The Effects of Steroid Therapy on Pulmonary Tuberculosis*

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The exact status of steroid therapy in the treatment of pulmonary tuberculosis is far from clear. In the beginning, active and inactive tuberculosis were considered contraindications of adrenal steroid use.1,4 In a second stage, treatment with them was admitted for non-tuberculous conditions in the presence of active tuberculosis always under antimicrobial coverage.5 We reached, at last, the present phase, where the hypophyseal-adrenal hormones have a definite place in the treatment of certain forms or localisations of tuberculosis, leading to extremely encouraging results. Such are the instances of tuberculous meningitis, miliary, pleural, peritoneal and pericardial forms.1,2,4,5,6 We will discuss further the effects of hormonal therapy on pleural effusion.

The status of steroid therapy in tuberculosis is still subject to discussion and thorough investigation. Although its responsibility in the enhancement of a preexistent tuberculous process is well established,5,6 it is also known that this detrimental effect may be overcome when used in conjunction with appropriate antimicrobial therapy.5,6 Such concurrent therapy, as a matter of fact, seems to be a definite approach whenever pulmonary tuberculosis is on adrenal hormones treatment. It must be borne in mind, however, that such combination only will be successful when tubercle bacilli reveal susceptibility towards chemotherapeutic agents. We have been able to demonstrate how tuberculostatic drugs fail to avoid the aggravating hormonal effect when tubercle bacilli show any degree of drug-resistance.

It has been an ultimate goal of therapeutics to use the favorable effects of hypophyseal-adrenal hormones in the treatment of pulmonary tuberculosis. The anti-stress effect, anti-allergic activity and the detoxifying effect in highly evolutive forms, besides their anti-phlogistic capacity and possible potentiation of antimicrobial drugs are some of the major advantages of these hormonal agents which make them so useful in the treatment of pulmonary tuberculosis.

In the present stage of experimental survey, it seems important to report our results in a series of 24 patients of the Institute of Phthisiology and Pneumology of the University of Brazil (Director — Prof. A. Ibiapina). The series include 13 cases reported in a previous paper.1 A greater number of cases was subjected to treatment, but some were excluded from this study as they did not fulfill the conditions required.

Material and Methods

The clinical material consists of 24 women hospitalized in the ward Affonso Penna, Jr. (Institute of Phthisiology and Pneumology of the U.B.). These are cases of active pulmonary tuberculosis confirmed by

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clinical, roentgenographic and bacteriological trials (five were found to have sputum negative for acid-fast bacilli at the term of combined therapy with prednisone, although the sputum had been positive prior to treatment).

a — Extent of disease:
  Moderately advanced ........................................... 4
  Far advanced ..................................................... 20

b — Bacteriological findings:
  Sputum positive .................................................. 19
  Sputum negative .................................................. 5

c — Tests for susceptibility to antimicrobial agents:
  Resistant (+) ...................................................... 7
  Susceptible ....................................................... 12
  Negative .......................................................... 5

(+) — Resistance level was assessed: 0.2 to INH, 2 to SM and 0.5 to PAS.

d — Clinical and miscellaneous tests:
  Roentgenographic tests and tomography, monthly.
  Sputum studies with culture and drug resistance tests, monthly.
  Determination of glycemias and potassium and sodium levels, monthly.
  Urine analysis, monthly.
  Pulse, temperature, blood pressure and weight daily.
  Routine diet.

e — All patients continued on associated treatment to which they were eventually submitted prior to present therapeutic procedures.

f — Therapeutic schedule was as follows: Prednisone 15 mg. daily during the first month, 10 mg. during the second and 5 mg. during the third month.

Antimicrobial coverage was performed with streptomycin at dosage of 1 g. daily and isoniazid, 10 mg. per kg. of body weight. (+)

  g — Indications for treatment were the following:

  1 — Drug intolerance with hypersensitivity reactions: 4 cases

  In all these cases, the administration of the drugs usually prescribed (INH, SM or PAS) caused severe eczematoid rash or urticaria which subsided when drugs were discontinued and recurred with a new course. This fact, no doubt, represents a significant impediment to adequate therapeutic measures.

  2 — Inefficacy of long-term therapy with the purpose of potentiation: 9 cases

  These are representative cases of far advanced tuberculosis on long-term therapy that should be labelled as failures as they still displayed active disease needing treatment.

  3 — Acute pulmonary disease: 8 cases

  This group consist of the most important instances including five cases of miliary tuberculosis (one with coexisting meningitis) one case of caseous bronchopneumonia and two acute episodes, highly evolutive, in patients with pre-existing chronic pulmonary tuberculosis.

  4 — Associated conditions: 3 cases

(+ ) The drugs employed in the present studies were: Meticorten, Streptomix and Ditubin kindly supplied by Schering Indústria Química e Farmacêutica S/A.
Two patients with pulmonary tuberculosis had associated asthma and in one, there was pleural effusion coexisting with the tuberculous disease.

With the above indications, an attempt was made to meet the following requirements:

a — In the cases of intolerance: anti-allergic effects.
b — In the cases of inefficacy: possible potentiating effect of prednisone on chemotherapeutic agents.
c — In the cases of acute disease: anti-inflammatory effects.
d — In cases of an associated disease: make use of prednisone when indicated in the treatment of coexisting conditions.

Results

Result will be evaluated by their clinical and roentgenographic aspects. Bacteriologic findings will not be assessed as the period of analysis was much too short to warrant any definite conclusion. The effects upon symptoms and roentgenologic changes are components capable of more accurate appraisal.

Results will be recorded only as:

a — Unchanged
b — Improved: whenever present symptomatic and roentgenographic improvement as a result of resorption of infiltrates and of improvement or closure of cavities.
c — Deterioration

Among the 24 cases placed on combined antimicrobial-steroid therapy eight became worse, 13 improved and three remained in the status prior to medication, as summarized below:

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>8</td>
<td>33.3</td>
</tr>
<tr>
<td>Worse</td>
<td>13</td>
<td>54.1</td>
</tr>
<tr>
<td>Unchanged</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>100.0</td>
</tr>
</tbody>
</table>

We shall discuss separately the distribution of these results in terms of bacterial susceptibility and clinical indications.

I — Worse (8)

As for susceptibility:

- Resistant: 6
- Susceptible: 2

As for indications:

- Intolerance: 2 (out of 4)
- Failure: 6 (out of 9)

II — Improved (13)

As for susceptibility:

- Resistant: 0
- Susceptible: 9
- Negative: 4

As for indications:

- Acute disease: 8 (out of 8)
- Intolerance: 1 (out of 4)
- Failure: 2 (out of 9)
- Association: 2 (out of 3)
III — Unchanged (3)

As for susceptibility:
- Resistant ........................................... 1
- Susceptible ........................................... 1
- Negative ........................................... 1

As for indications:
- Intolerance ........................................... 1 (out of 4)
- Failure ........................................... 1 (out of 9)
- Association ........................................... 1 (out of 3)

In the cases where intolerance to chemotherapy made patients eligible for prednisone program, or whenever associated disease occurred, results herein described refer to drug effects on pulmonary tuberculosis, but not on intolerance or associated disease. Effects of prednisone on hypersensitiveness to antimicrobials were dramatic in four cases without enhancement of the tuberculous process as shown in Case 1. (Figs. 1-4)

In case of concomitant disease (two cases of asthma and one of pleurisy), the effect of prednisone was strikingly marked without detrimental repercussion on tuberculous process. [This is not the opportunity to comment the effects of prednisone in instances of asthma or intolerance, which are already well known.]

We can ascertain from the above results that bacterial susceptibility to chemotherapy had a paramount influence on the outcome of prednisone therapy in pulmonary tuberculosis as shown in the table below:

<table>
<thead>
<tr>
<th>Category</th>
<th>Worse</th>
<th>Improved</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Susceptible</td>
<td>2</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

As for indications, antimicrobial drugs exerted extraordinary beneficial effects in acute instances chiefly in miliary form, where it is possible to observe a genuine resurgence of the patient. Cases 2, 3 and 4 are striking examples.

Distribution of results according to indication was as follows:

Intolerance (4)
- All patients improved as for hypersensitiveness making possible the institution of a safe antimicrobial program.

As for pulmonary tuberculosis:
- Worse ........................................... 2
- Improved ........................................... 1
- Unchanged ........................................... 1

Acute disease (8)
- Improvement ........................................... 8
- Unchanged ........................................... 0
**Associated disease (3)**

All those cases where prednisone was indicated for a coexisting disease improved by the treatment (2 of asthma and one of pleurisy).

As for associated pulmonary tuberculosis:

<table>
<thead>
<tr>
<th></th>
<th>Worse</th>
<th>Improved</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Failure (9)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td></td>
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</table>

No patient exhibited any other change attributable to prednisone.

**Case Reports**

**Case 1:** M. S. L., 21, white, Brazilian, unmarried, servant, was admitted on March 3, 1958 with far advanced pulmonary tuberculosis (Fig. 1) in the second month of pregnancy. Sputum was positive, susceptible to bacteriostatics. She had been taking INH (8 mg. per kg. of body weight) and PAS (12 gm.) daily. Because of drug intolerance evidenced by severe generalized urticarial rash (even when an approach with SM was tried) it was decided to give prednisone, (15 mg. daily) for one month, 10 mg. the second and 5 mg. the third month. With the use of prednisone, she showed perfect tolerance to bacteriostatics without exacerbation of tuberculosis. Three months after combined prednisone-antimicrobial therapy she showed marked improvement (Fig. 2). There was sputum "conversion," the infiltrate resorbed and the cavities showed a significant reduction of diameter.

**Case 2:** F. C. S., 21, white, unmarried, servant. Admission on February 13, 1958 with far advanced pulmonary tuberculosis, miliary form, and coexisting encephalomeningitis (Fig. 3). Sputum was negative on admission although it had previously been positive. The diagnosis of tuberculous meningitis was established by clinical examination and chemical and cytological findings in the spinal fluid, as *M. tuberculosis* was not detectable. The patient had a course of INH, SM and PAS prior to admission.

Examination on entry revealed an acutely ill woman with hyperpyrexia and some mental confusion. She was placed on a therapeutic course of INH (10 mg. daily per kg. of body weight), SM (1 gm. daily) and prednisone (15 mg. daily). It was not used...

**FIGURE 1 (Case 1):** M. S. L., Chest roentgenogram, March 4, 1958. Infiltrative process in superior right lobe and at upper lobe at left where cavitation with fluid level is noticeable.

**FIGURE 2 (Case 1):** M. S. L., Chest roentgenogram, June 13, 1958 after a three months course of combined therapy showing resorption of infiltrate and significant contraction of the cavities.
the intraspinal route. During the first 15 days her condition improved significantly. The neurological picture subsided, with normal values of cerebrospinal fluid. At the end of the first month, prednisone dosage was decreased to 10 mg. daily and at third month to 5 mg. daily, maintained until August. The miliary tuberculous process showed marked regression and a chest roentgenogram taken in June, 1958 showed the miliary picture had almost completely cleared (Figure 4).

Case 3: J. C., 28, white, unmarried, servant, was admitted on March 13, 1958 with far advanced miliary pulmonary tuberculosis (Figure 5). Her general condition was poor. Hyperpyrexia, sputum positive for tubercle bacilli susceptible to antimicrobials. She was started on therapeutic regimen of INH (10 mg. daily per kg. of body weight) SM (1 gm. daily) and prednisone (15 mg. daily). After two months of treatment (Fig. 6) radiography and tomography showed normal pulmonary fields. Clinical recovery was complete.

Case 4: M. C. O., 27, mulatto, Brazilian, unmarried, servant, hospitalized on October 29, 1957, with far advanced pulmonary tuberculosis, bronchopneumonic form (Fig. 7). Her general condition was poor: high fever, sputum positive for acid-fast bacilli susceptible to antimicrobial drugs. She was placed on combined therapy of INH (10 mg. daily per kg. body weight) SM (1 gm. daily) and prednisone (15 mg. daily) the first month, 10 the second and 5 mg. the third month. Two months later she exhibited excellent condition and the x-ray films (Fig. 8) showed marked resorption of parenchymal lesions, only a regressive picture remaining at the right pulmonary bases. Sputum became negative.

Comment

Results substantiate those attained with our first series and supply additional findings corroborating other writers' experience.

There is confirmatory evidence that adrenal hormones may have deleterious effects on pre-existent tuberculosis and that such enhancement of the disease may be overcome or prevented by the concurrent use of specific antimicrobials, provided that the tubercle bacilli are susceptible to these drugs. The greater number of aggravations occurred in carriers of drug-fast bacilli: of eight deteriorated cases, six were found to have such bacilli. In the improved group, none was resistant; nine were susceptible and four were negative at the beginning of prednisone regimen. Similar results are reported by Poppe et al., Rizzo, Warembourg and Gernez-Arieux and co-workers. On the basis of this review, it would appear therefore, that chronic types of pulmonary tuberculosis, already submitted to long-term therapy harboring a bacterial population predominantly drug-resistant, are not eligible for adrenal steroid therapy. It is true, however, that in our series, two patients with chronic disease treated without favorable response, improved by the prednisone although their sputum yielded susceptible tubercle bacilli.

On the other hand, it has been observed that acute forms of pulmonary tuberculosis, chiefly miliary and caseous bronchopneumonia, represent situations where corticoid therapy evidenced most spectacular results. The effect upon symptomatology is remarkable and the patients show rapid improvement.

![Figure 3](image1.png)

**FIGURE 3 (Case 2):** F. C. S., Chest roentgenogram, February 13, 1958 showing diffuse miliary process.

![Figure 4](image2.png)

**FIGURE 4 (Case 2):** F. C. S., Chest roentgenogram, June 6, 1958, four months after the beginning of the treatment, showing almost complete resorption of the miliary process.
It has been argued\(^{15}\) that it is difficult to establish whether favorable outcome of steroid and antimicrobial therapy could not be reached with chemotherapy alone. The consistent beneficial results and their rapid attainment warrant the belief that steroids at least potentiate chemotherapeutic activity. It can be said that such acute forms represent a formal indication for combined steroid-antimicrobial therapy. When intolerance to the tuberculostatic agents was present or there was another disease capable of improvement through prednisone, this drug in both contingencies afforded favorable results. The effects of prednisone upon pulmonary tuberculosis concomitantly depend on the disease features, time of previous treatment and the degree of bacterial susceptibility.

The length of prednisone course was close to three months. When evidence of deterioration was present before this term, the patients were taken off the drug. In miliary forms, the time-schedule was extended to three additional months with a maintenance dosage of 5 mg. daily. Improvement continued after the withdrawal of prednisone. Up to the present date, no relapses occurred in patients who continue under medical supervision.

The small number of cases does not yet permit definitive conclusions; these findings, however, suggest that steroid therapy already belongs to the therapeutical armamentarium of pulmonary tuberculosis, provided it is restricted to selected cases where miliary tuberculosis is an outstanding feature and that there is always concurrent specific antimicrobial coverage.

**FIGURE 5** (Case 3): J.C., Chest roentgenogram, March 17, 1958 showing very fine but diffuse and extensive miliary process.

**FIGURE 6** (Case 3): J.C., Chest roentgenogram, May 22, 1958, two months after she started therapy. Practically normal.

**FIGURE 7** (Case 4): M.C.O., Chest roentgenogram, October 29, 1957 showing extensive bilateral lesions and a great block of condensation at right lower lobes.

**FIGURE 8** (Case 4): M.C.O., Chest roentgenogram, January 30, 1958, three months after the treatment was started, showing marked improvement.
SUMMARY AND CONCLUSIONS

A series of four moderately advanced and 20 far advanced cases of pulmonary were given combined prednisone, streptomycin and isoniazid therapy. Indications were: intolerance to chemotherapeutics (acute pulmonary tuberculosis), inefficacy of long-term chemotherapy and presence of associated disease. Prednisone disclosed its powerful anti-allergic activity making possible resumption of the course of antimicrobial drugs for patients who had developed intolerance to these therapeutic agents. Chronic forms, chiefly those with drug-resistant bacilli, could not be treated with steroids. Instances with drug-fast bacilli frequently showed deterioration. Acute pulmonary tuberculosis such as miliary form and caseous bronchopneumonia vastly benefit by prednisone. In the presence of other diseases, prednisone exerts beneficial effects upon tuberculosis depending on the pathological form, period of previous treatment and the degree of susceptibility of tubercle bacilli. Three months of treatment with prednisone in a dosage of 15 mg daily during the first month, 10 mg daily during the second and 5 mg daily during the third month constitute an adequate regimen. In the acute, extremely severe forms as the miliary form, this may be increased to six months, with a dosage of 5 mg daily during the three additional months. Favorable response lasted even after withdrawal of the drug. With the last named dosage there was no untoward occurrence ascribable to the drug, with the exception of deterioration of tuberculous disease in certain cases.

RESUMEN Y CONCLUSIONES

Se administró la combinación de prednisona, estreptomicina e isoniazida a una serie de cuatro enfermos moderadamente avanzados y 20 muy avanzados de tuberculosis pulmonar.

Las indicaciones fueron por: intolerancia de agentes quimioterápicos, ineficacia de terapia a largo plazo, y presencia de enfermedad concomitante.

La prednisona demostró su poderosa acción antiinflamatoria haciendo posible reanudar el tratamiento con drogas antimicrobianas en enfermos que ya presentaban intolerancia a esas drogas.

Las formas crónicas, especialmente las que tenían drogo-resistencia no se pudieron tratar con esteroides. Los casos con bacilos drogo-resistentes mostraron deterioro. La tuberculosis pulmonar la forma miliar y la bronconeumonia hasta la tuberculosis se beneficiaron grandemente con la prednisona. En presencia de otras enfermedades la prednisona ejerce beneficia influencia sobre la tuberculosis dependiendo de la forma patológica, el periodo de tratamiento previo y el grado de susceptibilidad al bacilo tuberculoso.

Se considera un régimen adecuado el de tres meses proporcionando 15 mg. diarios. En las formas agudas como la miliar extremadamente severa, puede alargarse el término hasta seis meses dando 5 mg. diarios durante los segundos tres meses.

La influencia favorable persistió aún después de que la droga se suspendió. Con la dosificación mencionada al último, no hubo efectos adversos atribuibles a la droga con excepción de un deterioro de la enfermedad tuberculosa en algunos casos.

RESUMÉ

Les auteurs présentent un compte-rendu de ses études avec 24 malades traités par l'association prednisone-streptomycine-isoniazide, dont 4 présentaient une tuberculose modérément avancée et 20 la forme très avancée. Les indications étaient les suivantes: intolerance pour les chimiothérapiques, échec de la chimiothérapie prolongée, formes pulmonaires aiguës et la coexistence d'une autre maladie. La prednisona a démontré sa haute puissance anti-allergique permettant la reinstallation de la médication spécifique antibacillaire dans les malades qui présentaient intolerance à ces agents thérapeutiques. Les formes chroniques, surtout celles avec bacilles résistants à la chimiothérapie ne doivent pas être soumises à la corticothérapie. Dans la série des auteurs les cas résistants ont éprouvé aggravation symptomatique. Les formes aiguës de tuberculosis pulmonaire y compris la forme millaire et la bronchopneumonie caséeuse sont très favorablement influencées par l'administration de la prednisona. Aussi, dans les cas de tuberculose, la présence d'une maladie susceptible être améliorée par l'emploi de la prednisona, justifie l'indication de cet agent. Les répercussions thérapeutiques de la prednisona sur la tuberculose sont dans la dépendance de la variété clinique de la maladie, du traitement préalable e du degré de sensibilité des bacilles tuberculeux. Trois mois de traitement avec la prednisona dans un régime de 15 mg par jour le premier mois, 10 mg dans le second et 5 mg dans le troisième, constituent un programme convenable, selon confirment les résultats des auteurs. Dans les formes aiguës extrêmement graves, comme la forme millaire, cette période peut être augmentée de 3 mois dans les quels on fera l'usage de 5 mg par jour. Les améliorations obtenues se sont constatable après la suppression de la prednisona. Avec cette dose il n'y a pas eu des complications attribuables à la drogue, avec l'exception, dans quelques cas, de l'aggravation de la maladie tuberculeuse.

ZUSAMMENFASSUNG

Die Verfasser berichten über 24 mit der Kombination Prednison-Streptomycin-Isoniazid behandelte Kranke, von denen 4 eine mäßige und 20 eine weit vorgeschrittene Tuberkulose aufwiesen. Die Indikationen für diese Behandlung waren folgende: Uni-

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