Selecting the Streptomycin Regimen for Patients with Pulmonary Tuberculosis with Special Reference to the Intermittent Dosage Schedule*

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Streptomycin research in the treatment of patients with pulmonary tuberculosis has passed through a number of stages, and in the course of these investigations, an attempt has been made to answer the following questions:

1) Is streptomycin effective in the treatment of pulmonary tuberculosis?
2) In which phase of tuberculosis is streptomycin most useful?
3) How can we overcome the toxicity factor?
4) How can we reduce the incidence of, or avoid the loss of bacterial sensitivity to streptomycin?
5) Which type of regimen should be used for the various types of cases?

Numerous investigators have substantially answered the first three questions: 1) that streptomycin is effective in the treatment of pulmonary tuberculosis, 2) that it is most effective in the treatment of recent exudative lesions, and 3) that toxicity can almost be eliminated by reduction in the dosage and length of time the drug is administered. In this preliminary report, we are attempting to summarize recent developments pertaining to the remaining two closely associated problems, namely, 4) the reduction of “bacterial resistance” to streptomycin, and 5) the type of streptomycin regimen to use.

The matter of “bacterial resistance” to streptomycin should receive first consideration, because if we render the use of this remarkable chemotherapeutic agent impossible by improper administration, we are wasting one of the most important weapons we possess in the treatment of pulmonary tuberculosis. To properly evaluate this factor, careful bacteriological studies were conducted on various streptomycin regimens at Fitzsimons General Hospital (Chart 1). It was demonstrated by this work that the shorter

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CHART 1

The Incidence of Streptomycin Resistant Tubercle Bacilli Developing During the Treatment of Pulmonary Tuberculosis by Various Dosage Schedules

(a) *Comparison of All Schedules* (SM given intramuscularly)

<table>
<thead>
<tr>
<th>Regimen Number</th>
<th>Daily Dosage Schedules</th>
<th>No. of Cases (Total, 408)</th>
<th>Percentage Resistant*</th>
<th>Days after Beginning of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 gm, 120 days</td>
<td>100</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>1 gm, 120 days</td>
<td>37</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1 gm, 42 days</td>
<td>21</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>1 gm, 28 days</td>
<td>67</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>½ gm, 28 days</td>
<td>*</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>1 gm, 28 days; repeated after 6 weeks; a total of 56 gms in 98 days</td>
<td>35</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

*Definition of bacterial resistance: Cultures with growth comparable to the control (0 mcg/ml) on Herrold's egg-yolk agar containing 10 mcg. of streptomycin per ml.

**Dihydrostreptomycin.

(b) *The Intermittent Schedule* (Regimens 7 and 8 above).

Therapeutic application based upon a consideration of the "resistance factor."

<table>
<thead>
<tr>
<th>Days of Treatment</th>
<th>Per cent Resistant Cases</th>
<th>Treatment:</th>
<th>Use shortest course of intermittent streptomycin treatment which will accomplish results to reduce the number of cases developing &quot;bacterial resistance.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Short courses (30-60 days) of intermittent streptomycin Rx are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions. They may be definitive with rest, or adjunctive for operations, particularly temporary collapse. Other uses include symptomatic treatment and as a therapeutic trial. <strong>NOTE LOW INCIDENCE OF RESISTANT CASES (3.9 per cent at 60 days).</strong></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>8</td>
<td></td>
<td>Long courses (60-120 days) of intermittent streptomycin treatment are better and often required in the treatment of caseous pnemonic tuberculosis (particularly acute lobar or lobar pneumonia). Its greatest usefulness in these cases is as an adjunct to prepare the patient for temporary collapse or surgical procedures. <strong>NOTE PROGRESSIVE INCREASE OF RESISTANCE FROM 70th TO THE 120th DAYS.</strong></td>
</tr>
<tr>
<td>90</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Studies made by the Laboratory Service, Fitzsimons General Hospital, Denver, Colorado, on one hundred (100) cases averaging three (3) cultures weekly per patient.
Planning Definitive Treatment for Pulmonary Tuberculosis:
Based on Clinical Pathological Types.

| CLASSIFICATION OF PULMONARY LESIONS: Based on progress studies—x-ray, laboratory and clinical findings. DESCRIPTIVE TERMS USED IN CLASSIFICATION APPLY TO X-RAY FINDINGS. | MED RX | SURO RX |
|---|---|---|---|
| | SM | Regime | No. | Tem | Per | Exc |
| UNCLASSIFIED | | | | | | |
| New patients—evaluation incomplete | 1 | | | | | |
| NEW SOFT LESIONS | | | | | | |
| Resolving type—good resolution (exudative) | 2 | Short | × | | | |
| Non-resolving—poor resolution (caseous) | 3 | Long | × | | | |
| Mixed (exudative and caseous) | 4 | Long | × | | | |
| OLD HARD LESIONS | | | | | | |
| Cavitary (fibrocaseous cavernous) | 5 | | × | | | |
| Localized (tuberculoma) | 6 | Pro | | | | |
| OLD AND NEW MIXED LESIONS | | | | | | |
| New Component | 7 | S/L | × | | | |
| Old Component | 8 | | × | | | |
| MILIARY TUBERCULOSIS | 9 | Special | | | | |
| APPARENTLY CURED (NTA Standards) | 10 | | | | | |

KEY: SM—Streptomycin regimen: Short course (30-60 days; SM daily or q 3 days); Long course (60-120 days; SM daily or q 3 days); Pro—prophylactic (1 week before, 2 weeks postoperatively); S/L—Short or Long course, as indicated; Special—Special course (Long or Short courses of SM alternating with PAS).

X—Operations often required for definitive treatment.

TEM COL—Temporary collapse (pneumothorax or pneumoperitoneum).

PER COL—Permanent collapse (extra pleural thoracoplasty).

EXC SUR—Excisional surgery (segmental resection, lobectomy and pneumonectomy).

NOTE: A strict rest regime is an essential part of the management.

GENERAL PRINCIPLES OF THERAPY ILLUSTRATED IN THE CHART

(See Classification Number above)

(Great individualization is required in applying treatment and the principles summarized below are meant only to illustrate a broad viewpoint required in planning therapy. The conclusions on streptomycin are tentative, and based on current research).

1) **Unclassified:** The new patient falls in this group on admission to the hospital unless classified by previous clinical studies, serial x-ray examination or strong clinical evidence. As the clinical picture clarifies, the patient usually falls in one of the classifications below for treatment.

2) **New Soft Resolving Lesions—Good Resolution (Exudative):** Rest alone may prove to be definitive treatment. With unfavorable trend, persistent toxemia, positive sputum and/or cavitation, the plan of treatment should include streptomycin (Short regimen, 30-60 days, daily or intermittent schedules) and temporary collapse.

3) **New Soft Non-Resolving Lesions—Poor Resolution (Caseous):** As for
Number 2, except that extensive disease, particularly acute caseous pneumonia, constitutes a medical emergency and a Long course of streptomycin (60-120 days, preferably the intermittent regimen) is indicated. The fibrocoseous cavernous residuals must be treated as old hard lesions (see Numbers 5 and 6) after an appropriate period of stabilization by medical management.

4) Mixed New Soft Resolving and Non-Resolving Lesions: As described for Numbers 2 and 3.

5) Old Cavitary Lesions (Fibrocoseous Cavernous): Permanent collapse is usually required for persistent cavitary lesions, but some cases require excisional surgery when the type and location of the lesion make collapse therapy ineffective. Streptomycin is not advised except for "spreads" after thoracoplasty, or prophylactically for resection.

6) Old Hard Localized Lesions (Tuberculoma): Excisional surgery required. Short prophylactic course of streptomycin usually indicated (one week before, two weeks after operation).

7) Old and New Mixed Lesions—The New Component is usually given first attention. A short or long course of streptomycin, with or without temporary collapse, is prescribed as required.

8) Old and New Mixed Lesions—The Old Component may be controlled by the measures prescribed for the new lesions; if not, treatment must be surgical (see Numbers 5 or 6).

9) Miliary: Special long courses of streptomycin are required. This includes combinations of streptomycin and para-aminosalicyclic acid (PAS) and/or alternating months of therapy with these agents.

10) Apparently Cured (NTA Standards): No treatment. Periodic examinations (X-ray, etc.) are required.

the course of streptomycin and/or the smaller the daily dosage, the lower the incidence of "bacterial resistance." As compared with daily dosage schedules of similar lengths, the interrupted streptomycin schedules (streptomycin injected intramuscularly every third day) resulted in a marked delay in the emergence of resistant strains of tubercle bacilli. Other factors (cavitation, etc.) contribute to the early development of resistant strains of organisms; but when the drug is really needed, consideration of the method of administration is of paramount importance, as this factor lies within our control.

Keeping in mind the resistance studies just reviewed, consideration can now be given to other factors which influence the decision on the type of regimen to be selected for treating patients with pulmonary tuberculosis. First of all, it is of primary importance that certain principles of therapy based upon an evaluation of the pathological types of lesions be carefully reviewed before streptomycin is prescribed. Moreover, the place of this chemotherapeutic agent in the definitive treatment of pulmonary tuberculosis is largely determined by this factor, and a reasonable attempt must be made to classify the pulmonary lesions, if treatment is to be placed on a rational basis (Chart 2). It must be determined whether or not there is a new lesion which will respond to conservative measures of therapy, or an old lesion which will require a radical approach. Every effort must be made to make this and similar decisions if treatment is to be instituted promptly, effectively and safely.
THE PLACE OF SM IN THE PLAN OF TREATMENT
OF PULMONARY TUBERCULOSIS

The indication for the use of Streptomycin (SM) should be clearly defined at the time it is prescribed, and there should be a real need for its use:

I. DEFINITIVE WITH REST TREATMENT (Rx) (Streptomycin expected to give favorable result—arrested disease or apparent cure—without resort to other measures).
   1. New soft lesions (exudative, etc.).
   2. Some few cases of acute tuberculous pneumonia (treated early emergency).
   4. Miliary tuberculosis.
   5. Treatment for recent reactivation or spread in old cases.
   6. Post-hemoptoic spreads.
   7. Tuberculous complications preventing good pulmonary response to rest (bronchial, etc.).
   (Some of above may fail to respond to streptomycin and fall in other groups below).

II. ADJUNCTIVE TO OPERATIVE PROCEDURES OF ALL TYPES:
   1. Preparation for operative procedures (streptomycin used to improve operability).
      a. Lesions potentially suitable for temp coll (predom exudative, recent cavitation, etc., in which SM is used to reduce danger of complications).
         (1) To promote resolution and reduce symptoms (toxemla, sputum, etc.).
         (2) For endobronchial disease (reduce danger of tension cavities, atelectasis and/or blocked drainage).
      b. Acute and chronic caseous pneunonic cavitary tuberculosis.
         (1) If lesions are not extensive, SM may prepare for temporary collapse.
         (2) SM usually used to reduce inflammatory phase prior to permanent coll.
      c. Operable advanced bilateral disease.
         (1) Unilateral permanent collapse (worse side).
            (a) Opposite side controlled by streptomycin.
            (b) Opposite side controlled by streptomycin and temporary collapse.
         (2) Bilateral permanent collapse.
            (a) Both sides prepared by streptomycin.
            (b) Successful conversion.
            (2) Unsuccessful conversion (continue other Rx with or without SM).
               (a) Proceed with surgery if delay courts disaster.
               (b) Continue conventional therapy for better risk.
   2. Prophylaxis (Protection during and after operative procedures).
      a. Prevention of spreads during thoracoplasty for recent disease.
      b. Prevention of empyema and fistula after excisional surgery.
      c. Rx objective altered by unpredicted response to SM; combined uses of SM.
         a. "Definitive Rx" changed to "Adjunctive" if operation becomes necessary.
         b. "Adjunctive Rx" changed to "Definitive" if result warrants (unusual).
         c. "Symptomatic Rx" changed to "Adjunctive"—operation made feasible by unexpected response to streptomycin.
         d. Continuation of streptomycin for prophylaxis after use in "preparation."
   4. Other adjunctive uses.
SELECTING THE STREPTOMYCIN REGIMEN

a. Post-op reactivation or spreads (post-thoracoplasty, etc.).
b. Tuberculous complications preventing good pulmonary re-
   sponse (bronchial, etc.).

III. SYMPTOMATIC TREATMENT (Relief of distressing symptoms; no
    expected effect on the pulmonary lesions—far advanced "panic
    cases." Use cautiously!).
   1. Pulmonary complications.
      a. Severe painful productive cough, dyspnea, etc.
   2. Non-pulmonary complications (SM may be definitive for local
      extrapulmonary lesions).
      a. Painful ulcers of the mouth, larynx and respiratory passages.
      b. Tuberculous enterocolitis with abdominal discomfort.

IV. THERAPEUTIC TRIAL FOR PULMONARY TUBERCULOSIS SUS-
   PECTS (rarely necessary).
   1. Serious cases, e.g., millary suspect lacking bacteriologic proof.
   2. Serious progressive lesion, tuberculosis suspect, no bacteriologic
      proof.

The type of regimen to select in the treatment of pulmonary tuberculosis will be almost as varied as the indications for streptomycin (Chart 3). It is important, therefore, that we clearly indicate the purpose for which streptomycin is being given, and answer certain questions relative to its use. Is it being used for
1) definitive therapy in which there is a reasonable chance that
an apparent cure will result from the use of the drug (combined
with rest therapy) without resorting to operative procedures, 2) as
an adjunct to operative procedures in which streptomycin is pre-
scribed with a definite feeling that it alone (combined with rest)
will not bring about a favorable result, 3) for symptomatic treat-
ment in which the drug is expected to relieve severe, distressing
symptoms, even though the type of pulmonary disease present is
such as to resist treatment, or 4) as a therapeutic test in which
streptomycin seems indicated for urgent reasons (serious cases
such as millary tuberculosis suspects, etc.)? Viewed in this light,
the benefit from streptomycin is measured not so much by its
influence on the pulmonary lesion per se, but rather on its con-
tribution to the successful management of the case. This concept
is reflected in the present trend of streptomycin research, namely,
that of finding the place of streptomycin in the overall plan of
treatment of pulmonary tuberculosis.

It is not within the scope of this brief discussion to supply statis-
tical tables on the clinical and x-ray results attributed to the
various streptomycin regimens. In research studies made on more
than 1500 patients with pulmonary tuberculosis treated with strep-
tomycin at Fitzsimons General Hospital, the results were satis-
factory when the kind and length of the treatment schedule was
appropriate for the type of problem under observation (Charts
2 and 3). Aside from the long dosage schedules of one or two
grams of streptomycin daily for four months, which produced
marked toxic symptoms and resistant organisms in approximately 75 per cent of the cases, there were few serious draw-backs to the regimens (Chart 1) when they were properly prescribed.

Difficulties arose in using the short courses of streptomycin therapy, because the lag in x-ray evidence of improvement (resolution) made it difficult to determine the trend of the disease in less than six to eight weeks. An attempt to overcome this handicap was made by using interrupted short courses, that is, one gram of streptomycin daily for 28 days, followed by a six weeks interval without the drug, and finally, a similar 28 day course of streptomycin for those cases in which it appeared to be indicated clinically, roentgenologically and bacteriologically. A small percentage (8 per cent) of the more active lesions (e.g., acute caseous pneumatic cavitary lesions) relapsed during the six weeks interval without chemotherapy. At the 120 day observation point, the percentage of resistant cases rose to 30 per cent. With little reduction in therapeutic efficiency, therefore, this represented a considerable decrease in the number of resistant cases as compared to the 120 day regimens of continuous daily streptomycin therapy. Furthermore, the toxic reactions to the drug as prescribed in this manner, were practically nil. This same principle of therapy was applied successfully to the intermittent streptomycin schedule, using courses of one month and rest periods of one to two months. The number of cases so treated was too small, however, for statistical analysis; but the outlook for such streptomycin regimens appears to be quite promising.

**SUMMARY**

On the basis of current streptomycin research studies at Fitzsimons General Hospital, certain tentative conclusions regarding the type of streptomycin regimen to select in the treatment of patients with pulmonary tuberculosis seem justified, as follows:

1) We should use the shortest course of streptomycin therapy which will accomplish our purpose, in order that we may reduce the number of cases developing “bacterial resistance.”

2) That short courses (30-60 days) of streptomycin are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions.

3) That long courses (60-120 days) of streptomycin are better and often required in the treatment of patients with caseous pneumonic tuberculosis (particularly severe acute lobar or lobular pneumonia). In these cases where streptomycin may prove to be life saving, the danger of “bacterial resistance” must be disregarded.

4) That long courses of treatment or interrupted short courses
of streptomycin over a long period of time are required for miliary pulmonary tuberculosis with or without meningitis.

5) That the intermittent streptomycin schedule1 using one or two grams of the drug every third day for one to four months, will give clinical and roentgenological results comparable to those obtained by one or two grams daily dosage schedules over similar periods of time, without significant toxic reactions to the drug. In addition, the important factor of delaying the emergence of streptomycin resistant organisms is proved. In our series, no case with "bacterial resistance" developed in 42 days; only 3.9 per cent at 60 days; 4.2 per cent at 70 days; 8 per cent at 80 days; 18 per cent at 90 days; 24 per cent at 100 days; and 33 per cent at 120 days. In other words, this effective method of using the drug can be utilized for a prolonged period with less danger of encountering "bacterial resistance" than from any of the other regimens reported upon in this study. The intermittent regimen can be used for periods of from one to four months or longer, either continuously or in interrupted short courses, depending upon the purpose for which it is prescribed. Of all courses of streptomycin therapy studied at Fitzsimons General Hospital, it appears to have the greatest utility in the management of all forms of pulmonary tuberculosis (exclusive of miliary tuberculosis), whether its purpose be for definitive treatment, as an adjunct to operative procedures, for symptomatic relief, or as a therapeutic trial. (Research studies are now being made with the intermittent streptomycin schedules combined with 12 grams of para-aminosalicylic acid (PAS) orally daily, in the hope of still further delaying the emergence of drug resistant organisms).

CONCLUSION

Selecting the type of streptomycin regimen to use in the treatment of pulmonary tuberculosis must be based upon a careful case evaluation including especially an estimation of the type of pulmonary disease present, and its potentialities to respond to therapy.

Above all else, we must consider chemotherapy as only one of the many therapeutic measures available to us, and every effort must be made to define its exact place in the plan of treatment before this drug is prescribed.

RESUMEN

Basándose en la investigación sobre estreptomicina llevada a cabo en el Hospital Fitzsimons se pueden establecer algunas con-
clusiones preliminares sobre el régimen selectivo para los enfermos de tuberculosis pulmonar:

1) Debemos usar la serie más corta de tratamiento con estreptomicina para lograr nuestro propósito a fin de disminuir el número de casos con “resistencia bacteriana.”

2) Estas series cortas de 30 a 60 días son satisfactorias en la mayoría de los casos con lesiones exudativas recientes.

3) Las series largas de 60 a 120 días son mejores y a menudo requeridas en los enfermos con tuberculosis caseoneumónica (especialmente en la neumonía tuberculosa lobar aguda o lobular aguda). En estos casos cuando la estreptomicina puede ser heroica, la “resistencia bacteriana” puede no tomarse en cuenta.

4) Estas series largas o las cortas intermitentes por largo tiempo pueden ser necesarias en la tuberculosis miliar pulmonar con o sin meningitis.

5) El plan intermitente usando uno o dos gramos de droga cada tercer día por uno a cuatro meses, dará resultados clínicos y roentgenológicos comparables a los resultados obtenidos con el plan de uno a dos gramos diarios por periodos de tiempo similares sin reacciones importantes a la droga.

Además el factor importante para retardar la aparición de la estreptomicina resistencia está demostrado. En nuestras series no se encontró caso con resistencia bacteriana dentro de 42 días. Solo 3 por ciento se encontró a los 60 días; 4 por ciento a los 70 días; 8 por ciento a los 80 días; 18 por ciento a los 90 días; 24 por ciento a los 100 días y 33 por ciento a los 120 días. En otras palabras puede usarse este método efectivo de utilización de la droga por un período prolongado con menos peligro de encontrar “resistencia bacteriana” que en otros regímenes.

El régimen intermitente puede usarse por periodos de uno a cuatro meses o más, ya sea continuamente o en series pequeñas interrumpidas dependiendo del propósito que se tenga. De todos los métodos estudiados en el Hospital Fitzsimons parece que el más efectivo para todas las formas de tuberculosis pulmonar (excluyendo las miliars), es éste ya sea que su objeto sea como tratamiento definitivo o como adjunto del quirúrgico, como paliativo o como ensayo. (Se hacen investigaciones con la combinación de 12 gramos de Acido Para-aminosalicílico, (PAS) oralmente a diario, con la esperanza de demorar la aparición de resistencia del gérmen).

CONCLUSION

La selección del régimen de estreptomicina en tuberculosis pulmonar debe basarse en la cuidadosa valuación del caso especial-
mente del tipo de enfermedad presente y sus potencialidades de respuesta al tratamiento.

Sobre todas las cosas debemos considerar la quimioterapia como uno de los muchos recursos disponibles y todo esfuerzo debe hacerse para definir su lugar exacto en el plan antes de que la droga se prescriba.

REFERENCE