THE NORMAL BEHAVIOR OF THE PULMONARY BLOOD VESSELS WITH OBSERVATIONS ON THE INTERMITTENCE OF THE FLOW OF BLOOD IN THE ARTERIOLES AND CAPILLARIES

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In the work described in this paper, a method has been developed for direct microscopic observation of the smaller blood vessels of the mammalian lung in the unopened thorax. The behavior of these vessels and the flow of blood through them have been studied under a variety of conditions. We were particularly interested in their normal behavior, in the question of intermittence of the flow of blood in the arterioles and capillaries and the factors controlling it, and in the number of capillaries open at a given time and the variations in the circulation within them. Observations upon the actions of various drugs on the pulmonary vessels are also presented.

When this work was begun in 1924, Krogh (1919 and 1922) and Richards and Schmidt (1924) had reported the results of their brilliant work in which the Malpighian method of direct microscopic observation was used. The work of these investigators suggested the possibility of the re-adaptation and modification of the Malpighian method for use in studying pulmonary blood vessels in the cat.

Microscopic observations on the pulmonary circulation of the frog were first made and reported by Malpighi (1687). Stephen Hales (1733) and Tiemann and F. Roeder (1932) have also observed the flow of blood in the

1 The expenses of this investigation have been defrayed in part by a grant from the DeLamar Mobile Research Fund of the Harvard University Medical School and in part by the P. W. Harvey Research Fund in the Department of Medicine of Lakeside Hospital.

2 Doctors Barr and German, while fourth year students in the Harvard Medical School, spent a year in my laboratory and took part in developing the method as well as in some of the earlier experiments. Doctors Ernstene and Bromer, and Miss Zschiesche took part in a majority of the observations upon the behavior of the vessels and the action of drugs upon them.
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blood vessels of the frog's lung. No intermittence in the circulation was noted.

Cohnheim and Litten (1875) injected dye into the blood streams of rabbits and found that it was unevenly distributed in the lungs while evenly distributed in the other organs. This work, which is supported by that of Toyama (1925), furnishes the first evidence of an intermittent flow of blood in the pulmonary vessels.

Hall (1925) transilluminated the lung in cats and rabbits and observed the pulmonary circulation by opening the chest and drawing out and fixing a quiet lobe of the lung with small clamps. He described the blood flow in the arterioles, capillaries, and veins and, in the larger arterioles and venules in which the walls were thin enough to see the cellular elements of the blood, he observed a pulsatile flow. In the smaller arterioles and capillaries, the flow was steady. He reported no intermittence of arteriolar or capillary circulation. Following epinephrine he noted a reversal of direction of circulation and in some instances a constriction of arterioles.

Olkon and Joannides (1930) described the capillaries of the alveoli in the lung of a living dog and observed changes in blood flow with change in intrapulmonary pressure.

MacGregor (1933) modified Hall's method to study the pulmonary vessels in the cat and in the isolated, perfused lung. He reported alteration in the rate and a reversal of flow but no spontaneous intermittence of arteriolar or capillary blood flow. It is interesting that the reactions he observed in local vessels did not always agree with the general reaction of the vessels of the entire lungs as measured by the inflow and outflow.

Wiggers (1921) and Daly (1933) have published excellent reviews of the literature concerning the pulmonary circulation.

METHOD. In our experiments, the cat was used because its parietal pleura proved to be best suited to the method employed, the pleura of the dog being too thick and that of the rabbit too fragile. Amytal in a dosage ranging from 50 to 100 mgm. per kgm. was given intraperitoneally in sufficient amount to secure light but complete anesthesia. The normal body temperature, as determined by a rectal thermometer, was maintained by a heating pad.

The lung was brought into view by dissecting away the muscle in the mid-axillary line between the eighth and ninth ribs until only the parietal

Wearn, Barr, and German (1926); Wearn, Ernstene, Barr, and German (1927); and Wearn, Ernstene, and Bromer (1928) reported some of the experiments, the results of which are given in full in this paper.

The lung of the frog lends itself beautifully to microscopic study but repeated observations carried on for hours at a time revealed a steady blood flow through the pulmonary vessels. These results confirm those of Tiemann and F. Roeder. These observations were made while I was in the laboratory of Prof. A. N. Richards in the University of Pennsylvania in 1921-23. J. T. W.
pleura remained as a clear, transparent, intact membrane. The diameter of this pleural window usually ranged from 0.6 to 1.2 cm. Through such a window the lower edge of the lower lobe of the lung was usually revealed. The pleura was kept moist by frequent applications of normal salt solution at body temperature. Through a mid-line abdominal incision another window was made in the diaphragm by dissecting the muscle from the abdominal surface of the diaphragm until the parietal pleura was exposed. This window was placed immediately opposite the one in the chest wall so that the tip of the lung lay between them. A beam of light from an arc lamp was passed through a cooling chamber and a quartz rod and thrown through the diaphragmatic window in such manner as to transilluminate the tip of the lung and make possible observations of the pulmonary vessels with a microscope at the window in the chest wall (fig. 1). All observations were made with a Spencer binocular bi-objective microscope at a magnification of ninety or one hundred and seventeen diameters. The blood pressure was recorded by means of a cannula in the carotid artery and the femoral vein was exposed for the injection of drugs and other substances.

METHOD OF OBSERVATION. Our observations were carried out in two groups of experiments. In the first, the cats were breathing, while in the second group, the lungs were immobilized by the use of curare.

In the first group of experiments the difficulty of observing the moving lung grew less as our eyes became accustomed to the motion. Morphine was used to slow the animals respiratory rate, but even with the slow rate we did not feel secure in detecting the finer capillary changes and for this reason the lungs were immobilized in the second group of experiments.

Curare^4 was injected into the femoral vein in sufficient dosage (usually 1.0 to 1.5 cc. of a 1.0 per cent solution) to abolish respiratory movements. A small catheter was introduced into the trachea for inflation of the lungs.

^4 We are indebted to Dr. C. K. Drinker for the high grade curare used in our earlier experiments. We later obtained a high grade curare from Peru. The condition of the animals remained satisfactory for several hours after the use of each.
which amounted to a modification of Meltzer's method (1909). Air was passed through a water bottle and the pressure in the trachea was so regulated as to keep the tip of the lower lobe of the lung between the pleural windows. At short intervals the chest was compressed several times by hand to insure proper ventilation. This procedure did not interfere with the return to view of the air sacs under observation. By this method we secured a still lung which greatly facilitated our observations and gave us confidence in their accuracy.

The fact that the behavior of the vessels was the same in the moving and still lungs excludes the possibility of the vascular reactions being caused by the respiratory movements. Likewise the maintenance of good ventilation eliminates asphyxia as a causative factor in the reactions of the vessels described in this paper.

The following observations were made in both the moving and immobilized lungs. Observations which were not common to both groups of experiments will be so indicated.

Air sacs and blood vessels. The vessels selected for study lay on or immediately below the lung surface nearest the microscope. The air sacs and air cells with their borders sharply outlined by small blood vessels and dark pigmented lines were easily identified by their glistening, pinkish, semi-transparent walls (figs. 2 and 3).

The walls of all the smaller blood vessels were for the most part trans-
parent and therefore not visible, but the thickness of the wall of an arteriole could be judged with a fair degree of accuracy by the width of the transparent area lying between the line made by its outer wall against the adjoining structure and that formed by the blood column within the vessel. The walls of the larger arterioles were opaque.

Arterioles. Our observations were usually made upon arterioles of approximately one hundred and ten microns or less in diameter, inasmuch as the majority of the vessels of this size permitted a clear view of the blood cells within them. Gross changes were also recorded in larger vessels.

The flow of blood in the arterioles was sometimes pulsatile, more often steady and non-pulsatile but frequently changed from the steady to the pulsatile flow or vice versa. In a single microscopic field we often saw a rapid, steady flow in one arteriole, a sluggish steady stream in a second, and a slow pulsatile flow in a third. Indeed, a different type of flow may occur in two arteriolar branches of one parent arteriole. Moreover, in the smaller arterioles a variation in the cell volume of the circulating blood has been noted when the blood flow was sufficiently slow to permit such observations. The cells may be closely packed or they may pass through the arteriole in single file or two or more abreast with irregular clear spaces between them. Such spaces we interpret as the transparent circulating plasma. The moving blood column within an arteriole may stop suddenly or gradually, become pulsatile without moving forward, and then resume flow. As frequently observed, the blood flow in an arteriole and its capillaries may come to a stop and the cells may be expelled peripherally to leave the arteriole and capillaries invisible, or less commonly with the cessation of blood flow, the column may remain motionless in the arteriole.

Contractility of arterioles and intermittence of blood flow. In addition to the disappearance of arterioles, we have observed their spontaneous appearance with active circulation in a field where they had not been visible previously. Also in one instance pressure applied to the abdominal aorta resulted in the appearance of blood flow in an arteriole and several capillaries arising from it, which had previously been closed and invisible. After the pressure on the aorta was discontinued, blood flow ceased in the arteriole and the vessel began to constrict at a point about midway in its course across the surface of the air sac. The constriction divided the blood into two columns and the vessel emptied itself by expelling the columns in opposite directions until each portion disappeared from its side of the microscopic field.

In another experiment an arteriole resembling a capillary in that it permitted red blood cells to pass through it in single file, dilated sufficiently after an injection of epinephrine to allow corpuscles to pass through it eight or more abreast. (See sketch in fig. 10.)
In one arteriole—a branch of a larger arteriole in which there was a steady flow—a stationary blood column was observed which ended abruptly about one-third of the way across the surface of an air sac which it traversed. Beyond the point where the blood column ended, the vessel was invisible. Immediately after a small dose of epinephrine was injected, the blood column forced the vessel open and established a steady flow through it (see fig. 4, air sac H).

Fig. 4. Sketches of various types of circulation on air sacs. The broad dark lines represent arterioles and the finer lines capillaries (see text for special references).

In figure 4, air sacs A, B, and F are shown with an arteriole crossing their surfaces. When observations were first begun, these vessels were showing active flow but a few minutes later the arterioles closed and disappeared from view.

Another phenomenon observed frequently in the pulmonary arterioles is the spontaneous reversal of the direction of the circulation. In figure 4 the air sac F has arterioles lying on either side of it (the heavy black lines) with arrows indicating the direction of the blood flow at the beginning of
the observation. Suddenly the velocity of the blood flow decreased, the flow became pulsatile, stopped, and then began in the opposite direction. The direction of flow in the arteriole crossing the air sac did not change. After the reversal is once established the original velocity of flow may be resumed, and intermittence in the flow of the capillaries may occur. At times the blood flows in the reversed direction only momentarily, but in some experiments it has continued for several minutes. These changes are similar to those described by Hall and MacGregor after the use of epinephrine. We have produced them with epinephrine and various other drugs and these results will be described later.

**Capillaries.** The capillary walls were invisible, but the course and calibre of the vessel were determined by the blood column within it. With the lung immobilized, it was possible to make accurate sketches of the arterioles and capillaries on the visible surfaces of the air sacs (fig. 4).

![Fig. 5. Shows sketches of air sac and its vessels as observed at three different stages during experiment 8.](image)

Under the conditions of our experiments, the number of active capillaries per air sac varied widely. At times no active capillaries were visible, and again the air sac was covered with them. The general range, however, was from two to ten per air sac and the average number for each group of experiments (moving lungs and immobilized lungs) was six capillaries per air sac. When the number of capillaries was more than ten per air sac, branchings and anastomoses were so frequently encountered that accurate quantitation was no longer possible. Indeed, a single capillary on the surface of an air sac should be looked upon as one channel of a meshwork of vessels and not as an isolated conduit. In a few experiments when the circulation was failing, and on other occasions without obvious cause, we have seen what we consider to be the entire capillary bed of the air sac

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5 By “active capillary” is meant a capillary through whose lumen blood is circulating.

6 When we speak of the number of capillaries per air sac, we mean the number of active capillaries on the visible surface of an air sac.
filled with blood. In these instances, the surface of the sac did not appear to have individual capillaries, but resembled very closely a fine meshed netting made up of channels filled with blood (fig. 6-B). We have never been able to produce experimentally the state in which all the lung capillaries would open. As a general rule, when the heart began to fail, it was more common to observe a closure of all the lung capillaries.

Variation in capillary circulation. At first, the capillaries were extremely difficult to see because of their invisible walls. They appeared as processions of red blood corpuscles, usually in single file, but frequently two abreast, moving with such rapidity at times that they resembled blurred red lines. Again, the stream was sluggish, pulsatile, and moved very slowly, or, the most characteristic type of flow perhaps, was a single file of cells, almost invisible at first, but detected by their reflections of light as they either hurried or floated leisurely across the air sac in the plasma stream. Sometimes a single corpuscle entered and traversed the length of the capillary before the next cell appeared.

The final differentiation between an arteriole and a capillary was determined by the width of the blood column which its lumen would accommodate. A sharp classification must necessarily be an arbitrary one and in this paper all vessels whose lumens admitted three or less red blood cells abreast were called capillaries. Evidence of the difference in diameter of the various capillaries was furnished by the shape of the red corpuscles passing through them. When the vessel was constricted, the corpuscle seemed to be squeezed and in contact with the capillary wall, while other capillaries with the same parent arteriole allowed two corpuscles abreast without crowding.

Exact measurements of the length of the capillary channels have not been made but relative lengths of capillary channels have been determined in the following manner. Three sketches of the same air sac with a different circulation in each case were photographed and enlarged sufficiently to permit accurate measurement of the lines representing capillaries (fig. 5). Lead fuse wire was bent, superimposed over each capillary, straightened, and then measured. By this method, the length of the
capillary channels in figure 5-A was found to be approximately 3.6 times those in figure 5-C and 9.2 times those in figure 5-B.

In another experiment we were able to sketch an air sac which showed a few active capillaries in the beginning and which later showed what we believed to be its entire capillary network. Figure 6-A represents the air sac as it appeared at the beginning of the experiment. We were unable to trace the flow in the capillaries beyond the edge of the air sac, and venule (Ve) was not visible. At a later stage in the experiment, the entire capillary network on the air sac showed active flow and simultaneously the venule (Ve) opened to drain the flow into the venule (V) (fig. 6-B). Later all the capillaries closed. The arterioles supplying the capillaries were not visible at any time during the experiment. This and many similar observations furnish an excellent idea of the capillary reserve of the lungs. We do not claim that the sketches are exact, but we do feel that they are sufficiently accurate to justify our belief that the average number of active capillaries (six per air sac) represents a small fraction, perhaps one-tenth to one-fifteenth of the available capillaries per sac.

Spontaneous opening and closing of capillaries were observed in practically every one of our experiments. In order to study this behavior and the underlying causes of the intermittence of blood flow more intensively, we selected certain air sacs showing active arterioles and capillaries and recorded and timed the changes in them on the smoked drum. This was done with one individual at the microscope, another at the kymograph, and a third tending the animal. Changes in the circulation were frequently confirmed by a second observer at the microscope. When necessary, one took notes and kept time with a stop watch. A series of numbered keys, each connected with a signal magnet which recorded on a smoked drum, were arranged in a convenient place. Each capillary under observation was given a number and, when any change occurred in the capillary, the key of the corresponding number was so manipulated as to record the mark on the drum.

In the following experiment intermittence of blood flow in the capillaries was recorded. (Only excerpts from the protocol are quoted here.)

Experiment 2. April 4, 1927. Cat. Weight 2.01 kgm. Amytal 200 mgm. intraperitoneally. Curare 1 cc. 1.0 per cent solution I.V. Prepared as in method described above. After making several preliminary observations, an air sac was selected for study. (See fig. 4, air sac J.)

3:43  Capillaries 1 and 2 open; 1 shows rapid, steady flow; 2 slow, pulsatile flow.
3:46  Capillary 2 shows more rapid flow. Blood pressure 94.
3:48  Capillary 3 appears with rapid, continuous flow. Blood pressure 94.
3:49  Capillary 4 appears with rapid but intermittent flow. Blood pressure 94.
4:01  Respiratory movements beginning. Curare 0.25 cc. of 1.0 per cent solution given intravenously.
4:01:30  Flow in capillary 2 slow and pulsatile. Blood pressure 100.
4:03  Flow in capillary 2 becomes rapid and continuous. Others unchanged.
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4:17:36 Capillary 3 reappears and the flow in capillary 4 becomes very slow, only an occasional red corpuscle passing through. The flow in the arteriole from which this capillary arises remains unchanged. Blood pressure 80.

4:17:44 Capillary 4 disappears and almost immediately the flow in capillary 2 becomes slow and slightly pulsatile, while that in capillaries 1 and 3 remains unchanged.

4:27:40 Capillary 1 disappears as before. Blood pressure 81. Capillary 5 begins to show intermittent flow of cells which come in spurts of a dozen or so.


4:40:11 Capillary 4 appears with a rapid but intermittent flow. Apparently there is a rapid flow of plasma with single cells or groups passing through intermittently at irregular intervals. Flow in the parent arteriole unchanged. Blood pressure 75.

* * * * = Irrelevant parts of protocol omitted.

Fig. 7. Section of the kymographic record of experiment 2 showing blood pressure and time in seconds. The changes in the lines labelled Capillary 1, 2, 3, 4, 5, and 6 represent changes in the behavior of the capillaries under observation (see text). In = beginning of flow in the capillary. Out = cessation of flow. A = intermittent flow. Lever up = capillary showing active flow. Lever down = capillary closed.

A section of the original record of experiment 2 is shown in figure 7. The length of these records is such that publication of the entire records is impossible. They have been condensed and charted, therefore, as shown in figures 8, 9, 10, and 11.

This experiment shows quite clearly the intermittent flow in the capillaries of the lung as well as the variation of flow within them. Similar observations have been made repeatedly in our laboratory during all seasons of the year and at least seven observers have taken part. From these results and many other similar ones, we have concluded that inter-
mittence of blood flow in arterioles and capillaries of the lung represents
the normal behavior of these vessels.

Fig. 8. Chart showing variations in the behavior of capillaries as observed on one
air sac which is sketched in the chart. A dark line represents continuous flow, a
cross line pulsating flow, and interruption of the line represents cessation of flow.
This chart was constructed from data in the original kymographic record and
our notes.

Fig. 9. Chart showing the effect of a small dose of epinephrine and sketches of
the changes in capillary circulation before and after the drug.

It is generally agreed that the pressure curve in the pulmonary artery
follows and runs approximately parallel to that in the aorta. In the
protocol cited and in figures 7 and 8, in which the results of two experiments
Changes in circulation following 0.5 cc. of 1:10,000 solution epinephrine. The number of active capillaries increased and the vessel labelled capillary 3 which had shown a circulation of red cells in single file dilated to become an arteriole with 8 or more cells abreast.

Fig. 11. Constriction and closure of arterioles and changes in the capillaries are shown after injection of pituitrin. The blood pressure rise following epinephrine failed to overcome the constriction produced by the pituitrin (see text). The broad lines represent increase in the velocity of blood flow in the capillaries and arterioles, the narrow lines slowing of flow, and interruption of lines cessation of flow. The parallel lines in capillary 3 and arterioles 1 and 2 represent stationary blood cells in these vessels.
are charted, evidence is produced to show that intermittence of the pulmonary capillary flow is certainly independent of changes in the systemic blood pressure. Moreover, the number of capillaries open and showing circulation is not determined by the level of blood pressure in any given animal. In many of the experiments where either high or low pressures existed at the beginning, only one or two capillaries per air sac were found and the equivalent of fifteen or thirty capillaries per air sac was found in the presence of both high and low blood pressure.

There is the possibility of independent changes in the pressure within the pulmonary circulation which might play some rôle in causing the intermittence in the blood flow within the arterioles and capillaries. It is not likely, however, that changes of great magnitude occur in the pulmonary pressure with the animal under such constant conditions.

Another possible explanation is suggested by these observations; namely, that the contractility shown by the arterioles in the lungs may play some part in regulating the pressure in the pulmonary circuit. What governs the contractility is unknown, but in many of our experiments we were able to produce intermittence of blood flow in the pulmonary vessels by the injection of small doses of epinephrine into the blood stream. These experiments are described later.

Richards and Schmidt have produced intermittence in the flow of blood in the glomerular circulation in the frog's kidney by gentle faradic stimulation of the sympathetic nerve fibers to that organ; also by small doses of epinephrine. It has not been possible to separate the sympathetic fibers to the cat's lung, but it is an accepted fact that such fibers occur in the lung of this animal. It is possible, therefore, that epinephrine may have acted upon these fibers to produce the intermittence of blood flow in our experiments.

Hooker (1911) and Richards (1914-15) have shown that the deprivation of oxygen will cause dilatation of arterioles and capillaries and Richards believes that oxygen lack is one factor in the mechanism of the intermittence in the glomerular circulation in the frog's kidney. It is difficult to believe that oxygen lack is a factor in the dilatation phase of the intermittent blood flow in the cat's lung, for the arterioles, with walls of capillary thinness, and the capillaries lie on the surfaces of the air saecs where oxygen is more accessible than at any other place in the body. Moreover, the production of asphyxia, as described later in this paper, did not cause arterioles or capillaries to open.

In several experiments we distended the lung so that its lower border moved 1 or 2 cm. downward, but slight or moderate changes of this degree did not interfere with the capillary or arteriolar flow. We feel confident that such changes in the insufflation pressure can be disregarded as playing any rôle in the intermittent changes in the capillaries noted
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This observation is not in agreement with those of Hall who observed remarkable changes in the filling of minute vessels as a result of variable alveolar inflation. This might be explained by the difference in degree of inflation of the lungs. In our experiments, the lungs were inflated so slightly that the lower border moved no greater distance than it does in a full normal respiration. A closed chest enabled us to control this procedure accurately.

We were unable to determine the exact mechanism of the emptying of the capillaries, but certain observations which we have made on the pulmonary vessels agree closely with those of Krogh and Richards and Schmidt. In many experiments an arteriole was observed from which a number of capillaries on the surface of one air sac took their origin. Without obvious change in the flow in the parent arteriole, marked changes were observed in the blood flow in the capillaries. From such observations, both arterioles and capillaries appeared to empty themselves by contracting. Krogh and Richards and Schmidt, however, have shown that constriction of the entrance of the capillary may permit plasma only to enter, wash out the cells, and thus render the capillary invisible. Some of our observations lend support to this explanation. Repeatedly, we have noted the disappearance of a capillary except for occasional corpuscles which passed through it either rapidly or slowly in such a manner that they moved freely within the walls and showed no constriction in their shapes. At times one corpuscle would scarcely traverse the length of the capillary before another appeared. Between the corpuscles, however, the capillary was invisible.

In other experiments, some observations were recorded which at first glance suggested that pulmonary capillaries can contract with sufficient force to empty themselves. In experiment 9, while observing an air sac with three arterioles and eight capillaries, the rate of blood flow became much slower, then pulsatile in character, and finally the flow in seven of the capillaries stopped, although the blood remained in them. The eighth capillary and the arterioles continued to show pulsatile flow. The seven capillaries were gradually emptied without any pulsatile motion and disappeared. This observation might be interpreted as evidence that the capillaries emptied themselves by contracting, inasmuch as the pulsations were not transmitted to the blood column within them. On numerous occasions, however, we have observed pulsations in arterioles and a steady, constant flow in the capillaries arising from them. It is possible, therefore, that constriction of the entrances of the seven capillaries in the experiment just cited might have allowed the entrance of sufficient plasma to wash the cells out without showing pulsatile motion.

Still another observation is of great interest. In experiment 7, while watching the effect of an injection of pituitrin upon two arterioles and five
capillaries on an air sac, the circulation suddenly stopped in all the vessels. The blood remained stationary in both arterioles and in two of the capillaries. In the other three capillaries, the blood was gradually expelled peripherally. In this instance, the capillaries from the same parent arterioles behaved differently, but it is conceivable that the ostia of the first two capillaries were completely closed, while those of the three that were emptied were constricted sufficiently to permit the entrance of plasma only, which washed out the cells. It is also possible that these capillaries may have emptied themselves by contracting, but, inasmuch as we have not observed anything in the conduct of the capillaries which could be explained only by their ability to contract, our general conclusion drawn from these observations is that the behavior of the capillaries can be explained by the constriction at their ostia in such a manner as to permit “plasma skimming.”

When capillaries branch or take their origin from other capillaries, the explanation of their actions becomes more difficult. We have observed alteration and intermittence of flow in such capillaries in many experiments. In these instances, it is possible that very slight changes of pressure in the parent arteriole might explain the intermittent flow. If “plasma skimming” is offered as the explanation of this behavior, it would imply contraction of the capillary at the point of branching from the other capillary.

The behavior in the pulmonary vessels thus far described has been observed in an unopened thorax. In a number of experiments, accidental destruction of the pleural windows afforded us opportunities to observe the vessels under the pressure relations brought about by the open window. In some such experiments we have observed intermittence of arteriolar and capillary blood flow. In several other instances, following the opening of the thorax the flow became steady and no intermittence was observed. The reason for the difference in reaction in some animals after opening the thorax is not clear. It is well known, however, that on opening the abdomen certain physiological reactions are changed.

The limitations of our method confined our observations to the lower edge of the lung. Hall, however, with a much greater surface of the lung exposed, observed various areas and found that the circulation in the vessels was essentially the same in all parts at any given time. MacGregor, on the other hand, observed no local changes in the smaller vessels in the presence of appreciable alteration in the total pulmonary blood inflow and outflow.

The method used in the above experiments also lends itself admirably to the microscopic observation of the action of drugs upon the smaller pulmonary blood vessels. When studying the action of drugs, the observer at the microscope was kept in ignorance as to the nature of the drug or substance to be injected or applied locally. Frequent injections and
applications of normal salt solution were carried out as control observations and no change was noted at any time as a result of the salt solution. All solutions for injection and local application were kept at body temperature.

**Action of epinephrine.** Epinephrine was used in doses of various sizes and was injected intravenously or applied locally to the outer pleural window. The results were varied and inconstant, but certain effects were encountered with sufficient frequency to warrant their presentation.

The three effects most commonly observed were 1, increase in the velocity of blood flow; 2, intermittence of the capillary circulation, and 3, an increase in the number of active capillaries. Other less frequent effects were slowing or stopping of blood flow and reversal of the direction of the circulation, both of which were noted most commonly after large doses. All the effects noted, however, occurred after large and small doses. The range of dosage varied from 1.0 cc. of 1:10,000 solution to 0.2 cc. of 1:5,000,000 solution. (See figs. 9 and 10.)

In order to avoid the actions of epinephrine upon the heart and blood pressure and thereby eliminate the effect that these changes might have upon the pulmonary vessels, epinephrine was applied locally to the pleural window through which we were observing. It was felt that any changes in the vessels produced by this procedure would represent the direct action upon the vessels themselves. The following is an abstract from the protocol of experiment 10 (Feb. 7, 1927):

At 4:22, while I was observing the vessels of an air sac, J. T. W. touched the external window with a piece of cotton which had been dipped in a solution. (This was a 1:100,000 solution of epinephrine.) The large arteriole emptied itself of blood and flow within it ceased almost instantaneously. This cessation of flow lasted 45 seconds and at the end of a minute flow was again resumed, at first in an intermittent fashion. In 1½ to 2 minutes the flow was once more constant in character. At 4:26 the velocity of the blood flow through the arteriole seemed greater than before the application. Needless to say, when the blood disappeared from the arteriole, the four capillaries arising from it also disappeared. (A. C. E.)

In this observation the large arteriole apparently constricted following the application of epinephrine. We do not feel sure of this, however, for there may have been a constriction at its ostium which permitted plasma only to pass through it. (The entrance of the arteriole was not visible in our field.) In either event, it would be rendered invisible. The systemic blood pressure remained unchanged throughout when the epinephrine was applied locally.

Repeatedly we have obtained evidence of constriction of vessels elsewhere in the circuit and not visible in our field of observation, as shown by

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We used adrenalin chloride tablets and the solution adrenalin chloride which contained chloretone and found no difference in the actions. Both products were put out by Parke, Davis & Co.
a cessation or marked slowing with pulsatile motion of the circulation. These results are similar to those of MacGregor. In only three experiments have we actually seen an arteriole contract and in each instance the vessel apparently closed. Even in these plasma may have been circulating. The fact that we were unable to see the vessel constrict, however, cannot be given too much weight, for the most commonly observed change after injections and local applications of epinephrine was an increase in the velocity of blood flow. After the injections this might be explained by the action of the heart, but following the local applications there was no change in heart rate or blood pressure and it is quite possible that slight constriction of the arterioles under observation escaped our notice. This is not at all unlikely when one recalls that the walls of the arterioles are invisible for the most part and that the calibre of the vessel is judged almost entirely by the width of the blood column. In two experiments, arterioles were probably constricted at their openings, for their walls remained visible and open and plasma was flowing through them as shown by the passage of an occasional red corpuscle. In one of these experiments changes followed an injection, and in the other, local applications of epinephrine.

Arterioles which had been closed and invisible opened with a normal flow after epinephrine, and both arterioles and capillaries have been seen to dilate following its use. (See fig. 10.) Whether the dilatation was due to an increase of pressure within the vessels or to action on them, we are not able to say.

The inconstancy of the results is striking as evidenced by the fact that following the use of epinephrine, in eighteen instances there was no detectable effect on the pulmonary vessels, and even the most common effects were not constant.

Action of pituitrin. The action of pituitrin when injected or applied locally to the pleural window was much more constant than that of epinephrine. Constriction of the arterioles, ranging from a slight constriction after the injection of small doses to complete closure of the vessels after large doses, was the common effect observed. Partial or complete constriction of arterioles at their ostia was observed on several occasions and reversal of the direction of the circulation also occurred. The same results were noted when the drug was applied locally. Immediately after an injection or application, there was usually a transient increase in the velocity of flow, lasting a few seconds only, and followed immediately by a marked slowing or a complete cessation. Experiment 7, part 2 (see fig. 11) is a typical one.

As in the case of epinephrine, in a number of instances pituitrin failed

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8 "Infundin" of Burroughs and Wellcome was used in all experiments.
to produce any visible effect upon the vessels under observation. After the twenty-two injections of pituitrin, no effect on pulmonary vessels was noted in seven instances. Diminished velocity was noted after seven injections, flow was stopped completely four times, and capillaries only closed on four occasions. Reversed circulation was observed four times.

In experiment 7, part 2 (fig. 11) two injections of pituitrin were given in order to stop the circulation in the arterioles under observation. A large dose of epinephrine was then given for the purpose of raising the blood pressure in the pulmonary artery. Schafer and Lim (1919), Dixon and Hoyle (1929), and Berry and Daly (1931) have shown that a rise in the systemic or aortic blood pressure produced by epinephrine is accompanied by a rise in the pulmonary arterial pressure. The rise in aortic pressure in this experiment, therefore, was very probably accompanied by an appreciable rise in the pressure in the pulmonary artery. The actual rise of course is unknown, but the chart is presented to show that, if a rise in pulmonary pressure occurred after epinephrine, it was not sufficient to overcome the constriction produced by the pituitrin.

**Nitrites.** The nitrite group was administered intravenously as nitroglycerin or introduced into the ventilation system as amyl nitrite. Of thirty-nine administrations, no effect on the pulmonary vessels was observed after fifteen. In six instances, there was an increase in the number of capillaries. An increase in the velocity of blood flow in all vessels was noted in nine instances after the injection of a nitrite, while a definite slowing was observed on eight occasions. Flow in the visible vessels stopped entirely on two occasions and in one of these a reversal in the circulation occurred.

**Other substances.** Our eight observations upon the action of histamine on the pulmonary vessels are too few in number to justify any general conclusions. The most commonly noted action was a closure of arterioles and capillaries. In some instances evidence of constriction outside of our field of observation was obtained. This was shown by cessation of blood flow in the arterioles without obvious constriction. In one experiment, after a small dose of histamine, the velocity of flow increased, while in another with the same dose there was a decrease. At times no effect on pulmonary flow was noted.

Caffeine, digitalis, and atropine were given during the course of some of the experiments, but no noteworthy effects upon the pulmonary vessels were observed with the exception of an increase in the velocity of flow in the arterioles after atropine on two occasions.

Daly has recently summarized and discussed the lack of agreement in the reports of different workers concerning the action of epinephrine and other drugs on the pulmonary circulation. When we summarize our own results, we find them almost as variable as those in the literature. The
repetition of the same dose in the same animal may produce a different result.

One possible explanation of the variation in the action of the various drugs has been suggested by Daly, who advances the hypothesis that the difference in reaction is dependent upon the amount of the drug that reaches a given area in the lung. Our observations have shown that the number of arterioles and capillaries open in a given area of the lung at a given time may vary tremendously. Moreover, the blood flow within those vessels may be sluggish or rapid, and at times the blood column may even be at a complete standstill. This evidence would certainly indicate that a drug introduced into the blood stream would not reach every part of the lung in the same concentration and that some parts of the lung might escape its action entirely. It does not explain why the drugs do not act upon vessels showing active circulation.

**Oxygen, carbon dioxide, nitrogen, etc.** In the great majority of the experiments, air was used for the intratracheal inflation. Various mixtures of gas were tried in some of the experiments, however, in order to observe the effects, if any, upon the pulmonary vessels. Pure oxygen, nitrogen, carbon dioxide, and two mixtures of oxygen and carbon dioxide (O₂ 90 per cent, CO₂ 10 per cent and O₂ 95 per cent, CO₂ 5 per cent) were used. In general, we found that the blood pressure was maintained at a higher level and the animal’s general condition remained satisfactory for a longer period of time when oxygen or the oxygen-carbon dioxide mixtures were employed instead of air. Sudden changes from air to any of the other gases, with the exception of nitrogen, produced no effect upon the rate of blood flow or the number of visible pulmonary arterioles and capillaries. We have six observations on the effect of substituting nitrogen for air in inflating the lungs. In each instance, the blood pressure soon began to fall and the circulation gradually ceased in all vessels, frequently showing pulsatile flow and then stopping altogether. All arterioles and capillaries were usually emptied. In one experiment, in which the cat was breathing when the nitrogen was started, the result was the same. In no instance, however, did we note any increase in the number of arterioles or capillaries showing circulation. Moreover, when the nitrogen was continued until the heart stopped, the vessels remained closed. We have noted similar behavior of the pulmonary vessels when death resulted from a failing circulation from any cause.

It seems worthy of remark that in only one of the experiments with nitrogen did we observe an asphyxial rise in the blood pressure, and even in that instance, it was so slight as to be scarcely noticeable. In all these experiments the condition of the animal before beginning the nitrogen was excellent.

In those experiments where asphyxia was the result of the inflation of the
lungs with carbon dioxide, there was no constant or striking change in the pulmonary circulation. As a rule, there was a gradual failure of the circulation similar to that observed following nitrogen inhalation.

**DISCUSSION.** During the course of our work we have observed the opening and closing of arterioles and great variation of blood flow within them, as well as changes in calibre. Contractions of arterioles were infrequently seen but indirect evidence of contraction elsewhere in the pulmonary circuit was obtained repeatedly. In each instance the vessels were small, with walls approaching those of the capillaries in thinness, and they lay directly upon the surface of the air sacs. MacGregor's results were similar.

The wide variation of flow within the individual lung capillaries and the intermittence of flow in the arterioles and capillaries are more difficult to explain in the lung than in other structures. We made every effort to keep the lung as nearly as possible in its physiological state and we believe that our method with the thorax unopened does eliminate certain complicating factors which are introduced when the lungs are drawn out of the thoracic cavity or when they are perfused.

Our results are in agreement with several of the findings of Hall and MacGregor. On other points, however, we find our results at variance with theirs, and these have to do largely with the reactions and behavior of the blood vessels; Hall concluded that, provided the lung inflation and heart rate remain unaltered, the arterioles, capillaries, and venules do not show any changes in size and he obtained no evidence of disappearance and reappearance of active capillaries. It is our feeling that the difference in the two methods used will account for the different results obtained. Even with the lung in the chest and the pleura destroyed, the vessels failed to contract at times, so it may be that Hall's method of removing the lung from the chest, clamping it, and bringing it into contact with cotton and gauze will account for the failure of the vessels to react as they do within the closed thorax.

**CONCLUSIONS**

1. A method is described which makes possible direct microscopic observation of the smaller superficial pulmonary blood vessels and air sacs in the unopened chest of the cat.
2. The number of pulmonary arterioles through which the blood circulates at a given time is not constant. The rate and character of blood flow within them may change spontaneously or as the result of the injection of epinephrine and other substances.
3. Intermittence of blood flow has been observed in the arterioles.
4. The number of capillaries through which blood flows at a given time varies greatly and may represent a very small fraction of the total number of the capillaries in the lung.
5. The velocity of blood flow and the cell content of the blood may vary in capillaries arising from the same arteriole.

6. Intermittence of blood flow was commonly observed in the pulmonary capillaries, and we believe it to be the normal behavior of these vessels. It is also produced at times by epinephrine.

7. The changes in the capillary flow are probably governed by changes in the arterioles from which they arise and by slight changes in the pressure in the pulmonary circuit. No proof of contraction of the capillary walls was obtained.

8. The actions of epinephrine, pituitrin, nitrites, and histamine are described and the most commonly observed effects of these drugs are discussed.

REFERENCES


Daly, I. de B. Physiol. Reviews 13: 149, 1933.


Hall, H. L. This Journal 28: 440, 1925.


The anatomy and physiology of capillaries. New Haven. 1922.


Malpighi, M. Opera Omnia. Lugduni Batavorum, 2, Epistola ii, De Pulmonibus, 328, 1687.


Richards, A. N. and C. F. Schmidt. This Journal 71: 178, 1924.


Wearn, J. T., A. C. Ernstene and A. W. Bromer. This Journal 85: 410, 1928.