# Adrenal Cortical Dysfunction in Leprosy[1]

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Adrenal cortical dysfunction has been described in systemic mycotic diseases, such as histoplasmosis ([4,18]), coccidioidomycosis ([12]), cryptococcosis ([2]), blastomycosis ([8]) and paracoccidioidomycosis ([1,11]). In a survey of 1,200 cases one of the authors ([24]) reported adrenal cortical insufficiency with increased ACTH and MSH blood levels in the following conditions: Addison's disease, partial adrenalectomy, adrenogenital syndrome, rheumatoid arthritis, keratodermia, diabetes mellitus, hyperthyroidism, circulatory, psychologic and surgical stress and shock.

We shall now report on similar findings in leprosy.

## METHODS

Adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH) were assayed as described in an earlier report ([24]) by the melanophore reaction in tree frogs, *Hyla arborea* ([22]). This technic measures ACTH and MSH together and is therefore useful for the assessment of clinical conditions in which the adrenal glands are involved. The negative feedback mechanism of the inactive or incapacitated adrenal cortex induces an increase in both ACTH and MSH secretion ([10]). ACTH and MSH are measured in Frog Units (FU), one FU equaling 0.001 IU ACTH. A normal patient has less than one FU per 20 ml. blood, i.e., 50 FU/l. In untreated Addison's disease, values may well rise to 250 FU/l, and in Cushing's disease with a basophil pituitary adenoma to as much as 500 FU/l ([24]).

17-hydroxycorticoids (17-OHC) were assayed by the Porter-Silber method ([25,26])—minimal values for males 5 mgm./day, females 3 mgm./day—and 17-ketosteroids (17-KS) with the Zimmermann method ([23]), minimal values for males being 12 mgm./day, and for females 8 mgm/day.

The 25 leprosy patients, studied were hospitalized in the Government Hospital Hansen under clinical and dermatologic supervision. Their daily treatment consisted of 50-100 mgm. DDS (4 4'-diaminodiphenyl sulfone) and, when lepra reactions appeared, of 50-300 mgm./day thalidomide according to Sheskin ([19,20,21]). These patients suffered from lepromatous, tuberculoid or dimorphous leprosy.

## RESULTS

Table 1 shows blood ACTH-MSH, 17-OHC and 17-KS excretion of 25 leprosy patients, chosen at random, at various stages of their disease. Seven of the 25 patients (Nos. 3, 8, 12-15, 17) examined had normal levels of blood ACTH-MSH (<50 FU/l), the others had increased levels of blood ACTH-MSH. Some of the latter patients had normal blood ACTH-MSH levels at subsequent monthly examinations. In 20 of the 25 patients (Nos. 1-4, 6, 8-17, 20, 22-25) there was a positive correlation between clinical symptoms and ACTH-MSH blood levels. In 13 patients high ACTH-MSH blood levels coincided with the appearance of an exacerbation of the disease, such as lepra reaction, erythema nodosum leprosum (ENL), neuropathy, diarrhea and gouty arthritis. In six patients high ACTH blood levels were present while the disease was apparently in a quiescent state.

Values of 17-OHC were high when blood ACTH-MSH was low and were sometimes extremely low when blood ACTH-MSH was high. Especially low corticoid values and high ACTH-MSH values were observed in patients suffering from lepra reaction. As this condition, once extremely dreaded, is today favorably influenced

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TABLE 1. *Secretion of ACTH, MSH, 17-OHC and 17-KS in 25 leprotic patients.*

| Patient No. | Sex | Age | Date month/year | MSH ACTH FU/1 | 17-OHC mgm./1 | 17-KS mgm./1 | Diagnosis and condition | Treatment |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 28 | 6/66 | <50 | 4.4 | 20 | Lepromatous leprosy ENL<br><br><br><br><br>Diarrhea | Thalidomide—from 1/29/65 to 1/29/66 and from 3/1/66 to present. DDS—since 1/29/66. |
| | | | 7/66 | <50 | 3.6 | 18 | | |
| | | | 8/66 | 166 | 1.8 | 12 | | |
| | | | 9/66 | <50 | 3.4 | 15 | | |
| | | | 10/66 | <50 | 3.5 | 15 | | |
| | | | 11/66 | <50 | 3.6 | 15 | | |
| | | | 12/66 | <50 | 2.4 | 21 | | |
| | | | 1/67 | 83 | 2.5 | 14 | | |
| | | | 2/67 | 83 | 2.9 | 16 | | |
| | | | 3/67 | 83 | 4.4 | 18 | | |
| | | | 4/67 | <50 | 4.5 | 24 | | |
| 2 | M | 31 | 6/66 | 250 | 2.2 | 19 | Lepromatous leprosy with exacerbation in June '66 | Thalidomide—from 3/3/65 to 6/29/66 and from 2/20/67 DDS since 6/29/66 to present. |
| | | | 11/66 | <50 | 2.6 | 10 | | |
| | | | 12/66 | <50 | 2.7 | 6 | | |
| | | | 2/67 | 83 | 2.0 | 8 | | |
| 3 | M | 31 | 10/66 | <50 | 2.4 | 24 | Quiescent lepromatous leprosy | Thalidomide from 11/10/66 to 3/1/67. DDS starting 11/30/66 to present. |
| | | | 11/66 | <50 | 2.5 | 26 | | |
| | | | 12/66 | <50 | 2.2 | 21 | | |
| | | | 1/67 | <50 | 2.4 | 28 | | |
| | | | 2/67 | <50 | 2.3 | 26 | | |
| 4 | M | 26 | 5/66 | 500 | 1.6 | .7 | Lepromatous leprosy with polyneuritis since May '66 Exacerbation and ENL in March '67 | Thalidomide from 3/3/65 to 3/2/66 |
| | | | 6/66 | 500 | 1.8 | 6 | | |
| | | | 2/67 | <50 | 2.5 | 8 | | |
| | | | 3/67 | 166 | 4.2 | 1 | | |
| 5 | F | 54 | 4/66 | 166 | 3.1 | 9 | Quiescent tuberculoid leprosy. | Avlosulfone and DDS[a] |
| | | | 5/66 | 166 | 3.2 | 8 | | |

[a] Acetaldehyde-bisulfite of DDS.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 (cont'd) | | | 6/66<br>9/66<br>10/66<br>11/66<br>12/66<br>1/67 | 500<br>83<br><50<br><50<br><50<br>83 | 2.2<br>2.4<br>3.0<br>3.5<br>1.4<br>1.2 | 2<br>10<br>11<br>11<br>5<br>4 | | |
| 6 | M | 44 | 2/67 | 500 | 4.5 | 3 | Lepromatous leprosy with bucal necrotic inflammation | Thalidomide from 12/16/64 to 1/7/65 from 2/4/65 to 7/5/65 then from 7/5/66 to present, also DDS. |
| 7 | M | 38 | 3/67 | 166 | | | Quiescent promatous leprosy | DDS |
| 8 | F | 36 | 2/67 | <50 | 4.6 | 3 | Quiescent indeterminate leprosy | Thalidomide from 1/1/67 to 6/4/67 and DDS |
| 9 | M | 32 | 2/67 | 83 | 4.2 | 16 | Dimorphous leprosy with exacerbation | Thalidomide from 5/3/65 to 6/30/66 |
| 10 | F | 48 | 6/66<br>2/67 | 500<br><50 | 1.5<br>2.5 | 6<br>9 | Indeterminate leprosy with exacerbation in June '66 | DDS |
| 11 | M | 47 | 6/66<br>11/66<br>1/67<br>2/67<br>3/67 | 250<br>500<br>500<br><50<br><50 | 2.5<br>2.7<br>3.6<br>3.6<br>4.7 | 1<br>1<br>8<br>10<br>3 | Lepromatous leprosy with exacerbation in June '66 Nov. '66 and Jan. '67 (neuropathy arthritis, bronchitis) | Thalidomide from 8/29/64 to 6/2/65 and from 7/9/65 to 6/2/66 and DDS. |
| 12 | F | 59 | 2/66 | <50 | 2.2 | 7 | Quiescent lepromatous leprosy | Thalidomide from 1/3/67 to 1/6/67 and Ciba-1906 & DDS. |
| 13 | M | 30 | 2/67 | <50 | | | Quiescent lepromatous leprosy | Thalidomide from 1/5/65 to 1/19/65 and DDS from 7/2/65 to 7/15/65. |

TABLE 1. *Continued*

| Patient No. | Sex | Age | Date month/year | MSH ACTH FU/1 | 17-OHC mgm./1 | 17-KS mgm./1 | Diagnosis and condition | Treatment |
|---|---|---|---|---|---|---|---|---|
| 14 | F | 25 | 2/67<br>3/67 | <50<br><50 | 1.7<br>2.1 | 19<br>16 | Quiescent lepromatous leprosy | DDS |
| 15 | M | 45 | 2/67 | <50 | 5 | 14 | Quiescent tuberculoid leprosy | Thalidomide from 11/25/65 to 12/12/65 and DDS |
| 16 | F | 53 | 6/66<br>12/66<br>1/67<br>2/67<br>3/67 | <50<br>500<br>250<br>166<br><50 | 3.1<br>1.7<br>1.4<br>1.9<br>6.5 | 17<br>4<br>6<br>18<br>24 | Lepromatous leprosy with exacerbation in Dec. '66 and ENL in Jan. & Feb. '67. Resolution of symptoms in March '67 | Thalidomide from 3/5/65 to 6/15/66 then DDS. |
| 17 | M | 38 | 2/67 | <50 | | | Quiescent lepromatous leprosy | DDS |
| 18 | F | 26 | 2/67 | 166 | 2.3 | 11 | Quiescent lepromatous leprosy | DDS |
| 19 | M | 55 | 6/66<br>12/66<br>1/67 | 250<br>83<br><50 | 2.6<br>2.5<br>2.2 | 1<br>14<br>18 | Quiescent lepromatous leprosy | Thalidomide from 2/8/65 to 5/2/65 and DDS. |
| 20 | M | 66 | 2/67 | 83 | | | Lepromatous leprosy after exacerbation | Thalidomide from 1/4/65 to 3/23/66 |
| 21 | F | 66 | 3/67 | 83 | | | Quiescent tuberculoid leprosy | Thalidomide from 5/9/65 to 7/20/65 then DDS. |
| 22 | M | 77 | 4/66<br>6/66<br>11/66 | 500<br>500<br>83 | 0.5<br>0.6<br>1.4 | 7<br>4<br>8 | Tuberculoid leprosy and chronic lymphatic leukemia with gouty arth- | DDS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 22 (cont'd) | | | 12/66 | 83 | 2.5 | 12 | ritis in April & June '66 | |
| | | | 1/67 | 83 | 4.7 | 19 | | |
| | | | 2/67 | 83 | 3.4 | 6 | | |
| 23 | M | 27 | 2/67 | 83 | 5.2 | 14 | Active lepromatous leprosy | Ciba—1906 & DDS. Thalidomide from 1/26/67 to 2/12/67. |
| 24 | M | 36 | 2/67 | 166 | 7.2 | 1 | Lepromatous leprosy after exacerbation | Thalidomide from 10/1/65 to 6/1/66 then DDS. |
| 25 | M | 49 | 6/66 | 250 | 1.8 | 3 | Dimorphous leprosy with ENL in June '66. Clinical improvement in March '67 | Thalidomide from 2/8/65 to 6/22/66 then DDS. |
| | | | 9/66 | 83 | 2.3 | 9 | | |
| | | | 3/67 | <50 | 3.3 | 10 | | |

within a short time by thalidomide treatment ([3,19,20,21]), studies have become difficult because of its short duration. In 19 patients (Nos. 1-7, 9-12, 14, 16, 18-22, 25) urinary 17-OHC excretion was low with blood ACTH-MSH being increased; two other patients (Nos. 23, 24) had also increased blood ACTH-MSH, the urinary 17-OHC being normal.

Urinary 17-KS excretion was occasionally low in nine patients (Nos. 4, 6, 8, 10-12, 22, 24, 25); it cannot, however, be considered a reliable indicator of adrenal insufficiency as it may also indicate stress. In four patients (Nos. 1, 4, 16, 25) a positive correlation between clinical symptoms and adrenal dysfunction became evident on multiple occasions.

## COMMENT

Increase in ACTH or MSH with decrease in 17-OHC and 17-KS in leprotic patients has not hitherto been reported. Yet, Languillon *et al.* ([9]) recently reported cortical adrenal insufficiency in lepra reactions, using the Thorn test in their study. It is obvious that many chronic incapacitating diseases induce a stress reaction which may ultimately result in adrenal cortical exhaustion ([1,2,4,8,11,12,18,24]). A second possible factor, responsible for adrenal insufficiency, could be continuous drug treatment; this is, however, not known for DDS which was used in the treatment of all the above 25 patients. It is unlikely that DDS produces such an effect, since seven of the DDS-treated patients (Nos. 3,8,12-15,17) did not have increased blood ACTH levels. Moreover, the other 18 patients, too, had intervals in which they attained normal levels of adrenal activity. None of the 25 patients received corticoid treatment.

Another factor which may induce adrenal cortical insufficiency has been described by Oberdoerffer and Gehr ([17]) and confirmed by Muir ([16]). They reported a correlation between the occurrence of leprosy in the world and the intake of sapotoxins in the diet. The following five plants contain sapotoxins: *Colocasia antiquorum, Xanthosoma atrovirens, Chenopodium quinoa, Arum maculatum* and *Agrostemma githago*, the latter appearing mostly as a

contamination of flour (similar to ergot). A subclinical intoxication resulting from intake of sapotoxins with the food indeed induces strong adrenal cortical depression, but there is no evidence of such a factor being present in our patients.

The possibility should, therefore, be considered that leprotic infection as well as lepra reaction may be related to the occurrence of a hypoadrenal state. Inaba ([7]) has noted similarities between lepra reaction (ENL) and systemic lupus erythematosus. He believes that adrenal insufficiency, with a lowered basal metabolic rate, a transient rise in salt excretion, and a sharp drop in 17-KS excretion precedes a lepra reaction. In our cases exacerbation of the disease coincided with adrenal dysfunction in 17 patients.

The severe symptoms of lepra reaction are dramatically relieved by thalidomide ([19-21]). This may be due to its immunosuppressive properties described by Hellmann and his co-workers ([5, 6, 27]). Similarly, an antitumor growth effect has been observed by Mückter *et al.* ([13-15]). Thalidomide might compensate for a temporary cortisone deficit.

The fact that leprosy is associated with long periods of adrenal depression during which the patient becomes very sensitive to the disease, raises the qustion whether the rare patients who contract leprosy by contagion are not those who, during the time of exposure, suffered from adrenal insufficiency resulting in diminished immunity and defense reactions. Such proneness to secondary diseases is well-known in the Addisonian patient. This problem can only be solved by a prospective study using routine endocrine examinations of healthy people working or living in daily contact with leprotic patients.

The 25 patients studied in this series were examined for clinical symptoms of adrenal insufficiency, other than ACTH-MSH increase or 17-OHC and 17-KS decrease, with negative results. During and after lepra reactions there often is a darkening of the skin which might be related to the direct effect of ACTH or MSH on melanophore cells.


## SUMMARY

Adrenal cortical dysfunction has been observed in 19 of 25 leprosy patients. It was characterized by high blood levels of ACTH and MSH and low urinary excretion of 17-OHC. Two additional patients had increased ACTH and MSH blood levels, with normal urinary 17-OHC values. Urinary excretion of 17-KS was occasionally low in nine of the patients; this, however, cannot be considered a reliable parameter since it may indicate stress. The course of such adrenal cortical dysfunction is unpredictable; it is transient and sporadically recurrent. However, in 20 of 25 patients there was positive correlation between clinical symptoms and ACTH and MSH blood levels. In 13 patients high ACTH and MSH blood levels coincided with the appearance of exacerbations of the disease, such as lepra reaction, erythema nodosum leprosum, neuropathy and other complications. In six patients high ACTH and MSH blood levels were present while the disease was apparently in a quiescent state.

## RESUMEN

Se ha observado disfunción adrenocortical en 19 de 25 enfermos de lepra. Estaba caracterizada por niveles elevados de ACTH y MSH y baja excreción unrinaria de 17-OHC. Dos pacientes adicionales tenían aumento de nivel sanguíneo de ACTH y MSH con valores normales urinarios de 17-OHC. La excreción urinaria de 17-KS fué baja en forma ocasional en 9 de los enfermos; esto, sin embargo, no puede ser considerado como un parámetro fiel, ya que puede indicar stress. El curso de esta disfunción adrenocortical no se puede predecir; es pasajera y esporádicamente recurrente. Sin embargo, en 20 de 25 casos existía una correlacián entre sintomatología clínica y el nivel sanguíneo de ACTH y MSH. En 13 pacientes, niveles sanguíneos altos de ACTH y MSH coincidieron con exacerbación de la enfermendad tales como reacción leprosa, ENL, neuropatía y ostras complicaciones. En 6 pacientes, se encontrarou niveles sanguíneos altos de ACTH y MSH cuando la enfermedad aparentemente estaba quiescente.

## RÉSUMÉ

Un manuvais fontionnement de la cortico surrénale a éte observé chez 19 lépreux sur 25. Il étaite caractérisé par des teneurs élevées du sang en ACTH et en MSH, et une excrétion urinaire faible de 17 OHC. Deux autres malades présentaient une augmentation des taux sanguins d'ACTH et de MSH, avec des valeurs urinaires de 17 OHC normales. L'excrétion urinaire de 17 KS s'est montrée par moments fabile chez 9 malades, ce qui n peut cependant pas être considéré comme un paramétre sûr puis qu'elle peut aussi indiquer un stress. l'évolution de ce mauvais fonctionnement de la corticosurranale est imprévisible; il est passager et se manifeste sporadiquement. En depit de cela 20 malades sur 25 ont présenté une corrélation positive entre les symptômes cliniques et les taux sanguins d'ACTH et de MSH. Chez 13 malades, des taux élevés d'ACTH et de MSH coincidaient avec des périodes d'exacerbation de la maladie *telles* que: réactions lépreuse, erythema nodosum leprosum, neuropathies et autres complications. Six malades ont présenté des taux élevés d'ACTH et de MSH, alors que la maladie était apparemment en phase de rémission.


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