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Results of a Double Blind Study of the Influence of Thalidomide on the Lepra Reaction[1, 2]

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The first thalidomide experiments in this series ([1, 2, 3]) were aimed at evaluating the effectiveness of this drug in relation to a placebo, and were carried out on a small number of patients. The present double blind study extends the observations to a larger group of patients and expands the observational criteria.

In a preliminary report ([4]) data were presented on the procedure and results of the experiment which was carried out in Caracas in 1965-1966. The present paper presents the results of clinical and laboratory tests, notes side effects in detail, and includes a statistical evaluation.

METHODS

Patient selection. Patients with lepromatous leprosy were the subjects of the study and were included only if they presented clearly demonstrable dermatologic, neurologic or other manifestations of lepra reaction. These included erythema nodosum-like or erythema multiforme-like lesions; reactivation of old quiescent lesions and necrotic lesions of the Lucio phenomenon type; acute neuritis; acute iritis; acute iridocyclitis or acute orchitis.

Additionally the patients must have shown at least some of the following symptoms or signs: pyrexia, adenopathy, arthralgia, myalgia, bone pains, abdominal pains, nephritis, hepatosplenomegaly, rhinitis, epistaxis, anorexia, vomiting, insomnia. In the absence of the essential criteria, these latter symptoms and signs were not sufficient to warrent inclusion.

Fifty-two patients (37 males and 15 females) ranging in age from 17 years to 58 years were included in the study. Seven of these patients were reincorporated into the study after the completion of their four treatment regimens because their original treatment course did not include a pause after partial improvement. Statistically, they were regarded as new patients and this therefore increased the number of subjects to 59.

Forty-nine patients were hospitalized and 10 patients were ambulatory. The ambulatory patients had permanent residence in Caracas and were permitted to continue living at home during the experiment. They were requested to appear at the clinic daily.

The duration of the disease varied from eight months to 36 years: under one year, four patients; under 10 years, 23 patients; over 10 years, 25 patients.

Fifty of the patients showed both lepromata and reactive manifestations. Only two had reactive manifestations alone. Histopathologic evaluation coincided with the clinical assessment. Bacteriologic tests were positive in all patients. The Mitsuda test was negative in all patients.

Prior to this study all patients had received, at different times, singly or in combination: chaulmoogra oil, sulfones, diphenylthiourea, thiosemicarbazone, antibiotics.

The duration of the lepra reaction varied from three months to nine years: under one year in 12 patients, and more than one year in 40 patients. Forty-eight patients suffered from continuous lepra reaction. Two others

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suffered occasionally from recurrences, and the remaining two were incorporated into the study at the time of their initial lepra reaction.

The patients had received at different times, some continually and some intermittently, the following antireaction therapies: antimony, butazolidin, antihistamin, blood and plasma transfusions, steroids.

Clinical evaluation. Initially, complete history and physical examination was obtained for each patient. Clinical examinations by specialists in internal medicine, neuropsychiatry and gynecology were included because some of the patients had systemic manifestations such as anemia, gastrointestinal and mental disturbances. This participation by various specialists was of value in the assessment of side effects.

Physical findings were reviewed each day by at least two physicians and the intensity of lepra reaction assessed and recorded. A complete review of the findings was documented at the end of the seven-day treatment regimen, and included the findings of the various specialists where pertinent.

Women were treated only in hospital, while men were hospitalized, or treated as ambulatory outpatients if their condition permitted.

Female patients of childbearing age were examined to exclude pregnancy.

Laboratory evaluation. On admission, before beginning and on the last day of each regimen, the following investigations were performed:—leucocyte and erythrocyte counts, erythrocyte sedimentation rate (E.S.R.), liver function tests, biochemical blood examinations, bacteriologic and histologic examinations of selected lesions, urinalysis.

Treatment and dosage. Each lepra reaction was treated for a total of seven consecutive days; this being considered as a regimen unit. Patients weighing over 50 kgm. received 100 mgm. of either thalidomide or placebo four times a day. Patients weighing less, received 6 mgm./kgm./day. In all cases the drug was spaced by three equal intervals, with a night pause.

Those patients who showed no clinical improvement after seven days were considered therapeutic failures. They were immediately given a new regimen unit (additional seven days of the same treatment) as though they were suffering from their next lepra reaction.

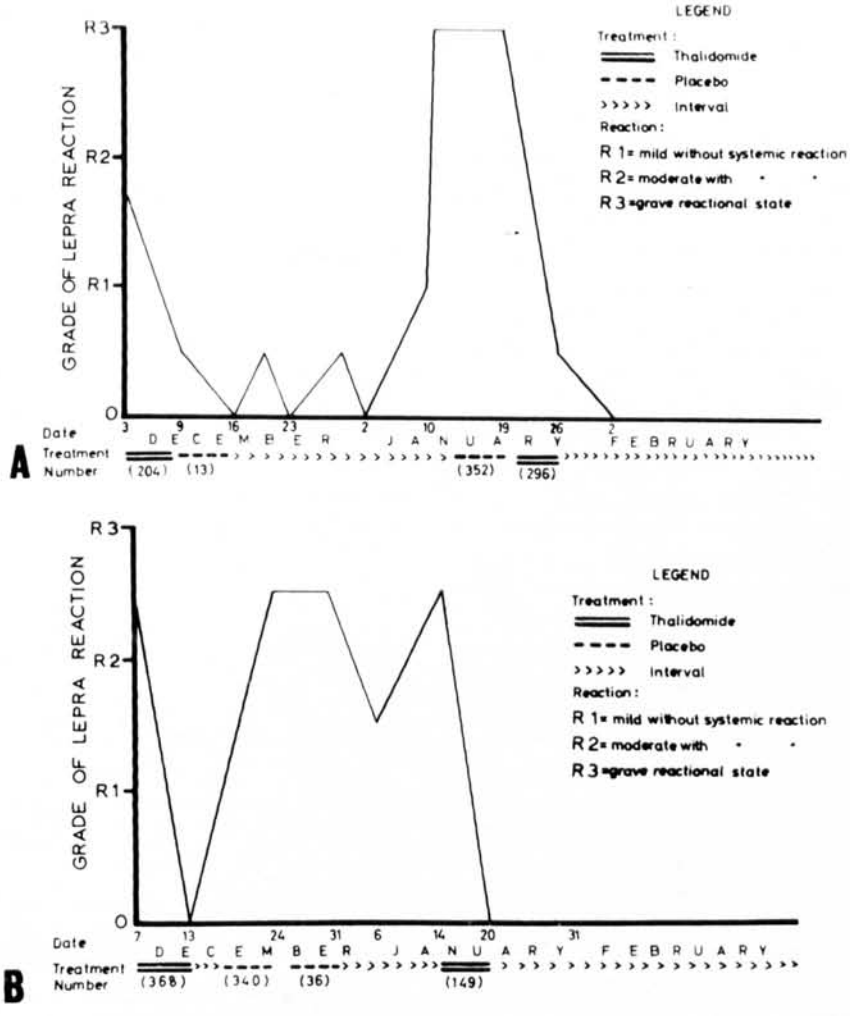
Treatment after a weekly regimen was discontinued after any favorable therapeutic response, even if only partial. This was done because if a subsequent regimen was administered immediately afterwards, and improvement continued, it would have been difficult to decide which regimen was responsible for the improvement. A new treatment regimen was started when a new skin eruption or neurologic symptoms of lepra reaction appeared. Up to four consecutive treatment regimens were given each patient.

Other therapy. Upon admission to the study, all drug therapy was stopped except that patients on sulfone therapy were continued on this therapy at the same continuing dosage throughout the study. Those patients not on sulfone therapy, were not given it.

Under no circumstances did patients included in the study receive antimony compounds, antihistaminic, antimalarials, blood transfusions, or local steroids. Patients who had been receiving systemic steroids or ACTH for prolonged periods continued to receive the same dosage. Such patients were included in the study only if new manifestations of lepra reactions appeared under this maintenance dose.

Patients whose clinical status made the administration of other drugs mandatory were not included in the study.

Allocation of therapy. Patients were given consecutive numbers in the order of their admission to the study and were treated with the contents of a numbered bottle as indicated on a Master Sheet, according to a prepared coded list. The code was unknown to the investigators and was kept at the Hebrew University, Jerusalem. Each bottle contained 31 tablets (28 for treatment, two to allow for accidental loss by vomiting and one to remain in the bottle for checking purposes). A different bottle was used for the treatment of each lepra reaction, as indicated on the Master Sheet. The sealed code was opened in the



FIGS. 1-A and 1-B. Response of patient with leprosy reaction to thalidomide and placebo.

presence of a committee only after the study was completed.

Where the clinical condition of a patient required that the code be broken to determine the contents of a particular bottle, the patient was dropped from the study.

Evaluation of reaction severity. R3. Intense reaction with many widespread, active, painful skin lesions of erythema nodosum or erythema multiforme whether severe arthralgia, myalgia, iridocyclitis and orchitis were present or not. These patients always had a severe general condition with headaches, pyrexia of more than 39°C, anorexia and insomnia. Loss of weight and vomiting were sometimes present.

R2. Lesser intensity of the above described signs and symptoms.

R1. Few elements of erythema nodosum as erythema multiforme. Subfebrile temperature. General condition good with or without mild degrees of pain. Note. When only isolated neuritic phenomena were present, they were classified as RN_1, RN_2, RN_3, according to their intensity.

The situation at the end of each regimen unit (seven days) was assessed as follows:

Total improvement. All dermatologic manifestations in an advanced state of remission. No new elements. Disappearance of the characteristic lepra reaction symptoms.

Striking improvement. Approximately 50 per cent of skin manifestations in an advanced state of remission. No new elements.

Partial improvement. Approximately 25 per cent of skin manifestations in remission. No new manifestations.

No change. Almost no change in the existing skin manifestations, with appearance of new elements.

Deterioration. Exacerbation of existing manifestations and appearance of new manifestations.

RESULTS

Clinical effects. Figures 1A & 1B and Tables 1-10 present summaries of the results of the treatment regimens as related to changes in reactional status and symptomatology.

The study extended over 129 days, during which time the patients received a total of 173 treatment regimens: 25 patients received four regimens; 13 patients received three, 13 patients two, and eight patients one.

Upon termination of the study and decoding, it was revealed that 85 regimens containing thalidomide and 88 containing placebo had been administered.

Laboratory findings. Fifty-six white blood cell counts were performed in 26 patients before and after thalidomide and placebo treatment. An elevated leucocyte count was usually found before treatment and ranged between 4,500 and 36,500.

In evaluating the leucocyte counts, a decrease or increase was considered only when there was a change of at least 2,000 white blood cells compared to the leucocyte count before the regimen was given. Of 30 counts performed in 22 patients who received thalidomide, 22 tests showed a significant decrease. In some cases leucocytosis due to lepra reaction had been very high and after thalidomide-containing regimen returned to normal values.

Hemoglobin values were examined in 13 patients before and after thalidomide and placebo. The range of hemoglobin before the regimen was between 6.1 to 11.9 gm. per cent. In five of the 15 hemoglobin examinations, after thalidomide treatment an increase of between 2-4 gm. per cent was observed. No change in the hemoglobin value was seen after placebo administration and the hemoglobin value rose from 11 to 13.5 gm. per cent in only one patient who received placebo.

No significant change of E.S.R. was seen after thalidomide or placebo. Most of the cases did not have a very high sedimentation rate.

In 10 patients, electrophoresis of proteins was performed before and after thalidomide administration. In four, electrophoresis of proteins was also done after placebo administration, in two of them twice. In 15 electrophoreses performed after thalidomide treatment of a decrease in globulin was found in eight, an increase in five and no change in two cases.

After placebo administration an increase in globulin was found in five cases, a decrease in two, and no change in two.

Because both the decrease and increase in gammaglobulin levels was slight only, no definite conclusions can be drawn.

Liver function tests were performed before and after thalidomide treatment. Thymol turbidity tests were performed in 10 patients before and after thalidomide administration: in seven there was an increase, and in three cases a decrease was seen. After placebo administration thymol turbidity increased in five cases and was unchanged in two.

Glutamic oxalacetic transaminase (G.O.T.) was examined 23 times before and after thalidomide administration and 20 times before and after placebo. After placebo no reduction of G.O.T. was seen. In seven instances the G.O.T. showed a significant reduction after thalidomide administration. Thalidomide caused a decrease in glutamic pyruvic transaminase (G.P.T.) in two patients, while decrease was seen after placebo. Conclusions cannot, however, be drawn because of the small numbers. Only those cases where either a significant increase or decrease had occurred were considered.

Bacteriology and histopathology. Bacteriologic examinations gave no evidence of changes that could be attributed to either the thalidomide or the placebo. Histopath-

TABLE 1. *Comparison of the results after thalidomide or placebo.*

	Total	Thalidomide		Placebo	
		No.	%	No.	%
Comp. Impr.	47	43	91.49	4	8.51
Striking Impr.	17	13	76.47	4	25.53
Partial Impr.	38	22	57.9	16	42.1
No change	51	7	13.72	44	86.28
Worsening	20	0	0	20	100
Total trials	173	85	49.14	88	50.86

TABLE 2. *Statistical analysis of results of treatment.*

	Total		Thalidomide		Placebo	
	No.	%	Real	Expected	Real	Expected
Improvement	102	59.0	78	50	24	52
No improvement or worsening	71	41.0	7	35	64	36
Total	173	100.0	85	85	88	88

ologic examinations carried out before and after administration of the drugs, showed that the placebo caused no evident changes in the histologic picture. On the other hand, after thalidomide administration a regression of the inflammatory infiltrate of the reactive lesion was seen, but there was no change in the specific lepromatous component of the infiltrate.

Side effects. The treatment regimens with thalidomide in the double blind study lasted a week at a time, and under these conditions side effects did not constitute a serious factor.

Dizziness appeared within two or three days of receiving thalidomide in eight cases; and nausea appeared in seven cases.

As far as gastrointestinal tract disturbances are concerned, such as dryness of the mouth, constipation and diarrhea, which existed in several of the patients prior to commencement of the study, no real differences were found between the thalidomide and the placebo group.

Drowsiness appeared after 20 thalidomide regimens, and in none after placebo.

Urticaria appeared only twice after thalidomide (never after placebo), and remitted spontaneously.

Tables 3-10 present additional observations. Neuritis first appeared during five treatment regimens with placebo; arthralgia in six placebo regimens; headache during two thalidomide regimens, and four with placebo; insomnia in 13 placebo regimens; lack of appetite in 11 placebo regimens; nausea in two placebo regimens.

STATISTICAL ANALYSIS

Table 1 presents a summary of the treatment results and Table 2 a statistical analysis of these results.

Fifty-nine per cent of all cases improved, 41 per cent were unaltered or worse. The number of treated and untreated cases shows a marked deviation of this percentu-

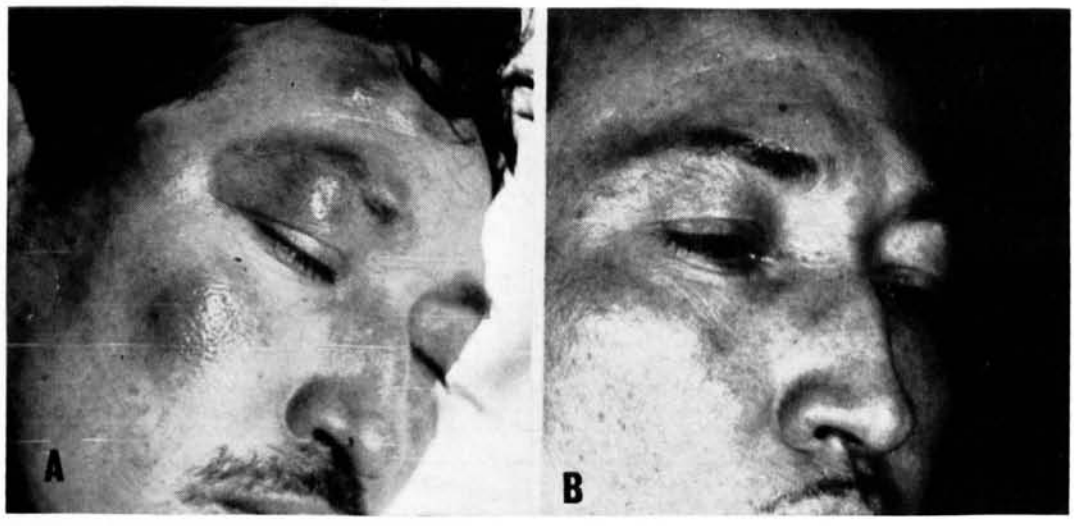


FIG. 2-A. Erythema nodosum lesions before treatment with thalidomide.

FIG. 2-B. The same patient, after completion of one treatment regimen.

al distribution: 28 vis–28. The x^2 value is 75., P 0.000001. Such a deviation from the expected distribution would happen by coincidence only in one of more than one million cases. In the absence of any special explanation for this deviation, treatment with thalidomide may be the causal factor in the present study.

DISCUSSION

Comparison of the charting and the code of the 24 lepra reactions in which improvement occurred after placebo treatment (Table 1), showed that thalidomide had been given in the previous regimen in nine patients and this could have been responsible for the partial improvement. In four of these, treatment had been continuous. This was before the decision that there should be an interval after each regimen even when the improvement was not total. In the remaining five patients there had been a 2-16 day interval. Although the improvement of these nine lepra reactions could have been attributed to the thalidomide that had been given prior to the placebo, the improvement was none the less attributed to the placebo.

Although the differences between the thalidomide and placebo groups with regards to total and striking improvement are evident, with partial improvement they are not (Table 1). Partial improvement after thalidomide occurred in 22 patients, four of whom were in a debilitated general condition, four others had severe anemia and three had been under the influence of steroids for a number of years. One of the latter had for nine years prior to this study received 20-60 units of ACTH, one to three times a week and 20-40 mgm. of meticortene a day almost continuously because of persistent lepra reaction. After the first treatment regimen, clear-cut improvement in the skin occurred but the general condition deteriorated dangerously. He was immediately removed from the study, and given thalidomide. Thereupon the lepra reaction and his general condition improved steadily. After decoding, it was found that the first treatment regimen given him in the double blind study had contained thalidomide, and that in error corticosteroids had been suddenly stopped at the beginning of the regimen and the patient thus entered a phase of adrenal insufficiency. This case illustrates the fact that when patients who are receiving steroids are to be treated with thalidomide, the steroids must be decreased gradually.

The condition of 51 lepra reactions remained unchanged; seven (13.72%) after thalidomide, and 44 (86.28%) after placebo (Table 1). It is possible that the standard

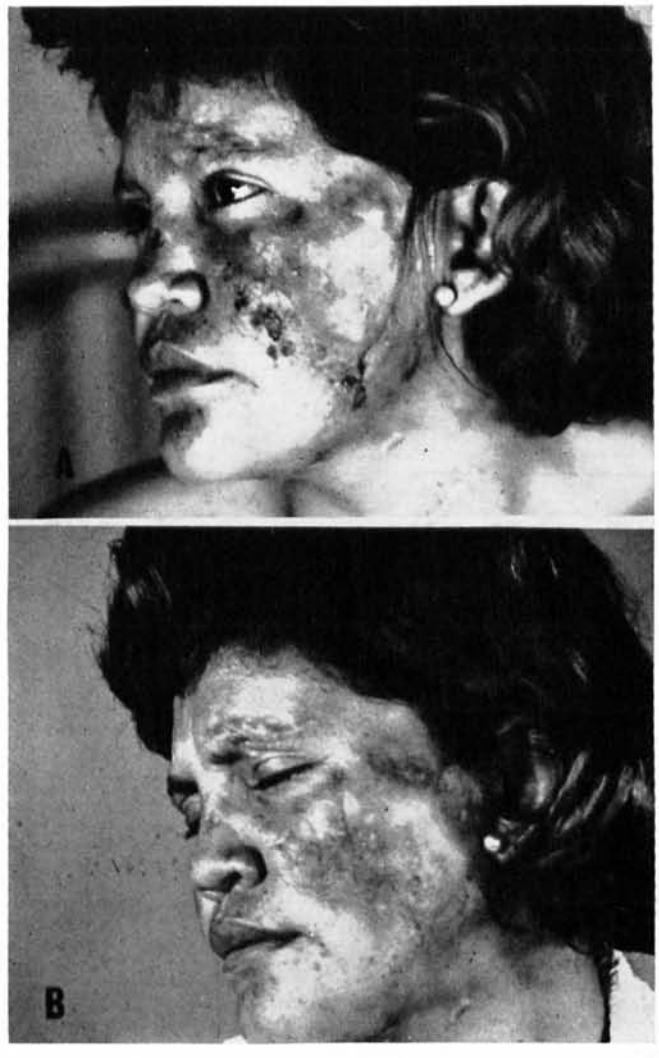


FIG. 3-A. Erythema nodosum lesions before treatment with thalidomide.

FIG. 3-B. The same patient, after completion of one treatment regimen.

dosage of 400 mgm. thalidomide daily, comprising the regimen, was not sufficient for these patients. There was not one case of deterioration following thalidomide, as compared to 20 (100%) after placebo.

Not all 59 patients received four series of treatments: 34 patients improved after only 1-3 regimens. Two patients were observed for 48 and 71 days respectively (until completion of the study) with no recurrences. These two patients previously suffered from continuous lepra reaction and required uninterrupted antireaction treatment.

In Table 4 the difference between the influence of thalidomide and placebo is clearly demonstrated in the "no change" group (5 with thalidomide and 44 with placebo), and it reaches a peak in the "deterioration" group (0 with thalidomide as compared to 28 with placebo). In all of these cases, the influence of thalidomide began to occur within 8-48 hours, but a period of one week was not sufficient for total resorption in all the patients.

In 58 lepra reactions, there was ulnar neuritis, and in one case also peroneal neuritis as noted in Table 5. In five lepra reactions, neuritis appeared while receiving placebo; this did not occur with thalidomide. In one-half of the 14 patients with total improvement following thalidomide, improvement occurred on the first or second day of treatment. In the remaining one-half it took up to one week. The pains disappeared and the limb movements were

TABLE 3. *General condition (appearance, pains, mood, alertness).*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	59	47	7	5	0
Placebo	60	4	8	28	20
Total	119	51	15	33	20

TABLE 4. *Erythema nodosum and multiforme.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	78	31	42	5	0
Placebo	88	2	14	44	28
Total	166	33	56	49	28

TABLE 5. *Neuritis and polyneuritis.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	28	14	11	2	1
Placebo	25	4	3	12	6
Total	53	18	14	14	7

TABLE 6. *Arthralgia.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	39	30	5	3	1
Placebo	38	0	10	18	10
Total	77	30	15	21	11

TABLE 7. *Headaches.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	13	11	1	0	1
Placebo	16	2	3	9	2
Total	29	13	4	9	3

TABLE 8. *Insomnia.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	44	38	2	3	1
Placebo	35	4	9	19	3
Total	79	42	11	22	4

TABLE 9. *Anorexia.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	51	43	2	6	0
Placebo	35	0	2	27	6
Total	86	43	4	33	6

TABLE 10. *Nausea.*

	Treatment regimens	Improvement		No change	Deterio-ration
		Total	Partial		
Thalidomide	7	6	0	0	1
Placebo	6	2	0	4	0
Total	13	8	0	4	1

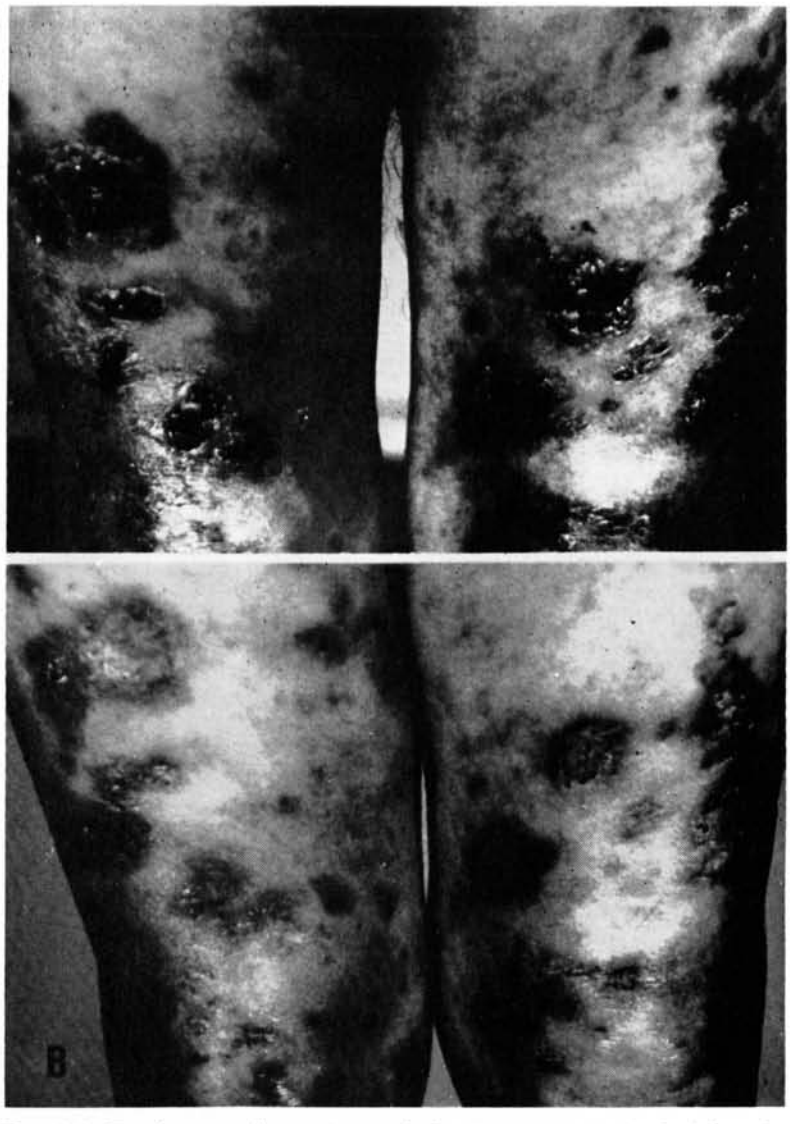


FIG. 4-A. Erythema nodosum lesions before treatment with thalidomide.

FIG. 4-B. The same patient, after completion of one treatment regimen.

free. The nerves, however, remained tender to touch.

Orchiepididymitis disappeared slowly in three lepra reactions where thalidomide was given. In three other lepra reactions where placebo was given there was no improvement.

Joint pains disappeared slowly, in comparison with other symptoms of lepra reaction. In 22 of 30 lepra reactions showing improvement who had received thalidomide, the improvement occurred within the first week, and in the remaining eight, during the "pause" after this regimen (Table 6).

It should be noted that disappearance of insomnia (Table 8) after thalidomide although not always accompanied by a general remission of the other symptoms, resulted in an improvement in the general and emotional condition. This was also observed in the 20 experiments in which sleep had been normal but drowsiness appeared after treatment with thalidomide.

The six cachectic patients had an increase of appetite and began to gain

weight during the thalidomide regimen (Table 9).

In 54 lepra reactions with dermalgia, 25 were given thalidomide and 29 placebo. There was striking improvement of dermalgia after thalidomide. This began within 48 hours and was complete by the sixth day. In comparison, following placebo, there was no improvement in one-half the patients and in two it became worse. In eight additional lepra reactions dermalgia appeared while they were receiving placebo.

In 10 lepra reactions there was myalgia especially of the limbs, before initiation of the regimen. In eight of the patients who received thalidomide, there was total remission of the myalgia. In two who received placebo, the condition remained unchanged, and in addition, muscle pains appeared in another four patients while they were receiving placebo.

Fourteen patients suffered from a burning sensation before commencement of the treatment regimen. In six of eight patients who received thalidomide, the burning sensation disappeared; this did not occur in the six who received placebo. In addition, in six other cases this symptom appeared while they were receiving placebo. One of the earliest side effects of thalidomide is said to be a burning sensation in the palms and soles. This was not substantiated in the present study. Seven days of treatment is, however, not a sufficient period in which to evaluate this phenomenon.

SUMMARY

In a double blind study of thalidomide and a placebo, 173 one-week trials were performed on 59 patients with lepra reactions. The age of the patients varied from 17-58 years. The duration of the disease was from eight months to 36 years, and of the lepra reaction from three months to nine years.

Due to the known dangers of thalidomide in pregnancy, the women included in these trials underwent constant gynecologic and laboratory tests, to insure that they were not pregnant.

After decoding, it was found that in 85 lepra reactions patients received thalidomide and in 88 they received placebo. After thalidomide there was improvement in 91.76 per cent and 8.24 per cent remained unchanged. Not a single case became worse. Following placebo there was improvement in 27.26 per cent while 50 per cent remained unchanged and 22.74 per cent deteriorated. Statistical analysis showed that such results could occur by chance only once in more than a million cases.

Improvement following thalidomide was seen after eight to 48 hours and continued steadily, although in some patients one week was insufficient for total remission of some of the symptoms.

Before and after each treatment regimen biochemical tests, bacteriologic and histologic tests did not show any significant changes. The histologic preparations showed that only under the influence of thalidomide was there regression of the inflammatory infiltrate of the reactional manifestation, though not of the leproma itself.

The side effects were not significant and did not influence the course of the seven-day treatment period.

Thalidomide is considered an effective drug against lepra reactions occurring in lepromatous patients.

RESUMEN

En un estudio doble ciego de thalidomida y placebo, 173 ensayos de una semana fueron realizados en 59 pacientes con lepra reaccional. La edad de los pacientes varió de 17 a 58 años. La duración de la enfermedad variaba de ocho meses a 36 años, y de la lepra reaccional de 3 meses a 9 años.

Debido al peligro conocido de la thalidomida en el embarazo, las mujeres incluídas en este ensayo estuvieron sometidas constantemente a examenes ginecológicos y pruebas de laboratorio, para asegurar que no estaban embarazadas.

Despues de clasificar, se encontró que 85 pacientes con lepra reaccional recibieron thalidomida y 88 recibieron placebo. Despues de la thalidomida se observó mejoría en el 91.76% y el 8.24% no experimentó cambio. Ni un solo caso empeoró. Siguiendo el placebo hubo mejoria en el 27.26% mientras que el 50% no mostró cambios y el 22.74% se empeoró. El análisis estadístico demostró que tales resultados podrian ocurrir por causa del azar solamente una vez en mas de un millon de casos.

La mejoría que siguió a la thalidomida fue observada despues de 8 a 48 horas y continuó regularmente, aunque en algunos pacientes una semana fue insuficiente para la remisión total de algunos de los síntomas.

Antes y despues de cada tratamiento, el esquema de ensayos bioquímicos, bacteriológicos e histológicos no demostró cambios significantes ninguno. Las preparaciones histológicas demostraron que solamente bajo la influencia de la thalidomida hubo regresión del estado inflamatorio de la manifestación reaccional, aunque no del leproma mismo.

Los efectos laterales no fueron significantes y no influenciaron el curso del tratamiento en el período de 7 dias.

Se considera la thalidomida como una droga efectiva contra la lepra reaccional que ocurre en pacientes lepromatosos.

RÉSUMÉ

Chez 59 malades atteints de réaction lépreuse, on a mené une étude comparée de la thalidomide et d'un placebo, par la méthode du double incognito. Cent soixante-treize essais d'une durée d'une semaine ont été pratiqués chez ces malades. L'âge des patients variait de 17 à 58 ans. La durée de la maladie s'étendait de 8 mois à 36 ans, et celle de la réaction lépreuse de 3 mois à 9 ans.

A la suite des dangers bien connus de la thalidomide lors de la grossesse, les femmes comprises dans ces essais ont été soumises à une surveillance gynécologique constante et à des épreuves de laboratoire, dans le but de s'assurer qu'elles n'étaient pas enceintes.

Quand l'incognito a été levé, on a trouvé que 85 malades atteints de réaction lépreuse avaient été traités par la thalidomide, et que 88 avaient reçu le placebo. Après thalidomide, on a noté une amélioration chez 91.76% des malades; 8.24% ne présentant pas de changement dans leur état. Aucun malade n'a vu son cas s'aggraver. A la suite de l'administration de placebo, on a enregistré une amélioration chez 27.26% des sujets, alors 50% ne présentaient pas de changement dans leur état, et que 22.74% ont empiré. L'analyse statistique montre que de tels résultats ne peuvent survenir par chance qu'une fois seulement sur plus d'un million d'essais.

L'amélioration notée avec la thalidomide a été observée après une période s'étendant de 8 à 48 heures, et s'est fermement poursuivie, encore que chez quelques malades une semaine n'a pas suffi pour observer une disparition totale de certains des symptômes.

Avant et après chacun de ces modes de traitement, des épreuves biochimiques, bactériologiques et histologiques ont été pratiquées, sans qu'il soit possible de relever aucune modification significative. Les préparations histologiques ont montré que, sous l'influence de la thalidomide seulement, il se produisait une régression de l'infiltrat inflammatoire caractéristique de manifestations réactionnelles, quoique non du léprome lui-même.

Les effets secondaires n'ont pas été significatifs; ils n'ont pas influencé la poursuite de ce traitement au cours d'une période de 7 jours.

La thalidomide est considérée comme un médicament efficace contre les réactions lépreuses survenant chez des malades lépromateux.

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