacquard 2015). Therefore, *Populus tremuloides* with its microbiome may be the individual, and *Populus tremuloides* itself with all its intricacies may be the organism. New organisms are created each time new boundaries are created. Different hierarchal levels will count as individuals across species, sometimes even within

the lifetime of a single clone. Intermediate levels of individuality are also possible (Clarke 2012).

Animals

The termite (*Macrotermes spp*) is an organism that exhibits a sophisticated social system. The main dietary component of termites is wood, which is hard to digest. Termites possess a gut microbiome, but some macrotermitine termites also construct an extracorporeal digestive system by cultivating a fungus (*termitomyces spp.*) on structures called "fungus combs" that are assembled in a "fungus garden" (Leuthold 1989). The termites then pass on finely divided wood fiber, which is their main food material, to the fungus combs along with fungal spores. The spores germinate, and the fungus then digests the wood fibers, providing the termites with the digestible diet they need to survive. The insect colony has a finite lifespan that usually corresponds to the life of the queen, although this lifespan can be several decades long. This feature of the termite colony distinguishes this colony from other insect colonies that last longer than particular insects. The termites construct a huge mound above the ground that acts as a ventilatory structure via the wind, based on differences in air pressure between the inside of the nest and atmosphere (Turner 2001). When the mound is wounded from the trauma of an external force, for example, a process of healing is initiated that then occurs in the form of distinct recruitment, repair, and remodeling phases. These three phases of mound healing are similar to the phases of healing when a large animal such as a human being is wounded.

What then are the boundaries of *Macrotermes*? The structure of the mound itself illustrates that the physiology of the insect extends beyond its apparent body. The termite's physiology clearly extends into the surrounding environment, and this extension serves to blur the boundary between the organism and its environment. By extension, the individual is the mound and all its functionally integrated contents including the insect, because it is the mound and not the insect that persists through time. Conversely, one may

claim that the termite and the environment it creates is what constitutes the individual, and only the termite itself is the organism. Although the mound lasts much longer than the termite, both the mound and the termite persist through time, just to a different length. It is unreasonable to claim that the termite does not persist though time. Unlike in the case of many other individuals, however, the mound has a special capability of persisting for a very long time.

The Hawaiian bobtail squid, *Euprymna scolopes*, provides another example from the animal kingdom that exemplifies a symbiotic relationship between an animal and a much smaller organism, and again brings into question the individuality of the larger animal. The Hawaiian bobtail squid contains light organs called photophores, which contain about 1 billion bacteria of a species called *Vibrio fischeri*. These bacteria are bioluminescent through a process involving quorum sensing and achievement of a certain density inside the organ. This bioluminescence prevents the squid from casting shadows that would identify the squid to potential predators. When the squid is the hunter rather than the hunted, potential prey below cannot see the squid either (Bouchard 2008). For these favors to the squid, the bacteria obtain their food supply from the squid. The squid expels about 80% of the bacteria each day, preventing a disease state in the squid occurring from prolonged contact with too many of the bacteria.

The bioluminescence is of no apparent direct benefit to the bacteria in enhancing their fitness, and the bioluminescence is not observable when the bacteria are free-floating in low concentrations in seawater. Conversely, there is no coding for bioluminescence in the squid's genome. Bioluminescence is a property of the squid-bacteria entity, which is a multi-species, multi-organism individual. Symbiosis and in turn bioluminescence lead to persistence of the *system* rather than reproductive success of an organism (Bouchard 2008). Regardless of the ontology involved in such systems, the number of organisms and individuals involved is open to question. Depending on the criteria one uses, one squid plus 1 billion bacteria can be counted as one billion-and-one individuals, two individuals

(squid and bacteria); one billion-and-three individuals (one billion bacteria, one bacterial *superorganism*, and one squid-bacterial superorganism), and so on (Bouchard 2008). In the latter two cases, there is an *emergence* of a so-called *superorganism*.

There are of course many more examples from the animal kingdom that can illustrate the problems inherent in analyzing the individual-organism distinction, but these examples will only serve to highlight subtle physiological distinctions among them without adding more philosophically. I will briefly remark here that the relationship of the Hawaiian bobtail squid to its bacteria moving in and out illustrates marked similarities to the relationship of human beings to their bacteria, which I will discuss in Chapter Three. However, I would like to emphasize that the exceptions these biological examples provide to the concept of individuality all pertain more to the physiological individual than the evolutionary individual. It might be helpful, therefore, to develop a concept other than simply a distinction between physiological individual and evolutionary individual (Pradeu 2016a).

2.6 Reconciling Species, Organism, and Individual

According to Godfrey-Smith (2013), a definition of individual involves acknowledgement of Darwinian fitness as mentioned previously (section 2.4). Fitness in a Darwinian sense is what distinguishes individual from organism. If the human being has such a proven fitness, then a human being counts as an individual. Since there is early germ line segregation in humans, the level of fitness can be assigned to the level of the organism, so by both Godfrey-Smith's and Goodnight's criteria a human being is both an organism and an individual.

However, one can distinguish an organism from an individual if prepared to put aside the *Darwinian* condition on individual (really an evolutionary individual) and focus more on the physiological individual. Godfrey-Smith claims that he does not know of cases that are multispecies Darwinian individuals but not organisms. Darwinian individuals can

evolve separately and then become associated at some later point in time. For example, the human immunodeficiency virus did not have a human host until the 20th century, but it began to infect human beings after a crossover event occurred from another species, probably the African green monkey. The human immunodeficiency virus transmits vertically from parent to child. The malarial parasite, as well as other bacteria and parasites with their much older history than human beings probably had other animal hosts before they started to infect human beings or cohabitate with them. It seems possible, therefore, that human beings have harbored different microorganisms throughout their history.

Euprymna scolopes provides us with a useful conceptual bridge from the animal kingdom to the human being. Like *Euprymna scolopes*, the human individual lives its life along with many microorganisms. Microbial metabolism is no doubt an important and likely indispensable contributor to the totality of human metabolism, but there are many more functions of metabolism in the human organism overall than there are in microorganisms overall. The human organism is larger and much more evolved than any microorganism. The human organism has many more complicated metabolic pathways than a microorganism does. In other words, *shared* metabolism constitutes only a small part of the total metabolism of the larger organism, or macroorganism. Although there are many products of the microbial genome, it is highly likely that most of these products benefit only the microorganisms themselves.

Microorganisms are primarily concerned with their own survival and not that of their human host. To ensure their own survival microorganisms must first compete with other microorganisms. In a disease process, these microorganisms will also compete with the human organism. Therefore, we should not allow the concept of *individual* to take anything away from the concept of *organism*. If we assign all the features of an organism to the individual, then we have no distinction between the two, and we have not made any progress in understanding the biological world. It is more reasonable to posit that an individual arises only incidentally by organisms (both macroorganisms and

microorganisms) competing among themselves for resources while forming rivalries and alliances in the process, ultimately to the evolutionary advantage of all.

Labeling the human being as an organism as Godfrey-Smith does, when it contains different individuals would imply that the human organism reinvents itself each time it takes on a new organism into its fold. The human organism in this instance can still be a bounded physical-chemical body which is or was a living agent at some point in its existence, is potentially but not necessarily capable of reproduction at some point in its living existence, and that uses energy to exchange resources with its environment in order to resist decay. However, the human organism in this case cannot be the *same* organism all along, for it becomes a different organism when it acquires or loses other organisms. The organism thereby has lost its ability to *persist* through time, and an organism needs to persist through time to be an organism. The organism has also lost its original boundaries each time it restores a boundary.

Let us consider the opposite instance, when an individual forms through the functional association of organisms. In this instance, the organism stays the same and persists through time according to its natural history, while the individual redefines itself as organisms enter and leave relationships with other organisms. The individual succeeds evolutionarily, without the need for passing organisms on to the next generation. Organisms can re-associate with each generation to re-form individuals. The organism can keep its boundaries and persist through time, leaving the individual to redefine its boundaries through its functional associations, in an ongoing process of reinvention. The separate metabolism of each organism is still respected, and the individual benefits from integrated metabolic pathways consisting of the metabolic pathways of two or more organisms. Each organism can also retain its status as a distinct species.

Instead of just calling the larger organism an organism, I propose that the larger organism with all its associated organisms is an *individual*, and the part of the larger

organism that derives from its own distinct lineage is the *organism*. We may call the larger organism the *macroorganism*, and call the smaller organism(s) *microorganisms* to fit our anthropocentric point of view. Both can retain their status as organisms. If all the appropriate criteria are met, as in the case of an isolated amoeba wandering about in the soil, then the living entity can conceptually be both an organism and an individual.

My proposal entails that the concept of individual is larger than that of organism. However, I had claimed earlier that lineage is not necessary to the definition of organism. I can easily address this concern. Historically, mitochondria and other cell organelles probably incorporated into human cells. These cell organelles may represent remnants of ancient organisms. Such cell organelles transmit from one generation to the next, according to a maternal lineage. Hepatitis B virus and the human immunodeficiency virus also transmit vertically, i.e. from parent to offspring, independent of the process by which the mother delivers her offspring.

Therefore, again, lineage *per se* does not appear necessary to defining the human organism. The human organism has acquired multiple lineages in its evolutionary history and it is impossible now to tell these lineages apart. Fortunately, we do not *need* to tell all the lineages apart, and we certainly do not need to acknowledge all of them when we describe the organism. Multiple lineages probably exist for all macroorganisms. Multiple lineages are likely even necessary for the persistence of the organism, and are therefore an integral part of the organism, but they do not have to *define* the organism, even if they are useful descriptors.

Organism and *individual* are two levels of biological organization. *Individual* is a scientific and philosophical concept. Terms such as *individual organism* include use of the word "individual" in its lay sense. We should therefore be careful to avoid *individual organism* in the future. There are single specimens of the same organism, but there is no such thing as an individual organism. There can be many individuals formed by

functionally integrating organisms, but there can be only one organism. The organism is a fixed entity in time while the individual is not. The individual can still be an evolutionary concept, which is in keeping with Godfrey-Smith's viewpoint (Godfrey-Smith 2013).

I do not claim to provide a solution to all the conceptual organism-individual distinction problems associated with every species on Earth. We can easily explain the concepts of organism and individual in the cases of the Hawaiian bobtail squid and the human being. There may not be a single separate concept for organism and individual which covers the entire natural world, and a pluralistic approach may be required to both concepts.

Nonetheless, we transplant organs between human beings, and if the human organism consists of multiple lineages derived from a multitude of other organisms while still maintaining functional relationships with yet other organisms, then transplantation science may need to view the procedure as one involving more than just the human organism alone.

2.7 Individual versus Superorganism

Recollect that an individual may be either an evolutionary individual or a physiological individual (section 2.4, Pradeu 2016a). Since for an individual to persist through time implies its evolutionary success, I propose that the concept *individual* be used for the evolutionary individual alone. We therefore need a new concept for the physiological individual, so that we may avoid the semantic confusion around *individual*. I propose that instead of *individual*, we call the physiological individual the *superorganism*.

If we use the above terminology, then the *superorganism* would have more features of an individual than an organism, and at the same time be easily distinguishable from both *individual* and *organism*. This distinction of the individual from other entities will be more important for the human being than for *Dictyostelium discoideum* or other organisms

for the simple reason that we use *individual* much more in the human context. The term "individual human being" is firmly embedded in the human lexicon and cannot be extracted. By using the term "superorganism", we can disambiguate the biological individual from every other instance where "individual" is used, while still acknowledging the functional unity exhibited by the biological entity. With *superorganism*, we can also separate *biological individual* from every other human-related use of *individual,* apart from its evolutionary use (Godfrey-Smith 2013, Goodnight 2013). Unlike for individuals, it is will also be made clear that superorganisms arise from organisms.

Superorganisms are localized in space and time, and as I will show later, are both established and maintained by the actions of the immune system.

In the case of the human being, which is the focus for most of the remainder of my dissertation, I will show that we can make a distinction between the human organism and the human superorganism. It is now time to bring the discussion closer to home. The major focus in the next chapter will therefore be the human being.

2.8 A Summary of Species, Organism, Individual, and Superorganism

In summary, life is not only diverse, but it interrelates. The concepts of *species*, *organism*, and *individual* at first all seem straightforward. However, it takes just some study of a few problematic examples from nature to illustrate that the organization of the natural world is far more complicated. Species taxa provide fixed and rigid boundaries in limiting the extent of SOT. We can only transplant solid organs within the same species. Regardless of the epistemic status of a species taxon, based on the criterion used to define a species, either an organism is a member of a species or it is not. At least for *Homo sapiens*, the potential for successful organ transplantation is the ultimate criterion of species membership.

An organism is a bounded physical-chemical body which is or was a living agent at some point in its existence, is potentially but not necessarily capable of reproduction at some point in its living existence, and that uses energy to exchange resources with its environment in order to resist decay. An organism does not require genetic lineage or autonomy, although lineage in some form is required when distinguishing among organisms. All organisms have boundaries, but organisms are not always individuals. In fact, most organisms are *not* individuals.

Biological individuals may be evolutionary individuals or physiological individuals. Evolutionary individuals persist through time, but we can directly study only physiological individuals. Organisms combine with each other through a process of functional integration that benefits all the organisms. This functionally integrated physiological individual is an emergent superorganism.

This survey of the philosophy of biology literature provides the background against which SOT is performed. The species, organism, and superorganism in which transplantation is being performed is a much more complicated concept than meets the eye. I propose that the current limitations of SOT arise from our limited understanding of these concepts. Surgeons perform organ transplants between organisms. Modern technology in the form of organ transplantation thereby provides us with a useful method to distinguish among species and organisms. This chapter emphasized literature from the philosophy of biology; the next two will emphasize the current science of the superorganism a bit more, to set the stage for understanding the emergent superorganism in Chapters Five and Six. Transplantation science may need to view the transplant procedure as a procedure involving more than the human organism alone. The biological human being on which we perform organ transplantation is an exemplar for the superorganism, which I will discuss further in Chapter Three.

Chapter Three

The Human Organism and the Human Superorganism

In Chapter Two, I described how nature provides interesting examples spread across phyla and kingdoms to demonstrate that the problems associated with arriving at a useful concept of organism and individual that is both precise and accurate are difficult to solve. These examples from nature provide accounts that are fascinating to philosophers of biology and may be useful to microbiologists, botanists, zoologists, and environmentalists, but they will be of little interest to philosophers of medicine or physicians unless the lessons learned apply by some means to better understand human beings. *Populus tremuloides* and *Euprymna scolopes* provide good sources of questions for a game of biological trivia, but their existence and physiology are of little interest to the average human being, let alone physicians or transplant professionals. There is also no meaningful biological interaction between either *Populus tremuloides or Euprymna scolopes* and humans. Fortunately, human beings do not need to look any farther than their own human body to understand the organism-superorganism distinction. Closer-to-home philosophical examination of the human being may even yield rewards for medical practice.

My goal for this chapter is simple: to demonstrate that members of *Homo sapiens* do not live in isolation from all the other species on Earth. This fact is not surprising to anyone even remotely aware of how ecosystems function. It is also not surprising to anyone who has experienced an infectious illness. In addition, however, I will demonstrate that other species do not just interact with us, or are essential for our survival, but that they constitute our very identity as superorganisms. I will also introduce the concept of the biological boundary, and show why human beings persist despite their boundaries.

Apart from a few examples of large worms that sometimes live in our intestines and which we can do without, these other species living alongside humans are microbial. We

call this collective of microorganisms the m*icrobiota*[10], which functionally integrates with the human organism as a physiological individual, or more accurately a human superorganism. This chapter is dedicated to the microbiota and its relationship to the human being.

Only one part of the human superorganism is the human organism. The human organism consists of all the structures and entities derived through its segregated germ line, even though it may include structures and entities derived from other organisms. The human superorganism consists of the human organism and its microbiota. I first provide scientific information to support these claims, and then integrate this information with the philosophical literature on boundaries to create a comprehensive picture of what it really means, biologically speaking, to be a member of *Homo sapiens*.

Whenever two organisms exist adjacent to each other, there must be a boundary between them. There will also be a boundary between the organism and its surroundings. Nature is full of biological boundaries. A separate metabolism distinguishes among organisms, but a boundary distinguishes among them as well. Boundaries and isolated metabolism go hand-in-hand.

It should not be surprising to anyone that humans have such a close relationship with microorganisms. Everyone has been ill at some time because of a microbial infection. Vaccination is a medical procedure meant to prevent infection and represents an important life event. Bacteria and larger animals share a very long period of the earth's history. The last common ancestor of plants and animals lived approximately one billion years ago. Animals diverged from plants about 800 million years ago, which is 3 billion years after bacteria originated and 1 billion years after the first eukaryotic cells appeared (McFall-Ngai 2013). Even primitive animals such as sponges associate themselves with numerous bacterial species (Land 2015). This long-shared history of animals and microorganisms is

[10] The microbiome refers to the genetic material that the microbiota contains. "Microbiome" and "microbiota" appear interchangeably in the literature.

readily apparent from genomic analysis. Contact and admixture is inevitable when there is this much contact.

Most life forms share approximately 37% of their genes, many of which are involved in critical life functions. Moreover, many animal genes are homologues of bacterial genes derived through descent and gene transfer (McFall-Ngai 2013). Approximately 28% of human genes have their origin in unicellular eukaryotes (Land 2015) and only 6% of human genes are exclusively primate (McFall-Ngai 2013). These shared genes are crucial to successful communication by signaling between bacteria and their animal hosts (Land 2015), and are required for the survival of both.

Before discussing the human superorganism, I will briefly discuss how the human superorganism compares to other superorganisms found in nature.

3.1 Types of Superorganisms

In the previous chapter, I discussed several instances from nature in which the status of the organism vis-à-vis the individual was left open to debate. I propose that superorganisms can be divided into two broad categories, based on whether the species of organism that constitute a superorganism are the same or distinct.

Type I Superorganisms

Type I superorganisms are superorganisms that are composed of organisms belonging to the same species. If we physically separate the constituent organisms of the superorganism from each other, then it will be possible to identify each of those organisms as a member of the same species, even if we cannot identify those organisms as such when they are still a part of the superorganism. These organisms may or not be capable of independent survival when separated from the superorganism, and correspondingly, removal of an organism may or may not permit the rest of the superorganism to persist in time.

In the case of *Dictyostelium discoideum,* the conglomerate of amoebae formed in response to unfavorable environments is all of the same species. Some cells within the conglomerate differentiate based on their role, but their status as *Dictyostelium discoideum* cells is not lost. Fitness differentiates cells capable of survival independent of other cells once the conglomerate dissolves, from others that are not so capable. The case with biofilms is less clear, although it is likely that the majority of bacterial cells within a biofilm belong to the same species in its initial stages. Biofilms promote survival of the species in harsh environments because of lateral gene transfer. As biofilms evolve over time, more bacterial species may attach to the biofilm, and the biofilm loses its status as a type I superorganism. *Populus tremuloides* may exist as a large forest, in which case the large forest counts as the superorganism. All the trees belong to *Populus tremuloides*. We can separate trees from the rest of the forest by severing their connection with the underground root system, and under favorable conditions, these separated trees should be capable of independent survival. Each tree also has its own symbiotic microorganisms, making it possible that each tree is itself a superorganism composed of different species. By this token, some superorganisms can form larger superorganisms in turn, and superorganisms can coexist.

Type II Superorganisms

Type II superorganisms consist of organisms belonging to two or more species. Since each species of organism provides its own unique contribution to the superorganism, it is likely that type II superorganisms possess a greater ability to persist through time because of the greater metabolic diversity its constituents provide. A biofilm or a coral reef, for example, might acquire a greater survival capability as its species diversity increases. Due to this increased capability for survival, type II superorganisms are more common in nature. *Populus tremuloides* with its symbiotic soil bacteria counts as a type II superorganism.

Euprymna scolopes contains its own cells as well as those belonging to *Vibrio fischeri*. Survival enhances for both these species when they relate to each other. There are two types of organisms in this superorganism, although it is possible (and perhaps likely) that there are more microorganisms associated with *Euprymna scolopes.* The termite (*Macrotermes spp*) associates with fungal gardens, making it a type II superorganism. The superorganism is also associated with a large non-living component (the mound) that possesses an extraordinary ability to persist through time. Therefore, a superorganism can possess an essential non-living component to enable its other constituents to persist.

The human being classifies as a type II superorganism. The human organism associates with a large microbial population that is essential to not only its persistence through time, but also its reproductive and evolutionary success, even when the microorganisms do not directly participate in the reproductive process. Classifying the human being with its associated microorganisms as a superorganism rather than as an individual permits more rational scientific study, disambiguates the human being from individuals like chairs and tables, steers clear of the misleading "individual organism", and, as I will show later, permits making better sense of the effects of intentional manipulation to the human organism as happens with organ transplantation.

I will next proceed with a scientific tour of the human superorganism, since this will enable a greater appreciation of its composition and more importantly for my purposes, an analysis of its function, over the later chapters of my dissertation.

A Multicellular Exception to Superorganisms

Modern technology has permitted the establishment and maintenance of germ-free animals under strict laboratory conditions (Al-Asmakh 2015). Germ-free animals can be contaminated very easily, and are more prone to developing infections and abnormalities affecting multiple organ systems (Al-Asmakh 2015). Nonetheless, germ-free animals have proven to be very useful models for studying brain development and behavior (Diaz Heijtz

2011). However, results from studies on germ-free animals have not been easily translated into treatment or prevention strategies in humans, because of the different anatomy and physiology of mice (Al-Asmakh 2015). Perhaps the most useful contribution of germ-free animals is their ability to serve as a model for studying host-microbiota interactions (Greer 2016). The ontological status of germ-free animals as superorganisms is debatable. On the one hand persistence through time is clearly possible, while on the other hand their status as organisms is unstable, since they will readily revert to a type II superorganism state when contaminated.

3.2 Size and Composition of the Human Microbiota

Size of the Microbiota

O'Hara (2006) calls the human microbiota the "forgotten organ" (O'Hara 2006). Estimates indicate that there are about 100 trillion bacterial cells, and one quadrillion viruses on the surface of, or inside the human body. These microorganisms constitute the microbiota, and the genes that these microorganisms encode constitute the microbiome (Clemente 2012). The term *microbiome* appears more frequently in the literature instead of *microbiota* since we learn most about microbial composition through ribonucleic acid and metagenomic analysis, owing in turn directly to the immense difficulty encountered in culturing these microorganisms. For our purposes, it is important to conceptualize the microorganisms themselves as biological entities with boundaries rather than just their genetic material, and so I will use the term *microbiota* as far as possible.

The human microbiota provides us with an illustration of how arriving at a definition for the *human organism* versus the *human individual* is not that straightforward, and why *human superorganism* may be a more appropriate term. We can liken the human being to the Hawaiian bobtail squid, with microorganisms regularly moving in and out of the confines of a large animal. For example, in humans, a very large number of microorganisms (10^{10}) enter the gut through the oral cavity from the environment every

day, and a large number leave the gut, passing into the surrounding environment with each bowel movement. All large animals have a microbiota, and even small animals such as termites possess a microbiota in their gut and on their skin.

I will more extensively describe the human intestinal microbiota since the large intestine is the largest location of microorganisms associated with the human organism, and the large intestine is the source of many human pathogens. I will also briefly describe the urogenital and skin microbiota because of their relevance to organ transplants.

About 90% of the cells associated with the human being do not strictly belong to the human lineage. All these cells belong to microorganisms, and these microorganisms contribute about 99% of the total gene content in the human (Dupre 2010). Based on an estimated microbial genome size of 3.4 mega base pairs, and the assumption that 92% of genes code for proteins, the gastrointestinal tract microbiome has been estimated to be about 47,000 mega base pairs in size, or 100-fold larger than the genome size of humans (Liolios 2010).

Microorganisms constitute up to 10^{12} cells per gram of intestinal luminal content, constitute about 30% of its volume, and microorganisms together weigh approximately 1.5 kg to 2 kg. This weight of microorganisms is significantly more than the weight of the pride of *Homo sapiens*, the human brain, which weighs about 1.4 kg or 2% of total body weight. Since the brain is the site of the mind, and the mind is often used to define personal identity in philosophy, this weight comparison between brain and microorganisms is a humbling reminder to *Homo sapiens*, or the wise man, that human brain size is really not all that impressive compared to the size of the microbial mass. On a gram-per-gram basis, microbes contribute more to biological personal identity than the brain. The concept of *Homo sapiens* therefore really refers to more than just the binomial nomenclature of a single organism.

For the microbial population to remain in a steady state there must be an equal number of organisms entering and leaving the body each day[11]. The number of microorganisms entering the gastrointestinal tract from the environment and born in the gastrointestinal tract must equal the number killed and digested, plus the number leaving the body as part of the fecal contents. Similarly, the number of microorganisms that land and then stay on the skin and are born on the skin each day must equal the number of microorganisms killed and/or washed off over the same time. Otherwise, a disease state is likely to occur from an excess or deficiency of microorganisms in any one of its ecological niches.

We can divide the human microbiota for both descriptive and research purposes based on anatomical location into distinct intestinal microbiota, urogenital microbiota, skin microbiota, and so on. Within the gastrointestinal tract, there is a progressive increase in the number of microorganisms from 100/ml in the jejunum to 10^8/ml in the terminal ileum (Walter 2011). All body surfaces that have exposure to, or that serve as a portal to external environments have a microbiota (Foxman 2013). Bacteria even occur in select internal environments such as the amniotic fluid (Clemente 2012). The composition of the microbiota in different locations differs significantly, more so within one person than across persons (Costello 2009). Only a small number of these microorganisms have been cultured so far, and it remains possible that only a small number of microorganisms can ever be cultured (Doolittle 2010). I will devote considerable further explanation to the intestinal microbiota, since the large intestines are the most likely sources of microorganisms associated with disease after SOT.

Associations of an infection in human beings with the source of the culprit organism seem relatively straightforward but usually remain circumstantial. It is hard to prove (and therefore the effort is rarely undertaken) to prove that a certain urinary tract infection, for

[11] I choose day as the unit of time for reconciling microbial numbers, since this length of time roughly corresponds with many natural biological rhythms. For example, many people have one major bowel movement and take one shower per day.

example, was caused by a bacterium from the intestines or from the skin. Besides, the source of an infection in a human being is more of medical than philosophical interest. A common cause of infections is a *misplaced* microorganism. A microorganism that does not cause disease in one body compartment can be the cause of a disease process when that microorganism locates to another body compartment. In other words, disease processes can result from a rearrangement in the spatial relationship between a microorganism and the human organism.

Composition of the Microbiota

The large intestine alone contains 15,000 species of bacteria distributed across 1800 genera, although only 40 species constitute 90% of the colonic microbiota. Attempts to classify microbiota into distinct patterns of associations among bacterial species called *enterotypes* will help to better ascertain their clinical and biological significance. Despite the abundance of bacteria in the intestinal microbiota, across the globe, human intestinal microbiota gathers into a small number of robust clusters. The enterotype is determined by both species composition and host functions.

In a study involving the genomic sequencing of human stool samples, most sequences derive from bacteria, with only small (under 10%) contributions from eukaryotes, archaea, and viruses combined (Arumugam 2011). We can therefore divide the human population into three large enterotypes, based on the pattern of intestinal microbial species that these groupings carry (Arumugam 2011). The composition of the microbiota and microbiome remains remarkably stable over time (Flint 2007). The walls of the colon do not hold bacteria due to the presence of a viscous layer of mucus, which acts as a physical and chemical barrier to bacterial entry into the intestinal walls. The adhesion of bacteria to the intestinal wall is therefore generally considered pathological.

Many factors affect the composition of the microbiota. The mode of delivery at birth (by the vaginal route or by Caesarian section) and the pattern of early feeding (breast

feeding, infant formula, and their combinations) determine initial microbiota composition. Later in life, the aging process, dietary patterns and habits; along with associated cultural practices that lead to those patterns and habits; disease states such as diabetes and obesity, a variety of inflammatory conditions, and genetic disorders can all exert effects on the microbial composition to varying degrees. Changes in the microbial composition may be temporary, such as after an acute infection, or more chronic, as when a human being changes his or her primary geographical region of residence. For example, it may take many months to recover the original microbial composition after a course of antibiotic therapy, or after moving back to an original geographical location. The composition of the microbiota is always changing, even if the overall pattern remains stable. Bacteria in humans have a 25-fold higher rate of lateral gene transfer than bacteria in other communities (Smillie 2011). Bacteria are metabolically very active. Eliminating the human microbiota is not compatible with human life.

We need to take into account two main considerations when analyzing the diversity of the intestinal microbiota. The first is the consistency with which a certain species of bacterium is present in the intestinal content. There is a high interpersonal consistency in the appearance of certain species of bacterium. The second consideration is the prevalence of a certain species or genus of bacterium relative to others. The numerical superiority of one species within the population may or may not be a sign of superiority in its importance. Rather, the importance of a certain species of bacteria to human health may equally be determined by the functioning of its genome, and its ability to interact with human-derived cells (in this case, the intestinal epithelium), along with the extent of that interaction (such as simple contact, or reliable penetration of the intestinal wall).

Species *diversity* of a microbial population is an expression of the relationship between the number of species and the number of microbes, while species *richness* refers to the number of species alone (Spellerberg 2003). The Shannon Diversity Index measures species diversity in ecology. It is a mathematical formulation based on the principle of

entropy used in communication theory. Shannon's Index 'H' in mathematics predicts the next letter in a message or communication. The mathematical details of this index are outside the purview of my dissertation. However, my point here is that analyzing communication between the human being and its microbiota becomes more complicated if there are more species for the human organism to have to communicate with.

The incidence for different bacterial species refers to the percentage of humans who harbor the concerned bacterium in their large intestine. The percentage composition of each bacterium within the large intestine, on the other hand, is more difficult to estimate with any degree of accuracy or precision because of the large inter-personal variability in species richness. However, bacteria from two phyla, namely *Bacteroidetes* and *Firmicutes*, constitute the vast majority of bacteria in the large intestine.

Examples of genera within the *Bacteroidetes* phylum include *Bacteroides*, while examples of genera within the *Firmicutes* phylum include *Clostridium, Enterococcus,* and *Lactobacillus*. *Bacteroidetes, Enterococcus, and Escherichia* genera are present in 100% of humans (Todar 2012). The bacteria most pathogenic to humans include *Escherichia coli* and *Proteus mirabilis*. Other equally pathogenic but much less common bacteria such as *Pseudomonas aeruginosa*, and *Salmonella enteritidis* belong to a different phylum, *Protobacteria*. Therefore, the amount of a particular bacterium in the large intestine does not necessarily correlate with its ability to cause disease[12]. Furthermore, a bacterium such as Escherichia coli O157:H7 causes serious, sometimes fatal disease in humans but is often harmless in cattle, from where it originates. Pathogenicity is therefore species-specific for both microorganisms and macroorganisms.

The urogenital microbiome consists of *Lactobacillus acidophilus*, as well as many other species of *Lactobacilli*, *Staphylococci*, *Ureaplasma*, *Corynebacterium*, *Streptococcus*, *Peptostreptococcus*, *Gardnerella*, *Bacteroides*, *Enterococcus*, and *Escherichia*, among others.

[12] Overgrowth of one particular type of bacterium may *predispose* to disease, however.

Particular to the female vagina is the normal presence of a fungus, *Candida*. By comparing this list of vaginal microorganisms to that in the large intestine, it is apparent that there are some species common to the vagina, particularly those that are capable of causing disease. The composition of the vaginal microbial community depends on age (based in turn on reproductive capacity) and ethnicity (Ravel 2011). Many of the same bacteria are also found as part of the male urogenital microbiota.

Another location of the human microbiota is the skin. The skin is the largest human organ by surface area, covering an area of 1.6 to 1.8 m^2 and contributing to approximately 16% of total body weight. The skin is exposed to the external environment, and is functionally and anatomically continuous with mucous membranes, such as those that line the gastrointestinal tract. Naturally, the skin is another large microbial reservoir in the body with its own great diversity. A biopsy of the skin can yield up to 1 million bacteria per cm^2 (Grice 2008). Microorganisms colonize the skin immediately after birth, regardless of the mode of delivery. The skin represents the final frontier of the human organism. It is a boundary between a specimen of the human species and numerous other species. This boundary is not visible to the naked eye, and does not correspond to the silhouette of the human body we see.

Just as in the gastrointestinal tract, there is some variation in number and specificity of bacterial genera on the skin, depending on the location of that skin. We know less about the skin microbiota generally than the intestinal microbiota, however, particularly in terms of its physiological role (Cogen 2008). More than 200 constituents of the skin microbiota have been isolated, including bacteria, viruses, and eukaryotes. There is diversity in microbial composition based on the skin component as well. For example, sweat glands and sebaceous glands, which are two important components of the skin structure, harbor a large microbial population particularly in adults. Most skin bacteria are present in these two types of glands, as well as on the most superficial layer of the skin (the epidermis) and in association with hair follicles.

Similar to the microbiota of the large intestine, there is great interpersonal variation in skin microbial diversity. This diversity of the skin microbiota is actually *greater* than the diversity seen in the gastrointestinal tract. There are also significant sex differences in the prevalence of specific bacterial species on the skin. Most bacterial species on the skin belong to *Staphylococcus*, *Corynebacterium*, *Propionibacterium*, and *Streptococcus*.

There appears to be very little overlap, if any, in the composition of the skin microbiota with the intestinal microbiota. However, most skin microorganisms are capable of causing disease states if they penetrate the skin. *Staphylococcus* for example is such an important pathogen to human beings that hospitals will isolate patients carrying a certain *Staphylococcus* species from other patients in the hospital even if they do not have any symptoms related to that bacterium. Bacteria on the skin are hard to quantify, and in principle, the presence of even one potentially pathological bacterium on the skin constitutes a positive test result.

Microbial composition thereby leads to social policy. A human being can be isolated from other human beings inside a hospital, because of the potential for harm associated with microbial transmission, even if the microorganism concerned in the intestines or on the skin is harmless to its current host. Most hospitals routinely screen admitted patients for the presence of certain bacteria in their rectum and on their skin, and will place patients in isolation whenever these bacteria are detected.

3.3 Functions of the Human Microbiota

It should be clear by now that the human being is not just the human organism. The human being is a superorganism. There are numerous microorganisms associated with the human organism in many locations (section 3.2). In this section, I will describe some of the many functions of these microorganisms.

The human microbiota through its associated genome (or microbiome) provides traits to humans that humans did not therefore need to evolve on their own (Turnbaugh 2007). Mammals have thus coevolved with their microbiota (Ley 2008) and so mammals and microorganisms may therefore have a linked fate. Due to the intimate relationship between microbiota and the human organism at all stages in life from delivery to after death, the status of our microbiota can be summarized in a slogan, "our microbiota are ourselves" (Foxman 2013). This is not strictly true of course, but without microorganisms, our bodies will not be able to develop or function properly (Dethlefsen 2007). The presence of microorganisms is essential to health.

Symbiosis is a signature of life on earth (Gilbert 2016). Symbiosis is not surprising, since the wealth of organisms on earth will lead to species contacting each other, and interactions developing among them. Harmful interactions cause disease states in at least one of the organisms, while beneficial interactions will be symbiotic to all the organisms in a relationship. The relationship between the human organism and its microbiota is *bidirectional*; just as the human organism relies on bacterial products for its survival, bacteria have also created pathways to metabolize molecules, such as halogenated hydrocarbons, that are produced by human beings (McFall-Ngai 2013). Biological assays have been developed to monitor human health based on measuring compounds that the microbiota normally produces, such as detecting radioactive carbon dioxide in the breath from ingested urea by *Helicobacter pylori* in the stomach. The major consideration in a symbiotic relationship is that both organisms contribute and benefit, even though the contributions and benefits do not always equal each other in importance.

Functions of the Intestinal Microbiota

Researchers unsurprisingly currently devote the most attention to the intestinal microbiota and microbiome, since the intestines contain our largest microbial population. It is also difficult for scientists to isolate the microbiota from body sites other than the

intestines without resulting in contamination by human cells (Turnbaugh 2007). The intestinal microbiota is therefore also the easiest to study. The intestinal microbiota reaches a stable pattern in terms of its composition by 2.5 years of age (Clemente 2012). The intestinal microbiota can be compared to the liver, a very large human organ, in terms of its metabolic capacity (Foxman 2013). We can use animal models to demonstrate the relationship of microbiota to diseases such as Crohn's disease, as well as autoimmune diseases including type 1 diabetes, multiple sclerosis, and rheumatoid arthritis (Clemente 2012).

Intestinal microorganisms can utilize any carbohydrate that reaches the large intestine for their own nutritional purposes, including dietary fiber and sugar alcohols. The energy so produced is also available to the rest of the human body for its use. Microorganisms in the intestine are responsible for producing the short-chain fatty acids acetate, propionate, and butyrate through their fermentation of dietary carbohydrates as well as proteins that the human body itself produces, such as mucin. Approximately 10% of our calories come from the microbiota. Organs distant from the intestines such as the heart and kidneys also benefit from these short-chain fatty acids. Short-chain fatty acids provide energy to the colonic epithelial cells themselves, promote the integrity of the epithelial barrier, and reduce inflammation as well as carcinogenesis.

The intestinal microbiome is also a major source of specific nutrients such as vitamin K, which is a factor critical for proper clotting of the blood. A vitamin by definition cannot be produced by the human body and must therefore be supplied through the diet. The intestinal microbiota is therefore a major contributor to our nutrition while not being a part of our diet or a part of our body either. The intestinal microbiota also modulates lipid metabolism as well as glucose metabolism and regulates blood glucose levels. The supply of nutrients and energy from ingested food depends on the ability of the intestinal microbiota to digest that food. The microbiota serves as an intermediary between the human organism and its nutrition. The microbiota contributes to maintaining normal

energy balance by promoting lipid breakdown, thereby preventing obesity and diabetes in turn. Disruption in the intestinal microbiota leads to conditions such as obesity from increased dietary energy extraction (Tsai 2009). Obesity is transferable by transplanting obesity-promoting microbiota into lean individuals (Clemente 2012). It is quite possible that we can develop treatments for obesity in the future based on our ability to modulate the intestinal microbiota composition (Tsai 2009).

In the small intestine, the microbiota is associated with the maintenance of a healthy villous structure, which in turn is required to regulate food absorption. The microbiota promotes healthy blood vessel formation in the small intestinal wall, and promotes mucin production, thereby further promoting intestinal integrity. The microbiota also regulates contraction of the intestinal musculature, so that the intestinal contents pass down in an appropriate manner. Metabolic products of the microbiome are helpful in the prevention of cancer along the intestinal wall, at least in part due to all these effects. The growth of early stage cancers may even be arrested.

The intestinal microbiota also metabolizes and activates or detoxifies drugs either directly or by changing the expression of genes in the host (Haiser 2012). The microbiota may even detoxify endogenous cancer-promoting compounds, thereby rendering them harmless. Even the ability of orally administered vaccines to provide protection against diseases may depend on how the intestinal microbiota handles them (Bjorksten 2012).

The intestinal microbiota plays a critical role in preventing colonization of the intestinal by pathogenic bacteria through their presence alone. Normal intestinal microorganisms also perform this function by producing compounds such as lactate that inhibit the growth of other bacteria. Acetate (a short-chain fatty acid) produced by normal intestinal microorganisms protects the intestinal endothelium from invasion by harmful bacteria. By also inhibiting the growth of pathogenic bacteria, inflammation is reduced and excess calorie absorption states are prevented.

Intestinal microorganisms may also influence human behavior. In animal models, the composition of the intestinal microbiota has been associated with the level of motor activity and anxiety. There are also claims that the composition of intestinal microorganisms is associated with psychological conditions such as stress and depression. Intestinal microorganisms produce hormones like serotonin and dopamine. Proprionate, another short-chain fatty acid, provides a feeling of satiety by the production of compounds such as proglucagon, which has the effect of further reducing caloric intake and preventing the development of obesity. Even if we associate personal identity with the mind, as philosophers are prone to do, we are still associating that identity partly with the activity of non-human organisms.

Functions of Non-Intestinal Microbiota

Lactobacilli in the vaginal tract produce lactic acid, which lowers the pH in the vagina and acts directly as an antimicrobial compound. The vaginal microbiota is also able to produce other antimicrobial compounds, as well as non-specific toxins such as hydrogen peroxide that destroy pathogens (Hawes 2010). The vaginal microbiota therefore serves a protective role in the female reproductive tract. In contrast to that of the vagina, the function of the male reproductive organ microbiota is very poorly understood, although its role may be similar to that of the microbiota of the female reproductive tract.

Colonization of the skin occurs immediately after birth, regardless of mode of delivery of the infant. Even though most known skin microorganisms are bacteria, other microorganisms including fungi, parasites, and viruses including bacteriophages have all been isolated from the skin. Our limited knowledge of these microorganisms simply reflects our inability to culture them all in vitro. Skin microorganisms obtain their nutrition from the skin's secretions, a human product, unlike intestinal microorganisms that obtain their nutrition through the diet, a non-human product. Normally present skin microorganisms prevent colonization from harmful microorganisms simply by

outnumbering them. They also secrete acids and antimicrobial peptides that directly inhibit the growth of pathogens. Therefore, the main role of the skin microbiota, in summary, is to prevent the growth of other microorganisms. Unlike in the case of the intestinal microbiota, there is no well-delineated role for the skin microbiota in nutrition, metabolism, or cancer prevention.

3.4 Relation of the Microbiota to the Human Body: The Intervening Boundary

What I have left unaddressed until now is the nature of the anatomical relationship of the microbiota to the human body. In the previous chapter, I described the confusion that exists between *organism* and *individual* using some well-known examples from the plant and animal kingdoms. In two instances, that of the Hawaiian bobtail squid and the human superorganism, there is a clear separation in space between different organisms. In the case of the Hawaiian bobtail squid, there is of course the squid itself (*Euprymna scolopes*) and there is the bacterium *Vibrio fischeri*; in the case of the human there is *Homo sapiens* and there are *Clostridium*, *Staphylococcus*, *Streptococcus*, *Escherichia coli*, and many other types of bacteria. These organisms associate regularly with each other and may exist in a mutually beneficial functional relationship, but they are still anatomically separated by seawater or intestinal contents and are fully capable at any time of going their own ways, both physically in space and functionally. The human superorganism is a type II superorganism. What then is nature of the boundary between the human organism and other organisms, within such a superorganism?

Boundaries are especially important to understanding the relationship between organisms. The nature of the boundary provides an explanation for the interaction that occurs; this interaction may be favorable and result in mutual association, or it may be unfavorable and result in either destruction of one of the entities or a separation and termination of the interaction. As I will later discuss, boundaries are also where communication can be understood. What then is a biological boundary?

According to Aristotle,

> "We call a limit the last point [το εσχατον] of each thing, i.e., the first point beyond which it is not possible to find any part [of the thing], and the first point within which every part [of the thing] is." [Aristotle 1984)

In the case of bacteria within the intestinal lumen, a space separates the bacteria and the intestinal wall. The bacteria are normally suspended within the fluids of the intestinal lumen, and are churned about due to intestinal peristalsis. There is no shared structural boundary between the bacteria and the intestinal wall. Adherence by bacteria to the intestinal wall is usually pathological, and such binding leads to a disease state. In the case of the skin microbiota however, the bacteria *are* physically adherent to the outer surface of the skin. In other words, there is a shared surface between the skin and the bacterial cell. There is a structural or anatomical boundary between the microbe and the human body in each instance. There is also a functional boundary between the two. In the case of the intestinal microorganisms, if they are truly incidental in presence and do not ever cause disease, then there should be no functional boundary between the human being and microorganisms. In the case of the skin, there is physical contact between the skin and the microorganisms but there is no direct functional relationship. The skin bacteria do not seem to be directly providing anything beneficial to the human apart from their ability to reduce colonization from harmful bacteria competitively through their presence alone.

The maintenance of health of the human organism requires the maintenance of health of all the microorganisms as well. One need not look beyond the confines of the human organism to a larger ecosystem to appreciate this fact. No effort is required to attract microorganisms to our bodies. These microorganisms cannot be expelled in their entirety either. There is an ongoing functional communication with microorganisms, yet

there is also an ongoing anatomical separation from them. The relationship between organisms is analogous to "action at a distance", similar to gravitational pull.

I will now evaluate some of the philosophical views on boundaries in general before turning to biological boundaries specifically. I will still evaluate these general views in the context of the human organism and its microbial organisms, which is a biological boundary. There are two main classes of theories about boundaries in general: the realist theories and the eliminativist theories (Varzi 2015). I will briefly evaluate each of these two classes of theories in turn, in the context of the human-microorganism boundary, and show that I favor one version of a realist theory of boundaries.

Realist theories of the boundary

The realist theory of boundaries posits that the boundary is a "lower dimensional entity", less real than the entity the boundaries contain, and from which it cannot be separated. According to the *realist* theory, there are four possibilities to a boundary. First, the boundary between the human organism and the microorganism may belong to neither of them. The human organism and the microorganism may or may not be in contact with each other, but they have a common outer boundary. Second, the boundary must belong to either the human organism or the microorganism, but we do not know to which one it belongs. In this case, the indeterminacy is either semantic or epistemic. Third, the boundary belongs to both, because the boundary does not take up any space. If the boundary does not truly belong to both, then the boundary does not possess the same properties as the human organism and the microorganism themselves. Fourth, there may actually be two boundaries, one belonging to the human organism and one belonging to the microorganism, in which case these boundaries are coincidental spatially but do not overlap in a mereological sense. Here also the boundary does not take up any space.

I will proceed to test these realist theories against the human-microbe boundary for the intestine and the skin in turn. The biological boundary in the genitourinary tract has

features similar to both the gastrointestinal tract and the skin, depending on the part of the genitourinary tract concerned, and so I will not discuss the genitourinary tract further.

It is undisputed in biology that from an anatomical perspective, the cells that line the intestinal wall are an integral part of the human organism, while the bacterial cell is a different organism. Cells of human origin such as those in the intestinal wall, and those of bacteria, carry their own cell organelles and DNA. The nature of the external boundary of the human cell and the external boundary of the bacterial cell is substantially different both structurally and functionally. At the most obvious, superficial level, a cell membrane surrounds all human cells, while a cell wall envelops bacterial cells. Cell walls have a physicochemical structure different from cell membranes. There is the likelihood of intermittent attachment, detachment, and reattachment of the bacterial cell to the human cell. The human cell on the other hand does not lose its attachment to other human cells, for to do so would be fatal to that cell. Finally, bacteria can freely attach and reattach to each other as part of processes involved in lateral gene transfer, but the structural relationship of human cells to each other in the intestinal wall is fixed. If the intestinal wall sheds a human cell, then another human cell takes its place because of rapid cell turnover.

In addition to the above four reasons for why there is a boundary between the human organism and bacteria, most importantly, *the intestinal lumen is not part of the human organism*. The lumen is contained within the body and the body surrounds the lumen. This lumen is hidden from external view, not visible except through an endoscope, without being a part of the human organism. Only the intestinal wall is an actual part of the human organism.

The gastrointestinal tract is one continuous tube from the oral cavity to the anal canal. It is possible at least theoretically to pass an endoscopic tube of sufficient length and flexibility through the mouth, and for the tip to appear externally again through the anal canal. Various chemical substances such as water, electrolytes including sodium,

potassium, chloride, calcium, and magnesium, and energy-containing dietary nutrient compounds traverse the intestinal wall to enter the blood circulation. Water and electrolytes also leave the blood circulation and enter the intestinal lumen by moving in the opposite direction. In other words, there is regular back-and-forth movement[13] of a variety of substances from the outside of the human body to the inside, and vice versa. Movement of substances also occurs in the opposite direction until the composition of the feces becomes final and appropriate for excretion. The lumen contains air, continuously swallowed and expelled, and can accommodate a variety of objects, some of great size.

The mucus membrane that lines the gastrointestinal tract is a boundary to the human organism as is the skin, and it is in physical continuity with the skin. This physical continuity of the mucus membrane and the skin is most easily visible around the lips, nostrils, and eyes. While the mucous membranes are permeable to water, the skin is not, or we would quickly balloon up whenever we bathe or go swimming. Medications such as ointments are absorbed through the skin by *dissolving* in its fat. The skin forms a simple structural boundary to bacteria entering the body, but the enforcement of a boundary by mucous membranes requires a more elaborate mechanism.

When the intestinal contents suspend bacteria, there should be no durable contact with the intestinal wall in a non-disease state. Therefore, there is no structural or anatomical boundary between the human and the bacterium. If the bacterium is producing a nutrient or an otherwise valuable energy-containing molecule that benefits the human, then there is a functional relationship between the two types of cells, and so they have a functional boundary. However, the nutrient molecule crossing the boundary is neither bacterium nor human. It must leave the outer boundary of the bacterial cell before the human cell takes it up. Therefore, in a physiological state, there is no common, outer boundary between the bacterial cell and the human cell. Both have boundaries and access

[13] An example of back-and-forth movement is enterohepatic recirculation, in which bile is secreted by the liver, and then reabsorbed in the intestine.

to the same fluid and air interfaces, which are not part of the other entity. There is a bacterium-fluid boundary and a human-fluid boundary, but a structural bacterium-human boundary either does not exist or is irrelevant. On the skin, however, there is physical contact between the bacterium and human. The line of demarcation is between the cell wall of the bacterium and the cell membrane of the human. The bacterium does not penetrate the skin. Since there is no exchange of material, the bacterium-human boundary continues to be two boundaries in a realist sense, similar to the case with the intestines with one boundary belonging to each, because they are not "joined at the hip". Each boundary continues to serve its own organism, despite contacting other boundaries belonging to other organisms.

The fourth realist theory described above, i.e., *there are two coincidental boundaries,* is therefore the most accurate as it applies to the human organism and its microorganisms. There are two boundaries, one belonging to the human organism and one belonging to the bacterium or other microorganism, in which case these boundaries are coincidental spatially but do not overlap in a mereological sense. The boundary itself does not take up any additional space. Since we know there is functional communication going on in the intestines, *we must divide the human being into two or more sub-entities*. Conceiving the human being as the human organism and the human superorganism provides a solution to this problem of the biological boundary. The boundary we have discussed is a biological boundary between the human organism and the microorganisms, but it is not a boundary between the human superorganism and the microorganisms. The intestinal and skin microorganisms are part of the human superorganism and can therefore have no boundary with it, because an entity cannot have a boundary with itself.

It is important to emphasize that the relationship I have described between the human organism and other organisms is not limited to microorganisms alone, although microorganisms are by far the most common organisms living in association with the human organism. There are also multicellular organisms occasionally present inside the

intestines. We consider these multicellular organisms as parasites, although we can consider some amoeba species to be parasites as well. A parasite is a living organism that receives nourishment and shelter from another organism in which it lives, but provides no benefit in return, unlike a symbiont. The other, larger organism then becomes the host. Parasites consume vital nutrients present in the intestinal contents for their benefit alone, and provide no nutrients or other advantages to the human organism in return. Parasites can even cause malnutrition. There are many worms fitting this criterion for a parasite. I will provide two examples of common parasites to illustrate a point about boundaries.

Some parasitic worms can grow to an enormous size inside the intestinal lumen. For example, the beef tapeworm, *Taenia saginata*, is capable of growing up to 10 metres in length. The worm resides in the small intestine, after acquisition through the consumption of undercooked beef. The worm fulfills part of its life cycle in the muscles of cattle, but reproduces in the intestinal lumen of its definitive human host. The worm then produces eggs excreted in the feces, cattle consume the eggs, and the worm's life cycle continues (Chatterjee 1975). One would hope that in return for the nutritional favors the human organism provides that these large parasites would at least respect the boundaries of the human organism. *Taenia saginata* provides an excellent example of an organism that can live first inside and then outside the boundaries of an organism, crossing these boundaries at will. *Taenia saginata* even crosses boundaries inside the human organism if left untreated, such as the muscle cell membrane, causing a disease process in the muscle.

Another example of a common parasite is the hookworm, *Ancylostoma duodenale*. This worm does not have an intermediate host, unlike *Taenia saginata*. The eggs of this worm similarly leave the human host via the feces, and the eggs then hatch in the soil. The larvae penetrate the skin of human organisms walking barefoot in the soil, enter the bloodstream, travel to the lungs, then to the trachea, crawl up and over into the pharynx, and are then swallowed, before maturing in the small intestine (Chatterjee 1975). *Ancylostoma duodenale* first lives outside the organism, then inside, then outside again.

Nature is full of such combinations of life cycle stages in organisms that do not respect the boundaries of other organisms. We consider these organisms pathological. *There is no known intact organism, microorganism or otherwise, which both violates the boundaries of the human organism and is harmless or capable of being always harmless at the same time.* Microbial genomes may incorporate into human germ cell lines, but these genomes are not intact organisms. However, this general rule about harmfulness may not be true of other organisms, which may contain harmless yet intact organisms inside their cells. Intact organisms possess boundaries that distinguish them from other organisms.

Eliminativist Theories of Boundaries

Now I will briefly discuss the eliminativist theories of boundaries (Varzi 2015). Eliminativist theories posit that boundaries are mere abstractions and we can divide them into smaller and smaller parts, or make them thinner and thinner without limit, because the universe consists of "atomless gunk" (Lewis 1991, Hawthorne 2004).

The first eliminativist theory states that material bodies are the material contents of open regions of space, and when two bodies contact each other, the closures of their receptacles are in contact (Cartwright 1975). We can approach the boundary from either the inside or the outside. However, *there is no true closure in biology* because there are holes in every boundary. Substances regularly enter and leave the cell, either by diffusion through the lipid bilayer of the cell membrane, in which spaces exist between the lipid molecules, or more quickly through special holes (called channels) in the cell membrane whose configuration permits the entry and passage of only certain molecules. A typical example of such a hole in the boundary is aquaporin 1, a water channel, which is a hole in the cell membrane through which water traverses (Preston 1992). Channels exist for many different types of molecules. All biological membranes are permeable to at least some types of molecules. Only through such permeability of biological membranes can cells persist in space and time.

The second eliminativist theory is that the boundary is some sort of "higher-order entity", different from the primary material bodies that form the boundary. We cannot extract this boundary. Since the human organism and the bacterium are real entities, their outer limits must be real, and so the eliminativist theories do not seem accurate. There is a point in space beyond which there is no human organism and no bacterium. Violation of the boundary of an organism triggers disease and even death. Therefore, there can be no higher entity beyond the cell wall and the cell membrane to explain the boundary. Both the cell wall and the cell membrane can easily be separated from the rest of the cell's contents by centrifugation, although unfortunately the cell will be killed in the process because there can be no other boundary created to replace them. In the case of the intestines and skin, the cell walls and cell membranes of different organisms may not even be in actual contact with each other because there is mucous and sweat dispersed everywhere as well. Biological boundaries are not higher-order entities. Any higher-order boundary would not also be relevant to the life of organisms.

Microorganisms Crossing Boundaries

Some organisms regularly cross boundaries of the human cell and take up an intracellular residence. We consider such microorganisms to be in a "latent" state if they do not cause disease immediately. The prime example among such organisms is the herpes family of viruses. These viruses are capable of reactivation at some future point in time, causing true disease. These viruses are always capable of causing disease; this is the reason why it is in their nature to violate[14] the human cell boundary. *An intact, live organism that violates the boundary of the human organism is never beneficial.* These viruses bear no similarity to the intestinal microorganisms which do not normally cross the human cell barrier and do not cause disease as long as they do not so. Certain intestinal bacteria, for example *Clostridium difficile*, may proliferate (multiply) excessively under antimicrobial or

[14] Throughout my dissertation, I use terms such as "violate", "breach" and "disrupt", along with "repair", "restore", and "reestablish" interchangeably, ignoring any subtle differences in their meaning.

other environmental pressures, and decrease intestinal diversity in the process, but their existence does not depend upon invasion of the human organism.

Whenever these bacteria have the potential to cause disease, such as is the case with *Clostridium difficile*, they do so by violating the human cell boundary when the opportunity presents itself. The most dramatic example of *Clostridium difficile* infection is a condition called pseudomembranous colitis, which can be fatal. Until such a violation of human cell boundaries occurs, these intestinal bacteria are non-pathogenic but once they do, they promptly become pathogenic. Boundaries are inherently protective to the organism.

Having posited that there are two real boundaries, one belonging to the human organism and one to the bacterial organism for us to grapple with, it is reasonable to state with confidence that the human organism and bacterium are two different organisms separated by at least two boundaries, consisting of the boundaries of each organism. This biological boundary between organisms is real but not necessarily fixed because organisms are usually in motion. The boundary between organisms is not an artificial boundary like, for example, the boundaries of the Atlantic Ocean or the boundaries of a particular constellation in the sky.

Biological Boundaries as Structural Boundaries and Functional Boundaries

In the physical world, we identify objects by their boundaries: the point in space of distinction between object and non-object. We usually identify biological entities by their boundaries as well, each limited in space and time because we equate biological entities with the physical entities we observe. In the case of biological entities, life is impossible without boundaries. Each organism has its own external structural boundary, whether formed by a cell membrane, cell wall, or inert material, separating the organism from non-organism. Cell boundaries are discernible as structural boundaries. We also identify entities larger than single cells such as the human organism easily by their structural boundary,

and in this sense, the structural boundary helps to reveal evolutionary lineage[15] (Tuma 2009).

Structural boundaries take time to develop but then persist, unless broken down through disease or as part of normal cell turnover. Structural boundaries become highly specialized when regulatory ion pumps and channels are inserted into them, adding to their function and stability in a niche environment. Each organism has its own metabolism contained within the boundary, and each organism has its own life cycle. The metabolism required to sustain life consumes energy, and one of the principal functions of boundaries is to contain that energy and prevent its dissemination into the environment. Containing energy efficiently allows the organism to perform work. Conversely, structural boundaries keep unwanted entities like toxins, excess water, and parasites on the outside of the organism. Internal structural boundaries add further efficiency to these processes. Contact between molecules inside and outside the organism is slowed by a boundary, but then preferentially sped up for certain molecules by pumps and channels.

There is also an interaction between two organisms in the case of the human organism and microorganisms, and this interaction contributes to the survival of both the human organism and bacterial organisms. Nonetheless, there is only an interaction between them, and some degree of separation between two organisms always maintains in their metabolism. A breakdown in the structural boundary of one organism through the mechanisms of another organism implies that *digestion* has taken place. The metabolism of the digested organism also ceases.

Structural boundaries perform other functions besides separating organisms from each other. Structural boundaries also separate organisms from their external environment. Structural boundaries prohibit contact between the internal cell contents of different organisms, yet also act as an interface between different cells (Tuma 2009). Structural

[15] There is an extensive literature on the evolutionary function of biological boundaries. My focus, however, is on the physiological function of biological boundaries.

boundaries slow down metabolic interactions between cells by regulating the duration of contact between molecules produced by those cells, and can make the outputs of such interaction more precise. Structural boundaries of cells are constantly being broken down and established in correspondence with normal cell turnover. Structural boundaries do not have to be only cell walls and cell membranes. They can be inert matrix as well.

Functional boundaries, on the other hand, can be discontinuous or distributed (Tuma 2009). Functional boundaries are also dynamic, with short survival times as they are constantly being decomposed and reinvented, and difficult to localize. Interactions occur at a distance when organisms separate from each other in space. Since different types of organisms contribute to functional boundaries, the effects of their creation are more diverse, but as a result functional boundaries are more adaptive than structural boundaries. New functions evolve when functional boundaries are breached (Tuma 2009). Functional boundaries also highly depend on feedback mechanisms (Goodwin 1963). Functional interaction can occur across structural boundaries through “transducers”, which translate actions on one side of the boundary to the other side of the boundary (Platt 1969). The boundary does not get destroyed in the process.

The human superorganism maintains though a functional boundary. In a perfect symbiotic relationship between organisms, the distance between the two organisms is not so close that it will cause disease or even destruction in one or both organisms, and the distance is not so far that there is no beneficial relationship at all. This separation in space is the functional boundary. Therefore, the functional boundary is an important element in maintaining the physical separation between the macroorganism and its microorganisms. When proven useful over time, some functional boundaries may evolve into structural boundaries.

There are two structural boundaries and one functional boundary between the human organism and a microorganism. Structural boundaries determine functional

boundaries, even though the latter can be vague. Conversely, functional boundaries precede structural boundaries, because structural boundaries evolve over time when functional boundaries become evolutionarily useful to the cell or organism.

Disease and Alteration in the Microbiota

I prefer the human superorganism concept because it explains many disease processes and can help to advance new technologies like xenotransplantation. There is another important variable to consider in the relationship between the microbiota and disease processes. Just as alteration in the microbiota can *cause* disease, alterations in the microbiota can be the *result* of disease. An example of the latter situation is chronic kidney disease, which in its most severe form leads to end-stage kidney disease. End-stage kidney disease is an indication for kidney transplantation. Kidney transplantation must accompany kidney disease, for the post-transplant state represents just one more stage along the chronic kidney disease continuum. Patients with kidney failure possess an intestinal microbiota different from that of healthy humans. Since we perform transplantation only in the later stages of chronic kidney disease, a new transplant recipient already has an abnormal intestinal microbiota. Nausea is a prominent symptom of advanced kidney disease related to the accumulation of nitrogenous waste products. These waste products are the result of breakdown of dietary protein in the intestines by the increased or altered microbiota. Functional boundaries are more complicated than structural boundaries, since disease in one organism can functionally affect other organisms related to that organism without identifiable structural invasion.

Patients with kidney failure have increased counts of both aerobic and anaerobic organisms in the upper small intestine, which is a part of the intestine that does not normally contain high bacterial counts (Ramezani 2014). In kidney failure, there is an overgrowth of aerobic bacteria in the lower intestine, as well as an overall decrease in the microbial diversity (Ramezani 2014). A local inflammatory response is generated, capable

of developing into a systemic inflammatory response. The toxins of kidney failure are mostly the toxins of the intestinal microbiota (Sirich 2017). Since kidney transplantation is a therapy for patients with kidney failure, it is important to recognize that the intestinal microbiota in kidney transplant recipients is not the same as that of healthy persons, at least at the time of transplantation. In kidney failure structural boundaries maintain, while functional boundaries alter because the relationship between the human organism and its associated microorganisms changes as a result of a disease process in the human organism.

3.5 Is the Human Being a Superorganism or a Community?

The human being is not equivalent to the human organism. That much is clear. There are numerous microorganisms living in association with the human macroorganism, to the extent that the number of microorganisms counted as individual cells outnumbers the number of human cells. However, the human organism is much larger than the sum of microorganisms in terms of the amount of space it occupies and its weight. Is it fair then to be anthropocentric and call the conglomerate a human superorganism, or is a concept of community of organisms more appropriate? I favor the concept of human superorganism over community as the most accurate description of a human organism with its microbiota.

The arguments in favor of the human superorganism, called by Skillings (2016) a holobiont (a group of organisms found together and in a functional relationship) actually being a community are several (Skillings 2016). First, there is an inherent disunity among the organisms, and one organism will quickly proliferate at the expense of other organisms if provided with the opportunity to do so. Microorganisms and macroorganisms are always in a relationship of cooperation and conflict (Skillings 2016). Second, microorganisms are transmissible vertically from parent to offspring, as well as horizontally from parent to offspring or from one organism to the next. In other words, microorganisms lead their own lives. Third, the holobiont as such does not reproduce as a single unit. Each organism reproduces in its own unique way. Human germ cell lines segregate not only from somatic

cells but from microorganisms as well. Fourth, each organism carries its own lineage. Finally, functional integration and metabolic dependency are features of a community in a symbiotic relationship, even though it may be an unequal relationship.

Each of these facts about the holobiont being a community has merit. If we view the holobiont as a community, it is certainly a community with unequal relationships. There is no doubt that the microbiota is extremely important to the health of the macroorganism. As human beings, however, we are not concerned about the health of the microbiota, if there is such a thing, *for its own sake*. We are concerned with the microbiota to the extent that it influences our own health.

Although the metabolic contribution of the microbiota is significant and indispensable, it is still only a small component of the overall metabolism of the macroorganism. To give one simple example, the microbiota synthesizes vitamin K, which the human organism needs for the proper clotting of blood. However, there is no known role for the microbiota in the metabolism of vitamin A, the B vitamins, or vitamins C, D, and E. Even vitamin K's contribution to human metabolism is limited to just one part of the coagulation cascade, and even then, it is possible that the development of the coagulation cascade as it exists today was determined *by* microbial metabolism rather than the microorganisms heroically arriving to fulfill some urgent human need. The size and extent of the macroorganism alone, compared to the sum of microorganisms, is sufficient to view the holobiont as a *human* holobiont, and therefore a human *superorganism*. Moreover, functional integrity and metabolic dependency can occur only when there is a mechanistic link between the human organism and its microbiota. In a community, there is no glue to attach the members together. The association between the human organism and its types of microorganisms would be random, and there would be far more than three major enterotypes (Arumugam 2011) in the world. A community has a more fluid structure than a superorganism. A superorganism, while still fluid, still persists within the framework that functional boundaries provide. Personal biological identity maintains in a superorganism.

The above argument in favor of the human holobiont being a community is more an argument against the human holobiont being an *organism* than it is against being a superorganism. The microbiota may be a community unto itself, but once the human organism enters the community, then the total entity is a human superorganism. A functional relationship holds both a community and a superorganism together. Holobionts do not meet the criteria for organisms or evolutionary individuals (Skillings 2016). However, holobionts do meet the criteria for physiological individuals (Pradeu 2016a).

The human superorganism is a physiological individual, in which functional relationships determine the rules of engagement between organisms. Although it is true that the microbiota can lead its own life, there is "glue" that holds them in association with the human organism as long as the human organism is alive. This glue is immunity, which I discuss in Chapter Four. However, I will now discuss some medical applications resulting from an understanding of structural and functional boundaries in the human organism and human superorganism.

3.6 The Human Superorganism and Therapy: Probiotics and Fecal Microbiota Transplantation

*Pro*biotics are organisms and substances that contribute to intestinal microbial balance (Parker 1974). Probiotics are living microorganisms that exert beneficial effects beyond nutrition. In contrast to probiotics, *pre*biotics are nutritional substances that can be chemically characterized and change the composition of the microbiota. *Syn*biotics are combinations of probiotics and prebiotics.

Organisms contained in probiotics obviously need to survive transit through the gastrointestinal tract including the highly acidic stomach, to reach the intestines. They should also not be capable of causing disease themselves. Probiotics are useful in restoring microbial balance when antibiotics have created an intestinal microbial imbalance leading to diarrhea. For example, administering *Saccharomyces boulardii* is effective for disease

caused by *Clostridium difficile* (McFarland 2006). These microorganisms remain separate from the human body, safe and well while maintaining their status as organisms without being digested. They locate within the intestinal lumen at some distance from the intestinal wall.

Since the microorganisms in probiotics remain alive and continue to function in a two-way interaction with the human organism, we can consider probiotic administration the most basic form of transplantation-based therapy. Probiotic administration is a form of transplantation that does not require a human donor. An in-vitro system is all we need to generate the microorganisms. Probiotic therapy is a form of transplantation in the human superorganism because otherwise the therapeutic product would be digested by the actions of the human organism. Most drugs other than antibiotics treat the organism only.

Probiotic administration of course has its limitations as a form of therapy for disease, due to the number and types of transplantable bacterial species available. Clinicians have long sought to manipulate the human intestinal microbiota in order to alleviate disease.

The next level of sophistication in transplantation therapy is fecal microbiota transplantation (FMT). FMT is the administration of donor fecal matter in the form of a solution directly into the intestinal tract of a recipient (Gupta 2016). FMT is a non-surgical transplant procedure. Similar to probiotic therapy, FMT also does not violate structural boundaries. Although other invasive procedures such as phlebotomy (otherwise known as venipuncture) and intramuscular or subcutaneous injections of live attenuated microorganisms do violate structural boundaries, phlebotomy and injections are considered non-surgical procedures because there is no repair (suturing) required afterwards. These procedures also do not cause disease.

The goal of FMT is to change the recipient's microbiota composition and thereby indirectly improve the recipient's health. The fecal solution is prepared by first selecting a

healthy donor, screening the donor for the presence of pathogenic organisms, collecting the donor's feces and mixing it with water, and then filtering the suspension to remove particulate matter. The recipient receives the solution through a retention enema or colonoscopy tube. FMT is not a technically challenging procedure to perform. The main challenges to FMT have been aesthetic in nature, which probably explains why FMT has lagged behind SOT in its implementation. I will briefly discuss some diseases treatable by FMT.

Clostridium difficile infection is a disease state characterized by decreased microbial diversity and an overgrowth of one particular bacterium. FMT is helpful in the case of *Clostridium difficile* infection by providing other bacteria to the intestinal lumen that then out-compete *Clostridium difficile* for nutrients, thereby creating an environment in which *Clostridium difficile* can no longer proliferate (Kelly 2015) through spore formation (Gupta 2016). FMT restores communities of *Firmicutes* and *Bacteroidetes*. The newly transplanted bacteria use sialic acid, thereby depriving *Clostridium difficile* of that vital energy source. After FMT, the fecal composition resembles that of healthy persons (Gupta 2016).

Another disease for which FMT may be helpful is inflammatory bowel disease, which includes serious disease processes like ulcerative colitis and Crohn's disease. Chronic inflammation of the gastrointestinal tract characterizes inflammatory bowel disease. Continuous antigenic stimulation of the intestinal mucosa-associated lymphatic tissue plays an important part of its pathology, in which intestinal microbial imbalance is an important part (Gupta 2016). There is again a decrease in microbial diversity, with a decrease in *Firmicutes* and *Bacteroidetes* presence. FMT is not as helpful in inflammatory bowel disease as it is in *Clostridium difficile* infection because of side effects like worsening infection. The etiology of IBD is multifactorial and microbial imbalance may only be one component. Taken in terms of the human organism-human superorganism distinction, however, inflammatory bowel disease may be more a disease of the human organism than the human superorganism, and so treatment of the human superorganism will not be

entirely successful. Diseases of the human organism like myocardial infarction and stroke will never be fully treatable by addressing the human superorganism. However, such diseases could conceivably be preventable if we can find pathogenic mechanisms in a causal pathway between the microbiota and the human organism.

Finally, FMT may be helpful in diseases not traditionally associated with the location of the intestinal microbiota, i.e., outside the gastrointestinal tract, where we can find the concerned mechanism. Excess fat (adipose) tissue is a key characteristic of metabolic syndrome, in which there is some combination among a constellation of diseases including central obesity, diabetes, hypertension, and hyperlipidemia. There are significant differences in the intestinal microbiota between twin mice that are lean and obese. Obese individuals have more *Firmicutes* than *Bacteroidetes* species, and an increased capacity for energy extraction from the intestinal content (Gupta 2016). Obesity can transfer to lean mice through FMT when the donor is obese, also by changing satiety (Gupta 2016). FMT is an example of a treatment directed to the human superorganism.

FMT represents an important conceptual advance in therapy of disease. Health Canada classifies FMT as a "new biologic drug" (Gupta 2016). Other therapies under development include selective personalized probiotic and prebiotic administration and narrow spectrum antibiotic treatment (Peterson 2015).

FMT acknowledges that not all disease processes originate within the human organism or result from other organisms invading the human organism. In FMT, we administer live organisms to a location outside the human body to alter the functional relationship among organisms. The expanded nature of therapy of the human being represented by FMT indicates that *there is more than one type of organism requiring therapy*. We treat the microbiota to benefit the human organism. FMT contrasts to live attenuated vaccination, where the vaccination process typically involves violating natural human boundaries in the form of a subcutaneous or an intravenous injection. With any

kind of vaccination, unlike with FMT, there is no intention to allow the injected microorganisms to proliferate and prosper in the causal pathway to immunity; there is just an attempt to stimulate species-specific host immunity using inter-species molecular interactions as the stimulus. We can assess the effectiveness of vaccination by measuring the titers of effective antibody generated by the immune system.

3.7 Xenotransplantation

Xenotransplantation represents a frontier of SOT medicine. Xenotransplantation is the transfer of organs, tissues, or cells from an animal of one species to an animal of another species or to a human being (Kumar 2000). We do not yet perform human xenotransplantation in human superorganisms, although there have been previous attempts (Starzl 1993). Biological boundaries limit xenotransplantation.

The first animal-to-human organ transplant with some measure of short-term success was that of a liver transplant from a baboon to a human with liver failure in 1992 (Starzl 1993). There had been several unsuccessful attempts at human xenotransplantation prior to this attempt, as far back as 1963 (Starzl 1996). Two such transplants performed lasted for about only two months (Starzl 1996). A clinical observation made from the first transplant was that the liver began to create for itself a chemical environment similar to that of the baboon donor. Circulating baboon DNA was detected 35 days after the liver transplant, and the serum concentration of chemical substances such as uric acid and cholesterol apparently changed to baboon values. Starzl also claimed that the pattern of serum proteins involved in immune reactions more closely related that of a baboon rather than human beings (Starzl 1993).

Since baboons and chimpanzees are in scarce supply, the most attention to an alternate animal species as a donor to humans has been the pig. As a large mammal, the pig bears significant physiological resemblance to human individuals, yet there are fewer ethical concerns with using pigs as donors because they are already a source of food (Gock

2011). Pigs are also easy to breed and to genetically modify. However, pigs are not yet ready to be a source of organs for SOT. There are currently two main limitations to the success of xenotransplantation: species incompatibility and the transmission of infections. I will discuss each of these two concerns in turn.

Xenotransplantation involves crossing a formidable species barrier. The status of an organism as a member of a species is non-modifiable. In other words, a pig will always remain a pig. However, genetic modification within a species is possible to create a special population of pigs. Unwanted genes can be removed, or "knocked out", and human genes can be introduced and overexpressed in the donor animal. Without these manipulations, rejection of the organ will be both immediate and severe, resulting in organ loss.

While important molecules such as galactose-α1,3 galactose present in pigs can be disrupted successfully, solving one barrier unmasks other barriers (Gock 2011). Xenotransplantation research uncovers new mechanisms of species differences. As a result, we need multiple generations of pigs to address newly discovered barriers. Moreover, these species barriers were discovered between pigs and non-human primate models. The barriers between pigs and humans still need to be tested. Costs then become prohibitive (Gock 2011). The innate immune response and cellular immune response cannot be easily suppressed (Li 2009). Another major problem with xenotransplantation is immediate clotting of the organ's blood supply not directly related to rejection (Gock 2011).

At least as far as large animals are concerned, therefore, the impossibility of xenotransplantation is the ultimate proof of difference in species. We do not have specimens of *Homo neanderthalis* or other *Homo* species to study xenotransplantation. It is unknown if all these barriers to xenotransplantation resulted from evolutionary divergence. However, evolutionary differences promote physiological differences, and evolutionary individuality invokes physiological individuality. Perhaps evolution anticipated xenotransplantation even less than allotransplantation. It is in a species' interest after all to

be poisonous to other species (for example, various plants and frogs are quite toxic to touch or to consume). The difficulty of xenotransplantation is another manifestation of species incompatibility that may serve as protection to one species against another species. A failure of human xenotransplantation will greatly benefit pigs.

A second major concern regarding xenotransplantation besides rejection is the transmission of infection. Concerns about infection from xenotransplantation have quickly overtaken concerns about rejection. It is possible to breed pigs without bacteria, fungi, and parasites that can cause human disease (Dwyer 2002). In other words, new pig superorganisms can be created. However, not all infections can be addressed by special housing. Porcine endogenous retroviruses (PERV) live in almost all pig cells, and are present in highest concentrations in the solid organs (Dwyer 2002). PERV is capable of infecting human cells (Patience 1997). In the past, several zoonotic infections in human farmers and abattoir workers have originated from pigs (Kumar 2000). The consequences resulting from the transmission of PERV to the human individual through SOT are unknown. However, such retroviruses by themselves are capable of inducing immunosuppression (Denner 1998). Eliminating galactose-α1,3 galactose in pigs to eliminate rejection of the transplant can make PERV even more infectious (Dwyer 2002). Unwanted immunosuppression can be very harmful in SOT recipients, since it may promote secondary infections and cancer. Furthermore, viruses that are harmless in one species can be quite harmful in other species. Simian retroviruses crossing over from chimpanzees into humans may have slowly adapted into becoming the group of human immunodeficiency viruses (Gao 1999).

A microorganism successfully integrated into the organism of one species may not be so benign once it is inside the boundaries of the organism of another species. In the case of the human organism, until it can be demonstrated that there are microorganisms inside the human organism that are as benign to human organisms as some microorganisms are to other animal species, it would be a great risk to proceed with xenotransplantation. For now, our concept of the human organism as being composed of

only human-lineage derived cells stands as a barrier to implanting organs from non-human species. A rare experiment of exposing human individuals to pig kidneys through dialysis did not result in PERV infection (Patience 1998). However, if the PERV genome incorporates into the human genome, then it may not be so easily detectable.

Since a microorganism that crosses the boundaries of the human organism brings with it a potential for harm, the introduction of a microorganism into the human organism may be quite harmful even if it is not harmful to pigs. We have not attempted FMT from animals to human individuals yet, although transplantation of human microbiota into piglets for the purposes of metabolism research and drug discovery has been performed (Pang 2007). Drugs for human use are already being produced in "humanized" mammals. FMT will preserve the organism-individual distinction without structural boundary violation. After FMT, *Bacteroides* species of human origin are reliably demonstrable in the pig intestinal microbiome (Pang 2007). If the success of human-to-pig FMT proves robust, then the demonstration of pig-to-human FMT may be the needed next step before xenotransplantation can be successful. Pig-to-human FMT might even be required whenever we perform xenotransplantation, assuming a favorable microbial environment is needed for a transplanted organ to escape rejection and for the transplanted organism to avoid infection.

Xenotransplantation redefines the human superorganism. Not only is the human organism redefined by the implantation of a non-human organ, but the ontology of the human organism-human superorganism distinction will need to be reevaluated in a context much larger than just understanding microbial disease, not just to achieve xenotransplantation success but to achieve health. For now, the human organism does not contain harmless microorganisms while the human superorganism does. A solid organ xenotransplantation recipient loses the human organism-human superorganism distinction when microorganisms like PERV are present on both sides of the human organism

structural boundary. The consequences of losing this distinction will remain unknown for the time being.

We might facilitate xenotransplantation if we tailor animal organs for acceptance by both the human organism and human superorganism, rather than by the human organism alone. Xenotransplantation violates both the boundaries of organism and the superorganism, and cannot be successful unless we understand the distinction between the types of boundaries that the organism and the superorganism possess.

3.8 Breakdown of the Superorganism

After the death of the macroorganism, the superorganism also ceases to exist as the process of putrefaction begins. The functional boundary between organisms is permanently broken. Perhaps not surprisingly, the intestinal microbiota drives putrefaction, and the intestines are among the first organs to putrefy. *Clostridium* species are the main bacteria responsible for putrefaction, although all the other components of the microbiota also contribute. Putrefaction is first noticeable over the area of the large intestine, because this corresponds to the area where a large microbial population normally resides.

The bodies of stillborn fetuses and small infants are the slowest to putrefy because their microbiota is non-existent or sparse. The conditions promoting microbial growth in general are those that promote rapid putrefaction, such as a high fat content, high moisture, and warm environmental temperatures. When the cause of death of the human organism is an infectious disease process, the process of putrefaction is also more rapid because microorganisms have already migrated beyond their normal boundaries, crossing over into the boundaries of the human organism. In addition, normal boundaries are broken when the cause of death is external or internal trauma, which permits bacteria to spread more rapidly.

Human putrefaction provides a stark reminder that the microbiota is beneficial to the human organism only under a tight set of conditions. The persistence of the human superorganism through time is only an incidental Darwinian benefit. The human superorganism breaks down when the human organism no longer exists, although this breakdown does not prevent other superorganisms from forming.

Death of the larger organism, in this case the human organism, actually becomes beneficial to the smaller organisms, in this case the intestinal microbiota, because the sources of food that the larger organism provide are no longer limited to the intestinal lumen. The larger organism itself becomes a food source, and the smaller organisms rapidly proliferate as a result. Other organisms and superorganisms like flies, not part of the human superorganism also become involved in putrefaction, laying their eggs on fertile grounds. The superorganism defines which organisms are allowed and to what extent, and which are not allowed. When the superorganism ceases to exist, the situation then becomes chaotic for other organisms and superorganisms.

Death of a smaller organism within the superorganism, on the other hand, is unnoticed by the larger organism or the superorganism. The death and putrefaction of a few bacteria is inconsequential, due to their miniscule metabolic contribution to the individual and the rapid rate of proliferation of bacteria in general. The larger organism routinely expels smaller organisms with each bowel movement. If there is mass extermination of bacteria, however, then the larger organism will notice because its health then becomes affected. Therefore, size and the metabolic contributions of the organisms involved direct the dependence in the relationship among the organisms constituting a superorganism.

Post-mortem putrefaction demonstrates that a superorganism, unlike an organism, is *not* what lives together and dies together. The superorganism lives together, but it does not die together. Only the parts of the organism die together. The speed with which

putrefaction occurs (the process starts in one or two days after death) indicates that the *priority* of the immune system is to protect the human organism, *not* the human superorganism. The human immune system fails with the death of the human organism, and the human superorganism consequently disintegrates.

3.9 A Summary of the Human Organism and Human Superorganism

The larger biological entity consisting of an organism with all its associated organisms is the superorganism, and any part of the superorganism that derives from its own distinct lineage is an organism. The human body contains many microorganisms, outnumbering human lineage-derived cells by 10:1 when microbial cells are counted numerically, and 100:1 when the microbial genome is quantified.

The human being as externally perceived has boundaries, distinguishing human being from non-human being, although the part of the human being containing human-derived cells organized in the form of organs and tissues has its own internal boundaries as well. The human organism delineates through a structural boundary, while the human superorganism delineates through a functional boundary. Biological boundaries are real and serve to separate organisms from one another, with each organism also having its own boundary to separate its internal contents from the external environment. Separation by boundaries is the key to survival of any biological entity. Destruction of the boundary leads to cell death even though there is no true closure of the biological boundary as evidenced by the presence of pores and channels.

Microorganisms reside outside of these human structural boundaries when they are beneficial, and they travel towards and away from the human organism, within the functional boundaries of the human superorganism. However, microorganisms that cross these boundaries can and will cause harm when they do so. The human organism requires the presence of different kinds of microorganisms outside of its structural boundaries to enable its own survival and persistence through time, but the human organism and the

microorganisms follow their own evolutionary history and natural history. Boundaries of organisms may be coincidental spatially as in the skin, but they do not overlap in a mereological sense. The boundary itself does not take up any space because cell physiologies are always distinct from each other. Probiotics and FMT are examples of therapy for the human superorganism, with the human organism only incidentally benefitting from these therapeutic interventions.

The human superorganism is therefore a *functionally integrated* entity consisting of the human organism and other organisms. We should avoid the ambiguity inherent in the word *individual* by staying clear of the term *individual organism*. We never see the term *individual individual* in the literature because it is so awkward at its face value. I argue that *individual organism* and *individual human being* are equally awkward and misleading.

The structure of the human superorganism demonstrates that functional integration does not depend on the integration of real boundaries. Instead, intact boundaries are more important for maintaining functional integration. The role of boundaries, both structural and functional, is to maintain separation, not integration in biology. Yet boundaries of biological entities such as organisms do occasionally merge. One organism usually perishes in this boundary interaction (i.e., it is digested), but sometimes both organisms persist. The new biological entity that results from this merger of boundaries "*e"* merges with new properties, as the boundaries now redefine. When boundaries redefine in this manner, a superorganism emerges. Digestion is prevented either by one organism protecting itself through the establishment of a new boundary (as in the case of large parasites), or organisms maintaining separation between boundaries while maintaining lines of communication between and across the two boundaries.

I propose that the term *single specimen* be used instead of *individual* when referring to a particular organism and describing its relationships to the environment, or other

specimens of the same organism in biological studies. For biological human beings, if the term *superorganism* is used, we can avoid the ambiguity of *individual* altogether.

Once we understand the concepts of *human superorganism* and *human organism* in this manner, as delineated by their boundaries, we no longer need the biological term *human being*. *Human being* loses its significance as a biological entity when it has no biological boundaries of its own. *Human being* still has a conceptual place in areas such as psychology, philosophy of mind, and law, but the concept of *human being* may not be relevant in biology or medicine.

By dismissing the entity of biological human being, I now conclude the first half of my dissertation. I moved from a description of examples in the natural biological world to illustrate organisms and superorganisms, to the human organism and human superorganism. I described the role of structural and functional boundaries in delineating the human organism and human superorganism. In the second half of my dissertation, I will discuss how biological boundaries are established and maintained, and describe what else happens when these boundaries are breached and reestablished.

Chapter Four

The Immune System in Organisms and Superorganisms

In previous chapters, I discussed species, organisms, individuals, and superorganisms in the natural world, and then argued that the human being is a human superorganism of which the human organism is just one constituent. The human organism is therefore a subset of the human superorganism. The human superorganism results from a functional integration between the human organism and a multitude of other organisms. Structural and functional boundaries maintain separation between organisms, but frequently alter to enable the persistence of organisms. Yet despite boundaries being breached and recreated, functional integration in superorganisms maintains throughout.

In this chapter, I will argue that the immune system through its mechanism of immunity maintains both the human organism and human superorganism. Although other mechanisms of maintenance such as physical adhesion, metabolic self-regulation, membrane enclosure, a genetic program, and reproduction can all occur in organisms, the mechanism of immunity can additionally distinguish *between* an organism and a superorganism. I will further argue that the clinical experience with transplantation of solid organs such as the kidney, liver, heart, and lungs can help to develop further our understanding of the human organism and the human superorganism.

Before embarking on these discussions about immunity as a communication mechanism of integration in the organism and superorganism, I will first clarify what I mean by phenomena and mechanisms in biology, by briefly referencing the rich literature on describing biological phenomena, as well as the features of a biological mechanism. The mechanism of communication in integrating superorganisms is especially important to discuss in the ontology of superorganisms because of its recognizable expression as phenomena at biological boundaries. But first, what are phenomena and mechanisms?

4.1 Searching for a Mechanism of the Human Organism and Superorganism

Describing Phenomena

A phenomenon is a product of observation. In biology, quorum sensing and lateral gene transfer in bacteria are phenomena; the vast geographical expanse of *Populus tremuloides* and the bioluminescence of *Euprymna scolopes* are other examples of phenomena. Phenomena however do not need to be so interesting. Most phenomena are mundane. A healthy human superorganism exhibits a certain set of phenomena while a sick human superorganism exhibits different phenomena. For example, a healthy human organism has a core body temperature of 37 degrees Celsius and is usually active, while a sick human organism might have a core body temperature of 34 or 39 degrees Celsius and be inactive. Biologists and clinicians expend great effort describing phenomena. Most scientific communication is about phenomena.

Describing phenomena alone, however, imposes significant limitations on scientific progress. Maintaining the human organism and the human superorganism as persistent entities requires mechanisms. A mechanism both produces and maintains a phenomenon. An understanding of a mechanism always relates to some phenomenon and *mechanism* carries no meaning without a phenomenon to go along with it. A phenomenon is a description of our perception of the end-result of one or more operational mechanisms. A phenomenon is always subject to explanation by a mechanism.

Phenomena need to be easily detectable, observable, and independently reproducible. Inputs to the phenomenon need to be known, and the set of conditions needed to manifest the phenomenon laid out. Criteria are established to confidently espouse that the phenomenon has occurred. The relevant modulating and inhibitory conditions on the phenomenon need to be known. Finally, it is helpful to understand how we perceive the phenomenon under non-standard conditions, since measured byproducts not actually related to the mechanism itself can provide vital clues about the mechanism

(Craver and Darden 2013). A proposed mechanism may need to be split into component mechanisms, or combined with other mechanisms into a singular mechanism of greater explanatory value to the phenomenon. Our drive to understand phenomena leads to the search for underlying mechanisms. This is how science progresses. Mechanistic papers are valued more highly than papers that report only phenomena.

What is a Mechanism?

We regularly invoke mechanisms to predict, explain, and ultimately control phenomena (Craver and Darden 2013). Addressing common clinical problems requires at least a partial understanding of the mechanisms involved in the disease process. Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions (Machamer, Craver and Darden 2000). A mechanism consists of both entities and activities. Entities are the parts of a mechanism, which when arranged under a given set of conditions perform the mechanism's work, otherwise called *activity*. Mechanisms exhibit productive continuity, in which each step gives rise to the next. A mechanism is also called a structure performing a function in virtue of its component parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena (Bechtel 2005). Mechanism schemas in biology play the role of theories.

Features of a Mechanism

All the entities in a mechanism may not necessarily be in place before the mechanism demonstrates its activity (Craver and Darden 2013). A mechanism may undergo modification as it performs its activity. One or more entities may insert at different places and times in the mechanism, thereby resulting in a modification of even the most basic activities of the mechanism. There is usually, but not always a start and a finish to the mechanism, since a mechanism can be linear or cyclical. Likewise, an environmental trigger

may or may not be required, and there may or may or not be a termination condition for the mechanism.

Mechanisms are regular because their workings are similar when the conditions are similar. A mechanism is organized, which means that a mechanism has spatial, temporal, and activity organization. Mechanisms exist at the molecular, cellular, tissue, organ, organism, population, and ecosystem levels. Mechanisms can also span different levels, with "top off" and "bottom out" limits of descriptive interest. This means that descriptions can become larger and larger in scope to the extent that we sacrifice detail, or entities can be broken down into their atomic or sub-atomic structure wherein further description is both impossible and meaningless. A mechanism ultimately has to be described both in terms of its function, as an integration with a higher-level mechanism, and in terms of its underlying mechanisms, or integration with lower-level mechanisms. Multi-level and multi-field integration is the overarching goal of mechanistic description.

We may also say that a mechanism consists of parts (Glennan 1996). Each part of a mechanism must have its own reality apart from the mechanism (Glennan 1996). The properties of a part should be ascertainable, at least to some extent, when the part is present outside the mechanism. The properties of a part may be hard to ascertain in a biological mechanism, since parts taken out of cells are not necessarily the same structurally or functionally as when they were inside the cell. Parts must be stable enough to be objects, and must be stable in the absence of interventions.

A mechanism is different from an aggregate. An aggregate of parts is one in which the parts can be freely rearranged without a change in any of the properties or behavior of the whole. We can take everything apart and put it back together again. In an aggregate, the relationship of the parts to one another is irrelevant. In the case of a mechanism, however, organization of the parts is essential. A liver cell will not function, for example, if placed in the skin. A transplanted organ and a recipient are not an aggregate when they are

combined. The relationship of the organ to the rest of the body parts is pre-specified, and this relationship must be respected if the organ is to function properly.

Mechanisms also require modularity, in which removing or disabling one part of the mechanism does not affect the other parts. A mechanism thus consists of distinctly separate, interacting parts. Components of a mechanism also combine to form more complex parts (Fagan 2012). Finally, mechanisms may also be ephemeral. This means that the organization of parts is of a looser kind, and the structures are not necessarily robust or stable. We often find new biological mechanisms expressing themselves once we suppress a known mechanism. The mechanism may have been present all along but simply did not express itself; it may be actively repressed, or it may be newly constituted from its component parts, in response to either the presence or absence of a signal. With regard to the last feature, components of a mechanism communicate among themselves through signals so that the mechanism can perform its function.

The Mechanism for Communication across Boundaries: Immunity

Biological interactions between human superorganisms involve exchanging microorganisms in a variety of social situations from activities as innocuous as shaking hands, to transplanting human solid organs. A single human superorganism in turn contains many self-serving organisms. The mechanistic output of superorganisms in which we are presently most interested is *communication* among its organisms.

Unicellular organisms communicate with other unicellular organisms and sometimes form superorganisms. However, multicellular organisms usually integrate functionally with other organisms to form superorganisms. Functional integration is the key process by which the superorganism holds together, for otherwise its constituent organisms would all quickly go their separate ways. In addition, a superorganism is much more than the sum of its organisms, both in terms of its structure and in what it is able to accomplish in its environment. This fact is very relevant to the success of organ transplantation.

A mutually beneficial relationship needs to exist among the organisms that constitute a superorganism. Otherwise, the relationship would be more of a master-slave or farming relationship between the macroorganism and its microorganisms. Putting unhelpful metaphors that imply intentionality aside, in order to establish such a mutually beneficial relationship, these organisms need reliable communication among themselves. Communication has to occur across intact boundaries. Exchange of crucial biological information in the form of a signal among the organisms enables the proper functioning of all of them, and ultimately the survival of all of them as well. *Communication enables functional integration*.

Although signaling occurs from one organism to the other, it is also important to note that signaling occurs inside the organism as well. Since integrity of the organism in turn enables the integrity of the superorganism, we can consider signaling within the organism as part of the same integrative biological process. Internal signaling likely differs in some respects from signaling between organisms even if there is some interdependency between them, but these differences do not impact the overall conclusions of my project.

The immune system is involved in all human biological interactions. The immune system plays an important role in regulating function both within, and at, the boundaries of the multicellular organism. *Immunity* is the output of the immune system. "Immunity" is a term that exudes strength and confidence, unlike "defense" where the prospect of defeat is as entailed as victory (Yatim 2015). The immune system is also central to many disease processes. All organisms and superorganisms require mechanisms to exist and persist through time. Organisms also require mechanisms to *form* superorganisms. Both of these major accomplishments of organisms, namely persistence and forming superorganisms, occur through the actions of the immune system. The immune system is the main determinant (physical proximity is also important) for how different organisms interact with each other to maintain themselves and form superorganisms. However, since we do

not perform SOT in non-human species, my discussion on how organisms become superorganisms will be mostly limited to the human species.

Why Care about a Communication Mechanism in Solid Organ Transplantation?

The history of SOT provides many examples demonstrating how understanding mechanism has led to major clinical advances. An understanding of mechanism also highlights dangers inherent in SOT research and practice if scientists pursue these without a sufficient understanding of mechanism. Applying scientific findings from the laboratory to clinical practice prematurely can lead to serious unintended consequences in SOT recipients. This is true of the side effects of anti-rejection medication, for example, when these medications are administered to different populations possessing unrecognized and substantive underlying metabolic differences from known populations.

A superorganism such as the human superorganism has boundaries separating its constituent organisms. Some form of communication always maintains across the separation between organisms, or the superorganism will not persist through time. It is important, therefore, to establish how such communication occurs between the human organism and a bacterium. Since a physical separation always maintains between the human organism and bacterium, microorganisms play as much of a role as the human organism in maintaining the superorganism. Microorganisms may act as scaffolds in determining the individuality of the host macroorganism, without being an actual part of that macroorganism (Chiu 2016). Maintaining this scaffold requires a mechanism for communication. Communication occurs across the physical separation between organisms.

In contrast to microorganisms located outside the human organism, a transplanted organ locates within the confines of the human organism. SOT adds complexity to mechanisms in superorganisms beyond what microorganisms provide because SOT creates new structural, not just functional connections between hitherto separate entities. We need a mechanism that can address the challenges posed both by microorganisms outside the

human organism's boundaries and the transplanted organ inside the boundary. The mechanism of communication acts in two directions: inwards and outwards.

A Communication Mechanism in Solid Organ Transplantation by Analogy to Microorganisms

Even though organ transplants and microorganisms reside in different compartments, microorganisms can still be very useful analogues to organ transplants. We can characterize the communication between any two organisms as *immunity*. As I will soon show in detail, immunity characterizes the relationship between both microorganisms and the human organism, *and* between a transplanted organ and the human organism. There is also a relationship between the transplanted organ and microorganisms. Other human mechanisms do not fulfill this multiple role. Therefore, analogous reasoning between these two relationships (human organism-microorganism and human organism-transplanted organ) might help advance our understanding of the human superorganism.

However, there are limitations to analogical reasoning. Bacteria are very different from human superorganisms and so have limited use for direct morphological comparison. On the other hand, large animals are widely used to generate data. A major concern in transplantation medicine is the great emphasis placed on gathering data from animal models and mapping the information obtained to humans as part of an analogical reasoning process. The 19th century physiologist Claude Bernard championed the concept of the *milieu interior*, still in use today as a characteristic that the organism is always seeking to preserve. According to Bernard (Desjardins 2014):

> Experiments on animals, with deleterious substances or in harmful circumstances, are very useful and entirely conclusive for the toxicology and hygiene of man...for as I have shown, the effects of these substances are the same on man as on animals, save for difference in degree.

Such analogies do not prove causation and certainly do not prove mechanism. They are not deductive inferences. There exists a complex interaction between every organism and its environment (Desjardins 2014). Such interaction with the environment is also unique to species and even populations within a species. Evidence for drug efficacy in one population may not provide the evidence for use of that drug in another population, even within the human species.

The environment in which two different organisms find themselves is not strictly identical, and the difference in environment between two organisms belonging to different species is likely to be even greater. Mice are used often in transplant research. Yet the basic cells involved in executing the effects of the immune system are quite different between mice and humans; while the majority of white blood cells in humans are neutrophils, the majority of white blood cells in mice are lymphocytes (Desjardins 2014). Therefore, purely reductionist approaches to understanding mechanisms in SOT are unlikely to provide rewarding insights. We need to contextualize biological mechanisms to understand phenomena in SOT. Furthermore, communication mechanisms may differ in different transplant organ types, even though the phenomenon may be very similar. Nonetheless, analogical reasoning between the microbiota and the organ transplant is helpful because the immune system is intimately involved in the relationship of both these entities with the human organism, as well as between the microbiota and the transplanted organ. The immune system is a multi-directional system of communication.

Therefore, we can justify analogical comparisons between microorganisms and organ transplants, because of shared mechanisms of immunity. Human evolution has already provided us with a useful model of existence with an entity other than the human organism in the form of the human microbiota. I have already discussed some science of the human microbiota. If we wish to know how to make organ transplants last better and longer, then understanding communication mechanisms common to organ transplants and the microbiota will be rewarding. There are many similarities between how the human

immune system responds to microorganisms and to a transplanted organ, because the human organism never evolved to handle SOT. The human organism must use immune systems already in place to relate to microorganisms for millions of years to now communicate with organ transplants.

Transplantation science follows what Mitchell describes as an *integrative pluralism* (Mitchell 2003), in which the less fundamental is not explainable in terms of the more fundamental, but rather scientific achievements are collaborative and piecemeal, slowly building up a picture of mechanism (Tabery 2004). SOT is an example of how different scientific disciplines (immunology, pathology, pharmacology, surgery, etc...) co-exist and serve to contribute to mechanistic explanation of phenomena. Transplantation medicine is no different from any other area in medicine in which knowledge accumulation is more piecemeal than sequential. The microbiota provides just one piece of information in this process of knowledge accumulation.

The immune system is central to health because its operations are involved in many different aspects of health and disease (Yatim 2015). The immune system contains many mechanisms needed to explain clinical outcomes before and after SOT. The immune system has the potential to explain many of the features of other disease processes as they evolve at varying times after SOT. It is likely that more mechanistic explanations for transplant-related phenomena than are currently available may become apparent once we appreciate the human superorganism as the larger entity that encompasses the human organism.

Our discovery of mechanisms in SOT whether they relate to communication or otherwise may have been limited in the past by our failure to account for the human organism-human superorganism distinction. In SOT evaluations, we may miss modulating and inhibitory conditions, redundant components may not all be located in one space, and pathological mechanisms may not truly be pathological, but rather only clinically deemed not acceptable. I will soon provide a specific example of the latter, namely organ rejection.

Mechanisms may also perform their activities and functions while actively destroying other healthy mechanisms in the body. In sickle cell anemia, which is a common disease in some parts of the world, a pathological mechanism may play a physiological role in a given environment where there is a high prevalence of malarial infection (Nervi 2010). Post-transplant events show that evolutionary arguments are not very helpful in daily medical practice when survival of the patient rather than the species is the priority. Patients with organ failure do not typically reproduce, and transplantation often restores fertility. Yet with an organ transplant, the priority is to preserve the patient, although this conflicts with the priority of the immune system in preserving the species. Good transplant function is not necessarily normal transplant function; it is suboptimal but it is acceptable under the circumstances. We need selective control of the immune system for a transplant to be successful. Communication compromise leads to suboptimal organ function and a variety of unwanted post-transplant phenomena.

Understanding Immune Mechanisms in Clinical Transplantation

Transplant immunology attempts to predict, explain, and control the success of SOT. The immune system is the messenger common to both the organism and superorganism. The products of the immune system act as signals for communication between organisms. SOT results from an interaction between two sets of human mechanisms, namely those of the donor and the recipient. Adding to this interaction is the complex milieu created by immunosuppressive medication and the possible microorganisms of both donor and recipient origin. Different mechanisms may be operational in different parts of the organ at different times, even if there is only one clinically apparent phenomenon. Dissecting out mechanisms from all the clinical noise becomes very difficult.

The etiology of many post-transplant events remains unexplained because their analysis is retrospective. We need to study mechanisms alongside the disease processes as

they occur. For example, antirejection medication designed to suppress the immune system are involved in many "non-immune" disease processes after a transplant, because those disease processes turn out to have an underlying immune mechanism. If we do not appreciate non-immune mechanisms as related to immune mechanisms, then therapy is likely to be haphazard and inaccurate, and therefore less effective. Clinical heuristics require mechanistic explanations be dropped; undesirable phenomena are described with limited study and interventions are prescribed based on the best possible explanation for the phenomenon. Quite often such interventions prove to be effective, and the search for mechanistic explanation loses scientific priority.

Knowledge of immune mechanisms will likely be the most useful heuristic in understanding not only how we can maintain an organ transplant, but how we maintain the human organism-human superorganism relationship as well. Understanding how organisms interact in creating superorganisms, and how exchanging microorganisms affects superorganisms may help us understand how organs and organisms interact in creating newer types of superorganisms. SOT is the most sudden and violent example of human cell exchange. SOT violates the boundaries of the human organism, and suddenly engages the immune system. *Boundary violations can trigger immune mechanisms.*

SOT is a non-standard condition of the human organism and the human superorganism because of this boundary violation. In addition, SOT creates several new boundaries. Evolution did not predict SOT. However, SOT provides us unique opportunities to study the immune mechanisms that evolution provided.

4.2 The Immune System as a Collection of Mechanisms

The human immune system contains many mechanisms relevant to communication. The immune system communicates with all other organ systems in the body. In this section, I will first describe the components of the immune system, followed by immune communication of the human organism with microorganisms and with organ transplants.

Understanding and learning to live with immunity is required for a superorganism to be successful as a healthy entity. "Immunity" is the output of the immune system, and includes both the immune reaction and immune response.

Components of the Immune System, Immune Reaction, and Immune Response

The Immune System

The *immune system* refers to a group of specific organs including the bone marrow, thymus, spleen, and lymph nodes, along with a circulation system that consists of the lymphatic system and blood system. The immune system also contains many different types of white blood cells (called *immune cells*), their molecules such as cytokines, and complement proteins (Pradeu 2012).

The bone marrow and thymus constitute the primary lymphoid tissues because they specialize in generating immune cells, and they transform immature cells into mature lymphocytes with a high specificity directed towards foreign antigens. The spleen, lymph nodes, and mucosa-associated lymphoid tissues are other parts of the immune system that are located throughout the body, and constitute the secondary lymphoid tissue. The function of these tissues is to trap foreign antigens and then present them to specialized white blood cells called T lymphocytes and B lymphocytes.

The immune system is a biological term widely used by immunologists and clinicians to denote the entities that perform the functions involved in immunity, such as the immune reaction and immune response. This description of the immune system applies to humans and other jawed vertebrates. A broader concept of the immune system that also encompasses systems contained in other types of organisms is that the immune system is any system of biochemically specific interactions leading to the rejection of some living entities (Pradeu 2012).

No matter how primitive an organism might seem, it always possesses an immune system. Even unicellular organisms such as bacteria have immune systems, although their immune systems components are understandably quite different from those of multicellular organisms (Pradeu 2013).

The Immune Reaction

The *immune reaction* refers to the biochemical interaction between an immune receptor and its ligand (Pradeu 2012). The immune reaction therefore includes any interaction that occurs between a receptor on any cell that is part of the immune system and what this receptor binds to, thereby enabling the immune cell to carry out its function. The immune reaction is a normal phenomenon that is always occurring. Immune reactivity is an ongoing process essential to survival.

The Immune Response

The *immune response* is the result of activation of an immune cell (Pradeu 2012). The immune response typically leads to selective immune cell proliferation and differentiation. Depending on the cell type involved, the end-result of the immune response may be either destruction of the target, or an inhibition of that destruction. Therefore, an immune reaction precedes every immune response, but not every immune reaction leads to an immune response (Pradeu 2012).

I will briefly summarize the immune response to establish the terminology needed for a subsequent philosophical discussion. The immune response essentially consists of three phases: recognition of the foreign antigen, activation of antigen-specific lymphocytes, and the effector phase of destruction.

The first phase of the immune response is most important from a philosophical perspective since we are most concerned with *how* a microorganism or transplanted organ becomes a recognized target for destruction. The genes that determine rejection or

acceptance constitute the major histocompatibility complex, or MHC, whose gene products are *antigens*. Differences in MHC between the recipient and the organ transplant are the stimulus to the immune response. The MHC encodes for a group of diverse proteins on cell surfaces, and their variation in structure and function (i.e., their polymorphism) makes each person immunologically unique (Danovitch 2005).

Peptides (small fragments of protein) from the microorganisms or transplanted organ bind to human leukocyte antigen molecules, and then so-called *antigen-presenting cells* present these peptides to helper T lymphocytes. This presentation of peptides occurs through their recognition via T lymphocyte receptors. Due to the polymorphism of MHC, the antigen-presenting cell efficiently binds many different microbial and other peptides and presents them to T lymphocytes. This manner of antigen presentation is called *direct* antigen presentation.

In the second, or activation phase of the immune response, more lymphocytes home in on their target through the up-regulation of several biochemical pathways. Cytokines, which are chemical products of the cell, lead to destruction of the microorganism or organ transplant. In addition to the all-important first signal, which is the MHC-T lymphocyte receptor interaction, several second signals result from different sites of binding between the antigen-presenting cells and the T lymphocyte.

In the third, effector phase of the immune response, T lymphocytes and *natural killer* cells proliferate (multiply). These two types of cells secrete several types of enzymes that perforate microorganisms and transplant cells. In addition, T lymphocytes produce a certain protein called *Fas ligand* that binds to a receptor called *Fas* on cells in the target and initiates a process called apoptosis, in which those cells self-destruct. We know apoptosis as “programmed cell death” because the target cells are being given instructions to die. The target cell thereby becomes a participant in its own destruction.

Finally, B lymphocytes transform into plasma cells (yet another type of white blood cell) and secrete a large amount of special proteins called *antibodies*. Antibodies react with other proteins collectively called *complement* to cause *cellular cytotoxicity*. B lymphocytes can be activated by T lymphocytes and vice versa, as part of the immune response.

The T lymphocyte-B lymphocyte interaction is just one example of communication between different cells of the immune system. The immune system operates through a system of checks and balances, each in turn regulated through other sets of checks and balances as part of an integrated communicative whole.

The Immune Self

Tauber (1994) popularized the term "immune self", although what this means, in shorthand, is the immune system with all its mechanisms. In contradistinction to the other "immune" terms, the immune self is a notoriously difficult concept to grasp scientifically, yet is philosophically very interesting since it links to other notions of the self. The immune system with its mechanisms distinguishes between self and nonself components in the body and thereby promotes selective immune responses. The immune self, if there is such a process, likely consists of at least some of the immune cells and their mechanisms. The immune self is more of a philosophical than biological term. Conceptually, the immune self is what underlies both the immune reaction and the immune response. The immune self is the self as distinguished from nonself by the immune system.

In the case of the human organism, the immune self recognizes microorganisms as nonself. However, in the case of the human superorganism, the immune self has a choice about whether to consider the structurally intact microorganism as self or nonself. The immune system protects the human organism from microorganisms, but also permits those same microorganisms to exist, or even allows them to proliferate under its umbrella, to protect the integrity of the human superorganism. This apparent dichotomy of goals of

destroying microorganisms or tolerating them raises two possibilities about the nature of the immune self.

The first possibility about the nature of the immune self is that there are two human immune "selves", one for the human organism and one for the human superorganism. To have two immune selves in this manner seems peculiar because "self" is supposed to be a unifying concept. There is only one human immune system, even if it acts in different directions. The second possibility is that there is only one immune self, but its sole purpose is to protect the human organism from danger. The immune self wants nothing to do with the human superorganism. The immune system tolerates microorganisms only incidentally as part of its protection of the human organism. If the microorganism threatens the human organism, only then will the immune self act. This possibility again seems unlikely since microorganisms are not always destroyed by the immune response, and may actually be encouraged to proliferate under the right circumstances because they can be very useful. Purely incidental tolerance to microorganisms seems highly improbable. The small number of enterotypes (Arumugam 2011) indicates that the microbiota assembly process is non-random.

We still face the question of what exactly is a human organism or human superorganism. We have a good idea of what entities the human organism and human superorganism consist of. However, for SOT to be truly successful and for the transplanted patient to be able to avoid acute rejection and chronic rejection, we should know more about the entity for whom we are performing the transplant, whether it is the human organism, the human superorganism, or both. We structurally perform the transplant on the human organism, but functionally the transplant affects both the human organism and the human superorganism. For SOT to be successful, we need to acknowledge the presence of the microbiota. Both similar and dissimilar interactions between the human being and the microbiota provide useful lessons for SOT, because the immune system considers the

transplanted organ very similarly to a microorganism. I will now provide some additional detail about the immune system.

The Innate and Adaptive Immune Systems

The innate immune system and the adaptive immune system together broadly comprise the immune system. Both immune systems consist of immune cells and produce immune reactions and immune responses.

The Innate Immune System

The innate immune system is primitive. Evolutionary principles dictate that nothing in the organism is invented from scratch. Rather, preexisting tools, even if they are primitive are preserved if they are useful, and then improved upon. When it comes to immunity, the best primitive defense mechanisms are preserved while the least useful mechanisms are discarded (Litman 2007). Innate immunity consists of mechanisms *encoded in the germ line*, and that therefore pass down from one generation to the next, requiring little modification along the way (Janeway 2002).

The innate immune system is 750 million years old and represents the first line of defense against infection, being able to recognize up to 1000 different molecular patterns. It is a rapid response system due to the urgency of the threat posed by infection to the organism, but as a trade-off for being rapidly responsive, the innate immune system is less diverse in its responses. The innate immune system also has no memory. The innate immune system is an off-the-shelf system whose responsiveness is towards danger signals, believed to be pathogen-associated molecular patterns, or PAMP. Pattern recognition receptors recognize pathogen-associated molecular patterns as nonself because host cells do not express PAMP.

Dendritic cells, which are antigen-presenting cells, form networks involved in *immune surveillance*, which is the active search for targets that do not meet the criteria for

self. Dendritic cells originate in the bone marrow. Dendritic cells digest unwanted intracellular proteins into small peptides by the MHC class I pathway, and engulf unwanted exogenous donor molecules from transplanted organs and bacteria by the MHC class II pathway. These molecules are then presented to T lymphocytes for further action. Natural killer cells directly induce the death of cells infected by viruses, through cytokines or direct lysis, *without* having to be first primed by other cells for that purpose. Natural killer cells respond to a *missing self, as opposed to a nonself,* by targeting cells in which MHC class I is absent. Macrophages engulf bacterial cells and kill them in a process called *phagocytosis*, and present the antigens of killed cells to T lymphocytes. Macrophages also present donor antigens from transplanted organs to T lymphocytes to initiate destruction of the target by producing reactive oxygen species.

In summary, the innate system is an old, powerful system designed to preserve the organism through time. In human organisms, the innate immune system is a defense system against microorganisms recognized as danger signals, and the innate immune system is the first responder to transplants when boundaries are violated.

The Adaptive Immune System

While the innate immune system can recognize up to 1000 different molecular patterns, the adaptive immune system can recognize up to 10 million different patterns (Akira 2006). This much more versatile adaptive immune system is both informed and regulated by the innate immune system (Iwasaki 2010). Specificities of the adaptive immune system to antigens are random. The adaptive immune system can also clonally expand, unlike the innate immune system, meaning that certain cells with high target specificity to certain antigens can multiply preferentially and rapidly. The adaptive immune system is probably a later evolutionary development, based on its degree of sophistication in response.

Differences between Innate and Adaptive Immunity

Self-nonself discrimination requires the participation of both the innate and adaptive immune systems. The innate immune system produces co-stimulatory molecules through the recognition of PAMP, while the adaptive immune system does so by recognizing molecular details expressed on its target cells (Medzhitov 2000). Innate immune responses often deal with bacteria, so a response by the adaptive immune system is not always needed. An organ transplant on the other hand will invariably engage the adaptive immune system.

T lymphocytes are especially important to the adaptive immune response, just as natural killer cells are to the innate immune response. Peptides from an organ transplant are presented to T lymphocytes just as microbial peptides are presented to trigger immune responses. Importantly, self-peptides belonging to the transplant recipient are also presented in this manner. However, T lymphocytes responding to such self-antigens are usually destroyed in the thymus gland (present in the chest) by a process of negative selection, while those cells whose reactivity is specific for foreign peptides proliferate by a process of positive selection. In addition to direct presentation, antigens can be presented *indirectly*, which means MHC molecules are shed from the donor cell surface, taken up by antigen-presenting cells, processed by them, and their peptides then presented on recipient MHC molecules instead of donor MHC molecules. Indirect antigen presentation blurs the self-nonself distinction between interacting immune cells.

Distinguishing between direct and indirect presentation is important because acute rejection depends mostly on direct presentation while chronic rejection depends on indirect presentation (Danovitch 2005). Molecules of the recipient mostly mediate chronic rejection because donor immune cells have a limited lifespan and soon cease to exist. However, these donor immune cells have communicated with the recipient's immune system before they die, so the immune response can reactivate in the future through a

recipient-borne mechanism. Nonself representation passes on from donor cells to recipient cells.

Whether any of these differences between the cell profiles of infection and organ rejection in terms of their clinical correlates are the result of differential activation of the innate and adaptive immune systems is unclear. However, the adaptive immune system clearly plays a more important role in SOT than in infection by microorganisms, in which the innate immune system plays the major role. Clinical phenomena after transplantation usually appear only after engagement of the adaptive immune response, at which time many different cell types belong to different arms of the immune response are found together.

In the next two sections (Sections 4.3 and 4.4) I will discuss the immune response of the superorganism to other organisms and to organ transplants.

4.3 The Immune Response to Other Organisms

The Immune System and Individuality in Unicellular Organisms

A specialized apparatus with cells dedicated to immune functions is not always necessary for immunity. Unicellular organisms also possess an immune system (Pradeu 2013). *Bacteriophages* are viruses capable of infecting bacteria. The clustered regularly interspaced short palindromic repeats/ clustered regularly interspaced short palindromic repeats-associated system (also called CRISPR/Cas9) in bacteria is responsible for their immunity against invading bacteriophages. Bacteria incorporate these genomic segments into their own genome ("spacer"), and then use an RNA interference-like mechanism to prevent viral replication. In effect, the invading nucleic acids are "silenced" (Jinek 2012). A subset of CRISPR/Cas9 is able to break down DNA as well (Jinek 2012). Ribonucleic acid silencing has previously been called the "genome's immune system" (Plasterk 2002).

Similarity in genome sequence between the spacer and the bacteriophage determines specific bacterial resistance to viruses (Barrangou 2007). CRISPR/Cas9 is therefore an *adaptive* immune system in unicellular organisms (Makarova 2011). Unicellular organisms are able to defend their integrity and cohesiveness from environmental threats such as viruses. Therefore, a unicellular organism such as a bacterial cell counts as an individual, because it is a functionally integrated entity whose integration links to the common fate of the system when faced with selective environmental pressures. The "individual" in bacteria functions effectively as a superorganism might in the case of multicellular organisms that form superorganisms. In this case, the integrity of the cell maintains by what counts as an immune response (Pradeu 2013).

The Immune System and Individuality in Multicellular Organisms

Multicellular organisms derive in their structure from unicellular organisms by evolution, but for them to remain as functionally integrated units, it is also necessary for them to possess a mechanism for maintaining cellular cohesion. *The immune system provides this cohesion mechanism.* The immune system facilitates the emergence of the multicellular individual (Pradeu 2013). If cohesion of the multicellular organism maintains once evolved, then the boundaries of the organism are successfully re-defined.

The development of a set of cells whose primary purpose is immune-related was an essential first step towards the development of cohesive multicellular organisms (Leslie 2007) that also have the characteristics of a superorganism. A useful first step to is to study an organism that is actually able to make such a transition as a part of its life cycle. The social amoeba, *Dictyostelium discoideum* (discussed in Chapter Two) elegantly displays the transition between a unicellular and multicellular organism, when driven by environmental circumstances. A certain bacterium called *Legionella pneumophila* can infect *Dictyostelium discoideum.* The amoeba defends itself from these bacteria through the actions of a population of sentinel cells, which circulate when the amoeba is in its slug

form. The sentinel cells adhere to the bacteria, and destroy them in a manner similar to neutrophils in higher multicellular organisms (Chen 2007). Based on this example of *Dictyostelium discoideum,* it appears that dedicating a subset of cells to immune functions is necessary for transitioning from a unicellular to a multicellular organism (Pradeu 2013).

By extension of the above example of *Dictyostelium discoideum*, once a cohesive multicellular organism or superorganism is established, the immune system then serves as a "policing" system inside its boundaries. The metaphor of policing is useful here, since a police system describes an internal law-and-order mechanism of a political state, as opposed to an army whose major role is to address threats external to the boundaries of that political state. Immune cells inside the boundaries of the organism destroy cells interested in their own proliferation at the expense of the rest of the organism. The immune system performs this critical function as part of a division of labor among the cells of the multicellular organism (Kirk 2005).

The innate immune system preserves the human superorganism by preserving the integrity of its largest organism. For the functional integrity of the human superorganism to be preserved, there needs to be ongoing immune responsiveness to the microbiota. Bacteria vary in the mechanism of their pathogenicity between two extremes: toxicity without invasiveness and invasiveness without toxicity. Toxicity without invasiveness is an attack against the organism without another organism breaching its boundaries, although toxic organisms (e.g., *Clostridium difficile*) secrete chemical products capable of breaching the boundary. Invasiveness without apparent toxicity occurs in humans infected by viruses (e.g., *cytomegalovirus, herpes simplex virus*), although *potential* toxicity always exists, and frequently occurs.

The first line of defense against the microbiota in multicellular organisms is the epithelial cell lining, which is part of the innate immune system. It may be a simple physical barrier as in the case of the skin. The outer layer of the skin contains several

layers of epithelial cells, upon which a layer of a protein called keratin rests. In addition, the secretion of fatty acids from the skin epithelium and immunoglobulins from the intestinal epithelium also help to curtail bacterial growth. The mechanical action of urine flow flushes away bacteria from the urinary tract. The acidity of the vagina is produced by the breakdown of glycogen into lactic acid. Commensal bacteria secrete compounds that kill pathogenic bacteria (Male 2006).

If bacteria pass this first line of defense, then PAMP molecules efficiently destroy bacteria and prevent the need for an adaptive immune response. Various cytokines prevent further penetration of the invading bacteria, increasing inflammatory cell adhesion to endothelial cells that constitute the inner lining of blood vessels. Phagocytes first migrate towards bacteria in response to chemical signals derived from both macrophages and bacteria. Ultimately, phagocytosis kills most bacteria. Other mechanisms of killing include the secretion of antimicrobial peptides, oxygen reactive species, and iron. Intestinal wall cells also directly secrete antimicrobial peptides.

There is an inherent immunological tension in the relationship between the microbiota and the human organism. On the one hand, the microbiota is useful, and so there is no outward reach of the structural boundary of the human organism to engulf or otherwise destroy the bacteria. On the other hand, bacteria also need to be kept at a safe distance from the boundaries of the organism, for to come into direct contact with the organism would significantly increase the chances of bacterial invasion or bacterial destruction, and therefore avoidable engagement of the adaptive immune system. However, at the same time the microbiota is safely contained within the functional boundaries of the human superorganism. As a result, there is an inner boundary and an outer boundary to the human: *the inner structural boundary belongs to the human organism while the outer functional boundary belongs to the human superorganism. The microbiota is located in between these two boundaries.*

The immune system senses the nature of the bacterial cell wall in determining the best method for killing the bacteria. To escape from the cells of the innate immune system, some pathogenic bacteria hide by entering the cells of the organism. Some bacteria can lyse the cell membrane of the phagocytic cell, while others enter non-phagocytic cells of the human organism such as epithelial cells. The entry of bacteria into the epithelial cell of the human organism is therefore always a cause for concern, because it may indicate that the functional integration of the superorganism has been compromised. The innate immune system defines and polices the boundary of the organism in order to preserve the structural organism, but in doing so the immune system also preserves the functional superorganism.

The Microbiota as Scaffolds of the Human Individual

An interesting philosophical perspective on the relationship between the macroorganism and its microbiota is the Equilibrium Model of Immunity (Chiu 2016, Eberl 2016). According to this model, the macroorganism cannot persist in time or function as an individual without its accompanying microorganisms, but immune processes between the macroorganism and its microorganisms promote individuality, rather than the functional contributions of the microorganisms themselves.

According to this model, there are three arms of immunity: *Type 1*, intracellular immunity that responds to intracellular signals from viruses, some bacteria, and cancers; *Type 2*, which responds to large extracellular signals from large parasites and tissue injury, and *Type 3*, which responds to small extracellular signals from fungi and most bacteria (Chiu 2016). These immune responses are not specific to the species of microorganism but only to their general category. All three arms of immunity express some activity all the time, but to a different extent. When one arm of immunity is activated, the other arms are down-regulated. For example, a viral infection activating type 1 responses downregulates type 3 responses, thereby increasing susceptibility of the host to bacterial infections.

Therefore, there is a regulated mutual inhibition and contextualization of the immune response (Chiu 2016). Microorganisms thereby participate as effectors of the immune responses. *Microorganisms are not simply targets of the immune response but are effectors as well.*

If the regulated mutual inhibition of the immune response is lost, then a disease process will result. Unregulated type 1 responses lead to certain autoimmune disease, unregulated type 2 responses to allergies and scarring, and unregulated type 3 responses to other types of autoimmune diseases. Increased susceptibility to allergies in children from excessive antibiotic administration or lack of microorganisms in the environment, which is the so-called hygiene hypothesis, can be explained by dysregulated type 1 and type 2 immune activity (Prioult 2005).

The Equilibrium Model of Immunity is an extension of the Discontinuity Theory (Pradeu 2012). According to the latter theory, the sudden detection of unusual antigen patterns stimulates the immune response, while a more gradual introduction of new antigens does not, at least not to the same extent. Microorganisms that act continuously with the macroorganism's immune receptors do not elicit exaggerated immune responses. Since microorganisms continually enter and leave the gastrointestinal tract, changes in composition within the class generating one type of immune response do not elicit a vigorous immune response (Chiu 2016). Equilibrium among the three types of immune activity maintains if a foreign antigen is introduced to the immune system gradually. Some pathogenic microorganisms manage to promote their own proliferation by *inducing* immune responses against other microorganisms (Lopez 2016).

The Equilibrium Model of Immunity thereby claims that microorganisms do *not* functionally integrate with the macroorganism to establish the biological individual (i.e., superorganism). Instead, the microbiota is a readily available environmental resource like a library, to which the immune system has access in carrying out its operations. Intracellular

organisms are accommodated in the model in the form of type 1 responses. Microbial stimuli from the environment are contextualized with respect to other microbial stimuli. The model however does not tell us what causes particular microorganisms to elicit a certain type of immune response. Moreover, the model requires the microorganisms to be alive. The model is also limited to organisms distinct from the macroorganism.

My primary interest is in the human superorganism. The Equilibrium Model of Immunity awaits formal evaluation as an explanation for phenomena in the context of organ transplantation, but it provides an interesting background to interpreting the clinical importance of microbiota assessments after SOT. The model is also presently not applicable for analyzing relationships other than with microorganisms, such as between organisms and organ transplants. A common clinical observation after organ transplantation is that infections and rejection do not often occur together. On the other hand, certain infections such as viral infections, but not others such as bacterial infections, are capable of increasing the likelihood of acute rejection themselves. However, the Equilibrium Model of Immunity points out to us that immunology is no longer a science of individuals; it is a science of communities (Gilbert 2016). In the case of humans, the Equilibrium Model of Immunity shows that immunology is a science of superorganisms. The model also shows that functional integration might vary according to the type of organism, and need not coincide with functional boundaries. Transplantation might create a fourth arm in the Equilibrium Model of Immunity, or be integrated across one or more of the existing arms of immunity.

The Immune Response and Boundaries

Having discussed at length the innate and adaptive immune responses, we can specify the role of the immune system in maintaining the boundaries of the organism. Both arms of the immune system transduce both structural and functional boundaries, enabling communication across them. The immune system also responds to breaches of both types

of boundaries to limit the pathological consequences and improve capabilities of persistence in an organism. The innate immune system predominantly establishes and maintains biological boundaries, while the adaptive immune system mostly repairs biological boundaries.

4.4 The Immune Response in Solid Organ Transplantation

Microorganisms versus Solid Organ Transplants

The immune system's intent is to protect the human organism from invasion by microorganisms, *but at the same time permit microorganisms to exist so that the human superorganism persists*. The limits to which microorganisms can wander are made very clear. By competing among themselves, microorganisms aid the human superorganism in achieving this task.

SOT helps by providing a unique window into the workings of the immune self that an understanding of microorganisms alone cannot. In SOT, we profoundly alter the human organism both anatomically and physiologically, but there is no danger of further invasion or proliferation by the transplanted organ, even though it does not originate from the same germ cell line. Microorganisms on the other hand can both invade and proliferate. The transplanted organ is also unmistakably of human origin. It is not easy for the immune system to destroy the organ because of its sheer size. The immune response to a transplanted organ is therefore slower and more protracted. The adaptive immune system assumes greater importance in transplantation. The transplanted organ carries its own antigen-presenting cells specialized to process peptides. Therefore, understanding the differences in the innate and adaptive arms of the immune response to microorganisms versus transplanted organs might help to facilitate greater insight into what the immune self is all about. Conversely, the shortcomings of transplantation medicine adequately illustrate how little we understand about the human organism and human superorganism.

The cells involved in innate immunity include antigen-presenting cells including dendritic cells, macrophages, neutrophils, and natural killer cells. Epithelial cells, which form an external boundary to the organism, are also part of the innate immune system. Epithelial cells are the type of cell experiencing first contact with microorganisms, but not with organ transplants. Consequently, entities such as natural killer cells may be helpful to SOT by promoting transplant tolerance through destroying immune reactive cells transplanted along with the organ. One of the most powerful cells in the immune response becomes an ally of the transplanted organ.

In the case of interactions between the immune system and solid organ transplants, the goal of the immune system is clearly the destruction of the transplanted organ. There is no ambiguity in this goal. It should not be surprising that if the tools used by the immune system are the same in every case of microorganism or transplant, then the outcomes of the immune response would be very similar as well, whether it be through the innate or adaptive arms. The interpretation of the human organism to an organ transplant is similar to that of the invading microorganism, but *not* that of a non-invasive microorganism that is part of the human superorganism and not part of the human organism. In successful transplantation, the immune system acts as if the transplanted organ belongs to the functionally integrated human superorganism, even though it has violated many boundaries of the organism and is not part of the organism. Proper communication between the immune system and the organ will make this desirable distinction. Unsuccessful transplantation indicates unsuccessful superorganism reestablishment.

Solid Organ Transplantation and Human Boundaries

SOT requires the placement of a solid organ inside the human organism. The operative procedure requires the services of a skilled surgeon who performs (depending on the organ involved) a three-to-six-or-more hour-long operation. The operation involves the use of intravenous lines, endotracheal tubes, bladder catheters, scalpels, forceps, suction

drains, scalpels, suture materials, heating probes, and other devices. Each of these instruments is designed to violate natural human boundaries. Even the cleaning solution for the skin kills microorganisms with precision. All the tools required to perform SOT violate human boundaries, leaving the newly minted human superorganism to start a new life with an organ transplant in an immunologically mangled state.

I will briefly describe only the core procedure involved in the kidney transplant, while ignoring aspects common to all surgical operations as well as more intricate details. A solution is used generously to clean the skin, and then the skin over the groin, not too far from the anal canal and the intestinal microbiota, is incised with a scalpel. A heat probe seals bleeding vessels, or they are tied with sutures. Scalpels cut deeper layers such as fat, muscle, and connective tissue, and a cavity is manually created, into which the kidney transplant is to be placed. The organ itself is by now far removed from its original home in its donor, having been already traumatized by cutting away connections to donor body parts that the donor still needs or which are not useful to the recipient. The donor kidney is then surgically connected to the urinary tract in the recipient so that any newly produced urine can be easily collected, and the venous and arterial connections for blood supply to the kidney are restored. If all has gone well up to this point, residual bleeding stops, and the cut layers of muscle and skin are reconnected.

The integrity of the human superorganism first alters when a cleaning solution is applied to the skin, and the integrity of the human organism is first violated when the skin is cut. Microbial entry is easily preventable at this point, but it will be much harder to do so after the operation is complete because of the persistent possibility of microbial recontamination before skin healing is complete. Once deep inside the human organism, a surgical connection is made, through the organ, as paradoxical as it might seem, to the exterior of the organism. Just as the gastrointestinal lumen is not part of the human organism, *the lumen of the urinary tract is not part of the human organism either*. However, determining the boundaries of the human organism here is much more complicated.

Although we can imagine the cavity of the urinary bladder as part of the human organism's exterior, the bladder leads up into the ureters, and thence into the kidney. But it is the entire kidney that is being transplanted. Therefore, the transplanted kidney contains parts which are both outside the human organism (the urinary tubules which lead to the ureter) and inside the human organism (the blood vessels of the kidney, the "parenchymal" cells of the kidney, and so on. In the human organism, the wall of the urinary bladder is not even metabolically active, but inside the kidney numerous ion pumps and channels exchange molecules between the interior and exterior. In kidney transplantation numerous boundaries besides the skin are transgressed.

Is the Immune Response to Transplants a Normal Mechanism?

In SOT, we consider organ rejection as pathological because SOT defies the therapeutic goal of restoring organ function as close to normal as possible. When considered as a reaction to a potentially harmful non-self antigen, however, the mechanisms involved are simply living up to their expected performance. We describe mechanisms in medicine in terms of their abnormalities, when a mechanism does not perform in the manner in it is supposed to. SOT provides no exception. Mechanisms causing disease are pathological mechanisms, as opposed to malfunctioning mechanisms (Nervi 2010). Pathological mechanisms do not work within a defined range unlike normal mechanisms, they exhibit ambivalence, and they have the potential to be either adaptive or maladaptive depending on different regulating factors (Nervi 2010). Undesirable mechanisms in SOT may not display any of the characteristics of pathological mechanisms. Rejection, strictly speaking, is not pathological because its mechanisms are normal mechanisms. The labeling of rejection as pathology reflects clinician judgment.

Internal Boundaries

Besides the boundaries that comprise the exterior of the organism, there are also numerous boundaries inside the organism. These boundaries form numerous

compartments. There is an intracellular compartment and an extracellular compartment. Within the extracellular compartment there is an intravascular compartment, consisting of the contents of the cardiovascular system such as blood and lymph, and an extravascular or interstitial compartment. Each of these compartments has a fluid composition different from the other compartments, tightly regulated by sophisticated pumping mechanisms to preserve the *milieu interior*. As an example, even a slight variation in the concentration of an electrolyte such as potassium in the extracellular compartment can be fatal to the organism. The type and number of cells found within each of these compartments is also distinct. Cells and molecules migrate from one compartment to another when driven by a specific purpose such as when they are part of inflammation.

Every cell of the organism in addition has a boundary of its own. Many types of cells combine to form tissue and other "connective" tissue surround tissues as a fascial plane, separating them from other tissues. These lines of separation are useful to surgeons for separating tissues when they need to reach a structure lying underneath them. Therefore, tissues also have boundaries. However, SOT requires that blood vessels and tissues first be cut and then re-sutured (a procedure that itself requires cutting). Therefore, surgery disrupts many different body compartments. An organ lifted out of the body has boundaries useful to isolate them from their surrounding structures. Its blood supply and other necessary connections are easily identified, and safe surgical cuts made. While all of this is true for any surgical procedure, including the organ procurement from the donor, in the case of SOT we also introduce an object capable of eliciting an immune response, and all the breached compartments are exposed to this new and unfamiliar object.

Clearly, the immune system will have much to consider in making its assessment of how to react in SOT, after the natural boundaries of the human organism are violated. If this violation of boundaries is simple trauma to the body without transplantation to go along with it, then the healing process starts. If the trauma is an autotransplantation procedure, then the same healing process starts even if the anatomy is disrupted severely.

The immune response however is likely to be significantly different and stronger, as well as more sustained, if the trauma involves allotransplantation or xenotransplantation.

The strength of the immune response in either allotransplantation or xenotransplantation does not depend much on the extent of trauma imposed by the surgical procedure. Some surgical procedures are much more traumatic than others. The unfamiliarity of the new antigens stimulates the immune response and sustains it. SOT creates a new self-nonself interface through the disruption of boundaries. Communication taking place at the interface between two organisms results in an activation of the immune system. Structural and functional boundaries come together, providing an opportunity to study the mechanisms of the immune response.

The immune response to transplants is a normal biological phenomenon resulting from normal mechanisms. “Rejection” is therefore a social construct of medicine. Boundary violations in many places trigger normal immune mechanisms, and these mechanisms serve to reestablish boundaries. This process of boundary violation and reconstruction creates new phenomena alongside.

The Immune Response to a Boundary Violation

SOT leads to a sudden and forceful engagement of the immune system. Most likely, the human superorganism receiving the transplant has never before experienced such a massive influx of unfamiliar cells and tissues entering its boundaries. The mass of an average human superorganism is 76 kilograms based on an autopsy series of healthy young adults dying from trauma (Molina 2012). The introduction of a 130-gram kidney transplant represents a 0.171 percent increase in the individual’s cell content, while a 1500-gram liver represents a 1.97 percent increase. If one considers the human organism alone, with a weight of 74 kilograms (76 kilograms minus the weight of the microbiota), the percentage weights contributed by the new kidney and liver are 0.175 and 2.02 respectively.

The immune system will provide a response to the transplant using the tools it has at its disposal for addressing invasions by microorganisms. It is understandable that the human organism will respond in this manner to microorganisms by using its innate immune response arm. The mechanisms for communicating with microorganisms were developed over hundreds of millions of years. Tolerance mechanisms, if needed, were probably already worked out. SOT by contrast has been taking place for less than a hundred years in human history. Very few human individuals will ever experience SOT, and the number of new human individuals created (i.e., born) to SOT recipients is even smaller. There will be no SOT lineages created in the future. Female SOT recipients give birth to regular human organisms who rapidly become regular human superorganisms. Male SOT recipients regularly become fathers to human organisms. SOT does not affect germ cell lines, except by the facilitation of a more favorable hormonal environment. Therefore, there was no need for evolution to make investments in SOT for the future. Human boundaries did not anticipate violation by entities other than microorganisms.

However, the adaptive immune system will respond differently from microorganisms to the organ. The organ is there to stay in the body. The organ is much larger than the largest cell mass invasion of the human organism possible (which is bowel rupture). The organ is also not that easy to destroy even with a massive immune response. The destructive process might be easier if there was a total mismatch for the MHC, but this is extremely unlikely to occur due to the well-established tissue typing procedures followed prior to SOT.

At best, fibrosis walls off the organ and creates a new structural boundary in response to a boundary violation. Fibrosis is retreat followed by building a new fortification. This fibrosis process is very similar in this respect to how the immune system would have to engage a large invading parasite such as a tapeworm invading the muscle tissues (section 3.4). Since the goals of treating a transplant in preventing rejection are quite different from treating an invading microorganism, which is to promote rejection and

destruction, there is a different *internal milieu* being permanently created as well. Immunosuppressive medication is introduced systemically and must remain as a part of the environment of the transplant for as long as it is functioning. Molecules of immunosuppressive medication can be delivered to the organ transplant only through the rest of the body, and not directly to the organ, because of the new structural boundaries around the organ.

The human organism rapidly alters after a transplant, but the human superorganism alters as well. Changes in the intestinal microbiota also occur after transplantation, and might affect the outcome of SOT through its interaction with the organ. The success of SOT is therefore likely to depend heavily on how well the human organism and the human superorganism are able to adjust to the influx of new human cells and tissues, which might be difficult because these cells and tissues originate from another specimen of an organism, even if it is of the same species.

The substantial change in composition of the microbiota post-transplantation is of only peripheral interest to my main thesis. Therefore, I will next discuss two important post-transplant events, acute rejection and chronic rejection, which relate to the organ transplant now present inside the boundaries of the human organism.

4.5 Rejection of the Organ Transplant

I will describe two common but closely related phenomena that can occur after SOT (but not before) and then explain some of the immune mechanisms behind these two common phenomena. I will then correlate these mechanisms to establish the ontology of the human organism and human superorganism that accounts for most clinical situations including those posed in the modern era of SOT.

Rejection of a microorganism is good for the human organism but may not be good for the human superorganism, while SOT rejection is clearly not good for either the human

organism and by extension, for the human superorganism either. When infection and rejection occur together in an unfortunate recipient, there arises a fundamental conflict in the management of the recipient. On the one hand, immunosuppression needs to be reduced to enable host defense mechanisms while on the other hand, immunosuppression needs to be enhanced to combat the rejection process that could lead to organ loss and furthering of the immunosuppressed state. Fortunately, rejection and infection rarely occur together, in keeping with the Equilibrium Model of Immunity (Chiu 2016).

It is currently impossible to diagnose acute or chronic rejection by analyzing the type or number of T lymphocytes, or any other cell type in the circulation. The cellular and even biochemical correlation between what is happening in the transplanted organ and what is detectable in the circulation is extremely poor. In other words, the biological information for rejection cannot be isolated from the cells that contain it and then pinpointed. The major entities, i.e., cells and molecules, involved in the rejection process, can be compared to those of control patients not experiencing rejection. Conversely, the diagnosis of an infection by an invasive microorganism through a blood sample is usually much simpler, because the microorganism does not belong there. Also, viral infections cause a depression in neutrophil counts while bacterial infections cause an increase in neutrophil counts. Past clinical experience indicates that isolating the microorganism is enough when the microorganism is found in a location where it does not belong. On the other hand, in organ rejection all the cells involved are normally present all the time, can even be present in unusual body compartments on occasion, and so we cannot ascertain the intentions of immune cells (malicious, protective, or innocent) ahead of time before their effect becomes apparent.

Apart from the SOT recipient undergoing profound structural change, the organ for SOT is removed from its native environment, away from its companion organs. Although SOT between identical twins entails identical lineage of the body part, transplantation between any other donor-recipient pair does not. These two sets of circumstances set up

the environment for both acute rejection and chronic rejection of a transplanted organ to occur. I will now discuss acute rejection and chronic rejection in turn.

Acute Rejection

Acute rejection involves a rapid deterioration in function of a transplanted organ brought about by the invasion of the organ by cells belonging to the recipient. Transplant clinicians have traditionally provided a significant amount of attention to acute rejection because if acute rejection is left untreated it can quickly lead to loss of the organ, regardless of the mildness of the initial immune response. Patients can become very sick and may even die. All the commonly used anti-rejection medications are immunosuppressive in nature and are designed to prevent acute rejection.

The specific biomarkers used to detect acute rejection vary by organ, and are measured regularly after SOT, although other biomarkers are typically also used to provide supportive evidence and put together a clinical picture in which organ dysfunction is the centerpiece of attention. Acute rejection obviously cannot occur before the SOT procedure itself occurs, but the likelihood of acute rejection after SOT can be estimated beforehand with the help of in-vitro laboratory tests that combine donor cells and recipient serum (a component of blood) and look for a biological reaction. Acute rejection occurring on a petri dish is taken as a surrogate for acute rejection occurring inside the boundaries of the human organism. Microbial tests before a transplant are limited, and never include the microbiota. In-vitro laboratory tests are imperfect representations of in-vivo events and are also not real-time test procedures.

It is not far-fetched to state that the human organism “acutely rejects” all microorganisms from entering its confines. There is never any willing acceptance of a microorganism. Similarly, the human organism never willingly accepts an organ transplant, even though clinicians have managed to violate the boundaries of the human organism and place the SOT right within its confines. The human organism still valiantly mounts an acute

rejection response, to dispose of the invading organ that it views in the same way as it does an invading microorganism.

The frequency and the severity with which acute rejection occurs can be mitigated by using powerful anti-rejection drugs that suppress the immune response. These drugs spurred the great success of SOT. These drugs are prescribed with finesse by transplant clinicians, to prevent rejection and minimize their side effects at the same time. All these drugs must be administered, however, to the *non-transplanted part of the human organism*. In other words, the entire human organism is exposed to immunosuppression that it does not need! This exposure is inevitable because the transplanted organ is now structurally located inside the boundaries of the human organism, and there are no means to access the organ without going through the rest of the human organism first.

Acute rejection of a transplanted organ caused from memory cell activation is especially severe. B lymphocytes are also involved in the adaptive immune response. Once B lymphocytes are activated, in addition to T lymphocytes, the rejection process is considered more advanced, and less likely to be treatable. B lymphocytes secrete antibodies as free-floating molecules into the circulation.

Acute rejection of a transplant can carry with it the force of a memory response. One definition of immune memory which maps on to the lay intuition is that memory is the "expression of learning from past experience" (Cohen 2000a). Immune dialogue and decision making is guided by the following principles: abstraction or representation, combinatorial signals, semantics (the semantics of immune molecules is easier to explain than the semantics of words), syntax (order of signals), and context, or the patterns of signals sharpening the meaning of a signal. Immune memory is one of the greatest mysteries in transplantation today; the fact that this metaphor from cognitive science is still widely used betrays our lack of understanding of the mechanisms involved in its genesis. Immune memory also defies regularity, which is integral to the processing of

information. However, it is not clear if the relationship between a mechanism and its phenomenon always needs to be regular. Regularity may exist along a spectrum, rather than being a dichotomous phenomenon of regularity or irregularity. If all the environmental conditions prevailing are the same, then it would be expected that the same mechanism will produce the same phenomenon each time.

More than one mechanism produces a phenomenon such as memory, and it is not always clear which mechanism is operating in each clinical situation. Rejection is an interaction between two different types of cells, not something that happens inside one cell. Each cell carries its own set of mechanisms, possibly with its own memory as well. The interaction between these cells is by itself yet another mechanism. A more suitable approach for studying a mechanism might be a retrospective one, namely that whenever a phenomenon is observed, it is duly noted (and proven) that a certain mechanism was acting. Malfunction of a mechanism is usually much more informative than normal function in mechanistic understanding, and the memory response exemplifies informative value. In transplant rejection, the observer imposes teleology using familiar metaphors such as memory. A correlative association of important clinical events with their risk factors is a common practice in clinical medicine, but this does not equal mechanism or a real understanding of the event. As long as mechanistic understanding in SOT remains so limited, particularly with regard to biological information, it is reasonable to study microorganisms as models analogous to transplants. Microorganisms provide no less biological information here than large animal xenotransplantation models would provide.

Clinicians vaguely account for the ongoing donor-recipient interaction in post-transplant care. Further clinical interventions alter mechanism outputs, which may increase or decrease. For example, a desired output from the organ is increased productivity, which in the case of a kidney transplant would be increased waste product removal, or decreased productivity, which would be decreased production of pro-inflammatory or pro-fibrotic cytokines. Acute rejection can occur at any time. Whenever acute rejection progresses to

chronic rejection, which will happen if acute rejection is especially severe or prolonged in duration, then macrophages accumulate in the rejecting tissue. These macrophages are also capable of attenuating the rejection response, depending on the types of cytokines that they produce.

Chronic Rejection

Chronic rejection represents a much slower response by the immune system to the transplanted organ than acute rejection represents. In chronic rejection, there is a steady deterioration in function of the organ transplant, typically occurring over many months or years and culminating in total loss of organ function. Acute rejection may predispose to chronic rejection, even though acute rejection is neither necessary nor sufficient for chronic rejection. The clinical features of chronic rejection again vary based on the specific organ concerned. The occurrence of chronic rejection cannot be predicted as readily as acute rejection before the transplant using standard laboratory tests. Even though the technology to predict chronic rejection is increasing, the urgency of the clinical situation necessitating transplantation may override that concern. In addition, the occurrence of chronic rejection also depends on many variables in the post-transplant environment, such as aging of the organ, cumulative anti-rejection medication exposure, concurrent infections, blood pressure and blood glucose control, and so on (Halloran 1999).

Chronic rejection reflects an admission on the part of the human superorganism that it cannot rid the organism entirely of the unwanted organ. Instead, the immune system attempts to create a new structural boundary within the confines of the human organism to exclude the organ the rest of its confines through scarring. This new boundary is comparable to a physical wall. Even anti-rejection medications do not work very well for chronic rejection. Chronic rejection likens among its microbial analogues to the immune response that occurs to an infection by a large invasive parasitic worm. The worm, like an organ, can be very large. In that instance the worm is too large to be annihilated by immune

cells, and so the human organism creates a wall of resistance by fibrosis to exclude the worm from the rest of the human organism, to deny the worm its nutrition. This system of fibrosis works well for the human organism because the worm is usually more interested in maintaining its ongoing nutritional source than in invading other areas of the human organism and proliferating. Chronic rejection, just like acute rejection, is a process of the human superorganism.

Rejection of a solid organ transplant represents success for the human organism in its goal of self-preservation in its environment, but represents a failure of the human superorganism to maintain its integrity because a signal from at least one of its constituent organisms has been misread by at least one other of its constituent organisms.

A few key observations are worth noting at this point. As already mentioned, without SOT to precede it, there can be no rejection. SOT itself is the environmental trigger. Rejection can be equally severe regardless of the degree of compatibility between donor and recipient. It is the *likelihood, not the severity* of rejection that is altered by degree of MHC compatibility. If we ignore rejection, however mild it may be to begin with, it will most likely ultimately lead to loss of the allograft. Rejection can act as if it is the result of a memory response if it is ignored, even if that is not the case. A massive amount of the T lymphocyte repertoire (by some estimates, up to 5%) is capable of reactivity in this manner (Cohen 2000b).

Foreign antigen activates a strong immune response whenever an antigen looks like an altered self-antigen. The degree of difference between donor and recipient does not matter. Rather, what the immune system deems to be an appropriate (but not necessarily greater) degree of difference from the recipient ultimately determines the severity of the initial immune response. Handling the altered self is part of the body's ongoing maintenance, but throughout life there is a slower, permanent alteration to the self as well. *An allograft rejection response is therefore actually an anti-altered self-response*, and

represents an extreme form of an autoimmune reaction. Response to an infection, on the other hand, is the result of a reaction against the most self-like antigens in the infectious organism. Cohen (2000) puts this in a slogan: "By learning to know yourself, you know your enemies" (Cohen 2000b). There can be no knowledge of nonself without knowledge of the self. Organ rejection reflects the superorganism's self-knowledge. Transplantation might succeed if there is no immune system, except that immune reactiveness is essential to life.

Therefore, there is an important difference between the immune response to microorganisms and organ transplants. The immune response to microorganisms is an anti-nonself reaction, while the immune response to transplanted organs is an anti-altered self reaction.

4.6 Interactions between the Transplanted Organ and Non-Human Organisms

I discussed the interactions between the human organism and microorganisms, and between the human organism and organ transplants. Now I will discuss the *parts* of the human organism that communicate with microorganisms, perhaps leading ultimately to acute rejection and chronic rejection. There is an extensive interaction between the immune system of the human organism and the intestinal microbiota (Tabibian 2017).

In the innate immune system, both macrophages and dendritic cells need to be primed by an exposure to microorganisms to give them the signals required to exert their effects (Bartman 2015). This exposure enables these two types of cells to travel to locations where they are required in the case of infections (Ichinohe 2011). In SOT, there may be "pro-rejection" and "anti-rejection" (pro-regulatory) microorganisms in both the donor and recipient (Bartman 2015). Microbial influence may be at the time of presentation of the foreign antigen by antigen-presenting cells to T lymphocytes, or it may be at the time of T lymphocyte differentiation. Short-chain fatty acids produced by intestinal microorganisms may play an important role in this regard (Maslowski 2009). The responsiveness of cell receptors on T lymphocytes to antigens is increased (Alegre 2014). Natural killer cell

responsiveness to nonself antigen requires signals that the microbiota normally sends to phagocytes (Ganal 2012). By extension, the transplant's communication with the microbiota involves both T lymphocytes and natural killer cells.

In the adaptive immune system, molecules produced by an enterotype of the microbiota may be more conducive to the proliferation of anti-rejection T lymphocytes (Bartman 2015). Polysaccharide A from *Bacteroides fragilis* promotes regulatory T lymphocytes, and restores balance in various T lymphocyte subtypes (Alegre 2014). Certain skin microorganisms can also induce favorable T lymphocyte proliferation (Naik 2012). T lymphocytes specific to intestinal microorganisms may cross-react to other antigens such as viruses. If this cross-reactivity is possible, then cross-reactivity to antigens in the transplanted organ is also possible. Immunoglobulins secreted by the intestinal mucosa in response to specific microorganisms may also provide feedback signaling to the adaptive immune system (Bartman 2015). There is no corresponding "mucus" to surround a transplant organ to contain it, so an immune reaction must always proceed.

Mechanistic studies as above have not yet been performed to-date in SOT recipients. However, changes in the intestinal microbiota composition have been noted in recipients of lungs, livers, kidneys, and small intestines. In lung transplants two different patterns of intestinal microorganisms were associated with different post-transplant clinical outcomes (Dickson 2014). Diarrhea, a very common complication of kidney transplantation, is associated with changes in the intestinal microbiota (Lee 2014). An increased rate of infections in liver transplant recipients associates with decreased intestinal microbial diversity (Lu 2013). Highly selective antibiotic therapy in any population provides an opportunity to study the interaction of the microbiota with the immune system, because we can study immune cell products before and after such treatment (Peterson 2015).

The above brief scientific review indicates to us that we should not consider the human organism in isolation, when analyzing the role of specific cell lines or cell products

from the innate or adaptive immune system in post-transplant outcomes. The human superorganism that includes the microbiota needs to be taken into account if post-SOT outcomes are to be optimized. Not only are both arms of the immune system in the human organism engaged by the microbiota, but the products of this engagement such as the differentiation of specialized cells and their products can affect the transplanted organ as well. The immune system considers the transplanted organ to be just another microorganism. *The immune system belongs to the human superorganism.* The immune system engages both the microbiota and the transplanted organ. Engaging alone does not produce belonging; however, the microbiota and the transplanted organ are both in a co-dependent relationship with the human organism. The microbiota and transplanted organ may even be co-dependent on each other because the microbiota alters after transplantation. Immunity mediates all this co-dependence.

If the immune system belonged only to the organism, then altering the immune system should not alter the superorganism. However, altering other organ systems of the organism, e.g. producing kidney failure, alters the microbiota because of immune effects. The immune system acts as the communicator between the organ systems of the organism and the organism's exterior. Similarly, altering the microbiota can affect many organ systems such as the cardiovascular system; the oral microbiota contributes importantly to cardiovascular disease. This connection may be through the immune system.

The immune system decides that the transplanted organ is a part of the human superorganism but is not a part of the human organism, even though it situates inside the confines of the human organism. If it became a part of the human organism, it will not reject ever, except as part of an autoimmune process. However, rejection is not an autoimmune process. The transplanted organ is acting as a representative for another human organism. After transplantation, therefore, *an organ is performing the role of an organism, like a microbe*. The organ does not display all the features of an organism (section 2.3) however, but it is capable of eliciting an immune response in its new

environment and has its own immune cells, unlike inert prostheses. Its immune function is preserved even when other features (such as plasticity) are absent or severely impaired. This transplanted organ had once been part of a human organism, that of its donor, but it cannot ever achieve that full status in the recipient. Until our technology permits the human organism to consider the transplanted organ as part of itself, its "nonself" status entails that rejection always remains possible. The possession of an immune system is perhaps the most robust characteristic of an organism, because the immune system maintains a part of the organism that has been disconnected from the rest of the organism.

Transplantation of the Small Intestine

Transplantation of the small intestine is the least commonly performed and least successful form of SOT (Sudan 2014). Although the frequency of SOT is generally increasing across all the organ types, the number of small intestinal transplants (with or without the large intestine) is actually decreasing. It has been extremely difficult to achieve sustained success with intestinal transplants. This decrease in number of transplants is an illustration of the great difficulty inherent in overcoming the significant barriers to acceptance of nonself entities. Even the most successful clinical transplant programs in the world have not been able to establish robust small intestine transplant programs.

The technical challenges of small intestine transplantation are not especially different from other types of transplants. Some bacteria transplant along with the small intestine. The microbiota accompanying the organ may prime antigen-presenting cells, resulting in antigen presenting more efficiently to T lymphocytes (Alegre 2014). However, the major difficulties associated with intestinal transplantation include the high rates of acute rejection and cancer, besides infection. It is quite difficult to distinguish rejection of the organ from infection as a cause for diarrhea in intestinal transplant recipients (Sudan 2014). In the case of the intestines, there is an abundance of lymphatic tissue. The extent of this lymphatic tissue is so large that we consider it an organ itself. Not only do the

intestinal walls contain lymphatic tissue, but the lumen of the intestine normally contains, as we have seen, numerous microorganisms which are part of the superorganism. Intestinal transplantation therefore causes an extreme disruption of boundaries; the boundary of the human superorganism (the human organism and its microorganisms) disrupts, rather than just the boundary of the human organism.

Even though the boundary of the superorganism is more tolerant of disruption, the extent of the disruption is very large in small bowel transplantation. Small bowel transplantation is an example of an instance in which the microorganisms also face a new human environment, so in this respect small bowel transplantation is technically xenotransplantation. It is also possible that the disruption in the superorganism becomes more significant when the largest organism disrupts at the same time, which is not the case with the regular movement of microorganisms in and out of the intestines. We can trace the great difficulty encountered in achieving long-term success with small bowel transplantation to all these possibilities.

4.7 Accessing the Messages of the Immune System

A lot of messaging occurs after an organ transplant. In this section, I will explain how we might localize these messages so we can understand them.

A *message* is a specific type of information that provides a resolution to uncertainty. The amount of information that a message bears relates to the possible number of alternative messages carrying alternative information in that system. The vehicle for a message is a *messenger*. As one example of communication within the immune system, hormones such as cortisol suppress the immune system. Hormones are chemical compounds produced in one part of the body, and enter the bloodstream to reach a site distant from where these chemicals were originally produced, before they exert their biological actions. These actions occur from interacting with *receptors* on a cell surface or in the cell's cytoplasm.

Drugs similar to cortisol, such as prednisone, both prevent and combat acute rejection of a transplanted organ. Cortisol suppresses many different components of the immune system. Hormones like cortisol in this context of their function are considered chemical signals. No intelligence is required for the hormone to carry out its actions. Information bears *meaning*, which in this example of cortisol is an instruction to suppress the functioning of the immune system. Messages transmit when chemicals bind to receptors. Chemical messages block other chemical messages.

The end-result of carrying information is that a message in some form passes on to another cell. The cell that provided the initial information may or may not be working in conjunction with its target cell. The first cell may not even be alive when the message reaches the second cell. The first cell may be instructing a second cell to destroy or not destroy a third cell. Alternatively, the first cell may intend to destroy the second cell by instructing self-destruction. In the immune system, there may be many more immune reactive cells along such a pathway, with each link between two cells carrying its own protective or destructive message. The same message carrying the same information may also provide a different message to different cells. Communication among the cells of an immune network may rival communication among cells in a synaptic neural network in terms of its complexity.

Unfortunately, the information contained and processed in the immune system is not directly accessible to the clinician. The information is only accessible to the cellular target of the message containing that information. Blunt clinical tools to alter the immune response such as cortisol can only target the cells that produce and receive information, not the information itself. The molecule carrying the information, such as a molecule of cortisol, may be measurable but its information is not measurable. At every stage of the immune response, *the message is isolated from access by a boundary*, to which the clinician does not have direct access. In the case of SOT, all we see is the end-result of acute or chronic rejection. The boundary, in other words, acts as a shield to information.

According to Godfrey-Smith, biological information may not even be matter (Godfrey-Smith 2016). If it is true that information is not matter, then clinicians may never have access to biological information, or in this case, "immune information". Yet the immune cells themselves appear to have perfected the method for transmitting information across such cellular boundaries. Information might be stored as energy inside the cell rather than matter, and be transmitted from one entity to the next in the form of a message. In this case, a chemical molecule is matter, and its information is its energy.

For us to have any chance of accessing the information contained within a cell would mean having to destroy the boundaries of that cell. When the cell gets destroyed, the information contained within that cell is also lost[16]. The inadequacy of the concept of *information* in genetics as conveyed by the genetic code is quite clear through its description as inferential (Godfrey-Smith 2016). Information in immunity is no different; it can only be inferential, because our knowledge about information bases on the downstream biological effects of the information conveyed. Transplantation science has developed to the extent we know the cell types involved in the innate and adaptive immune systems, the points of connection between the innate and adaptive immune systems, and the end-results of different types of cells receiving different signals. However, information conveyed in each of these messaging systems remains strictly inferential until we can develop the means to access a living cell's cognitive apparatus.

Despite this gloomy outlook for accessing information within a cell, there is still some hope for accessing or capturing the information as it transmits between organisms. In Chapter Three, I discussed how the boundaries between the human organism and the bacterial organisms associated with the human organism maintain, but communication still occurs to the benefit of both organisms in the course of setting up the functional integration of the superorganism. The lifespan of the human organism and the human superorganism as a whole is much longer than the lifespan of its single cells. Even if

[16] One example of an information source inside a cell is the genetic code.

bacterial cells have as short of a lifespan as single cells in the human organism, we may still have direct access to at least one part of the message.

Structural boundaries can obviously present a physical obstacle to the transmission of information in many parts of the body. For example, the cornea of the eye represents a structural and functional boundary which a ray of light must cross between the external environment and the brain. An irregularly shaped cornea will distort the light ray entering the organism and consequently distort the information received by the brain. An opaque cornea causes blindness. In both these cases, we can localize the information during its transmission, to the site of its distortion. By manipulating the cornea, we understand the light source better as the image alters until it is accurate.

Clinical medicine has provided the means to circumvent these two types of corneal obstacles by creating external lenses and corneal transplants, because we can "catch" the information being transmitted. Similarly, if some day we can find the right "immune meter" by which we can measure the *immune responsiveness* of one organism to another, as well as its direction (either helpful or harmful), then we will be a lot further along in understanding how and why an immune response occurs, and more usefully, before it occurs. For now, we are limited to measuring only the products of the immune response such as a proliferation of certain cell lines, and various secreted chemical cell products, after the immune response occurs. In both acute and chronic rejection, there are no cell lines and chemical products that are present but should never be measurable. All cell types and chemical products are normally present at all times, only in different amounts and proportions.

The boundary may be just the spot at which we might catch biological information. Even if this biological information is just a part of the mathematical description of matter, it needs to be localized to some real space if we are to access it. The boundary may be the location where biological information such as immune information is accessible, analogously to how neurological information is accessible at the synaptic cleft between

neurons, not inside the neuronal cell. This localized point in space is the *immunological synapse* (Davis 2004).

Communication across Boundaries

There are three major levels of communication across the boundaries among organisms and superorganisms that require the actions of the immune system.

In the first level of communication, boundaries between organisms are transcended by sending signals in an accurate and precise manner but not causing any harm to the boundary, with the result that benefit is promoted to the organisms on both sides of the boundary. On the other hand, if the organism on one side of the boundary "decides" that the organism on the other side of the boundary is harmful to its interests or, conversely, so beneficial to its interests (such as being a source of nutrition), then it may cause that second organism harm. The individuality of the organism relative to its environment containing other organisms is preserved, promoting superorganism formation.

In a second level of communication, individuality within the organism may be manifest at lower levels such as at the level of the cell (Goodnight 2013). In this instance, the boundaries exist within the organism. An internal policing mechanism exists whereby cells that are part of the organism by lineage but are not beneficial (or even harmful) to the organism are destroyed. Individuality within the organism is decided at the cellular level, with each cell being assigned compatible individuality status or not. It is quite possible for a given cell's status of individuality to change over time, as defined by its boundaries, and be addressed by the organism's immune system to promote organism formation.

A third level of communication occurs when the organism's boundaries are violated in a manner that is inconsistent with evolution, in contrast to the other two levels. In SOT, the boundaries of the organism are deliberately disrupted, in order to connect a body part originating from another organism, which may or may not be a member of the same species. This body part did not only originate from another organism, but it also originated

from another human superorganism. The special challenge posed to the immune system in this instance is the forced, sudden redefining of the boundaries of both the organism and the superorganism. The threat posed to the integrity, and therefore the life of both the organism and the superorganism by the violation of their boundaries is significant and immediate. There is clear and present danger, akin to the situation where a microbe such as *Clostridium difficile* crosses the intestinal wall to enter the human organism. This type of communication is the most complicated to study but in principle provides the most opportunity to access biological information because both the organism and superorganism are reliably disrupted.

In all these three instances of communication, the role of the immune system is to preserve both the organism and the superorganism. Why is it that the cells of the immune system can even coordinate their activities to produce an effective immune response? This immune response is clearly quite effective against both dangerous microorganisms and transplanted organs. Understanding the mechanisms by which such signaling occurs might provide the means to prevent immune responses against a transplant, in a situation wherein clinical intentions do not coincide with the intentions of the immune system. Understanding signaling requires a philosophical understanding not just of information, but of the mechanism behind boundaries themselves.

Where is the Boundary in Transplantation?

The boundary of the human organism with microorganisms is in the intestinal wall and the skin. However, with transplants the boundary is harder to find. Blood transfusions and bone marrow transplants are not very helpful as exemplars to study communication across boundaries because the separate identity of the transfused blood is lost immediately upon transfusion. We cannot extract transfused blood or bone marrow in the same way we can extract (explant) a transplanted solid organ. In addition, after blood transfusions, there are no structural boundaries to study afterwards, apart from the boundaries of individually

transfused cells if we could isolate them afterwards. We also cannot study signal transmission across cells without destroying those cells.

Tissue transplants such as corneal transplants and heart valve transplants are also not particularly helpful to studying organisms and superorganisms, not because they do not violate the boundaries of the human organism, which they do, but because they do not typically engage the immune system. Either these tissues do not contain cells capable of activating the immune system, or these tissues may be completely decellularized. Another type of transplant, the vascularized composite transplant (face, hand) is heterogeneous in the types of tissues it contains. The tissues may have very different functions, e.g. the nerves and the blood vessels, and so their immunological "outputs" are not easily measured. Moreover, the technology of vascularized composite transplants is still in its infancy and consequently, very few have been performed to-date. Vascularized composite transplants have not yet been studied enough from an immunological perspective either, to be subject to an ontological analysis of boundaries.

The organs of SOT (kidney, pancreas, heart, lung, liver, small intestine) are the more promising exemplars for demonstrating boundaries in organisms. Boundaries between the transplanted organ and the organism maintain, the immune system engages at a known point in time, there is some predictability to the resultant immune response, and there is some hope for successful analogical mapping of the immune response to organ transplants with the immune response to microorganisms. Since the immune response to microorganisms determines the human superorganism generally, studying the immune response to SOT may also contribute to understanding human individuality, but more accurately and precisely because structural and functional boundaries coincide.

Molecules are the bearers of messages in SOT but are not the messages themselves. The diversity of antibodies creates new information as these antibodies are able to recognize a diversity of antigens. The amount of information created by this diversity is

much more than what a single antibody can create (Atlan 1998). The interface between the organ and the organism is the antigen-presenting cell-T lymphocyte interface. The direct immune response shifts over to the indirect immune response, which is analogous to the response to microbes (Danovitch 2005). The self-nonself interface thereby also shifts, but the immune response otherwise remains the same. This interface is where there are known cell receptors and drug targets for those receptors. This is the boundary between self and nonself, akin to the boundary between microorganisms and the intestinal wall or skin. This interface is where pharmacological intervention seems most rewarding (Halloran 2004). It is therefore the site where capturing biological information is also likely to be most rewarding. Current laboratory assays do not reproduce the interface, and this remains a significant obstacle to improving post-transplant outcomes. We only measure cell lysis (destruction) as a downstream effect using cross-matching technology.

The immune system establishes and maintains the organism's boundaries by including and excluding entities. The immune system operates throughout the organism, both within its anatomical confines and on its external boundary, relating to the environment. Organisms remain coherently bounded in space and remain recognizable by the actions of the immune system (Gould 1999). In SOT, the interface is where the boundaries of organ and organism meet.

The boundary between self and nonself does not directly correspond to the boundary of the physical organ with the rest of the body, but it corresponds to the cell interface between the antigen-presenting cell and the T lymphocyte. The location of this interface is always changing; it might be in a lymph node or the bone marrow, in the peripheral circulation, or somewhere within the transplanted organ itself. Once blood circulation to the organ reestablishes, the continuity of blood vessels between donor organ and recipient instantly blurs the interface location. The boundary between self and nonself does not always correspond to the interface between donor and recipient either. In the case

of indirect allorecognition, cells that belong to the recipient present antigen, so the functional boundary is actually a recipient-recipient interface.

The antigen-presenting cell-T lymphocyte boundary is both structural and functional. The molecules are the signals. Communication occurs across boundaries and the boundary in this case the immunological synapse, where information as molecules can be captured. These molecules include adhesive molecules and "accessory proteins" (Delon 2000). Dustin (2000) described the steps of adhesion between the antigen-presenting cell and the T lymphocyte are described (Dustin 2000a). First, the T lymphocyte polarizes, meaning it becomes asymmetrical in shape. The T lymphocyte then adheres to the antigen-presenting cell through multiple proteins. Next, MHC molecules stabilize the molecular interactions by rearranging them, so they do not fall apart. Multiple "second" messengers emerge from the interaction to strengthen the initial bond between cells. Finally, the interaction terminates when the antigen-presenting cell dies (Ingulli 1997) or the T lymphocyte divides to generate new T lymphocytes (Dustin 2000b). In summary, abundant scientific data exists to localize biological information, in the form of a message that leads to an act or event in the recipient of the message, to the immunological synapse that is *both the structural and functional boundary* between self and nonself. Information pervades biological systems, but we can capture information at biological boundaries. Transplantation provides the great advantage over the microbiota of coincidental structural and functional boundaries, making SOT a much easier method to study the human organism-human superorganism distinction.

To summarize, science allows us to find the boundary where molecules are the messengers and molecular *arrangements* become the message. In this manner, biological information becomes a process rather than being either matter or energy. Information is accessible when structural and functional boundaries coincide at the site of its exchange to create unique molecular arrangements.

4.8 Transplant Tolerance and Immune Privilege

We desire to avoid anti-rejection medications to avoid their side effects. Transplant tolerance strives to achieve the goal of avoiding anti-rejection medications, but transplant tolerance is not yet been clinically attainable. *Immunological* tolerance is a state of unresponsiveness for a particular antigen (Male 2006). Since the immune system randomly generates diverse receptors for a variety of antigens, tolerance mechanisms are required to curb autoimmunity. Therefore, we can view tolerance as opposing autoimmunity. Tolerance is required so that we may absorb food from our gastrointestinal tract, and not react to air-borne particles entering our lungs. Tolerance is also required to self. Immunological tolerance is readily inducible in animal experiments through selective breeding strategies and transgenic technology. True transplant tolerance is not yet possible.

The original definition of *transplant* tolerance was a non-responsiveness to antigens (Billingham 1953). Transplant tolerance is defined as a state of lasting antigen-specific, immunologic unresponsiveness in the absence of chronic immunosuppressive therapy. Therefore, transplant tolerance is a much more pragmatic definition than the broader definition of immunological tolerance. However, transplant tolerance is not a naturally occurring phenomenon. It has proved impossible to-date to achieve true tolerance to a specific donor that is both robust and long-lasting.

The adaptive immune system was traditionally the target for mechanisms involving tolerance (Murphy 2011). However, the innate system may be more promising than the adaptive immune system as a target for achieving tolerance (Wu 2012). Understanding how the innate immune system functions *during* transplantation may lead to more success in achieving tolerance (Murphy 2011). *Operational* tolerance is the term given to the state of a few patients who manage to live with functioning transplants without anti-rejection medication, but this does not equal true tolerance.

There are two types of tolerance, called central tolerance and peripheral tolerance.

Central tolerance is the ability to distinguish self from nonself. Self-reactive lymphocytes are eliminated and inappropriate self-recognition of tissue is thereby avoided. Therefore, the process of central tolerance is negative selection (Salisbury 2014). Central tolerance begins in the primary lymphoid organs. B cells develop in the bone marrow, while T cells migrate to the thymus, where they are "educated" and then selected for their immune reactivity and maturation. The thymus destroys T lymphocytes which possess dangerous autoreactivity. The function of peripheral tolerance, on the other hand, is to capture self-reactive lymphocytes that escape destruction by the mechanisms involved in central tolerance. In peripheral tolerance, self-reactive T lymphocytes are eliminated by inducing programmed cell death, or *apoptosis* in them.

For true immunological tolerance to be present, all the alloreactive cells need to be either eliminated, or be made tolerant. Even if alloreactive cells are depleted through a variety of strategies, they quickly become repopulated due to a strong memory response. In addition, the mechanisms required to induce tolerance are not necessarily the same mechanisms required to maintain tolerance. Even a minor subsequent challenge to the immune system such as an infection can activate an immune response to antigens to which the immune system was previously tolerant.

Understanding the constitution of the human superorganism may help promote the cause of transplant tolerance. In this context, one type of mucosa-associated lymphoid tissue in the intestinal deserves additional description. Peyer's patches are organized collections of lymphoid tissue that lie just beneath the intestinal mucosa. Antigens are transported to Peyer's patches from the intestinal lumen so that the primary immune response can take place. Effector B and T lymphocytes leave Peyer's patches and enter the circulation. At the same time, interactions also occur in Peyer's patches in order to promote tolerance to harmless and useful antigens, such as food. Peyer's patches are associated with microorganisms (Gilbert 2016). The microbiota can promote T lymphocyte

development in the intestine (Duan 2010). An important role for the microbiota in B lymphocyte development has also been demonstrated (Wesemann 2013).

Identifying pro-rejection microbial phenotypes in the intestine may help to create a favorable environment to acceptance of the transplanted organ (Bartman 2015). Alternatively, if the active molecules from these intestinal microorganisms can be isolated, we can develop methods to either encourage the further synthesis of favorable molecules or reduce the synthesis of unfavorable molecules. With transplantation, the molecules of the donor are not directly exposed to microorganisms. The intestinal immune system and the microbiota need more attention if transplant tolerance is to be achieved. Our current focus is on circulating lymphocytes, but more focus on intestinal lymphocytes may yield greater reward.

Mixed chimerism, in which there is an admixture of cells of donor and recipient origin, is demonstrable in transplantation and is believed to be essential to the acceptance of an organ transplant (Starzl 1992a, Starzl 1992b). Such patients who exhibit "operational tolerance" are extremely rare (Salisbury 2014). Chimerism also induces tolerance to organ and tissue transplants (Billingham 1953). In chimerism, new lineages of cell lines are established in the bone marrow of the recipient (Salisbury 2014). This finding, if it is reproducible and extendable to clinical SOT, implies that the organ transplant recipient is really an admixture of human-derived cells from different organisms without clearly demarcated boundaries. Recipient chimerism is normally transient (Ochando 2014). Inducing mixed chimerism requires ablation of the bone marrow by irradiation to go along with SOT. Of course, this therapy is very toxic, since all immunity is lost. We need a much less toxic means of reliably establishing mixed chimerism to induce tolerance. Such mixed chimerism may be achievable if we account for composition of the human superorganism.

There is no reason for the microbiota not to participate in tolerance. We can selectively manipulate the microbiota for subjects in tolerance-inducing protocols. Natural

killer cells and other cells of the innate immune system have established relationships with the microbiota (Murphy 2011). A simple approach to achieving operational tolerance might be to perform FMT from the same donor, and create a mixed chimera of the intestinal microbiota when trying to induce operational tolerance of a transplanted organ. Whether the microbiota acts as a scaffold or whether certain microorganisms are preferable to others in the microbiota is a secondary question. Ignoring microbiota function may be a reason for why achieving even operational transplant tolerance is so difficult. Non-selective tolerance is disastrous to the superorganism, and selective tolerance to the transplant will be difficult without affecting relationships with microbes. The human superorganism is so large that selective tolerance will not be achievable by targeting selective microbial species. We can only target the microbiota enterotypes to allow the microorganisms to then perform their integrative physiological function on their own.

If the role of the microbiota in promoting tolerance is established, then it becomes clear that tolerance is a state of the human superorganism and not a state of the human organism alone. It will also prove that the human being is really a human superorganism. The initial focus on achieving tolerance through affecting the actions of the adaptive immune system may have been due to the successes achieved in reducing the rates of acute rejection using anti-rejection medication targeting the human organism.

The lack of success to-date in achieving tolerance demonstrates however that the mechanisms for one phenomenon need not to be the same as the mechanisms for its inverse phenomenon, in this case rejection. Tolerance and rejection may be two sides of the same coin clinically, but they do not bear the same type of opposing relationship mechanistically. This may be why transplantation has hit a roadblock to achieving tolerance. Targeting the innate, rather than adaptive immune system may be a better route to achieving tolerance, even though the innate immune system is not the target to prevent rejection.

I will analogize a state of tolerance to military peace[17] between two armies. We do not achieve peace by annihilating the most prominent entities in one or both armies, but by affecting their interactions. Those interactions occur at the interface where the armies exchange information in their headquarters, which may not correspond to the location of the battlefield. Similarly, we can achieve transplant tolerance if we understand the interface between the human organism and the organ, and so we need to understand the interface between the organism and the microorganism that lies elsewhere.

Immune Privilege

A potential alternative analogue to microbial interactions for studying tolerance is the phenomenon of immune privilege. Immune privilege refers to the ability of certain body tissues to be exempt from the immune response. These tissues might provide a suitable alternative to the microbiota as an analogue to organ transplants. Immune privilege is the corollary of transplant tolerance. The known immune privileged sites in the body are the brain, anterior chamber of the eye, testis, the fetal-maternal interface of the placenta in the pregnant uterus, and joint cartilage. The principal purpose of immune privilege is presumably to protect vital organs from the damage that might occur from an immune response. The concepts of immune privilege and immune tolerance overlap, since immune privilege, just like tolerance, is an active process rather than just passive ignorance by the immune system (Hong 1999).

Anatomical sequestration from the circulation is partly responsible for the immune privilege enjoyed by certain body areas. Sequestration of a part of an organism can be created by structural boundaries within an organism, but to a more important extent immune privilege is the result of very weak immune responses generated from the interactions of immune cells with the privileged tissue concerned (Forrester 2008). There is an increased expression of inhibitory cytokines such as transforming growth factor-β,

[17] The use of military metaphors was common in early discussions about the self-nonself distinction, but the use of such metaphors is now rare in the immunology literature.

which inhibits inflammation. Privileged tissues secrete anti-migration chemicals that inhibit natural killer cells. Apoptosis[18] eliminates lymphocytes able to enter such privileged sites (Male 2006). Therefore, immune privilege arises not by the absence of an immune system, but by multiple active processes that create functional boundaries.

Immune privilege comes in degrees. The relative degree of immune privilege enjoyed varies from tissue to tissue, depending on the number and strength of each of the mechanisms of immune reactivity that are contained within that tissue. Immune privilege can even generate in tissues not ordinarily immune privileged. For example, skin tissue is rejected if transplanted on to nonself skin, but it is possible in animals to transplant skin tissue into the brain, where it will escape rejection because of the privileged environment of the brain.

Immune privilege is more than just a curiosity. It has clinical significance. Immune privilege permits corneal transplants and cartilage transplants to proceed unhindered, From a mechanistic point of view, the natural consequence of immune privilege is tolerance. Therefore, in addition to central and peripheral tolerance mechanisms, there is a *third* route by which the organism promotes a non-reactive state to self-antigens, namely that which is based on the specific properties of each tissue. Tolerance may therefore also be a context-dependent local phenomenon (Forrester 2008). Immune privilege is the effect of successful functional boundary maintenance.

Like immune tolerance, immune privilege has its drawbacks. The anterior chamber of the eye is a privileged tissue. When minor injury occurs to the eye, potential antigens are efficiently handled by local dendritic cells and there is no further immune response. However, if one eye is severely traumatized, antigens escape from the eye, enter the systemic circulation, and can cause a severe autoimmune reaction leading to blindness in the opposite eye.

[18] Apoptosis is programmed cell death.

Like tolerance, it is unlikely that immune privilege will be relevant to SOT in which we implant organs only in non-immune privileged sites. Many organs (kidney, lung, small bowel) are also exposed to the external environment, containing parts outside the structural boundaries of the human organism. Even if some organs are not outside structural boundaries (e.g., heart, liver); they are just too large to find an immune privileged site to accommodate them. If the cells and molecules involved in immune privilege are known, their mechanisms may be different when contextualized outside immune privileged sites. Immune privilege is not particularly useful as an operational model of tolerance. The size of the microbiota may be a better source of reward in investigation about tolerance than difficult-to-access immune privileged sites in the body.

4.9 A Summary of the Immune System in Organisms and Superorganisms

The immune system, preserved over millions of years, is central to the identity of both organisms and superorganisms. Every organism has an immune system. The immune system determines the structural boundaries of the human organism and functional boundaries of the human superorganism. Organ transplantation brings these boundaries into sharp focus by engaging the immune system through a novel method. Since organ transplantation has no role in evolution, the mechanisms that the immune system uses to engage organ transplants are the same as those used by the human organism to engage microorganisms in establishing the human superorganism. Therefore, microorganisms are useful analogues to organ transplants.

Maintaining the human organism and the human superorganism as persistent entities through time requires communication through immune mechanisms. Transplantation adds complexity because it creates new connections between hitherto separate organisms, but also adds simplicity by bringing boundaries together. SOT is the most dramatic example of exchanging human cells. Our discovery of mechanisms in SOT

may have been limited in the past by our failure to account for the human organism-human superorganism distinction.

SOT is a non-standard condition of the human organism and the human superorganism because it violates many different structural and functional boundaries. Communication taking place at the interface between two organisms results in an immune response. In SOT, this interface corresponds to the immunological synapse.

The immune self of the human organism recognizes microorganisms as nonself. However, the human superorganism has a choice about whether to consider the microorganism as self or nonself. The immune system protects the human organism from microorganisms, but also permits those same microorganisms to exist, or even allows them to proliferate, to protect the integrity of the human superorganism. The immune system responds to organ transplants using the tools it has at its disposal for addressing invasions by microorganisms. If SOT is to become more successful, the immune system needs to be convinced that the transplanted organ belongs to the human superorganism and not just the organism, even though it has violated many boundaries of the organism.

Rejection of a transplant represents success for the human organism in its goal of self-preservation in its environment, but represents a failure of the human superorganism to maintain its integrity because a signal from at least one of its constituent organisms has been misread by at least one other of its constituent organisms. The interpretation is one of harm where none exists. Transplant rejection reaction is an anti-altered self-reaction, and represents an extreme form of an autoimmune reaction. The likelihood but not the severity of rejection is altered by the degree of MHC compatibility between donor and recipient.

There is an extensive interaction between the immune system and the intestinal microbiota. The human organism should not be considered in isolation when we analyze the role of specific cell lines or cell products of the innate or adaptive immune systems in

post-transplant outcomes. The immune system belongs to the human superorganism, engaging both the microbiota and the transplanted organ. Successful treatment and reintegration of the superorganism after disruption may also be relevant to many health and disease processes outside of SOT, and therefore to the goals of medicine in general.

Communication in all biological systems including the immune system encounters several boundaries along its pathway. In SOT, the boundaries between the organ and organism are disrupted and reestablished, the immune system engages with some predictability, and there is some hope for successful analogical mapping of the immune response to microorganisms to the immune response to organ transplants. Molecules are the bearers of messages in SOT. The diversity of antibodies creates new information. The amount of created from this diversity is much more than what can be created from a single antibody. We cannot capture information itself, except perhaps at the self-nonself interface where that information may be the process of molecular rearrangement.

Immunological tolerance is a state of unresponsiveness to a particular antigen. Transplant tolerance is a state of lasting antigen-specific, immunologic unresponsiveness in the absence of chronic immunosuppressive therapy. It is unproven whether the intestinal microbiota participates in tolerance. If this is true, then the microbiota composition needs to be selectively manipulated in subjects being considered for protocols of inducing tolerance. If the role of the microbiota in promoting tolerance is established, then it becomes clear that tolerance is a state of the human superorganism and not a state of the human organism alone. The lack of success in achieving tolerance demonstrates that the mechanisms for one phenomenon need not be the same as the mechanisms for its inverse phenomenon. Tolerance and rejection may be two sides of the same coin clinically, but they do not bear the same type of relationship mechanistically.

It is important to identify molecular events before a clinical event in the form of organ dysfunction or visible microscopic changes in the transplanted organ occur (Bontha

2017). Molecular associations with disease are a major thrust of medical research. Molecules carry the messages. We now recognize that it will not be helpful to follow a purely reductionist approach to changes in the organ. A systems-wide approach that focuses on the dynamic interactions within biological systems will be rewarding if it is extendable to the human superorganism.

In summary, boundaries separate the organism from its environment, and separate organisms from each other. The mechanism of functional integration across boundaries consists of the immune system's reactions and responses, or immunity. Functional integration across boundaries already exists with microorganisms through immunity, but organ transplantation creates several new boundaries including between the organism and organ, and between organ and microorganism. By doing so, organ transplantation provides new opportunities for studying the functional integration of biological entities. The signal, borne by molecules as part of a message, is accessible at the boundary between organisms through the molecules of communication recombining into new patterns and arrangements. Transplant tolerance is unachievable if viewed as just preventing rejection. Instead, tolerance should be viewed as an exchange of the correct type of biological information at the functional boundary between organisms, but localizable by science to the structural boundary.

The structural boundary may be more easily localizable for organ transplants than for microorganisms. Transplantation provides the great advantage over the microbiota of coincidental structural and functional boundaries, making SOT a much easier method to study the human organism-human superorganism distinction.

Chapter Five

Transplantation and Biological Emergence

A typical human superorganism contains a human organism and the microbiota. A human transplant recipient in addition has a transplanted organ that is part of neither the human organism nor the microbiota. Instead, the transplanted organ is contained within the boundaries of a human organism but belongs to another human organism. In this chapter, I will show how this unique relationship of entities leads to emergent biological phenomena in the human organism.

Data suggest that there is a functional connection between the transplanted organ and the microbiota, so in this sense, the transplanted organ is also part of the human superorganism. In addition, there are connections between the transplanted organ and the other organs of the human organism. In a regular, non-transplanted human superorganism, functional connections between the heart and the kidney, or the liver and the kidney, for example, are widely recognized[19]. These connections among native organs continue to function in the transplant recipient as well. Yet the newly transplanted organ is different from all the other organs of the human organism in one important respect. The body will always reject the transplanted organ, potentially or actually. This rejection occurs through the physiological mechanism of an anti-altered self reaction, in which the immune system handles the organ as not belonging to the self. Occasionally, other organs will lose their self-status and then become subject to autoimmune disease, which is a form of anti-altered-self reaction in which the targeted organ is no longer a part of the same organism to which all its companion organs still belong. In autoimmune disease, the mechanisms involved are clearly pathological, not physiological. However, rejection of a transplanted

[19] The corresponding disease processes in these organ interactions include the cardiorenal syndrome and hepatorenal syndrome. Severe dysfunction in one organ can result in severe dysfunction in another organ, even if the latter remains structurally normal. Transplanting one organ can result in normal function being restored in the other.

organ is physiological just as rejection of a microorganism is physiological, for there are no known diseases caused by rejecting microorganisms.

Due to the fundamental difference in the manner by which the immune system handles the transplanted organ compared to all other organs, we need to classify the transplanted organ in a category different from any other organ in the body. The origin of the transplanted organ is a different organism and by extension, a different superorganism. Since the human transplant recipient was just like all other non-transplanted human transplant recipients before the transplant, there emerges a *different* type of human superorganism after the transplant. This entity is a redefined human organism, and a redefined human superorganism.

In this chapter, I argue that such emergence in biology is the expression of otherwise normal processes facilitated by the right environment for those processes, but it is also the emergence of other processes that would not otherwise express. I will first describe biological emergence generally and then explain why the transplant recipient displays interesting emergent phenomena within the overall scheme of the living world, characterized by the constant redefining of biological boundaries.

5.1 Emergent Processes in Solid Organ Transplantation

According to Wimsatt (2006), four conditions determine whether the property of a system as a whole is the aggregate sum of its parts. When one or more of these conditions is not satisfied, the property can be said to be emergent. These conditions include: the system property being invariant with the inter-substitution of its parts with one another (e.g., mass); size scaling of qualitative properties even though values may differ when parts are substituted; invariance under the decomposition and re-aggregation of parts; and no cooperative or inhibitory interactions among the parts of the system. Conversely, an emergent property is a system property that is dependent upon the mode of organization of the system's parts (Wimsatt 2006). In other words, it is the manner by which the parts

relate to each other that leads to emergence. Campbell (2015) developed this concept of emergence further. A property is emergent iff it is a system property that is necessarily dependent upon the mode of that system's organization (Campbell 2015). According to Campbell, an emergent property *also* exists in the same time and place as its parts, and has distinctive properties and types of interactions among its parts that are also dependent on how those parts are organized.

Emergent phenomena result from interactions among the parts from which they arise. Yet the emergent whole is different from the sum of its parts. When wholes possess properties that their parts lack, such global properties are said to be emergent. Energy of a whole is distributive across the entire system, yet emergent properties are not distributive but global. Some of the key features of emergence are irreducibility, unpredictability or the inability to explain, novelty, and holism. Not all of these features need to be present for emergence to occur.

The transplant recipient can never go back to being a non-transplanted human superorganism, even if the transplant is subsequently explanted. The effects of the transplant last for the rest of the recipient's life. Antibody production against foreign antigens can persist for a lifetime, greatly hindering future transplants. This irreducibility of status leads to unpredictability of events. In the case of an organism, emergent properties arise from the interactions of its parts (Bunge 2003). The transplant recipient is a later emergent of the same general kind of human superorganism presumably as healthy as that superorganism was before the onset of disease in the organ whose function was replaced, but who now displays newly emergent properties.

Ontological emergence is the occurrence of qualitative novelty, while epistemological emergence refers to its unpredictability based on the properties from lower levels (Bunge 2003). Transplant recipients demonstrate both ontological and epistemological emergence. Although the function of the human organism after SOT is

qualitatively novel, because organ function is directly provided by another organism, scientists should still be able to predict post-transplant outcomes when all the inputs are known. Yet the function of the transplanted organ remains unpredictable to even the most experienced transplant physician. There are numerous studies of the effect of some "risk factor" or another that coincides with the occurrence of some post-transplant disease or another, as well as organ survival or patient survival. A statistical effect is computed to the risk factor around which a range of probability of the effect being a chance effect is constructed. This effect guides clinical decisions in situations ranging from donor-recipient matching to balancing post-transplant immunosuppression between the opposing outcomes of preventing rejection and disease from over-immunosuppression. However, we can never truly know in advance an outcome for a particular recipient. I argue that this unpredictability arises from our epistemic shortcomings of the human organism-human superorganism distinction. Emergence arises out of a certain degree of biological complexity. Emergence is predictable through induction, but is not derivable by deductive reasoning.

Emergence inherently opposes reductionism. A simple (and oft-quoted) example of emergence is the water molecule (di-hydrogen oxide), which bears none of the properties of its constituent hydrogen or oxygen molecules. Wetness, an emergent characteristic of water, requires more than one molecule of water to emerge. Emergence results from both the interactions between hydrogen and oxygen atoms, and between whole water molecules. Similarly, although we view transplantation as simply the implantation of one organ into a recipient, transplantation is actually the *combination* of organs originating from two different superorganisms to create a new superorganism. In other words, the organ and the recipient are biological equals in the relationship despite their enormous size difference. In this case, the original disease process of the transplant recipient attenuates while new post-transplant diseases processes emerge. Therefore, the "original" person loses his or her original biological properties after transplantation because of reorganizing, reattaching,

and new communication pathways among some of his or her parts. The transplant recipient is more than just an aggregate of parts, some of which are new to the whole[20].

Modularity opposes emergence. Modules are separable from the whole without losing their properties, are biological "individuals", and delineate from other entities with which they interact (Luttge 2012). Modules compare to the knots of networks (Luttge 2012). Qualitative novelty does not occur in a modular system. If the transplant recipient were to be a modular organism, then the properties of the transplant recipient would be easily describable, and all post-transplant outcomes would be easily predicted based on the structural similarity of the transplanted organ with the original organ.

The more rare, complicated, or well-designed an entity is, the less likely it is that the entity occurred by chance (Deacon 2006). This well-known argument dates back to William Paley's famous metaphor of the watch. Although the disease causing organ failure might have indeed occurred by chance, such as through some environmental interaction of the organ with its environment (e.g., a toxin or microbe), there is no doubt that organ replacement through transplantation does not occur by chance. Transplantation is a deliberate human action. By extension, the transplant recipient as an entity is not a chance occurrence of nature either. It may be more helpful to consider the transplantation procedure a *process* with membership along the spectrum of organ failure processes, that also includes chronic organ disease and procedures like dialysis. By viewing transplantation as a process instead of a combination of entities, then size discrepancies among body parts no longer become a consideration when deciphering post-transplant pathophysiology.

The decay of the human organism that occurs from most forms of disease as well as aging, ultimately leading to the failure of the human superorganism (i.e., death), conforms to the second law of thermodynamics because entropy is increased. With death, the

[20] The new part interacts differently from the original part when it is part of a new whole.

molecules of the human body, which were always non-living, return to a non-living environment where they do not participate in life processes until they incorporate into another organism. Disease is a process caused by the disruption of normal mechanisms, the activation of pathogenic mechanisms, or both. Successful disease treatment means to reverse the entropy of the human superorganism, usually by repairing dysfunctional mechanisms such as anti-diabetic agents that increase the sensitivity of tissues to insulin, or antibiotics that add new mechanisms to counter microbial mechanisms. Transplantation is a process that reverses entropy not by reversing or countering mechanisms, but by *adding matter* to the human superorganism in the form of a solid organ. The goal of transplantation is to add tissue whose mechanisms are identical to those that have been lost to disease. Processes are restored. Prior to organ implantation, we consider the solid organ as living even while it is not performing its most important function. Within a solid organ are innumerable tissue processes, molecular or otherwise, that resist entropy. These processes continue for as long as there is life in the organ. Emergence of organ function is the most visible and recordable expression of these processes.

Clinicians expect that the transplant recipient will possess the same properties as the human superorganism without organ failure through inductive reasoning. If a non-transplant recipient with a certain amount of organ function x has a certain property, then a transplant recipient with the same amount of organ function x should express that same property. However, this is never the case. Their system properties might be acceptably described, as being "within normal limits" of organ function. Administering anti-rejection medication helps to achieve good post-transplant organ function even though the mechanisms of those medications typically situate outside normal human physiological processes. Since organ function after transplantation originates from *another* human superorganism, novel properties emerge in the transplant recipient. Organs are not modular entities.

5.2 The Transplant Recipient with Emergent Processes

Transplantation biology defies the self-nonself dichotomy (Tauber 2000). The immune system is not a patrol unit, but is intimately involved with the function of every cell in the body (Howes 2000). The transplant recipient is a human superorganism with a transplanted organ without which there is a high probability of death. It is not possible to restore the function of the failed organ itself, and so outsourcing of the organ's function becomes necessary for life sustenance. In a dialysis patient, the outsourcing of the kidney's function is external to the human organism, so there is no involvement of the immune system in establishing functional connectivity to a machine unless there is an allergic reaction to one of the machine's components. A dialysis machine is not part of the human superorganism since the human organism contributes nothing to the machine's survival.

After transplantation, on the other hand, the organ locates internal to the human organism and so the immune system becomes intimately involved in establishing functional connections between the organ and the rest of the human organism through a two-way mechanism. Many other properties of the recipient emerge as a result. These properties did not exist in the recipient before, would not exist if the transplant had not been performed, and are both irreducible and unpredictable. Unpredictability is an especially daunting obstacle to post-transplant success despite enormous advances in understanding the physiological, pathological, and pharmacological principles of transplantation science. Immunity is a mechanism of biological emergence. Before I discuss post-transplant emergent processes, however, I will first describe some other life events leading to biological emergence.

Life Events Leading to Emergence

There are of course other situations in life where parts from different human organisms mix. Mixture of parts from different organisms occurs physiologically in

pregnancy, pathologically in infection, and therapeutically in blood transfusion. The resultant emergent properties differ from those after transplantation.

Many female human superorganisms become pregnant in their reproductive years with a product of conception that is only half their own organism, the other half of course originating from another human organism[21]. In pregnancy a placental barrier always separates the embryo or fetus from the mother. There is a physiological mechanism in place for the expulsion of the fetus by the uterus when appropriate. Unlike the mother, the fetus is not a superorganism because it does not have a microbiota. The fetus also does not violate any human organism boundaries from conception to delivery, because it is inside the uterine cavity and the mother can expel it without violating maternal boundaries. Mother and child each have their own circulatory systems. Each has its own immune system as well. Nutrient molecules cross this placental barrier from mother to child, and some waste products also cross in the opposite direction, although waste molecules from the fetus enter the surrounding amniotic fluid that belongs to the fetus. The child becomes a superorganism once it acquires its microbiota, to which it is tolerant. The structural boundary between mother and fetus is unbreachable without fetal expulsion, and amniotic membrane rupture serves as the initial exteriorizing event prior to delivery. Immune sensitization resulting from pregnancy occurs from some admixture of fetal blood and its constituent molecules across the placental barrier, but this structural boundary between mother and fetus nonetheless exists. Blood cells along with their antigens and other molecules are no longer part of the fetus *after* they leave the fetal organism but *before* they enter the mother. In transplantation, most molecules of the organ *remain* part of the organ all along, from before the transplant to many years afterwards. Some molecules do enter the rest of the recipient, thereby provoking the transplant recipient or the pregnant woman to form antibodies.

[21] Human cloning is not yet possible.

Another example of an event leading to new processes emerging is blood transfusion. Both females and males sometimes receive blood transfusions. A blood transfusion is a process used to treat or (rarely) to prevent a disease process called anemia. Unlike in transplantation, the purpose of a blood transfusion is to enhance, *not replace*, the function of the recipient's own blood. Unlike pregnancy, a blood transfusion directly violates the boundaries of the human organism when a needle penetrates the blood vessel wall and the first red blood cell enters the organism. Similar to pregnancy, immune sensitization can occur and persist long afterwards. Unlike transplantation, however, the separate identity of the transfused blood is instantaneously lost. There are no longer any discernible boundaries between the blood and the rest of the organism. Measurement of the hemoglobin concentration determines success of a blood transfusion but this measurement is really a combination of the recipient's own hemoglobin and the hemoglobin of the transfused blood. A bag of blood contains life similar to an explanted organ, but it is not an organism. The transfused blood itself may have even originated from multiple donors, since it is not intact blood but only processed and concentrated red blood cells. Two-way or multi-way communication among the different blood sources in a bag of blood, even if it occurs, is not measurable. Even the lifespan of the transfused blood cells is short. Sensitization, the most quantifiable outcome of this admixture of blood, results only from activation of the recipient's own immune system after the blood is transfused.

A third life event leading to emergence is infection. I discussed infections extensively in previous chapters, and so I will only briefly reiterate that infectious diseases emerge when organisms of another species violate the boundaries of the human organism. With infection, in general, an intact organism violates the boundaries of another organism. In transplantation, an intact organ violates the boundaries of an organism separate from the organism from which the organ originated. In both cases, disease processes emerge from the violation and reestablishment of boundaries. Reestablishing boundaries is an attempt of the human organism to restore health.

It is possible that structural boundary violation can still result in "benign" relationships between microorganisms and the human organism, especially in the case of viruses. More research will determine if there are indeed benign viruses located inside the confines of the human organism, serving as biomarkers of immunity. Bacterial associations from "colonization" at structural boundaries of the human organism do not result in disease processes, because they do not result in a breach of the structural or functional boundary between organisms.

The common link among these three life events (pregnancy, blood transfusion, infection) is that in each case biological boundaries are breached. In each case, emergence is the result. Therefore, *biological emergence occurs when boundaries are breached and reestablished*. Emergent phenomena arise from boundary reestablishment. These boundaries may be structural, functional, or both. The virulence of an organism reflects its ability to breach biological boundaries and cause disease processes. Restoration causes either disease or health processes. But what are these processes?

Emergent Processes after Kidney Transplantation

Organ transplantation is a sudden and deliberate breach of the boundaries of the human organism. Therefore, we might expect emergent processes to result when these boundaries reestablish. Organ transplantation provides novel examples of emergence. I will first briefly describe how disease and health processes emerge after an organ transplant.

Organ failure leads to profound effects on the entire human organism, and kidney failure is no exception. I will provide a few examples of diseases in other organ systems resulting from kidney failure.

Cardiovascular disease is especially common in kidney failure and follows a natural history different from cardiovascular disease in the general population. Similarly, infections are much more common in kidney failure because kidney failure itself is an

immunosuppressed state. The normal core body temperature is lower in kidney failure. There are increased circulating concentrations of some hormones, decreased circulating concentrations of other hormones, and decreased tissue sensitivity to yet other hormones. Successful pregnancy is all but impossible. Cognitive dysfunction is very common. Unmanaged kidney failure profoundly affects psychomotor behavior, memory, speech, perception, and emotion, making it difficult to distinguish from organic brain syndromes. Intellectual dysfunction occurs without any anatomical lesions in the central nervous system (Kowalik 2005). The intestinal microbiota alters significantly. Mortality from kidney failure is higher than that of almost any other disease due to the profound disruption of multiple organ systems.

Transplantation brings about immense change to this scenario of kidney failure. The risk of cardiovascular disease reduces and many of its features differ[22] to resemble those of the general population again. Cognition improves, fertility improves and pregnancy becomes possible, and mortality lowers. Rare types of infections and cancer occur more commonly. All these changes do not directly depend on the environmental presence of anti-rejection medication. Diabetes control improves after kidney failure compared to before kidney failure, to the point that medications are often not required. However, somewhat paradoxically, diabetes control promptly worsens after a successful kidney transplant.

Although the natural history of some existing disease processes accelerates after transplantation, it is a mistake to assume that those disease processes are the same as those of non-transplant patients just because they carry the same epistemic label. Some disease processes causing kidney failure recur in the transplant and follow a different natural history. Diabetes, hypertension, and cancer, for example, may have an etiology

[22] This is quoted as being a "reversal of reverse epidemiology". For example, obesity is a risk factor for cardiovascular disease in the general population, is protective in dialysis patients, and again becomes a risk factor after kidney transplantation.

different from the general population, and therefore a different treatment[23]. As one example, Kaposi's sarcoma, a kind of cancer, is extremely rare in the general population but occurs much more commonly in transplanted patients. Transplantation brings out the ambiguity inherent in our limited disease nomenclature. Diabetes for example has many causes, all leading to the common phenotype of hyperglycemia.

Our limitation in mechanistic understanding of disease sometimes compels us to place widely disparate diseases into the same bin for descriptive and therapeutic purposes. The molecules we measure to diagnose and monitor disease are rarely the cause of the disease, or even participants in the process. Molecules are only surrogates of disease processes because they are entities performing some activity as part of a mechanism. All entities such as molecules are surrogates of disease processes when they interact with other entities to produce output in the form of activity.

Beyond these widely appreciable clinical outcomes after transplantation, there are two especially interesting aspects to emergence in kidney transplantation: the emergence of life, and the emergence of organ function. Although emergence is a common phenomenon in the human organism and in transplant recipients as well, these two forms of emergence are unique to the post-transplant situation. I will briefly discuss each of these in turn.

The Emergence of Longevity in Solid Organ Transplantation

Longevity is the least controversial global outcome encompassing all other measures of health and disease processes. Even though multiple diseases processes exert their own effects on the superorganism, *the survival of the human superorganism increases overall after transplantation.* In other words, *there is an emergence of new life expectancy in the transplant recipient.* Transplantation restores years of life lost from organ failure not by a

[23] The exact nature of the differences between specific diseases in organ transplant recipients and the general population lies outside the scope of this discussion. However, the medical literature abounds in epidemiological studies of organ-specific diseases.

reversal of the disease process, but by the material supplementation of a new organ containing normally functioning mechanisms. An increase in normally functioning mechanisms does not however fully explain enhanced longevity.

In the case of deceased donor kidney transplantation, it is not difficult to understand how new longevity emerges. The deceased organ donor is obviously dead. However, the organ soon to be transplanted is still living and has normal function, even though it has very little time left to live. This potential lifespan of the organ must shorten even more once the organ is removed from the donor and is situated outside a human body, such as in a box of ice. Once the organ is implanted in the recipient, the potential lifespan of the organ recipient is suddenly increased, sometimes to the normal lifespan of a human superorganism without kidney disease. Therefore, there is a transfer of potential life from the donor to the recipient, carried in the form of a solid organ (an entity). The recipient can expect to live a normal lifespan for his or her current age even if the deceased organ donor was much older than the recipient is, at the time of the transplant. The donor might otherwise have expected to have a much shorter lifespan than the recipient did, such as from age alone, even if the donor did not have the condition that led the donor to become an organ donor in the first place, such as cerebrovascular disease leading to a stroke. The sum *total* life of the donor and recipient is therefore increased.

In the case of living donor kidney transplantation, the approved donor can expect to live a normal lifespan, or even a longer lifespan than average because of his or her superior health status. This normal lifespan stays preserved after kidney donation. When a recipient who has a reduced lifespan receives the donated organ, the recipient's lifespan is increased. Again, the *total* expected years of life for the donor and recipient has increased. Years of life have emerged, all of which belong to the recipient.

What are the reasons for this emergence of life? The higher the overall state of health is for a population, the longer a member of that population can expect to live. This

comparative life expectancy measure is widely compared across countries. Average life expectancy mirrors overall socioeconomic health, which in turn is determined by investments in health care, and so on. Transplantation represents a very large healthcare investment. Transplantation therefore represents a stark example of monetary resource "conversion" into years of life for a population. Mechanistically, we might explain that these emergent years of life are the result of relief from all the pathological events, both psychological and physical, that result from organ failure. It is a mistake, however to think that the transplanted organ itself restores or adds to life-years. The kidney is an entity, but relief from kidney failure is a process involving the whole superorganism. Healthy relationships between the kidney and other organs are restored. Increased process expression provides relief from the entropy of death. Increased longevity results from a redistribution of organs within a population: a changed relationship of parts to wholes.

The Emergence of Organ Function in Solid Organ Transplantation

That biological emergence is an expression of process becomes clearer with the recognition that transplantation results not only in years of life emerging. Organ *function* emerges as well. This is because the sum total of organ function in the living organ donor and the corresponding organ recipient is more than the total organ function of the donor before donation. In other words, new function emerges in the other kidney of the donor without any long-term adverse consequences to that kidney. New function would not have expressed itself in the donor without donation.

Kidneys have a proper function of removing toxins from the blood, based on their evolutionary history. By doing so, the kidneys adjust their function to the functioning of other organ systems. The kidneys are the representative of toxin removal provided by evolution, because kidneys serve that purpose well. Kidneys will remove toxins whenever they are situated in the right environment. Transplantation is a process of changing environments, and the transplanted kidney adapts accordingly in its changed environment,

always performing its function within the range that evolution provides. Sometimes this kidney function is at the lower end of that range in the donor and at the higher end of that range in the recipient. We define the kidney's function only around the purposes with which it serves us. Emergent life "provided" by the transplanted kidney is nothing but the changed environment it provides to the recipient, which in turn allows that potential for life to express itself. The *process* in emergence is what is primary, not the entity. Environment determines the expression of process. In the case of living liver donation, a small remaining liver in the donor is sufficient to "regrow" and restore liver function.

When one kidney is diseased, function in the other kidney does not increase to the same extent as in a healthy remaining kidney after donation. On the other hand, certain kidney diseases can occur in the healthy kidney when the other is diseased, leading to it becoming diseased as well. The overall environment changes with kidney disease because multiple processes including those situated outside the kidneys have become diseased as well. Since a kidney donor is a healthy person, the kidney remaining after donation has a greater capacity to permit new function to emerge. Such emergence depends on the health of surrounding organs. Emergence depends on support from the surrounding environment that all organs together create.

An internal organ such as the kidney cannot survive outside the body for very long. As with all organs, it is very dependent on a continuous, reliable, external blood supply. The "cold ischemia period", during which time there is no blood flow to the kidneys, cannot exceed 36 hours, or else the damage to the kidney becomes too severe and the organ then becomes useless for transplantation. Shorter cold ischemia times are always better. The loss of life can be slowed to some extent, but not stopped, by cooling down the kidney with ice to reduce its metabolic processes, and also by pumping the kidney with a special preservative fluid to mirror normal nutritive processes. When the kidney is rewarmed before implantation in the recipient, its blood flow must then be restored quickly (in a matter of minutes). Therefore, while the kidney is in vitro awaiting its new

owner, it constitutes a living part of the body that is not in structural continuity with the rest of the organism, but with plastic, ice and the atmosphere. This kidney could also be transported thousands of kilometers away to its new owner, under fantastic circumstances. The kidney may be at high altitude in an aircraft, for example, around which there is no other life present apart from the pilot. A kidney outside the confines of a human body is therefore not really a kidney because it is not performing kidney processes.

Once transplanted into the recipient, the kidney is not placed in an ideal anatomical location either. Its new home is decided by the convenience of the surgeon, in a place typically far removed from the original kidneys. The kidney is usually grafted onto an artery and vein connected to a lower limb, while the original kidneys are usually retained far up in the abdomen. Thus, the structural "self-organization" of the body has been effectively disrupted. The rest of the body is no longer fully self-organized, but rather, structurally re-organized. The kidney is still expected to perform as a normal kidney would albeit now in a new, alien environment, with what may be suboptimal blood supply or urine drainage. Along with chronic rejection, these anatomical imperfections of the environment cause slow scarring of the kidney. Despite these imperfections, the function of the kidney increases in the recipient, compared to when it was in slush, which is an even more imperfect situation. The "re-emergence" of kidney function relates not to the organ structure itself, which is largely unchanged, but to the environment which permits that function to be expressed. We are adding more self-organized matter to the human body, not process *per se* even though it is the process which restores health. That process was non-existent at organ implantation. We add function to the recipient because there is more *expression* of process.

In living donor kidney transplantation, the total kidney function of one human superorganism is divided between two human superorganisms. This division is possible because there are two kidneys and one kidney can be spared. The functional process of the kidney is indeed "split" between individuals, but their combined function is never split in

the same proportion as their mass (which is presumably equal) because of the different environment in which the two organs now find themselves, in the donor and in the recipient. The kidney remaining in the donor assumes more function than the kidney transplanted into the recipient because the donor's environment is inherently more favorable to the full expression of its processes.

In summary, the emergence of both life and organ function in transplantation demonstrates that emergence is a manifestation of properties, resulting from the recordable manifestation of processes. Processes (life and function) can be transferred via entities (such as organs). Entities such as organs possess properties and processes.

The organ's environment determines the expression of its processes including life and function. The emergence of biological function is determined therefore by the *relationship* of parts to a whole (Wimsatt 2006). This whole is also the environment in which the part finds itself. I will next discuss the relationship of parts to the whole in the context of SOT in the next section.

5.3 The Organ Transplant as a Part of a New Whole

A cell and an organism must be contained within some sort of boundary, outside of which there is a space without life, and this space separates one individual cell or organism from the next individual cell or organism. In the case of animal cells, as we move from the centre of a cell towards its periphery, we encounter first the semi-permeable membrane that forms the outer boundary at the cellular level, beyond which is an intercellular lifeless space before the next semi-permeable membrane is encountered. When we scale this up to the level of the entire organism, beyond unicellular and small multicellular organisms of course, this boundary comes to be defined by specialized organs like the skin.

Although there are no constraints on the internal structure of atoms or molecules themselves when they are contained within biological organisms, significant restraints are

placed on their movement and behavior. Their states of ionization are regulated by the acidity or alkalinity of their environment. Membranes further restrict ionic movement both within and outside the cell, creating gradients for their movement that in turn is restricted by the presence of pumps and channels contained in those membranes. Even water and gaseous molecules require special channels to traverse cell membranes. Structural boundaries are present everywhere.

What lies outside the skin or mucous membranes is exposed to air and does not constitute part of the human organism. While accommodating for growth (and shrinkage with aging) this integumentary structure is considered as fixed. However, the outermost layer of skin consists of dead cells that are regularly shed, as these cells move upwards and towards the exterior from the basal layer of the skin. These skin cells are dead in that they contain no life and were previously living (thereby distinguishing them from non-living entities), yet serve the useful purpose of protection from the exterior (just as fingernails and hair do). Body parts can thus serve a useful function without being alive. The human organism consists of a harmonious combination of living and non-living parts. Each organ in turn also consists of living and non-living parts. Living parts require non-living parts for their normal functioning. By extension, in SOT, both living parts and non-living parts are being transplanted. Only then can the processes of transplantation emerge. Life arises in the emergent processes of living cells (Thompson 2001). However, maintaining life requires support from non-living entities. Without living cells, there would be no life, but at the same time cell components alone do not constitute life. Life depends on the *organization* of the cell's components and a non-living environment.

The human body consists of numerous organs and tissues that are loosely although accurately referred to as "parts". An organ consists of two or more tissues that combine in such a way that a more complex function emerges (Findlay and Thagard 2012). The relationship of an organ to the organism has greater clarity than the relationship of a tissue to the organism, due to our ability (at least visually) to delineate the outer boundaries of an

organ. We also have the ability to explant an organ from the organism, and implant that organ in another organism while still preserving its shape and structure. If the shape and structure of the organ are not preserved, then the organ becomes useless to the recipient. After transplantation, a part of one organism has now become a part of another organism. I will now evaluate the relationship of the parts to the whole, but in the context of transplantation.

The organization of entities at multiple levels is relevant to explaining biological operations (Findlay and Thagard 2012). *Parts* are units that together assembled form a *whole*. Parts have properties called *tags* giving them structural and functional identities, brought together by forces or processes called *organizers*. Parts hold together by forces, processes, or entities called *attachers*, and they interact with other parts by specialized components called *communicators.* When parts are joined in this manner to other parts, the parts all form a whole that operates as a *system* (Findlay and Thagard 2012). Although the human organism can be compared to a machine (section 2.3), the analogy of a human organism to a machine falls apart quickly. The analogy falls away because parts are constantly being synthesized, tagged, organized, attached, and replaced in biological systems to maintain their structural and functional integrity, thereby maintaining the whole (Findlay and Thagard 2012). The relationship of organs to other organs is of particular interest in transplantation because of the reorganization, reattachment, and replacement of parts in the organism.

The tags of cells are the molecules that they express on their surface. Cell adhesion molecules and proteoglycans enable cells to stick together. Polarity of the cell, the cell's secretions, and surface receptors for hormones and other molecules produced by other cells all count as cell tags. Cells that migrate throughout the body, such as immune cells (lymphocytes, macrophages, natural killer cells, and so on, discussed previously), serve as communicators among the organism's cells. These tags are constantly being synthesized and degraded, during all the steps of transplantation. These tags belong to, or intimately

connect with, the immune system. Much research effort is directed towards increasing the expression of favorable tags and decreasing the expression of less favorable tags.

Cells undergo constant turnover. New cells are being produced, and old, dead cells are being shed, so that if an organism is simply defined as a collection of cells, then we are not really considering the same organism at two different points in time. New cells need to be tagged, organized, attached, and sometimes moved (Findlay and Thagard 2012). With transplantation the cells of the organ are moved spectacularly in relation to cells of other organs. We do not know how a membrane comes to surround the rest of the living system, such as whether it comes from the inside of the system or comes to envelope it from the outside. It is more helpful to view the transplanted organ as containing a set of processes within some boundary defined by the immune system. These processes are obviously carried out by cells, but it is the processes themselves in which we are most interested.

When the organism is viewed as a unified whole entity, everything is fixed in a sense. While we have energy input in the form of food, and output in the form of innumerable body processes, and notwithstanding cell turnover, we continue to have one heart, two lungs, one stomach, two kidneys, and so on, throughout our life. When the body is alive, all these organs are expected to be alive as well. It is strictly not possible to be alive while having dead kidneys, even if they are totally non-functional, because the relationship of those kidneys to other body parts continues. Conversely, when the whole organism is dead, the expectation is that all these organs are dead too. What we call life coincides with organ function, which goes together with life of the body as a whole. All these internal organs connect to other organs in the organism, and perform their function when they are ideally situated. For example, the heart's functional tags determine its position within the chest (Findlay and Thagard 2012).

All vital thoracic and many abdominal organs are protected by the strong yet flexible rib cage. Each organ is situated in the location most suited for its function. The

heart is ideally located in the thorax and not the abdomen or an arm, while the liver and kidneys work best when situated in the abdomen. They work best when considered as part of a unified whole. Specific connections exist between and among the organs. Structural attachments of organs include body cavities, their supportive connective tissues, and their lining membranes. Body cavities provide a low friction environment for organs to move about and even rub against each other (Findlay and Thagard 2012).

In transplantation, organs are indeed replaced by substitute organs "waiting in the wings" (Findlay and Thagard 2012). Structural attachments are determined by the constraints of evolution. Transplantation demonstrates that some structural attachments of organs are not essential to their function, while other structural attachments are more essential. A kidney transplant could theoretically be placed anywhere in the body, and still function as long as its connections are preserved.

Organ transplantation defies the evolutionary relationship that developed among organs. If an organism is to be described in evolutionary terms, then the transplant recipient counts as another *type* of organism because the recipient's expression of organ processes is superior to that of a diseased but still "normal" individual.

Medical practice in its division of labor follows the parts-to-whole approach. Some medical specialties are defined by their anatomical region of interest. For example, cardiologists are interested in the heart, pulmonologists are interested in the lungs, hepatologists are interested in the liver, and nephrologists are interested in the kidneys, even if they all have an interest in how the body functions as an integrated whole. Other specialists however do not have their body "part" with which they can easily identify themselves. Their specialties are defined by physiology rather than anatomy. Endocrinologists and rheumatologists do not have special organs of interest, so they must constantly keep the entire body in perspective. By extension, transplanted organ function does not typically match that of a native healthy organ. Organ dysfunction may be the

result of improper structural attachments, rather than defects in the organs themselves. In other words, *the expression of processes in a part is determined by the relationship of that part to a whole*. It is the whole sustained by the proper function of the part. Likewise, the proper function of the part depends on the sustained maintenance of the whole. In turn, medical practitioners are really interested in organ systems rather than organs alone. A cardiologist needs to know more about the heart's function than its structure because his or her goal is to provide relief from disease processes. Knowledge of function requires knowledge of structure, but knowledge of structure does not entail knowledge of function. A surgeon's extensive knowledge of structure is useful only in his or her ability to restore function.

Understanding the intrinsic purposiveness of the kidney requires it to be connected to the bladder, which is its most visible connection to the rest of the body and the outside world. The parts (kidney and urinary bladder) mutually determine each other as well, since there is little use for a bladder without a functioning kidney. Even if the blood supply of the kidney transplant comes from the leg artery[24] and not the renal artery, it still needs the bladder to collect its product, namely urine. Organ systems function as a whole, and the organs of that system are its parts. The kidney is organized by connecting it so that we can know what it does. Emergence can occur only in what is called an "open system" (Campbell 2015). This functional relationship among organs is parallel to the concept of organism, according to which there must be an ongoing exchange of resources with the environment, resisting entropy. Exchange of resources occurs across boundaries, and boundaries keep these resources including energy contained.

While an organism is quite dissimilar to a machine, a machine can be realized in many different manners. This is certainly true of a transplant; it can be realized in the same person or any number of different persons. It is common practice to first allocate a kidney to one recipient, and then to another if the first recipient is medically ineligible for

[24] The transplanted kidney most commonly connects to the external iliac artery.

whatever reason. The kidney itself has no interest in who its eventual recipient is going to eventually be. We can only describe a living system in terms of its utility or purpose to ourselves, but not what pertains to the system itself. A non-functioning kidney transplant is essentially treated as junk, even if it is still alive. It is quickly removed once it is determined that is of no use to the recipient, as long as it is surgically safe to do so.

If living systems direct their own organization, then they clearly did not account for transplantation, which is a special non-evolutionary case in which the new organization of the body is not determined by the body itself or its environmental success. Once the kidney knows it is in a favourable environment after re-implantation, it begins to perform its function of producing urine again. Structural connections in the form of blood or lymphatic supply along with supporting connecting tissue enable the functional connections that the immune system needs to keep all the organs working together harmoniously.

An artificial (such as a biosynthetic) kidney would be able to relieve patients of kidney failure, as long it was both anatomically and physiologically suitable by its size and immunological inertness. Dialysis as a form of artificial replacement of kidney function is external to the organism's boundaries. However, dialysis is not only inefficient, but leads to complications like blood clotting. To solve these problems, it might be possible to grow what looks like a kidney using what are called *stem cells*, derived from other body parts such as the skin. However, enabling that kidney to function in the way it is supposed to is another matter altogether. Attempts are being made to grow hearts by growing cardiac muscle cells on top of an inert matrix used as a scaffold (Taylor 2017). Even if we were able to grow such an organ in vitro, enabling the organ to properly perform all its functions is another matter altogether. Therefore, the function of the organ will not emerge from its structure alone. Function can only arise from the organ's processes.

Transplantation shows that organs can exist alive outside the organism at least temporarily, and so structural continuity with the other organs is not essential to their short-term existence. The organized entity of an organ does have a purpose in the organism that cannot be changed. Self-organization at the cellular level has to be preserved at all costs, if a transplant is to be successful, and so cell self-organization becomes the foremost requirement of life, over self-organization at the macroscopic level. Preservation of internal structural boundaries precedes that of external structural boundaries in importance. Attempts to derive a plausible account of emergence of life are still quite short of adequate explanation, although developing such an account remains a laudable goal in the philosophy of science. Studying biological boundaries is a good place to start.

According to Bechtel (2013), vitalists correctly objected that mechanistic explanations in biology lacked the resources to explain important features of biological phenomena. Emergentism has faced other setbacks (Malaterre 2013). Quantum chemistry complicates the calculations required to deduce properties of a system from its organization, since it overturns the in-built assumptions about unpredictability and non-deducibility of chemical properties from physical properties. Bechtel (2013) proposes that mechanistic science can be coupled with dynamic modeling to yield dynamic mechanistic explanations such as those being proposed in systems biology. It is important to subject existing problems in transplantation to mechanistic explanation, so that emergent properties are better understood, or we are left with only describing phenomena as novel.

5.4 Boundaries and Biological Identity after Organ Transplantation

Entities undergo recordable changes over time while still maintaining their identity. This is certainly true of the human superorganism, which maintains its biological identity both as a member of the species *Homo sapiens* and as a socially contextualized human being named so-and-so. In a biological sense, the human superorganism is in a continuous dynamic process of resisting entropy through its metabolism. Organs provide specialized

metabolism that can be duplicated by other organs only rarely. A transplanted organ correspondingly provides specialized metabolism when the failed organ does not provide the amount of metabolism required to maintain the milieu interior. If the failed organ retains some function and the organ is not removed when the new organ is implanted, then the functional output of the native and transplanted organs merge into a single organ system with measurable output in the form of function. Metabolism is a process arising from the functional cohesion of numerous sub-processes at the cellular level, coupled with the functional cohesion of numerous cells and even organs, not all of which provide the same type of function.

Self-maintenance is essential for the persistence of a biological entity through time. Without self maintenance, a biological entity quickly disintegrates. "Recursive" self maintenance refers to the internal processes that enable persistence of an entity through time (Campbell 2015). These processes are organized in a manner that permits the ongoing expression of function, and this organization constitutes biological identity. The persistence of an entity depends on processes whose purpose is maintaining it in existence (Campbell 2015). Transplanted organs resume their ability for self-maintenance once they are transplanted, although this ability is of course not perfect. Transplanted organs are more prone to environmental injury, for example, besides being subject to rejection and anti-rejection drug toxicity. Nonetheless, recursive self maintenance is sufficient to enable the identity of the organ, and in turn the organism to persist. The organism with a transplanted organ acquires a new biological identity from its new processes. This identity is different from the identity of both donor and the pre-transplant patient with organ failure. Persistence in time and biological identity go hand-in-hand.

The transplanted organ is not a static entity, just like the organism is not a static entity. The organ requires nutrition and oxygenation via a reliable blood supply, and access for excretion of its metabolic waste products. Although the organ's metabolic function varies over time, its immune status as the representative of a different organism does not

change. Immune function is not subject to metabolic change, even though metabolic change contributes significantly to both persistence and identity. The immune response situates functionally outside cell metabolism; entities of the immune system including all its cells have their numerous metabolic pathways similar to those of other cells, but those metabolic pathways by themselves do not provide the biological information of self-nonself discrimination. Rather, this information is contained within soluble molecules like the MHC and cytokines. This location of information in soluble molecules may be a reason why the immune system is ubiquitous, and hard to localize in visible entities such as organs.

Organ transplantation redefines structural and functional boundaries. Emergent phenomena require that boundaries come into contact with each other, which in the case of transplantation is the contact between the organ and the organism. Sometimes, these boundaries come into contact with each other through molecular movement. In all cases of biological boundary contact, directly or through molecular intermediaries, emergent phenomena can result. *Emergence results from self-reorganization, and therefore new biological identity, when real biological boundaries are violated*. The creation of new boundaries results in emergent processes. Unicellular organisms fuse to form multicellular organisms with redefined boundaries. Functional boundaries may fuse before structural boundaries, but when such fusion is successful, emergent properties result. The emergent organism possesses properties different from the organisms it emerged from, at least some of which are novel and unexpected.

Not all biological boundaries can fuse successfully with each other, of course. The structural and functional boundaries between species are too different to permit the survival of cells on both sides of these boundaries when these boundaries are in continuous contact. If cell components successfully fuse, however, then emergence will be the result. Xenotransplantation provides a stark reminder of how limited success can be when fusing the structural and functional boundaries between different species of organisms.

In the human organism, all organ systems operate within their biological boundaries. The immune system is unique among organ systems because the immune system operates across many different boundaries, extending to the entire superorganism. The immune system serves as a communication mechanism across boundaries. The immune system communicates not only among organ systems within the human organism, but between the human organism and microorganisms to establish the human superorganism.

Organ transplantation adds to our knowledge of boundaries and emergence by virtue of the organ's location inside the organism, thereby creating unique forms of biological emergence amenable to scientific study. New organ properties emerge beyond what microorganisms create, and unique health and disease processes can also emerge at the same time as new boundaries form. The new boundaries may not correspond to the disrupted boundaries in location, size, or shape. The unpredictability of emergent phenomena reflects the unpredictability of the nature of the new boundaries formed. Organ transplantation nicely demonstrates that new properties emerge when new boundaries are created. Organ transplantation provides some experimental proof to a philosophical supposition about the relationship between biological emergence and new boundaries.

5.5 A Summary of Emergence in Organ Transplantation

New structural and functional connections between the transplanted organ and other organs characterize the organ transplant recipient. Due to the fundamental difference in the manner by which the immune system handles the transplanted organ compared to all other organs, we need to place the transplanted organ in a category different from any other organ in the organism. The transplant recipient becomes a redefined human organism, and by extension a redefined, emergent type of human superorganism because the transplanted organism is much more than an aggregate of native and transplanted parts. Organ transplantation allows for the emergence of unique biological phenomena,

some of which are desirable such as improved cognitive function or improved general performance of all organs, and others not so desirable such as heightened immune sensitivity, reactivated infections, or unique forms of cancer.

Disease promotes, and treatments for disease reverse the entropy of the human superorganism. Transplantation reverses entropy not by reversing disrupted mechanisms, but by adding matter to the human organism in the form of a solid organ. However, there is an emergence of both increased life and increased organ function after transplantation, because this transplanted matter contains potential processes. Years of life emerge, all of which belong to the recipient, because donor years of life are still preserved at the same time. Similarly, after living kidney donation, the sum total of kidney function in the donor and recipient is increased. Many health-related parameters belonging to numerous other organs systems also improve. These novel organ system properties emerge because of the relationships between the organs and their environment. Properties and processes can be transferred via entities even if they are not manifest at the time of transfer, but do require an entity with structural boundaries such as an organ that contains them. The organ's stability in its environment, enabled by the functional tags, attachers, and communicators of the immune system, permits the full expression of its life and function.

A property is emergent iff it is a system property that is dependent upon the mode of that system's organization, i.e., the manner by which those parts relate to each other. The human organism has numerous organs and tissues that are loosely although accurately referred to as "parts". After transplantation, a part of one organism has now become a part of another organism, and therefore part of a different "whole" set of organs. A transplanted organ will function only when it connects properly to the other organism parts, both structurally and functionally. The re-emergence of organ function relates not to the organ structure itself, which is largely unchanged, but to the environment which permits that function to be expressed. The transplanted organ provides more function because we are

adding more self-organized matter to the human organism. We are adding life to the recipient because of more process expression initially and emergent years of life later.

The immune system responds to boundary violation to re-establish boundaries. Emergent phenomena, both desirable (health) and undesirable (disease) result alongside the more (although not fully) predictable processes that result from the transplantation of matter into a favorable environment. Unpredictability of emergent phenomena results from the unpredictability of new boundary formation in the human organism and the human superorganism.

In summary, emergent phenomena in biology result from the reestablishment of a disrupted self-organization that the violation of boundaries produces. Emergence is always occurring in organisms and superorganisms. Organ transplantation produces its own unique emergent phenomena, but it also adds to our knowledge of the relationship between boundaries and emergence by virtue of its location inside the organism, accurately timed boundary disruption, and the availability of a self-nonself interface to study.

Chapter Six

Disease, Health, and the Human Superorganism

In the previous chapter, I mostly focused on emergent phenomena in the human organism. In this chapter, I propose that in order to make progress in our understanding of health and disease, a focus on the human organism alone will not be helpful. Instead, I propose that health and disease can both be understood better when the human superorganism and not the organism alone is taken as the subject for consideration of emergent processes. In this chapter, I argue that it is important to consider *health as the result of harmonious interactions among the components of the superorganism*. I acknowledge the great physiological diversity of the biological world (Chapter Two), but will limit my discussion here to the human superorganism with an emphasis on SOT. I will also discuss some of the challenges that successful organ transplantation poses to normative accounts of health.

I claim that definitions of health and disease warrant consideration of the integrity (for health) or failed integrity (for disease) of the human superorganism's boundaries in the broader theorizing on the topic. In a healthy human superorganism, the microorganisms locate at some distance from the human organism, separated by structural and functional boundaries. Disease results when microorganisms enter the confines of the human organism. Similarly, transplanted organs are placed inside the human organism. The immune system responds similarly in both cases to repair the disrupted boundaries. How these boundaries are restored determines the nature of the resulting emerging processes. Some of these processes will be health-promoting and others will be disease-promoting. Transplantation helps us understand health better by bringing the role of boundaries in emergence into sharper focus. Structural and functional boundaries coincide. There is a constant two-way communication between the organism and the organ (part of another organism), all within the superorganism, and if this communication can be better

understood, we may be able to achieve tolerance to the organ similar to the manner by which tolerance to non-invasive microorganisms is achieved. When tolerance is achieved, health can be achieved, so tolerance maybe along the causal pathway to health.

While claiming that health and disease can be better understood through biological processes, I do not claim that such an approach is a replacement for normative approaches to defining health. I am simply providing an addendum to the health-disease debate rather than a robust replacement. Normativity can be helpful in understanding health for predictive purposes, such as for life and disability insurance, or military service. Yet simply comparing the health of one person to the next does not lend itself to a mechanistic understanding of health. Acknowledging and examining the human organism-human superorganism distinction is a useful heuristic to understanding the mechanisms of health and disease.

Health and well-being are needs of the organism because they are required for the organism to stay alive. Organisms may stay alive for a long time without perfect health of course, for no organism is ever in a state of perfect health, yet many organisms can live perfectly adequate lifespans. An organism in a state of perfect health may expect to live forever. Immortality is impossible, and so perfect health is impossible as well. Loss of health is usually also the first step towards death of the organism, for even if a particular form of organ dysfunction is not a direct part of the causal pathway towards death, it might be least associated in some way with more direct causes, however remotely. Even with sudden traumatic death of a healthy individual, apart from instant vaporization in a nuclear blast, there intervenes a period, however brief, of imperfect health.

A discussion of disease must accompany a discussion of health, because disease is the other side of the same coin in any debate. Definitions for disease abound. In some definitions of disease, comparisons are made to other members of a species. There is general agreement that absence of disease by itself does not constitute health. The link from disease to the absence of well-being is circumstantial at best. Many diseases have

been “defined” in clinical medicine by listing their features in textbooks or consensus conferences. Although the presence of disease implies the absence of perfect health, it is quite possible to feel well and function well, and compare favorably to other members of the species in the presence of a disease. Many diseases processes arise long before they cause symptoms or display signs. The features of a disease, namely its symptoms and signs, may never even be detected before death occurs. The goal of clinical medicine therefore is to restore well-being, not perfect health. Illness and sickness, being socially constructed concepts, are not amenable to analysis through the human organism-human superorganism distinction.

The human organism can stay alive only as part of a superorganism, when it is in a functional relationship with all its associated microorganisms. The human organism cannot stay alive if it is suddenly sterilized of all these smaller organisms, so in this sense the human superorganism is an individual. The microbiota is relevant not only when it causes disease, since it provides many functional contributions to the human organism in health. The human superorganism quickly disintegrates when the human organism dies. Since the human organism always has disease, it may be helpful to look for means beyond the organism’s pathophysiology to conceptualize, if not define, health.

A useful starting point for understanding health and disease is to acknowledge the definition taken from the World Health Organization’s 1948 constitution that links health and disease:

> Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.

This concept of health aims to include multiple components, and move beyond health as being merely the strict opposite of disease. Well-being and infirmity are introduced into the definition as ancillary concepts, and each of these is linked to the physical, mental, and social components of health. This concept of health although

comprehensive is vague, is of little practical use because it is not achievable by anyone and leaves much to discuss about each component. Despite being so broad, the World Health Organization definition has been considered by some as being not broad enough (Boddington 2009).

An alternative approach to understanding health is to start with disease first.

6.1 Disease and Health as Emergent Processes

Two Concepts of Disease: Disadvantage and Limitation

Concepts of disease are mostly normative. According to Scadding (1968):

> A disease is the sum of the abnormal phenomena displayed by a group of living organisms in association with a specified common characteristic or set of characteristics by which they differ from the norm for their species in such a way as to place them at a biological disadvantage.

Scadding's concept of disease uses other members of the population of a species as the comparator. Scadding emphasizes phenomena, which in turn require observation and the value judgments of another person. Biological disadvantage to an organism means that other organisms are advantaged, and therefore healthier. This is a major assumption, for the health of one organism cannot directly determine whether another organism is healthy or not.

A second concept of disease from Boorse (1977) conceptualizes disease according to ability and efficiency, but also includes contributory effects from the environment. According to Boorse (1977):

> Disease is a type of internal state which is either an impairment of normal functional ability, i.e. a reduction of one or more functional abilities below typical efficiency, or a

> limitation on functional ability caused by environmental agents.

These two examples of definitions illustrate and emphasize the types of components used in developing a concept of disease. Developing such concepts of disease is often driven by the desire of the theorist to be all-encompassing, and provide an ability to handle all the nuances of disease, and perhaps be applicable to all living beings in all situations. Biostatistical theories of disease are often defended (Schwartz 2014). There is also a desire to extend the concepts of disease into associated areas of concern such as illness and sickness. Illness and sickness are not my focus here, since they are more dependent upon subjective experience as well as normativity. Conceptual analysis of disease is useful, but an alternative is to naturalize the concept of disease so that the value of normativism can be better ascertained (Lemoine 2013).

Two Concepts of Health: Ability and Adaptability

Commonly quoted definitions of health include well-being as a part of the definition, although well-being is a consequence of health, and this still begs the question of what health is. Naturalistic definitions of health also use comparisons to other members of a species. However, such comparisons have nothing to do directly with the actual events taking place in the organism or superorganism whose health is being defined.

Health is commonly understood based on ability and adaptability. A prominent naturalistic view of health is that of Boorse (1977), according to which:

> Health in a member of the reference class is normal functional ability: the readiness of each internal part to perform all its normal functions on typical occasions with at least typical efficiency.

Boorse's view is based on the statistical normality of function, as well as the goal-oriented needs of the organism contextualized to the needs of the population in which the

organism is a legitimate member. The human species does not have clearly defined boundaries from other species although humans do understand them[25], while clinical medical practice still reflects value-laden social judgments about health that involve comparisons and that can vary over time. Ability and efficiency of the organism, which are integral to Boorse's concept, are actually comparisons to peers and mostly depend on mental states or capacities which in turn depend most on the nervous and musculoskeletal systems. Although naturalistic in its flavor, bio-statistical theories such as Boorse's account are not necessarily value-free (Kingma 2014).

A second concept of health is an action-theoretic account. According to Nordenfelt (1995):

> A is healthy iff A has the second-order ability, given standard circumstances, to realize all the goals necessary (and jointly sufficient) for his minimal happiness.

The major feature of Nordenfelt's concept is the adaptability of an organism rather than its ability alone, which along with efficiency was emphasized by Boorse. This ability to achieve one task or another varies widely across the members of a population. Health is therefore helpfully contextualized by Nordenfelt to the environment in which the organism finds itself. Normality is specific to situations that reflect homeostasis in an environment (Dussault 2015). However adaptability, similar to ability, also depends on mental states and social norms. Nordenfelt's concept gives primary importance to the functioning of the central nervous system, to the exclusion of other organ systems. Moreover, adaptability (and even ability) reflects well-being more than health *per se*.

Scadding and Nordenfelt have conceptualized well-being adequately, but they did not in my view conceptualize health quite as well. A psychological component to health is emphasized, and comparisons to other members of a species are also prioritized. Health

[25] It is important to remember (Chapter 2) that *Homo sapiens* does not have any close extant relatives to create confusion of identity.

requires well-being and well-being requires health. Therefore, an opportunity to re-examine health in the light of a more adequate but strictly biological understanding of the organism-superorganism distinction exists without circularity. The organism-superorganism distinction has the potential to avoid concepts such as well-being, illness, and sickness entirely, as well as avoid circularity between health and well-being. Yet another concept of health involves functional efficiency (Hausman 2012), proposed as being more important than the absence of pathology (Hausman 2014) but again, it is difficult to avoid normativity and comparisons to predetermined performance standards for the members of a species. Health "capability" is a combination of health and the ability to make health-related choices (Ruger 2010).

Disease and Health in the Superorganism

A concept of disease and health does not need to encompass all life forms, but it does need to acknowledge the relationships among organisms because we are human superorganisms. A formulation of disease does not need to be also encompassing of all human experience, but to at least be applicable to a significant subset of human disease processes. When the superorganism is understood as a functional integration of organisms, it is theoretically possible for the human organism to have disease while still maintaining normal functional relationships with other organisms. It is also possible for the human organism to be healthy but have dysfunctional relationships with other organisms.

Organs within the human organism can be morphologically and functionally normal while still in a dysfunctional relationship with other organs. For example, one might have a healthy liver and a healthy spleen, but if there is even the slightest dysfunction in the heart, for example, then health is lost. Even if we ranked the organs by their importance to total organism physiology, with the brain ranking much higher in this hierarchy than the spleen, health is still lost when the spleen is removed[26] or even if the big toe is stubbed.

[26] Splenectomy is a common surgical procedure, and is fully compatible with life.

Less trivially, it is common to experience kidney dysfunction after severe diarrhea because vital body fluids are depleted, but such dysfunction is readily corrected once the fluids replete. Severe kidney function without any abnormalities seen in tissue histology is seen in the presence of severe liver or heart dysfunction. Disease processes in the kidney such as hepatorenal syndrome and cardiorenal syndrome arise from abnormal relationships between the kidney and other organs rather than any anatomical or physiological abnormalities in the kidney itself.

Similar to what happens inside the human organism, a change in the intestinal microbiota leading to the proliferation of one type of bacterium (*Clostridium difficile*) causes serious disease in the human superorganism. As medical knowledge expands, associations and then mechanisms are detected between diseases in the human organism and alterations in the human microbiota. New associations are being found between organ transplants and the microbiota, some of which are surprising. For example, bacteria in the stomach (*Helicobacter pylori*) are linked to stomach ulcers, and bacteria in the mouth are linked to cardiac disease including myocardial infarction. Both health and disease emerge as the superorganism emerges from the organism.

Although it is true that many human diseases have not been linked to the microbiota based on our current state of medical knowledge and may never be so linked, a definition of health based on the human organism-human superorganism distinction cannot be accused of vagueness. Many non-infectious diseases of the human organism might link to microorganisms, and so the distinction of infectious diseases from non-infectious diseases might lose relevance. As a consequence, many more diseases emerge with the human superorganism rather than belong to the human organism alone. This seems expected since the human superorganism is a more complicated entity than the human organism. There is less need for normativity, and so human biology will be in a better position to inform the concept of health by supplementing work from the social sciences.

6.2 Using Solid Organ Transplantation to Understand Health and Disease

Comparing Transplant Recipients to the General Population

Since we cannot ever study the relationship between each bacterium and the human organism, organ transplantation provides an opportunity to evaluate disease and health in the context of the human organism-superorganism distinction. Most microorganisms cannot be cultured. Certain diseases such as *Clostridium difficile* proliferation and invasion clearly belong to the superorganism, while diseases such as embolic stroke clearly belong to the organism. For many other diseases, however, this distinction is not so clear. Rather, there are emerging data to indicate disease processes such as myocardial infarction, through a relationship to the oral flora, actually belong to the superorganism. A list of diseases related to the superorganism rather than the organism alone is likely to become longer as our medical knowledge expands.

Successful SOT provides a counter-example to normativity of health in many respects. Organ transplant recipients are healthier than their end-stage organ failure counterparts, and healthier than many, but not all members of the general population[27]. Laboratory values of chemical compounds in the blood accepted as normal differ between transplant recipients and the general population. The starting point for change towards the transplanted state was not a healthy state. Transplant recipients possess health processes in some respects and disease processes in others.

As I described in Chapter Five, the organ transplant recipient enjoys many benefits from a successful transplant. Overall well-being is improved, and the natural history of existing diseases may be favorably altered. However, recipients experience many complications related to the transplant as well[28]. Physicians and other providers who care for SOT recipients are typically more experienced in diagnosing, treating, and otherwise

[27] There is a transplant Olympics, and transplant recipients are known to perform amazing physical feats.
[28] Some of these complications are unique, such as recurrent disease in the transplanted organ.

managing non-transplanted patients. As a result of this vast experience, concepts related to health and diseases are carried over from general medicine to transplant medicine. Since the transplant recipient carries emergent processes not seen in non-transplanted patients, a different approach to understanding their health and disease processes is needed. By extension, transplantation might help to illustrate how our understanding of health and disease can be refined and improved, because any disease process is actually a set of multiple processes leading to a common phenotype.

It is quite reasonable to group transplant recipients together by their common characteristic of possessing a solid organ transplant for data registry-based analyses of outcomes and clinical trials of interventions. However, this characteristic of possessing an organ transplant also sets transplant recipients apart from other human superorganisms. Transplant recipients are healthier than patients with organ failure, but more diseased than non-transplanted humans with functioning organs. If we consider the transplant recipient as having a disease process because they still have lesser organ function, both qualitatively and quantitatively than the general population, and must consume medication that others do not need, then we are compelled to view the organ as a pathological entity and the recipient as diseased, even though it is that organ's normal function that was the basis for its selection for elective implantation.

A transplanted *healthy* organ being pathological is inconsistent with disease being an abnormal phenomenon and conferring a biological disadvantage. After transplantation, there is always some impairment of the organ's function below typical efficiency, despite the emergence of increased combined organ function in the donor and recipient. Comparison of transplant recipients to other human superorganisms with regards to their organ function is uninformative because transplantation does not *cause* impairment or limitation in either function or ability.

On the other hand, transplanted organ and other organ function can slowly improve over time, reproductive success can be restored, and the composition of the microbiota changes favorably after transplantation. Transplant recipients are not incapacitated, but re-capacitated by transplantation. Organ function can steadily improve with time, sometimes over a period of many years.

Therefore, the transplant recipient does not have health, but at the same time does not have disease in the organ, at least in the tradition of Scadding and Boorse. If anything, new function and life expectancy emerge in the organ and the recipient. Like all others, transplant recipients can of course never be truly healthy even if we set aside all other organ function, since organ replacement is simply considered one phase along the spectrum of serious organ disease.

Disease and Health in the Transplant Recipient

The transplant recipient is prone to many different disease processes. At the same time, the immune system is central to health and disease after SOT. Many of these disease processes link to the altered immune state that the new environment creates. Immune process alteration results from the disease that caused organ failure in the first place, the location of the organ transplant itself, the presence of drug molecules that alter the immune response, and the presence of microbes that also affect the immune system. All of these serve to create a dynamic, continuously shifting milieu within the transplant recipient.

The primary goal of clinical medicine is to discover the mechanisms of disease and enable cures, and to achieve health. Discovering mechanisms of disease exceeds discovering entities in importance; discovery of a bacterium is rarely significant unless that bacterium links mechanistically to some disease process. Direct causal links to disease processes are very difficult to establish, and the murkiness of the transplant environment further impedes finding causal links to disease processes. As a result, there is a tendency

in clinical medicine to use the labels of disease processes from non-transplant states to the post-transplant state. However, this transposition of terms really reflects an epistemic limitation of taking diseases to be entities rather than processes, when the pathogenesis of those diseases can be quite different after transplantation. Disease is a process that actually consists of multiple processes leading to a common set of phenomena.

New diseases that manifest after SOT may result from the acceleration of preexisting conditions such as heart disease in the recipient. However, many "de novo" diseases occur in transplant recipients, some of which are very rarely or never described in the general population. Links between the immune system and both these categories of post-transplant diseases processes are identifiable. The full mechanism of a disease is often unknown and need not be fully known. A sufficient extent of knowledge about a mechanism may lead to effective therapy or even cure of a disease. Since need drives therapy development, therapeutic success might even impede mechanistic understanding.

I will now return to two processes that commonly occur after transplantation, to help further understand post-transplant disease: acute rejection and infection. These two conditions often balance each other and are immune process-related, so I will discuss them together.

Acute Rejection and Infection

In acute rejection, there is a coordinated effort by the immune system to destroy the organ contained within the confines of the human organism because it has been determined to be a representative of another organism. In this respect, the immune system likens the transplanted organ to an organism. If left untreated, even if the acute rejection process was initially mild, graft failure eventually ensues. *There is a normative component to describing acute rejection because it is inherently undesirable.* However, acute rejection is an expression of a *normal* process even though it affects patient well-being through various symptoms, and affects organ longevity. Acute rejection of a transplanted organ is not a

disease process any more than aging is, even though it warrants prevention and treatment. Just as we should not treat some diseases because their treatment might worsen health, we should also treat some non-diseases because they worsen health. Disease is clearly not the inverse of health.

Opportunistic infection is the paradigm example of immune imbalance. All human superorganisms experience infection, only because survival of an organism requires living in an environment with other organisms. The human organism invariably contacts other organisms, and infection in some instances is inevitable when other organisms cross the structural boundaries of the organism. Latent infections occur when the invading organism, through many possible mechanisms, is able to avoid the immune surveillance of the larger organism it has invaded. Common examples of invading microorganisms include bacteria such as *Mycobacterium tuberculosis* and viruses such as *cytomegalovirus*. Disease is still present in this instance, even if there are no symptoms. Latent infection can be treated before transplantation in anticipation of the emergence of a new human superorganism.

Anti-rejection medication induces immune imbalance, but since it is impossible to quantify the actual level of immunosuppression achieved because there is no instrument for its measurement, we cannot predict the risk for infection with much accuracy. Rough guides such as anti-rejection medication dose (which is often not even titrated to body weight), or blood molecular concentrations are simply snapshots of drug exposure in time and do not directly reflect overall tissue drug exposure. It is also impossible to measure drug exposure at the donor-recipient interface, or the drug exposure to different types of cells, whether they are immune cells or other types of cells. The type of infection seen in the transplant recipient varies, and there are only rough guidelines available to predict the type of infection based on the extent of immunosuppression achieved and the time that has elapsed since the transplant. I will provide one example of an infection for illustration.

Viral infections are important early after the transplant, especially in the period between one and six months post-transplant. This period is when the level of immunosuppression is kept relatively high in order to prevent acute rejection, whose incidence is also high during that time. DNA viruses reside dormant in the body long after initial infection, and sometimes cause trouble by proliferating in the early post-transplant period. BK virus[29] is an example of a DNA virus that normally resides in the urinary tract. Within about three months after transplantation, the virus reactivates in 30-50% of kidney transplant recipients (Bressollette-Bodin 2005, Brennan 2005), and sometimes causes organ failure. Equilibrium between the human organism and BKV obviously existed before the transplant because there was no BKV nephropathy in the native kidneys. The immune system may have failed to contain BKV, or BKV has switched from self to nonself status.

One important observation is that viral infections appear more commonly in the transplanted organ than in the corresponding native organ, even if the environment of immunosuppression in both organs is the same. BKV perhaps understandably has little interest in the failed native kidneys after a kidney transplant. The native organs are not affected. BKV nephropathy is a disease of modern times that Burnet's era did not encounter. Another example of a post-transplant infection is that of cytomegalovirus. Unlike with kidney transplants where the native kidneys are retained, the native liver and lungs are removed when liver and lung transplants are performed. Due to post-transplant immunosuppression, cytomegalovirus causes hepatitis in liver transplants and pneumonitis in lung transplants without affecting the other healthy native organs. These observations indicate that the organism remains intact while the superorganism is disrupted after the transplant, and the immune response is directed towards this disrupted superorganism.

Anti-rejection medication effectively prevents acute rejection, but since the transplanted organ is located inside the confines of the human organism, molecules of

[29] BK virus is named after a patient.

these medications must travel through the recipient's body to reach the organ and the immune cells involved in the immune response. Organ systems having little to do with post-transplant immune reactivity produce "side" effects from immunosuppressive medication. This blunt, non-specific medication exposure of multiple organ systems creates disease processes. The need to prevent disease must balance the need to prevent acute rejection, while remembering at the same time that acute rejection is not a disease process but a physiological process. It does not make sense to reduce the risk of acute rejection to zero percent, for the risk of both medication side effects and opportunistic infections then becomes overwhelming. The balance needed reflects the fine-tuned titration of the degree of immunosuppression required to achieve both goals. Too much anti-rejection therapy invariably causes disease. Yet if acute rejection indicates health, then any move to suppress acute rejection regardless of motivation promotes disease. In fact, drugs used to treat all diseases cause disease. How then do we get past the quandary of having to cause disease to promote health?

To solve the puzzle that immune imbalance poses requires the recognition that *acute rejection is a process of the superorganism and not the organism*. The organism is moving closer to a state of health after transplantation because transplantation restores the function of multiple organs. Physiological processes in the recipient quite distant from the organ become functional again through emergence. The organism therefore clearly benefits from the transplant. However, the organ is not, and can never be, an integral part of the recipient's organism. The organ does not assume the organism's identity. The superorganism recognizes that the transplanted organ has disrupted its integrity, just as a microorganism disrupts the superorganism's integrity when it crosses boundaries and enters the organism. The superorganism does *not* ignore events taking place inside its constituent organisms because the immune system belongs to both the individual and the organism. The immune response appears directed both outwards towards non-organism and inwards towards organism, but these two seemingly opposite directions are really

towards the superorganism in all directions. The seemingly inward direction of acute rejection in the organism is actually an outward immune response to the superorganism. The immune response belongs to the superorganism because the immune system, unlike other organ systems, belongs to the superorganism.

If we are prepared to accept that acute rejection belongs to the superorganism, then the reason behind the problem of side effects seen with immunosuppressive medication becomes apparent. We administer immunosuppressive medication to the *organism*. Side effects belong to the organism experiencing medication-related side effects. Immunosuppression causes infection because the medications abrogate normal immune responses of the superorganism, allowing microorganisms normally present in the individual but outside the organism to enter the confines of one of its organisms. *We need to direct immunosuppression efforts towards the superorganism instead, in a way that the organism accepts the transplanted organ as part of the superorganism.*

Health reflects harmony in the human superorganism and not just the organism. Microorganisms need to remain in their proper place, situated at just the right distance from the human organism. If microorganisms get too close, then they cause pathology in the human organism. If microorganisms keep too far a distance, then they are of little use to the human organism. Immune responses maintain the functional boundaries of its contained organisms and those of the superorganism. Transplantation, through redefining structural and functional boundaries, affects interactions between the human organisms and non-human organisms, and disrupts the human superorganism in the process. Acute rejection and infection further disrupt the already disrupted superorganism. This sequence of events from organism to superorganism within disease processes may apply to non-transplant related disease processes as well.

Post-transplant health will be closer to fulfillment if we can disrupt the human organism without disrupting the human superorganism. Disruption of the organism seems

inevitable because sustenance of the transplanted organ requires its implantation deep within the organism. We also know that transplantation alters the intestinal microbiota in a significant manner. So only technology that "sterilizes" the donor-recipient interface can help to achieve an immune state in which there is still normal immune reactivity through the rest of the superorganism, which still remains essential to health, while at the same time maintaining non-reactivity towards the transplanted organ.

Selective immune reactivity is the cornerstone of transplant tolerance. Transplant tolerance may be achievable if we can determine the means to maintain immune reactivity to non-invasive microorganisms without mounting an immune response, while readily maintaining the immune response to invasive microorganisms. The Equilibrium Model of Immunity (Chiu 2016) may help to guide us in this regard. Also, post-transplant diseases may be the result of our misguided approach to organism and superorganism. It may even be possible to determine that alterations in the intestinal microbiota lead to diseases in transplant patients before we can determine such links in the general population.

Creating the Immune System in the Superorganism

I must support my assertion that the immune system belongs to the superorganism and not the organism. The immune system is an emergent biological system (Cohen 2000b). The immune system is a product of evolution, but the immune system differs substantially from how other human organ systems evolved. Other organ systems (the nervous system, cardiovascular system, reproductive system, to name a few) were products of natural selection in the organism, with the current function of these systems presumably being the best suited for survival of the organism concerned.

Yet survival in a broad sense includes both survival in a physical environment and survival in conflicts with other organisms. All organ systems are arguably concerned with survival in both these contexts, such as the nervous and musculoskeletal systems that are concerned with building homes and hunting for food while avoiding predators, or the

cardiovascular system that circulates blood to and from these organ systems. While other organ systems are mostly concerned with survival in physical environments, the immune system's major concern is with biological environments. Consequently, the organism's own signals drive the development of other organ systems but besides these signals, signals from other organisms also drive development of the immune system. This much seems reasonable, but I propose in addition, based on the example of the phagocyte and amoeba, that *combining different organisms* creates at least some parts of the immune system.

The first immune cell discovered was the macrophage. Metchnikoff championed the macrophage and its mobile version, the phagocyte, as the primary agents of defense in both vertebrates and invertebrates (Cohen 2000b). Macrophages and phagocytes are mainly involved in innate immunity. Once adaptive immunity was discovered, lymphocytes then became the focus of attention, but recently macrophage-lymphocyte communication is considered very important in immune maintenance (Cohen 2000b). *Macrophages closely resemble amoebae in shape, size, and function. They do not look like any other human cell.* Perhaps amoeboid organisms "infiltrated" the human organism at some point in the evolution of the human individual to perpetuate themselves, independent of the rest of the human organism, subsequently finding their way into the germ cell line in the process (Lappe 1997). While this fascinating hypothesis lacks proof, it intriguingly speculates that non-human cells infiltrated the human organism in the past and now serve the human organism by actively responding to biological nonself on behalf of the self.

Macrophages can engulf entire microorganisms like amoebae, and hundreds of macrophages can fuse together to form giant cells to engulf particularly resistant bacteria like *Mycobacterium tuberculosis* (Lappe 1997). This fusion behavior of macrophages is very reminiscent of how *Dictyostelium discoideum* behaves, as discussed in Chapter Two. Macrophage-like cells function as antigen-presenting cells in the human organism. Besides this remarkable analogy of the function of macrophages to that of amoebae, it is possible that other immune cells also originated from non-human organisms. After all, cell

organelles such as mitochondria may also have been originally non-human. Since functionally combining organisms creates the superorganism, it is reasonable to suppose that the immune system also belongs to the superorganism.

How Can We Target the Superorganism Therapeutically?

This discussion brings us back to the original question posed about disease and health: how can we target the superorganism but not the organism to prevent acute rejection, as well as prevent the infections that result from the attempts to prevent acute rejection. How can we access the immune system without harming the organism, and how can we create the true tolerant state? As human superorganisms, we need to account for all our organisms. Health of the organism might still be an unattainable goal, but the closest we might get is to be a healthy superorganism and the closest a transplant recipient might get to this ideal would be to achieve a true tolerant state toward the organ. Health in the superorganism means a state of compatibility among all its organisms, although not necessarily the health of each organism.

Targeting immune cells alone does not seem to be the solution to transplant tolerance because these cells situate inside the organism. Targeting microorganism populations selectively also seems difficult particularly when their profile is evanescent. Matching donors and recipients based on their enterotypes (Arumugam 2011) is one possibility to making progress. An approach of "de-immunizing" the transplanted organ before its implantation by extinguishing its contained antigen-presenting cells, is clearly impossible. Lymphocytes in the gut at the human organism-microorganism interface may be more rewarding targets for intervention than circulating blood lymphocytes.

A current technology that we can examine more closely in terms of a therapeutic target is islet cell transplants, which are used to treat Type 1 diabetes. The smallest transplantable cells are pancreatic islet cells. These islet cells can be "encapsulated" by a physical barrier, excluding immune system components while permitting oxygen and

nutrients to pass through to them (Yang 2015). This approach of islet cell encapsulation is akin to creating an immune privileged site in the organism, but this would not be possible for large organ transplants. Redefining the superorganism can alternatively be achieved by creating "micro-chimeras', by simultaneously transplanting bone marrow from the same donor as the solid organ, although success with this technique has been limited to a few patients followed for short periods of time (Starzl 2008). Simultaneous fecal transplantation might be an alternative option.

The human superorganism is always evolving and this evolution constitutes human biological identity. A consequence of the increased hygiene and less microbial exposure over the past century of human development may be an increased incidence of autoimmune diseases, resulting from the altered microbiota. This is part of the so-called "hygiene hypothesis" (Rook 2012). Suppressing immune reactivity even indirectly therefore can have deleterious consequences for the human superorganism, because it now interacts differently with the environment in which it situates. Although well-being of entire populations of human superorganisms may improve with improved hygiene, this does not uniformly translate into improved overall health for every superorganism taken in isolation.

The human organism is also prone to developing diseases that have little to do with immune causes even if there is intense immune system involvement afterwards (e.g., traumatic injury and subsequent healing), so the human organism-human superorganism distinction will be of little help in refining the concept of those sorts of diseases. Yet there are associations between the microbiota composition and numerous diseases, so invasion by intact microorganisms may not be essential to all disease processes in which the microbiota is involved.

In summary, the concept of the healthy superorganism differs from the concept of the healthy organism. Previous concepts of disease and health over-emphasize the role of

the central nervous system, and require comparisons of organisms to other organisms. By doing so, these concepts also emphasize the importance of the organism over the superorganism. The human organism-human superorganism distinction helps point out that the superorganism can remain functionally integrated while the organism can have a disease. Health of the superorganism is a state of harmonious relationships among all its organisms. We will hopefully develop the ability to guide the human organism and human superorganism selectively towards emergent health processes rather than disease processes, perhaps through an understanding of how biological boundaries are violated and restored in each case.

6.3 Establishing and Maintaining the Healthy Human Superorganism

The Need for a Concept Larger than Superorganism

I have argued that the human superorganism consists of the human organism and all its associated microorganisms, and that disease processes occur when microorganisms cross the boundaries of the human organism. Immunity is the mechanism by which organisms hold together by themselves and with other organisms despite structural and functional boundaries. The immune response protects the integrity of the human organism, and thereby the human superorganism, whenever the relationship between organisms alters. Microorganisms possess their own immunity to which the superorganism's immune system responds. Microorganisms are equal partners in the microorganism-human organism immune relationship. The integrating process of the human superorganism is therefore the human immune response and the sum of the microbial immune responses. Thus, there is an expanded list of processes, both human and microbial, about which our present state of knowledge is deficient.

Listing all the immune processes in the superorganism will be epistemically challenging, and is likely both impossible and unnecessary. Can we then characterize the

immune system's role in maintaining the superorganism by a unifying process? Doing so will require understanding further the entity that such an immune process holds together.

The Human Superorganism as a Distributed Entity

The human superorganism is an entity that contains all the processes displayed by the human organism and its associated microorganisms. Disrupting the integrity of the human superorganism by invading microorganisms leads to disease processes, but these disease processes are located in the human organism based on various symptoms and signs displayed by the human organism, such as a fever, rash, or delirium. It is not however possible to diagnose a diseased human superorganism without diagnosing a diseased organism first.

Acute rejection is the immune response of a disrupted superorganism but it is not a disease process by itself, by virtue of its being only the cause of symptoms and signs in the human organism that are in turn part of other disease processes as well. Therefore, it seems useful and reasonable to consider the human organism as an entity and treat it accordingly when it is diseased. Infections get treated with antibiotics, and transplant rejection is treated with immunosuppressive drugs.

Diseases caused by invasive or toxic microorganisms count as diseases of the human superorganism but we cannot diagnose these either[30], except at the organism level. Identifying a disease process requires identifying the entity in which the disease process is occurring. Diagnosis is simple for the human organism but not the human superorganism. Even the most severe over-proliferation of a microbial species can be diagnosed only when it begins to affect the human organism. Microorganisms are continuously expending and replacing themselves unnoticed. Whether we consider an isolated microorganism or an entire population of microorganisms as an individual, the constant turnover of the

[30] Most symptoms and signs of acute rejection such as pain and fever are easily suppressed with immunosuppressive medication that affects processes in the human organism.

microbiota indicates that the human superorganism is continually being reinvented both in terms of the organisms that compose it and its functional boundaries. As a consequence emergent phenomena constantly arise.

The entity of the human superorganism is obviously much more than what can be described by immune processes, whether they are human or microbial. Body trauma, aging, nutrition, excretion, reproduction, and any other process associated with life constantly alter the human organism. Microbial turnover mirrors the constant turnover of cells in the human organism over time, throughout which the human superorganism persists. The microbial composition also alters with age. The human superorganism persists despite constant cell turnover in the human organism and its microorganisms because it occurs by the *relationship* among cells. In other words, the human superorganism depends on intact functional boundaries established by the immune system. The human superorganism is therefore a distributed entity, akin to a university. Just as educational processes, administrative processes, and research processes define a distributed entity such as a university, immune processes are central to defining a superorganism.

Extending cell-to-cell relationships such as human cell-human cell interactions to the interactions of human cells with microorganisms enables us to further understand what happens when a disease process occurs. The immune system facilitates cell-to-cell relationships among the cells of the human organism as well as between cells of the human organism and microorganisms. Immune cells, besides being key components within the human organism as transducers across biological boundaries, are also therefore key players in similarly maintaining the human superorganism that consists of multiple organisms. Immune cells are the only human cells that can fulfill this role because they are qualified to do so by their multi-organism origin. Cardiac myocytes, neurons, hepatocytes, the vascular epithelium, and perhaps all other cell types can act only within the confines of the human organism.

It would be a mistake to equate the processes sustaining the human superorganism with life itself. The human organism consists of *non-living* cells and tissue as well. Non-living cells and tissue, besides undergoing turnover as living cells do, maintain functional relationships among themselves and with living cells. Non-living cells and tissues also display processes enabling them to persist through time. We need to account for the *relationship* among living cells, dead cells, and non-living structures in the human superorganism, in which all cell types can be either healthy or diseased. We possess not only diseased living cells, but healthy dead cells as well. Dead cells and non-living structures[31] do not react, but can cause reactions in living cells. The functional relationships among cells are biological processes and they all end at some point, when the entities themselves end.

It would also be a mistake to equate the human organism-human superorganism distinction with a soul-body dualism. All biological processes must ultimately be explainable by mechanisms. The human superorganism is a distributed entity about which our mechanistic knowledge is limited, but the immune system's reaction and responses might be a good place to start looking for mechanisms. The chief output of the immune system is immunity, through a mechanism that includes inflammation, which is my next topic.

Inflammation as an Integrating Process

In my dissertation, I discussed species, organisms, individuals, and superorganisms. I then examined boundaries, emergence, disease, and health. Based on the work of Cohen (2000b), I propose that inflammation is ultimately the mechanism that holds the human organism and the human superorganism together to preserve biological personal identity. Inflammation is more than just the immune response; unlike an immune response, it is

[31] Non-living cells are synonymous with dead cells, because they were once living cells. Non-living structures, on the other hand, were never alive.

more easily measurable throughout the body[32] even though its stimulus is local. Inflammation is a larger process than the immune response because it also includes tissue and organ healing, which are processes that follow the immune response.

Some amount of inflammation is always present in the body, waxing and waning in intensity. The immune system is an important enforcer of the structural and functional boundaries of the human superorganism, and inflammation provides those boundaries with the flexibility to tolerate disruption and then re-establish. There are obviously significant species differences in how superorganisms are held together, but these differences exist only because the mechanisms employed may differ across species.

Disease processes may result from misguidance that can occur at any one or more of the steps along the inflammatory pathway. Misinformation results not only from mimicry of human tissue content such as RNA or DNA brought about by invading microorganisms. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the initial inflammatory process, and to initiate tissue repair. These three processes can occur simultaneously. Cell injury and necrosis are physiological processes, as long as they are kept within reason. Likewise, tissue repair is physiological. Conversely, excessive cell injury and necrosis are pathological, and excessive tissue repair can be pathological since it can lead to organ fibrosis, hypertrophic scars, and in the worst cases, result in keloids forming and invading normal tissue. Both the innate and adaptive immune systems regulate inflammation, and in turn, inflammation regulates both self-maintenance and defense (Cohen 2000b). Inflammation is intimately involved in the healing from wounds and repair of tissues. Inflammation occurs in the parts of the body that need it most even though it is systemic in nature. Inflammation also relates in its mobilization to both biological (cellular) and physical (molecular) entities, even though it is a biological process.

[32] A non-specific surrogate serum biomarker called C-reactive protein, synthesized by the liver, is often used to measure inflammation. However, other biomarkers, both positively and correlated with degree of inflammation can be used.

Organ transplantation creates inflammation because it elicits a greater need for asserting the biological self. In the case of transplantation, the origin of information is the human organism-human organism interface, which corresponds to the self-nonself interface. A molecule messages other effector components of the immune response, whether they are cells or other molecules, and of either donor or recipient origin. The immune system thereby engages in "discrimination and dialogue" as part of its normal function (Cohen 2000b). Discrimination and dialogue are just other words for information. Biological boundaries cannot co-exist in a location together without accompanying inflammation to communicate across those boundaries.

The physical location of the interface between the donor organ and the recipient does not change, since the solid organ obviously does not move around inside the body. This interface is accessible, is reasonably stable in duration, and is deliberate, since it engages the immune system at a known point in time. If we are able to understand all the processes at this interface, then we just might be able to take a snapshot of the process of the immune recognition, and the initiation of inflammation. Other interactions occur of course throughout the body between cells and invading microorganisms. However, it might be simpler, since microorganisms have a much short lifespan, to study the interface of the solid organ instead. The peptides presented by the antigen-presenting cells activate the T lymphocyte, but these cells are again just entities. The cumulative sum of all the processes at the antigen-presenting cell-T lymphocyte interaction might reflect the process of the immune response and inflammation, particularly if the antigen-presenting cell represents another organism, having crossed over in evolution from another species. In short, inflammation at the immunological synapse is the glue of the human superorganism.

The difference between normal repair and disease processes depends on the intensity of inflammation and its timing; however, the immune cells involved are identical in both cases (Cohen 2000b). The immune system "examines and repairs the self" (Schwartz 2000) but this implies that the self is an entity, and an entity separate from the immune

system. More accurate might be an assertion like “the process of the immune reaction contributes to the process of maintaining the superorganism”.

Inflammation is a bidirectional like immunity: it directs inwards towards routine body maintenance and outwards as a defense against pathogens. Inflammation is the means of communication across structural and functional boundaries and is the sum of all human and microbiota responses involved in immunity, *as well as* those of tissue repair. Tissue repair is considered a distinct process from immunity (Eming 2009, Laurent 2017). The immune response can either favorably or unfavorably affect the repair response (Eming 2009). A transplanted organ is not just an entity representing another organism, but it is also an *injured* organ, in need of repair, and so there are *two* distinct reasons for the immune system to demonstrate a high degree of interest in the transplanted organ.

The immune system does not just perceive the organ as a danger, but it perceives it also as an adopted child, which now needs the repair of its boundaries. A transplanted organ always sustains some degree of damage during the transplantation procedure. The human organism is also damaged during the surgical procedure. Both the invader and the invaded cells promote inflammation (Zhang 2010). Macrophages, whose origins I have posited as being non-human, play an important role in tissue repair (Wynn 2016). Transforming growth factor-β is a key molecule involved in healing, but it also causes scarring of the transplanted organ. Immunosuppressive drugs such as cyclosporine, which contribute to transplant success by preventing acute rejection, enhance transforming growth factor-β production and cause scarring of the organ. We suppress transforming growth factor-β with anti-rejection medication such as cyclosporine because rejection is considered inherently undesirable, even though rejection is a healing process.

The distinction between helpful and harmful immunity is relative and shifting. Inflammation is simply the physiological output of the immune system (Schwartz 2000).

What more can transplantation teach us about the human superorganism?

Until now, I have extensively discussed how organ transplantation informs the human organism-human superorganism distinction. In this last subsection, I will include some additional thoughts about transplantation and the human superorganism.

Transplantation brings the self-nonself distinction into sharp focus because transplantation breaches existing boundaries while creating new boundaries, causing immune responses in each case. The functional boundary defines the domain in space and time within which the processes of the superorganism occur. Establishing boundaries for new entities such as an organ transplant recipient creates the additional challenge of ongoing self-nonself discrimination. Self-nonself discrimination expresses differently in different organs; some organ transplants are more easily rejected than others and therefore require more intense immunosuppression to prevent rejection. Therefore, biological personal identity need not express itself uniformly throughout a biological entity, but can express itself in some parts more than others.

Transplantation radically alters the boundaries of the human organism and the human superorganism, and so both need to readjust their processes to persist through time. Transplantation shows us that a disease process is disarray in the superorganism, which is a distributed entity. Human superorganisms differ from one another not because the cells which they produce are different, but because the molecular expression of those cells is different, indicating that the underlying processes of each human superorganism differ as well, however slightly. These different cell processes reflect in the wide variety of the major histocompatibility complex (MHC) molecules they produce. MHC, again an entity like the cells that express them, is the most prominent expression we know of the biological self, and is the expression of the self with the most clinical applicability. Human superorganisms are even more diverse than human organisms.

Transplanting immune cells from one human superorganism to another, performed in bone marrow transplantation, can lead to serious graft-versus-host disease if performed against MHC matching rules. MHC is so varied because combining organisms (i.e., sexual reproduction) creates new biological information about the organism, and each organism is different both genetically and epigenetically. Bone marrow transplantation is an extreme form of MHC recombination and so great care is taken to avoid MHC mismatch. The extent of alteration in the composition of the microbiota and the proliferation of harmful bacteria like *Escherichia coli* (Eriguchi 2012) in bone marrow transplantation may dictate the severity of graft-versus-host disease further indicating graft-versus-host disease, another form of acute rejection, belongs to the superorganism and not the organism.

The transplant recipient is continually in an inflammatory state. This inflammation is true of autoimmune diseases as well. In all cases of inflammation, scarring is the end-result, and so all transplanted organs scar. Inflammation is a mechanism of correction; the immune system takes on the transplant challenge as its predetermined function of a correction and readjustment of the self-process. Our current knowledge of inflammation limits our understanding of the superorganism. We use limited tools such as the serum C-reactive protein concentration to measure inflammation that are remarkably non-specific. However, these markers are always measurable, even if they lack accurate correlation with inflammation. Specific cytokines may be more helpful to determine activation of certain types of immune cells, but what we really need instead are better biomarkers to distinguish autoimmunity from alloimmunity. Transplant recipients have a higher C-reactive protein concentration than “normal”, but this increased concentration is not always obviously pathological.

Just as inflammation is required for organ rejection, inflammation is also required for immune tolerance. If tolerance in the transplant recipient equals health, then inflammation is required for health as well. Tolerance is a process that contributes to the health process of all organisms and superorganisms. Improving success with tolerance

protocols will require a more refined understanding of not just the human organism-human superorganism distinction, but of inflammation as well. Inflammation, even though it is a process of the superorganism, is still expressed by the organism, and will therefore be an achievable concept for a full understanding. Transplantation provides the "time zero" for the start of inflammation as well as the interface to study inflammatory responses. A tolerant patient may have either more or the "right kind" of inflammation. The organism constantly communicates with the transplanted organ, which represents another organism now within the superorganism. If communication among the parts of the superorganism can be better understood, then it may be possible to achieve tolerance to the organ similar to how tolerance to non-invasive microorganisms is achieved, because health is an emergent process arising from the mode of arrangement of the superorganism's parts.

While there is hope for achieving transplant tolerance, there is less hope in my view that xenotransplantation will ever be successful. Differences in cell processes and the mechanisms by which structural and functional boundaries are maintained across species are simply too great. The extent to which a pig needs to be genetically modified means that it can no longer be a pig, Pig cells can be modified to the extent that there is no immune responsiveness to those cells, but for pig cells to be accepted by the human superorganism as being unworthy of a forceful immune response causing rejection, the cells would have to be modified to the point of being incompatible with a pig's own life. Pig cells would need to be altered to the extent that many basic cellular processes would no longer be possible. Mutations in human cells can only occur to a limited extent before life becomes impossible. Severe errors in basic cell metabolism and respiration are invariably fatal. Inflammation reigns supreme in severe organ rejection because it is physiological towards the organ even though it leads to disease processes elsewhere. Every living entity displays inflammation in the presence of every other living entity.

The boundaries of the superorganism are never distinct, implying that both the self and the nonself are continuously changing. There may be differential rate of change of the

self and nonself, and so the balance between self and nonself ultimately becomes the primary determinant of whether a health or disease state exists. Molecules in the body constantly switch between self and nonself status (Grignolio 2014). The teleology of the immune system is preserving fitness of the superorganism. Self and nonself are merely the token assignments of the biological self that are accessible to us. Biological processes other than immune processes may be part of the biological self as well. Both the psychological and physical accounts of the self are equally compelling (Howes 2000). I have emphasized the physical self in my dissertation.

The metaphoric self-nonself terminology is still required so that we may understand the working of the immune system (Howes 2000). The self-nonself terminology is also required so we may better understand emergent health and disease. The human superorganism contains ongoing processes that change with evolution. "Self" was first introduced by Burnet in 1940, and self-nonself distinction in 1949 (Tauber 2000). Both these terms persist in the immunology literature due to their heuristic utility to scientists.

A theory should be heuristic and explanatory. A theory should act as a guide for experimentation, serving as a template around which we can rationally introduce specific interventions or therapies. Given the inaccessibility of the donor-recipient interface where inflammation first occurs, scientists attempt to reproduce the interface in the laboratory. We capture the specificity of the immune response not through what it recognizes but in how it responds (Cohen 2000b). Immune responses and inflammation are our best-known determinants of biological personal identity: what it means to be an organism, species, and individual. Transplantation gives us the location and the self-nonself interface.

I will conclude by reconciling the phenomenon of organ transplant rejection with the clinical need to prolong the life of the patient with organ failure. Rejection preserves the human superorganism in both cases: it is a defense against the transplanted organ and microorganisms. Since the immune system belongs to and protects the human

superorganism, enabling the superorganism to persist through time, the immune system does not consider preserving the organ transplant in its mechanisms. The organ transplant is treated as just one more organism in the superorganism. Rapid microbial turnover indicates that the persistence of any one of its organisms is not specially prioritized. Therefore, organ transplant rejection is compatible with prolonging life by recognizing that the immune system belongs to the human superorganism. All other organ systems adapt to a new organ because they are part of the same human organism; the immune system cannot because it is part of the human superorganism.

Transplanting organs in a manner compatible with preserving the human superorganism and not just the human organism will be more effective in maintaining biological personal identity, where transplant tolerance alone indicates a fully restored biological personal identity. By understanding that organ transplant recipients are not just non-transplanted patients with an extra part, but are newly emergent human superorganisms, we can understand both post-transplant health and disease better and we can also possibly target our therapies more effectively.

Chapter Seven

Summary and Conclusion

Medicine is largely concerned with the diagnosis, causes, and treatment of disease. In my dissertation, I intended to demonstrate that a new technology in medicine, organ transplantation, informs philosophical concepts such as human beings, organisms and superorganisms, emergence, and disease and health in new ways. I also intended to demonstrate conversely that philosophy, which is a discipline from the humanities, has the potential to inform medical practice, which is based mostly on scientific principles. The extant philosophical view of the human being as a single organism is no longer tenable. Rather, the current biological-philosophical view of the human being as a functionally integrated, emergent human superorganism in which the human organism is the largest constituent appears much more tenable.

I started by distinguishing between evolutionary and physiological individuals, and developed the concept of physiological individual further by describing the interactions of the human organism and its structural boundaries with microorganisms, to create the human superorganism with its functional boundaries. I then extended that idea by looking at the somewhat similar interactions between organ transplants and the human organism. I examined the nature of biological structural and functional boundaries, and provided some science of the immune system to determine the means for communication across biological boundaries. Immune responses result from the interaction of boundaries, and act to preserve and restore boundaries in the form of inflammation. Inflammation provides the biological information of restoration. By reestablishing boundaries, biological self-organization is preserved. I also showed that violating biological boundaries triggers emergent properties in the organism once these biological boundaries are reestablished after disruption. Organ transplantation intervenes on biological boundaries, and creates novel forms of emergence not seen with other forms of boundary interventions. The

success of organ transplantation might be improved and even extended into new areas such as transplant tolerance and xenotransplantation if the human superorganism is taken as the target of therapy rather than the human organism alone. We may even be able to guide the human organism and human superorganism towards emergent health processes rather than emergent disease processes if we understand the nature of the relationship between boundaries and emergence.

I will now provide a summary according to the highlights of each chapter. I will also discuss the limitations of my dissertation, along with topics that I think are ripe for future philosophical inquiry.

Summary

In Chapter One, I provided an outline to human biological personal identity. I explained how human beings differ from other species and from each other. I also related how human beings are able to transform themselves using means not available to other species: through solid organ transplantation. I showed that organ transplants are able to transform human beings outside evolutionary constraints, leading to improved health and prolonged life, but in the process also setting up an apparent conflict with the immune system whose role is to preserve the integrity of biological entities. I described two important limitations of solid organ transplantation: the shortage of available organs and post-transplant disease, both of which relate to mismatched organ donors and recipients, and the workings of the immune system.

In Chapter Two, I introduced the superorganism as a biological entity consisting of physiologically integrated organisms of the same or different species with different lineages. I first described the concepts of species, organism, individual, and superorganism in the biological world in turn, while highlighting the controversies around each method of categorizing living beings from the philosophy of biology literature. I provided several examples from nature to discuss why the distinction between organism and individual is

not always clear-cut. I discussed one useful method to distinguish types of individuals from the available literature to help move past this controversy: I emphasized the distinction between the evolutionary individual and the physiological individual. I explained why the physiological individual is more useful to further study the biological human being by using analogous models from nature. I proposed that the term *superorganism* replace *physiological individual* because the former term better distinguishes a multi-organism entity from an individual, which might be evolutionarily defined, of multiple lineage, unicellular, a part of a cell, or even non-living.

In Chapter Three, I explained how the biological human being consists of the human organism derived from species-specific DNA, and the intact microbiota, which together with the human organism constitutes the human superorganism. Humans are superorganisms because the human body consists of the human organism physiologically integrated with numerous microorganisms. The localization of superorganisms in space and time is defined by their boundaries. There are structural and functional boundaries to the various components of the organism and the superorganism. The microbiota is required for the health of the human superorganism, and disease processes result when microorganisms violate the boundaries of the human organism. Biological boundaries are real boundaries, and must hold intact for organisms to co-exist. I gave the example of fecal microbiota transplantation to show how a technically simple therapy can improve human health when we understand the concept of boundaries and the human superorganism. I explained that the concept of superorganism is more appealing than that of a community in describing the human superorganism because of the superorganism's inherent tendency towards disunity and entropy. I also explained why transplanting animal organs (xenotransplantation) is unlikely to be successful unless we include the superorganism, i.e., both the organism and the microbiota, in our mechanistic considerations. All human biological concepts relate to either the human organism or the human superorganism.

In Chapter Four, I started by describing how mechanisms are important to understanding phenomena such as the establishment and maintenance of superorganisms. I described the immune system, immune reaction, and immune response, and discussed how the immune system through its output of immunity is the means by which communication occurs across intact boundaries. The immune system establishes and maintains biological boundaries. I explained how organ transplantation violates the boundaries of the human organism, and leads to immune responses in the human superorganism because the immune system, unlike other human organ systems, belongs to the human superorganism, serving to maintain the human superorganism through time. I related how the human superorganism emerges from immune reactivity and immune responses. I drew an analogy between the innate immune response to microorganisms and the adaptive immune response to organ transplants, discussing the interactions among human organism-microorganism, human organism-human organ transplant, and organ transplant-microorganism, to show that expected post-transplant phenomena such as organ transplant rejection and infections result from structural and functional boundary violation and restoration. I explained why post-transplant complications such as acute rejection represent success for the human organism but failure for the human superorganism. Clinical problems such as organ rejection are physiological and serve to reestablish the boundaries of the organism. Biological information locates in molecules, and information transmits across boundaries separated from each other. I described how we might access biological information at the donor-recipient interface, and more specifically at the antigen-presenting cell-T lymphocyte interface, the immunological synapse. Transplant tolerance is not only the prevention of rejection, but the active exchange of the correct type of information across boundaries.

In Chapter Five, I described the native organ as one part of a whole, and the transplanted organ as a new part of a new whole. I discussed why the output of the immune system is the mechanism to maintain the relationship of the part to a whole though tags,

attachers, and communicators. I explained that emergence results from structural and functional boundary disruption, and follows the consequent process of boundary restoration in reestablishing biological self-organization. Both organisms and superorganisms contain a multitude of emergent processes. I discussed some emergent phenomena unique to the transplant recipient, including increased longevity and organ function as well as improved cognitive function, and compared emergence after organ transplantation with emergence after other life events. Biological emergence results from self-reorganization, and therefore new biological personal identity, whenever real biological boundaries are violated. Emergence is always occurring in the human organism and human superorganism, more predictably from the addition of matter, but less predictably from boundary restoration. Organ transplantation adds to our knowledge of the relationship of biological boundaries to emergence by its location inside the organism, timed boundary disruption, and its emphasis on prioritizing the maintenance of internal structural over external structural boundaries for successful emergence to occur.

In Chapter Six, I reviewed the limitations of some current concepts of human disease and health. I discussed how to consider disease and health as processes of the human superorganism, not just the human organism. I showed that successful transplantation challenges normative accounts of disease and health. Understanding the human organism-human superorganism distinction can help inform the discussion about the nature of health and many types of disease. I explained organ transplantation as a therapy of the human superorganism, which is a distributed entity. However, we direct post-transplant management towards the organism instead, and cause treatment side effects. We also direct the therapy of organ rejection towards the human organism. To improve post-transplant outcomes, we must direct our treatment toward the human superorganism, for which I described some possible methods. Even though transplanted organs do not function at their full efficiency, the function of the human superorganism improves overall. I described how immune imbalance leads to rejection on one hand and

infection on the other, but reducing the risks of both requires their balance rather than elimination. I then described inflammation as the measurable physiological output of immunity in the human superorganism. I explained how inflammation might be heuristically useful in understanding how to maintain the integrity and identity of the human superorganism by tissue repair in both infection and after organ transplantation. By understanding that organ transplant recipients are more than just non-transplanted patients with an extra part, but are newly emergent human superorganisms, we can understand both post-transplant health and disease better and also possibly be able to target our therapies more effectively.

In sum, I have brought a new perspective into an understudied area in the philosophy of biology and medicine: the metaphysics of organ transplantation. To understand the ontology of the human superorganism, we need to understand biological boundaries in the superorganism, since this is where communication occurs by immune processes. The extant philosophical and biological views of boundaries have been limited to the nature of biological hierarchies and the members of those hierarchies such as *species*, *organism*, and *individual*. The cell membrane is viewed as a structure essential to life and as the outer boundary of the organism. The philosophical understanding of emergence in individuality, such as the evolution of multicellular organisms from unicellular organisms and the development of superorganisms, rests on immune functions. In my dissertation, I have developed this view much further by bringing into consideration an existing medical technology, solid organ transplantation, for the evaluation of boundaries, emergence, and biological personal identity. Through considering the available evidence, I analyzed the human being as a human superorganism, and demonstrated through analogy the relationship of microorganisms and organ transplants to the human organism, and between microorganisms and organ transplants themselves. In the process, I showed the importance of the immune system in emergent phenomena in the human superorganism. I discussed that biological emergence rests on the disruption and

reestablishment of biological boundaries through the actions of the immune system, and that novel phenomena emerge in unique situations such as organ transplantation. I also demonstrated how a philosophical understanding of boundaries and emergence might help improve post-transplant outcomes and extend transplantation science into new areas such as transplant tolerance and xenotransplantation.

Limitations of the Dissertation

In my dissertation, which focused on organ transplantation, I did not discuss at any length some equally fascinating forms of function and dysfunction of the human organism and superorganism, including autoimmune disease and cancer. Autoimmune diseases and cancer are two groups of very serious disease processes afflicting the human superorganism. Biological research in those areas is rapidly advancing, and these sets of disease processes will hopefully be some day curable, but they manifest deep within the confines of the human organism and cannot ethically be intentionally elicited in human superorganisms in the way that organ transplantation can. I chose organ transplantation as my example for studying the human superorganism because unlike other conditions, organ transplantation is an established and successful therapy for serious disease but not a disease process itself. Organ transplantation engages the immune system at a known point in time, and provides us with an opportunity to examine the self-nonself interface at the immunological synapse, analogous to the microorganism-human organism interaction.

There are many other post-transplant diseases such as diabetes, hypertension, malignancy, and many specific infections; although I could not address these diseases at any length, the omission of their description from this dissertation does not diminish their importance to post-transplant health. I discussed bone marrow transplantation only briefly. The philosophically rich post-transplant phenomenon of graft-versus-host disease seen after bone marrow transplantation exemplifies the bi-directional nature of the immune response, and its study will complement my project with solid organ transplantation well.

I have also deliberately excluded other means of studying forms of personal identity besides biological identity, including by neuropsychological, social, and legal constructs. There are clearly many other methods to study personal identity, even in transplanted populations (Sharp 1995, Svenaeus 2012). Alternative methods of describing a human being are without doubt as philosophically interesting as describing the human being through biology. In particular, I excluded accounts from a body of literature that blurs the biological and phenomenological to produce a theory of embodiment. Feminist embodiment theorists advance the notion of "leaky" bodies and boundaries. For example, one feminist philosopher describes the human body to be permanently open to its surroundings and capable of being composed, recomposed, and decomposed by other bodies (Gatens 2000). Another contends that scientific discourse, which forms the core of my thesis, is inseparable from the means by which we understand and live our bodies (Richardson 2006). Nonetheless, careful scientific inquiry is an indispensable part of feminist inquiry into culture, history, and language (Wilson 1999). Feminists contend that the boundaries of neither the subject nor the body are secure (Shildrick 1997). Complete understanding of personal identity therefore requires an understanding of biological personal identity combined with an understanding of other forms of personal identity. It is likely that boundaries in some form are important in forms of personal identity apart from biological personal identity.

I believe, however, that even though there are many ways to understand the human being, the biological human being emphasized in this dissertation will be of most interest to philosophers of science and medicine because the human being is a product of biology; all other human experience follows from this fact.

Achieving human health is a great motivator for scientific and philosophical inquiry, and understanding the position of the human organism in relation to other organisms is where the search for human health and biological personal identity should begin.

Conclusion

A study of organ transplantation can inform the philosophy of biology generally and the nature of the human organism-human superorganism distinction especially. The human organism-human superorganism distinction can guide therapeutic advances to specifically enhance post-transplant health and ultimately human health in non-transplant situations. The paradox of having to improve human health and extending human life by confronting the immune system resolves when we consider the immune system part of the human superorganism and not part of the human organism.

The immune system with all its mechanisms is the means for communication across biological boundaries, both structural and functional, through its output of immunity. Biological boundaries are constantly breached and reestablished, and this continuous cycle leads to emergent properties. Inflammation provides the biological information of self-reorganization and restores boundaries. Biological information can be captured at boundaries. In the case of the human superorganism, the immunity-mediated relationship between the human organism and its microorganisms enables its persistence through time, but capturing biological information is difficult because the human superorganism is a distributed entity, and the relationship between microorganisms and the human organism is fleeting. Solid organ transplantation deliberately breaches biological boundaries that are then reestablished, and so can provide the timed experimental evidence that boundaries relate closely to information and emergence, as well as biological personal identity.

To improve post-transplant outcomes, we must treat the human superorganism instead of the human organism. Success in challenging areas such as transplant tolerance and xenotransplantation requires understanding structural and functional biological boundaries in the human superorganism, the processes that sustain biological boundaries, and through the disruption and reestablishment of these biological boundaries the emergence of other favorable processes.

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