EXPERIMENTAL STUDIES ON RAPID BREATHING

II. TACHYPNEA, DEPENDENT UPON ANOXEMIA, RESULTING FROM MULTIPLE EMBOLI IN THE LARGER BRANCHES OF THE PULMONARY ARTERY

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INTRODUCTION

In Paper I (1) of this series it was shown that multiple emboli of the pulmonary arterioles and capillaries experimentally produced in dogs by the intravenous injection of a suspension of potato starch cells, resulted in rapid and shallow breathing, which occurred independently of anoxemia but was aggravated by it. The primary cause of this type of tachypnea was attributed to anatomical changes in the lung parenchyma in the nature of congestion, edema and atelectasis with reduction of lung volume and diminution in the normal elasticity of lungs. The limitation of respiratory excursion thus produced led to acceleration of rate through the action of the vagus nerves (Herring-Breuer reflex).

An analogy was drawn between this type of rapid and shallow breathing and that seen in such clinical conditions as acute and chronic passive congestion of the lungs, lobar pneumonia, and pulmonary fibrosis.

The object of this present study was to determine whether obstruction to the larger branches of the pulmonary artery would lead to similar effects, or whether they were inherently related to lesions of the arterioles and capillaries. We shall see in this paper that tachypnea does result from obstruction to the larger branches of the pulmonary artery, but that it is different in character and origin from the tachypnea following obstruction to the pulmonary arterioles and capillaries.

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EXPERIMENTAL

In this, as in the previous study, dogs anesthetized with Luminal Sodium were used as experimental animals. To produce obstruction of the larger pulmonary vessels, we resorted to the intravenous injection of seeds of various sizes. The seeds used and their average diameters were as follows:

cm.

Poppy.. 0.1
Rape... 0.2
Radish... 0.25
Pea.. 0.5

The method of injecting all seeds except pea seeds was to fill short lengths of glass tubing with a known number of the seeds. The tubing was just wide enough to hold the seeds single file and was of approximately the same bore as the venous cannula. The glass tube and cannula were then filled with 0.85 per cent NaCl solution and the seeds were forced into the vein by flushing out the tube with 10 cc. saline from a syringe. To inject the pea seeds, single peas were fixed on a pointed steel wire threaded through a French woven catheter No. 8. The seed was then pushed down the right jugular vein into the right heart. By holding the catheter in place and drawing back the wire the pea was dropped into the cavity of the right heart.

Embolism of the pulmonary circultaion produced in dogs by the intravenous injection of seeds

Rapid but labored and rather deep breathing associated with progressive cyanosis of the tongue and mucous membranes is the characteristic response of dogs to intravenous injections of seeds. This is true no matter what kind of seed is employed, but with the smaller seeds many more are necessary to bring about this effect than with the larger ones. For example, to raise the respiratory rate from 12 to 29 breaths per minute in one dog, 1000 poppy seeds, averaging 0.1 cm. in diameter, had to be injected. Whereas, with pea seeds, which average 0.5 cm. in diameter, after 13 had been injected in another animal the rate rose from 12 to 22 breaths per minute. Seeds of intermediate diameter such as rape, averaging 0.2 cm., produced rapid breathing and cyanosis after an intermediate number (122 in one experiment) had been injected. As with starch embolism, so with seeds—a certain dosage had to be injected before any apparent

changes in the animal's condition occurred. For example, in one dog after 50 rape seeds had been injected the respiratory rate and percentage saturation of arterial blood remained unchanged, but with the additional injection of 150 seeds, the respiratory rate trebled and the saturation fell from 89.3 to 72.7 per cent.

In another experiment the injection of 400 poppy seeds had no effect whatever on the respiratory rate and was not accompanied by cyanosis, and marked tachypnea and anoxemia did not occur until nearly 1000 seeds had been injected.

Once tachypnea and anoxemia had arisen there was a tendency for both to progress, with the gradual deterioration of the animal and death from respiratory standstill, the heart continuing to beat for a short period after breathing had ceased. Additional seed injection in a dog already cyanotic and breathing rapidly usually resulted in sudden death.

The fact that a critical number of seeds had to be injected before tachypnea and anoxemia occurred, together with the fact that the greater the number of seeds the severer the effect and, furthermore,that the number of seeds necessary to produce such an effect was in inverse ratio to their diameters, all suggested that we were dealing with a phenomenon directly dependent upon mechanical obstruction to the pulmonary circulation. It remained to show the relationship existing between the two changes that ensued, namely tachypnea and anoxemia, and the causes for their existence. To accomplish this a more precise analysis of the various factors involved was necessary.

(a) *Changes in pulmonary ventilation following seed embolism.* Unlike starch embolism, seeds produce breathing which is usually labored and deep as well as rapid, and though the rate may rise to 70 or 80 breaths per minute it does not reach the extraordinary degree of rapidity occasionally observed after starch injection. In four experiments the average rate before seed embolism was 14 and after it was 40. This was associated with an average increase in tidal air from 180 to 198 cc. and a resultant change in volume of pulmonary ventilation from 2.62 to 7.97 liters per minute.

(b) *Arterial anoxemia following seed embolism.* The cyanosis which the dogs exhibited has .already been mentioned. That this was dependent upon arterial anoxemia, often of profound degree, was re-

peatedly demonstrated by blood gas analyses.   In 12 dogs the average arterial O_2 content before embolism was 16.25 volumes per cent, after embolism it had fallen to 11.59.   In these dogs the average capacities remained almost unchanged—the figure before embolism being 18.19 volumes per cent as compared with 18.74 volumes per cent after. This resulted in a decrease in the percentage saturation of arterial blood of nearly 25 per cent, or from an average of 87.56 per cent to one of 62.68 per cent.

(c) *Effect of O_2 inhalation on anoxemia and tachypnea following seed embolism.*   It was shown in Paper I (1) of this series that oxygen administration to a dog after embolism of the pulmonary arterioles and capillaries reduced the respiratory rate but little, and that oxygen inhalation before embolism did not prevent the occurrence of tachypnea which, under such circumstances, arose even without the existence of anoxemia.   With embolism of the larger branches of the pulmonary artery the effect of oxygen inhalation is quite different from this.   To our surprise, in these dogs the respiratory rate was brought down to a normal level on allowing them to breathe oxygen rich mixtures and, furthermore, tachypnea was wholly prevented when oxygen was given prior to the production of emboli.   For example, in one dog while breathing room air the respiratory rate was 71 to the minute and the arterial blood was only 53.5 per cent saturated after the intravenous injection of 200 rape seeds.   Breathing a 90 per cent O_2 mixture reduced the respiratory rate to 19 and increased the arterial saturation to 97.0 per cent.   In another animal the respiratory rate was 13 and the percentage saturation of arterial blood 90.2 before oxygen inhalation and seed injection.   The dog was then permitted to breathe 90 per cent O_2, with the result that his respiratory rate fell to 8, and his arterial blood rose in percentage saturation to 99.2.   While in this condition rape seeds were injected intravenously to a total number of 250.   The respiratory rate remained at 8 and the saturation fell only to 92.0 per cent which was still in excess of the original.   Oxygen inhalation was discontinued, the dog again breathing room air.   There resulted a gradual acceleration of respiratory rate and progressive decrease in percentage saturation of arterial blood, these changes occuring simultaneously.   In two hours the dog's respirations had reached 57 to the minute, and his arterial blood had decreased 23.7 per cent in saturation with O_2.

The data of this experiment are presented in table 1.

These facts lead to the obvious conclusion that the cause of tachypnea resulting from seed embolism is anoxemia.

(d) *Effect of vagal freezing upon tachypnea and anoxemia following seed embolism.* The effect of vagal freezing was discussed in Paper I (1). Here we showed that not only the rapid and shallow breathing of starch embolism was converted into slow, deep breathing by freezing the vagi, but that other types of tachypnea resulting from presumably central stimuli, such as low alveolar oxygen or high CO_2 tensions, were similarly checked by this procedure.

We suggested that an animal without vagal control was unable to accelerate his respirations. It was reasonable to anticipate that

TABLE 1

Experiment 36. Intravenous injection of rape seed preceded by oxygen inhalation

Time	Total number of seeds	Gas inhaled	Respiratory rate per minute	Arterial blood			
				O_2 content	O_2 capacity	Saturation	CO_2 content
				vol. per cent	*vol. per cent*	*per cent*	*vol. per cent*
2:19	0	Room air	13	18.73	20.77	90.2	41.52
3:15	0	90 per cent oxygen	8	18.50	18.66	99.2	48.0
4:55	250	90 per cent oxygen	8	16.16	17.57	92.0	52.6
5:05		Room air	29	13.70	17.36	78.9	48.7
6:08		Room air	42	12.31	17.26	71.3	43.48
6:35		Room air	57	12.49	18.28	68.3	43.2

the rapid breathing following seed embolism, which has been shown to be a sequel of anoxemia, would in like manner be stopped by vagal freezing. This, indeed, is a fact, concerning the truth of which we have repeatedly satisfied ourselves.

Experiment 11. A female collie, weighing 16 kg., was given 1.95 grams Luminal by stomach tube. Three and one half hours later the dog was ready for the experiment, being relaxed and insensitive. The right femoral vein was cannulated for seed injection and the left femoral artery for securing blood samples. The vagus nerves were isolated in the neck.

A pneumographic tracing was obtained, the respiratory rate being 24 per minute. At this time the arterial blood was 89.0 per cent saturated. Radish seeds were then injected intravenously, the respiratory rate accelerating to 76 and the saturation of arterial blood falling to 62.7 per cent. While in this state

the dog's vagi were frozen with the prompt cessation of tachypnea. Respirations now became deep and at the rate of 16 per minute. In spite of the slow, deep breathing the arterial anoxemia progressed, the percentage saturation falling to 34.9 per cent.

Table 2 presents the data of this experiment and figure 1 shows the pneumographic record after anoxemia and tachypnea had progressed to still greater degree. The tracing shows the effect of alternate periods of freezing and thawing the vagus nerves. This experiment shows that the tachypnea resulting from embolic anoxemia can be checked by vagal freezing, and that anoxemia persists in spite of the slow, deep breathing. It suggests, therefore, that the anoxemia is not the result of rapid breathing but of some other cause which will be discussed later.

TABLE 2

Experiment 11. Intravenous radish seed injection followed by vagal freezing

Time	Total number of seeds	Respiratory rate per minute	Arterial blood			
			O_2 content	O_2 capacity	Saturation	CO_2 content
			vol. per cent	*vol. per cent*	*per cent*	*vol. per cent*
1:18	0	24	18.0	20.24	89.0	39.6
2:00	227	76	13.63	21.77	62.7	37.5
2:11		16 (Vagi frozen)	7.85	22.49	34.9	39.9

In another experiment a rate varying from 6 to 9 breaths per minute was maintained for twenty minutes after the intravenous injection of 244 rape seeds in spite of profound oxygen want as indicated by 26.4 per cent oxygen saturation of the arterial blood. The vagi were then thawed and in the succeeding thirty-seven minutes the respiratory rate had accelerated to 76 per minute.

The fact observed thus far in this work and the conclusions to be derived therefrom may be summarized as follows:

1. After a certain critical number of seeds are injected intravenously into dogs there results a marked decrease in percentage saturation of arterial blood associated with increase in the repiratory rate.

2. The greater the number of seeds, the more severe the reaction; and the smaller the seeds, the greater the number required to bring it about.

3. With small seeds (0.1 cm. in diameter) as many as 500 have been injected without producing anoxemia or tachypnea.

4. A point is reached, however, when anoxemia occurs and there is an associated acceleration of respirations. These changes tend to be progressive. When anoxemia and tachypnea are established further seed injection frequently results in the death of the animal.
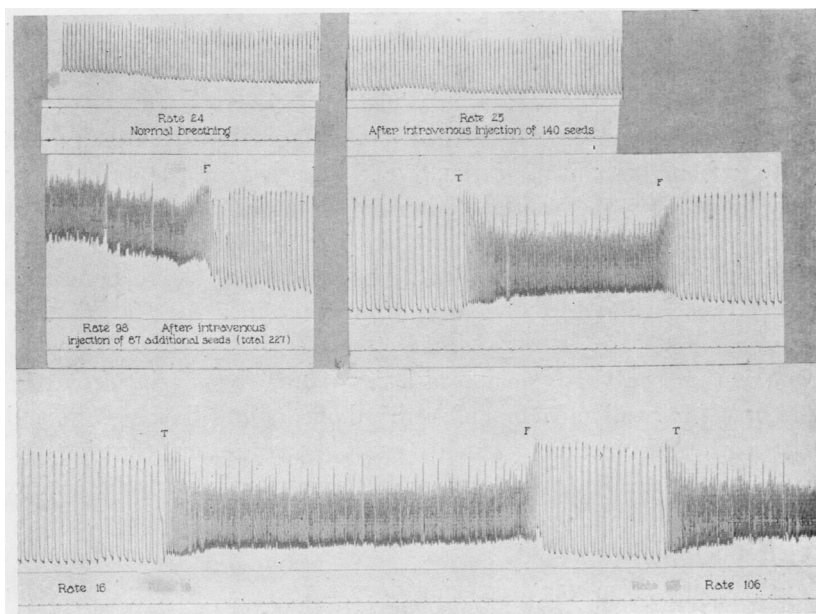

FIG. 1. EXPERIMENT 11. PNEUMOGRAPHIC TRACING OF DOG BEFORE AND AFTER SEED EMBOLISM, SHOWING MARKED TACHYPNEA.

The letters F and T indicate alternate periods of freezing and thawing of the vagi. Time marker indicates 5 second intervals. The pneumograph used was made by Joseph Becker, Department of Pharmacology, Columbia University Medical School, N. Y.

These facts all point to the physiological changes being due primarily to obstruction of the pulmonary circulation and coincide with the observations of Haggart and Walker (2) who showed that quantitative occlusion of the pulmonary artery in cats resulted in no significant changes in the circulatory system until from 52 to 66 per cent of the pulmonary circulation is cut off when a sharply defined point

of circulatory collapse occurs involving both pulmomary and systemic pressures.

5. Administration of O_2 to a dog thus rendered anoxemic and tachypneic, causes a return of the arterial blood to more or less complete saturation with O_2 and reduction in the respiratory rate to a normal level. On subsequent withdrawal of O_2, the animal again breathing room air, tachypnea and anoxemia recur simultaneously.

6. Administration of O_2 prior to and during the production of seed embolism prevents the occurrence of both anoxemia and tachypnea. But these occur as soon as O_2 administration is stopped.

These conditions establish clearly the fact that the tachypnea resulting from embolism of the larger branches of the pulmonary artery is wholly the result of anoxemia, thereby differentiating it from the tachypnea resulting from embolism of the pulmonary arterioles and capillaries, which was shown in Paper I (1) to be due to another cause, though, to be sure, often intensified by the existence of anoxemia.

7. Freezing the vagus nerves of a dog which is suffering from the rapid breathing and anoxemia of seed embolism immediately slows and deepens the respirations, which again accelerate on thawing the nerves. In spite of slow, deep respirations following vagal freezing, no amelioration of oxygen unsaturation occurs, which progresses as if tachypnea had persisted.

The slowing from vagal freezing does not necessarily indicate the blocking of a peripheral irritative stimulus in the lung, as it was shown in Paper I (1) that rapid breathing resulting from central chemical stimuli could be checked similarly by vagal freezing. The general proposition was put forward that an animal without vagal control is unable normally to accelerate his respirations.

The fact that slow, deep breathing does not ameliorate the condition of anoxemia indicates that the anoxemia is not the result of tachypnea.

It remains for us, therefore, to determine what is the cause of anoxemia following multiple emboli of the larger branches of the pulmonary artery. For this purpose a study of the pathology of the ''seed'' lungs, both gross and microscopic, has been made, and an attempt, with the aid of numerous injection preparations, to visualize the extent and distribution of the circulatory obstruction.

The characteristic feature of these lungs which differentiates them clearly from the "starch" lungs is the absence of generalized congestion, edema, exudate and atelectasis, and the presence of areas of relative ischemia and emphysema.   It is probable that in the areas in which circulation persisted, a certain degree of vascular distension and alveolar atelectasis did exist, though this was not definite except in the lungs of dogs surviving several hours after embolism.   This latter change corresponds to the congestion observed by Underhill (3) and by Schlaepfer (4) and also by ourselves in the right lungs of animals, of which the left pulmonary artery had been occluded by ligation.

PATHOLOGY

Twenty-two animals, injected with different kinds of seeds, were autopsied, the trachea being clamped and the thorax opened immediately after death. The dogs died spontaneously, or were bled to death, or killed by intravenous injection of from 10 to 20 cc. of a saturated magnesium sulphate solution.

Gross pathology

Lungs. Disregarding animals which were injected intravenously with dyes before death, notes on the morbid anatomy of the lungs were obtained in 11 animals.   Free fluid in the pleural cavity was not present in any instance.   In the 3 animals which died within 2 hours after the first seed injection, the lungs showed hypostasis in the dependent (dorsal) parts of the caudal lobes, the remainder of the lobes being salmon pink, well distended, but collapsing readily on removing the tracheal clamp.   They were, in fact, normal in appearance.   The lung-heart ratio in one of these three dogs was 1.11, i.e., normal (see Paper I).   In the remaining 8 dogs in which death occurred from $3\frac{1}{2}$ to $5\frac{3}{4}$ hours after the initial seed injection, hypostasis was more marked than in the previous group.   The lungs in the distended state, before the tracheal clamp was removed, showed pale pink areas along the periphery which contrasted with the light reddish areas about the hilum.   The lungs collapsed throughout but less so at the periphery than at the hilum.   After collapse the surfaces near the hilum were of a dark red color, the periphery remaining pale and emphysematous.   The lung-heart ratio in 4 dogs was 1.22, 1.29, 1.34 and 1.55, respectively, while in the animal which lived longest ($5\frac{3}{4}$ hours) it was 2.02.   This was the only ratio definitely outside the normal range, the increased lung weight being probably due to the hypostatic congestion.   In no instance was edema evident.

Other organs. The right heart was usually dilated. The kidneys, liver and spleen showed no pathological changes referable to the seed injection.

Examination of injected lungs

Eight lungs were injected through their pulmonary arteries with barium sulphate gelatine (6 per cent). Examination of the cleared specimens and the x-ray stereoscopic photographs show definitely the areas where the circulation has been blocked (figs. 2 and 3).
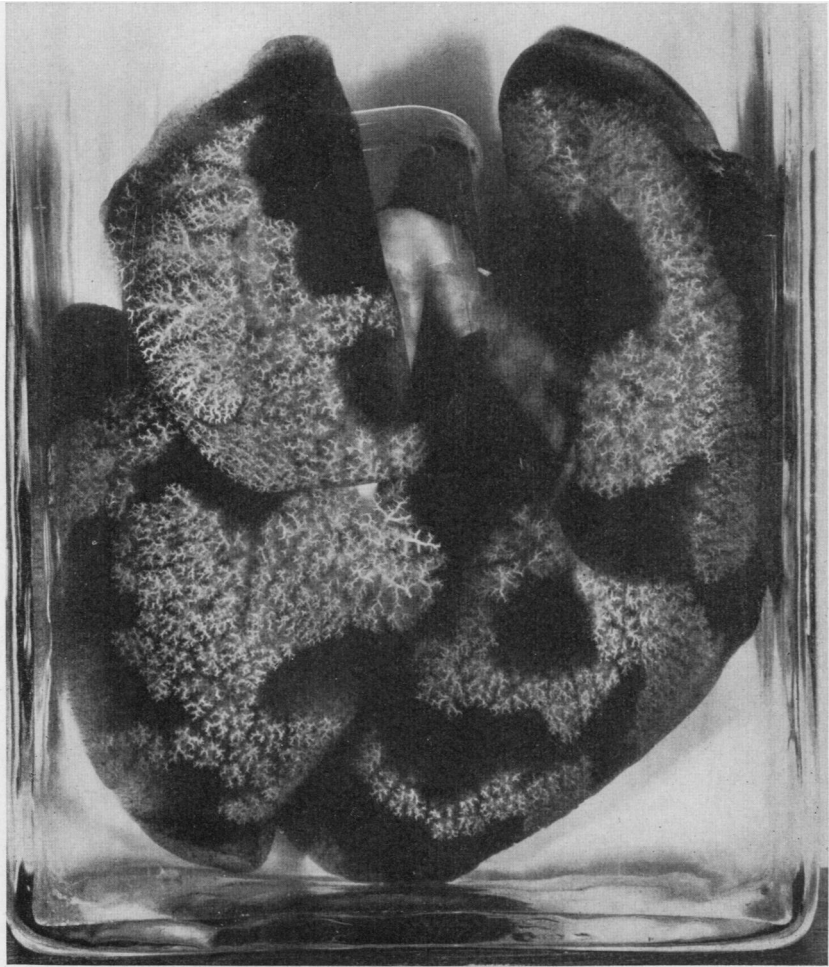

FIG. 2. DOG 8–2. RAPE SEED EMBOLISM. PHOTOGRAPH OF SURFACE OF INJECTED LUNGS AFTER CLEARING IN OIL OF WINTERGREEN

Note the numerous blocked areas where the barium sulphate gelatine has not penetrated.

The pulmonary arterial bed of one other lung was washed out with saline and the lung dehydrated and cleared in oil of wintergreen.   In this transparent specimen the seeds may be clearly seen.   They are widely distributed but tend to line up in rows, one behind the other, in the main peripheral vessels.   The distribution of the seeds may, however, best be seen in 4 specimens in which the pulmonary artery was injected with celloidin and the lung tissue digested away
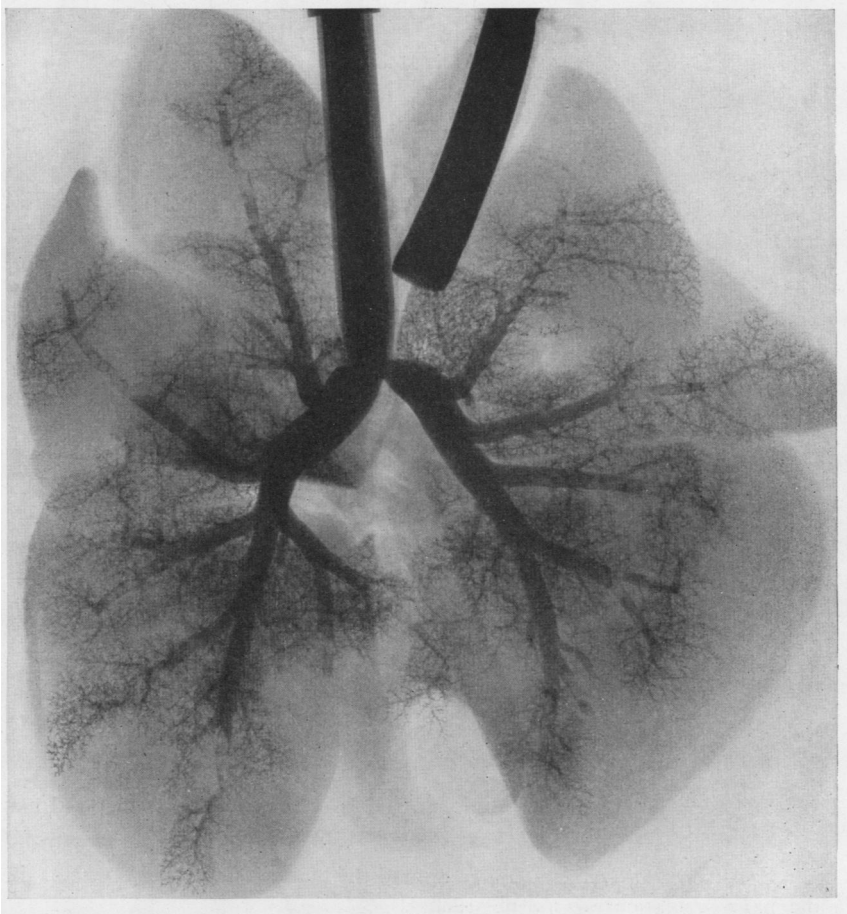
FIG. 3. DOG 9–2. RAPE SEED EMBOLISM. X-RAY PHOTOGRAPH OF LUNGS INJECTED WITH BARIUM SULPHATE GELATINE

Note the numerous uninjected areas.   These are mostly at the periphery as the seeds tend to follow and lodge in the main arterial trunks, the diameters of which gradually decrease in size.

with muriatic acid (Hinman, Morison and Lee-Brown (5)).   The seeds adhered
to the celloidin and remained undigested.   Their exact situation could, there-
fore, be observed.

To obviate the artificial conditions of postmortem injections, 3 dogs were
infused intravenously during life with from 65 to 100 cc. dialyzed India ink
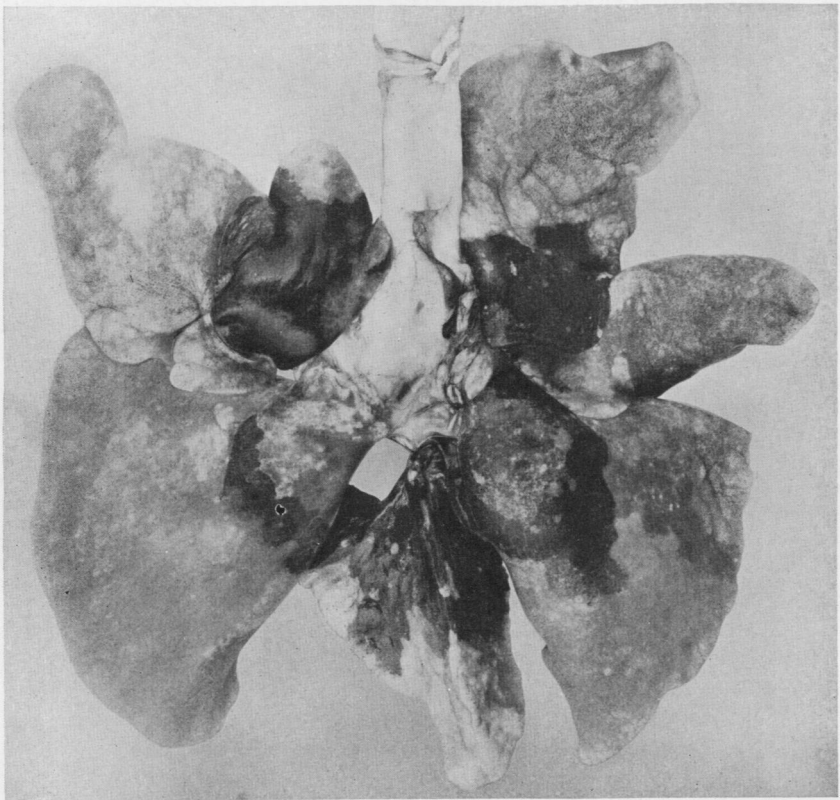
FIG. 4. DOG 55–2.   PEA SEED EMBOLISM.   PHOTOGRAPH OF SURFACE OF LUNG
AFTER ANTEMORTEM INTRAVENOUS INJECTION OF INDIA INK

Note the comparatively small area around the hilum stained black where the
pulmonary circulation was not obstructed.

(Krogh (6)).   Examination of their lungs within 5 minutes showed that large
parts of the peripheral portions were unstained, in contrast with the remainder
of the lungs which were black.   This corresponded to the picture in postmortem
injections.   A photograph of such an India ink preparation is reproduced in
figure 4.

Microscopical pathology

Lungs. Histological examination was made in 7 cases. In no instance was edema or exudate noted. The branches of the pulmonary artery were frequently completely blocked by the presence of seeds and enveloping clots, the calibre of the artery obstructed being dependent on the size and number of seeds injected. In the 4 instances in which the experiment was concluded within 2 hours of seed injection, it was difficult to distinguish the blocked from the unobstructed vascular areas. It appeared as if the obstructed areas were relatively ischemic and emphysematous and, by contrast, the vessels of the unobstructed areas appeared congested and the alveolar walls partially collapsed. This contrast was more pronounced in the 3 dogs which survived longer than 2 hours.

The hypostatic areas were not included in the above description. The muscular contractions noted in the bronchiolar walls of normal and "starch" lungs were also observed here.

EMBOLIC ANOXEMIA

In their monograph Lundsgaard and Van Slyke (7) have made a detailed theoretical study of the factors which contribute to the occurrence of cyanosis. Whereas the appearance of clinical cyanosis should be differentiated from anoxemia as measured by the percentage saturation of the arterial blood, it is nevertheless true that many of the same factors are involved in the production of both. An enumeration and analysis of these will help us to understand the causes which give rise to embolic anoxemia.

Of the factors which may be responsible for arterial anoxemia the more important are these:

1. Low alveolar oxygen tension due to (*a*) diminished atmospheric oxygen pressure, (*b*) inefficient ventilation.

2. Retardation of diffusion of oxygen from alveoli into blood due to presence of edema or exudate.

3. Shunt or passage of a fraction of blood through unaerated channels from the venous to the arterial system. This may be (*a*) complete, in which no aeration of shunted fraction occurs, or (*b*) partial, in which partial aeration of shunted fraction occurs.

4. Increased reduction of oxygen during flow through the tissue capillaries due to (*a*) greatly increased rate of oxygen consumption by the tissues, (*b*) decreased rate of flow through the tissue capillaries.

5. A change in the total content of haemoglobin, which if increased would tend to decrease the percentage saturation of the blood passing through the lungs.

6. A change in the quantitative relation of blood flow to vascular diffusion area in the lungs.

An analysis of the rôle played by these various factors in the production of *embolic anoxemia* follows.

1. Low alveloar oxygen tensions

(a) *Diminished atmospheric oxygen pressure.* There can be no question of this entering as a cause of the type of anoxemia here described as in all the experiments the dogs breathed either room air or gas mixtures with a higher partial pressure of oxygen than exists in room air.

(b) *Inefficient ventilation.* On page 157 it was shown that the response of breathing to seed embolism is characterized by increased depth as well as accelerated rate. Under such circumstances there should be no diminution of the effective ventilation. From this alone one might conclude that anoxemia was not the result of inefficient ventilation. Further evidence for this is furnished by the vagal freezing procedure in which a 37 per cent increase in the depth of tidal air did not increase the percentage saturation of arterial blood.

In addition to these observations the following experiment was performed to eliminate inefficient ventilation as a cause for the anoxemia observed.

Experiment 68. A dog was rendered anoxemic by the intravenous injection of 169 rape seeds. His respiratory rate, which had been 9, rose to 37 and his arterial blood, which had contained 15.54 vol. per cent of O_2, now contained 10.27 vol. per cent. The resulting decrease in percentage saturation was from 96.00 to 61.01 per cent, the capacity having increased by only 0.60 vol. per cent. While in this condition, artificial ventilation by the intratracheal insufflation of air at the rate of 27 liters a minute was maintained for 15 minutes, when another sample of arterial blood was drawn. This showed no amelioration of the anoxemia. The O_2 content was 9.99 vol. per cent and saturation 59.10 per cent.

This experiment together with the foregoing observations we believe definitely rules inefficient ventilation as the cause of embolic anoxemia.

2. Retardation of diffusion of oxygen from alveoli into blood due to presence of edema or exudate

The solution of this phase of the problem depended largely upon the gross and microscopic pathology of the embolized lungs. In postmortem examination of twenty-two dogs rendered anoxemic by intravenous injection of seeds, none was found in which there was free fluid in the pleural cavities or gross evidence of interstitial edema. The cut surfaces of the lungs were not more moist than normal, nor did fluid exude from the trachea or bronchi. Furthermore, the weight ratios of lungs to heart were normal in those dogs in which this observation was made at autopsy.

In the microscipical examination of the lungs of seven dogs which had been rendered anoxemic by intravenous seed injection, no evidence was found of intra-alveolar exudate or of change in the appearance of the alveolar wall other than a certain degree of emphysema.

An actual measurement of the diffusion constant as has been made in the human subject by Marie Krogh (8) was not possible, as this method requires precise coöperation on the part of the subject and is, therefore, not applicable to experimental animals. Krogh has shown that the rate of diffusion of a gas through the alveolar epithelium depends upon its partial pressure and is directly proportional to the surface of epithelial tissue and inversely proportional to its thickness or to the thickness of the alveolar wall. The surface area of epithelial tissue Krogh expressed as the two-thirds power of the mean alveolar lung volume (usually called the mid capacity). She showed that increase of the alveolar lung volume above the mean increased the diffusion constant, but decrease below the mean did not alter it because, she argued, that such a decrease, in the normal lung, was due to folding and wrinkling of the alveolar walls which would not reduce their surface area. This argument was substantiated by experimental observations.

Though the actual diffusion constant could not be measured in these experiments, it was thought desirable to measure the lung volume. It was believed that lung volume estimation might furnish at least indirect evidence of any changes in the area of alveolar epithelium available as a diffusion membrane.

In each of three experiments an *increase in lung volume (functional residual air)* (9) accompanied the anoxemia following seed embolism. These changes in lung volume, respiratory rate and percentage

saturation of arterial blood are presented in table 3. This augmentation of lung volume is consistent with the gross and miscroscopic evidence of emphysema. It should be compared with the successively constant lung volume determinations made on a control dog, and the decreasing lung volumes resulting from congestion, edema and atelectasis following starch injection (see Paper I of this series).

In the absence of gross or microscopic evidence of edema or of exudative changes, and in the presence of an increase in lung volume suggesting no diminution in the surface area of alveolar epithelium available for the diffusion of gases, it seems reasonable to

TABLE 3

The effect of seed embolism on lung volume, respiratory rate and arterial O_2

Experiment number	Time	Total seeds injected	Functional residual air	Respiratory rate per minute	Arterial blood		
					O_2 content	O_2 capacity	Saturation
			liters		*vol. per cent*	*vol. per cent*	*per cent*
34	1:42	0	0.48	28	11.17	15.33	72.9
	2:39	155	0.51	33	9.18	16.15	56.8
35	12:44	0	0.56	8	15.15	17.02	89.0
	1:41	50	0.61	9	15.00	16.80	89.3
	3:18	200	0.70	27	12.82	17.64	72.7
	4:07		0.87	71	10.39	19,43	53.5
36	2:30	0	0.73	13	18.73	20.77	90.2
	6:40	250	0.78	57	12.49	18.28	68.3

conclude that anoxemia of embolic origin is *not the result of retardation of diffusion of oxygen from the alveoli into the blood due to changes in permeability of the alveolar walls.*

3. Shunt of blood through unaerated channels

(a) *Complete shunt or passage of a fraction of blood through completely unaerated channels from the venous to the arterial system.* As a possible cause of embolic anoxemia this may be quickly disposed of by the experiments with inhalation of high concentration of O_2. On page 158 it was shown that breathing 90 per cent O_2 raised the saturation of the arterial blood from 53.5 to 97.0 per cent. This increase in

saturation was repeatedly observed. Were blood being shunted from the venous to the arterial system through completely unaerated channels, raising the alveolar O_2 tension alone could not thus cause the O_2 unsaturation to disappear.

(b) *Partial shunt or passage of a fraction of blood through partially unaerated channels from the venous to the arterial system.* That this is not responsible for the occurrence of arterial anoxemia after pulmonary embolism is difficult to establish definitely. There is, however, strong persumptive evidence against it:

1. There is no morphological appearance of partial obliteration of alveolar spaces, nor is there any evidence of bronchiolar or atrial spasm.

2. There is no decrease but, in fact, an increase of lung volume after seed embolism (see table 3).

3. There was no apparent delay after embolism in obtaining equilibrium between lung air and the hydrogen-oxygen mixture contained in the spirometer used for lung volume determinations. This suggests that the alveolar air was accessible to atmospheric air and that partially unaerated portions of the lung did not exist.

4. The fact that artificial respiration by intratracheal insufflation did not relieve the arterial O_2 unsaturation is strong evidence against the existence of unaerated areas as these would in all probability have been ventilated by the method of intratrachial insufflation.

4. Increased reduction of oxygen during flow through the tissue capillaries

(a) *Increased rate of oxygen consumption by the tissues.* By actual measurement of the metabolic rate existing before and after seed embolism it was shown that there was no consistent change in oxygen consumption by the tissues. In one dog 74.55 cc. O_2 were consumed per minute when the arterial blood was 90.8 per cent saturated, and 74.40 cc. O_2 were consumed when the saturation had fallen to 73.3 per cent. In another dog, a drop in percentage saturation from 82.2 to 42.5 per cent was accompanied by a decrease in O_2 consumption from 80.06 to 72.77 cc. per minute, and in a third dog a decrease in percentage saturation from 97.7 to 59.2 was associated with a rise

in O_2 consumption from 101.53 to 134.33 cc. per minute. For data of these three experiments table 4 should be consulted. They indicate that the type of anoxemia with which we are dealing is not the result of increased tissue metabolism.

(b) *Decreased rate of flow through the tissue capillaries.* That this in itself can be a cause of arterial anoxemia is improbable without the concomittant changes in the pulmonary circulation which will be discussed under heading 6.   A slowing of rate of flow through the tissue capillaries might result in anoxemia of the capillary blood, but it is difficulty to see how it could result in arterial anoxemia.   A slow

TABLE 4

Measurement of O_2 consumption before and after anoxemia following seed embolism

Experi-ment number	Rectal tempera-ture	Total number of seeds injected	Respira-tory rate per minute	O_2 con-sumption per minute	Arterial blood			
					O_2 content	O_2 capacity	Saturation	CO_2 content
	°C.			cc.	vol. per cent	vol. per cent	per cent	vol. per cent
49	38.0	0	12	70.85	18.31	18.10	100	49.01
	38.2	205	24	74.55	16.89	18.61	90.8	49.09
	38.0	255	34	74.40	13.68	18.67	73.3	46.1
50	38.5	0	12	80.06	14.33	17.44	82.2	43.2
	36.8	235	46	72.34	11.04	16.56	66.7	44.62
	35.5		42	72.71	7.44	17.51	42.5	46.28
51	39.2	0	22	101.53	17.24	17.65	97.7	42.23
	38.0	300	48	125.95	13.19	18.40	71.7	
	38.5		46	134.33	12.55	21.20	59.2	39.22

rate of flow through the systemic capillaries, if accompanied by a slow rate of flow through the pulmonary capillaries, should enable the reduced hemoglobin to be reoxygenated in the lungs.

That there is no such actual decrease in rate of flow through the tissue capillaries is suggested by the following facts:

1. No marked decrease in output of the heart per beat or per minute was observed after seed embolism (see below under 6).

2. No marked fall in systemic blood pressure was observed after the production of anoxemia due to seed embolism as is shown in figure 5, the mean arterial pressure before embolism being 81 mm. Hg and after 79 mm. Hg.

5. A change in the total content of hemoglobin which if increased would tend to decrease the percentage saturation of the blood passing through the lungs

That such an increase is not the cause of embolic anoxemia is shown by the following facts:

In 12 dogs in which embolic anoxemia was produced the average changes in arterial blood were as follows: Before embolism the arterial O_2 content was 12.25 vol. per cent as compared with 11.59 vol. per cent after. The O_2 capacity, on the other hand, had increased very slightly, being 18.19 vol. per cent before as compared with 18.74
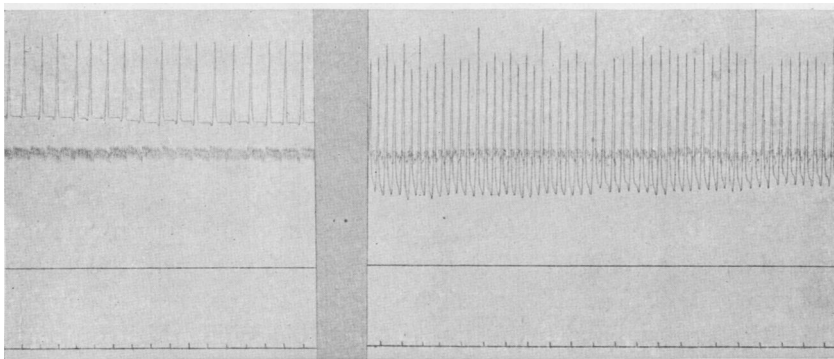
FIG. 5. BLOOD PRESSURE AND PNEUMOGRAPHIC TRACINGS BEFORE AND AFTER TACHYPNEA FOLLOWING SEED EMBOLISM

Time marker indicates 5 second intervals

vol. per cent after embolism. This represents an increase in hemoglobin of only 0.3 per cent whereas the decrease in percentage saturation was from 87.56 to 62.68 or approximately 25 per cent.

A control experiment to check this point was done by bleeding a 9 kg. dog 150 cc. of arterial blood at the height of embolic anoxemia when his blood was 59.10 per cent saturated. No increase in percentage saturation resulted but, in fact, a decrease to 56.20 per cent.

At this point in the paper a résumé of the foregoing argument may appear desirable. It has been shown that multiple experimental emboli of the larger branches of the pulmonary artery in dogs gives rise to *anoxemia* and thus to *tachypnea*. An effort to explain the cause of this anoxemia has shown that it is not related to:

1. Low alveolar oxygen tension.

2. Retardation of diffusion of oxgyen from alveoli into blood due to edema or exudate.

3. Shunt or passage of fraction of blood through either completely or partially unaerated channels from the venous to the arterial system.

4. Increased reduction of oxygen during flow through the tissue capillaries.

5. Increase in the total content of hemoglobin.

It is believed that embolic anoxemia results from the sixth cause enumerated above, namely, *a change in the quantitative relation of blood flow to the vascular diffusion area in the lungs*. The following experimental data and discussion will essay to establish this point.

It should be stated at the outset that anything approaching a quantitative estimation of the size of the capillary diffusion area of the lungs has not been possible and we have had to depend upon the morphological appearance of injected specimens to give us a conception of the extent of obstruction to the pulmonary circulation caused by seed embolism. Photographs of such specimens are shown in figures 2, 3 and 4. There can be no doubt from these specimens that the emboli have set up an effective blockade which prevents the passage of blood and thus much diminishes the vascular diffusion area. In the specimen shown in figure 4 it may be estimated that approximately two thirds of the vascular bed of the lungs has been obstructed.

The relation between blood flow and the area of the pulmonary vascular bed has been expressed by Stewart (10) in the following formula:

$$T \approx \frac{Q}{rQ'}$$

where Q = capacity of the pulmonary circulation,

Q' = average output of the right ventricle,

r = the number of beats of the heart per second, and

T = the pulmonary circulation time

It appears from this that a reduction in Q such as we are here dealing with, r and Q' remaining constant, would result in a diminution of T or, in other words, in a more rapid flow of blood through

the pulmonary circulation.   The possibility should be borne in mind that the rate of flow may be so fast that the blood cannot take up its usual load of oxygen.   Indeed from the recent considerations of L. J. Henderson and his co-workers (11) on the time of the diffusion process in the lung this interpretation may be the correct one.

An actual estimation of the changes in Q' or at least of the changes in cardiac output per beat, was made in three experiments before and after seed embolism by the method of Barcroft, Boycott, Dunn, and Peters (12).   In these experiments temporary changes in volume of cardiac output and in the volume of blood flowing through the lungs occurred after seed embolism which did not persist in spite of the persistence of anoxemia.   It is safe to say, therefore, that such transitory changes were not responsible for the occurrence of anoxemia. In the first experiment of the three, the cardiac output per beat decreased from 11.3 to 9.9 cc. before and after seed injection, respectively. This amounted to a reduction in blood flow through the lungs per minute from 1.61 to 1.35 liters.   In the second experiment the changes were of a similar order of magnitude.   Before seed embolism the cardiac output per beat was 19.1 cc. after 17.0 cc. and the blood flow per minute through the lungs was 2.73 liters as compared with 2.18 liters.   In the third experiment 12.5 cc. of blood were being delivered from the heart before embolism as compared with 11.6 cc. after, and 2.51 liters of blood were flowing through the lungs per minute before embolism as compared with 2.32 liters after.   The data of these three experiments are persented in table 5.   In each case a slight diminution in cardiac output per beat and in minute volume blood flow through the lungs resulted.   If we pool the data of these three experiments we obtain the figures in table 6.

Let us assume that in these three experiments half of the total pulmonary vascular bed has been obstructed by seeds and that 100 arbitrarily represents the capacity of the pulmonary circulation, Q, before embolism.   We have then:

Before embolism   Circulation time:

$$T \eqsim \frac{100}{37.18} = 2.69$$

After embolism   Circulation time:

$$T \eqsim \frac{50}{32.00} = 1.56$$

TABLE 5

The effect of seed embolism

Experiment number	Time	Total number of seeds injected	O₂ content of blood Arterial (vol. per cent)	O₂ content of blood Venous (vol. per cent)	O₂ capacity of blood Arterial (vol. per cent)	O₂ capacity of blood Venous (vol. per cent)	Saturation of blood Arterial (per cent)	Saturation of blood Venous (per cent)	CO₂ content of blood Arterial (vol. per cent)	CO₂ content of blood Venous (vol. per cent)	Respiratory rate per minute	Heart rate per minute	Tidal air (cc.)	Minute volume (liters)	O^*	$A-V^*$	F^*	Cardiac output per beat (cc.)	CO₂ produced per minute (cc.)
49	11:27	0	18.31	13.93	18.10	18.09	100.00	77.00	49.01		12	142	170.0	2.05	70.85	0.044	1,610	11.3	60.24
	2:44	205	16.89	10.45	18.61	18.76	90.80	55.70	49.09	48.30	24	144	189.0	4.54	74.55	0.064	1,164	8.1	75.38
	4:07	255	13.68	9.18	18.67	20.04	73.30	45.80	46.10	50.70	34	136	186.0	6.32	74.40	0.055	1,352	9.9	67.36
50	1:24–1:34	0	14.3	11.40	17.44	14.66(?)	82.20	77.80(?)	43.20	46.10	12	143	187.5	2.25	80.06	0.0293	2,730	19.1	70.47
	3:14–3:24	235	11.04	5.41	16.56	16.11	66.70	33.50	44.60	44.78	46	139	172.4	7.93	72.34	0.0563	1,284	9.2	3.51
	3:55–4:05		7.44	4.10	17.51	18.34	42.50	22.34	46.28	48.52	42	128	164.0	6.89	72.71	0.0334	2,177	17.0	3.67
51	2:03–2:13	0	17.24	13.02	17.65	16.78	97.70	77.60	42.23		22	192	179.0	3.94	101.53	0.0422	2,405	12.52	77.05
	4:49–4:54	300	13.19	8.67	18.40	19.40	71.70	44.69		43.63	48	186	217.0	10.42	125.95	0.0452	2,786	14.96	5.60
	5:37–5:44		12.55	6.77	21.20	21.39	59.20	31.62	39.22	43.05	46	200	229.7	10.57	134.33	0.0578	2,324	11.61	5.68

*In this table $F = \dfrac{O}{A-V}$ where $A-V$ = the difference in content of O_2 between arterial and venous blood in cubic centimeter per 1 cc. blood. O = the total O_2 in cubic centimeter used per minute, and F = the cubic centimeter of blood flowing through the lungs per minute.

This represents a 42 per cent decrease in time (increased rapidity) of blood flow through the pulmonary vessels. Such a change alone, according to Henderson's approximations, would be responsible for, roughly, a 10 per cent decrease in volume per cent O_2 content of arterial blood. There is, however, another factor involved besides increased rapidity of blood flow. For the argument we have advanced assumes that no compensatory dilatation of unobstructed vessels has occurred. But our whole knowledge of the behavior of capillaries leads us to believe that this is not the case.

The postmortem findings of Underhill (3) and of Schlaepfer (4) give definite evidence for the occurrence of a compensatory dilatation of vessels in the intact lung after the artery to the other lung has been ligated. Since under these conditions there is usually a 40 per cent rise in pulmonary blood pressure with no effect on carotid pressure,

TABLE 6

	Heart rate per second	Cardiac output per beat	r.Q. or cardiac output per second
		cc.	cc.
Before embolism................	2.6	14.3	37.18
After embolism................	2.5	12.8	32.00

pulse rate, output of the heart or state of its dilatation, Underhill concludes that the healthy heart can accommodate itself by sending the same volume of blood through one lung in a given time as it previously sent through both. In our own experiments, which were of relatively short duration, difficulty in differentiating histologically the obstructed from the unobstructed areas in uninjected specimens made the actual demonstration of such dilated vessels somewhat uncertain. It is reasonable however, to assume the existence of a compensatory dilatation in the unobstructed vessels. Though in a lung, such as that shown in figure 4, it is scarcely conceivable that dilatation could be sufficient to restore the vascular bed to its original capacity. In such dilated capillaries crowded with corpuscles the inward diffusion of O_2 should be impaired and this should form a contributing cause to the type of anoxemia with which we are dealing here. Both these causes, which result in anoxemia, i.e., increased

rate of flow and increased blood bulk in the capillaries, could be corrected by raising the alveolar oxygen tension.

It should be stated here that Underhill (3) observed the occurrence of anoxemia in the blood of cats after ligating the artery to the left lung. Artificial ventilation did not relieve this anoxemia when the chest was closed. Underhill made no attempt to explain the cause of the anoxemia, but stated, as we have already mentioned, that under these conditions the right lung contained more blood than normal. With the chest open he found it was possible for the blood to be 90 to 95 per cent saturated provided sufficient ventilation were being given.

CO_2 CONTENT OF ARTERIAL BLOOD FOLLOWING SEED EMBOLISM

In spite of the impaired inward diffusion of oxygen due to the diminution of the vascular area, the carbon dioxide content of the arterial blood in these dogs remained remarkably constant. In 10 dogs in which seed embolism and the resulting anoxemia was produced the average content in CO_2 of the arterial blood before embolism was 44.46 volumes per cent as compared with 43.26 volumes per cent after embolism. The fact that there was no "piling up" of CO_2 in the blood can best be explained by (a) the existence of hyperventilation, (b) the greater diffusibility of CO_2 than O_2 due to its greater solubility coefficient. A normal or low CO_2 content of arterial blood in the presence of anoxemia is commonly seen in patients with lobar pneumonia.

DISCUSSION

As is suggested by the title of this paper and Paper I two distinct causes of rapid breathing have been encountered: (a) resulting from embolism of pulmonary arterioles and capillaries; (b) resulting from embolism of the larger branches of the pulmonary artery. The first is dependent on reflex changes arising from structural modifications in the pulmonary parenchyma. The nature of these is a generalized congestion and edema which produces a reduction in lung volume and an impairment of the normal elasticity of the lungs. This tends to limit the extent of the respiratory excursion and, as we have explained, thereby to quicken respirations. The second cause of rapid breathing, with which we have dealt in this paper, is anoxemia which results from a reduction in the vascular diffusion area. This second

type may be a complicating factor of the first.   To both there are clinical analogies.   Acute and chronic congestion of the lungs, lobar pneumonia, pulmonary fibrosis, are clinical conditions characterized by rapid respirations resulting, we believe, in part at least, from reflex effects due to the mechanical limitations to inflation and deflation.   Each of these conditions may be associated with anoxemia which, if present, will tend to a further acceleration of respiratory rate.

The causes of cyanosis and anoxemia as clinically seen have been fully discussed by Lundsgaard and Van Slyke (9).   That obstruction to the pulmonary circulation *per se* may constitute such a cause was not emphasized by them, and yet in such conditions as postoperative pulmonary embolism where there is often intense cyanosis accompanied by rapid breathing, which can and should be relieved by continuous oxygen therapy, there can be little doubt that we are dealing with a phenomenon analagous to the one experimentally produced in this work.   To what extent the obliteration of the branches of the pulmonary artery which exists in pneumonia is responsible for the occurrence of anoxemia and cyanosis, we are not prepared to say, but it is probable that it plays a rôle.

SUMMARY AND CONCLUSIONS

1. Multiple emboli of the larger branches of the pulmonary artery experimentally produced in dogs by the intravenous injection of seeds of various sizes results in tachypnea and anoxemia.

2. The tachypnea is due to the anoxemia and can be stopped or prevented by oxygen inhalation.

3. The anoxemia has been attributed to a change in the quantitative relation of blood flow to the vascular diffusion area in the lungs. The nature of this changed relationship is twofold: (a) an increased rate of flow through the capillaries, the flow being so rapid that the blood cannot assume its normal load of oxygen; (b) a compensatory dilation in the capillaries which are crowded with corpuscles in columns so thick as to interfere with the normal inward diffusion of oxygen. Each of these defects in O_2 diffusion can be remedied by raising the alveolar O_2 tension.

4. Changes of this sort occur in such clinical conditions as lobar pneumonia and pulmonary embolism where cyanosis and rapid breathing are commonly encountered and where oxygen therapy is indicated.

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