Chloramphenicol* in the Control of Bronchopulmonary Suppuration*

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In chronic broncho-pulmonary suppuration purulent sputum, the result of bronchitis or pneumonitis, is a common presenting complaint. It may be a complication of chronic pulmonary disease, such as fibrosis and emphysema. Following bacteriologic and clinical arrest, it may be the basis for continued symptoms in tuberculosis, especially arising distal to broncho-stenoses. Finally, purulent sputum is seen in bronchiectasis, which despite advances in surgical technic continues to be a medical problem.

In a bronchographic survey of 383 patients at the Los Angeles County Hospital 161 proved to have bronchiectasis. Of these, 64 (39 per cent) proved to be bilateral and therefore unsuited for surgery unless extensive bilateral attack was to be considered. Further, 76 (48 per cent) were over 40 years of age. In addition, there must be added to the burden of medical management those patients with bronchiectasis in whom surgery has not eliminated all disease, and in whom residual dilations and bronchial stumps result in continuation of cough and purulent expectoration.

In 1946 one of us reported before this section from the bronchiectasis clinic of the Los Angeles General Hospital the successful control, over periods up to six months, of the purulent sputum and broncho-pulmonary complications of bronchiectasis by the daily administration of 1 gram doses of sulfa drugs. The limited range of antibacterial action, patient intolerance, adverse effects on the bone marrow, and the necessity of detailed laboratory control, limited this procedure's usefulness to 25 per cent of the 32 patients studied.

Since that time, the antibiotics, beginning with penicillin, later streptomycin, alone or in combination, systemically, or by aerosol, have been employed with an enthusiasm proportional to the disappointment experienced when allergic reactions to the drugs, bacterial resistance, or over-growth of non-affected organisms have necessitated discontinuance of therapy.

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Without exploring in detail the shortcomings of therapy to date one might summarize as follows the characteristics of the ideal antibiotic for control of chronic broncho-pulmonary suppuration:

1) Safety, without detailed laboratory control.
2) Wide range antibacterial activity.
3) Persistence of effectiveness.
4) Convenience of administration.
5) Economy.

The advent of the so-called wide-spectrum antibiotics, of which chloramphenicol is the first to be synthesized, seemed to satisfy all these criteria except that of economy. This obstacle was made less formidable by an observation made by a patient with residual bronchiectasis who had frequent rises of temperature. It was noted that the 1.0 gram doses he took once or twice weekly not only controlled his fever, but also kept his sputum at a greatly decreased level. The same dosage was finally extended to a total of 62 patients who received the drug in doses of 1 gram two or three times weekly for periods of two to six and one-half months. Observations of the effect of this dosage constitute the basis for this report.

The concept of intermittent antibiotic therapy is not without precedent. In 1948 Parker and Luse observed that following a short exposure of a culture of staphylococci to penicillin a variable period of no growth (lag period) occurs. During this period the damaged (if not destroyed) organisms fail to multiply and become susceptible to the continuing action of the host. It is this period of host action (and ineffective penicillin level) that allows for the discontinuous method of administration of penicillin. Interrupted dosage with penicillin has been employed in a variety of infections. Recent experiences with intermittent streptomycin therapy in pulmonary tuberculosis further suggest the utility of this concept.

A single oral dose of 1 gram of chloramphenicol is absorbed rapidly from the gastro-intestinal tract, producing an effective blood level in one hour (See Table I). This level persists for at least six hours which is as long as we have observed it. The drug also can be detected in traces in the sputum but not in levels that can be considered effective. For the determination on which these statements are based we are indebted to Dr. Eric Stern of the research staff of the Los Angeles Sanatorium.

Early in the study it became quite evident that the facilities at our disposal would not permit sufficient bacteriologic study to correlate clinical changes with factors of native bacterial susceptibility and acquired resistance. Early observations demonstrated we could not predict the clinical response by cultural studies,
since the same organisms were not always present in the same patient. Moreover, it was impossible to determine which organisms were responsible for symptoms. In addition we have had the experience of isolating from a surgical specimen organisms which were never found in the sputum. We, therefore have, in general, contented ourselves with smears and gram stains of the sputum during the periods of observation. These have not been without value, for we can say from these data that no radical change usually takes place in the flora. None of the overgrowth of gram negatives such as is seen in penicillin therapy was observed. It appears more likely that what we have accomplished is a depression of bacterial activity over a wide range without accomplishing disappearance of one group and overgrowth of another. In addition, no evidence of fungus invasion such as is sometimes seen in intensive therapy has been encountered.

The results are summarized as follows (See Table II):

Eleven patients with active or arrested tuberculosis, in eight of whom major bronchial stenosis was present received the drug as

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hour: Zero</th>
<th>One</th>
<th>Two</th>
<th>Four</th>
<th>Six</th>
</tr>
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<tbody>
<tr>
<td>C.M.</td>
<td>0</td>
<td>7</td>
<td>12</td>
<td>11.5</td>
<td>17</td>
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<tr>
<td>L.W.</td>
<td>0</td>
<td>17</td>
<td>34</td>
<td>50</td>
<td>24</td>
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<tr>
<td>I.C.</td>
<td>0</td>
<td>22</td>
<td>19</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>H.C.</td>
<td>0</td>
<td>44</td>
<td>39</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>B.B.</td>
<td>0</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>J.W.</td>
<td>0</td>
<td>65</td>
<td>65</td>
<td>80</td>
<td>60</td>
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</table>

**TABLE II**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
<th>Excellent</th>
<th>Good</th>
<th>Poor</th>
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</thead>
<tbody>
<tr>
<td>Emphysema and Chronic Bronchitis</td>
<td>13</td>
<td>4</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary Tuberculosis with Broncho-stenosis and Bronchiectasis</td>
<td>11</td>
<td>6</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>Bronchiectasis**</td>
<td>38</td>
<td>25</td>
<td>66</td>
<td>11</td>
</tr>
<tr>
<td>TOTAL</td>
<td>62</td>
<td>35</td>
<td>56</td>
<td>15</td>
</tr>
</tbody>
</table>

*Excellent—75 per cent reduction in sputum. Good—50 per cent reduction in sputum. Poor—0 to 50 per cent reduction in sputum.
**Twelve patients had received initial therapy with other antibiotics.
follows: two for two months, three for four months, and six for six months. Six experienced a 75 per cent or more reduction in sputum output. This effect was sustained throughout the period of treatment. One had 50 per cent reduction in sputum. Four had a poor result or no reduction in sputum or cough. Of these four, two had active pulmonary tuberculosis and most likely tuberculous bronchiectasis.

Of 13 with chronic bronchitis and emphysema, four received the drug for two months, four for four months, and five for six months. Excellent result, or a 75 per cent decrease in sputum occurred in four, a 50 per cent reduction or good result in three. In six the result was poor or unsatisfactory. In three of the six poor results, purulence of the sputum decreased but the total amount of sputum was unchanged.

In 26 cases of bronchiectasis treated intensively with chloramphenicol for one week followed by intermittent therapy for four months in 17, six months in nine, there were excellent results in 14 (75 per cent reduction), good results in 10 (50 per cent reduction) and poor or unsatisfactory results in two.

In 12 bronchiectatics with initial one week treatment by penicillin or penicillin and streptomycin, four received chloramphenicol for four months, and eight for six months. Excellent results were obtained in 11, and a good result in one. There was no failure.

At the conclusion of the study, 14 patients were given placebos, the remainder abruptly discontinued. Essentially all maintained their status for two months with a partial relapse occurring in most patients in the third month.

In the entire group only five who were finally classified as unsatisfactory had a good initial response. Thus clinically, evidence of acquired resistance appears infrequently and for the most part, a good initial response is sustained.

Complications

Gastro-intestinal complications such as nausea and diarrhea were not important side effects nor were skin reactions encountered with the doses employed.

Of a more serious nature, two cases of aplastic anemia were encountered. One of these was fatal, the other is in a chronic improving phase. These are being reported elsewhere. Chloramphenicol as the etiologic agent is strongly implicated although the evidence may not be considered absolutely conclusive.

Discussion

The experiences related here indicate that oral administration of chloramphenicol for both intensive therapy and prolonged
maintenance of bacteriostasis is an effective drug in chronic broncho-pulmonary suppuration. It fulfils the qualifications of easy administration, sustained wide-range effectiveness, and in the doses used, of economy. However, unless the blood reactions can be attributed to other causes, it does not fulfill the qualification of safety without detailed rigid laboratory control. Now that the effectiveness of intermittent dosage has been demonstrated, it remains to be seen if others of the wide spectrum antibiotics will better qualify in this and other requirements.

SUMMARY
1) Oral administration of chloramphenicol is effective in broncho-pulmonary suppuration.
2) Sustained improvement in the volume of purulent sputum is possible on intermittent dosage of the drug.
3) The drug fulfills essentially the requirements of an ideal antibiotic except that of safety without detailed laboratory study.

RESUMEN
1) La administración oral del cloramfenicol es efectiva en los casos de supuración broncópulmonar.
2) Es posible obtener una mejoría sostenida en el volumen del esputo purulento, con dosis espaciadas de la droga.
3) La droga satisface esencialmente los requisitos de un antibiótico ideal, excepto aquellos que se refieren al margen de seguridad sin estudios detallados de laboratorio.

RESUME
1) L'administration par la bouche de chloramphenicol donne de bons résultats dans les suppurations broncho-pulmonaires.
2) Grâce à l'utilisation intermittente de la dose, on peut obtenir une diminution très nette de la quantité de crachats purulents.
3) Ce produit répond à ce qu'on demande à un antibiotique parfait quand on ne peut avoir des résultats de laboratoires précis.

REFERENCES