Summary of Normal Inflammatory Response to Implant Administration

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For years, we’ve implanted cattle and realized a significant weight gain advantage in implanted over non-implanted cattle. We know these implants last or “play out” in varying periods of time and in different ways, depending upon the product selected. Implant technology has advanced over the years with the approval of many new products. However, until recently, very little was known about the implant site. All we really knew was that some sites swelled, and some didn’t, some abscessed and some didn’t. The entire industry focused on proper implant techniques and sanitation. Animal health companies did studies to determine the percent of implant abscesses and other defects and calculated the economic impact that defects had on cattle producers and the industry. This figure was not only significant but, in fact, staggering. However, no one had a clear understanding of what actually happens at the implant site. A description of the normal physiological events, and a summary of the impact on the implant site, follows.

When the skin is broken and the implant is deposited, bacteria, dirt particles, hair and other contaminants inevitably are carried under the skin, where the animal recognizes two things. First, the animal has lost the integrity of the skin, which will trigger the body to bring in cells to fight the inevitable infection, even if it’s very low grade. These cells are associated with the inflammatory process. Second, the foreign body, which has just been introduced, needs to be walled off since it is not part of the normal “body system” and needs to be contained. It is important to understand that this inflammatory response happens in every animal any time the integrity of the skin is broken, even with such a minor event as a vaccination injection.

The inflammatory response is characterized by heat, swelling, redness and pain, and happens to some degree every time the skin is broken. It is the primary job of the inflammatory cells to fight off the bacteria, viruses and other “invaders.” The cells involved in this inflammatory process are called non-lymphocytic leukocytes, and they have the task of killing, consuming and destroying (if possible) foreign objects and particulate debris, microbes, damaged tissue and dead cells. Leukocyte numbers normally range between 6,000 leukocytes/mL and 10,000 leukocytes/mL of whole blood. Leukocytes are classified by the intracellular granules present (neutrophils, eosinophils and basophils or granulocytes), lobed nuclei (polymorphonuclear cells) and types of histological staining. The bone marrow contains three times as many granulocytes (precursor cells) as the blood. These granulocytes are involved in the inflammatory response and can be mobilized via chemotaxis within just a few hours to the blood and then into the tissues, where they typically release heparin, histamine, bradykinin and serotonin. The neutrophils’ main function is to engulf bacteria and other foreign invaders (phagocytosis). Neutrophils are the first responders to tissue injury (see photos 2 and 3). The more bacteria that are present, the greater the numbers of neutrophils recruited to the site (see photo 3). Neutrophils are short-lived and when they die, they release enzymes and oxygen radicals that destroy the surrounding tissue. Pus is composed primarily of dead neutrophils and tissue debris. Eosinophils fight parasites by releasing lethal enzymes and superoxides and can actually engulf and consume an antigen/antibody complex. Monocytes or mononuclear cells are immature cells in the blood but can swell up to five times their normal size, taking on a granular appearance. They also are known as macrophages and their main function is phagocytosis. Macrophages reproduce at the injury site and can consume microbes, damaged tissue, and dead cells, as a first line of defense. Failure on the part of these cells can result in abscesses or even overwhelming infection.
After implantation, the implant pellet itself is treated as a foreign body and is encapsulated as the animal attempts to isolate, segregate and actually separate it from the body to minimize its impact. This happens by a process called neovascularization. The formation of new blood vessels brings in the cells necessary to create a scar tissue nest — more correctly termed a “capsule.” The capsule initially is composed of granulation tissue, which contains all of the above-mentioned cells as well as many small blood vessels and fibroblasts that are precursors to the actual capsule. This granulation tissue “template” is soon replaced by fibrous connective tissue — the true fibrous capsule. The thickness of this capsule is dependent on the number of bacteria and, hence, the degree of inflammation present at the site. It is safe to assume that with every implant, a number of bacteria, viruses and other contaminants are carried into the implant site. These organisms probably number in the thousands or even tens of thousands. The inflammatory/encapsulation process begins shortly after every implant is administered (see photos 4 and 5).

Low-power view of an implant site on day 1. Blood surrounds the implant. The body recognizes a foreign body via chemotaxis and has begun the inflammatory response.

Magnified view of day 1 implant site. Neutrophils, the first responders to tissue injury, are seen in the blood (dark dots).

This implant site had a bacterial challenge, which resulted in a large number of neutrophils being recruited to the site. The implant is surrounded by a thick layer of densely packed dead neutrophils and tissue debris (pus).

Capsule formation generally begins by day 7. Lymphocytes, plasma cells and mononuclear inflammatory cells* are seen in the outer portion of the capsule.

*Note: Peripheral blood mononuclear cells (PBMCs) are a heterogeneous population of immune cells that are present in human peripheral blood.
A human medical study\(^1\) conducted in Finland measured inflammatory response. In this study, \textit{Staphylococcus aureus} was inoculated at different concentrations into a sterile implant, which was then deposited subcutaneously in rats. The results of this study clearly show that when more than 1,000 organisms are introduced at the implant site, infection develops and healing is delayed. Infection increased the total number of wound fluid leukocytes by 10- to 100-fold. In controls, as well as infected implants, wound fluid leukocytes consisted mainly of neutrophils (85% to 95%) and lymphocytes (5% to 15%), whereas in implants inoculated with 100 organisms, monocytes or phagocytizing macrophages were also detected. Histologic examination of the tissue specimens showed that infiltration of inflammatory cells, especially polymorphonuclear leukocytes, increased with the increasing number of staphylococci in the inoculum. Also of importance was that wound fluid oxygen concentration approached zero in infected implants. Not surprisingly, the study demonstrated that the more severe the inflammatory process and the more pronounced the infection, the more granulation tissue and hence the thicker the fibrous capsule that would be present long-term.

In an Iowa State University veterinary study, implant sites were evaluated using histopathology. Researchers looked at numbers of leukocytes present at implant sites and measured the thickness of the capsules in what would be considered relatively non-reactive sites, as well as increasingly reactive sites all the way to abscessed implants. The conclusion of the study was that the more inflammation at the site, as evidenced by increased numbers of leukocytes (neutrophils), the thicker the fibrous capsule. This study almost mirrors the human study mentioned earlier and clearly demonstrates that the most desirable site is one with a minimal inflammatory response and with a minimal amount of fibrous capsule around the implant.

**Summary**

- The inflammatory/encapsulation process begins shortly after every implant is administered and is meant to protect the animal from the inevitable infection that occurs as a result of breaking the skin under non-sterile conditions.

- The animal’s defense mechanisms recognize the implant as a foreign body and because of the associated infection, attempts to segregate the implant from the rest of the body by forming a non-vascular fibrous capsule around the implant.

- Human and veterinary histopathology research has demonstrated that if the degree of infection at the implant site is increased, the number of wound fluid neutrophils will increase, as will the thickness of the fibrous capsule surrounding the implant.


\(^2\)Elanco Reference No. 1948.
