ON THE PHYSIOLOGICAL ACTION OF PEPTONES AND ALBUMOSES[1]. By S. POLLITZER, A.M., M.D., *New York.*

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While engaged in studying the destiny of the proteid products of digestion, Schmidt-Mülheim[2] discovered that injections of peptone into the veins of a living animal are followed by a series of remarkable phenomena. The animal sinks at once into a deep narcosis, the blood-pressure falls to such an extent that the animal may die as from asphyxia, and the coagulation of the blood drawn from the vessels is delayed for a period which may extend to several days.

Our increased knowledge of the products of digestion which has followed the investigations of Kühne and Chittenden[3], has shown us that heretofore most of the so-called peptone has consisted of mixtures of peptones and the hemialbumoses, the latter being usually in large excess. The peptone of Schmidt-Mülheim and of Fano, from which only a part of the albumoses had been precipitated by ferric acetate, was of this nature. And Fano[4] found that injections of anti-peptone—(called by him Tryptone), which, in contradistinction to his "peptone", probably contained a large proportion of peptone,—were not followed by effects similar to those which resulted from injections of his pepsin-"peptone". It seemed desirable therefore to repeat these experiments with each of the hemialbumoses, and with pure peptones.

The albumoses were prepared strictly after Kühne and Chittenden. 500 grms. of Witte's "peptone" were rubbed up in a mortar with 1500 grms. NaCl and dissolved in 5 c.c. water. A few large crystals of rock salt were added and after 24 hours the precipitate was collected, dissolved in water, again precipitated, dissolved, and the solution dialysed with

[1] A preliminary notice of the results in this paper was in part published in the *Verhandlungen d. Naturhist. Med. Vereins zu Heidelberg.* N.F. III. Bd. 4 Hft.

[2] *Arch. f. Anat. und Phys.* 1879.

[3] *Zeitschr. f. Biol.* XIX and XX.

[4] *Arch. f. Anat. und Phys.* 1881.

addition of a little thymol till it no longer gave a reaction for NaCl. From the clear fluid taken from the dialysor the protalbumose was precipitated by alcohol, collected on a filter, extracted with alcohol and ether, and obtained as a fine white powder. The heteroalbumose being insoluble in pure water was precipitated during the process of dialysis, and was easily removed from the parchment walls of the dialysor. The deuteroalbumose was precipitated by the addition of acetic acid from the first filtrate from which the prot- and heteroalbumose were obtained, dissolved in H_2O, again precipitated with NaCl and $C_2H_4O_2$, dissolved, and the solution dialysed till every trace of NaCl and $C_2H_4O_2$ had disappeared. It was then precipitated by alcohol and extracted with alcohol and ether.

The peptone was prepared after Wenz[1]. A large quantity of carefully cleaned fibrin was digested for 8 days in artificial gastric juice made from the stomachs of six pigs. The fluid having been freed from neutralization-precipitate was saturated with ammonium sulphate. After 24 hrs. the precipitated albumins (mainly albumoses) were removed, the $(NH_4)_2SO_4$ decomposed at the boiling temperature by barytic hydrate and, towards the end of the process, barytic carbonate. The baryta-peptone was then decomposed by cautious addition of dilute sulphuric acid, and the peptone precipitated from the thick syrup to which the solution had been evaporated, by absolute alcohol.

The antipeptone used was some which had been placed at my disposal by Prof. Kühne (to whom I desire to express my deep obligations for much kind help)—and was free from all other proteids and from the amidated-acids.

With the albumoses and peptones prepared in this way, the experiments of Schmidt-Mülheim and of Fano were to be repeated. In determining the quantity of proteid to be injected, the statement of Fano, that 0·3 grammes per kilogramme of weight of animal sufficed to bring about complete narcosis and to prevent the coagulation of the blood, served as a guide. If that quantity of his mixed peptones and albumoses had the required effect, then a similar proportion of any one of these bodies would suffice to bring about the observed phenomena, if they were ascribable to that particular proteid.

For the injections, 5 % solutions of the proteid in ½ % solutions of sodium carbonate were employed. The $NaCO_3$ was used because it was necessary for the solution of the heteroalbumose, and as com-

[1] *Zeitschr. f. Biol.*

parative observations were to be made, the same solutions had of course to be used in every case. The solutions were injected into the external jugular, or the crural vein, and at a temperature of about 40° C. Samples of blood taken to test its coagulability were drawn from either the crural, the carotid or the axillary artery. The cannula connected with the mercury manometer for determining changes in the blood-pressure, was inserted into either the carotid or the crural artery. The animals employed in the experiments were for the greater number dogs. In every case (except before a few injections of peptone) the animal had received no food for 24 hours. The observation of Fano, that the rabbit is not susceptible to the action of these bodies, was corroborated. A few experiments were made with cats, with the same general result as in the case of dogs, except that the cat seems to require a relatively larger dose to bring about the same degree of effect.

It would serve no purpose to give the details of all the experiments made; a few cases will suffice:

EXPERIMENT II. Dog, 8 kilos. Injected 100 c.c. of a filtered solution of Witte's *peptone* into jugular vein. The injection was promptly followed by marked signs of distress; defaecation; micturition; after 2 minutes, deep narcosis; complete anaesthesia; reflexes preserved. Pulse first slow and full, then rapid and feeble. After 20 minutes the animal still unconscious was killed by puncture through the medulla. On post-mortem examination, the intestines were found highly congested, the villi appearing beautifully injected under the microscope. The peritoneal cavity was filled with a bloody serum which showed traces of albumoses. A sample of blood drawn from the carotid before the injection coagulated normally; samples drawn at 5, 10 and 15 minutes after the injection, remained wholly free from coagula for over three days.

EXPERIMENT V. Dog, 24 kilos. Blood pressure in carotid, 110 mm. Hg. Injected 0·75 grm. *amphopeptone* in 15 c.c. $NaCO_3$ solution 0·5%. The blood pressure sinks rapidly to 28 mm., and 3 minutes after the injection it is 22. From this point it soon begins slowly to rise:

after 7 min. the pressure is 30,
„ 12 „ „ „ „ 40,
„ 17 „ „ „ „ 66,
„ 22 „ „ „ „ 94,
„ 33 „ „ „ „ 105,

at which it remains constant for 15 min. The injection was followed by symptoms of narcosis &c. as in Exp. II., only apparently less intense. The

recovery from the narcosis was coincident with the restoration to the normal blood pressure. Three samples of blood, drawn at 3, 7 and 12 minutes after the injection, were firmly coagulated within 10 minutes.

EXPERIMENT XV. Dog, 28 kilos. Blood pressure in crural art., 120 mm. Injected 0·8 grm. *heteroalbumose* in 16 c.c. of a 0·5% $NaCO_3$ solution, into jugular vein. The pressure fell at once to 20 mm., and

2	min.	after	the	injection,	it	is	16 mm.
6	„	„	„	„	„	12	„
9	„	„	„	„	„	20	„
12	„	„	„	„	„	40	„
15	„	„	„	„	„	94	„
20	„	„	„	„	„	103	„

Narcotic and other symptoms as in other experiments, but very strongly marked. Samples of blood drawn at 2, 6 and 10 minutes after the injection remained free from clots for 24 hours. A cruor which had by this time settled at the bottom of the vessels in which the blood was contained was found on examination under the microscope to consist of blood-corpuscles and numerous minute clots of fibrin.

The results of all the experiments may be summed up under the following heads:

A. *Narcotic action.* All the substances employed in these experiments (excepting antipeptone), exercised without fail a strong narcotic action on the dogs and cats into whose veins they had been injected. With regard to the intensity of this action it would be difficult to express an opinion as there seem to be considerable individual differences in the different animals. Fano reports that in 6% of his cases, injection of his peptone failed to produce its usual effects. In one of my cases, injection of the usual dose of deuteroalbumose caused the death of the animal (the autopsy revealing nothing of value) while in the others the narcosis was slight. Without being too positive, it seems that heteroalbumose possesses the strongest action, protalbumose next, amphopeptone least.

Immediately following the injection there occurs a stage of excitement, with more or less marked manifestations of pain and distress, due no doubt to strong intestinal peristaltic action. There is usually passage of faeces and of urine. This stage lasts from one to two minutes, and is followed by the narcosis. With regard to the nature of the narcosis, it may suffice to say that it resembles that produced by chloroform. The animal seems to be in a deep sleep, from which it

cannot be aroused. There is no motor paralysis, and the reflexes are perfectly preserved. The muscles nevertheless seem often affected in an unusual way; the extremities offer that peculiar "waxy" resistance which they sometimes possess in catalepsy; they will remain in any position in which they are placed.

Only two injections of antipeptone were made. In the one a deep narcosis followed; the other had not the slightest visible effect. Fano reports a similar irregularity in the action of his antipeptone. Something like this I found in the effect of amphopeptone on the coagulability of the blood.

A word as to the cause of the poisonous action of these bodies and the view of Brieger[1] that it is due to the admixture of a ptomaine. Indeed Brieger claims to have obtained from Witte's and other "peptones" a substance which he calls "*peptotoxine*" and with which he poisoned dogs and rabbits. That the physiological action of the proteids is not due to this "peptotoxine" is sufficiently clear from the fact that the latter exercises a poisonous action on rabbits, and, as already mentioned, the albumins in question are without the slightest effect on these animals. A simple experiment, however, decides the question definitely: 10 grammes of Witte's peptone were treated after Brieger to extract the peptotoxine. Of the residue, free from peptotoxine, the usual dose was injected into the crural vein of a dog. The injection was followed by the same train of symptoms that follow an injection of a like quantity of the proteid which still contains its "peptotoxine."

As bearing on this question of causation, the following experiment may be worth recording. The peptone formed in the alimentary canal must pass through the liver before entering the general circulation. To follow out this natural course, an injection of Witte's peptone was made into the portal through the splenic vein. The injection was followed by the narcotic and other effects already described. It must however be said that the time occupied in the injection was relatively so short, that it cannot be assumed to have imitated the absorption process, in which the peptone is introduced into the circulation (if indeed it be not converted into other albumins in the process of absorption itself) very gradually.

B. *Effect on the coagulability of the blood.* The remarkable property of delaying or entirely preventing the coagulation of the blood drawn from the arteries of an animal into whose circulation an injection

[1] *Ueber Ptomaine.* Berlin, 1885.

has been made, is shared by all the hemialbumoses, and is wanting to the antipeptone; the action of amphopeptone being inconstant. The period during which the blood remains unclotted after an injection of the stated quantity of the proteid varies from twenty minutes to several days. Heteroalbumose seems in this respect again to exercise most constantly the strongest action, the blood never showing any clots within 24 hours after an injection. Both the other albumoses, however, have in single cases wholly prevented the coagulation for an indefinite period. In the two cases in which injections of antipeptone were made, the blood coagulated normally;—a result which agrees with the observations of Fano. Seven injections in all were made with amphopeptone. In three of them the blood clotted normally; in four, its coagulation was delayed for 10, 20, 30 minutes, and 12 hours respectively in the different cases. The peptone was the same preparation in all the experiments, and the dose constantly 0·3 grammes per kilogramme of animal; four of the injections with inconstant results were made into the veins of the same dog, at intervals of time which allowed for the healing of the last wounds. The action of amphopeptone then depends on some unknown and inconstant factor. That this factor is not the quantity of proteid matter present in the blood at the time of the injection is evident from the fact that the coagulation of the blood occurred normally or was delayed independently of the condition of the dog as to the time of his last meal. Nor can it be held that the admixture of the inactive antipeptone in the amphopeptone can be the cause of this inconstance, for in one case in which 0·9 grammes per kilogramme of weight of animal was injected, the blood coagulated normally. Assuming the anti- and hemipeptone to be in equal proportion in amphopeptone, considerably more of hemipeptone than the usual dose of proteid (0·3 grammes per kilogramme) was here injected without effect.

Schmidt-Mülheim found that when he caused blood from the artery of a dog to flow into a vessel containing an equal portion of blood from another dog, into whose veins an injection of his peptone had been made, the coagulation of the whole was prevented. I have made a series of somewhat similar experiments. Normal blood from an artery was caused to flow into vessels containing aqueous solutions of the different peptones and albumoses. The quantity of blood drawn in each case was 5 c.c. and it was instantly and thoroughly mixed with an equal volume of a 0·5 % solution of $NaCO_3$ containing 0·2 grammes of the different proteids. This quantity 0·2 grammes was selected as

being ten times the weight of the proteid that would fall to 5 c.c. of blood when 0·3 grammes per kilogramme are injected[1]. As a control, a similar mixture of blood was made with a 0·5 solution of $NaCO_3$ which contained no proteid. In this there was firm coagulation in from 3 to 5 minutes; the blood mixed with the antipeptone solution clotted quite as promptly, as did also that mixed with the protalbumose. In the deuteroalbumose solution the blood remained fluid for 5 to 15 minutes in the different experiments. In the amphopeptone solution it was unclotted for from 10 minutes to 3 hours; in the heteroalbumose, from 20 minutes to 24 hours. The clot in the different cases too is characteristic. That in the deuteroalbumose solution is not to be distinguished from that in the $NaCO_3$ solution; that in the protalbumose like that in the amphopeptone is soft and ill-formed; that in the antipeptone is unusually firm and contracted, while in the heteroalbumose, no true clot is formed at all, there being simply at the bottom of the vessel after a time a cruor containing numerous minute coagula.

C. *Effect on the blood pressure.* The effect on the tone of the blood-vessel walls noticed by Schmidt-Mülheim is a common property of all the proteids used in these experiments, excepting perhaps antipeptone, the action of which is doubtful. Immediately after an injection of the stated dose, the blood pressure sinks to a degree which would be fatal to the life of the animal were it to continue at its lowest point for a considerable period. In this respect the heteroalbumose again seems to exercise the most powerful effect, amphopeptone the least. That the fall in pressure is due to vaso-motor paralysis cannot of course be questioned, and that the action is manifested chiefly if not wholly on the splanchnic region is reasonably certain. After an injection of one of these proteids, the mesenteric vessels are always strongly congested, to such an extent, that there is sometimes a bloody serum in the peritoneal cavity. Indeed it seems not unlikely that the narcotic action which these bodies exercise is due simply to this accumulation of the blood in the great veins of the abdomen, thus producing anaemia of the brain. The narcosis lasts only as long as the blood pressure is under the normal.

One property in which peptone is sharply differentiated from the albumoses may here be mentioned. A sufficiently large dose of any of

[1] There being 70 grammes of blood for each kilogramme of body weight in the dog, 0 3 grammes of proteid per kilogramme are about 0·004 grammes for each c.c. blood. For 5 c.c. then, 0·02 grammes of proteid, which multiplied by 10 gives the quantity used,—0·2 grammes.

the albumoses (something more than 0·3 grammes per kilogramme) is inevitably fatal. Peptone however can never produce this result so long as the kidneys of the animal are intact. In its solubility and diffusibility, peptone resembles the crystalline rather than the colloid bodies, and like the former it is a diuretic. If the blood pressure of an animal be lowered, as by stimulation of the cardio-depressor nerve till the renal secretion is stopped, and an injection of a crystalline diffusable body—e.g. urea—be made into the blood, the kidneys will at once begin to act, though the blood pressure remain unchanged. $2\frac{1}{2}$ grammes of peptone (0·3 grammes per kilogramme) were injected into the jugular vein of a dog; the pressure fell at once from 120 to 56 mm. As soon as the pressure began to rise, 5 grammes of peptone more (0·6 grammes per kilogramme) were injected, and were followed anew by a fall in pressure to 45 mm. Ten minutes later, the pressure still being under the normal, the animal was killed. The bladder was found enormously distended with urine which, judging from the intensity of the biuret reaction, contained a large proportion of peptone. After an injection of a smaller quantity of peptone, or of any quantity of the albumoses, the renal secretion is in abeyance during the reduction in blood pressure.