STUDIES IN ASTHMA.

VII. THE PULMONARY CIRCULATION IN THE GUINEA PIG DURING ANAPHYLACTIC SHOCK.*

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In 1924, Drinker and Bronfenbrenner (1) measured the pressure in the pulmonary artery of the rabbit, the cat, the dog and the monkey during and for a brief period after the intravenous injection of small doses of sheep serum. The animals in question had received antecedent doses of this protein. It was found that in rabbits, anaphylactic shock is characterized by a notable degree of pulmonary vasoconstriction, great enough in some instances to cause the death of the animal. The same reaction but in lesser degree was observed in cats. Shock in dogs was without expression in the pulmonary circuit and as has been the invariable experience; no gross phenomena of any sort followed the second injection in monkeys.

At the time these experiments were made, measurement of the pulmonary arterial pressure in the guinea pig under good physiological conditions had not been accomplished. During the past spring the authors (2) have devised a method for making this measurement, which is so simple and reliable as to induce them to carry out the missing experiments upon this animal.

Auer and Lewis (3) in their paper on the immediate reaction of anaphylaxis in the guinea pig measured the systemic blood pressure during “shock” as have also Anderson and Schultz (4) and Loewit (5). All these authors have shown a rise in this pressure, coincident with the development of asphyxia. The absence of pronounced changes in the action of the heart constituted presumptive evidence that

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nothing notable occurred in the pulmonary blood circuit during shock, but without explicit experiment this could not be considered certain.

**Technique.**

*Anesthesia.*—All of the guinea pigs were anesthetized by intraperitoneal injections of 5 per cent sodium-barbital. It seems certain that this anesthetic, in common with others, somewhat reduces the acuity of anaphylactic shock but does not alter the fundamental nature of the reaction.

*Measurement of Pulmonary Arterial Pressure.*—In accordance with the technique described in our previous paper (2) a small L-shaped glass cannula was passed into the arch of the pulmonary artery without interrupting or obstructing the pulmonary blood flow. This cannula was connected with a water manometer containing red ink and the animal given an intravenous injection of heparin to prevent blood coagulation. In earlier experiments the level of the manometer was read at close intervals but in order to make recording entirely automatic, a Bell Howell 16 mm. motion picture camera was equipped with a small solenoid, operating a plunger, arranged to strike the starting button of the camera. By means of an ordinary laboratory timer the current in the solenoid could be made for an instant at selected and regular intervals, thus providing a series of photographs of the height of the manometer. By including an ordinary watch in the photographic field, strips of film were obtained carrying all the data necessary for plotting the pulmonary pressure curve of the experiment. With the apparatus described photographs could be made as rapidly as sixteen per second. In actual experiment it was found that a photograph every 5 seconds recorded the experiment in ample detail.

*Artificial Respiration and the Record of the Onset of Bronchial Obstruction.*—The anterior mediastinal partitions in the guinea pig are widely separated and with a fine dental saw to split the sternum it would undoubtedly be possible to cannulate the pulmonary artery without artificial respiration. But since it was our desire to find out whether the pulmonary vessels contracted during anaphylactic shock as a distinctive phenomenon similar to the contraction observed in the rabbit, and not secondary to the convulsive and asphyxial changes so characteristic of shock in the guinea pig, it was necessary to prevent convulsions and delay asphyxia by the use of curare and artificial respiration. The curare employed was from a lot used in this laboratory in many different series of experiments during the past 4 years and known to be without circulatory effect. For artificial respiration the quantitative respiration pump described by Drinker and Agassiz (6) was utilized. This pump delivers a gentle blast of air for lung inflation and expiration follows passively. In order to identify anaphylactic shock in the guinea pig one must have assurance that interference with the entrance of air into the lungs has occurred and the anesthetized, curarized guinea pig gives no early gross indications of such a situation. If, however, one places a T-tube in the inflow line to the
tracheal cannula from the respiration pump and connects from this T to a tube, the lower end of which is immersed in mercury in a small bottle, an arrangement is provided which records with fair sensitivity any obstruction to the entrance of air in the lungs. In actual practice we used a 90 cc. specimen bottle containing mercury and provided with a rubber stopper pierced by two glass tubes, one long, the other just through the cork. The lower end of the long tube was pushed through the cork and beneath the surface of the mercury just far enough so that no air escaped during the positive stroke by the pump. The shorter tube was connected with a small Krogh spirometer which wrote upon a kymograph. As long as conditions remained constant in the chest of the animal no air entered the spirometer and the writing point made a straight line, but with even very slight obstruction in the respiratory passages, air at once began to overflow into the spirometer and the rise in the writing point signaled the onset of the reaction. In our experiments anaphylactic shock invariably produced a degree of bronchiolar obstruction sufficient eventually to shunt all the air which had been reaching the animal into the overflow spirometer. The rate at which complete deprivation of air took place varied from animal to animal and was never rapid enough to make asphyxia a complicating factor in the distinctive circulatory change seen early in shock.

Sensitization.—All the animals received 2 cc. of sheep serum intraperitoneally and were used for acute experiment from 2 to 5 weeks following this injection.

EXPERIMENTAL.

In the paper (2) describing the technique of pulmonary arterial pressure measurement in the guinea pig, the fact that horse serum given intravenously produces a notable degree of constriction, is described. This is the reaction noted first by Brodie (7) and later explored by Schultz (8) and Edmunds (9). It occurs most markedly in cats. Drinker and Bronfenbrenner (1) found that from a variety of proteins sheep serum proved most innocuous but in some cats even this material gave an occasional reaction. Horse serum, given intravenously to the guinea pig, gives Brodie reactions with somewhat less regularity than in the cat. Sheep serum in doses below 0.3 cc. proved entirely inoffensive and as a consequence animals were sensitized with this material and given a "shocking" injection of 0.1 to 0.2 cc. of the same substance in 1 cc. of physiological saline.

In order to show the great difference between the Brodie reaction and that of anaphylactic shock, a typical experiment of the former type is given.
Fig. 1. Pulmonary arterial pressure in a normal guinea pig, which received 1 cc. horse serum intravenously at mark 1. Ordinates, pressure in millimeters of water. Abscissae, time in seconds. At mark 2, a moderate amount of exclusion of air began.
August 8, 1928. Experiment 1.—Intravenous injection of 1 cc. horse serum. Normal guinea pig. Weight 390 gm. 10:20 a.m. 4 cc. 5 per cent sodium-barbital intraperitoneally. 11:15. Cannulation of external jugular vein and pulmonary artery finished. Animal curarized, heparinized and under artificial respiration with connection to Krogh spirometer. Pressure record begun as shown in Fig. 1. Immediately following the injection of horse serum there is a slight rise in pressure, a volume effect and then an enormous increase which is well sustained. At the mark 2 overflow of air began, indicating difficulty of air entrance into the lungs. This did not increase to a serious degree and is possibly a vascular rather than a bronchiolar phenomenon. The exact vascular site of the Brodie reaction is undetermined. If it is to any degree upon the venous side of the capillary bed the degree of pulmonary congestion produced would readily exclude air as shown by Drinker, Peabody and Blumgart (10) in experiments bearing upon this point.

The contrast between this experiment and those which follow indicates the entire lack of identity between the simple protein and anaphylactic reactions in the guinea pig.

August 9, 1928. Experiment 2.—Intravenous injection of sheep serum in a sensitized animal. Guinea pig, weight 415 gm. Received 2.0 cc. sheep serum intraperitoneally, July 17, 1928. 3:15 p.m. 4 cc. 5 per cent sodium-barbital intraperitoneally. 4:25 p.m. Cannulation of external jugular vein and pulmonary artery finished. Animal curarized, heparinized and under artificial respiration with connection to Krogh spirometer. Pressure record begun as shown in Fig. 2. At the mark 1, 0.1 cc. sheep serum was given intravenously. At 2 air began to escape through the overflow tube indicating the onset of bronchial obstruction. The fall in pulmonary blood pressure was interrupted momentarily, and then progressed into a long decline accompanied by increasing exclusion of air from the lungs so that by the 400th second the lungs showed practically no movement. At mark 3, the possibility of air overflow was prevented and the artificial respiration adjusted so that a moderate amount of air was entering the lungs, and at mark 4, 1.0 cc. of horse serum was given intravenously. There is the large increase in pressure characteristically due to horse serum, but owing to the poor condition of the animal, not well sustained.

There is a marked contrast between this experiment and the one preceding. A fall in pulmonary arterial pressure characterizes anaphylactic shock in the guinea pig.

August 10, 1928. Experiment 3.—Intravenous injection of sheep serum in sensitized animal. Guinea pig, weight 440 gm. Received 2.0 cc. sheep serum intraperitoneally July 17, 1928. 1:10 p.m. 4.0 cc. 5 per cent sodium-barbital
Fig. 2. Pulmonary arterial pressure in a sensitized guinea pig, which received 0.1 cc. sheep serum intravenously at the mark 1. Ordinates, pressure in millimeters of water. Abscissa, time in seconds. At mark 2 exclusion of air began. At mark 3 air exclusion prevented by forcing overflow tube deeper in mercury. At mark 4, 1.0 cc. horse serum intravenously.
intraperitoneally. 2:04 p.m. Cannulation of external jugular vein and pulmonary artery finished. Animal curarized, heparinized and under artificial respiration with connection to Krogh spirometer. Pressure record begun as shown in Fig. 3. At mark 1, 0.2 cc. of sheep serum was given intravenously. The animal was in very good condition with the pulmonary pressure rising when the injection was given. At mark 2, air escape into the Krogh spirometer indicated bronchial obstruction, which was rapid and complete. The final rise in pressure is asphyxial and in experiments where systemic pressure was also recorded invariably accompanied the rise in systemic blood pressure, noted by other observers in "shocked" guinea pigs.

![Fig. 3. Pulmonary arterial pressure in a sensitized guinea pig, which received 0.2 cc. sheep serum intravenously at mark 1. Ordinates, pressure in millimeters of water. Abscissae, time in seconds. At mark 2 exclusion of air began.](image-url)
August 8, 1928. Experiment 4.—Intravenous injection of sheep serum in a sensitized animal. Guinea pig, weight 310 gm. Received 2.0 cc. sheep serum intraperitoneally July 17, 1928. 3:25 p.m. 6.0 cc. 5 per cent sodium-barbital intraperitoneally. 4:28 p.m. Cannulation of external jugular vein and pulmonary artery finished. Animal curarized, heparinized and under artificial respiration with connection to Krogh spirometer. Pressure record begun as shown in Fig. 4. At mark 1, 0.2 cc. of sheep serum was given intravenously and at mark 2 bronchial obstruction was recorded. This condition became complete almost immediately as noted by the subsidence of lung movement. Asphyxial rise in pulmonary pressure began promptly and could be but slightly checked by adjusting the respiration pump so as to attempt to force air into the lungs. The final drop in the curve occurred just before death.
August 8, 1928. Experiment 5.—Intravenous injection of sheep serum in a sensitized animal. Guinea pig, weight 450 gm. Received 2.0 cc. sheep serum intraperitoneally July 17, 1928. 3:18 p.m. Anesthesia and preparation identical with former experiments. Shocking injection of 0.2 cc. sheep serum given intravenously at mark 1, Fig. 5, and at mark 2 bronchial obstruction was recorded. There was the usual fall in pulmonary blood pressure followed by a slight asphyxial rise before the death of the animal.

![Fig. 5](image.png)

Fig. 5. Pulmonary arterial pressure in a sensitized guinea pig, which received 0.2 cc. sheep serum intravenously at mark 1. Ordinates, pressure in millimeters of water. Abscissae, time in seconds. At mark 2 exclusion of air began. The secondary rise in pressure is asphyxial and is followed by a decline leading to the death of the animal.

DISCUSSION.

The experiments cited show that as a very early phase of the anaphylactic disturbance there is a fall in pressure in the pulmonary circuit. Given a normal heart, and all observations of anaphylaxis in the guinea pig as well as in other animals¹ indicate minimal effects upon the actual pumping power of the heart; the great factor affecting

¹ Drinker and Bronfenbrenner (1) showed that the serious effects of anaphylactic shock on the heart of the rabbit were secondary to pulmonary obstruction and not a primary ventricular phenomenon of distinct importance as postulated by Auer (11).
pressure in the pulmonary circulation is the flow of blood into the right ventricle. The fall in pulmonary pressure observed in our experiments would thus appeal to the physiologist as due to some reaction in the animal which interfered with cardiac filling. This is exactly what happens in the dog, where owing to interference with blood flow through the liver, blood pools in the abdominal vessels, the pulmonary pressure falls and as the left ventricle begins to receive less blood the systemic pressure drops sharply.

But neither in our experiments nor in those of others has there been any fall in systemic blood pressure, and while the criterion is not absolutely delicate, it is sufficiently so to cause us to feel that the fall in pulmonary pressure is more probably due to a gradual widening of the pulmonary vascular bed with an increase in the pulmonary blood volume not great enough to fail of compensation by vasoconstriction on the systemic side of the circulation, and so unaccompanied by fall in systemic blood pressure.

Examination of Figs. 2 to 5 shows that with the exception of Experiment 2 and in this it would seem as if the characteristic fall in pulmonary pressure is but broken temporarily by a slight rise, the pulmonary vascular reaction precedes evidence of bronchiolar obstruction. Possi-

**SUMMARY.**

1. Sheep serum in doses below 0.3 cc. intravenously produces no pulmonary vasoconstriction in the guinea pig. Guinea pigs have consequently been sensitized with this substance and anaphylactic shock produced by doses of 0.1 and 0.2 cc.

2. Pressure in the pulmonary artery has been measured by the method of Drinker and Went (2) and recorded photographically in a new and convenient manner.

3. At a very early stage in anaphylactic shock the pulmonary arterial pressure falls markedly and this fall seems to precede the appearance of bronchiolar obstruction.

4. The fall in pulmonary blood pressure in anaphylactic shock is in marked contrast to the rise in pressure resulting from intravenous injection of toxic foreign protein, such as horse serum.
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BIBLIOGRAPHY.