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SUBSEQUENT EVOLUTION OF THE INDUCED
MITSUDA REACTION IN CLINICALLY AND
BACTERIOLOGICALLY NEGATIVE
LEPROMATOUS CASES

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In few diseases does the factor of the organic terrain play so preponderant a role as it does in leprosy, in which it controls the entire pathology, evolution and prognosis of the disease. The polar types of leprosy are nothing other than very different clinical, bacteriological, histological and immunological manifestations provoked by the same bacillus but in terrain that is not only different but opposite: one is resistant (the tuberculoid type) and the other nonresistant (the lepromatous type).

This lack of defense in patients with the lepromatous type is what gives most concern to leprologists, and I believe it no exaggeration to say that when we are able to convert a nonresistant individual to a resistant one, then we will have almost solved the problem of leprosy.

One of the best known and most widely accepted expressions or indexes of the presence and degree of this specific organic resistance to leprosy is the reaction to lepromin. This reaction is frankly negative in cases which lack this specific defense, while on the other hand the more strongly positive the reaction the higher is the degree of defense possessed by the patient. Hence the various attempts to make positive the lepromin reaction in healthy persons, done successfully with BCG by Fernandez (3), Souza Campos, Rosemberg and Aun (10), and others; and also in active lepromatous cases by Schujman (6, 7, 8), and in clinically and bacteriologically arrested lepromatous cases by Convit and associates (2), by Azulay and associates (1), by Schujman (8), and by Lowe and McNulty (4).

ATTEMPTS TO INDUCE LEPRONIN POSITIVITY IN PATIENTS

I. *In active lepromatous cases.*—In a communication presented to the Argentine Dermatological Association in May 1947 (6) I reported the results of my first attempts to make positive the lepromin reaction in active lepromatous cases—i. e., cases with skin lesions and positive smears—using as the stimulating or sensitizing agent a Stefansky antigen prepared from rat lepromas by the Mitsuda-Hayashi method. In none of the cases did I succeed in inducing the early Fernandez reaction, but in 55 per cent the late reaction (Mitsuda phenomenon) became positive, the reaction nodules showing the tuberculoid structure. In that com-

munication I made no claim for a protective value of the induced Mitsuda reaction, because at that time I had no experience in the matter.

Subsequent observations of these cases permitted me to say later, (1) that the lepromin test repeated five months after the vaccination gave negative results in all cases in which positivity had been induced, and (2) that the induced Mitsuda reaction had no favorable influence on the later course of the disease in those cases, and therefore that it had no protective value. For these reasons I abandoned the experiment.

II. *In arrested lepromatous cases.*—Because of the studies of Convit and coworkers and of Azulay and associates, who induced lepromin positivity in cases that had become clinically and bacteriologically negative, I undertook similar work with such cases.

Convit's group, giving BCG intradermally, saw 43 per cent of their cases become positive, 25 per cent in those whose tuberculin reaction was negative, and 62 per cent in tuberculin positives. The structure of the reaction nodules was tuberculoid. Azulay, using oral BCG, found that the early reaction became positive in 80 per cent of the cases, and the late reaction in 35 per cent.

My own work was with 40 lepromatous cases (mostly L_2 and L_3) which had become clinically and bacteriologically negative after several years of treatment, some by sulfones and some by chaulmoogra derivatives. For the vaccination I used the Stefansky antigen in 13 cases, oral BCG in 19 cases, and intradermal BCG in the remaining 8 cases. The results of this work, which was reported at the Madrid congress (8), were briefly as follows:

(a) In none of the cases was the Fernandez reaction induced. (b) The Mitsuda reaction was induced in 47 per cent of the cases vaccinated orally with BCG, in 50 per cent given intradermal BCG, and in 69 per cent receiving the Stefansky vaccine. (c) Histologically, the induced reaction nodules revealed a tuberculoid structure in the majority of the cases.

IMPERMANENCE OF THE INDUCED REACTION IN ARRESTED CASES

As has been said, the positive Mitsuda reactions induced in active cases were transitory, and no favorable influence in the course of the disease was observed. It was therefore of interest, to complete the experiment, to observe the reactions in the arrested cases that had been made positive, and especially to find out if the induced reactivity would be helpful in maintaining the recovery achieved.

In my first report on this subject (8) it was said that the test, repeated three months after the vaccination, still gave late reactions in all of the induced positives. These cases were tested again in February 1954, six months after the vaccination. In all of them, whether they had been vaccinated with BCG or the Stefansky suspension, the reactions were frankly negative.

In April of the same year, for the purpose of again inducing reactivity, I revaccinated the same group of patients with the same antigens they had received before. Again they became positive, showing as before only the late reaction, not the early one. To ascertain how long the positivity would persist the reactors were then tested once a month. It was found that after the fourth month the majority did not respond to lepromin, and none after the fifth month.

With respect to the subsequent evolution of the disease in these arrested cases in whom the Mitsuda reaction had been induced, some of them were seen to develop new, bacteriologically positive lesions.

Thus, the same thing was seen in these arrested cases as had been seen in the active ones, that is, that the induced Mitsuda reaction was only transitory and without protective value.

DISCUSSION

From the experience of other workers and myself in attempts to induce lepromin positivity in lepromatous cases, active or arrested, the following facts emerge:

1. That it is not possible to induce lepromin reactivity in all such cases. The results of different workers have varied, but the proportion of cases that have been made positive is approximately 50 per cent. In the remaining 50 per cent it has not been possible to achieve positivity by any of the methods of vaccination that have been used for that purpose: BCG, oral and intradermal, and the Stefansky antigen.

2. That some authors have reported that both the early and late reactions were made positive, whereas in my own experience only the late reaction has appeared, that is, the Mitsuda phenomenon in which a nodule of tuberculoid structure is produced after three weeks. I have been unable to induce the early reaction.

3. That the induced Mitsuda reaction, the new capability of responding positively to lepromin obtained in lepromatous cases by means of vaccination with other kinds of acid-fast bacilli, has in my case been of short duration. It began to decline in three months, disappearing completely in all cases within five months after vaccination.

4. That the induced lepromin reactivity in lepromatous cases has no protective value. In active cases, if treatment is neglected, the disease continues to progress despite the induced positive responses to the Mitsuda test. In arrested cases, clinically and bacteriologically negative, we have seen relapses with appearance of new, positive lesions despite the induced reactivity.

From these observations there arises the following question: Can we be sure that the induced Mitsuda reaction in healthy persons or contacts has the same protective value as the spontaneous positive reaction? Some authors give it the same value. I have not had enough experience to confirm or deny this, but what I have observed in patients

—although the problem in them is different since I was able to induce positivity in only 50 per cent while in healthy persons it can be induced in over 90 per cent—I am inclined to maintain that it is necessary to obtain more evidence than we have, especially facts based on long experience, before we can be assured of a protective influence of induced positivity.

All observers agree that almost all lepromin-negative children given BCG vaccination become Mitsuda positive. It should not be forgotten, however, that in a high percentage of individuals the lepromin reaction becomes positive spontaneously with age, so much so that in adults, even in nonendemic countries, around 80 per cent give positive Mitsuda reactions. This spontaneous positivity, which some authors attribute to cross sensitization by the Koch bacillus, I interpret as an expression of organic resistance against the leprosy bacillus possessed by the majority of adults. The reactivity to lepromin may or may not be influenced by cross sensitization by the Koch or other acid-fast bacilli, but that influence is not essential to possess or explain the resistance with which we are concerned. It is normal for adults to possess the capability of responding positively to lepromin with the Mitsuda phenomenon; it is abnormal, and fortunately less common, to be lepromin negative.

I believe that there is no reason why, for prophylactic purposes, contact children should not be submitted to mass vaccination with oral BCG because of its ease of administration and the lack of contraindications. However, in order to be able to establish in a really scientific way whether or not the induced Mitsuda reaction has the same protective value as spontaneous reactivity, I believe there must be selected a group of frankly and persistently negative contacts, the negativity shown to persist for at least two years, place them in the same epidemiological conditions, and then vaccinate one group of them and keep the others for a control, in order to make a comparative study of them and to observe their subsequent experience for several years.

CONCLUSIONS

My attempts to change the negative lepromin reactivity to positive in active and arrested lepromatous cases by vaccination has led to the following conclusions:

1. The induction of lepromin positivity in either active or arrested cases has been achieved in only 50 per cent of the cases, using either BCG or the Stefansky antigen.
2. In my cases I obtained only induced positive late reactions (Mitsuda phenomenon), with discreet nodules of tuberculoid structure; I have not seen induction of the early, or Fernandez, reaction.
3. The induced Mitsuda reaction in lepromatous cases has no protective value. For one thing, it is transitory. Furthermore, it has no

favorable influence on the evolution of the disease in active cases, and it has not prevented relapse in some of my arrested cases.

4. Although in healthy persons the problem is different, yet I believe that in order to be assured that the induced Mitsuda reactivity has the same protective value as the spontaneous reactivity it is necessary to select individuals who are frankly and persistently lepromin negative, place them in the same epidemiological conditions, and vaccinate one part of them and leave the other part unvaccinated as a control. These groups should then be observed for developments over a period of several years.

CONCLUSIONES

Nuestros intentos de positivizar la leprominoreacción en los casos lepromatosos en actividad (en el año 1947) y en los "arrested" ó sea clínica y bacteriológicamente negativizados (año 1953); nos permite llegar a las siguientes conclusiones:

1). La inducción de la Mitsuda en los casos lepromatosos ya en actividad ó ya "arrested," la hemos logrado solamente en el 50 por ciento de los vacunados (ya con B. C. G. ó ya con Stefansky).

2). En nuestros casos hemos obtenido únicamente la positivización de la reacción tardía (Fenómeno de Mitsuda) con un nódulo discreto de estructura tuberculoide; pero no logramos en cambio inducir la reacción precoz de Fernández.

3). La Mitsuda inducida en los casos lepromatosos no tiene valor protector. Porque es de duración transitoria y además no ejerce ninguna influencia favorable en la evolución ulterior de los casos, ya que observamos progresión del proceso en los enfermos en actividad y recaída en algunos de los clínica y bacteriológicamente negativizados.

4). Si bien en las personas sanas el problema es diferente, juzgamos que para poder asegurar que la Mitsuda inducida en ellas tiene el mismo valor protector que la Mitsuda positiva espontanea, hay que seleccionar casos franca y persistentemente leprominonegativos (por lo menos durante 2 años) y colocados en las mismas condiciones epidemiológicas, someter un núcleo a la vacunación, dejando el otro sin vacunar, de control, para observar en ellos comparativamente y durante varios años su evolución ulterior.

REFERENCES

- ✓ 1. AZULAY, R. D., DE MOURA, A. and MOURAO, G. A viragem da reação lepromínica pelo BCG administrado aos doentes lepromatosos em condições clínico-bacterio-scópico-histopatológicas de "transferencia para dispensario." *Rev. brasileira Leprol.* **20** (1952) 178-182.
- ✓ 2. CONVIT, J., RASSI, E., CANTO RODRIGUEZ, F. and CONTRERAS, R. Changes in the lepromin and tuberculin reactions of lepromin-negative leprosy patients after vaccination with BCG. *Internat. J. Leprosy* **20** (1952) 347-354; also (*in Spanish*), *Bol. Hosp. (Caracas)* **51** (1952) 13-21; *Mem. III Conf. Pan-Americana Leprol.*, Buenos Aires, 1951, Vol. 1, 1953, pp. 286-291.
- ✓ 3. FERNANDEZ, J. M. M. Sensitization to lepromin in presumably non-leprous individuals. *Internat. J. Leprosy* **11** (1943) 15-22.
- ✓ 4. LOWE, J. and McNULTY, F. Tuberculosis and leprosy; immunological studies. *Leprosy Rev.* **24** (1953) 61-90.
- ✓ 5. DE PAULA SOUZA, R., DE TOLEDO FERRAZ, N. and BECHELLI, L. M. Influencia do BCG vivo e morto sobre a reação de Mitsuda. (Observações preliminares.) *Rev. brasileira Leprol.* **21** (1953) 43-50.

- ✓ 6. SCHUJMAN, S. Intradermorreacciones con leprominas y otros antígenos con bacilo ácidoresistentes en enfermos de lepra. *Rev. argentina Dermatosif.* **32** (1948) 148-149 (Soc. Trans.).
- ✓ 7. SCHUJMAN, S. Intentos de positivar la reacción de Mitsuda en los casos lepromatosos; nuestros primeros resultados. *Rev. argentina Dermatosif.* **32** (1948) 149-151 (Soc. Trans.).
- ✓ 8. SCHUJMAN, S. Intentos de positivar la leprominorreacción en los casos lepromatosos; (a) en los casos en actividad, (b) en los casos negativizados o "arrested." *Mem. VI Congr. Internac. Leprol.*, 1953; Madrid, 1954, pp. 509-517; *also*, *Semana Méd.* **106** (1955) 401-408.
- ✓ 9. SOUZA CAMPOS, N. BCG in the prophylaxis of leprosy; a preliminary report. *Internat. J. Leprosy* **21** (1953) 307-312.
- ✓ 10. SOUZA CAMPOS, N., ROSEMBERG, J. and AUN, J. N. Da relação imunobiológica entre tuberculose e lepra. II. Da inter-relação entre as reações tuberculínica e lepromínica em filhos de doentes de lepra. *Rev. brasileira Leprol.* **18** (1950) 117-127.

DESCRIPTION OF PLATE

PLATE (1)

FIG. 1. Positive Mitsuda reactions in a lepromatous case, induced by oral BCG vaccination, as seen after 21 and 50 days.

FIG. 2. Showing the negative result of a Mitsuda test in the same case, made six months after the vaccination.

FIG. 3. A positive Mitsuda reaction, after 21 days, induced by intradermal BCG vaccination, the lesion of which is also shown.

FIG. 4. Negative Mitsuda reaction in the same case, made six months after the vaccination.

FIG. 5. Positive Mitsuda reactions induced by inoculation with the Stefansky antigen. The upper two lesions are the reactions 21 and 52 days after the tests; the lowermost lesion is the site of the Stefansky injection.

FIG. 6. Negative result of repetition of the Mitsuda test in the same case after six months.

FIG. 7. One of the lepromatous cases of the experiment, before treatment. (A picture taken after three years of sulfone treatment, when the patient was clinically and bacteriologically negative and the lesions shown in this picture were completely cleared up, cannot be used for lack of space.)

FIG. 8. The same case two years after suspension of treatment, showing the appearance of new lesions, bacteriologically positive, in spite of the fact that distinct lepromin positivity had been induced in the patient.

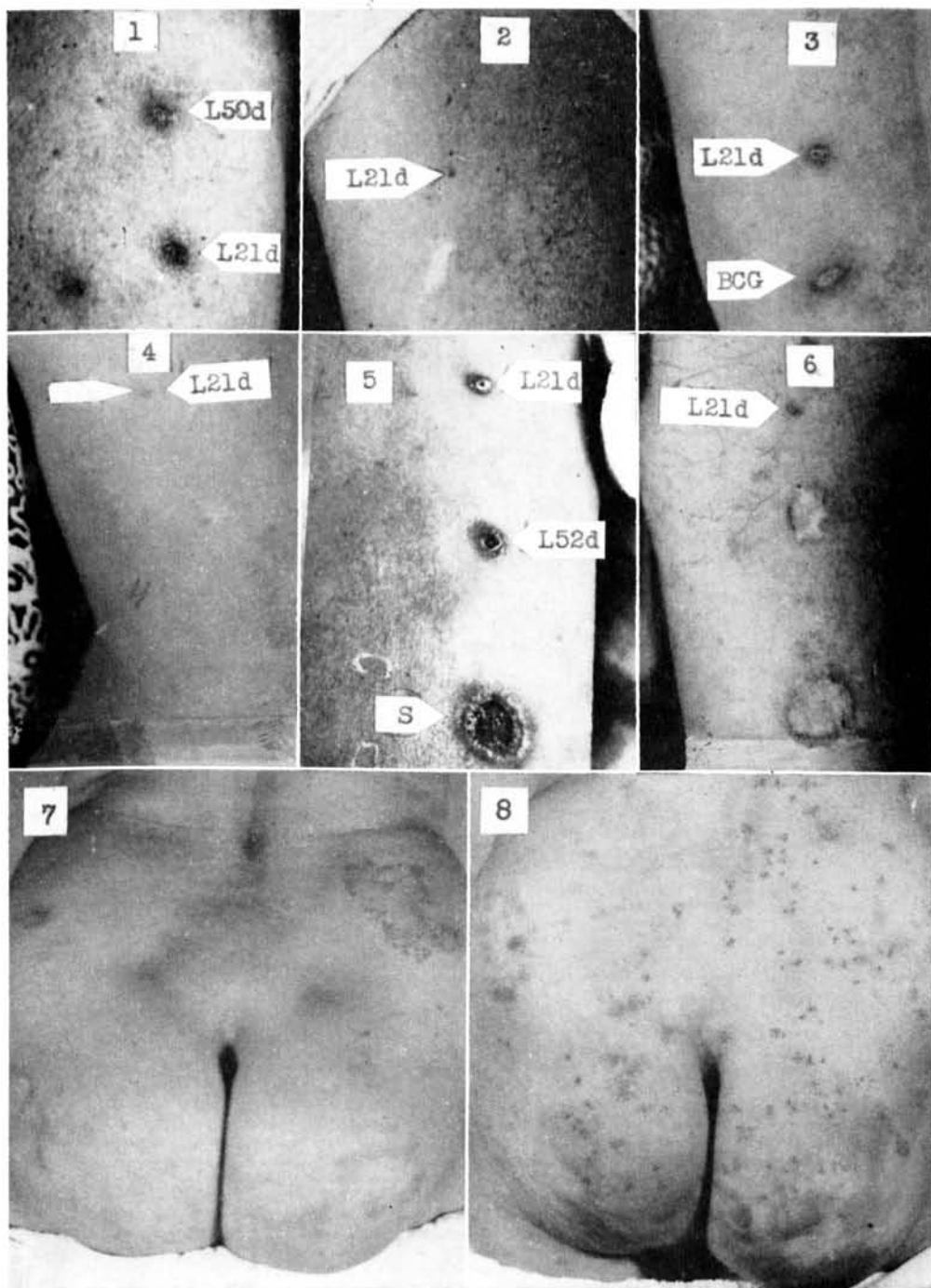


PLATE 1