THE EFFECT OF MULTIPLE EMBOLI OF THE CAPILLARIES AND ARTERIOLES OF ONE LUNG.

By CARL A. L. BINGER, M.D., DOUGLAS BOYD, M.D., AND RICHMOND L. MOORE, M.D.

(*From the Hospital of The Rockefeller Institute for Medical Research.*)

INTRODUCTION.

The striking fact (Dunn (1), Binger, Brow and Branch (2)) that obstruction to the pulmonary arterioles and capillaries leads to a marked disturbance of the respiratory mechanism with the development of rapid and shallow respirations, and an increase in the minute volume of pulmonary ventilation, presents a pathological state which we have attempted to analyze further. Interest in this effect lies partly in its clinical application to such conditions as lobar pneumonia in which accelerated respirations are an important physical sign; and partly in the opportunity for investigating the difficult problem of respiratory rhythmicity and some of the factors influencing it. The reasons for thinking that an analogy exists between the rapid breathing due to multiple emboli of the arterioles and capillaries and the rapid breathing occurring in lobar pneumonia are several. In the first place in both conditions rapid breathing may occur independently of anoxemia. In the animal with multiple emboli this fact has been experimentally shown (2). And we have frequently observed patients with pneumonia continuing to breathe at the rate of 40 or more to the minute even after oxygen want has been relieved by oxygen administration. The occasional persistence of rapid respirations after crisis, when pulse and temperature have returned to normal, has suggested that the stimulus for accelerated respirations may be a local one resulting from the pulmonary lesion. A probable occurrence of capillary fibrinous thrombi has been described in pneumonic lungs by Kline and Winternitz (3), and that obstruction to the circulation may

occur in the consolidated lobe is known. This last fact again suggested a possible similarity in causes operating to produce similar effects.

Moreover, it has been found in experimental pneumonia produced in dogs by intratracheal insufflation of cultures of *B. friedlænderi* (Porter and Newburgh (4)) that the dyspnea which resulted could be checked by sectioning the vagi or blocking vagal impulses with cocaine. A similar slowing of accelerated respirations has been demonstrated for the tachypnea resulting from multiple experimental emboli. In this condition either vagal section (1) or vagal freezing (2) immediately brings about slow, deep breathing.

Quite aside from its immediate application to disease, a study of changes in respiratory rate has appeared important to us from the point of view of the nervous control of respiration. Of this subject not much is known. We know that the so called respiratory center sends out impulses which vary in strength and frequency, according to certain changes, physical and chemical, occurring either in the blood stream or in the center itself. And we know that the character of breathing, *i.e.* rate and depth, is influenced in some manner by impulses travelling along the vagus nerves (Le Gallois (5), Hering and Breuer (6), Head (7)). That these impulses are of a centripetal nature may be assumed from the studies of Einthoven (8) in which he demonstrated electrical changes in the thoracic end of the cut vagus occurring synchronously with changes in distension of the lungs. Whether there are centrifugal vagal impulses important to the control of respiration is not known. The vagus nerves in the dog, more than in the cat and rabbit, are not pure nerves, but are colonies containing sympathetic and depressor fibers as well. These nerves supply both heart and lungs. Cutting and freezing experiments are therefore necessarily varied in their effects and difficult to interpret.

The perhaps undue emphasis which we have placed on respiratory rate rather than on the minute volume of pulmonary ventilation lies in our interest in the nervous mechanism, where change in rate must represent a reversal in impulse occurring either peripherally in the breathing apparatus or in the respiratory center.

We must again emphasize the great difficulties introduced by the use of anesthetics. One is indeed caught between the horns of a

dilemma. To study the respiration in animals without an anesthetic is often impossible when concerned with changes involving the circulation in the lungs. We have previously (2) alluded to the effects of emotional and other adventitious stimuli which may confuse an experimental procedure. And yet equally confusing may be the sometimes excitatory, sometimes depressing influences of the anesthetic used to obviate the other effects. We have varied our technique, using luminal sodium by stomach tube, or barbital-sodium given intravenously or again ether with sterile technique and survival, in animals previously trained to lie still and breathe quietly. In the interpretation of results we have had constantly to keep in mind the effects of anesthetics.

The characteristic gross and microscopic pathology of the lungs of dogs in which multiple emboli of arterioles and capillaries have been produced by injection of suspensions of starch cells is congestion, edema and atelectasis. This is associated with a diminution in lung volume as determined by a measurement of the functional residual air (2). It seemed not improbable that these changes resulted in a decrease in elasticity of pulmonary tissue producing a shallow tidal air and thus, through the mechanism of the Hering-Breuer reflex, a rapid respiratory rate. Could the phenomenon be reproduced by causing similar lesions in one lung? If so, this would tend to establish more clearly the analogy with rapid and shallow breathing as it occurs in pneumonia. Experiments were planned with an eye to answering this question. It must be stated in advance that because of the technical difficulties involved and the necessary operative trauma the answers were not as unequivocal as was hoped.

EXPERIMENTAL.

Experiment 1. Effect of the Injection of Starch Suspension into One Lung.—
A female dog, weighing 7 kilos, was given by slow intravenous injection 2.50 gm. barbital-sodium dissolved in distilled water, or 0.34 gm. of the drug per kilo of body weight. Within ½ hour the dog was quiet and relaxed, and breathing regularly at the rate of 13 respirations per minute. The animal was then intubated and artificial respiration started by the intratracheal insufflation of an interrupted current of air. With the dog lying on its right side the thorax was opened by incising the skin, muscles and pleura in the 4th left intercostal space. The ribs were separated by mechanical retractors, and with very little blunt dis-

section the artery to the left lung was freed. By a method to be described below a suspension of starch grains (sufficient ordinarily to produce rapid and shallow breathing when injected intravenously) was injected directly into the artery supplying the left lung. Thereupon the animal's thorax was closed by approximating the 4th and 5th ribs by three stout ligatures, care being taken to distend the lungs and drive all air out of the pleural space before closing the chest. The muscle and skin layers were next repaired by suturing, the dog turned on its back and allowed to breathe spontaneously after removing the tracheal tube. To avoid the complications of anoxemia a stream of oxygen was blown through a funnel placed over the dog's muzzle. In this animal the preoperative respiratory rate varied from 16 to 20 breaths per minute. The postoperative rate, after the temporary acceleration had subsided, varied from 24 to 21. Following a steady respiratory rate at this level for 25 minutes the dog was killed by the intravenous injection of 20 cc. of a saturated solution of magnesium sulfate, and autopsied. The abdominal cavity and its viscera were normal. On opening the thorax the left lung, containing the starch grains, was mottled and paler than the right, which appeared normal. Frozen sections of the lungs, stained with Lugol's solution, showed the four lobes of the right lung to be free from starch grains, whereas in the small vessels of the left lung, especially in the upper and ventral lobes, they were thickly distributed.

From this experiment the following tentative conclusion can be drawn: Embolism of the capillaries and arterioles of one lung (the left) does not result in rapid and shallow breathing, when the other lung is functioning normally. The phenomenon is therefore not of an irritative nature due, solely, to the presence of the embolic material in one lung.

There is one important criticism to this experiment which obviously makes it inconclusive, namely: Was there actually enough embolic material introduced into the left lung to produce rapid and shallow breathing? It has repeatedly been observed that with intravenous starch suspension injections into the intact, unoperated animal a certain volume of suspension is necessary before accelerated respirations start. This fact was interpreted as indicating that the phenomenon was in some manner related to the degree of obstruction to the pulmonary circulation rather than the result of irritative, local stimuli set up in the lungs.

Method of Injecting Starch Suspensions Directly into the Artery Supplying One Lung.

As this method may prove to be of use to others it seems worth describing in detail. The method has the advantage of allowing the injection to proceed without clamping the artery or interfering with the circulation in the lung. The injection apparatus consists of a graduated burette to which about 10 inches of rubber tubing are attached. The tubing passes through a du Noüy* pump, which operates by rotating a wheel, designed to compress and decompress alternately
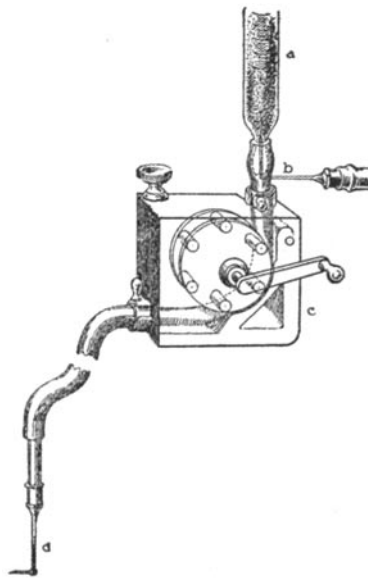
TEXT-FIG. 1. Apparatus for injecting suspensions into the pulmonary artery or its branches. *a*, burette; *b*, hollow needle through which a stream of air is blown to keep suspended particles from settling; *c*, du Noüy pump; *d*, bent needle with ball of solder in place.

the rubber tubing, thereby ejecting the fluid which enters the tubing from the burette. The speed and force of injection can be varied at will by varying the number of rotations of the wheel.

---

* This very useful pump, which was devised by Dr. du Noüy, of The Rockefeller Institute, has not previously been described in the literature. It was manufactured by the Central Scientific Company. We are indebted to Dr. du Noüy for its use.

The distal end of the rubber tube connects with a No. 21 gauge Luer needle 3 cm. long. 1 cm. from its point this needle has been bent at right angles by heating to a dull red, bending with a pair of nippers and then retempering. A small ball of solder is fused on to the needle at the right angle bend. Before thrusting the needle point through the arterial wall a small piece of muscle is "baited" on to the needle in much the same manner as baiting a fish hook. The ball of solder keeps the fragment of muscle from sliding around the bend and up the shank of the needle. This muscle fragment serves the double function of a flap valve over the puncture wound and of supplying tissue extracts which act as coagulants. With this equipment the arterial wall can be punctured with little hemorrhage and the needle kept in place for 15 to 20 minutes or more, without interfering with the flow of blood through the vessel. On removing the needle, the bleeding which usually occurs at the puncture wound can be controlled by the application of a fragment of muscle and cotton pledgets moistened in warm saline. Text-fig. 1 illustrates the burette, pump and needle used for injecting suspensions into the pulmonary artery or its branches.

Experiment 2.—An important corollary to the foregoing experiment, and one free from the criticism applicable to it, is the following, in which a dog, similarly anesthetized with barbital-sodium, was prepared for the experiment by ligating the left branch of the pulmonary artery. After the thorax had been closed, the animal was allowed to breathe oxygen. The respiratory rate at this time was 10 to the minute. A starch suspension of the same strength as in the previous experiment was then introduced into the circulation through a cannula in the right jugular vein. Since the left branch of the pulmonary artery had been ligated, all the starch entered the vessels of the right lung. The result was rapid and shallow breathing, the rate reaching a level of 58 to 60 per minute, where it remained for 1 hour before the animal was killed. The absence of anoxemia, as a contributing cause to the rapid breathing, was established by analysis of the dog's arterial blood at the close of the experiment, the percentage oxygen saturation being 100.

At this point, the tentative conclusion can be drawn that emboli in the capillaries and arterioles of one lung do not produce rapid and shallow breathing when the circulation through the other lung is normal. Or, in other words, the presence of embolic material, such as starch grains in one lung, does not excite this change in respirations. When, however, the circulation to the other lung is cut off by ligating its artery, emboli of capillaries and arterioles of one lung do produce rapid and shallow breathing in spite of the absence of oxygen want. Under the conditions of the experiment, the "embolized" lung adequately satisfied the animal's oxygen needs, but, even so, respirations assumed a definitely abnormal and accelerated character.

In an effort to surmount our own objections to the first experiment of this pair (Experiment 1), a new approach was devised.

A method was employed by which the left branch of the pulmonary artery could be occluded after the thorax had been closed and while the animal was breathing naturally. The occlusion was accomplished by inflating a pneumatic rubber cuff which had been previously placed about the left branch of the pulmonary artery. The method is given in detail in another paper in this *Journal* (9). Starch suspensions were then injected intravenously so that the emboli lodged in the vessels of the right lung. The left branch of the pulmonary artery was then released. By so doing, blood was allowed to circulate through the left lung after emboli, sufficient to produce rapid and shallow breathing, had lodged in the right lung. Under these conditions, does reestablishing the circulation through the left lung restore the respiratory rate to its original level? It should be stated that in these experiments too, anoxemia was prevented by oxygen inhalation.

The results of this series of experiments were variable. In some, reestablishing the circulation to the left lung (after production of rapid and shallow breathing by intravenous injection of starch granules which had lodged in the capillaries of the right lung) was accompanied by a definite slowing of respiratory rate. In others, the rate remained accelerated. In only one experiment (No. 3), was the respiratory rate restored to its slow, preoperative level.

In this experiment, the dog breathed at the rate of 16 per minute before it was operated upon, and the arterial blood was 97 per cent saturated with oxygen. The thorax was then opened and a pneumatic cuff placed about the left branch of the pulmonary artery. After closing the thorax, and allowing the animal to breathe naturally, the rubber cuff was inflated through a tube which projected through the chest wall. Inflation of the cuff completely shut off the flow of blood to the left lung. This resulted in no increase in respiratory rate. Indeed, at this stage of the experiment, the dog was breathing 13 times per minute. A starch suspension was thereupon injected intravenously, with the result that the respirations became shallow and accelerated to the rate of 61 per minute, despite the fact that the arterial blood was still 95 per cent saturated. The obstruction to the left branch of the pulmonary artery was next released by allowing the cuff to deflate, with the result that within 4 minutes the respiratory rate had dropped to 11 per minute.

This experiment is a clean-cut one and is more susceptible of interpretation than the others of this series. The dog breathed normally with only one lung, the right. When small emboli were introduced into the right lung, the respiratory rate accelerated to nearly 5 times

its previous rate. When, however, circulation was reestablished in the left lung, the respiratory rate returned to normal. Clearly, then, from this experiment too, one could conclude that emboli in the capillaries of one lung alone (the right) do not produce rapid and shallow breathing, unless the other lung is thrown out of the circulation, or, (as is suggested below), otherwise structurally damaged. That this last may account for the variable results referred to above is suggested by the following observations. In several experiments, the left lung, which had been temporarily deprived of its arterial blood, was, at autopsy, found to be bright red in color, instead of the normal salmon-pink. We know that depriving an organ of its blood supply may result in hyperemia from dilated capillaries, when the blood is again admitted (10). It is our opinion, though this fact is not definitely established, that in those animals in which accelerated respirations persisted after reestablishing the circulation to the left lung, some such capillary damage had been produced.

Experimental evidence for this statement is supplied by histological studies of the left lungs of Dogs 3 and 4. In Dog 3 (the experiment cited above in which the rate returned to normal on release of the cuff) the microscopic anatomy of the left lung is essentially normal. In Dog 4, however, in which the left lung, at autopsy, was noted to be bright red and granular in appearance, the respiratory rate remained at 61 per minute even after release of the obstruction to its artery. Here the microscopic picture is definitely abnormal, the thickness and distortion of capillaries being plainly visible. We reproduce photomicrographs of two typical regions of the left lungs of these two dogs which show clearly this difference in them (Figs. 1 and 2).

It should be stated that the variable behavior of different animals could not be correlated with variations in the percentage of oxygen saturation of the arterial blood, nor in the CO_2 tension or pH of the blood (11). Since this is true, we have not considered it worth while to present these data in this publication.

DISCUSSION.

When a suspension of potato starch grains is intravenously injected into a dog, the grains lodge in the finer arterioles and capillaries of the lungs. No change in the dog's respirations occurs until a certain, somewhat variable (in different animals) dose has been given. The

dog then develops rapid and shallow breathing, the respiratory rate often reaching 60 or more per minute. This phenomenon has interested us, partly because of an apparent analogy to the accelerated respirations seen clinically in cases of lobar pneumonia, partly because we believed that an understanding of this condition might throw some light on the problem of the rhythmicity of respiratory movements, and in particular upon the so called Hering-Breuer reflex.

Previous work has not revealed the cause of this abnormal type of breathing. It has not been correlated with (1) changes in arterial or venous blood pressures, (2) changes in percentage saturation of the arterial blood with oxygen, (3) changes in carbon dioxide tension or pH of the blood. It was found, however, to be associated with a reduction in lung volume, as expressed by measurement of the so called functional residual air, or that volume of air remaining in the lungs at the end of a quiet, normal expiration. And it was found that the characteristic pathological picture associated with this abnormal type of breathing was congestion, atelectasis and edema of the lungs.

The present study was undertaken to discover whether similar emboli introduced into one lung would result in a similar change in breathing. To accomplish this, that is, introduction of emboli into one lung, we had to resort, not only to the use of anesthetics, but to difficult and drastic operative procedures. Such procedures, of course, have drawbacks, and we have previously dwelt on the care necessary in interpreting results in the face of them.

Experimental evidence here presented appears to us to justify the conclusion that emboli lodged in the arterioles and capillaries of one lung produce an accelerated type of breathing only when the other lung has been excluded from the circulation by ligating or clamping its artery, or when the capillaries of the other lung have been abnormally distended by depriving them of blood for a period and then again admitting the blood.

The phenomenon would, therefore, appear to be in some manner related to the condition of diminution of the pulmonary vascular bed, to congestion in the lung or to resistance to the flow of blood through the lungs.

SUMMARY AND CONCLUSIONS.

1. Injection of a suspension of potato starch cells into the left branch of the pulmonary artery, in quantity sufficient ordinarily to give rise to markedly accelerated respirations, resulted in no change in respiratory rate.

2. A method for injecting substances into the pulmonary artery or its branches without interfering with the blood flow to the lungs has been described.

3. Injection of similar material into one lung when the other is excluded from the circulation either by ligation or by temporary clamping does give rise to rapid and shallow breathing (from a rate of 10 to 15 per minute to one of 60 or over) identical in character to that brought about by introducing emboli into both lungs.

4. A method for clamping and releasing the pulmonary artery or its branches in a dog breathing normally with closed thorax has been devised. This is described in detail in another paper.

5. After rapid breathing has been initiated by the effect of emboli lodged in the arterioles and capillaries of the right lung, reestablishing the circulation in the other lung by releasing the clamp on its artery may or may not restore the respiratory rate to its original, normal level.

6. This discrepancy in results has not been correlated with any difference in oxygen saturation of the arterial blood, or in carbon dioxide tension or pH of its plasma.

7. It is, however, believed to be related to the gross and microscopic anatomy of the lung of which the artery has been temporarily clamped. Photomicrographs are published, showing in one dog (No. 3), in which the respiratory rate returned to normal, a normal histological picture of the left lung, and in another dog (No. 4), in which the rate remained rapid after release of the clamp, a picture characterized by congestion and dilatation of arterioles and capillaries.

8. The fact that accelerated respirations result from emboli in the pulmonary capillaries and arterioles only after a certain quantity of material has been introduced, and the fact that emboli in one lung do not occasion accelerated respirations unless the circulation through the other lung is occluded or abnormal, leads us to the conclusion that

the phenomenon is not an irritative stimulus due to foreign bodies, but is in some manner related to (*a*) diminution of the pulmonary vascular bed, (*b*) resistance to the blood flow through the lungs or (*c*) congestion or dilatation of the arterioles and capillaries of the lungs.

BIBLIOGRAPHY.

1. Dunn, J. S., *Quart. J. Med.*, 1920, xiii, 129.
2. Binger, C. A. L., Brow, G. R., and Branch, A., *J. Clin. Inv.*, 1924, i, 127.
3. Kline, B. S., and Winternitz, M. C., *J. Exp. Med.*, 1915, xxi, 311.
4. Porter, W. T., and Newburgh, L. H., *Am. J. Physiol.*, 1916, xlii, 175; 1917, xliii, 455.
5. Le Gallois, C. J. J., Expériences sur la principe de la vie, Paris, 1812.
6. Hering, E., and Breuer, J., *Sitzungsber. k. Akad. Wissensch., Math.-naturw. Cl., Wien.*, 1868, lvii, pt. 2, 672; lviii, pt. 2, 909.
7. Head, H., *J. Physiol.*, 1889, x, 279.
8. Einthoven, W., *Arch. ges. Physiol.*, 1908, cxxiv, 246.
9. Moore, R. L., and Binger, C. A. L., *J. Exp. Med.*, 1927, xlv, 655.
10. Krogh, A., The anatomy and physiology of the capillaries, New Haven, 1922, 141.
11. Binger, C. A. L., and Moore, R. L., *J. Exp. Med.*, 1927, xlv, 633.

EXPLANATION OF PLATE 23.

Figs. 1 and 2. Photomicrographs of sections of lungs from Experiments 3 and 4. × 130.

Fig. 1. Experiment 3. Section from left upper lobe. The histological picture is essentially normal.

Fig. 2. Experiment 4. Section from left upper lobe. The picture shows marked engorgement and tortuosity of alveolar capillaries.

Both preparations were made with similar technique, the dogs being killed by the intravenous injection of a saturated solution of magnesium sulfate. The lungs were fixed by immersion in Helly's fluid, after they had been distended *in situ* by the intratracheal injection of about 1 liter of Helly's fluid.
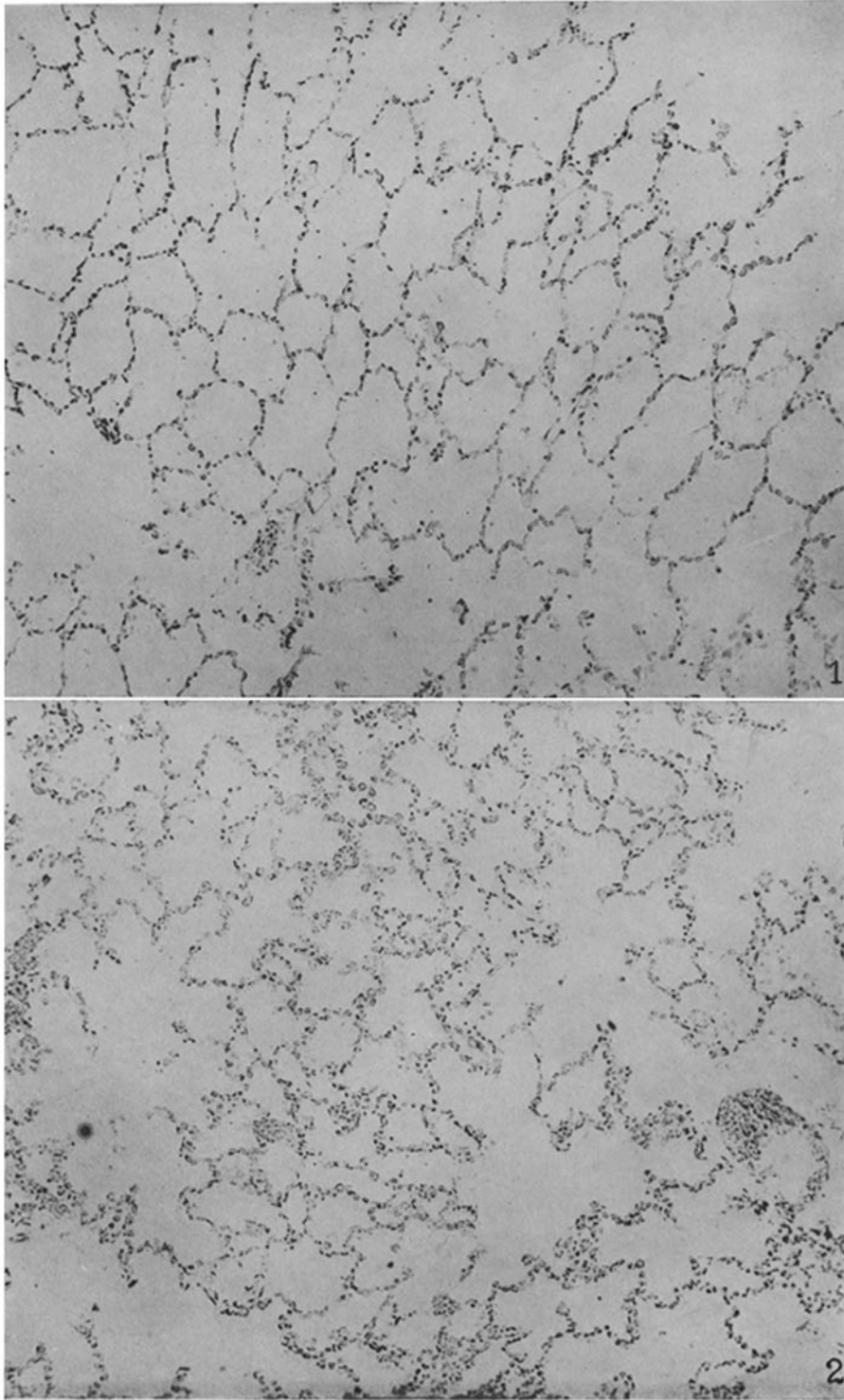
(Binger, Boyd, and Moore: Effect of multiple emboli in one lung.)