Adrenal Function in Chronic Pulmonary Tuberculosis*

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The frequency, extent and importance of adrenal involvement in pulmonary tuberculosis, and the role of the adrenal in the clinical symptomatology of this disease have been the subject of widely divergent opinions for many years. This lack of unanimity has a variety of reasons, some of fundamental importance. All too often, judgment as to the presence or absence of adrenal cortical hypo-function has been based solely on clinical criteria such as gastrointestinal disturbances, asthenia, hypotension, and so forth; these symptoms, though usually present in severe adrenal insufficiency, are by no means pathognomonic, and their significance is particularly difficult to interpret in a disease such as tuberculosis where intestinal lesions, malnutrition, and debility are so common. Thorn¹ states, as a matter of fact, that the differential diagnosis of Addison's disease may present great difficulty "in patients with established tuberculosis elsewhere (i.e., not in the adrenal) whose excessive weakness, gastrointestinal symptoms or pigmentation raises the question of adrenal involvement" unless detailed studies of adrenal function are performed. The small, globular heart which forms part of the clinical picture of the now discredited "habitus phthisicus" and which was thought to bear some relationship to the small heart commonly found in Addison's disease has been shown by us to have no relation to adrenal function, as far as could be judged by available criteria.² Even isolated biochemical data may be misleading in this problem, for low serum sodium values have been observed in patients with chronic pulmonary tuberculosis but without any evidence of adrenal failure.³ Other biochemical attempts to study adrenal function by highly roundabout means have served only to confuse the picture further. Trautweln,⁴ studying liver glycogen in tuberculous patients by indirect tests, found that depletion of liver glycogen exists in such patients, and that repletion could be induced by the administration of adrenal cortical substance. This and similar data were considered to be evidence of adrenal cortical insufficiency. Actually, they merely demonstrate well-known physiological effects of adrenal cortical hormones, and can be observed clinically as well as in starved nonadrenalectomized animals. Experiments of this type, then, cannot add to our knowledge of the adrenal status in tuberculosis. Abderhalden and Abderhalden⁵ claim that certain urinary proteases reflect adrenal cortical activity. On the basis of this measurement, they state that nearly all severe cases, as well as 36 per cent of "mild" cases of tuberculosis show disturbance of adrenal function.

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The other major difficulty in arriving at unequivocal results has been the manner in which the clinical data were studied. Tuberculous individuals cannot simply be lumped together and treated as a homogeneous group; such a procedure, commonly employed, serves only to produce "statistically insignificant" average values and to mask useful information. Several recent investigations have proved particularly fruitful by their avoidance of this treatment. Pfeffer et al. studied eight individuals with respect to adrenal function and found, in five febrile patients with cavitation and active disease, positive Kepler and Cutler-Power-Wilder tests. The urinary hormone excretion, studied by an unspecified method, was found to be decreased. By contrast, three patients responsive to chemotherapy and improving steadily gave negative tests and normal urinary hormone excretion.

De FIGueroa Taboda studied 17-ketosteroid excretion of 79 patients whom he classified carefully according to the degree and activity of their disease, and found that the average values for ketosteroid excretion diminished with increasing severity. Unfortunately, no consideration seems to have been given to sex and age distribution of patients in the various groups; neglect of these factors makes it almost impossible to assess the validity of these ketosteroid measurements.

The most careful report to date is that of Bastenie and Kowalewski, who studied 35 males and 10 females with tuberculosis. All were under 60 years of age. Significant differences were found between the average ketosteroid excretion of normal controls as against the tuberculous patients. However, a breakdown of the clinical material gives a more important insight into their findings: of the 15 with "moderately active" tuberculosis, 14 showed normal urinary ketosteroid excretion, whereas of the 20 classified as "severe," only six were in the normal range and the rest showed decidedly low values. These workers state, "It may be that the tuberculous infection plays the same nonspecific role in depressing adrenal cortical function as other debilitating conditions do."

It is hardly surprising, in view of these diagnostic difficulties, that therapy with adrenal cortical preparations has given inconstant results, and the recent availability of synthetic adrenal steroids such as cortisone has increased the complexity of the problem even further. The data presented by us will attempt to evaluate adrenal function by means of urinary hormone excretion, keeping in mind the possible influence of variables such as age, sex, extent and activity of disease, etc., and may provide indications for adrenal hormone therapy in tuberculosis.

Materials and Methods

Material: A total of 68 patients, 49 males and 19 females, were investigated. In the group under 20 years of age there were three females; in the 21 to 30 year age group there were eight females; in the 31 to 40 year age group there were four females and seven males; in the 41 to 50 year age group there were two females and 11 males; in the 51 to 60 year age group
there were one female and 20 males; in the 61 to 70 year age group there was one female and 11 males. The nature and extent of the tuberculous process was classified according the criteria of the American Tuberculosis Association. One patient was classified in group 2-A, six in group 2-B, one in group 3-A, nine in group 3-B, and 43 in group 3-C.

As a quantitative measure of disease activity the sedimentation rate (Westergren) was used as a convenient index. Seven had a sedimentation rate of less than 10 mm. per hour; nine showed 11 to 25 mm. per hour; 16 showed 26 to 50 mm. per hour; 16 showed 51 to 75 mm. per hour; nine showed 76 to 100 mm. per hour; and 11 a rate greater than 100 mm. per hour.

As major indices of adrenal cortical function, the urinary excretion of 17-ketosteroids and neutral reducing corticoids are used throughout this paper. It should be emphasized, however, that these two parameters do not provide an absolute quantitative nor even qualitative measure of the active function, let alone the reserve strength of the adrenal cortex. Thus any conclusion to be drawn in this investigation regarding adrenal function must be made with this reservation in mind.

Methods: Sedimentation rate was determined by the Westergren method. Total eosinophil counts were determined by chamber count after staining in the pipette with phloxine-methylene blue in propylene glycol. Urinary 17-ketosteroids were determined from pooled 48 hour urines by the method of Drekter et al. Neutral reducing ("11-oxy") corticoids were determined on these same urines by a modification of the method of Heard and Sobel. Blood pressure and weight measurements were performed by the same observer throughout. Determination and evaluation of the cardiothoracic ratio was conducted in the manner described previously. Statistical evaluations were carried out by means of the t-test using the formula:

\[ \sigma = \left[ \frac{\sum (x - \bar{x})^2}{n-1} \right]^{1/2} \]

FOR THE STANDARD DEVIATION IN GROUPS OF LESS THAN 35 PATIENTS, AND CALCULATING t ACCORDING TO THE FORMULA:

\[ t = \frac{M_1 - M_2}{s} \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \]

WHERE

\[ s = \sqrt{\frac{\sum (x - \bar{x})^2 + \sum (x - \bar{x}_2)^2}{n_1 + n_2 - 2}} \]

\[ M = \text{MEAN} \]
\[ n = \text{NO. OF CASES} \]
\[ x - \bar{x} = \text{DIFFERENCE OF ACTUAL VALUE FROM THE MEAN.} \]
Results

Urinary Hormone Excretion. 17-Ketosteroids:

The excretion of urinary 17-ketosteroids is known to vary with age. Moreover, in the male it represents the combined product of testicular and adrenal secretion while in the female the ovary does not contribute to the urinary 17-ketosteroid output. Evaluation of this quantity must, therefore, consider the age and sex factors. Figure 1 shows the individual ketosteroid values of our group of patients distributed according to age and sex. Average values obtained from a considerable number of normals and a range of variation representing approximately one standard deviation is also shown. It is evident that the vast majority of the values obtained fall within the normal range. Sixteen males showed values somewhat higher than one standard deviation above normal; this is not particularly meaningful, for the upward variation in males is quite wide due to the increment of testicular secretion. None of the values fall into the pathologically elevated range. The 10 values in females which appear to be low are actually within the normal range for this sex: to avoid confusion, the normals and normal range for females have been omitted from the diagram. Actually, none of the values for women fall in the abnormally low range. Only four male patients in the 55 to 69 year old age group have low values, and of these
only two values are substantially lowered. It may be concluded that urinary 17-ketosteroid excretion (when corrected for sex and age) does not yield evidence of profound adrenal cortical insufficiency in this group of tuberculous patients.

**Urinary Hormone Excretion. Neutral Reducing Corticoids (NRC):**

As this urinary metabolite is an index of adrenal cortical (and not of testicular) function, males and females show similar levels of excretion. Individual values, plotted against age, are shown in Figure 2. The average value for NRC excretion with age is indicated by a line; the data indicate only approximately the normal range. Once again it is evident that there is no significantly large group of patients whose NRC excretion is abnormally high or low. In this respect the two steroid excretion patterns are in agreement.

**Relation of the Sedimentation Rate to Urinary Hormone Excretion:**

The sedimentation rate as a convenient quantitative index reflects to a certain extent the activity of the infectious process. To study the rela-
tionship of tuberculous activity to urinary hormone excretion, the patients were divided into two groups: those having a sedimentation rate of less than 30 mm. per hour and those with a rate greater than 50 mm. per hour. Each group was adjusted for age and sex distribution. The actual data are summarized in Table I, and their significance is shown in Figure 3.

Statistical analysis of the 17-ketosteroid excretion in these two groups showed a significant difference (t=2.1), which agrees with the findings of other investigators.6-8 There was also a significant difference in the NRC excretion of the two groups (t=2.0). It may be concluded that adrenal cortical function (as judged by ketosteroid and NRC excretion) is diminished in patients with considerable activity compared to those with minimal or moderate activity as judged by the sedimentation rate.

<table>
<thead>
<tr>
<th>TABLE I</th>
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<table>
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<tr>
<th>Sed. Rate in mm./hr.</th>
<th>Number of Patients</th>
<th>Average Excretion in mg. per day</th>
<th>Significance (t-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 KETOSTEROIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30</td>
<td>14</td>
<td>18.6 ± 7.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Over 50</td>
<td>32</td>
<td>14.5 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>NEUTRAL REDUCING CORTICOIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30</td>
<td>19</td>
<td>3.5 ± 1.05</td>
<td>2.0</td>
</tr>
<tr>
<td>Over 50</td>
<td>33</td>
<td>2.9 ± 0.99</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 3**
Relation of Weight Loss to Urinary Steroid Excretion:

In addition to the sedimentation rate, changes in body weight provide some indication of the activity of the tuberculous process and its effect on the organism. In connection with other studies (to be described elsewhere) the weight was recorded at weekly intervals over a minimum period of six weeks. For purposes of analysis, the patients were divided into two groups: those showing progressive weight loss and those with constant or increasing weight. The data for the urinary hormone excretion of these two groups are shown in Table II.

### TABLE II

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Average Excretion in mg. per day</th>
<th>Significance (t-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17 KETOSTEROIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss (males only)</td>
<td>6</td>
<td>14.0 ± 2.5</td>
<td>1.3 (n.s.)</td>
</tr>
<tr>
<td>No weight loss (males only)</td>
<td>33</td>
<td>17.6 ± 6.8</td>
<td></td>
</tr>
<tr>
<td><strong>NEUTRAL REDUCING CORTICOIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>11</td>
<td>2.6 ± 0.65</td>
<td>1.9</td>
</tr>
<tr>
<td>No weight loss</td>
<td>42</td>
<td>3.3 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

The t-value for the comparison between these two groups as regards neutral reducing corticoid excretion is 1.9. Although t±2 is usually selected as the lower limit of statistical significance (equivalent to the 5 per cent level of confidence), one may say that such a correlation is, at least, suggestive. This conclusion would confirm the correlation with sedimentation rate, namely, that increased activity of the disease constitutes an exhausting strain on the adrenal cortex, with a consequent diminution of adrenal activity and decrease in excretory products. And as has been pointed out previously, the lack of confirmation in studies of the 17-ketosteroids is most probably due to the factor of testicular hormone excretion, which is of unknown and variable amount.

Relation of Blood Pressure to Urinary Steroid Excretion:

Hypotension is one of the characteristic findings in adrenal cortical insufficiency and therefore an attempt was made to correlate this clinical sign with evidence of adrenocortical hypofunction as measured by urinary excretion studies. The patients were divided into two groups: the "normotensives" with blood pressure of 100/65 or more and the hypotensives with less than 100/65. Hypertensives were excluded for obvious reasons.

A scattergram of blood pressure vs. hormone excretion failed to reveal any obvious correlation, and therefore a more detailed study by means of the t-test was undertaken. The 17-ketosteroids (corrected for the proportion of males and females) and the NRC values were compared statistically as shown in Table III.
TABLE III

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Average Excretion in mg. per day</th>
<th>Significance (t-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17 KETOSTEROIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>43</td>
<td>17.0 ± 5.7</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>14</td>
<td>12.0 ± 4.2</td>
</tr>
<tr>
<td><strong>NEUTRAL REDUCING CORTICOID</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>43</td>
<td>3.2 ± 1.1</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>17</td>
<td>2.7 ± 0.8</td>
</tr>
</tbody>
</table>

In each instance the difference between the two blood pressure groups was such as could have occurred by chance alone (t=0.99 and 1.6 respectively). It may be concluded that hypotension in the majority of cases, and certainly hypotension alone, cannot be taken to indicate adrenal cortical deficiency in these patients.

*The Relation of the Cardiothoracic Ratio to Adrenal Function:*

The meaning of the small, spherical heart and the cardiothoracic ratio has been studied previously by one of us as a possible index of adrenal function. By the criteria of that study² no correlation could be found. In the present work a further attempt was made to relate the cardiothoracic ratio to adrenal activity, using the urinary hormone excretion as an index of function. A substantial number of patients had to be excluded because of mediastinal deformation due to pulmonary disease; only 40 patients yielded x-ray films in which a determination of the cardiothoracic ratio was meaningful. A scattergram of the cardiothoracic ratios plotted against 17-ketosteroid or NRC excretion failed to reveal any correlation. Because of the nature of the scatter, no further statistical attempt was made to verify the point and we can confirm our previous findings that the small heart in the tuberculous patient is no sign of adrenal cortical hypofunction.

*Total Eosinophile Count as a Measure of Adrenal Cortical Function:*

It is well known that changes in adrenal cortical activity are reflected in changes of the total eosinophile count. For example, the eosinopenia which follows administration of ACTH has become the basis of a clinical test for the study of adrenal cortical function. The eosinophil counts of these patients were therefore examined in relation to their NRC and 17-ketosteroid excretion. Scattergram analysis failed to reveal any significant correlation. In general, this was to be expected, for it has been observed that absolute values of eosinophiles are not useful as an index of adrenal cortical function except in extreme instances. It is usually necessary to study changes of total eosinophile count during acute adrenal stimulation. The wide range of the normal total eosinophile count precluded obtaining statistically significant data.
Discussion

Perhaps the most important observation to emerge from these studies is that the adrenal cortex is able to withstand and compensate for the stress of chronic pulmonary tuberculosis in so many cases. This statement, we must emphasize, applies only to the particular type of patient investigated by us, and not to those with an acute, hectic, or rapidly downhill course. The data reveal that patients with a substantially elevated sedimentation rate or progressive weight loss as evidence of active disease do show diminished steroid excretion, indicating adrenal damage and decreased function. In acute febrile conditions generally, the adrenal is known to suffer injury, and this has been shown by others to be true of the acute phases of tuberculosis as well. We agree with Bastenie and Kowalewski that this is not a specific manifestation of tuberculosis in any sense, but a general response to stress whether of infections, toxic, traumatic or other origin.

It seems also that adrenal insufficiency cannot explain the symptoms of asthenia, hypotension or gastrointestinal disturbances in most instances, judging from the efficient adrenal compensation observed in our cases. On the other hand, it must be admitted that minor degrees of adrenal failure, sufficient to produce symptoms but not enough to change steroid excretion (which represents less than 10 per cent of the actual adrenal steroid output) could exist. Investigation of this point must await the development of more refined tests for adrenal activity and reserve.

Lastly, our findings confirm the observation of others, that the adrenal is more or less exhausted in the acute and febrile stages of tuberculosis. As it is solidly established that the adrenal is an important cog in the defense mechanisms of the body, this is a clear indication for the use of adrenal cortical extracts with the potentiating adjuvants thiamine, ascorbic acid and pyridoxine. In this present medical era it is necessary to emphasize that cortical extract therapy is not by any means synonymous with the use of cortisone or desoxycorticosterone acetate (DCA). The former substance particularly, when used in the unphysiological doses currently favored, is known to have just the reverse effect on certain phases of tissue resistance, permitting rather than inhibiting the spread of infection. DCA, in turn, requires constant, careful supervision of electrolyte balance lest edema or potassium depletion be induced, and does not restore normal carbohydrate metabolism or immune response. Cortical extracts by contrast do not produce these side effects even in massive dosage.

In chronic tuberculosis compensated from the adrenocortical standpoint, on the other hand, there seems to be no physiological indication for adrenal substitution therapy.

SUMMARY

The adrenal cortex shows biochemical evidence of damage only during the acute and/or febrile phases of tuberculosis, just as in other stressful situations. In the material studied, which has been carefully defined as to age and sex distribution, type and activity of disease, etc., the degree of
adrenal damage correlated with elevation of the sedimentation rate and progressive weight loss. Clinical symptoms of hypotension (and probably asthenia, gastrointestinal disturbances and so on, as well) cannot be ascribed to adrenal failure without careful biochemical studies. The indications for adrenal cortical therapy are discussed.

Acknowledgments: We wish to express our deepest appreciation to Miss Annabel Schuman and Mr. Edward L. Richman for their management of the nursing and administrative aspects of this project, and to Miss Kate Pollack, Mr. Robert Scism and Mr. Sidney Stern for valuable technical assistance.

RESUMEN

Solo durante las fases agudas y/o febriles de la tuberculosis la corteza suprarrenal muestra evidencias bioquímicas de daño, tal como ocurre en otras situaciones de esfuerzo. En el material estudiado que ha sido cuidadosamente definido en lo referente a edad y sexo, tipo de la enfermedad y actividad de ella, etc., el grado de correlación del daño suprarrenal estuvo de acuerdo con la sedimentación globular y con la pérdida de peso. Síntomas clínicos de hipotensión (así como astenia, trastornos gastrointestinal, etc.) no pueden ser atribuidos a falla suprarrenal a menos que se hagan estudios bioquímicos cuidadosos. Las indicaciones para el tratamiento suprarrenal se discuten.

RESUME

Il est démontré par les examens biochimiques que la cortico-surrénale est atteinte exclusivement pendant la période aigue ou fébrile de la tuberculose. Elle se comporte exactement comme dans les autres affections graves. Dans les cas étudiés, qui ont été parfaitement précisés au point de vue de leur âge, de leur sexe, du type et de l'activité de l'affection, le degré de l'atteinte de la corticale est parallèle à l'élévation de la vitesse de sédimentation et à la chute progressive de poids. Les symptômes d'hypotension (et probablement aussi bien l'asthénie, les troubles gastro-intestinaux) ne peuvent être attribués à une insuffisance cortico-surrénale sans que soient pratiquées des études biochimiques attentives. Les auteurs discutent les indications du traitement par les extraits cortico-surrénaux.

REFERENCES


