Evaluation of Results After the Administration of Drugs in the Presence of Resistant Mycobacterium Tuberculosis*

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Introduction

Current literature is rich in reports on resistance developed by tubercle bacilli to antituberculous drugs in vitro and its possible significance. Efforts are being made in order to correlate resistance in vitro with clinical findings.

Some authors believe that drugs should be discontinued once an absolute resistance is demonstrable (100 mcg./ml.) since thereafter there will be no improvement imputable to them; others taking the opposite view, feel that even in the presence of apparent resistance, it is possible for the patient to harbor strains susceptible of being affected by the continued action of therapeutic agents. This study analyzes the results of the continuation of the drugs in the confirmed presence of resistant bacilli in order to determine:

1. Time of appearance of resistance.
2. Clinical and radiological changes.

A limited experience with Viomycin is also reported.

Material and Methods

Two hundred and seventy seven patients with active pulmonary tuberculosis with positive sputa and/or gastric washings for Mycobacterium tuberculosis admitted to the Chest Service, Gorgas Hospital, from June 1, 1949 through December 1954 have been evaluated.

No attempt was made to classify the disease according to extent or type of lesions, since our only object was to observe changes under the conditions described previously.

Every six weeks, the patients were submitted to periodic examinations or evaluations consisting of: clinical observations (fever, cough, weight, toxicity, etc.); x-ray films of the chest (postero-anterior); three sputa examinations on direct smears and concentration for M. tuberculosis followed, if negative, by three gastric or bronchial washings.

Each specimen was submitted to the following tests:


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2. **Concentration**: Using standard digestive mixture.
3. **Culture**: The culture on Petragrani media was observed for a total of 90 days before discarded as negative.
4. **Sensitivity test**: Two dilutions (10 mcg. and 100 mcg.) of the drug used were done. Seven tubes were inoculated with the growth from the original culture. Two tubes for each drug to be studied and one plain tube with culture media that served as a control. Positive growth in any tube that was confirmed morphologically, by the Ziehl-Nielsen stain gave us the sensitivity for that particular drug. Growth of acid-fast bacilli in a dilution of 100 microgram/ml. was considered absolute resistance to the drug.

**Results**

A total of 277 patients were evaluated according to the following criteria:
1. Those who received one or more drugs
2. Those who developed resistance to one or more of the drugs used.
3. Observation of patients on whom drugs were continued in the presence of resistant bacilli, as to:
   A. Clinical and radiological changes.
   B. Permanent bacteriological conversion.
   C. Toxicity due to the drugs.
   D. Other forms of treatment and changes attributable to them.
   E. Reactivations and deaths.

Three cases received only streptomycin. After 30 to 90 days, with an average of 40 days, they all developed resistant bacilli. On continued administration of the drug, no clinical or radiological improvement was observed and sputa continued positive in all three patients. They received at the same time pneumoperitoneum with no demonstrable benefit.

**TABLE I**

<table>
<thead>
<tr>
<th>resistance</th>
<th>Streptomycin</th>
<th>PAS</th>
<th>SM—PAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 cases</td>
<td>6.7%</td>
<td>3 cases</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

All resistances were permanent.

One hundred and sixty-two patients received the combined and intermittent treatment of streptomycin and para-aminosalicylic acid. Of these, 80 (49.3 per cent) developed resistant bacillus to one or both drugs. Eleven (6.7 per cent) were resistant to streptomycin; three (1.8 per cent) to PAS and 66 (40.8 per cent) to both drugs.

**TABLE II**

<table>
<thead>
<tr>
<th>resistance</th>
<th>Streptomycin</th>
<th>PAS</th>
<th>SM—PAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td>average</td>
<td>days</td>
<td>average</td>
</tr>
<tr>
<td>0—240</td>
<td>130</td>
<td>30—360</td>
<td>260</td>
</tr>
</tbody>
</table>

0 = Natural or spontaneous resistance.

The average time for the development of resistance to streptomycin was 130 days; to PAS was 260 days and for both drugs simultaneously was 133 days.
TABLE III
DRUGS CONTINUED IN 42 CASES

<table>
<thead>
<tr>
<th>Clinical Improvement</th>
<th>Radiological Improvement</th>
<th>Permanent Bacteriological Reversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No. of Cases</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Per Cent</td>
<td>69 31</td>
<td>33.2 66.6</td>
</tr>
</tbody>
</table>

These drugs were given to 42 of the 80 resistant cases, noticing that 29 (69 per cent) showed clinical improvement; 14 (33.2 per cent) radiological improvement and 22 (52.3 per cent) a permanent bacteriological conversion.

TABLE IV
OTHER THERAPY

<table>
<thead>
<tr>
<th>Other Therapy</th>
<th>Cases</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Thoracoplasties</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Segmental Resection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Reactivation: 4
Deaths: 4

Thirty of the 42 cases received pneumoperitoneum; five pneumothorax; three thoracoplasties; one was submitted to segmental resection and in two cases isoniazid was added. The clinical and radiological improvement and bacteriological conversion can be attributed in some cases to the following: two cases to isoniazid; five, to lobectomies; and in one, to pneumonectomy. In this group there were four reactivations and four deaths due to tuberculosis.

TABLE V
TOTAL CASES: 17

<table>
<thead>
<tr>
<th>Resistance to INH</th>
<th>15 (88.2 Per Cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of Permanent Resistance</td>
<td>0-180 Days</td>
</tr>
<tr>
<td></td>
<td>Average: 123 Days</td>
</tr>
</tbody>
</table>

0 = Natural or spontaneous resistance.

Seventeen patients received only isoniazid. Of these, four were initial cases while 13 had already shown resistant bacilli to streptomycin and to PAS. Isoniazid was started on these patients as a last resort because they had chronic, advanced, and predominantly productive lesions. Fifteen (88.2 per cent) developed resistant bacilli to INH in an average of 123 days. Two of these showed resistant bacilli before starting the drug, presenting so called natural or spontaneous resistance.
Of the 15 resistant cases, 13 (86 per cent) showed marked clinical improvement; one (6 per cent) radiological improvement; while three (20 per cent) had permanent bacteriological conversion.

Seven received pneumoperitoneum as additional treatment and only two cases improved. One had lobectomy showing clinical, radiological and bacteriological improvement after surgery.

Forty-nine patients received combined treatment of isoniazid and streptomycin. Nine (18.3 per cent) developed resistant bacilli to either drug. Four (8.1 per cent) were resistant to streptomycin; two (4 per cent) to isoniazid and three (6.1 per cent) to both drugs simultaneously.

One hundred and five days was the average time for the appearance of resistant bacilli to streptomycin; 125 days for isoniazid and 83 days for both drugs at the same time.
The time for development of resistance to each drug was approximately the same.
TABLE XIV

DRUGS CONTINUED IN 14 CASES

<table>
<thead>
<tr>
<th>Clinical Improvement</th>
<th>Radiological Improvement</th>
<th>Bacteriologic Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

| Per Cent             |                          |                        |
| 78                   | 22                       | 50                     |
| 50                   | 50                       | 43                     |
| 57                   |                          |                        |

After continuing the administration of these drugs, only 11 (78 per cent) showed clinical improvement. Seven (50 per cent) had slight or marked radiological improvement and six (43 per cent) permanent bacteriological conversion.

TABLE XV

<table>
<thead>
<tr>
<th>Other Therapy</th>
<th>Cases</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumoperitoneum</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

| Reactivation:     | 0     | Deaths:     | 4     |

Besides the mentioned drugs, three patients received pneumoperitoneum without improvement; two with lobectomies and one with pneumonectomy improved. There was no reactivation in this group, but four deaths; two, due to tuberculosis; one, to an anaphylactic shock due to cocaine during bronchoscopy and the other of tension pneumothorax after lobectomy.

Viomycin*

Viomycin is an antituberculous agent derived from a strain of streptomycin puniceus, discovered by Finlay and collaborators. According to some authors it is effective against streptomycin-sensitive as well as resistant tubercle bacilli.

The original studies completed in animals and human beings indicated that in adequate therapeutic concentrations the drug is toxic. Nevertheless, more recent investigations have revealed that used in lower dosages and employing an intermittent regimen, toxicity does not represent a problem. It has an antituberculous effectivity greater than PAS but less than streptomycin or isoniazid.

On the strength of favorable reports, such as those of Tucker, Amberson, et al, and those of the Tenth and Eleventh Veteran Transaction on the Chemotherapy of Tuberculosis, 10 patients were started on treatment with this drug, in May of 1953. These patients were suffering from pulmonary tuberculosis, far advanced, of mixed type and with resistant bacilli to isoniazid, streptomycin, and para-aminocallicilic acid. They were as it can be readily seen "cases in extremis." Two daily doses of 2 grams each of viomycin sulphate intramuscularly, three times a week were administered. After four months on this regimen, no clinical, nor radiological improvement was observed and all the cases continued with positive sputum.

*The Viomycin used in this investigation was donated by Pfizer Corporation.
No apparent toxicity caused by the drug was observed, however all patients complained of marked pain at the site of injection, making it necessary to add novocaine to the solution prior to injection. This observation does not constitute an adequate evaluation of the drug, because the cases, besides being few in number, were all “abused” with the other chemo-antibiotic agents. Even so, results seem to confirm partially the fact that viomycin should not be employed alone, and it should not replace the other antituberculous drugs in use today.

Discussion

It is again confirmed that the appearance of resistances occurs much earlier when the chemo-antibiotic agents are administered alone, than when given combined with one or more other drugs. It is therefore deduced that from a purely medical standpoint, the administration of a single drug in the treatment of tuberculosis is not to be recommended.

Once absolute resistance is demonstrable, there is no clinical, radiological improvement, nor bacteriological conversion attributable to the continuation of drugs. The improvement obtained from the time of appearance of resistances must be considered as due to other factors, such as complete bed rest, temporary interventions, such as artificial compression therapy or permanent ones, as surgery. In some cases of resistance to one drug the improvement is observed upon changing to another chemo-antibiotic agent. It is to be accepted that in cases that have received more than one drug the improvement is due to all drugs until resistance is demonstrated, and from then on to those agents to which the bacilli are still susceptible.

Notwithstanding the above statements, it is admitted that when the drugs were continued in the presence of resistances, and surgical interventions were performed, extensions and disseminations were practically unknown, particularly if compared with the frequency of this type of complication in the pre-antibiotic era. In the administration of isoniazid, it is observed that the clinical improvement continues, and becomes permanent in spite of the presence of resistant bacilli and even if there is no evidence of radiological improvement or bacteriological conversion. With the patient in a better general condition and having increased considerably his organic resistance, it is possible to perform surgical procedures with success and less possibilities of complications.

Other patients, not subjected to surgical interventions become stabilized and chronified and although there is no further progress in their improvement they do not seem to get worse becoming what has been termed “good chronics,” which continue to constitute a serious therapeutic challenge and public health problem that remains without solution.

The dosages and drug administration routines followed were the ones accepted internationally. Maybe with the idea of obtaining greater clinical radiological or bacteriological benefits the dose could have been increased, but it has been proved that by so doing, only greater toxicity without more efficiency is obtained, as we were able to demonstrate in a previous paper.
In this study, only four (1.4 per cent) of the patients presented evidence of toxicity. Two reacted to streptomycin, one of them showing irreversible injury to the eighth nerve, and the other, together with the patients that reacted to isoniazid and PAS, the symptoms disappeared entirely on discontinuation of the drugs.

It is convenient to point out that in some samples of sputa which were positive on direct smear and concentration, no positive culture was obtained. Maybe if other culture media would have been employed together with the Petragnani, which was used in this observation, a higher percentage of positive cultures would have been obtained. This phenomenon could also be explained by the fact that some strains of Mycobacterium tuberculosis lose their vitality and virulence with the appearance of resistance and their growth becomes more difficult. Today, there is under discussion in the literature, the theory that with an increase in resistance there is decrease in the degree of virulence of these organisms to such an extent that some resistant strains lose their capacity to produce progressive disease in highly susceptible animals. We injected 10 guinea pigs with material in which resistant bacilli to all drugs used were demonstrated. When these animals were sacrificed at the end of six weeks, generalized tuberculosis was found in eight while in two, there was no demonstrable disease. These results do not seem to confirm the aforementioned theory.

CONCLUSIONS

1. Two hundred and seventy patients with pulmonary tuberculosis admitted to the Chest Service of Gorgas Hospital from June 1949 through December 1954 were evaluated.

2. Clinical, radiological and bacteriological results were analyzed on those patients that developed resistant bacilli to the antituberculous drugs. 

3. The fact that the development of resistance occurs earlier when these agents are administered alone than when given combined with one or more is again confirmed; therefore, from a purely medical standpoint, the use of one drug alone, including viomycin is not to be recommended.

4. Once resistance appears, there is no clinical, radiological, or bacteriological improvement that can be attributed as due to the chemo-antibiotics agents.

5. Even in the presence of resistant organisms, the chemo-therapeutic agents prevent extensions and disseminations as the result of surgical interventions and they stabilize the lesions on the so called “good chronics.”

6. Toxicity to the drugs was found in four (1.4 per cent) of the cases. Only one had permanent damage.

CONCLUSIONES

1. Se estudiaron doscientos setenta enfermos de tuberculosis pulmonar que se admitieron en el Servicio de Tórax del Hospital Gorgas de Junio de 1949 a Diciembre de 1954.

2. Se analizaron los resultados de estudios clínicos, radiológicos y bacteriológicos de aquellos enfermos que presentaron bacilos resistentes a las drogas antituberculosas.
3. Se confirmó nuevamente el hecho de que la resistencia a las drogas ocurre más temprano cuando se administra una droga sola que cuando se administran combinadas una o más. Por tanto, desde el punto de vista meramente médico, el uso de una sola droga, incluyendo de la Viomicicina, no se recomienda.
4. Una vez que aparece la resistencia, deja de haber mejoría clínica, radiológica o bacteriológica atribuible a los agentes quimioterápicos.
5. Aún en presencia de organismos resistentes, los medicamentos quimioterápicos evitan las extensiones y diseminaciones como resultados de las intervenciones quirúrgicas y estabilizan las lesiones de los llamados “buenos crónicos.”
6. Se encontró toxicidad de las drogas en cuatro casos (1.4 por ciento). Sólo en uno hubo daño permanente.

RESUME
1. L'étude porte sur 270 malades atteints de tuberculose pulmonaire, admis au service des affections thoraciques du Gorgas Hospital entre juin 1949 et décembre 1954.
2. Les auteurs ont noté les résultats cliniques, radiologiques et bactériologiques obtenus chez les malades dont les bacilles étaient résistants aux médications antituberculeuses.
3. Ils confirment de nouveau le fait que le développement de la résistance survient plus précocément lorsque les agents chimio-thérapeutiques sont administrés isolément que lorsqu'ils sont donnés en association de deux ou de plusieurs produits. C'est pourquoi, du strict point de vue médical, l'utilisation d'un produit isolé, y compris la viomycine, ne doit pas être recommandé.
4. Une fois que la résistance est apparue, il n'y a aucune amélioration clinique, radiologique ou bactériologique qui puisse être attribuée aux agents chimio-antibiotiques.
5. Même quand les microbes sont résistants, les agents chimio-thérapeutiques empêchent l'extension et la dissémination après les interventions chirurgicales, et ils stabilisent les lésions des malades que l'on considère comme de "bons chroniques."
6. La toxicité des produits ne se révèle que chez quatre malades (1.4%). Dans un seul cas, elle causa des troubles définitifs.

SCHLUSSFOLGERUNGEN
2. Klinische, röntgenologische und bakteriologische Befunde wurden bei denjenigen Kranken näher untersucht, bei denen sich gegen antituberkulösé Heilmittel resistente Bazillen entwickelt hatten.
3. Die Tatsache wird wiederum bestätigt, dass die Entwicklung einer Resistenz früher einsetzt, falls diese Medikamente allein gegeben werden, als wenn sie mit einem oder mehreren anderen Mitteln kombiniert werden;
es kann daher vom rein ärztlichen Standpunkt die Verwendung einer Substanz allein einschliesslich Viomycin nicht empfohlen werden.

4. Tritt erst einmal Resistenz ein, dann kommt es zu keiner klinischen, röntgenologischen oder bakteriologischen Besserung, die den chemotherapeutischen oder antibiotischen Substanzen zugeschrieben werden kann.

5. Selbst bei Vorliegen resisterter Keime verhindern die chemotherapeutischen Stoffe Ausbreitung und Streuung im Gefolge chirurgischer Eingriffe, und sie stabilisieren die Herde zu den sogenannten chronischen Asylierungs fälle.


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