Pathogenesis of Spontaneous Pneumothorax*
With Special Reference to the Ultrastructure of Emphysematous Bullae

Masaaki Ohata, M.D., F.C.C.P.† and Hiroshi Suzuki, M.D.

We have performed 253 thoracotomies among a total of 334 cases of spontaneous pneumothorax during the past 17 years, subjecting 126 of these surgical cases to histologic examination by light microscope. Recently, we have classified 54 emphysematous bullae as Reid type 1 or 2 and have examined these, as well as giant bullae, by scanning electron microscope. This revealed exterior surface differences among the three types of cysts: type 1 exhibits a marked absence of mesothelial cells, whereas type 2 and giant bullae do not. At the bases of bullae, deteriorated pulmonary parenchyma, exposed to alveolar space, shows reticulated trabecula-like structures. Our study supports the possibility of air leaking through the wall of the bullae into the pleural cavity at a certain level of pressure, thus emphasizing the role of pleural mesothelial cells in the genesis of spontaneous pneumothorax.

The incidence of spontaneous pneumothorax has been shown to have increased in Europe during the decade from 1960 to 1970.1,2 A similar increase has been observed in Japan since 1965, continuing to the present.3 It seems generally accepted that the pathogenesis of spontaneous pneumothorax involves emphysematous bullae which develop just beneath the pulmonary pleura. It remains still debatable, however, in what manner such bullae develop and under what circumstances pneumothorax occurs.

With the intention of elucidating the mechanism of the genesis of pneumothorax and of emphysematous bullae immediately underlying the pulmonary pleura as the cause of spontaneous pneumothorax, histologic studies of bullae removed by thoracotomy in cases of pneumothorax have been made for several years at the thoracic surgical division of Nihon University Hospital. This article discusses mainly the ultrastructure of emphysematous bullae as classified into three different types: Reid type 1 and type 2 and giant bullae not accompanied by pneumothorax.

Materials and Methods

We have treated 334 cases of spontaneous pneumothorax during the 17 years from 1960 through 1977. In 253 of these, we performed thoracotomy and found emphysematous bullae

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Table 1—Classification of Emphysematous Bullae according to Reid*

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<th>Under 40 yr</th>
<th>Over 40 yr</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Reid type 1</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>(18)</td>
<td>(20)</td>
<td>(18)</td>
<td></td>
</tr>
<tr>
<td>Reid type 2</td>
<td>33</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>(73)</td>
<td>(40)</td>
<td>(65)</td>
<td></td>
</tr>
<tr>
<td>Reid type 1 and 2</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>(9)</td>
<td>(7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant bullae</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>(45)</td>
<td>(40)</td>
<td>(10)</td>
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*Percentages in parentheses.
To obviate the sloughing of mesothelial cells as a result of surgical procedures, in each case the bulla was excised in an inflated state after having been blocked off from the lung with forceps. All contact with the surface of the bulla was avoided. The bulla was then immediately washed in physiologic saline solution to remove blood components and then fixed in 2.5 percent glutaldehyde, or in some cases, in 10 percent formaline. In preparation for electron microscopic procedures, a specimen excised from each bulla was dehydrated with a series of alcohol solutions, dried in the critical point dessicator, then adsorbed with gold-palladium by vacuum evaporation, and finally submitted to observation and photography using a scanning electron microscope.

RESULTS

Examination of the emphysematous bullae by light microscope revealed elastofibrosis, scar formation both in the pulmonary pleura and beneath it, and foreign body reaction (Table 2). However, we found bronchiolitis in the specimens of only 50 percent of the cases. In Reid type 1 emphysematous bullae, the predominant change is that which Miller has named the “bleb” formation. As Miller indicates, the bleb forms between the lamina elastica interna and externa of the pulmonary pleura. Under further examination with the electron microscope at low power, the narrow passageway between the Reid type 1 bullae and the lung parenchyma could be seen (Fig 1).

The surface of the pleura around the Reid type 1 bullae was seen to be in a nearly normal state when examined with the electron microscope. Viewed microscopically, the membrane seemed to become thinner in the vicinity of the bulla, and electron microscopic examination of the exterior surface of the bulla itself revealed a sparsity, or in some areas, a total absence of mesothelial cells, with the underlying collagen fibers consequently becoming naked. Small pores or crevices of several microns could be seen.

Figure 2 shows a pore causing air leakage which was observed microscopically during surgery. Elec-

<table>
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<th>Table 2 — Light Microscopic Findings of Resected Specimens (Given in Percent)</th>
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<tr>
<td>Thickness of pleura</td>
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<tr>
<td>Elastofibrosis of underlying of pleura</td>
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<tr>
<td>Dilatation of bronchioli</td>
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<td>Bronchiolitis</td>
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<tr>
<td>Emphysematous change of lung parenchyma</td>
</tr>
<tr>
<td>Thickness of the wall of pulmonary arteriola</td>
</tr>
<tr>
<td>Anthoracosis</td>
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Electron microscopy revealed a complete absence of the mesothelial cells around the pore.

In Reid type 1 bullae, there were no cell materials on the inner surface, where we noticed, instead, a

Figure 2 (left). Pore causing air leakage which was observed microscopically during surgery (original magnification, × 80). (Right), complete sloughing off of mesothelial cells around pore (original magnification, × 1,000).

Figure 3. Inner surface of a Reid type 1 bulla. Wave is noticeable in fiber bundle of the collagen, and between the fiber bundles there is a crevice formation of a few microns (original magnification, × 1,000).
wave in the fiber bundle of the collagen (Fig 3). Between the fiber bundles, we found crevices of a few microns. The wall at the bases of these bullae was flat, composed of an amorphous material, and interspersed with small round or oval pores, varying in size though small in number.

Our examination by light microscope of Reid type 2 bullae confirmed the findings of Miller (who uses the term “bulla” only in this case, distinguishing it from the “bleb formation,” as we noted above). However, we noticed in addition that these bullae were often accompanied by blebs.

Figure 4 shows the ultrastructure of the surface of the pulmonary pleura of a Reid type 2 bulla. The mesothelial cells of the pleura were relatively well preserved and short microvilli were visible. But there still were some areas devoid of the mesothelial cell covering, as in the case of the Reid type 1 bullae. At the base of the Reid type 2 bullae, the deteriorated pulmonary alveoli had been exposed to the space within the bulla, and a reticulated, trabecula-like structure was observed. In some places, the alveoli had retained a relatively normal structure, and the Cohn pores could still be seen.

Six cases of giant bullae, which did not accompany pneumothorax, were examined. The walls of such giant bullae, when observed microscopically during surgery, were seen to be thin and translucent. Further examined by scanning electron microscope, the surface of the giant bullae showed a nearly normal state, with normal sized mesothelial cells and short, thick microvilli.

We found neither sloughing off of mesothelial cells nor crevice formations in the collagen bundles. The collagen fiber bundles which formed the walls of the bullae were thick. As seen in Figure 5, the bases of the giant bullae had deteriorated to a much greater degree than the bases of the Reid type 2 bullae. Many trabecula-like structures were visible in these cases.

**DISCUSSION**

There are many existing theories with regard to the developmental mechanism of emphysematous bullae directly beneath the pulmonary pleura, and these bullae are in turn, commonly held to be the cause of spontaneous pneumothorax. Commonly held opinions include the congenital theory, inflammation of the bronchiole, disturbance of collateral ventilation, etc. However, there is as yet no clearly established theory. Although several histologic studies\(^4\) of emphysematous bullae have been undertaken previously, these have relied exclusively on light microscopy.
Miller,\textsuperscript{4} Reid,\textsuperscript{6} and Lichter and Gwynn,\textsuperscript{7} for example, have reported such light microscopic findings as elastofibrosis within and directly beneath the pulmonary pleura, scar formation, bronchiolitis, and focal emphysema. In our examination by light microscopy, we also observed elastofibrosis in the pulmonary pleura and beneath it in almost 100 percent of the cases, as well as alveolar macrophagocyte and marked anthracosis. However, we found bronchiolitis in the specimens of only about 50 percent of the cases.

In 1973 Masshoff and Höfer\textsuperscript{8} advanced the "Neo-membrane Theory" of the etiology of emphysematous pulmonary bullae, which was based on histologic findings from specimens taken in a number of cases of spontaneous pneumothorax. Masshoff's suggestion that the mesothelial cells in an affected area proliferate to form a "pneumatization chamber" in response to air leakage seemed plausible to us. However, the problem of whether direct communication between the bulla and the lung parenchyma exists or not was not clarified by their findings. Using light microscopic procedures, we ourselves located only one example of a dilated bronchiole opening directly into the bulla. For more detailed examination, we have turned in the present research to observation by scanning electron microscopy, focusing on the exterior and interior surfaces and the base of the emphysematous bulla, as well as the pulmonary parenchyma beneath it, following in general the classification of Reid.\textsuperscript{6} On the exterior surface of the Reid type 1 bullae, we observed a scarcity or absence of the mesothelial cells of the pleura with the underlying collagen fibers consequently becoming naked, and many small pores or crevices of several microns appearing between the bundles.

Masshoff's experimental findings that mesothelial cells of the pulmonary pleura tend to proliferate when exposed to air, suggest at least that the sloughing of mesothelium may not necessarily be the result of pneumothorax. On the interior surface of the bulla, we observed that in many cases, there were no cell materials whatever. The interior surface was lined instead by thick bundles of collagen fiber.

At the base of the Reid type 1 bullae, we found the inner surface to be amorphous with numerous small pores of 10$\mu$ to 20$\mu$ in approximate diameter. The alveolar structure was clearly visible through these pores. In contrast, the mesothelial cells on the exterior surface of Reid type 2 bullae were relatively well preserved. In some places, partial absence of the mesothelial cells was observed, though the microvilli were generally intact. In the Reid type 2 bullae, deteriorated alveolar structures were seen to constitute the base, and it is therefore clear that communication between the bullae and the emphy-
sematous alveolar area exists.

When the base was, in turn, examined under high power magnification, we found that the number of type 2 alveolar epithelial cells in the alveolar septa was greater than normal. (Tueller et al\textsuperscript{10} indicate the same). In several areas of the alveolar wall we also found type 1 alveolar epithelial cells, which have no microvilli.

The exterior surface of the giant bullae, which were not accompanied by spontaneous pneumothorax, were covered with nearly normal mesothelial cells having microvilli, while the interior surface was lined with collagen bundles in the same manner as the Reid type 1 bullae. However, in some places we noticed alveolar epithelial cells, particularly those of type 2. At the base of the bullae, deteriorated trabecular structures were seen along with an increase in the number of type 2 alveolar epithelial cells.

From this examination of the three types of emphysematous bullae summarized above, we have indicated that there are differences in the exterior surface of the three types of emphysematous bullae (Reid types 1 and 2 and the giant bulla), most notably that the Reid type 1 bulla exhibits a marked absence of mesothelial cells, whereas Reid type 2 and the giant bulla do not. In addition, as stated above, considerable differences exist in the basal structures of the three types, although electron microscopic examination of the ultrastructures has made it clear that direct communication between the bulla and the alveolar area immediately beneath it nonetheless exists in each case.

In 1959, Sattler\textsuperscript{11} pointed out that leakage of air into the pleural cavity could occur without rupture of an emphysematous bulla. Our study also supports the possibility of air leaking through the wall of the bulla into the pleural cavity at a certain level of pressure. The difference in the ultrastructure of pleural mesothelial cells observed among the three types of emphysematous bullae cited above suggests that a major role in the pathogenesis of spontaneous pneumothorax may be played by the sloughing of mesothelial cells.

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