Immunologic Aspects of the Lepromin Reaction

Positive "Lepromin" Reactions With a Cow Spleen Suspension

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I will confine myself to the late (Mitsuda) lepromin reaction, which is read three or four weeks after the intradermal injection of lepromin. It must be kept in mind that the various lepromins used may vary much in strength, as can be seen in Table 1.

As is well known, lepromin contains leprosy bacilli *and* tissue. In this paper I will discuss chiefly the part played by the tissue in the lepromin reaction. It is now generally accepted that with suspensions of normal tissue, without leprosy bacilli, positive Mitsuda reactions can be obtained in tuberculoid leprosy and negative ones in lepromatous leprosy ([1, 3, 4, 11, 12, 13]). The results of our own recent experiments with normal tissue suspensions in tuberculoid leprosy are as follows. Klokke and coworkers ([8]) in India tested, on my request, a normal *human* spleen suspension, treated with chloroform and ether (Dharmendra method of preparation) in seven patients with tuberculoid leprosy. The results are shown in Table 2.

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TABLE 1. *Average readings (in mm) of reaction papules evoked with various substances read after 4 weeks (0.1 cc).*

	Lepromins (0.1 cc)						
Prep.	PI	PII	Z	Y	F	T	U
Tuberculoid	6.8	8.0	10.0	7.8	3.3	0	0
Lepromatous	0.4	0.5	1.6	1.1	0	0	0

PI = Mitsuda-Wade prep. from lepromatous ear lobes.
PII = another Mitsuda-Wade prep. from lepromatous ear lobes.
Z = very crude Mitsuda-Wade prep. from lepromatous liver.
Y = "standard" lepromin (Wade).
F = Dharmendra lepromin from lepromatous ear lobes.
T = bacterial filtrate from prep. Z.
U = bacterial filtrate from prep. F.

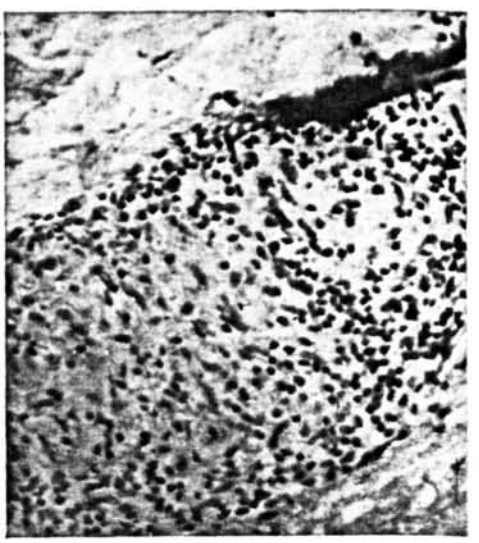

FIG. 1. Epithelioid cell granuloma evoked by an intradermal injection of a normal *human* spleen suspension in tuberculoid leprosy.

In three out of four patients with major tuberculoid leprosy and in one out of three with minor form, a papule (2-4 mm. in diameter) was observed at the end of 30–50 days after the injection. In three of these reaction papules on histologic examination an epithelioid cell granuloma was seen (Fig. 1).

We prepared also, from a *cow* spleen by extraction with saline, a suspension, 0.2 ml. of which was injected intradermally in six patients with tuberculoid leprosy in the Westfort Institution (Pretoria) in cooperation with Dr. Schulz. In all six a papule (2-6 mm. in diameter) developed after 4-5 weeks (Table 3). In three of them histologically an epithelioid cell granuloma was seen (Fig. 2).

With this same cow spleen suspension positive "Kveim" reactions were obtained in patients with sarcoidosis ([10]). The (late)

TABLE 2. *Tissue response to suspension of a normal tissue (spleen).*

Patient no.	Clinical diagnosis	Histology of reactive granuloma[a]		Size of papule (mm.)
		Infiltrated tuberculoid leprosy		
308131	Major tuberculoid	Tuberculoid	(35)	3
1708 G	" "	Multiple tuberculoid	(45)	4
1695 G	" "	Tuberculoid	(50)	2
1769 G	" " (regressing)	No biopsy	(40)	—
1186 G	Minor tuberculoid	Nonspecific infiltration	(30)	2
1683 G	" "	No biopsy	(50)	—
1739 G	" "	" "	(40)	—

[a] The figure within parentheses indicates the number of days after introduction.

Mitsuda lepromin reaction and the Kveim reaction have many things in common, especially its timing and gross appearance. In comparing the results of lepromin tests and Kveim tests, one must realize that the criterion for a positive Kveim test is histologic and for the lepromin test macroscopic. Positive Kveim reactions have been obtained also in tuberculoid leprosy ([2, 6, 9, 14]) Hirako used an antigen prepared from a Banti disease spleen. The Kveim test, like the lepromin reaction, has no etiologic value. With Kveim antigen one can detect certain immunologic changes.

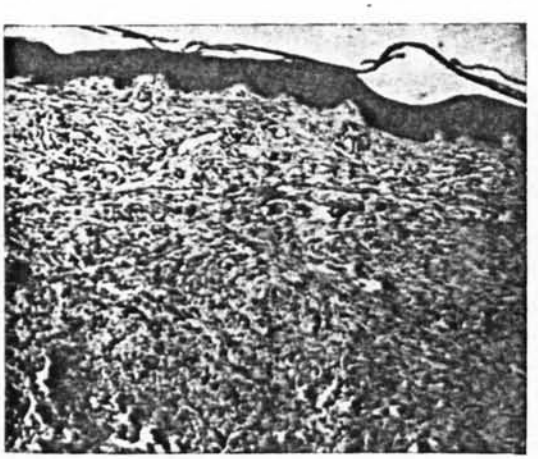

FIG. 2. Epithelioid cell granuloma evoked by an intradermal injection of a normal *cow* spleen suspension in tuberculoid leprosy.

Kveim antigen is prepared from sarcoid tissue by extraction with saline in the same way as lepromin from infected lepromatous tissue. Sometimes with nonsarcoid tissue suspensions positive Kveim reactions can be obtained in sarcoidosis ([7, 10]) However not every nonsarcoid tissue suspension can evoke positive Kveim reactions. But even preparations from sarcoid tissue often fail to produce positive Kveim reactions [for particulars refer to Kooij ([9])]. The same applies for "lepromin" prepared from normal tissue; the activity of these suspensions varies; not every suspension in active.

The above results show that with suspension of homologous and heterologous tissue one can evoke lepromin-like reactions in tuberculoid leprosy. These tissue components may act as antigen and it is now well known that tissue components, if sufficiently altered by infection, irradiation or heat, or by treatment with denaturizing agents, may induce a kind of autoimmunization as described by Waksman ([15]). Apart from the resemblances of the lepromin reaction and the Kveim reaction, there is also some point of contact with the homograft reaction. The tissue components of the lepromin and the homograft both contain various tissue (transplantation) antigens. With every lepromin test transplantation antigens are injected. This might give rise to similar immunologic changes as

TABLE 3. *"Lepromin" reactions with a cow spleen suspension.*

Patient no.	Clinical features	Histology reaction papule (biopsy taken after 5 weeks)	Size of papule (mm.)
5534	Raised lesions Mitsuda reaction 8 mm.	slightly tuberculoid	5
16408	Circumscribed lesions with scaling edges Mitsuda reaction 5 mm.	non-specific	2
16426	Raised lesions with succulent edges. Mitsuda reaction 5 mm.	lympho-histiocytic	6
16429	Major tuberculoid Mitsuda reaction 4 mm	tuberculoid	2
16438	Spongy erythematous lesions. Mitsuda reaction 3 mm.	lympho-histiocytic	3
16488	Hypopigmented macule with raised margin Mitsuda reaction 3 mm.	slightly tuberculoid	3

observed in the homograft reaction.

Knowledge of the mechanism of the homograft reaction, which is based on cellular immunity, might be applicable to the reaction evoked by the tissue components of lepromin. Even histo-compatibility of the tissue components of lepromin might be of importance and also genetic differences of the individuals. One must not forget that with each lepromin test one injects foreign tissue into an individual. This might give rise to special immunologic changes, especially on repeated injections.

In the lepromin reaction the tissue components change the effect of the leprosy bacilli and vice versa. Floch ([5]) observed that reactions to highly diluted lepromin are strengthened by adding an extract of normal skin. One can probably consider lepromin as a kind of Freund adjuvant. As long as lepromin cannot be freed of tissue the immunologic changes caused by the bacilli *and* the tissue components of lepromin must be studied with all modern immunologic methods available. I hope the discussion at this colloquium will stimulate and coordinate further investigations in this direction.

SUMMARY

Although lepromin contains *M. leprae* and tissue, I will confine myself chiefly to the part played by the tissue in the lepromin reaction. There is some resemblance between the lepromin test and the Kveim test. Like lepromin, Kveim antigen contains tissue components. Positive Kveim tests have been obtained in tuberculoid leprosy. Positive Kveim tests have been obtained also with suspensions of normal human and animal tissue, prepared in the same way as Kveim antigen, in sarcoidosis and tuberculoid leprosy. Furthermore there is some resemblance with the homograft reaction. Lepromin and Kveim antigen also contain tissue (transplantation) antigens. Histocompatibility might be of importance in the lepromin reaction. Knowledge of the nature of these reactions, which are all based on cellular immunity, might be applicable to the part played by the tissue in the lepromin reaction.

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