A STUDY OF LOW BLOOD PRESSURES NOT ASSOCIATED WITH TRAUMA OR HEMORRHAGE *

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In the course of studies on anaphylactic shock in the dog it was found that during the period of low blood pressure the pressor effect of nicotin may be greatly augmented at a time when epinephrin produces little or no result.¹ Exactly similar reactions were found in peptone shock. Low blood pressures from hemorrhage are sharply distinguished from the above by the fact that in them, while the effect of nicotin may be exaggerated, that of epinephrin remains unchanged, as shown by Hoskins, Rowley and Rosser.² It seems not improbable, therefore, that the mechanism of these phenomena may be different.

It was suggested in connection with the study of anaphylactic shock that the augmented action of nicotin in that condition was due largely if not entirely to its effect on respiration. Further observations on this point are here reported, partly because they may have some bearing on the question of the effect of respiration on blood pressure, and partly because they may find practical application in the treatment of certain forms of shock.

The technic employed was that used in the previous study, namely, that described by Hoskins and Wheelon.³ The animals were anesthetized with ether. A canula in the carotid or femoral artery was connected with a mercury manometer. A second canula in the femoral vein was connected with a buret containing physiologic salt solution, with a pinch-cock on the rubber connection immediately above the canula. Standard doses of nicotin (1 c.c. of 1 to 4,000 solution) and of epinephrin (1 c.c. of 1 to 20,000 solution) were administered by inserting the needle of the syringe into the rubber tube immediately above the pinch-cock. After being injected into the tube the drug was quickly and completely washed into the vein with from 6 to 8 c.c. of salt solution. The normal reactions of the animal to standard doses of nicotin and epinephrin were first determined. Known amounts of Witte's peptone in solution, or, in the case of sensitized animals, of normal horse serum, were then injected. After the blood pressure

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1. Simonds, J. P.: *Jour. Infect. Dis.*, 1916, xix, 746.

2. Hoskins, Rowley and Rosser: *THE ARCHIVES INT. MED.*, 1916, xvi, 456.

3. Hoskins and Wheelon: *Am. Jour. Physiol.*, 1914, xxxiv, 81.

had reached its lowest level the injections of epinephrin and nicotin were repeated at frequent intervals.

The results are shown graphically in Figures 1 to 4. In Figure 1 sections of the blood pressure tracing of Dog *A14-p* are shown. This animal was given 1 c.c. of normal horse serum subcutaneously on Feb. 3, 1915. On February 24 the normal reactions to epinephrin and nicotin were recorded, and 5 c.c. of normal horse serum were injected intravenously. There was no fall in blood pressure during the following twenty minutes and 2 gm. of Witte's peptone in salt solution were given intravenously. The blood pressure fell promptly, but during the period of fall the animal made several violent respiratory efforts, at which time the decline became less steep and even almost ceased for a few seconds. The first injections of nicotin and epinephrin given two and three minutes, respectively, after the administration of the peptone produced no effect either on respiration or blood pressure. (The tracing for epinephrin is not shown.) An injection of nicotin given six minutes after the peptone caused some dyspnea and a rise in pressure greater than the normal for that animal (Fig. 1, 5). One minute later epinephrin caused only a slight rise in pressure (Fig. 1, 6). Two minutes afterward, that is, nine minutes after the injection of the peptone, nicotin gave a markedly exaggerated reaction, the pressure reached almost normal and did not fall again (Fig. 1, 7). It may be noted in passing that the effect of dyspnea in increasing the amplitude of the swing of the manometer is not so evident in these conditions of low blood pressure as when the pressure is at its normal level and the heart filling and emptying itself properly at each beat. This is shown especially well in Figure 4.

Small openings were made between the ribs into the pleural cavities in Dog *P C O 1* (Fig. 2) and artificial respiration was employed. The normal reactions to epinephrin and nicotin were then recorded. This animal was very sensitive to epinephrin. Two grams of Witte's peptone dissolved in 20 c.c. of salt solution were washed into the femoral vein with 60 c.c. of salt solution. The volume rise was quite marked, but was followed by an immediate fall in blood pressure. During the following thirty minutes none of the frequently repeated injections of nicotin produced anything like the normal response. In most instances the only perceptible result was the slight transient rise that was due to the volume of fluid with which the drug was washed into the vein. The effect of epinephrin, to which this animal was especially sensitive, was evident from the first injection. The last injection of this substance caused a rise in pressure equal to about one-half the normal response for this animal, but it brought the pressure back to approximately its original level, where it remained.

In Dog *P C O 2* (Fig. 3) the normal reactions to nicotin and

Fig. 1.—Dog A 14p: On February 3, 1 c.c. normal horse serum was injected subcutaneously, and on February 24, 5 c.c. were injected. No fall in blood pressure occurred. Twenty minutes later 2 gm. of Witte's peptone dissolved in salt solution were given intravenously. Division 1 shows normal reaction to epinephrin; 2 shows normal reaction to nicotine; in 3 there were given 2 gm. of peptone intravenously at 11:22 a. m.; in 4 nicotine was injected at 11:24 a. m., with no reaction. There was no reaction to epinephrin injected one minute later (not shown on tracing). At 5 nicotine was injected (11:28 a. m.). There was dyspnea and an augmented rise in blood pressure, which remained higher than before. At 6 epinephrin was injected (11:29 a. m.). There was decreased reaction to less than one-half the normal. At 7 nicotine was injected (11:31 a. m.). There was dyspnea and exaggerated rise in pressure, which was subsequently sustained at this level.

Fig. 2.—Dog P C O 1: To determine the effect of opening the chest and the use of artificial respiration on the reaction to nicotine small openings were made between the ribs into both pleural cavities at 9:35 a. m. At 1 is shown the normal reaction to nicotine with the chest open; at 2 is shown the normal reaction to epinephrin with the chest open. This animal was very sensitive to epinephrin. There were given at 3 Witte's peptone, 2 gm., in salt solution, injected at 9:43 a. m. There was marked volume rise with sharp fall in pressure. At 4 nicotine was injected at 9:44 a. m., and at 5 epinephrin was injected at 9:45 a. m. Again at 6 nicotine was injected with 12 c.c. salt solution at 9:50 a. m.; at 7 epinephrin was injected at 9:52 a. m.; at 8 nicotine was injected at 9:59 a. m.; at 9 epinephrin was injected at 10:01 a. m.; at 10 nicotine was injected at 10:13 a. m.; at 11 epinephrin was injected at 10:15 a. m.; at 12 nicotine was injected at 10:17 a. m.; and at 13 epinephrin was injected at 10:20 a. m.

Fig. 3.—Dog P C O 2: This experiment was undertaken to determine the effect of opening the chest on the reaction to nicotine. At 1 is shown the normal reaction to nicotine before opening chest, and at 2 the normal reaction to epinephrin before opening the chest. Small openings made between the ribs into both pleural cavities at 9:35 a. m. At 3 is shown the reaction to nicotine after opening the chest, and at 4 the reaction to epinephrin after opening the chest. At 5 were given 3 gm. Witte's peptone in salt solution at 9:42 a. m. At 6 nicotine was injected at 9:43 a. m.; at 7 epinephrin was injected at 9:44 a. m.; at 8 epinephrin was injected at 9:58 a. m.; at 9 nicotine was injected at 10:04 a. m., with volume rise only. At 10 epinephrin was injected at 10:10 a. m.; at 11 nicotine was injected at 10:12 a. m.; at 12 nicotine was injected at 10:26 a. m., and at 13 epinephrin was injected at 10:27 a. m. The openings in the chest wall were closed with clamps at 10:30 a. m., and the animal breathed spontaneously. At 15 epinephrin was injected at 10:33 a. m., and at 16 nicotine was injected at 10:34 a. m.

Fig. 4.—Dog P R 1: This experiment shows the effect of violent respiratory effort on blood pressure in peptone shock. The upper tracing shows the respiration, the lower one, blood pressure. (While taking this tracing, at a point on the chart between *a* and *b* the rubber tube connecting the tracheal cannula with the Marey tambour became kinked and only a straight line was registered, although the animal was still in a condition of dyspnea. An attempt was made without much success, to trace this in afterward.) At 1 is shown the normal reaction to nicotine, and at 2 the normal reaction to epinephrin. At 3 there were given 2 gm. Witte's peptone in salt solution, injected intravenously, at 10:29 a. m. At 4 nicotine was injected at 10:30 a. m.; at 5 epinephrin was injected at 10:32 a. m.; at 6 nicotine was injected at 11:04 a. m.; at 7 nicotine was injected at 11:30 a. m.; at 8 nicotine was injected at 11:36 a. m., and at 9 nicotine was injected at 11:56 a. m. Five minutes previously the chest had been opened and artificial respiration started.

epinephrin were obtained before (Fig. 3, 1 and 2) and after (Fig. 3, 3 and 4) opening the chest and using artificial respiration. The results show that the process of opening into the pleural cavities and the use of artificial respiration did not materially affect the normal reactions to these drugs. Three grams of Witte's peptone in 30 c.c. of salt solution were then injected intravenously, which caused a prompt and marked fall in blood pressure. The first doses of epinephrin and nicotin caused no perceptible rise. It was only after sixteen minutes had elapsed that epinephrin began to give a reaction (Fig. 3, 8). After twenty-two minutes nicotin still caused no response (Fig. 3, 9). After forty-four and forty-five minutes, respectively, both nicotin and epinephrin gave subnormal reactions, the latter being proportionally stronger than the former. At no time did a standard dose of nicotin cause its normal response.

Figure 4 shows the respiration curve, taken with a Marey tambour, and the blood pressure curve of a dog which was given 2 gm. of Witte's peptone. The effect of dyspnea on the action of nicotin in low blood pressures of this type is well shown. Figure 4, 8 shows the effect of a standard dose of nicotin, given nearly an hour after the onset of shock, which did not, for some reason, affect the respiration. Just why similar doses of nicotin should act on respiration differently at different times in the same animal cannot now be stated. It may have been due to variations in the depth of anesthesia, although there is no particular reason why, in this instance, the degree of anesthesia should have varied greatly. Figure 4, 6 and 8, shows the marked effect of nicotin when dyspnea is produced.

The results of these observations may be stated briefly thus: In conditions of low blood pressure due to anaphylactic shock and peptone poisoning the exaggerated reaction to nicotin frequently observed is associated with violent respiratory effort. Opening the chest and employment of artificial respiration effectively prevent this result, although they do not materially affect the reaction to nicotin before the condition of shock has been induced. It is believed, therefore, that this augmented effect in these two conditions is due to its action on respiration rather than any action on the vasomotor apparatus itself.

Swale Vincent⁴ has shown that under conditions of normal blood pressure violent dyspnea has a distinctly depressor effect. Henderson and Barringer⁵ believe that "the utmost assistance which respiration can afford to the circulation is to maintain a venous pressure sufficient to distend the right ventricle as rapidly as it relaxes and as fully as the duration of the diastole allows." The "critical venous pressure"

4. Vincent, Swale: *Quart. Jour. Physiol.*, 1915, ix, 45.

5. Henderson and Barringer: *Am. Jour. Physiol.*, 1912-1913, xxxi, 399.

necessary to accomplish this is "not more than 50 mm. of saline."⁶ The negative pressure maintained around the heart by the elasticity of the lungs, according to these observers, is approximately equal to the critical venous pressure. Lewis⁷ found that in man "a deep intercostal inspiration, which is not prolonged, yields a pure fall in blood pressure; a deep diaphragmatic inspiration, which is not prolonged, gives a pure rise in blood pressure. The rise in blood pressure in abdominal breathing is due to the raised intra-abdominal pressure."

It appears to be generally accepted, therefore, that in the normal animal increased respiration produces little if any rise in blood pressure and may even cause a fall. This is true for several reasons: First, the veins are uniformly filled, venous pressure is normal, and as Henderson and Barringer⁸ have pointed out, any suction that might be produced by respiratory effort cannot be transmitted through these collapsible tubes to any distance outside the thorax. Second, with the heart normally filling and emptying itself at each beat, the percentage of blood that could be added by respiratory effort would be small. Third, there is no reservoir of accumulated blood comparatively near the heart on which suction can be exerted.

In anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the venous pressure is low and the heart is not filling normally. There is room, therefore, for a considerable increase in the percentage of blood that could be added to the heart during each diastole if a source of supply were available. Such a supply is at hand in the overfilled venous trunks and in the veins of the liver and splanchnic area. Even in the process of collapsing under the influence of suction such turgid vessels would deliver to the heart a larger volume of blood than normally filled vessels could do. Furthermore, the veins of the liver are not readily collapsible, and Edmunds⁸ has shown that in anaphylactic shock there is a very marked increase in the volume of the liver due to the accumulation of blood in that organ. Suction exerted on the dilated hepatic veins by increased respiratory effort would not cause their collapse, but would draw from them a much greater amount of blood than could thus be extracted from the normal liver. The increased intra-abdominal pressure in dyspnea would help to keep the dilated veins of the liver filled by pressing into them blood from the veins of the splanchnic area.

Low blood pressures due to hemorrhage and to circulatory shock of the type under discussion are, as shown by Henderson,⁹ identical

6. Henderson and Barringer: *Am. Jour. Physiol.*, 1912-1913, xxxi, 352.

7. Lewis: *Jour. Physiol.*, 1908, xxxvii, 233.

8. Edmunds: *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, Original, 1914, xxii, 181.

9. Henderson: *Am. Jour. Physiol.*, 1910, xxvii, 152.

in mechanism, in that in both the venous supply to the right side of the heart is the critical factor. In both the venous pressure is low and too little blood reaches the right side of the heart. But there is this sharp difference, that in the circulatory shock there is a large reservoir of stagnant blood in the veins of the liver and splanchnic region, while after hemorrhage no such reservoir is present. This distinction is important from a therapeutic standpoint and in the interpretation of the results of the injection of nicotin reported above.

In low blood pressure from hemorrhage, as shown by Hoskins, Rowley and Rosser¹⁰ there is an increased irritability of the vasomotor center as manifested by the augmented reaction to nicotin. This phenomenon, in this case, is undoubtedly chiefly if not wholly of central origin. The mechanical effect of increased respiratory effort under such conditions would be slight because of the absence of any reservoir of accumulated blood on which suction could be exerted; and because the veins, being already underfilled, would collapse all the more readily and suction could not be transmitted through them even to the slight extent to which it is transmitted through normal veins.

In the case of low blood pressure from anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the greatly reduced response to injections of nicotin that are observed when, for any reason, dyspnea is not produced, is suggestive of a condition of reduced irritability of the vasomotor center (Fig. 4, 7). When, however, dyspnea is produced, suction is exerted on the overfilled veins of the liver and sufficient blood is drawn into the heart to cause an exaggerated rise in pressure.

In human patients in the treatment of shock associated with low blood pressure not due to hemorrhage, Pearce and Eisenbrey¹¹ recommend the use of epinephrin and intravenous injections of salt solutions. Neither of these procedures was effective in my animals, although it is quite possible that they might be more so in human cases. In my animals the paralysis of the nerve endings in the vessel walls was too great for the epinephrin to cause a rise in pressure. Intravenous injections of comparatively large quantities of salt solution yielded relatively slight increase in pressure. The added fluid apparently went chiefly to increase the dilatation of the splanchnic vessels. For example, a dog in peptone shock with a blood pressure of 32 mm. of mercury received, during a period of two minutes, 225 c.c. of salt solution at 40 C. As a result of this treatment, the highest pressure reached was 48 mm. of mercury, and by the end of three minutes

10. Hoskins, Rowley and Rosser: *THE ARCHIVES INT. MED.*, 1915, xvi, 456.

11. Pearce and Eisenbrey: *THE ARCHIVES INT. MED.*, 1910, vi, 218.

from the beginning of the injection, the pressure had sunk to 40 mm., above which it did not again rise, and the animal ultimately succumbed.

In such cases the injection of nicotin, on the other hand, by causing increased respiratory effort, led to rise in blood pressure and frequently saved the life of the animal, even when death seemed imminent.¹² In the treatment of this type of circulatory shock in man it is possible that any measure which will excite more or less dyspnea (not necessarily nicotin) would raise blood pressure and improve the condition of the patient. Perhaps, when possible, voluntary deep and rapid breathing on the part of the patient at frequent intervals might work good results. It might at least help to prevent a serious loss of tonus from a too long-continued overdilatation of the vessels concerned.

SUMMARY

The condition of low blood pressure due to anaphylactic shock and peptone poisoning is characterized by absence or marked diminution of the reaction to epinephrin, and an exaggerated response to nicotin. It would appear that there is a condition of reduced irritability on the part of the vasomotor center, and that the increased reaction to nicotin is largely mechanical, resulting from the effect of the drug on respiration. The dyspnea so produced causes suction on the overfilled non-collapsible veins of the liver and brings sufficient blood to the under-filled right side of the heart and ultimately to the systemic vessels, in which the pressure is raised. It is suggested that in cases of shock in man, associated with low blood pressure not due to hemorrhage, the artificial production of dyspnea or the voluntary increase of the rate and depth of respiration by the patient may lead to improvement.

12. Simonds, J. P.: Footnote 1, Chart 2.