An article which will be of special interest to workers concerned with the histopathology of the Mitsuda reaction to lepromin, and especially in the question of whether size of the reaction nodule can be depended upon for determining positivity of the reaction or whether it can be determined only by histopathology, is the report of a study of the microscopic features of the Kveim-test reactions by workers at Columbia University in New York, one of whom is Carl T. Nelson[1] who is known for his clinical use of the test.

The two tests, Kveim and Mitsuda, are closely related at least superficially, because the antigens of both are suspensions of the lesion tissues, and the positive reactions are both "late" ones, slow to develop. In the Kveim test antigen, however, the antigenic element is unknown since it contains no detectable microorganism or virus, whereas in lepromin the essential antigenic element is the leprosy bacillus. The reactions in both cases are nevertheless granulomata which are mainly of tuberculoid nature.

Attempts have been made to correlate the histopathology of the lepromin reaction with the clinical criteria of positivity (nodules beyond

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[1]STEIGELDER, G. K., SILVA, A., JR. and NELSON, C. T. Histopathology of the Kveim test. Arch. Dermat. **84** (1961) 828-834. (See summary in the Current Literature section of this issue.)

a certain size after 2 or 3 weeks), but the reported findings [2, 3] have been so inconclusive that at the time of the Tokyo Congress (1958) the Committee on Immunology could only say:

"It is recommended that histologic studies of the late reaction be pursued to determine whether or not [the prescribed limits of size] agree with histologic factors."

The authors of the Kveim-reaction article under discussion point out that the development of that reaction depends so much on individual factors that Putkonen believed that the reaction lesion ("papule") should be biopsied when it attains maximal size rather than after a given interval of time. Practically, to follow that rule would at least be inconvenient, and often impossible. Yet if the examinations are made after a given time—6 weeks after the injection was the usual time—there will be found in some cases an immature granuloma, not fully developed, and in others a granuloma with severe degenerative changes and necrosis. "In other words, we may expect to find a high number of borderline cases which are subject to more than one interpretation."

The authors' study was based on 165 specimens of reaction lesions, age at time of removal not stated but apparently about 6 weeks as a rule, taken from 165 patients tested with Nelson's antigens prepared from sarcoidal spleens. The patients themselves were divided into 5 groups:

Group A.—Definite sarcoidosis, proved histologically
Group B.—Probable sarcoidosis, but not proved histologically
Group C.—Probably not sarcoidosis, but with suggestive findings
Group D.—Patients with pulmonary tuberculosis
Group E.—Patients with other diseases.

The histologic findings were divided into 7 classes, 4 of which were considered negative with respect to the Kveim test, while 3 were regarded as positive. The negative group: (1) banal inflammatory reaction, (2) lymphoreticular reaction (lymphocytes and histiocytes), (3) fibrosis (including, rarely, keloid formation), and (4) foreign body granuloma. The positive group: (5) tuberculoid granuloma without fully developed epithelioid cell tubercle, (6) tuberculoid granuloma with epithelioid cell tubercles with necrosis and banal inflammatory reaction, and (7) granuloma indistinguishable from or very similar to sarcoidosis.

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[2]The references given in an article by R. D. Azulay *et al.* in THE JOURNAL [**28** (1960) 38-43] recall reports on the subject by Schujman (1936), Alayon (1939), Nagai (1939), Tachikawa (1939), Nolasco (1940), Piñeyro (1950), Yokata (1953), and the authors themselves (1956).

[3]BECHELLI, L. M., SOUZA, P. R. and QUAGLIATO, R. Prepared papers with identical titles, presumably different papers but under identical titles for the Madrid and Tokyo congresses, which were published in the *Rev. brasileira Leprol.* **25** (1957) 21-55 and **27** (1959) 172-182, and also in the *Internat. J. Leprosy* **26** (1958) 426.

The results are shown in a detailed table which is condensed as follows:

Histologic groups	*Clinical groups*		
	Sarcoidosis	*Not sarcoidosis*	*Total*
Negative Kveim test			
Group I	2	13	15
Group II	—	10	10
Group III	6	6	12
Group IV	8	36	44
Totals	16	65	81
Positive Kveim test			
Group V	24	1	25
Group VI	27	—	27
Group VII	32	—	32
Totals	83	1	84

Silicate crystals were found in some of the foreign-body granulomas from early experiments in which they had been introduced experimentally into the antigen suspension, but usually the doubly refractile material represented debris of hair structure (keratin). In 16 instances the reactions were considered false negatives, against only 1 false positive (Group V). The negatives were sometimes due to technical errors (e.g., missing the reaction site in removing the specimen), and also probably comprised some cases that had reacted either unusually slowly or unusually quickly to the antigen.

It was concluded that the Kveim test is valuable in the diagnosis of sarcoidosis, and of considerable specificity when properly performed and evaluated. It is said that:

"Some investigators allegedly have obtained a positive [Kveim reaction] in diseases other than sarcoidosis, especially in leprosy.[5] This may be explained by the use of an inadequate antigen,[6] since Wade[7] and Nelson[8] have not encountered positive reactions in leprous patients."

In that connection the question arises whether or not there would be a difference between lepromatous and tuberculoid cases in the matter of reactivity to the Kveim antigen. Wade tested, besides 7 lepromin-positive normal controls, only 10 leprosy cases, none typical tuberculoids but some lepromin positive. In all persons tested the reactions were essentially negative clinically at 5 weeks to both of the two Kveim

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[5]Kooij, R., Pepler, W. J. and Wainwright, J. Histopathology of the reaction papules evoked by intradermal injection of normal tissue suspensions and Kveim antigen. Dermatologica (Basel) **119** (1958) 105-114.

[6]The senior author has explained (personal communication) the term "inadequate antigen" as follows: "That term was used to describe every antigen that gave nonspecific results as well as any that had low reactivity or was nonreactive. If an antigen loses its specificity it is just as inadequate as one that loses its reactivity."

[7]Wade, H. W. Leprosy and sarcoid: The Kveim test in leprosy patients and contacts. J. Invest. Dermat. **17** (1951) 337-347.

[8]Nelson, C. T. (unpublished data).

antigens used. The cases tested by Nelson, it is said (personal communication), were of all types, tuberculoid, lepromatous and indeterminate. No information about the work and findings of Kooij *et al.* is available.

In the study of the histopathology of the reactions to lepromin, students of the matter might be well advised to follow the example of Steigleder *et al.* in the grouping of the findings. It would be especially interesting to observe whether the foreign body granuloma, shown in one of their pictures as an example of a negative reaction, is ever encountered in lepromin reaction lesions. —H. W. WADE