

Granulomatous Inflammation of Domestic Mammals

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WHEN you began the study of inflammation in your sophomore year you were given a detailed description of the histopathological changes which occur throughout this defensive reaction of the body against an irritant. In that introduction to inflammation you became acquainted with the acute non-suppurative form of the process. From that first description it was easy and logical to go on to a detailed account of the alterations which occur in the tissues in chronic non-suppurative inflammation. After that it was not difficult to add the special tissue reactions which appear in acute and chronic suppurative inflammation. After disposing of non-suppurative and suppurative inflammation there remained a third type which called for special consideration. It was granulomatous inflammation. This type of reaction called for special handling because it appeared so different from the other two types.

You were soon struck by the fact that granulomatous inflammation is quite different from non-suppurative and suppurative inflammation. You were also impressed by the fact that several important and usually fatal chronic diseases of animals have granulomatous inflammation as the basic histopathological re-

action. You learned that actinobacillosis, actinomycosis, so-called botryomycosis, blastomycosis, porcine brucellosis, coccidioidomycosis, glanders, histoplasmosis, John's disease, toxoplasmosis, and tuberculosis belong to this group of diseases and that they are caused by microorganisms which are either bacteria, yeasts, molds, fungi or protozoa.

Vascular and exudative changes

In the conventional description of inflammation emphasis is placed on the vascular and exudative changes. The same underlying alterations occur in granulomatous inflammation but the vascular changes are at a minimum and the exudative changes are characterized by a scant amount of fluid but an excessive accumulation of inflammatory cells, particularly large mononuclear phagocytes. There is such an extensive accumulation, and also proliferation of large mononuclear phagocytes, that there is often a tendency for nodules of inflammatory tissue to form. These phagocytes, as you remember, belong to the so-called reticuloendothelial system. They are derived both from the blood and tissue spaces. There is no complete agreement among histologists as to their origin but three things about them are certain; they are phagocytes, they are capable of rather rapid proliferation, and they display metamorphosis. By metamorphosis is meant the interesting epitheloid nature and the multinucleated giant cell forma-

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tion which these cells assume in most of the granulomatous diseases.

Chronic inflammation

In all three types of chronic inflammation — non-suppurative, suppurative and granulomatous — the same inflammatory cellular elements are present, i.e., lymphocytes, plasma cells, large mononuclear phagocytes, and neutrophils, but the relative number and the distribution of each kind of cell is entirely different and quite characteristic for each type of inflammation.

In the pure chronic non-suppurative inflammation there is a mixture of lymphocytes and plasma cells with some large mononuclear phagocytes and few neutrophils. In chronic suppurative inflammation the chief cell of course is the neutrophil. In the chronic granulomatous inflammation there is an accumulation and proliferation of large mononuclear phagocytes.

All three types of inflammation may progress to the healing stage which consists of a fibrosis followed by scar formation. In some diseases the centers of the granulomatous areas may undergo caseation necrosis either with or without calcification, as in porcine brucellosis and bovine tuberculosis. Later fibrosis and scar formation, sometimes with hyalinization, may be the terminal process. In histoplasmosis of the liver of the dog there is a distinct coagulation necrosis.

While the neutrophil is the first cell to appear in an area of invasion of the specific agent in granulomatous inflammation, as in the other two types of inflammation, the most prominent cell and also the most important cell eventually is the large mononuclear phagocyte, but the response of this cell to the different causative agents is not exactly the same. Some of the specific irritants such as *Mycobacterium tuberculosis* and *Mycobacterium paratuberculosis* stimulate principally the accumulation and proliferation of very large numbers of the large mononuclear phagocytes. Other causative agents like *Brucella suis*, *Malleomyces mallei*, *Actinobacillus lignieresii*

and *Actinomyces bovis* do not stimulate the formation of as many macrophages but do attract sufficient numbers of neutrophils so that suppuration occurs. This type of inflammation therefore is not a pure granulomatous one but a mixture of granulomatous and suppurative. *Staphylococcus ascoformans*, the cause of so-called botryomycosis, also causes a mixed granulomatous and suppurative inflammation.

While some diseases like bovine tuberculosis and Johne's disease are characterized by a pure granulomatous inflammation and others like actinobacillosis, actinomycosis, botryomycosis, glanders and porcine brucellosis present a mixture of the granulomatous and suppurative types, there is one disease which displays a variation of types. The disease is coccidioidomycosis caused by the mold *Coccidioides immitis*. The variations of types of inflammation in this disease are explained on the basis that the three developmental stages of this mold in the body incite different inflammatory reactions.

Function of the macrophage

The function of the macrophage in granulomatous inflammation is obviously phagocytosis of the invading microorganism. The outcome of the attack on the invader however is quite variable; that is, the invader may be phagocytized and destroyed, or after ingestion the invader may kill the phagocyte, or after engulfing the invader the latter may continue to live within the phagocyte, an example of a strange type of intracellular parasitism. In the latter instance the most peculiar reaction occurs in that the intracellular parasite seems to stimulate the phagocyte to proliferate, to migrate and undergo metamorphosis. In Johne's disease, histoplasmosis, toxoplasmosis, and coccidioidomycosis in particular one observes these phenomena. One wonders how the macrophages can gorge themselves with such large numbers of the causative agent and still remain alive. Furthermore one wonders why the chronic inflammatory process is not ac-

accompanied by conspicuous connective tissue proliferation.

The eventual outcome of most cases of granulomatous inflammation is death of the animal. The process kills by displacing tissue in vital organs or by obstructing hollow or tubular shaped organs. In this respect the action of the areas of inflammation resembles that of tumors, and in fact masses of granulomatous tissue are often referred to as granulomas. Death may be postponed for months or years however because many of the lesions often have a tendency to heal but by metastasis the causative agent gradually spreads to other areas in the body.

Diagnosis of granulomatous inflammatory diseases is often difficult. For the most part there are no distinguishing characteristic symptoms. The course is usually long — measured in weeks, months or years. Fever is not constant or high unless there is suppuration. There is usually gradual wasting, and progressive weakness and anemia. Symptoms related to obstruction or compression of vital organs may become apparent. Chills and prostration may occur before death.

In some of the diseases characterized by granulomatous inflammation sensitizing antibodies are produced by the lymphocytes and reticuloendothelial cells in sufficient numbers to give a reaction to skin sensitizing tests. This is particularly true in tuberculosis, Johne's disease and glanders. To some extent it is true also in coccidioidomycosis and histoplasmosis.

The clinical laboratory can give some assistance in diagnosis. In histoplasmosis circulating monocytes sometimes contain histoplasmae. Examination of pus from suspected lesions of actinomycosis, actinobacillosis, botryomycosis, porcine brucellosis and glanders may reveal the causative agent. Fecal examination of suspected Johne's disease cases may be useful. In pets an exploratory abdominal opening for the purpose of obtaining biopsy material or cultures is of value.

Treatment of animals having any of the granulomatous diseases listed above with the exception of actinobacillosis and actinomycosis is of little value. In fact

the hazards of keeping affected animals is great. Wherever possible they should be destroyed and autopsied, but the prospector should bear in mind that the specific agent causing several of these diseases is transmissible to man.

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