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OXYGEN POISONING IN MAMMALS.

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Plates 27 and 28.

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INTRODUCTION.

The increasing use of oxygen in clinical medicine would seem to make worth while a study of the toxic effects which may result from its prolonged inhalation in high concentrations. The observation that oxygen inhalation may lead to pathological states is not a new one. And yet it has seemed important to us, because of our own constant use of oxygen inhalation as a therapeutic measure, to investigate this problem further, giving particular attention to the nature of the injury and the mechanism of death. The fact that many of the experiments done in the past were performed on animals housed in small containers with inadequate ventilation made it appear especially desirable to repeat experiments under conditions in which CO_2 removal, temperature, humidity and air motion were controlled, and to rule out definitely the possibility of death resulting from respiratory infections so prone to occur in caged animals and in rabbits in particular. It seemed not improbable that some of the pulmonary lesions described in the literature might be the result of respiratory infections perhaps resulting from a lowered resistance of lung tissue when exposed to an abnormal mixture of atmospheric gases.

Lavoisier is said to have remarked the poisonous effects of oxygen inhalation shortly after the discovery of this gas in the atmosphere. Regnault and Reiset (2) in 1849 demonstrated that the respiration of different species of animals in an atmosphere containing two or three times the normal concentration of oxygen remains unchanged. They found no alteration in the amount of oxygen consumed, in the respiratory quotient, or in the general behavior of the exposed animals. No further investigation in this field appears to have been made until the

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classical experiments of Paul Bert (3) established the fact that oxygen at high tensions is a powerful poison. Bert showed that sparrows exposed to atmospheric air at 15 to 20 atmospheres pressure developed convulsions and died. If pure oxygen were used in the compression chamber only one-fifth as much pressure was needed to produce the same effects. On the other hand, if oxygen-poor air were used in the compression chamber the sparrows survived until overcome by the accumulated CO_2. Bert concluded that the toxicity of highly compressed air was due to the high tension of the contained oxygen, which he believed exerted a direct toxic effect upon the central nervous system. He was unable to reproduce the symptoms by the injection into a normal dog of a large amount of blood taken from a dog in oxygen convulsions. From this he argued that the status epilepticus which he described was not the result of a circulating poison secondarily produced by the oxygen. He found that high oxygen tensions had a similar effect on other laboratory animals and was also injurious to insects, arachnids, myriapods, molluscs, earthworms and germinating seeds. It inhibited the putrefaction of meat and delayed the souring of milk.

20 years later the problem was taken up by Lorrain Smith (4), who was the first to test out the effect of prolonged exposures to moderately high oxygen tensions. He found that mice suffered no ill effect from exposure for 8 days to 41.6 per cent of an atmosphere of oxygen, but that with 70 to 80 per cent of an atmosphere some mice died in 4 days of "congestion and consolidation" of the lungs, while others survived. At 1.14 to 1.50 atmospheres of oxygen all the mice died of consolidation of the lungs in 40 to 70 hours. At 1.66 to 1.89 atmospheres of oxygen mice, guinea pigs and larks died at 7 to 27 hours, the lung changes being similar. At 3.55 to 3.57 atmospheres of oxygen mice died in 5 hours. Mice which had begun to show dyspnea on exposure to this tension of oxygen died at once on being taken out of the chamber. Two larks exposed to 3.017 atmospheres of oxygen developed convulsions in 10 minutes. They were taken out of the chamber after 2 hours but both died. There was nothing noteworthy in their postmortem appearances. Lorrain Smith showed that by a previous short exposure to a high oxygen tension or by raising the oxygen tension very slowly the exposure could be carried distinctly beyond the point which usually produces convulsions. He also aimed to show that the toxic effect of oxygen is related to its tension in the inspired air and not its quantity in the blood. In a chamber containing 0.4 per cent carbon monoxide as well as 3 atmospheres of oxygen larks developed convulsions as usual, although the arterial blood at the end of the experiment was only 38 per cent saturated with oxygen.

In brief, Lorrain Smith demonstrated that moderately high tensions of oxygen produce an inflammation of the lungs, while very high tensions have an irritating effect on the central nervous system. He believed that the inflammatory reaction of the lung protected the central nervous system from pathological changes through interference with the diffusion of oxygen into the tissues. There is considerable variation between species and between individuals of the same

species in their susceptibility to oxygen. The minimum tension necessary to produce stimulation of the central nervous system is always well above that required to bring about pulmonary inflammation, but if the tension is sufficient the nervous symptoms develop rapidly and death may occur before there are any demonstrable changes in the lungs.

In 1903 Hill and McLeod (5) considered the question of the effect of compressed air on the respiratory exchange. From their experiments on mice they concluded, in agreement with an observation of Paul Bert, that a partial pressure of oxygen equal to 1 atmosphere does not increase, but rather lessens the processes of oxidation.

On the other hand, experiments in lower animal forms (6) have shown that the metabolism of many lower invertebrates, both marine and terrestrial, and some of the higher invertebrates such as the lobster and annelid worm is proportional over a wide range to the oxygen tension. This does not appear to be true of vertebrates.

Curiously enough, Lavoisier's original observation of the toxic effects of breathing high concentrations of oxygen at atmospheric pressure did not receive the attention of later workers (with the exception of Lorrain Smith) until Schmiedehausen (1) and David (7) confirmed his findings. They reported that pure oxygen supplied to a dog through a tracheal cannula produced a mild pulmonary hyperemia in as short a period as 15 minutes. 1 hour's exposure of a dog to 90 per cent oxygen in a chamber brought about definite hyperemia and extravasation of blood into the bronchi and alveoli. Similar results were noted in mice and guinea pigs, particularly after longer exposures. One guinea pig was exposed to 40 to 60 per cent oxygen at atmospheric pressure for 69 hours and 37 minutes. 6 hours after being taken out of the chamber into room air the animal died. Postmortem examination showed bronchopneumonia. This is the only case we have found recorded in the literature of pulmonary inflammation following exposure to increased oxygen tensions of less than 70 per cent of an atmosphere.

Benedict and Higgins (9), in 1911, carried out a series of experiments on the effect of inhalation of oxygen-rich mixtures for short periods of time on normal young men. With 40, 60 and 90 per cent oxygen they found no change in metabolism or respiration but a definite decrease in the pulse rate, which was more or less proportional to the percentage of oxygen breathed.

Bornstein and Stroink (10), in 1912, report the first case of experimental oxygen poisoning in man. Bornstein placed himself in a pressure chamber exposed to 2 atmospheres of pure oxygen. After 50 minutes he began to have cramps, first in the right, then in the left arm. The cramps ceased as soon as the pressure was lowered. These investigators also carried out a series of experiments on the effect of high oxygen tensions on dogs, apes, cats and rats. A dog and an ape, kept for several months in 0.6 atmosphere of oxygen, showed slight anemia,—an interesting observation in view of the opposite effect of low oxygen tensions.

Retzlaff (11), in 1913, found that the inhalation of oxygen produces vasoconstriction of the pulmonary blood vessels in the cat, and he suggests that the

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beneficial effect of oxygen administration in cardiac failure with pulmonary edema may be ascribed to the improved pulmonary circulation thereby produced.

In 1916, Karsner (12) made an extensive study of the pathology of oxygen poisoning in rabbits, and recorded the time relationships of the various changes and gave a definition of the type of pneumonia occurring. He found that "80 to 96 per cent oxygen under normal barometric pressure produces in 24 hours, or more commonly 48 hours, congestion, edema, epithelial degeneration and desquamation, fibrin formation, and, finally, a pneumonia, probably of irritative origin," and described by him as a "fibrinous bronchopneumonia." He also found a certain degree of congestion in all of the abdominal organs which he believed to be secondary to the damage done to the pulmonary circulation. There were no demonstrable changes in the hematopoietic system other than congestion.

In a later work (13) Karsner and his coworkers showed that high partial pressures of oxygen are definitely inhibitory to the growth of certain strains of bacteria, while on other strains they may have no effect. The growth of pneumococcus was not inhibited by high oxygen tension.

Cleveland (14), in 1925, reported a series of ingenious experiments which indicated that oxygen in high concentrations is peculiarly toxic to intestinal protozoa. In cockroaches, for instance, the oxygen is 135 times as toxic for flagellates and 26 times as toxic for ciliates as for the host cockroaches. Similar effects are seen in termites and to a less marked degree in frogs, salamanders and goldfish, so that the intestinal tracts of these animals can be cleared of protozoa by simply exposing them to a sufficient oxygen tension. This test is impossible to carry out in warm blooded animals because the host is more susceptible than the parasite.

Barach (15), in 1926, published a series of carefully controlled experiments on the effect of oxygen-rich atmospheres on normal rabbits and on rabbits with pulmonary tuberculosis. He found that 60 per cent oxygen produced no effect on the general appearance, activity and weight or growth of normal rabbits over periods as long as 1 to 4 months. Furthermore, no gross or microscopic pathological change was observed for periods as long as 1 to 2 months. Attempts to increase the resistance of the pulmonary epithelium to atmospheres containing 80 to 85 per cent oxygen by previous exposure to lower concentrations were unsuccessful. In one case pulmonary edema followed the inhalation of 70 per cent oxygen for 12 days. On the basis of these observations Barach states that the highest concentration of oxygen compatible with safety for therapeutic use should be regarded as 60 per cent.

EXPERIMENTAL.

Our own studies on the toxic effects of oxygen began with observations on three dogs and three rabbits kept in an atmosphere of approximately 80 per cent oxygen. The animals were placed in cages in a large oxygen chamber used ordinarily for the treatment of pneumonia patients. In this chamber it was possible to maintain satisfac-

tory cleanliness and isolation of one animal from the other and to provide for the proper removal of carbon dioxide and moisture, and maintenance of fairly constant conditions of temperature, relative humidity and air motion. Daily observations of the weight, body temperature and behavior of the animals, and more frequent records of the room temperature, humidity and oxygen concentration were made. After a 4 day control period with the chamber open to the atmospheric air the doors were closed and oxygen was admitted into the chamber. The oxygen content of the chamber was raised at once to a little over 50 per cent of 1 atmosphere and then gradually, during the next 30 hours, to 80 per cent, where, with minor fluctuations, it was maintained throughout the remainder of the experimental period.

Experiments on Dogs.

The first abnormal sign noted in the dogs was the refusal of food. This was observed on the 3rd day after exposure to 70 to 80 per cent oxygen in Dog 1, a young, immature dog, on the 4th day in Dog 2, and on the 5th day in Dog 3. All of the dogs lost weight after the 3rd day. *Vomiting* occurred on the 5th day in Dog 1, on the 6th day in Dog 3 and was absent in Dog 2. *Drowsiness* was first recorded on the 6th day in all three dogs. *Labored breathing* was first noticed on the 6th day in Dog 3, on the 7th day in Dog 1 and was absent throughout in Dog 2. This respiratory distress became progressively worse during the rest of the experimental period. It had the character of slow, labored, deep breathing often associated with an apparent expiratory effort. There were no seemingly significant variations in the body temperature. Text-fig. 1 shows the variations in body weight and temperature in relation to O_2 and CO_2 content of the chamber.

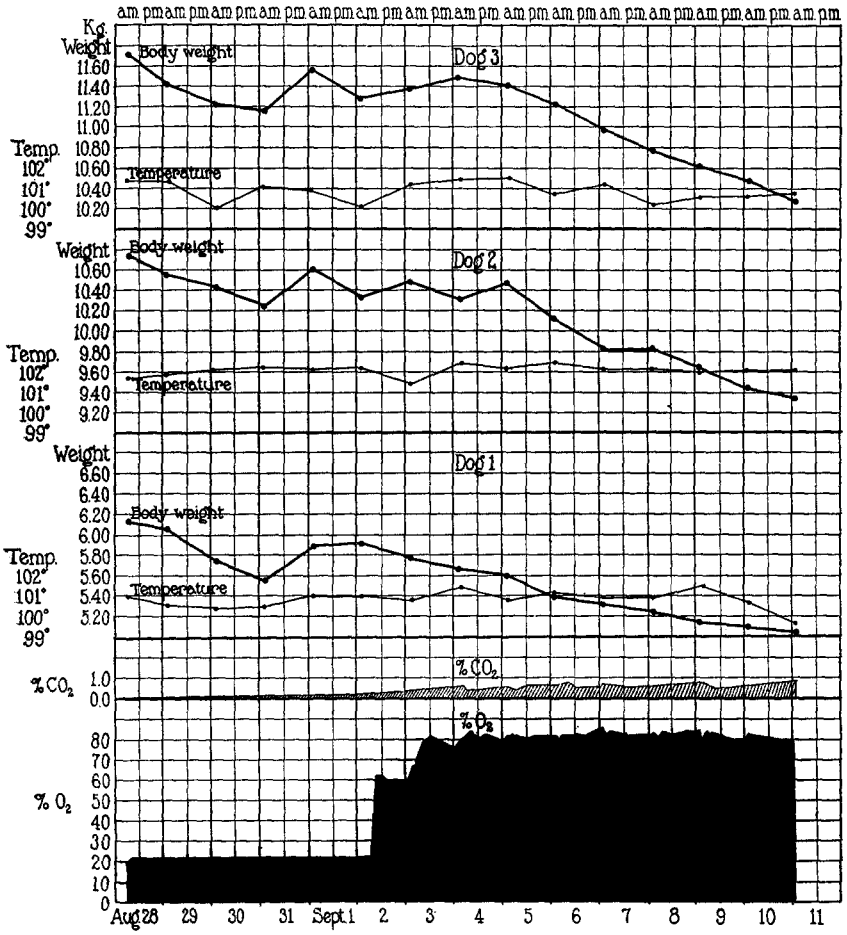
After 8 days exposure to 70 to 80 per cent of an atmosphere of oxygen the dogs were removed from the chamber and samples of their arterial blood were drawn for oxygen analysis by puncturing the femoral arteries.

Dog 1 was markedly cyanosed. There was a cardiac arhythmia, shown by electrocardiograph to be the result of extrasystoles. Blood-stained froth was pouring from the mouth. Breathing was labored. At each inspiration the flanks were sucked in and expirations were grunting. When turned on its back respiratory distress became very great. Analysis of the arterial blood showed an oxygen saturation of only 40 per cent.

Dog 2 showed no evidence of anoxemia or respiratory distress. The arterial blood was 94.6 per cent saturated with oxygen.

Dog 3, like Dog 1, though far less markedly, manifested respiratory disturbance. Respirations were slow and labored. The flanks sucked in with inspiration and expiration was accompanied by a prolonged groan. There was, however, no definite arterial anoxemia, the blood being 93.7 per cent saturated with oxygen.

The three dogs were then immediately and painlessly killed by the intravenous injection of from 10 to 20 cc. of a saturated solution of magnesium sulfate. This



TEXT-FIG. 1. Chart showing loss of weight of three dogs confined in chamber containing 80 per cent oxygen. The oxygen concentration is represented by the black area; the carbon dioxide by the narrow shaded area. Carbon dioxide concentration remained below 0.8 per cent throughout the experimental period.

method is admirable for the study of pulmonary pathology, as the heart beat and respirations are arrested simultaneously and at once, unaccompanied by an antemortem struggle.

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Autopsies on Dogs.

The gross and microscopic appearance of the lungs in the three dogs showed changes in keeping with the severity of their response to oxygen. When examined by a pathologist* who was unfamiliar with the symptomatic course of these three animals the lesions were graded in order of intensity thus: Dog 1, Dog 3, Dog 2, which will be seen to correspond to the manifestations cited above.

Description of Lesions in Lungs of Dog 1.

When the thorax was opened the lungs were found to be collapsed. They were mottled, beefy red—bright in some areas and dull red in others. There were no normally pink lobes. The trachea was full of blood-tinged froth. There was no free fluid in the pleural cavities. The lungs were disturbed as little as possible, except for punctures made for the purpose of making cultures. They were fixed *in situ* by distending them with Helly's fluid injected through a tube tied in the trachea. The roots were then ligated and the lungs carefully removed from the thorax and placed in Helly's fluid. Histological preparations were made by the usual paraffin technique, sections being cut at 7 μ and stained with Giemsa and hematoxylin and eosin. The sections revealed a general destructive process of a non-infectious character involving all parts of both lungs, the chief features being: (1) capillary engorgement with some hemorrhage; (2) the presence of interstitial and intraalveolar serum; (3) hypertrophy and desquamation of alveolar cells; and (4) interstitial and intraalveolar infiltration of mononuclear cells.

No microorganisms were seen in any of the sections examined. It will be shown later that these lesions, though not so marked in the dog, are pronounced in the lungs of the rabbits exposed to oxygen in the same chamber with the dogs. A photograph of a characteristic section of lung tissue from Dog 1 is shown in Figs. 1 to 3.

Description of Lesions in Lungs of Dog 2.

On opening the chest wall the lungs were collapsed and of essentially normal appearance, being uniformly coral-pink. There was no evidence of infiltration or consolidation; nor was there any free fluid in the pleural cavities. The lungs were treated in the same manner as those of Dog 1. Microscopic examination showed little change except for an apparent capillary engorgement.

Description of Lesions in Lungs of Dog 3.

Both lungs were collapsed. The right lung was, for the most part, normally pink in color, but there were a few small hemorrhagic areas near the periphery, especially on the anterior borders of the ventral lobe. The left lung had several small hemorrhagic areas on the surfaces of all lobes which were otherwise of normal

* Dr. L. T. Webster of the Staff of The Rockefeller Institute, whom we wish to thank for his help in interpreting the nature of the lesions.

appearance. There was no free fluid in the pleural cavities. Microscopic examination showed capillary engorgement with some hemorrhage. Fig. 4 shows a photomicrograph of a characteristic region taken from the right lower lobe of Dog 3.

The gross appearance of all the other viscera was essentially normal.

Attempts at Cultivation of Bacteria.

Broth cultures taken from the heart's blood in all three dogs were sterile, and material from the lung punctures streaked on blood agar also showed no bacterial growth.

Experiments on Rabbits.

Three rabbits, housed in separate cages, were placed in the same chamber with the dogs just described, and exposed to identical atmospheric conditions as the dogs. Daily observations of body temperature and weight were made as well as careful inspection of behavior. No significant fluctuation in temperature occurred. All of the rabbits showed a slight loss of weight during the experimental period. *The first symptom of significance was marked dilatation of the alæ nasi accompanying respiration.* This was noticed on the 6th day after exposure to 70 to 80 per cent oxygen in Rabbit 1; on the 6th day in Rabbit 2; on the 5th day in Rabbit 3. From their general appearance at this time the prediction was made that they would die in the order in which they eventually did die, namely No. 3 first, then No. 1 and finally No. 2. The dilatation of alæ nasi was followed by definite signs of respiratory distress, gasping inspirations with the use of the accessory muscles of respirations, the mouth opening wide with each inspiration. This was accompanied by definite cyanosis of the tissues about the nose and of the ear tips. These symptoms appeared from the 6th to 7th day in all three animals. The intensity of the respiratory distress grew worse, the animals showing marked orthopnea when turned on their backs for the purpose of taking their temperatures. Rabbits 1 and 3 died on the 7th day after exposure to 70 to 80 per cent oxygen.

From the appearance of cyanosis and the low oxygen saturation found in the arterial blood of Dog 1 it was believed that the immediate cause of death was probably anoxemia resulting from the lesion of the respiratory membrane. To test this point further it was decided to take Rabbit 2 out of the chamber, with the anticipation of its being immediately asphyxiated by the sudden lowering of alveolar oxygen tension. When this was done the animal at once had a convulsive seizure and died in a few moments after exposure to atmospheric air.

Autopsies on Rabbits.

With minor variations in intensity of reaction the gross and microscopic appearance of the three rabbits' lungs were closely similar. All three showed mottled dull to beefy red discoloration—with much gross edema, and either froth or fluid in the trachea. Rabbit 1 had 2 to 3 cc. of blood-tinged fluid in both pleural cavi-

ties, which, on direct smear, showed many lymphocytes and leucocytes and fibrin, but no bacteria. A few cc. of a similar but not blood-tinged fluid was found in the pleural cavities of Rabbit 2. None was seen in Rabbit 3.

Microscopic examination of the lungs of the three rabbits showed in varying degrees of severity the same reaction as seen in Dog 1, though on the whole a more intense one, *viz.*: capillary engorgement with hemorrhage, interstitial and intra-alveolar serum, hypertrophy and desquamation of alveolar cells, interstitial and intraalveolar infiltration of mononuclear and of a few eosinophilic cells. No microorganisms were found in any of the sections examined. Photomicrographs of sections from the lungs of Rabbits 1 and 3 are shown in Figs. 5 and 6. Heart's blood cultures were sterile. With the exception of an occasional mold and colony of large spore-bearing bacillus most of the plates streaked with material obtained from lung puncture were likewise sterile.

Experiment on a Guinea Pig.

Protocol.—December 3. A guinea pig was placed under a bell jar, so arranged on a wooden platform that oxygen could be blown into the jar at the desired rate. A basket containing soda-lime, for the removal of CO_2, was suspended in the jar. At 4.25 p.m. the flow of oxygen through the jar was begun at the rate of 1 liter a minute.

December 4. The guinea pig looks normal. There is no dyspnea. Analysis of sample of gas in the bell jar: Oxygen, 99 per cent. Carbon dioxide, 0.67 per cent.

December 6. 12 noon. Respirations deep.

5 p.m. No apparent dyspnea. The guinea pig has eaten lettuce and some oats.

December 7. 9 a.m. Found dead. Autopsy showed the lungs to be a deep, dull red, resembling liver in appearance. Sections of the lungs placed in 10 per cent formalin sank to the bottom of the container.

Experiments on Mice.

Four full grown mice were placed by pairs into two dialyzing jars which were found to be convenient receptacles for subjecting them to the desired gas mixtures. The jars were partly filled with wood shavings to serve as bedding for the mice and provide for their warmth. Two of the mice acted as controls and two of them were to be subjected to a high concentration of oxygen. Compressed air was run into the control jar from a pressure tank at a rate of 1 liter per minute and oxygen into the other. This rate of flow provided for an adequate removal of CO_2 and moisture. It was believed that any harmful influence which might result from the effect of compression and commercial handling of oxygen might be controlled by the use of air compressed to the same degree in cylinders identical to those containing the oxygen.

Protocol.

Control Mice.

Mouse marked with mercurochrome. Weight 25 gm.

Unmarked mouse. Weight 19 gm.

Nov. 16, '25, 4.30 p.m. Air flow started at 1 liter per min.

Nov. 17, '25. Mice active. Buried in shavings most of the time. No condensation of moisture on walls of jar.
Analysis of air in jar: O_2 = 22.09 per cent.
CO_2 = 0.22 per cent.

Nov. 18, '25. Mice appear normal.
Analysis of air in jar: O_2 = 21.58 per cent.
CO_2 = 0.25 per cent.

Nov. 21, '25. Mice appear normal.

Nov. 22, '25. Mice appear normal.
Analysis of air in jar: O_2 = 21.68 per cent.
CO_2 = 0.4 per cent.
4.30 p.m. Compressed air tank nearly empty. Jar connected with house air pressure system and air run in at the same rate of flow, *viz.:* 1 liter per min.

Oxygen Mice.

Mouse marked with picric acid. Weight 19.6 gm.

Mouse marked with carbolfuchsin. Weight 20 gm.

Nov. 16, '25, 4.30 p.m. O_2 flow started at 1 liter per min.

Nov. 17, '25. Mice appear normal.
O_2 concentration in jar 98 per cent.

Nov. 19, '25. Mice appear normal. They are lively and restless. They remain on top of the shavings, whereas control mice are buried.
O_2 concentration in jar 98 per cent. CO_2 0.39 per cent.

Nov. 20, '25. Mice appear normal.
O_2 concentration 98.5 per cent.

Nov. 21, '25. Mice appear normal.

Nov. 22, '25, 11.30 a.m. Mouse marked with picric acid is found dead. Weight 15.8 gm. Mouse marked with carbolfuchsin is gasping for breath. Its mouth opens wide and its whole body shakes at each inspiration. Cyanosis of tail, feet and nose. 2.45 p.m. Mouse dead. Weight 15.3 gm.

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Nov. 23, '25. Mice appear normal.

Nov. 24, '25. Mice appear normal.

Nov. 25, '25. Mice appear normal.
Mouse marked with mercurochrome now weighs 27.6 gm. Unmarked mouse now weighs 20.6 gm. Jar cleaned and fresh wood shavings put in. Flow from compressed air cylinder again begun at rate of 1 liter per min.

Nov. 27, '25. Mice appear normal.

Nov. 28, '25, 8.40 p.m. Mice appear normal.

Nov. 29, '25, 10.30 a.m. Mice appear normal.

Nov. 30, '25. Mice removed from jar. They are active and normal in appearance.
Mouse marked with mercurochrome weighs 27.1 gm.
Unmarked mouse weighs 20.5 gm.

Autopsy of both these mice showed the lungs to be uniformly discolored a deep red, almost indistinguishable from liver. The lungs sank when placed in Zenker's fluid.

The experiments thus far reported demonstrate quite clearly, we believe, that for several mammalian species, the mouse, guinea pig, rabbit and dog, inhalation of commercial oxygen in concentrations greater than 70 per cent of an atmosphere may lead to a train of physiological changes consisting of drowsiness, loss of appetite, loss of weight, dyspnea and cyanosis, usually culminating in death from extreme oxygen want. The cause of the oxygen want is undoubtedly to be sought for in the acute pulmonary changes, to be characterized as a diffuse hemorrhagic edema of the lungs found in all these species.

Is it possible that this destructive process is due not to the oxygen itself but to some impurity in it introduced in the process of manufacture? The oxygen used thus far in this work was commercially prepared by a method now commonly employed, namely: the fractional distillation of liquid air. Before concluding that the pathological effect is due to oxygen and not to the presence of impurities, parallel experiments were done on mice kept in jars containing oxygen prepared in two differing ways: (1) by the so called "air reduction" process, (2) by the electrolytic dissociation of water.

This experiment shows that mice confined in a jar containing 96 to 98 per cent oxygen electrolytically prepared show the same physiological and pathological reactions as mice confined in equivalent concentrations of oxygen prepared by the "air reduction" process.

Burrows (16) reported the observation that oxygen was inhibitory to the growth of tissue cultures only when the gas had been led through rubber tubing, and believed that the toxic effect was due to a substance formed by the reaction of oxygen or ozone with rubber. Burrows, however, prepared his oxygen by the electrolysis of dilute H_2SO_4. By this method there is usually a contamination with ozone, which Burrows removed by bubbling the gas through olive oil. Under these circumstances it was not inhibitory to the growth of his culture material.

To control this factor two mice were placed in a dialysis jar connected with a tank of electrolytically prepared oxygen. The oxygen from the cylinder was led through glass tubes and bubbled successively through three wash bottles containing respectively 2M H_2SO_4, 2M NaOH and an approximately 10 per cent solution of K_2MnO_4. 4 days after the flow of oxygen was begun both mice were gasping for breath and incoordinated in their motions. The following day one of

Protocol.

Air Reduction Oxygen.

Nov. 24, '25. Two mice put in dialyzing jar. One stained with safranine, the other unmarked.
3.50 p.m. O_2 flow started at 1 liter per min.

Nov. 25, '25, 2.20 p.m. Both mice appear normal.
O_2 concentration 96 per cent.
CO_2 concentration 0.27 per cent.

Nov. 27, '25, 11.50 a.m. Mice appear drowsy and inactive.
O_2 concentration 99 per cent.
CO_2 concentration 0.41 per cent.

Nov. 28, '25, 8.40 p.m. Mice alive but very dyspneic.

Nov. 29, '25, 10.30 a.m. Safranine-marked mouse is dead. Second mouse living but very dyspneic. Moves about actively, however. Coat is ruffled.
O_2 concentration 97 per cent.
CO_2 concentration 0.11 per cent.

Nov. 30, '25. The surviving mouse breathing very rapidly, but not gasping.
O_2 concentration 98 per cent.

Dec. 2, '25. Died at 11 a.m. Autopsy shows usual picture of red liver-like appearance of lungs. The removed lungs sink when placed in distilled water.

Electrolytic Oxygen.

Nov. 24, '25. Two mice put in dialyzing jar. One stained with safranine, the other unmarked.
3.50 p.m. O_2 flow started at 1 liter per min.

Nov. 25, '25, 12.30 p.m. Mice lively. Appear normal.
O_2 concentration 96 per cent.
CO_2 concentration 0.55 per cent.

Nov. 27, '25, 11.30 a.m. Mice appear normal, but drowsy.
O_2 concentration 98 per cent.
CO_2 concentration 0.50 per cent.

Nov. 28, '25, 8.40 p.m. Both mice very dyspneic.

Nov. 29, '25, 10.30 a.m. Severe dyspnea.
4.30 p.m. Unmarked mouse gasping. Lower jaw drops with each inspiration. Other mouse looks sick but is not gasping. Both move about when jar is shaken. Coats are ruffled.
O_2 concentration 96 per cent.
CO_2 concentration 0.18 per cent.

Nov. 30, '25. Both mice gasping. Noses and tails dusky bluish. Have eaten very little.

Dec. 1, '25. Both mice found dead. Lungs are deep purple-red the color of liver. Sink in water.

them was dead and the other, when moribund, was etherized. The lungs of both showed the usual changes.

In another experiment oxygen was bubbled through olive oil for the purpose of removing traces of ozone, even though its presence could not be shown by the starch-iodine test on the gas as it emerged from the cylinder. Mice exposed to this oxygen died of the same symptoms and showed the same autopsy findings as all the others described above.

DISCUSSION.

The phenomena described in this paper seem to have general application. The mammalian organism can survive exposure to oxygen concentrations varying roughly from 6 per cent to 60 per cent of an atmosphere. Beyond these limits it rapidly deteriorates, and at each extreme, death results from oxygen deprivation. At the lower limit oxygen want results from the diminished alveolar oxygen tension. At the upper limit, although alveolar oxygen tension is far above normal, the diffusion membrane of the lung is so damaged that in spite of the increased head of pressure in the alveoli, the arterial blood remains unsaturated, and the animal dies from anoxemia. This process possibly is of a "protective reaction" nature on the part of the organism, but going too far culminates in death. The organism, in its unsuccessful effort to achieve a new equilibrium, is kept alive by the very environmental condition which ultimately destroys it.

SUMMARY AND CONCLUSIONS.

1. Oxygen in concentrations of over 70 per cent of an atmosphere is poisonous to dogs, rabbits, guinea pigs and mice.

2. The poisonous effects manifest themselves in drowsiness, anorexia, loss of weight, increasing dyspnea, cyanosis and death from oxygen want.

3. The cause of oxygen want is a destructive lesion of the lungs.

4. The lesion may be characterized grossly as an hemorrhagic edema. Microscopically there is to be seen in varying degrees of intensity (*a*) capillary engorgement with hemorrhage, (*b*) the presence of interstitial and intraalveolar serum, (*c*) hypertrophy and desquama-

tion of alveolar cells, (*d*) interstitial and alveolar infiltration of mononuclear cells.

5. The type of tissue reaction is not characteristic of an infectious process and no organisms have been recovered at autopsy from the heart's blood or from lung puncture.

6. The poisonous effects of inhalations of oxygen-rich mixtures do not appear to be related to impurities in the oxygen, nor are they related to faulty ventilation, excessive moisture or increased carbon dioxide in the atmosphere of the chambers in which the experimental animals were confined.

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EXPLANATION OF PLATES.

PLATE 27.

FIGS. 1 and 2. Photomicrographs of sections of right lower lobe of lung of Dog 1. Magnification × 130. The pictures show the intraalveolar transudation of serum and red blood corpuscles.

FIG. 3. Section of right lower lobe of Dog 1. Magnification × 500. The picture shows desquamated alveolar epithelial cells.

PLATE 28.

FIG. 4. Section of lower lobe of right lung of Dog 3, showing engorged and tortuous alveolar capillaries. Magnification × 130. This probably represents the initial hyperemic stage before hemorrhage and edema have occurred.

FIG. 5. Section of lung of Rabbit 1. Magnification × 130. The picture shows transudation of serum and cells as well as cellular exudate.

FIG. 6. Section of lung of Rabbit 3. Magnification × 500. The picture shows desquamation of alveolar epithelial cells as well as an exudate consisting chiefly of mononuclear and a few eosinophilic cells.

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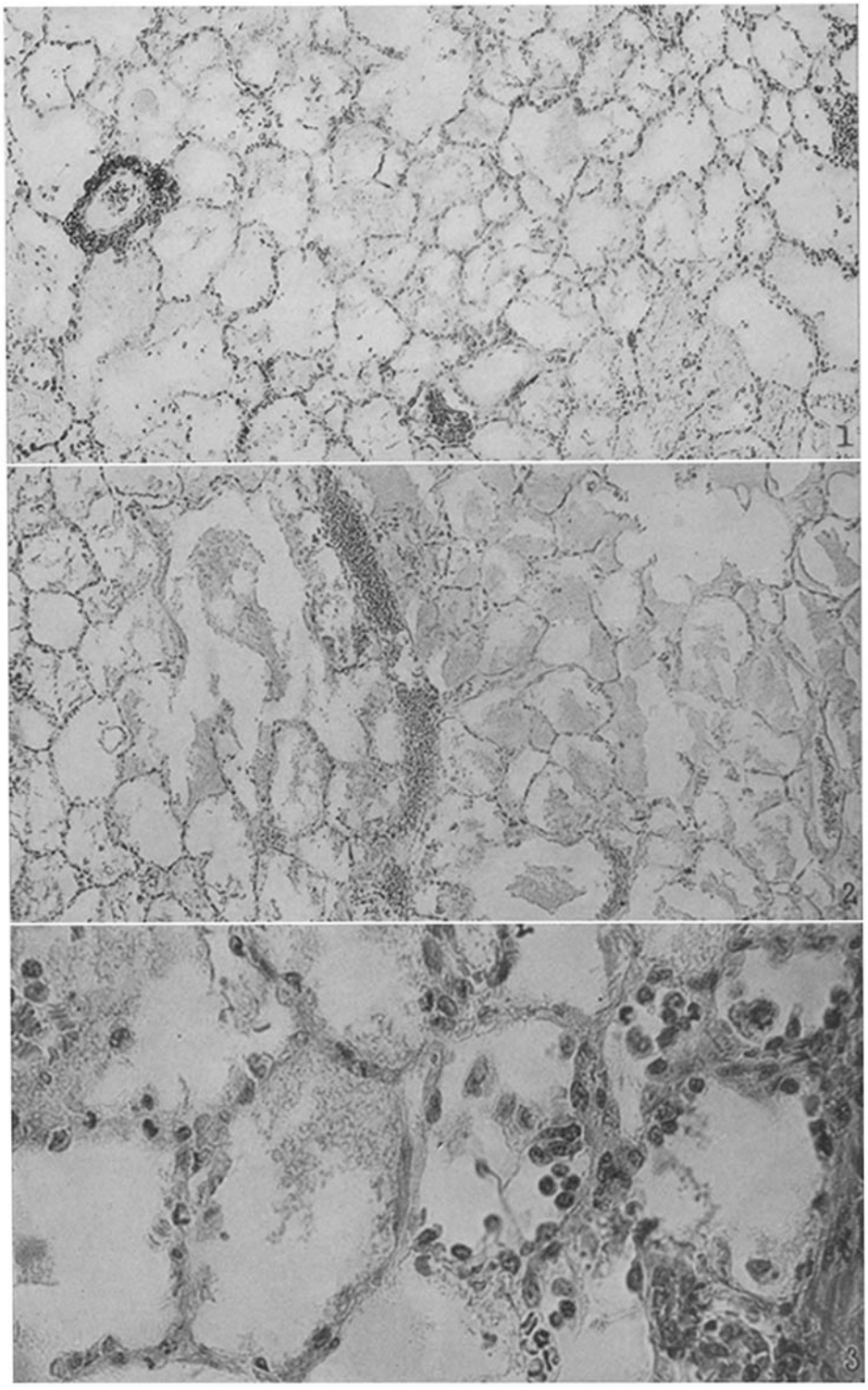

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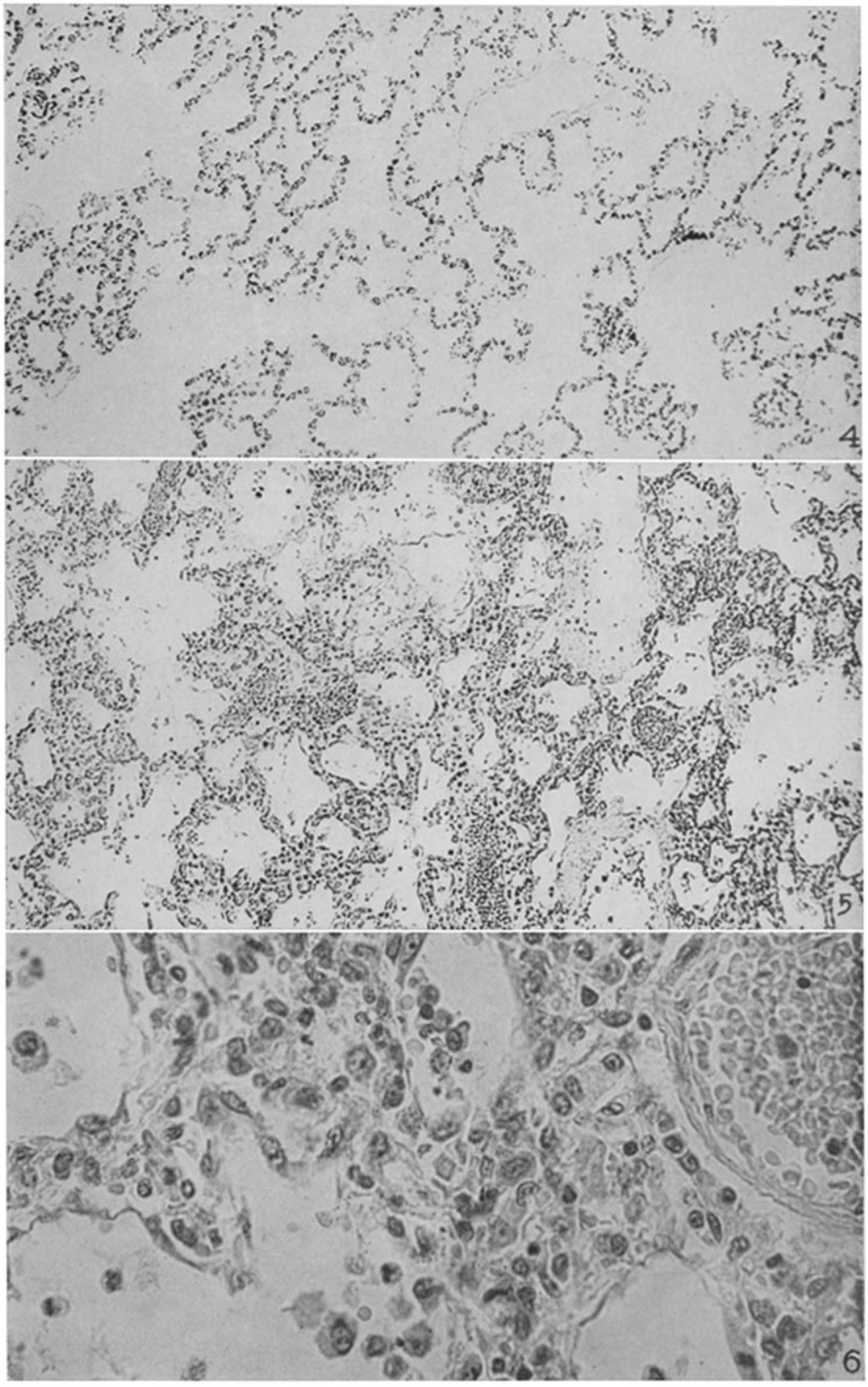

(Binger, Faulkner, and Moore: Oxygen poisoning in mammals.)