RESULTS OF SIX MONTHS SUPPLEMENTARY TREATMENT OF LEPROMATOUS PATIENTS WITH *MYCOBACTERIUM MARIANUM* VACCINE[1]

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Early in this decade, Sr. Marie-Suzanne and associates, in Lyon, reported (7, 8) that she had cultivated, from a leproma, an acid-fast bacillus which was called—in the name of the person from whom the specimen had come—the "Chauviré strain" (*souche Chauviré*). After having been studied in Rome by Penso, it was formally named *Mycobacterium marianum*, in honor of the Marist order to which Sr. Marie-Suzanne belonged (9). From this culture a vaccine was prepared for the treatment of leprosy patients, and it has been widely distributed for therapeutic trials.

Favorable results were reported in an early period by Blanc and associates (1, 2) who were among those to whom the "antigen" was first given for large-scale trials. It was injected intradermally in doses of 0.1 cc. once a month for three months, followed by two months rest, then a new course of three monthly injections. Severe local reactions occurred in 8.4 per cent, and there were very severe reactions accompanied by constitutional symptoms in an additional 1.4 per cent. The percentages of cases classified as improved after two to three years of treatment were: for lepromatous, 76.0; for tuberculoid, 84.7; and for indeterminate, 70.5. Only 4.2 per cent of the lepromatous cases became worse, 5.6 per cent of the indeterminate, and none of the tuberculoid. About 50 per cent of the cases had received sulfones during treatment with the antigen; the other half were given antigen therapy alone. There was no control series.

Favorable results following 9 months treatment with this antigen were also reported in the same period by Gaté and Rousset (6). Vaccinations were made intradermally at intervals of 3 to 15 days. Lepromatous cases showed subsidence of nodules, but there was less marked improvement of leprides in nonlepromatous cases.

In another publication, Blanc *et al.* (3) reported that three intradermal injections of 0.1 cc. each of the Chauviré vaccine were given at monthly intervals to 73 patients with lepromatous leprosy. Of 63 who were originally negative to lepromin, 32 became reactive, while of 10 who were positive, 8 remained positive but 2 became negative. The first Mitsuda test was performed one month before the first Chauviré vaccination, the second one two months after the third vaccination.

PRESENT STUDY

For the present study a supply of the vaccine, labelled "Antigen Marianum," was received for trial in the treatment of some of the leprosy patients at the Eversley Childs Sanitarium in Cebu.

A total of 47 patients were brought into the study, most of them lepromatous but some of them advanced borderline of the sort often regarded as lepromatous. All were bacteriologically positive, and most of them gave negative or doubtful

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reactions to lepromin, as will be seen later. One group, 22 patients, received the vaccine and also the regular DDS treatment. The other group, 25 patients, carefully matched with the vaccinated one in respect to age, sex, and severity of lesions, was treated with DDS only and served as control. On the average, the disease was less advanced clinically and the lesions contained less numerous bacilli than in patients included in the clinical evaluation studies of the Leonard Wood Memorial (4, 5).

Comparison of smears made from loopsful of the vaccine with those of lepromin suspensions showed that the density of acid-fasts was something like seven to eight times as great in the marianum suspension as in the lepromins. From some limited observations by Dr. E. Mabalay, of the Eversley Childs Sanitarium, it contained many times the number of bacilli that are present in standard concentrations of the BCG vaccine.

The vaccinated patients were given 0.1 cc. of the marianum antigen intradermally in the deltoid region, at the beginning of the study and monthly thereafter for five months, or six injections in all. Treatment and observation were continued for 28 weeks, from late in June 1955 to early January 1956. Of the vaccinated patients one became demented and another absconded, while one of the control group absconded, so those three did not complete the treatment.

All patients of both groups were tested with lepromin before treatment, and those who completed the course were tested again after treatment. The same lot of lepromin, prepared by the Mitsuda-Hayashi method, was used. Sixteen of the vaccine-treated patients were also tested with tuberculin.

The DDS used, Avlosulfone, was given in the following dosage schedule:

50 mgm. 3 times a week for 2 weeks
50 mgm. daily except Sunday for 2 weeks
100 mgm. daily except Sunday for 2 weeks
150 mgm. daily except Sunday for 2 weeks
200 mgm. daily except Sunday till the end.

A clinical evaluation was made of each patient before and after therapy. Skin lesions on the face, trunk, buttocks and extremities were classified as macules, plaques, nodules and infiltrations, and were graded as negative, 1+, 2+, or 3+ on each examination. Smears were made before and after the treatment from 8 sites, including with each patient one from each earlobe and one from each side of the nasal septum. The results of the bacteriological examinations were graded as in the clinical evaluation studies (4).

RESULTS

Clinical changes.—Of the 20 patients who received the full course of injections of the marianum vaccine as a supplement to the regular DDS treatment, 14 or 70.0 per cent showed clinical improvement of skin lesions; in 4 patients there was no detectable change in the lesions, and in 2 they got worse. Of the 24 patients who received DDS only, 19 or 79.2 per cent showed clinical improvement, while in 5 there was no change.

Bacteriological changes.—Of the 20 patients in the vaccine group, only 2 showed bacteriological improvement, whereas such improvement was noted in 8 of the 24 patients on DDS alone. No significance is attached to this difference between the groups.

Changes in reactivity to lepromin.—The results of the repeated lepromin tests are summarized in Table 1. Of the 6 patients in the marianum antigen-DDS group who were quite negative to lepromin before treat-

ment, the reaction remained negative in 2, became doubtful in 1, and in 3 it became weakly (1+) positive. Of the 4 whose reactions were doubtful at the beginning, the reaction remained doubtful in 1 and became 1+ in 3. Of the 10 in whom the original reaction was 1+, it increased to 2+ in 1, and remained 1+ in 6, while in 3 it became doubtful.

TABLE 1.—*Results of lepromin tests before and after the six months treatment, (A) patients treated with the marianum vaccine and DDS, and (B) those treated with DDS only.*

Before treatment		After treatment							
		Negative		Doubtful		One plus		Two plus	
Grade of reaction	No. of cases	A	B	A	B	A	B	A	B
Negative	17	2	7	1	4	3	0	0	0
Doubtful	11	0	2	1	4	3	1	0	0
One plus	16	0	1	3	0	6	5	1	0
Total	44	2	10	5	8	12	6	1	0

Of 11 patients in the DDS group who were negative before treatment, the reaction remained negative in 7 and became doubtful in 4. Of 7 whose reactions had been doubtful, 2 became negative, 4 remained doubtful, and 1 became 1+. Of 6 in whom the original reaction was 1+, the reaction became negative in 1 and remained the same in 5.

Thus the changes in lepromin reaction were not of a striking nature. The difference between the groups is slight, with possibly a greater tendency towards increase of reactivity in the vaccinated group than in the other one.

Reactions to the marianum antigen.—The marianum antigen produced local reactions in all of the vaccinated patients. In 5 the nodules at the site of injection varied in size from 3 to 6 mm. in diameter; in 8 from 7 to 10 mm., and in 7 they were over 10 mm., the largest being 40 x 45 mm. There was a tendency for the nodules to become larger with succeeding injections. In all patients some of the nodules ulcerated, and in 4 they were accompanied by malaise, chilliness, slight fever and anorexia.

An interesting question arises as to a possible relationship between local reactions to the marianum antigen and hypersensitivity to tuberculin. Of the 20 vaccinated patients who completed the treatment, 16 had received a preliminary tuberculin test as well as the lepromin test. Of these 16, 6 were negative to 5 TU of PPD, and of these all but one were also negative to lepromin; the exception showed a doubtful reaction. Local reactions to marianum vaccine were somewhat bigger in the tuberculin-positive patients than in the negatives (see Table 2), and were not more severe in those showing doubtful reactions to lepromin than in others.

This finding was unexpected because the marianum vaccine, being made from an acid-fast bacillus, would be expected to share in group antigens common to mycobacteria. The explanation may lie in the very high concentration of bacilli in the vaccine, which has been noted.

TABLE 2.—*Comparison of local reactions to the marianum vaccine, in millimeters, with the results of the tuberculin test (PPD) in 16 cases.*

Reactions to tuberculin	Reactions to marianum vaccine				
	0-4	5-9	10-14	15-19	20+
Negative	0	2	2	2	0
Positive, 1+	0	0	1	3	2
Positive, 2+	0	0	1	0	2
Positive, 3+	0	0	1	0	0
Total	0	2	5	5	4

SUMMARY

Twenty leprosy patients were each given intradermal injections of 0.1 cc. marianum antigen, at monthly intervals for six injections, as a supplement to the regular treatment with DDS. Twenty-four other patients treated with DDS only, constituted a control group. These patients were all classified as lepromatous, but in actuality some of them were borderline far advanced toward lepromatous.

Clinical improvement occurred in 70 per cent of the vaccinated patients and in 79 per cent of the control group. No significant bacteriological improvement occurred in either group during the period of about six months.

Changes in reactivity to lepromin were not of a striking nature. Such differences as were noted are not of statistical significance, although, on their face, the figures suggest a tendency toward greater increase of reactivity among the vaccinated patients.

There appears to have been a tendency for the tuberculin-positive patients to exhibit bigger local reactions to the marianum vaccine than the tuberculin negatives. There is no relation between the sizes of the reaction to marianum and that to tuberculin, they being of very different natures.

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RESUMEN

Veinte leprosos recibieron inyecciones intradérmicas de 0.1 c. c. de antígeno *marianum*, a plazos mensuales hasta seis inyecciones, como complemento del tratamiento

regular con DDS. Otros 24 enfermos tratados únicamente con DDS constituyeron un grupo testigo. Todos estos enfermos estaban clasificados como lepromatosos, pero en realidad algunos de ellos eran casos limítrofes muy avanzados hacia la forma lepromatosa.

Hubo mejoría clínica en 70 por ciento de los enfermos vacunados y en 79 por ciento del grupo testigo. No se observó mayor mejoría bacteriológica en uno u otro grupo durante el período de unos seis meses.

Las alteraciones en la reactividad a la lepromina no fueron de orden notable. Las diferencias que se notaron no revestían importancia estadística, aunque a primera vista las cifras indican una tendencia hacia mayor aumento de la reactividad entre los sujetos vacunados.

Parece que hubo una tendencia de parte de los enfermos positivos a la tuberculina a manoifestar mayores reacciones locales a la vacuna *marianum* que los negativos a la tuberculina. No existe relación alguna entre los tamaños de la reacción a la *marianum* y a la tuberculina, siendo de naturaleza muy distinta.

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