LATE TUBERCULOID GRANULOMATOUS REACTIONS

Orthodox discussions of allergic reactions and their mechanisms recognize only two general classes of them, the "immediate" reactions, including anaphylactic and urticarial, and "delayed" reactions, including tuberculin-type reactions and contact dermatitis; and the mechanism of all is ascribed to interactions of antigens with antibodies, free or fixed.[1] The student of the Mitsuda reaction to lepromin, a "late" phenomenon appearing after a much longer interval than the ordinary "delayed" reactions, finds no recognition of that type of phenomenon, and nothing to aid him to an understanding of its mechanism.

In recent years two dermatologists in Philadelphia, H. J. Hurley and W. B. Shelley, have become interested in such reactions, which they recognize as having been previously overlooked and regard as extending the "frontiers" of allergy. Abstracts of four papers in this field published by them appear in the Current Literature section of this issue, and the fourth paper is reprinted in full (136-138). (88-98).

The first report was in effect a preliminary one by Shelley [2] on the occurrence in an occasional person of late-appearing and long-persisting papular lesions of tuberculoid ("sarcoid") nature appearing in the axilla as a result of specific sensitization by a zirconium compound in a deodorant stick. This condition had been seen in 4 clinical patients and had been produced experimentally in 2 of 30 volunteers. The second report [3] dealt with these 6 cases and 64 others found in the literature, and listed the many foreign bodies which may give rise to tuberculoid granulomas and the many disease conditions in which such granulomas may be found. Mention is made of the lepromin and Kveim tests. The demonstration of the allergic nature of the zirconium lesions the authors regarded as "... an entirely new facet of immunological response ..." which may bear on granulomatous processes generally, including that in (tuberculoid) leprosy.

The third report [4] bore largely on the question of whether or not patients with sarcoid granulomas (35 of which were included in the

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[1] See for example an up-to-date review entitled "The allergic reaction," in Therapeutic Notes (Parke, Davis & Co.) **67**E (1960) 265-269. This note contains two definitions by the Nomenclature Committee of the International Association of Allerology that may be noted. Allergy, or the allergic state, is "... an acquired, qualitatively altered capacity of living tissue to react, induced by a specific allergen." An allergen (or antigen) is "... any substance capable of producing a state or manifestation of allergy." (Quoted from an editorial in *Ann. Allergy* **16** (1958) 680.)

[2] SHELLEY, W. B. Some reflections on certain new granulomata. Trans. St. John's Hosp. Dermatol. Soc. (1957) No, **39**.

[3] SHELLEY, W. B. and HURLEY, H. J. The allergic origin of zirconium deodorant granulomas. British J. Dermat. **70** (1958) 75-101.

[4] HURLEY, H. J. and SHELLEY, W. B. Comparison of the granuloma producing capacity of normals and sarcoid granuloma patients: experimental analysis of the sarcoid diathesis theory. American J. Med. Sci. **237** (1959) 685-692.

study) would give sarcoid reactions to any of the various substances used in test injections more frequently than normal persons (300 tested). They did not. The only granulomatous reactions seen at all were in their 6 zirconium-reactive cases, and in them only in the sites of injection of a water-soluble zirconium salt. The delayed appearance of this granulomatous reaction was likened to those resulting from the Kveim test in sarcoidosis and the lepromin test in patients with tuberculoid leprosy. It was postulated that in these diseases, and perhaps others, a specific granulomagenic agent is responsible for such tissue reactions.

Most recently, the study was extended [5] to the occasional late development of persistent epithelioid granulomas at the sites of tuberculin tests, about the cause of which there has been some speculation that they might result from tissue breakdown secondary to an intensely positive 48-hour reaction. Out of 50 normal Negro volunteers tested with one-half the normal dose of the first PPD dilution, 5 showed the tuberculoid papular reaction. All of them had shown positive tuberculin reactions earlier, but those graded from 1+ to 3+ in a 4-grade reading scale so there was no correlation with the degree of the 48-hour reaction. Retests gave the same results. Further tests with larger doses of PPD gave larger papular reactions in these subjects, not however commensurate quantitatively with the stronger 48-hour reactions; but these larger doses did not induce the papular reaction in subjects who had not shown it after the first, low-dose test. The authors hypothesize that this delayed type of reaction in a small proportion of subjects may be due to a special type of hypersensitivity, one that is analogous to that of patients with zirconium and other sarcoid granulomas, and distinct from the ordinary tuberculin hypersensitivity. It is believed that sarcoid granulomas represent a reaction pattern which may be induced by various agents "through the mechanism of a newly described type of hypersensitivity which manifests itself as a granuloma."

It may be suggested that the term "reactivity" might well be substituted for "hypersensitivity," to provide a distinction from the tuberculin type of allergy to which the latter term is usually applied. In the zirconium-sensitive (or reactive) cases there was no early (48 hour-type) response whatever before the late appearance of the granulomatous papular reaction, even after repeated testing; and in the delayed reaction to tuberculin—although in the authors' experiment it was seen only in tuberculin-positive cases—there was no correlation with the degree of reaction to tuberculin either at first with the low dose or later with larger doses. A probably significant feature is that

[5] Hurley, H. J. and Shelley, W. B. Sarcoid granuloma after intradermal tuberculin in normal human skin. Arch. Dermat. **82** (1960) 65-72.

(apparently) there was no acceleration of those granulomatous reactions to either antigen on repeated testing of the reactive cases.[6]

To one who has long held that there must be a special kind of allergy involved in the mechanism of the Mitsuda reaction to lepromin, not dependent on the "early" (48-hour) type of hypersensitivity although undoubtedly affected by it when it is present and strong, the studies here reviewed bring hope that specialists in immunology (if not perhaps clinical "allergists" as well) may sometime pay attention to this type of reaction and arrive at an explanation of its mechanism. In the meantime, however, leprologists who concern themselves with the problem of the mechanism of the late reaction to lepromin might with profit take this newly-defined phenomenon into consideration. To do so might at least lead them to agree with Kinnear Brown in his dissatisfaction with the facile foreign-body-effect explanation, which seems so plausible because lepromin contains leprosy bacilli and tissue elements and because filtrates and extracts which do not contain bacilli do not elicit the Mitsuda phenomenon. The problem is obviously complex and difficult—which should not make it less challenging.

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[6] About that matter Hurley has written more recently (personal communication) that they had not particularly studied the point, but that their observations would allow the following statements:

1. It is possible that with repeated testing some degree of acceleration of the reaction, from four to three weeks perhaps, may be seen. However, we are not firm in this view and feel that the matter requires further study.

2. Acceleration of this response to a time approaching 48-72 hours was *never* seen, and in our opinion is not to be anticipated. This granulomatous reaction is a more delayed response and we would doubt that the time required for its development could be shortened to less than two to three weeks even after repeated testing or in cases of unusual sensitivity.