Meticorten as Adjuvant Therapy
in Chronic Pulmonary Tuberculosis with Emphysema

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Introduction

The action of prednisone on a group of active pulmonary tuberculosis patients was studied. Some unexpected effects were noted with Prednisone used as an adjuvant drug in the chemotherapy of chronic, pulmonary Tuberculosis. The effect of steroids in tuberculosis has been subjected to a great deal of experimentation and clinical study for the past several years. Controversy still rages as to its actual therapeutic value. The wide disagreement among qualified clinical workers is not surprising, when one considers the effect of steroids on host parasite relationships, the hormonal balance of the organisms, and more specifically, the action on connective tissue itself. Numerous previous studies have been primarily related to the effect of steroids on other forms of tuberculosis; meningeal and miliary tuberculosis and effusions.

This study was initiated to determine the therapeutic value of prednisone with anti-microbial drugs on patients with chronic active, pulmonary tuberculosis with emphysema.

Materials—Methods

Forty-four patients with chronic pulmonary tuberculosis were selected from the wards of Metropolitan Hospital. All had received at least two years of chemotherapy with no clinical or x-ray improvement. These were so-called "good chronics" and not terminal, as has been described in previous literature on this subject. Bacillary susceptibility was pre-determined in all cases. They were then equally divided into prednisone and control groups.

Background Factors*

The age of the patients varied from 24 to 76 years with an average of 50. Forty-two patients were men and two were women. Race distribution presented 19 Whites, seventeen Negroes, seven Puerto Ricans, and one Chinese.

Thirty-four had far advanced pulmonary tuberculosis and 10 presented moderately advanced disease. Tubercle bacilli were present in all but three. All patients had clinical evidence of pulmonary emphysema.

Regimen

(1) Each patient was placed on a group of anti-tuberculosis drugs as determined by sensitivity studies. Drugs used were streptomycin, INH, aminosalicycic acid, cycloserine and viomycin. Twenty-two received, in addition, 20 milligrams of prednisone daily, in four divided doses.

*See Table I.
(2) X-Ray films done prior to therapy, then bi-weekly for two months, and monthly thereafter. Tomograms were done as indicated.

(3) Complete hematological, urine and liver function tests were performed bi-weekly. Similarly, blood sugar, urea nitrogen, serum potassium, sodium and chlorides were determined.

(4) Ventilatory function studies, including maximum breathing capacity and timed vital capacity were done monthly.

(5) Serial electrocardiograms and weekly body weight and blood pressure were recorded.

**Therapeutic Results**

The primary phase of this study was to determine whether prednisone produced any extension of the disease in these patients and to weigh these results against the hazards of induced hypercorticism.

(a) *Clinical*

Improvement was noted soon after starting therapy by eight patients. Ten remained unchanged. Four became worse, demonstrating increasing dyspnea, and/or early congestive failure. At the end of therapy, an average increase of 10 pounds in body weight was noted in 13 patients.
TABLE II—BACKGROUND DATA

<table>
<thead>
<tr>
<th></th>
<th>Duration of Treatment</th>
<th>Bacteriology</th>
<th>X-Ray Appearance</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Range (Months)</td>
<td>Mean (Months)</td>
<td>Positive</td>
</tr>
<tr>
<td>Prednisone</td>
<td>22</td>
<td>2-10</td>
<td>5.5</td>
<td>20</td>
</tr>
<tr>
<td>Control</td>
<td>22</td>
<td>5-10</td>
<td>6</td>
<td>21</td>
</tr>
</tbody>
</table>

Nine lost an average of six pounds during the same period. Sixteen of the 20 controls showed no improvement or were worse. Four presented clinical improvement. Ten lost an average of eight pounds, while the other 10 gained an average of two pounds in this same period.

(b) Bacteriology

Twenty prednisone treated patients had tubercle bacilli in their sputa and two were bacilli free. After 24 weeks, 11 patients had bacilli in their sputa. Four did not complete the six month survey. Five had no tubercle bacilli in sputa on direct microscopy. Cultural methods did not reveal tubercle bacilli in two of these patients. Of the controls, at the end of 24 weeks, only two were bacilli free; the remainder were unchanged.

(c) X-Ray Changes

Fourteen patients showed no change roentgenographically in six months. Five improved. Of the remaining three, two demonstrated fresh exudative lesions. In one, steroid therapy was discontinued for disciplinary reasons, (unco-operativeness). The x-ray film lesions cleared within four weeks in both patients. Steroid therapy was maintained throughout this phase. The third prednisone treated patient demonstrated a progressively enlarging cavity, which to date, has persisted. There was no case of improve-

FIGURE 3: R. M. Spirographic tracing of vital capacity of the same patient before and after prednisone therapy. After 24 weeks of treatment, a 43 per cent increase in the vital capacity was observed.
TABLE III—RESULTS

<table>
<thead>
<tr>
<th>Clinical Improvement</th>
<th>Weight</th>
<th>Bacteriology</th>
<th>X-Ray Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Improvement</td>
<td>No Improvement</td>
<td>Worse</td>
</tr>
<tr>
<td>Prednisone</td>
<td>18</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

ment noted roentgenographically in the controls, although 19 of 20 cases presented a fairly static x-ray film. There was one patient who developed an extension of disease during this control period.

(d) Ventilatory Function

Ventilatory function studies were done regularly on 15 patients for 24 weeks. Eight of these had an average increase of 25 per cent in vital capacity. Four presented no change as compared to pre-treatment values, while the remaining three showed a slight decrease.

Thirteen of the same 15 patients showed a substantial increase in their maximal breathing capacity. The average improvement observed was 41 per cent. The remaining two showed no change.

Ventilatory function studies done on the control patients presented no change in the vital capacity in 10 patients. Five showed an average increase of 10 per cent in their vital capacity and of these, only three showed a definite increase in their maximal breathing capacity. This average improvement was about 15 per cent.

(e) Hemoptysis

One unexpected and intriguing finding was the complete absence of hemoptysis in the prednisone patients. Ten of them had had a previous

![Before Meticorten vs. After Meticorten](image)

**FIGURE 4**: R. M. Spirographic tracing of maximal breathing capacity of the same patient. An increase of 163 per cent was observed in this patient after the 24 weeks of prednisone therapy.
history of repeated hemoptysis. None bled throughout therapy. One, who discontinued prednisone after 10 weeks, developed hemoptysis one month later. Nine of the 22 controls had varying bouts of hemoptysis. Two of these attacks were severe and exsanguinating, requiring blood replacement.

Toxic Reactions

1. **Carbohydrate Metabolism**
   Two known diabetics of the prednisone group presented much more lability after steroids. One patient manifested persistent hyperglycemia and glycosuria, and in spite of doubling his insulin, prednisone had to be discontinued after two weeks of therapy.
   Three other prednisone treated patients had a relative hyperglycemia, which was not treated and only one of these presented glycosuria which was transient.

2. **Electrolyte Metabolism**
   Sodium and potassium levels remained unchanged. Serum chlorides were elevated in four patients. Urea nitrogen was elevated in two and serum calcium in one.

3. **Liver Function Tests**
   Many of these patients had abnormal studies prior to institution of prednisone. (Many of our patients are chronic alcoholics.) No variation in cephalin flocculation, serum proteins or serum albumin was noted. Five developed progressive rise in serum globulin fraction.

4. **Cardiovascular System**
   Serial electrocardiograms showed no changes as compared with pre-prednisone tracings.

*Figure 5:* H. W. Chest roentgenogram taken at the onset of prednisone therapy showing extensive tuberculous involvement of the upper two thirds of the left lung and infiltration of the right base. An old thoracoplasty can be seen on the right side.—*Figure 6:* H. W. Chest roentgenogram taken nine months after the start of prednisone therapy showed clearing of most of the pathology leaving a cystic area at the left upper lobe.
However, four developed cardiac decompensation, which responded to the usual regimen. No electrolyte changes were observed in these four patients.

5. Formed Elements of Blood

Marked leukocytosis was seen in 18 of the 22 patients. This developed within one week after prednisone therapy and has persisted to date.

Three showed a reduction in lymphocytes. Eighteen of the 22 had eosinophils prior to prednisone. After 24 weeks, only two of these showed the presence of eosinophils.

6. Fat Metabolism

Abnormal deposition of fat in the body characterized by "moon face" and/or "buffalo hump" were noted in two patients.

7. Central Nervous System

No euphoria was noted. Three patients complained of insomnia. This was controlled by giving the last dose of prednisone at 4:00 p.m instead of bedtime. Weakness of the lower extremities was noted by three patients.

Confusion and early schizoid reactions were observed in three. Concurrently, all three were receiving cycloserine and/or INH, either of which may produce similar symptoms.

Discussion of Steroid Therapy in Tuberculosis from the Point of View of Pathologic Physiology

Chemotherapy in recent years, has revolutionized the treatment of tuberculosis, but in the light of present knowledge and experience, chemotherapy certainly is not the answer for the eradication of the disease. Many factors are against it. The most important of them being the foci of caseous necrosis which alter the morphology of the bacilli and the fact that resting forms of bacilli escape the action of all antibiotics in use today. Clinical detection of the disease and its treatment thereof, before caseating occurs, is an unattainable ideal.

Thus, attacking this problem from a different point of view, seems meaningful. The anatomical and structural changes that can be produced by steroid therapy can so alter the conditions of bacterial nutrition and respiration as to stimulate the metabolic activity of the resting forms. This enhancement of the metabolic activity might stimulate these resting forms to multiply; thus making them amenable to antibiotics. A reduction in the number of resting forms in caseous lesions will in its turn, reduce the number of relapses.

Silver impregnation methods have demonstrated the presence of a fine network of reticulin fibers within all caseous lesions. These probably are the precursors of collagen fibers and aid in fibroblastic proliferation. The action of cortico-steroids on connective tissue is well known. It can be summarized as expressed by Albright in 1942, seven years before Hench and Kendall introduced the drug to clinical medicine; that its action is anti-anabolic, rather than catabolic. There is an increase in the urinary excretion of hydroxyproline, a failure of fibroblastic proliferation. But, where fibroblasts are already present, collagen and ground substances are normally laid down and immature connective tissue becomes mature.
The administration of prednisone might be expected to reduce fibroblastic activity in a growing lesion; thus reducing the extent of fibrosis with emphysema, a crippling complication. In a chronic lesion, a metabolic instability of the matrix with a consequent depolymerization might exert an action not unlike that of hyaluronidase. The loosening of the matrix as a result of depolymerization might enhance the diffusability of antibiotics as well as that of immune bodies to where the bacilli are enmeshed within the fibrous walls. In addition, sufficient nutriment and oxygen may reach the site at the same time, thus stimulating the multiplication of the resting bacilli. If one bears this in mind, it is not difficult to conceive why, in the absence of effective antibiotics to act at this stage of bacillary proliferation, steroid therapy can be potentially dangerous.

In a chronic disease such as tuberculosis, the part played by antigen antibody reaction cannot be underestimated. Tuberculin allergy plays a decisive role in the evolution of the tubercle. The ability of the steroids to counteract all types of allergic manifestations at the cellular level is well known. It has been definitely proven in animals that administration of steroids results in a considerable reduction of tuberculin sensitivity. This probably occurs in man also, especially when one considers the action of steroids on lymphocytes and mast cells. Degeneration of lymphoid follicles and actual lysis of lymphocytes occur under steroid therapy. This might partially account for the rise in serum protein, especially the globulin fraction. The theory that lysis of lymphocytes releases a flood of antibodies that are contained in them, has been discounted, but a certain rise in the titre of circulating antibodies does take place as evidenced by the fact that serial per-cutaneous tests with PPD have shown a decreasing amount of reaction.

The presence of lymphocytes in great abundance at the site of chronic inflammation has given rise to a great deal of speculation. Their appearance at the same time as the development of hypersensitivity cannot be discounted as mere coincidence. Their exact function is still unknown but many workers have claimed that they are capable of transforming themselves into fibroblasts. If that is so, the advantage of reducing the number of lymphocytes becomes apparent at once. Mast cells contain a large proportion of pre-formed histamine and heparin and these cells, under steroid therapy, appear to lose their granules and degenerate. This decrease in heparin level in the circulating blood may be reason for the lowering of the coagulation time. This may explain the absence of hemoptysis in our group of patients.

Recently Handley report similar findings in a small series noting the absence of hemoptysis in prednisone treated tuberculous patients.

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SUMMARY

A group of 22 patients with chronic, active, pulmonary tuberculosis with emphysema was treated with anti-tuberculosis drugs and prednisone for an eight to 12 month period. Twenty-two controls were followed simultaneously. These were not terminal but so-called "good chronics." Complete studies were done prior, during and after therapy. Severely untoward effects were noted, primarily diabetes in three patients
and cardiac decompensation in four others. No significant roentgen deterioration was observed. Ventilatory function studies were moderately to markedly improved. One unexpected and intriguing finding was the complete absence of hemoptysis in the prednisone treated group of which 10 had history of repeated hemoptysis.

RESUMEN

Se trataron 22 enfermos de tuberculosis pulmonar crónica activa con enfisema, mediante las drogas antituberculosas y Prednisona por un término de 8 a doce meses. Se observaron simultáneamente 22 testigos. Estos no eran casos terminales sino de los llamados "buenos crónicos." Se hicieron estudios completos antes, durante y después del tratamiento. Varias efectos dañosos se observaron consistentes en diabetes en tres enfermos y descompensación cardíaca en otros cuatro. No hubo deterioro visible a los rayos X. La función ventilatoria mejoró moderada o marcadamente. Un hallazgo inesperado y que causó perplejidad fue la ausencia completa de hemoptisis en los tratados con prednisona, diez de los cuales tenían antecedentes de repetidas hemoptisis.

RESUME

Un groupe de 22 malades atteints de tuberculose pulmonaire chronique, active, avec emphysème, fut traité par les médications antituberculeuses et la "Prednisono" pendant une période de 8 à 12 mois. 22 malades témoins furent suivis en même temps. Ceux-ci n'étaient pas des malades stabilisés, mais de sol-dissant "bons chroniques." Des études furent effectués pendant et après le traitement. Des effets indésirables furent d'abord notés chez trois malades qui eurent du diabète, et chez quatre autres chez lesquels on constata une décompensation cardiaque. Aucune perturbation radiologique importante ne fut observée. Des études de la fonction respiratoire furent effectuées d'une façon modérée ou nette. Une constatation inattendue et intrigante fut l'absence complète d'hémoptysie dans le groupe traité à la Prednisono, dans lequel 10 malades avaient des antécédents d'hémoptysies répétées.

ZUSAMMENFASSUNG


REFERENCES