Treatment of Tuberculosis with Promizole: A Clinical Investigation with Matched Controls

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Beginning in 1940, it appeared likely that derivatives of diamino-diphenylisulfones, such as promin offered new hope for the development of specific antibacterial agents against this most common of chronic infectious diseases of the human race. Very quickly chemists instituted a program to develop synthetic drugs of increasing efficacy and decreasing toxicity. The compound named “4, 2'-diaminophenyl-5'-thiazolesulfone” (promizole) was subjected to extensive experimental studies at the Institute of Experimental Medicine, Mayo Foundation and was shown to be a moderately effective drug of low toxicity for animals. Preliminary clinical studies at the Mayo Clinic and Mineral Springs Sanatorium demonstrated that it was a drug of low toxicity to human beings but that its therapeutic efficacy was not demonstrable to a degree adequate to permit recommending the drug. Therefore a controlled clinical study appeared necessary.

In carrying out this study our group had three objectives:

(1) To explore the possibilities of evolving a technic of clinical study to evaluate therapeutic agents in a protein disease such as tuberculosis. (2) To determine if promizole exerts a recognizable antibacterial effect in certain clearly definable types of pulmonary tuberculosis. (3) To make available to the inmates of mental hospitals of Minnesota any therapeutic benefits possible. These unfortunate persons have access to little or no direct therapeutic measures such as collapse treatment and surgery and are often unable to cooperate with bed rest treatment.

This project was instituted in the autumn of 1943. At that time, there was a population of approximately 14,000 inmates in the hospitals for the mentally ill of Minnesota. Of this group there were over 2,000 who showed some evidence of reinfection type tuberculosis by x-ray. More than 1350 films extending through

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The Promizole used in this study was furnished through the courtesy of Parke, Davis and Company, Detroit, Michigan.
several years of observation were available on patients in nine mental hospitals with facilities to cooperate in the study.

Patients were selected for inclusion in this study on the basis of x-ray findings primarily. All patients whose disease had tended to improve spontaneously were excluded and those patients whose disease was of chronic nature were excluded. We felt it necessary to prove by serial films that the disease process was unstable and progressive and that there was a substantial component of exudative bronchopneumonic tuberculosis of apparently reversible type before a patient could be included in this investigation. After a patient had been selected for this study it was then necessary to pair him with another patient of about the same age whose disease was of similar quality, extent and distribution and to secure unanimous agreement of the investigators that the outlook of each one of the pair was apparently the same. Needless to say, many highly interesting and otherwise suitable cases were excluded because it was not possible to find a comparable patient to pair with the candidate for treatment. When a pair of patients had thus been matched to the approval of the group, a coin was tossed to determine which of the two patients would receive treatment with promizole and which would be given a placebo treatment consisting of Brewer's yeast tablets.

Adequate clinical records were maintained and films on each patient taken at monthly intervals. A number of patients selected for treatment were excluded due to their inability to cooperate because of their psychiatric condition. Oral medication was often refused. Others were excluded because of toxic reactions which did not permit treatment in adequate dosage for sufficiently long periods of time.

Evaluation of Results:

Results were evaluated on the basis of roentgenographic improvement alone. Films were reviewed without the observer having knowledge as to whether the patients belonged in the treated or in the control group. Because of the type of disease in the cases selected the progression was usually so obvious and death so frequently occurred during the period of study that no particular difficulty was encountered in evaluation.

Results Obtained:

The following table shows the status of the project when it was concluded in December 1944. It will be noted that only 24 pairs (48 patients) finally qualified for inclusion in this table. Reference to the last column will show that two-thirds of all patients were either dead or worse by that time and that only 15 per cent
had shown improvement, which was usually of only slight degree. It will also be noted that there is little detectable difference between patients in the treated series and those in the control series.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients Treated</th>
<th>Total Patients</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died early (within 30 days)</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Died later</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>66</td>
</tr>
<tr>
<td>Worse</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>3</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL PATIENTS</strong></td>
<td><strong>24</strong></td>
<td><strong>24</strong></td>
<td><strong>48</strong></td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY**

Evidence developed by his study indicated that the severe progressive, potentially fatal type of bronchopneumonic tuberculosis selected for treatment with promizole did not respond to such medication given under the conditions of this experiment.

It is quite possible that the handicaps imposed were too severe to be overcome. It is also possible that patients with associated mental disease are less likely to respond favorably to therapy than individuals with normal mentality.

Subsequent experience with streptomycin has demonstrated to the satisfaction of this group of investigators that a large percentage of the patients selected for this study would have made at least temporary improvement with streptomycin therapy had this drug been available at that time.