

ABSORPTION FROM THE PULMONARY ALVEOLI

By CECIL K. DRINKER, M.D., AND ESTHER HARDENBERGH

(From the Department of Physiology, Harvard School of Public Health, Boston)

PLATE 3

(Received for publication, March 25, 1947)

The ways in which molecules of different sizes, and finally visible particles, including bacteria, are absorbed from the lungs, present recurring problems to those concerned with many aspects of medicine and surgery. In this communication findings are recorded which have been gathered through the last four years with the advantage of new technical methods.

The routes of absorption from normal lung alveoli require passage through the epithelial lining of the alveoli and then the crossing of endothelium-lined blood capillaries into the blood or, if the second available route is to be followed, penetration of a lymphatic capillary through a delicate endothelial wall into the lymph stream. There is no doubt that bronchiolar absorption occurs, but both from the surface area available and the anatomical barriers imposed, it is of little importance compared with the absorption from the alveoli.

Experimental Technique

In every case dogs have been the experimental animals and have been anesthetized with 35 mg. per kilo of pentobarbital sodium (nembutal) given intravenously and repeated whenever necessary. The route of absorption into the blood capillaries in the lungs needs no comment. Absorption through the lung lymphatics is not so familiar and the anatomical considerations governing this pathway for removal of foreign material require explanation, since the validity of the experiments which will be described depends upon knowledge of the variable arrangements of the lung lymphatics and ability to cope with these variations.

Lymph from the lungs enters the blood through the right lymphatic duct, only a very small part of the left upper lobe being drained by the thoracic duct. Although it is true that right duct lymph invariably represents drainage of the lungs, it is unfortunately the fact that connections between the thoracic duct and the right lymphatic duct are frequent. In the dog, Freeman (1) found that in 12 out of 25 animals there were connections between the two ducts. This, for man, if true, is of the highest importance when thoracic duct obstruction occurs, or when it becomes necessary to tie the thoracic duct near to entrance into the left subclavian vein. But for the investigator who wishes to collect lung lymph with no additions except an inevitable small increment from the heart, it becomes very trying to encounter a series of animals in which the right duct lymph is grossly similar to that of the thoracic duct, in that both contain chyle. But with patience and experience, it eventually develops that in about one experiment in three, the right lymphatic duct can be cannulated and will deliver no lymph save that from the heart and lungs. There are no reliable directions for finding the right lymphatic duct. The technique could be made to seem quite simple by directing the dissector to follow the right cervical lymphatic vessel down to its junction with the right duct. The difficulty is that this direct means of finding the right duct is reliably unreliable. The right duct in the dog usually joins the axillary vein just above the first rib. With sufficient fre-

quency to alleviate discouragement, one sees the right duct come clearly into view just above the first rib, and the entrance into the vein is plain. But lymphatics in all parts of the body have a versatile irregularity of position and connection, and consequently the right lymphatic duct may be found emptying into different veins in unexpected planes at the base of the neck. Fortunately, as has been described in some detail by Drinker (2), it is possible to ascertain whether the lymph being collected from the right duct is actually from the lungs. This is learned by the simple expedient of instilling 5 to 10 cc. of 0.5 or 1 per cent T-1824 in Ringer's solution into the lung alveoli. It will be found that this intense blue dye will usually color the right duct lymph in 20 to 30 minutes but will not be detectable in the thoracic duct lymph until much later. This latter development expresses the absorption of the dye by the blood passing through the lungs, and is merely an indication of the generalized distribution of the blue compound in the tissue fluid all over the body. What is of consequence is the fact that if T-1824 reaches the pulmonary alveoli, it is seen in a short time in lymph coming from the lungs. A further control of the situation provided by right duct cannulation can be gained by subcutaneous injection of a graphite or very dilute India ink solution into a hind foot. If the site of this injection is massaged and the foot moved passively, the black injection mass appears promptly in the thoracic duct lymph and is not evident in right duct lymph, unless there is connection between the two sides.

In summary, it is apparent that if the thoracic duct and right lymphatic duct are cannulated, and if diffusible foreign materials readily identified in low concentrations are instilled into the lung alveoli, the observer can ascertain whether absorption has been into the blood or into the lymph, and the time required for the beginning of removal as well as an approximation of the rate and probable success of alveolar clearance can also be obtained.

EXPERIMENTS

The ease with which water and solutes up to about the dimensions of egg albumin are absorbed from the lungs is not adequately realized by physiologists and clinicians. The facts are that water leaves the pulmonary alveoli to pass into the blood capillaries with a degree of rapidity quite consonant with the profuse blood capillary area available for absorption in the lungs. Winternitz and Smith (3) instilled physiological salt solution into the trachea of an anesthetized dog and found prompt removal of large amounts of fluid. When phenol-sulfonphthalein was added to the salt solution it appeared in the urine at once. These experiments mean that there is no alveolar barrier to the passage of water nor of small molecules and that the lung capillaries carrying blood at a relatively low pressure are easily accessible and very effective as a means of absorption. It will enforce this statement to summarize a simple experiment:—

A dog anesthetized with nembital was prepared for observation by cannulation of the thoracic and right lymphatic ducts. The obvious presence of chyle in the thoracic duct lymph and absence in right duct lymph indicated lack of communication between lung lymphatic and thoracic duct drainage. Ten cc. of a 1 per cent solution of T-1824 in physiological salt solution was instilled intratracheally, the dog being inclined head up at about a 30° angle during the instillation and for some minutes afterwards. Within 20 minutes the right duct lymph became blue and in a short time blood specimens showed a faint blue tinge in the plasma. This meant that in a dog with no possibility of lymphatic delivery of dye into the blood, molecules of this

dye passed through the alveolar epithelium to reach the alveolar blood capillaries and then entered the blood. At the same time dye molecules reached the lung lymph on the way to the right duct and delivery into the right axillary vein. Cannulation of the right duct disclosed this path of removal from the lungs, but though the concentration of dye in the lymph was very high, so that the fluid collected was an opaque deep blue, one could not escape the fact that simultaneously with lymph absorption of dye molecules there had been a steady and efficient absorption directly into the blood. Had there been no interference with lymph delivery to the blood through the normal route, blood concentrations of dye might have become higher, but this obvious point is not the true concern of the experiment.

It is the fact that intraalveolar molecules, even of fairly large size as represented by the dye T-1824, enter the blood capillaries quickly and the main route for lung clearance of such foreign instillations is the blood. If lymphatic connections are normal, that is, unbroken by the cannulations possible to the experimenter, additional increments of dye absorbed by the lung lymphatics will reach the blood through the right duct and to a very minor degree through the thoracic duct.

These facts are of more than experimental significance. For example, penicillin by inhalation was advocated early in the history of the drug for direct medication of bronchiectatic cavities and suppurative conditions in the lungs. It is doubtful how far inhaled mists containing penicillin reach suppurative foci which it is hoped they will affect favorably. At the same time there cannot be any question that the intrapulmonary absorption of inhaled penicillin is extremely effective and one can rely on high blood titres of penicillin administered by inhalation.

It is now known (4) that T-1824 forms some sort of combination, chiefly with albumin, and in this way the molecule of blue dye is effectively increased in size and diffuses through living membranes very slowly. If T-1824 is vaporized in watery solution and a dog breathes the blue mist, which is wholly non-irritating, the blood plasma becomes strikingly blue in a short time. There is absorption by the lung lymphatics, as cannulation of the right lymphatic duct shows, but it is insignificant in amount compared with the ready entrance into the blood.

In contrast to the experiments upon ready absorption of T-1824 in water, a number of experiments have been done in which the dye, in 0.5 to 1 per cent concentration, has been dissolved in Ringer's solution and then various proteins added, giving in each case a concentration of 2.0 to 5.0 per cent of protein. At the start, fresh heparinized dog plasma was used; later, highly purified serum albumin; and finally, egg albumin. In all these cases the dye combines with protein, and on dialyzing the blue solution against Ringer's solution many hours are required before the salt solution shows recognizable traces of blue color. In addition to these proteins, experiments were also made with hemoglobin solutions. Hemoglobin does not combine with T-1824. It was our hope that

if absorption into the lymph occurred, it would be evident through red color in the right duct lymph. This did not happen to a recognizable degree.

Typical experiments are as follows:—

1. *Blood Plasma Plus T-1824.*—

Dog weight, 11.8 kg.

9:15 a.m. 9 cc. of 5 per cent nembatal, intravenously.

10:05. Intratracheal injection of 6.0 cc. of a solution which contained 0.5 per cent T-1824 plus heparinized dog plasma making an eventual concentration of 4.4 per cent protein.

10:15. 5 cc. same solution intratracheally. During these instillations the board was elevated for 15 minutes so as to give a 30° angle, head up position.

10:35. 200 cc. Ringer's solution intravenously—slowly.

11:25. Thoracic duct cannulated. Lymph flow rapid.

11:30. Right lymphatic duct cannulated. Lymph flow excellent.

11:42. Blood pressure record from left femoral artery.

11:48. Second blood pressure record.

11:49. Artificial respiration given through tracheal cannula by means of a pump supplying air under positive pressure for inspiration, expiration being normal, that is, without suction. The pump used can be set for rate and minute volume of delivery where the animal ceases all efforts to breathe in its natural manner.

12:10 p.m. 5 cc. of blood from left external jugular vein. Centrifuged at once. No blue color.

12:56. 1 cc., 5 per cent nembatal, intravenously.

1:13. 1 cc., 5 per cent nembatal, intravenously.

1:32. Third blood pressure record.

1:56. 1 cc., 5 per cent nembatal, intravenously.

2:10. Fourth blood pressure record.

2:11. Dog bled to death from femoral artery. Blood specimen centrifuged. No blue color.

Autopsy.—The largest part of the blue solution given intratracheally entered the lower right lobe which was intensely blue. There was a small degree of blue color posteriorly in all the other lobes on both sides.

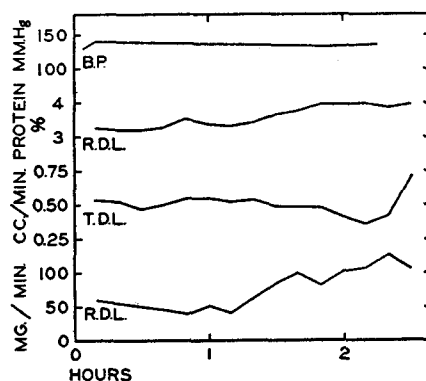
The right lymphatic duct and the vessels combining to form it showed no blue discoloration. The right tracheobronchial lymph node was very faintly blue, indicating slight absorption but not enough to pass through the node and reach the draining trunks leading eventually to the right lymphatic duct, the lymph from which never showed blue color.

Comment.—In this animal, observed for 4 hours after intratracheal instillation of a T-1824 and blood plasma solution, there was no delivery of the solution to the blood nor to the right lymph duct and thoracic duct. Experience has shown that had the solution been protein-free, right duct lymph would have become intensely blue in about 20 to 30 minutes and the blood appreciably so within the first hour.

The animal remained in excellent condition throughout the entire experiment. Positive pressure artificial respiration was applied, not because the condition of the dog required it, but because the squeezing effect on the lungs of the positive inspiratory blast of air greatly intensifies lymph drainage from the lungs

and assures the appearance of the blue solution in the right duct lymph, since it is forced out into the interstitial tissue of the lungs and then into capillary lymphatics. When such an injection is made directly into the lung parenchyma, though part of the blue solution is intraalveolar, the protection against absorption offered by the normal alveolar epithelium is lost to a fair degree and even if the solution does contain protein, lymphatic entrance is readily accomplished. This fact must be clear enough since one of the functions, indeed, possibly the most important function under normal conditions, of the capillary lymphatics is to remove excess protein which has escaped from the blood capillaries.

In Text-fig. 1, the details of blood pressure, protein content and flow of right duct lymph, and flow of thoracic duct lymph are given for the experiment in which plasma plus T-1824 was given intratracheally.



TEXT-FIG. 1. The details of Experiment 1 in which T-1824 in a Ringer-plasma solution was given intratracheally to a dog. Curves from top to bottom: *B.P.*, blood pressure in millimeters of mercury; *R.D.L.*, right duct lymph protein in grams per cent; *T.D.L.*, thoracic duct lymph in cubic centimeters per minute; *R.D.L.*, right duct lymph in milligrams per minute. Ordinates, as designated. Abscissae, time in hours.

2. Serum Albumin.—

In this experiment the animal was anesthetized with nembutal, the thoracic and right lymphatic ducts cannulated, and 11 cc. of a 4 per cent solution of purified bovine serum albumin, obtained from Dr. Charles A. Janeway, was instilled intratracheally.

The serum albumin employed was a crystallized bovine albumin prepared by Dr. Walter L. Hughes, from the Department of Physical Chemistry at the Harvard Medical School, and in use by Dr. Janeway for immunological experiments. It was a 24 per cent solution in isotonic saline with a pH of about 6.8. It contained merthiolate, 1 to 15,000, as a preservative. Dr. Janeway considered that the preparation contained about 0.1 per cent of globulin, being, thus, 99.9 per cent pure albumin. This stock solution was diluted to 4.0 per cent prior to use in the lung absorption experiments. No T-1824 was added.

Dr. William H. Batchelor, a student in Dr. Janeway's laboratory, determined the bovine

albumin content of blood and lymph specimens as follows: The crystallized bovine albumin content of the specimen received was determined by precipitation, using rabbit antiserum in the range of antibody excess. The nitrogen content of the washed precipitate was determined by a micro-Kjeldahl technique. Using a calibration curve, prepared for the particular antiserum, these nitrogen values (actually the equivalent of the nitrogen values in terms of the amount of N/70 HCl needed to neutralize the ammonia) were compared with those gained by using known amounts of protein. Dog serum proteins do not yield precipitates with the antiserum. The error is probably within 20 per cent.

Artificial respiration was employed intermittently in order to accelerate the flow of lung lymph.

Specimens of lymph from the right duct and the thoracic duct were taken at approximately hourly intervals for 4 hours following intratracheal administration of the albumin solution. Blood specimens were secured before, during, and at the close of the 4 hour period of observation.

Five samples of thoracic duct lymph were all negative for albumin as were the blood samples.

The results relative to the right duct lymph were as shown in Table I.

TABLE I
The Detection in Right Duct Lymph of Crystalline Bovine Albumin Dissolved in Saline and Introduced Intratracheally in the Dog

Time	No. of specimen	Albumin (+ or -)	Amount of specimen	Remarks
<i>p.m.</i>		<i>mg. per cent</i>	<i>gm.</i>	
12:15-1:25 1:40	1		1.3	Instillation of albumin solution
1:25-3:00	2	Trace	1.2	
3:00-4:30	3	5.75	1.4	
4:30-5:40	4	25.75	1.3	

Comment.—In this case it is evident that a small degree of transfer of intra-alveolar albumin to the right lymphatic duct began shortly after instillation and increased over the next few hours but never reached high values. It must be remembered that right duct lymph drainage was forced by artificial respiration and would have been less under normal conditions of breathing. Also, it is significant that even at the close of this experiment the blood did not contain a detectable amount of albumin.

3. Egg Albumin.—

In this experiment a dog was given nembutal intravenously and the thoracic duct and right lymphatic ducts were cannulated. A cannula was inserted in the trachea to permit artificial respiration. Purified egg albumin, supplied by Dr. Gertrude E. Perlmann from the Massachusetts General Hospital, was made from fresh eggs, the egg white being recrystallized three times and stored at 3°C. under a saturated solution of ammonium sulfate. Before use, the preparation was dissolved in distilled water and dialyzed for 24 hours against running

distilled water, and then against smaller volumes of distilled water until ammonium sulfate-free. The dialysis was carried out at 3°C. The eventual solution was found to contain 6.9 per cent egg albumin. This solution was then diluted to 4 per cent albumin and 1 per cent T-1824 in 0.9 per cent saline. It was in turn dialyzed against 0.9 per cent salt solution and no release of T-1824 occurred. One can, therefore, conclude that in the case of egg albumin, there is a combination of T-1824 with the protein, and the blue dye serves as an indicator of the movement of the egg albumin molecule. In this experiment 11 cc. of 4 per cent albumin plus 1 per cent T-1824 were given intratracheally at 12:40 p.m., the dog being inclined head up during the instillation and for a short time thereafter. The results in right duct lymph are summarized in Table II.

Comment.—In the case of purified egg albumin there is evidence that slight traces of the protein did pass through the alveolar walls and reach the right duct drainage route, but absorption was just recognizable and no blue color was detected in thoracic duct lymph nor in blood plasma.

TABLE II
Results Obtained in Right Duct Lymph When a Solution of Purified Egg Albumin Plus T-1824 Was Instilled Intratracheally

Time	Lymph	Protein	Remarks
<i>p.m.</i>	<i>gm.</i>	<i>per cent</i>	
12:25-12:40	0.54	3.12	
12:40- 1:40	1.3	3.08	Intratracheal instillation egg albumin plus T-1824 at 12:40
1:40- 2:40	1.5	2.72	
2:40- 3:40	1.3	3.01	Questionable grey-blue color in lymph
3:40- 4:40	1.6	3.00	Definitely blue lymph
4:40- 4:58	0.73	3.08	
4:58- 5:05	0.31		All specimens very slight bluish tint
5:05- 5:18	0.22		
5:18- 5:25	0.20	3.03	
5:19			Blood specimen shows no blue color

4. Hemoglobin.—

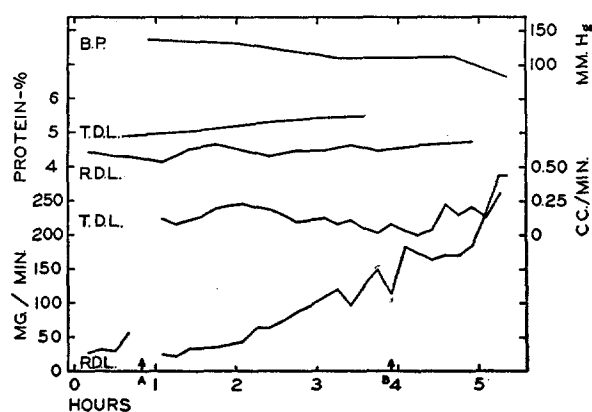
In several experiments crystalline hemoglobin in Ringer's solution and crude hemoglobin from washed red cells were given intratracheally. If absorption occurred during 4 hours, it was so slight as to be masked by the usual slightly yellow color of the right duct lymph.

5. Visible Particles.—

Lymph from the right duct of the dog does not contain visible foreign particles even if the lung lymphatics and lymph nodes are plentifully loaded with black dust of microscopic dimensions. To determine the absorption of particles from the alveoli of the normal dog, it is necessary to examine sections of the

lung and lymph nodes, and since all dogs except extremely young puppies show black particles in lung lymphatics and nodes, it becomes impossible to be sure whether what is seen was in the lungs prior to intratracheal injection or resulted from it. Accordingly, search was made for visible particles of distinctive appearance. These were furnished by Dr. Leslie Silverman of the Department of Industrial Hygiene.

Dr. Silverman had been making dusts by grinding pyrex glass to extremely fine dimensions and then blowing the glass powder across an oxygen and gas jet. The heat encountered by the particles in this transit converts them into perfect spheres. For our purpose Dr. Silverman furnished glass spheres averaging 4 micra in diameter. These were suspended in distilled



TEXT-FIG. 2. The effect of alpha-naphthyl thiourea on the flow of lung lymph and the times of injection both of the drug and the glass sphere suspension. *Arrow A*, time of intravenous ANTU injection. *Arrow B*, time of intratracheal injection of glass sphere suspension. Curves from top to bottom: *B.P.*, blood pressure in millimeters of mercury; *T.D.L.* and *R.D.L.*, thoracic and right duct lymph protein, respectively, in grams per cent; *T.D.L.*, thoracic duct lymph in cubic centimeters per minute; *R.D.L.*, right duct lymph in milligrams per minute. Ordinates, as designated. Abscissae, time in hours.

water plus T-1824 and shaken vigorously just prior to intratracheal administration. Dogs were prepared in the usual manner; anesthetized with nembutal, and the trachea, the right lymphatic duct, and the thoracic duct cannulated.

After control examinations of the right duct lymph, which disclosed nothing except large numbers of lymphocytes, the glass sphere suspension plus T-1824 was delivered by intratracheal instillation. Flow of lymph from the right duct was free, and artificial respiration was used to make it maximal. Examinations of right duct lymph, representing lung drainage, showed blue coloration 72 minutes after giving the intratracheal suspension of glass spheres and T-1824. But though the lung lymph showed dye absorption, which became more pronounced as time passed, specimens of the lymph examined microscopically never, during 4 hours, showed the glass spheres, which are so unique in appearance as to be quite unmistakable. In sections of lymph nodes, through which the lung lymph must pass on the way to the blood, no glass spheres were detected at the end of 4 hours. It is of interest that lung sections, as

seen in Fig. 1, showed spheres attached to typical lung phagocytes, but in the space of 4 hours none of these cells carrying foreign particles had made visible progress along the conventional line of lymph drainage, and no spheres were seen in lymph nodes.

This result, in which a distinctive particle was employed, does not permit wide generalization. Because glass spheres averaging 4 micra in diameter were not moved in 4 hours from the alveoli, even to lymph nodes at the root of the lung, does not mean that other foreign particles might not make a quicker entrance in the lymph stream and a more rapid movement to lymph nodes. There can be no doubt that different physical and chemical characteristics of foreign particles in the alveoli influence the rapidity of removal by the lymphatic route.

In order to see whether great increase in lymph flow might cause movement of the glass spheres, dogs were given alpha-naphthyl thiourea (ANTU) which causes a huge outpouring of lung lymph. In a typical experiment (Text-fig. 2) the glass bead suspension was given intratracheally 3 hours and 5 minutes after intravenous ANTU injection had begun to increase lymph flow. This animal died 1 hour and 27 minutes later. At autopsy, the pleural effusion and lung edema which are caused by ANTU were found; but, on microscopic examination of lung tissue and lymph nodes, presence of the glass spheres in the lymphatic system could not be detected. Text-fig. 2 shows the details of this experiment.

DISCUSSION

Drinker, Warren, and MacLanahan (5) investigated the absorption of protein solutions placed in the alveoli of anesthetized dogs. Contrary to their expectations, they found that detectable traces of protein appeared in the blood some time before they were found in the thoracic duct lymph. The technique of preparing the animals for these experiments was inadequate in view of what has been learned relative to lymphatic drainage of the lungs in the last few years.

In 1937, it was thought that if the right lymphatic duct was tied where it makes venous entrance and the thoracic duct cannulated, all material absorbed from the lungs would be found in the thoracic duct lymph or in the blood. Although the right duct and the thoracic duct are often connected, the anastomosing vessels are usually very small and of little significance unless the thoracic duct is obstructed, when the increased lymph pressure forces dilatation, and eventually they become large enough to carry all of the thoracic duct lymph to the right subclavian vein. Under normal conditions of breathing the flow of lymph from the lungs is small, and if the right duct, into which the lung lymph flows, is obstructed, there is a large enough distribution of lymphatics in the lungs so that there is lymph accumulation in the lungs and practically no tendency to force the fluid into the thoracic duct through the small connecting vessels which may be present. One cannot expect in a brief experiment to obtain material absorbed from the lung alveoli in thoracic duct lymph. It is

necessary to cannulate the right lymphatic duct in order to accomplish this, just as has been done in the experiments described in this paper. Drinker, Warren, and MacLanahan (5) used qualitative immunologic methods for detecting horse serum, crystallized hemoglobin, and crystallized egg albumin after instilling large amounts (20 to 50 cc.) of solutions of these proteins into the alveoli by the tracheal route. Frequently the experiments lasted 24 hours, and it was found that after several hours all these proteins could be detected in the blood and later in thoracic duct lymph to which they had undoubtedly been delivered by the blood. These results, though inadequate for uncovering all the possible methods of absorption from the alveoli, do, however, indicate that so far as removal by the blood capillaries is concerned, exceedingly small amounts of foreign protein pass through the alveolar epithelium and then the blood capillary endothelium.

In the experiments reported in the present paper it is apparent that in 4 hours' time small protein molecules, notably serum albumin and egg albumin, do find their way into the lung lymphatics, though by using artificial respiration with a positive pressure delivery of air for inspiration, advantage has been taken of the measure found most effective in promoting absorption from the alveoli into lymphatics and the flow of lung lymph. The conclusion to be drawn is that unchanged transudates and exudates resulting from lung injury are removed from the lung alveoli in minute amounts. To clear the lungs of plasma proteins requires breakdown of molecules by enzymatic action until products are formed which are small enough to diffuse readily into the blood. The prolific supply of lymphatics in the lungs is apparently for the purpose of slowly moving wholly insoluble substances into the lymph stream, with the usual result of imprisoning them in lymph nodes prior to a possible entrance into the blood and general distribution throughout the body. The chief barrier to absorption is apparently the alveolar epithelium, since, when proteins are injected directly into the lung tissue and so diffuse widely in the alveolar walls, delivery of these substances by the right lymphatic duct is very prompt.

The results reported in this paper and accumulated over a number of years, accord with and extend those obtained by Cameron and Courtice (6) and by Courtice and Phipps (7).

SUMMARY

Experiments upon dogs anesthetized with nembutal and lasting 4 hours, in which the right lymphatic duct and thoracic duct have been cannulated and collection of lung lymph and blood specimens was accomplished after intratracheal instillation of dog plasma, purified bovine serum albumin, crystallized egg albumin, and hemoglobin, have shown that the absorption of such molecules is slight. Experiments in which pyrex glass spheres averaging 4 micra in

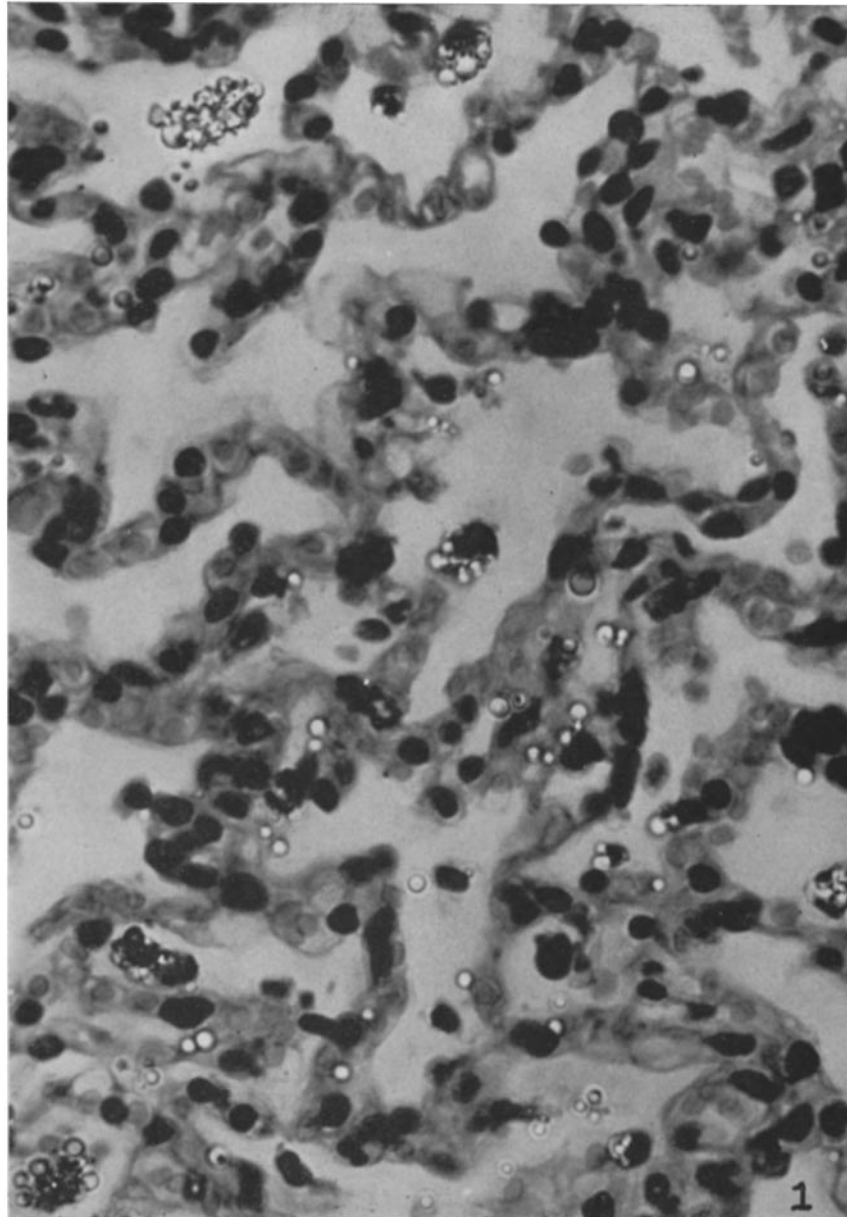
diameter were instilled failed to disclose entrance of these distinctive foreign particles into the lymph stream, though the fact that lung phagocytes were often found containing the particles or covered with them, indicated that eventually these particles would be found in lung lymphatics and in lymph nodes. The protection against absorption from the lung alveoli is in the main due to intact alveolar epithelium through which molecules of the dimensions of the proteins commonly entering the alveoli, as a result of trauma or disease, pass very slowly and are found in small traces in lung lymph and even to a less degree in blood.

BIBLIOGRAPHY

1. Freeman, L. W., *Anat. Rec.*, 1942, **82**, 543.
2. Drinker, C. K., *Pulmonary Edema and Inflammation*, Cambridge, Harvard University Press, 1945.
3. Winternitz, M. C., and Smith, G. H., Preliminary studies in intratracheal therapy, in *Collected Studies on the Pathology of War Gas Poisoning*, New Haven, Yale University Press, 1920, 143.
4. Rawson, R. A., *Am. J. Physiol.*, 1942-43, **138**, 708.
5. Drinker, C. K., Warren, M. F., and MacLanahan, M., *J. Exp. Med.*, 1937, **66**, 449.
6. Cameron, G. R., and Courtice, F. C., *J. Physiol.*, 1946, **105**, 175.
7. Courtice, F. C., and Phipps, P. J., *J. Physiol.*, 1946, **105**, 186.

EXPLANATION OF PLATE 3

FIG. 1. Photomicrograph of the lung of a normal dog into which glass spheres, 4 micra in average diameter, have been instilled intratracheally. Many spheres have been collected by phagocytes, many are free in the alveoli, and here and there one sees possible but not certain entrance of a sphere into the alveolar wall. $\times 550$.



(Drinker and Hardenbergh: Absorption from pulmonary alveoli)