

## UNIT I

# Sense of Being: The Concept of Self and Self/Nonself Recognition

ΓΝΩΘΙ ΣΑΥΤΟΝ (*“Know thyself”*)

Words originally inscribed in gold on the pronaos of the Temple of Apollo at Delphi

This dictum—short in length but deep in meaning—encapsulates a basic need for all forms of life.

In a way, most organisms in our world live alone. They are composed of single cells or particles, and as such, their need to distinguish themselves is seemingly simple. Their single cell or particle is “*I*,” and all else is “*them*.” They need to sense which of “*them*” is appropriate to mate with or perhaps to congregate with, but otherwise their version of self is limited by their own membrane.

Multicellular organisms faced a new problem as they evolved. They gave up some of their independence to reap the advantages of being part of a greater whole—an organism composed of multiple semi-independent units. Initially, any such unit was pretty much like every other one within the greater structure, so extending the concept of self to include others that were essentially identical was perhaps a relatively small leap. “*I*” became “*us*” but only as multiples of “*I*.” As organisms became more complex and the different cells within a single organism began to engage in a division of labor, they generated an array of cells with different forms and functions. Distinguishing “*I*” or “*us*” from “*them*” became increasingly complex: *Is that adjoining cell, which seems so different from “I,” really a part of “us,” or is it an intruder from “them”?*

The development of commensal arrangements between organisms (e.g., moss and fungi combining to form lichens, humans and normal bacterial flora in the gut and on the skin) required yet more questions: *If there is an intruder, does it represent a threat or can it safely be ignored? If it represents a threat, what should be done to eliminate it?*

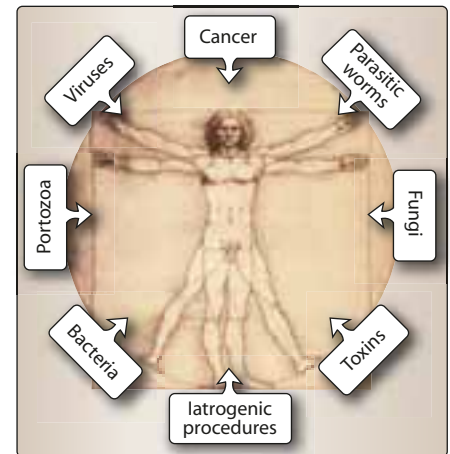
These questions are the starting points from which the immune system operates. The human immune system utilizes a variety of methods to ask and answer these questions. Some of these methods have been widely used for eons; others have been developed more recently by more restricted groups of organisms. This unit introduces how the human immune system deals with these questions.

# The Need for Self Recognition

## I. OVERVIEW

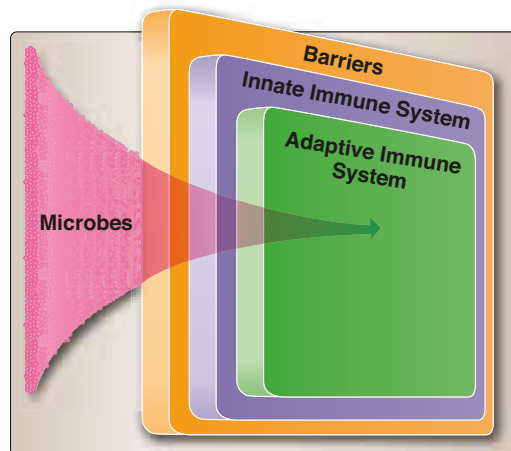
A wide variety of organisms and their associated molecules pose a constant threat to the human body. The human immune system—the defensive mechanisms that identify and neutralize these threats—is able to distinguish “**nonself**” organisms and molecules from “**self**,” that which belongs within the body (Fig. 1.1). Threats may enter the body from the outside (e.g., infectious organisms or toxic agents) or may arise from potentially harmful changes occurring within the body (e.g., the malignant transformation of a previously normal cell into a cancer cell). Fortunately, the immune system consists of three layers of defense (Fig. 1.2). The first line of defense is provided by a set of mechanical, chemical, and biologic barriers that protect the body. If these barriers are breached, the second and third lines of protective systems are activated: first the innate immune system and then the adaptive immune system.

The innate and adaptive immune systems utilize cell-surface and soluble receptors to sense potential threats. These receptors of the innate and adaptive systems are generated in different ways, however, providing a major distinction between the two systems (Fig. 1.3).



**Figure 1.1**

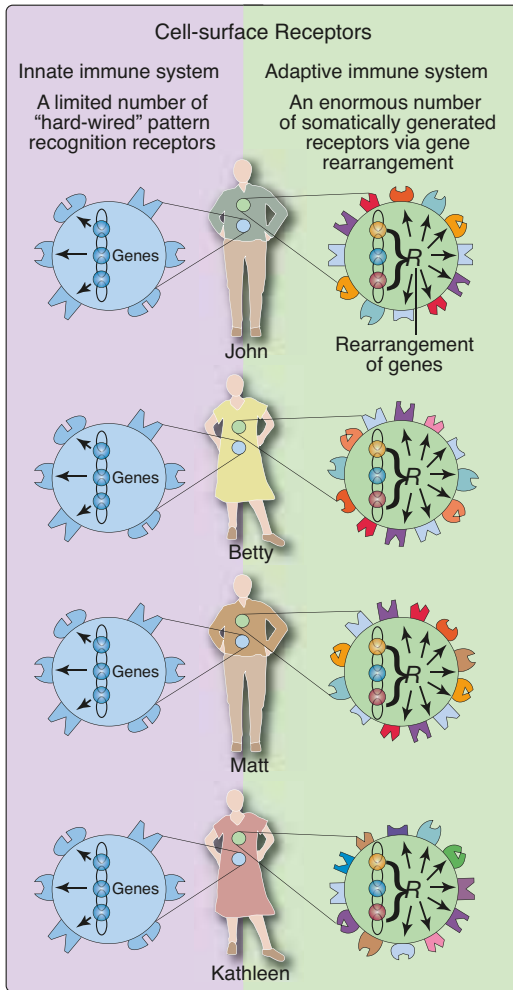
Threats to the individual. The body is continuously exposed to many infectious agents, cancerous cells, toxic molecules, and even therapeutic drugs.



**Figure 1.2**

Protection from and response to microbial invasion. Initial protection is provided by a set of barriers. When breached, invading microbes trigger the innate immune system and, if necessary, the adaptive immune system.





**Figure 1.3**

Innate pattern recognition receptors and adaptive somatically generated receptors. Each individual expresses pattern recognition receptors (innate immune system) and somatically generated receptors (adaptive immune system).

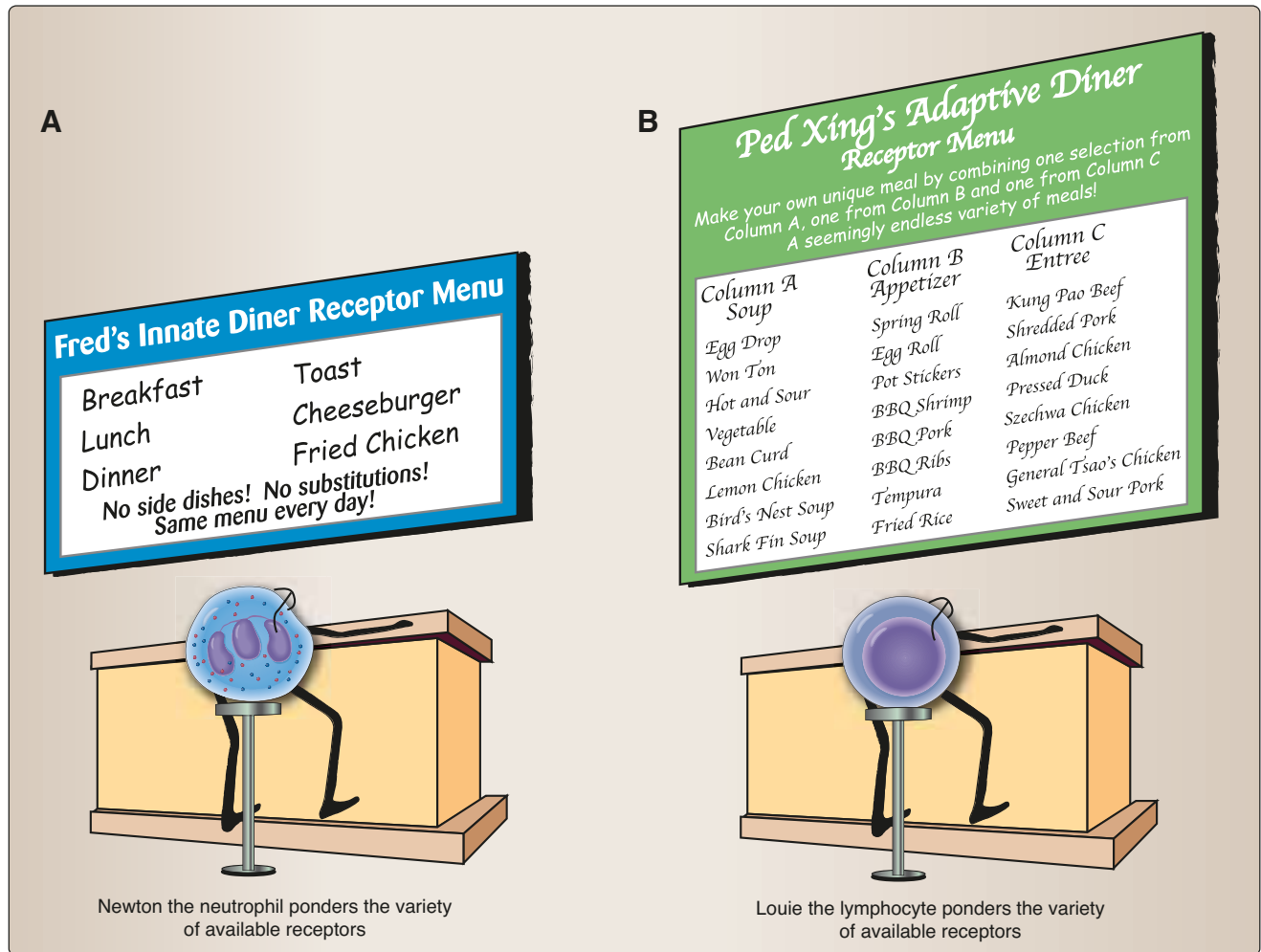
Some receptors recognize and bind to self molecules. Other receptors recognize and bind to nonself molecules. Some receptors for nonself are limited in number and are “hard-wired” in the genome, common to all normal individuals. They specifically detect molecules produced by a wide variety of other organisms (e.g., molecules commonly found on bacterial cells but not on human cells). These “common” receptors, called **pattern recognition receptors** (PRRs), number perhaps a hundred or so and are part of the **innate immune system**, the second line of defense (Fig. 1.4A). Cells and molecules of the innate immune system respond rapidly to a microbial invasion and are often sufficient for defense.

The **adaptive immune system** (Fig. 1.4B), with its unique cells and molecules, is the third level of defense against these potential threats to the body, following the barriers and the innate immune system. Bone marrow-derived and thymus-derived lymphocytes (B cells and T cells, respectively) generate distinct receptors during development. Each lymphocyte randomly generates a unique receptor through the rearrangement and rejoining of a relatively small number of genes into a “combination gene” encoding the receptor. These receptors, called **somatically generated receptors**, are generated randomly prior to any contact with self or nonself; the process is described in detail in Chapter 8. By combining multiple genes, therefore, each individual can generate enormous numbers of B and T cells, each with a unique receptor. A subsequent process, in which the receptors are uniquely vetted by each individual, results in the retention of a set of receptors that is individualized to that particular self and his or her nonself environment. In addition, the initial responses of the cells of the adaptive immune system to a given threat or stimulus can lead to enhanced or depressed responses during subsequent encounters with the same threat or stimulus. This ability to modify the immune response to substances encountered on multiple occasions is the basis for **immunologic memory**, one of the hallmarks distinguishing the adaptive from the innate immune system.

Both the innate and adaptive immune systems involve a variety of molecules and cells. Some of these are unique to one or the other system, while some contribute to both innate and adaptive responses. For example, cells of the innate system can act by themselves to resist infectious organisms. But some of them are also critical for activation of cells in the adaptive system and can in turn have their activity elevated and directed by activated cells from the adaptive system.

The immune system employs several defense mechanisms against foreign agents: killing them, consuming them, and isolating them. Many of these mechanisms also involve the proliferation of relevant host cells, following recognition of the intruders, to provide sufficient numbers for defense. Like many biologic systems, the immune system employs redundancy—multiple mechanisms with overlapping functions—to ensure that if one mechanism is not effective, another may be.

Through time, hosts and microbes have repeatedly changed their tactics. Some microbes have developed means of evading some immune responses. Hosts, in return, have developed additional defensive strategies. These strategies could eventually be evaded by some microbes. These new microbial innovations again drive development

**Figure 1.4**

Diversity of receptors of the innate and adaptive immune systems. **A.** Receptors of the innate immune system (pattern recognition receptors) are limited in number and diversity and are consistent from one normal individual to another. **B.** The somatically generated receptors of lymphocytes in the adaptive immune system use random combinations of genes to assemble a very large number of different receptors.

of yet additional defensive mechanisms, and so on. Thus the relationship between host and microbe is essentially an ever-spiraling arms race.

## II. THE IMMUNOLOGIC CONCEPT OF SELF

If you were to describe what makes you unique as an individual, you might list the attributes you possess (e.g., eye, hair, and skin color, blood type). You might also list or imply the attributes you would never have (e.g., lipopolysaccharides, hemagglutinins, feathers, scales, wings). The immune system makes similar distinctions. For example, the hard-wired receptors of the innate immune system have been selected over

evolutionary time only to recognize nonself molecules whose presence indicates an intruder, such as the lipopolysaccharides found on the surfaces of numerous types of bacteria. On the other hand, the highly variable receptors of the adaptive immune response, generated anew within certain somatic cells of each individual, recognize both self and nonself. As a result, the cells that express them must undergo a process of selection or “education” first to learn what self is for that particular individual, then to consider (by default) that all other elements constitute nonself.

#### **A. Recognizing self**

Recognition of self is used by the body’s cells to determine whether an encountered molecule or cell has the appropriate structures to show that it is a part of the body. This is important for several purposes. The ability to recognize self enables the cells of multicellular organisms to know whether other cells with which they come into contact actually belong to the same organism and whether interactions with them are safe. In many immune functions, recognition of such self structures among cells is absolutely critical to their ability to interact successfully to carry out some function. These self structures are normally absent from invasive microbial cells and may also be absent from some abnormal cells of the body (e.g., some cancer cells) and from cells of other individuals of the same species (e.g., a transplanted graft).

#### **B. Recognizing the absence of self**

In addition to permitting productive interaction, the absence of such self indicators can trigger an attack upon any cells that lack these indicators. For example, certain cells (natural killer cells) of the innate immune system bear receptors that recognize stress signals expressed by infected or cancerous cells. Using a second set of receptors, natural killer cells then examine the stressed cells to determine whether they possess sufficient levels of a particular set of cell surface molecules called MHC I that should be present on every normal nucleated cell of the body. Cells that become abnormal owing to cancer or certain viral infections may greatly reduce (or eliminate entirely) the expression of these molecules. Natural killer cells can detect this decreased MHC I expression and destroy the abnormal cells.

#### **C. Recognizing nonself**

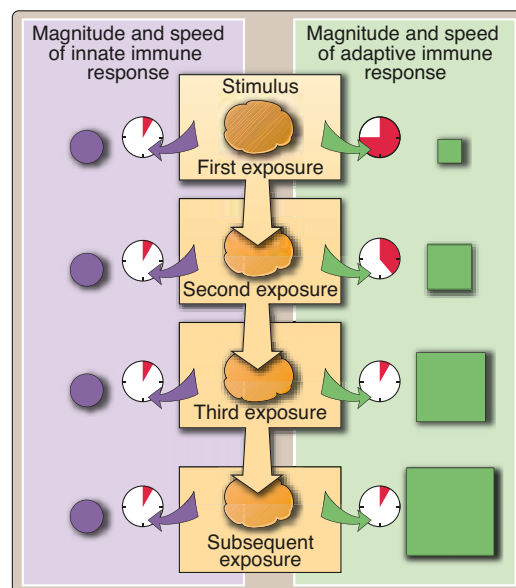
The ability to recognize something that is nonself and has not yet been encountered represents a significant biologic challenge. The immune system meets this challenge through two approaches utilizing the pattern recognition receptors and the somatically generated receptors that were mentioned previously (see Fig. 1.3). The first is a genetically stable set of receptors that has been evolutionarily selected to recognize and bind structures that are produced by distantly related organisms (e.g., microbes) or are produced by host cells in response to stress (e.g., infection or injury). The extremely variable somatically generated receptors of lymphocytes are based on a relatively small number of genes that are routinely transmitted from one generation to the next but are then rearranged somatically within each lymphocyte of each individual to construct a vast and

randomly generated set of receptors, some of which will be capable of recognizing and binding to nonself.

1. **Via pattern recognition receptors:** PRRs are designed to recognize and bind to only nonself structures that are not normally present within the body but are abundant in the microbial world. The structures of these receptors are directly encoded (hard-wired) in the genome. Thus they are transmitted across generations and expressed in each individual within a species in an essentially identical form. This type of recognition is characteristic of the innate immune system. PRRs identify structures that are typically associated with microbes but not with host cells. Some PRRs (e.g., the toll-like receptors) are found on the membranes of various cell types, while others (e.g., complement molecules) exist in a soluble form. The role of PRRs is introduced in more detail in Chapters 2 and 5 concerning the innate immune response.
2. **Via somatically generated receptors:** A subset of white blood cells, the T and B lymphocytes, are the only cells capable of producing somatically generated receptors of the adaptive immune system. Each T or B cell utilizes the rearrangement of DNA (and in some cases, somatic mutation) to develop an enormous number of different receptors. While each cell produces only a single type of receptor able to recognize only a single structure, the total number of such cells undergoing this process permits the development of a pool of receptors capable of recognizing more than  $10^{10}$  different structures. Because each such cell generates its receptor in a random manner, some cells develop structures capable of recognizing self, and others develop receptors capable of recognizing nonself. As a result, T and B lymphocytes undergo processes (“education”) to remove those bearing receptors that could potentially recognize and attack normal structures within the body. In addition, some lymphocytes develop receptors that are not capable of properly interacting with other cells within the body, and these are eliminated as well. Once activated, the remaining T and B lymphocytes can launch powerful and lethal immune responses designed to eliminate nonself cells and molecules.

### III. IMMUNOLOGIC MEMORY

Cells and molecules of the innate immune system treat each encounter with a particular microbial invader as if they were meeting it for the first time. The adaptive system, on the other hand, has the capacity to use the initial encounter with a particular stimulus (e.g., a specific microbe) to modify or adapt its response(s) to any subsequent encounters with that same stimulus (Fig. 1.5). This **immunologic memory** allows the adaptive immune system to tailor its responses to cells or molecules that it encounters on multiple occasions. In some cases, as in common microbes, subsequent responses may be increasingly rapid and vigorous to speedily eliminate the microbes, often before their presence can be detected by other means. In other cases, immune responses may be depressed against other commonly encountered nonself entities, such as harmless cells and molecules present on our skin, in the air we



**Figure 1.5**

Immunologic memory. The innate immune system reacts to a given stimulus with a consistent intensity, regardless of how many times it has been exposed to that stimulus. The adaptive immune system can adapt and modify its response after each exposure to a given stimulus.



**Figure 1.6**

Immune defense mechanisms. The immune system utilizes an arsenal of protective mechanisms to inhibit or destroy invading microbes. The illustration presented includes some of them, and their sequence can vary.

breathe, or in the food and water we consume. Immunologic memory thus provides the body with an ability to deal differently with threatening or nonthreatening nonself.

## IV. DEFENSE MECHANISMS

The immune system is, along with the nervous system and the endocrine system, one of the great communication systems of the body. Most immune responses require successful interactions between multiple cells and molecules.

Once the immune system decides to eliminate a particular threat, it relies on three general approaches. The threat may be isolated, it may be disrupted, or it may be ingested and consumed; or some combination of these actions may be used. Within these general categories, many types of mechanisms are available (Fig. 1.6) to inhibit the spread or growth of microbial intruders or to kill them. Mechanical barriers (e.g., skin and mucous membranes), chemical barriers (e.g., microcidal molecules), and biologic barriers (e.g., the presence of commensal microbes) resist the initial entry of microbes into the body. Invasive microbes may be walled off within structures (e.g., granulomas) to restrict their ability to spread to other parts of the body. Disruption of nonself cells may occur through physical damage inflicted on their membranes or by inducing them to undergo a process of programmed suicide (**apoptosis**) in which they destroy their own nucleic acids. **Phagocytic** cells capture and ingest microbes and cellular debris. The ingestion and subsequent degradation of microbes or cellular debris also triggers some phagocytic cells to secrete molecules that selectively activate other elements of the immune system. Natural killer cells can detect and destroy host cells that display certain abnormal characteristics (e.g., stemming from viral infection). Antibodies (produced by B lymphocytes) and complement molecules can attach to microbes and initiate their destruction, while T lymphocytes can directly or indirectly attack microbes and infected cells. Many cells of the immune system also proliferate rapidly upon perceiving the presence of a threat to ensure sufficient numbers to cope with that threat.



## Chapter Summary

- The immune system distinguishes cells and molecules that belong within the body (**self**) from those that do not (**nonself**), using the **innate** and **adaptive** immune systems.
- Both the innate and adaptive immune systems use cell-surface and soluble receptors to sense potential threats.
- Cells and molecules of the innate immune system respond rapidly to a microbial invasion and are often sufficient for defense.
- Recognition of self is used by cells to determine whether an encountered molecule or cell has the appropriate structures to show that it is a part of the body.
- The recognition of something that is nonself and has not yet been encountered is achieved through pattern recognition receptors and somatically generated receptors.
- **Immunologic memory** allows the adaptive immune system to tailor its responses to things that it encounters on multiple occasions.
- The immune system can eliminate threats by **isolation**, **disruption**, or **ingestion** (consumption) or by a combination of these actions.

## Study Questions

- 1.1 Immune recognition of molecules belonging to self is important to
- activate natural killer cells of the innate immune system.
  - determine the safety of interacting with the molecule.
  - induce somatic generation of a B or T lymphocyte receptor for the molecule.
  - stimulate binding by pattern recognition receptors.
  - trigger an attack upon the cell expressing the self molecule.
- 1.2 Natural killer cells assess whether other cells are abnormal by detecting types and levels of surface-associated
- MHC I molecules.
  - nonself molecules.
  - pathogen-associated molecular patterns.
  - pattern recognition receptors.
  - somatically generated cell surface receptors

The correct answer is B. Identification of self tells the immune system that the cell or molecule recognized is not a foe. Natural killer cells use this mechanism of self recognition to halt their attack on cells that they perceive to be abnormal. Receptor generation by B and T cells occurs independently of initial encounter with self molecules. Pattern recognition receptors, on the other hand, are genetically programmed to recognize nonself. By triggering an attack upon a cell expressing the self molecule, an immune recognition molecule violates its "nonaggression pact" with the cells and molecules of the host and establishes an internal coup known as autoimmunity.

The correct answer is A. MHC class I molecules are self-identification molecules found on all nucleated host cells. Natural killer cells, after making contact with cells expressing stress signals, make the decision whether to kill them or not by assessing whether they express the appropriate types and levels of MHC I molecules. Although they are members of the innate immune system, natural killer cells do not recognize nonself, pathogen-associated molecular patterns or pattern recognition receptors. Natural killer cells are unable to recognize somatically generated cell surface receptors.

## 1.3 Pattern recognition receptors bind to

- A. B and T lymphocytes.
- B. host cell-associated molecules.
- C. MHC I molecules.
- D. natural killer cells.
- E. pathogen-associated molecular patterns.

The correct answer is E. Pattern recognition receptors (PRRs) are genomically determined to bind to molecules widely expressed by microbes but not by host cells. Consequently, PRRs cannot recognize host-associated molecules such as MHC class I molecules or cells of host origin such as B, T, or natural killer lymphocytes.

## 1.4 Somatically generated receptors found on B and T lymphocytes are

- A. bound only to MHC I molecules.
- B. encoded in the germline to recognize pathogen-associated molecular patterns.
- C. first produced after an initial encounter with nonself.
- D. identical among individuals.
- E. randomly generated during development.

The correct answer is E. Bone marrow-derived (B) and thymus-derived (T) lymphocytes somatically generate receptors during development. Unlike natural killer cells, B cells and T cells are unable to assess the quantity of MHC class I molecules on nucleated cells. Unlike innate immune system receptors, B and T lymphocyte somatic receptors are randomly generated and vary greatly between individuals. B and T lymphocytes receptors are formed prior to antigen stimulation.

## 1.5 Immunologic memory refers to

- A. activation of phagocytic cells to ingest microbial invaders.
- B. changes in adaptive immune responses with subsequent encounters with antigen.
- C. constancy of the response of the innate immune response to a particular microbe.
- D. recognition of pathogen-associated molecular patterns by pattern recognition receptors.
- E. stimulating a defective host cell with reduced MHC I molecules to commit suicide.

The correct answer is B. A hallmark of the adaptive immune system is that it progressively alters its response upon reexposure to an antigenic stimulus, and in doing so, it must recall the previous exposure, a process known as memory. Although they are members of the innate immune system and do not possess immunologic memory, phagocytes may be influenced by the adaptive immune system. Consistency in immune response from initial to subsequent encounters is a hallmark of the innate immune response. Immunologic memory of the adaptive immune system is not passed genetically from one generation of individuals to the next. Detection of diminished MHC class I expression is a function of natural killer cells, members of the innate immune system.

## 1.6 Influenza viruses infect humans and elicit an immune response that is often insufficient to protect the individual from sickness or death. Which of the following structures are on influenza viruses, allowing them to be recognized by the human immune system?

- A. MHC I molecules
- B. MHC II molecules
- C. pathogen-associated molecular patterns
- D. pattern recognition receptor
- E. somatically generated receptors

The correct answer is C. The molecules on the virus that are not on host cells are the pathogen-associated molecular patterns. The pattern recognition receptors are found on host cells and molecules. MHC I and II molecules are present on all nucleated host cells but not on viruses. The somatically generated receptors are on host T and B lymphocytes.