Pulmonary Reimplantation Response

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REIMPLANTATION or autotransplantation of the lung is a formidable procedure involving division of many structures. In the past, reimplantation of the canine lung presented technical problems which resulted in high surgical mortality and appreciable compromise of the bronchial and vascular anastomoses with consequent functional impairments in surviving animals.[3,6,11,18,20,24] Recent technical improvements have made it possible to minimize defects at the bronchial and vascular anastomoses;[2,22] a reimplanted lung can now recover normal morphology and function remarkably well if the bronchus and major vessels are adequately reconstructed.[10,20,23] After technically flawless reimplantation, however, functional defects may occur in the early postoperative period. These defects are largely reversible[13,21] and may be attributed to disruption of nerves, lymphatics and bronchial vessels and/or to ischemic injury.[1,7,12,18]

We have been investigating the mechanisms of pulmonary allograft rejection in dogs using serial chest roentgenography and pulmonary angiography with simultaneous lung biopsy.[15,16] Serial chest roentgenography is an important means of monitoring the status of the allograft in the postoperative period. Since the anticipated responses to autotransplantation have not been adequately defined, it may be difficult to determine whether a postoperative pulmonary roentgenologic abnormality is due to rejection or reimplantation. The present study was undertaken to allow us to establish the radiologic and histologic manifestations of pulmonary reimplantation.

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Methods

Reimplantation of the left lung was carried out in eight mongrel dogs. Details of operative technic and perfusion were similar to those described elsewhere.[21,22] The pulmonary artery was divided obliquely and reconstructed by use of a meticulous technic which approximated 1 mm. bites of vessel wall with each stitch.

Four animals received 2–3 mg./Kg./day of azathioprine, 2–4 mg./Kg./day of prednisone, and rabbit anti-dog lymphocyte serum. The latter agent was given in doses of 10–20 ml./Kg. three times preoperatively and daily postoperatively for 2 weeks. The other four animals were not treated.

During the postoperative period, frontal (posteroanterior) roentgenograms of the chest were obtained daily of the unanesthetized animals in the prone position. Extensive examinations were performed on each animal on four occasions: in the early postoperative period (day 1–3), 1 week postoperatively (day 7–9), 2 weeks postoperatively (day 14–16), and 3 to 4 weeks postoperatively (day 22–31). The animals were anesthetized with intravenous pentobarbital and plain chest roentgenograms were obtained in the frontal (anteroposterior) and right posterior oblique (supine oblique) projections. A polyethylene catheter with side holes was then introduced into the right jugular vein and guided under fluoroscopic control into the main pulmonary artery. Serial angiograms were then obtained with the animals in the right posterior oblique position, using 1.75 ml./Kg. of 60% methylglucamine diatrizoate injected at

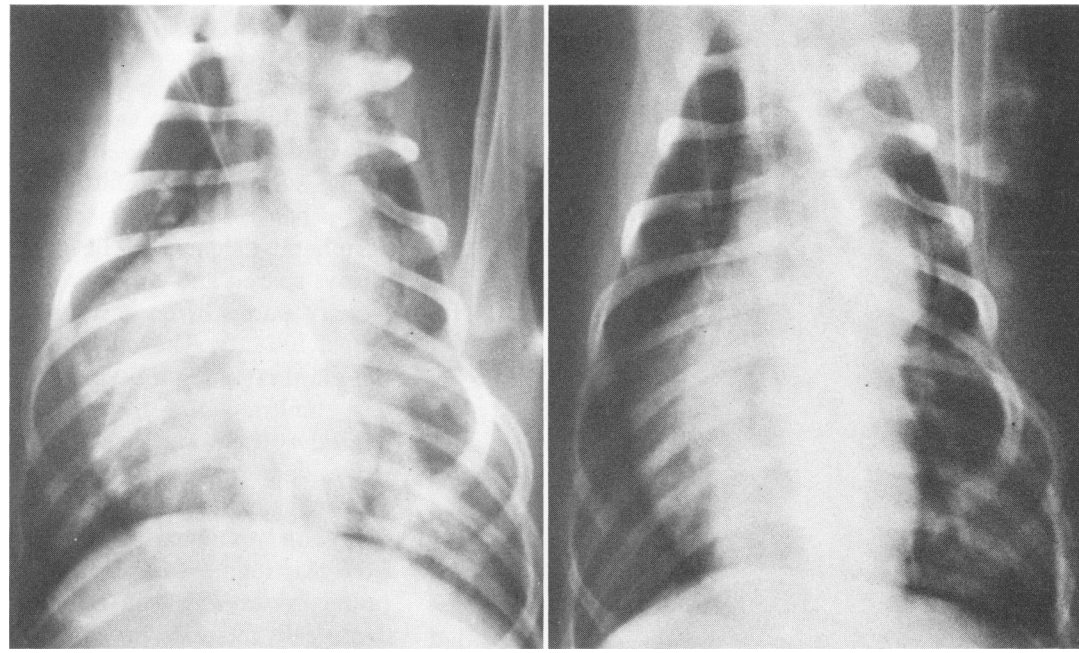

FIG. 1. Usual reimplantation response. Chest roentgenograms following autotransplantation of the left lung. Dog 1. (A. left) Second postoperative day. The left lung contains an alveolar infiltrate in the diaphragmatic (lower) lobe and in the central portion of the upper lobe. A linear density at the left cardiophrenic angle represents thickening of the inferior aspect of the major pleural fissure. The peripheral margins of the lung are normal. (B. right) Eleventh postoperative day. The infiltrate has cleared completely. Slight pleural thickening persists.

a rate of 15–20 ml. per second with filming at the rate of two films per second for 8 seconds. Following the angiographic examination, thoracotomy was performed and the left lung was inspected and biopsied. All biopsies were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin.

After the fourth examination, the animals were sacrificed and autopsied. The lungs were examined grossly. All anastomoses were inspected from within. The lungs were then fixed by inflation with and immersion in formalin. Multiple sections were taken and stained with hematoxylin and eosin.

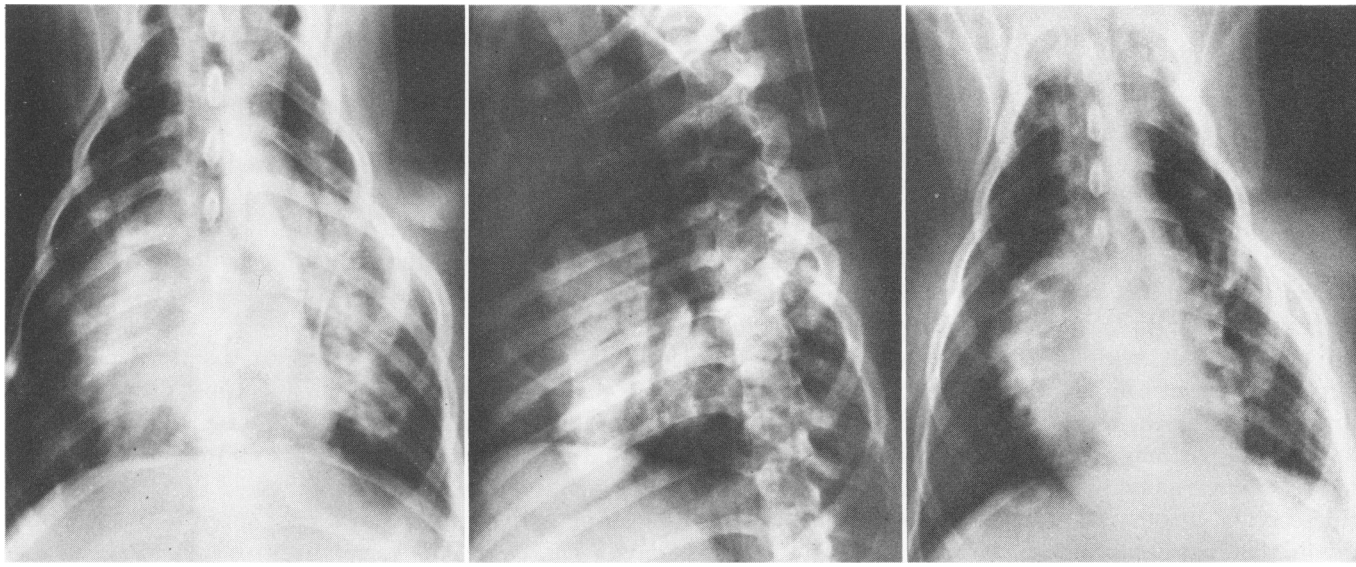

FIG. 2. Maximum reimplantation response. Chest roentgenograms following autotransplantation of the left lung. Dog 2. (A. left) Third postoperative day. Alveolar infiltrates are present in the proximal portion of the diaphragmatic lobe and the perihilar region of the upper lobe. The infiltrate is bordered by a peripheral crescent of uninvolved well aerated lung. A curved linear density extending from the mid portion to the base of the left lung represents thickening of the pleural fissure. (B. center) Third postoperative day. Right posterior oblique projection. The perihilar distribution of the infiltrate is demonstrated. (C. right) Seventh postoperative day. There has been extensive peripheral clearing. Some central perihilar patchy infiltrate remains in the upper and diaphragmatic lobes. The inferior aspect of the pleural fissure remains prominent.

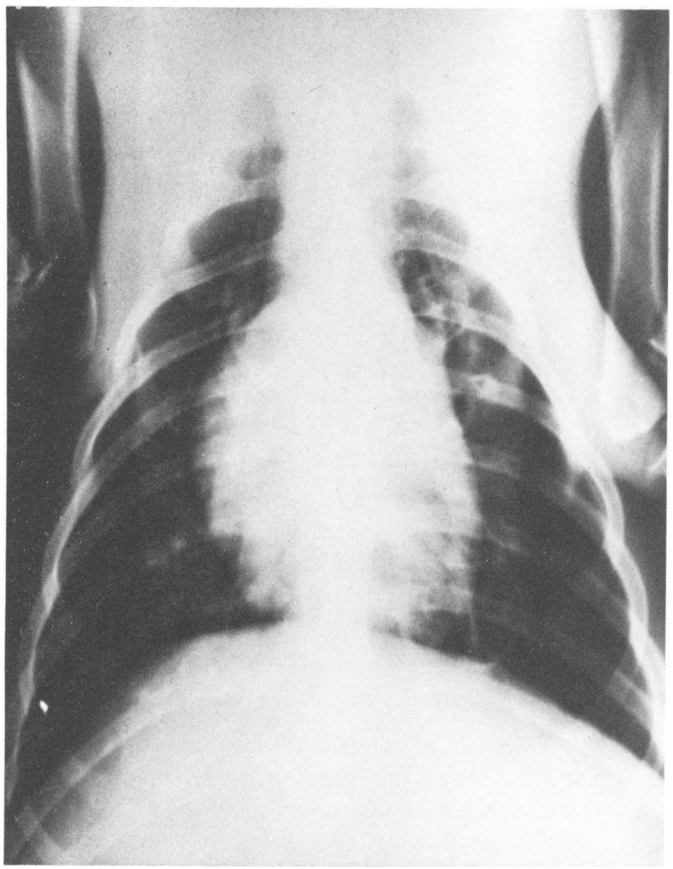

FIG. 3. Minimal reimplantation response. Dog. 3. Fifth postoperative day. There are minimal patches of infiltrate in the diaphragmatic lobe behind the heart and in the proximal portion of the left lower lobe. The chest roentgenogram returned to a normal appearance on the seventh postoperative day.

Results

The findings on chest roentgenography, pulmonary angiography and lung biopsy were the same in treated and immunosuppressed animals.

Plain Chest Roentgenography: There was a characteristic pattern and a definite timing of the roentgenographic abnormalities which appeared in the reimplanted left lung. The initial chest roentgenogram on the first postoperative day was always abnormal, although the degree and extent of abnormality varied. An alveolar infiltrate originated in the hilar region and extended into the proximal portions of the apical, cardiac and diaphragmatic (lower) lobes. On the second day the infiltrate coalesced as it progressed along a peribronchial and perivascular pathway to involve larger segments of the lung (Fig. 1A). The greatest involvement occurred on the third postoperative day when the lesions reached maximum development (Figs. 2A, 2B).

The areas of consolidation which constitute the pulmonary reimplantation response have the characteristics of *alveolar infiltrates*.[8,14] The lesions change rapidly during evolution; they follow a lobar pattern, and their margins are fluffy and vaguely defined. The *air bronchogram* phenomenon, in which the larger air passages are seen as linear radiolucent pathways contrasted by the opacified air spaces, is a feature of the lesion.

The segments of infiltration radiate from the hilum into a flame or fan shaped configuration with a limited peripheral extension. The outer third of the lung was always spared and a clear zone of normal-appearing pulmonary parenchyma surrounded the involved segments (Figs. 1, 2, 3). The most commonly involved area was the diaphragmatic lobe behind the heart (Figs. 1, 2, 6). The infiltrate never extended to the diaphragmatic pleural surface and hence the diaphragm remained in sharp definition. The second predilected site was the proximal portion of the apical lobe directly adjacent to the main pulmonary artery. The peripheral extension from this segment approached the pleural surface but a preserved crescent of clear lung always remained to demarcate the outer margin of the lesion. Thus the pulmonary autotransplantation response was never manifested by total consolidation of any lobe. Although there was no variation in the nature of the infiltrate in the autotransplanted lung, there was a considerable range in the degree of involvement. The roentgenograms illustrated in Figure 1 represent the usual response. The reaction of maximum magnitude is shown in Figure 2. In several animals the pulmonary reimplantation response was confined to a minimal patchy infiltrate in the diaphragmatic and upper lobes (Fig. 3).

The roentgenograms also contained evidence of reactive pleural change. An oblique, vertically oriented linear density at the medial aspect of the lung base represented thickening of the inferior aspect of the oblique fissure (Figs. 1A, 6A). Occasionally small amounts of fluid produced increased prominence of the superior segments of the fissure manifested by thin, sharp linear densities adjacent to the hilum (Fig. 2A). A collection of pleural fluid yielding a detectable density lateral to the lung was an unusual finding seen in only one animal.

Following the peak reaction on the third postoperative day, the abnormalities in the chest roentgenogram gradually resolved at a variable rate. Three dogs exhibited extensive clearing of the infiltrate by the seventh postoperative day, three dogs showed slight to moderate clearing between the third and seventh postoperative days (Fig. 2). In the remaining two animals no change was detected during this period. After the seventh day there was progressive clearing of all residual infiltrate. The infiltrate receded centrally and the proximal perihilar involvement was the last to disappear. Thus, complete dissolution of all abnormalities occurred between the seventh and twenty-first days. Despite the trauma of

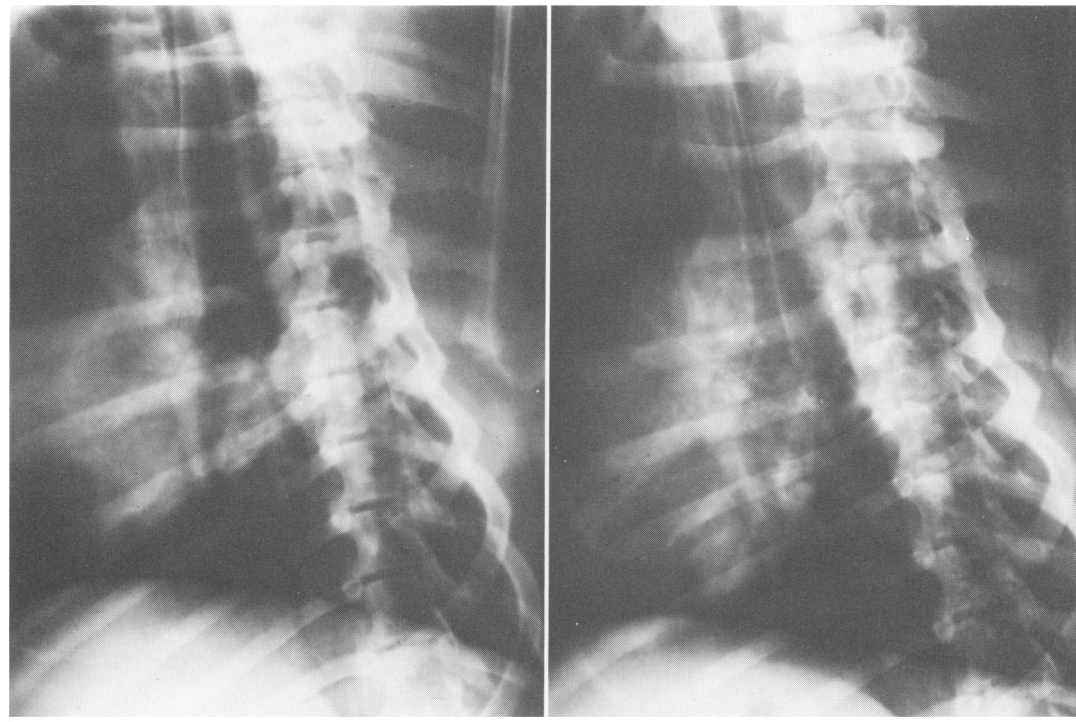

FIG. 4. Bronchial narrowing. Dog 4. (A. left) Right posterior oblique projection, fifth postoperative day. Narrowing of the proximal portion of the left main bronchus at the site of surgical anastomosis. (B. right) Right posterior oblique projection, 28th postoperative day. The lumen of the bronchus has returned to a normal calibre.

repeated thoracotomy and biopsies, the process of progressive reabsorption of infiltrate was never reversed; increase in pulmonary infiltrate in serial roentgenograms was never observed after the third postoperative day.

Plain chest roentgenography also offered a means of evaluating the bronchial anastomosis. The left mainstem bronchus is not well seen in frontal roentgenograms because it is obscured by cardiovascular structures. However, a series of four oblique plain chest roentgenograms (immediate postoperative, 1 week, 2 weeks, and 3–4 weeks postoperative) provided an opportunity to assess the contour of the air column in the proximal left bronchial tree. Narrowing of the lumen beginning at the site of the bronchial anastomosis was evident in each case. The magnitude of narrowing of the bronchial lumen was maximum in the first postoperative week when it

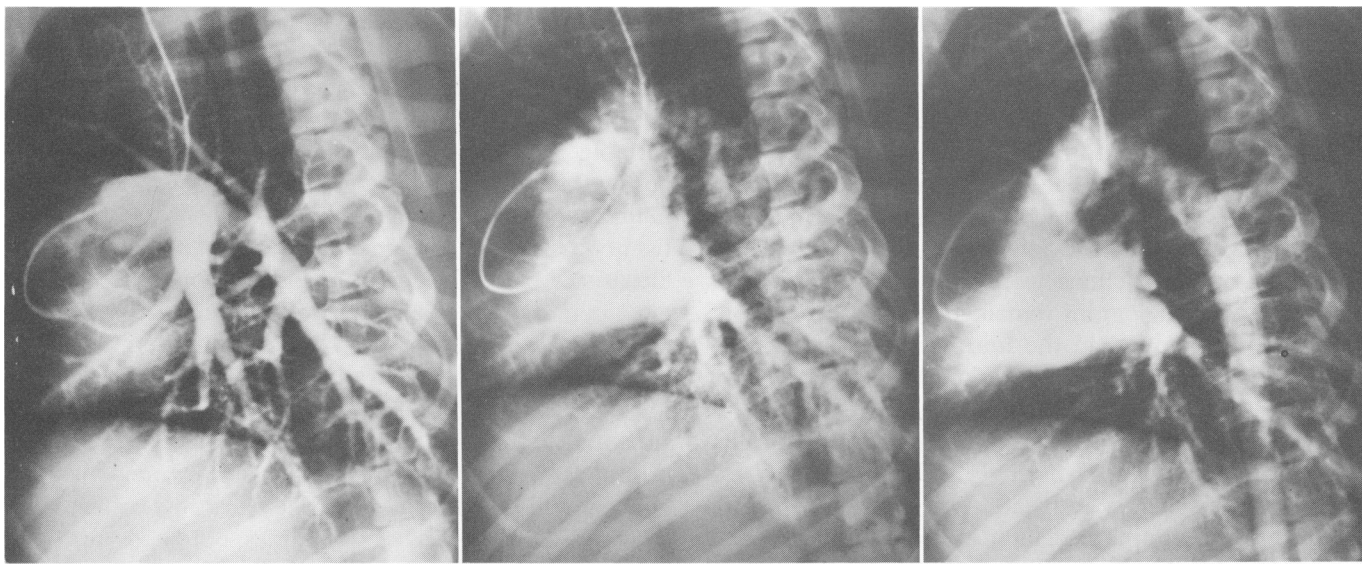

FIG. 5. Pulmonary angiography. Dog 2. (Same as dog in Fig. 2), 16th postoperative day. (A. left) Early arterial phase showing patent pulmonary arterial anastomosis and an equal distribution of contrast material to each pulmonary artery following injection into the main pulmonary artery. (B. center) Capillary phase. (C. right) Venous phase with filling of pulmonary veins of each lung, left atrium, left ventricle and aorta.

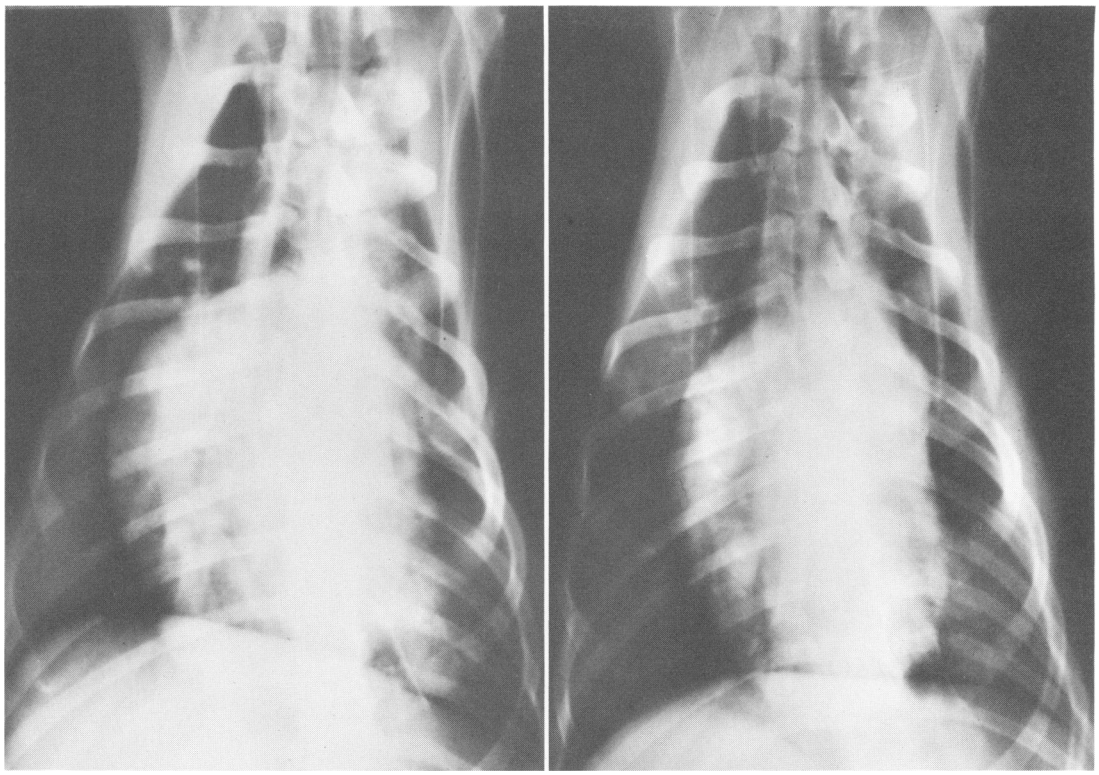

FIG. 6. Pulmonary reimplantation response in an allotransplanted lung. (A. left) Chest roentgenogram 7 days after autotransplantation of the left lung. There is a left lower lobe infiltrate and thickening of inferior aspect of the pleural fissure. (B. right) Same animal on the 14th postoperative day. The infiltrate has cleared completely.

approximated 50% of baseline measurements (Fig. 4A). The narrowing regressed considerably in the second week and a restoration toward a normal calibre bronchial lumen was noted in the third and fourth postoperative weeks (Fig. 4B). No significant narrowing was present at autopsy.

Pulmonary Angiography. Pulmonary angiography disclosed a patent pulmonary arterial anastomosis with no detectable narrowing (Fig. 5A), equal distribution of contrast material to each lung following injection into the main pulmonary artery, a normal capillary blush (Fig. 5B) and excellent filling and emptying of the pulmonary veins (Fig. 5C). The right posterior oblique position facilitates visualization of the junction of the left pulmonary veins with the left atrial cuff anastomosis.[9] No defects or obstructions were present at the anastomotic site. The angiogram remained normal throughout the study: the findings in the fourth week were no different from the findings in the immediate postoperative period.

Gross and Microscopic Morphology. Grossly the reimplanted lung appeared normal at all times when examined in the early and late postoperative period. Biopsies of the reimplanted lung in the early postoperative period (1-3 days) revealed traces of alveolar edema in six of the eight dogs. Biopsies of the remaining two animals in this period and all biopsies after this period were completely normal.

Discussion

The pulmonary reimplantation response consists roentgenologically of a coalescing alveolar infiltrate which is usually associated with and probably due to the presence of edema fluid within the air spaces. The process involves the central portions of the lung and extends into the pulmonary parenchyma along a peribronchial and perivascular pathway. The peripheral portions of the lung are not involved. The maximum expression occurs by the third postoperative day. This is followed by a variable improvement between the fourth and seventh postoperative days and a gradual disappearance of the infiltrate which is complete between the seventh and twenty-first days. The edema and resultant alveolar infiltrate are probably due to a combination of factors, the most important of which are ischemia, operative-trauma, and lymphatic interruption. During the clearing phase, the infiltrate recedes centrally so that the peripheral portions of the lung are the earliest to be restored to a normal appearance. The phenomenon of peripheral sparing and central regression may explain the discrepancy observed between the lung biopsies and the chest roentgenograms. In some animals the lung biopsies obtained from the outer third of the lung were entirely normal whereas the chest roentgenograms contained evidence of residual central pulmonary infiltrate.

The findings in our present study are consistent with

the few published observations on the roentgenographic appearance of the autotransplanted lung. Trummer *et al.*[18] performed occasional roentgenographic studies on six dogs which survived more than 1 month following autotransplantation. They described progressive pulmonary opacification which became maximal on the third postoperative day. Thereafter sporadic chest roentgenograms revealed extensive clearing on the eighth to nineteenth days. The appearance of the autotransplanted lung in the baboon has also been studied at weekly intervals by chest roentgenography.[19] The findings were those of a diffuse alveolar process produced by edema and congestion which cleared gradually in a 4 to 6-week period. The variability between our results and those of others may be due to differences in technic or species variations.

The radiologic observations of transient alveolar infiltration and bronchial narrowing in the autotransplanted lung have their counterpart in physiological derangements which occur during the early postoperative period. The reimplanted lung exhibits a definite decrease in ventilation and oxygen uptake followed eventually by a restoration of normal respiration if all the anastomoses are functioning adequately.[5,13] In a recent study, a fall in autograft ventilation in the second and third postoperative days was associated with findings on inhalation scanning suggesting obstruction at the bronchial anastomosis.[4] Recovery of function began at the end of the first postoperative week and stable ventilation was restored at the end of the third week. Transient bronchial narrowing at the anastomotic site is presumably produced in part by the intraluminal protrusion of edematous bronchial mucosa. Extensive mucosal edema distal to the level of division of the bronchus has been observed by bronchoscopy of the reimplanted canine lung.[12] These findings would coincide with our observation of the appearance and regression of both bronchial narrowing and edematous infiltration of the air spaces. It has yet to be shown, however, that bronchial narrowing alone is capable of producing impaired ventilation. It is conceivable that the bronchial narrowing may represent the reflection of impaired ventilation due to other factors. In a separate completed study, serial postoperative plain chest roentgenograms and serial bronchograms were performed at weekly intervals following autotransplantation of the left lung in a different group of mongrel dogs.[17] The plain oblique chest roentgenogram has proved to be an effective means of assessing the status of bronchial anastomosis.

Our documentation of a characteristic radiological appearance of autotransplanted canine lungs must be considered in any comparable study of lung allografts. Obviously allotransplanted dog lungs will exhibit a reimplantation response. This has been the case in a group of dogs subjected to allotransplantation of the left lung that were treated with immunosuppressive agents and studied with serial chest roentgenography and lung biopsy.[15] In three animals, rejection was completely suppressed for several weeks. The roentgenograms and lung histology revealed the typical reimplantation response. In these dogs during the first postoperative week, a coalescing alveolar infiltrate was noted (Fig. 6A) while lung biopsy showed transient pulmonary edema. In the second week the infiltrate cleared completely (Fig. 6B).

Coalescing alveolar infiltrates in the allotransplanted lung which do not conform to the distribution or timing of the reimplantation response can be considered due to other disorders. Total consolidation of the lung in the first three postoperative days should lead to an investigation for thrombosis of the pulmonary arterial or venous anastomosis. The appearance of a new area of infiltrate or the extension of a previous infiltrate after the fourth postoperative day should be attributed to rejection or pneumonia. The infiltrates associated with rejection and pneumonia are more apt to extend to the outer third of the lung, thus producing total consolidation of an entire lobe, a phenomenon which has not been observed in successfully allografted lungs.

Summary

Chest roentgenograms, pulmonary angiograms and lung biopsies were studied serially in a group of dogs following reimplantation of the lung. Reimplanted lungs exhibited centrally located coalescing alveolar infiltrates immediately following operation. The infiltrate, which corresponded to pulmonary edema in lung biopsies, extended peripherally as it progressed to maximum expression on the third postoperative day. Thereafter abnormalities resolved at a variable rate with complete clearing between the seventh and twenty-first days. Transient narrowing at the bronchial anastomosis was also observed. Pulmonary angiography was entirely normal.

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