IMMUNODEFICIENCY

Howard M. Lederman

Patients with a defective immune system often have an increased susceptibility to infection as one of their major problems.

The immune system has two major functions: (1) to recognize substances that are foreign to the body and (2) to react against them. These foreign substances (or antigens) may be microorganisms that cause infectious diseases, transplanted tissues or organs from another individual, or even "foreign" tumors that arise within one's own body. Adequate functioning of the immune system provides protection from infectious diseases, is responsible for the rejection of transplanted organs, and may provide some protection from cancer.

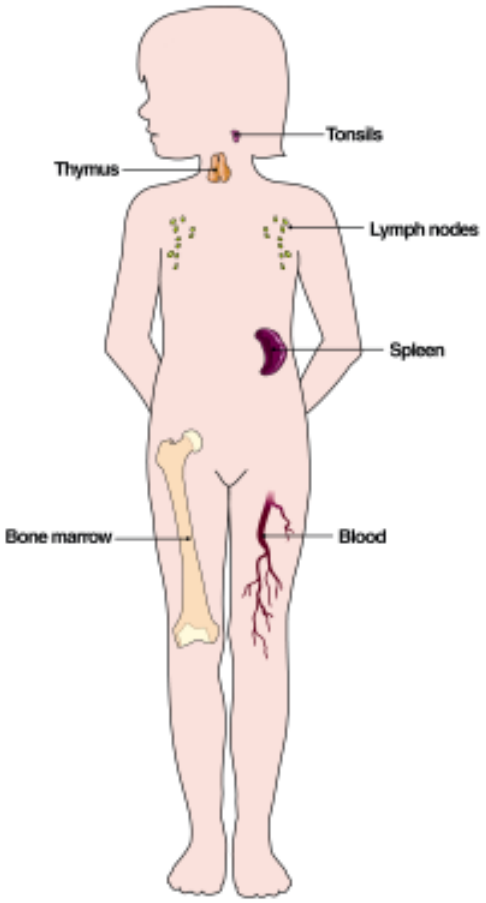

Fig. 5-1: Important components of the immune system.

One of the most important functions of the immune system is to protect against infectious diseases. The body is constantly challenged by a variety of infectious microorganisms such as bacteria, viruses and fungi. These microorganisms can cause a variety of infections - some relatively common and usually not serious, and others less common and more serious. For example, the average individual has a number of "colds" each year caused by a variety of respiratory viruses. Other viruses can cause more serious liver infections (hepatitis) or brain infections (encephalitis). Common bacterial infections include "strep" throats, some skin infections (impetigo) and ear infections (otitis). Occasionally a bacterial infection may be very serious as when it affects the covering of the brain (meningitis) or involves the bone (osteomyelitis) or joints (pyogenic arthritis).

Whatever the infection, the immune system is responsible for defending the individual against the invading microorganism. A normal immune system

provides a person with the ability to kill the invading microorganism, limit the spread of infection and ultimately recover. An abnormal immune system is unable to kill the microorganism effectively. The infections may spread and, if untreated, ultimately be fatal. Thus, patients with a defective immune system often have an increased susceptibility to infection as one of their major problems. In some individuals with defective immune systems, the infections may occur infrequently and be of relatively little consequence. In others, the infections may be unusually frequent, unusually severe, or be caused by unusual and/or rare microorganisms.

Because all parts of the body need to be protected from microorganisms or other foreign material, the immune system is located in, or has access to, virtually all parts of the body. Thus, important components of the immune system are concentrated in the blood, thymus, lymph nodes, bone marrow and spleen. If an infection starts in a location that has only a few components of the immune system, such as the skin, signals are sent throughout the body to call in large numbers of immune cells to the site of infection. This is the reason that lymph nodes in the neck may swell during a throat infection and that pus (formed by the activity of protective white blood cells) develops at a skin infection.

The major components of the immune system are:

- √ B-lymphocytes
- √ T-lymphocytes
- √ Phagocytes
- √ Complement

COMPONENTS OF THE NORMAL IMMUNE SYSTEM

The immune system is composed of a variety of different cell types and proteins. Each component performs a special task aimed at recognizing and/or reacting against foreign materials such as germs. For some components, recognition of germs is their primary and only function. Other components function primarily to react against the germs. Still other components function to both recognize and react against germs and other foreign materials.

Since the functions of the immune system are so critical to survival, many of them can be performed by more than one component of the system. This redundancy acts as a back-up mechanism so that if one component of the whole system is missing or functioning poorly another component can take over at least some of its functions.

The major components of the immune system are:

B-lymphocytes
T-lymphocytes
Phagocytes
Complement

B-lymphocytes: B-lymphocytes (sometime called B-cells) are white blood cells system whose major function is to produce antibodies (also called immunoglobulins or gammaglobulins). B-lymphocytes develop from primitive cells (stem cells) in the bone marrow. When mature, B-lymphocytes can be found in

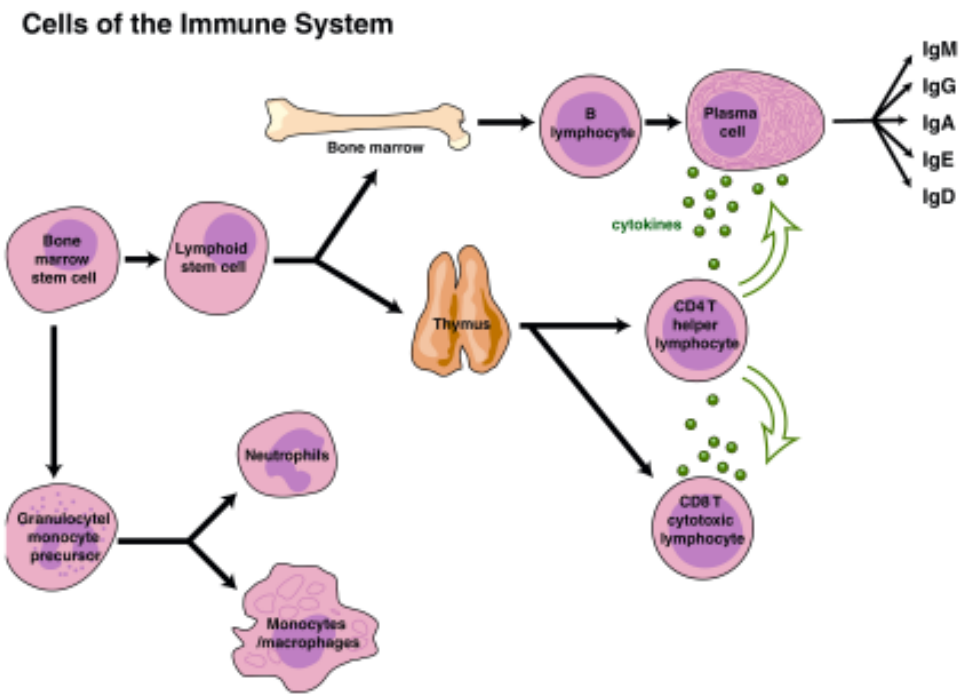

Fig. 5-2: Cells of the immune system arise in the bone marrow and are then distributed throughout the body.

Antibodies protect each of us from infection in a number of different ways.

the bone marrow, lymph nodes, spleen, certain areas of the intestine and, to a lesser extent, in the bloodstream. When B-lymphocytes are stimulated by a foreign substance or antigen, they respond by maturing into plasma cells that produce antibodies. These substances find their way into the bloodstream, respiratory and intestinal secretions and even tears.

Antibodies are highly specialized serum protein molecules. For every foreign antigen to which the body has been exposed, there are antibody molecules that specifically recognize antigen. Thus, there are antibody molecules that fit the polio virus like a lock and key, others aimed specifically at the bacteria that causes diphtheria, and still others that match the measles virus. The variety of different antibody molecules is so extensive that B-lymphocytes have the ability to produce antibodies against virtually every possible microorganism in our environment. When antibody molecules recognize a microorganism as foreign, they physically attach to the microorganism and set off a complex chain of reactions involving other components of the immune system that eventually destroys the microorganism.

The chemical names for antibody proteins are “immunoglobulins” or “gammaglobulins.” Just as antibodies can vary from molecule to molecule with respect to which microorganisms they bind, they can also vary with respect to their specialized functions in the body. This kind of variation in specialized function is determined by the antibody’s chemical structure, which in turn determines the class of the antibody or (immunoglobulin). There are five major classes of antibodies or immunoglobulins:

Immunoglobulin G	(IgG)
Immunoglobulin A	(IgA)
Immunoglobulin M	(IgM)
Immunoglobulin E	(IgE)
Immunoglobulin D	(IgD)

Each immunoglobulin class has special chemical characteristics, that provide it with certain advantages. For example, antibodies of the IgG class are formed in large quantities and can slip out of the bloodstream into the tissues. IgG immunoglobulins (antibodies) are the only class of immunoglobulin that cross the placenta and pass immunity from mother to fetus. Antibodies of the IgA fraction are produced near mucus membranes and find their way into secretions such as tears, bile, saliva and mucus, where they protect against infection in the respiratory tract and intestines. Antibodies of the IgM class are the first antibodies formed in response to infection and, therefore, are important in protection during the first few days of an infection. Antibodies of the IgE class are responsible for allergic reactions. The function of IgD is still not understood.

Antibodies protect each of us from infection in a number of different ways. For example, some microorganisms must attach to body cells before they can cause an infection, but antibodies on the surface of a microorganism can interfere with its ability to adhere to body cells. Antibodies attached to the surface of some microorganisms can activate a group of proteins called "complement" that directly kill bacteria and viruses. Antibody-coated bacteria are also much easier for phagocytic cells to ingest and kill than bacteria that are not coated with antibody. All of these actions of antibodies prevent microorganisms from successfully invading body tissues where they may cause serious infections.

T-lymphocytes: T-lymphocytes (sometimes called T-cells) are another type of immune cell. T-lymphocytes do not produce antibody molecules. Instead, the specialized roles of T-lymphocytes are to directly attack foreign antigens such as viruses, fungi, or transplanted tissues, and to act as regulators of the immune system.

T-lymphocytes develop from stem cells in the bone marrow. Early in fetal life, these immature cells migrate to the thymus, a specialized organ of the immune system that is in the chest. Within the thymus, lymphocytes develop into mature T-lymphocytes ("T" for the thymus). The thymus is essential for this process, and T-lymphocytes cannot develop if the fetus has no thymus. Mature T-lymphocytes leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow and blood.

Each T-lymphocyte reacts with a specific antigen, just as each antibody molecule reacts with a specific antigen. In fact, T-lymphocytes have molecules on their surfaces that are like antibodies and recognize antigens. The variety of different T-lymphocytes is so extensive that the body has T-lymphocytes that can react against virtually any antigen. T-lymphocytes also vary with respect to their function.

There are "killer" or "effector" T-lymphocytes, and "helper" T-lymphocytes: Each has a different role to play in the immune system.

Killer or effector T-lymphocytes are the T-lymphocytes which perform the actual destruction of the invading microorganism. These killer T-lymphocytes protect the body from certain bacteria and viruses that have the ability to survive and even reproduce within the body's own cells. Killer T-lymphocytes also respond to foreign tissues in the body, such as a transplanted kidney. The killer T-lymphocytes migrate to the site of an infection or the transplanted tissue. Once there, the killer cell directly binds to its target and kills it.

The most common immune system abnormalities are deficiencies of antibody and a reduction in the number of lymphocytes circulating in the bloodstream.

Helper T-lymphocytes assist B-lymphocytes in producing antibody and assist killer T-lymphocytes in their attack on foreign substances. The helper T-lymphocyte helps or enhances the function of B-lymphocytes, causing them to produce more antibodies and giving instructions for making IgG, IgA or IgE. Helper T-lymphocytes also help or enhance the function of killer T-lymphocytes and some phagocytic cells, especially macrophages.

Phagocytes: Phagocytes are specialized cells of the immune system that function to ingest and kill microorganisms. These cells, like the others in the immune system, develop from primitive stem cells in the bone marrow. When mature, they migrate to virtually all tissues of the body but are especially prominent in the bloodstream, spleen, liver, lymph nodes and lungs.

There are a number of different types of phagocytic cells. Polymorphonuclear leukocytes (neutrophils or granulocytes) are commonly found in the bloodstream and can migrate into sites of infection within a matter of minutes. It is this phagocytic cell that increases in number in the blood during infection and is in large part responsible for an elevated white blood cell count during infection. It also is the phagocytic cell that leaves the bloodstream and accumulates in the tissues during the first few hours of infection, and is responsible for the formation of "pus." Monocytes are another type of phagocytic cell found circulating in the bloodstream, and lining the walls of blood vessels in the liver and spleen. Here they act to capture microorganisms as they pass by in the blood. When monocytes leave the blood stream and enter the tissues, they change shape and size and become macrophages.

Phagocytic cells serve a number of critical functions in the body's defense against infection. They have the ability to leave the bloodstream and move into the tissues to the site of infection. Once at the site of infection, they ingest the invading microorganism. Ingestion of microorganisms by phagocytic cells is made easier when the microorganisms are coated with either antibody or complement or both. Once the phagocytic cell has engulfed or ingested the microorganism, it initiates a series of chemical reactions within the cell, which result in the death of the microorganism.

Complement: The complement system is composed of approximately 20 serum proteins, that function in an ordered and integrated fashion to help defend against infection and produce inflammation. Some of the proteins in the

complement system are produced in the liver, while others are produced by macrophages.

In order to perform their protective functions, the complement components must be converted from inactive forms to activated forms. In some instances, microorganisms must first combine with antibody in order to activate complement. In other cases, the microorganisms can activate complement without the need for antibody. Once activated, the complement system can perform a number of important functions in defense against infection. One of the proteins of the complement systems coats microorganisms to make them more easily ingested by phagocytic cells. Other components of complement act to send out chemical signals to attract phagocytic cells to the sites of infection. Finally when the whole complement system is assembled on the surface of some microorganisms, a complex is created which can puncture the cell membrane (outer envelope) of the microorganism and kill it.

Having a deficiency of IgG_2 in addition to a deficiency of IgA compounds the risk for infections of the respiratory tract.

THE IMMUNE SYSTEM IN A-T

Many, but not all, A-T patients have abnormalities of immune function. The most common abnormalities are deficiencies of antibody and a reduction in the number of lymphocytes circulating in the bloodstream.

IMMUNODEFICIENCY IN A-T

- Most problems are not progressive
- There are many laboratory abnormalities
  - IgA deficiency
  - IgG_2 deficiency
  - Impaired ability to respond to vaccines
- Many patients do NOT have a significant predisposition to infection

Abnormalities of Antibody

Approximately two-thirds of A-T patients have a deficiency of IgA. This immunoglobulin is particularly important for host defense along mucosal surfaces that come in contact with the environment, such as the lining of the sinuses, the bronchi and smaller airways of the lung, and the intestines. IgA is not an important part of host defense in the blood or organs without connections to the outside such as the brain, liver and bones.

Selective deficiency of IgA - that is, normal immune function except for the lack of IgA - is actually a relatively common problem among healthy individuals, occurring in approximately 1 of 500 people. Most of those people are healthy and do not have any significant symptoms, but a small number of IgA deficient patients

have recurrent infections along mucosal surfaces that manifest as sinusitis and bronchitis. It is not known for certain why only some people with IgA deficiency have problems with infection, but it is suspected that those patients who get infections have other abnormalities of their immune function (especially deficiencies of other immunoglobulin classes such as IgG_2). Most A-T patients with selective IgA deficiency do not have problems with infection. Those that do, usually have additional problems with immune function or another predisposition to develop infection (for example, aspiration of food and fluid into the lung).

There are no known therapies to increase the amount of IgA produced by a person, nor is there a way of manufacturing synthetic IgA or effectively purifying it from normal people. Other strategies, such as reducing contact with infected individuals and/or prophylactic antibiotics during the winter months, are sometimes used in these patients.

All A-T patients should have at least one comprehensive immunologic evaluation that measures the number and type of lymphocytes in the blood.

Another common problem in A-T patients is a deficiency of IgG_2. This particular type of IgG molecule is most important for the body's defense against encapsulated bacteria. These are bacteria that are surrounded by a protective and slippery sugary coating (a capsule) and include many of the common causes of ear infections, sinusitis, bronchitis and pneumonia.

Sometimes these problems with immunity can be overcome by immunization. Vaccines against common bacterial respiratory pathogens such as Hemophilus influenzae and the pneumococcus are commercially available and often help to boost antibody responses, even in individuals with IgG_2 deficiency. If the vaccines do not work and the patient continues to have problems with infections, gammaglobulin therapy (IV infusions of antibodies collected from normal individuals, see below) may be of benefit.

In a very small percentage of A-T patients, there are severe abnormalities of antibody production. Those patients will make little or no IgG, IgA or IgM and be very susceptible to a variety of respiratory and gastrointestinal infections. In these cases, gammaglobulin therapy is absolutely necessary.

Finally, 10 to 15 percent of all A-T patients will have an abnormality in which one or more types of immunoglobulin are increased far beyond the normal range. In a few cases, the immunoglobulin levels can be increased so much that the blood becomes thick and does not flow properly. Therapy for this problem must be tailored to the specific abnormality found and its severity.

For the most part, the pattern of immunodeficiency seen in an A-T patient early in life (by age five) will be the same pattern seen throughout the lifetime of that individual. It is probably not worthwhile to repeat measurements of serum immunoglobulin levels at regular, fixed intervals. However, if an individual patient's susceptibility to infection increases, it is important to reassess immune function in case deterioration has occurred and a new therapy is indicated. (If infections are occurring in the lung, it is also important to investigate the possibility of dysfunctional swallow with aspiration into the lungs.)

Low Lymphocyte Counts

Most A-T patients have low lymphocyte counts in the blood. This problem seems to be relatively stable with age and very few patients have progressively decreasing lymphocyte counts as they get older. In general, patients with very low lymphocyte counts are at significantly increased risk for infection. They may develop complications of live viral vaccines (measles, mumps, rubella and chickenpox), chronic or severe viral infections, yeast infections of the skin and vagina, or opportunistic infections (such as pneumocystis pneumonia that do not occur in individuals with normal immune function). Fortunately, although lymphocyte counts are often low in A-T patients, these problems with infection are virtually never seen. The one exception to that rule is that many A-T patients have chronic or recurrent problems with warts on the hands and feet.

Individuals who are unable to produce adequate amounts of immunoglobulins or antibodies may benefit from replacement therapy with gamma globulin.

GENERAL RECOMMENDATIONS

- Every A-T patient should have at least one comprehensive immunologic evaluation.
- If he/she has normal antibody responses to killed vaccines [diphtheria, tetanus, or H. influenzae (Hib)], all standard childhood vaccines (including measles/mumps/rubella and varicella) should be administered.
- Influenza virus vaccine and pneumococcal vaccines may be particularly helpful.
- If there is an increase in infections later in life:
  - Re-evaluate the immune system
  - Evaluate for dysfunctional swallow and pulmonary aspiration

Specific Recommendations

All A-T patients should have at least one comprehensive immunologic evaluation that measures the number and type of lymphocytes in the blood (T-lymphocytes and B-lymphocytes), the levels of serum immunoglobulins (IgG, IgA, and IgM) and antibody responses to T-dependent (e.g., tetanus, Hemophilus influenzae B) and T-independent (23 valent pneumococcal polysaccharide) vaccines. The tests need not be repeated unless the patient develops more problems with infection.

If the tests show significant abnormality, your doctor will be able to discuss various treatment options. Absence of immunoglobulin or antibody response to vaccine can be treated with replacement gammaglobulin (IVIG) infusions, or can be managed with prophylactic antibiotics and minimized exposure to infection. If immune function is normal, all routine childhood immunizations including live viral vaccines (measles, mumps, rubella and varicella) should be given. In addition, several "special" (that is, licensed but not routine) vaccines should be given to decrease the risk that an A-T patient will develop lung infections. The patient and all household members should receive the influenza (flu) vaccine every fall. A new 7-valent pneumococcal conjugate vaccine has just been licensed. For A-T patients less than two years old, three doses of the new vaccine should be given at two month intervals. For A-T patients older than two years old, two doses of the new vaccine should be given over a two month interval. Six months after the new vaccine has been given and after the child is at least two years old, the standard 23-valent pneumococcal vaccine should be administered. Immunization with the 23-valent pneumococcal vaccine should be repeated every five years after the first dose.

There are two forms of gamma globulin that can be given to patients:

√ Intramuscular (IM)

√ Intravenous (IV)

In patients who have low levels of IgA, further testing should be performed to determine if the IgA level is low or completely absent. If the latter, there is a slightly increased risk of a transfusion reaction. "Medical Alert" bracelets are not necessary, but the family and primary physician should be aware that if there is elective surgery requiring red cell transfusion, the cells should be washed to decrease the risk of an allergic reaction.

Finally, it is important to emphasize that if an A-T patient develops an increase in respiratory tract infections, particularly if accompanied by increased problems with drooling, coughing or choking when eating, or very slow eating, that the physician should think about dysfunctional swallow and pulmonary aspiration as causes for infection.

GAMMAGLOBULIN THERAPY

Individuals who are unable to produce adequate amounts of immunoglobulins or antibodies may benefit from replacement therapy with gamma globulin. The term gamma globulin refers to the chemical fraction of blood that contains immunoglobulins or antibodies. Gamma globulin therapy is not used for patients with isolated IgA deficiency.

Mature B-lymphocytes (plasma cells), when encountering antigens, manufacture antibodies and release these molecules into the bloodstream. To commercially prepare antibodies that can be given to patients, the antibodies must first be purified (extracted) from the blood of normal healthy individuals. Blood from each donor is carefully tested for evidence of transmissible diseases, such as AIDS or hepatitis, and any sample that is even suspected of having one of those diseases is discarded. Blood is collected from approximately

10,000 people, then pooled together. Since different individuals are exposed to different germs, collecting blood from so many different people is the best way to ensure that the final gamma globulin product will contain antibodies to many different types of germs.

The first step in gamma globulin production is to remove all red and white blood cells. Then, the immunoglobulins are chemically purified in a series of steps involving treatment with alcohols. The process results in the purification of antibodies of the Immunoglobulin G (IgG) class, but only trace amounts of IgA and IgM survive.

The purification process removes other blood proteins and is also very effective at killing viruses and other germs that may be in the blood. Purified gamma globulin has been used for approximately 40 years and is extremely safe. On only one occasion has a gamma globulin product manufactured in the United States ever transmitted an infectious disease. Due to a change in manufacturing process during the mid-1990s, one company produced gamma globulin contaminated by hepatitis C virus. Since the outbreak of hepatitis C, every U.S. manufacturer has been required to add additional steps to inactivate any viruses that may have escaped the alcohol purification process. The U.S. Food and Drug Administration has tested the manufacturing processes and found that they completely kill the virus that causes AIDS. No subsequent infections have occurred.

There are two forms of gamma globulin that can be given to patients - a form to be injected into muscle (intramuscular, IM) and a form to be injected directly into the bloodstream (intravenous, IV). Gamma globulin products for intramuscular use have been used for decades and continue to be used to give normal individuals a boost of antibodies after exposure to some specific diseases such as hepatitis. The same products were used for many years to treat immunodeficient patients. Unfortunately, immunodeficient patients required frequent injections with much larger doses of gamma globulin than those used in normal individuals. These intramuscular injections were very painful, and only modest amounts of gamma globulin could be given in this way - there simply was not enough room inside the muscle for more.

In the early 1980s, new manufacturing processes were developed to make gamma globulin products that could be injected intravenously (called IVIG or IGIV). There are now many different gamma globulin preparations licensed in the United States for intravenous use. For the most part, the products are equivalent. There are some minor differences which may make one particular preparation most suitable for a given individual. Your doctor is your best source of information about which product is best for you.

The new intravenous gamma globulin products are usually very well tolerated by patients. They can be administered either in an outpatient clinic or in the patient's home. A typical infusion will take two to four hours from start to finish. Use of intravenous products allows physicians to give larger doses of gamma globulin than could be given intramuscularly. Most patients have no side effects

from the IV infusions, but low grade fever or headache sometimes occur. These symptoms can usually be alleviated or eliminated by infusing the gamma globulin at a slower rate.

The dose of gamma globulin varies from patient to patient. In part, the dose is determined by the patient's weight. It is also determined by measuring the blood level of IgG in the patient at some interval after infusion, and by determining how well a given dose of gamma globulin is treating or preventing symptoms. Intravenous infusions of gamma globulin are usually given every three to four weeks, but they may be given more or less frequently depending on the needs of the individual patient.

It is important to remember that although our current gamma globulin products are very good, they do not duplicate exactly what nature normally provides. The manufactured gamma globulin is almost pure IgG, so essentially no IgA or IgM is transferred to the patient. The specific protective functions of these immunoglobulins are therefore not replaced. At least part of the reason that antibody-deficient patients remain somewhat more susceptible to respiratory infections, even though they are receiving gamma globulin, may be that the IgA on the mucosal surfaces of the respiratory tract is not being replaced.