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IFAS EXTENSION

The Immune System ¹

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Immunity and Livestock Herds

Immunity is the ability of an animal to resist disease. Fortunately, immunity is a basic fact of nature; unfortunately, we take it for granted. In reality, immunity culminates from the activity of a very complex and intricate system of the body - the immune system; a system that we can to some extent enhance and manipulate to provide various degrees of protection against most disease-causing bacteria and viruses.

Present-day livestock management systems and practices may allow the immune system to be overwhelmed by either a significantly high disease challenge or by weakening the existing immune system. Large herds, transportation, confinement and commingling of animals from different operations are practices causing greater exposure to disease agents. These management practices also increase stresses on the animals and contribute to weakening the immune system. A weakened immune system can allow clinical disease to occur that would otherwise be controlled by a non-impaired immune system.

Proper management of nutrition, sanitation, enhancement of the animal's immune system through vaccination, and the reduction of stress and existing

disease challenges can optimize the immune status of our livestock herds. Disease cannot be adequately prevented when management systems focus only on one of these factors. To provide the herd with a comprehensive disease prevention program all factors contributing to a herd's immune status must be addressed.

Disease threats are ever-present; infectious agents can be brought into a herd by birds, wild animals, insects, trucks, water sources and replacement animals. The two chief infectious agents which cause disease are bacteria and viruses which damage tissue or organs and interrupt normal body functions, all of which may be exhibited as disease symptoms. Some infectious diseases strike herds abruptly and dramatically causing acute illness and even death; other infectious diseases, while not as severe, cause obvious disease symptoms and severe reductions in production. However, most infectious diseases in a herd are actually subclinical, that is, they cause only subtle symptoms or no symptoms, reduce profits by delaying production cycles, increase feed and management cost and are often not noticed until a comprehensive review of the producer's financial records is conducted.

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The immune system consists, in part, of a variety of specialized cells, enzymes, and other serum proteins which are spread throughout the blood and tissues of the body. The specialized cells are concentrated within the spleen, thymus, lymph nodes, bone marrow, blood and parts of other organs and glands.

To simplify the discussion of the immune system, we have divided the immune system into two major components - the Innate (or Native) Defense System and the Acquired (or Adaptive) Immune System. However, the immune system is an integrated system and all components must work in harmony to provide maximum protection for the animal. The failure of any one component of the immune system could prevent the animal from achieving maximum protection against infectious diseases.

The Innate (Native) Defense System

This is the first line of defense; it is naturally occurring, is functional in the healthy animal, and does not require vaccination to initiate the system. The components of the innate defense system are not disease specific and begin responding almost immediately when an infectious agent enters the body. The major components of the innate defense system are the natural defense system, the complement system, the phagocytic cells, and the interferon system.

Natural Defense System

Each species of livestock has natural immunity to certain diseases. Atrophic rhinitis, for example, affects only swine and does not cause disease in cattle, while blackleg affects cattle and not swine.

The Phagocytic Cells

There are two primary phagocytic cell types; the *granulocytes*, which include the neutrophils and eosinophils, and the *mononuclear phagocytes*, which include monocytes circulating in the blood and macrophages located in tissue. Phagocytic cells are responsible for engulfing, killing and digesting invading bacteria; they also have an important role in controlling viral infections. Phagocytic cells are

attracted to infected or inflamed sites by chemotactic substances which may be produced by certain microorganisms, be generated by cleavage of certain complement components, or be released by sensitized lymphocytes. As the phagocytes arrive at the infected area, they begin to engulf the infectious agent if it is susceptible to phagocytic activity. Most disease-causing microorganisms must be opsonized before they can be engulfed by a phagocytes; bacteria are opsonized by the attachment of a specific antibody and/or complement to their surface. This in turn allows for easier destruction of the bacteria by phagocytic cells. Enzymes within the phagocytic cell will attempt to destroy the bacterium after they have been engulfed.

Phagocytes may also play an important part in controlling certain viral infections. Since it is necessary that viruses be within a cell (intracellular) to replicate and thus cause disease, the phagocyte will attempt to destroy the infected target cell if it has been properly tagged by a specific antibody produced by the *acquired immune system* (discussed later). Even though the mechanism of destruction is not completely understood, the antibody presumably creates a bridge between the phagocyte and the infected target cell; the phagocyte will then attempt to destroy the infected target cell and thus destroy the virus. All phagocytic cell types are capable of the activities described above; however, the granulocyte and most specifically the neutrophil is the most proficient of all the phagocytes in these activities.

Mononuclear phagocytes originate in the bone marrow as monocytes and are released into the blood stream where they circulate before migrating into the tissues to become macrophages. Even though macrophages are capable of all the activities of the neutrophil, macrophages are described as the second line of defense. They are not as aggressive as the neutrophil and are much slower to arrive at the sites of infection. Macrophages, however, are capable of much more sustained activity than neutrophils and are able to kill certain types of bacteria that are resistant to killing by the neutrophils. In addition, macrophages process engulfed microorganisms and present fragments (antigens) of them to specialized cells for initiating the *antibody-mediated (humoral) immune* response and the *cell-mediated immune*

response (described below) to infectious diseases agents.

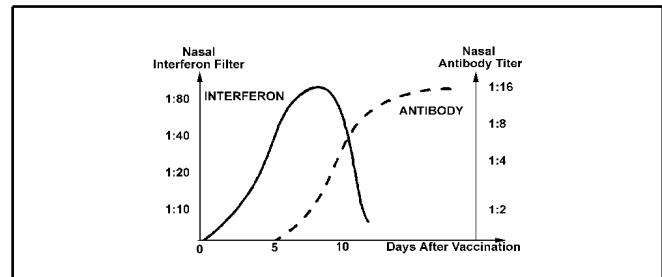
The Complement System

The complement system consists of at least 20 serum proteins which, when stimulated, respond with a series of chain reactions similar to the "domino effect," i.e., something happens to activate the first component which in turn activates the next component which in turn activates the next component, etc., until the reaction is complete. The primary effect of this chain reaction is to increase blood flow to an injured area of the body or an area that has been invaded by an infectious agent; the increased blood flow to the area is accompanied by fluid loss from the blood vessels. This "rush" of blood and the accumulation of leaked fluids in the affected area results in redness and swelling of the tissues and is recognized in/on the animal as a "hot and painful" area. This complement system reaction, which at times appears to be detrimental, hastens the accumulation of disease fighting cells (phagocytes) to the area by providing a fluid "pathway" and by producing chemotactic substances which attract phagocytes. Components of the complement system may also be able to lyse (rupture) the microorganism or opsonize (tag) the infectious agent which renders the infectious agent more vulnerable to a phagocytic cell.

The Interferon System

Interferons are small proteins that cells immediately secrete when they are invaded by infectious agents, especially viruses. Interferon controls replication of certain viruses by inhibiting production of required viral protein in the infected cells and signals other body cells to initiate defenses which prevent replication of viruses in cells if they should be attacked. Interferon further enhances the immune system by increasing the activity of phagocytes in the destruction of engulfed microorganisms and engulfed infected cells. Interferons are not viral-specific, that is, interferon will cross-protect against a variety of viruses. In addition, interferon levels secreted by invaded cells can reach protective levels very quickly, thus preventing replication of viruses in other cells.

These latter two properties of interferon are in part the reasons for our use of intranasal vaccines when we are in need of rapid resistance against certain respiratory viral infections (Figure 1). Interferons also function in the *active immune* system, which will be discussed below.



(Figure 1).

The Acquired Immune System

Acquired immunity is the protection a previously susceptible animal 1) *actively* develops because of a "triggering" of the immune system by foreign agents such as viruses, bacteria, extracts or metabolites of infectious agents, or vaccines; or 2) *passively* receives by transfer of protective substances such as antibodies and/or other cellular factors from a previously immune animal. Hence, acquired immunity can be either *active* immunity or *passive* immunity.

Active Immunity

While the innate defense system, which becomes immediately functional when an infectious agent enters the body, is capable of killing some bacteria and viruses it is not capable of protecting the animal from high levels of disease challenges. In addition, passive immunity (of particular importance for protection of the newborn) is also not useful in controlling high levels of disease challenges. *Active immunity* is usually required to stimulate protection against high levels of disease challenges. Active immunization involves the administration of a disease antigen derived from an infectious agent to stimulate specific immune responses to achieve resistance to the disease. It also became apparent that different diseases required different types of active immunity to stimulate protection in the animals.

Antibody-mediated immunity (also known as *Humoral immunity*) functions primarily to control

"extra-cellular" infectious agents; *cell-mediated immunity* is generally required to kill intra-cellular infectious agents; and *mucosal immunity* is necessary for mucosal membranes to resist invasion by infectious agents.

Specialized macrophage cells called *Antigen Presenting Cells* roam the animal's body, seeking out, ingesting, and partially digesting foreign (disease) material. The *antigen presenting cells* in turn display fragments of the disease antigen, combined with special molecules produced in the cell, on their surface. This combination (antigen fragment & cellular molecules) is then "screened" by a specialized group of white blood cells called *Helper T-Cells*.

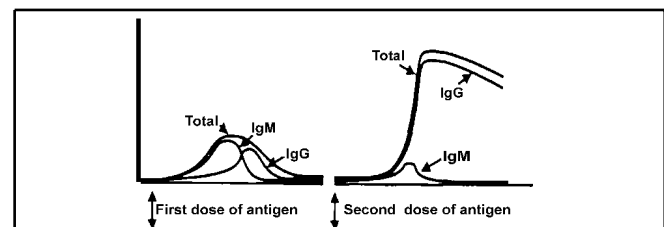
When a helper T-cell encounters the one combination it is programmed to recognize, it secretes messenger molecules (Lymphokine) that in turn excite other components of the immune system. Among the excited components are *B-lymphocytes* that carry receptors that recognize one particular disease antigen. When a B-lymphocyte recognizes an antigen in the presence of *lymphokine*, it begins to divide; some daughter cells become *Plasma Cells* that produce antibodies against the antigen, others become *Memory Cells*. The antibodies are very specific; each B-lymphocyte produces an antibody that binds to a specific antigen. When initially exposed to disease antigens the immune system responds with low levels of IgM antibodies. As the antigen-specific IgM antibody concentration begins to increase in the blood, the helper T-cells signal some of the B-lymphocytes to switch from producing IgM antibodies to production of IgG, IgA or IgE antibodies. Which type of antibody the switched B-lymphocytes produce depends largely upon the origin of the stimulating helper T-cell. If the stimulating helper T-cell originated in a lymph node or the spleen (through which tissue fluids and/or blood flows) then IgG would probably be produced. If the stimulating helper T-cell originated under a mucous-producing surface then IgA would tend to be produced.

The antigen-stimulated B-lymphocyte cells retain a "memory" of each specific antigen and, following a subsequent exposure to the same antigen,

respond rapidly and produce a large quantity of antibody. The source of the antigens can either be naturally occurring, as in a disease challenge, or by vaccination. Antibodies alone are not capable of killing infectious agents; however, the antigen-specific antibodies help to control disease by binding the infectious agents for destruction by the complement or phagocytic immune systems. They can also attach to and neutralize toxins produced by infectious agents.

Humoral Immunity

Humoral immunity (antibody-mediated immunity) involves the production of antigen-specific IgM and IgG antibodies. The IgM antibody is the first antibody type to be produced following the initial exposure to a disease antigen; however, it is the largest of the antibody types produced by the humoral immune system, which makes it difficult to move out of the bloodstream. IgM antibodies provide some low levels of early protection; however, because of their size, they are of limited value in providing any degree of protection outside the bloodstream. IgG antibodies, on the other hand, are smaller and are produced in large amounts following a second exposure to a disease antigen. Because of the size and the amounts produced, the IgG antibodies can readily leave the bloodstream in sufficient amounts to attack disease antigens in the tissues of the body. Most killed vaccines use this principle to build immunity by requiring a second dose (Figure 2). The *memory cells* provide the immune system with a long-lived mechanism to remember previous antigen encounters and respond more quickly to subsequent invasions by the same disease antigen or vaccine antigen.



(Figure 2) .

This "memory" mechanism can persist for months to years and usually requires a booster vaccination to keep the memory system primed. The frequency of the booster vaccinations depends upon

the disease antigen and the level of the disease challenge to the animal.

Mucosal Immunity

Mucosal surfaces are those that line the internal passages of the body; they include the duct system of the mammary glands, the lining of the mouth, the salivary duct system, the esophagus, the stomach and the intestinal tract and the duct system of the gland of the eye. Mucosal surfaces are moist and warm and thus provide an excellent environment for bacterial growth. The antibodies responsible for humoral immunity (mainly IgG) are found in the blood stream and tissue fluids, including those tissues under the mucosal surfaces; even though they are helpful in controlling disease agents that have penetrated the mucosal membranes, they are not very effective at controlling infection on the mucosal surfaces. If a disease organism penetrates the mucosal membrane, the disease agent is engulfed by a macrophage and presented to B-lymphocytes.

The B-lymphocytes, in turn, will begin producing IgM antibodies against the disease organism, some of which will be switched by helper T-cells originating from lymph glands and the blood system to produce IgG antibodies; however, because of the close proximity to the mucosal surface, helper T-cells that originated in the submucosal tissues stimulate the IgM producing B-lymphocytes to switch to IgA production. IgA is then transported across the cells lining the mucosal surface and extruded onto the mucosal surface. As the IgA is being transported across the cellular lining it combines with a cellular secretion and forms a substance called "secretory IgA." Secretory IgA is highly resistant to destruction by mucous secretions and will remain on the mucosal surface to interfere with the ability of disease agents to attach to and penetrate the mucosal lining.

Some of the activated IgA-producing B-lymphocytes are able to enter the blood system and be transported to other mucosal areas of the body where they will also colonize and produce more IgA in the new location. This mechanism allows more than just the invaded mucosal surface to receive protection from the disease agent; other mucosal surfaces also receive the needed protection.

Cell-Mediated Immunity

All disease-causing viruses and some disease-causing bacteria invade, live and replicate within selected cells of the body. Eventually the infected cells may rupture and the released disease organisms will invade other cells. In some diseases, the infected cell may "bridge" with susceptible cells thus allowing the disease organism to enter other cells without the infected cell being ruptured. In the first scenario, the disease organisms may briefly become extra-cellular and can be exposed to the humoral (antibody) immune system; however, when the disease organism invades a susceptible cell through the "bridge" mechanism, the disease organism will not become extra-cellular and thus is never exposed to the humoral immune system. The *cell-mediated immune* system is stimulated to react against intra-cellular viruses and intra-cellular disease causing bacteria.

When an animal is exposed to a disease or vaccine that stimulates cell-mediated immunity, B-lymphocytes and *T-lymphocytes* are activated by specialized helper T-cells. The activated B-lymphocytes respond as described under humoral immunity; however, the T-lymphocytes respond by dividing to produce daughter cells, by destroying the disease-infected tissue cells, or by secreting chemical messenger molecules that signal the invasion of additional susceptible cells by the disease organism or direct and encourage macrophages to destroy the disease-infected cell. The daughter cells will mature to function in the same manner as the activated parent T-lymphocyte and retain a memory of the specific disease antigen. Once the infected cell is destroyed, the replication of the disease organism within the cell is halted and the organism is released into the surrounding tissue fluid. Upon their release into the extra-cellular environment, the disease organisms become susceptible to the activated humoral (antibody) immune system. Like the humoral immune system, cell-mediated immunity is much stronger when subsequent exposures to a particular antigen occur.

When attempting to stimulate the active immune system by vaccination, the selection of the vaccine should depend upon the type of active (humoral or cell-mediated) immunity needed to protect against a

specific disease. In general, killed vaccines are noted for stimulating a humoral immune response and modified live vaccines that are capable of replicating in the animal's body are needed to stimulate a cell-mediated immune response; however, recent research has indicated that certain adjuvanted killed vaccines can stimulate a cell-mediated response (adjuvants are materials added to vaccines that help introduce vaccine antigens to the immune system in such a way that stimulates stronger and longer-lasting immunity). It should be noted that adjuvants which have historically been used in animal vaccines have not been very effective at inducing cell-mediated responses; however, new adjuvants have been and continue to be developed that have the ability to induce cell-mediated immunity. In addition, killed vaccines stimulate very little production of IgA to protect the mucosal surfaces; hopefully, new adjuvants and/or technology which will stimulate the mucosal immune system will soon be developed.

Hypersensitive Reactions

Normal immune responses are important in providing the host animal with some degree of protection against disease organisms; to some degree the animal's immune system will also respond to foreign tissues and other extraneous substances. Unfortunately, these usually protective responses can, under certain circumstances, have a harmful effect on the animal. These harmful reactions are referred to as "allergic" or "hypersensitivities" and can manifest ranging from simple swelling of the eye lids, runny eyes/nose and vaccine injection sites reactions such as granulomas, to life-threatening episodes such as anaphylactic shock. Hypersensitive reactions are caused by chemical mediators that are released from specialized granulocytic cells of the body called basophils or mast cells when they become bound by IgE antibodies. IgE antibodies are produced by the humoral-antibody immune system when the immune system overreacts to certain foreign antigens. IgE antibodies, while potentially of detrimental value, probably evolved as a specialized defense mechanism against parasitic infections. Certain individual animals, because of a genetic predisposition, overreact to non-parasite antigens by producing high levels of IgE antibodies when exposed.

The severity as well as the nature of the clinical manifestations that occur following the interaction of the foreign antigen and the mast cell bound IgE varies with the dose of the antigen, the route by which the antigen enters the body, and the location of the IgE coated mast cells. The hypersensitive reaction may be localized or generalized and be manifested as mild to severe respiratory distress; abdominal pain, vomiting or diarrhea; pooling of blood in the intestines and liver; or skin disorders such as hives.

The most severe type of hypersensitive reaction is a generalized reaction known as anaphylactic shock. This type of reaction occurs in animals previously sensitized against certain vaccines or drugs, as a result of ingestion of foods, or after insect bites. Clinical signs of anaphylactic shock occur within seconds after the antigen enters the body. Immediate treatment with epinephrine is prescribed to counteract respiratory distress and pooling of blood in the intestinal and liver blood vessels or death of the animal may occur. The milder forms of hypersensitive reactions such as swelling of the eyelids, runny eyes/nose and hives are usually controlled by the administration of antihistamines.

All in all, hypersensitive reactions in animals are not frequent, however, neither are they a rarity. Be prepared to respond to hypersensitive reactions should they occur; especially the life-threatening reactions. Keep a bottle of epinephrine in your supplies when you process livestock (vaccinating or treating) and be sure you understand how much and how to administer epinephrine to an animal exhibiting anaphylactic shock.

Passive Immunity

Passive immunity is so named because the animal merely receives another animal's antibodies and/or other cellular factors. Protection ceases once the received supply is exhausted. The most common example of passive immunity in cattle is the transfer of the dam's antibodies (maternal antibodies) to the newborn calf in colostrum (the "first" milk). As parturition (calving) nears, high levels of antigen-specific antibodies are secreted into the dam's colostrum and are passively transferred to the nursing calf. If the calf suckles colostrum within the first 12 hours after birth, it can absorb some of these

protective antibodies into its bloodstream; other protective antibodies will remain in the calf's intestinal tract to provide some local protection. Any delay in suckling immediately after birth will significantly reduce the amount of maternal antibodies a calf will absorb into its bloodstream. Maternal antibodies have a half-life of approximately 21 days; that is, in 21 days a calf will have only one-half the amount of maternal antibodies it absorbed from the colostrum. In another 21 days, the calf will have only one-fourth the original amount ($1/2$ of $1/2$), etc. Because of the rapid reduction in maternal antibodies in the calf, it is important that we stimulate the dam (by vaccination to stimulate a humoral immune response) to produce as high a level of colostral antibodies as possible ("fortify" the colostrum) to prolong passive immunity in the newborn. IgG, IgA and IgM antibodies are major components of colostrum; IgG antibodies are readily absorbed through the intestinal wall of the newborn calf and provide "passive immunity" to the calf. IgA antibodies tend to remain on the surface of the intestinal tract and provide some protection against invading disease agents. IgM antibodies are too large to be absorbed through the newborn calf's intestinal wall and will also remain, for a short time, in the intestinal tract and provide some protection against disease agents that gain entry to the gut.

Another example of the use of passive immunity in the livestock industry is the utilization of antiserums and antitoxins. Like maternal antibodies, antiserums and antitoxins are produced in other animals; however, they are administered to the animal by injection rather than being absorbed from the colostrum. In general, antiserums and antitoxins are administered after the animal has been exposed to a disease challenge, is sick with the disease or, in the case of some newborns, did not receive an adequate amount of colostral antibodies to protect against disease.

Conclusion

Different diseases as well as different livestock management systems require different types of immunity to protect your livestock. Do not become entrenched in your thinking by utilizing only one type of immunity to provide or stimulate protection for

your livestock; be flexible, open-minded and consult with an animal health professional when selecting the type of immunity that meets your management and animal's needs.