CLINICAL AND THERAPEUTIC STUDY OF AN ANTIGEN PREPARED WITH *MYCOBACTERIUM MARIANUM*, APPLIED TO 457 LEPROSY PATIENTS [1]

DR. M. BLANC AND MILLE PROST
With the Assistance of
MME MICHEAL, MLLE LEMAIRE, EMILE KUNA
JOSEPH ESSELE AND JEAN-MARIE NKOA
Nden Leprosarium, Cameroun

A year ago we presented two reports (1, 2) on the immunological results obtained with an antigen prepared by Sr. Marie-Suzanne from her "Chauviré" culture.[2] The results obtained—73.3 per cent of Mitsuda positives in 6 months to 1 year—led us to make a closer follow-up of the same patients, and to apply the method of treatment to all new cases that came under our care. Our experimentation, which began two and a half years ago, has now involved a total of about 1,000 patients. The present report deals with 457 of these cases; the others will be analyzed after completion of the work.

The present report has to do with, (1) the general clinical evolution; (2) details of the various reactions caused by the antigen; (3) the influence of this antigen therapy on the clinical condition of the patients.

GENERAL CLINICAL EVOLUTION

The marianum antigen has been employed in the manner previously described: intradermal injection of 0.1 cc. on the external surface of the left arm once a month for three months, followed by two months rest, then a new course of three monthly injections. At present we tend to do courses of 6 consecutive injections without the rest of two months that previously was taken to permit making the Mitsuda test. As before, the Mitsuda test was performed before and after each course of antigen.

All of the intradermal injections were given by the same staff of four nurses, usually in the mornings. The reading of the results and the observations of the patients were done by the present authors. The classification of each case was discussed by at least three of us.

In total, more than 7,000 injections were given, but the results of only 2,638 are considered here. We have observed the following clinical evolution when the reaction is positive.

First day: A few hours after the injection the patient complains of more or less severe headache, and burning pain on the site of the injection. Often there is also moderate fever after a few hours, about 38-39°C. In

---

[1] This article, written in 1954, is based primarily on an English translation supplied by Sr. Marie-Suzanne, checked against a copy of the French original. The figures given in the original text are used throughout, although certain discrepancies will be seen in the tables, which have been prepared to conserve space.—EDITOR.

[2] This culture, as stated in the title, is a mycobacterium which has been named *Mycobacterium marianum* (3, 4).—EDITOR.

some cases this febrile state starts only on the second or third day. It disappears more or less quickly, but may last up to 8 days.

Second to fourth days: Besides the symptoms mentioned above, there appears at the site of the injection a small papule which may disappear quickly but which, more often, continues to develop for some days. At the same time one very often observes the beginning of a lepra reaction, with turgescence of patches and lepromas, modifications of color of these elements, and disturbance of the general condition. This reaction has generally disappeared within 8 to 10 days.

Seventh to thirtieth days: Usually there occurs a generalized and more or less intense pruritus. Clinical examination shows a dry skin covered with almost invisible but very numerous micropapules. The papule at the site of the injection is erythematous and increases up to the 20th or 28th day, developing into a nodule which may become 2 to 3 cm. in diameter. Usually this nodule softens and ulcerates about the 15th day. Later it forms a scar which, if not very marked, disappears in two months; but if the ulceration has been severe, of large size and deep-seated, the scar may last for many months or may be permanent.

The reading of the results was made a month after the injection of the antigen. In this way we have eliminated the weakly positive or doubtful reactions, in order that the results might be clear-cut.

THE DIFFERENT DEGREES OF REACTION TO THE ANTIGEN

Considering the details of the reactions shown by the patients, whom we especially followed for this purpose, we shall now see the different modalities which they have presented. They are classified as nil or weak, moderate, strong, and very strong. The figures are assembled in Table 1.

TABLE 1.—*The degrees of reactions to injections of the* M. marianum *antigen, in the different type groups of patients.*[a]

Type of case	No. of injections	Reactions observed							
		0		1+		2+		3+	
		No.	%	No.	%	No.	%	No.	%
Indeterminate	1,599	324	20.2	1,107	69.2	118	7.3	14	0.9
Tuberculoid	482	50	10.3	384	78.6	48	9.9	8	1.2
Lepromatous	557	82	14.7	402	72.1	58	10.4	15	2.8
Totals	2,638	456	17.5	1,893	72.5	224	8.6	37	1.4

a The figures here given are those stated in the text, it being impossible to correct discrepancies. The figures in the total line at the bottom are supplied, and they are correct for the figures given, the total number of injections being 2,610 instead of the stated 2,638.—EDITOR.

Negative or weak reactions (symbol 0).—The very weak type of reaction placed here consists, apart from the effect of the puncture, in at most a micronodule which disappears in a few days. There is no focal reaction; the patches and lepromas show no congestive eruption (*poussée*), nor do they itch. There is no general reaction, and particularly there is no fever.

This absence of reaction was recorded 456 times out of the 2,638 injections, or in 17.2 per cent of the total. It will be seen from Table 1 that there was no uniformity in the different types of case.

Lack of reaction does not mean lack of clinical effect, however, for patients who did not present any reaction have shown improvement of their condition during the course of the injections. We think that it is only a lack of external manifestation of internal phenomena.

Moderate reactions (1 +).—The moderate grade of reaction consists of a local response which starts on the 3rd or 4th day and goes on to the formation of a nodule 0.5-1.0 cm. in diameter. This nodule may remain as such, to disappear within two months; or it may undergo central necrosis, and then dry and cicatrize within the same length of time. There is also focal reaction: itching and congestion of all macules (*tâches*) and other lesions, lasting about a week. From the first day there is a general reaction of mild degree: headache, generalized but moderate pruritus, *courbatures*,[3] and rise of temperature to about 38°C.

This variety of reaction has been observed in 1,893 times out of 2,638 injections, or 71.7 per cent, with a type frequently as shown in Table 1.

Strong reactions (2 +).—The strong reaction consists of a local reaction, starting on the 3rd or 4th day, which goes to the formation of a nodule 1.5-2 cm. in diameter that always undergoes central necrosis. This necrosis causes an ulceration 3 to 4 mm. in diameter, surrounded by a superficial zone of erythema confined largely to the subjacent nodule. At the same time there is a focal reaction: pruritic painfulness of the leprotic lesions with congestion and turgescence, sometimes leprotic rhinitis, and often a lymph-node reaction within the territory of the injection. The general reaction is marked: headache from the first day, which may persist for three days, *courbaturé* fever to 38°C for 4 to 5 days, generalized itching, adenitis apart from any leprotic lesion, and general malaise.

This severe reaction has occurred in only a small proportion of our observations. It has been seen only 224 times out of 2,638 injections, or 8.4 per cent—less than 1 in 10. The type distribution is shown in Table 1.

---

[3] Apparently the nearest English equivalent of *courbaturé* is "malaise," but patients are said at one point to suffer both conditions. According to Soeur Marie-Suzanne *courbaturé* has a meaning quite similar to malaise, best described by the French colloquial phrase, "I feel like I had been beaten all over," or by the American phrase, "I feel like I've been drawn through a knothole."—EDITOR.

Very strong reactions (3 +).—In this case the local reaction is very early, with intense irritation at the site of the injection, and a papule developing rapidly into a nodule attaining as much as 3 cm. in diameter. Central necrosis of the nodule commences toward the 20th day. The ulcer is a little deeper than in the milder forms of reaction, involving the whole thickness of the dermis; the size is larger, attaining 1 cm. in diameter; the edge is elevated above the skin level, and is surrounded by a large inflammatory zone. A crust which covers it completely is rapidly formed over the ulceration, and under this crust cicatrization occurs in two or three months, leaving a permanent scar about 1 cm. in diameter. The nodule itself, as in the less severe reactions, disappears completely.

The focal reaction is also very intense. This first affects the lymph nodes in the region of the injection, which become enlarged, hard and painful. The macules and lepromas undergo congestion and become painful; one may even see bleeding of the lepromas. There may also be a more or less severe rhinitis. Usually those symptoms disappear completely in 8 to 10 days.

The general reaction, too, is very marked: the headache is intense and persists for many days; the patient is *courbaturé* and is bed-ridden; there is fever, which may reach or even exceed 39°C, persisting for 8 to 10 days. There is also an intense generalized pruritus, and palpation of the skin shows the presence of very numerous micropapules which may persist up to the 30th day after the injection. Marked adenitis, again, is found.

These focal and general phenomena always terminate a month after the injection, at which time there remains only the crust—evidence of the local reaction—which gives place to a permanent scar.

There have been very few of these reactions, only 37 out of 2,638 injections, or 2.7 per cent, with a type distribution shown in Table 1. Of 1,000 patients treated with this antigen, we were obliged to discontinue the treatment of 4 of them on account of the severity of the focal and general reactions.

Such are the different reactions met with in our experimentation. As seen, in 15-20 per cent of the injections the reactions have been weak or nil, and in 70-75 per cent they have been only moderate. This has permitted us to use the method with a large number of patients without any risk to them. They not only accepted the treatment willingly, but they even asked for it as they came to realize that after two or three injections a marked regression of leprotic lesions was taking place, and their general condition was improving.

INFLUENCE OF THE ANTIGEN THERAPY ON THE CLINICAL CONDITION

To determine the influence of this method of treatment on the evolution of the disease, we naturally have made day-to-day observations of the changes in the lesions of numerous patients, with appropriate records.

It would be tedious to include here another description of the different stages of an aggravation of the disease, or of those of an amelioration; they are too well known for it to be necessary for us to do so. Let us only say that the changes for the better have seemed to be more rapid and stable than those obtained with the sulfones; and we have observed that the patients have fewer leprotic reactions with the antigen than with the sulfones.

We have thought it would be more useful to study the general results in as large a number of patients as possible. To this end we have carefully examined the 457 patients who could be most easily reached, whose previous condition we knew, who had regularly followed the injection for a sufficient length of time (in principle, 6 injections), and for whom circumstances permitted us to judge the stability of their present condition.

The therapy was first used in cases in which the sulfones had stopped giving further improvement after 2 or 3 years of treatment, or in which they were not well tolerated. As a measure of prudence, at the beginning of our trials we did not stop the sulfones while using the antigen. These cases constitute 50 per cent of the patients dealt with here. Later on, however, because of the very favorable results obtained in patients who had not benefited from the sulfones, we stopped that practice and have put all our new cases on the antigen therapy alone, without any other active antileprosy treatment.

The results obtained in the two groups, i.e., those given the antigen with or without sulfones, have been the same, with the same number of cases that have become aggravated, have remained stationary, or have improved. We have not, therefore, made any distinction, the sulfones seeming to have had no action in these cases as regards improvement.

Clinically, however, the difference between these two methods is striking. The antigen acts the more quickly: the leprotic lesions disappear more rapidly, the general condition is improved rapidly, appetite and energy return, the skin regains its normal condition. With the sulfones, on the other hand, there is often a greyish complexion which reveals the toxicity of the drug. The antigen seems to stimulate activity, and thus to create an active defense in the organism.

For greater precision and convenience in reporting the results we have grouped the patients into 7 categories, according to the changes occurring in the course of the trial to the time of this report:

1. Deceased.
2. Leprosy aggravated and general condition deteriorated (Ag).
3. Leprosy unchanged, general condition poor (St).
4. Leprosy improved (*amélioré*), general condition fair (Am).
5. Leprosy improved, general condition quite good (Am+).
6. Leprosy markedly improved, general condition good (Am2+).
7. Leprosy very markedly improved, general condition excellent (Am3+).

These categories will now be considered seriatim. The data are assembled in Table 2.

1. *Deceased patients.*—Ten of the 457 patients under consideration died, or 2.2 per cent, none of them because of the new therapy. The causes of death were: Indeterminate cases (7): cardiac conditions, 3; cancer of the liver, 1; pulmonary tuberculosis, 1; and unknown, 1 (probably pulmonary; died in his village). Tuberculoid cases (2); cancer, 1; and unknown, 1 (died in his village). Lepromatous (1): the only death of a patient of this type was due to polytoxicomania—alcohol, India hemp, and probably native therapy. None of these patients had had severe reactions, and their deaths did not occur during the course of treatment. The records show reactions to the injections in these cases as shown in Table 2.

TABLE 2.—*Degrees of improvement in the antigen-treated cases reported on, by type of case and category of results, and the reaction to the injections in those categories.*

Type of case and of reaction	Category of case							Totals
	1 (Dead)	2 (Ag)	3 (St)	4 (Am)	5 (Am+)	6 (Am2+)	7 (Am3+)	
Indeterminate	7	15	64	27	19	99	44	275
Tuberculoid	2	0	13	8	4	33	27	87
Lepromatous	1	4	19	13	4	35	21	97
Totals, cases	10	19	96	48	27	167	92	459
Per cent	2.1	4.1	21.0	10.5	5.9	36.5	19.9	100.0
Reaction 0	7	28	126	31	24	166	70	452
Reaction 1+	26	65	391	161	122	686	416	1,867
(Subtotal, %)	(82.4)	(92.0)	(89.4)	(87.7)	(93.7)	(90.5)	(91.6)	(90.3)
Reaction 2+	7	6	51	27	10	79	38	218
Reaction 3+	0	2	11	0	0	12	7	32
Totals	40	101	579	219	156	943	531	25,69

This number of deaths is quite normal, even low for a leprosarium whose cases are mainly advanced.

2. *Patients become worse (Ag).*—Nineteen cases are in this category, 15 indeterminte and 4 lepromatous; none of them was tuberculoid. This proportion of cases, 4.1 per cent of the treated ones under consideration, is relatively low considering that the patients were not especially selected for this experiment, and that many of them had serious complications of leprosy or presented other conditions (e.g., toxicomanias) the treatment of which was difficult or gave little results because of the poor condition of the patients.

No less than 92 per cent of the reactions to the injections of the antigen in these cases were nil or weakly positive (Table 2).[4]

3. *Patients remaining stationary* (*St*).—The patients in this group are more numerous than those in the two groups already mentioned; 96 in all, or 20.9 per cent. These cases were classified as: indeterminate, 64; tuberculoid, 13, and lepromatous, 19. The reactions to the injections were as shown in Table 2.

If we pause at this stage of our exposition, we see that 125 patients out of 457, or 27.2 per cent, did not benefit from this therapy. If to these cases are added the 10 that died—from other conditions than leprosy —our percentage of failures is slightly increased.

4. *Patients improved, condition fair* (*Am*).—This group comprises 48 patients, 10.5 per cent of the total; 27 were indeterminate, 8 tuberculoid, and 13 lepromatous. The reactions to the injections are shown in Table 2.

5. *Patients improved, condition good* (*Am* +).—Twenty-seven patients (5.9%) are in this group: 19 indeterminate, 4 tuberculoid and 4 lepromatous. The reactions to the injections are shown in Table 2.

6. *Patients markedly improved, condition good* (*Am2*+).—This is the largest group of all: 167 patients, or 36.5 per cent. They were classified as indeterminate, 99; tuberculoid, 33; and lepromatous, 35. The reactions to the injections are shown in Table 2.

7. *Patients very markedly improved, condition excellent* (*Am3*+).—This group, important because of the results obtained, is also important because of its size: 92 cases, or 19.9 per cent. They were classified as: indeterminate, 44; tuberculoid, 27; lepromatous, 21. The reactions to the injections are shown in Table 2.

In summary, the number of improved cases is 332, or 72.8 per cent. We may note the similarity of this figure to that of 73.3 per cent, the one of conversion of the Mitsuda reaction obtained in a different experiment. It should also be noted that the two last groups, Am2+ and Am3+, together constitute 56.4 per cent of the cases. In other words, more than one-half of the patients were markedly or very markedly improved. This test in itself seems to us important.

There seems to be no parallelism between the intensity of the reactions and the figures on improvement. We have encountered very strong reactions in patients whose leprosy remained stationary or got worse, as well as improvement in nonreacting patients.

CONCLUSIONS

We have attempted to treat 457 patients with an antigen prepared

[4] The percentages of these two reaction classes in the other categories of patients, not mentioned in the original manuscript, have been added in the table for completeness. —EDITOR.

with the culture of *Mycobacterium marianum,* employing monthly intradermal inoculations, and have observed:

1. A general evolution during thirty days after the injections, consisting of a more or less intense local reaction, a focal congestive reaction of leprotic lesions, and a general reaction consisting of fever and various symptoms.

2. The various types of this reaction are classified as: nil or slight (17.2%), moderate (71.7%), strong (8.4%), and very strong (2.7%). Each of these types has its own modalities of local, focal and general reactions.

3. This method of treatment is not dangerous. The 10 deaths which we have had in the course of more than two years were all due to conditions other than complications of the antigen therapy.

4. The clinical efficiency of this method is seen in the following results: 21.7 per cent of the patients did not benefit, while in 79.9 per cent the state of the leprosy and the general condition improved; in 56.4 per cent this improvement was of considerable degree.

5. Improvement has been more rapid and stable (i.e., with fewer lepra reactions) with the antigen than with the sulfones. In many cases the antigen therapy has given relief where sulfone therapy failed or was badly tolerated.

In resumé, this method, the immunological efficacy of which has been demonstrated, has proved equally active from the point of view of therapy. Its efficacy is comparable to that of the sulfones, the action of which it simulates, and which it can replace advantageously. In the treatment of a disease as complex as leprosy, it is valuable to have at our disposal a new therapeutic agent of no toxicity and of specific activity.

CONCLUSIONS

Nous avons essayé de traiter 457 malades avec l'antigène préparé à partir de la culture de *Mycobacterium marianum.* Nous avons observé:

a) Une évolution générale durant une trentaine de jours et comportant une réaction locale plus ou moins intense, une réaction focale congestive des éléments lépreux et une réaction générale consistant en fièvre et phénomène divers.

b) Divers types de réactions que nous avons classé en nulles (17.2%), intensité moyenne (71.7%), fortes (8.4%), et très fortes (2.7%), ayant chacune leurs modalités de réactions locales, focales et générales.

c) Cette méthode n'est pas dangereuse, les 10 décès que nous avon constaté au cours de plus de deux ans sont tous dus à l'évolution d'affections graves autres que des complications de l'antigénothérapie.

d) L'efficacité clinique de cette méthode se traduit par les résultats suivants: 21.7 pour cent des malades n'ont tiré aucun bénéfics de la méthode, 72.9 pour cent ont vu leur état lépreux et leur état général s'améliorer, et pour 56.4 pour cent d'entre eux l'amélioration a été considérable.

e) Les améliorations ont été plus rapides et plus stables (moins de réactions lépreuses) avec l'antigène qu'avec les sulfones. Dans bien des cas l'antigénothérapie est venue prendre avec succès la relève d'une sulfonethérapie défaillante ou mal tolérée.

En résumé cette méthode, dont nous avions vu l'efficacité immunologique, se montre également active au point de vue thérapeutique. Son efficacité peut être comparée à celle des sulfones dont elle stimule l'action et qu'elle peut remplacer avantageusement. Dans le traitement d'une maladie aussi complexe que la lèpre il est intéressant de pouvoir disposer d'un nouvel agent thérapeutique dont la toxicité est nulle et l'activité spécifique.

REFERENCES

1. Blanc, M., Prost, M. T. and (Soeur) Marie-Suzanne. Influence de l'injection d'une suspension d'un mycobacterium isolé d'un cas de lèpre (souche Chauviré) sur la réaction de Mitsuda. Bull. Soc. Path. exot. **46** (1953) 1009-1015.
2. Blanc, Prost, Lemaire, Kuna, E. and Nkoa, J. M. Etude immunologiques de l'antigène Chauviré. J. Sci. Méd. de Lille **71** (1953) 584-590.
3. Marie-Suzanne (Soeur), Noel, R. and Sohier, R. Le *Mycobacterium marianum.* (Recherches anatomopathologiques sur les lésions provoquées par cette mycobacterie.) Mem. VI Congr. Internac. Leprol., 1953. Madrid, 1954, pp. 833-837; *abstract* in Internat. J. Leprosy **21** (1953) 623.
4. Marie-Suzanne (Soeur), Noel, R. and Sohier, R. Etude des lésions obtenus après injection du *Mycobacterium marianum* sur les rats blancs préalablement inoculés avec une suspension autoclavés de même germe. Rev. lyonnaise Méd. **2** (1953) 401-404.