GRANULOMATOUS INFLAMMATION

WILEY D. FORBUS, M.D.

GRANULOMATOUS INFLAMMATION

ITS NATURE
GENERAL PATHOLOGICAL SIGNIFICANCE
AND CLINICAL CHARACTER

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Introduction

We have known for a long time that all pathological processes can be dealt with successfully only at the level of the individual cells which make up the body. In this lecture, which deals with inflammation, a basic pathological process without peer in importance to the preservation of the individual, it will be necessary therefore to say much about cells and their morphology. However, the purposes of this presentation will not be accomplished unless the reader appreciates fully that cell morphology in its details is dependent upon the functional state of the cell, and that our interest in morphology lies, therefore, not in morphology for its own sake, but in morphology as an indicator of the functions of cells as they change from time to time under the influence of a variety of pathological stimuli. Thus, although we shall discuss granulomatous inflammation chiefly from the point of view of what can be seen under the microscope, it is to be kept constantly in mind that it is not what the microscope *shows,* but what it *reveals,* that is important to us.

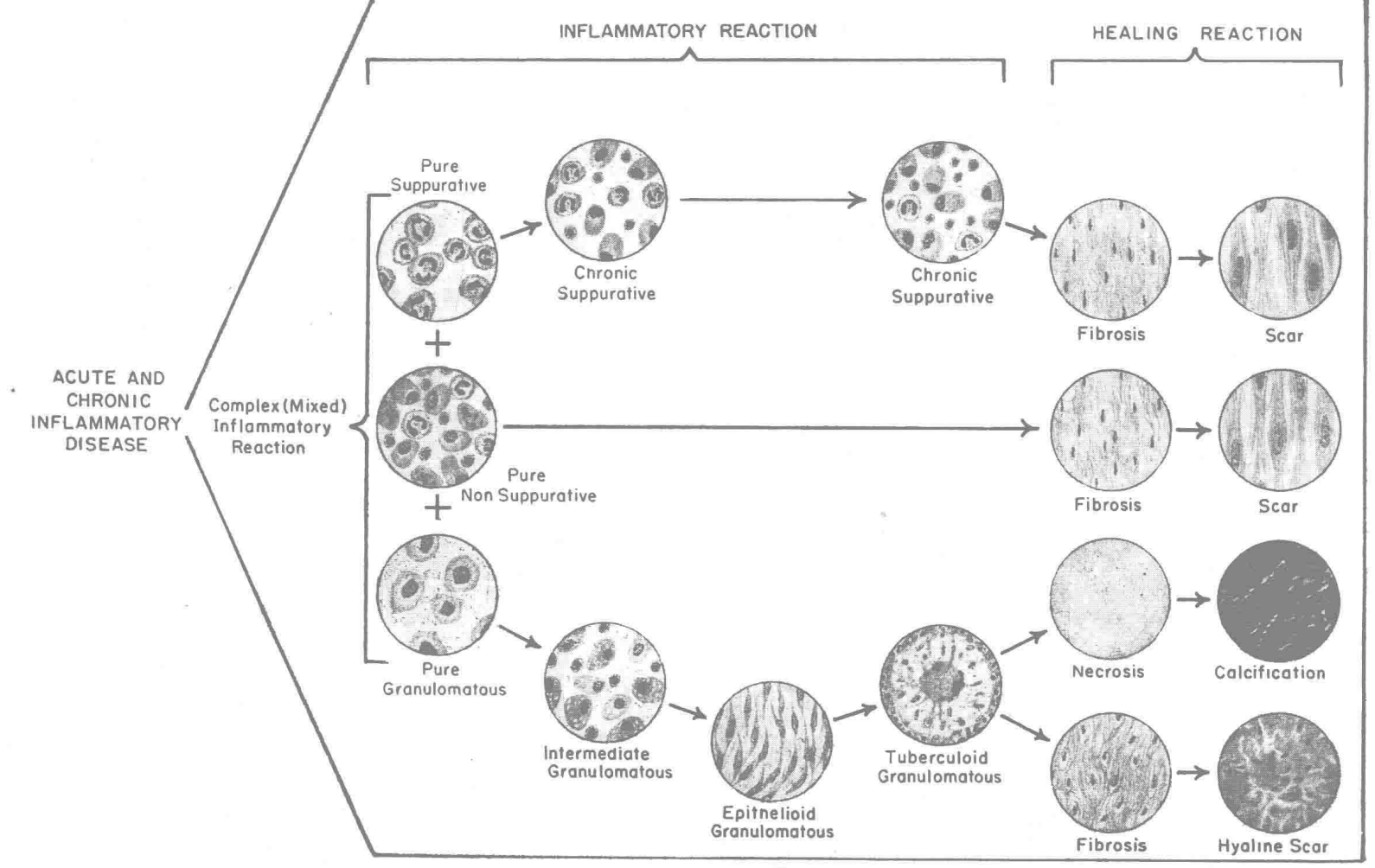
In the discussion that is to follow I hope to accomplish what may be called a partial reorientation of some of the problems common to those extraordinary disease entities which we are accustomed to call the infectious granulomata. This will not be difficult, since little other than a change in emphasis in the matter of granulomatous inflammation

seems to be required. I think this can be readily accomplished by adhering closely to a discussion with the following five main objectives: 1) the presentation of a brief review of the basic pathological processes involved in granulomatous inflammation; 2) the reorientation of certain basic pathogenic factors involved in granulomatous inflammation; 3) the illustration of the proposed change in emphasis necessary to the reorientation of the question of granulomatous inflammation by means of a description of certain observations recently made in our own work on one of the more unusual infectious granulomata; 4) a brief statement of the importance and general pathological significance of granulomatous inflammation; and 5) the brief description of the distinguishing clinical characteristics of granulomatous disease.

The Nature of Granulomatous Inflammation

Nowhere in the literature have I been able to find a more lucid description of the basic pathological process which we call inflammation than that so cryptically stated some years ago in these words by Dr. Opie: Inflammation is "the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it." This simple statement of the matter has two great virtues, the one being the emphasis placed upon the two important components of all inflammatory reactions—cells and fluid—and the other being the freedom of thought which the definition allows anyone who would understand this most important biologic mechanism. If this definition of inflammation has any fault, it appears to lie in the lack of specification of the injurious agents essential to the development of "the process." For the purposes of this discussion, I wish to bring into relief this potential fault, and thus, from the very beginning, point directly to that highly specific relationship which always exists between the injurious agent and the type of cellular response in inflammatory reactions. It is a discussion of this relationship that is the chief burden of my presentation.

Knowing that you will understand my omission of a general discussion of the classification or typing of inflammation, and with full acknowledgment of and appreciation for the various classifications and definitions of inflammation that are current, for our immediate purposes I should like for you to think of inflammation as occurring in the following three forms (Fig. 1) : 1) acute and chronic suppurative


INFLAMMATORY REACTION
HEALING REACTION
ACUTE AND CHRONIC INFLAMMATORY DISEASE
Complex (Mixed) Inflammatory Reaction
Pure Suppurative
Chronic Suppurative
Chronic Suppurative
Fibrosis
Scar
Pure Non Suppurative
Fibrosis
Scar
Pure Granulomatous
Intermediate Granulomatous
Epitnelioid Granulomatous
Tuberculoid Granulomatous
Necrosis
Calcification
Fibrosis
Hyaline Scar

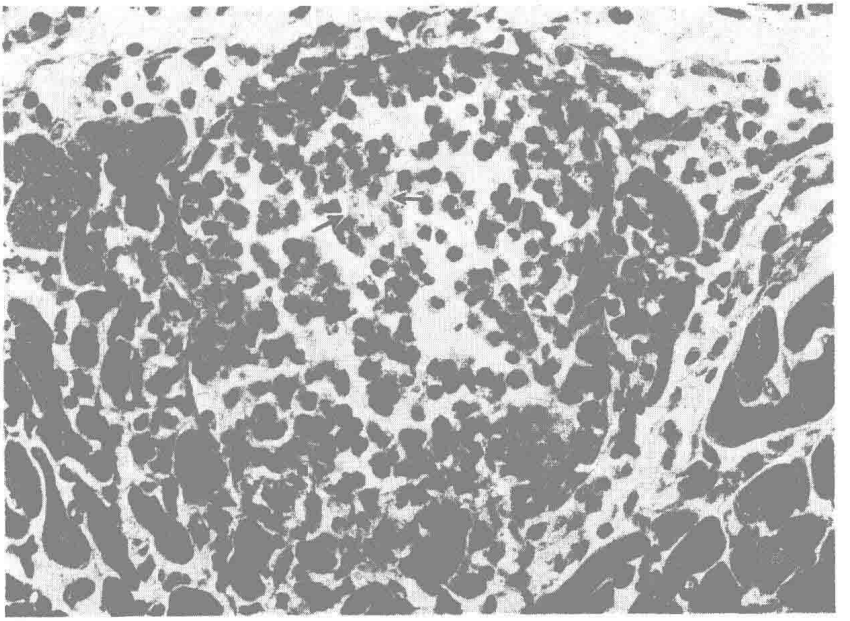


FIGURE 2

Basic inflammatory reaction types: the pure suppurative reaction as shown in a simple acute abscess of the myocardium resulting from the deposition in the muscle of a mass of endospores of Coccidioides immitis. The reacting cells are exclusively polymorphonuclear leukocytes. The organisms are minute black dots indicated by arrows. (See also Figure 6) (From Forbus and Bestebreurtje: Coccidioidomycosis, The Military Surgeon, Nov. 1946, 99:653. U. S. Army Medical Museum Neg. No. 92925, X200).

(Fig. 2), 2) acute and chronic non-suppurative (Fig. 5), and 3) acute and chronic granulomatous (Fig. 4). Distinction between these basic types of inflammatory reaction can be drawn on both morphologic and physiologic bases, but it is obvious that a completely satisfactory classification of an inflammatory reaction must involve a consideration of the character of the stimulus provoking the reaction. Our broadening experience with disease during the war years has given us familiarity with a variety of etiologic agents which previously were hardly more than names to most of us. A

←— FIGURE 1

Schematic representation of the four basic types of inflammatory cellular reaction which underlie the various acute and chronic inflammatory diseases. (See text for description).

major consequence of this has been a greater appreciation of the importance of the more subtile etiologic factors in determining the character of the inflammatory reaction.

Accepting the risks of oversimplification, I have found it possible to center the morphologic differentiation between the suppurative, non-suppurative, and granulomatous inflammations about the reactions of three groups of cells (Fig. 1)—the polymorphonuclear leukocytes (Fig. 2), the large mononuclear phagocytic wandering cells (reticuloendothelial cells) * (Fig. 4), and the small mononuclear wandering cells (Fig. 5). A brief description of granulomatous inflammation from the morphologic, functional, and etiologic points of view will reorient the problem of classification along these lines and indicate the change in emphasis which modern investigations seem to justify.

The Morphology of Granulomatous Inflammation

Two very old concepts relating to inflammation, dating from the description of the tubercle by Virchow, have made and continue to make difficulties for us in our studies of the inflammatory reaction. One of these is that inflammation is either "productive" or "exudative." The other is that the inflammatory reaction is a process which involves *active* participation of the fixed tissue cells. According to the earliest conception of the process, and indeed in that of some

*Throughout this discussion "reticuloendothelial cell" is used synonymously with "large mononuclear phagocytic wandering cell." These cells are found in all the tissues, where they occur in varying numbers and in various forms. They also occur in the circulating fluids, blood and lymph. In the tissues they go by a number of names, including clasmatocyte, tissue macrophage, histiocyte, etc. In the circulating fluids they go by the name monocyte. Their specific origin is still a matter of controversy, but there is general agreement regarding their function, which is chiefly phagocytosis. These cells have a remarkable proliferative capacity and are also capable of changing their form. From them are derived the epithelioid cells and the large multinucleated giant cells, combinations of which are seen most commonly in the lesions of tuberculosis and similar infectious diseases. The large mononuclear phagocytic wandering cells and their derivatives constitute the reticuloendothelial system, as described and first outlined accurately by Aschoff and Kiyono in their studies based upon the vital staining of tissues.

modern workers, productive inflammation is any inflammatory process characterized by the growth of new tissue, irrespective of the character of the growing cells. In the case of certain early workers, particularly Baumgartner, the most active production of new cells was believed to take place in the fixed tissues of the body, thus sharpening the difference between this type of inflammation and that which was described as exudative. In the case of exudative inflammation, the emphasis was placed upon the accumulation of fluid in the injured tissue from the circulation. This early conception of inflammation took little account of two important facts, the one being that the exudation of fluid is essentially

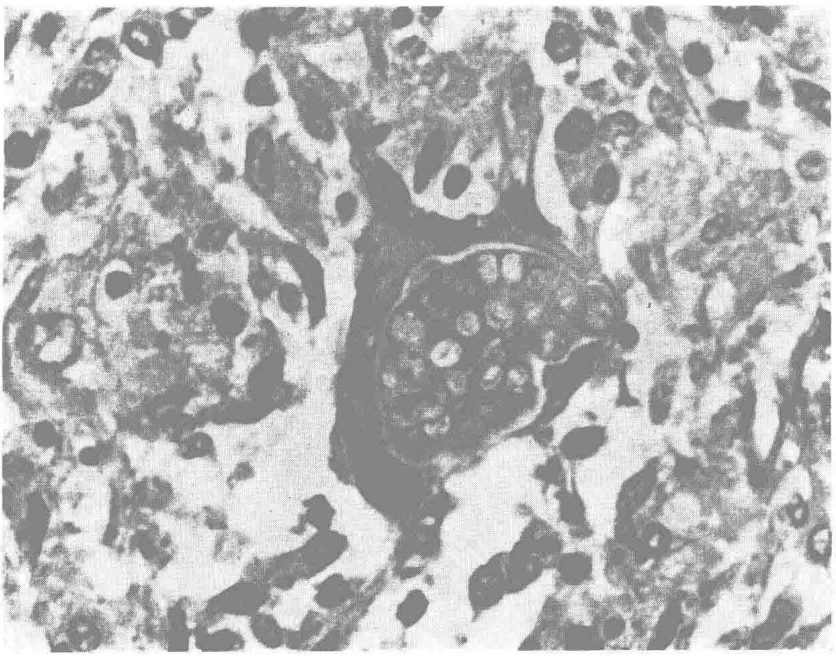


FIGURE 3

Basic inflammatory reaction types: the tubercloid granulomatous reaction with its periferal zone of epithelioid cells and its centrally situated giant cell. The giant cell contains within its cytoplasm a large mature **Coccidioides immitis** spherule with its multiple, fully developed endospores. (**Compare with** Figure 2) (From Forbus and Bestebreurtje: Coccidioidomycosis, **The Military Surgeon**, Nov. 1946, **99**:653. U. S. Army Medical Museum Neg. No. 92923, X1000).

a passive process—the inescapable result of injury to the blood vessels—and the other being that the proliferative reaction which characterizes the productive form of inflammation involves a type of cell not belonging to the fixed tissues. The proliferative response of cells in the productive type of inflammatory reaction was observed by the early workers to give rise to the development of little granules in the inflamed area. It was this development of granules of new tissue that led to the conception of tumor-like inflammatory reaction or, in the words of the early Germans, inflammatory "neubildung," and, in our own early literature, "infectious granuloma." It is hardly desirable any longer to describe inflammation as "exudative" or "produc-

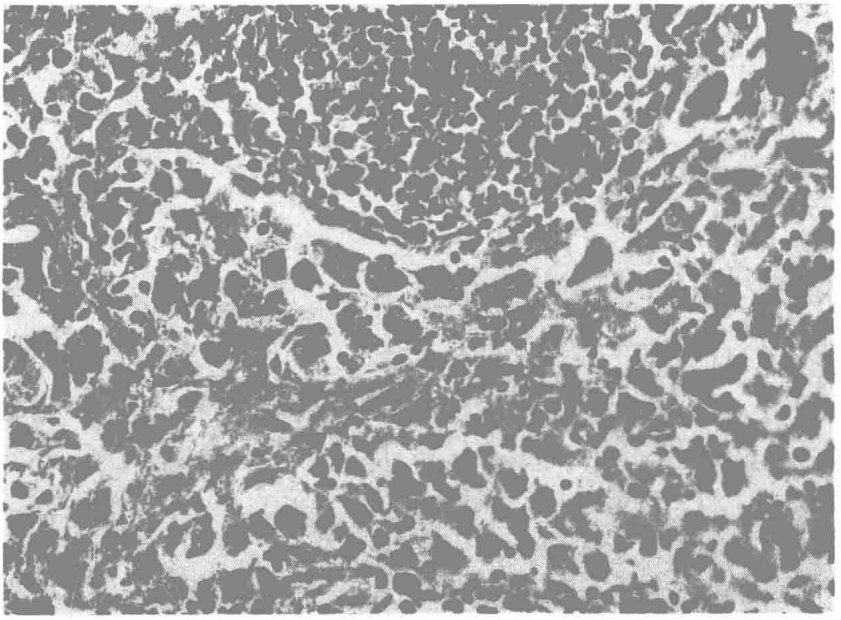


FIGURE 4

Basic inflammatory reaction types: the pure granulomatous reaction consisting exclusively of large mononuclear macrophages—reticuloendothelial cells—replacing the lymphoid tissue of a lymph node. The macrophages are filled with little black dots, each surrounded by a clear zone. These are the yeast-like forms of **Histoplasma capsulatum**. This is a good example of intracellular parasitism produced by a fungus (X450).

tive," since we know now that all inflammation, in the sense of Opie's definition, which we have accepted, is "exudative," and the "productive" concept is confusing in view of its original meaning. However, if one uses the term "productive inflammation" in strict reference to the proliferation of the reticuloendothelial cells, and thus identifies the "productive" process with the tumor-like granules of certain specific etiologic types of inflammation, the concept then becomes a useful one, since it is indeed synonymous with granuloma. Pure granulomatous inflammation, morphologically and functionally speaking, is then an "exudative" and "productive" reaction in the tissues characterized by the accumulation and proliferation in the injured tissues of reticuloendothelial cells, some being from the circulating

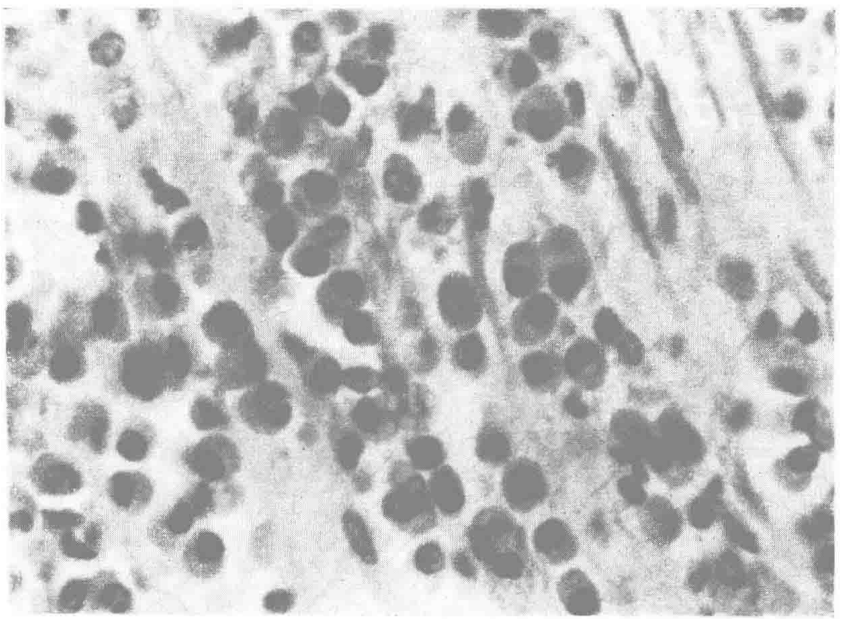


FIGURE 5

Basic inflammatory reaction types: the pure non-suppurative reaction consisting almost exclusively of plasma cells, one of the most commonly occurring small mononuclear wandering cells. A few lymphocytes and an occasional large mononuclear wandering cell constitute the other components of this reaction, which appears in a field of fibrous tissue. The lesion is from a case of chronic nasal sinusitis (X1182).