The Foundations of Immunology and their Pertinence to Medical Interventions

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Do not let yourself be tainted with barren scepticism.
—Louis Pasteur

We are drowning in information, while starving for wisdom.
—Edward O Wilson

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

PREFACE

This book has two aims: to influence immunologists in how they think about the immune system and to provide a text that is both accessible and engaging to non-specialists. I imagine non-specialists to include medical students, clinicians and members of the general public. I have been told that successful books are those for which the author has a well-defined target audience in mind. I wish to express upfront why I feel it important to go against such advice in this case.

The scientific research culture has dramatically changed over the last few decades. The increased investment, since WW II, in many fields of science, including immunology, has led to what can be referred to as the information overload. Many argue that this information overload has impeded the evolution of foundational concepts (1-4). Researchers are simply too busy to assimilate the implications of all the new findings. Some argue that these circumstances inevitably lead to an "ossification of the canon" (2). I have argued this is not necessarily so (5). The feelings and considerations leading to this contrarian view have inspired my writing of this book. A consequence of the "ossification of the canon" is the accumulation of paradoxes in the context of the currently popular and dominant frameworks (5). A focus on finding and resolving these paradoxes leads, I suggest, to novel frameworks of ever broader plausibility and applicability, thus transcending the information overload (5,6). To experience this transcendence is inspiring. I believe a focus on, and description of how foundational scientific concepts have evolved, allows one to encapsulate these concepts and their rationale. Such a description makes the foundational ideas accessible to the non-specialist. Such a description serves as a platform for discussion by all and so enables the further evolution of the canon. My agenda for this book is to achieve such a description. I hope the above considerations explain why I anticipate the book will be of interest to specialists and non-specialists alike. I feel there is a story to tell.

I hope a few more philosophical considerations will allow all readers to appreciate the vision underlying the contents of this book. I begin such considerations with the question of whether there is a highly developed scientific method, resulting in certain knowledge, or whether science is just the sophisticated expression of everyday exploration and reasoning? It

might seem surprising to raise this as the first question in the book. However, I believe its consideration will provide both immunologists and the interested non-specialist with confidence that they can understand the ensuing discussion of ideas on how the immune system operates and their relationship to medicine (6, 7). Moreover, a consideration of this question has both inspired the science I do and provided me with the motivation to write this book.

Science has led to knowledge of which we can be surprisingly confident. For example, there are prescriptive manuals on how to calculate the strength and stability of different kinds of bridge. These manuals are the result of past scientific endeavors. However, they reflect technical information rather than current scientific enquiry. When science is so successful that it can be reliably used for practical purposes, we recognize that it has given birth to technology. Large manuals are written. When consulting such a manual on bridges, few question the basis of the knowledge on which the strength and stability of different types of bridge are calculated. Such manuals are usually only accessible to specialists.

Current bridge manuals are based on Newtonian physics. From a modern perspective, they are strictly speaking invalid. No modern physicist thinks about the physical world primarily in terms of Newtonian concepts. This example illustrates the difference between practical utility and live scientific enquiry, where in principle nothing should be taken for granted, and the struggle to have valid foundations is paramount.

The history of science teaches us that the framework in which our scientific knowledge is cast needs to be changed, often radically, when foundational paradoxes are recognized. This is most apparent when scientific theories have evolved to be remarkably successful in their accounting of a wide body of natural phenomena but are also found to be strikingly deficient in some other respect, for example, being incompatible with some well-established observations that are expected to be explicable within the theory's mandate. Alternatively, the theory may be unsatisfactory by being in conflict with some principle appealing to investigators. The history of physics of the last century is replete with such scenarios. However, anyone familiar with the history of other scientific disciplines, immunology included, can see the same kind of pattern. The persistent reader will recognize such scenarios in the pages that follow.

A moral can be drawn from these considerations. No scientific method can be employed to mechanically crank out certain knowledge. If there is no

such method, how is science different from everyday reasoning and exploration? The most significant science is usually done within the context of a contemporary culture. We have learnt from the giants of science and of philosophy just how subtle and significant reasoning and the exploration of ideas, whether through experiment or thought, can be. I argue that such an appreciation is an essential component of scientific culture, with the result that subtle arguments are seriously considered and paid attention to by the scientific community. This culture also reflects the virtue of making and testing predictions of different frameworks to assess their utility in understanding nature. To relive the past experiences of science, by becoming familiar with its history, is empowering. It is appropriate to refer to such collective empowerment as the culture supporting scientific endeavors.

Different scientific styles lead to different types of contribution. Some contributions, made within the context of a generally accepted framework, explore the framework's utility to account for the breadth of known and of new observations. To follow in detail the arguments of such contributions often requires considerable training in the discipline and extensive knowledge of the field. The extreme form of such contributions is like employing a prescriptive manual for building bridges. Such considerations are certainly not readily accessible to the non-specialist and can even be daunting to the specialist with a slightly different area of expertise

At the other end of the spectrum are contributions that challenge the nature of the currently accepted solutions to basic issues of the field, and that propose novel solutions. These high-risk potential contributions typically either fall flat with time or can result in a dramatic reorientation of research. This has happened in the last fifty years of immunology a few times, as I shall relate.

It is perhaps not surprising that basic issues are rather few in number, because they are foundational. The proposed solutions to these issues provide the axioms or framework on which explanations are developed. Indeed, foundational studies require the ability of the investigator to identify what issues are truly basic and whose solutions are consequently seminal.

A consideration of foundational ideas does not require a detailed knowledge of all the observations that the framework can explain, nor of the technical developments on which such explanations are based. Foundational ideas can usually be simply expressed. Moreover, an appreciation of just one clear and simple paradox can show a framework to be unsatisfactory, requiring a re-examination of the framework's foundations. Thus, the considerations

involved in addressing foundational ideas are open to understanding by a non-specialist with only moderate knowledge.

In the recent past, by which I mean the period of two hundred to one hundred years ago, western science was inevitably much more foundational than much of today's science. It was less developed and so more accessible to the non-specialist. We are in the era cursed with overspecialization. Charles Darwin's foundational *Origin of Species*, published in 1859, was accessible to the broadly educated individual. This was a time when gifted individuals could attain a valid grasp of diverse aspects of the culture in which they lived.

This book describes how foundational concepts of immunology have evolved over the last two and a half centuries. It traces how, in the late 1700s, Jenner established a safe means of vaccinating against smallpox, and how this success in public health led, in the 1800s, to the establishment of two new sciences, immunology and the study of infectious diseases. These advances led to a characterization of immune responses in the late 1800s and early 1900s. The Clonal Selection Theory, developed in the 1950s, was formulated to explain how some of these major characteristics could be realized at a mechanistic level. It is no accident that this formulation occurred at roughly the same time that molecular biology was becoming established. This new science had a decisive impact.

The Clonal Selection Theory inspired an explosion of studies in the field for the next three decades. Later investigations tended to examine the minutiae of the system and led immunologists to view the immune system as extremely complex. This assessment was fostered by an exponential increase in the number of immunologists and their publications.

This book is an update of an earlier one (7). Both books attempt to transcend contemporary overspecialization by returning to and focusing on foundational concepts. I anticipate this feature will make this book accessible to interested clinicians and non-specialists. Most today consider the immune system to be highly complex. I believe that a focus on foundational concepts reveals the immune system to be sophisticated. By this, I mean that its limited complexity can be understood to serve physiological needs, and so the need for this complexity becomes understandable; these features are then seen as sophistication on the part of Mother Nature and of evolution. I shall deal with some controversial foundational concepts and will sometimes argue for ones that have not found favor or have been abandoned by the immunological community at large.

I wish to make a final comment on style. I have striven to achieve accessibility, brevity, and clarity. The clarity I seek here is at the conceptual level. I do not, for the most part, attempt to justify concepts in terms of extensive observations that support them, or by comprehensively delineating observations that conflict with opposing concepts. I employ observations more to illustrate concepts than attempt their rigorous justification. This might be regarded as constituting more of a poetic than of a scientific approach. Circumstances allow me to be comfortable with writing a book in this style. I have justified most of the concepts elaborated upon here on a more documented and observational basis in my more technical book, *Rediscovering the Immune System as an Integrated Organ* (8). The references here are primarily chosen for their conceptual contributions to the field. I refer herein to my more technical book simply as *Rediscovering*.

I conclude this Preface with an admission. I thoroughly enjoy focusing on foundational ideas rather than discussing at length the observational pros and cons for different views. I hope the text conveys my enthusiasm. I am also excited. A change in perspective could, I believe, have a dramatic impact on world health. I hope some readers will share this vision and help to bring it into reality.

Finally, I wish to express my gratefulness to two colleagues, Preston Dennett and Ted Steele, who gave me careful comments on an earlier draft. I and the final text benefited from these comments. However, I did not incorporate all their suggestions. I wanted to keep the text as short as possible consistent with it being accessible and not misleading. Their help should not be construed as their agreement to all that is said.

A NOTE ON TECHNICAL TERMS

My teaching experience has led me to try to develop ways of minimizing the barriers that technical terms present in achieving a valid understanding. This book has a glossary at the end, but it does not provide definitions of terms used. Instead, it notes the page(s) in which the term is defined and its use shown in context. The term, when first used in the text and its meaning explained, is ***bolded and italicized***. I believe it is critical to use terms as precisely as possible to foster clear discussion and understanding. However, precision is only possible in a context, and so definitions can become somewhat elaborate, circular, and so not absolute. I hope this way of defining terms in context will facilitate the reader's understanding.

ABBREVIATIONS

BSA	bovine serum albumin
Co	costimulatory
CoM	costimulatory molecule
CoS	costimulatory signal
CTL	cytotoxic T lymphocyte
DAMP	danger-associated molecular pattern
DC	dendritic cell
DTH	delayed-type hypersensitivity
HIV	human immunodeficiency virus
HSA	human serum albumin
Ig	immunoglobulin
MHC	major histocompatibility complex
mIg	membrane immunoglobulin
PAMP	pathogen-associated molecular pattern
PLL	poly-L-lysine
PPD	purified protein derivative
SRBC	sheep red blood cells
TcR	T cell receptor

CHAPTER 1

HOW THE IMMUNE SYSTEM WAS DISCOVERED AND ITS ATTRIBUTES RECOGNIZED

Circumstances leading to the exploitation of immunity and to the birth of the science of immunology

Smallpox was, in the 1700s, a prevalent and deadly disease in Europe. It is estimated that sixty of every hundred Englishmen were infected, of which twenty died and twenty bore the everlasting scars that often followed infection. Voltaire reported in the mid-1700s on practices in China and the Middle East whereby protection could be achieved against smallpox. Material was harvested from the crusts of the pocks of an infected individual, and this material was administered by a prescribed method to a healthy individual, with the aim of protecting them from subsequent disease. This process led to the death of one in a hundred of the individuals so infected (9).

Milkmaids, according to folk knowledge in England at this time, were protected against smallpox through exposure to cows suffering from cowpox, a disease similar to the human variety. In the late 1700s, Edward Jenner started systematically vaccinating against smallpox by exposing individuals to material obtained from cowpox lesions. He scarified the skin before exposing the individual to this material. This process resulted in reliable protection against smallpox, with no untoward consequences.

This landmark of western medicine was followed about fifty years later by the studies of the German, Robert Koch, and the Frenchman, Louis Pasteur. Their work over a number of years provided a context for understanding Jenner's success. They demonstrated that some diseases are caused by infectious agents. This demonstration required Koch and Pasteur to isolate the causative pathogen, to find conditions under which they could grow the pathogen in the laboratory, and then to show that infection of an animal with the organism resulted in the symptoms characteristic of the disease.

One animal model used by Pasteur was chicken cholera. This bacterial disease results in various symptoms, including violent diarrhea. Pasteur had found conditions under which he could grow the responsible bacteria in the lab. On returning from a summer vacation, he found a plate on which the bacteria had grown. He had accidentally left this plate on his laboratory bench. Pasteur discovered that these bacteria, when injected into chickens, would no longer cause disease. The bacteria had lost their ***virulence***. However, infection with these bacteria could protect against a subsequent challenge of bacteria virulent in unexposed chicken. The bacteria had, over the summer holidays, become ***attenuated***. Following this chance finding, Pasteur developed different means of culturing pathogens under conditions less than optimal for their growth, resulting in their attenuation. An attenuated pathogen could be used to protect against the corresponding infectious disease. Pasteur called this process ***vaccination*** in honor of Jenner's discovery with cowpox virus, also called vaccinia virus. The name vaccinia is derived from vacca, the Latin for cow (9).

Two further findings made in the late 1800s were seminal and can be seen as the culmination of the discoveries that led to the establishment of two new and related sciences, immunology and the study of infectious diseases. First, Roux and Yersin reported in 1888 that the bacteria-free supernatants of cultures of diphtheria bacilli could cause the symptoms of the disease. This finding led to the recognition that some bacterial pathogens cause disease by their production and secretion of ***toxins.*** In time, it was found that toxins could be chemically or physically treated in such a way that they were no longer toxic. Such modified non-toxic molecules are called ***toxoids***. They can be used to vaccinate individuals against a normally pathogenic challenge of the toxin. The treatment thus "attenuates" the toxin (9).

The second seminal finding arose from an attempt to characterize the nature of the protection provided by vaccination. Von Behring and Kitasato attempted to determine if there are protective molecules in the blood of immune animals. They drew blood from an animal immune to tetanus toxin, allowed it to clot, and harvested the honey-colored, cell-free serum. They reported in 1890 that a naïve animal, given serum derived from an immune animal, is resistant to a normally lethal challenge of tetanus toxin (9), see Figure 1.1.

This demonstration led to the conclusion that components in the humor, the non-cellular component of blood, were responsible for protection. These protective molecules were called ***antibodies***, and their presence is referred to as ***humoral immunity***. Substances recognized by antibodies are called ***antigens***.

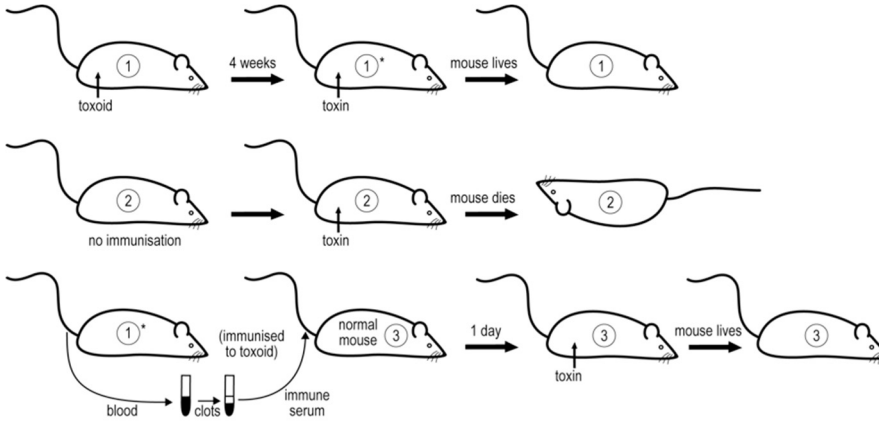

Figure 1.1 Passive transfer of humoral immunity

These investigations led to an explosion of important discoveries. Immunology as a science was born.

The immune system's four attributes

Innate and immune defense mechanisms

All forms of life, from single cells to multi-cellular organisms, have mechanisms of defense to protect them from the environment and from foreign invaders. Immune systems are a unique form of defense only found in vertebrates. We refer to the evolutionary older mechanisms of defense as ***innate defense***. Vertebrates have both innate and immune defense mechanisms.

Four attributes of immune systems distinguish them from the systems of innate defense. I first outline the nature of these four attributes. Understanding them is essential to appreciate the uniqueness of immune systems. This recognition will provide a context for analyzing how these attributes are realized. The understanding so gained will provide a conceptual foundation to devise strategies for the prevention and treatment of clinical conditions in the five areas of medicine related to the immune system.

i) The immune system's adaptability

Innate mechanisms of defense are present either at the time of an insult or are mobilized within minutes. These mechanisms are said to be ***constitutive***,

that is, part of the constitution of the organism as always present. The expression of the defense mechanisms of the immune system is, in contrast, regulated. Immune responses are said to be ***adaptable***. This adaptability is evident in three distinct forms of regulation of the expression of immune effector mechanisms.

Firstly, it takes days if not weeks to develop effective immunity against a foreign invader. Secondly, the Greek Thucydides, the first recognized western historian, noted in about 500 BCE a different form of immunological memory. He recorded that individuals who had survived a previous epidemic were resistant to becoming ill during a similar epidemic, often occurring decades later. He reported that those who had previously survived the plague could tend the sick with impunity. This observation reflects a prevalent finding. The immune systems of animals and people usually respond much more rapidly and with greater intensity on a second than a first infection by the same pathogen. It is said that the ***secondary immune response*** generated upon a ***secondary infection*** is greater than the ***primary immune response*** generated upon a ***primary infection***. This form of adaptability is different from that associated with a state of immunity. It reflects an enhanced ability to *generate* a potent state of immunity. Secondary immune responses are both more rapid and larger than primary responses. This memory response is the basis of most vaccination, as we shall shortly see.

A third form of adaption is different from the previous two. The first two reflect ***positive memory*** in that they reflect a state of immunity that takes time to develop, or an enhanced ability to generate such immunity. It turns out that previous exposure to an antigen can, under some circumstances, reduce the immune response to a subsequent exposure to this same antigen. Such a state is usefully referred to as ***negative memory***. We shall later consider the physiological significance of adaptive forms of negative memory.

ii) The immune system's specificity and universality

It was shown in the late 1800s that antibodies are fairly specific. When honey colored and transparent, cell-free serum is obtained from an animal immune to tetanus toxin and is added to a transparent solution of this toxin, the mixture goes cloudy. This precipitation is due to interactions between the antibody and the toxin molecules. This phenomenon is referred to as the ***precipitin reaction***. When anti-tetanus toxin antibody is added to diphtheria toxin, no precipitate forms. Thus, the interaction of antibody with antigen

expresses some specificity.

Landsteiner, in the early decades of the 1900s, found a means to raise antibodies to small, organic molecules whose structures had been elucidated in the late 1800s (10). A molecule able to induce the formation of antibody is said to be ***immunogenic***, capable of generating an immune response. Landsteiner showed that when he chemically coupled a small molecule, the size of a benzene ring or two, to an immunogenic protein and immunized rabbits with this conjugate, he could raise antibodies able to bind this small molecule. The small molecule is called a ***hapten*** and the large immunogenic molecule, to which the hapten is coupled to raise anti-hapten antibody, is usually referred as a ***carrier***. Thus, anti-hapten antibody can be raised by immunizing with a ***hapten-carrier conjugate***.

Landsteiner also examined whether these anti-hapten antibodies could bind to other small molecules whose structure was closely related to the hapten. He found most often that the antibodies were less able to bind the related molecule. Landsteiner's observations led to the recognition of the highly specific nature of antibody/antigen interactions. An everyday analogy of key and lock is often employed to appreciate this ***specificity***, with antibody binding to antigen likened to the fact that keys usually only open their corresponding locks.

A second aspect of the antibody response became apparent from Landsteiner's work. Antibody could be raised to virtually any small foreign molecule that organic chemists devised. This remarkable ability of the immune system is referred to as ***universality***. It appeared that the immune system was able to respond to the unexpected and unanticipated. To illustrate how remarkable this attribute is consider a key shop that has keys to all locks now existing and to all possible locks, some of which have not yet been invented! We will later see how universality is achieved.

The exquisite specificity of antibodies and the universality of the immune system must mean that the immune system has the capacity to produce an incredible number of distinct antibody molecules. It is estimated that humans and vertebrates can each produce billions!

iii) Self-nonself discrimination

All defense systems have an ability to preferentially attack foreign invaders rather than self-cells or molecules. This attribute is referred to as ***self-nonself discrimination***. The mechanisms by which innate defense and immune systems achieve self-nonself discrimination are radically different.

Self-nonself discrimination by innate defense mechanisms

It is evident that the ability to distinguish ***self*** from ***nonself*** has to rely on properties that distinguish self from nonself cells and molecules.

There are receptors in non-vertebrates, as well as in vertebrates, called ***pattern recognition receptors (PRR)***, which can bind to ***pathogen-associated molecular patterns (PAMPs)***. These PAMPs are present on infectious pathogens, and often also on their benign counterparts, but are not present on self-cells or molecules. Consider an insect as an example of a non-vertebrate with only innate mechanisms of defense. The different PAMPs it encounters can be regarded as flags characteristic of different classes of invaders, such as viruses, bacteria, or protozoa. The interaction of the insect's PRR with a PAMP initiates an attack by the insect upon the PAMP-bearing invader.

This kind of self-nonself discrimination is realized because the PRRs bind to structures uniquely present on foreign but not on self-cells or molecules. The PRR are nearly always proteins. The particular proteins an organism produces are determined by its genes. Genes thus directly define most of the PRRs, and the PRRs recognize PAMPS expressed by some nonself but not by self-entities. Thus, the ability to discriminate nonself from self is ***germline encoded***, in other words, due to the nature of the organism's genes.

Self-nonself discrimination by the immune system

Consider how self-nonself discrimination might be achieved by the immune system. An attribute of the immune system is its universality—the ability to respond to virtually all foreign molecules. This means that an individual grafted with a kidney from his non-identical sibling can reject it, as this sibling has different genes from the individual. In the luck of the draw that occurs at conception, the grafted individual could have inherited the genes that make his sibling's kidney foreign. In this case, these antigens would have been self. This example illustrates that an individual has the ability to respond to something that could have been self. We therefore conclude that we have the intrinsic ability to respond to self-antigens. In order to achieve self-nonself discrimination, this intrinsic ability must be ablated, or somehow held in check. This tolerance towards self-antigens is not germ-line encoded, but the result of an ***adaptive process***. The nature of the adaptive process leading to self-nonself discrimination by the immune system is thus radically different from the germline encoded mechanism of innate defense.

There must be properties distinguishing self from foreign antigens if the immune system is to reliably respond to these antigens differently. Burnet and Fenner suggested in the late 1940s that the property that distinguishes self from foreign antigens was their first appearance early in development (11). Support for this idea came from the studies of Hasek (12) and Medawar (13) and their colleagues in the early 1950s. It was found that the deliberate exposure of developing animals to a foreign antigen could ablate the ability of the animal, as an immunologically mature individual, from making an immune response to this antigen. It thus appeared that *early* exposure to a foreign antigen, in the *life history* of an animal, could result in the animal's immune system regarding this foreign antigen as a self-antigen. This idea is referred to as the ***Historical Postulate***. This acquired unresponsiveness to an antigen is a form of negative adaption on the part of the immune system, as the ability to respond to self-antigens is ablated.

iv) Immune class regulation

The recognition that there are distinct classes of immunity grew out of Koch's attempts to develop a treatment for tuberculosis in the late 1800s.

Koch had isolated from tissues of tuberculosis patients the causative pathogen, ***Mycobacterium tuberculosis,*** and found conditions under which he could grow these bacteria in the lab (9). Koch tried to stimulate the patients' immune system by injecting them with a protein preparation obtained from *M tuberculosis*, called ***purified protein derivative (PPD)***. Such treatment led to inconsistent results; in some cases, it appeared to lead to an improvement in the patient's condition and in others to a rapid deterioration and sometimes even to death (14,15). Koch had to abandon this experimental treatment.

However, Koch made a seminal discovery during these studies. He observed a particular kind of inflammation on injecting PPD into the skin of his patients. He saw reddening and a swelling at the site of injection that first became apparent at twelve hours post-injection and peaked between twenty-four and forty-eight hours (9). This inflammatory response is referred to as ***delayed type hypersensitivity (DTH)***, distinguishing it from acute inflammation. ***Acute inflammation*** is observed within minutes following the injection of antigen into the skin of an individual allergic to the antigen, as we shall shortly see. This latter inflammation is referred to as reflecting ***immediate hypersensitivity***.

Studies in animals demonstrated that DTH is a highly specific reaction, similar to the specificity of the antibody/antigen interaction. Studies also showed that, in contrast to humoral immunity against a toxin, a state of DTH could *not* be conferred upon a naïve animal by giving it serum from an immune animal. It was surmised that cells are needed to mediate the DTH reaction. It was not possible to test this idea until the 1940s when inbred strains of various experimental animals, such as inbred strains of mice and guinea pigs, were developed. Mice and guinea pigs of the same sex and same strain are genetically identical, and are said to be ***syngeneic***, meaning having the same genes. In this case, cells can be transferred between syngeneic animals without the recipient making an immune response against the donated cells. With the existence of inbred strains, it was possible to show that a naïve animal would express DTH if given cells, but not serum, derived from a syngeneic animal that had been immunized to express DTH (16). Thus, DTH is mediated by cells and is referred to as a form of ***cell-mediated immunity***.

It might be thought that the immune system would direct all the weapons in its arsenal against a foreign invader. Diverse observations in both animals and people show this not to be the case. The immune system has a decision-making mechanism that determines whether a cell-mediated or humoral response is induced. We refer collectively to all the processes that determine the class of immunity induced as ***immune class regulation***. We shall see that understanding the basis of such regulation is central to devising strategies of immunological intervention in many areas of medicine related to the immune system.

The significance of immune class regulation: recruiting different mechanisms of innate defense

Immune systems first appeared, evolutionarily speaking, in vertebrates. The animals from which they arose had innate mechanisms of defense. The immune system exploits these evolutionarily older mechanisms. I outline four such mechanisms as a prelude to illustrating how the immune system commandeers them.

Single cell amoebae have the ability to ingest some other single cell organisms and then destroy them. They use the resulting small molecules to build their own larger molecules. This process of taking in other organisms is appropriately likened to eating and is called ***phagocytosis*** from the Greek *phago*, meaning I eat. All multicellular organisms have specialized cells

with similar functions, and these defensive cells are called ***phagocytes***.

A second form of innate defense is mediated by a group of molecules called ***complement***. Complement has diverse functions, one of which is to insert a donut-shaped assembly of molecules into the membranes of invading cells, including those of bacteria. Moderately sized molecules can pass through the doughnuts' holes, leading to the bacterium's death. Figure 1.2 shows an electron microscopic photograph of a bacterial membrane with holes caused by complement.

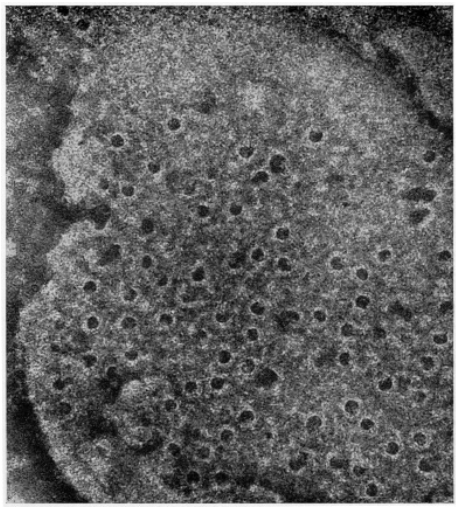

Figure 1.2. Holes in a bacterial membrane produced by complement.

A third mechanism of innate defense is responsible for the inflammation that occurs when we get a substantial scratch on our skin. The redness around the scratch forms within one minute and the scratch will, if substantial, swell along its length within several minutes. Nerve cells close to the skin's surface, which respond to pressure, release a substance when the scratch is made. This substance activates ***mast cells***, resident close by, to release several substances, one of which is called histamine. Histamine in turn causes nearby blood vessels to dilate and become leaky, leading to inflammation along the length of the scratch. This inflammation results in fluid containing protective molecules and cells, including phagocytes, to accumulate at the site of injury and deal with any invaders. This process is called ***acute inflammation***, to distinguish it from delayed-type hypersensitivity, which is a different form of inflammation.

Lastly, cells infected by viruses trigger the production of ***interferon***. This is secreted by the infected cells and induces neighboring cells to produce anti-viral proteins that interfere with viral replication, thereby protecting them.

The structure of antibodies

A knowledge of the structure of antibodies is essential to understand how they commandeer innate mechanisms of defense to attack an invader. Understanding the process of commandeering is central to explaining the full significance of immune class regulation.

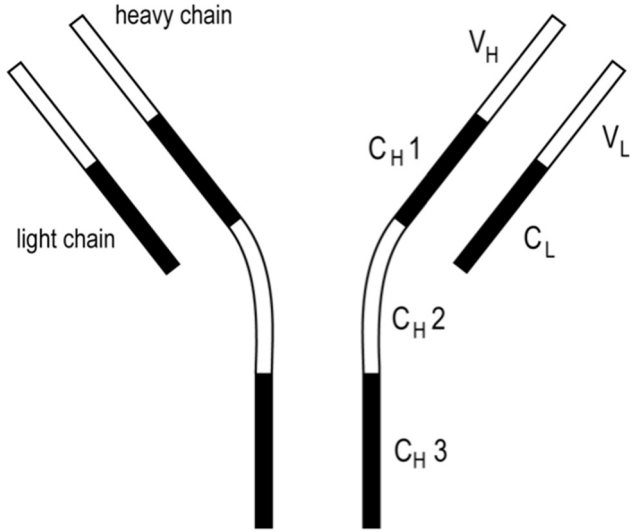

Figure 1.3. The prototypical unit of an antibody molecule

Antibodies are proteins, and all proteins are made up from polypeptide chains. The prototypical antibody unit consists of two identical light and two identical heavy chains, and thus has two identical halves, as shown Figure 1.3. The antibody chains themselves are made up of distinct ***domains***, represented in the figure as contiguous white and black regions. Each domain contains about 120 amino acid residues. Light chains have two domains, while some heavy chains have four and others have five. The first domain of the light and the first of the heavy chain are called the variable domains, as there is much variability between the corresponding domains of different antibody chains. These two variable domains are close together in space and interact to form the binding site of the antibody that interacts

with antigen. Thus, the prototypical antibody unit, shown in Figure 1.3, can bind two antigen molecules, meaning it is divalent.

There are seven types of heavy chain in people, as defined by their different constant domains, and seven classes/subclasses of antibody. The nature of the constant domains of an antibody molecule's heavy chain defines the class or subclass of antibody to which the molecule belongs. The classes are IgM, IgA, IgE, and IgG, the latter containing the IgG_1, IgG_2, IgG_3, and IgG_4 subclasses.

Molecules belonging to the IgM class consist of five prototypical units, and so have a valency of 10 (2x5). The IgE and IgG molecules all contain just one unit, and so are divalent. IgA molecules can consist of one or more units, but the number is variable.

The function of antibodies

The reason why these classes and subclasses of antibody are so important is that they activate different effector functions. For example, IgM is efficient at activating complement, leading to the lysis of a cell to which it is attached. IgE molecules do not activate complement but bind to ***mast cells*** and, when they interact with antigen, the mast cell degranulates, resulting in release of histamine and other substances, which in their turn initiate a local and acute inflammatory reaction around the site where the mast cells are degranulated. IgA is predominantly induced by *chronic exposure* at ***mucosal surfaces***. These are internal surfaces of the body to which access is possible without disruption of the skin. Examples are the lungs, the gastrointestinal tract, and the urogenital systems.

IgA does not activate known effector functions such as acute inflammation, complement, or phagocytosis. The IgG subclasses have different and diverse activities, such as facilitating phagocytosis and initiating the activation of complement to lyse cells to which the antibody is attached. Moreover, these different classes and subclasses of antibody are optimally produced under different conditions. We shall see how significant such differential production is in understanding different clinical conditions.

CHAPTER 2

THE IMMUNE SYSTEM'S PERTINENCE TO MEDICINE

Five areas of medicine are related to the immune system. I now list them and give an indication of why I think an understanding of the basis of immunological tolerance and immune class regulation is so medically important. I argue that such an understanding will likely provide a platform to develop strategies to prevent and treat clinical situations in each of these areas.

Autoimmunity and transplantation

In the early 1900s, Paul Ehrlich raised antibodies against the red blood cells of one goat by injecting them into another goat. The antibodies so raised reacted with the red blood cells of the donor goat but not with the red blood cells of the recipient. This finding struck Ehrlich. It led him to suppose there must be a mechanism to prevent immune responses against self-antigens, leading to the attribute now known as self-nonself discrimination. He surmised, if this were not the case, that the immune system would be a greater internal threat to an individual than all external threats (17).

Ehrlich's views were shown to be prescient in the late 1930s, when it first became clear that some diseases were due to an immune attack against parts of the patient's own body. Such damaging immune reactivity is referred to as ***autoimmunity***. One of the earliest autoimmune diseases to be recognized was ***autoimmune hemolytic anemia*** (18). In this disease, antibodies are produced against the patient's own red blood cells, resulting in their destruction. The patient thus becomes anemic. Other common autoimmune diseases are ***autoimmune diabetes*** and ***multiple sclerosis***.

A second area of medicine related to the immune system is transplantation. We will have a much better chance to prevent autoimmunity and immune rejection of a graft, or intervene to ameliorate such immune responses once they have occurred, if we understand how antigen acts differently to ablate