A Physiologic and Anatomic Study After Pulmonary Irradiation in Dogs*

A 52 Week Report

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Physiologic and anatomic changes following unilateral pulmonary irradiation up to 6,000 rads in dogs were studied. Fractionate irradiation was given to the right lung of 11 dogs divided into three groups which received 2,000, 4,000 and 6,000 rads respectively. Differential bronchospirometry was serially performed at approximately four week intervals for one year. There was no significant change in the relative distribution of ventilation and oxygen uptake between the irradiated and the contralateral control lungs. Upon diversion of the entire cardiac output through the irradiated lung by temporary unilateral pulmonary artery occlusion, pulmonary artery pressure and left atrial pressure remained within normal limits. Thus, there was no suggestion of increased pulmonary vascular resistance as a consequence of irradiation. Neither adhesions nor abnormalities of the bronchial vessels were observed. The microscopic findings consisted of focal organized pneumonia which was found only in the 4,000 and 6,000 rads groups, and mild focal interstitial fibrosis plus focal vascular sclerosis found in representatives of each of the three groups. We conclude that no significant physiologic abnormalities following unilateral pulmonary irradiation up to 6,000 rads in dogs were demonstrated.

The treatment of primary and metastatic malignancies with pulmonary irradiation is well-established. In recent years, preoperative irradiation has been advocated, and irradiation has also been utilized to modify and arrest tissue transplantation rejection. Therefore, correlative physiologic and anatomic study of the effect of irradiation on canine lungs was begun in our laboratory in 1966, and our findings during the first six weeks following the conclusion of unilateral irradiation have been previously reported.1 The total dosage given to three groups of four dogs each was 2,000, 4,000 and 6,000 rads. Serial differential bronchospirometry, diffusion determinations, bronchial arteriography, lung scans and pulmonary arteriograms, during the first six weeks after completion of irradiation showed no meaningful differences between the irradiated lung and the contralateral control lung. The expected skin changes, consisting of epilation and erythema, appeared at the end of the second week of irradiation and at six weeks there was induration in the irradiated area. Histologic sections obtained from the irradiated lung and from the contralateral control lung of one dog (6,000 rads) showed interstitial fibrosis. Because there were surprisingly few physiologic or anatomic changes found, observations were continued in order to quantitate possible delayed effects. From the original group of 12 dogs, one who had received 2,000 rads to the right lung died six weeks following the end of irradiation as a result of technical difficulties encountered during bronchial arteriography; the remaining 11 animals were followed for a full year. Our purpose is to present observations during the period from six

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to 52 weeks after unilateral right pulmonary irradiation in dogs.

METHOD

The right lung of 11 dogs, randomly divided into three groups, had been irradiated from a 2,000 Curie source of Cesium\(^{137}\) with a source-to-subject distance of 25 cm. A 12.5 × 5 cm portal on the right posterior thorax was used, and the total dosage given to each group of dogs was 2,000, 4,000 and 6,000 rads to the right lung respectively, the left lung having been carefully shielded. Radiation schedules similar to those used for patients were employed. All dogs received 1,000 rads to the right lung weekly, equally divided during five days of therapy. Treatment was continued until the desired total dosage was reached. A representative entrance portal and the calculated isodose curve are shown in Figure 1.

All studies were performed under general anesthesia, using an average induction dosage of 15 mg/kg of sodium thiopeptal supplemented with additional injections of 12.5 to 25 mg as required in order to maintain a steady state as closely as possible. The routine use of premedication with 30 mg of morphine sulfate and 0.65 mg of atropine sulfate minimized the barbiturate requirements and greatly facilitated approximating the desired steady state.

Differential bronchospirometry was performed at approximately four week intervals for one year, using a flexible silicone rubber tracheal divider,\(^3\) and a Gaensler-Collins double spirometer, modified for canine use. Ventilation, \((V_E)\), and oxygen uptake, \((V_{O_2})\) were determined while the dogs breathed 100 percent oxygen.

The tests scheduled at 32 weeks were omitted because the animals were in transit from Madison, Wis. to Torrance, Calif.

Pulmonary vascular resistance of the irradiated lung was estimated one year after the conclusion of irradiation by monitoring the main pulmonary artery pressure and the left atrial pressure with the thorax open, before, during and after temporary diversion of the entire cardiac output through the irradiated lung by occluding the left pulmonary artery. Indwelling polyvinyl catheters, inserted into the main pulmonary artery via segmental branch of the left artery and into the left atrium through a branch of the inferior pulmonary vein, were used to measure pressures which were recorded with Statham transducers and a Honeywell polygraph. Flow and cardiac output were not monitored.

Pathologic examination was made when the dogs were killed at 52 weeks following the completion of irradiation. Representative specimens were obtained from each lobe on the nonirradiated left side, as well as from the right side which had been irradiated. The tissue was fixed in buffered 10 percent formaldehyde (formalin) and microscopic sections were stained with hematoxylin and eosin. In selected cases, trichrome stain for connective tissue and fuchsin stain for elastic tissue were also made.

RESULTS

Differential Bronchospirometry

The mean ventilation \((V_E)\) of the right lung 52 weeks after irradiation was 1.28 liters per minute representing 56 percent (50 to 61) of the total. Before irradiation, mean \(V_E\) for all animals was 1.30 liters per minute (0.89 to 2.31) accounting for

Figure 1. (A, upper) X-ray showing 12 × 5 cm entrance port outlined on the right posterior thorax, encompassing essentially all of the right lung in the radiation field. (B, lower) Isodose curve showing distribution and gradation of irradiation delivered to the right hemithorax with a calculated dosage depth of 6 cm. \(\text{The Annals of Thoracic Surgery, 4:399, 1967}\)

56 percent (45 to 61 percent) of the total. During the year of observation, \(V_E\) of the right lung ranged from 51 percent to 59 percent of the total in 160 tests. The mean value for oxygen uptake \((V_{O_2})\) of

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the right lung one year after irradiation was 52.9 ml per minute (33.4 to 70.6) which was 57 percent (53.5 percent to 62.5 percent) of the total. Before irradiation, the mean value for $V_O_2$ of the right lung was 59 ml per minute, representing 56 percent (52 percent to 60 percent) of the total $V_O_2$. During the year of observation $V_O_2$ of the right lung ranged from 51 percent to 62 percent of the total. These data indicate no significant change in the relative distribution of ventilation and oxygen uptake following unilateral pulmonary irradiation ranging from 2,000 to 6,000 rads as compared to before irradiation. Furthermore, no difference was detected between the maximally and minimally irradiated animals.

**Vascular Resistance Estimate**

Following temporary occlusion of the left pulmonary artery, the mean pressure in the main pulmonary artery in the entire group of 11 dogs rose 4.3 (1 to 6) mm Hg. Concomitant pressure measurements in the left atrium remained essentially stable during temporary occlusion of the left pulmonary artery. Thus, no significant changes from normal were observed in any of the animals following temporary diversion of the entire cardiac output through the irradiated lung. Pulmonary vascular resistance could not be precisely calculated since flow measurements were not made, but no suggestion of alteration from normal was found.

**Pathologic Examination**

Neither adhesions nor macroscopic changes were revealed in the bronchial vessels by pathologic examination. No parenchymal abnormalities were seen on gross inspection. Microscopically, the lungs showed numerous minor focal abnormalities bilaterally, ie, peribronchiolar chronic inflammation, bronchiectasis, subpleural alveolar macrophage infiltration, anthracosis, alveolar duct muscular hypertrophy, metaplastic bone formation and focal emphysema. These changes were regarded as non-specific and not related to the irradiation, since they were found on both sides. However, significant additional microscopic changes found only in sections taken from the right lung included organized pneumonia and focal interstitial fibrosis. Foci of organized pneumonia were found in three dogs receiving 6,000 rads and all four dogs receiving 4,000 rads. Except for one dog who had received 6,000 rads and two animals to whom 4,000 rads had been given, the degree of parenchymal change was slight. Organized pneumonia was characterized by dense collagen deposits in the lumen of bronchioles and alveolar ducts (Fig 2). These intraluminal scars were attached to alveolar duct walls at some points, which contained capillaries. They were often lined by swollen septal cells. The focal interstitial fibrosis found in the irradiated lungs was characterized by fibrous thickening of alveolar walls, associated with intra-alveolar macrophage infiltration (Fig 3). There was swelling of the septal cells lining the fibrous thickened alveoli. Focal interstitial fibrosis was found in one dog from each group, but it was minimal except for the animal who had received 6,000 rads.

**DISCUSSION**

The paucity of physiologic abnormality following unilateral pulmonary irradiation up to 6,000 rads in dogs has been surprising to us, although we are aware of previous suggestions in the literature that pulmonary tissue is relatively radioresistant.3-5 Although there has been general agreement in

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21469/)

**Figure 2.** Cross section of an alveolar duct from a dog who received 4,000 rads to this lung. Note that the lumen is obstructed by a mass of fibrous tissue containing capillaries typical of organized pneumonia. Hematoxylin and eosin $\times 450$.

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21469/)

**Figure 3.** Interstitial fibrosis of alveolar walls from a dog who received 6,000 rads to this lung. Note the markedly thickened avascular walls, the prominent septal cells lining the dwarfed alveolar spaces and the presence of histiocytes within the alveolar lumens. Hematoxylin and eosin $\times 450$. 

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previous physiologic studies of postirradiation pneumonitis that respiratory rate increases if vital capacity is reduced.6 Rigler on the basis of unpublished observations made years ago, concluded that radiation pneumonitis in dogs occurs only when there is accompanying infection.7 Certainly, the focal parenchymal changes found bilaterally in the lungs of our animals suggests that they have been subject to intermittent respiratory tract infections commonly found in laboratory dogs. The abnormalities we have demonstrated in the radiated canine lungs were not present on the contralateral side, and we have, therefore, certainly induced unilateral radiation changes. It is difficult to explain why the degree of abnormality varied considerably between dogs who received the same calculated dosage by identical techniques, except perhaps by postulating varying degrees of mild subclinical chronic or recurrent pulmonary infection. We have limited our physiologic testing to differential bronchiospirometry and to a simple technique for estimating pulmonary vascular resistance by temporarily diverting the entire cardiac output through the irradiated lung because more extensive measurements, including diffusion determinations, closely paralleled the bronchiospirometry data in our earlier report compiled six weeks after irradiation.1 One year after irradiation, neither the ability of the irradiated lung to ventilate and to take up oxygen, nor its capacity of accepting a sudden increase in pulmonary blood flow were impaired. This can be correlated with the microscopic findings because the pulmonary reserve in normal dogs is sufficiently great to compensate adequately for the focal changes induced in our experimental animals.

Neither differential bronchiospirometry nor bronchial arteriography nor diffusion studies at the end of six weeks after the completion of irradiation demonstrated any significant impairment of function, and similarly we observed no meaningful abnormalities over the course of an entire year. Thus, we probably have not derived any information applicable to patient care. However, current interest in pulmonary transplantation includes the use of irradiation for the purpose of supplementing other means of modifying the rejection response. Therefore, it is important that the relative radioresistance of canine lung be brought to the fore.

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