

## Hydrocortisone Production in Lepromatous Patients with Insulin Load<sup>1</sup>

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It is well known that a functional incapacity of the adrenal glands or experimental adrenalectomy markedly increases any animal's sensitivity to various pathogenic factors, particularly to different infections or endotoxins (<sup>1,2</sup>), and favors the development of both allergic and autoimmune diseases (<sup>7</sup>).

We have not found in the available literature any studies on the production of glucocorticoids in patients with lepromatous leprosy under the influence of stress, in spite of the obvious significance of such investigations to a better understanding of such a severe and prolonged disease. Some authors (<sup>3,4,5,6</sup>) have determined 17-ketosteroids and 17-oxycorticoids in urine in order to evaluate the functional state of the adrenal cortex in leprosy. However, the methods utilized did not allow precise and differentiated assessment of the levels of the various steroids synthesized by the adrenals, particularly the levels of glucocorticoids.

The aim of our work was to study hydrocortisone production in leprosy patients with an insulin load as a stress factor.

### MATERIALS AND METHODS

**Subjects.** Thirty-six patients with lepromatous leprosy without endocrine pathology, aged 30–59 years, were studied. None of them had received any corticosteroids previously. Twenty-two of the subjects were women and 14 were men. Twenty-three of the patients showed signs of the early stage of regression of the disease. They had small skin infiltrates and hyperpigmented and cyanotic macules. Histological investigation showed residual granulomas, sometimes with a predominance of elements with non-

characteristic structure containing few, disrupted mycobacteria (Group I). The remaining 13 outpatients had no active skin eruptions and were bacteriologically negative by skin smears (Group II). At the time of investigation, all the patients were being treated with sulfones in combination with either prothionamide or rifampin. Fourteen of the cases had a history of relapses in the past. By "relapse" we mean the appearance of skin eruptions and the emergence of acid-fast bacteria in skin smears after a period of apparently clinical cure and bacterial negativity. Some of the patients relapsed in this way twice or even three times during the seven to ten years prior to our investigation.

Eight healthy volunteers, 32–58 years old, served as controls.

Because of the possible adverse effects of insulin-induced hypoglycemia on the cardiovascular system, potential subjects with clinical signs of atherosclerosis or cardiovascular disease were excluded from the study.

**Hydrocortisone determinations.** Serum hydrocortisone levels were estimated using a competitive radioassay (Amersham kits, England) before and after insulin injections. Insulin was administered in doses of 0.2 IU per kg of body weight. Hydrocortisone concentrations were expressed in nanomoles per liter of serum (nmole/l).

To exclude the possible influence of circadian rhythm on hydrocortisone production, blood samples from leprosy patients were taken at two strictly determined time intervals: 10:00–11:00 a.m. and two hours after insulin injection. Some of the patients were studied two or more times (in different seasons of the year), so that the total number of investigations was 44.

In the control group, 14 paired hydrocortisone determinations were carried out at various seasons of the year following the same scheme as that used in the leprosy patients.

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## RESULTS AND DISCUSSION

The results obtained are presented in Table 1. Basal levels of hydrocortisone (before insulin load) are higher in the leprosy patients than in the healthy subjects ( $p < 0.05$ ). Insulin stress induced increased hydrocortisone concentrations in healthy subjects an average of 1.9 fold ( $p < 0.001$ ). On the other hand, in most leprosy patients there was a decrease in the serum hydrocortisone concentration after insulin load (noted by asterisks in Table 1). The decrease in serum hydrocortisone levels in many of the leprosy patients following insulin, in contrast to its increase in healthy persons, suggests an acute exhaustion in the capacity of the adrenal cortex to produce this hormone in leprosy patients [paradoxical reaction type response (PRT)]. PRT was observed in 23 of the 36 leprosy patients under insulin stress (64%).

In order to clarify the role of the activity of the leprosy process in exhausting the hydrocortisone-producing capacity of the adrenals, we compared the results obtained between the leprosy patients in Group I (active disease) and Group II (inactive disease). The degree of hydrocortisone production was expressed in percents as a ratio of hydrocortisone concentration after insulin load over its basal level (Table 2). Hydrocortisone production in the patients of Group I with active disease was significantly lower ( $p < 0.05$ ) than that in Group II patients with inactive disease. The test groups did not differ significantly in other clinical parameters which could influence the results, i.e., the number of relapses, age, and concurrent diseases. Hence, we may state that the active leprosy process depresses the hydrocortisone-producing capacity of the adrenals. Partial recovery of this capacity is observed in the period of clinical cure. At the same time, many of the cases showed PRT responses of the adrenal cortex, suggesting that depression of hydrocortisone production in leprosy patients may be due to more than one factor.

To identify these factors, several clinical aspects of the patients with PRT were compared with those of patients showing a normal reaction type (NRT) response of the adrenal cortex. It was found that 12 of the 23 patients with PRT had relapsed in the past; while only two of the 13 patients with

TABLE 1. Serum hydrocortisone concentrations from leprosy patients and healthy volunteers before and after insulin load (nmoles/l).

	Before insulin load	After insulin load
Leprosy patients	325.5	353.1
	212.4	413.8
	193.1	408.3
	162.8	482.8
	300.7	411.0
	286.9	400.0
	322.8	662.1
	320.0	353.1
	242.8	300.7
	482.8	695.2
	248.3	300.7
	201.4	366.9
	229.0	278.6
	267.6	400.0
	281.4	325.5
	300.7	364.1
	366.9	350.3*
	524.1	405.5*
	160.0	118.2*
	256.5	157.2*
	364.1	140.7*
	248.3	184.8*
	482.8	419.3*
	455.2	449.6*
	248.3	193.1*
	281.4	190.3*
	377.3	248.3*
	259.3	217.9*
	408.3	317.2*
	377.9	198.6*
	377.9	240.0*
	264.8	237.2*
	297.2	264.8*
	353.1	267.6*
	342.1	165.5*
	662.1	270.3*
	333.8	110.3*
	510.3	264.8*
	300.7	240.0*
	397.2	350.3*
	358.6	336.6*
	253.8	173.8*
	369.7	273.1*
	344.8	223.4*
	326.3 ± 15.3 <sup>a</sup>	307.4 ± 18.8 <sup>a</sup>
Healthy controls	253.8	648.3
	284.1	791.7
	275.9	786.2
	372.4	394.5
	361.4	422.1
	195.9	560.0
	137.9	499.3
	173.8	469.0
	187.6	485.5
	74.5	195.9
	240.0	281.4
	297.9	380.7
	353.1	400.0
	309.0	386.2
	251.2 ± 23.6 <sup>a</sup>	478.6 ± 45.8 <sup>a</sup>

\* Paradoxical reaction type response.

<sup>a</sup> Mean ± Standard Error of the Mean.

TABLE 2. Ratios of hydrocortisone concentrations after insulin load to basal levels (in percents) in leprosy patients in relation to the degree of activity of the leprosy process and the occurrence of relapses in the past.

Group I (active disease)		Group II (inactive disease)
Relapses	No relapses	
33.1	38.6	63.5
40.8	61.3	74.4
48.4	65.7	77.4
51.9	67.6	77.8
52.6	73.9	84.0
64.8	74.1	88.9
68.5	75.8	89.6
79.8	77.7	98.8
86.5	121.1	108.5
88.2	121.1	115.7
93.8	121.7	136.7
95.5	123.9	194.8
110.3	139.4	205.1
	144.0	211.4
	149.5	296.6
	182.2	
70.3 ± 6.6 <sup>a</sup>	102.4 ± 10.1 <sup>a</sup>	128.2 ± 17.5 <sup>a</sup>
	88.0 ± 6.9 <sup>b</sup>	

<sup>a</sup> Mean ± Standard Error of the Mean.

<sup>b</sup> Mean ± Standard Error of the Mean for Group I (active disease) patients as a whole.

NRT had had relapses. These patients did not differ significantly in any other clinical parameter. We therefore subdivided the patients with active disease (Group I) into those who had experienced relapses and those who had not, and analyzed their production of hydrocortisone in response to insulin. These results are also presented in Table 2. The level of hydrocortisone production in the patients with a history of relapses in the past is lower than in patients with no relapses ( $p < 0.02$ ). Thus, relapses are among the factors exhausting the reserve hydrocortisone-producing function of the adrenals.

The data obtained suggest great perspectives for further studies on the associations between the hydrocortisone-producing function of the adrenal glands and the leprosy relapses, both for extending our knowledge of the pathogenesis of leprosy and for improving methods of nonspecific therapy. At present, we may definitely outline the principles of steroid treatment of patients with active lepromatous leprosy and a past

history of relapses. Glucocorticoids, which are often used in high doses (for instance, for erythema nodosum leprosum) according to the feed-back mechanism, would further depress an already deficient synthesis of endogenous glucocorticoid (hydrocortisone). Thereby, the background is created for the development of various diseases associated with glucocorticoid deficiency. Thus active lepromatous leprosy patients with a history of relapses who have been treated with glucocorticoids may be particularly vulnerable to glucocorticoid deficiency during times of stress, e.g., cooling, nutritional disorders, psychic traumata, etc.

### CONCLUSIONS

1. Basal levels of hydrocortisone are higher in patients with lepromatous leprosy than in healthy individuals.

2. Reserve hydrocortisone-producing adrenal function in most patients with lepromatous leprosy, revealed under insulin load, is exhausted. The marked degree of such exhaustion expressed as a "paradoxical reaction" is found in 64% of patients.

3. The lowest levels of reserve hydrocortisone production were observed in patients with signs of active disease. The patients with clinical regression showed higher levels. Leprosy relapses are one of the active factors exhausting the reserve hydrocortisone-producing function of the adrenals.

### SUMMARY

Hydrocortisone production was studied in 36 patients with lepromatous leprosy before and after insulin load as a stress factor using a competitive radioassay. Twenty-three patients showed a so-called paradoxical type of hydrocortisone production suggestive of markedly exhausted hydrocortisone-producing function of the adrenal cortex. Reserve hydrocortisone production was depressed in most of the patients with active disease; while cured patients showed a partial restoration in reserve hydrocortisone production. Leprosy relapses seem to be among the factors affecting the reserve hydrocortisone-producing function of adrenals. The question of reassessment of the principles of steroid therapy in lepromatous patients with relapses is raised.

### RESUMEN

Se estudió la producción de hidrocortisona en 36 pacientes con lepra lepromatosa antes y después de la administración de un pulso de insulina como factor de stress. Se usó un radioensayo competitivo para su medición. Veintitrés pacientes mostraron un tipo "paradójico" de producción de hidrocortisona sugestivo de una marcada depresión en la función productora de hidrocortisona por la corteza adrenal. La producción de la reserva de hidrocortisona estuvo deprimida en la mayoría de los pacientes con enfermedad activa. Los pacientes curados mostraron una restauración parcial en la producción de la reserva de hidrocortisona. Las recaídas leprosas parecen estar entre los factores que afectan la función productora de la reserva de hidrocortisona por las adrenales. Se plantea la necesidad de reestudiar los principios de la terapia con esteroides en los pacientes con cuadros reaccionales.

### RÉSUMÉ

Chez 36 malades atteints de lèpre lépromateuse, on a étudié la production d'hydrocortisone avant et après une charge d'insuline, utilisée comme un facteur de stress. Cette étude a été menée au moyen d'une épreuve radioactive compétitive. Chez 23 malades, on a observé une production d'hydrocortisone du type appelé paradoxal, ceci suggère un épuisement prononcé de la fonction de production d'hydrocortisone dans le cortex des surrénales. La réserve de la production d'hydrocortisone était déprimée chez la plupart des malades souffrant d'une maladie active; alors que les malades

guéris présentaient une restauration partielle de cette réserve. La récurrence de la maladie paraissait constituer l'un des facteurs agissant sur la réserve de la fonction de production d'hydrocortisone dans les surrénales. Ceci soulève le problème d'une nouvelle évaluation des principes sur lesquels est basée la thérapeutique par les stéroïdes chez les malades lépromateux atteints de récurrence.

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