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Steroid Therapy for Pneumonitis Induced in Rabbits by Aspiration of Foodstuff

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The instillation of gastric contents, 0.5 ml/kg (*p*H 4.3), containing small food particles into the left diaphragmatic lobe of the lungs of 49 rabbits caused severe aspiration pneumonitis. Administration of methylprednisolone, 30 mg/kg, intramuscularly, every eight hours for three days to 26 of the 49 rabbits did not alter the rate of roentgenographic resolution of the pneumonitis. Corticosteroids did decrease the fibroblastic response of the lung to the aspirate, but also interfered with healing of granulomatous lesions. (Key words: Complications: aspiration. Hormones, adrenal: corticosteroid. Lung: aspiration.)

ALTHOUGH CORTICOSTEROIDS are often recommended for the treatment of aspiration pneumonia,[1–3] their use is controversial.[4,5] Clinical impressions have been almost entirely anecdotal and based on uncontrolled factors.[6–8] Experimental studies have yielded conflicting results.[9–13] However, all experimental studies have used solutions of either hydrochloric acid or filtered gastric contents adjusted to a *p*H of less than 2.5 to induce aspiration pneumonitis. Acid is believed to be the major determinant of the severity of aspiration-induced pulmonary injury,[14] and *p*H 2.5 has been identified as the critical level of acidity necessary to damage the lung.[15–17]

On the other hand, experimental studies suggest that the aspiration of gastric contents containing small food particles can also cause severe pulmonary damage, even when the *p*H of the aspirate is well above 2.5.[15,18] This injury appears to be similar in severity to that caused by acid, but differs histologically. The cellular response to gastric contents containing food matter is more mononuclear and granulomatous than when clear acid is aspirated. The possible effectiveness of administering corticosteroids for pneumonitis induced by aspiration of foodstuff has not been evaluated. In the present study we used roentgenographic and pathologic criteria to evaluate the extent of damage induced in the rabbit lung by aspiration of gastric contents containing small food particles, and to determine whether steroid treatment altered this response.

Materials and Methods

Healthy New Zealand white rabbits (mean weight ± SD, 2.3 ± 0.2 kg) were anesthetized with chlorpromazine, 25 mg, intramuscularly, and pentobarbital sodium, 25 mg/kg, intravenously, and were secured in the supine position with their heads elevated 30 degrees above the examining table. Using sterile technique, a 19-gauge intravenous catheter was inserted percutaneously between two tracheal rings into the trachea and was advanced under fluoroscopic control into the diaphragmatic lobe of the left lung at the level of the eighth rib. The animals were randomly divided into three groups (table 1). Group I (19 animals) received an aspirate of saline solution, 0.5 ml/kg, via this catheter. Group II (23 animals) received gastric contents, 0.5 ml/kg (*p*H 4.3), which had been obtained from the stomach of a normal human volunteer 90 min after a meal of one-quarter pound of ground beef, eight ounces of mixed vegetables, and two slices of bread. The aspirate was drawn into syringes through a 17 g needle to ensure that it was free of large food particles. Group III (26 animals) received gastric contents, 0.5 ml/kg, but in addition were treated with methylprednisolone, 30 mg/kg, intramuscularly, three times a day. Treatment was begun one hour after aspiration and was continued for three days in survivors. Following administration of the aspirate, the animals were kept with their heads

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TABLE 1. Classification of Experimental Animals According to Number of Animals in the Group, Aspirate Received, Treatment Received, and Days on Which the Animals Were Sacrificed

	Aspirate (0.5 ml/kg)	Treatment	n	Number of Animals Sacrificed			
				Day 1	Day 3	Day 7	Day 21
Group I	Physiologic saline solution	None	19	6	7	6	0
Group II	Gastric contents	None	23	6	5	7	5
Group III	Gastric contents	Methylprednisolone, 30 mg/kg, im, every 8 hours for three days	26	7	7	6	6

elevated for 20 min. They were then returned to their cages and maintained on a routine diet.

Animals from each group were sacrificed by rapid intravenous infusion of sodium pentobarbital, 60 mg/kg, one, three, seven, and 21 days after aspiration. The whole lungs and tracheas of the sacrificed animals were immediately excised and fixed by inflation according to the method of Markarian.[19] Air-dried lungs were then cut into 5-mm-thick frontal slices and were x-rayed. Sections from all lung slices were prepared for histologic examination.

The extent of roentgenographic opacification induced by the aspirate was quantitated by placing a transparent grid over the roentgenograms of the left lung of each animal. Grid squares overlying areas of increased density were counted and divided by the number of grid squares overlying the total area of the left lung. The resulting ratio was expressed as the percentage of the left lung damaged by the aspirate. Roentgenograms of animals sacrificed on day 1,3, or 7, with their identifying marks obscured, were assessed independently by two of the authors (JWW and JCR); the resulting correlation coefficient was 0.95. Roentgenograms of animals sacrificed at 21 days were assessed by one author (JWW).

The histologic sections from each animal—the identifying marks obscured and their order disarrayed—were examined by a third author (CIH). The slides of sections from animals sacrificed one, three, or seven days after aspiration were ranked on a scale of 0–3 in terms of 15 histologic findings felt to be characteristic of aspiration of foodstuff (table 2). Slides of sections from animals sacrificed at 21 days were scored only on the percentages of necrotic granulomas.

The results of the roentgenographic and histologic analyses for each group of animals were then compared by analysis of variance and least-significant difference. Histologic changes at 21 days were compared by Fisher's randomization test. $P < 0.05$ was regarded as significant.

Results

Only four of the 19 animals in Group I had abnormal roentgenograms. Mean percentages of roent-

TABLE 2. Histologic Findings Typical of Aspiration Pneumonitis Induced by Foodstuff, and Ranking Scale Used to Grade Findings

Histologic Findings	Ranking Scale			
	0	1	2	3
Alveoli				
Septal edema	None	Slight	Moderate	Marked
Alveolar edema	None	Slight	Moderate	Marked
Architectural disruption in involved area	None	Slight	Moderate	Marked
Septal metaplasia	None	Slight	Moderate	Marked
Septal inflammation	None	Slight	Moderate	Marked
Septal fibrosis	None	Slight	Moderate	Marked
Neutrophils	None	Few	Many but not predominant	Dominant cell type
Macrophages	None	Few	Many but not predominant	Dominant cell type
Fibroblasts	None	Few	Many but not predominant	Dominant cell type
Fibrous matrix	None	Slight	Moderate	Marked
Giant cells	None	Rare	Few	Numerous
Bronchi				
Aspirate present	None	Slight	Occluding much of airway	Occludes airway
Inflammatory reaction	None	Slight	Moderate	Extensive
Fibrosis	None	Occasional fibroblasts	Moderate	Extensive organized fibrosis
Epithelial metaplasia	None	Mild atypia	Mixed	Entirely squamous

genographic abnormality (±1 SD) of the left lung for animals in Group I were 10 ± 13 per cent at day 1, 4 ± 8 per cent at day 3, and 0 at day 7. The lungs of all animals in Groups II and III were abnormal. Mean percentages of roentgenographic abnormality for Group II were 64 ± 19 per cent at day 1, 50 ± 21 per cent at day 3, 37 ± 31 per cent at day 7, and 40 ± 11 per cent at day 21. For Group III these values were 49 ± 16 per cent at day 1, 52 ± 20 per cent at day 3, 30 ± 24 per cent at day 7, and 40 ± 11 per cent at day 21. The mean percentages of areas of the left lung damaged were significantly greater in Group II and Group III animals than in Group I animals at each time examined during the first week. However, there was no statistically significant difference in the extents of roentgenographic abnormality between Groups II and III at any time. Review of the roentgenograms revealed that most of the aspirate was confined to the diaphragmatic lobe of the left lung, the most extensive involvement being dorsal (fig. 1). Occasionally there was a small amount of spill-over into the right lung, which was otherwise uniformly normal.

The lungs of all animals receiving the saline aspirate were histologically normal, except that at three days two animals had what appeared to be viral pneumonia and at one day two other animals had slight accumulation of edema fluid without evidence of inflammation. Histologic abnormalities that closely paralleled in location and extent the roentgenographic abnormalities were seen in the lungs of all animals receiving foodstuff aspirate. On day 1 the lungs of Group II animals showed an inflammatory reaction consisting almost entirely of polymorphonuclear cells in both the small airways and alveolar spaces of the left diaphragmatic lobe. Many of the terminal and respiratory bronchioles were either partially or completely obstructed by this reaction. Although food particles were present, they did not themselves cause obstruction (fig. 2). In the more severely involved areas, usually surrounding airways, there was often extensive hemorrhagic necrosis and edema and dense polymorphonuclear infiltration of the air spaces. Also found were areas of coagulative necrosis surrounded by a dense zone of inflammatory cells and, more peripherally, inflammatory edema.

Group II animals sacrificed on day 3 had more discrete bronchiolitis and necrotizing pneumonitis. One feature that distinguished this reaction from that seen on day 1 was the presence, especially in the air spaces, of macrophages, often in numbers equal to or greater than the numbers of polymorphonuclear cells. In addition, spindle-shaped fibroblastic cells were already present in both the airways and the air spaces (fig. 3). This fibroblastic reaction was especially evident surrounding large food particles. Peripheral wedge-shaped areas of hemorrhage and necrosis were also present in some sections, and were associated with thrombosed pulmonary arteries, suggesting pulmonary infarction (fig. 4). By day 7 many discrete, well-organized granulomas were present. These were

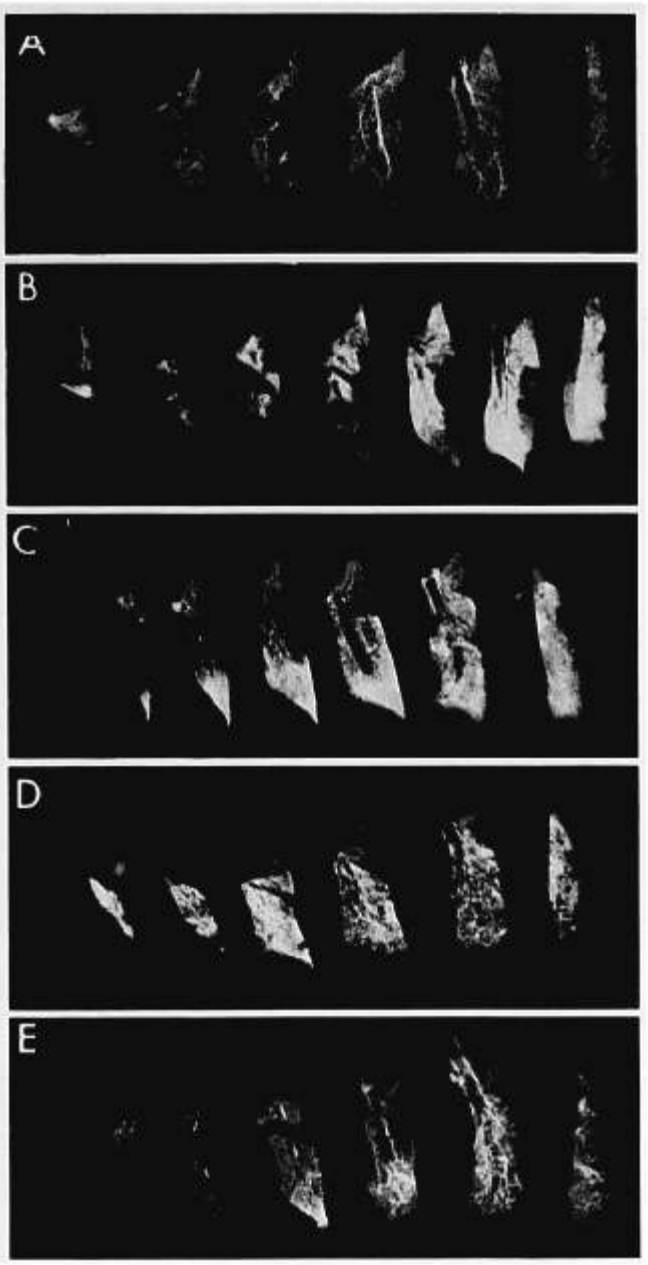

FIG. 1. Roentgenograms of serially sectioned left lungs. Each panel contains the left lung sections from a single animal. The most anterior (ventral) section is to the left and the most posterior (dorsal), to the right. *A*, Group I animal sacrificed on day 1; *B* through *E*, Group II animals sacrificed on days 1, 3, 7, and 21. Note the dense infiltration 24 hours after aspiration of foodstuff *B*, with gradual resolution over the ensuing 20 days, *C* through *E*.

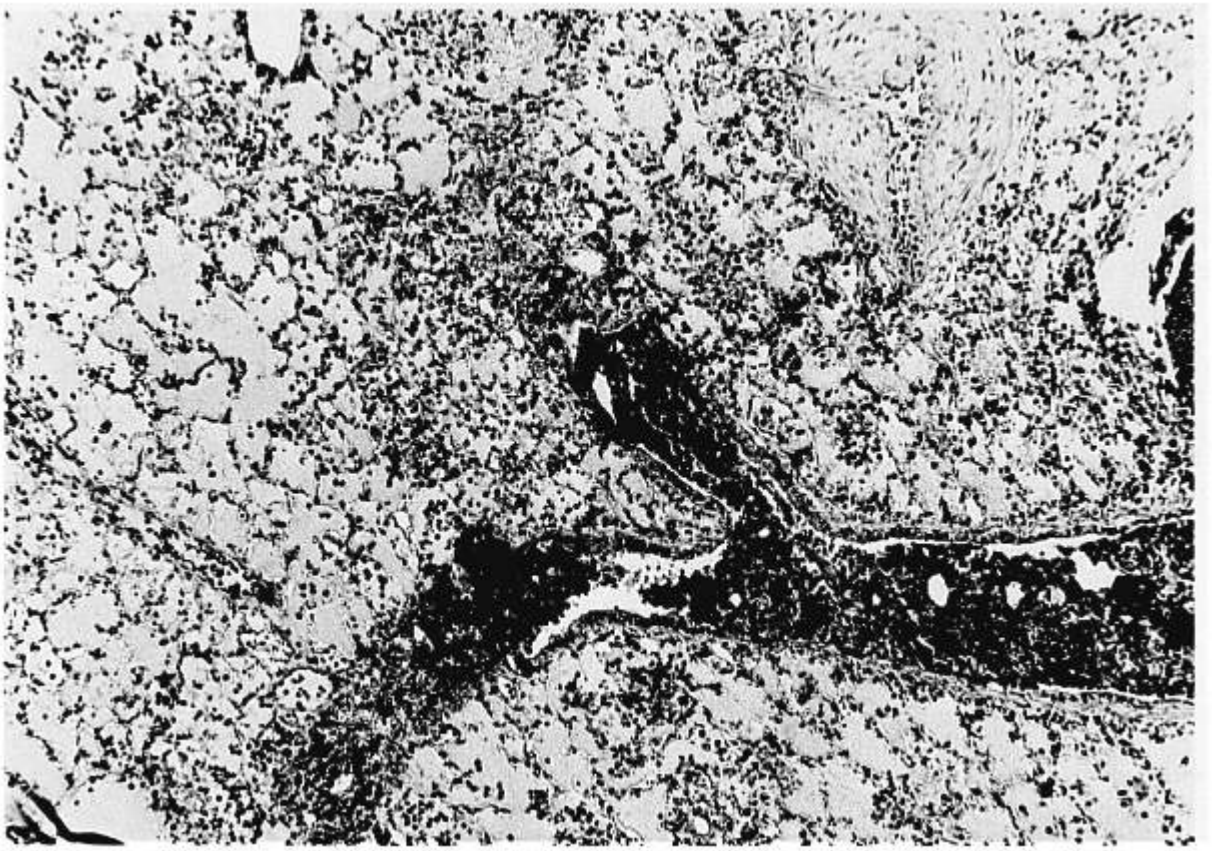

FIG. 2. Section of lung from an animal in Group II 24 hours after aspiration of gastric contents. Note the terminal bronchiole obstructed by inflammatory cells and food matter with peribronchiolar edema and inflammation (hematoxylin–eosin, ×110).

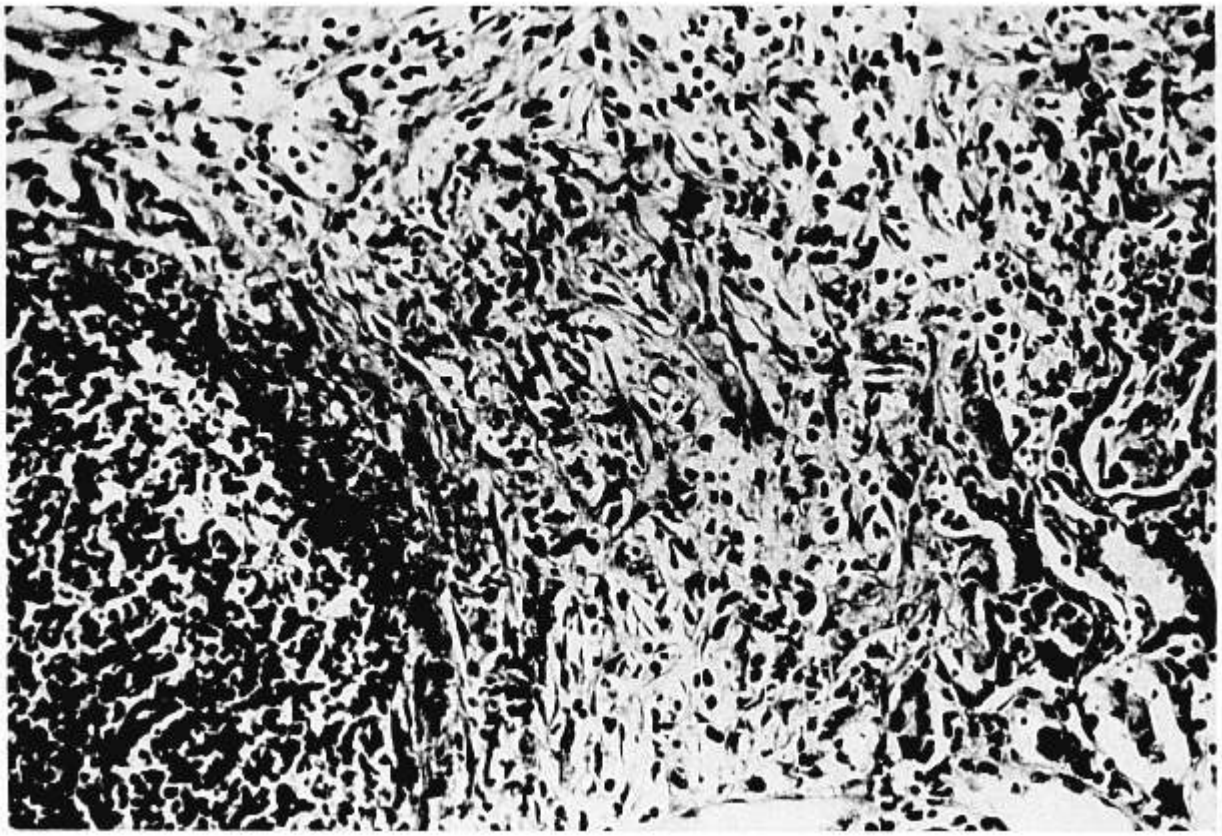

FIG. 3. Section of lung from an animal in Group II three days after aspiration. An inflamed bronchiole is visible at the lower left. Note the necrosis of the bronchiolar wall and the fibroblastic peribronchiolar reaction (hematoxylin–eosin, ×142).

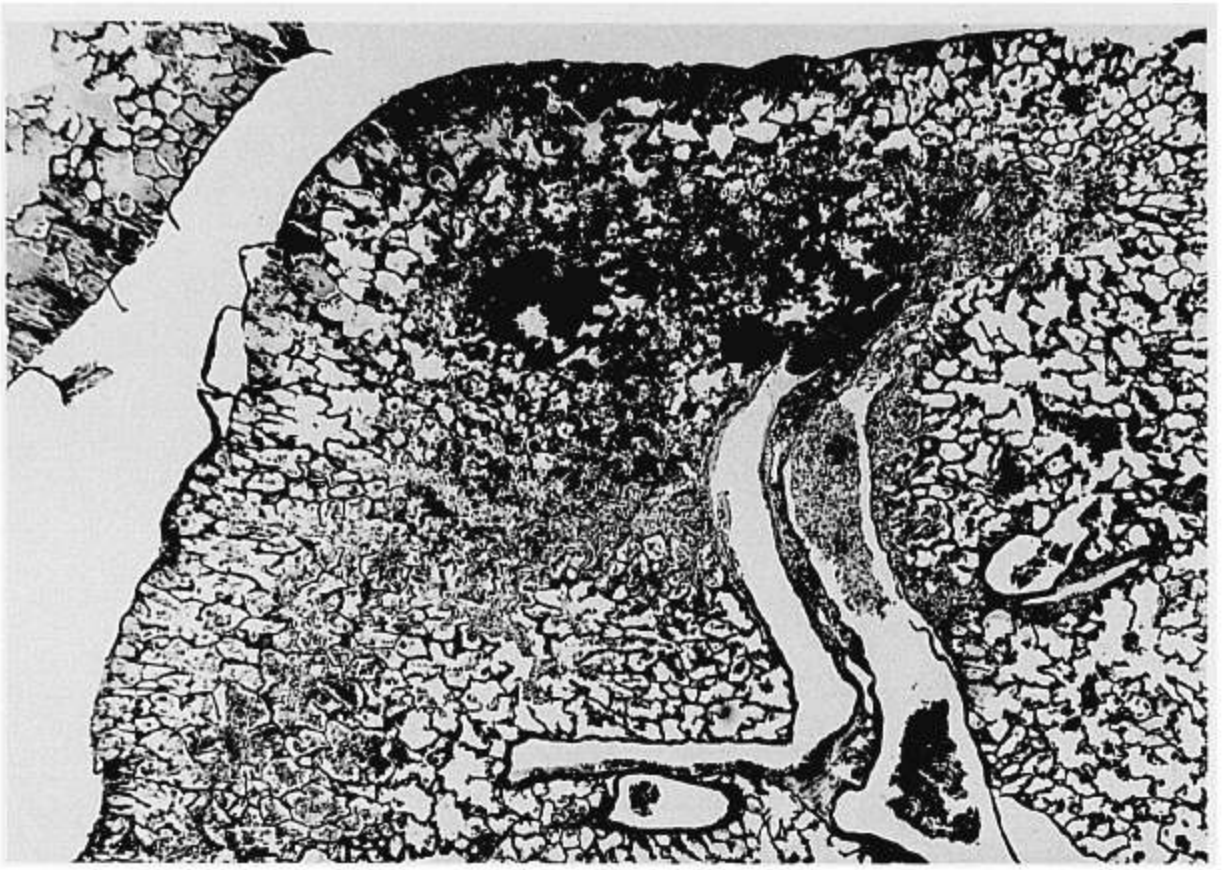

FIG. 4. Section of lung from an animal in Group II three days after aspiration of gastric contents. The arrow identifies an organizing thrombus occluding a small pulmonary artery. The thrombus is adjacent to an inflamed bronchiole occluded by inflammatory cells. A wedge-shaped, pleural-based zone of hemorrhage and necrosis, suggesting pulmonary infarction, can be seen distal to the thrombus (hematoxylin–eosin, ×48).

sparse in some areas, numerous in others, and in some areas, confluent. Multinucleate foreign-body-type giant cells were numerous. Vegetable and meat particles were identifiable in some, but not all, granulomas. In the larger areas of confluent granulomas there was often a center of granulation tissue and fibrosis, and in the largest, residual foci of necrosis were still present. Finally, in the small airways there was organization of the inflammatory reaction with either partial or complete obliteration of the lumen.

In the five animals in Group II sacrificed 21 days after aspiration, histologic abnormalities consisted mostly of patchy areas of granulomas and obliterative bronchiolitis. This reaction was minimal in light of the extensive changes that had been present earlier. This response varied; in some areas granulomas occurred singly, while in others they were confluent. The focal nature of the response seen at 21 days made histologic ranking virtually impossible, since random sampling of microscopic fields missed significant pathologic conditions. Therefore, statistical comparison of the 15 histologic findings was performed only for days 1, 3, and 7. Statistical comparison of Groups II and III at day 21 was made only in terms of necrosis of granulomas, which is discussed below.

Comparison of histologic ratings for Groups II and III one to seven days after aspiration revealed statistically significant differences between the groups in 11 of 15 categories (fig. 5). In only two categories (architectural disruption and alveolar septal metaplasia) were there significant differences between the groups on day 1. However, in these two categories and in nine others there were differences at days 3 or 7, or both. Animals treated with steroids had significantly less bronchial and septal fibrosis, formation of fibrous matrix, and bronchiolar metaplasia than did animals that were not treated. In addition, treated animals had fewer fibroblasts, giant cells, and macrophages. On the other hand, the percentage of polymorphonuclear cells was greater in Group III animals. There was no significant difference between the two groups that aspirated foodstuff on any day in the amounts of aspirate present, the extents of bronchiolar inflammation, or the extents of septal or alveolar edema.

Histologic examination of the lungs of animals sacrificed at 21 days revealed intense central necrosis of many of the granulomas seen in animals receiving steroids. The centers of these granulomas contained large amounts of nuclear debris and many polymor-

phonuclear leukocytes. Often necrosis was so severe as to cause dystrophic calcification (fig. 6). In contrast, necrosis was rarely present in animals that aspirated foodstuff but were not treated with steroids, and when present, was minimal. Necrosis was present in 14 per cent of granulomas studied in animals receiving steroids and in only 0.5 per cent of granulomas in animals not receiving steroids, a difference that was statistically significant.

Finally, aerobic, anaerobic, and fungal cultures from the gastric contents used in the experiment and from sections of lungs of two additional animals that had received the foodstuff aspirate and had been sacrificed 48 hours after aspiration revealed no consistent or significant growth of bacteria or fungus. In addition, tissue sections obtained from the left diaphragmatic lobe of six rabbits in Group II and six in Group III that had particularly severe histologic changes at day 3 or 7 were resectioned and Gram-stained. Bacteria could not be seen in any of these sections.

Discussion

Our study has indicated that the aspiration of gastric contents containing small food particles can severely injure the lung, even when the *p*H of the aspirate is above 2.5. This pulmonary injury is not caused by infection, but appears to be a reaction of the lung to the aspirated material. Our work confirms results of earlier studies by Teabeaut[15] and Moran[18]; however, by localizing the aspirate to a single lobe of the lung, by substantiating the histologic involvement with roentgenograms, and by consistently sampling the same portions of the left diaphragmatic lobe in all animals, we eliminated problems of interpretation that might result from sampling errors or from unequal distributions of the aspirate. The volume of aspirate we delivered to the left diaphragmatic lobe was proportionate to 2 ml/kg of aspirate dispersed throughout the entire lung and is approximately that used in many other experimental studies of acid aspiration.[20]

The histologic changes we found in animals receiving the foodstuff aspirate were similar to those described by Teabeaut.[15] In many respects, the edema, hemorrhage, and polymorphonuclear infiltrates present on day 1 also resembled those described to occur after acid aspiration.[20] However, by three days the inflammatory reaction had changed from the polymorphonuclear response characteristic of acid

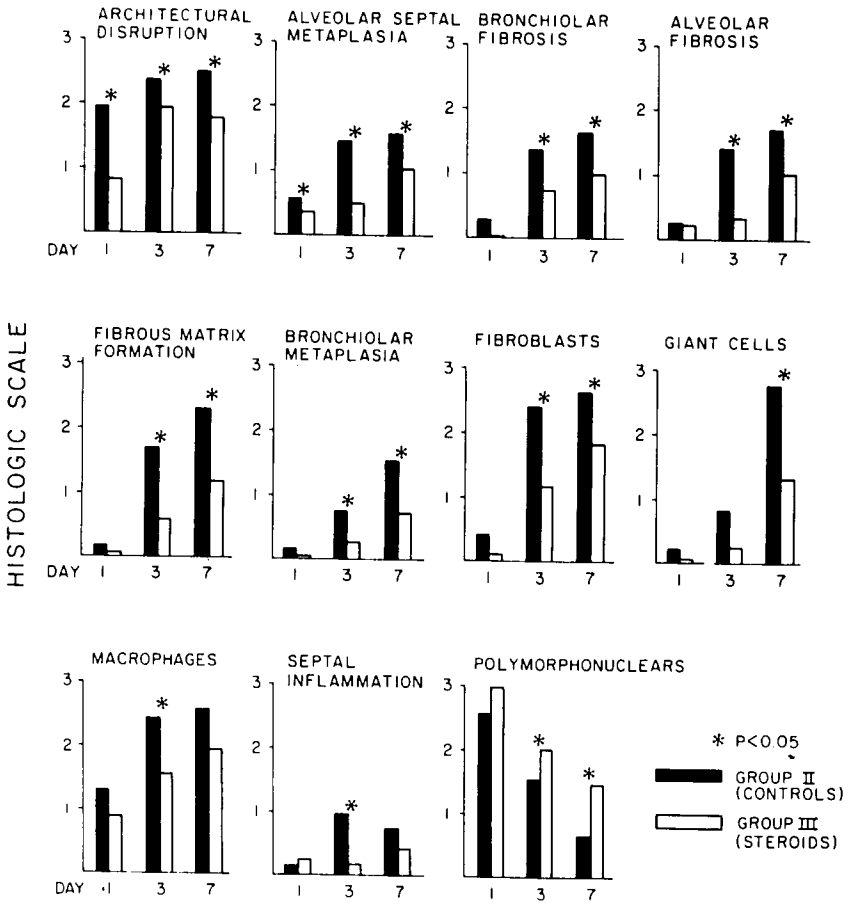

FIG. 5. Comparison of histologic ratings for Groups II and III in the 11 categories in which there were significant differences between groups.

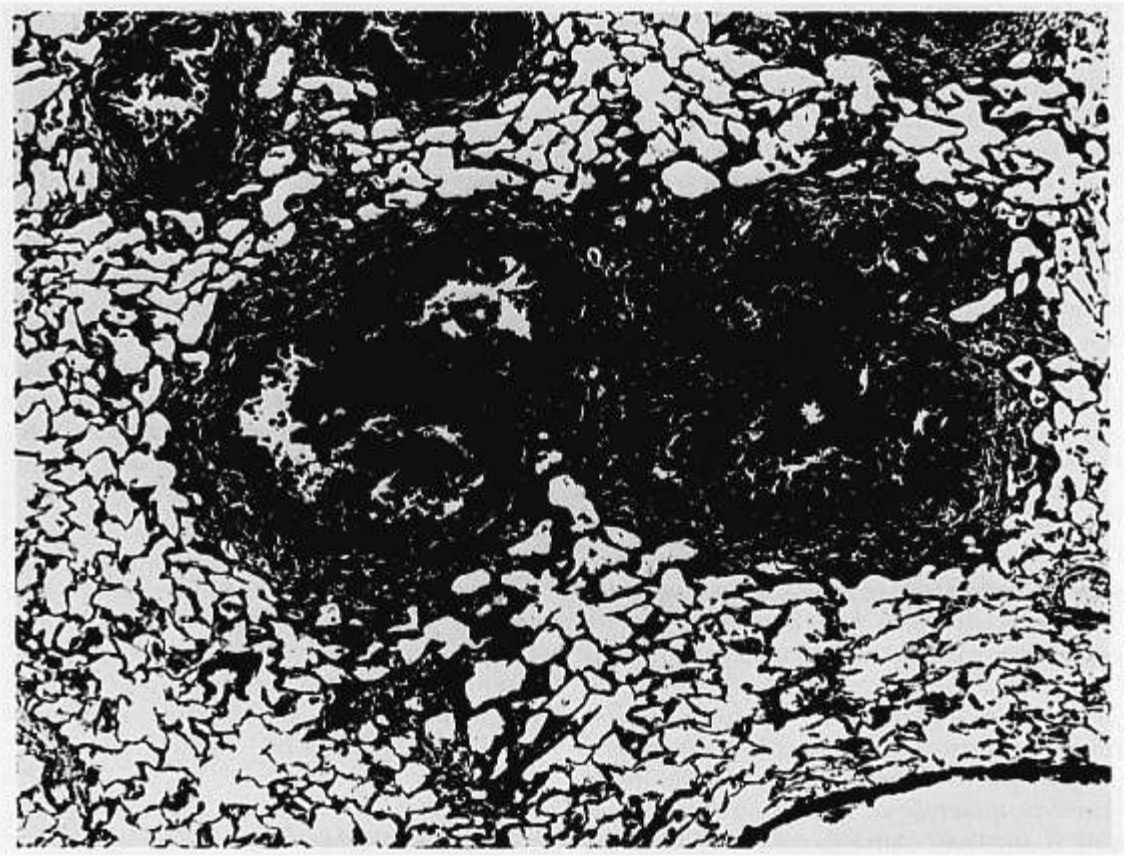

FIG 6. Lung tissue from an animal in Group III 21 days after aspiration. Note the severe central necrosis of the granulomas (hematoxylin–eosin, ×76).

aspiration to a mononuclear and granulomatous response. Also, hyaline membranes, which are frequently present after acid aspiration, were not seen. Despite the extensive area of the left lung originally involved by the aspirate and the presence of fibroblasts on days 3 and 7, the overall amount of fibrosis present at day 21 was minimal. This suggests that the long-term effects of foodstuff aspiration may be limited.

Of particular note in our animals were areas of hemorrhage and necrosis with accompanying *in-situ* pulmonary arterial thrombosis suggestive of pulmonary infarction. Similar changes have been seen in dogs following aspiration of 0.1 hydrochloric acid,[21,22] but have not previously been described to occur following aspiration of foodstuff. Another important finding in our animals was the extensive bronchiolitis induced by the foodstuff aspirate, leading to obstruction of the airways as well as the subsequent development of obliterative bronchiolitis. This reaction is also similar to that seen after aspiration of acid,[23] although the damage to large airways does not appear to be as severe. The obstruction of smaller airways could have important physiologic consequences, and the subsequent development of bronchiolitis obliterans may be the only important major residual effect of foodstuff aspiration.

Although we made no attempt to prove that this pulmonary reaction was caused by the food particles themselves, we strongly suspect this was the case. The work of previous investigators supports this contention. Mendelson,[14] for instance, administered neutralized liquid gastric contents into the lungs of rabbits and found no significant histologic change. Moran,[18] on the other hand, introduced finely ground food particles suspended in saline solution into rabbit lungs and found changes virtually identical to those we reported. Finally, Teabeaut[15] filtered gastric contents containing both meat and vegetable matter and introduced the filtered gastric juice into the lungs of rabbits. He observed only minimal histologic changes. The animals had no alveolar exudates and no areas of granulomatous reaction.

The significance of our observations, along with those of Teabeaut and Moran, pertains to the fact that much of the current knowledge of the pathophysiology and treatment of aspiration pneumonia has been gained from animal experiments using hydrochloric acid to induce pulmonary damage. The

realization that small particulate foodstuff at a more neutral *p*H can also damage the lung may make much of this previous work incomplete.

The effects of corticosteroid treatment for foodstuff aspiration have not been evaluated. However, corticosteroids might be expected to be of benefit in treating the granulomatous, fibroblastic reaction induced by this type of aspirate. Corticosteroids are known to diminish the influx of mononuclear phagocytes from peripheral blood to sites of inflammation,[24,25] to depress phagocytosis by macrophages,[26] to interfere with the processing of particulate antigens by macrophages,[27] and to affect the complex interactions between macrophages and lymphocytes involved in formation of granulomas.[28,29] Steroids have also been used for granulomatous diseases of the lung such as sarcoidosis, and in the early cellular phase of interstitial pneumonitis.[30] Since the optimum dose of corticosteroids for treating aspiration pneumonitis has not been established, we chose a high-dose multiple-injection regimen that was used in a previous study.[13]

Our experiment was designed to avoid problems of interpretation arising from sampling errors and from unequal distributions of aspirate in the lung, and to provide quantitative measurements suitable for statistical analysis. Analysis of our histologic findings suggests that corticosteroids did indeed exert their expected effects. During the first week after aspiration, animals treated with steroids had less fibroblastic proliferation and fewer macrophages and giant cells than did control animals. However, although the magnitude of mononuclear cell infiltration and granuloma formation was decreased, there was instead a persistent inflammatory response in the form of large numbers of polymorphonuclear leukocytes. As a result, the extents of pneumonitis, as measured by roentgenographic evaluation, were the same in treated and untreated animals. The histologic findings in the lungs of animals sacrificed at 21 days suggest the continuation of this inflammatory process in the group treated with steroids. Severe necrosis of granulomas with large amounts of cellular debris and dystrophic calcification was significantly more prevalent in animals receiving steroids.

In light of these findings, it would appear that the pneumonitis seen after aspiration of food matter may represent a housekeeping effort on the part of the lung to ingest, eliminate, or isolate foreign material. For the most part, this effort is successful, for by 21 days very little remains of the initial intense cellular response except localized foreign-body granulomas and scarred small airways. Extensive interstitial or alveolar fibrosis is also not a notable consequence of foodstuff aspiration, although a substantial number of fibroblasts can be seen early in the course of the reaction. This fibroblastic activity appears to be more directed at walling off and isolating foreign material than a precursor of extensive fibrosis. In this sense, corticosteroids appear to interfere with this clearing process and thus may prolong a state of acute inflammation in response to the aspirated material.

We view the fibroblastic granulomatous response of the lung to aspirated food matter as a protective mechanism. By interfering with this process, administering corticosteroids would appear to be detrimental. However, even if one accepts this view, it is not clear whether the histologic changes seen in the animals treated with steroids are important to their eventual recovery and function. We feel, however, that our study has demonstrated no clear benefit from administration of steroids, and that this should be considered when treating patients who have aspiration pneumonia. Our study also emphasizes the value of examining the effects of therapy over an extended period of time. If our evaluation had ended after a week, our conclusion might have been entirely different.

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