EXPERIMENTAL APPROACHES

The Pulmonary Lymph Flow after Irradiation of the Lungs of Dogs*

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The pulmonary lymph flow, measured by our previously published method, is reported in ten dogs after irradiation to anterior mediastinal portals which included the medial one-third of both lungs. In group A (six dogs) the lymph flow of the lung was measured immediately after the course of radiation and in group B (four dogs) a period of about five months elapsed. Our results show that the lymph flow in the lungs of dogs after exposure to radiation is not altered appreciably either immediately after the completion of a course of radiation or after a delay of several months. The implication is that neither the initial radiation nor the later fibrosis significantly interferes with the lymphatic channels. Alterations in the parenchyma of the lung such as patchy edema and severe chronic pneumonitis are not quantitatively reflected in the pulmonary lymph flow.

We have studied the role of the pulmonary lymphatics in experimental acute and chronic pulmonary edema. An improved method has been developed in our laboratory for the collection of lymph from the lungs by cannulation of the right duct. Since the response of the pulmonary lymphatics to radiation is not clear, we applied our method to a study of the effects of irradiation on the pulmonary lymphatics. There is considerable evidence that lymphatic vessels are relatively resistant to radiation, but that histologic damage to the lung consistently occurs particularly in the cells of the alveolar wall and endothelium of the pulmonary capillaries. The purpose of the present experiments was to study the influence of radiation to the lungs on the pulmonary lymph flow immediately after a course of radiation and after a period of approximately five months.

**METHODS**

Healthy mongrel dogs were treated with 4150 to 5025 r (air) to 4 x 10 cm anterior mediastinal portals which included the medial one-third of both lungs. This gave an exposure of 3,400 rads (midline). All courses of treatment were completed in 32 to 49 elapsed days. Treatment factors were 250 KVP, 50 cm TDS, HVL 3.05 mm copper.

The right duct lymph flow was measured with our method which we have used for more than ten years. The right lymph channels are visualized by the endobronchial instillation of 4 ml of Evans blue dye (T-1824) since these must be recognized and preserved in the subsequent dissection of the veins. The right external jugular vein is carefully dissected and the axillary and brachiocephalic veins isolated and ligatures passed around them. The axillary and brachiocephalic
Table 1A—Pulmonary Lymph Flow of Dogs Immediately after Irradiation of Lungs

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Irradiation r/air</th>
<th>Period of irradiation (days)</th>
<th>Right duct lymph flow ml/hr</th>
<th>Interval in days after course of irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.2</td>
<td>M</td>
<td>4800</td>
<td>35</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>13-64</td>
<td>16.8</td>
<td>F</td>
<td>4800</td>
<td>35</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>15.8</td>
<td>M</td>
<td>5025</td>
<td>36</td>
<td>2.9</td>
<td>4</td>
</tr>
<tr>
<td>7-64</td>
<td>11.3</td>
<td>M</td>
<td>4800</td>
<td>46</td>
<td>1.8</td>
<td>4</td>
</tr>
<tr>
<td>16-24</td>
<td>12.7</td>
<td>F</td>
<td>4800</td>
<td>45</td>
<td>5.5</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>12.7</td>
<td>F</td>
<td>4800</td>
<td>46</td>
<td>5.5</td>
<td>6</td>
</tr>
<tr>
<td>8-14</td>
<td>13.8</td>
<td></td>
<td>4838</td>
<td>42</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Av</strong></td>
<td></td>
<td></td>
<td><strong>4838</strong></td>
<td><strong>42</strong></td>
<td><strong>3.5</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

Veins are ligated and the external jugular vein ligated distally and divided proximally to the ligature. A plastic cannula (PE 160) is inserted into the open proximal end of the vein and tied in place. The external jugular vein acts as a collecting chamber for the leash of fine lymphatics which makes up the right duct and which empty into the junctional area of the jugular and brachial veins. The cannula drains all of the right duct lymph (about 3.0 ml/hr, vide infra) and has advantages over the method of collecting pulmonary lymph in which only one of the small right lymph ducts11,12 is cannulated.

The animals were divided into two groups consisting of those studied early and late after a course of irradiation (group A and B). In the first group of six dogs (Table 1A) the right duct lymph flow was measured within a few days (average four) after completion of the exposure to roentgen rays. A one cubic centimeter biopsy of the right lung was removed through a small intercostal incision for microscopic study immediately after the lymph flow was completed and under the same anesthetic (29 mg/kg sodium pentobarbital). Ninety-six to 132 days later, unsuccessful attempts were made to repeat the measurement of the right duct lymph flow through the same cervical approach. A second similar lung biopsy was taken at this time.

In the second group of four animals (Table 1B) the lymph flow was measured 115 to 129 days (average 157) after completion of the exposure to irradiation. The lung was biopsied in only two animals at the time of this delayed lymph flow study since a large number of late biopsies had already been prepared for histologic study.

**RESULTS**

A total of 14 dogs were irradiated over a period of six weeks (32 to 49 days, average 41). There were ten satisfactory experiments (Tables 1A and B). Table 1A illustrates the pulmonary lymph flow (right duct) in six dogs, one to six days after irradiation of the mediastinum and medial thirds of both lungs to a midline exposure of 3,400 rads. The average flow was 3.5 ml/hr (range 1.8–5.6). Table 1B shows the pulmonary lymph flow of a second group of four dogs measured five months after irradiation. In this group, studied an average of 157 days (range 115–229) after the course of irradiation was completed, the average lymph flow was 3.05 ml/hr (range 1.4–4.5). The pulmonary lymph flow in both groups was within the normal range reported from this laboratory12,13 and by others.14

Four other animals were radiated, but excluded from the results. In two of these, the right duct could not be cannulated. A third (No. 21-64) animal became severely ill with a profuse sanguino-
PULMONARY LYMPH FLOW AFTER IRRADIATION OF LUNGS

FIGURE 1—Microphotographs of lung 149 days after irradiation with 4800r over a period of 46 days (dog 20-64). A (upper): This field shows septal thickening, narrowing of some alveolar spaces by hyperplasia of pneumocytes which line the alveoli, exudate in some alveoli which contains lymphocytes, plasma cells and hemorrhage. There is partial collapse of pulmonary tissue and alveolar spaces and in these areas there appear to be proliferation of spindle shaped stromal cells (x 350). B (lower): At higher magnification the arrangement of swollen pneumocytes (probably type II) around the alveolar walls is well seen. The thickened septa, obliteration and collapse of alveoli, filling of some alveoli with proteinaceous material and cellular elements, and hemorrhagic areas are again seen (x 560).

purulent nasal discharge. Radiation was stopped after 4,250 r (air) had been administered over an extended period of 60 days. An elevated pulmonary lymph flow of 6.5 ml/hr was obtained 146 days after radiation was completed. Twenty-six days after the lymph flow study the animal was sacrificed and extensive inflammation and consolidation of the lungs were noted at autopsy. Blue dye was visible in the right lower lobe where it had been instilled 26 days earlier. The fourth experiment excluded from Table 1 was a healthy dog (No. 4-65) in which the right duct lymph flow, measured 180 days after completion of radiation therapy, was unusually high—15.3 ml/hr. This high flow suggested an anomalous connection between the thoracic duct and the right duct.11,12 Since such flows are encountered occasionally in normal dogs, it would probably be incorrect to assume such a high flow was due to the radiation which the animal had received.

One of the limitations encountered in the study of the lymph system is the difficulty in the recannulation of lymphatics for a second study. This is particularly true for the right duct which differs anatomically from the thoracic duct, a larger and often a single trunk. Recannulation of the right duct was not possible in eight dogs in which it was attempted through a second cervical incision. In one of the eight animals, an intercostal approach was used after abandoning the cervical approach and it was possible in this dog (No. 4-65) to cannulate a lymph channel in the right upper mediastinum which lay between the trachea and the superior vena cava11 and which appeared to be part of the right duct complex. This experiment is not included in our results for the reason stated above; however, it is mentioned here since the method may prove to be useful for re-study of the pulmonary lymph flow.

Twenty-two lung biopsies were performed in 12 dogs. They were taken immediately after the course of irradiation was completed and repeated two to four and a half months after radiation in group A and five to seven months after radiation in group B. The biopsies were obtained at variable distances from the hilum of the lung and the pathologic changes varied from none to severe radiation effects. Many biopsies exhibited the changes described as characteristic of radiation pneumonitis,6,7 which include enlargement of pneumocytes, an increase in the number of pneumocytes with thickening of the alveolar septa, alveolar macrophages, septal fibrosis, diffuse exudative pneumonitis, chronic bronchitis, focal hyaline membrane formation, varying degree of organization and fibrosis, obliteration of alveolar spaces with patchy atelectasis and patchy foci of edema (Fig 1). Some of these changes are nonspecific and associated with pulmonary infections which not infrequently occur in laboratory animals; many of the histologic changes are the result of radiation.4

Slight hyperemia of the skin usually appeared following exposure to radiation in the animals. Depilation occurred in one case and a superficial ulceration 3 cm in diameter in another.

DISCUSSION

Our results show that the lymph flow of the lungs of dogs after exposure to radiation is not altered

*We are indebted to Dr. Paul Ortega, Associate Chief of Pathology, Mount Zion Hospital and Medical Center, for the microscopic description of the biopsies.
Flow measured concurrently was 18.5 (range 9.5–18.0). The average right duct flow was 3.14 ml/hr (range 0.7–5.0). The average thoracic duct flow measured concurrently was 18.5 (range 10.4–29.4). All flows were measured for one hour.

Pathologic changes in the lung which follow irradiation in man have been described by Warren et al as outlined previously. Recently Leroy et al defined electronmicroscopic changes in the lungs of dogs during the first weeks after irradiation. In this period changes were noted "in the alveolar epithelium, the septal walls, and, to a lesser extent, the capillary endothelium. . . ." Focal interstitial edema was consistently noted.

Studies of peripheral lymph vessels in dogs have shown no evidence of anatomic disruption after high exposure levels of ionizing irradiation. Other experiments in rats on the function of peripheral lymph vessels and nodes after substantial exposure to radiation showed a breakdown of the barrier function of lymph nodes, but no interference to flow even when the nodes become fibrotic.

It has been suggested that, in contrast to radiation damage, fibrotic residua of inflammation may interfere with the lymphatic drainage of the lungs and accentuate pulmonary edema in areas of lung so damaged.

Hooykass et al reported no significant physiologic abnormalities in lung function in dogs following unilateral pulmonary irradiation up to 6,000 rads studied at four week intervals up to one year. There was no suggestion of an increase in pulmonary vascular resistance. The microscopic findings consisted of mild focal interstitial fibrosis and focal vascular sclerosis. In animals with larger doses of 4,000 to 6,000 rads, focal organized pneumonia was found. A report from the same laboratory gave similar results after irradiation (up to 6,000 rads) at two week intervals for six weeks.

The conclusions of Teates were similar and indicated that there is "a nonspecific reduction in the function in the irradiated lungs (of dogs) which was reflected on all the indices measured," including compliance, inspiratory capacity and diffusing capacity. The proportion of pulmonary blood flow to the irradiated lung decreased. He concluded that "patients usually remain relatively free of symptoms of respiratory insufficiency unless a large volume of lung is irradiated, or there has been a reduction of the normal respiratory reserve of function due to other disease processes."

The effects of radiation on the heart have been noted by Stewart et al who have summarized their study of 25 patients as follows: "Acute pericarditis, often with pericardial effusion and tamponade, chronic pericardial effusion, and chronic constrictive pericarditis sometimes associated with myocardial and/or endocardial fibrosis or fibroelastosis were most commonly seen." The majority of patients developed heart disease after a delay of several months. In our animals, gross changes in the heart or pericardium, such as pericarditis or pericardial effusions, were not observed at autopsy up to 15 months after radiation.

Histologic examination of radiated lungs indicates that the primary effect is on the alveolar wall and capillary endothelium, in both short and long-term observations. Physiologic methods show little or no interference with alveolar capillary exchange of gases following irradiation. The development of an improved method for measurement of the lymph flow of the lungs of dogs made it possible to evaluate this function also.

REFERENCES

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Self-Imposed Termination of Creativity in Two Famous Composers

Gioacchino Rossini (1792-1868) produced some thirty-five operas, ranging from one-act pieces of trivial character to tragedies on a grand scale. Rossini curbed the liberty of the singers to improvise upon what the composer had written for them. Hence arose the appearance of greater floridity in Rossini's vocal writing. He also followed Simon Mayr in giving greater prominence to the orchestra. After settling down in Paris in 1823, Rossini set himself to accommodate his music to Parisian tastes. Based upon Schiller's drama, Guillaume Tell was a typical product of Franco-Italian culture in 1820s. Musically it combined Italianate vocal melody and sharp characterization of opera buffa with solid choral style of French grand opera. It established a model for the grand opera of the succeeding period and its influence appears no less in the early works of Wagner than in those of Meyerbeer and Verdi. Rossini had a meteoric career beginning in Venice at the age of eighteen and ending in Paris in 1829, nearly forty years before he died.—The Kalevala, the Finnish national epic, is the literary source of Sibelius's (1865-1957) four Legends for orchestra (one of which is The Swan of Tuonela), of the symphonic fantasy Pohjola's Daughters and several other works. Direct Finnish patrician associations are carried by the popular Finlandia. Sibelius in his symphonies makes great play with short motives of a few notes, and he is a composer with distinctive fingerprints—among them rushing string passages in contrary motion (some parts moving up while others move down), and falling two-note figures with the first note accented. He is a great master of orchestration. His seven symphonies span less than three decades (1898-1924). Though Sibelius lived to pass his ninetieth birthday, he published nothing in his last thirty years.

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