Leprosy and the Concept of *Granuloma*

Indiscriminate use of the word *granuloma* in writings about leprosy, when the histopathologic discrimination between tuberculoid and lepromatous leprosy is based on the concept of *granuloma*, suggests frequent lack of awareness of the significance of the leprosy model to the concept.

The term *granuloma* is an imprecise designation (e.g., *cholesterol granuloma, rheumatic granuloma, granuloma venereum, granulomatosis infantiseptica, beryllium granuloma, eosinophilic granuloma, lethal granuloma,* etc.) originally derived from gross morphology and descriptive of a "small nodule tumor." Virchow originally defined it as a tumor or neoplasm made up of granulation tissue. Its use has, however, largely been reserved for the designation of proliferative inflammatory processes as contrasted with exudative, or pyogenic inflammation, though some confusion continues with the concept of reparative, proliferative "granulation tissue." The term *granuloma* is accepted by common usage, not because the nodule is necessarily like granulation tissue either grossly or microscopically, but rather because of the occurrence of a nodule or granule. These nodules develop as an inflammatory response to pathogens which have characteristics that stimulate a predominantly chronic, macrophage (histiocyte) response. This classically, as in tuberculosis and sarcoidosis, results in the formation of a more or less specific, tubercle-like structure, the *granuloma.* Morphologically it consists of macrophages turned epithelioid and accumulated in small, nodular entities (which may, however, conglomerate) surrounded by varying quantities of lymphocytes and often incorporating multinucleated giant cells, usually of the Langhans variety. Caseation may occur but neither caseation nor giant cells are essential to the concept of *granuloma.* Vascularity may, as in the luetic gumma, or may not, as in the tubercle of tuberculosis, be a feature.

The concept of *granuloma* is related to that of the epithelioid cell, and both have long been regarded as responses to some common or related substance or substances possessed or induced by the pathogenic agents concerned in their genesis. The tubercle bacillus, as well as other pathogens, has repeatedly been fractionated and the tissue response to its various fractions studied. Sabin and associates[1] noted tuberculoid reaction in experimental animals which had received a total of 192 mgm. of the fatty acid derived from tuberculophosphatide and Rich[2] commented that it would take 19 gm. of tubercle bacilli to

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1 SABIN, F. R., DOAN, C. A. and FORKNER, C. E. Studies on tuberculosis. J. Exper. Med. **52** (1930) Supplement no. 3.

2 RICH, A.R. *The Pathogenesis of Tuberculosis.* Oxford: Blackwell Scientific Publications, 2nd ed., 1951. pp. 3-27.

yield that amount of the fatty acid. Rich noted further that a single tubercle bacillus can cause giant cell formation and several bacilli will cause the formation of a tubercle. The intact tubercle bacillus possesses far greater power of evoking characteristic inflammatory response than that which has been shown to be possessed by any or all of the tuberculolipids. Refvem[3] in an extended study concluded that phospholipids are responsible for the genesis of epithelioid cells and *granuloma* formation. He postulated that such phospholipids could be derived from the pathogen, from tissue breakdown, or from antibody reaction with pathogen antigens. Lurie[4] and others have noted that the transformation of macrophages into epithelioid cells is constantly associated with the retardation of growth or the destruction of bacilli. He also noted that the greater the resistance of experimental animals to the pathogen, the more rapid is the transformation of macrophages into epithelioid cells. He concluded, however, that, "It is not that the epithelioid cells destroy the bacillus but rather that the transformation of the mononuclear phagocytes into epithelioid cells results from the disintegration of bacilli or their products."

Leprosy provides a unique model for the study of these problems as related to the *infectious granulomata*. Its immunopathologic spectrum encompasses classical epithelioid cell *granuloma* formation in tuberculoid leprosy and complete absence of *granuloma* and epithelioid cells in active lesions of lepromatous leprosy, with a broad, interconnecting spectrum of intermixed inflammatory manifestations in intermediate (dimorphous, borderline) disease. The same bacillus, and presumably similar breakdown products, are involved in evoking this entire reactional spectrum of inflammatory response. Phospholipids are found in lepromatous tissues, as well as other bacillary breakdown products, but in lepromatous disease there is no true epithelioid cell transformation and no structural *granuloma* formation. Additionally, though there appears to be no deficiency in pathogen phagocytosis, there is striking failure to destroy the engulfed bacilli. Morphologically the immunopathologic scale from lepromatous through intermediate to tuberculoid leprosy demonstrates the validity of the assertion that the transformation of macrophages into epithelioid cells is constantly associated with degradation and destruction of bacilli. This same progression suggests that epithelioid cells do destroy bacilli and that the epithelioid transformation is a morphologic reflection of enhanced intracellular activity which is manifest in hyperplasia and hypertrophy of intracellular organelles. The electron microscopic contrasts between lepra cells of lepromatous and epithelioid cells of tuberculoid leprosy noted by Nishiura[5] support this concept. The increased density, opacity and eosinophilic staining of cytoplasm which is characteristic of epithelioid cells is a reflection of these intracellular changes and is apparently not due to intracellular accumulation of bacillary or other breakdown products, or even of epithelioid stimulating phospholipids. Several histochemical studies, including those of Davison and associates[6] and Harada[7] indicate that in leprosy the accumulation of pathogen lipids occurs in lepromatous and not in tuberculoid cells and such accumulation seems to be evidence of slowed, ineffective or incomplete enzymatic digestion of bacillary lipids.

To speak of the macrophage accumulations of lepromatous leprosy and of tuberculoid leprosy indiscriminantly as *granulomas* is to ignore both the morphologic and immunologic characteristics of *granuloma* to which the leprosy model points. Indeed, it was against the background of these differences in morphologic expression as

[3] Refvem, O. The pathogenesis of Boeck's disease (sarcoid). Acta Med. Scandinavian Suppl. (1954) 9-146.

[4] Lurie, M.D., *Resistance to Tuberculosis*. Cambridge, Mass., Harvard University Press. 1964, pp. 4-29.

[5] Nishiura, M. The electron microscopic basis of the pathology of leprosy. Internat. J. Leprosy **28** (1960) 357-400.

[6] Davison, A. R., Kooij, R. and Wainwright, J. Classification of leprosy. II. The value of fat staining in classification. Internat. J. Leprosy **28** (1960) 126-132.

[7] Harada, K. The mode of formation of lepra cells. La Lepro **25** (1966) 21-27.

correlated with immunologic behavior that Wade,[8] many years ago, sketched the contrasting histopathologic characterizations of the polar forms of leprosy in terms of "tuberculoid" and "lepromatous." Use of the term *granuloma* for the usual morphologic lesion of tuberculosis is consistent, for the human tuberculosis model does not present the dichotic problem posed by the contrasts of lepromatous and tuberculoid leprosy. Some immunopathologic implications of these differences between tuberculosis and leprosy were noted in a previous editorial discussion.[9] Occasionally, when under conditions of severe immunologic debilitation cellular immunity in the tuberculosis patient is eliminated, the tubercle bacilli proliferate apace. The macrophages then are packed with bacilli and appear less like epithelioid cells and tubercles are poorly, if at all, developed. The morphology is so akin to that seen in lepromatous leprosy that it has recently been suggested that it is appropriate to term this response "lepromatoid tuberculosis."[10] In the lepromatous leprosy model and in "lepromatoid tuberculosis" there is then, no *granuloma* but only unstructured accumulations of ineffective macrophages containing engulfed pathogens and degradation debris. The nature of this debris will, of course, differ with the pathogen and the macrophages may, or may not, show varying degrees of foaminess.

The tuberculoid granuloma is a true granuloma, as is the cellular response found in much intermediate (borderline, dimorphous) leprosy, both morphologically and immunologically. These contrast distinctly with the masses of vacuolated, bacilli and debris laden macrophages seen in lepromatous leprosy. It would seem more discriminating to refer to these masses as "nodules" rather than as *granulomas*. This will, accordingly, be the editorial practice of this JOURNAL. There is good historical precedent for such practice since lepromatous leprosy was long designated as "nodular leprosy."

If it be accepted that there are essential morphologic and immunologic differences between the nodules of lepromatous leprosy and the granulomas of tuberculoid leprosy, then leprosy stands as a relatively unique, single-pathogen model for the comparative study of granuloma formation. Either end of the leprosy spectrum serves as an automatic control for the other.

Since the same pathogen elicits both polar manifestations in leprosy, the possibility exists that, if some chemical entity is responsible for epithelioid conversion and *granuloma* formation, the two differing polar macrophage reactions result in bacillary degradation to or through the responsible chemical entity in tuberculoid disease and failure to achieve similar degradation in lepromatous disease. Since phospholipids are demonstrable in lepromatous lesions this possibility seems unlikely, though it is not excluded by specific evidence. Alternatively, it is possible that the failure in epithelioid conversion and tubercle formation is part of the manifestation of the immunologic or cell enzyme defect that is responsible for this form of inefficient response. In other words, the failure of phospholipid to stimulate epithelioid conversion and granuloma formation in lepromatous leprosy may help to define the nature of the macrophage defect which is a manifestation of immunologic defect. Recalling the greater effectiveness of the tubercle bacillus, as compared to its chemical fractions, in eliciting these cellular responses, the leprosy defect is the more striking by virtue of its manifestation in the presence of masses of bacilli.

In pointing up the immunologic dichotomy of leprosy, Lowe[11] noted that humoral antibodies to a variety of related antigens are demonstrable in lepromatous leprosy and not, or with difficulty, in tuberculoid. Further, erythema nodosum leprosum

[8] WADE, H. W. Tuberculoid changes in leprosy. I. The pathology of tuberculoid leprosy in South Africa. Internat. J. Leprosy **2** (1934) 7-38.

[9] SKINSNES, O. K. First infection leprosy. Internat. J. Leprosy **37** (1969). (Editorial).

[10] SKINSNES, O. K. Comparative pathogenesis of the mycobacteriosis. Ann. New York Acad. Sci. **154** (1968) 19-31.

[11] LOWE, J. The leprosy bacillus and the host reaction to it. *In* Experimental Tuberculosis, G. E. W. Wolstenholme & M. P. Cameron, Eds. CIBA Foundation Symposium, J. & A. Churchill, Ltd., London, 1955, pp. 344-354.

(ENL) carries the morphologic characteristics of immediate type (anaphylactoid) hypersensitivity whereas tuberculoid reaction is characterized by morphologic changes usually associated with delayed type (cellular) hypersensitivity. In the latter the granulomatous expression is often enhanced. Apparently granuloma formation in leprosy is not associated with humoral antigen-antibody reactions but is related to the mechanisms of cellular immunity and hypersensitivity, and is associated with macrophage ability to degrade and eliminate the pathogen.

The leprosy model, therefore, presents a need for a more precise characterization of *granuloma* and use of this designation, and suggests that this can be achieved in correlative morphologic and immunologic terms. Indeed, in this desideratum lies its recommendation as a uniquely contributive model for further significant contributions to an understanding of *granuloma*.

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