A STUDY OF THE LOW BLOOD PRESSURES ASSOCIATED WITH ANAPHYLACTIC AND PEPTONE SHOCK AND EXPERIMENTAL FAT EMBOLISM, WITH SPECIAL REFERENCE TO SURGICAL SHOCK.

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PLATES 17 TO 21.

(Received for publication, November 28, 1917.)

In a preliminary report attention was called to certain fundamental differences between the low blood pressures associated with peptone shock and experimental fat embolism. Consideration of these differences is important because they have a direct bearing upon certain theories as to the etiology and mechanism of surgical shock. It is proposed in this paper to give in detail the experimental data upon which some of the statements made in that report were based, to add new observations, and to discuss the results obtained. The theories concerned are that surgical shock is due to loss of vascular tone in the splanchnic region, that it is due to loss of peripheral vascular tone, and that it is due to fat embolism.

Mann is of the opinion that "the cause of shock is an actual loss of red cells and fluid from the circulating blood through stasis, diapedesis, exudate, and endothelial changes brought about by the reaction of the great delicate splanchnic area to irritation." Janeway and Jackson concluded from their study of low blood pressures induced by compression of the inferior vena cava, that the dilatation of the peripheral venules and capillaries as a result of the increased venous pressure caused such a loss of tone, that even after normal pressure was restored by release of the compression, they became overfilled with blood. As a

result of this, the arterial pressure fell to a very low level and the animal died in a few hours. Warthin,\textsuperscript{4} Bissell,\textsuperscript{5} and Porter\textsuperscript{6} are convinced that fat embolism is "a cause" of surgical shock.

\textit{Technique.}

All the experiments here reported were made upon dogs under ether anesthesia. Altogether, more than thirty-five animals have been used in the study of the problems involved. The arterial pressure was taken from the carotid artery according to the usual technique. The fat, in the form of neutral olive oil, was injected through a cannula in the femoral vein, being washed into the vessel with 5 or 6 cc. of isotonic salt solution. Witte's peptone (0.5 to 1 gm., according to the size of the dog) was dissolved in 10 cc. of salt solution and injected through the same cannula. Standard doses of nicotine (1 cc. of a 1:4,000 solution) and of adrenalin (1 cc. of a 1:50,000 solution) were also administered intravenously in the same manner.

In making a record of the venous pressure the following method was employed. The external jugular vein was exposed as low down in the neck as possible. Into it a wide cannula with a large bulb completely filled with 10 per cent solution of sodium carbonate was inserted. The long proximal end of the cannula, measuring 4 to 6 cm., was pushed well down into the subclavian vein and even in some instances into the superior vena cava. Before inserting the cannula into the vessel, a rubber tube was attached to the distal end and closed with a screw clamp to prevent the carbonate solution from running into the vein. The cannula was then connected by rubber and glass tubing (including a T-tube) with a manometer of the type described by Hoskins and Gunning.\textsuperscript{7} All connections were made air-tight, because air transmission was used. In the manometer there was a solution of zinc chloride with a specific gravity of 1.36; that is, one-tenth the specific gravity of mercury.\textsuperscript{8} The float in the manom-

\textsuperscript{5} Bissell, W. W., \textit{Surg., Gynec. and Obst.}, 1917, xxv, 8.
\textsuperscript{7} Hoskins, R. G., and Gunning, R. E. L., \textit{Am. J. Physiol.}, 1917, xliii, 298.
\textsuperscript{8} For the preparation and the accurate measurement of the specific gravity of this solution I am indebted to Professor J. H. Long.
eter was attached by a thread to the longer branch of a light heart lever exactly half way between the fulcrum and the writing point. After all the connections had been made, it was necessary to produce a slight negative pressure in the apparatus. This was readily done through the T-tube. The screw clamp at the cannula was then cautiously released. The apparatus was so adjusted that the column of liquid forced out of the cannula in high venous pressures did not rise above the level of the vein. In other words, the column of liquid was kept parallel with the axis of the vessel. The respiratory and other changes in the venous pressure were recorded as shown in Figs. 1, 2, and 3. The change in position of the writing point of the heart lever represented ten times the change in pressure expressed in millimeters of mercury, because the fluid in the manometer had a specific gravity one-tenth that of mercury.

EXPERIMENTAL.

The three following protocols of experiments are typical. All operative procedures were carried out under ether anesthesia, and the animal was killed at the end of the experiment without recovery from the anesthetic. A cannula was placed in the trachea and connected with an ether bottle. The remainder of the technique has been sufficiently described above.

Dog 1.—Male; weight 18 pounds. October 15, 1917.
10.07 a.m. Blood pressure 130 mm. of mercury.
10.07 to 10.09 a.m. 12 cc. of olive oil injected in doses of 2 cc. each.
10.10 a.m. Blood pressure 110 mm.
10.13 a.m. Blood pressure 130 mm.
10.13 to 10.15 a.m. 8 cc. of olive oil injected in doses of 2 cc. each.
10.14 a.m. Blood pressure 125 mm.
10.16 a.m. Blood pressure 105 mm.
10.20 a.m. Blood pressure 95 mm. 4 cc. of olive oil injected.
10.21 a.m. Blood pressure 80 mm.
10.25 a.m. Blood pressure 70 mm. 2 cc. of olive oil injected.
10.26 a.m. Blood pressure 65 mm. 2 cc. of olive oil injected.
10.27 a.m. Blood pressure 50 mm. Respiration ceased. Artificial respiration started. Heart stopped beating at 10.29 a.m.

Autopsy.—Dilatation of the right side of the heart; left side contains small amount of blood. General venous stasis. Very slight edema of the lungs.
Dog 2.—Male; weight 14 pounds. June 29, 1917.
1.20 p.m. Blood pressure 180 mm. of mercury. 1 gm. of Witte's peptone injected intravenously. Blood pressure fell within 30 seconds to 55 mm.
1.40 p.m. Blood pressure 130 mm.
1.50 p.m. Blood pressure 170 mm.
1.50 to 1.52 p.m. Three injections of olive oil, 2 cc. each.
1.53 p.m. Blood pressure 170 mm. 2 cc. of olive oil injected. Respiration became slow and shallow and blood pressure began to decline very slowly.
1.57 p.m. Blood pressure 120 mm. Respiration continued to become slower and slower. Blood pressure fluctuated but had a general downward tendency. Reaction to adrenalin and nicotine normal.
2.25 p.m. Blood pressure 70 mm. Respiration slow and labored.
2.40 p.m. Blood pressure 85 mm.
2.55 p.m. Respiration stopped entirely. Blood pressure 50 mm. Artificial respiration begun and ether removed. Blood pressure steadily rose during the artificial respiration until 3.05 p.m.
3.05 p.m. Blood pressure 95 mm. Respiration became spontaneous and artificial respiration was stopped. Immediately upon stoppage of artificial respiration the pressure rose rapidly.
3.10 p.m. Blood pressure 140 mm. Ether given again because of return of corneal reflex. Respiration again became slow and labored. During the next 50 minutes the blood pressure fluctuated between 140 and 70 mm.
4.05 p.m. Blood pressure 90 mm. 5 cc. of olive oil injected. Blood pressure fell to 80 mm.
4.06 p.m. Blood pressure 90 mm. 5 cc. of olive oil injected. Blood pressure fell to 75 mm.
4.07 p.m. Blood pressure 80 mm. 3 cc. of olive oil injected. Blood pressure fell to 70 mm.
4.08 p.m. Blood pressure 70 mm.
4.09 p.m. Blood pressure 60 mm.
4.10 p.m. Blood pressure 55 mm. Respirations very slow and shallow.
4.11 p.m. Blood pressure 40 mm. Respiration stopped.
4.13 p.m. Heart stopped.

Dog 3.—Male; weight 42 pounds. October 18, 1917.
11.33 a.m. Blood pressure 130 mm.
11.36 a.m. Blood pressure 125 mm. 1 gm. of Witte's peptone injected.
11.37 a.m. Blood pressure 55 mm. Venous pressure fell during this time approximately 14 mm.
11.47 a.m. Blood pressure 120 mm. Venous pressure at its former level.
11.47 a.m. to 12.06 p.m. 40 cc. of olive oil injected in doses of 5 cc. each.
12.08 p.m. Blood pressure 110 mm. The reactions of the venous and arterial pressures to the injections of oil are shown graphically in Fig. 3.
12.10 to 12.11 p.m. 10 cc. of olive oil injected in doses of 5 cc. each.
12.12 p.m.  Blood pressure 105 to 110 mm.
12.13 p.m.  5 cc. of olive oil injected.
12.14 p.m.  Blood pressure 95 to 100 mm. The pressure steadily declined and heart stopped beating at 12.16 p.m. During the fall of arterial pressure the venous pressure constantly rose (Fig. 3).

Autopsy.—Dilatation of the right side of the heart; left side contains very little blood. General venous stasis. Slight edema of the lungs.

The characteristic feature of anaphylactic and peptone shock in the dog is a marked and abrupt fall in arterial blood pressure. Experiments by Edmunds,9 Manwaring,10 Denecke11 Jaffé and Pribram,12 and Weil13 have shown that the liver is an essential element in the production of this type of shock in this animal14 (Figs. 1 and 4). Although Robinson and Auer,15 by means of the electrocardiograph, found disturbances in the conduction of the heart and abnormalities in the ventricular contractions, it is evident that the action upon the heart is of relatively minor importance. The cause of the low blood pressure is a stagnation of the blood in the liver and splanchnic region which prevents the right heart from receiving sufficient blood to keep the left ventricle supplied with an amount adequate to maintain the arterial pressure at its normal level.16

The studies of blood pressures in experimental fat embolism reported in the literature are meager and for the most part give too few details to be satisfactory. Warthin injected 7 cc. of olive oil directly into the heart of a dog, and observed a rapid fall in arterial pressure and an increase in pressure in the auricle and jugular vein, "as shown in the charts." But no "charts" appear in the article. He states further that "repeated injections cause large systolic pulsations in the right auricle, the arterial pressure steadily falls, and that in the auricle and jugular steadily goes up. Finally there is delirium cordis and death." The weights of

9 Edmunds, C. W., Z. Immunitätsforsch., Orig., 1913, xvii, 105; 1914, xxii, 181.
14 Loewit, M., (Arch. exp. Path. u. Pharm., 1913, lxxiii, 1) has pointed out certain alleged differences between anaphylactic and peptone shock.
the animals, the quantities of oil used in the "repeated injections," and the time allowed to elapse between them are not stated.

Bissell gives one chart showing the arterial and venous pressures in a dog weighing 7.4 kilos (16.3 pounds) which received 17 cc. of olive oil in doses of 7, 5, and 5 cc. within 2 minutes. After the first injection (of 7 cc.), there was only a "volume change" in arterial and venous pressure; after the second, there was a very transient fall in arterial pressure and an equally transient rise in venous pressure; after the third injection, the venous pressure went up very abruptly while the arterial pressure gradually fell and the animal quickly died.

Porter mentions experiments upon eight cats. One received 3 cc. of "official emulsion" of olive oil injected slowly into the jugular vein. Very soon there followed a fall in carotid pressure. In two other experiments thick cream was used, and in the remainder, olive oil. "2 to 4 cc. of olive oil in a large cat has never failed to produce a fall in blood pressure to one-half or less the normal level." In one experiment the diastolic pressure fell from 140 to 65 mm. of mercury and later to 40 mm. "In this cat the tracing showed that the fall in blood pressure could not be ascribed to changes in the heart beat. The same is usually true when the injection is not made too rapidly. The clinical picture is essentially that of traumatic shock in human beings."

It appears that in the above instances cited from the literature relatively large amounts of oil in proportion to the body weight of the animal were injected within the space of a few minutes. Graham, on the other hand, made repeated small injections of small amounts of olive oil into the veins of rabbits over a period of days, but no blood pressure tracings were taken.

The presence of fat embolism in some cases of surgical shock has been established by the work of Bissell. But it has also been found by Flournoy, and by Katase, in a variety of other pathological conditions.

In experimental fat embolism, the fall in blood pressure is gradual and progressive. But the beginning of the fall in pressure is not synchronous with the beginning of the injections of the oil. A remarkably large amount of oil can be introduced into the veins of an anesthetized dog without producing more than a very slight and temporary fall in arterial pressure. There appears to be a roughly quantitative relation between the body weight of the dog and the amount of olive oil that must be injected to cause the arterial pressure to start downward permanently. In the experiments of this series it was

19 Katase, A., *Cor.-Bl. schweiz. Ärzte*, 1917, xlvi, 545.
necessary to inject approximately 1 cc. of oil for each pound of body weight in order to bring about a fall of pressure of any duration. The results in twelve animals are shown in tabular form in Table I. In this table are shown the weight of the animal and the number of cubic centimeters of oil that were injected before the arterial pressure was permanently and materially lowered. It was somewhat difficult to establish a standard. But for the purposes of this tabulation, it was considered that the pressure had been permanently and ma-

### TABLE I.
The Quantity of Oil Necessary to Reduce Permanently and Materially the Arterial Pressure in Anesthetized Dogs.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Weight (lbs)</th>
<th>Amount of oil necessary to reduce arterial pressure (cc)</th>
<th>Amount of oil per pound of body weight</th>
<th>Dosage of oil injections</th>
<th>Frequency of injections</th>
<th>Total amount of oil injected (cc)</th>
<th>Initial injection of Witte's peptone</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>19</td>
<td>21</td>
<td>1.1</td>
<td>2-5</td>
<td>1-2</td>
<td>26</td>
<td>No injection.</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>29</td>
<td>0.8</td>
<td>2</td>
<td>2-4</td>
<td>37</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>23</td>
<td>0.9</td>
<td>2</td>
<td>3-4</td>
<td>23</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>35</td>
<td>1.0</td>
<td>5</td>
<td>1-5</td>
<td>55</td>
<td>Injection.</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>28</td>
<td>1.0</td>
<td>2</td>
<td>2</td>
<td>28</td>
<td>No injection.</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>42</td>
<td>1.4</td>
<td>2</td>
<td>1</td>
<td>44</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>25</td>
<td>0.8</td>
<td>2-4</td>
<td>1</td>
<td>38</td>
<td>Injection.</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>20</td>
<td>1.1</td>
<td>2</td>
<td>1</td>
<td>28</td>
<td>No injection.</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>16</td>
<td>1.0</td>
<td>1-2</td>
<td>1</td>
<td>19</td>
<td>Injection.</td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>18</td>
<td>1.0</td>
<td>2</td>
<td>1-2</td>
<td>18</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>70</td>
<td>2.3</td>
<td>2-10</td>
<td>1-9</td>
<td>70</td>
<td>No injection.</td>
</tr>
</tbody>
</table>

Average (omitting Dog 13) . . . 1.0+
animal; that is, a 25 pound dog would require about 25 cc. of oil, and a 150 pound man about 150 cc., to induce a lasting fall in pressure, if the same quantitative relations hold for man as for the dog.

It apparently makes only slight difference whether this critical quantity is injected in amounts of 1 or 2 cc. of oil at intervals of 1 or 2 minutes, or in quantities of 5 to 10 cc. at a time. When the larger amounts are injected, with short intervals between the injections, the mechanism of adaptation is put to a greater strain, the critical point may be slightly lowered, the immediate fall is more marked, and the recovery more slow (Fig. 5). But even when relatively enormous quantities of oil are injected at one time and fairly rapidly (for example, in one experiment, 75 cc. of oil were injected very rapidly into a 29 pound dog from a burette connected with the cannula in the femoral vein) the fall in pressure is much more gradual than in the case of peptone or anaphylactic shock (Fig. 6).

Several factors of safety, which in peptone shock appear to be entirely useless, are thoroughly effective in fat embolism in the dog. In the first place, many years ago, Lichtheim\(^{20}\) showed that three-fourths of the pulmonary circulation may be occluded without affecting the systemic pressure. Tigerstedt\(^{21}\) and Gerhardt\(^{22}\) have both confirmed this observation, although Gerhardt, who worked with spontaneously breathing rabbits, questioned Lichtheim's explanation of the phenomenon. More recently, Kuno\(^{23}\) has shown that the lungs may contain from 8.8 to 19.44 per cent of the amount of blood in the body, depending upon the condition of the circulation.

It is evident, therefore, that much of the vascular space of the lungs can be closed without causing a fall in arterial pressure, a conclusion amply justified by the results here reported. This is due in part to the presence of an excessively large vascular area in the lungs in which there is probably ordinarily much dead space where the circulation is not active. But the occlusion may involve more than this

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excess of vascular area, and the systemic pressure may still be maintained at the normal level by increased work on the part of the right ventricle. Gerhardt observed a rise in pressure in the pulmonary artery under these conditions. Furthermore, the capillaries of the lungs are capable of very great distention, and by dilatation the still unoccluded capillaries can permit the passage of an undiminished or only slightly diminished supply of blood to the left side of the heart.

A more detailed analysis of the curve of arterial pressure obtained during the successive injections of small amounts of olive oil into the veins of a dog shows it to be more complex than the simple curve of peptone shock. In Fig. 2 is shown the effect of injecting a 15 pound dog with 1 or 2 cc. doses of olive oil at intervals of 1 to 2 minutes, until a total of 19 cc. had been injected. It is seen that the first one or two injections produced hardly any perceptible effect. With each succeeding injection the immediate fall in pressure became greater and greater and the return to normal slower and slower. Finally, a point was reached at which, after each injection, the pressure did not again reach its former level. In the case of this particular animal, an injection of peptone had been given, from the effects of which it had not completely recovered when the injections of oil were begun. This accounts for the fact that the arterial pressure continued to rise slowly for some minutes in spite of the injections of oil (see also Fig. 3).

After the critical point had been reached, each succeeding dose of oil brought the pressure lower and lower. If the injections were stopped soon enough, however, the animal could usually be kept alive for some time and the various phases of the condition studied. In all the animals, when the arterial pressure showed a permanent and material depression, however slight at first, the condition gradually became worse, and the animal died in from 1 to 3 hours. If the injections were continued, the animal succumbed very quickly. The anesthetic doubtless played a part in the progressively fatal course.

The interpretation of these results is, perhaps, obvious. It would seem to be a legitimate conclusion that the oil first injected merely filled some of the excess vascular space in the lungs. When this excess was used up, the unoccluded capillaries dilated sufficiently to permit the passage of an undiminished or only slightly diminished
LOW BLOOD PRESSURES

volume of blood. When the capillary area was still further reduced, the right ventricle was still able, by increasing its work, to deliver the necessary amount of blood to the left side of the heart. It is not to be supposed, however, that each of these factors of safety came into action separately and in the order named. They probably all became active early, but in varying degrees. The increasing extent of fall and slower recovery after each succeeding injection was due to the increasing difficulty of readjustment of these various factors to the augmented load placed upon them. A point was ultimately reached at which the fall in pressure induced by each injection was roughly proportional to the amount of reduction in the remaining vascular space in the lungs by that injection. That this was probably true was indicated by the great difference in the amount of fall in pressure induced by the same volume of oil injected before and after the critical quantity had been reached (Figs. 2 and 3). The progressively downward course was probably the result of a break in compensation on the part of the various adaptive factors of safety.

Differences in the Effect of Peptone Shock and Experimental Fat Embolism upon Venous Pressure.

The differences in the effects of peptone shock and experimental fat embolism upon venous pressure are equally striking. In the former, there is usually a slight preliminary rise due to the volume of fluid suddenly injected into the veins with the peptone. This is followed by a precipitate fall. The arterial and venous pressures thus run practically parallel (Fig. 1). While the arterial pressure is gradually rising as the animal recovers, the venous pressure also rises. The onset of dyspnea during peptone shock causes a further fall in venous pressure and a rise in arterial pressure as already described.

In experimental fat embolism, the venous and arterial pressures change in opposite directions. During the successive injections of small amounts of oil there occurs usually a slight temporary rise in venous pressure simultaneously with the slight evanescent fall in arterial pressure. But both quickly return to normal. It is not until the critical quantity of oil has been injected that there is a lasting rise in venous pressure. A relatively small amount of oil in-
jected at this time will cause a rapid rise in venous pressure synchronous with the marked fall in arterial pressure described above (Figs. 2 and 3).

In peptone shock the venous pressure falls because of the sudden stagnation of blood in the liver and organs of the splanchnic area. It does not reach the larger veins which are relatively collapsed. In fat embolism the blood cannot reach the systemic circulation because of the blocking of its passage through the lungs. The blood of the body, therefore, accumulates in the veins. Since all the vessels still retain their normal tone, the venous pressure rises.

It seems obvious that if a sufficient amount of fat has entered the lungs to cause a fall in arterial pressure in any case of surgical shock, there should also be present at the same time an elevation of venous pressure, for in experimental fat embolism in the dog the venous pressure begins to rise only when the arterial pressure begins to fall. There has not been opportunity to make observations upon this point on human cases of shock.

Effects of Dyspnea in Peptone Shock and in Experimental Fat Embolism.

In two papers published in 1916, it was shown that dyspnea will cause a rise in arterial pressure in anaphylactic and peptone shock. Weil, who appears to have seen only the first of these papers in which the idea was not fully developed, has recently stated that "this novel hypothesis is quite unsupported by confirmatory experiments." It seems advisable, therefore, to restate briefly the evidence upon which this claim was made. The phenomenon was first observed in the course of experiments to determine the state of vasomotor irritability in anaphylactic shock in dogs. It was noticed that during the stage of low blood pressure, doses of 1 cc. of a 1:4,000 solution of nicotine sometimes produced a greatly exaggerated reaction. When this occurred the percentile rise varied from 30 per cent to more than 200 per cent, as contrasted with a percentile rise of 10 to 17 per cent before the induction of shock, and with an average percentile rise of less than 10 per cent after its production in those instances in which nicotine did not bring about dyspnea (Table II). It was observed further, that whenever this augmented reaction occurred, the injection of nicotine was invariably followed by more or less dyspnea, and that the rise in pressure was roughly proportional to the severity of the dyspnea.
Dyspnea induced by other means, such as increasing the amount of carbon dioxide in the inspired air, and stimulation of an afferent nerve, has given similar results. But there is no method of causing dyspnea in an anesthetized dog that is entirely free from criticism. Asphyxia is known to cause a rise in blood pressure in the normal anesthetized animal. In the stimulation of an afferent nerve it is not always easy to determine for a given animal the exact strength of current that will produce the maximum of dyspnea with a minimum of pressor or depressor effect.

There is reason to believe that for the purpose of determining the effect of dyspnea upon the low blood pressure associated with peptone shock, that induced by the injections of nicotine may be freer from criticism than that brought about by any other method. It has been shown by Hoskins and Ranson\(^2^6\) that nicotine causes vasoconstriction chiefly by its action upon the sympathetic ganglia, but partly by its action upon the vasomotor center. Adrenalin, on the other hand, produces a rise in blood pressure as a result of its action upon the nerve endings in the vessel wall.\(^2^7\) Hence nicotine, as a rule, cannot produce a rise in blood pressure in those conditions in which adrenalin is completely ineffective. In anaphylactic shock and in peptone poisoning, injections of adrenalin are without appreciable effect until the blood pressure has begun to rise. Even when the reaction does return, the percentile rise is reduced, and only gradually approaches the normal for the given animal as the absolute pressure nears its former level. The reaction to nicotine, when unaccompanied by dyspnea, follows an exactly similar course; that is, the actual and percentile rises in blood pressure following nicotine injections (without dyspnea) gradually increase from zero to their pre-shock values as the absolute pressure rises to its normal, as shown in Table II. This is especially evident when the results of injections of nicotine in spontaneously breathing animals are compared with those obtained in dogs similarly treated but with the thorax open and artificial respiration employed. The fact that the actual and percentile rises caused by injections of adrenalin and nicotine, when


TABLE II.
Effects of Injections of Nicotine* with and without Dyspnea upon Low Blood Pressure Associated with Anaphylactic and Peptone Shock.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Before induction of peptone or anaphylactic shock</th>
<th>After induction of peptone or anaphylactic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial pressure</td>
<td>Maximum resultant pressure</td>
</tr>
<tr>
<td>14</td>
<td>110 mm</td>
<td>125 mm</td>
</tr>
<tr>
<td>15</td>
<td>105 mm</td>
<td>115 mm</td>
</tr>
<tr>
<td>16</td>
<td>125 mm</td>
<td>145 mm</td>
</tr>
<tr>
<td>17</td>
<td>140 mm</td>
<td>150 mm</td>
</tr>
<tr>
<td>18</td>
<td>180 mm</td>
<td>200 mm</td>
</tr>
<tr>
<td>19</td>
<td>100 mm</td>
<td>110 mm</td>
</tr>
<tr>
<td>20</td>
<td>160 mm</td>
<td>175 mm</td>
</tr>
</tbody>
</table>

* Standard dose, 1 cc. of a 1:4,000 solution of nicotine intravenously.
unaccompanied by dyspnea, in anaphylactic and peptone shock run parallel courses, indicates that the direct pressor action of nicotine is inhibited by the same condition that renders adrenalin ineffective. It is for these reasons that in anaphylactic and peptone shock we consider the exaggerated rise in blood pressure induced by nicotine as a more purely mechanical effect than a similar rise accompanying dyspnea brought about by any other method.

We may summarize the evidence that the augmented reaction to nicotine frequently observed in the condition of low blood pressure associated with peptone poisoning is due wholly to the mechanical effect of the dyspnea, as follows: (1) It occurs only in the stage of low blood pressure, and only when the dose of nicotine causes dyspnea. It does not appear when the blood pressure is normal even if dyspnea is produced. (2) It has not been observed in any animal in which the chest has been opened and artificial respiration employed. (3) It is not due to any cumulative effect because of the slowed circulation, for a double dose of the drug will not cause such an augmented reaction before the condition of shock is induced. During the condition of shock a 2 cc. dose is more likely to produce dyspnea and is therefore more frequently followed by a magnified rise in pressure.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Initial pressure</th>
<th>Max. resultant pressure</th>
<th>Absol. rise in pressure</th>
<th>Per. cent rise in pressure</th>
<th>Initial pressure</th>
<th>Max. resultant pressure</th>
<th>Absol. rise in pressure</th>
<th>Per. cent rise in pressure</th>
<th>Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>100</td>
<td>110</td>
<td>10</td>
<td>10</td>
<td>55</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>Chest open. Artificial respiration.</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>47</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>70</td>
<td>5</td>
<td>8</td>
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</tr>
<tr>
<td></td>
<td>52</td>
<td>56</td>
<td>4</td>
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than is a 1 cc. dose. A double dose without dyspnea does not yield the normal, i.e. pre-shock, percentile rise. (4) This augmented reaction occurs at a stage in the condition of shock when adrenalin is without effect, and when, from our knowledge of the pharmacologic action of nicotine, no response to injections of that drug is to be expected. (5) With a large reservoir of stagnating blood in the liver, conditions are favorable for the most effective results from increased respiratory suction and from the force-pump action of the vigorously contracting diaphragm. The distance from the right auricle to the point of entry of the hepatic vein into the inferior vena cava is short. The latter vessel is prevented from collapsing by its attachment to the central tendon of the diaphragm through which it passes. By this pump-like action increased amounts of blood are brought to the underfilled right ventricle and delivered at once through the unimpeded pulmonary circulation to the left ventricle and thence to the systemic circulation, with the resultant rise in pressure. When the blood pressure is normal, dyspnea does not cause this marked rise because there is no large convenient reservoir of blood for respiratory suction to act upon, and because the right side of the heart is already filling properly with each diastole.

During the first \( \frac{1}{2} \) minute or so after the blood pressure approaches or reaches its minimum in anaphylactic or peptone shock, dyspnea frequently is not effective in causing a rise in pressure. This is especially well seen by contrasting the results of injections of nicotine in Dogs 17 and 19 (Table II). With a pressure of 20 mm. of mercury immediately before the injection of the second dose of nicotine (11 minutes after injecting 5 cc. of normal horse serum) in Dog 17, a violent dyspnea produced a rise of 250 per cent. With the same initial pressure in Dog 19, between \( \frac{1}{2} \) and 1 minute after giving 5 cc. of horse serum, a rise of only 25 per cent was produced in spite of the marked dyspnea which the injection of nicotine caused.

The type of the rise in blood pressure which accompanies dyspnea in peptone shock varies with the severity of the dyspnea. If this is violent, as in Dog 14 (Fig. 4), the rise is rapid; if only moderate, as in Dog 17, the rise is somewhat less steep.\(^{28}\) The degree of dyspnea does

\(^{28}\) The tracing from this dog was published in connection with the paper on "Anaphylactic shock in dogs," *J. Infect. Dis.*, 1916, xix, 746.
not affect the percentile rise so much as it affects the rate at which the rise occurs. In either case, there is, in the early stages, a tendency for the pressure to fall again, but usually less rapidly than it rose. As a rule, the pressure does not again return to its former low level, unless the dose of peptone was very large. It then not infrequently falls to a still lower plane. For example, Dog 17, with a blood pressure of only 20 mm. of mercury at the time of the induction of the second period of dyspnea, by nicotine, was apparently in extremis. The dyspnea was violent and induced a rise in pressure of 250 per cent, and the animal recovered in a relatively short time. Similar results, although usually less spectacular, have been obtained in many animals.

Dyspnea is, therefore, an important therapeutic agent in low blood pressures of the type present in anaphylactic and peptone shock. By bringing the pressure above the danger zone at frequent intervals by the repeated induction of short periods of dyspnea, the life of the animal can usually be saved. Whether equally beneficial results will follow its use in surgical shock in human patients will depend upon the mechanism of that condition. If the low blood pressure in surgical shock resembles that in peptone poisoning in that it is accompanied by a reservoir of stagnating blood in the liver, it would seem reasonable to expect salutary results from the frequent induction of periods of dyspnea by some method which can be applied with safety in human cases, such as increasing the carbon dioxide content of the inspired air. If, on the other hand, surgical shock has an entirely different mechanism, as, for example, fat embolism, little permanent benefit can be expected from the use of dyspnea. Incidentally it may be remarked that the study of the effects of dyspnea in surgical shock in man may yield information of value in determining the nature and mechanism of that condition.

Since I had observed that dyspnea causes a rise in blood pressure in anaphylactic and peptone shock, Porter's report that dyspnea causes a rise in the low blood pressure accompanying fat embolism led to the present comparative study of these two conditions. My experiments have confirmed Porter's observation, although the re-
sults are far less striking than in peptone shock. The character of
the curve is different from that obtained in peptone shock. In ex-
perimentional fat embolism, the rise induced by dyspnea is usually less
marked, the ascent is more gradual, and the decline usually slower.
The pressure tends to fall progressively lower between the periods
of dyspnea, so that the tendency to recover is lacking. All the ani-
mals of this series whose blood pressures showed a permanent fall in-
variably succumbed. In several instances dyspnea appeared to hasten
the end by causing acute pulmonary edema. The increased negative
intraalveolar pressure as a result of the deeper and more forcible
inspirations may have been a factor in the production of this edema
as in the case of adrenalin pulmonary edema in rabbits described
by Auer and Gates.30

Artificial respiration with a bellows has been found to cause a
rise in pressure in experimental fat embolism in some dogs. This
rise, when it does occur, is very gradual (Figs. 7 and 8).

In view of the marked differences in the state of the circulation
in these two conditions, to explain the rise in arterial pressure accom-
panying or following dyspnea in fat embolism upon the same basis
as the similar phenomenon in peptone shock, namely as a result of
respiratory suction, as is done by Porter,39 would hardly seem justified.
Conditions are certainly not favorable in fat embolism for the activity
of this force. (1) There is no convenient large reservoir of stagnating
blood upon which respiratory suction can be exerted. Instead, there
is a general venous stasis. The distribution of the blood in the body
can be influenced by gravity. Thus, if the foot of the operating board
is raised, the venous sinuses of the brain will be found at autopsy
greatly distended with blood. If at autopsy the skull is opened before
the thorax is disturbed, enormous quantities of blood flow from the
opened sinuses, indicating the extreme degree of venous stasis. This
does not occur in anaphylactic and peptone shock. (2) The right side
of the heart is already overfilled with blood. To add more blood
would only increase its burden and augment the tendency, already
present, to acute dilatation. (3) A large portion of the vascular
bed of the lungs is occluded. Any additional blood brought to the

heart by respiratory suction or any other force could not be delivered to the left ventricle where it is needed to raise arterial pressure. (4) The venous pressure rises when the arterial pressure falls (Figs. 2 and 3). (5) The vessels still retain their functional integrity as shown by the reaction to adrenalin (Fig. 8).

A more reasonable explanation, but one difficult to verify, is that in experimental fat embolism dyspnea, and perhaps artificial respiration with a bellows, in some way facilitates the passage of blood through the lungs. Cloetta\(^{31}\) has called attention to the effect of inflation of the alveoli upon the caliber of the interalveolar capillaries. When the lung is collapsed, the capillaries are reduced in diameter. With moderate inflation there is radial traction upon these vessels and their lumina are increased in size. With marked inflation, the capillaries are narrowed, both by compression and by linear extension. In dyspnea this cycle is repeated in rapid succession, so that a milking action upon the capillaries is produced which would tend to dislodge mechanically the occluding droplets of oil from these vessels. But the question of the mechanism by which dyspnea and artificial respiration cause a rise in blood pressure in experimental fat embolism must remain for the present without a satisfactory answer.

We may summarize the effects of dyspnea upon the low blood pressures in peptone and anaphylactic shock and in experimental fat embolism as follows: In the former, the rise in pressure is relatively sharp; there is a tendency to decline, but the pressure does not usually reach its former low level unless the dose of peptone was exceptionally large; and the animal generally recovers if the periods of dyspnea are repeated with sufficient frequency to prevent serious damage to the vital centers of the brain by the anemia. In experimental fat embolism, the rise in pressure accompanying dyspnea and the subsequent decline are usually more gradual than in peptone shock; the tendency is for the pressure to sink progressively lower, after each paroxysm of dyspnea; and no permanent benefit has been observed from the employment of dyspnea after the arterial pressure has once been materially and permanently reduced. If permanent

improvement in surgical shock is found to follow repeated periods of dyspnea, this would appear to be indirect evidence that this condition is not due to fat embolism.

Further Differences between the Low Blood Pressure Associated with Peptone Shock and Experimental Fat Embolism.

In peptone and anaphylactic shock the respiration is usually not affected except for the temporary dyspnea that occasionally occurs during the fall in pressure. In experimental fat embolism, on the other hand, two very unlike changes in respiration have been observed in different animals. Sometimes both conditions have developed in the same animal at different stages of the experiment. In a number of dogs a violent dyspnea occurred, lasted for several minutes, and usually resulted fatally. This was almost always accompanied by edema of the lungs. The condition closely simulated the clinical picture of fat embolism sometimes seen after fractures of long bones. In several instances the difficulty of respiration became so extreme that it was necessary to disconnect the tracheal cannula from the ether bottle. With each violent expiration a shower of frothy fluid was blown from the cannula. The degree of edema appeared to bear a direct relation to the severity of the dyspnea.

In other animals a condition of apnea not infrequently developed unexpectedly without any change in the amount of anesthetic being given. This may occur before the critical quantity of oil has been reached in the injections, and therefore before the arterial pressure has begun to fall. The onset of apnea may be sudden, but usually it is somewhat gradual. The respirations become more shallow and less frequent until they stop entirely, as in fatal ether poisoning. If the anesthetic is removed promptly and moderate artificial respiration instituted at once, the animal can usually be revived, and after a varying period of time will begin to breathe spontaneously again. If the artificial respiration is not started without delay, the blood pressure quickly falls and the heart stops beating within a few minutes. A delay of $\frac{1}{2}$ minute has appeared, in some instances, to result in the death of an animal that might have been revived. This apnea has not been observed in peptone shock.
The similarity of this series of events to ether poisoning, and the recovery of the animal upon the removal of the anesthetic and the institution of artificial respiration, has led to the tentative explanation that the toxicity of ether may be enhanced in experimental fat embolism. The recovery of the dog under the conditions noted would seem to exclude the possibility of any organic damage to the respiratory center by the lodgment therein of an embolus of oil. Careful postmortem examination, gross and microscopic, of the region of the floor of the fourth ventricle has not revealed evidence of such a lesion.

Janeway and Jackson reduced arterial pressure by compressing the inferior vena cava. Release of the compression after 2 hours was followed by a prompt rise in arterial pressure, which slowly fell again, and the animal died in about 12 hours. They consider that the dilatation of the peripheral venules and capillaries as a result of the increased venous pressure caused such a loss of tone that even after normal pressure was restored they became overfilled with blood. Too little blood was thus permitted to reach the heart to keep the arterial pressure above the danger zone of 40 to 50 mm. of mercury, and the animal died.

The animals used in this series of experiments were observed for varying periods of time after the injection of oil. In most instances the experiments did not last longer than 5 hours. Hence from the observations of Janeway and Jackson, it might be objected that an amount of fat in the lungs less than the critical quantity may cause a fall in pressure more than 5 hours after the injection. That there is a rise in venous pressure in experimental fat embolism is known from the work of Warthin, and of Bissell, and from the results here reported. But as far as these experiments go, it would seem that a rise in venous pressure of a lasting character or of a degree greater than the fluctuations observed in dogs without any further treatment than the administration of an anesthetic, does not begin until the critical quantity of oil has been injected and the arterial pressure has begun to fall. Even then the venous pressure (external jugular-superior vena cava) may be lowered by dyspnea. The conditions present in experimental fat embolism do not, therefore, appear to be analogous to those in the experiments of Janeway and Jackson until a relatively large amount of oil has been administered. After
this point has been reached, that is after the venous pressure has begun to rise, progress to a fatal termination is usually rapid. Hence there is no reason to consider this possible objection valid.

SUMMARY.

1. In peptone shock there is a marked, precipitate fall in arterial pressure. At the same time there is a fall in venous pressure.

2. In experimental fat embolism, (a) the fall in blood pressure is always gradual; (b) approximately 1 cc. of oil for each pound of body weight must be injected before a lasting fall in arterial pressure is produced; (c) it makes only a slight difference whether this amount is injected in small doses at a time or in relatively large quantities; and (d) when the arterial pressure falls, but not till then, the venous pressure rises.

3. In peptone shock, dyspnea, by its suction and force-pump action upon the reservoir of stagnating blood in the liver, brings more blood to the heart and causes a rise in arterial pressure. By repeatedly inducing short periods of dyspnea at frequent intervals, permanently beneficial results are obtained and the life of the animal can be saved.

4. In experimental fat embolism, dyspnea will cause a rise in blood pressure. But permanently beneficial results have not been obtained by this method. If dyspnea is found to bring permanent improvement in surgical shock, it is indirect evidence that this condition is not due to fat embolism. Respiratory suction is probably not responsible for the rise in blood pressure in experimental fat embolism. It seems more likely that the dyspnea in some way facilitates the passage of blood through the embarrassed pulmonary circulation. Artificial respiration with a bellows will also frequently cause a rise in blood pressure in experimental fat embolism.

5. In peptone shock the respiration is usually not affected, although there is some evidence that the respiratory center may be in a state of increased irritability. In experimental fat embolism, in some animals a violent dyspnea develops spontaneously. This is usually accompanied by edema of the lungs. In other instances, an apnea occurs, even before the blood pressure has begun to decline.
EXPLANATION OF PLATES.

PLATE 17.

Fig. 1. The fall in arterial and venous pressures associated with peptone shock. Dog 3; weight 42 pounds. The writing point of the venous pressure manometer was recording 1 inch in advance of that of the arterial manometer.

Fig. 2. The effect on arterial and venous pressures of injecting small doses of oil at frequent intervals. This animal had been previously subjected to peptone shock, which accounts for the gradual rise in arterial pressure in the first section of the tracing (a), in spite of the injections of oil. Between the first and second (b) sections of the tracing, 4 minutes elapsed and 6 cc. of oil were injected. After the arterial pressure had begun to fall, the respiration became slow and four inspirations with the bellows were used as shown in the second section of the tracing. Dog 11; weight 15 pounds.

PLATE 18.

Fig. 3. The effect on arterial and venous pressures of the injection of small doses of oil at frequent intervals. The same animal as in Fig. 1. Between the first (a) and second (b) sections of the tracing 20 minutes elapsed. During this time a clot formed in the venous cannula. In removing this clot some fluid was lost from the system of transmission. This probably accounts for the lower level of the venous pressure tracing in this section of the figure. In the second section the arrows indicate corresponding positions of the writing points of the two manometers.

PLATE 19.

Fig. 4. Dog 14. The effect of nicotine on arterial pressure in peptone shock with and without the production of dyspnea. a and b, injections of adrenalin and nicotine, respectively, before the induction of shock; c, peptone injected; d, adrenalin; e, nicotine without dyspnea; f, nicotine with marked dyspnea. Dosage 1 cc. of 1:50,000 adrenalin, and 1 cc. of 1:4,000 nicotine.

Fig. 5. The effect of rapidly injecting large single doses of oil at frequent intervals, the total amount being less than the critical quantity. Moderately rapid fall in pressure with gradual rise to previous level. Dog 23; weight 30 pounds. The time covered by the tracing, including the period during which the drum was stationary, was 18 minutes.

PLATE 20.

Fig. 6. Gradual fall in arterial pressure after rapid injections of large amounts of olive oil (75 cc.). The effect on respiration is also shown. Female dog; weight 29 pounds. Time covered by entire tracing, 7 minutes.
FIG. 7. The effect of artificial respiration with a bellows upon low blood pressure (arterial) in experimental fat embolism. The animal was breathing spontaneously when the artificial respiration was instituted. Time covered by tracing, 4 minutes.

PLATE 21.

FIG. 8. The effect of artificial respiration with a bellows upon low arterial pressure in experimental fat embolism. The respiration became very slow and finally stopped. Rapid fall in pressure, followed by gradual rise during artificial respiration. Between the first (a) and second (b) sections of the tracing 3½ minutes elapsed. During this time the pressure continued to rise gradually. Respiration became spontaneous while the drum was stopped. The rise in pressure indicated by the perpendicular line occurred very quickly upon the suspension of artificial respiration before the drum could be started. This tracing also shows the reaction to adrenalin in the low blood pressure due to experimental fat embolism in contrast to the absence of this reaction in peptone shock.