Effects of the Restriction of the Pulmonary Artery on the Blood Pressure and on the Volume of some Organs, and the Cause of the Fall of the Arterial Blood Pressure, due to the so-called "Paradoxical Vasodilatatory Substances."

By

KATSUMA ABE.

(阿 部 勝 馬)

(*From the Pharmacological Laboratory of the Tohoku Imperial University, Sendai.*)

CONTENTS.

Introduction.

According to many previous reports, many substances, such as peptone, organ extracts, blood serum, anaphylatoxin, β-iminazolylethylamine etc., cause a vasodilatatory fall of the systemic blood pressure, if injected intravenously, and vasoconstriction, when perfused through isolated organs. They are, therefore, called "paradoxical vasodilatatory substances." Is this apparent discrepancy in their actions, under conditions of natural circulation and of artificial perfusion, a real one? It cannot be believed that the substances cause vasodilatation in the natural circulation, notwithstanding that they have a vasoconstrictor effect on the excised blood vessels. I rather suspected that they might inhibit the pulmonary circulation, for they all constrict bronchial muscles, and in consequence of this the systemic blood pressure may fall.

In order to ascertain the truth or otherwise of my suspicion, the effects of the restriction of the pulmonary circulation on the volumes of such organs, as the small intestine, limb and kidney, which have not yet been clearly pointed out must be known. So I shall describe first these effects and then those of the so-called "paradoxical vasodilatatory substances" on the blood pressure and blood vessels.

I. The effects of mechanical restriction of the pulmonary artery on the arterial blood pressure and on volumes of some organs.

It is to be assumed a priori that if the pulmonary artery be obstructed, and the flow of blood be restricted, the left heart receives and discharges a less amount of blood, and consequently the arterial blood pressure falls and the venous blood pressure rises. For this reason owing to the obstruction of the pulmonary artery the volumes of the peripheral organs, varying with the amount of blood contained in them, may undergo two opposite effects. Therefore owing to the obstruction of the pulmonary artery the volume of the peripheral organs, which vary in volume with the amount of blood contained in them, are subjected to two distinct interferences, one increasing, the other decreasing their volume. Then how do the volumes of such organs as the small intestine, limb and kidney change as a result of

these two interferences? Up to the present there have been no reports of any experiments dealing with this point.

Bayliss and Starling[1] observed that an obstruction of the inferior vena cava was followed by a fall of the arterial blood pressure, a rise of the blood pressure in the inferior vena cava and in the portader, congestion of the liver and anaemia of the small intestine. Though this investigation does not justify us in accepting the conclusions arrived at with regard to the changes in volume in the organs, yet it may be inferred that the organs may vary in volume as the result of constriction of the vena cava inferior.

In my expeiments cats and rabbits were used, kept anaesthetised with A.C.E. mixture under artificial respiration. The arterial blood pressure was measured in the carotid artery by a mercury manometer. Arrangements were then made for the measurement of the volumes of such organs as the small intestine, limb and kidney, with an air plethysmograph of suitable size for each organ. In order to obstruct the pulmonary artery, the breast and pericardium were opened and then the pulmonary artery was separated from its surroundings with great care, so as not to injure the surrounding organs, such as the heart, lungs and aorta, and then a string was put round the artery. Both ends of this string were tied to a spiral to regulate the obstruction at will. At the time when these operations were finished, both the blood pressure and volumes of organs were unstable, but after several minutes had elapsed they returned to the stable conditions.

The change in the volumes of the organs varies with the degree and duration of the obstruction of the pulmonary artery. In this paper I shall describe in detail the changes in the organ volumes, when the obstruction occurs in a moderate degree. Under such conditions, (1) the volume of the limb enlarges during the fall of the arterial pressure, and when the obstruction is removed little by little, the carotid blood pressure rises gradually and proportionately to its original height and the volume comes back also gradually to the normal size. (2) The volume of the kidney (left side) diminishes simultaneously with the fall of the carotid blood pressure, and when the obstruction is relaxed and the blood pressure recovers correspondingly, its volume recovers also, but sometimes at the moment of this recovery it becomes somewhat greater temporarily than the original size, especially when the obstruction is rapidly removed; and then

returns to its normal expansion. (3) The change in the volume of the small intestine varies with the strength and the duration of the obstruction of the pulmonary artery. If the obstruction is little and short, and the fall of the blood pressure is not considerable, the volume of the small intestine diminishes during the obstruction and recovers when the obstruction is relaxed, as in the case of the kidney. However, when the degree and the duration of the obstruction are great, the volume of the small intestine also diminishes a little, but after a short while, it enlarges more and more and becomes larger than its original size, and when the obstruction is relaxed and the blood pressure returns to the normal height, the volume becomes still greater, especially when the obstruction is removed rapidly, but soon after it comes back to the original size (Fig. 1). The degree of the

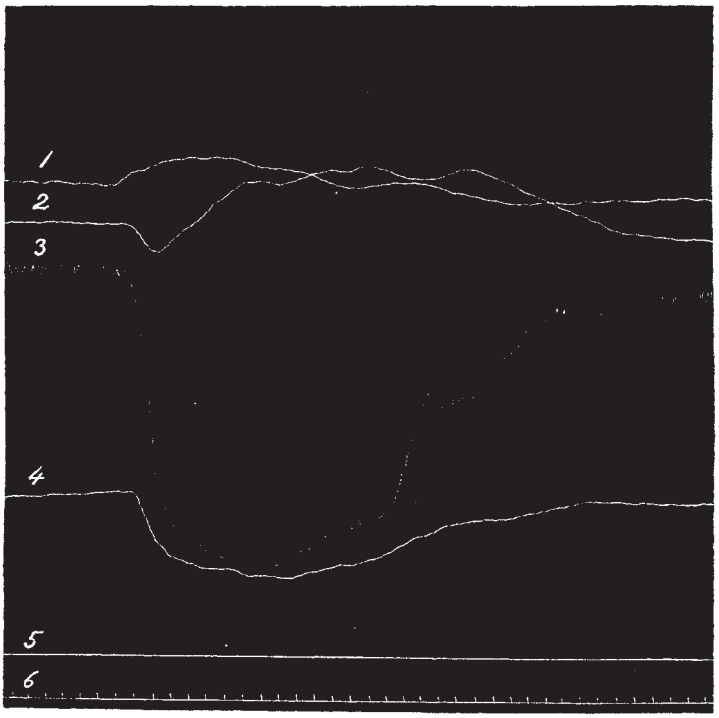

Fig. 1. Cat. A.C E. mixture. Artificial respiration.
1, volume of the right leg. 2, volume of the small intestine. 3, carotid blood pressure. 4, volume of the left kidney. 5, zero line. 6, time in 5 seconds.

preliminary diminution of the volume of the small intestine corresponds with the height of the arterial blood pressure before the

obstruction. The higher the blood pressure before the obstruction, the less the preliminary diminution. It must be noticed that even in a case where the preliminary diminution can hardly be recognized, the commencement of the expansion of the small intestine is always 2–3 minutes later than that of the fall of the blood pressure. Heidenhain[2] had previously pointed out that after the obstruction of the inferior vena cava the intestine looks branched and anaemic. Bayliss and Starling[1] also have obtained the same results in the same experiments as Heidenhain did. They have observed the changes in the small intestine only immediately after the obstruction of the vein.

From the above experiments it is clear that the fall of the arterial blood pressure, due to the obstruction of the pulmonary artery, is not always attended by the decrease of the volumes of all the organs, but sometimes by increase of the volumes of certain organs, though the degree and the course of the fall vary according to the height of the blood pressure and to the manner of the obstruction.

Many observers are apt to attribute the fall of the blood pressure to a vasodilatatory effect of some substances, when they cause a fall of the blood pressure and expansion of the volumes of such organs, as the small intestine and limbs. Of course vasodilatation may be one of the causes of the pressure fall, but not the only cause. As above mentioned, the inhibition of the pulmonary circulation may also cause a fall of the blood pressure and expansion of such organs as the small intestine and limbs. Therefore it is far too hasty a conclusion to suppose without taking other possible causes into consideration that the substances have a vasodilatatory effect, since they may cause a fall of the blood pressure and a large expansion of such organs as the small intestine and limbs. Much more is this the case with the substances that inhibit the pulmonary circulation.

II. The cause of the fall of the blood pressure, due to the so-called "paradoxical vasodilatatory substances."

Peptone, extracts of organs, blood-serum, anaphylataxine, β-iminazolylethylamine etc., if injected intravenously, cause a considerable fall of the blood pressure. Since these substances do not so inhibit the heart's activity, to such an extent as to cause the pressure fall, the cause of this has been attributed by many writers to

their vasodilatatory effect on such organs as the small intestine and limbs, for the volumes of these organs enlarge during the pressure fall. Further, as they cause also the fall of the blood pressure, even if injected into the pitched animal, so the vasodilatation has been ascribed to direct peripheral action of these substances. Nevertheless, if perfused through isolated organs, they cause vasoconstriction. What strange effects they have! They are, therefore, called "paradoxical vasodilatatory substances."

To explain their paradoxical vasodilatatory action, some observers formed a hypothesis that the blood vessels are supplied by "non-surviving vasodilatatory nerves," on which those substances act; others supposed that those substances contain the so-called "vasodilatin" or can liberate a substance like "vasodilatin" if injected intravenously.

All these hypotheses are based on the supposition that the fall of the blood pressure may be due to vasodilatation, for it is always accompanied by large expansion of such organs, as the small intestine and limbs. However, it is not right to persist in assuming a "vasodilatatory" effect of these substances, without ascertaining whether, when injected intravenously, they really cause vasodilatation, and whether these substances cause inhibition of the pulmonary circulation or not. I have already shown that the fall of the blood pressure, even though it is accompanied by a large expansion of such organs as the small intestine and limbs, does not mean only dilatation of the blood vessels of those organs, for it may be caused by inhibition of the pulmonary circulation. For this reason I have to investigate the cause of the pressure fall, due to the so-called "paradoxical vasodilatatory substances" and to settle the question whether these substances really cause vasodilatation in living animals, notwithstanding that they cause vasoconstriction when perfused through isolated organs.

It has been already pointed out by many observers that the effect of peptone on the blood pressure resembles those of organ extracts, blood serum and anaphylatoxine. Recently Dale and Laidlaw[3] have reported that the effect of β-iminazolylethylamine is not only analogous to those of peptone, organ extracts etc., but the extract of the small intestine contains β-iminazolylethylamine as its acting substance. For this reason there are some who suppose that the fall of the blood pressure due to many other organ extracts, may be caused by β-iminazolylethylamine, contained in them. I do not

know whether their supposition is correct or not, but it can be assumed a priori, that as β-iminazolylethylamine is a chemically pure substance, its action may be simpler, and consequently the investigation of it may be easier than that of the other substances. And accordingly if the cause of the pressure-fall, due to β-iminazolylethylamine, is determined, it will contribute not a little to the investigation of the effects of many other chemically impure substances, which resemble that of the former. I will, therefore, bring forward first the effects of β-iminazolylethylamine on the blood pressure and blood vessels.

1. The cause of the fall of the blood pressure, due to β-iminazolylethylamine (Histamine).

Histamine is an amine produced when carbon-dioxide is split off from histidine, and is present in putrified meat, cornu secale etc. Its action on the vascular system was investigated first by Ackermann and Kutscher[4] and then more minutely by Dale and Laidlaw[3]. According to the latters, the effect of histamine on the blood pressure is complicated and is not easily to be explained. It not only varies in different species of animals, but shows a very wide variation in individuals of the same species, especially in rabbits; in the case of cats and dogs the effect of injecting a small dose of histamine intravenously is almost always a considerable fall of the systemic arterial pressure, accompanied simultanously by a large expansion of the small intestine and limbs, and by a diminution of the volumes of the kidney and lung. As these investigators could not attribute the pressure fall to the direct depression of the heart's activity, the fall of the blood pressure was ascribed by them to the general vasodilatation, in which the arterioles of the kidney do not participate. Dale and Laidlaw having observed that the pressure fall and the expansion of such organs as the small intestine and limbs are caused by histamine even after section of the splanchnic, or right stellate ganglion, or after injection of nicotine in a dose sufficient to block the impluses through the automatic ganglia, stated their belief that the "vasodilatatory" effect of histamine was peripheral in origin.

They added, moreover, that by extirpating the stellate ganglion and allowing a sufficient time for the subsequent complete degeneration of the peripheral neurons, the vasodilatatory effect was intensified in the corresponding limb, if altered at all. For this reason they

concluded that the fall of the blood pressure is due to vasodilatation in the small intestine and limbs, and that the vasodilatatory effect of histamine in the dog, cat and some other animals is a primary action, peripheral in origin, independent of the integrity of the sympathetic neurons. However, they could not detect any vasodilatatory effect in the artificially perfused organs, but found a vasoconstrictory effect. Believing that this apparent discrepancy is a real one, they stated that histamine may act on their hypothetical "vasodilatatory nerves," which do not survive excision and artificial perfusion. They observed further that monkeys and fowls, as do cats and dogs, respond to the intravenous injection of histamine also by a typical fall of the blood pressure and a large expansion of some organs, while most rabbits do so rather by a rise of the blood pressure. They seem to attribute the rise of the blood pressure in rabbits to the failure of their hypothetical "non-survival vasodilatatory nerve."

To explain these discrepant facts, Popielski[5] stated his belief that histamine is one of the series of substances, which liberate his hypothetical "vasodilatin," and causes a fall of the blood pressure by liberating this substance, if injected into the cat, dog and some other animals, but when injected into rabbit, it does not cause a fall, but a slight rise, for it can not liberate the "vasodilatin" in this animal. However his argument are not based on his own experiments, but on Dale and Laidlaw's. Since I can not believe all these explanations, I have performed the following experiments, to discover the real cause of the fall of the blood pressure due to histamine.

All the experiments here described were made with histamine prepared from histidine by a chemical process, which was imparted by Dr A. R. Cushny, F.R.S., professor in the University of Edinburgh, to whom I, with Dr S. Yagi, professor of our laboratory, am indebted for his kindness.

(a) Effects on the arterial blood pressure.

According to Dale and Laidlaw the effect of histamine on the blood pressure varies with different species of animals; in cats and dogs, the drug causes a fall of the blood pressure, but in rabbits, it causes a rise. So I used cats and rabbits and attempted to ascertain whether the effect of the drug really varies in different species of animals. All the animals were usually kept anaesthetised with A.C.E. mixture under artificial respiration. The arterial blood pressure was

measured in the right carotid artery by a mercury manometer. The drug was dissolved in each case, in 1·0 c.c. Ringer's solution and injected into the left jugular vein.

(1) *The cat.* Dealing first with cats, the effect of injecting 0·5 mgrm. per kgrm. of histamine is almost always a considerable fall of systemic blood pressure. The degree of the pressure fall is independent of the dose, as described by Pilcher and Sollmann[6], but dependent on the rate of the injection (Oehme[7]); the more rapid the rate of the injection of the drug, the more considerable is the fall of the blood pressure. With dose of 0·5 mgrm. injected for about 20–30 seconds, fall of the blood pressure amounts to 50–60 mm. Hg (Fig. 2). As pointed out by Dale and Laidlaw[4], in the course of

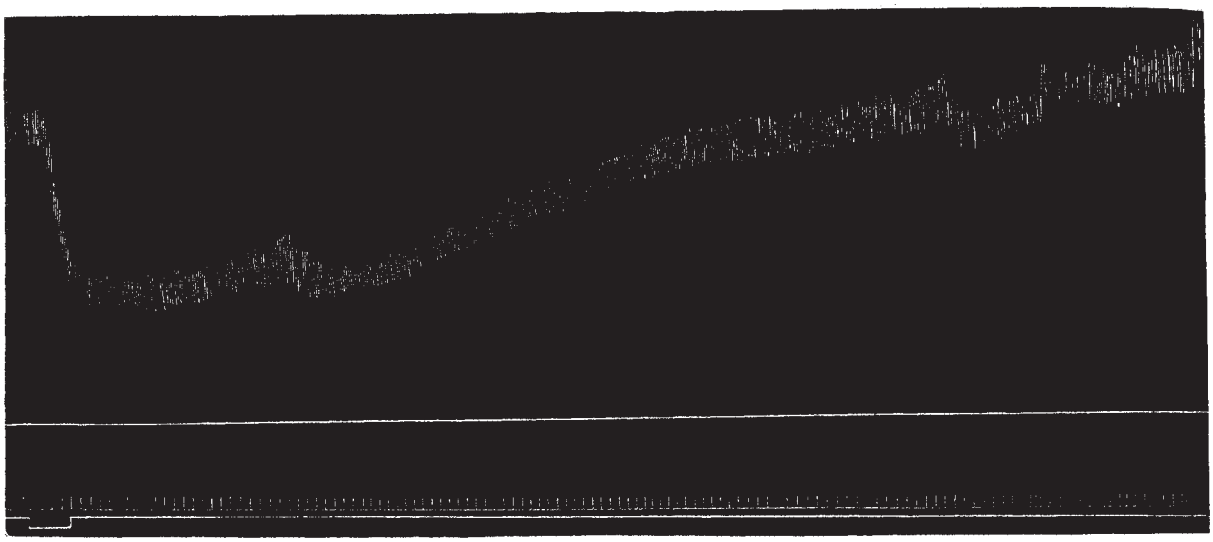

Fig. 2. Cat. A.C.E. mixture. Carotid blood pressure.
At the signal 0·5 mgrm. of histamine was injected into the left jugular vein. Time in 5 seconds.

the pressure fall it can sometimes be observed to occur in two stages, viz. there is a preliminary fall, lasting about ten seconds, succeeded by a more marked secondary fall, the duration of which varies with the dose of the drug. With 0·2 mgrm. recovery soon begins, and after the recovery the blood pressure is higher than the original height; while, with 1·0 mgrm. or more, the secondary fall is much more prolonged and, though the lowered blood pressure begins to rise, the rise gives way again to a grandual fall.

Moreover the degree of the fall of the blood pressure and its rise after the recovery are correlated to the intensity of narcosis and the maintenance of artificial respiration. If the cat has been completely anaesthetised with a large quantity of chloroform or urethane and artificial respiration is maintained, it responds to the injection of histamine, even if a great dose has been injected, with less fall of the pressure, but with a more distinct rise after the recovery from the fall (Fig. 3).

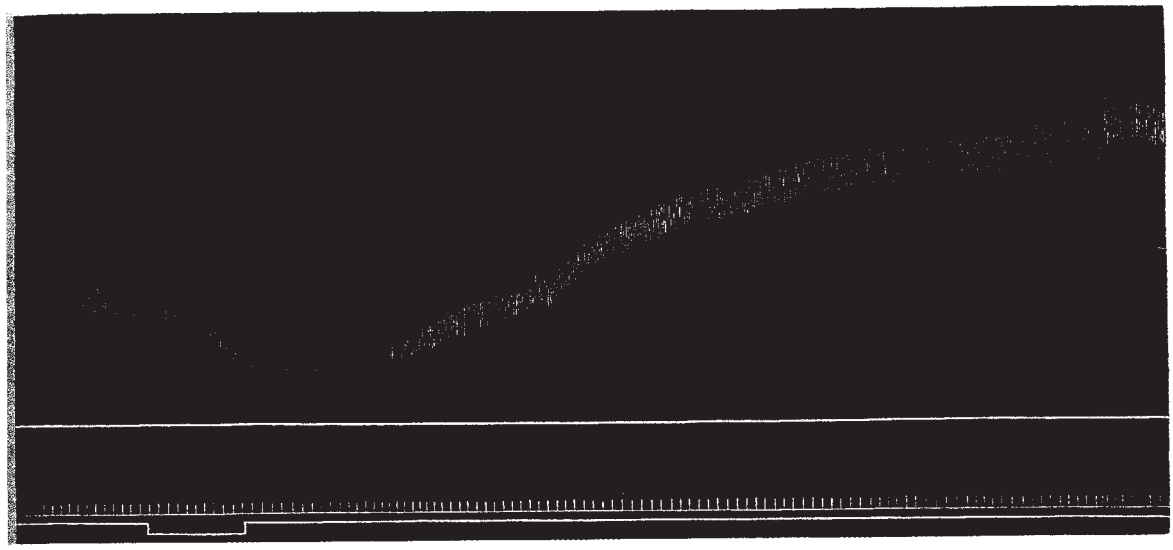

Fig. 3. Cat. Chloroform. Artificial respiration. Carotid blood pressure. At signal 0·5 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

(2) *The rabbit.* In rabbits the effect of histamine is more greatly modified by the condition of narcosis and artificial respiration, especially by the former; when narcosis is not deep, the fall of the blood pressure and rise after its recovery are also produced by the injection of 0·5 mgrm. per kgrm. of the drug as in the case of cats, but when it is intense, rabbits respond to the injection of the drug with only a slight initial fall, succeeded by a more prolonged rise, as shown in Fig. 4. Moreover, if the rabbit be left for a long time (30 minutes or more) under the full influence of urethane or A.C.E. mixture, and artificial respiration be maintained, the injection of the drug causes only a more prolonged rise of the blood pressure (Fig. 5).

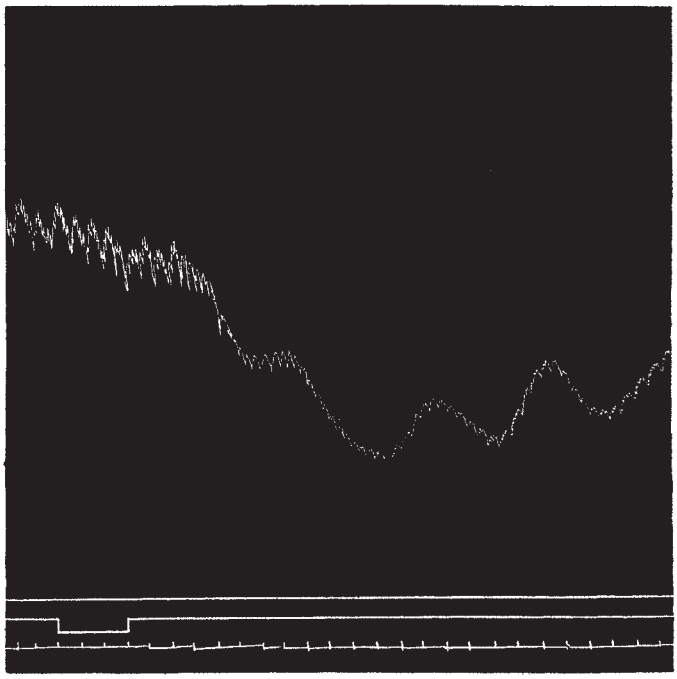

Fig. 4. Rabbit. A.C.E. mixture. Carotid blood pressure.
At signal 0·5 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

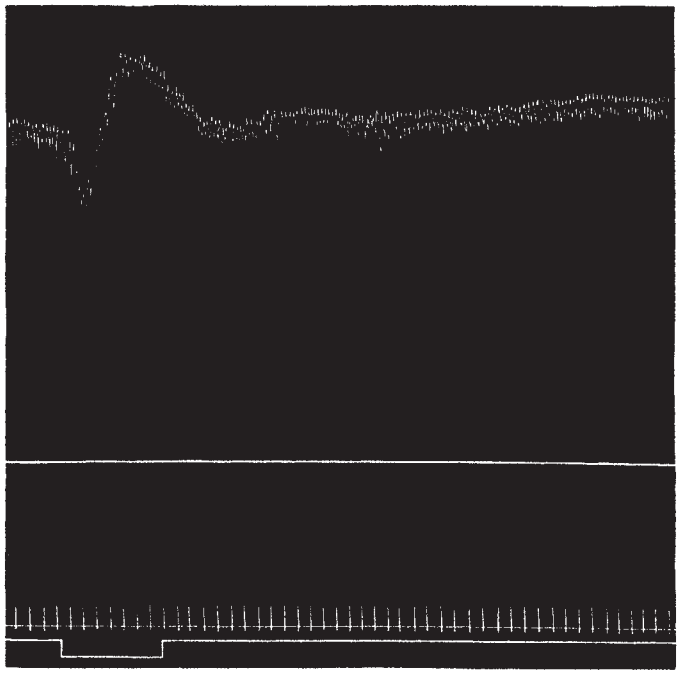

Fig. 5. Rabbit. Urethane. Carotid blood pressure.
At signal 0·5 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

Though the results, obtained by injecting histamine in rabbits, vary in individuals, as stated by Ackermann and Kutscher and by Dale and Laidlaw, all these variations are due only to the conditions of anaesthesia and artificial respiration and not to the age or indiosyncrasy of the animal, to which they are attributed by Dale and Laidlaw.

Conclusively, histamine, injected into animals, causes first a fall and then a rise of the blood pressure, and the degree of the fall of he blood pressure varies not only with the rate of injection of the drug, but with the conditions of anaesthesia and artificial respiration. If narcosis is not deep, and artificial respiration is not maintained, the fall of the pressure is considerable, but in other conditions, viz. if narcosis is complete and artificial respiration is maintained, the fall is reduced and the rise after the recovery from this fall is more marked. And it does not matter, whether a cat or a rabbit be used in the experiment. It must be, however, added that the rabbit is more markedly sensitive to those influences than the cat.

Now to investigate the cause of the fall and the rise of the blood tpressure after the recovery from the fall, I examined separately th action of the drug on the heart, the pulmonary circulation and the systemic vessels.

(b) Effects on the heart.

Dale and Laidlaw, having observed in the cardiometer experiment in situ after the vagi had been cut, the fact that the rate of the heart beat is slightly less after the injection of the drug, while the volume of the heart increases, stated their belief that even though the rate is slightly less, the output per beat is more than proportionately increased, so that the output per unit time is greater, and for this reason the fall of the blood pressure must be due to some other cause than the action of the drug on the heart. However that may be, it is not rational to attribute the expansion of the heart to the increase of the output. There is no doubt that when both the right and left ventricles expand, and their beat is not inhibited, the output per beat increases; but the expansion of the heart does not always mean the enlargement of both ventricles: if congestion should occur in the right ventricle, even if the left ventricle had not dilated, this might also cause expansion, which does not mean the increase of the output. Previously Führer and Starling[8], having experimented on the

action of histamine on the heart-lung-coronal circulation of dogs, observed that the drug causes a large expansion of the heart and a fall of the arterial blood pressure. From their experiments it can be also supposed that the expansion, caused by the drug, does not mean any increase of the output, but rather a diminution of it.

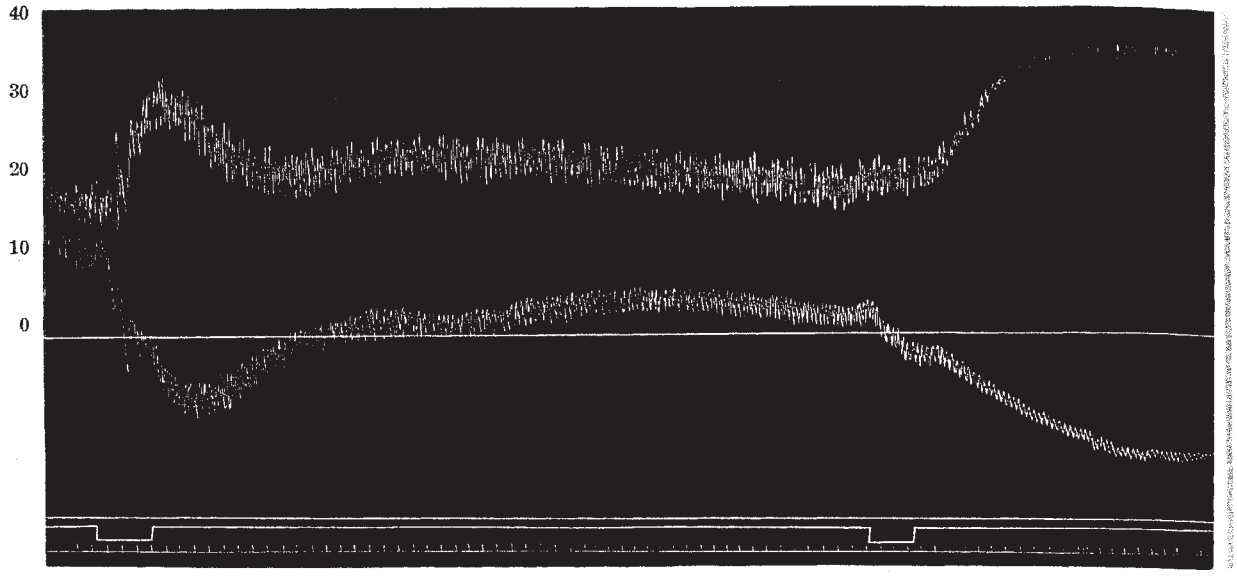

Fig. 6. Cat. Hering's heart-lung-coronal circulation. Pulmonary (upper) and carotid blood pressure (lower curve).
At signal 0·5 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

I have prepared also the heart-lung-coronal circulation of cats by Hering's method[9], and measured the blood pressure in the carotid and the pulmonary artery. As Fig. 6 shows, the drug, injected into the jugular vein, causes a rise of the pressure in the latter and a fall in the former as observed by Führer and Starling. Even in this experiment I could sometimes observe the preliminary fall and secondary fall of the carotid blood pressure. In rabbits the same results were obtained, but to obtain marked results a dose double that injected into cats was necessary.

These experimental results prove that the drug causes a decrease of the output of the heart and not an increase of it. All the evidences, therefore, are definitely against the explanation of Dale and Laidlaw. The cause of the fall of the blood pressure must be in the effect of the drug on the heart, or on the pulmonary circulation, or on both.

According to Dale and Laidlaw, the action of the drug on the hearts of cats and rabbits, isolated and artificially perfused, is to produce an increase in both the rate and the force of the beat, accompanied simultaneously by the constriction of the coronary vessels. Rabe[10], having experimented on a cat's heart, observed also the increase of the former, but not always the decrease of the coronary flow. F. Meyer[11] found, after giving histamine intravenously in the living dog, a decreased flow from the coronary veins, which he attributed to the fall in general blood pressure (not having investigated the factor of local vaso-constriction). Einis[12], working on the isolated and perfused heart, observed, after giving the drug, a short and slight slowing, followed by considerable quickening with increased exclusions. In the living dog Pilcher and Sollmann[6] observed, after injecting the drug, that the amplitude of the cardiac exclusions is not sufficient to account for the fall in the blood pressure and the heart rate is variable, either unchanged, or somewhat increased or lessened.

I have also perfused the isolated hearts of cats and rabbits with warm (37°C.) oxygenated Ringer's solution, the drug being dissolved for exchange with the perfusion fluid in the same Ringer's solution. In a concentration of 1:10000, the rate and force of the cat's heart is almost unchanged, and the outflow from the coronary veins is retarded a little, but in concentrations of 1:5000–1:2000 both the rate and the force of the beat are increased, and the diminution of the coronary outflow is more distinct. The effect of the drug on the rabbit's heart is almost similar, but somewhat weaker than that on the cat's.

From these experimental results it is not rational to attribute the fall of the blood pressure to the effect of histamine on the heart, as F. Meyer did. Histamine has not a depressing action on the heart. Now there must be some other cause to produce the pressure fall of the drug. It can be assumed a priori that the drug must have an inhibitory effect on the pulmonary circulation, for the pressure fall can be caused even in the heart-lung-coronal circulation.

(c) Effects on the pulmonary circulation.

As above described, histamine, injected intravenously, causes a fall of the arterial blood pressure, and at the same time a rise of the pulmonary pressure. Dale and Laidlaw, having observed that,

following the injection of 0·5 mgrm. of the drug into cats, the pulmonary pressure rose,—amounting to about 40 mm Hg at its maximum, and preceding the systemic fall by about 2–3 seconds,—stated that, though the pulmonary vessels are constricted by the drug, its effect, in diminishing the output of the left ventricle, when it is perceptible at all, must be limited only to the initial stage of the systemic fall, for it is clear from the time relations of the two effects: the pulmonary rise of the blood pressure having already passed its maximum, when the systemic fall is but beginning. But I regret that I can not agree with them, as the following experimental results show.

I have measured the pulmonary pressure with a mercury manometer from a branch of the art. pulmonaris (which leads to the left under lobe of the lungs) of a cat by the method described by Bradford and Dean[13], the animal being anaesthetised with A.C.E. mixture and artificial respiration maintained.

The pulmonary and carotid pressure respond to the injection of 0·2 mgrm. of the drug with a rise and a fall respectively, and the former not only precedes the latter by about 2–3 seconds, as observed Dale and Laidlaw, but both changes correspond, in duration and intensity, but in contrary direction, differing from that described by them (Fig. 7). And it is observed only in cases where the drug is rapidly injected or a large dose of it is used, that the rise of the pulmonary pressure gives way to a fall to its original

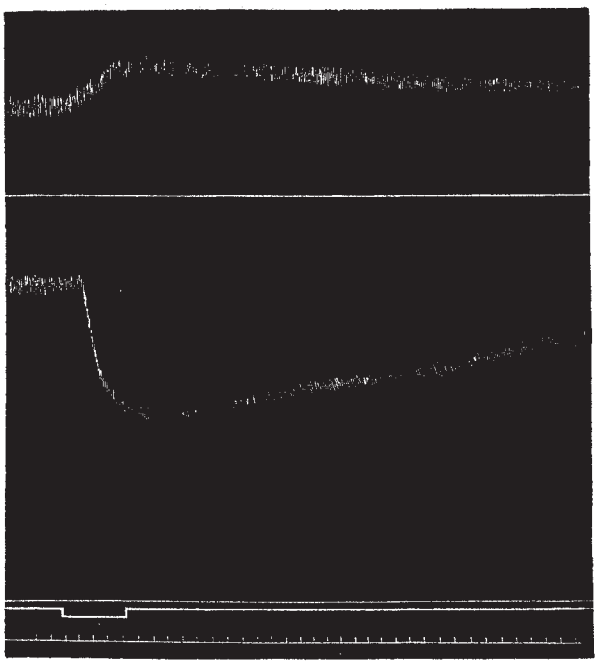

Fig. 7. Cat. A.C.E. mixture. Artificial respiration. Pulmonary (upper curve) and carotid blood pressure (lower curve).
At signal 0·5 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

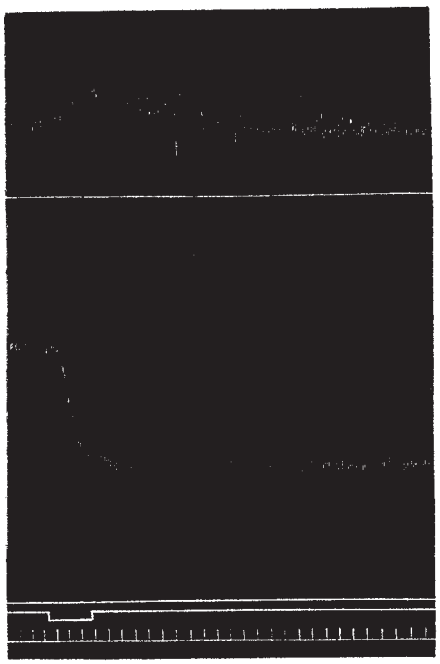

Fig. 8. Cat. A.C.E. mixture. Artificial respiration. Pulmonary (upper) and carotid blood pressure (lower curve).
At signal 1·0 mgrm. of histamine into the left jugular vein. Time in 5 seconds.

height, as soon as its maximum is reached, and in these cases, of course, the pulmonary rise and the systemic fall do not agree in duration (Fig. 8). In serting an arterial cannula into the pulmonary artery and letting warm Ringer's solution flow into it upstream to the right ventricle, I could ascertain the disturbance to the pulmonary valves of such animals, as respond to the injection of the drug with only a short rise of the pulmonary pressure, in spite of a long fall of the systemic pressure. This failure to function of the pulmonary valves is produced by the rapid and enormous rise of the pulmonary pressure. The short duration of the pressure of the pulmonary artery, after the injection of histamine, must therefore be explained thus:—The rise due to the action on the pulmonary vessels is interrupted by the failure of the valves.

Dale and Laidlaw's observation, that the pulmonary rise lasts for only a short duration, may perhaps be due to their neglect of these facts. If the drug is injected carefully, the pulmonary rise lasts as long as the fall of the systemic pressure and the former always precedes the latter. This is a fact that cannot be ignored.

This great rise of the pulmonary pressure can only be attributed to the inhibitory effect of the drug on the pulmonary circulation, since the effect of it on the heart is too feeble to cause the rise.

As reported by Dale and Laidlaw, Baehr and Pick[14] and Berezin[15], I have also found, as a result of the perfusion experi-

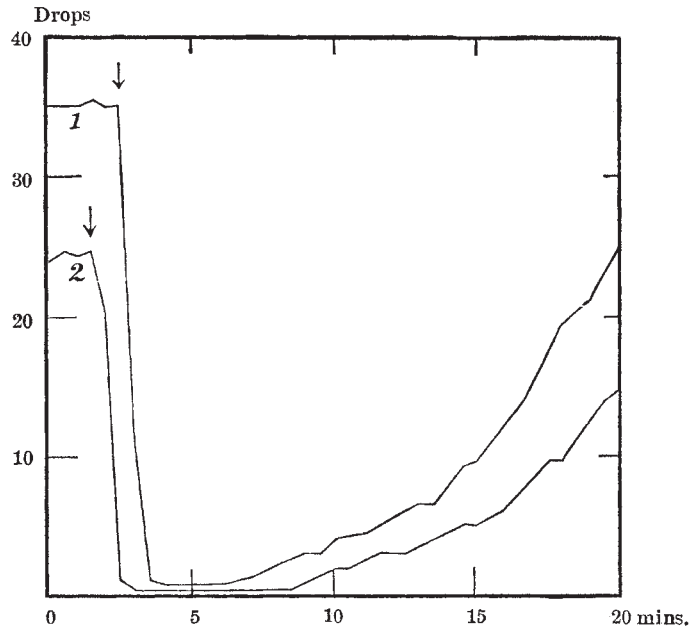

Fig. 9. Graphs of the amount of fluid passing through the vessels of the cat's (1) and rabbit's (2) lungs, perfused with Ringer's solution.
At the arrows 0·2 mgrm. of histamine into the inflows canula.

ment of the lungs (left under-lobe) of the cat and the rabbit, that the drug, injected into the cannula from which they are perfused, causes a considerable diminution of the drops from the venous side (Fig. 9). By the previous observers this decrease of the venous outflow is ascribed to the constriction of the pulmonary vessels, but I can not agree with them, until it is decided whether the effect of the drug on the bronchial muscles participates in this inhibitory effect or not, for the degree of the diminution of the drops observed by perfusion of the lungs is, by no means, to be compared with that caused by the perfusion of many other excised organs, as described in what follows. There is no doubt from the experiment made by Barbour[16] on the rings of the pulmonary artery, that the drug causes a constriction of them. But generally the pulmonary vessels are less sensitive to many drugs than other vessels, while histamine inhibits especially the pulmonary circulation. So it is very questionable if the drug causes the remarkable inhibition only by its effect on the pulmonary vessels. According to the investigations of Dale and Laidlaw, Januschke and Pollak[17], Jackson[18] and Titone[19], histamine causes a contraction of the bronchial muscles by its peripheral action, and Lohmann and Müller[20] observed that the pulmonary circulation was inhibited by this drug. So I suppose that the main cause of the inhibition of the pulmonary circulation must be due to the effect of the drug not on the pulmonary vessels, but on the bronchial muscles;

for the latter can be considerably constricted by the direct peripheral effect of the drug. And this supposition was ascertained by the following experiment: I measured the intrapleural pressure of a curarized cat, artificial respiration being maintained, with a tambour, and found that the intrapleural pressure responded to the injection of the drug with a considerable fall, almost simultaneously with the fall of the arterial pressure, and as the former recovered, the latter came back also, and the duration of the fall of both pressures almost agreed in time relation.

For this reason I have to attribute the cause of the blood pressure to the inhibitory effect of histamine on the pulmonary circulation, which is due to the constriction of the bronchial muscles. Now it will be clearly understood, why the fall of the blood pressure, caused by histamine, is influenced by the conditions of anaesthesia and artificial respiration, for various anaesthetics, such as urethane, depress the response of the bronchial muscles (Brodie and Dixon[21], and Trendelenburg[22]) and artificial respiration obscures mechanically the broncho-constrictory effect of the drug. Moreover, as regards the partial antagonism between the effects of histamine and adrenine on the blood pressure, which was discovered by Dale and Laidlaw, it is also easily explained from my results, for though adrenine has an effect on the bronchial muscles, which are constricted by histamine, the former cannot reduce the constriction, caused by the latter, as Januschke and Pollak, and Jackson have pointed out.

Briefly stated, histamine has a constrictory effect both on the pulmonary vessels and bronchial muscles, and these effects cause a considerable inhibition of the pulmonary circulation, which produces the rise of the pulmonary pressure on the one hand and the fall of the arterial blood pressure on the other. If the inhibitory effect of the drug appears successively, the fall of the arterial pressure occurs in two stages; a preliminary and secondary fall, and if the response of the bronchial muscles is reduced physically and pharmacologically by the artificial respiration and narcotics respectively, the inhibitory effect of the drug on the pulmonary circulation is also reduced and consequently the degree of the fall of the arterial blood pressure is lessened.

(d) Effects on the systemic vessels.

I have shown above that the fall of the arterial blood pressure is not of cardiac origin, but is due to the inhibitory effect of the drug

on the pulmonary circulation. Now it is very interesting to discuss whether, as Dale and Laidlaw described, "non-survival vasodilatatory nerves" exist in the blood vessels of cats and whether, as Popielski supposed, histamine injected intravenously liberates such substances as "vasodilatin."

In the first place, before proceding with this discussion, I have to confirm the fact that histamine actually does cause a vasoconstriction in reality, when perfused through isolated organs. Dale and Laidlaw, by perfusion of the isolated small intestine and limb of a cat, Barbour, by experiments on the arterial rings of rabbits, cats and dogs, and Kaufmann, by perfusion of the ears of rabbits, all observed the vasoconstrictory effect of histamine.

I have also perfused various organs such as small intestines, kidneys, lungs, and limbs of cats and rabbits with warm oxygenated Ringer's solution or with their own blood serum, diluted about 5–10 times with Ringer's solution and obtained the same results as many previous observers did, viz. vasoconstriction (Fig. 10). The degree of the diminution of the outflow from the venous side by the injection of

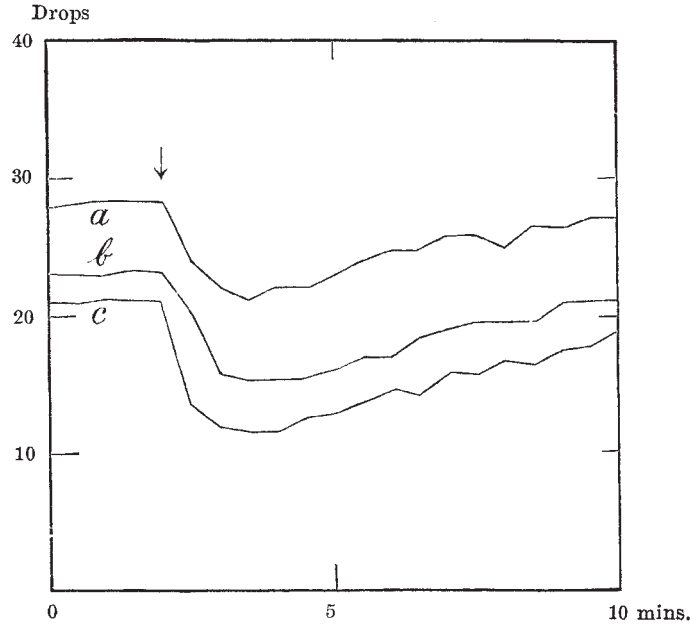

Fig. 10. Graphs of the amount of fluid passing through the vessels of the cat's fore limb (*a*), kidney (*b*) and intestine (*c*) perfused with Ringer's solution.
At the arrow 0·2 mgrm. of histamine into the inflow cannula.

the drug is most remarkable in the lungs, as described above, and the blood vessels of rabbits respond to the drug more vigorously than those of cats.

If it is true, that the blood vessels of cat are supplied by "non-survival vasodilatatory nerves," how feebly they persist in surviving! To preserve the response of the so-called "non-survival vasodilatatory nerves," I have performed an experiment with an artificial heart on a cat, its heart and lungs being excised. Fig. 11 shows the arrangement of the artificial heart.

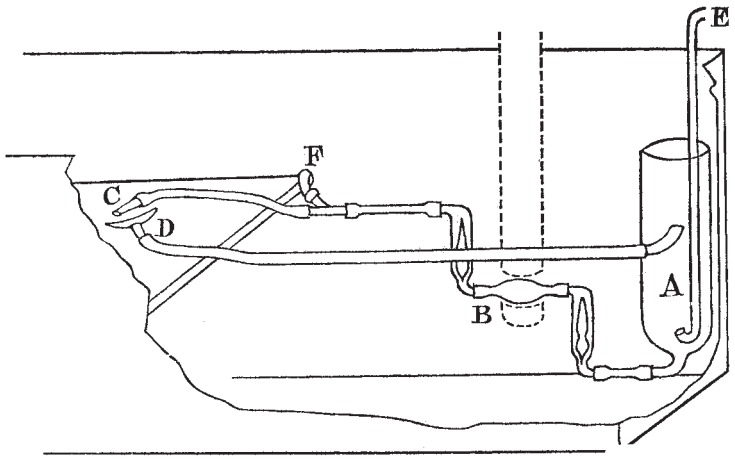

Fig. 11. The arrangement of the artificial circulation.

In this figure, A is a reservoir of blood, its base having a cannula leading with a rubber tube to a rubber ball B, which has a valve on each side and is substituted for the heart, which is rhythmically compressed by means of a motor; the other side of B being connected with a rubber tube to an arterial cannula C, which is to be inserted into the aorta of the animal. D is a T-cannula, to be inserted into the inferior and superior vena cava and connected with a rubber tube on the other side to the side of the blood reservoir A. F is connected with a mercury manometer to measure the pressure in the arterial system.

At the beginning of the experiment the blood reservoir A is to be filled with hirudinized cat's blood and B rhythmically compressed, to fill the system from A to C with the blood. Then a cat is narcotised with urethane and a sufficient dose of hirudine is injected. The breast is opened widely in the middle line and then the cannulae C and D are inserted into the aorta and vena cava inferior and superior respectively. After these arrangements have been completed, the blood pressure is regulated so as to show about the normal height, and histamine is introduced into the reservoir A.

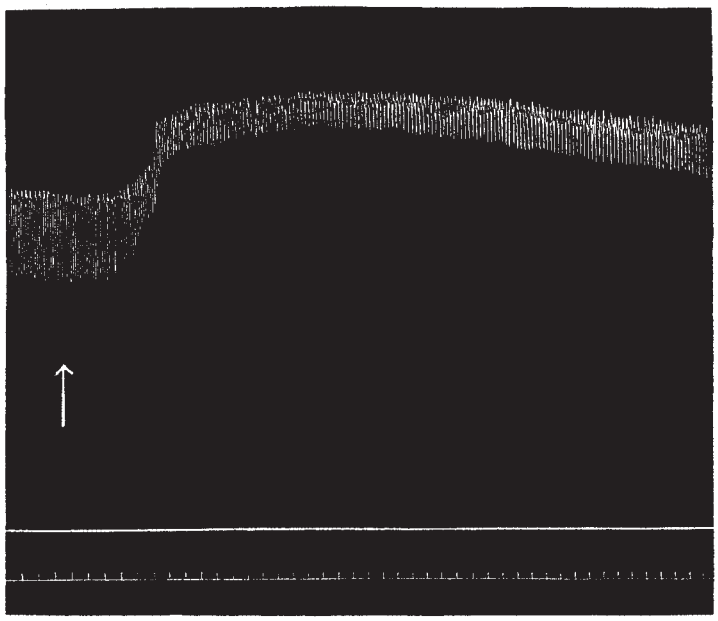

Fig. 12. Cat. Artificial circulation. Arterial blood pressure. At the arrow 2·0 mgrms. of histamine are introduced.

As Fig. 12 shows, the effect of the injection of the drug is always a vasoconstriction. Since this experiment is very simple and the duration from the beginning of the operation to the injection is only about several minutes, and since hirudine does not prevent the fall of the blood pressure, due to the injection of histamine, the so-called "non-survival vasodilatatory nerves," if they exist in reality, must still survive this experiment. And since hirudine does not prevent the liberation of a substance like "vasodilatin,"—for histamine, even when injected into a hirudinized cat, can cause the typical fall of the blood pressure,—histamine must liberate the hypothetical substance in this experiment. All the evidences, however, are against these hypotheses. There is no reason to accept the hypothesis of Dale and Laidlaw or that of Popielski.

By plethysmographic experiments, Dale and Laidlaw have observed the volume of the small intestine undergoing a large expansion, preceded by an initial decrease, after injecting the drug; while the volume of the limb increases and that of the kidney greatly decreases, both changes corresponding to the fall of the blood pressure, and they pointed out from these observations that the fall of the blood pressure is due to vasodilatation in such organs as the small

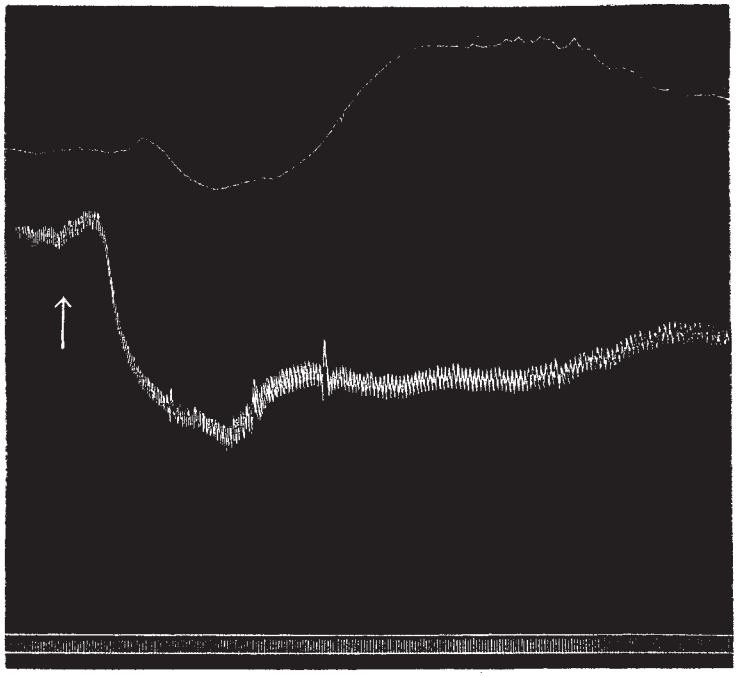

Fig. 13. Cat. A.C.E. mixture. Intestine volume (upper curve) and carotid blood pressure (lower curve).
At the arrow 0·5 mgrm. of histamine into the left jugular vein. Time in seconds.

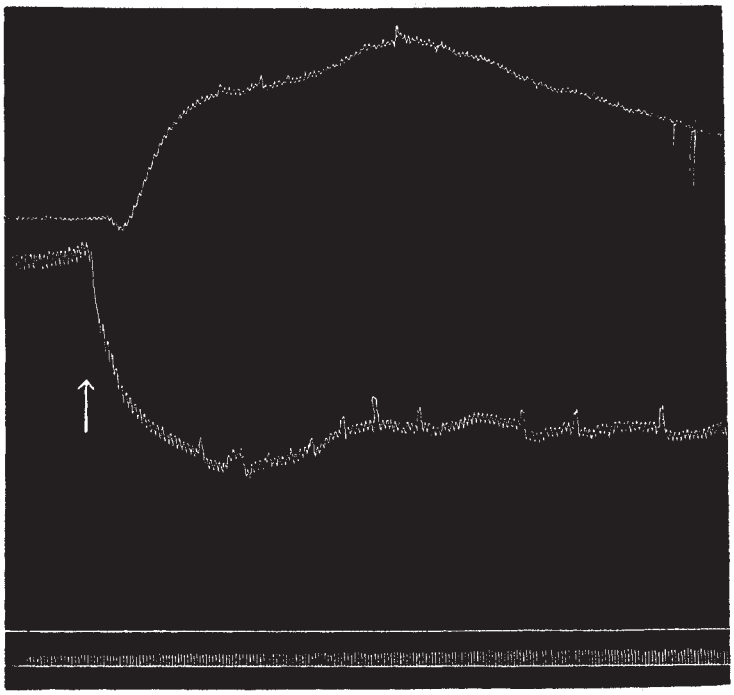

Fig. 14. Cat. A.C.E. mixture. Leg volume (upper curve) and carotid blood pressure (lower curve).
At the arrow 0·5 mgrm. of histamine into the left jugular vein. Time in seconds.

intestine and limb, in which the blood vessels of the kidney do not participate. I can confirm their observations as Fig. 13 and 14 show, but, before accepting their explanation, it must be discussed whether the increase of the volume of the small intestine and limbs is really caused by vasodilatation. For the expansion of these organs is not concerned only with vasodilatation, but also with congestions of the venous system, and the latter, though the arterioles are always a little constricted, can cause an increase of the volume of those organs, as I have mentioned in part I. And it is more probable that the large expansion of the volume of such organs as the small intestine and and limb may be due to congestion of the venous system, since the drug in all other experiments does not cause any dilatation, but on the contrary causes vasoconstriction, and indeed, the inhibition of the pulmonary circulation.

To confirm the truth of this probability, I performed the following experiments. A cat was anaesthetised as usual with A.C.E. mixture, and the arrangements for the measurement of the carotid blood pressure and of the volume of one fore limb were made. After these, hirudine was injected to prevent blood coagulation and then the outflow of the blood from the vena brachialis of the other fore limb, all subcutaneous veins being ligatured, was recorded. When the outflow of venous blood became constant, the drug was injected into the jugular vein. The injection caused the slowing of the rate of the outflow, while the blood pressure fell and the volume of the fore limb increased as usual (Fig. 15). I performed the same experiment on the mesenterial veins, and obtained the same results. It must be noticed, however, that, if the venous anastomoses have not been ligatured, there is sometimes an increase in the outflow of blood from the veins.

There is no doubt that the fall of the arterial blood pressure may cause a retardation of the rate of the venous outflow, but if the cause of the fall in pressure be due to the dilatation of the arterioles, there must be some increase of the rate at least at the beginning of the fall. However, the evidence is contrary to this consideration, and the outflow diminishes. There is, therefore, no escape from the conclusion that histamine has a vasoconstrictory effect, even if injected into the natural circulation, and the enlargement of the volume of such organs as the small intestine and limbs, is due to congestion of the venous system, produced by the inhibition of the pulmonary circulation, and

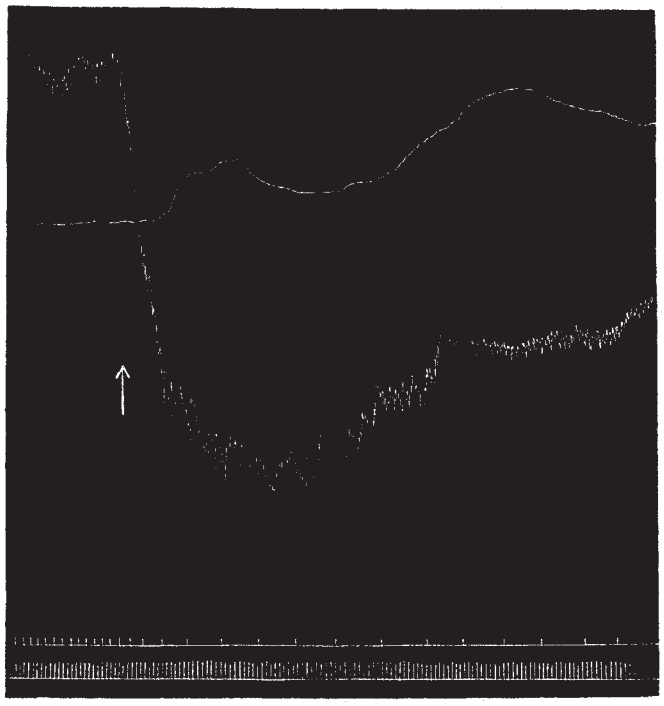

Fig. 15. Cat. A.C.E. mixture. Carotid blood pressure (upper curve), volume of the right fore limb (middle curve) and drops of blood from the vena brachialis (lower line).
At arrow 0·5 mgrm. of histamine into the left jugular vein. Time in seconds.

not to vasodilatation to which it is attributed by Dale and Laidlaw, and the fact, that if the venous anastomoses are not ligatured, the venous outflow increases, confirms my view.

Histamine has always a vasoconstrictory effect, and it makes no difference whether it is injected into the natural or into the artificial circulation. Now it becomes clear, why the drug causes the rise of the blood pressure after the previous fall, especially in the case of such animals as are fully influenced by narcotics or by artificial respiration.

Thus there is no reason to form such a hypothesis as Dale and Laidlaw or Popielski have done, and the explanation of the formers, appears to me to be inconclusive. The explanation of the latter is based on the observations of the formers and not on his own; there is no necessity for further discussion.

(e) Conclusion.

(1) Histamine has a vasoconstrictory effect not only when perfused through isolated organs, but also when injected into the animal intravenously.

(2) Histamine constricts pulmonary vessels on the one hand, and bronchial muscles on the other, both of which cause the inhibition of the pulmonary circulation directly and indirectly, and in consequence of this the output from the left ventricle is reduced and the arterial blood pressure falls. Though the systemic arterioles are constricted by the drug, the constriction is too feeble to prevent the pressure fall, caused by the inhibition of the pulmonary circulation. If the two causes of that inhibition appear successively, the fall of the arterial blood pressure occurs in two stages, a preliminary and a secondary fall. The inhibition of the pulmonary circulation causes, on the other hand, a considerable rise of the blood pressure in the pulmonary artery, the right ventricle and the venous system, and the venous congestion developes the volume of such organs as the small intestine and limbs which undergo a large expansion.

(3) Various anaesthetics, such as urethane or chloroform, and artificial respiration are able somewhat to restrict the fall of the blood pressure, caused by histamine, for they can depress the response of the bronchial muscles to the drug pharmacologically and physically respectively.

(4) There is no evidence that vasodilatation is caused by histamine. The arguments of Dale and Laidlaw are due to the inconclusiveness of their observations. Accordingly the hypothesis of Popielski that the liberation of some substance like vasodilatin occurs, is groundless, for his arguments are based entirely on the observations of Dale and Laidlaw.

(5) The effect of histamine on the blood pressure does not vary in character in the different species of the animals, and in the case of rabbits the same results can be obtained as in that of cats. However it must be noticed that the influences of anaesthetics and artificial respiration upon the fall of the blood pressure caused by histamine is more marked in rabbits than in cats, and this is the only difference between the response in each case to the intravenous injection of the drug. The rise of the pressure in rabbits observed by Dale and Laidlaw, is due to the strong influence of urethane.

2. The cause of the pressure fall, due to peptone.

Since Schmidt and Mühlheim[24], and Fano[25] discovered that peptone, introduced intravenously into the dog, causes a considerable fall of the blood pressure. The cause of this pressure fall has been the subject of much investigation and discussion. Schmidt and Mühlheim, Fano and Pollitzer[26] noticed that after the injection of peptone the intestines were highly congested, and state their belief that the fall of the blood pressure is chiefly, if not wholly, due to dilatation of the blood vessels of the splanchnic region. Grosjean[27] also attributed the fall of the blood pressure to this cause. He raised the further question as to how the vascular dilatation is brought about, and expressed his belief that the chief cause is that peptone affects the respiratory and cardio-inhibitory centres, the two bulbous mechanisms being situated close to the vasomotor centre. No experiments were, however, performed by him to decide this point. Thompson[28], having proved experimentally that the fall of this blood pressure can be produced by peptone after dividing the spinal cord and splanchnics, attributed the fall to the loss of "vasomobility," caused by a direct or peripheral action of peptone and shown by failure of the normal constrictory response to stimulation of the splanchnic nerves. After him, Hamburger[41], Popielski[29], Biedl and Kraus[35] also ascribed the fall caused by peptone to the paralysis of the splanchnics.

More recently, however, Dale and Laidlaw[4] expressed their belief that peptone also stimulates their so-called "non-survival vasodilatatory nerves," for the reason that the fall of the blood pressure caused by peptone resembles that caused by histamine. But as above mentioned, I have proved that histamine causes the fall in pressure by its inhibitory influence on the pulmonary circulation, notwithstanding that it has a vasoconstrictory effect on the peripheral blood vessels. So I have supposed that if the effect of peptone on the blood pressure and blood vessels resembles that of histamine, peptone may also cause inhibition of the pulmonary circulation. But referring to my supposition many writers report the failure of the normal constrictory response to stimulation of the splanchnic nerves. I have therefore endeavoured radically to investigate the cause of the fall of the blood pressure due to peptone.

(a) Effects on the arterial blood pressure.

According to previous observers, cats and dogs respond to the intravenous injection of peptone with a considerable fall of the blood pressure, while rabbits and guinea pigs do not. For this reason I used first a cat, to investigate the effects, and then, a rabbit. Peptone, prepared by Friedrich Witte of Rostock, was dissolved in Ringer's solution in each experiment.

1. *The cat.* As usual, the animal was anaesthetised with A.C.E. mixture, and the blood pressure was measured in the carotid artery by a mercury manometer. As previous observers have detailed, when 0·2–0·4 grm. peptone is injected into the jugular vein, the blood pressure falls considerably, and after several minutes it comes back gradually to its original height, and after recovery it rises still higher, but only slightly and for a short while. The fall of the pressure can be observed to occur in two stages, a preliminary fall, succeeded by a more considerable secondary fall (Fig. 16). With dose of 1·0 grm. of peptone the secondary fall is more marked in degree and duration, but recovers finally.

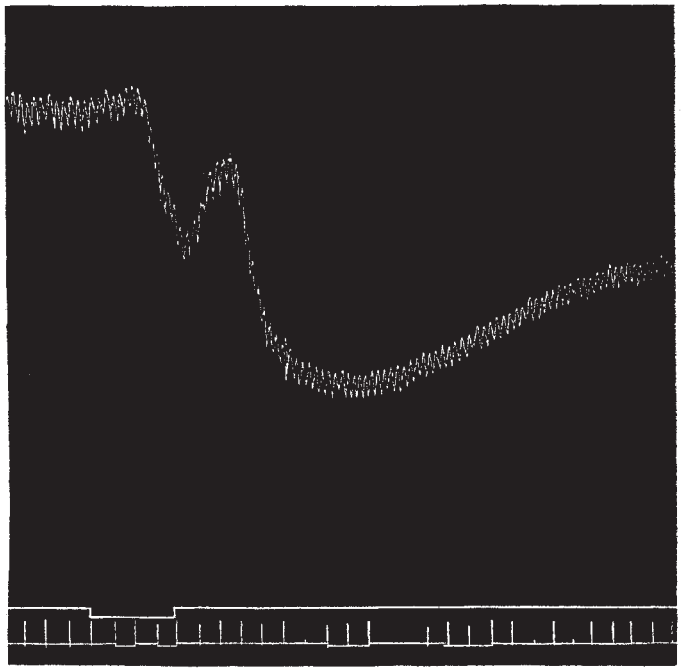

Fig. 16. Cat. A.C.E. mixture. Carotid blood pressure.
At signal 0·2 grm. of peptone into the left jugular vein. Time in 5 seconds.

The effect of peptone on the blood pressure is also restrained by anaesthetics and by artificial respiration. If the animal was fully under the influences of urethane (1·5 grms. per Kilo) or chloroform, and artificial respiration was maintained for a long time (about an hour) 0·2–0·4 grm. peptone does not cause the usual fall of the blood pressure and even with does of 0·5–1·0 grm. the blood pressure falls slightly or rises slightly without the typical fall (Fig. 17).

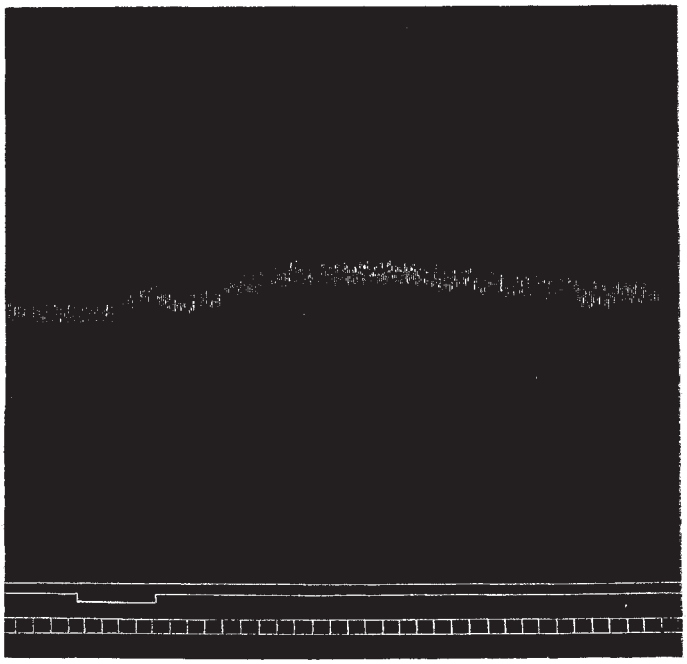

Fig. 17. Cat. Urethane. Carotid blood pressure.
At signal 0·2 grm. of peptone into the left jugular vein. Time in 5 seconds.

2. *The rabbit.* Considering the possibility, that in the case of rabbits, as in that of cats, the effect of peptone on the blood pressure may be also restrained by anaesthetics and artificial respiration, a rabbit in a state of slight anaesthesia with A.C.E. mixture and without artificial respiration is injected intravenously with 1·0 grm. peptone. Then it responds to the injection of the drug with the same considerable fall of the blood pressure as the cat does (Fig. 18).

On the other hand, under the full influence of the narcotics, urethane or chloroform, and with artificial respiration, the same doses of peptone, as above detailed, cause only a slight fall of the pressure, if any, or some times a slight rise (Fig. 19).

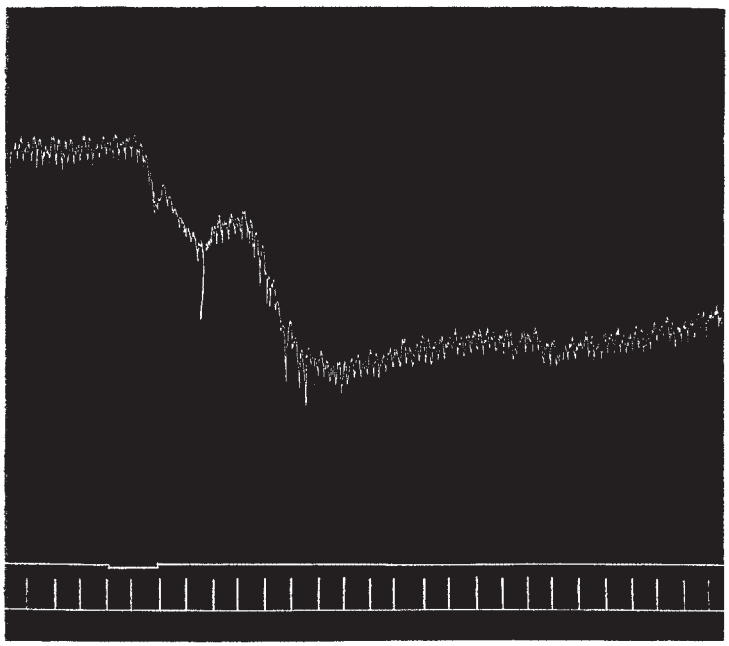

Fig. 18. Rabbit. A.C.E. mixture. Carotid blood pressure.
At signal 0·5 grm. of peptone into the left jugular vein. Time in 5 seconds.

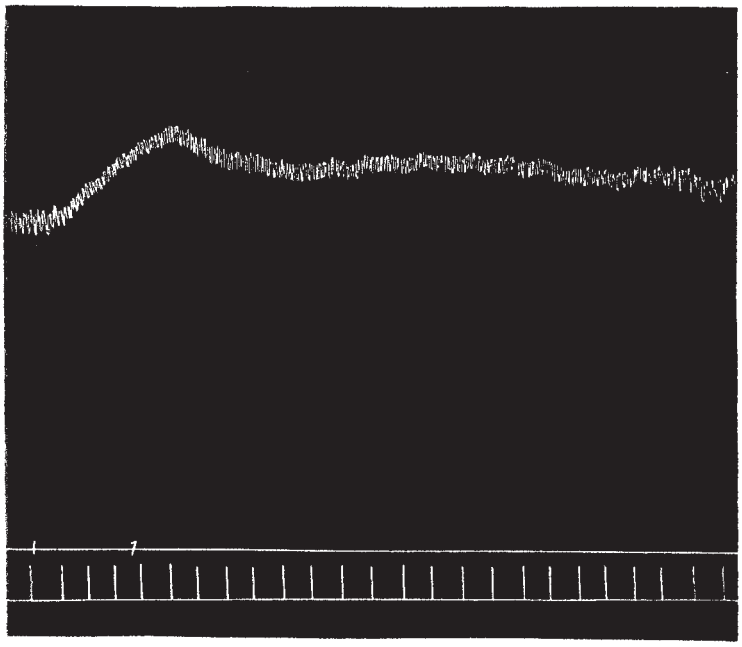

Fig. 19. Rabbit. A.C.E. mixture. Carotid blood presure.
At signal 0·5 grm. of peptone into the left jugular vein. Time in 5 seconds.

From these experimental results, we see that both the cat and the rabbit respond to the injection of peptone with a considerable fall of the blood pressure, and their response is restrained by anaesthetics or artificial respiration, especially in the case of the rabbit. To conclude that the rabbit does not respond to the injection of peptone with the pressure fall, while the cat does so, seems to be due to lack of observation on the part of the previous observers.

(b) The effects on the heart.

1. *The heart of the frog.* Popielski[29] pointed out that peptone increases both the rate and force of the beat of the heart, while Friedberger and Mita[30] observed that the excised frog's heart is inhibited and arrested by peptone.

I have also perfused the excised heart of a Rana esculenta using an apparatus inducing artificial circulation with Ringer's solution. If small doses of peptone (0·01–0·05 grm.) are added, both the rate and the force of the beat of the heart are increased and the drops from an arterial cannula are more in number. With doses of 0·1 grm. or more of the drug, the rate and the force of the beat increase for a short while, but soon the heart beat decreases in rate and is then arrested. Finally the heart stands still in the diastolic period. It may perhaps be due to the effect of large does of the drug that Friedberger and Mita have observed an inhibitory effect of it upon the frog's heart.

1. *The heart of the cat and of the rabbit.* Popielski stated that in the excised heart of a cat both the rate and force of the beat are increased by the drug. Yoshimura[31] observed that the drug has a beneficial effect upon the heart's activity in the dog. Yanagawa[32] observed that the drug causes the heart of the rabbit to decrease in rate but increase in the force of the beat. According to Pissemsky[33] the excised mammalian heart is weakened by concentrations of 1:1000 to 1:10000; stimulated by 1:200.

I have also perfused excised hearts of cats and rabbits, first with warm (37°C) oxygenated Ringer's solution for 10–15 minutes, and then substituted for the perfusion fluid a 5·0 per cent peptone solution in Ringer's at the same pressure and temperature. The results of my experiments are as follows:—

When the duration of the substitution is short, the rate and force of the beat increase, but if it is long, the rate becomes slower, and

finally the heart stands still in the diastolic phase. If the solution of the drug is more diluted, it has a merely good effect on the heart's activity, and if still more diluted, viz. 0·005 per cent, the effect is hardly observed at all.

These experimental results show that peptone in moderate doses has a good influence upon the heart's activity and does not inhibit the heart, unless very large doses are used. Pearce and Eisenbrey[34], after observing the heart's activity during the pressure fall after injecting peptone, stated their belief that the pressure fall caused by this drug is not due to its effect on the heart's activity. For the above reasons this view is, in my opinion, correct.

(c) The effect on the pulmonary circulation.

What effect has peptone on the pulmonary circulation? Though it is necessary to know it's effect, in order to decide the cause of the pressure fall due to peptone, there is no one who has experimented on it. I have performed the following experiments, to observe the effects of the drug on the pulmonary circulation and the pulmonary vessels. The method of these observations is the same as that used in the case of histamine. As Fig. 20 shows, the pulmonary pressure rises

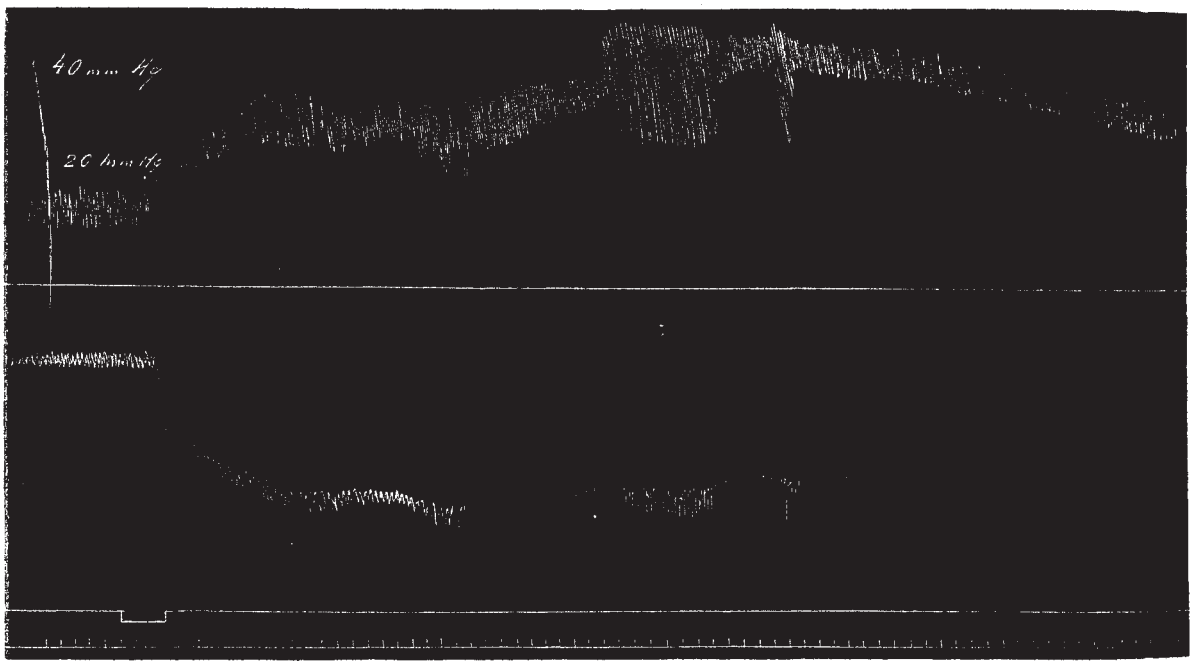

Fig. 20. Cat. 1 A.C.E. mixture. Artificial respiration. Pulmonary blood pressure (upper curve) and carotid blood pressure (lower curve). At signal 0·4 grm. of peptone into the left jugular vein. Time in 5 seconds.

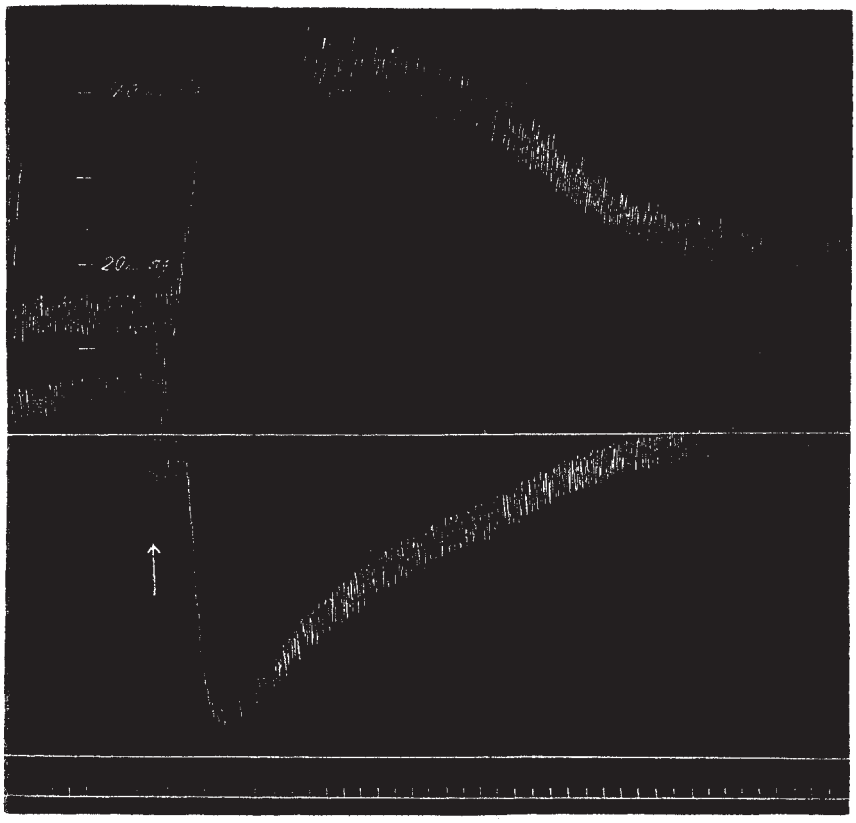

Fig. 21. Cat. Hering's heart-lung-coronal circulation. Pulmonary (upper curve) and carotid blood pressure (lower curve).
At signal 1·0 grm. of peptone into the left jugular vein. Time in 5 seconds.

considerably after the injection of the drug, preceding the fall of the systemic pressure by about 2 or 3 seconds, and the rise of the pulmonary pressure is observed to occur always in two stages, a preliminary and then a secondary, and a more prolonged rise. Further the rise of the pulmonary pressure and the fall of the systemic pressure can be seen even with Hering's heart-lung-coronal circulation, as Fig. 21 shows. But in this case larger doses of the drug must be used for injection, for in such cases the breast must be opened and artificial respiration maintained a long time.

From these results it follows that the cause of the fall of the arterial blood pressure due to peptone must be searched for in its effects either on the heart or on the pulmonary circulation or on both. But since it has been already pointed out that the drug does not

inhibit the heart's activity, the fall of the blood pressure must be due to its inhibitory effect on the pulmonary circulation.

Now I have perfused the excised lungs (left under lobe) of cats and rabbits with warm (38°C) oxygenated Ringer's solution. The drops of the perfusion fluid from the pulmonary vein decrease considerably after injecting 0·2 grm. peptone, which is dissolved in the same solution. The drop-record shows sometimes the two stages, the preliminary and the secondary diminution of the perfusion fluid (Fig. 22). There is, therefore, no room for doubt that the cause of the rise of the pulmonary pressure and accordingly the fall of the systemic blood pressure caused by the drug are due to this inhibitory effect upon the pulmonary circulation.

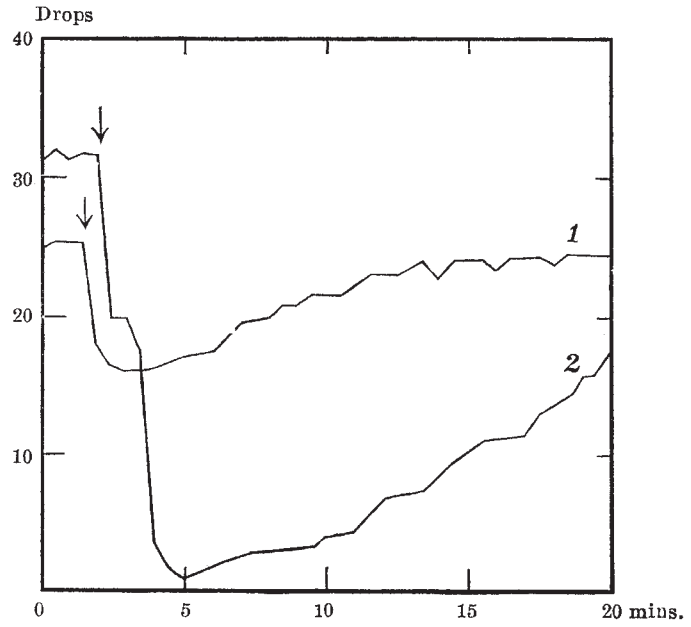

Fig. 22. Graphs of the amount of fluid passing through the vessels of the cat's intestine (1) and left under lung-lobe (2) with Ringer's solution.
At arrow 0·2 grm. of peptone into the inflow cannula.

Then what is the cause of the inhibition of the pulmonary circulation due to the drug? It has been already pointed out by many previous observers that the dyspnoea of the animal after the injection of peptone is due to its broncho-constrictory effect, peripheral in origin. The inhibition of the pulmonary circulation also may be perhaps due to this broncho-constrictory effect, for the reason that constriction of the

bronchial muscles causes indirectly the reduction of the calibre of the pulmonary vessels (see the paragraph on histamine). Though it was not ascertained whether the drug has a direct vasoconstrictory effect upon the pulmonary vessels or not, I suppose that it may perhaps constrict them, because it has a vasoconstrictory effect upon other vessels as will be shown in what follows, and this direct vasoconstrictory effect of the drug upon the pulmonary vessels may also be connected to some extent with its inhibitory effect on the pulmonary circulation. And if these two inhibitory effects of the drug upon the pulmonary circulation appear separately in time relation, the rise of the pulmonary pressure and consequently the fall of the systemic blood pressure may occur in two stages.

It will be decided in the following paragraph, how the systemic circulation or the systemic vessels participate in the fall of the blood pressure caused by peptone.

(d) Effects on the systemic blood vessels.

Up to the present, it was considered by all previous writers that peptone dilates the systemic vessels and in consequence of this, the arterial blood pressure may fall after the intravenous injection of the drug.

Popielski[29], and Biedl and Kraus[35] attributed this supposed vasodilatatory action of the drug to the effect of their hypothetical "vasodilatin" contained in it. However, peptone, when perfused into isolated organs, does not cause vasodilatation, but on the contrary, vasoconstriction. To explain this apparent discrepancy, Dale and Laidlaw[4] have ascribed the effect of the drug to the same mechanism as that of histamine, viz., to its stimulant effect on their hypothetical "non-survival vasodilatatory nerves."

Before criticising their hypothesis, the statement, that the drug has in reality a vasoconstrictory effect when perfused into isolated organs, must be confirmed.

(1) *The frog's blood vessels.* After perfusing the frog's (Rana esculenta) blood vessels by Läwen-Trendelenburg's method, I recorded the rate of the drops from the vein cannula. The drops decreased slightly but distinctly on the injection of peptone 0·05–0·1 grm. These results agree with those of Hirschfeld and Modracowski[37]. According to Handovsky and Pick[36] peptone dilates the frog's blood vessels, which are already constricted by adrenine,

but in their protocol there is no evidence that the drug causes vasodilatation, since the blood vessels, which are already constricted by adrenine, respond with vasodilatation even on the exchange of the poison with Ringer's solution.

(2) *The blood vessels of cats and rabbits.* I have perfused many organs of cats and rabbits, such as the limb, small intestine and kidney, by the method described in Part I. All the drop records show vasoconstriction after injecting 0·1 grm. peptone, which was dissolved in the same solution as the perfusion fluid. These results agree with Dale and Laidlaw's, Kaufmann's[38] and Lönning's[39], and the vasoconstriction is the main effect of the drug upon isolated blood vessels.

Having supposed, as some writers did, that there may be some conditions in the body, which are necessary to the vasodilatatory effect of the drug, if it should really cause vasodilatation when injected intravenously, I have also performed the experiment with an artificial heart, as is already shown, to decide this question. But I could not observe any fall of the pressure after the injection of peptone, but on the contrary, always a rise as Fig. 23 shows.

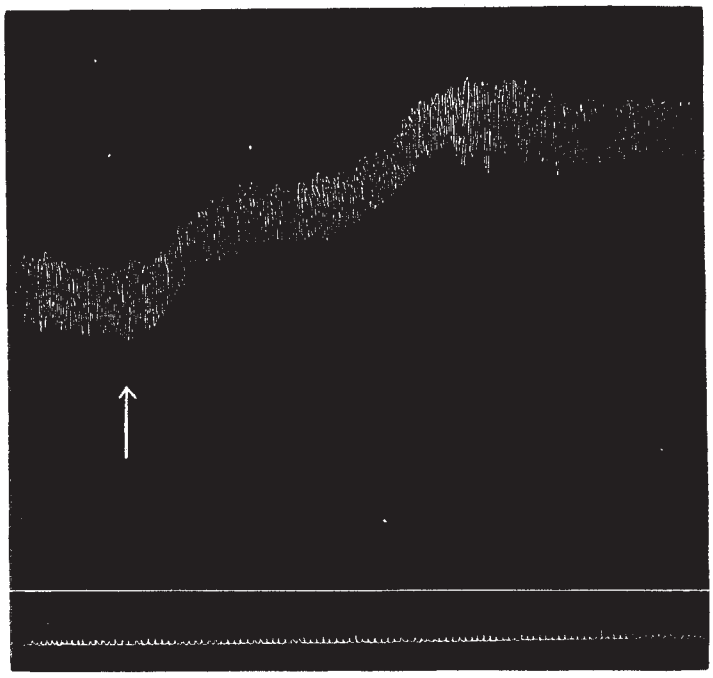

Fig. 23. Cat. Artificial circulation. Arterial blood pressure.
At arrow 2·0 grms. of peptone are introduced. Time in seconds.

Further, I have counted the number of drops of blood from the right brachial vein, while the volume of the other fore limb and the carotid blood pressure were measured. But I could not see any increase of the number of drops on the injection of peptone, but on the contrary, always a remarkable decrease of it, notwithstanding that the fall of the blood pressure and the large expansion of the limb occurred as usual. There is no evidence that peptone dilates the blood vessels in the body and all the evidence is, therefore, definitely opposed to such an explanation as that of previous observers that the fall of the blood pressure, caused by the intravenous injection of peptone, may be due to a vasodilatatory effect of it. Peptone has always a vasoconstrictory effect and it does not matter whether the blood vessels are in a condition of natural circulation or of artificial perfusion.

According to Heidenhain[2] he could not observe the usual fall of the blood pressure by injecting such doses of peptone, sufficient to cause the fall if given intravenously, into the aorta from the carotid artery. This fact confirms also the vasoconstrictory effect of peptone.

Now I will criticize the explanations of many previous observers regarding the cause of the pressure fall due to peptone.

Schmidt and Mühlheim, and Fano and Pollitzer having observed the congestion of the small intestine after injection of the drug, state their belief that the fall of the pressure is chiefly due to vasodilatation of the blood vessels of the splanchnic region. However it must be noticed that the congestion can be also caused by the inhibition of the pulmonary circulation. Their reason is so feeble that further argument is not necessary.

Thompson, having observed after injecting the drug the increase of the volume of the liver, small intestine and limbs, states that these volume changes are due to vasodilatation. But it is not correct to attribute the expansion of the volume of such organs to vasodilatation, without examining another possible cause, for as I have already described the inhibition of the pulmonary circulation can also cause a large expansion of such organs. It is too hasty to ascribe the expansion of such organs to vasodilatation. Much more is this the case with such a substance as peptone, which causes a considerable inhibition of the pulmonary circulation. Even in his reports the course of the volume changes resemble that which is caused by inhibition ef the pulmonary circulation.

Thompson, and Camus and Grey[40] and more recently Popiel-

Fig. 24. Cat. A.C.E. mixture. Artificial respiration. Carotid blood pressure.
At signals splanchnic nerve was stimulated; coil distance 10 cms. Time in 5 seconds.

ski[29] have attributed the fall of the blood pressure, caused by peptone, to vasodilatation, due to paralysis of the endings of the splanchnic nerves, since after injection of the drug, they could not observe any usual rise of the blood pressure caused by the stimulation of the nerves. Their conclusion is, however, correct only in such cases, as those where the stimulus of the splanchnics has no effect on the blood pressure, when the blood vessels are full of blood. But in their experiments, there is no evidence, that the blood vessels contained sufficient blood. And even if any other cause but systemic vasodilatation, e.g. the inhibition of the pulmonary circulation, should cause the fall of the blood pressure, one can not expect the distinct vasoconstrictory response of the blood vessels to electrical stimulus of the vasoconstrictory nerves, as in normal cases, even though their activity is not inhibited. In the experiment on an animal bled from the carotid artery with the blood pressure falling in nearly the same way as the fall of the blood pressure caused by obstruction of the pulmonary vessels, I observed the effect of the stimulus of the splanchnic nerves at various heights of the blood pressure. As Fig. 24 shows, the effect of the stimulus is proportionate to the height of the blood pressure and when that falls extremely,—to 30–40 mm. Hg,—the change of pressure caused by the stimulus is hardly observed, but at this time, there is of course no paralysis of the splanchnics. When the blood pressure rises gradually by injecting Ringer's solution into the jugular vein, with the rise of blood pressure, a proportionate

response to the stimulus appears.

From these experimental results we can draw the conclusion that the activity of the splanchnics is maintained, when the stimulus causes a normal vasoconstrictory effect on the blood pressure, but on the other hand it is not right to consider that the vasomobility is lost, when there is no normal vasoconstrictory response to stimulation of the splanchnic nerves. I can not therefore approve of such an explanation as Thompson, Camus and Grey, and Popielski give.

Experiments by Hamburger[41] appear to show that post-ganglionic degeneration of the sympathetic nerve abolishes the vasodilatatory effect of peptone. However that may be, the facts available appear only to indicate that, as Meltzer[42] demonstrated, the vasoconstrictory action of adrenine on the blood vessels, whose vasoconstrictory nerves had degenerated, appears more distinctly than on the normal blood vessels.

By the following experiments I can prove that the drug does not inhibit the activity of the splanchnic nerves.

The excised small intestine of a cat was perfused as usual and the drug injected into the inflow cannula, and when the blood vessels were constricted, the splanchnic nerves were stimulated. Then the blood vessels responded to the stimulus with more distinct vasoconstriction. Further I have found by experiment that the blood vessels of the excised small intestine, after perfusion with 1·5 per cent peptone solution for about 2 hours, can still respond to the stimulation of the splanchnic nerves by vasoconstriction.

All the evidences are, therefore, opposed to the explanation that peptone paralyses the splanchnic nerves or "vasomobility."

There are many investigators, who have attributed the cause of the pressure fall due to peptone to peripheral vasodilatation, since various vasoconstrictory drugs, such as adrenine (Hamburger and Popielski), strychnine (Camus and Grey), barium chloride (Popielski, and Biedl and Kraus), can prevent the pressure fall caused by peptone. However, by their experiments it has been only proved that such vasoconstrictory drugs can cause the rise of the blood pressure and there is no evidence that peptone causes vasodilatation.

Since such drugs as adrenine (Januschke and Pollak[17], Trendelenburg[22]) and strychnine (Trendelenburg), especially relax the bronchial muscles, which are constricted by peptone, so they can prevent the pressure fall due to peptone not only by their more

considerable vasoconstrictory action, but also by the relaxing action on the bronchial muscles.

Pearce and Eisenbrey[35] could not observe the large expansion of the volume of the small intestine during the pressure fall after injecting peptone and attributed the fall of the blood pressure to its inhibitory effect on the liver circulation by a remarkable constriction of the liver vessels. If their conclusion, however, is a true one, the arterial blood pressure must rise in consequence of obstruction of the portal vein, as Bayliss and Starling found by experiment.

In short, all the explanation, given by many investigators that peptone has a vasodilatatory effect, if injected intravenously, are based on imperfect observation. There is, however, no evidence that can prove the vasodilatatory effect of peptone. On the contrary all the evidences show vasoconstrictory action of the drug, though injected intravenously, or perfused into organs exised. Consequently there is no reason to accept the hypothesis which asserts the existence of the "non-survival vasodilatatory nerves" and the so-called "vasodilatin."

(e) Conclusion.

(1) Peptone always has a constrictory effect upon the blood vessels, and it does not matter whether it is applied under natural or under artificial circulation.

(2) The cause of the fall of the arterial blood pressure due to peptone resembles that caused by histamine, and there is no foundamental difference between them. The drug constricts the pulmonary vessels on the one hand and the bronchial muscles on the other, and in consequence of this the pulmonary circulation is so inhibited directly or indirectly by the drug, that the arterial blood pressure falls. Though the peripheral arterioles are slightly constricted by peptone, it is too weak to prevent the fall of the blood pressure caused by the inhibition of the pulmonary circulation. The large expansion of the volume of such organs as the small intestine, limb, and liver is due to congestion caused by the inhibition of the pulmonary circulation.

(3) The effect of peptone on the blood pressure can be arrested by artificial respiration and by some drugs such as those anaesthetics, which prevent the constriction of the bronchial muscles mechanically or pharmacologically.

(4) These effects can be observed not only in cats but also in

rabbits, although, according to previous investigators, the latter do not respond to the intravenous injection of peptone with the fall of the blood pressure. But the influences of artificial respiration and anaesthetics upon the effects of peptone are much more marked in rabbits than in cats.

3. The cause of the pressure fall, due to organ extracts and blood serums.

Many investigators have examined the effects of organ extracts and blood serums on the animal. And though they all agree in their opinion to the extent that these substances, if injected intravenously, cause a symptom complex, such as dyspnoea and considerable fall of the blood pressure, they differ in their opinions about the cause of the pressure fall.

(a) Organ extracts.

Dixon[43], having used orchitic extract, and Halliburton[44], nerve tissue extract, attribute the cause of the pressure fall, due to them, to their inhibitory effect on the heart. However according to Hedbom[45], Cleghorn[46], Popielski[47] etc. the activity of the heart is not inhibited by such doses of any organ extracts, as can cause the fall of the blood pressure, when injected intravenously, but is inhibited with large doses of them.

Leichtenstein[48] has stated his belief that organ extracts may obstruct the pulmonary vessels mechanically and in consequence of this the blood pressure may fall. But his hypothesis has been denied by Foa and Pellacani[49], Dold and Ogata[50], and more recently by Goto[51].

Dold and Ogata, Yoshimura[52], Ichikawa[53] etc. have attributed the cause of the fall of the blood pressure due to organ extracts to formation of thrombosis in the pulmonary vessels, for they have found by experiment that the blood coagulability is quickened after injecting organ extracts, and moreover that in the section of the animal, poisoned by organ extracts, they have often observed thrombosis in the pulmonary vessels. However there is no one who has clearly demonstrated the relation between the cause of the pressure fall and the formation of thrombosis in the pulmonary vessels. Though often found, thrombosis is not so constant as to be always found in

the section of such animals. For these reasons their conclusion is not yet generally accepted.

Besides these, there is a still another probable hypothesis that the cause of the fall of the arterial blood pressure may be due to the peripheral vasodilatatory effect of organ extracts, and according to Popielski[47], Modrakowski[57], Studzinski[58] etc. the vasodilatation is caused by their hypothetical "vasodilatin" contained in organ extracts, which is not specific to each organ.

However, according to Oliver, Dixon[43], Farini and Vidoni[55], Kaufmann[56], Yoshimura, Ichikawa etc. many organ extracts, when perfused into isolated organs, cause vasoconstriction.

Dale and Laidlaw[59], having regarded this apparent discrepancy between the effects of organ extracts under the conditions of natural circulation and artificial perfusion as being a real one, appear to attribute the cause of the pressure fall also to their stimulating effect on their hypothetical "non-survival vasodilatatory nerves" and moreover, Dale and Barger, having proved that the pressure fall caused by the extract of the small intestine is due to the histamine contained in it, stated their belief that the hypothetical "vasodilatin" contains histamine.

I don't know whether, as Popielski etc. assert, all the substances in many organ extracts, which cause a fall of the blood pressure, are the same or not, and accordingly it cannot be rashly decided as Dale and Laidlaw stated, that "vasodilatin" contains histamine. But it is a fact that the effect of many organ extracts not only resemble one another, but also those of histamine and peptone, which I have investigated. It can be therefore easily understood that the fall of the blood pressure, caused by the extract of the small intestine, may be due to its inhibitory effect on the pulmonary circulation, since Dale and Barger have pointed out that the substance, which causes a pressure fall in the extract of the small intestine, is histamine. For this reason I have supposed that the pressure fall, caused by many other organ extracts, may be also due to their inhibitory effect on the pulmonary circulation.

Now I have to investigate further the cause of the pressure fall, due to organ extracts other than that of the small intestine, suspecting that the discovery of the main cause of the pressure fall due to a few organ extracts may contribute not a little to demonstrating the effects of other organ extracts, which resemble each other in this respect.

For this purpose I have prefered the extract of lungs, which was prepared by the following method.

The freshly excised lungs of a rabbit were cut fine, added with a double volume of Ringer's solution, stirred for about ten minutes and then filtered through cotton wool. The filtrate was centrifugated and thus a clear extract of lungs was obtained.

The animals which I used in these experiments were cats and rabbits, anaesthetised with A.C.E. mixture, and I measured the carotid and the pulmonary blood pressure by such a method as that described in the foregoing.

If 0·5 c.c. of the extract is injected intravenously, the pulmonary pressure rises considerably, amounting to 30–40 mm. Hg, or still more at the maximum, and then the carotid blood pressure falls about 2–3 seconds later, after the beginning of the rise of the pulmonary blood pressure. And as the pulmonary blood pressure returns to its original height, the fall of the carotid blood pressure returns to its normal height, but at the moment of this recovery the systemic blood pressure is higher than the original height (Fig. 25). The rise of the pulmonary blood pressure and the fall of the systemic blood pressure

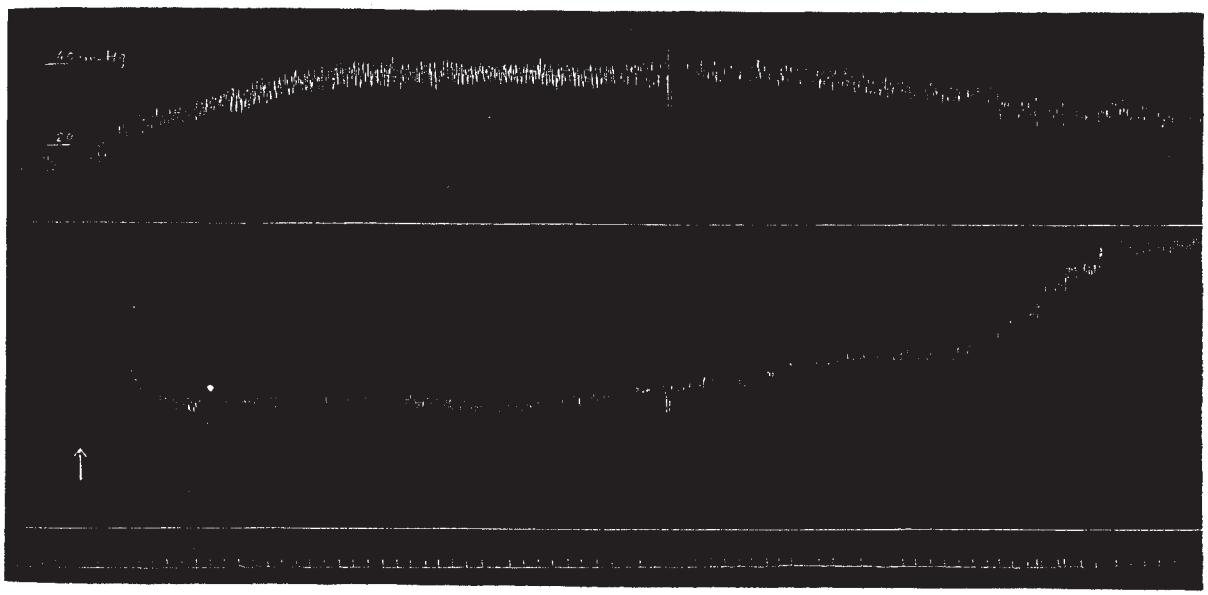

Fig. 25. Cat. A.C.E. mixture. Artificial respiration. Pulmonary (upper curve) and carotid blood pressure (lower curve).
At signal 0·25 c.c. of lung extract into the left jugular vein. Time in 5 seconds.

can be sometimes observed to occur in two stages, the preliminary rise or fall being succeeded by a more prolonged secondary rise or fall respectively.

The same changes of the pulmonary and systemic blood pressure caused by the extract can be also observed in the experiments with Hering's heart-lung-coronal circulation.

The effect of the extract on the blood pressure is also arrested, though but slightly, by anaesthetics such as urethane and chloroform and by artificial respiration, especially in the case of rabbits. Into a rabbit, anaesthetised with 1·5–2·0 grms. of urethane, respiration being maintained artificially for about an hour, 0·2 c.c. of the extract was injected intravenously. The blood pressure of this animal did not fall as usual, but on the contrary rose slightly, and the rise of the pulmonary blood pressure was also but slighter than usual, notwithstanding the fact that 0·2 c.c., if injected into the normal animal, caused a usual fall and rise of the pulmonary and carotid blood pressure. It may perhaps be due to this fact that previously Goto on inspecting the extract could not observe any change of the blood pressure in the right ventricle.

From my experimental results it seems as if the fall of the systemic blood pressure has an intimate relation to the rise of the pulmonary blood pressure. Then to what cause may the rise of the pulmonary blood pressure be due? I must look for the cause of it in the effect of the extract on the heart or on the pulmonary circulation.

(1) *The heart of cats and of rabbits.* Dealing first with the heart of a cat, which is excised and perfused with Ringer's solution (37° and oxygenated). Though large doses of the extract inhibit the heart's activity and cause a diastolic arrest, with moderate doses of the extract, such as used in the experiments and cause a fall of the blood pressure, the heart increases in rate and force of the beat. The results of the experiment with the heart of the rabbit are almost similar to that in the case of the cat.

It can be easily understood that the fall may not be due to the inhibitory effect of the extract on the heart, for the heart's arrest can not cause a considerable rise of the pulmonary blood pressure. And the cause of the pressure fall must be looked for in the effect of the extract on the pulmonary circulation.

(2) *The pulmonary circulation.* To investigate the effect of the extract on the pulmonary circulation, I have performed the perfusion

experiment with the excised lungs of cats and rabbits, the method of which has been already described. The results of these experiments are that if 0·1–0·2 c.c. of the extract is injected into the inflowing cannula, the drops from the pulmonary vein diminish considerably. The degree of this diminution of the outflow is so considerable as not to be compared with that caused by perfusion of other organs, such as the small intestine and limbs.

From these experimental results we see that the extract of the lung of a rabbit has a marked inhibitory effect on the pulmonary circulation.

And this considerable inhibitory action on the pulmonary circulation can be also observed in a section of the animal which has been poisoned by the extract.

There is, therefore, no doubt, that the considerable rise of the pulmonary pressure is due to this inhibitory effect.

Then, how does the extract cause the pulmonary inhibition? Is it due only to the constriction of the pulmonary vessels or to another action?

The extract may somewhat constrict the pulmonary vessels, for it causes constriction of all other vessels, and moreover, it can constrict bronchial muscles as many previous investigators observed. By these two effects the extract inhibits directly and indirectly the pulmonary circulation (see the paragraph on histamine). There is no doubt that the extract of the lung of a rabbit causes an inhibition of the pulmonary circulation, by which, when it is injected intravenously, the pulmonary pressure rises and the systemic blood pressure falls.

Then it must be decided, how the peripheral blood vessels behave themselves during the fall of the systemic blood pressure, due to the extract: Are they constricted or dilated?

(3) *The systemic circulation.* I perfused the excised small intestine and limb of a cat and a rabbit by the method as already described. The result of these experiments was that all the blood vessels of perfused organs responded to the extract (0·05–0·1 c.c.) with constriction. Besides these, I also observed the rise of the pressure after the experiment of injecting the extract in connection with the the artificial heart (see foregoing).

There is, therefore, no evidence of vasodilatation, caused by the extract, but on the contrary all the blood vessels are constricted by the extract.

In spite of the explanations of many previous investigators, who have ascribed the cause of the fall of the blood pressure due to organ extracts to vasodilatation of the peripheral blood vessels, there is no proof that organ extracts cause vasodilatation, when injected intravenously into the living animal. Bayliss and Starling[60], Oliver and Schäfer[61], Dixon[43], Halliburton[44], Osborne and Vincent[62], Vincent and Sheen[63] etc. having observed during the pressure fall the large expansion of such organs as the small intestine and limbs, attributed the changes of organ volume to vasodilatation in these organs, without considering other possible causes. But their explanation cannot always be correct, as I have already described in the foregoing. Much more is this the case with such a substance as organ extracts, which cause a considerable inhibition of the pulmonary circulation.

Popielski has attributed the fall caused by many organ extracts to their paralytic effect on the peripheral nerve structures of the splanchnic nerves, since he found that adrenine caused a rise of blood pressure after injecting organ extracts, and he regarded the former as acting more peripherally. But it is clear from what I have already mentioned, that his experiments do not show any vasodilatation and paralysis of the splanchnic nerves.

Thus there is no reason to accept the hypothesis of a vasodilatatory effect of organ extracts.

On the other hand, as far as the cause of the pressure fall is concerned with the inhibitory effect of organ extract, my explanation resembles the hypothesis that the cause of the pressure fall may be due to thrombosis formed in the pulmonary vessels by organ extracts. But it must be noticed that to cause the inhibition of the pulmonary circulation by such extracts there is no necessity for those thrombosis, for the inhibition can be caused by these extracts even with the perfusion experiment, when there are no thrombosis formed. Moreover, in a section of the lungs of an animal poisoned by organ extracts the distinct constriction of the pulmonary vessels and bronchial muscles can be always observed, while it is not always possible, even though often so, to discover thrombosis in the pulmonary vessels. It is a fact that for some time after the injection of organ extracts, the blood coagulability is accelerated and consequently it is obvious that if there is considerable vasoconstriction, thrombosis can be easily formed. However, the formation of thrombosis in the

pulmonary vessels is not the main cause of the pressure fall due to organ extracts, but a secondary effect caused by the inhibition of the pulmonary circulation. Accordingly the formation of thrombosis is but an accidental occurrence when organ extracts are injected, and this is the reason why one cannot discover thrombosis in the pulmonary vessels in every case, though they are often found after injecting organ extracts.

The fact that, even though the blood coagulability has been already retarded by various means, the usual fall of the blood pressure can be also caused, is definitely opposed to the hypothesis of the formation of thrombosis.

I don't know whether the pressure fall resulting from the extract of lungs and from histamine (active substance of the extract of the small intestine) is similar to that caused by many other organ extracts, but if their actions all resemble each other in character, the pressure fall, which is caused by many other organ extracts, might be explained as due to the extract of lungs or histamine.

(b) Blood serums.

Since Mosso[64], Weiss[65] etc. have discovered a considerable fall of the blood pressure after injecting the blood serums of animals of other species, many investigators have examined the cause of this pressure fall, but they do not agree in their opinions about this cause and their explanations of it vary, just as do those about the cause of the pressure fall due to organ extracts. Brodie[66] attributed the cause to the inhibitory effect of blood serums on the heart's activity, Popielski[49] and Studzinski[58] to their vasodilatatory effect, by liberating their hypothetical vasodilatin, if injected intravenously, and Loeb, Strickel and Tuttle[67] to thrombosis in the pulmonary vessels on injection of blood serums.

However the bases of these arguments are too feeble to be accepted, as are those of the cause of the fall of the blood pressure due to organ extracts. That is to say, such doses of blood serums as cause a fall of blood pressure, when injected intravenously, do not inhibit the heart's activity as the experiments of Tatum[68], Lannoy[69], Leyton and Sowton[70], Cushny and Gunn[71], Yanagawa[72] etc. prove, and do not cause vasodilatation, as the experiments of Ludwig and Schmidt[72], Mosso[73], Bernstein[74], Battelli and Mironi[75], Handovsky and Pick[36], Zucker and Stewart[76], Kaufmann[77],

Cubarj[78], Lönning[39] etc. prove. And it is not always possible, though often so, to discover thrombosis in the pulmonary vessels in a section of an animal poisoned by blood serums.

I also investigated the effect of the blood serum of a rabbit on the blood pressure and blood vessels of cats by repeating the same experiments, as performed in the research for the cause of a pressure fall due to organ extract, and obtained about the same results as in that case. For these reasons the pressure fall, caused by blood serums, is also due to their inhibitory effects on the pulmonary circulation, and the pulmonary inhibition is caused by their broncho-constrictory and vasoconstrictory effect on the pulmonary vessels. There is no evidence of their depressing action on the heart's activity and of dilatatory action on the peripheral blood vessels.

The hypothesis regarding the formation of thrombosis in the pulmonary vessels by blood serums resembles my explanation so far as the cause of the pressure fall is concerned with inhibition of the pulmonary circulation, but thrombosis is not the main cause of the inhibition corresponding to the pressure fall and is produced secondarily by the inhibition of the pulmonary circulation, which is caused by the constrictory effect of blood serums on the bronchial muscles and pulmonary vessels.

Recently Schultz[79] attributed the cause of the pressure fall after injection of blood serum, to its inhibitory effects on the pulmonary circulation and the heart's activity. His explanation may be a correct one, but it is due to his imperfect observation that he considered that the arrest of the right heart (without observing the left heart's activity) is due to the primary direct inhibitory effect of blood serums on the heart. But the arrest of the right heart after injecting blood serum is caused secondarily by the inhibition of the pulmonary circulation.

General conclusion.

I. If the pulmonary artery is obstructed and the amount of the blood through it restrained, the arterial blood pressure falls and the volume of the small intestine and limbs increases, while the volume of the kidney decreases.

II. Many authors having observed the large expansion of such organs as the small intestine and limbs during the fall of the blood pressure, are apt to attribute the cause of this large expansion to vaso-

dilatation in those organs, without considering another possible cause of it. But such an explanation is premature.

III. The so-called "paradoxical vasodilatatory substances," such as histamine, peptone, extracts of organs, blood serums etc. always have a vasoconstrictory effect and it does not matter whether they are injected into the natural circulation or artificial perfusion. In spite of this effect, these substances, if injected intravenously in the living animal, cause a considerable fall of the arterial blood pressure. The cause of this pressure fall is due to their broncho-constrictory effect, for a considerable constriction of the bronchial muscles causes indirectly inhibition of the pulmonary circulation. For this reason, these substances, if injected intravenously, cause a rise of the pulmonary blood pressure and a fall of the arterial blood pressure, and moreover a large expansion of such organs as the small intestine and limbs. Accordingly the large expansion of these organs after the injection of these substances is due to the congestion of venous blood in consequence of the inhibition of the pulmonary circulation and not to vasodilatation in these organs.

IV. The explanations of many investigators that the cause of the fall of the blood pressure is due to vasodilatation of such organs as the small intestine and limbs, are based on imperfect observations. But there is no evidence to show vasodilatation caused by these substances.

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