

THE EFFECTS OF ADRENOCORTICOTROPIC HORMONE (ACTH) IN LEPROMATOUS LEPROSY REACTION¹

MARCEL ROCHE, M. D.
JACINTO CONVIT, M. D.
JOSÉ A. MEDINA, M. D.

AND ELENA BLOMENFELD, M. D.

*From the Cabo Blanco Leprosarium, Maiquetía and the
Universidad Central, Caracas, Venezuela*

Leprosy reaction in lepromatous leprosy is a most troublesome acute incident in the chronic, drawn-out course of the disease. So far, there has been no way of controlling satisfactorily the characteristic fever, malaise, joint and muscle aches, and cutaneous lesions which periodically beset many of these patients. Since adrenocorticotrophic hormone (ACTH) has produced marked symptomatic benefit in conditions regarded as "allergic" (5, 7), its trial in leprosy reaction appeared to us logical.

A small supply of the purified substance was obtained,² and a group of patients at the Cabo Blanco colony who were suffering from lepromatous leprosy and were undergoing reactions of varying degrees of severity and duration were selected for treatment. All patients were kept in the infirmary under careful medical and nursing supervision. Most of them were receiving antileprosy medication; this was continued unchanged during the period of observation, but all other medication was discontinued. ACTH was administered intramuscularly every six hours, dissolved in sterile saline solution. Eosinophil counts were performed by the direct method (4). The determination of 17-ketosteroid were made according to the method of Callow and co-workers (1). Sedimentation rates were measured by the method of Westergren. Changes in the more important laboratory findings are indicated in Table 1.

CASE REPORTS

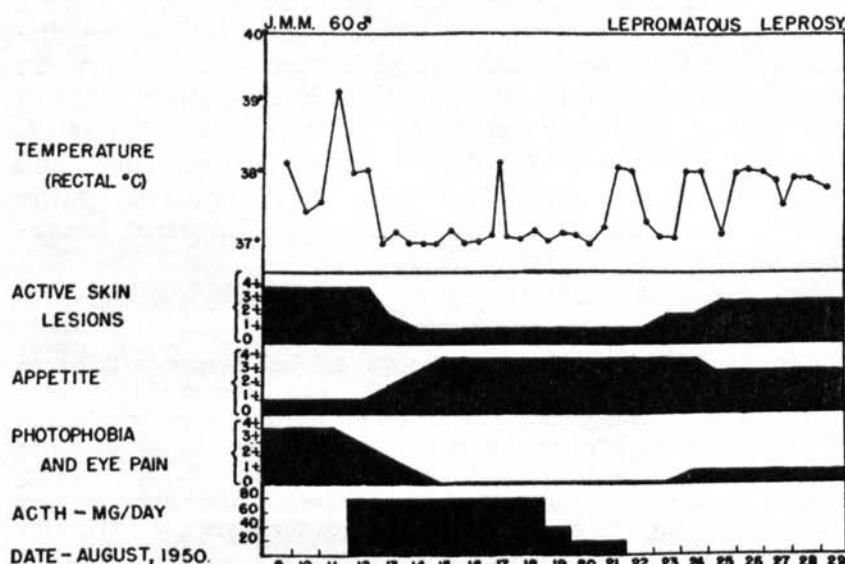
CASE 1. J. M. M., male, white, age 60. Clinical disease in this case began in 1931, and the diagnosis was established in August of that year; skin biopsy showed the picture of lepromatous leprosy. Since then he has had prolonged periods of treatment with chaulmoogra oil, but only one temporary, asymptomatic, bacteriologically-negative episode. His present admission began in 1947, since when he has had one reaction after another, some of them extremely severe. He was treated for a year, in 1947, with

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² From the Armour Company, through the courtesy of Dr. J. E. Mote.

promin. In March 1950 he was started on tibione (acetamidobenzal thiosemicarbazone) and was taking 250 mgm. per day at the time of ACTH administration. Approximately two months before the present observation a severe reaction began, with marked generalized infiltrations of the skin and many erythema nodosum elements, malaise, fever, anorexia and pain in the left eye with photophobia. Examination on August 12, 1950 showed a burgundy-wine-colored infiltration of the face and ears. Over the trunk and back there were numerous tender, erythematous, subcutaneous nodules. The gluteal region and the legs were covered with a diffuse infiltration. There were erythema nodosum elements on the forearms. The left sclera was markedly injected, there were several posterior synechiae, and marked photophobia was present. General physical examination showed only bilateral gynecomastia and a smouldering epithelioma on the left nostril, which had been present for several years. Blood pressure, 120/65.

Treatment and course.—On August 12, the patient was started on ACTH, 20 mgm. being injected every six hours (80 mgm. per day). After 24 hours the appetite had begun to increase, the skin lesions showed improvement, and the photophobia was distinctly better. The response of the temperature may be seen in Text-fig. 1. Improvement continued throughout the period of treatment. After seven days, the erythema nodosum elements had lost their bright hue and their tenderness, and most of them had been replaced by pigmented spots. The cheeks no longer had a cardboard-like consistency and had become soft and pliable. Photophobia had disappeared and the sclerae were no longer injected. The temperature remained normal except for a small peak on the fifth day of treatment. The dosage of ACTH was gradually lowered. Three days after the dose had been reduced to 20 mgm. per day there appeared over the back and trunk new, painful erythema nodosum nodules, mixed with the older pigmented ones, which did not flare up again. After a week the infiltra-

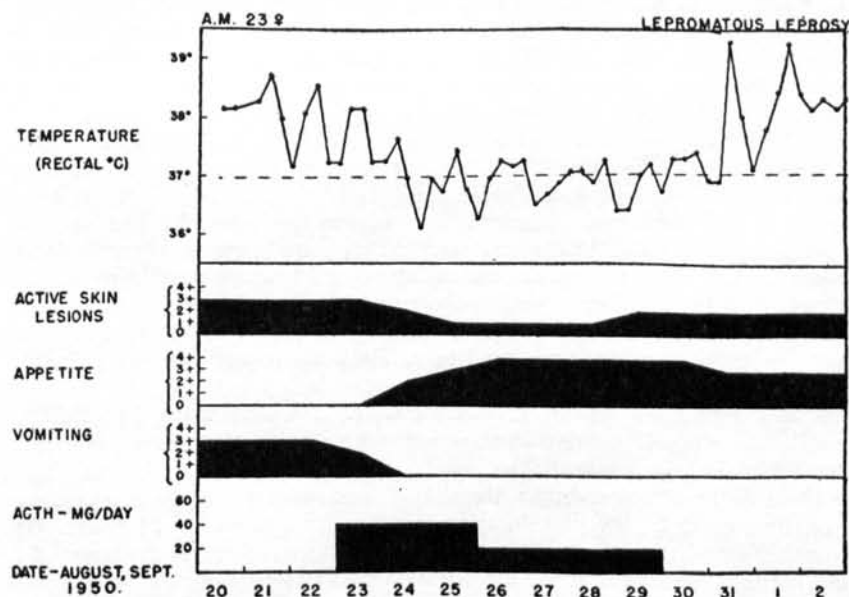


TEXT-FIG. 1. The effect of ACTH treatment of lepra reaction in Case 1.

tion of the cheeks and ears had returned, although not as severe as before treatment. The symptoms of iridocyclitis, however, remained practically under control, only slight photophobia and inflammation making their appearance at this time. The patient continued to eat well and to feel better. Gradually, however, the full-blown reaction came back—except for the iridocyclitis, which stayed latent—and after one month the patient had returned to approximately his pretreatment state. It is felt, however, by both the patient and the observers, that his present reaction is far less severe than it was.

CASE 2. A. M., female, age 23 years. Clinical onset of the disease in 1946, during her first pregnancy. Skin biopsy: lepromatous leprosy. She was given promin and later diasone for nearly three years. In March 1950, diasone was stopped and she was started on tibione, the dose of which was gradually worked up to 200 mgm. per day and was continued throughout the ACTH treatment. The present reaction began approximately one week after the start of tibione treatment and was characterized by fever, anorexia and exacerbation of the erythema nodosum. In addition, the patient experienced frequent pains in the right hypochondrium and almost daily episodes of vomiting. Examination on August 23 showed a thin female with, over the cheeks, chin, gluteal region, arms and forearms, dorsum of hands, and legs, many elements of erythema nodosum. Over the face, forearms, pectoral region, gluteal region and legs there were many pigmented spots, remnants of former reaction lesions. Over the right forearm, as well as on the dorsum of the left hand, some of the subcutaneous nodules had become ulcerated.

Treatment and course.—ACTH was started on August 23, in doses of 10 mgm. every six hours (40 mgm. per day). The patient felt better within four hours. Improvement in appetite and well-being was rapid, beginning



TEXT-FIG. 2. The effect of ACTH treatment of lepra reaction in Case 2.

on the same day. The temperature quickly went down to normal and remained so, as shown in Text-fig. 2. In 24 hours the appetite had greatly increased; pain in the right upper quadrant and vomiting had ceased. There was frank regression of the erythema nodosum elements except for a few which persisted over the left forearm, and ulcerated elements healed completely. Within three days the improvement had become quite dramatic, and the dosage of ACTH was halved. There was no return of the pre-treatment state, and the patient continued to feel well. After seven days of treatment ACTH was discontinued, after which there was a gradual return of the fever over a four-day period. Symptoms reappeared more slowly, however, and did not reach a state comparable to the pretreatment state until one week after discontinuation of therapy.

CASE 3. A. T. M., female, age 29. Clinical onset of the disease in 1945. Skin biopsy in April 1947: lepromatous leprosy. In March 1950, she was started on tibione and the dose was worked up to 200 mgm. per day. One week after the start of this medication a lepra reaction began which has persisted, with fever, anorexia, malaise and erythema nodosum. On examination the woman was of sickly appearance; there were painful erythema nodosum nodules over the left cheek, back, gluteal region, and a diffuse infiltration over the face and ears, back, gluteal region and legs.

Treatment and course.—ACTH was administered in doses of 10 mgm. every six hours for seven days. Regression of the lesions and of the symptoms was perhaps a little slower than in the other patients, but essentially of the same nature. After discontinuation of the treatment there was some return of the skin lesions, and of the anorexia and other symptoms, over a period of seven days, but the patient remained distinctly better than before therapy.

CASE 4. C. M., female, white, age 32. Clinical onset of the disease in 1946. Diagnosis by positive nasal scrapings and by skin biopsy: lepromatous leprosy. Chaulmoogra oil was given for one year, followed by diasone in March of 1947. This drug gave rise immediately to a severe reaction which lasted for four months; since then she has never been quite free from reaction, has felt badly at all times, and has had painful nodules over both forearms. On August 5, 1950, treatment with diasone had to be suspended, but she continued to have mild fever, malaise, anorexia, and erythema nodosum. For about one year she has had, in addition, pain in the left elbow and wrist, which becomes particularly severe during the reactions. Examination revealed an adequately nourished woman with infiltrations over the cheeks and ears and two red, infiltrated spots over the left scapular region. Other infiltrated spots were present over the gluteal region, arms and legs. Both ulnar nerves were palpable and tender; there was marked pain in the left wrist on flexion. The general examination was otherwise negative. Blood pressure, 138/88.

Treatment and course.—Treatment with ACTH, 40 mgm. per day, was begun on August 19. The results were essentially similar to those obtained in the other patients: the skin lesions regressed and the symptoms partially subsided; the pain in the wrist disappeared within 24 hours. On the other hand, the slight fever which was present before treatment did not respond. One week after discontinuing treatment the skin lesions had returned, although definitely not as painful or evident as before treatment; the pain in the wrist remained under control.

CASE 5. L. M. U., female, age 30 years. Clinical onset of the disease in August 1949. Skin biopsy in January 1950: lepromatous leprosy. The patient was started on diasone, 0.90 gm. per day. Within a month there was accentuation of the existing skin lesions and an erythema nodosum eruption appeared. Two weeks later there was brawny edema over the dorsa of both hands and the entire legs and the dorsa of both feet, accompanied by marked pain and burning and numbness over both feet and anterior tibial regions, which made her quite unable to walk. There was general malaise and marked anorexia. Examination in August 1950 revealed an obese woman, with erythematous infiltration over the face, trunk, and extremities, a few elements of erythema nodosum over the back and arms, and brawny edema as mentioned. Subjectively, there was intense burning, pain and inability to move the feet. General examination was otherwise negative. Blood pressure, 135/70.

Treatment and course.—On August 8, the patient was started on ACTH, receiving first one dose of 25 mgm., followed by 20 mgm. every six hours (80 mgm. per day). Within six hours of the first injection the patient began to feel a distinct subjective improvement. In 24 hours, appetite and well-being had increased markedly and definite regression of the skin lesions could be observed; burning and pain in the feet had diminished. Within three days the skin lesions had lost their marked erythema and bright hue; the patient was willing and able to walk; there was improvement in the temperature; a distinct euphoria had appeared. The edema had totally disappeared. The temperature, which had fluctuated between 37.0° and 38.6°C. in the pretreatment period, never rose above 37.6°C. while the ACTH was being given. After seven days of treatment there was some return of the burning of the feet, but improvement was otherwise continued.

Immediately after ACTH administration was stopped there was a sharp, temporary rise of the temperature to 39.2°C., but the patient continued to feel well and there was no exacerbation of the lesions. To date, improvement has been continued: there has been no return of the neuritic pains and the skin lesions appear stationary; appetite is excellent. Diasone therapy has been continued.

CASE 6. E. B., male, age 28. Clinical onset of the disease in August 1948. Skin biopsy in September 1948: lepromatous leprosy. The patient was started on diasone at the time, and he has had a total of 14 reactions. Four months ago the patient had a severe reaction, with marked erythema nodosum, fever and malaise, which lasted three and one-half months and subsided somewhat two weeks ago before examination on August 18, 1950, when the patient was ambulatory, feeling fairly well, afebrile. There were only two painful nodules on each of the forearms; the patient complained of occasional muscle and bone pains. Although he experienced a few symptoms, he was essentially reaction-free.

Treatment.—It was decided to give this patient ACTH for 48 hours (80 mgm. per day) and to stop the drug abruptly to see if, in the "rebound" period, a full-blown lepra reaction would be induced analogous to what takes place, for instance, in gout (2). During the 48 hours of ACTH administration, the patient reported that he felt extraordinarily well. Far from developing a reaction after ACTH was stopped, he continued to feel much improved for at least a month.

TABLE 1.—*Effects on certain laboratory findings of ACTH treatment in lepra reaction.*

Patient	Laboratory determinations/ <i>a</i>	Findings		
		Before treatment	At end of treatment	3-5 days after treatment
J.M.M. (Case 1)	Circulating eosinophils	718/ <i>b</i>	25	210
	Urinary 17-ketosteroids	2.1	3.4	
	Sedimentation rate	108	67	100
A.M. (Case 2)	Circulating eosinophils	528	182	337
	Urinary 17-ketosteroids	5.8	10.7	
	Sedimentation rate	129	112	114
A.T.M. (Case 3)	Circulating eosinophils	80	25	86
	Urinary 17-ketosteroids	4.4	8.2	
	Sedimentation rate	132	115	128
C.M. (Case 4)	Circulating eosinophils	60	38	87
	Urinary 17-ketosteroids	5.5	7.1	
L.M.U. (Case 5)	Circulating eosinophils	209/ <i>c</i>	256	156
	Urinary 17-ketosteroids	1.3	1.6	
	Sedimentation rate	48	50	86
E.B. (Case 6)	Circulating eosinophils	214	40	214

a Circulating eosinophils are expressed as the number per cubic centimeter of blood urinary 17-ketosteroids as milligrams per day, and the sedimentation rate as millimeters in one hour.

b Four hours after the first injection of 20 mgm. of ACTH the eosinophil level fell to 25.

c Four hours after the first injection of 25 mgm. of ACTH the eosinophil level fell to 110.

COMMENTS

In all of the patients treated with ACTH the response was rapid, definite and striking, even with as relatively low a dose as 40 mgm. per day. One of the patients (Case 2), after an initial satisfactory response on 40 mgm. per day, showed continued improvement on only 20 mgm. per day. In all cases there was some return of the symptoms within from two to five days after ACTH was discontinued; nevertheless, all but one (Case 2) remained better than they had been before treatment. Two

of the patients (Cases 5 and 6), were distinctly benefited, the former being brought back from an invalid to an ambulatory, nearly normal state, and the latter being given the well-being necessary to continue his antileprosy treatment.

The response of the adrenals to ACTH in these patients appears to have been as a rule rather subnormal (See Table 1). Many of them were, of course, in a debilitated state. Since the clinical response was so striking, however, it may be deduced that lepra reaction is unusually sensitive to the actions of adrenal steroids.

In Case 5 the adrenal response, as measured by the laboratory determinations, was virtually nil. These results suggest that the striking clinical betterment of this patient may have been due to a spontaneous change in the disease. In the others, however, the improvement could hardly have been ascribed to coincidence.

The sedimentation rates show a distinct tendency to become lower. It is likely that, had the therapy been prolonged, they would have fallen to normal, as is the case in rheumatoid arthritis (3).

Because of the possibility that the poor eosinophil response in Cases 4 and 5 might have been due to intestinal parasites, the feces of all patients were examined. In Cases 1, 3 and 5, *Trichiura trichiuris* was found, while Case 4 harbored ascaris and *Strongyloides stercoralis*. We do not believe that these parasites influenced the eosinophil response in an important way.³

DISCUSSION

The importance of the control of the acute lepra reaction need not be elaborated upon. Particularly since the use of the sulfone drugs, and now tibione, the reaction has been one of the major obstacles to treatment.

Among the diseases upon which ACTH or cortisone has exerted a beneficial modifying influence, these drugs have been most useful in those processes which by their very nature are self-limited and wherein a low dosage is effective. Lepra reaction varies widely in duration. It may be prolonged, but usually it is transient. From the point of view of sensitivity to the

³ Skin biopsies were made in all cases before and at the end of treatment. No striking change was noted, except for disappearance of interstitial edema. It is our feeling that more prolonged treatment should lead to a decrease in cellular infiltration.

therapeutic action of ACTH, lepra reaction appears to rank high, together with such diseases as rheumatoid arthritis and some of the allergic states (7). This represents a distinct advantage, since with this drug it is essential to reduce the dosage to a minimum, for economic reasons and because of the unpleasant effects which usually result from prolonged administration of large doses.

It has been thought that lepra reaction is essentially a useful thing, its occurrence in a patient representing a favorable sign. It might then be argued on theoretical grounds that to suppress such a reaction represents a dangerous step. On the other hand, it appears that "the action of ACTH and Cortisone may dissociate the harmful effects of hypersensitivity from the beneficial reaction of immunity" (7). A clear-cut example of this state of affairs appears to be the effect of ACTH in typhoid fever, in which the drug can suppress almost completely the clinical manifestations while allowing the antibodies to develop normally (6). Similarly, then, in lepra reaction we might be suppressing the outward, useless manifestations without modifying whatever immunological good may arise from the reaction.

Even though the beneficial effects of these hormones may last only during and shortly following the period of their administration, the advantages of being able to give debilitated patients periods of rest without symptoms is evident.

It is hoped that by alleviating the reactions, and particularly those brought about through the use of active chemotherapeutic agents, ACTH or cortisone may eventually contribute to an earlier and easier total cure or control of leprosy. The modifying effect of these drugs, if any, on the course and final outcome of the disease remains to be determined.

SUMMARY

Six patients with lepromatous leprosy undergoing lepra reaction were given adrenocorticotrophic hormone (ACTH, Armour) in doses of 40 to 80 mgm. per day for a maximum of seven days. In all cases there occurred a rapid regression of the reaction symptoms, and in most of them the temperature fell to normal within 24 hours. Iridocyclitis present in one of the patients, and peripheral neuritis present in two others, were rapidly benefited. Most of the symptoms returned a few days after cessation of therapy.

It is felt that, through the rapid control of the reaction symptoms, ACTH may contribute in an important way to the

treatment of leprosy, particularly in those cases where the reaction is an obstacle to continued administration of a chemotherapeutic agent.

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RESUMEN

Los autores administraron la hormona adrenocorticotrópica (ACTH, Armour) en seis casos de lepra lepromatosa con brote leproso agudo. Las dosis empleadas fueron de 40 a 80 mgm. por día y el tiempo máximo de tratamiento siete días. En todos los enfermos se manifestó una regresión rápida de los síntomas, y en la mayoría la temperatura volvió a la normal en veinte y cuatro horas. Una iridociclitis presente en uno de los enfermos y una neuritis periférica presente en dos otros mejoraron rápidamente. Casi todos los síntomas reaparecieron a los pocos días de suspenderse el tratamiento.

Los autores opinan que el ACTH pudiera contribuir de manera importante al tratamiento de la lepra, controlando efectivamente los brotes leproso, particularmente en aquellos casos en los cuales el brote forma obstáculo al uso prolongado de agentes quimioterapéuticos.

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