Several options are available for treatment of malignant pleural effusions in patients with non-small-cell lung cancer. Repeat thoracentesis may be appropriate for the patient with limited survival and a slowly recurrent effusion. Pleurodesis with a sclerosing agent administered via a chest tube is the most widely used therapy, though controversy exists as to which drug produces the best results. Pleuroperitoneal shunting remains an option for those patients whose lung is trapped by tumor. Video-assisted thoracoscopy is likely to change the treatment patterns of malignant pleural effusion. Thoracoscopic pleurectomy can be performed with minimal morbidity. Alternatively, sclerosing agents such as talc can be easily and uniformly introduced into the thoracic cavity under thoracoscopic control. Future therapy is likely to entail a diagnostic thoracentesis followed by a definitive thoracoscopic procedure.

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The surgeon's role in the treatment of non-small-cell lung cancer is not limited merely to resection, but extends to management of local complications. Conditions requiring palliative care are often more complicated than simple tumor extirpation, taxing both ingenuity and technology. The most common reason for requesting surgical consultation in patients with nonresectable lung cancer is pleural effusion.

Perhaps because the treatment is palliative, there are a variety of therapeutic options. Consequently, the literature is often voluminous, confusing, and indeterminate. There is, however, sufficient information to allow an effective approach to the treatment of pleural effusion.

Not all pleural effusions associated with lung cancer are neoplastic. Therefore, before embarking on therapy, a firm diagnosis must be established. This can often be difficult, particularly with a malignant effusion. The different techniques that are available include thoracentesis, needle biopsy, thoracoscopic biopsy, and open biopsy. A malignant effusion is usually hemorrhagic in appearance and is an exudate: fluid protein, >3 g/dl; pleural fluid-serum protein ratio, >0.5; lactate dehydrogenase (LDH) levels, >200 IU; and pleural fluid-serum LDH ratio, >0.6.1 Only with cytologic or histologic documentation, however, can malignancy be firmly established.

There are several treatment options for patients with malignant pleural effusions. For a small minority of patients with effusions that recur slowly, repeat thoracentesis is a reasonable approach. Strict attention to sterile conditions should prevent introduction of bacteria and the development of empyema. Though pleurodesis remains the standard therapy, a cohort of patients in whom pleurodesis is unsuccessful or not feasible may be palliated with a pleuroperitoneal shunt. Pleurectomy is rarely indicated.

**LITERATURE REVIEW**

During the past few decades, a number of different agents have been used to achieve pleurodesis. An exhaustive review by Hausheer and Yarbro6 summarizing the extant literature appeared in 1985. Only those studies in which response rates could be calculated were included. Response was defined as no fluid reaccumulation for at least 1 month as determined by chest x-ray and/or no further requirement for thoracentesis within 1 month (Table 1).

### Tetracycline

Six published reports using tetracycline contained sufficient data to allow analysis. Of the 65 total patients, 45 (69 percent) responded to tetracycline. Included in this group were 22 patients randomized to receive tube thoracotomy plus placebo or tube thoracotomy plus tetracycline. A solution of acidified multivitamins with a pH similar to the tetracycline solution was injected into patients randomized to the control group. Response was seen in only 11 percent of the control group compared with 70 percent (9 of 13 patients) of the tetracycline group. This provides convincing evidence that it is not merely the pH of the tetracycline that causes pleurolymphymosis.

### Bleomycin

Four studies using bleomycin17-20 in 232 patients were evaluated: 71 percent responded. Interestingly, patients treated with thoracentesis followed by immediate bleomycin instillation appeared to have a lower response rate than those who underwent thoracostomy.11

### Talc

Talc was instilled in a total of 216 patients from eight trials. Overall, 96 percent met the response criteria. The

| Table 1 — Summary of Trials Using Compounds for Pleurodesis |
|----------------------------------|-------------------|------------------|
| **Compound** | **Range of Response, %** | **Total No. Responders/ Patients (%)** |
| Tetracycline | 65-100 | 45/65 (69) |
| Bleomycin | 62-85 | 164/232 (71) |
| Talc | 72-100 | 208/216 (96) |
| Quinacrine | 64-100 | 84/98 (86) |

*Adapted from Hausheer and Yarbro.4

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talc was commonly insufflated either during thoracoscopy under general anesthesia or during a limited thoracotomy.

**Quinacrine**

The antimalarial agent quinacrine was administered to 98 patients enrolled in eight studies.34-37 Though objective responses were excellent, excessive morbidity, including pain, fever, nausea, and mental status changes, rendered this drug unpopular.38

**Randomized Trials**

Hundreds of reports have documented the anecdotal use of sclerosing agents within the pleural cavity. The number of prospective, randomized trials, however, is much more limited (Table 2). Bayly et al39 compared a single dose of tetracycline, 500 mg, with five daily doses of quinacrine. The drugs were administered the day following tube thoracostomy. Chest tubes were clamped for 6 h and removed when drainage was <60 ml/24 h. Control of the pleural effusion was achieved in 66 percent of patients in both groups. However, the patients who received quinacrine had a much higher incidence of pain and fever. The authors, therefore, concluded that tetracycline was the preferred sclerosing agent.

Gupta et al40 published an abstract in the 1980 Proceedings of the American Society of Clinical Oncology comparing bleomycin with tetracycline. (A full manuscript never appeared.) Twelve patients received tetracycline and 13 bleomycin. The response rates in each group approximated 55 percent. Complications were also similar. The authors concluded that bleomycin and tetracycline were equally effective. It is difficult to support this conclusion with such a small number of patients; certainly the power to detect the difference between the two groups was not large.

Both studies by Fentiman et al41,42 were performed solely in patients with breast cancer. Following thoracoscopy, talc was insufflated. A chest tube was left in place for 5 days. Patients who received mustine also underwent thoracoscopy. However, the drug was instilled following surgery. Chest tubes were removed when drainage had ceased, usually within 3 days. In the talc group, 90 percent of the patients responded, while only 56 percent of those in the mustine group achieved control of the effusion.43 In a separate group of patients, talc was instilled in a similar fashion.44 Tetracycline, 500 mg, was administered in the recovery room following thoracoscopy. Again, 92 percent of the patients in the talc group responded, while only 48 percent of those receiving tetracycline had control of pleural effusions.

Kessinger and Wigton45 compared tetracycline, 500 mg, with bleomycin, 99 U, administered through a chest tube without thoracoscopy in 34 patients. Chest tubes were left in place until drainage had slowed to <40 ml/24 h or 7 days had passed. Response was seen in 8 of 16 patients (50 percent) who received bleomycin and 11 of 26 patients (45 percent) who received tetracycline (8 patients had more than one drug or multiple administrations of the same drug). These differences were not statistically significant. There are numerous difficulties with this trial. The most prominent is the small number of patients and the corresponding small statistical power present to determine a difference between the groups. In addition, the method of randomization, which seems to have been literally a coin toss, was questionable.

The randomized prospective trial by Masuno et al46 involved 95 patients with lung cancer only, of whom 76 were evaluable. Approximately one half received doxorubicin, and the other one half received doxorubicin plus the biologic response modifier LC9018, prepared from heat-killed and lyophilized *Lactobacillus casei*. The response rate for the combination therapy was 74 percent, compared with 40 percent for doxorubicin alone. It is difficult to compare this trial with the others for a number of reasons, among them the fact that chest tubes were left in situ for up to 4 weeks. Patients who received the combined therapy also had a substantial incidence of fever, anorexia, chest pain, and nausea with vomiting.

The study by Ruckdeschel et al47 was designed to determine whether bleomycin performed better than tetracycline in the therapy of malignant pleural effusions. It contained the largest number of patients of any randomized trial and had the advantage of being conducted at different locations, avoiding the criticisms inherent in a single-institution trial.

Patients with any pleural effusion were eligible to participate. Recurrence was defined as pleural fluid accumulation greater than baseline. A chest tube was inserted, and when drainage was <100 ml/24 h, either tetracycline, 1 g in 100 ml normal saline solution, or bleomycin, 60 U in 100 ml normal saline solution, was administered via the chest tubes, which were removed several hours later.

Recurrence was assessed at 30- and 90-day intervals. At 30 days, 10 of 28 evaluable patients (36 percent) who received bleomycin had pleural fluid recurrence, while 18 of 27 patients (67 percent) who received tetracycline had pleural fluid recurrence. The difference was statistically significant (p<0.025). Similarly, at 90 days, 11 of 37 patients (30 percent) who received bleomycin had evidence of recurrent fluid, whereas 19 of 36 patients (53 percent) who received tetracycline had pleural fluid recurrence. This was also statistically significant (p<0.05).

The median time to pleural fluid recurrence in patients who received tetracycline was 32 days, while the median time to recurrence for patients who received bleomycin had not been reached. There was no apparent difference in survival between the two groups (p>0.05). The authors

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**Table 2—Comparison of Sclerosing Agents: Randomized Trials**

<table>
<thead>
<tr>
<th>Investigators, yr</th>
<th>Sclerosing Agents</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayly et al, 1978</td>
<td>Tetracycline* vs quinacrine</td>
<td>21</td>
</tr>
<tr>
<td>Gupta et al, 1980</td>
<td>Bleomycin vs tetracycline†</td>
<td>25</td>
</tr>
<tr>
<td>Fentiman et al, 1983</td>
<td>Mustine vs tetracycline</td>
<td>46</td>
</tr>
<tr>
<td>Fentiman et al, 1986</td>
<td>Talc* vs tetracycline</td>
<td>33</td>
</tr>
<tr>
<td>Kessinger and Wigton, 1987</td>
<td>Bleomycin vs tetracycline†</td>
<td>34</td>
</tr>
<tr>
<td>Masuno et al 1991</td>
<td>Doxorubicin vs doxorubicin</td>
<td>76 + BRM††</td>
</tr>
<tr>
<td>Ruckdeschel et al 1991</td>
<td>Bleomycin* vs tetracycline</td>
<td>85</td>
</tr>
</tbody>
</table>

*Treatment judged superior.
††Treatments equally effective.
††BRM = biologic response modifier (LC9018).
concluded that bleomycin was more effective than tetracycline in the treatment of malignant pleural effusion. The relative cost of bleomycin vs tetracycline is often raised as a contraindication to the use of bleomycin. However, if bleomycin prevents even one additional day of hospitalization, the cost is recovered. The results of the study might have assumed greater importance if not for the fact that the manufacture of injectable tetracycline was discontinued.

**Tetracycline Derivatives**

Now that injectable tetracycline is no longer available, attention has turned to using a tetracycline derivative. Minocycline was used in seven patients with a reported 96 percent response rate. The details of drainage and timing of chest tube insertion were not given in the English abstract of this Japanese article.) Administration of doxycycline, 500 mg via the chest tube, was sufficient to control effusion in 11 of 18 patients (61 percent) with cancer. Approximately 50 percent of the patients required multiple instillations of doxycycline before the chest tubes were removed. Another article in the French literature reported 90 percent control of the effusion with a single administration of doxycycline.

**Treatment Failures — Therapeutic Options**

What is the best method of management of patients who are treatment failures? This depends on whether the lung is fully expanded and pleurosis is achievable or whether the lung is trapped in a peel of tumor. If the lung is fully expanded, repeat sclerotherapy with either the same or a different agent is possible. If the lung is trapped by tumor, repeat pleurosis is doomed to failure. These patients may be treated by pleuroperitoneal shunt or by pleurectomy and decortication. Finally, a palliative approach with acceptance of fluid within the pleural space is reasonable.

**Pleurectomy**

In the past, the principal objection to pleurectomy, the most efficacious therapy, was the need for major surgery in patients with a brief life expectancy. However, the recent availability and popularization of video-assisted thoracoscopic surgery may increase the use of this procedure. Video-assisted thoracoscopy will permit visualization of the entire pleural space through small incisions. Furthermore, via video-assisted thoracoscopy, it is possible to perform a pleurectomy and decortication, allowing definitive treatment with minimal morbidity.

**Pleuroperitoneal Shunt**

The pleuroperitoneal shunt was first proposed and used by Weese and Schouten in 1982. There have since been numerous reports of its use in patients with pleural effusions of various etiologies. The largest series is that by Little et al in 1988. Success, measured by prevention of symptoms and long-term patency of the shunt, has been excellent.

The pleuroperitoneal shunt consists of a pumping chamber that can transport 1.5 ml fluid with each compression. There are two one-way valves. One end of the device is inserted into the chest cavity and the other into the abdomen. The pumping chamber is inserted subcutaneously into a pocket developed away from the skin incision site. This procedure can be performed under local anesthesia. It avoids the need for chest tube drainage and allows for a rapid hospital discharge. Though the valves theoretically allow spontaneous drainage if the appropriate pressure differential exists, the majority of investigators have failed to demonstrate spontaneous flow. While most surgeons who use this device have reserved it for patients with trapped lungs, some investigators are sufficiently enthusiastic to recommend it as primary treatment for patients with malignant effusions.
Proposed for Failure Management

The future management of patients with malignant pleural effusions will likely be similar to that illustrated in Figure 1. Thoracentesis will be performed to establish the diagnosis and provide temporary relief of symptoms. If the patient is able to tolerate general anesthesia, then he or she will go to the thoracoscopy suite, where video-assisted thoracoscopy will be performed. Adhesions between the lung and the chest wall will be lysed, and a pleurectomy or decortication will be performed. If these procedures are successful and the lung is fully expanded, a sclerosing agent may be instilled and the chest tube removed shortly thereafter. If the lung does not completely fill the pleural space, either a pleuroperitoneal shunt can be inserted during the same operative procedure or the decision can be made not to pursue further therapy.

If the patient is unable to tolerate general anesthesia, a pleuroperitoneal shunt can be inserted under local anesthesia. Alternatively, a chest tube can be placed in the usual fashion, and if the lung is fully expanded, a sclerosing agent such as bleomycin infused. The chest tube would be removed when drainage was <100 ml/24 h. If, however, the lung remains trapped following chest-tube insertion, either a pleuroperitoneal shunt could be inserted or no further care offered.

Malignant pleural effusion is a common occurrence in the 160,000 patients who develop lung cancer each year. Its appropriate treatment will contribute to ameliorating the symptoms in many patients with disseminated disease.

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