tion in the acid base balance of the blood produced a deviation from normal in the citric acid of the serum. Martensson(6) showed that citric acid is normally oxidized by the kidneys and, therefore, any change in kidney function from whatever cause could affect the level of citric acid in the serum. Thunberg (8) and Sjöström(9) found elevated levels of citric acid during hepatitis. We, however, did not do plasma electrolyte studies nor liver or kidney function tests on our subjects, and hence cannot relate abnormal serum citric acid levels to dysfunction of these organs.

Summary. The level of citric acid in the serum was determined in 50 patients with Hodgkin's disease, 10 with lymphosarcoma, 7 with leukemia, and in 19 with various forms of carcinoma. Sixty patients with a variety of non-malignant disease and 37 normal persons served as controls. No disease, malignant or non-malignant, was associated with a characteristic value, though variations from normal occurred in all disease categories.

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Cortisone Effect on Pneumonitis Produced in Mice by Exposure to a High Oxygen Atmosphere.* (19617)

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Application of cortisone and adrenocorticotropic hormones to the treatment of such pulmonary diseases as pneumonia(1) and bronchial asthma has focussed interest upon its effect on the inflammatory responses of the lung. The adverse effects of cortisone on experimental tuberculous disease have been reported(2) and have since been confirmed by reports of similar effects in clinical cases(3). However, since the pulmonary responses to tuberculous infection differ so markedly from those induced by other inflammatory diseases, it seemed desirable to investigate the effects of cortisone on acute pneumonitis.

Bacterial pneumonia was avoided in this study in order to eliminate the complicating factors of inhibition by cortisone of the usual host responses to infections(4). A fatal acute pneumonitis has been induced regularly in animals by prolonged continuous residence in atmospheres of 100% oxygen(5,6).

Materials and methods. In all experiments, the mice used were of a heterologous albino and Bartonella free strain, examined bacteriologically for freedom from enteric and respiratory infections. They were 8 to 10 weeks of age and averaged about 25 g in weight. Each group contained an equal number of males and females. For continuous maintenance of a 100% oxygen atmosphere, a special chamber was constructed. The bottom of the chamber was divided into compartments to permit the separation of the groups of mice. One compartment was used for the storage of the drugs and instruments needed for the experiment. The top was made of a transparent plastic material to permit observation of the animals, and was provided with a gasket so that airtight closure was possible. Two tubes were inserted into opposite ends of the chamber, one

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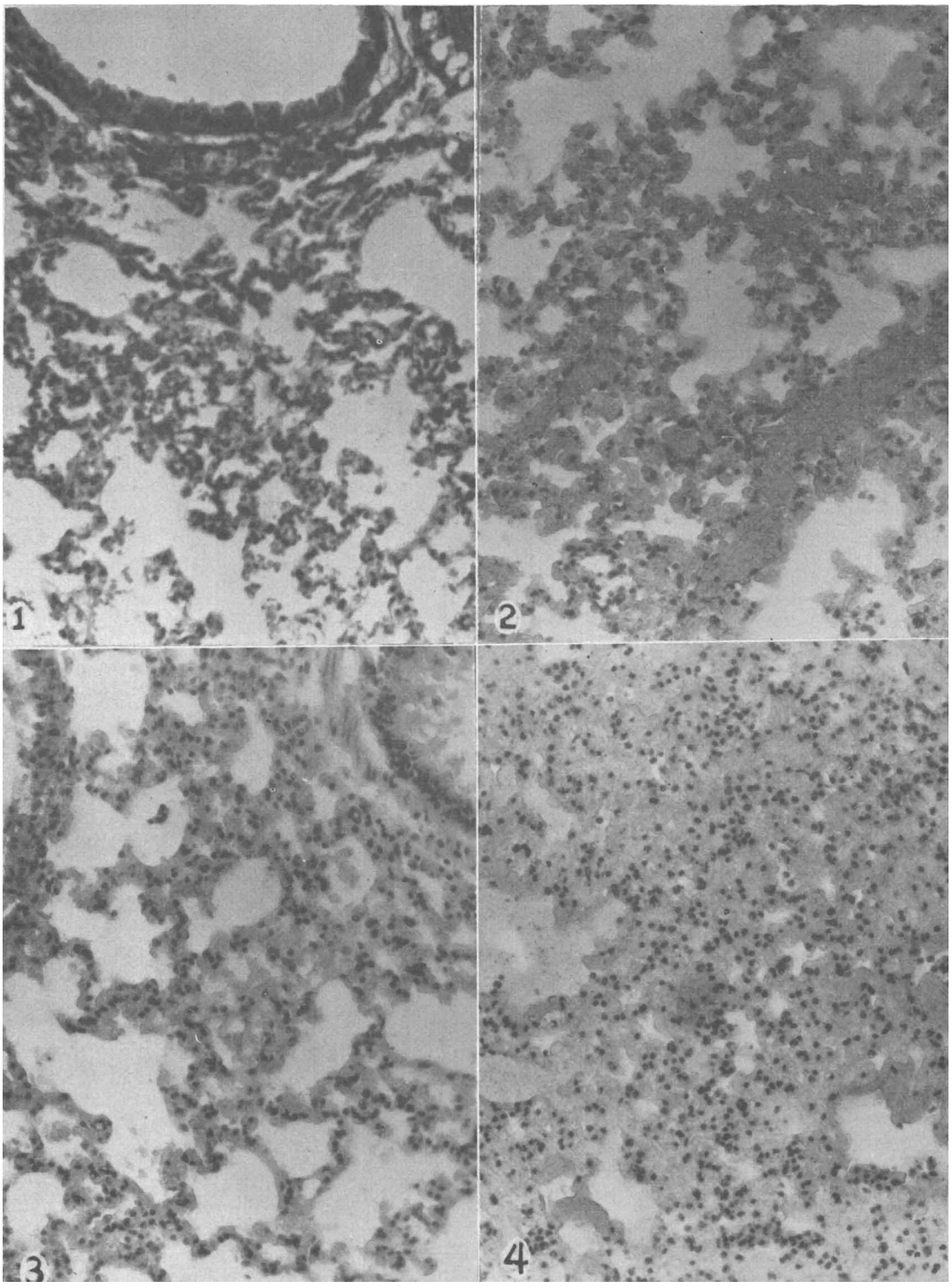

FIG. 1. Photomicrograph of lung of control sacrificed after 3 days in 100% O_2, showing a relatively normal appearance. Mag. × 350.

FIG. 2. Photomicrograph of lung of cortisone treated animal sacrificed after 3 days in 100%

O_2 showing intense engorgement of alveolar capillaries. Mag. × 350.

FIG. 3. Photomicrograph of lung of control sacrificed after 6 days in 100% O_2, showing engorgement of alveolar capillaries. Mag. × 350.

FIG. 4. Photomicrograph of lung of cortisone treated animal that died after 6 days in 100% O_2 showing alveolar exudate, fibrin, hyaline membranes and occasional leukocytes. Mag. × 350.

through which oxygen was supplied and the other through which it overflowed. Long-sleeved rubber gloves were sealed into portholes on two sides to permit handling and injection of the animals without opening the chamber. The animals were placed in the chamber together with supplies of food and water sufficient for the duration of the experiment. The drugs and the syringes and needles necessary for their administration were also placed in the chamber. The top was sealed and 100% oxygen was introduced at a high rate of flow for a time sufficient to purge the interior of the chamber of nitrogen. The oxygen flow was then reduced and then maintained at 5 liters per minute for the duration of the experiment. The constant overflow provided the means of removing carbon dioxide. Samples of the chamber atmosphere were tested twice daily to assure maintenance of the oxygen concentration above 99%.

In the first experiment, 32 mice were given a daily injection of 1 mg of cortisone while 20 additional mice received daily injections of identical amounts of the sterile diluent used to suspend the cortisone. These injections were continued for the duration of the experiment. On the fifth day, 20 of the cortisone treated animals and all of the control group were placed into the chambers and maintained in an atmosphere of 100% oxygen. The remaining 12 cortisone treated mice were kept in cages open to room air.

Results. The results of this experiment are presented in Table I. It will be noted that the cortisone treated animals proved to be much more susceptible to the lethal effects of prolonged exposure to a 100% oxygen atmosphere, all but one of this group having succumbed before the first deaths occurred among the controls. The prolonged survival of the cortisone treated animals maintained in room air is evidence that the increased rate of mortality cannot be attributed to the cortisone alone.

In the second experiment, essentially the same procedure was followed. A daily injection of 1 mg cortisone was given to each of 27 mice while the 26 controls received daily injections of comparable amounts of the diluent. All animals were placed in the chamber on the fourth day of the experiment. Commencing the second day of oxygen exposure, the chamber was opened just long enough to permit removal of the dead mice and of a number of the survivors which were sacrificed for histological study of their lungs. Sacrifices were made by cervical fracture. After resealing the lid, oxygen was admitted at a high rate of flow to purge the chamber of nitrogen and reestablish the 100% oxygen atmosphere.

The mortality rates (Table II) were similar to those of the first experiment, the cortisone treated animals proving to be less resistant to the toxic effects of the high oxygen atmos-

TABLE I. Effects of Cortisone on Survival of Mice Continuously Exposed to 100% Oxygen.

Day of exp.	Days in 100% O_2	No. dead: Cortisone treated	No. dead: Controls	No. dead: Air controls: Cortisone treated and maintained in room air
4	—	—	—	—
5	1	3	—	—
6	2	5	—	—
7	3	11	—	—
8	4	—	—	—
9	5	—	2	—
10	6	1	10	—
11	7	—	6	—
12	—	—	2	2
13	—	—	—	1
14	—	—	—	—
15	—	—	—	—

TABLE II. Effects of Cortisone on Survival of Mice Continuously Exposed to 100% O_2. Started 4th day of experiment.

Days in 100% O_2	Cortisone treated: No. dead	Cortisone treated: No. sacrificed	Controls: No. dead	Controls: No. sacrificed
1	—	—	—	—
2	1	5	—	6
3	3	2	—	5
4	5	1	1	5
5	5	—	2	2
6	2	—	1	4

phere. The lungs of the control animals sacrificed on the third day of exposure to 100% oxygen were normal on both gross and microscopic examination (Fig. 1) while those of the cortisone treated animals sacrificed on the same day showed intense engorgement of the alveolar capillaries (Fig. 2). The same early findings were not observed in those sacrificed animals in the control group until the sixth day of exposure, by which time all of the cortisone treated animals had died (Fig. 3).

The lungs of the cortisone treated animals that died were dark red in color and grossly congested. Microscopic examination (Fig. 4) revealed intense engorgement of the alveolar capillaries. The alveoli contained an exudate with mononuclear cells and polymorphonuclear leucocytes and fibrin which, in many instances, had formed a hyaline membrane. There was some perivascular exudate. The same changes were present in the peribronchial areas. Essentially the same finding was noted in the lungs of the control animals that died. Thus, the final picture was the same in both groups of animals except that all of the pathological alterations occurred significantly earlier in the cortisone treated animals.

Discussion. The demonstration of the effectiveness of cortisone in controlling status asthmaticus has resulted in wide use in the treatment of bronchial asthma. The fact that many asthmatic patients also have concurrent infectious disease of the lungs, as well as the fact that a patient treated with cortisone for non-pulmonary conditions may develop an independent pulmonary infection, prompts a consideration of the effects of cortisone on such pulmonary diseases.

Mice treated with cortisone have been shown to have increased susceptibility to pneumococcal and influenza A infections(7) and similar results have been demonstrated in streptococcal infections in rabbits(8,9). The enhancement of the lethal effects of an acute pneumonitis of non-infectious origin as shown by the above report emphasizes that cortisone depresses resistance to pulmonary inflammation. These data suggest that cortisone is contraindicated in the treatment of patients with pulmonary infections and that patients who are susceptible to acute pulmonary infection should be kept under careful observation when given this drug for other diseases.

While exposure to 100% oxygen at atmospheric pressure is not deleterious to humans, the finding that cortisone increases the susceptibility of lower animals (Rodentia) to its toxic effects suggests that consideration be given to the possibility that high concentrations of oxygen be administered cautiously to patients receiving cortisone.

Summary. 1. Cortisone was shown to increase the susceptibility of mice to acute pneumonitis induced by high oxygen atmosphere. 2. Pathologic changes appeared earlier in the lungs of the cortisone treated animals and the mortality rate was accelerated. 3. The terminal histologic findings in the lungs of the cortisone treated animals and the controls were qualitatively similar. 4. It is suggested that cortisone is contraindicated in the treatment of acute pulmonary infections. 5. Attention is called to the possibility that high oxygen atmospheres may be deleterious to patients receiving cortisone.

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