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The Immune System

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Abstract
The immune system comprises a variety of components that cooperate to defend the host against infectious agents. These components generally can be divided into nonspecific (or native) immune defense mechanisms and specific (or acquired) immune defense mechanisms. The nonspecific defense mechanisms are not antigen specific. They are present in a normal animal without previous exposure to antigen, and they are capable of responding almost immediately to an infectious agent. The major components of the nonspecific immune system are complement, phagocytic cells (macrophages, neutrophils, and eosinophils), natural killer cells, and some types of interferon. These components are very important in controlling an infection during the first few days after an initial exposure to an agent. This is the time when the specific immune response system is gearing up to produce antibody and a cell-mediated immune response.

Disciplines
Large or Food Animal and Equine Medicine | Veterinary Microbiology and Immunobiology | Veterinary Preventive Medicine, Epidemiology, and Public Health

Comments
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The immune system comprises a variety of components that cooperate to defend the host against infectious agents. These components generally can be divided into nonspecific (or native) immune defense mechanisms and specific (or acquired) immune defense mechanisms. The nonspecific defense mechanisms are not antigen specific. They are present in a normal animal without previous exposure to antigen, and they are capable of responding almost immediately to an infectious agent. The major components of the nonspecific immune system are complement, phagocytic cells (macrophages, neutrophils, and eosinophils), natural killer cells, and some types of interferon. These components are very important in controlling an infection during the first few days after an initial exposure to an agent. This is the time when the specific immune response system is gearing up to produce antibody and a cell-mediated immune response.

B and T lymphocytes and their products are the components of the specific immune response system. This antigen-driven system requires 2–3 weeks to reach optimal functional capacity after the first exposure to antigen. Upon second exposure to antigen, the specific immune response system reaches optimal activity much more rapidly due to the anamnestic, or memory, response. A major mechanism by which B and T lymphocytes enhance resistance to disease is by activating the nonspecific defense mechanisms (phagocytic cells, natural killer cells, and complement) to be more efficient. The immune response in mammals has been shown to be influenced by genes in the major histocompatibility complex (MHC). In pigs, this is referred to as the swine leukocyte antigen (SLA) complex. Genetic influences on susceptibility to disease in the pig are discussed in Chapter 64 of this book.

Providing immunity at mucosal surfaces and to the newborn piglet are especially difficult challenges for the immune system and for the swine producer. The nature of these special problems will be discussed as well as generalities about vaccination to improve immunity at mucosal surfaces and in newborn pigs.

If an animal is immunosuppressed due to stress, pre-existing viral infection, immunotoxicants, or nutritional factors, the nonspecific defense mechanisms may not function optimally. In addition, the specific immune response may be slow to develop or inadequate, which can result in clinical disease due to an infectious agent that would otherwise be controlled by a nonimpaired immune system.

The immune system has potent mechanisms for protecting the pig from infectious and neoplastic diseases. If the immune system is overstimulated or is not appropriately regulated, it may cause hypersensitivity reactions. This can occur in response to infection, vaccination, or environmental or dietary antigens, or even against normal host tissues.

**PHYSIOLOGY OF THE IMMUNE SYSTEM**

**Native Defense Mechanisms**

**PHYSICAL, CHEMICAL, AND MICROBIAL BARRIERS.** Physical, chemical, and microbial barriers to infection at body surfaces are a very important part of resistance to disease. These factors include squamous epithelium, bactericidal fatty acids, normal flora, the mucus layer and the flow of mucus, low pH, bile, and numerous enzymes. The antibacterial peptides are a relatively newly described family of molecules that help to form a chemical barrier to infection at epithelial surfaces. At least five antibacterial peptides have been isolated from the epithelium in the small intestine of the pig (Lee et al. 1989; Agerberth et al. 1991; Agerberth et al. 1993; Boman et al. 1993). Three of these peptides are bactericidal for *Escherichia coli*. More detailed information on physical, chemical, and microbial barriers to infection may be found in chapters dealing with specific organ systems.

**COMPLEMENT.** The complement system is an enzyme cascade system similar to the coagulation system and is composed of at least 20 serum proteins. In a cascade system something happens to activate the first component, which in turn activates the next component, which in turn activates the next component, and so on, until the reaction is completed. Since the sequential steps involve enzymes, the system is greatly amplified as it proceeds. The components of the mammalian complement system can be divided into different groups: the classical pathway, the alternative pathway, the membrane attack pathway, and regulatory proteins. All nine components of the classical and membrane attack pathways have been individually titrated in swine sera (Barta and Hubbert 1978). The complement system is very im-
important in mediating the inflammatory response and controlling bacterial infection. It also plays a prominent role in many types of allergies and hypersensitivity diseases. The classical pathway is triggered primarily by antigen-antibody complexes (IgG and IgM). The alternative pathway may also be activated by antigen-antibody complexes (IgA and IgE), by certain bacterial products, such as endotoxin, and by proteases released by tissue damage. Both the classical and the alternative pathways end in the splitting of the third component of complement (C3) and start the formation of the membrane attack complex.

The complement system has many important biologic activities. Activation of either the classical or alternative pathway causes vasodilation and increased vascular permeability, resulting in serum components (including antibody and complement) entering the tissues to help control infection. Complement components produced during activation are chemotactic and attract phagocytic cells to the site of infection. They also coat infectious agents so they can be more easily phagocytized by phagocytic cells. A very important function of the membrane attack pathway of complement is the destruction of cell membranes, including some bacterial cell membranes.

The complement system is important for mediating inflammation and controlling bacterial infection. However, since it is so potent, it is also capable of causing serious and even life-threatening damage if it is activated in an unregulated fashion. Therefore, numerous regulators of complement are present in the serum. These regulators help to control and stop the complement reaction once it has started.

**PHAGOCYTIC CELLS.** Phagocytic cells are responsible for engulfing, killing, and digesting invading bacteria. They also play an important role in controlling viral and fungal infections and in killing cancer cells. There are two main types of phagocytic cells: (1) the granulocytes (polymorphonuclear leukocytes), which include the neutrophils and the eosinophils, and (2) the mononuclear phagocytes, which include the circulating monocytes in the blood and the tissue macrophages. All these cell types are phagocytic and are capable of all the reactions described below for neutrophils. In addition, macrophages play a very important role in processing antigens and presenting them to lymphocytes to mitiate and facilitate the cell-mediated and humoral immune responses.

**Granulocytes.** Neutrophils are produced in the bone marrow and are released into the blood. The half-life of neutrophils in the bloodstream is approximately 8 hours; they then enter the tissues. In the healthy individual the neutrophils are lost into the intestinal tract and lung primarily. Neutrophils migrate into the intestinal tract very rapidly in response to *E. coli* infection in the pig (Sellwood et al. 1986). Neutrophils in the circulation tend to marginate in the capillaries by loosely associating with the endothelial cells. In swine, neutrophils seem to have a high affinity for margination in the capillaries of the lung (Oghami et al. 1989).

The principal function of the neutrophil is the phagocytosis and destruction of invading microorganisms. The neutrophil is well equipped to perform this function and has several mechanisms for destroying microorganisms. To be effective, the neutrophil must first come into the vicinity of the invading microorganism. This is achieved by the chemotactic attraction of the neutrophil to the site. Chemotactic factors may be produced directly by certain microorganisms, be generated by the cleavage of certain complement components, or be released by sensitized lymphocytes at the site of infection or inflammation. The chemotactic factors will diffuse away from the site to form a gradient, and when they reach a capillary, they cause the endothelial cell membrane and the neutrophil membrane to increase the expression of adhesion proteins. The neutrophils then adhere to the endothelial cells and leave the capillary by diapedesis. Once in the tissues, the neutrophils migrate along the chemotactic factor gradient toward the source of the chemotactic factor and thus arrive at the site of infection; they will begin to ingest the microorganisms if those agents are susceptible to phagocytic activity. Most pathogenic microorganisms must be opsonized before they can be ingested; bacteria are opsonized by the attachment of specific antibody and/or complement to their surface. The opsonization process facilitates ingestion. When a neutrophil comes into contact with an opsonized particle, it will attempt to surround the particle with pseudopodia and ingest it by the process of phagocytosis. The ingested particle will be within a membrane-bound vesicle called a phagosome.

The neutrophil cytoplasm contains two main types of membrane-bound lysosomes (granules): (1) primary, or azurophilic, granules and (2) secondary, or specific, granules. These lysosomes contain numerous hydrolytic enzymes that have been quantitated in porcine neutrophils (Chibber and Castle 1983) and at least six cationic antibacterial peptides (Kokryakov et al. 1993; Shi et al. 1994; Storici et al. 1994; Zanetti et al. 1994) that are important to the bactericidal activity of the neutrophil. After a particle is ingested and is inside a phagosome, the neutrophil "degranulates"; some of the lysosomes fuse with the phagosome and release their contents into the phagosome with the ingested particle. The hydrolytic enzymes and antibacterial peptides can function under aerobic or anaerobic conditions to attempt to destroy the ingested microorganisms. The antibacterial peptides act by rendering the bacterial membranes permeable. Neutrophils die after a short time at sites of inflammation. The hydrolytic enzymes are released and contribute to the inflammatory response and tissue destruction.

In addition to having hydrolytic enzymes and anti-
In addition to its important role in the phagocytosis and destruction of pathogenic bacteria, the neutrophil may also be important in controlling certain viral infections via a mechanism referred to as antibody-dependent cell-mediated cytotoxicity. As the name implies, this mechanism requires antibody, which presumably forms a bridge between the neutrophil and the virus-infected target cell. The neutrophil will then attempt to destroy the target cell. The mechanism of this cell destruction is not known but is thought to involve a direct membrane-to-membrane interaction. Porcine neutrophils are very active at antibody-dependent cell-mediated cytotoxicity, even in the fetus and newborn (Zarkower et al. 1982; Yang and Schultz 1986). They are the only cell type capable of antibody-dependent cell-mediated cytotoxicity against African swine fever virus (Norley and Wardley 1983a).

Several steps are involved in the neutrophils' attempt to control invading microorganisms: (1) adherence of neutrophils to vascular endothelium and exit from the blood vessel via diapedesis, (2) random migration and directed migration along a chemotactic gradient, (3) the engulfment of opsonized microorganisms, (4) degranulation, (5) the generation of oxygen-free radicals and 

\[ \text{H}_2\text{O}_2 \], (6) the myeloperoxidase-catalyzed reaction, and (7) antibody-dependent cell-mediated cytotoxicity. Assays can be conducted for each of these processes. If any of these processes are impaired in the neutrophil, one would expect that the neutrophil would not be able to perform its function of controlling microbial infection as efficiently. This would make the animal more susceptible to microbial infection. Depressions neutrophil function has been associated with increased susceptibility to experimentally induced E. coli mastitis in sows (Löfstedt et al. 1983).

The eosinophil is capable of the same phagocytic and metabolic functions as the neutrophil, but to a different extent. The eosinophil is not as active as the neutrophil in destroying bacteria but is important in the host's defense against the tissue phase of certain parasitic infec-

\[ \text{H}_2\text{O}_2 \], oxygen free radicals and hydrogen peroxide, superoxide anion (O_2^-), the hydroxyl (OH^-), and perhaps singlet oxygen (O_2). All of these components can damage microbial organisms. The 

\[ \text{H}_2\text{O}_2 \] formed after phagocytosis may also react with halide ions in a reaction catalyzed by a myeloperoxidase enzyme that is released from the primary granules. This reaction is one of the most potent bactericidal mechanisms of the neutrophil and is also potentially fungicidal and virucidal.

in destroying bacteria, it can efficiently attach to and kill migrating parasites that are too large to be ingested. Eosinophils are also important in helping to control certain types of allergic responses.

Mononuclear Phagocytes. The mononuclear phagocytic system is made up of circulating monocytes, fixed macrophages, and wandering macrophages (histiocytes). Monocytes are produced in the bone marrow and released into the bloodstream, where they circulate before migrating into the tissues to become macrophages. The fixed macrophages are found lining the endothelium of capillaries (particularly in the lungs) and the sinuses of organs such as the spleen, bone marrow, and lymph nodes. These fixed macrophages are important for trapping and removing foreign antigens from the bloodstream and lymph. Wandering macrophages are derived from blood monocytes and are found throughout the tissues of the body. In certain locations, they differentiate into specialized types of macrophages such as the glial cells in the nervous system, Langerhans cells in the skin, and Kupffer cells in the liver.

Macrophages are capable of all the activities described above for neutrophils. Macrophages are said to be the second line of defense. They are slower to arrive at the site of inflammation and are not as aggressive as neutrophils. Macrophages have been activated by cytokines secreted by T lymphocytes. As the name implies, this mechanism requires antibody, which presumably forms a bridge between the neutrophil and the virus-infected target cell. The neutrophil will then attempt to destroy the target cell. The mechanism of this cell destruction is not known but is thought to involve a direct membrane-to-membrane interaction. Porcine neutrophils are very active at antibody-dependent cell-mediated cytotoxicity, even in the fetus and newborn (Zarkower et al. 1982; Yang and Schultz 1986). They are the only cell type capable of antibody-dependent cell-mediated cytotoxicity against African swine fever virus (Norley and Wardley 1983a).

A very important function of macrophages is the processing of antigen and presentation of antigen to T lymphocytes. This is an essential step in the initiation of a cell-mediated immune response and for facilitating an efficient antibody response by B lymphocytes. The interaction of macrophages with antigen and T and B lymphocytes is described below.

Alveolar macrophages are found normally in the alveoli of the lung (Chitko-Mckown et al. 1991). They migrate into the alveoli, where they phagocitize inhaled particles, including low numbers of bacteria that they may encounter. After ingesting the particles, they leave the alveoli either through the airways, where they move up the mucociliary escalator, or by migrating out of the alveoli between alveolar epithelial cells and being carried through lymphatic drainage to local lymph nodes. There, they present the antigens they have captured to lymphocytes to initiate an immune response.
Kown and Blecha 1982). They are prominent in pigs and some other species and are believed to be important for phagocytizing and removing infectious agents from the blood. Since all of the blood passes through the pulmonary vasculature on each pass through the body, this is a good location for macrophages responsible for removing bacteria from the blood. The pulmonary intravascular macrophages are therefore primarily involved in defense against septicaemia rather than protection from respiratory disease. Pulmonary intravascular macrophages that are actively clearing bacteria from the bloodstream (especially gram-negative bacteria or free endotoxin) may release cytokines and arachidonic acid metabolites, which contribute significantly to pulmonary inflammation (Crocker et al. 1981 a,b; Bertram 1986).

**NATURAL KILLER CELLS.** Natural killer (NK) cells are lymphoid cells capable of "natural cytotoxicity"; that is, they can kill a variety of nucleated cells without previous antigenic stimulation. They are part of the native immune system and can kill some (but not all) tumor cells and some (but not all) virus-infected cells. NK cells in most species are also called large granular lymphocytes because of the presence of granules in their cytoplasm. NK cells in most species are part of the null-cell population because they are distinct from B cells, T cells, and macrophages. In most species NK cells have Fc receptors for IgG and can mediate antibody-dependent cell-mediated cytotoxicity (ADCC) against most antibody-coated mammalian cells. When mediating ADCC, these cells have been called killer (K) cells.

NK cells in the pig differ markedly from NK cells found in other species. NK activity in swine is mediated by small granular lymphocytes that have the CD2 T-cell marker (Ferguson et al. 1986; Duncan et al. 1989) and are, therefore, not null cells (Duncan et al. 1989). Swine NK cells are slower in initiation of the lytic process against typical target cells (YAC-1 lymphoma and K-562 myeloid leukemia cells) than cells responsible for NK activity in other species (Ferguson et al. 1986). In swine there is evidence that NK-cell activity and K-cell activity are from two distinct populations of lymphocytes (Kim and Ichinura 1986; Yang and Schultz 1986). Swine NK cells are capable of lysing cells infected with transmissible gastroenteritis virus and pseudorabies virus (Evans and Jaso-Friedmann 1993).

The activity of NK cells in many species is increased in the presence of interferon-γ and interleukin-2 (IL-2). Swine NK cells have been shown to respond to an interferon inducer (poly I:C), IL-2, human interferon-α, and human IL-1α with enhanced NK activity (Lesnick and Derbyshire 1988; Knoblock and Canning 1992; Evans and Jaso-Friedmann 1993). Therefore, NK cells are an important part of native defense mechanisms and also participate in a cell-mediated immune response by enhanced activity through cytokine activation.

**Humoral and Cell-Mediated Immunity.**

**CLONAL SELECTION AND EXPANSION.** An important concept that is basic to understanding the immune response is the clonal selection process. Each mature T or B lymphocyte in the body has receptors on its surface that it uses to recognize antigens. All the antigen receptors on one lymphocyte recognize exactly the same antigen (or small group of antigens). All the lymphocytes that recognize exactly the same antigen make up a "clone" and have all arisen from the same ancestor cell. There are millions of clones of T and B lymphocytes. Each clone may contain from a few hundred to a few million cells. The lymphocytes are in a resting stage as they circulate through blood, enter the lymph nodes through the postcapillary venules, percolate through the lymph nodes, and reenter the bloodstream.

In the lymph nodes (or other secondary lymphatic tissues), lymphocytes come in contact with antigens that arrived through the afferent lymphatics and are trapped by macrophages. Each lymphocyte can respond only to the one specific antigen that it can recognize through its antigen receptors. Therefore, the vast majority of lymphocytes that contact an antigen in the lymph node cannot respond to it. In an animal that has never been exposed to a particular infectious agent before, relatively few lymphocytes will recognize that particular antigen. The first step, therefore, in producing an effective primary immune response is to expand the clone of lymphocytes that recognize the antigen. The T and B lymphocytes that recognize the antigen are stimulated to undergo a series of cell divisions so that within a few days there will be enough lymphocytes in the clone to mount an effective humoral and/or cell-mediated immune response. If the animal has been exposed to the antigen previously, the clone of lymphocytes has already been expanded, so not nearly as many cycles of cell division are needed to produce enough lymphocytes to mount an immune response. This can result in a degree of protection from vaccination or exposure even if there is no remaining detectable antibody. The cells present in the expanded clone are called memory cells. If the previous exposure has been relatively recent, there still will be circulating antibody and effector T lymphocytes that can act immediately to begin to control the infection.

**CELLULAR INTERACTIONS IN THE INDUCTION OF THE IMMUNE RESPONSE.** The induction of clonal expansion and the immune response requires a complex interaction of macrophages, T lymphocytes, and B lymphocytes. Macrophages attempt to phagocytize and destroy infectious agents. After the infectious agent is partially degraded by the macrophage, antigenic fragments are taken up by macrophages and presented to the T lymphocyte. This interaction results in the production of helper T cells (Th cells) that produce cytokines, such as IL-2 and interferon-γ, which stimulate the B lymphocytes to differentiate into antibody-secreting plasma cells. The antibody-secreting plasma cells then produce large quantities of specific antibodies, which are transported to the site of infection by the blood and lymphatic systems. The antibodies bind to the antigen, neutralizing its activity and marking it for destruction by macrophages. The macrophages then phagocytize the antigen-antibody complexes, destroying the antigen and preventing its further spread. The macrophages also release cytokines, such as interleukin-1 and tumor necrosis factor, which activate and recruit other cells of the immune system, including cytotoxic T lymphocytes, which can directly destroy infected cells. This coordinated interaction of macrophages, T lymphocytes, and B lymphocytes is essential for the effective induction of an immune response.
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from it are bound to MHC class II molecules on the macrophage surface, where they can easily be contacted by T lymphocytes. Macrophages (and other specialized antigen-presenting cells) have a high density of MHC class II molecules on their surface.

T-helper (T<sub>h</sub>) cells are needed to help initiate the immune response. They can efficiently recognize only foreign antigens that are on a cell surface bound to an MHC class II molecule. Cytotoxic T (T<sub>c</sub>) cells are important for killing cells infected with intracellular pathogens and cancer cells. They can recognize only foreign antigens that have been processed intracellularly and transported to a cell surface bound to an MHC class I molecule. T<sub>h</sub> and T<sub>c</sub> cells cannot respond to free soluble antigen or to whole bacteria or viruses.

Because the MHC class I and class II molecules play a key role in antigen presentation to T lymphocytes, they are capable of significantly influencing the nature of the immune response. The MHC molecules in all species are highly polymorphic; that is, genetically different individuals inherit different types of MHC molecules. The MHC molecules in swine are called the swine leukocyte antigen (SLA) complex molecules. The type of SLA molecules that a pig inherits has some influence on its immune response to pathogens and its ability to resist infectious diseases (Lunney 1993, 1994).

To be fully activated, the T<sub>h</sub> cell also requires the presence of cytokines released by the antigen-presenting cell or by other T cells and contact with co-stimulatory molecules on the surface of the antigen-presenting cell. Interleukin-1 (IL-1) is an important molecule released by macrophages that are processing antigen. IL-1 is a protein molecule (formerly referred to as lymphocyte activating factor and endogenous pyrogen) that is a key mediator of the host response to infection through its ability to induce fever and neutrophilia, among other things. A very important function of macrophage-produced IL-1 is its action on T<sub>h</sub> cells to cause them to secrete IL-2. IL-2 is a protein molecule (formerly called T-cell growth factor) secreted by activated T<sub>h</sub> cells. IL-2 is needed for T cells to undergo mitosis and produce more cells in the clone. B cells are also capable of processing antigen and presenting it to T<sub>h</sub> cells on MHC class II molecules. During secondary immune responses, B cells are thought to be the main type of antigen-presenting cell.

T<sub>h</sub> cells are very important in initiating the B-cell response resulting in antibody production. B cells contact antigen through immunoglobulins bound to their surface, which act as receptors. Antigens do not have to be presented on MHC class II molecules by macrophages for a B cell to recognize them. An optimal B-cell response to antigen requires the help of soluble factors released by T<sub>h</sub> cells and contact with co-stimulatory molecules on the T<sub>h</sub>-cell surface. This T<sub>h</sub>-cell help is needed for B-cell mitosis and clonal expansion and for switching the class of antibody produced from IgM to IgG, IgA, or IgE.

LYMPHOCYTE SUBPOPULATIONS. Lymphocyte subpopulations are defined by the presence of certain molecules on their surface. These molecules are identified by a standardized nomenclature and given a CD number which designates similar molecules in all species. CD stands for "cluster of differentiation." This terminology arose because the surface molecules were differentiated from each other by "clusters" of monoclonal antibodies. At least 19 CD molecules have been identified on the surface of porcine leukocytes (Saalmuller et al. 1996). Over 130 CD molecules have been identified on human or mouse leukocytes, and there are probably at least that many on porcine leukocytes also.

Lymphocyte subpopulations in the peripheral blood of pigs are markedly different from those of other species. Young pigs have higher blood lymphocyte counts than most other mammals (approximately 10<sup>7</sup>/mL). Up to 50% of these lymphocytes are null cells, which lack most surface markers characteristic of B or T cells. They are usually identified on human or mouse leukocytes (Chien et al. 1994). These null cells do not recirculate between the blood and lymphatic tissues, and they differ from null cells in other species in that they do not have NK-cell activity.

The majority of these null lymphocytes have recently been shown to be gamma delta (γδ) T cells. The T cells that predominate in the blood of humans and mice and that recognize peptide antigens presented on MHC molecules are called alpha beta (αβ) T cells. Their antigen receptor is made up of an α and a β chain and they have either a CD4 or a CD8 molecule to assist in their interactions with MHC molecules. The antigen receptors on γδ T cells are made up of a γ and a δ chain. They do not have CD4 or CD8 molecules associated with them because they apparently are capable of recognizing intact antigen molecules, similar to the way antibodies recognize antigen. Unlike the αβ T cells, they do not require antigen processing and presentation on MHC molecules (Chien et al. 1996). Pigs and other ungulates have a much higher population of γδ T cells in the blood than do other mammals that have been studied. The functional significance of γδ T cells and their role in resistance to disease are poorly understood but are an active topic of research in the pig (Hirt et al. 1990; Bians 1994; Thome et al. 1994).

Swine T lymphocytes have at least three unusual properties compared to other species (Lunney and Pescovitz 1987). (1) Approximately 25% of swine peripheral-blood T cells express both the CD4 and CD8 antigens on their surface. It has been suggested that many of these dual expressing T cells are memory cells; however, the functional significance of having both CD4 and CD8
on the same cells is not known (Pescovitz et al. 1994; Zuckermann and Husmann 1996). (2) The ratio of CD4+ to CD8+ T cells is normally about 0.6 in pigs, which is a reversal of the expected ratio in other species. A normal ratio of CD4+ to CD8+ in humans is 1.5–2.0. Both of these properties are very unusual in other species and only occur in pathological conditions in humans. (3) Resting CD8+ cells in swine preferentially express MHC class II antigens. The significance of these differences between swine T lymphocytes and those of other species is not completely understood.

LYMPHOCYTE CIRCULATION. Lymph node structure and lymphocyte circulation are markedly different in the pig compared to humans or to other domestic species (Binns 1982). Recirculation of lymphocytes from blood to lymphoid tissues is very important for bringing an antigen into contact with the rare lymphocytes that are able to recognize it. Circulation of B cells, T cells, and macrophages through lymph nodes is also important for facilitating cellular interactions needed for the induction of the immune response as described above.

Lymphocytes are produced in the bone marrow as well as in the thymus and in all secondary lymphoid tissues in the pig. Lymphocytes are released from the site of production into the bloodstream. T and B lymphocytes circulate in the blood for an average of approximately 30 minutes before entering the tissues. Null cells in the pig apparently remain in the bloodstream and do not recirculate between blood and lymphoid tissues. Porcine lymph nodes are structurally inverted compared to other domestic species. Lymphatics enter the node through the hilus, and the lymph passes through the node and leaves through the periphery. The lymph node has a dense medulla which lacks sinuses and cords. The germinal centers are located in the interior of the node. Other lymphoid organs such as the Peyer’s patches, tonsils, and spleen are similar to those found in other species (Binns et al. 1986; Pabst and Binns 1986).

Lymphocytes in swine and other species enter the lymph node through two routes. Lymphocytes leaving the bloodstream and entering the subcutaneous tissues are carried to the lymph node in the afferent lymphatics. Lymphocytes may directly enter the lymph node by adhering to high endothelial cells in the venules of the lymph node. The high endothelial cells phagocytize the lymphocytes and transport them into the lymph node. In other species, the lymphocytes exit the lymph node in the efferent lymphatics and are carried through the thoracic duct back to the circulatory system. In swine, the efferent lymph contains very few lymphocytes. The lymphocytes in the lymph node directly reenter the circulation in swine (Binns et al. 1986). The emigration of lymphocytes from blood into lymph nodes can be increased by antigenic stimulation.

In addition to migrating from blood to lymphoid tissues, lymphocytes in swine migrate into most other tissues as well (Binns et al. 1986). Lymphocyte subpopulations in swine show a distinct preference for circulation to either gut-associated lymphoid tissues or surface nodes (Binns et al. 1986). For instance, mesenteric lymph node cells (both T and B lymphocytes) preferentially home to the gut (Salmon 1986). In rodents the majority of the lymphocytes found in the mammary gland also come from gut-associated lymphoid tissue, whereas in swine approximately equal numbers of lymphocytes in the mammary gland come from gut-associated lymphoid tissue and from peripheral lymph nodes. The dual origin of mammary lymphocytes in swine suggests that the local mammary immune response may not depend solely on oral immunization (Salmon 1986, 1987).

ACQUIRED IMMUNE DEFENSE MECHANISMS. An important component of lymphocyte activity in host defense is mediated by soluble products released by stimulated lymphocytes. T lymphocytes secrete a variety of cytokines, and B lymphocytes differentiate into plasma cells that secrete antibodies (B lymphocytes are also able to secrete some cytokines). Antibodies are specific for the antigens that induced them, whereas cytokines are not. These soluble products produced during the immune response play an important role in orchestrating host defense against pathogens partially through their direct activities and partially by enhancing the activity of the nonspecific defense mechanisms (i.e., complement, phagocytic cells, and NK cells).

The cytotoxic T lymphocytes (Tc cells) are an important part of the cell-mediated immune response to virus infection and tumors. Most Tc cells have the CD8 marker on their surface and only recognize antigen associated with MHC class I molecules on a cell surface. MHC class I molecules present peptide antigens derived from proteins synthesized within the cell, such as viral proteins. The Tc cells directly attack host cells that have foreign antigen (e.g., viral antigen) presented on MHC class I molecules on their surface. These cells do not attack free bacteria or viruses. Tc-cell activity specific for hog cholera virus and African swine fever virus has been demonstrated in pigs that have recovered from infection (Martins et al. 1993; Pauly et al. 1995). Tc cells kill target cells by making direct contact, releasing granzymes onto the cell surface, and inducing apoptosis (programmed cell death) in the target cells.

IMMUNOGLOBULINS
Production of Immunoglobulins. B lymphocytes from clones that have never been stimulated by antigen have monomeric IgM antibody molecules on their surface that act as antigen receptors. All of the IgM molecules on one B cell are specific for the same antigen. When a B cell is appropriately stimulated by the antigen it recognizes (along with soluble products from a Tc cell), it begins to undergo mitosis. This results in the formation of many more B cells with IgM receptors that also...
recognize the same antigen. Some of these newly formed B cells differentiate into plasma cells that secrete IgM antibody. The increasing antigen-specific IgM antibody concentration in the blood signals the T\(_h\) cell to in turn signal some of the B cells to switch from IgM production to IgG, IgA, or IgE production. These B cells then rearrange their genetic material that codes for antibody production and produce antibody molecules with the same antigenic specificity (i.e., the same light-chain structure and variable portion of the heavy chain) but of a different antibody class (i.e., the constant heavy portion of the antibody molecule is changed). Changing the antibody class gives the antibody molecules different properties. The class of antibody that the T\(_h\) cells cause the B cells to switch to depends to a large extent upon the nature of the antigen and the location in the body where the antigen was trapped. T\(_h\) cells located in lymph nodes and the spleen tend to induce B cells to switch to IgG production. T\(_h\) cells located in Peyer’s patches or under other mucosal surfaces tend to induce B cells to switch to IgA and/or IgE production, depending on the nature of the antigen and the genetic predisposition of the individual.

Antibody molecules have a variety of activities in host defense, although they alone cannot kill infectious agents. Antibody molecules can coat infectious agents to prevent them from attaching to or penetrating host cells, they can agglutinate infectious agents to reduce their infectivity, and they can directly bind to and neutralize toxins. A very important function of antibody is that it marks infectious agents for destruction by complement, phagocytic cells, and/or cytotoxic cells.

**Classes of Immunoglobulins.** Characteristics of the various classes of porcine immunoglobulin were thoroughly reviewed in a previous edition of this book (Porter 1986).

IgG is the predominant Ig class in the serum of the pig and other species. It accounts for more than 60% of the Ig in serum and colostrum (Table 56.1). The two main subclasses of IgG are IgG1 and IgG2 (Metzger and Fougerau 1968), with IgG1 predominating in serum and colostrum. The IgG3 and IgG4 subclasses are found in lesser concentrations. An 18S Ig has been described that is antigenically similar to IgG2 and is found in low levels in normal serum and colostrum (Kim et al. 1966). Newborn piglets also possess a 5S IgG, which may not have light chains and may not be functional (Stertzl et al. 1960; Franek and Riha 1964).

IgM accounts for approximately 5–20% of the total Ig in serum and colostrum (Table 56.1). IgM is a pentamer held together by disulfide bonds and has a sedimentation coefficient of 17.8S (Porter 1969).

The porcine immune system produces far more IgA than any other class of antibody; however, most of the IgA is found on mucosal surfaces rather than in the serum. IgA is present in swine serum as dimers which are two monomers bound together with a J chain (Halpern and Koshland 1970; Mestecky et al. 1971; Porter and Allen 1972). IgA at mucosal surfaces is mostly dimeric IgA with a J chain and associated secretory component (see the section on mucosal immunity below).

Porcine IgE has recently been purified and characterized (Roe et al. 1993). It was shown to have physicochemical properties similar to IgE in other species, including the characteristic of losing biologic activity when serum is heated to 56°C. The investigators produced monoclonal polyclonal antisera for porcine IgE. The antisera inhibited a passive cutaneous anaphylaxis reac-

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**Table 56.1.** Concentration of porcine immunoglobulins (mg/mL) in body fluids

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgG2</th>
<th>IgM</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult sow serum</td>
<td>24.3 ± 0.9</td>
<td>14.1 ± 0.5</td>
<td>2.9 ± 0.2</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Colostrum</td>
<td>61.8 ± 2.5</td>
<td>40.3 ± 1.6</td>
<td>3.2 ± 0.2</td>
<td>9.6 ± 0.5</td>
</tr>
<tr>
<td>Milk (24 hours)</td>
<td>11.8 ± 4.8</td>
<td>8.0 ± 3.2</td>
<td>1.8 ± 0.3</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>Milk (48 hours)</td>
<td>8.2 ± 3.2</td>
<td>5.0 ± 1.8</td>
<td>1.8 ± 0.4</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>Milk (3–7 days)</td>
<td>1.9 ± 0.6</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.2</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Milk (8–35 days)</td>
<td>1.4 ± 0.6</td>
<td>1.00 ± 0.45</td>
<td>0.90 ± 0.25</td>
<td>3.05 ± 0.74</td>
</tr>
<tr>
<td>Intestinal fluid</td>
<td>Piglet</td>
<td>0.002</td>
<td>0.065</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Sow</td>
<td>0.001</td>
<td>0.001</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>Urinary tract</td>
<td>4.7</td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Follicle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diestrus</td>
<td>18.1</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrus</td>
<td>25.1</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Uterine secretions</td>
<td>Diestrus</td>
<td>0.32</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrus</td>
<td>0.34</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Cervicovaginal mucus</td>
<td>Diestrus</td>
<td>6.7</td>
<td>8.60</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Estrus</td>
<td>2.0</td>
<td>0.06</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Used with permission from Veterinary Clinical Immunology, R. E. W. Halliwell and N. T. Corman, editors. (Philadelphia: W. B. Saunders Co., 1989).
tion, identified a sparse population of plasma cells in the lamina propria of the gut and mesenteric lymph nodes of parasitized pigs, and reacted with human IgE in Western blotting. There are apparently no reports of the production of monoclonal antibodies specific for porcine IgE. Antibodies against human IgE and bovine IgE have been shown to react with a homocytotropic immunoglobulin in swine serum (Barratt 1972; Nielsen 1977).

**Polyclonal and Monoclonal Antibodies.** Antibodies produced by an animal in response to an infection or vaccination are polyclonal antibodies. Infectious agents are complex antigens with many different antigenic specificities on their surface; therefore, they stimulate many clones of B and T lymphocytes to respond. This results in a heterogeneous mixture of antibodies that recognizes a wide variety of surface molecules on the microorganism. This broad spectrum of antibodies that are produced and are present in the serum are very helpful to the animal in overcoming infection. The broad spectrum is sometimes a disadvantage, however, if one wishes to use the serum for developing diagnostic reagents. The polyclonal antibodies produced in response to one infectious agent may cross-react with another infectious agent and thus interfere with the specificity of the assay. The majority of the protein present in a polyclonal antiserum produced against an infectious agent is not antibodies directed against the agent. Therefore, the amount of specific antibody in relation to the amount of protein present is low. This is a disadvantage when attempting to protect an animal from disease by administering antisera.

Monoclonal antibodies are now commonly produced in research laboratories and are used to overcome many of the disadvantages of polyclonal antisera for diagnostic and, less commonly, for therapeutic purposes. Monoclonal antibodies are produced by one clone of B lymphocytes and therefore are all identical. All of the antibody molecules present in a monoclonal antibody preparation are specific for the same antigenic determinant; therefore, the antibody can be present in extremely high concentrations, which reduces the problem of cross-reactivity between microorganisms in diagnostic tests. If monoclonal antibodies can be produced against a protective antigen on a microorganism, the monoclonals can be used in therapy or prevention of disease. Since they can be produced in very high concentration and purity, a much lower volume of monoclonal antibody than of polyclonal antibody solution can be used to passively immunize animals. This reduces the risk of serious reaction to the passively administered antibody and its extraneous protein.

**CYTOKINES.** Cytokines are small protein or glycoprotein molecules that are secreted by cells and serve as intercellular signaling molecules. All cells of the immune system are capable of secreting some cytokines and of being influenced by some cytokines. Cytokine secretion is usually transient and occurs in response to specific stimuli. The cytokines that are secreted may act locally if they are secreted in low concentrations, or they may have systemic effects if they are secreted in higher concentrations. A cytokine will act only on a cell that has specific receptors for it. Regulation of cytokine receptor expression is an important mechanism for regulating the response to cytokines.

Information regarding cytokine biology has increased rapidly in recent years. Most of the new information on cytokine biology is from research on mice or humans. However, because of the economic importance of pigs, and their importance in biomedical research, considerable information has been published recently regarding porcine cytokines (Murtaugh 1994; Murtaugh and Foss 1997). The porcine cytokines that have been studied are generally similar to their homologues in humans or mice. Over 30 porcine cytokines have been described and partially characterized (Murtaugh 1994; Murtaugh and Foss 1997).

The cytokines can generally be categorized into four groups based on their functions (Abbas et al. 1994). One group of cytokines is important in mediating natural immunity. This includes the type I interferons (α and β) and the pro-inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α (TNFα). These are produced by macrophages and some other cell types and can be produced without previous exposure to antigen. The type I interferons are produced mainly in response to viral infection and can be produced by many cell types. They can be detected within a few hours of viral infection. The type I interferons make cells resistant to infection by some viruses, they increase NK-cell activity, and increase the efficiency of antigen presentation to T cells by increasing MHC molecule expression on cell surfaces.

The pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) are produced primarily by macrophages in response to bacterial infection. They may also be produced in response to viral, protozoal, or fungal infections or in response to tissue damage. These cytokines have several biologic activities. They stimulate the liver to produce acute-phase proteins; they stimulate the release of amino acids from muscle tissue and may induce cachexia or wasting in chronic infections; they induce fever, fatigue, and loss of appetite if present in high enough concentrations. Low levels of these cytokines promote leukocyte adhesion to endothelial cells and diapedesis of leukocytes into the tissues.

The second group of cytokines regulates lymphocyte activation, growth, and differentiation. These are produced mainly by T_{h} lymphocytes in response to antigen recognition. Three important cytokines in this group are
IL-2, IL-4, and transforming growth factor-β (TGF-β). IL-2 stimulates the proliferation of T and B cells that have recognized antigen. It also increases the cytotoxic activity of NK lymphocytes. IL-4 is important for effective IgE–mast-cell–eosinophil inflammatory reactions. This is needed for control of some parasites and may result in symptoms of allergy if the response is to nonparasite antigens. TGF-β is mainly a negative regulator of the immune response. It inhibits many activities of lymphocytes and may be a signal for shutting off the immune response.

A third group of cytokines is composed of those that regulate immune-mediated inflammation. They are produced mainly by T effector and Tc cells and their primary function is to activate the cells of the native defense system. The activation of the effector cells of the native defense system is a major component of cell-mediated immunity. Interferon-γ causes cells to be resistant to virus infection (similar to interferon-α and -β), and it is also a potent activator of macrophages, neutrophils, and NK cells. TNF-β often acts synergistically with interferon-γ to activate phagocytic cells. TNF-β can also activate endothelial cells, which results in diapedesis of leukocytes into sites of inflammation. IL-5 is secreted by Th2 cells and increases eosinophil production and their ability to kill parasites. IL-12 is a very potent activator of NK cells and it assists in the maturation of CD8+ cells into Tc cells.

The fourth group of cytokines stimulates hematopoiesis. This group of cytokines stimulates expansion and differentiation of bone marrow progenitor cells, which are called colony stimulating factors (CSFs). IL-3 is a CSF which stimulates the production of all of the types of leukocytes. Granulocyte-macrophage CSF (GM-CSF) stimulates the production of granulocytes and macrophages, whereas granulocyte CSF (G-CSF) stimulates the production of granulocytes only. The CSFs also may enhance the antimicrobial activities of mature neutrophils and macrophages.

**Mucosal Immunity**

Providing immunity at mucosal surfaces is a difficult problem. Mucosal surfaces are frequently exposed to infectious agents. The components of the immune system described previously may not function well in the microenvironment on the mucosal surface. The degree to which the various components of the immune system contribute to protective immunity varies with the mucosal surface. For instance, IgG class antibody, complement, and phagocytic cells may function efficiently in the lower respiratory tract and in the uterus but not in the lumen of the gut.

An important component of immunity at mucosal surfaces is the secretory IgA system. Antigen that enters the body through a mucosal surface tends to induce an IgA class antibody response at the mucosal surface. It may also induce secretory IgA at other mucosal surfaces. Specialized epithelial cells called dome cells or M cells are found overlying aggregations of gut- and bronchus-associated lymphoid tissues. These dome cells pinocytose antigen and transport it across the epithelial layer. The antigen may then be processed by antigen-presenting cells and presented to T and B lymphocytes.

Lymphocytes in the bloodstream tend to segregate into two populations: those that circulate between the bloodstream and the systemic lymphoid tissues of the lymph nodes, spleen, and bone marrow, and those that circulate between the bloodstream and lymphoid tissues associated with mucosal surfaces. Because of the nature of the Th cells, which home to mucosal surfaces, antigens entering through mucosal surfaces tend to induce an IgA or IgE class antibody. In some cases antigens entering through the intestinal tract may induce oral tolerance, resulting in suppression of IgG class antibody responses.

In the mucosal lymphoid tissues, B cells that have been stimulated by antigen and induced by Th2 cells to switch to IgA class antibody production will leave the submucosal lymphoid tissue and reenter the bloodstream. These lymphocytes exit the bloodstream at submucosal surfaces and locate in the lamina propria, where they differentiate into plasma cells that secrete dimeric IgA. Many of these cells return to the same mucosal surface from which they originated but others can be found at other mucosal surfaces. Therefore, oral immunization can result in the migration of IgA precursor cells to the bronchi and subsequent secretion of IgA onto the bronchial mucosa. Oral immunization with live or inactivated *Actinobacillus pleuropneumoniae* has also been shown to result in the migration of Th cells and IgG positive lymphocytes to the bronchoalveolar space and production of IgA there (Delventhal et al. 1992; Hensel et al. 1994; Pabst et al. 1995). Lymphocytes that have been sensitized in the gut of the sow have a special affinity for migrating to the mammary gland to become plasma cells and secrete IgA into the milk. The IgA in the milk helps to protect the piglet from intestinal pathogens while it is nursing. This is an important mechanism for transferring from the sow to the piglet immunity to enteric pathogens that the sow has been exposed to.

The dimeric IgA secreted by the plasma cells in the lamina propria bind to secretory component on the basement membrane of mucosal epithelial cells. The dimeric IgA and secretory component are then transported to the mucosal surface of the epithelial cell, and this complex is released onto the mucosal surface. Secretory component is important for protecting the IgA molecule from proteolytic enzymes and also serves to anchor the IgA into the mucous layer so that it forms a protective coating on the mucosal surface.

Secretory IgA plays an important role in immunity at mucosal surfaces by agglutinating infectious agents, preventing the attachment of infectious agents to epithelial
cells, and neutralizing toxins. Other components of the immune response may also be important in protection against various types of infection at mucosal surfaces. For example, neutrophils in the pig can migrate into the intestinal lumen in large numbers within a 4-hour period in response to antigen-antibody complexes. The recruitment of neutrophils into the intestinal lumen is dependent upon the presence of antibody, which may be circulating IgG antibody (Bellamy and Nielsen 1974), colostral antibody (Sellwood et al. 1986), or locally induced IgA class antibody (Bhogal et al. 1987). Neutrophils in the lumen have been shown to be actively phagocytic (Bhogal et al. 1987). The immigrating of neutrophils into the lumen of the gut and their subsequent destruction have been shown to result in an increased concentration of lactoferrin, lysozyme, and cationic proteins. These substances may also contribute to immunity to bacterial infections in the gut.

T lymphocytes are important mediators of immunity at mucosal surfaces (Dunkley et al. 1995). This is especially true for respiratory infections with facultative intracellular bacterial pathogens. T lymphocytes also play a role in immunity in the intestinal tract. Salmon (1987) has shown that a high proportion of the intraepithelial lymphocytes in the intestine are of the T<sub>C</sub> phenotype. He speculates that these T<sub>C</sub> cells in contact with intestinal epithelial cells may be important in destroying virus-infected epithelial cells.

More detailed information on aspects of immunity at mucosal surfaces may be found in chapters in this book dealing with specific organ systems or specific pathogens. See Pabst and Binns 1994 for a review of the role of lymphocytes in immunity in the lung of the pig.

**Immunity in the Fetus and Neonate**

All components of the native and acquired immune systems develop in utero and are functional at birth. However, they are generally less efficient than in the adult (Hamberberg et al. 1989). Since the normal newborn piglet has not yet been exposed to antigen, it has not yet developed a humoral or cell-mediated immune response to any infectious agents. After exposure to infectious agents, it takes 7–10 days for a primary antibody or cell-mediated immune response to develop. During this time, resistance to infection depends upon the actions of the native defense mechanisms and the antibody that is passively transferred from the sow to the piglet. In the pig virtually no transfer of antibody occurs across the placenta. The epithelialoclar placenta of the sow has several tissue layers between maternal and fetal circulation, which prevents antibody transfer. In the sow, as in other large domestic species, passive transfer of antibody from mother to offspring occurs through the colostrum. The sow concentrates antibody in the colostrum during the last several days of gestation. This antibody is largely transferred intact across the gut epithelial cells into the circulation of the newborn piglet. The passive transfer of antibody from sow to piglet in the colostrum and milk is very important for neonatal survival and is discussed in more detail below.

**NATIVE DEFENSE MECHANISMS.** The newborn piglet has low levels of hemolytic complement activity at birth. Hemolytic complement activity is related to birth weight: heavier pigs have significantly higher concentrations of complement in the serum (Rice and L'Ecuyer 1963). In colostrum-deprived pigs, hemolytic complement activity gradually increases during the first 36 days of life. Piglets allowed to suckle colostrum have higher titers of hemolytic complement than colostrum-deprived piglets during the first 3 weeks of life. This suggests that some of the complement components that are present in limiting amounts are transferred through the colostrum to the piglet (Rice and L'Ecuyer 1963).

The third component of complement (C3) plays a central role in complement activity. Newborn piglet serum has approximately 25% of the C3 levels found in adult swine serum. The C3 concentration increases until it reaches adult levels at 14 days of age. The C3 component of complement is apparently not transferred through the colostrum (Tyler et al. 1988, 1989). In one study, the authors made the paradoxical observation that the neonatal pigs with the lowest amount of C3 had the highest survival rate (Tyler et al. 1990).

The level of natural interferon-α production by porcine blood mononuclear cells was shown to be low at birth and to gradually increase until adult age, with a significant increase around puberty (Nowacki et al. 1993).

Phagocytic cells are present in newborn animals but generally have reduced phagocytic activity compared to adult animals (Osburn et al. 1982). Alveolar macrophages from 1-day-old pigs have reduced chemiluminescence (a measure of oxidative killing mechanisms) compared to alveolar macrophages from adult pigs. By 7 days of age, these aspects of alveolar macrophage function have reached adult levels of activity (Zeidler and Kim 1985). Neonatal pigs have low numbers of pulmonary intravascular macrophages, which increase 14-fold by 30 days of age (Winkler and Cheville 1987). Since phagocytes depend on complement and/or antibody to opsonize many infectious agents, the overall efficiency of phagocytosis may be reduced due to inadequate levels of complement and antibody. Neutrophils from fetal pigs have been shown to have antibody-dependent cell-mediated cytotoxicity activity against chicken red blood cells that is comparable to that of adult pigs. Neutrophils from neonatal pigs have also been shown to rapidly migrate into the lumen of the gut in response to the presence of E. coli and colostral antibody (Sellwood et al. 1986; Yang and Schultz 1986).

**ACQUIRED IMMUNE MECHANISMS.** The percentage of CD2<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T lymphocytes increases
with age during the first several weeks of life in specific-pathogen-free pigs (Bianchi et al. 1992; Joling et al. 1994). The lymphocyte blastogenic responsiveness to mitogens has been shown to be low after birth and to increase by 4 weeks of age (Becker and Misfeldt 1993). The mucosal lymphoid system is also less developed at birth and matures over the next few weeks of life (Jericho 1970; Ramos et al. 1992).

NK-cell activity has been shown to be absent in the peripheral blood of fetal pigs and to be low in pigs of less than 2 weeks of age (Yang and Schultz 1986).

**PASSIVE TRANSFER IN THE NEONATE.** Pigs are born with almost no serum antibody and absorb IgG, IgM, and IgA from sow colostrum. Sow colostrum is richer in IgG, IgG2, and IgA than serum is. It has approximately the same concentration of IgM as serum (Table 56.1). When the pig suckles, the colostrum is replaced by milk, which has a much lower Ig content. From 3 days of age until the end of lactation, IgA is the predominant antibody found in sow milk. The percentage of Ig in the mammary gland derived from serum and the percentage of Ig locally produced in the mammary gland differ in colostrum and milk and vary with the Ig class (Table 56.2).

All three major classes of Ig (IgG, IgA, and IgM) are absorbed from the colostrum into the circulation of newborn pigs (Porter 1969; Curtis and Bourne 1971). IgA, however, is absorbed less efficiently than the other classes of antibody (Porter 1973; Hill and Porter 1974), apparently because much of the IgA in porcine colostrum is dimeric IgA lacking secretory component (Porter 1973). The neonatal colostrum-deprived piglet has been shown to express secretory component in the gut which tends to localize in the mucus of the crypt areas (Allen and Porter 1973). Because of the affinity of the dimeric IgA and IgM for secretory component, it has been suggested (Butler et al. 1981) that IgA and IgM are bound in association with secretory component and held in the mucus of the crypt areas and are, therefore, less efficiently absorbed from the colostrum. The IgA present in sow's milk throughout the suckling period may also bind to the secretory component in the crypt areas and thereby provide relatively continuous protection against intestinal pathogens.

Intestinal absorption of immunoglobulin from the colostrum normally ceases by 24–36 hours after birth. If pigs suckle normally, the efficiency of absorption decreases with a half-life of about 3 hours (Speer et al. 1959). Lecce et al. (1961) found that the period of time that the intestine could absorb antibodies was extended up to 5 days in starved pigs that were maintained by parental administration of nutrients. Therefore, piglets that have not had an opportunity to eat during the first 24–36 hours may still benefit from colostrum ingestion.

Neonatal pigs have been shown to absorb colostral lymphocytes from their intestinal tract into the bloodstream (Tuboly et al. 1988; Williams 1993). By 24 hours the colostrally derived cells were found in the liver, lung, lymph nodes, spleen, and gastrointestinal tissue. Pigs that had absorbed the colostral lymphocytes had higher lymphocyte blastogenic responses to mitogens than control pigs. It is not clear if the passively transferred lymphocytes also transfer clinically significant cell-mediated immunity from the sow to the piglet.

**HYPERSENSITIVITIES**

Hypersensitivities are conditions in which there is excessive responsiveness to antigen to which the animal has previously been exposed. The clinical signs are due to the immune response to the antigen rather than to a direct action of the antigen. The hypersensitivity conditions can be divided into four types based on their mechanism of action.

Type I (or immediate-type hypersensitivity) involves the synthesis of specific IgE (reaginic or cytotoxic) antibodies. The IgE preferentially binds to Fc receptors on the surface of tissue mast cells. When the same antigen is encountered subsequently, it will bind to the IgE on the mast-cell surface (if there is a sufficiently high concentration of IgE specific for the antigen) and cause the mast cell to release numerous pharmacologically active substances which are responsible for the clinical signs (e.g., histamine, serotonin, kinins, prostaglandins, and others). Type I hypersensitivities may be localized to a particular region or organ or may be systemic (anaphylaxis) (Eyre 1980).

Type II hypersensitivity (or cytotoxic-type hypersensitivity) involves the presence of antibodies directed against cell-membrane antigens. These may be normal tissue antigens in the case of autoimmune diseases or foreign antigens (e.g., drugs or viral or bacterial antigens) that have adhered to the cell surface.

Type III hypersensitivity (or immune complex–type hypersensitivity) involves the presence of antigen-antibody complexes in the circulation or tissue. These immune complexes can fix complement and, therefore, may initiate the inflammatory response, attract neutrophils to the site, and damage cell membranes.

Type IV hypersensitivity (or delayed-type hypersensi-

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Table 56.2. Origin of porcine colostral and milk immunoglobulins

<table>
<thead>
<tr>
<th></th>
<th>Derived from Plasma (%)</th>
<th>Locally Synthesized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colostrum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>IgG</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>IgA</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>IgG</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>IgA</td>
<td>10</td>
<td>90</td>
</tr>
</tbody>
</table>

Source: Stokes and Bourne 1989.
tivity) is mediated by sensitized T cells releasing cytokines. It does not involve antibody. The tuberculin skin test is a classic type IV hypersensitivity reaction.

It is not unusual for clinical hypersensitivity conditions to involve more than one of the four types of hypersensitivity. Hypersensitivity conditions that have been studied in the pig will be briefly reviewed here.

**Immediate-Type Hypersensitivity**

Information on naturally occurring localized type I hypersensitivities in pigs is not readily available, although it has been reproduced experimentally (Roe et al. 1993). Acute systemic anaphylaxis in pigs is due primarily to systemic and pulmonary hypertension, leading to dyspnea and death. In some pigs the intestine may be involved also (Tizard 1987).

**Cytotoxic-Type Hypersensitivity**

Type II hypersensitivities have been reported in pigs in which autoantibodies have formed against erythrocytes, thrombocytes, or neutrophils. This results in a depletion of the respective cell type and the associated clinical signs that one would expect (anemia, bleeding diathesis, or increased susceptibility to infection, respectively). These autoantibodies may arise from blood transfusions, from the use of vaccines that contain blood products, or in multiparous sows that develop antibody against the alloantigens shared by the sire and the fetus. In the last case, one would not expect clinical signs to appear in the sow since she would only produce antibody against cell-alloantigens shared by the sire and the fetus. In the last case, one would not expect clinical signs to appear in the sow since she would only produce antibody against cell-surface allotype antigens that are not found on her cells. When the piglet suckles and receives colostral antibody, the passively transferred antibody will cause clinical signs in the pig if it has inherited the sire's alloantigens. Thrombocytopenia purpura in baby pigs due to passively transferred antiplatelet antibody seems to be rather common. Pigs appear normal at birth. Death usually occurs between 10 and 20 days of age. The most striking pathologic feature is the presence of hemorrhages in the subcutaneous tissues and internal organs. Castration during the period of thrombocytopenia may greatly increase the death rate.

Antibodies against erythrocytes, thrombocytes, and neutrophils may be present in the same piglet. In one report, 50% of the dams of litters affected with thrombocytopenia purpura had erythrocyte isoantibodies in their serum (Linklater et al. 1973). The concurrent presence of hemolytic disease with thrombocytopenia purpura in the piglets will exacerbate the anemia. The degree of severity of these conditions may vary between piglets in one litter depending on the erythrocyte and platelet isoantigens that they have inherited from the sire and the amount of colostrum ingested.

**Immune Complex–Type Hypersensitivity**

Immune complex-mediated glomerulonephritis is a common sequela to chronic hog cholera virus infection or African swine fever virus infection. The lesion associated with these two infections is moderately severe membranoproliferative glomerulonephritis. The immune complexes found in these diseases may also cause polyarteritis nodosa, a systemic vasculitis. Immune complex deposition in swine kidneys is apparently common. One study evaluated 100 kidneys collected at slaughter and having no gross lesions. Ninety-seven of the kidneys had IgG deposits and 98 had C3 deposits as demonstrated by immunocytochemistry. The significance of these immune complex deposits in the kidney is unknown; however, the clinical diagnosis of glomerular disease in swine is rare (Shirota et al. 1986).

**Delayed-Type Hypersensitivity**

Delayed-type hypersensitivity is believed to play a role in some cases of food hypersensitivity in pigs (see below). Very little work has been reported on other clinical conditions involving delayed-type hypersensitivity in pigs. Transfer of delayed-type hypersensitivity between genetically matched pigs by transfer of lymphocytes has been demonstrated (Binns et al. 1996).

**Food Hypersensitivity**

Food hypersensitivity is thought to be responsible for some cases of postweaning diarrhea and reduced growth performance in piglets (Stokes et al. 1987; Stokes and Bourne 1989; Li et al. 1990, 1991; Friessen et al. 1993). This apparently involves the formation of IgG antibodies and a type IV (delayed-type) hypersensitivity. Following the introduction of a new protein antigen to the diet, a small proportion (<0.002%) of that protein is absorbed intact. This may induce an antibody and/or cell-mediated response. Typically the systemic antibody response (IgG) will be subsequently suppressed (oral tolerance) and a local mucosal antibody will persist. The local antibody prevents further absorption of the intact protein. The oral tolerance that develops is a specifically acquired ability to prevent responses to any of the proteins which may be absorbed. Therefore, following the introduction of new dietary antigen, animals may pass through a brief phase of hypersensitivity before the development of a protected state of tolerance.

In pigs weaned abruptly and placed on a soya-containing diet, soya protein was detected in the sera of all animals for up to 20 days postweaning. A delayed-type hypersensitivity skin test reaction to soya proteins was transiently positive in the soya-fed group. The changes in gut morphology (crypt hyperplasia and villous atrophy) and the malabsorption associated with early weaning have been characterized. Evidence exists that suggests that these changes occur as a result of a transient hypersensitivity to antigen in the postweaning diet. These intestinal changes can facilitate the growth of and disease production by *E. coli*. Feeding of large amounts of soya
prior to the withdrawal of milk prevented the postweaning malabsorption and diarrhea (Stokes et al. 1987).

**IMMUNODEFICIENCY AND IMMUNOSUPPRESSION**

Primary or secondary immunodeficiency increases the susceptibility of animals to infectious disease. A primary immunodeficiency is defined as a disorder of the immune system for which a genetic basis is proven or suspected. A secondary immunodeficiency is a disorder in which the animal is genetically capable of normal immune function, but some secondary factor is impairing resistance to disease.

Clinical findings associated with immunodeficiency include the following:

1. Illness from organisms of normally low pathogenicity or from an attenuated live vaccine.
2. Recurrent illnesses that are unusually difficult to control.
3. Failure to respond adequately to vaccination.
4. Unexplained neonatal illness and death affecting more than one animal in a litter.
5. A variety of disease syndromes occurring concurrently in a herd.

A large number of primary immunodeficiencies have been reported in humans, and a few have been reported in other domestic species; however, there are apparently no reports of primary immunodeficiencies in pigs. This is probably due to the relatively low value of the individual piglet and the expense and difficulty associated with diagnosing a primary immunodeficiency. In addition, sows and boars that produce nonvigorous litters are not kept in the breeding herd.

A common cause of secondary immunodeficiency is failure of passive transfer of adequate levels of maternal antibody through the colostrum to the piglet. This has been discussed earlier in this chapter. Other potential causes of secondary immunodeficiency (or immunosuppression) include (1) physical or psychological distress, (2) immunosuppressive infectious agents, (3) inadequate nutrition, and (4) immunotoxic substances. The influence of most of these factors on the porcine immune system has not been adequately studied.

**Physical or Psychological Distress**

There is ample evidence that both physical and psychological distress can suppress immune function in animals, leading to an increased incidence of infectious disease. Excess heat or cold, crowding, mixing, weaning, limit-feeding, shipping, noise, and restraint are stressors that are often associated with intensive animal production and have been shown to influence immune function in various species (Kelley 1985). Distress-induced alterations in immune function are mediated by interactions between the neuroendocrine and immune systems. The study of these multisystem interactions initially focused on the secretion and influence of glucocorticoids, which suppress several aspects of immune function. However, pigs are more resistant to the immunosuppressive effects of glucocorticoids than some other species (Flaming et al. 1994). It is now recognized that there are many mechanisms by which the neuroendocrine system can alter immune function; in addition, the immune system is capable of altering the activity of the neuroendocrine system (Breazile 1987; Dunn 1988; Kelley 1988).

The neuroendocrine and immune systems communicate in a bidirectional manner via direct neural, as well as hormonal, signaling systems (Griffin 1989). Neuroendocrine signals that are capable of directly altering the function of cells of the immune system include (1) direct sympathetic innervation to the parenchyma of the thymus, spleen, and bone marrow; (2) glucocorticoids produced by the adrenal cortex after pituitary adrenocorticotropic hormone (ACTH) stimulation; (3) catecholamines produced by the adrenal medulla; (4) endogenous opiates (endorphins and enkephalins) produced by the pituitary, adrenal medulla, sympathetic terminals, and lymphocytes; (5) vasoactive intestinal peptide released by sympathetic neurons of the intestine and perhaps other sites; and (6) substance P released by sympathetic nerve terminals (Breazile 1987; Dunn 1988; Kelley 1988). Receptors have been detected on lymphocytes and thymocytes for a variety of hormones, including corticosteroids, insulin, testosterone, estrogens, β-adrenergic agents, histamine, growth hormone, acetylcholine, and metenkephalin. Some of these substances have been demonstrated to stimulate lymphocyte differentiation and affect their activity. Recombinant porcine somatotropin, at dosages used for growth promotion, did not have any clinically relevant effects on immune function in growing pigs (Goff et al. 1991).

Conversely, the immune system can influence the function of the neuroendocrine system. Upon antigenic stimulation, lymphocytes have been shown to produce small amounts of ACTH, β-endorphin, metenkephalin, thyroid-stimulating hormone (TSH), and other classically "neural" peptides (Blalock et al. 1985; Griffin 1989). Activation of the immune system, as during the response to an immunizing antigen, results in a change in neural firing rates in certain parts of the hypothalamus. Some evidence indicates that certain cytokines (interleukins) can promote hormone release by pituitary cells. Thymic hormones (thymosin-α1 in particular) seem to affect the central nervous system (CNS) as well as the immune system and, in turn, are regulated by the CNS. Thus, the interaction between the immune and neuroendocrine systems is reciprocal, and feedback loops have been described.

Weaning is certainly a stressful event for domestic an-
imals. Piglets are usually separated from their sow, handled extensively, regrouped with unfamiliar pigs, and shifted from a liquid to a solid diet. Weaning at 2, 3, or 4 weeks of age (but not at 5 weeks of age) has been shown to decrease the in vivo and in vitro response of porcine lymphocytes to phytohemagglutinin (Blecha et al. 1983). This is considered to be a measure of the pigs’ ability to mount a cell-mediated immune response. These same parameters were suppressed in artificially reared neonatal piglets compared to their sow-reared littermates (Blecha et al. 1986; Hennessy et al. 1987). Early weaning of pigs at 3 weeks of age suppressed the ability of mesenteric lymph node cells to produce IL-2 (Bailey et al. 1992). Weaning (at 5 weeks of age) 24 hours after the injection of sheep red blood cells (RBCs) decreased the antibody response to the sheep RBCs. Weaning 2 weeks prior to injecting the sheep RBCs did not decrease the antibody response (Blecha and Kelley 1981).

Regrouping of pigs at the time of weaning or at 2 weeks after weaning significantly increased their plasma cortisol concentration. However, there were no measurable changes in lymphocyte blastogenesis or antibody responses at the time of elevated plasma cortisol concentration (Blecha et al. 1985).

Crowding or restraint may also stress pigs sufficiently to decrease their immune responsiveness. Housing 8 pigs (11.5–18 kg) per group in pens with 0.13 m² of floor space per pig significantly reduced their phytohemagglutinin skin test response compared to pigs given twice as much space (Yen and Pond 1987). When young pigs were restrained for 2 hours per day over a 3-day period, they had a significantly elevated plasma cortisol concentration, which correlated with a decrease in the size of the thymus gland and with a reduction in the phytohemagglutinin skin test response (Westly and Kelley 1984). Another report indicated that tethering of sows suppressed antibody synthesis to sheep RBCs. It also resulted in a reduction in the amount of antigen-specific antibodies that were transmitted through the colostrum into the blood of the piglets (Kelley 1985).

**Immunosuppressive Infectious Agents**

Certain infectious agents are capable of suppressing immune function sufficiently to make the animal more susceptible to secondary infections. For example, infection with *Mycoplasma hyopneumoniae*, *Actinobacillus pleuropneumoniae*, virulent or vaccine strains of hog cholera virus, porcine reproductive and respiratory syndrome (PRRS) virus, or pseudorabies virus increases the susceptibility of pigs to severe *Pasteurella multocida* pneumonia (Smith et al. 1973; Pijoan and Ochoa 1978; Fuentes and Pijoan 1986, 1987; Chung et al. 1993; Done and Paton 1995). The mechanism of the immunosuppression induced by these agents has not been completely characterized. A cytotoxin from *A. pleuropneumoniae* is toxic for alveolar macrophages (Dom et al. 1992; Chung et al. 1993; Tarigan et al. 1994). The pseudorabies virus has been shown to replicate in monocytes and alveolar macrophages and to impair their bactericidal and cytotoxic functions (Iglesias et al. 1989a, b, 1992; Chinsakchai and Molitor 1992). Porcine parvovirus replicates in alveolar macrophages and in lymphocytes and has been shown to impair macrophage phagocytosis and lymphocyte blastogenesis (Harding and Molitor 1988). The swine influenza virus and PRRS virus also replicate in alveolar macrophages, and the swine influenza virus kills the macrophages (Charley 1983; Bautista et al. 1993).

The African swine fever virus causes a peripheral lymphopenia and necrosis of lymphoreticular organs (Wardley and Wilkinson 1980). This virus replicates in both lymphocytes and the mononuclear phagocytic system and presumably impairs their function (Wardley et al. 1979). It has also been shown to strongly reduce NK-cell activity by 2 days after infection (Norley and Wardley 1983b).

*Mycoplasma hyopneumoniae*, *Salmonella typhimurium*, and *Salmonella choleraesuis* have each been shown to alter porcine neutrophil function (Coe et al. 1992; Roof et al. 1992a, b; DeBey et al. 1994).

**Nutritional Influences on Immunity**

Both malnutrition and overfeeding may result in impairment of immune function and increased susceptibility to disease due to a deficiency or excess of proteins or calories or to a relative imbalance in vitamin or trace mineral content. Animals under intensive production conditions typically have a completely controlled diet. Therefore, it is very important that the diet, especially the vitamin and trace mineral content, be optimally formulated. Key vitamins and minerals for optimal immune function include vitamins A, C, E, and the B complex vitamins, copper (Cu), zinc (Zn), magnesium (Mg), manganese (Mn), iron (Fe), and selenium (Se). The balance of these constituents is especially important since an excess or deficiency in one component may influence the availability or requirement for another (Tengerdy 1986).

It is difficult to predict the optimal diet for immune function. Very little research in this area has been performed that pertains to swine. The dietary requirements for optimal immune function may differ from the requirements to prevent deficiencies as judged by traditional methods. Relatively small imbalances of a particular nutrient may suppress immune function, whereas a more severe deficiency must occur before the classic clinical evidence of deficiency of that nutrient is recognized. In addition, stress or the demands of rapid growth may change dietary requirements for optimal immune function.

Dietary and injectable vitamin E and selenium have
been evaluated for their influence on antibody levels in young pigs. Dietary vitamin E supplementation increased the antibody response to E. coli (Ellis and Vorhies 1976). Supplemental (dietary or injectable) vitamin E and/or selenium treatment in pigs beginning at 4-5 weeks of age increased their antibody response to sheep RBCs (Peploowskii et al. 1981). Dietary vitamin E and selenium also increased the blastogenic response of pig lymphocytes to phytohemagglutinin (Larsen and Tolleronsrud 1981).

Other investigators demonstrated that injection of sows with vitamin E and/or selenium at 100 days of gestation resulted in increased serum IgG concentrations in their piglets at 2 weeks postpartum, but not at 20 hours or 4 weeks postpartum (Hayek et al. 1989). In contrast, other studies found no influence of dietary vitamin E or selenium on the immune response of young pigs (Blodgett et al. 1986; Kornegay et al. 1986).

**Immunotoxic Substances**

In other species, various compounds, including heavy metals, industrial chemicals, pesticides, and mycotoxins, have been shown to be immunosuppressive at very low levels of exposure. These compounds may be detrimental to the immune system and predispose animals to infectious diseases at levels that do not cause other symptoms of toxicity (Koller 1979). Very little immunotoxicology research has been conducted in swine. Aflatoxin in the feed of young pigs has been shown to impair immunity to erysipelas, to enhance the severity of clinical signs due to salmonellosis, and to enhance susceptibility to an oral inoculation with Serpulina hydysen-teriae (Cysewski et al. 1978; Mellor et al. 1978; Joens et al. 1981).

**GENERAL PRINCIPLES OF VACCINATION**

For nearly 100 years scientists have known that animals may develop immunity to diseases if exposed to either the killed infectious agent or a live strain of the agent that has been modified so it does not cause disease. This approach led to the development of many successful vaccines in the early 1900s. However, it soon became apparent that for certain diseases this simple approach was not effective. An animal, for example, might produce antibody in response to vaccination but still develop the disease. These are diseases for which circulating antibody alone is not protective or for which the vaccines do not induce antibody against the important antigens of the pathogen. The challenge for these diseases is to understand the basis for successful immunity, then to develop vaccines which induce this type of immunity.

The basic types of immune defense mechanisms against infectious agents (as discussed earlier in this chapter) are (1) native defense mechanisms, the first line of defense and already operational in the nonvaccinated animal; (2) humoral immunity, due to the presence of antibodies in the bloodstream; (3) cell-mediated immunity, caused by the action of various types of white blood cells and orchestrated by T lymphocytes; and (4) the secretory IgA system, important for resistance to diseases at mucosal surfaces such as the gastrointestinal tract, the respiratory tract, the mammary gland, and the reproductive tract.

It is apparent that different diseases require different types of immunity for protection and that the type of vaccine (modified live vs. killed), route of administration, and type of adjuvant make a difference in the type of immune response.

General principles regarding vaccine efficacy and vaccine failure will be discussed here. It must be remembered that there are exceptions to these general principles for specific vaccines and specific diseases. Information regarding protective immunity and vaccination for specific diseases may be found in other chapters of this book.

**Selective Induction of Different Types of Immunity**

It is relatively easy to develop a vaccine that will cause the production of IgG and IgM antibody in the bloodstream. However, the vaccine may not induce antibodies against the important antigens of the infectious agent. Antibody alone is not capable of killing infectious agents. The presence of circulating IgG and IgM may help to control disease by

1. agglutinating infectious agents, thereby reducing the number of infectious particles (for viruses) and facilitating removal by phagocytosis;
2. binding to and neutralizing toxins;
3. binding to infectious agents and blocking attachment to cell surfaces;
4. binding to infectious agents and initiating the classical pathway of complement activation;
5. opsonizing infectious agents and facilitating phagocytosis; and
6. mediating attachment of cytotoxic cells to the surface of infected cells so the infected cells may be destroyed by antibody-dependent cell-mediated cytotoxicity.

Some disease-causing organisms, however, are resistant to control by these activities of circulating antibody. These organisms must be controlled by the cell-mediated immune system or the secretory IgA system. It is more difficult to develop a safe and effective vaccine that induces these types of immunity.

Protecting the animal from infection at mucosal surfaces such as the intestinal tract, respiratory tract, mam-
mary glands, and reproductive tract is especially difficult for the immune system. The antibodies responsible for humoral immunity and the white blood cells responsible for cell-mediated immunity are found in the bloodstream and in the tissues to some extent. However, they are not found on some mucosal surfaces. Therefore, they can help to prevent invasion through the mucosal surface but are not very effective at controlling infection on the mucosal surface. Even in the lung and the mammary gland, where IgG and white blood cells are found in relative abundance, they are not able to function as effectively as in the bloodstream and tissues. Protection on mucosal surfaces is due in large part to secretory IgA. Secretory IgA is secreted onto mucosal surfaces, where it may bind to mucus and be present in fairly high concentration. Secretory IgA is resistant to destruction by the proteolytic enzymes on mucosal surfaces that are capable of breaking down IgG and IgM.

The nature of the vaccine and the route of administration are important for influencing the type of immunity induced. Subcutaneous or intramuscular injection of a killed vaccine will stimulate the immune system to produce IgM and IgG classes of antibody. However, there is very little production of IgA to protect the mucosal surfaces. In addition, the killed vaccines are not very effective at inducing cell-mediated immunity.

The induction of cell-mediated immunity generally requires a modified live vaccine capable of replicating in the animal or a killed vaccine with a highly effective adjuvant. Adjuvants that have traditionally been used in animal vaccines are not very effective at inducing cell-mediated immunity. New adjuvants are being developed that show promise for inducing cell-mediated immunity using killed vaccines. There are killed vaccines that have been available for many years and have been effective in controlling certain systemic-type diseases. These are generally diseases that can be controlled by the presence of IgG in the circulation.

The route of vaccine administration is important when attempting to induce mucosal immunity. To get secretory IgA produced at mucosal surfaces, it is best for the vaccine to enter the body through exposure to a mucosal surface. This can be accomplished by feeding the vaccine to the animal, aerosolizing the vaccine so the animal will inhale it, or intramammary exposure. If a sow is exposed to an infectious agent in her intestinal tract, she may respond by producing secretory IgA not only in her own intestinal tract but also in her mammary gland. The sow passes the IgA against the infectious agent to the piglet when it suckles. Therefore, the secretory IgA in the sow's milk can protect the piglet from infectious agents present in the sow's intestine. This protection will only last as long as the piglet continues to suckle. Enteric infections by many organisms are not controlled by the presence of IgG and IgM in the bloodstream or by cell-mediated immunity. If a modified live vaccine is given by injection but goes to a mucosal surface to replicate, it may also induce a secretory IgA response.

**Vaccination Failure**

There are many reasons why animals develop disease even though they have been vaccinated. Disease occurs because (1) the animal was incubating the disease when it was vaccinated; (2) something happened to the vaccine to make it ineffective; (3) the physiologic status of the host makes it unresponsive or hyporesponsive to the vaccine; or (4) the host was exposed to an overwhelming challenge dose of infectious agent. By being aware of these factors, veterinarians and producers can help to minimize the occurrence of vaccine failures.

**OCCURRENCE OF DISEASE SHORTLY AFTER VACCINATION.** The host requires several days after vaccination before an effective immune response will develop. If the animal encounters an infectious agent near the time of vaccination, the vaccine will not have had time to induce immunity, and the animal may come down with clinical disease, resulting in an apparent vaccination failure. In this situation, disease symptoms will appear shortly after vaccination, and the disease may mistakenly be attributed to vaccine virus. Modified live vaccine viruses have been attenuated to be of reduced virulence. The attenuation must be shown to be stable; therefore, reversion to virulence is thought to be a rare event. However, the attenuated vaccine strains may be capable of producing disease in immunosuppressed animals.

**ALTERATIONS IN THE VACCINE.** Improperly handled and administered vaccines may fail to induce the expected immune response in normal, healthy animals. Modified live bacterial and viral vaccines are only effective if the agent in the vaccine is viable and able to replicate in the vaccinated animal. Observing proper storage conditions and proper methods of administration are very important for maintaining vaccine viability. Failure to store the vaccine at appropriate conditions and proper methods of administration can lead to stored under appropriate conditions, the vaccine loses viability over time. Therefore, vaccines that are past their expiration date should not be used. The use of chemical disinfectants on syringes and needles can inactivate modified live vaccines if there is any residual disinfectant. The use of improper diluent or the mixing of vaccines in a single syringe may also inactivate modified live vaccines. Diluents for lyophilized vaccines are formulated specifically for each vaccine. A diluent that is appropriate for one vaccine may inactivate a different vaccine. Some vaccines and diluents contain preservatives that may inactivate other modified live vaccines. For these reasons, multiple vaccines should not be mixed in a sin-
HOST FACTORS CONTRIBUTING TO VACCINE FAILURE. Vaccine failures may occur because a vaccinated animal is not able to respond appropriately to the vaccine. Vaccine failure in young animals may be due to the presence of maternal antibody which prevents adequate response to vaccination. It can also be due to immunosuppression from a variety of causes.

Maternal antibodies derived from colostrum are a well-known cause of vaccine failure. These antibodies in the piglets' circulation may neutralize or remove the antigen before it can induce an immune response. Typically, virulent infectious agents are capable of breaking through maternal immunity earlier than modified live or killed vaccines. This means that even if young animals are immunized frequently, there still is a period when they are vulnerable to infection. Vulnerability occurs between the time that young animals lose their maternal antibody and before they develop their own active immune response. This period can be shortened by the use of less-attenuated modified live vaccines or the use of killed vaccines with high antigenic mass. A high challenge dose of infectious agents will break through maternal immunity sooner than low exposure to infectious agents. Therefore, overcrowding and poor sanitation exacerbate the problem of inducing immunity in young animals before they come down with clinical disease.

Veterinarians commonly recommend that puppies and kittens be vaccinated every 3 weeks between approximately 6 and 18 weeks of age. However, for large domestic animals, a single vaccination is commonly recommended to induce immunity during the first few weeks or months of life. There is no inherent difference between large and small domestic animals in their response to vaccination in the face of maternal immunity. The frequent vaccinations recommended in puppies and kittens minimize the period of vulnerability to infectious diseases.

Because only one vaccination is commonly recommended for large domestic animals, the timing of the vaccination is important. If the vaccine is administered too soon, it may be ineffective because of the presence of maternal antibody. If the vaccine is administered after all maternal antibodies are gone from animals, there may be a prolonged period of vulnerability before they develop their own immune response. Most veterinarians and producers decide that because of time and expense considerations it is impractical to vaccinate young pigs frequently. However, frequent vaccination may be justified in cases of unusually high disease incidence.

Immunosuppression due to a variety of factors, including stress, malnutrition, concurrent infection, or immaturity or senescence of the immune system, may also lead to vaccination failure. If the immunosuppression occurs at the time of vaccination, the vaccine may fail to induce an adequate immune response. If the immunosuppression occurs sometime after vaccination, then disease may occur due to reduced immunity in spite of an adequate response to the original vaccine. Therapy with immunosuppressive drugs (e.g., glucocorticoids) may also cause this to occur.

Another concern is that some modified live vaccines are capable of inducing disease in the immunosuppressed animal. Modified live vaccines are tested for safety in normal, healthy animals. They are not recommended for use in animals with compromised immune systems. Therefore, these vaccines should not be used in animals that are immunosuppressed for any reason. This includes animals in the first few weeks of life unless the vaccine has been specifically tested in animals this young. When it is necessary to vaccinate animals under these conditions, killed vaccines should be used.

OVERWELMING CHALLENGE DOSE. Most vaccines do not produce complete immunity to disease. They provide an increased ability to resist challenge by infectious agents. If a high challenge dose of organisms is present due to overcrowding or poor sanitation, the immune system may be overwhelmed, resulting in clinical disease.

Vaccine Efficacy

Vaccines that are licensed by the U.S. Department of Agriculture have been tested to determine that they are safe and effective. However, "effective" is a relative term. It does not mean that the vaccine must be able to induce complete immunity under all conditions that may be found in the field. This would not be realistic, since the immune system is not capable of such potent protection under adverse conditions.

To be federally licensed, the vaccine must have been tested under controlled experimental conditions. The vaccinated group must have had significantly less disease than the nonvaccinated control group. This testing is typically done on healthy, nonstressed animals under good environmental conditions and with a controlled exposure to a single infectious agent. Vaccines may be much less effective when used in animals that are under stress, incubating other infectious diseases, or exposed to a high dose of infectious agents due to overcrowding or poor sanitation.

It is important to remember that for most diseases the relationship between the infectious agent and the host is sufficiently complicated that vaccination cannot be expected to provide complete protection. The vaccine can increase the animals' resistance to disease, but this resistance can be overwhelmed if good management practices are not followed.
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