Basic and Clinical Aspects of Granulomatous Diseases

Editors:
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Proceedings of the Workshop on Basic and Clinical Aspects of Granulomatous Diseases held June 18-20, 1980 in Bethesda, Maryland

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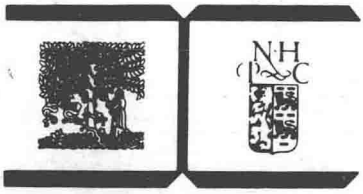

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Preface

Granulomatous tissue responses have been observed and described by pathologists over a century ago. Yet, the function of this chronic inflammatory response remained an enigma in the ensuing decades. In the past fifteen years, thanks to the efforts of the dedicated few, many of whom participated in this Workshop, a great deal of progress has been made. Experimental models succeeded to better delineate the differences which exist between foreign body as opposed to immune-induced granulomatous lesions. The "infectious" hypersensitivity-type granuloma has been conceptually identified as one of the diverse manifestations of the cell-mediated arm of the immune response. The central role of the thymic-derived lymphocyte in the generation, maintenance, and possibly healing of hypersensitivity granuloma has been established. The dual role of the macrophage in antimicrobial resistance and local tissue destruction is now appreciated. The activity of the fibroblast, hitherto a rather neglected component of the lesions, is rapidly gaining the attention of researchers. The program of this Workshop reflects the prevailing trends in granuloma research and points to future approaches. Descriptive histopathology gave way to cellular immunology, molecular biology and immunopharmacology. Interest is focused on cellular subpopulations, cell-cell interactions, cellular receptors, signals carried by mediators and regulatory mechanisms. Though emphasis is placed on the exploration of basic mechanisms active in the various facets of the granulomatous response, the essential goal, an improved handling of granulomatous disorders, should never be lost. Despite efforts, the etiologic agents of several granulomatous diseases are still unknown. Whereas some disorders are benign and may resolve spontaneously, others

progress to dangerous tissue liquefaction, extensive fibrosis and rarely, to rapid death. Granulomatous inflammations may also be influenced by the genetic background of the diseased individuals. Clinically, granulomatous diseases are treated by broad-action anti-inflammatory drugs such as corticosteroids with often harmful side effects. Thus a better understanding of the cellular and molecular basis of the granulomatous response should help clinicians in at least three major aspects: (a) restoration of the granulomatous response to patients succumbing to disseminating infectious agents; (b) regulation of the intensity of the inflammatory response and (c) curtailment of tissue damage and prevention of irreversible fibrosis.

Granulomata have been compared to a battleground between indigestible agents and macrophages. To extend this metaphor, we'd like to learn more about the battle plan, the generals who lead the fight, the mobilization of infantry and their weaponry, the communication systems of the fighting forces, prevention of devastation and restoration of the damaged area.

The proceedings of this Workshop presented in this book deal with many of these questions. We hope that this book will become a stimulus to the future investigations of basic and clinical researchers in granulomatous inflammation.

Finally, we wish to express our gratitude to the National Institute of Allergy and Infectious Diseases and the National Heart, Lung and Blood Institute for so generously sponsoring this Workshop, thereby helping to realize an ambitious idea and reaffirming that granuloma research has come of age.

July, 1980

Dov. L. Boros at Detroit, Michigan

Takeshi Yoshida at Farmington, Connecticut

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Contents

Boros/Yoshida, eds. Basic and Clinical Aspects of Granulomatous Diseases

The Granulomatous Inflammatory Response: An Overview*

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Introduction

The granuloma is a chronic inflammatory reaction to persistent irritants. Granulomatous tissue inflammations have been observed and described by pathologists more than a century ago. Though a great deal of progress has been made since in understanding this complex tissue reaction, basic problems regarding the etiology, clinical management and prevention of these tissue destructive disorders still remain to be solved. The detection and identification of a causative agent which induces the granulomatous condition often poses major difficulties. The dual, protective/destructive role of the granuloma can baffle clinicians who want to develop a uniform strategy of treatment.

The example of the "classic" granuloma evoked by tubercle bacilli encapsulates the pitfalls, misinterpretations and conceptual difficulties which researchers encountered in the past. Tubercle bacilli have been identified by Koch as the etiologic agents of tuberculosis, which cause granulomatous tissue inflammations and induce a state of hypersensitivity in the infected host. In subsequent decades, these two phenomena have been regarded as separate entities—granulomata being tissue responses to irritating, toxic mycobacterial lipids, whereas dermal reactions to soluble tuberculin represented the "allergic," delayed hypersensitive response of the previously exposed individual. Basically, this assumption was correct because experimentally fractionated lipids or waxes were shown to induce granulomata whereas soluble tuberculin products were ineffective.

Today we recognize that a variety of subcellular fractions of mycobacteria including fatty acids, waxes, cord factor, methanol extraction residue and muramyl

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dipeptide all induce foreign body type granulomata, which are morphologically very similar to lesions induced by intact bacilli. This paradox—the induction of a dual, irritative/immune-inflammatory response by a single infectious agent remained a source of confusion and error till today. The toxic, irritative properties of subcellular mycobacterial products and the florid tissue inflammation which they evoked diverted the attention from the protective role of the granuloma. It is a tribute to Metchnikoff, a pioneer of the discipline of cellular immunology, who alone recognized and defined the protective role of the infectious granuloma by stating: " . . . tubercule is composed of a collection of phagocytes mesodermic in origin which move towards the spot where the bacilli are situated and englobe them." (Metchnikoff, 1891). This statement made at the dawn of immunologic research is still valid today. During the past decade several attempts were made to classify granulomatous responses. Pathologists believed that the presence of epithelioid cells, (a transformed macrophage) and their organized arrangement within the lesions provides a reliable criterion for distinguishing hypersensitivity from foreign body lesions (Epstein, 1967). This is no more tenable because implanted plastic sheets (van der Rhee et al., 1979) and muramyl dipeptide (Tanaka and Emori, 1980) can also elicit the formation of epithelioid cells in normal animals. Macrophages being the major components of any granulomatous response, their multiplication, longevity and death in a given lesion was taken as a basis for classifying granulomata into active (high) or quiescent (low) turnover lesions. This functional approach unfortunately is applicable mostly to experimental systems and would lump together such widely divergent lesions as the mycobacterial tubercles and the silica granuloma (Spector, 1974). A third approach emphasizes the degree of activation of the macrophages within the granulomata as means of classification (Adams, 1976). The diverse manifestations of the activated macrophage (morphological, membranous, biochemical, microbicidal, secretory, cytotoxic) which can be selectively expressed in some but not other granulomatous lesions makes this classification tenuous. A fourth classification emphasizes the immune, cell-mediated or nonimmune foreign body etiology of the lesions (Boros, 1978). This helped to conceptualize the role of the hypersensitivity granuloma within the overall picture of cell-mediated immunity. This classification can be applied to clinical practice only if the state of delayed hypersensitivity of the patient is verifiable by the appropriate reagents and tests.

Though as yet, no satisfactory classification has been devised, advances made in the fields of inflammation and cell-mediated immunity provided important conceptual frameworks for the understanding of the various granulomatous inflammatory responses. This brief review intends to summarize recent advances in the various facets of the chronic granulomatous tissue inflammatory responses.

Granuloma-Inducing Agents

It is generally held, that granuloma-inducing agents persist in the tissues because they are insoluble or poorly degradable (James and Neville, 1977; Adams, 1976; Boros, 1978). The agents may be of microscopic or macroscopic size ready to be

ingested or surrounded by macrophages. The intra- or extracellular residence of the irritant may have important influence on the intensity and duration of the ensuing inflammatory response. An additional major factor is the physicochemical properties of the inciting agent. Nonantigenic, inanimate agents such as metal salts, sutures, plastic beads, sponges, etc., would induce a tissue inflammation more limited in intensity, duration and tissue-destructive effect than antigens which initiate a cell-mediated immune reaction. A notable exception is the silica granuloma, which though generated by inanimate particles, develops an inflammation of high intensity and is accompanied by pronounced tissue destruction. This indicates that in foreign body type tissue responses the intrinsic cytotoxic properties of the inciting agent(s) may decide whether the lesion will develop into an active or quiescent inflammatory response. Soluble antigens may also induce granuloma formation in specifically sensitized animals provided they are adsorbed or bound to insoluble carriers (bentonite, latex, plastic bead particles) (Boros, 1978) or rendered insoluble by chemical cross-linking (McGee et al., 1978). Naturally forming granulomagenic aggregates are large immune complexes which at equivalence or in antibody excess are insoluble and once ingested by macrophages, may persist intracellularly for long periods of time (Spector and Heesom, 1969). Formation of immune complexes and their deposition in blood vessel walls was shown to cause a variety of clinical disorders known as granulomatous vasculitides, which may be highly destructive (Fauci, 1978). An additional "man-made" granulomatous condition of recent years is the spermatic granuloma which forms around extravasated spermatazoa in the spermatic cord, in a percentage of vasectomized individuals (Alexander and Schmidt, 1977). This type of lesion is of special note, because the condition is induced by ill-resorbed or digested "self" components. It is conceivable that some granulomatous disorders for which no etiologic agent(s) have been yet identified may well have an autoimmune basis. If it is indeed so, then the search for transmissible agents in certain granulomatous disorders of unknown etiology may prove to be futile. That the granulomatous condition is essentially induced and perpetuated by the inability of the macrophage to degrade the ingested material is excellently illustrated by the activity of muramyl dipeptide (MDP). This organic molecule is a water soluble component of the wax D moiety of the mycobacterial cell wall. The compound can substitute as an adjuvant for whole mycobacteria, activates macrophages and the reticuloendothelial system and induces foreign body type epithelioid cell-containing granulomas (Tanaka and Emori, 1980). The biologic activity of the compound derives from its unnatural L-alanyl-D-isoglutamine linkage, which unlike the L-L stereoisomer configuration cannot be broken down by macrophage enzymes (Chedid et al., 1978).

A new dimension added recently to the scope of granuloma research is the genetic background of the granuloma-bearing individual. Though individuals or experimental animals are exposed to the same granuloma-inducing agents, the inclination as to whether to develop a granulomatous response, the intensity of the inflammation and the speed of resolution may all be under genetic control. A tentative genetic influence has been established in humans with leprosy (Hastings, 1977), hypersensitivity pneumonitis (Flaherty et al., 1975), sarcoidosis (James and Neville