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Supplement to  
*The Art of Getting Well*  
**Immune System Protection from Foreign Invaders**

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Throughout 4.5 billion years our cellular and multi-cellular ancestors struggled to survive, creatively developing and utilizing a marvelously complex immune system. Throughout these aeons it has been eat or be eaten.

Our bodies utilize an extremely diverse army of cells and other molecules designed especially to protect us from the strategies of all of those would-be eaters. (See Diagram I.) These finely tuned protective cells also work well as a team.

Researchers continue to uncover new and amazingly complex ways whereby protection from "outsiders" has developed. What is already known may sound complex, but please have patience. There's a point of great understanding in what follows.

There's an "innate" immune protective system. We're born with the ability to recognize certain microbes on sight, so to speak, and we can then destroy them.

There is an "adaptive" immune protective system. The "receptors" (as a lock is to a key) activated in the adaptive immune response are formed by piecing together gene segments, like piecing together a jigsaw puzzle. The available pieces are used by each cell in a different way to make a unique receptor, enabling cells to collectively recognize infectious organisms confronted during our lifetimes.

The end-point target of all immune processes is to destroy or otherwise protect from an "antigen," usually a foreign molecule from a microorganism.

The end-object of vaccinations is to confront the immune system with an antigen forcing the immune system to adapt to the foreign invader; that is, the immune system must learn to identify the invader and to retain the memory of this knowledge for the purpose of destroying the invader now and in the future.

One major end-result of such vaccinations is to develop a signal to specialized blood components, called "complement" (an enzyme substance) which is used to overwhelm and to destroy foreign invaders. (See Diagram II.)

Specialized "antigen-presenting" cells, such as macrophages, roam throughout our bodies literally ingesting the antigens (invaders) and fragmenting them. These fragments are called "antigenic peptides."

Pieces of these peptides are layered on the surface of the cell called "major histocompatibility complex" (MHC). This joining produces a peptide-MHC combination.

Other specialized white cells called "T lymphocytes" have receptor cells that "recognize" different peptide-MHC. (The designa-

tion "T" means cells from the thymus gland.)  
The T cells that are activated by that "recognition" begin to divide, and they also secrete a substance called "lymphokines." Lymphokines are chemical signals that mobilize other components of the immune system.

One set of those cells that responds to the lymphokine signals are the "B-lymphocytes" each of which also have receptor molecules of a single specificity on their surface. (See Diagram III.) (The designation "B" means cells from bone marrow.)

However, unlike the receptors of T cells, those of B cells can recognize parts of antigens that are free in solution without the MHC molecules attached.

When the B-lymphocytes are activated, they divide and differentiate into plasma cells that secrete "antibody" proteins, water soluble forms of their receptors.

These antibodies bind to whatever antigens they find, neutralizing them or precipitating their destruction by enzymes derived from the molecule called "complement." Complement is a blood protein which can destroy pathogens on first encounter.

Complement activity -- the end point of adaptive immunization, to develop a "complement" to antibodies -- can be triggered in three ways. (See Diagram IV.)

(1) One type of complement called C3 can bind to any protein. Once bound to the microbe the C3 molecule causes other complement molecules to bind to the bacterium. This is called the "complement cascade." Their joint action overwhelms the bacterium. Our body's cells are protected from C3 by proteins that inactivate this molecule.

(2) Antibodies produced as a result of infection can also activate complement. After detecting an infection, a macrophage secretes a substance called "interleukin-6." As it's carried through the blood stream, interleukin-6 reaches the liver, causing the secretion of a "mannose-binding protein." (Mannose is a sugar formed by the oxidation of manitol.) Mannose-binding protein binds to the capsule of a bacterium, and this protein then triggers the complement cascade, thus overwhelming the bacterium.

(3) Antibodies produced as a result of infection also activate complement. B cells are activated if they bind to the bacterium and are stimulated by a so-called helper T cell. The binding stimulates the B cell to proliferate and to secrete antibodies. The antibodies bind to the bacterium and activate complement protein called C1Q, which activates other complement molecules -- the "complement cascade" -- thus overwhelming and killing the bacterium.

**To make a rather long, complex story short, the many major immune defensive mechanisms we've inherited usually results in producing a complement cascade, which, working together with antibodies, overwhelms an invading organism.**

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### THE LYMPH SYSTEM IS A DECENTRALIZED IMMUNITY DEFENSE

The lymph system consists of many organs and tissues that are scattered throughout the body, providing lymphocytes that are responsible for "specific immunity." Specific immunity is the special affinity between antigen and its corresponding

antibody. (1) Lymphocytes are born in the *primary lymphoid organs* -- the *thymus* making T cells and the *bone marrow* making B cells. (2) T and B cells leave their birthplace, circulating in the blood until they reach one of the numerous *secondary lymphoid organs*. *Lymph nodes*, *spleen* and *tonsils* are examples. (3) T and B cells exit the blood stream through specialized blood vessels named *high endothelial venules*. Each gram of lymph node contains  $10^9$ , or one billion, lymphocytes. Despite their density, the lymphocytes move about freely. (4) These two facts explain why the lymph nodes are excellent locations for the activation of antigens and antigen presenting cells which enter through *afferent lymphatic vessels*. Antigens in the *paracortex* generally activate T cells. The B cells, antibody producing cells, generally are activated in areas such as the *germinal centers of the lymphoid follicles*. (5) Lymphatic vessels carry activated

lymphocytes from the nodes through *efferent lymphatics*, by means of fluid, until they reach the blood stream where they provide protection around the body. (6) Eventually the lymphocytes flow into other lymph nodes, whence the cycle repeats.

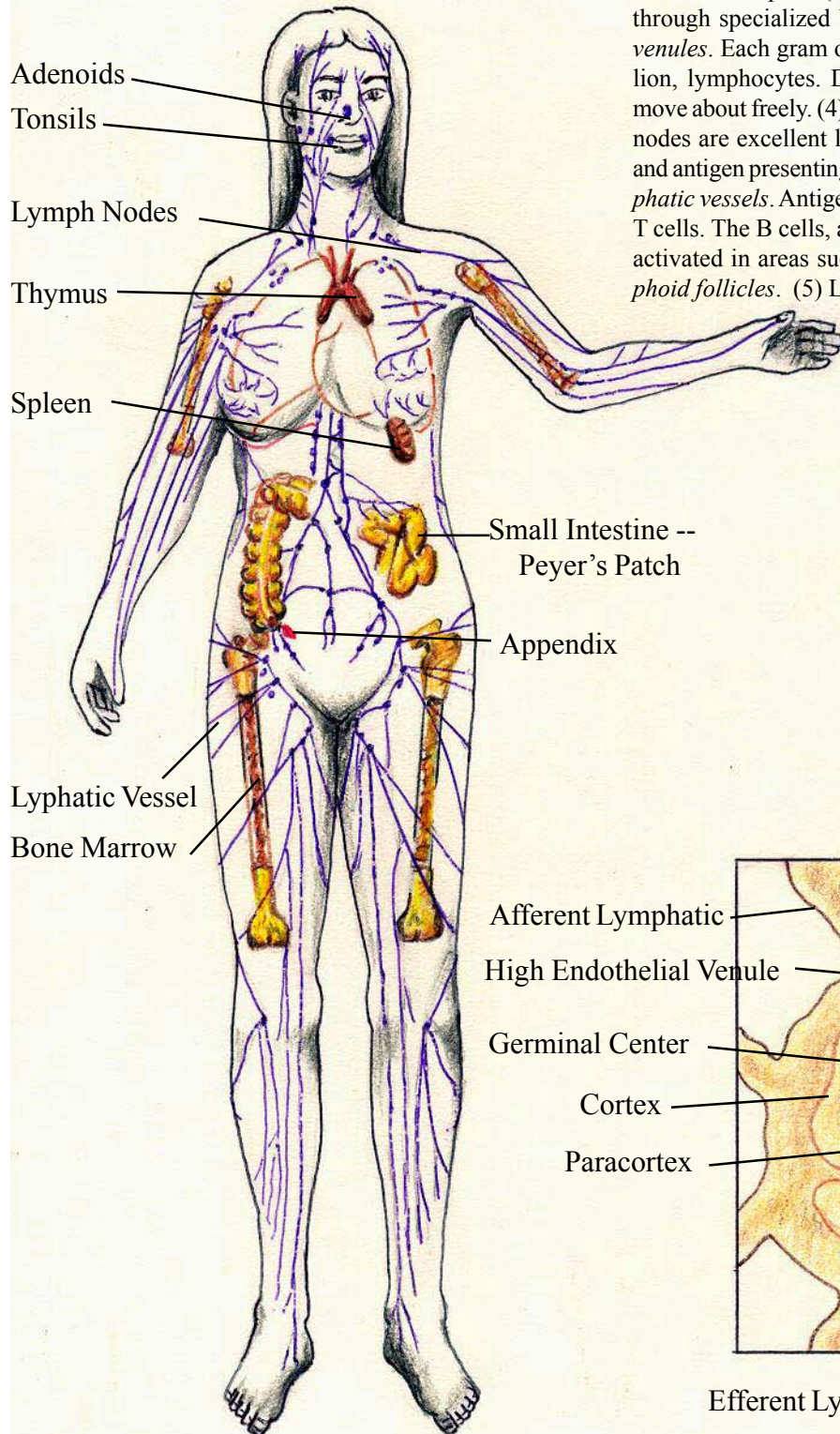
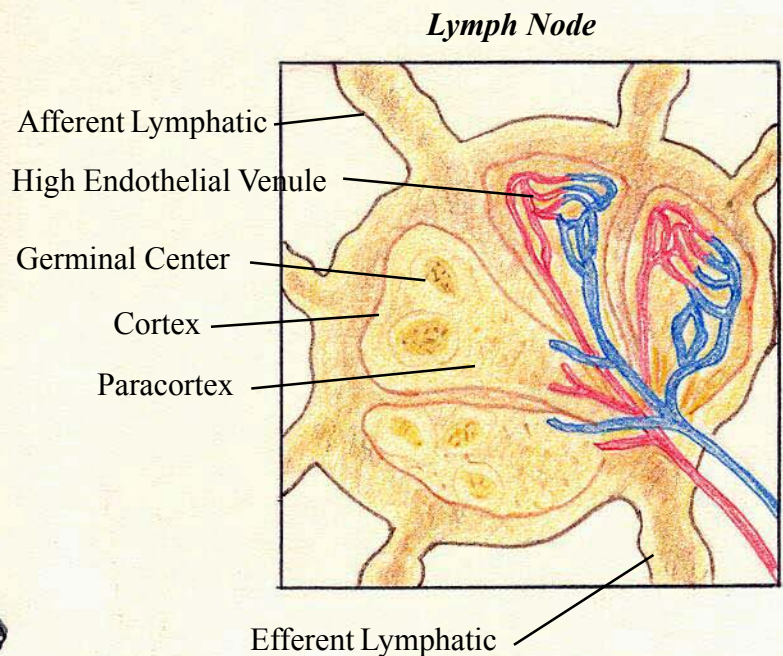


Diagram I



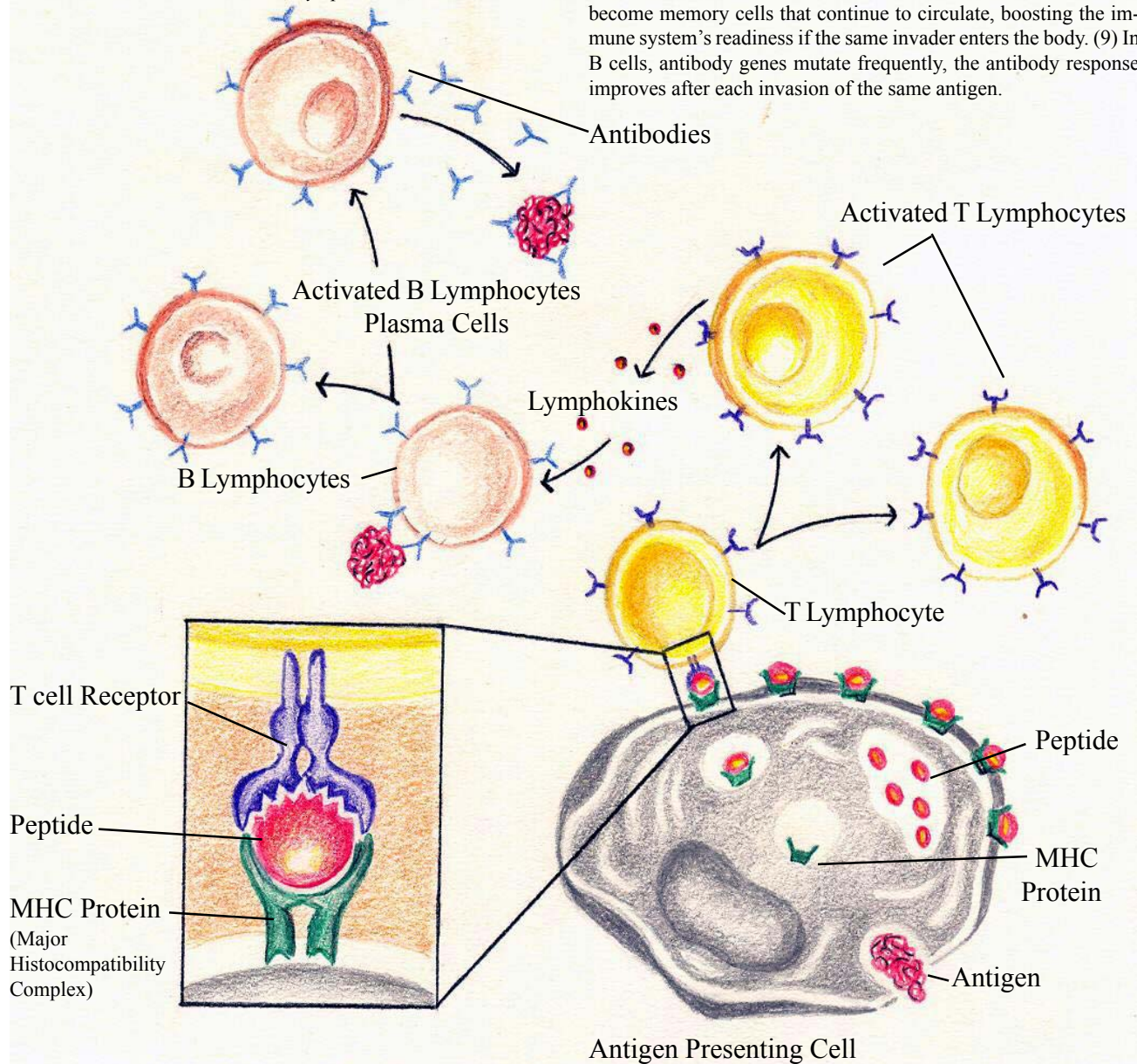
Adapted from Sir Gustav J.V. Nossal, "Life and Death of the Immune System," *Scientific American*, Sept. 1993, p. 56. Artwork originally by Dimitry Schildlovsky and Tomo Narashima, but readapted and drawn by France Watts.



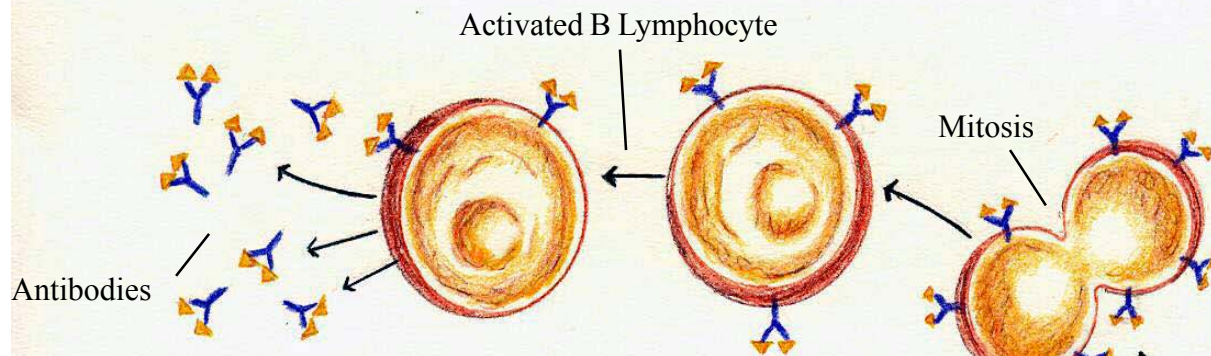
## DEFENDING THE BODY WITH A WIDE VARIETY OF MOLECULES AND CELLS

An *antigen* is a molecule usually from a foreign microorganism or other invader. (1) Macrophages, also called antigen-presenting cells, roam throughout the body ingesting antigens. (2) Macrophages fragment antigens into *antigenic peptides*. (3) These fragments are joined to *major histocompatibility complex (MHC)* molecules, which are displayed on the surface of invading cells. (4) *T lymphocytes*, which are also white cells, have receptor sites that enable each one to recognize different peptide-MHC combinations. These activated T cells divide and secrete *lymphokines*, which are chemi-

cal signals that activate other components of the immune system. (5) Among cells that respond to lymphokines are B lymphocytes. These have specific receptor molecules on their surface, and unlike T cells can recognize parts of antigens free in a solution without MHC molecules. (6) Once activated, B cells divide, differentiating into plasma cells that secrete *antibody* proteins which are also soluble forms of their receptors. (7) The antibodies can neutralize antigens by binding to them or trigger their destruction by means of complement enzymes or even by scavenging cells. (8) Some T and B cells become memory cells that continue to circulate, boosting the immune system's readiness if the same invader enters the body. (9) In B cells, antibody genes mutate frequently, the antibody response improves after each invasion of the same antigen.

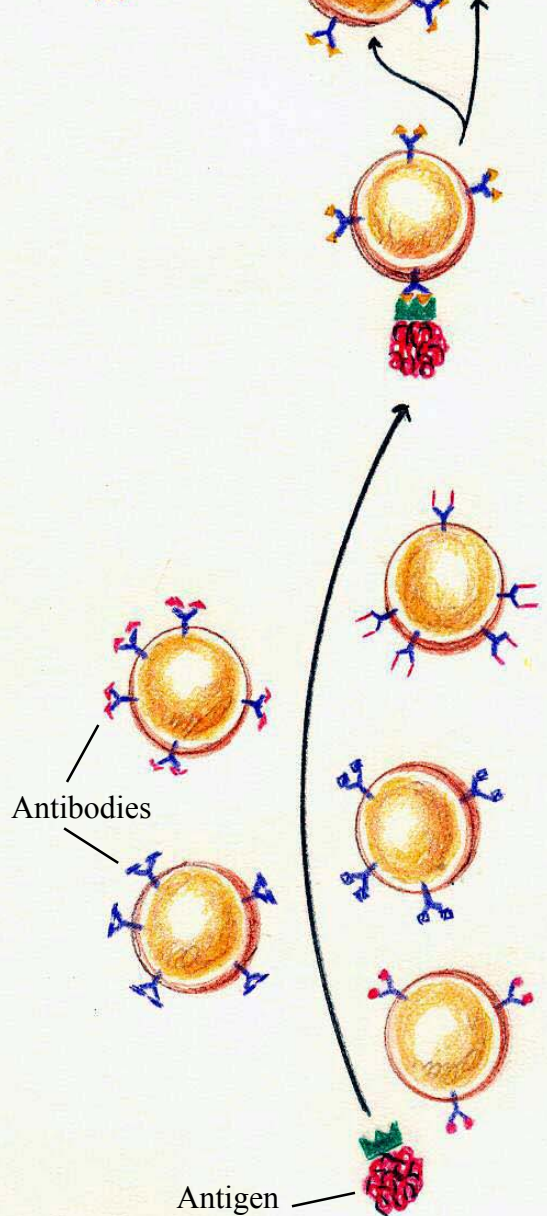


**Diagram II**



(1) Having millions of possible surface antibodies, lymphocytes constantly roam throughout the body. (2) When a matching antibody meets its matching antigen (bottom), the lymphocyte swells and then begins to rapidly divide. (3) Once maturity is reached, B cells secrete antibodies that attack an invader (top). (4) T cells produce lymphokines. Lymphokines are chemicals that increase the activity of other immune system cells.

**Diagram III**

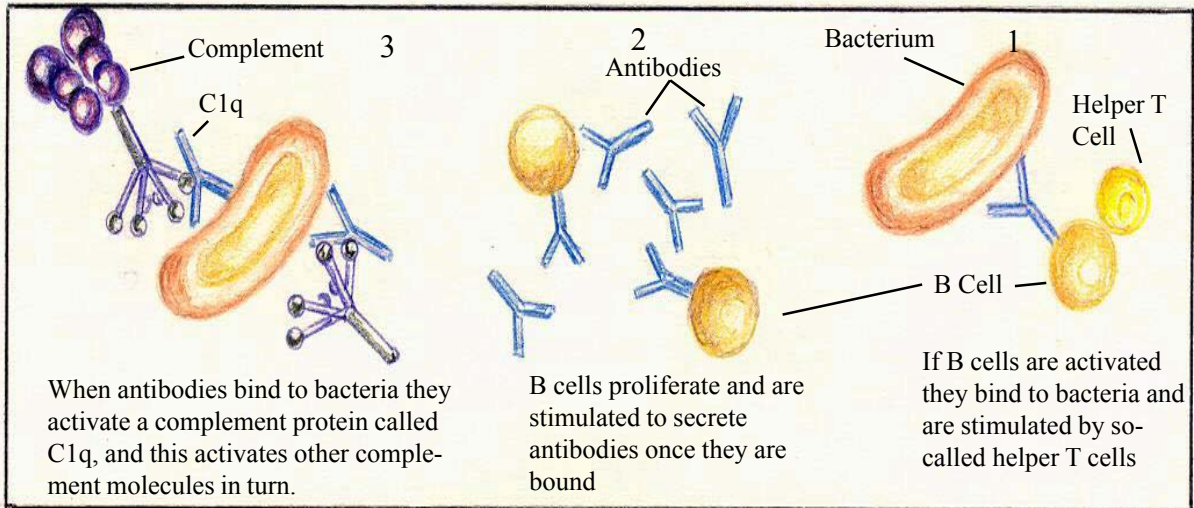


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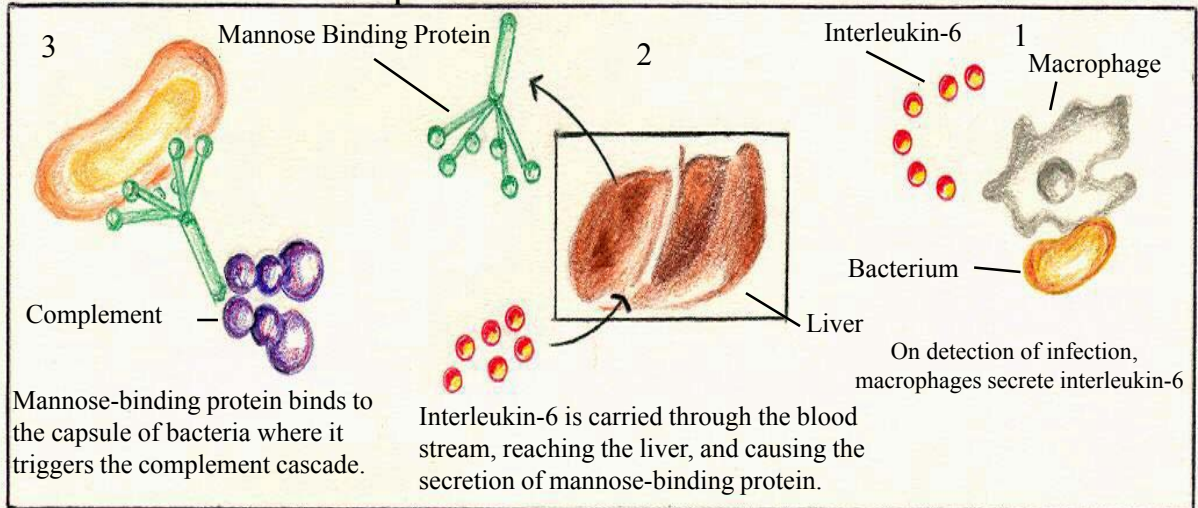


**THREE WAYS BY WHICH COMPLEMENT ACTIVITY CAN BE TRIGGERED**  
 COMPLEMENT EITHER KILLS BACTERIA OR RECRUITS OTHER IMMUNE SYSTEM CELLS, SUCH AS PHAGOCYTES

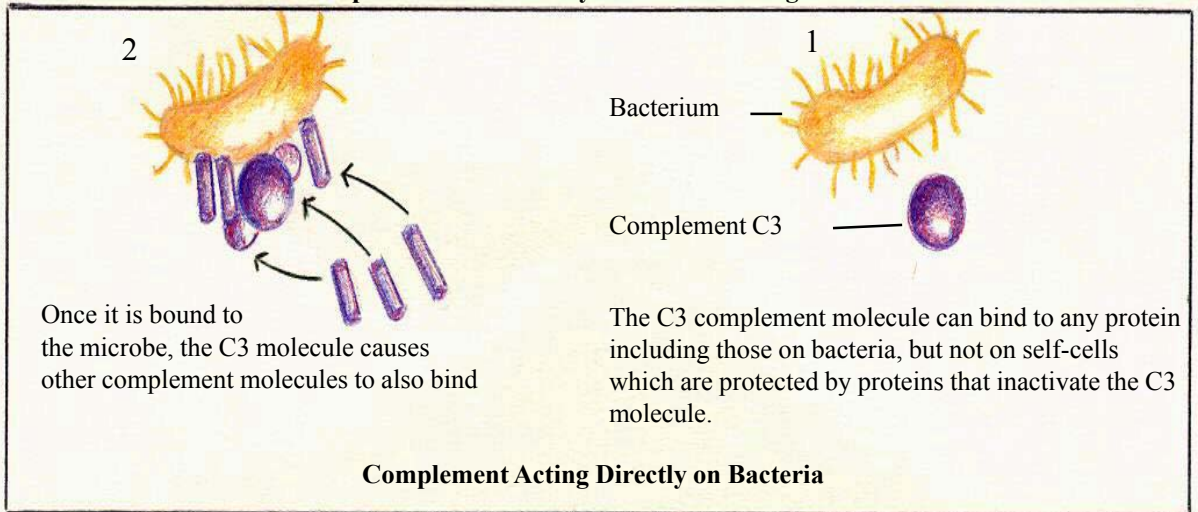
**Diagram IV**



**Complement Produced as Result of Infection**



**Complement Activated by Mannose-binding Protein**



Adapted from Charles A. J aneway, Jr., "How the Immune System Recognizes Invaders," *Scientific American*, Sept. 1993, p. 74. Artwork originally by Ian Warpole, but readapted and drawn by France Watts.