THE EFFECT OF PEPTONE ON THE PERIPHERAL CIRCULATION.*

BY J. P. SIMONDS, M.D., AND S. W. RANSON, M.D.

(From the Laboratories of Pathology and Anatomy t of Northwestern University Medical School, Chicago.)

PLATE 21.

(Received for publication, May 11, 1923.)

In a previous paper by one of us1 it was stated that experiments were being carried out to determine (1) what influence, if any, the large mass of smooth muscle in the hepatic veins of the dog has on the fall in arterial blood pressure in anaphylactic and peptone shock; and (2) what other factors, if any, may be concerned in this reaction. The present paper pertains to the latter of these problems, and presents a study of the effect of peptone on the peripheral blood vessels.

The literature on this phase of anaphylactic and peptone shock is meager and the results reported are not uniform. Thompson2 described a peripheral dilatation of the blood vessels of the dog, which he believed to be due to depression of the irritability of the vascular neuromuscular apparatus, rendering it irresponsible to vasoconstrictor influences.

Kaufmann3 used the isolated rabbit's ear kept alive by perfusion with Ringer-Locke solution. Wite's peptone in concentration of 1:200 in this solution caused first a dilatation of the vessels, followed by a vasoconstriction which was of relatively long duration. He believed that the vasoconstriction represented the active phase of the effect of peptone because it disappeared if the vessels had previously suffered a severe irritation or if they were repeatedly subjected to the action of peptone. Pissemsky4 studied the action of peptone on rabbit ears and

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* This work was aided by a grant from the Fenger Memorial Fund.
† Contribution No. 106.
2 Thompson, W. H., J. Physiol., 1896, xx, 455; 1899-1900, xxv, 1.
3 Kaufmann, P., Centr. Physiol., 1913-14, xvii, 724.
obtained vasoconstriction with all concentrations and with any kind of peptone. Kondo reports that peptone injected intravenously has a constricting action on the vessels of the legs and ears of rabbits, while it dilates the splanchnic vessels.

More recently Manwaring has perfused the hind quarters of dogs with Locke solution containing 0.5 per cent filtered defibrinated blood from the same animal, under a perfusion pressure of 80 to 110 mm. of mercury. He found that the canine hind quarters, isolated by his method, usually showed a marked reduction in vascular tone, on control perfusion with Locke solution, but in one-third of his animals the vascular tone was fairly well preserved, at least during the initial stages of the perfusion. Manwaring found a uniformly increased perfusion flow from the hind quarters of his dogs varying from 10 per cent increase in the vascular atonic hind quarters, to 150 per cent increase in the vascular tonic hind quarters. At the height of the peptone reaction the rate of flow was identical with the perfusion rate with amyl nitrite. It appears that the reaction reached its maximum by the end of 1 minute, but with less tendency to recovery by the end of 8 minutes than in the isolated intestines similarly perfused.

It would seem, therefore, that most of the information available concerning the effect of peptone on the peripheral circulation has been obtained by perfusion experiments. Such procedures are handicapped by the complication that the tissues being perfused suffer from a coincident deficient oxygenation. Furthermore, in some of the experiments at least the perfusion pressure was maintained at a constant level. In our experiments these difficulties have been overcome, and they appear, therefore, to represent more accurately what actually takes place in the intact limb of a dog with the normal blood supply undisturbed.

Method.

In the present experiments now to be described the carotid blood pressure was taken in the usual manner with a mercury manometer, and the leg volume by means of a plethysmograph, the manometer and plethysmograph writing on the same kymograph. The plethysmograph used was one devised and previously described by one of us. The technique differed from the usual method of plethysmographic study in two important respects: first, the instrument is so constructed that it obviates the necessity of making an air-tight joint

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between the leg and the plethysmograph; and second, the peptone was injected in such a way that its effects on the vessels in the leg were not confused with changes due to vascular reactions in other parts of the body.

The dog is anesthetized with morphine and ether and the amount of anesthetic regulated so that the depth of anesthesia is constant throughout the experiment. The abdomen is opened and the right iliac artery isolated. The branches of this vessel are severed between double ligatures. The middle sacral artery is also ligated. The right iliac artery is doubly ligated and cut just above Poupart's ligament, and the free end brought out through an opening in the right flank. The abdominal incision is then closed. A pair of bulldog forceps is placed on the exposed iliac artery and there is inserted into the severed end and tied a large caliber blunt needle (for a Luer syringe) about the tip of which a small mass of solder has been fixed to prevent the needle from slipping out of the artery. The injections of peptone solution are made by attaching the syringe containing the solution to the needle, loosening the bulldog forceps, and forcing the liquid backward through the iliac artery to the bifurcation of the aorta whence it is washed into the left leg with the blood stream. By this method the peptone exerts its effects upon the vessels of the limb while they are supplied with normal blood in the normal manner, before it acts upon the vessels in any other part of the body. In this manner it is possible to determine the direct action of the peptone on the vessels of the leg uncomplicated, for a few seconds at least, by any general effect or by any special local effect that it may have upon any of the viscera.

The plethysmograph is essentially a flattened truncated cone. An air-tight rubber stocking is made of the same shape and size as the plethysmograph. The open end of the former is drawn over the open end of the latter and securely tied in place, the connection being made air-tight with a little beeswax in the groove around the open end of the instrument. The plethysmograph and stocking are filled with air and the left foot and leg of the animal are made to invaginate the small end of the stocking until the leg, covered by the invaginated stocking, is within the plethysmograph. The instrument is of such size that when the foot rests against the inside of the small end, the large end is at about the middle of the thigh. When supported by clamps and an iron stand with the leg held rigidly outward and backward no constriction is exerted on the femoral artery. When the instrument with the leg inside is in position warm water (40°C.) is introduced through a tube opening into the side while the air escapes through another tube attached to the small end of the instrument. A little air is allowed to remain in the upper end of the plethysmograph, and the tambour and connections contain air. With the instrument applied in this manner it is not only possible to record graphically the volume changes in the leg but the pulsations in the limb as well.
The peptone used in the experiments was the same as that employed in the experiments previously reported dealing with the simultaneous changes in blood pressure in the carotid artery and jugular and portal veins. It was found to give uniformly a typical peptone shock in the dog.

RESULTS.

The results of the experiments are shown graphically in Fig. 1. The time relations between the changes in leg volume and carotid blood pressure are tabulated in Table I. Of the eight animals included in Table I, five suffered fatal peptone shock; two showed a non-fatal form, one of the animals receiving repeated injections of peptone recovering within a few minutes after each injection; and one dog which had been sensitized to normal horse serum was given 5 cc. of this serum, injected into the right iliac artery, in the same manner as the peptone.

From these experiments it is seen that the injection of peptone directly into the arteries of the hind limb of a dog causes an abrupt increase in the size of the leg due to vasodilatation. The increase in leg volume begins in from 5 to 9 seconds after the beginning of the injection of peptone and reaches its maximum in from 8 to 16 seconds after the beginning of the injection. The volume of the limb then becomes less almost as rapidly as it had increased and reaches its previous size in from 17 to 25 seconds after the beginning of the injection. In one animal the leg volume remained permanently slightly above its initial size. It was nearest its original volume 50 seconds after the beginning of the injection. In all the other dogs the leg volume showed a definite diminution, the minimum being reached in from 33 to 70 seconds from the beginning of the injection.

The arterial pressure in these animals showed, in almost all instances, a very slight fall of less than 10 mm. of mercury coincident with the beginning of the increase in leg volume. A permanent fall in arterial pressure occurred slightly later, or from 12 to 23 seconds after the beginning of the injection of the peptone, in all except one dog. This animal received three injections of peptone at short intervals and showed a beginning permanent fall in arterial pressure in 8, 9, and 8 seconds, respectively, after the beginning of the injections of the peptone.
It is thus seen that the permanent fall in arterial pressure in peptone shock in the dog begins after the leg volume has reached its maximum and is diminishing in size. The subsequent reduction in leg volume cannot, therefore, be due exclusively to the fall in arterial blood pressure. It is evident, furthermore, that the permanent fall in arterial pressure is not the result of peripheral dilatation, for this has been shown to be of very short duration, and has started to disappear before the arterial pressure begins to show its characteristic fall.

### TABLE I

**Time Relations between the Changes in Leg Volume and Arterial Blood Pressure.**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Injection time</th>
<th>Beginning increase in leg volume</th>
<th>Maximum leg volume</th>
<th>Return of leg volume to normal level</th>
<th>Minimum leg volume</th>
<th>Beginning permanent fall in arterial pressure</th>
<th>Minimum arterial pressure</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>19 sec.</td>
<td>6 sec.</td>
<td>12 sec.</td>
<td>39 sec.</td>
<td>51 sec.</td>
<td>18 sec.</td>
<td>120 sec.</td>
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<tr>
<td>2</td>
<td>15 sec.</td>
<td>6 sec.</td>
<td>12 sec.</td>
<td>19 sec.</td>
<td>65 sec.</td>
<td>13 sec.</td>
<td>150+ sec.</td>
</tr>
<tr>
<td>3</td>
<td>12 sec.</td>
<td>9 sec.</td>
<td>14 sec.</td>
<td>25 sec.</td>
<td>40 sec.</td>
<td>16 sec.</td>
<td>40 sec.</td>
</tr>
<tr>
<td>4</td>
<td>12 sec.</td>
<td>7 sec.</td>
<td>10 sec.</td>
<td>17 sec.</td>
<td>70 sec.</td>
<td>13 sec.</td>
<td>120 sec.</td>
</tr>
<tr>
<td>5</td>
<td>15 sec.</td>
<td>5 sec.</td>
<td>8 sec.</td>
<td>17 sec.</td>
<td>33 sec.</td>
<td>23 sec.</td>
<td>90 sec.</td>
</tr>
<tr>
<td>6</td>
<td>18 sec.</td>
<td>8 sec.</td>
<td>13 sec.</td>
<td>50 (?)</td>
<td>50 sec.</td>
<td>12 sec.</td>
<td>28 sec.</td>
</tr>
<tr>
<td>7a</td>
<td>13 sec.</td>
<td>6 sec.</td>
<td>16 sec.</td>
<td>28 sec.</td>
<td>63 sec.</td>
<td>8 sec.</td>
<td>30 sec.</td>
</tr>
<tr>
<td>7b</td>
<td>17 sec.</td>
<td>6 sec.</td>
<td>14 sec.</td>
<td>28 sec.</td>
<td>60 sec.</td>
<td>9 sec.</td>
<td>37 sec.</td>
</tr>
<tr>
<td>7c</td>
<td>12 sec.</td>
<td>7 sec.</td>
<td>13 sec.</td>
<td>26 sec.</td>
<td>60 sec.</td>
<td>8 sec.</td>
<td>32 sec.</td>
</tr>
<tr>
<td>8</td>
<td>17 sec.</td>
<td>14 sec.</td>
<td>24 sec.</td>
<td>93 sec.</td>
<td>190 sec.</td>
<td>80 sec.</td>
<td>270 sec.</td>
</tr>
</tbody>
</table>

**Nos. 1 to 5, fatal peptone shock.**

**Nos. 6 and 7, non-fatal peptone shock.** 7a, b, and c represent injections into the same animal at short intervals after the leg volume and arterial pressure had returned to normal following the preceding injection.

**No. 8, non-fatal anaphylactic shock.** Dog immunized with normal horse serum and injected with 5 cc. of the serum after 3 weeks.
The decrease in leg volume below its original level shows that the blood does not accumulate in the peripheral vessels in peptone shock and must, therefore, be impounded elsewhere in the body.

With suitably regulated doses of peptone the results described above can be repeated several times in the same animal (see Dog 7, Table I). The arterial pressure and leg volume are allowed to return to normal before the injection is repeated. In this respect, therefore, peptone shock differs from anaphylactic shock. The fundamental physiologic reaction appears, however, to be the same in both conditions.

The single instance of anaphylactic shock in this series indicates that changes occur in that condition similar to those in peptone shock (Dog 8, Table I). The peripheral dilatation was less marked in this dog than in those showing peptone shock. Furthermore, the fall in arterial pressure was later in manifesting itself than in other dogs in which the serum to which they had been sensitized was injected into the femoral artery instead of into the iliac artery.

The vasodilatation produced by the intraarterial injection of peptone may be due to the presence of a small amount of histamine as an impurity.

It has been shown by Abel and Kubota\(^8\) and by Hanke and Koessler\(^9\) that Witte's peptone contains appreciable amounts of this toxin, in one sample as much as 0.0335 mg. per gm. Since the intraarterial injection of 0.025 mg. of histamine is sufficient to produce a maximum vasodilation in the hind leg of a dog\(^10\) it is obvious that the amount of this substance in peptone is sufficient to account for its dilator action. Moreover, peptone, as shown by Kaufmann\(^8\) and Kondo\(^9\) and confirmed by us in one experiment, has a vasoconstrictor instead of a vasodilator action in the rabbit. Since histamine also causes vasoconstriction instead of vasodilatation in the rabbit\(^11\) the action of peptone on the peripheral vessels seems to be identical with that of histamine. Although it is possible that the transient vasodilator action of peptone may be due to contamination with histamine, Hanke and Koessler\(^9\) have shown that histamine and peptone shock are not identical, since a typical peptone shock is obtained by the injection of histamine-free peptone.

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SUMMARY.

1. Injection of a solution of peptone directly into the artery of the leg of a dog is followed by an abrupt increase in leg volume. This is of short duration and is quickly followed, usually in less than \( \frac{1}{2} \) minute, by a decrease in the volume of the limb below that previous to the injection.

2. The phases of the leg volume curve bear a fairly definite relation to the changes in arterial pressure.

3. These results, therefore, indicate that the long continued low arterial pressure in peptone shock, and probably in anaphylactic shock, may be hastened but is not maintained by peripheral dilatation, and suggest that there is an impounding of the blood in some other part of the body.

EXPLANATION OF PLATE 21.

**Fig. 1.** Arterial blood pressure \((A)\) and leg volume \((L\ V)\) of Dog 7 in Table I. Time marked in seconds.
(Simonds and Ranson: Effect of peptone on peripheral circulation.)