

INTERNATIONAL JOURNAL OF LEPROSY

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION
PUBLISHED WITH THE AID OF THE
LEONARD WOOD MEMORIAL

Publication Office: 1832 M St., N.W., Washington 6, D. C.

VOLUME 31, NUMBER 2

APRIL-JUNE 1963

EDITORIALS

Editorials are written by members of the Editorial Board, and opinions expressed are those of the writers.

OLMOS CASTRO ON THE LEPROMIN REACTION

This issue of THE JOURNAL contains, exceptionally, a series of three articles on the reactions of the lepromin class, by the Argentinian students of the subject, Drs. Norberto Olmos Castro and Pascual B. Arcuri. These articles are the last to be written by this team and, taken together, constitute a summation of their views. By chance, they were received on January 1, 1963, which—discounting the effect of the International Date Line—was the day that Olmos Castro died, December 31, 1962, of a rapidly-growing fibrosarcoma of the mediastinum.

The letter from him that came with the manuscripts, dated December 15th, follows:

Some years ago you asked me what, precisely, was my view of the Mitsuda reaction. I believe I am now in a position to reply with assurance, because of the three last reports prepared in collaboration with Dr. Pascual B. Arcuri. Of these, the one entitled "Our Immunologic and Clinical Interpretation of the Lepromin Reaction," will I believe interest you particularly. I think that the publication of these articles in the *International Journal* would be of interest.

There is no indication in that letter of any disturbance of the author's equanimity, and the news of his death was entirely unexpected. Dr. Arcuri has written that Olmos Castro wrote these articles on his bed, where he was because of weakness and torturing pain, and that "up to the very day of his death he talked with me about plans for further investigations."

Although there are features of these papers which are new, the main theses will be familiar to anyone who has followed the work of Olmos Castro and his group.¹ Two of their reports have appeared in

¹At one time Olmos Castro had enlisted several other persons (see the second following footnote) in a group given the ambitious name, "Agrupación Para el Estudio de la Hiper-sensibilidad e Inmunidad de Lepra (A.P.E.H.I.L.)."

THE JOURNAL, one as a reprinted article.^{2,3,4} The papers discussed here represent their thoroughly-considered views.

I. LEPROLIN VERSUS LEPROMIN

Discussing first the effects of *leprolins*, which like tuberculins do no more than reveal the existence of a certain kind of hypersensitivity, and of *lepromins*, which reveal or induce "tissue sensitivity," this article reports an experiment made to determine the effect of a lepromin test on the pre-existing leprolin positivity. In a group of 23 known leprolin positives tested with lepromin, a high degree of concordance of positivity was observed. Retesting the same group with leprolin 3 weeks after the lepromin injections, it was observed that the degree of leprolin positivity (i.e., of hypersensitivity) had been increased materially. It was increased much more 3 weeks later, in those individuals the data of whose 6th-week tests are given—this late increase being a particularly interesting point not specially discussed by the authors.

They then diverge from the subject of the title. For years, they say, they have insisted that the two most important observations in the immunology of leprosy have been (1) the demonstration by Wade, in experiments on dogs, of the sensitizing capacity of the leprosy bacillus, and (2) the demonstration by Fernandez of the tuberculin-reaction type of hypersensitivity in leprosy. Apparently regarded as of a similar category is the authors' observation of a nodular reaction by the 7th day in previously sensitized persons, which reaction they call the "accelerated formation of the tubercle" and regard as having the same significance as the 21-day Mitsuda reaction.

It is held that testing should begin with leprolin. In cases found positive to that antigen, the use of lepromin is harmless, but in leprolin-negative cases its use is usually inadvisable because of its artificial sensitizing effect. It is also held that the positive leprolin (or Fernandez) reaction demonstrates the existence of resistance. All this would seem tantamount to saying that the results of the leprolin test are sufficient to determine what results the lepromin test would give, with which view—if our inference is correct—few would agree.

This conclusion obviously pertains to persons sensitized by (tubercloid) leprosy infection, or by injection of some sensitizing antigen. Nothing is said of the small proportion of normal children tested who give the early reaction but do not give late Mitsuda reaction (10% in

²OLMOS CASTRO, N. and ARCURI, P. B. Attempts to obtain an antigen (LPT) suitable for study of hypersensitivity in leprosy. *Internat. J. Leprosy* **26** (1958) 51-56.

³OLMOS CASTRO, N., ARCURI, P. B., USANDIVARAS, R., BONATTI, A. A., LEBRON, E., TORANZOS, L. and CONEJOS, M. Hipersensibilidad de vacunación y de infección por *Mycobacterium leprae*. *Arch. argentinos Dermatol.* **3** (1958) 221-229; *reprinted in Internat. J. Leprosy* **27** (1959) 148-156.

⁴The most ambitious of the products of Olmos Castro and Arcuri was a 52-page, 7-chapter manuscript of monographic length and arrangement entitled *The Wade Phenomenon*, which was submitted to THE JOURNAL in 1958 but was not used for reasons of practicability.

the report of Guinto and Wade.)⁵ In the next article (to anticipate a bit), mention is made of a small proportion of tuberculoid cases (3 out of 28, also 10%) who failed to give early reactions but nevertheless gave the later reactions. Cases of this latter sort constitute Type B of the third report.

II. ACCELERATED TUBERCLE FORMATION

In this report there is included an experiment with three "lepromins," one of which was a new one which hardly merits that name but gave results that, although they were not specially discussed by the authors, are really noteworthy.

The "accelerated formation of the tubercle" in response to the injection of lepromin, which Fernandez has called the "Olmos Castro phenomenon," is (again) explained. It is described as an erythematous tubercle, minimal size 3 mm., which may or may not be surrounded by an inflammatory halo. In a *previously unsensitized* lepromin reactor an injection of lepromin causes the appearance, on about the 14th day, of a nodule which becomes a mature late reaction by the 21st day. In a *previously sensitized* reactor, in contrast, the lepromin injection induces—besides the early reaction—the production of a reactional tubercle by the 7th day (or earlier in particularly strong early reactors) which tubercle progresses to produce the mature Mitsuda reaction lesion by the 14th day. The 7-day reaction, therefore, has the same significance as the Mitsuda reaction.

It is passing strange that, in the nearly fifty years since the lepromin reaction was first observed, and in the thirty years and more that it has been widely used, the 7-day reaction and its significance have not been appreciated. We must admit missing it in our own experiments in patients and animals, in which readings were frequently recorded on the 2nd, 4th, 7th, 10th, 14th and 21st days; but practically none of the patients tested by us, a good share of whom were positive Mitsuda reactors, were of the straightforward tuberculoid type.

It is not possible to determine the validity of this thesis from the literature. We cite only an article by the authors' group already mentioned³ in which is shown the contrast of average sizes of the reactions to lepromin in two groups tested, normals (6 cases) and tuberculoid patients (11 cases).

	2nd day	7th day	14th day	21st day
Normals	3.4 mm.	4.2 mm.	6.5 mm.	7.5 mm.
Tuberculoids	20 mm.	16 mm.	11 mm.	11 mm.

The measurements tell nothing of nodule formation in the previously sensitized (tuberculoid) cases, in which the early reactions were

⁵GUINTO, R. S. and WADE, H. W. Results of tests with serial dilutions of lepromin in separate groups of normal young children; with a comparison of two lepromins and the Dharmendra antigen. Trans. VII Internat. Congr. Leprol., Tokyo, 1958; Tokyo, 1959, pp. 193-206; Internat. J. Leprosy **26** (1958) 328-345.

evidently very strong and the late reactions were stabilized by the 14th day. However, it was stated that in 7 of the 11 tuberculoid cases the nature of the reaction had changed from erythematous infiltrations on the 2nd day to nodules on the 7th day; in the other 4 cases that change took a week longer.

This observation by the authors of 4 exceptions out of 11 cases cannot arouse much confidence that the 7-day reading would be sufficient to determine positive reactors, but a supplementary reading on the 14th day of the patients negative on the 7th day might suffice. There would obviously be an advantage in being able to decide the results at 7 days, in any material proportion of cases tested, instead of waiting for the 14th or the 21st day—a point not discussed by the authors. This matter should be carefully and widely investigated in the near future.

As for the experiment reported in the paper under review, all of the 28 tuberculoid cases used as subjects gave the early and 7th-day accelerated reactions—and of course the late reaction—when injected with bacillus-body antigens (the classical Mitsuda-Hayashi lepromin and the bacillary suspension of Fernandez and Olmos Castro).⁶ With a newly-devised nonbacillary antigen, called a “whole-leproma (integral) antigen” (better called an extract), and described as “devoid of whole bacillus bodies and cellular detritus,” the accelerated-tubercle reaction and the subsequent Mitsuda reaction were also positive in 25 of the cases.

Except for one step, the method of manufacturing this antigen is the same as that of their “leprolin,”⁷ which is supposed to be non-allergenic. In the process used in the experiment the product of the grinding of the leproma in chloroform is not extracted with ether. In making leprolin, that is done to remove the lipids, “which have no antigenic value in the hypersensitivity test.”

It would seem, since both the early and the later reactions (see table), are given by the product which *does* contain the ether-soluble lipids—of the bacillus and the leproma tissue—that the lipids do, when in combination or association with the bacillary proteins, have an antigenic effect. This is a matter worthy of further attention.

III. INTERPRETATION OF THE LEPROMIN REACTION

Unorthodox, and peculiarly limited, is the authors' definition of a positive lepromin reaction. It is “characterized by the accelerated formation of the tubercle” by the end of the first week. This occurs only in persons previously sensitized by tuberculoid leprosy, or by the injection of lepromin, or BCG or the like. The late nodular (Mitsuda)

⁶FERNANDEZ, J. M. M. and OLMOS CASTRO, N. Estandarización de la lepromina. *Rev. argentina Dermatosisif.* **25** (1941) 435-446.

⁷OLMOS CASTRO, N. and ARCURI, P. B. Lepromin hypersensitivity induced by integral lepromin in persons presumably free from leprosy. *Internat. J. Leprosy* **25** (1957) 375-379.

reaction, said to be complete in such cases by the 14th day, "is nothing but the terminal evolution of the accelerated formation of the tubercle."

Four types of reactions are systematically set forth, of which only Types A and B have late reactions which are regarded as proper lepromin (or Mitsuda) reactions. These signify pre-existent tissue sensitization, both types exhibiting the essential 7-day accelerated tubercle.

The order of Types C and D seems anomalous. The former being entirely negative, and the latter being positive for the late (Mitsuda) reaction (only), it would seem that the order should be reversed. The Type D reaction is placed last because they hold it not to be a proper Mitsuda reaction, but a "Wade phenomenon." It does not signify pre-existing sensitization, but sensitization resulting from the lepromin injection itself. (The term "Wade phenomenon" was originally applied by these authors to the reactions in dogs^{8,9} by means of which it was demonstrated experimentally that the suspension of heat-killed leprosy bacilli is capable of inducing sensitization. Its application was later extended to the Type D reaction in man.)

Be all that as it may, last place (D) still seems a more appropriate location than third place (C) for the wholly negative reactions, because total negativity signifies both: (1) lack of pre-existing sensitivity, and (2) incapability of being sensitized—at least by a single injection of the lepromin employed in the dosage used.

The whole point of this article is based on the two revolutionary concepts, (1) that only the late reactions that occur in the cases with positive 7-day accelerated nodular reactions actually represent the significant Mitsuda reaction, the 7-day reaction signifying the existence of tissue hypersensitivity (*histic hipersensibilidad*), and (2) that the 21-day reactions in cases not showing first the 7-day reaction should not be considered in the same category as the Mitsuda reaction. It is a "different biologic phenomenon" corresponding to matters of vaccination, immunization, etc.

The validity of this concept will depend, in the first place, on the occurrence—and regularity of occurrence—of the 7-day reaction in positive cases. As for the significance that should be given the late reactions that result from tests of unsensitized persons (or animals), that seems likely to be a moot question for some time to come.—H. W.