

The physiological effects of peptone and its precursors when introduced into the circulation : interim report ... / E.A. Schäfer [and others].

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The Physiological Effects of Peptone and its Precursors when introduced into the Circulation.—Interim Report of a Committee, consisting of Professor E. A. SCHÄFER, F.R.S. (Chairman), Professor C. S. SHERRINGTON, F.R.S., Professor R. W. BOYCE and Professor W. H. THOMPSON (Secretary). (Drawn up by the Secretary.)

THE present report is to be regarded as a continuation of work the first results of which were communicated by the Secretary of this Committee to the British Association (Section I) at its meeting in Liverpool last year, and afterwards published in the 'Journal of Physiology,' vol. xx., December 1896, p. 455.¹

The chief conclusions then arrived at concerned the effects of Witte's 'peptone,' and were—(1) That this substance in small doses—below 0.02 grm. per kilo—hastens the coagulation of blood in the dog, while in larger doses retardation is brought about, as other investigators have found. (2) That the well-known fall of blood-pressure produced by this substance when injected into the circulation is due to a peripheral influence upon the neuro-muscular apparatus of the blood-vessels. No influence on the vaso-motor centre was detected. (3) That the vasodilating influence of Witte's 'peptone' is not confined to vessels of the splanchnic region, but extends to other vessels also.

This last conclusion was arrived at in an indirect way by observing the effects of Witte's 'peptone' on carotid blood-pressure when injected during excitation of the spinal cord (after complete section), at the level of the third cervical vertebra, the great splanchnics on both sides having been previously divided. Neither time nor circumstances had then permitted the checking of this result by similar injections made during excitation of the sciatics, nor of the observation of plethysmographic variations of limb volume under similar conditions of experiment.

Accordingly, in the work carried out during the past year which has been entrusted to the Secretary, this was the first point to which attention was given. A similar method of observation was then applied in turn to the effects of Witte's 'peptone' on the blood-vessels of the kidney and spleen. This was succeeded by an analysis of the effects (a) on blood-coagulation, (b) on general blood-pressure and peripheral vaso-motor mechanism, (c) on local vascular areas (limb, kidney, spleen) of the following substances—pure peptone, anti-peptone, deuterio-albumose, proto-albumose and hetero-albumose. The investigation as regards the latter two substances is as yet too incomplete for publication, nor indeed can it be looked upon as more than preliminary for any of the substances mentioned.

The contents of the present abstract may therefore be summarised as follows:—

I. *Effects of Witte's peptone*—

- (a) On the blood-vessels of the limb;
- (b) On the blood-vessels of the kidney;
- (c) On the blood-vessels of the spleen.

¹ Thompson, 'Contribution to the Physiological Effects of "Peptone" when injected into the Circulation,' *Journ. of Physiology*, vol. xx. December 1896, p. 455.

II. *Effects of pure peptone—*

- (a) On blood-coagulation ;
- (b) On blood-pressure and peripheral vaso-motor irritability ;
- (c) On the blood-vessels of the limb, kidney, and spleen respectively.

III. *Effects of anti-peptone—*

- (a) On blood-coagulation ;
- (b) On blood-pressure and vaso-motor irritability.

IV. *Effects of deutero-albumose* dealt with in the same way as have been the effects of pure peptone.

I. *Effects of Witte's Peptone.*

(a) *On the blood-vessels of the limb.*—Plethysmographic observations of the volume of the limb were taken by Mosso's method and compared with a simultaneous tracing of carotid blood-pressure. One or both sciatic nerves were divided and excited by a faradic current. In the earlier experiments an injection of Witte's 'peptone' was made during this excitation, the excitation being also repeated subsequent to the injection. Later it was found more suitable to compare the results of an excitation of definite strength, made after the injection, with the results of an excitation of the same strength made before the injection.

Five experiments were performed, on dogs varying from 7.6 to 10.8 kilos in weight, and employing Witte's peptone in doses of 0.1, 0.15, and 0.2 gm. per kilo of body weight.

The conclusions arrived at by this method support those expressed last year, viz., that Witte's peptone produces a decided dilating effect on limb blood-vessels by lowering the irritability of the peripheral neuromuscular apparatus, to centrifugal impulses. The effect, however, does not appear to be so pronounced on these blood-vessels as upon those of the splanchnic area. A dose of Witte's peptone which is sufficient to completely abolish the effect of vaso-constrictive impulses on abdominal blood-vessels is only able to weaken their effect on blood-vessels of the limb.

(b) *On blood-vessels of the kidney.*—A record of kidney volume was taken by means of Roy's oncometer and oncograph. This was accompanied by a tracing of blood-pressure. A solution of Witte's peptone was injected into the saphenous vein. In the earlier experiments one or both splanchnic nerves, or occasionally the spinal cord, was faradically excited during, and after the injection. This procedure was subsequently modified, and the effects of an excitation of certain strength made before the injection, were compared with the results of the same strength of excitation made after the injection.

Seven experiments were performed. The dogs employed varied in weight from 7.8 to 16.4 kilos, and the dose used in most cases was 0.1 gm. per kilo. In a few experiments double this dose was employed.

The conclusions arrived at from these experiments are similar to those deduced concerning the influence of Witte's peptone on limb blood-vessels. This substance produces a vaso-depressing influence on the blood-vessels of the kidney to a considerable degree, especially in the larger doses employed. The degree to which this influence extends is probably even less than that upon the blood-vessels of the limb, certainly less than that upon other vessels in the abdomen.

(c) *On the blood-vessels of the spleen.*—A spleen curve was taken by

means of Schäfer's spleen box, or by a modification of it, made for the writer of this report, which allowed the organ to be surrounded by a layer of warmed oil, and thus prevented a loss of heat, otherwise liable to occur. This method of recording splenic undulations of volume was found to be much more satisfactory than that of Roy, and fully merits all that Professor Schäfer has elsewhere said about it. Side by side with the spleen curve a tracing of carotid blood-pressure was recorded.

Six experiments were performed, the dogs varying in weight from 7 to 11·7 kilos. In most of the experiments a dose of 0·15 gm. per kilo was employed. In one this was increased to 0·2 gm. The left splanchnic nerve in two of the experiments was divided and excited during the injection. In the remainder either the spinal cord or the splanchnic nerves were excited, before and after the injection, with the same strength of stimulus, and the results compared.

The results showed that the effects of Witte's peptone on the blood-vessels of the spleen were somewhat different from the effect of the same substance on renal and limb blood-vessels.

In the first place it was noted that the spleen volume suffers less of a diminution from the fall of blood-pressure which immediately succeeds an injection of Witte's peptone, and that this fall of the lever was soon replaced by a return to its ordinary level.

Agreeing with this, it was found that the early effects of this substance on the peripheral irritability of splenic blood-vessels was very slight, decidedly less than the same effect on splanchnic vessels generally. Later, however, the contrary result was observed; the splenic blood-vessels seemed then to be more influenced by Witte's peptone than other vessels in the abdominal cavity. This was shown in the later stage by a decided rise of carotid blood-pressure on excitation of the spinal cord, unaccompanied by any effect on spleen volume, while the contrary obtained at an earlier part of the same experiment.

II. *Effects of Pure Peptone.*

(a) *On blood coagulation.*—This was observed in four experiments, the peptone used being prepared according to the directions of Grosjean¹ and supplied to me by Dr. G. Grüber. The dogs used weighed from 8·5 to 18·45 kilos, and in each case a dose of 0·2 gm. per kilo was employed.

In all four cases coagulation was delayed from two to several hours. In one case coagulation occurred at the end of the former period; in two others it had supervened next morning, the experiments having been performed in the afternoon. In the fourth case the onset of coagulation was not observed.

These results agree with those of Grosjean, who found that pure peptone delayed but never wholly destroyed the coagulability of blood. Previous to Grosjean, Pollitzer had obtained inconstant results with amphotone—sometimes no effect, sometimes a variable amount of delay, on the whole his experiments leading to the conclusion that amphotone exerts but slight influence on blood-coagulation.

Whether peptone in smaller doses is capable of producing hastening of coagulation has not as yet been investigated.

¹ Grosjean, 'L'action physiologique de la propeptone et de la peptone,' *Travaux du laboratoire de Léon Frédéricq*, tome iv. 1891-92, p. 45.

One other noteworthy effect appeared in the samples of blood drawn in three of the above four experiments—viz., an unusually rapid sinking of the red corpuscles, leaving a perfectly colourless and clear plasma above. Within half-an-hour, plasma to the extent of one-third of the whole blood drawn appeared above the corpuscles, and within one hour this was increased to almost half, after which very little further subsidence was observed. It was in this condition that the blood and plasma coagulated.

In the exceptional case curare had been administered ; the other dogs were not curarised.

(b) *On blood-pressure and vaso-motor irritability.*—Seven experiments, involving a record of blood-pressure, were made with Grosjean's peptone. The dose employed was in all cases 0.2 gm. per kilo, and the weights of the dogs varied from 7.4 to 18.45 kilos.

The general results obtained were the same in all, and showed that pure peptone causes a considerable fall of blood-pressure, and with this a lowering of vaso-muscular irritability to central impulses. The degree and duration of the fall were neither so great nor so lengthened as with corresponding doses of Witte's peptone, nor was the peripheral vaso-motor irritability depressed to the same degree. Thus, after a dose of 0.2 gm. per kilo of pure peptone, blood-pressure had usually returned to its normal level, and with it the response to vaso-motor excitation had likewise, almost, if not fully reappeared.

These results are in accord with those of Grosjean.

(c) *On blood-vessels of the limb, kidney, and spleen respectively.*—In three of the above experiments a record of the volume of each of one of these organs was taken, with the object of noting the effect of peptone on its blood-vessels.

In all three organs it was found that the dose employed produces a distinct lowering of peripheral vaso-motor irritability immediately following the injection. This, however, soon commenced to pass off, and within a short period the response, by a gradual return, assumed its normal proportions.

With regard to any difference shown by the blood-vessels of these organs, little positive can be said based on a single experiment for each. So far, however, as this justifies remark, it would appear that limb blood-vessels are more affected by pure peptone than either renal or splenic.

III. *Effects of Anti-peptone.*

(a) *On blood coagulation.*—This was observed in seven experiments on dogs which varied in weight from 8.7 to 23.95 kilos. The doses employed per kilo were 0.1 gm. in one experiment, 0.2 gm. in four, and 0.3 gm. in two experiments.

In all of these, with one exception, blood coagulation was hastened, in some markedly so. Thus, in one experiment with a dose of 0.2 gm. per kilo, coagulation time was reduced from 9 m. 30 sec. to 2 m. 0 sec. ; in another, with a dose of 0.3 gm. per kilo, from 3 m. 0 sec. to 1 m. 15 sec. ; and in a third, with a dose of 0.1 gm. per kilo, from 5 m. 10 sec. to 2 m. 45 sec.

In the exceptional case, with a dose of 0.3 gm. per kilo., blood-coagulation-time was practically unaltered ; before injection time 3 m. 30 sec., after 3 m. 55 sec..

This result stands in marked contrast to those published last year in

the paper before referred to, concerning Witte's peptone.¹ It was then found that this substance, in doses of 0.1 grm. per kilo, retards coagulation almost invariably, and the same effect was observed to be the rule with doses as low as one-fifth this quantity. Grosjean² had also found coagulation to be delayed from one to ten hours by propeptone in doses of 0.1 grm. per kilo. Below 0.02 grm. per kilo a hastening of blood-coagulation was the rule.

The result, however, is corroborated by those of Spiro and Ellinger,³ published during the course of this research. These observers found a reduction of coagulation-time from eight to four minutes with a dose of 0.6 grm. per kilo. With regard to former investigators, it is to be remarked that Pollitzer⁴ did not find that anti-peptone (tryptone) produced any effect on the rapidity of coagulation, agreeing in this with Fano.⁵ It is probable that neither of these experimenters used very pure products.

Nor can the hastening effect of Witte's peptone on blood-coagulation, in small doses, be attributed solely to an admixture with anti-peptone, since deutero-albumose in certain doses, as will be shown later, has been found to hasten this process, while in other doses coagulation is markedly retarded.

(b) *On blood-pressure.*—Pollitzer evidently had noted that the effect of anti-peptone (tryptone) on blood-pressure was different from that of albumoses, since he makes an exception of it, stating that its effect is doubtful. In the present research it has been found that anti-peptone in its action on blood-pressure likewise contrasts with other products of proteid digestion. In doses of 0.2 grm. per kilo, after a very transient fall immediately following the injection, blood-pressure returns to a level, as a rule, somewhat higher than before the injection. This was observed also in one of two experiments with doses of 0.3 grm. per kilo each. In the other, the fall lasted somewhat longer, but even here the duration of lowered blood-pressure was very temporary when compared with that of Witte's peptone, minutes as compared with hours.

Spiro and Ellinger⁶ also state that they have found essential differences in the effects of this substance, amongst other things, on blood-pressure as contrasted with albumoses. They, however, reserve their results for future publication. It is interesting, as these observers point out, to note the contrast of this substance with that of the albumoses, out of which it arises, in view of the possibility that toxins and anti-toxins are similarly related as to origin.

(c) *On peripheral vaso-motor irritability.*—As might be anticipated, this substance was not found to possess any depressing action on the tone of blood-vessels, either abdominal or general. On the contrary, in many cases a decided increase of irritability was shown.

¹ Thompson, *op. cit.*

² Grosjean, 'L'action physiologique de la propeptone et de la peptone,' *Travaux du laboratoire de Léon Frédéricq*, tome iv. 1891-92, p. 45.

³ Spiro and Ellinger, 'Der Antagonismus gerinnungsbefördernder und gerinnungshemmender Stoffe im Blut, &c.' *Hoppe-Seyler's Zeitschrift f. physiologische Chemie*, Bd. xxiii. (1897), Hft. 2, p. 121.

⁴ Pollitzer, 'On the Physiological Action of Peptones and Albumoses,' *Journ. of Physiology*, vii. (1886), p. 283.

⁵ Fano, 'Das Verhalten des Peptons und Tryptons gegen Blut u. Lymphe,' *Archiv f. Physiol.*, 1881, p. 277.

⁶ Spiro and Ellinger, *op. cit.*

Plethysmographic observations on the blood-vessels of the limb, spleen, and kidney in this respect gave concordant results.

IV. *Effects of Deutero-Albumose.*

(a) *On blood coagulation.*—With regard to influence on blood-coagulation, this substance has been found to produce a marked hastening in certain of the experiments, while in others a marked retardation was observed. Nor can the difference be attributed to the amount of dose. So far this has proved irregular.

Thus hastening has been obtained as follows :—

Dose per kilo	Coagulation Time	
	Before	After
	M. S.	M. S.
0.05 grm.	12 0	3 0
0.20 "	5 0	1 30
0.20 "	4 40	4 5
0.30 "	9 30	1 0

While retardation has been obtained as under :—

Dose per kilo	Coagulation Time	
	Before	After
	M. S.	
0.075 grm.	28 0	Several hours
0.1 "	10 0	" "
0.1 "	6 30	" "
0.1 "	7 30	Not after 1 hour
0.2 "	5 50	" "
0.2 "	4 45	Not after three hours. Coagulated next morning.

In the first two of the latter group of experiments there is reason to believe a somewhat overdose of curare had been administered, and also that this substance produces an effect on blood-coagulation. A new supply of this substance had just been obtained which proved to be very active. In these two experiments, with dogs 9.4 and 8.5 kilos respectively, the dose actually given was only two cubic centimetres of a 1-per-cent. solution.

Further experiments are in progress which it is hoped will throw light on the want of uniformity in the effects of the above doses.

(b) *On blood-pressure and vaso-motor irritability.*—Ten experiments were made in blood-pressure and recorded. The dogs varied in weight from 7 to 18.1 kilos, the doses employed being 0.2 grm. per kilo in four experiments, 0.1 grm. in three, 0.3, 0.075, and 0.05 in one experiment each respectively.

The general conclusion arrived at is that this substance produces a more profound and enduring influence on blood-pressure than pure peptone, but less than the same dose of Witte's peptone. Deutero-albumose cannot therefore be regarded as the most potent constituent of Witte's peptone. The experiments here recorded are in agreement with those of other observers on this point.

(c) *On blood-vessels of the limb, kidney, and spleen respectively.*—Observations were made on the effect of deutero-albumose on limb blood-vessels in two experiments, using Mosso's plethysmograph; on those of the kidney also in two, employing Roy's apparatus; and on those of the spleen in four, with the modified Schäfer's spleen-box.

The results showed that the vaso-motor mechanism of these organs

is without doubt affected by doses of 0.1 grm. per kilo and upwards. The influence is not very marked, and is probably less than that on splanchnic blood-vessels other than those of the spleen or kidney. Nor did the effect last long; as a rule it had begun to disappear within five minutes, and had almost if not wholly disappeared at the end of half an hour.

In all the foregoing experiments the animals were fully anæsthetised during the whole experiment by means of morphine and atropine administered hypodermically prior to its commencement. Afterwards, when necessary, a mixture of ether and chloroform was employed to maintain the anæsthesia. Curare was given when the spinal cord or nerves other than the splanchnics were excited.

The products employed were furnished to me by Dr. George Grüber, Dresden, and were with few exceptions injected into the external saphenous vein, dissolved in 50 to 60 c.c. of normal saline.

It will be apparent that a considerable amount of work has yet to be done to make even the part of this research now reported upon complete; while a large extent of the research has not as yet been carried sufficiently far for publication owing to want of time. When this is finished it is proposed to publish the whole, including the present part more fully written, with tracings, tables, and protocols of experiments.

The history of the United States of America is a story of the growth of a nation from a collection of colonies to a great republic. It is a story of the struggles of the people for freedom and justice, and of the triumphs of the American spirit.

In the beginning, the colonies were small and weak, but they were determined to fight for their rights. They fought the Revolutionary War, and they won. They became a nation, and they grew.

The people of the United States have always been a people of courage and determination. They have fought for their rights, and they have won. They have built a great nation, and they will continue to build it.



