incidence of lung cancer induced by asbestos exposure would be expected to be higher than that based on the data of Blot et al.

5. We have previously reported the histologic types of lung cancer induced by asbestos exposure in our study group: there were 26 cases of adenocarcinoma, 13 cases of squamous cell carcinoma, and one case of small cell carcinoma of peripheral origin. We are currently preparing these data in detail for submission.

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Small-Volume Nebulizers versus Metered-Dose Inhalers

To the Editor:

Several recent articles in Chest have suggested that economy and quality assurance demand switching from small-volume nebulizers (SVNs) to metered-dose inhalers (MDIs). We believe that, when viewed critically, these studies do not support that conclusion.

In the February 1992 issue of Chest, Alvine et al made much about the mechanical unreliability of SVNs. No comparison data were presented regarding the mechanical reliability of MDIs, nor were there data reported about the clinical reliability. We have performed weighing and puff-counting on six each of professional-sample MDIs from four prominent manufacturers. The results are shown in Table 1. Using radioaerosol techniques, we compared the lung deposition of these devices (expressed as a percentage of medication placed in the SVN or as a percentage of medication in five puffs from the MDI) in six trained subjects. Radioaerosol results are shown in Table 2. It is apparent that MDIs are mechanically reliable, but in terms of lung deposition, the SVN reliability is superior. The coefficient of variation for SVN is 20 percent, compared to 45 percent for MDI, presumably because the latter is more difficult to use. Possibly the use of a spacer with MDIs would lessen this difference.

The articles by Bowton et al and Tenholder et al, in the February and March 1992 issues, respectively, purport to show cost savings.

Table 1—Characteristics of MDI Samples*

<table>
<thead>
<tr>
<th>MDI</th>
<th>Weight of Contents, g</th>
<th>No. of Puffs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventolin</td>
<td>8.3 ± 0.4</td>
<td>101 ± 8</td>
</tr>
<tr>
<td>Alupent</td>
<td>8.8 ± 0.3</td>
<td>119 ± 3</td>
</tr>
<tr>
<td>Proventil</td>
<td>8.7 ± 0.2</td>
<td>110 ± 7</td>
</tr>
<tr>
<td>Maxair</td>
<td>8.6 ± 0.2</td>
<td>129 ± 3</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD.

Table 2—Lung Deposition of Aerosol

<table>
<thead>
<tr>
<th>Subject</th>
<th>SVN, %</th>
<th>MDI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>10 ± 2</td>
<td>13 ± 6</td>
</tr>
</tbody>
</table>

Both fail to use equivalent dosing, giving only three or four puffs from the MDI. In addition to the data presented above, there is abundant evidence that the equivalent of one SVN treatment is about ten puffs from an MDI whether studied with radioactive aerosol particles, bronchoprovocation, or relief of bronchospasm.

Since the claimed cost savings are largely in technician time, recalculation using ten puffs at 1-min intervals actually makes supervised MDI therapy relatively expensive. Moreover, the practical realities are ignored. For most patients, technicians really do have to supervise MDI therapy, whereas commonly the SVN is set up and the patient is left on his own. Switching from an SVN to three or four puffs from an MDI is the equivalent of the hospital pharmacy reducing by mandate the prescribed dose of any medication by 60 to 70 percent simply to save money. Few patients or physicians would tolerate such intrusion.

Modern aerosol therapy is actually relatively simple. About 10 percent of aerosol inhaled is deposited in the lungs. For example, albuterol delivered by MDI at 0.09 mg per puff x 10 puffs x 0.1 lung deposition equals a 0.09-mg lung dose and a 0.9-mg total-body dose. In a typical SVN there is a "dead volume" of retained droplets of about 0.8 ml. Albuterol, 2.5 mg in 3-ml volume, produces about 2.2 ml of aerosol, half of which is lost to the environment during exhalation (inspiratory-expiratory ratio = 1:1), producing a 1.1-ml, or 0.9-mg, inhaled total-body dose and a similar 0.09-mg lung dose. The 90 percent of the inhaled dose that is extrapulmonary and may promote toxicity may be lessened by the use of a spacer or baffle to reduce the larger "nonrespirable" particles.

The message is clear that we are probably vastly underdosing the lungs. There is preliminary information that higher doses of aerosol are safe and effective. Our clinical experience supports this, especially if the devices used are configured to maximize pulmonary deposition and minimize pharyngeal deposition.

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Chylous Transport of Amiodarone

To the Editor:

We found interesting the observations of Strange et al.,1 which appeared in the February 1992 issue of Chest. They reported that amiodarone reached significant levels in the pleural fluid of the patient they described. However, it is unlikely that chest tube drainage represented a major clearance mechanism.

The data of Table 1 in their report suggest that average levels of amiodarone in pleural fluid were about 2.2 µg/ml. Thus, the 9 L of chylous pleural effusion drained over 6 days accounts for perhaps 20 mg of amiodarone. Over 6 days the patient would have received 2,400 mg of amiodarone, and even if oral bioavailability was as low as 20 percent,4 480 mg of drug should have entered the systemic circulation. In this patient, after 1 year of treatment, steady-state conditions should have prevailed. Therefore, 480 mg would have been eliminated over a 6-day period, and the amount appearing in pleural fluid would have represented no more than 4 percent of the total amount eliminated.

The conclusion that pleural fluid levels remain constant in the face of declining serum (plasma?) concentrations is based on scant data. Intrasubject variability, bioanalytical complexities, and a lack of information about blood sampling relative to dosage times on days 1 and 6 make it difficult to assess whether the plasma level on day 6 represents a true decline over the period of drainage. We fully recognize the difficulties involved in generating more detailed pharmacokinetic data under pressing clinical circumstances, but a full understanding of this phenomenon does not appear possible without additional information.

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Definitions for Sepsis and Organ Failure

The ACCP/SCCM Consensus Conference Committee Report

To the Editor:

I applaud the members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee on their report on sepsis and organ failure, which appeared in the June 1992 issue of Chest.1 I believe this to be a sentinel document in the critical care literature.

There are two small but, in my opinion, important points in the article that I would like to take issue with. On page 1647, under the definition of "septic shock," the phrase "despite adequate fluid resuscitation" is used without any qualification. Also, there is no mention of the role of technology in the monitoring of and therapy for these conditions.

As the authors indicate, much of the confusion in the literature regarding sepsis and organ failure is due to differences in the definitions used. There are also, however, significant discrepancies among articles in establishing hemodynamic parameters for both diagnostic and therapeutic purposes. Admittedly, there is controversy over the applications of invasive and noninvasive technology in monitoring critically ill patients, particularly those with "sepsis" and "organ failure." Nevertheless, an extensive body of literature exists that addresses cardiovascular parameters in these conditions. Additionally, there is growing evidence that by utilizing specific hemodynamic therapeutic end points, one may be able to significantly enhance outcome in the critically ill.2

I urge the authors to consider the role of monitoring in the definition of these conditions; "adequate fluid resuscitation" just is not an adequate qualifier and will be a likely source of continuing confusion in interpreting studies. Also, the use of monitoring in these conditions may have innovative potential for prevention and therapy that has not been addressed in this report.

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To the Editor:

As we pointed out in the editorial1 that was published concurrently with the Consensus Conference report, until very recently there was little practical consequence to the diverse uses of the various terms sepsis, shock, and organ failure. With the development of potential new treatments, more precise language and improved understanding of that language became critical.

It was the aim of the conference to take a "snapshot in time"—the outcome was meant to provide definitions of sepsis that would "provide maximum flexibility in classifying patients for identification and treatment in both the clinical and research settings."7 It must be borne in mind, however, that these are concepts in evolution. All suggestions are well-meant; such discussion contributes to the evolutionary process. In the future, as new data become available, it may be appropriate to convene a new consensus conference to revise and update these definitions.

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