The two agents most commonly used for producing a pleurodesis are tetracycline and bleomycin. Tetracycline is no longer available due to more stringent requirements on the manufacturing process. The objective of this project was to determine whether bleomycin is an effective sclerosant in an experimental model in rabbits. The following medications were instilled intrapleurally in anesthetized male rabbits: tetracycline, 35 mg/kg, or bleomycin, 1.5 or 3.0 IU/kg diluted to a total volume of 1 ml with bacteriostatic saline solution. Twenty-eight days after the instillation, the animals were killed, and the pleural spaces were assessed grossly for evidence of pleurodesis and microscopically for evidence of fibrosis and inflammation. The intrapleural injection of bleomycin was ineffective in creating pleural fibrosis, either grossly or microscopically. The mean degree of gross pleurodesis in the six rabbits who received tetracycline was 2.7 ± 1.5 (scale 0 to 4), while that in the rabbits who received the highest dose of bleomycin was 0.0 ± 0.0. Based on this study, we recommend that bleomycin not be used as a pleural sclerosant in patients with nonneoplastic pleural disease, eg, those with pneumothorax, congestive heart failure or cirrhosis, and pleural effusion.

(Chest 1993; 104:1582-84)
The degree of microscopic changes in the underlying lungs was minimal in all three groups (Table 3). The degree of fibrosis in the underlying lung was significantly greater (p<0.05) in the tetracycline group than in either of the bleomycin groups on the injected side.

**DISCUSSION**

The present study demonstrates that bleomycin at a dose of 1.5 or 3.0 IU/kg does not produce significant pleurodesis when injected into the pleural spaces of normal rabbits.

Bleomycin is an antineoplastic agent that is thought to exert its antitumor effects by the inhibition of DNA synthesis. Paladine and coworkers first reported that it was effective in the management of malignant pleural effusions in 1976. Since that time, there have been multiple reports concerning the treatment of malignant pleural effusions with this agent with contradictory results. Bitran and coworkers reported that bleomycin was effective in 17 of 20 patients with malignant pleural effusions. However, Hillerdal and associates compared bleomycin, 60 IU, with *Corynebacterium parvum* in a randomized study and concluded that *C. parvum* was better because it was effective in 11 of 15 patients, while bleomycin was only successful in 2 of 15 patients. Ostrowski and coworkers more recently randomized patients to receive *C. parvum* or 60 IU bleomycin. They reported that the response rate with bleomycin (18 of 25, 72 percent) was superior to that with *C. parvum* (9 of 19, 47 percent). Kessinger and Wigton randomized patients to receive 89 IU bleomycin or 500 mg tetracycline and found that the response rates were comparable in the two groups. They concluded that tetracycline was the sclerosing agent of choice because of the lower cost of tetracycline and reports of bleomycin-associated deaths in the literature. More recently, Ruckdeschel and associates concluded that bleomycin is the sclerosant of choice. They reported that recurrence rate at 30 days was 10 of 28 (36 percent) after the intrapleural instillation of 60 IU bleomycin and 18 of 27 (67 percent) after the intrapleural instillation of 1,000 mg tetracycline.

In view of the above studies, there is no doubt that intrapleural bleomycin is an effective treatment for at

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**Table 1 — Macroscopic Examination of the Right Side**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/kg</th>
<th>n</th>
<th>Gross</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>35.0 mg</td>
<td>6</td>
<td>2.7±1.5</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>1.5 IU</td>
<td>7</td>
<td>0.1±0.4†</td>
</tr>
<tr>
<td></td>
<td>3.0 IU</td>
<td>5</td>
<td>0.0±0.0†</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SD.
†p<0.01 when compared to tetracycline.

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**Table 2 — Results With Microscopic Examination of the Pleural Changes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/kg</th>
<th>n</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>35.0 mg</td>
<td>6</td>
<td>3.3±1.2</td>
<td>0.5±0.5</td>
<td>1.8±0.8</td>
<td>1.0±0.0</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>1.5 IU</td>
<td>7</td>
<td>1.6±0.5†</td>
<td>0.7±0.7</td>
<td>1.1±0.4</td>
<td>0.9±0.7</td>
</tr>
<tr>
<td></td>
<td>3.0 IU</td>
<td>5</td>
<td>1.5±0.6†</td>
<td>0.9±0.9</td>
<td>1.2±0.5</td>
<td>1.3±0.5</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD.
†p<0.05 when compared to tetracycline.
‡p<0.01 when compared to tetracycline.
least some patients with malignant pleural effusions. Why didn’t bleomycin produce a pleurodesis in our animal model? Sahn and Good\(^1\) also reported that pleurodesis does not result after intrapleural bleomycin. However, the only dose they studied was 1.5 IU/kg.

There are several possibilities for the discrepancy between the results in the rabbit model and in patients with malignant pleural effusions. First, the dose of bleomycin that we used in our rabbits may have been insufficient. This explanation appears unlikely to us. With a dose of 60 IU, there have been responses to bleomycin in the clinical situation.\(^4,10\) This is equivalent to approximately 1 IU/kg, and we used doses as high as 3 IU/kg in the present study. It should be noted, however, that Yamaguchi and associates\(^11\) recently reported that the intrapleural injection of 10 to 20 IU/kg to hamsters did produce pleural fibrosis at 28 days.

A second possibility is that the pleura of the patient with a malignant pleural effusion is altered such that the bleomycin does produce a pleurodesis. This could easily happen if the clearance of bleomycin from the pleural space was slowed in patients with malignancy. For example, due to decreased lymphatic clearance, the drug might stay in the pleural space longer in the patient with disease. Previous studies have demonstrated that in patients with malignant pleural effusions, the clearance of pleural fluid is diminished.\(^12\)

A third possibility is that the mechanism of action of bleomycin in producing a pleurodesis is directly related to its antimutator action. If intrapleural bleomycin controls the pleural effusion by eliminating the tumor cells, then no pleurodesis need result for it to be effective in patients with malignant pleural effusions. Indeed, when bleomycin is added to cultured mesothelial cells, no growth-factor-like activity for fibroblasts is produced. When tetracycline is added to the same system, a growth-factor-like activity for fibroblasts is released.\(^13\)

Based on the results of the present study, bleomycin cannot be recommended as a sclerosing agent in patients who have nonneoplastic conditions, such as those with pneumothorax, cirrhosis with pleural effusion, congestive heart failure with pleural effusion, etc. The mechanism by which bleomycin produces pleurodesis in patients with malignant pleural effusions remains to be defined.

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**Table 3—Microscopic Examination of the Alveolar Changes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/kg</th>
<th>n</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>35.0 mg</td>
<td>6</td>
<td>1.8±1.2</td>
<td>0.2±0.4</td>
<td>1.2±0.4</td>
<td>0.5±0.6</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>1.5 IU</td>
<td>7</td>
<td>0.4±0.5†</td>
<td>0.3±0.5</td>
<td>1.1±0.4</td>
<td>0.7±0.4</td>
</tr>
<tr>
<td></td>
<td>3.0 IU</td>
<td>5</td>
<td>0.3±0.6†</td>
<td>0.3±0.4</td>
<td>1.0±0.0</td>
<td>0.8±0.4</td>
</tr>
</tbody>
</table>

\(*Values expressed as mean±SD.\

†p<0.05 when compared with tetracycline.

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References