THE ACTION OF DRUGS IN THE DETERMINATION OF INTRINSIC PULMONARY VASCULAR MECHANISMS.

By

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APPENDIX.

Action of drugs on the pulmonary circulation of the rat.

INTRODUCTION.

The amount of blood contained in the pulmonary vascular bed has been shown by recent work to be affected to a marked degree by nervous stimulation, powerful vasoconstriction being brought about by stimulation of the pulmonary sympathetic fibres (Daly and Euler, 1932). Weak dilatation was obtained on stimulating the thoracic vagosympathetic nerves.

The vasoconstrictor effects appeared to be due to the activity of adrenergic fibres, whereas the dilator effect was due to the activity of cholinergic fibres. The nature of the nervous supply to the lungs has been worked on by many investigators with somewhat differing results. Further work on this question appears to be necessary.

Elliott, in 1904, made the suggestion that sympathetic nerves acted by the peripheral liberation of adrenaline. The neuro-humoral theory received support in 1921, by experimental evidence obtained by Loewi for both parasympathetic and sympathetic nerve impulses. Further evidence has been accumulated by a large number of workers that chemical substances are liberated at the terminations of autonomic fibres; these fibres have been called by Dale cholinergic or adrenergic according to the nature of the transmitters which appear to be closely allied to acetyl choline and adrenaline/

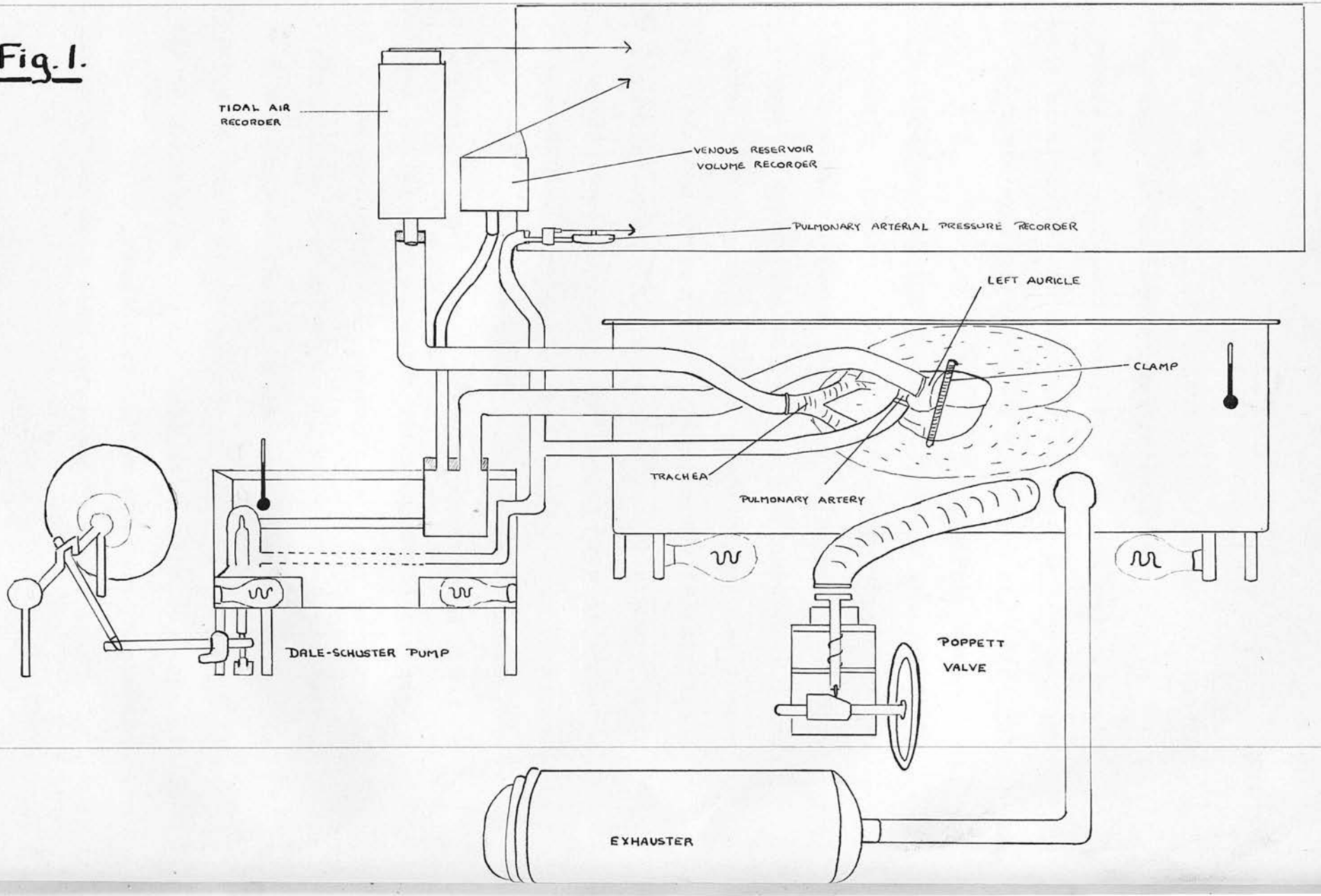
adrenaline respectively (Dale, 1933).

Experiments were planned therefore in order to discover the site of action of adrenaline and acetyl choline on the isolated perfused lung vessels of the dog, with the object of throwing light on their autonomic control.

Also, in the intact animal and on the isolated perfused lungs adrenaline causes a rise of pulmonary arterial pressure. Exercise, however, shows little or no such rise in spite of the increased cardiac output and the presence in the circulation of large quantities of adrenaline. The problem arises as to whether there are factors determining the nature of the response to adrenaline, or possibly factors which inhibit this response. It has been found (Gaddum and Holtz, 1933; Alcock, Berry and Daly, 1935) that although adrenaline injections into the pulmonary artery raise the pressure there is also in the vast majority of cases an increase in venous outflow. The question therefore arises as to whether part of the adrenaline response is due to vasodilatation and part to vasoconstriction, in which case it might be possible to alter conditions so that either the pressor or the depressor component would predominate.

The effects of histamine were also tested with regard/

Fig. 1.


TIDAL AIR RECORDER
VENOUS RESERVOIR VOLUME RECORDER
PULMONARY ARTERIAL PRESSURE RECORDER
LEFT AURICLE
CLAMP
TRACHEA
PULMONARY ARTERY
DALE-SCHUSTER PUMP
POPPETT VALVE
EXHAUSTER

regard to its role in pathological conditions, particularly that of anaphylactic shock.

METHOD.

The method used was the same as that described by Alcock, Berry and Daly (1935). In all the experiments the isolated lungs of the dog were perfused with defibrinated blood taken from the same animal and the lungs were inflated by rhythmical negative pressure variations applied to their outer surfaces. Fig.1 shows the arrangement of the apparatus. The animals were for the most part bled from the femoral artery under local anaesthesia; in a few cases they were bled from the carotid artery under general anaesthesia (chloroform and ether).

The isolated lungs were perfused at constant blood inflow through the pulmonary circulation alone. The changes in the volume of blood in the lungs were recorded by the difference method of measuring the blood content of the venous reservoir (Daly, 1928). The pulmonary arterial pressure was usually recorded by a Marey tambour in order to eliminate blood pooling in the instrument during a rise in pulmonary arterial pressure.

When a constant adrenaline infusion was given to the/

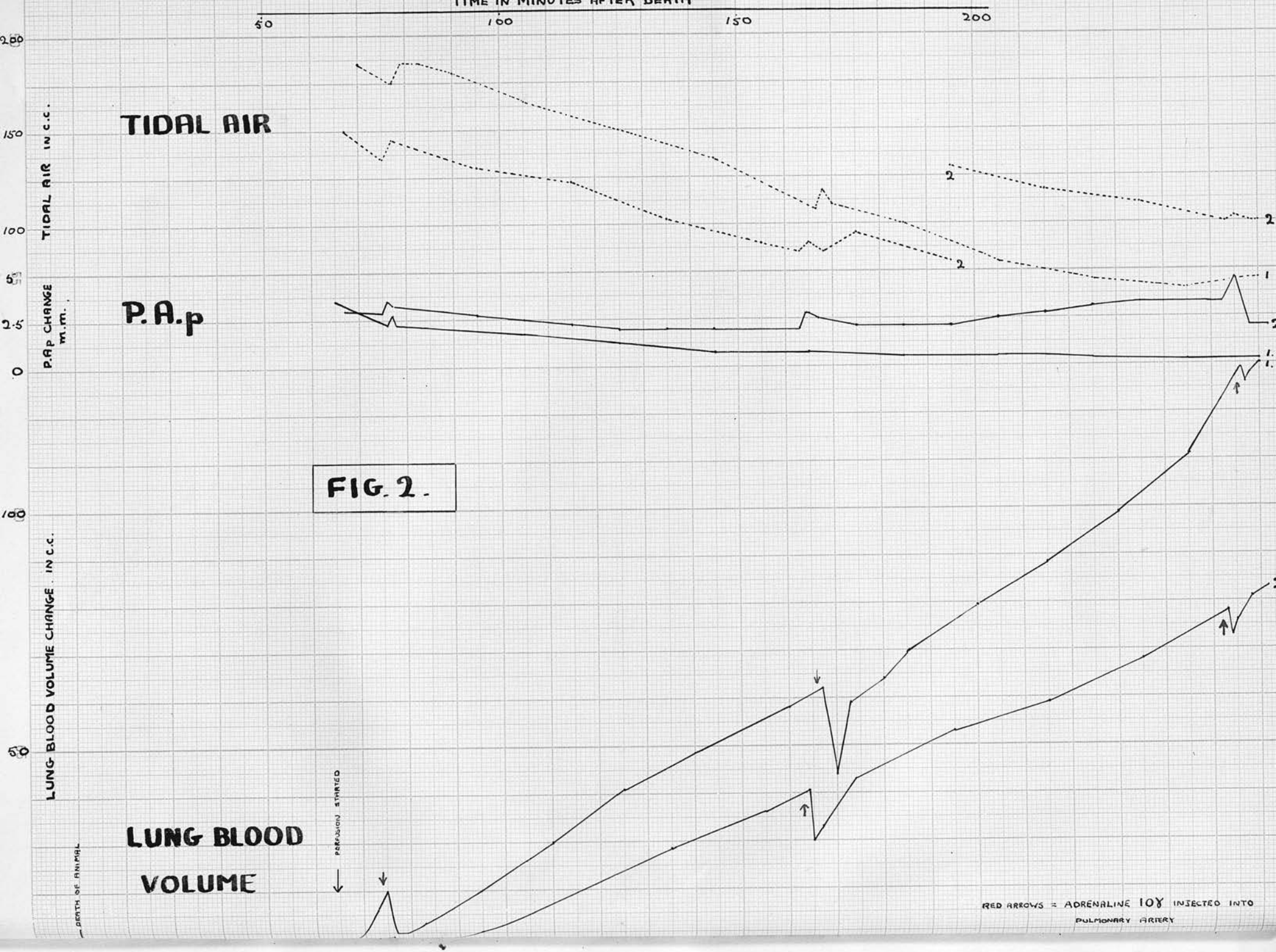

TIME IN MINUTES AFTER DEATH
50
100
150
200
TIDAL AIR
TIDAL AIR IN C.C.
200
150
100
5
2·5
0
2
2
2
1
1
1
P.A.p
P.Ap CHANGE m.m.
100
50
LUNG BLOOD VOLUME CHANGE IN C.C.
LUNG BLOOD VOLUME
DEATH OF ANIMAL
PERFUSION STARTED
RED ARROWS = ADRENALINE 10γ INJECTED INTO PULMONARY ARTERY

FIG. 2.

the preparation, a mechanically propelled syringe was used, which injected four cubic centimetres of the solution an hour into the venous reservoir.

All drugs were given by injection into the tube leading to the pulmonary artery except where otherwise stated.

ADRENALINE.

Introduction.

The most usual effects of injecting adrenaline on the isolated perfused lungs of the dog are a rise of pulmonary arterial pressure and a fall in the blood volume of the lungs (Berry and Daly, 1931; Gaddum and Holtz, 1933). Tracings from two experiments showing the effect of injecting adrenaline into the pulmonary arterial tubing at intervals of 1½ hours are shown in Figs. 2 and 3. From these it will be seen that the effect of adrenaline on the pulmonary arterial pressure and on the venous outflow show the same qualitative changes throughout the experiment. There is a slight increase in sensitivity of the preparation after 2 hours perfusion, thereafter the sensitivity declines.

In interpreting this result the following possibilities arise: the rise of pulmonary arterial pressure might/

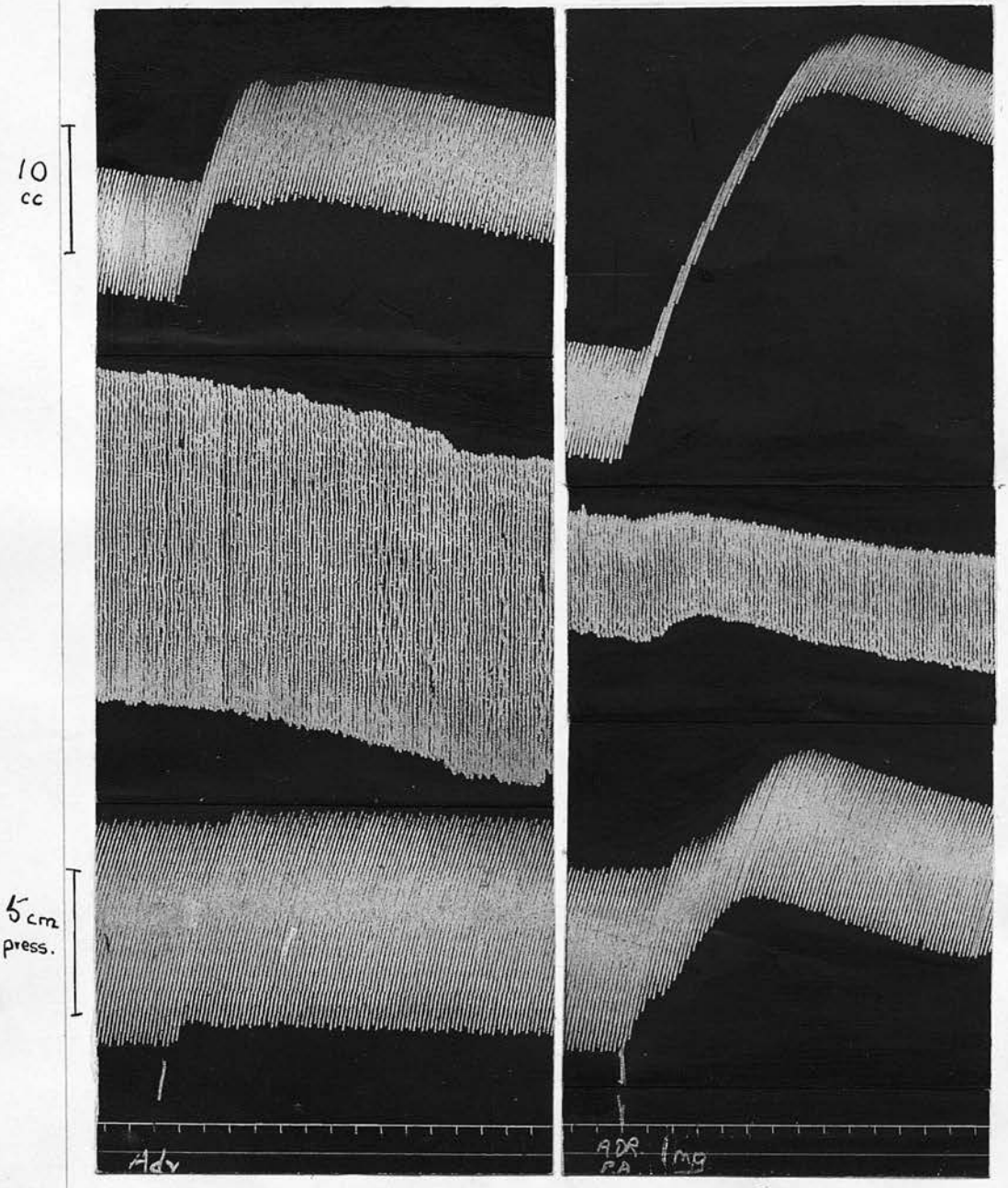


FIG 3.

EXPT 11.12.36. DOG. ♂ 22 Kg. ISOLATED PERFUSED LUNGS. BLED UNDER LOCAL ANAESTHESIA. TOP TRACING VOLUME OF VENOUS RESERVOIR, 2ND TIDAL AIR, 3RD PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR) 4TH · TIME 30SECS

(a) ADRENALINE 10γ : INTO PULMONARY ARTERY

(b) ADRENALINE 1mg : INTO PULMONARY ARTERY

might be due to vasoconstriction of the pulmonary arterioles, capillaries or veins. This statement is made because the total resistance of the pulmonary vascular bed is extremely small and it has been found by experiment that slight changes in venous pressure are reflected in the pulmonary arterial pressure. It is conceivable therefore that the action of adrenaline in increasing the pulmonary arterial pressure and the venous outflow may be due to simple venous constriction, the increase in outflow being caused by the squeezing out of blood from the veins. It is equally true that a similar adrenaline response might be produced by capillary constriction, the resistance and capacity components being reflected in the rise of pulmonary arterial pressure and increase in venous outflow. From the same line of argument the arterioles may be the responsive vessels. We have therefore three possible interpretations and when it is considered that the venous outflow increase might also be due to venous dilatation which releases blood from the capillaries the complex nature of adrenaline action becomes evident. It will be clear that in lungs perfused at constant inflow any interpretation placed upon/

upon a venous outflow change would be greatly facilitated by a previous knowledge of the relative quantities of blood in the arterioles, capillaries and veins. Unfortunately, this knowledge is not available and therefore experiments have to be devised which will determine whether any given outflow change is due to a resistance or to a capacity effect. By capacity effect ~~is meant~~ we mean the squeezing of blood from vessels owing to a diminution in their calibre. The calibre change may be of sufficient magnitude to cause a significant change in the vessel resistance, or it may have little or no effect on the total vascular resistance. Thus widely dilated veins, if slightly constricted by adrenaline, may squeeze blood out and cause an increase in venous outflow, but the diminution in their calibre may not be large enough to cause ~~an~~ a significant and measurable increase in resistance to blood flow. It should be pointed out that with constant inflow perfusion the changes in venous outflow due to any cause whatsoever are temporary. Thus, venous constriction will cause a temporary diminution in outflow with pooling of blood in the lungs; dilatation, a temporary increase in venous outflow with depletion of capillary blood.

To/

on the ~~temporary~~ retention of blood by virtue of their dilatation.

To return to the specific action of adrenaline in increasing the outflow, it should be mentioned that this is not an invariable result. It was found by Gaddum and Holtz that adrenaline gave an increase in outflow in five out of ten experiments. In two experiments they found that adrenaline gave a decrease in outflow. Alcock, Berry and Daly have already shown that a decrease in outflow only occurred in three experiments out of 44, and my own experiments show that in 15 experiments in which 98 tests were made no case of adrenaline diminution of outflow occurred.

2/5

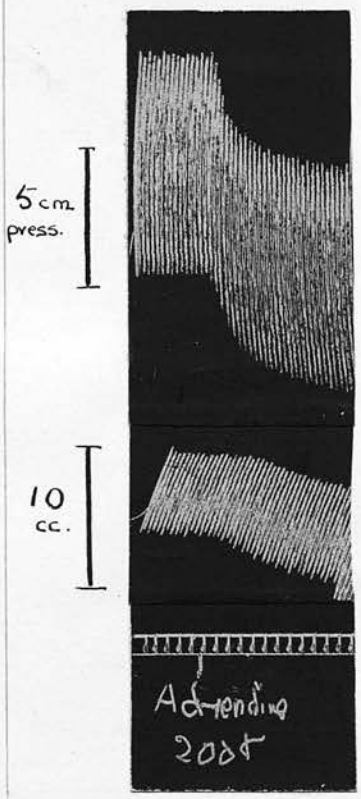
3/59

It would appear therefore that venous outflow diminution resulting from adrenaline injections seems to be a relatively rare event. Indeed in our experiments it has occurred so infrequently that we have not had a full opportunity of investigating it.

RESULTS.

The effect of ergotoxine on the adrenaline response.

The adrenaline pressure response has been shown to be reversed by ergotoxine in the isolated perfused lungs of the dog (Daly and Euler, 1932). These investigators did not determine whether the adrenaline outflow response was modified to ergotoxine and therefore a number of experiments were conducted in ergotoxinised preparations and special attention paid to/



P.A.p.

V.R.vol.

EFFECT OF ERGOTOXINE ON THE ADRENALINE RESPONSE.

EXPT. 17.9.35. DOG ♂ WT 12.5 Kg. BLED UNDER LOCAL ANAESTHESIA. PUMP AT CONSTANT FLOW. TOP TRACING PULMONARY ARTERIAL PRESSURE (P.A.p.) RECORDED BY MAREY TAMBOUR, SECOND VOLUME OF VENOUS RESERVOIR, THIRD TIME = 10 secs INTERVAL, FOURTH SIGNAL.

ERGOTOXINE 2 mg HAD BEEN GIVEN PREVIOUSLY TO THE ANIMAL.

AT SIGNAL, ADRENALINE 200γ WAS GIVEN. (P.A.).

FIG. 4.

to the action of adrenaline on the outflow. It was found in confirmation of Daly and Euler that ergotoxine suppresses or reverses the pressor response of adrenaline. Out of 20 experiments and 35 injections, 26 gave no change in outflow, 7 gave a fall and 2 gave an increase in outflow, one of these being very slight. When therefore a change in outflow was obtained after ergotoxine the effect was usually a decrease (Fig.4).

It would appear then that the more common effects of adrenaline action are as follows: in the normal preparation it decreases the inflow (or raises the pulmonary arterial pressure) and increases the outflow, whereas in ergotoxinised preparations it increases the inflow (or diminishes the pulmonary arterial pressure) and decreases the outflow.

On the hypothesis that adrenaline stimulates the action of excitation of sympathetic nerves and that ergotoxine paralyses sympathetic motor nerves and leaves the sympathetic dilator nerves functionally intact, then it would appear that the action of adrenaline on those vessels of the pulmonary vascular bed responsible for the resistance change is upon vessels supplied with both sympathetic constrictor and sympathetic dilator fibres.

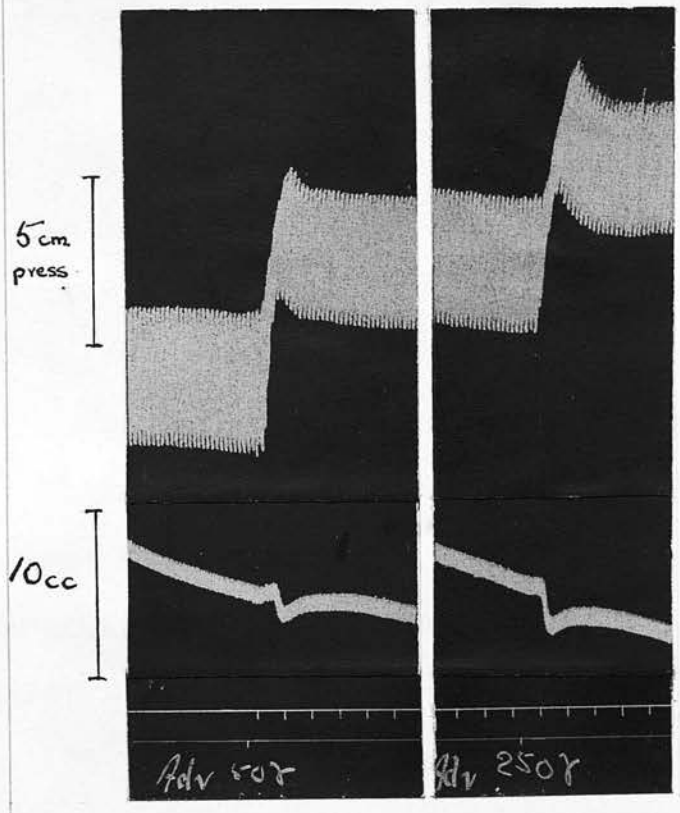
One/

If adr. raised the P.A.P. by venous constriction and also squeezed blood out of the veins the result P.A.P.↑ and venous outflow ↑ would be expected. After ergotoxine then the venous dilatation would cause P.A.P.↓ (resistance effect) and venous outflow diminution (capacity effect)

One explanation of the action of adrenaline in raising the pulmonary arterial pressure and in raising the outflow would be that the pulmonary arterioles constrict and increase the vascular resistance but at the same time squeeze blood from the arterioles, thus causing an increase in venous outflow. On this view adrenaline in ergotoxinised preparations should by dilation of the pulmonary arterioles increase their capacity for blood and also cause a temporary diminution in outflow, an effect which was obtained in 7 experiments. The absence of a venous outflow response in ergotoxinised preparations which was obtained in a large number of experiments is difficult to explain on this hypothesis alone, as is also the increase in venous outflow obtained in two experiments.

In order to test whether adrenaline is acting upon the arterioles, a number of experiments were conducted in which the lungs were perfused backwards through the left auricle, the blood being collected from the pulmonary artery.

It was argued that if the pulmonary arterioles were responsible for the increased resistance, then in "reverse" perfusion experiments adrenaline should cause a rise in inflow pressure and a fall in the outflow. It was found in the "reverse" perfusion experiments that/



P. A. p.

V. R. vol.

EFFECT OF ADRENALINE DURING REVERSE CIRCULATION

FIG 5

EXPT 6.4.36. DOG. ♂ 14 Kg. ISOLATED PERFUSED LUNGS. BLEO UNDER LOCAL ANAESTHESIA. TOP TRACING PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR), 2ND VOLUME OF VENOUS RESERVOIR, 3RD TIME ½ 30SECS, 4TH SIGNAL PREPARATION IN REVERSE CIRCULATION.

1ST SIGNAL. ADRENALINE 50γ: INJECTED INTO INFLOW (LEFT AURICULAR) TUBE

2ND SIGNAL. ADRENALINE 250γ: INJECTED INTO INFLOW (LEFT AURICULAR) TUBE.

that adrenaline in small doses gave an increase in the inflow pressure and an augmentation on the outflow. With large doses the inflow pressure was increased but the outflow was diminished. There is then this difference between the action of adrenaline in normal "forward" perfusions and in the "reverse" perfusions, the larger doses producing a diminution in outflow in "reverse" perfusion, whereas in normal "forward" perfusion the outflow is augmented. We have attempted from time to time to test on one and the same preparation the effect of small and large doses in "forward" and in "reverse" perfusion but owing to the fact that preparations quickly lose their sensitivity to adrenaline after the exhibition of large doses, it has not been possible to obtain a clear cut result.

With "reverse" perfusion a small dose of adrenaline increases the outflow, a large dose diminishes the outflow (Fig.5); switching over to "forward" perfusion both small and large doses of adrenaline produce an increase in outflow. When, however, adrenaline is given once more with "reverse" perfusion, then both small and large doses of adrenaline either produce an increase in outflow or have no effect.

Apart/

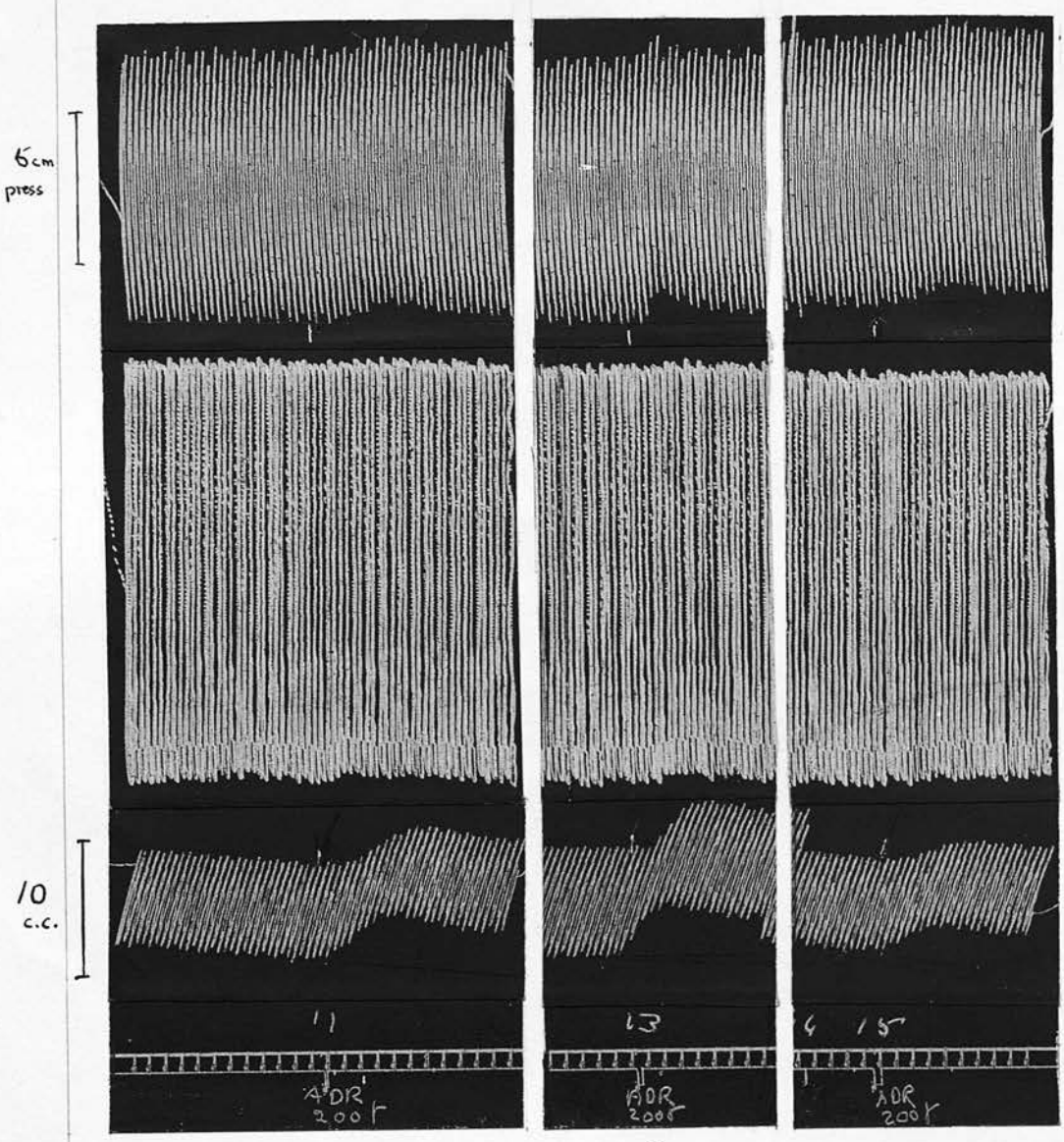


Fig. 6

EXPT 6.11.36. DOG. ♂ 18kg. ISOLATED PERFUSED LUNGS. BLED UNDER LOCAL ANAESTHESIA. TOP TRACING PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR), 2ND TIDAL AIR, 3RD VOLUME OF VENOUS RESERVOIR, 4TH TIME = 30SECS, 5TH SIGNAL PREPARATION IN REVERSE CIRCULATION DURING (a) AND (c), NORMAL CIRCULATION DURING (b)

1ST SIGNAL (a) ADRENALINE 200γ INTO INFLOW (LEFT AURICULAR) TUBE

2ND SIGNAL (b) ADRENALINE 200γ INTO PULMONARY ARTERY

3RD SIGNAL (c) ADRENALINE 200γ INTO INFLOW (LEFT AURICULAR) TUBE

Apart from these distinctions between the action of adrenaline on "forward" and "reverse" perfusions, it was found that in comparing equal doses of adrenaline the latent period of the response, both pulmonary arterial and venous outflow, was longer with "reverse" perfusion than with "forward". Moreover, both responses in "reverse" perfusions were not so large as in "forward" (Fig.6).

The interpretation of these phenomena is a difficult matter. But they appear to lend support to the view that adrenaline is acting on blood vessels on the arterial side rather than on the venous side of the capillaries. If for the purposes of argument we assume that these vessels are the pulmonary arterioles then the action of small doses of adrenaline during "reverse" perfusions would be arteriolar constriction causing an increase in outflow by squeezing the blood from their lumen, which is greater than the diminution in outflow which would tend to occur as the result of blood being banked up in the capillaries due to the increased arteriolar resistance. On the other hand with the larger doses of adrenaline, the resistance effect on the arterioles predominates over the capacity effect and the amount of blood banked up in the capillaries which causes a diminution in outflow is greater than/

than that squeezed out from the arterioles tending to cause an increase in outflow.

In view of the fact that on occasion large doses of adrenaline during "reverse" perfusions may increase the outflow, the explanation given above does not explain all the experimental facts and further experiments were devised in the hope that more light might be thrown upon the mechanisms involved. It may be stated in passing that one explanation of the failure of large doses of adrenaline to cause a diminution in outflow in some of the "reverse" perfusion experiments may be that the preparations are relatively insensitive to adrenaline and that the effect upon the arterioles is so small that the adrenaline only succeeds in squeezing a small amount of blood from them, their reduction in calibre being insufficient to introduce the resistance component. It would naturally be expected that the resistance component would come into action more strongly the smaller the initial calibre of the vessels.

It was considered that the action of adrenaline on the lungs in the collapsed and in the expanded (under negative pressure) state might throw some light upon its point of action. There is a considerable amount of evidence to show that lungs under negative pressure increase their blood capacity by augmentation in the filling/

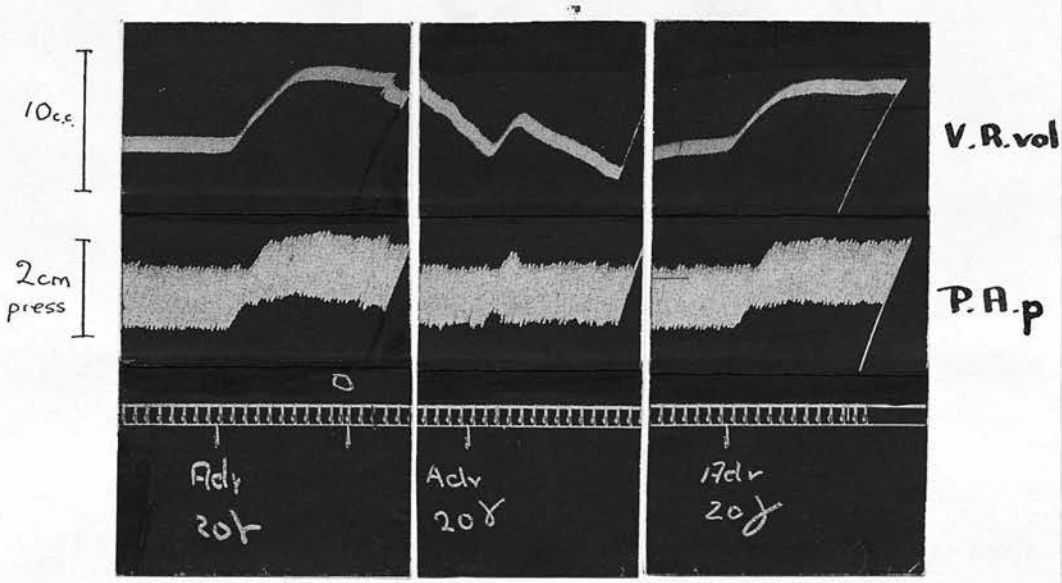


Fig. 7.

EXPT 21.1.36. DOG ♂ 16Kg. ISOLATED PERFUSED LUNGS. BLED UNDER LOCAL ANAESTHESIA. TOP TRACING VOLUME OF VENOUS RESERVOIR, 2ND PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR) 3RD TIME = 10 SECS, 4TH SIGNAL DRUGS INJECTED INTO THE PULMONARY ARTERY.

1ST SIGNAL ADRENALINE 20γ. LUNGS DEFLATED

2ND SIGNAL ADRENALINE 20γ. LUNGS INFLATED

3RD SIGNAL ADRENALINE 20γ LUNGS DEFLATED

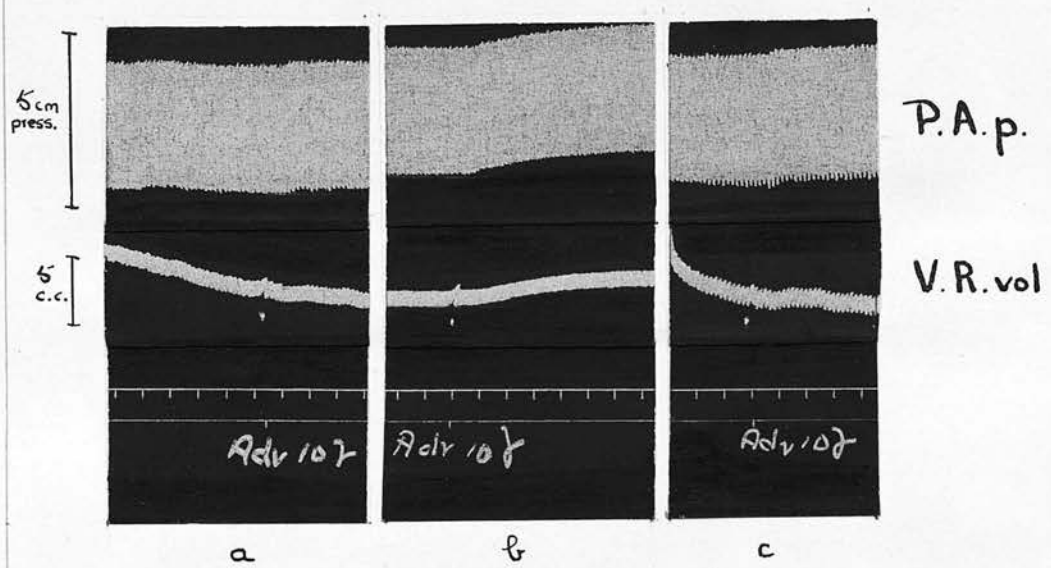
Neg: pressure inflation

filling of the lung capillaries. If adrenaline acts by contracting the capillaries, then it would be expected that more blood would be squeezed out of the expanded lung than out of the collapsed, and therefore the venous outflow increase would be greater in the expanded than in the collapsed lung. On the same line of argument adrenaline administered to lungs under rhythmic negative pressure ventilation with the expansion (inspiratory) phase greater than the collapsed (expiratory) phase would have a greater effect in increasing the venous outflow than in lungs respired with the expiratory phase greater than the inspiratory phase.

It was found that adrenaline injections into the pulmonary artery of lungs kept steadily inflated by negative pressure have a smaller response than similar doses injected into collapsed lungs (Fig.7).

In both cases, however, the pulmonary arterial pressure rose and the venous outflow increased.

This result might have been due to the fact that with intra-arterial injections of adrenaline the concentration of the drug in the lungs would be smaller when the lungs were expanded than when collapsed, since the blood volume of the lungs is greater in the expanded condition than in the collapsed. Further experiments/



This tr. is not convincing

FIG. 8.

EXPT. 18.3.36. DOG. ♀ 14 Kg ISOLATED PERFUSED LUNGS. BLED UNDER LOCAL ANAESTHESIA. TOP TRACING PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR) 2ND VOLUME OF VENOUS RESERVOIR, 3RD TIME = 30secs, 4TH SIGNAL. ALL DRUGS INJECTED INTO THE VENOUS RESERVOIR

1ST SIGNAL (a) ADRENALINE 10γ LUNGS ~~DEFLATED~~ well infl.

2ND SIGNAL (b) ADRENALINE 10γ LUNGS ~~INFLATED~~

3RD SIGNAL (c) ADRENALINE 10γ LUNGS ~~DEFLATED~~ infl.

Negative pr. resp.

experiments were therefore carried out and injections made into the venous reservoir and the responses compared on the lungs in the collapsed and in the expanded condition. It was found even then that the pulmonary arterial pressure increase and the venous outflow augmentation were greater when the lungs were collapsed than when expanded (Fig.8).

Here again this result which is entirely unexpected presents considerable difficulties in interpretation. It might be said, however, that they appear to rule out definitely the possibility that adrenaline is exerting its action on the capillaries, for if this was so, we would expect a very mugh larger increase in venous outflow under negative pressure expansion when the capillaries are full than in the collapsed lung when the capillaries are comparatively empty. There appears to be some other factor at work which is causing a diminution in the response to adrenaline when the lungs are expanded. If the reactive vessels are arterioles it is difficult to see from the knowledge we have of their anatomical arrangement how expansion of the lungs can affect them; the only suggestion I have to make is that expansion of the lungs stretches the pulmonary arterioles and diminishes their calibre, thus leading to a smaller contractile response when the adrenaline reaches them.

The/

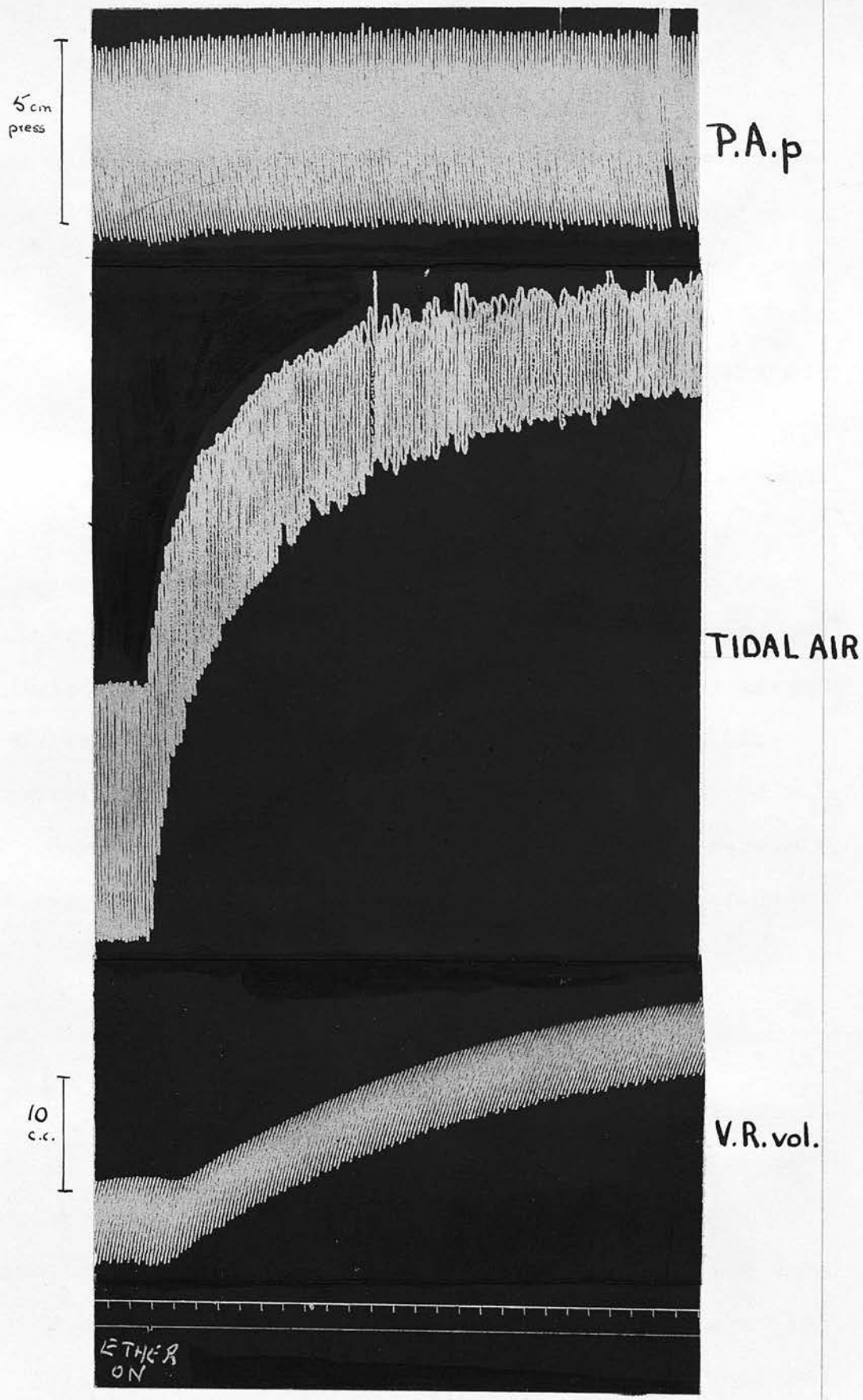


FIG 9. EXPT 13.3.36 DOG. ♀ 12 kg. I.P.L. BLED UNDER LOCAL ANAESTHESIA

TOP TRACING PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR) 2ND TIDAL AIR,

3RD VOLUME OF VENOUS RESERVOIR, 4TH TIME = 30 SECS, 5TH SIGNAL

AT SIGNAL, ETHER BOTTLE INTRODUCED INTO CLOSED CIRCUIT BETWEEN TRACHEA AND VOLUME RECORDER

The next series of experiments was conducted to determine whether the action of anaesthetics modified in any way the adrenaline response. It was found that the administration of ether by the introduction of an ether bottle into the closed circuit between the trachea and the volume recorder had no effect upon the adrenaline response. This result was all the more remarkable because the effect of ether alone was to increase the pulmonary arterial pressure slightly and to diminish considerably the blood volume of the lungs (Fig.9).

In view of the fact that there is no adremaline circulating in the blood of isolated perfused lungs and that normally the suprarenal glands have a certain output of adrenaline, it is of interest to discover whether the constant infusion of small amounts of adrenaline into the perfusion during circulation has any effect upon the vascular response to single injections of adrenaline.

Experiments were carried out in which adrenaline was infused into the circulation at the rate of 2-50 γ per minute. As infusion was continued it was found that the pulmonary arterial pressure and the venous outflow gradually increased but after $\frac{3}{4}$ hour to $1\frac{1}{4}$ hours the pulmonary arterial pressure level became stabilised and the venous outflow showed no further rise. Thus the effect of such an infusion was an

increase/

A. EFFECT OF ADRENALINE IN NORMAL ANIMAL.

DATE	DOSE	P.A.p. m.m.	V.R. VOL. C.C'S CORRECTED.	WHERE INJECTED.	P.A.p. RECORDER	OUTFLOW. P.A.P.
25.6.36.	2γ	+ 10	+ 1.5	P.A.	MAREY TAMBOUR	0.15
	2γ	+ 2	+ 1	P.A.		0.5
	10γ	+ 6	+ 1.8	P.A.		0.3
13.2.35	50γ	+ 20	0	P.A.		0
	40γ	+ 14	0	P.A.		0
15.3.35	500γ	+ 40	+ 2.5	P.A.		0.06
8.7.35	50γ	+ 1	+ 1.4	P.A.	WATER MANOMETER	1.4
	60γ	+ 3	+ 1.9	P.A		0.6
9.7.35	2γ	+ 3	+ 0.9	P.A.	WATER MANOMETER	0.3
	5γ	+ 2	+ 0.8	P.A.		0.4
	10γ	+ 3.5	+ 0.7	P.A.		0.22
16.7.35.	100γ	+ 3.5	− 0.3	P.A.	WATER MANOMETER	− 0.4
	20γ	+ 1.5	− 0.3	P.A.		− 0.6
13.9.35.	200γ	+ 17	+ 3.8	P.A.	WATER MANOMETER	0.2
	50γ	+ 2.5	+ 1.6	P.A.		0.6
28.6.35	100γ	+ 1.5	+ 1.2	P.A.	WATER MANOMETER	0.8
3.7.35.	50γ	− 7	+ 1	P.A	WATER MANOMETER	
	50γ	+ 11	− 0.6	P.A.		−0.4
5.6.35	2γ	+ 1.5	0	P.A.	MAREY TAMBOUR	0

B. EFFECT OF ADRENALINE GIVEN DURING CONSTANT ADRENALINE INFUSION

DATE	DOSE	P.A.P mm	V. R. vol c.c.'s	P.A.P RECORDER	STRENGTH OF INFUSION	WHERE INJECTED	OUTFLOW / P.A.P
30935	25γ	+ 1.5	+ 1.5	MAREY TAMBOUR	20γ/min	P.A	1
	50γ	+ 1.5	+ 1.5			P.A	1
	250γ	+ 3	+ 2			P.A	0.66
1.10 35	25γ	+ 0.5	+ 0.25	MAREY TAMBOUR	20γ/min	P.A	0.5
	100γ	+ 1.5	+ 0.25			P.A	0.16
	500γ	+ 2	+ 1			P.A	0.5
2 10 35	100γ	+ 2	+ 1	MAREY TAMBOUR	5γ/min	P.A	0.5
	250γ	+ 1	+ 1.25			P.A	1.25
7/10 35	2γ	− 0.5	0	MAREY TAMBOUR	5γ/min	P.A	
	10γ	+ 0.5	0			P.A	
	30γ	+ 1.5	+ 1			P.A	0.66
9 10 35	200γ	+ 2	+ 1	MAREY TAMBOUR	50γ/min	P.A	0.5
	500γ	+ 1.5	+ 1			P.A	0.66

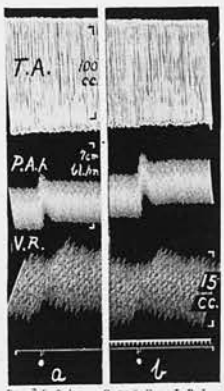
NOTE I. ANIMAL IS LESS SENSITIVE TO ADRENALINE INJECTIONS

II P.A.p RESPONSE SMALLER IN RELATION TO OUTFLOW RESPONSE.

increase in vascular tone leading to a rise of vascular resistance and a diminution in blood volume of the lungs.

The response to single adrenaline injections during such an infusion was qualitatively the same as in the isolated perfused lungs without adrenaline infusion. The preparations, however, were much less sensitive to the single doses of adrenaline for even with very large doses of adrenaline (100γ to 1 mg.) only small effects were seen. Moreover, single injections of adrenaline in the infused preparations had a relatively smaller effect in increasing the pulmonary arterial pressure than in raising the venous outflow (see tables). I am not at all clear what is the reason for the relatively greater effect on the venous outflow in the adrenaline infused preparations. The observations should be interpreted with caution because it might be that the method of recording the pulmonary arterial pressure was not adequate to detect very small alterations and since both pressure and outflow changes in the infused preparations were small, a false idea of their relative values may have been obtained. At first sight it might be argued that adrenaline is acting on capillaries and squeezing blood out, so giving/

Fig. 10.



10.6.38. Dog♂ 8.0 kg. C and E. I.P.L. Constant inflow. Top tr. = tidal air; 2nd = P.A.p. (Marey tambour.; 3rd = vol. of venous reservoir; 4th = 10 sec.; 5th = signal. 1st signal = adrenaline (cryst.) 4Y; 2nd = adrenaline 4Y. Between "a" and "b" cocaine 300Y was injected into the P.A.

EFFECT OF COCAINE ON THE ADRENALINE RESPONSE

giving rise to an increased venous outflow but causing little change in the total vascular resistance. Against this, however, is the fact that experiments on expanded and collapsed lungs indicated that adrenaline had no action in constricting the capillaries. On the whole, therefore, these experiments on perfused preparations throw little light upon the site of action of adrenaline.

According to Fröhlich and Loewi (1910) and also Burn and Tainter (1931), cocaine enhances the action of adrenaline; a series of experiments were therefore carried out on cocainised preparations. It was thought that there was the remote chance that cocaine might not only enhance the general action of adrenaline on the isolated perfused lungs but might even have a selective enhancing effect on one portion of the vascular bed and thus throw some light on the point of action of adrenaline.

Contrary to expectation cocaine had only a slight action in enhancing the pressor effect of adrenaline on the pulmonary vascular bed. This slight effect was seen in four experiments, but in two experiments no enhancement was obtained. The greatest enhancement of the pressor response is shown in Fig. 10.

In/

In ergotoxinised preparations cocaine had no effect on the adrenaline response.

Discussion.

The response to adrenaline in the isolated perfused lungs (under negative pressure ventilation) of the dog appeared in these experiments to be a rise in pulmonary arterial pressure and a decrease in lung blood volume; there were only rare exceptions. Apart from its action in the ergotoxinised animal, adrenaline did not cause a fall in pulmonary arterial pressure under any conditions in spite of the teleological advantages of such an effect. When single injections of adrenaline were superimposed on a constant adrenaline infusion, thus somewhat reproducing the adrenalaemia of exercise, they still caused a rise of pulmonary arterial pressure; the whole effect, however, was very much diminished and it is possible therefore that the action of adrenaline in increasing pulmonary resistance is much lessened when there is already a large amount of adrenaline in the blood.

The action of adrenaline in raising the pulmonary arterial pressure might be due to three causes, namely vasoconstriction of the arteries, capillaries or veins. From the experiments on the reverse circulation it appeared that the main action of adrenaline was on the arterioles. These experiments suggest that the same/

same vessels might be responsible by their reduction in diameter for the rise in resistance as well as for the squeezing out of blood, resulting in the increase in outflow. If this hypothesis were correct, then there would be no necessity to assume that adrenaline increases the venous outflow by causing a venous dilatation, a mechanism which has been suggested by Gaddum and Holtz.

It must be admitted that the various lines of approach which have been planned and carried out in order to discover the site of action of adrenaline have yielded results of very little profit. Notwithstanding, the various experiments which have been carried out indicate that however simple the action of adrenaline may be, the complex nature of the arteriole-capillary-venous haemodynamical relations renders any sure interpretation of the results a matter of great difficulty. It may be said that all the results may be explained upon the view that adrenaline causes simple arteriolar constriction which gives rise to an increased vascular resistance and a squeezing out of blood from the lungs. Perhaps the main criticism which could be levelled at this view is that the blood capacity of the pulmonary arterioles is probably insufficient to account/

account for the amount of blood which adrenaline releases from the lungs. It may be, therefore, that adrenaline has an action in dilating the pulmonary venules. If so, the experiments performed are unable to discriminate between this action and that on the arterioles mentioned above. The time relationships of the pressure changes due to adrenaline injections in the preparations perfused in the reverse direction rather suggest that the constrictor action of adrenaline is exerted on the arteriolar side of the capillaries and not on the venules. There is, however, in the reverse perfusion experiments nothing against the interpretation that adrenaline might be causing an inflow (venous) dilatation as well as an arteriolar constriction. Indeed the smaller response to adrenaline as compared with that in forward perfusion experiments might well be due to the venous dilatation component.

The experiments on ergotoxinised preparations suggest that there is a pulmonary vasodilator nerve supply to the lungs, but the results are not conclusive, for reasons that adrenaline might itself be causing relaxation of the pulmonary arterioles by its action on the muscle. The fact that stimulation of the pulmonary sympathetic nerves in ergotoxinised preparations/

preparations causes vasodilatation (Daly and Euler) does not of necessity prove the existence of adrenergic vasodilator nerves because there may have been cholinergic dilator fibres in the sympathetic nerve bundle stimulated.

The experiments on collapsed and expanded lungs give no evidence that adrenaline is acting by dilating the capillaries, although it should be mentioned that Wearn et al.(1934) have produced some evidence that adrenaline does act in this way.

Finally it should be mentioned that the vast majority of experiments in lungs under negative pressure ventilation show an increase in venous outflow to adrenaline. In collapsed lungs Gaddum and Holtz found in 10 experiments that 5 showed an increase in outflow with adrenaline, 3 no effect in outflow and 2 a diminution in outflow. Whether the adrenaline outflow increase is better shown in negative pressure ventilated lungs than in collapsed lungs is hard to judge, but there is no question that venous outflow diminution in lungs under negative pressure ventilation is an extremely rare occurrence, for the reason that in 59 experiments which have been performed in this laboratory and/

and in Birmingham, 56 showed a venous outflow increase to adrenaline and only 3 an outflow diminution.

ACETYL CHOLINE.

Introduction.

The action of acetyl choline on the isolated perfused lungs of the dog shows some interesting features. Both vasopressor and vasodilator effects may be obtained; the vasodilator response appears to be most readily obtained with small doses, and vasoconstriction with large. The question arises as to whether the large doses are having a toxic effect, but both vasodilator and vasoconstrictor effects are increased with eserine and abolished by atropine (Daly and Euler; Gaddum and Holtz).

It appeared possible that one of these two actions of acetyl choline might be peripheral, and the other ganglionic. Chemical transmission occurs at the synapse of a sympathetic ganglion, the transmitter being indistinguishable from acetyl choline (Feldberg and Gaddum, 1933). This action of acetyl choline (or some closely allied substance) has been called "nicotine-like" (Dale, 1933). It was proposed to give injections of acetyl choline after massive doses of/

of nicotine, so that with the ganglia paralysed, the peripheral action alone should be obtained.

It is seen that acetyl choline in large doses has an action similar to adrenaline on the isolated perfused lungs of the dog. It was planned to try the effect of ergotoxine on this adrenaline-like response.

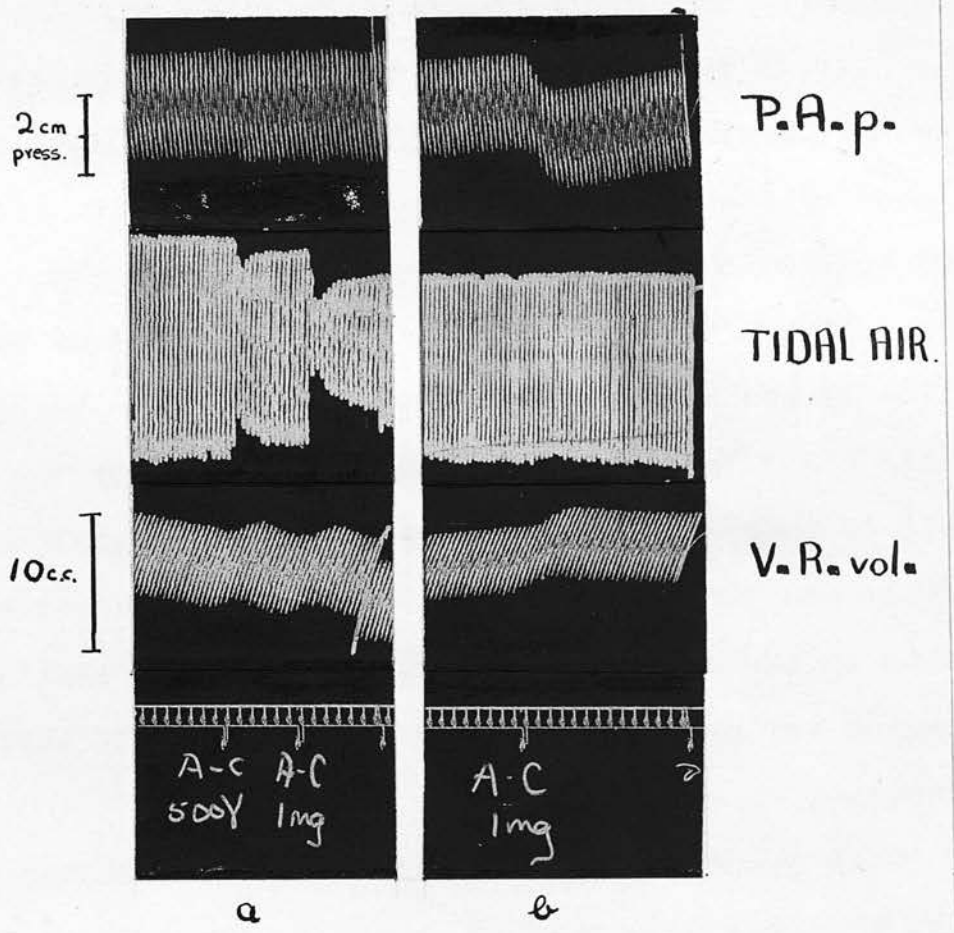
It was also proposed to try the effect of adrenaline on the acetyl choline response. Adrenaline has been found in the isolated perfused lungs of the guinea-pig to increase the pressor response of acetyl choline (Dale and Narayana, 1935). It was proposed to repeat this on the dog in particular to see if adrenaline caused any change of the dilator response to acetyl choline.

It was also proposed to give acetyl choline with the circulation reversed, but these experiments have not yet been done.

Results.

1. The effect of injections of acetyl choline (crystalline, B.D.H.) on the pulmonary arterial pressure is sometimes to cause a rise and sometimes a fall, thus confirming Daly and Euler, Gaddum and Holtz, and Alcock, Berry and Daly (1936). The effect on the outflow was either an increase, no change or a decrease.

Any/



EFFECT OF ADRENALINE ON THE ACETYL-CHOLINE RESPONSE

EXPT 13.9.35. DOG ♂. wt 13·5 Kg. I.P.L. BLED UNDER LOCAL ANAESTHESIA. PUMP AT CONSTANT FLOW. TOP TRACING PULMONARY ARTERIAL PRESSURE (WATER MANOMETER), SECOND TIDAL AIR, THIRD VOLUME OF VENOUS RESERVOIR, FOURTH TIME = 10 secs interval, FIFTH SIGNAL

1st signal - Acetyl Choline 500γ

2nd signal Acetyl Choline 1mg

3rd signal Acetyl Choline 1mg

Between the 2nd and 3rd signal Adrenaline 200γ was given.

FIG. 11.

Any one, therefore, of four effects may be seen (ignoring no change in outflow): one, a fall of pulmonary arterial pressure and a fall of outflow; two, a rise of pulmonary arterial pressure and a fall in outflow; three, a fall of pulmonary arterial pressure and a rise in outflow; four, a rise in pulmonary arterial pressure and a rise in outflow.

2. The effect of dosage. As found by Gaddum and Holtz, the smaller doses tended to give a fall of pulmonary arterial pressure, and the larger a rise (see table). The sensitivity of the preparation to acetyl choline was increased by eserine; after administration of atropine no effects from acetyl choline were seen.

3. The effect of single doses of adrenaline on the response to acetyl choline was tried. In 5 experiments the dilator response of acetyl choline, that is the fall in pressure, was increased by injection of adrenaline (Fig.11). In one experiment the pressor response of acetyl choline was converted to a depressor response.

4. The effect of acetyl choline during a constant infusion of adrenaline (see Table).

Out of 18 injections of acetyl choline given during constant adrenaline infusion, on 6 animals, 14 gave a fall/

A. EFFECT OF INCREASING ACETYL CHOLINE DOSAGE IN NORMAL ANIMAL.

DATE	DOSE	P. A. p.	V.R. vol	TIDAL AIR	P. A. p RECORDER	ESERINE	WHERE INJECTED
25 6 35	50 γ	—	0	0	MAREY TAMBOUR	Abs	P.A
	200 γ	+	0	—		Abs	P.A
28 6 35	50 γ	—	+	—	WATER MANOMETER [1.]	Pres.	V.R.
	100 γ	+	0	cc		Pres.	V.R.
	500 γ	+	+ —	cc		Pres.	V.R.
12 7 35	100 γ	—	0	—	WATER MANOMETER	Pres.	V.R.
	200 γ	+	—	—		Pres.	V.R.
19 7 35	200 γ	+	+	0	WATER MANOMETER	Abs.	P.A
	50 γ	—	0	0		Abs	P.A
30 7 35	50 γ	—	+	—	MAREY TAMBOUR	Pres.	V.R.
	100 γ	+	0	cc		Pres	V.R.
13 9 35	250 γ	—	+	cc	WATER MANOMETER	Pres.	P.A
	1 mg	+	+	cc		Pres.	P.A

EFFECT OF REPEATING EQUAL DOSES.

6 2 35	200 γ	+ —	0	—	MAREY TAMBOUR	Abs	P.A
	200 γ	+	0	—		Abs	P.A
25 7 35	500 γ	— +	+	—	WATER MANOMETER	Abs	P.A
	500 γ	+	+	—		Abs	P.A

1. CC = BRONCHI ALREADY COMPLETELY CONSTRICTED.

B. EFFECT OF INCREASING ACETYL CHOLINE DOSAGE DURING CONSTANT ADRENALINE INFUSION.

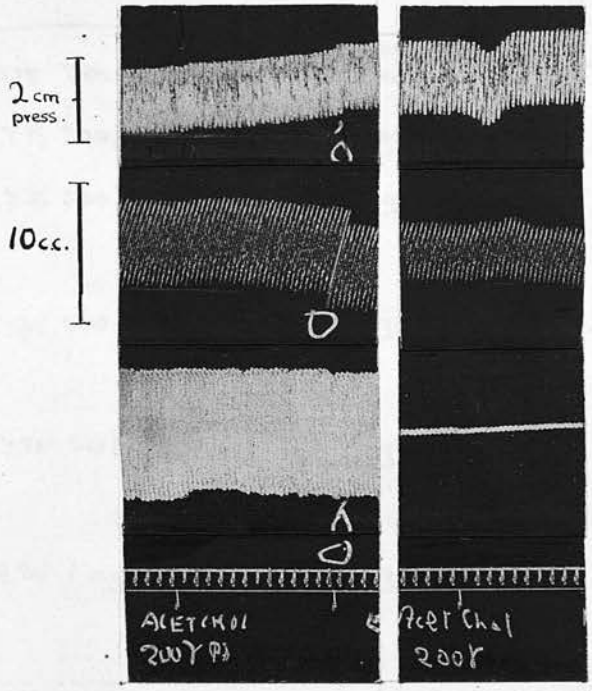
DATE	DOSE	P.A.p	V.R.vol	TIDAL AIR	WHERE INJECTED	P.A.p RECORDER	ESERINE	STRENGH OF ADRENALINE INFUSION PER MINUTE
30935	100γ	0	–	0	P.A	MAREY TAMBOUR	Abs	20γ
	650γ	0	–	–	P.A		Abs	
	100γ	–	+	–	P.A		Pres	
	500γ	+	+	cc	P.A		Pres	
1.10.35	100γ	–	0	0	P.A	MAREY TAMBOUR	Abs	20γ
	500γ	–	+	–	P.A		Abs	
	1 mg	–	+	–	P.A		Abs	
	500γ	–	+	–	P.A		Pres	
2.1035	500γ	–	+	–	P.A	MAREY TAMBOUR	Abs	5γ
	1 mg	–	+	–	P.A		Abs	
	750γ	–	+	cc	P.A		Pres.	
71035	10γ	–	0	0	P.A	MAREY TAMBOUR	Abs	5γ
	50γ	–	0	–	P.A		Abs	
	100γ	–	0	–	P.A		Abs	
	500γ	–	+	cc	P.A		Pres	
	1mg	–	+	cc	P.A		Pres	
91035	1mg	–	0	–	P.A	MAREY TAMBOUR	Abs	50γ
161035	500γ	+	+	cc	P.A	MAREY TAMBOUR	Pres	5γ

fall of pulmonary arterial pressure, 2 no change and 2 gave a rise. The doses were large (from 100γ to 1 mg., with 2 exceptions); eserine was present for 7 of the injections. Compared to the normal preparation without adrenaline, this showed a large preponderance of the pulmonary arterial dilator response. All doses large enough to cause a change in pulmonary arterial pressure except two gave a rise in outflow. In one experiment one milligram of acetyl choline caused a rise in pulmonary arterial pressure before the adrenaline infusion and a fall during the infusion. In another experiment the same dose of acetyl choline caused no effect before the infusion and a fall in arterial pressure during. In a third experiment acetyl choline before the adrenaline infusion caused a fall of pulmonary arterial pressure and a fall in outflow; the same dose during the infusion caused a fall of pulmonary arterial pressure but no change in outflow. Apparently, therefore, the presence of adrenaline increased the occurrence of a depressor response to acetyl choline (see Table). In one experiment evidence was also obtained that adrenaline converted an outflow diminution response to acetyl choline to an outflow increase.

5. Action of ergotoxine on the acetyl choline response (see/

EFFECT OF ERGOTOXINE ON THE ACETYL CHOLINE RESPONSE

ACETYL CHOLINE BEFORE ERGOTOXINE					ACETYL CHOLINE AFTER ERGOTOXINE				PREVIOUS DRUGS.		
DATE	DOSE	P.A.p	V.R.vol	DOSE OF ERGOTOXINE	DOSE	P.A.p	V.R vol	WHERE INJECTED	ESERINE	NICOTINE	OTHER DRUGS
19.7.35	200γ	+	0	2·5mg	200γ	−	0	P.A	Abs	Abs	None
24.7.35	500γ	+	+	3 mg	500γ	−	+	P.A	Abs	Abs	None
					500γ	−	+	P.A	Abs	Abs	None
25.7.35	500γ	+	+	2 mg	500γ	−	+ −	P.A	Abs	Abs	None
					500γ	−	+	P.A	Pres	Abs	None
26.7.35	50γ	−	+	3 mg	50γ	−	0	V.R	Pres	Abs	None
					750γ	−	+	V.R	Pres	Abs	None
29.7.35	1 mg	+	+	3 mg	1 mg	0	0	P.A	Pres	Pres	None
					3 mg	+	+	P.A	Pres.	Pres	None
					3 mg	−	0	P.A	Pres	Pres	ADRENALINE
17.9.35	200γ	+	+	2 mg	200γ	−	+	P.A	Pres	Pres	None
				3 mg	200γ	−	+	P.A	Pres	Pres	None
					500γ	−	+	P.A	Pres	Pres	None
18.9.35	100γ	+	+	3 mg	100γ	+	0	P.A	Pres	Pres	None
					400γ	+	+	P.A	Pres	Pres	None
23.9.35	500γ	+	+	5 mg	500γ	0	0	P.A	Pres	Pres	None
						+	−	P.A	Pres	Pres	None



P.A.p.

V.R. vol.

TIDAL AIR.

EFFECT OF ERGOTOXINE ON THE ACETYL CHOLINE RESPONSE

EXPT 19.7.35. DOG. ♂ wt 8.5 Kg. I.P.L. BLED UNDER LOCAL ANAESTHESIA. PUMP AT CONSTANT FLOW. TOP TRACING PULMONARY ATERIAL PRESSURE (WATER MANOMETER) SECOND VOLUME OF VENOUS RESERVOIR, THIRD TIDAL AIR, FOURTH TIME = 10 SECS INTERVAL, FIFTH SIGNAL.

1st signal. Acetyl Choline 200γ

2nd signal Acetyl Choline 200γ

Between 1st and 2nd signal Ergotoxine 2.5 mg was given.

FIG. 12

(see table). In three experiments the administration of ergotoxine converted a pressor response (rise of pulmonary arterial pressure) of acetyl choline to a depressor response; in one the response was already depressor and was not altered by the ergotoxine. Out of four experiments when the animal was nicotinised, one showed the pressor response reversed by ergotoxine, two showed the pressor response suppressed, and in one the pressor response remained although reduced in size. In the two experiments in which the response was suppressed, increasing the dose to 3 mg. produced a small rise of pulmonary arterial pressure. There is then a tendency for ergotoxine to convert a pressor response to acetyl choline to a depressor (Fig.12).

5. Effect of nicotine. After massive paralysing doses of nicotine both effects, pressor and depressor, of acetyl choline on the pulmonary arterial pressure were seen, and therefore these responses are not dependent upon a nicotine-like action on the pulmonary ganglia.

Discussion.

Both pressor and depressor responses were obtained from acetyl choline, smaller doses giving the depressor, and larger doses the pressor, confirming Gaddum and Holtz.

Adrenaline appeared to increase the dilator response/

response of acetyl choline. It is suggested as a hypothesis that adrenaline is giving tone to the arterioles so that they dilate more readily to acetyl choline. Adrenaline may here be having a similar action to that shown by Dale and Richards, who found the presence of adrenaline to be necessary in obtaining vasodilator effects of histamine in the perfused vessels of the cat.

The type of acetyl choline response which appears to be increased by adrenaline in this preparation is that o of a fall in pulmonary arterial pressure with possibly a rise in outflow. If the hypothesis is put forward that this effect is due to dilatation of arterioles together with constriction of capillaries, then it might be that adrenaline constricting the arterioles made them more ready to dilate, and dilating the capillaries made them more ready to constrict. Here then acetyl choline and adrenaline would be acting in opposition as is the case on most tissues of the body. In view of the fact that the acetyl choline pressor response is inversed, diminished or suppressed by ergotoxine, it may be that acetyl choline is either stimulating adrenergic nerve fibres or has an adrenaline-like action.

It is seen that acetyl choline has predominantly a depressor/

depressor action or at any rate little or no constrictor action during constant adrenaline infusion. It might be argued from this that stimulation of cholinergic fibres would lead to a fall rather than to a rise in pulmonary vascular resistance during exercise, when adrenaline is released. This supposition has the support that it would obviously be of advantage to the animal.

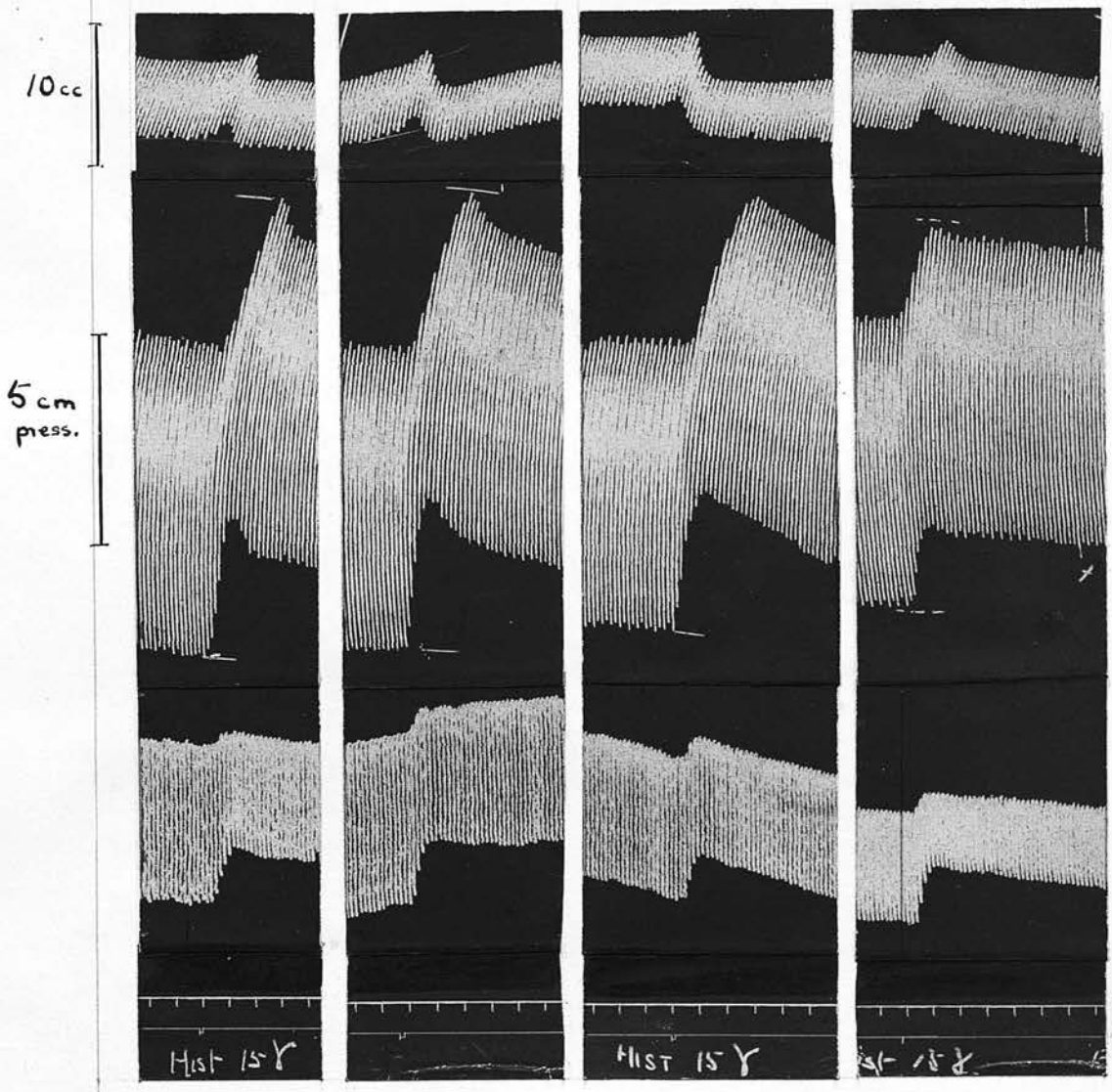
HISTAMINE.

Results.

1. The action of injections of histamine on the pulmonary arterial pressure was pressor. No depressor response has been seen from histamine. The action of histamine was as follows: in the earlier experiments the response was a decrease in outflow (one exception, one injection only). These experiment were done during June and July. Experiments done during September, October, November, December and January, showed sometimes an inflow increase and sometimes a decrease.

2. Effect of dosage. The preparation used was crystalline histamine acid phosphate (B.D.H.), dosage being given in terms of the base.

In no experiment was a fall of pulmonary arterial pressure seen, the minimum effective dose of histamine giving a rise. In some experiments the smallest dose of/



EFFECT OF ETHER ON THE HISTAMINE RESPONSE.

EXPT 29. 1. 36 DOG ♂ WT 13·5Kg. I.P.L. BLED UNDER LOCAL ANAESTHESIA. PUMP AT CONSTANT FLOW. TOP TRACING POLUME OF VENOUS RESERVOIR SECOND PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR), THIRD TIDAL AIR, FOURTH TIME = 30 secs INTERVAL, FIFTH SIGNAL.

Signal 1. Histamine 15γ. No ether.

Signal 2. Histamine 15γ After 10 minutes of ether.

Signal 3. Histamine 15γ Immediately after removal of ether

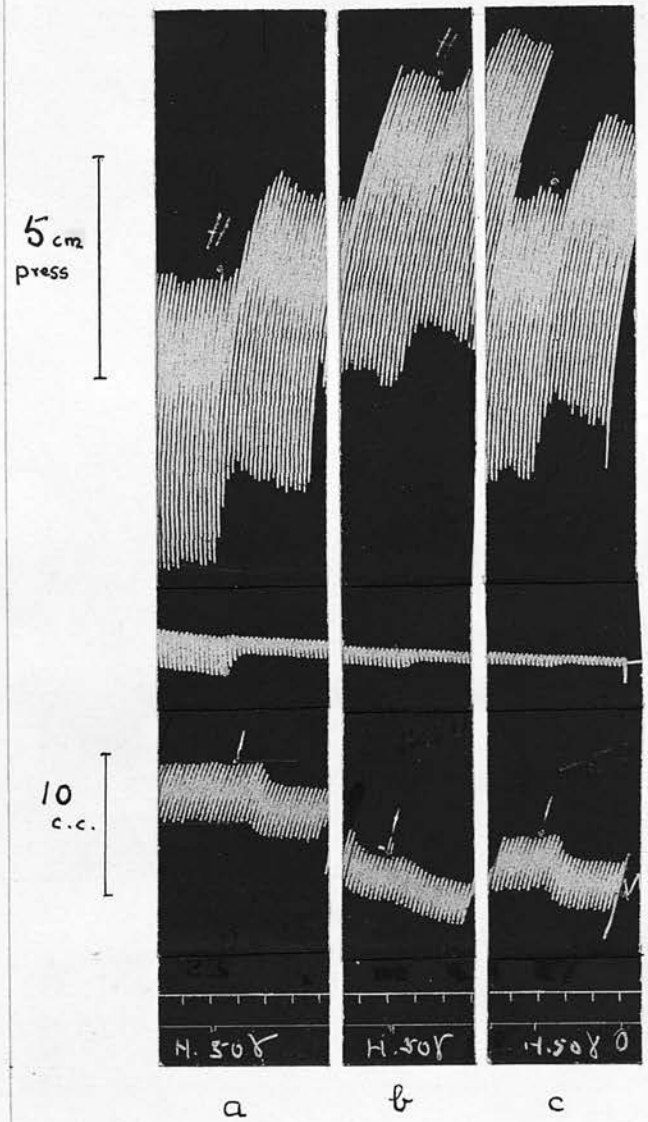
Signal 4. Histamine 15γ 30 minutes after removal of ether.

FIG. 13.

of histamine gave a fall in outflow, but in some a rise in outflow was changed to a fall by increasing the dose.

3. In the earlier experiments, those done during June and July, the typical outflow response was a fall with a rise in pulmonary arterial pressure. In the experiments done during the winter months the outflow response was usually a rise. This gave the impression of a possible seasonal variation, but it was found that in the earlier experiments the animals had been induced by a general anaesthetic (50/50 ether + chloroform). In the later experiments the animals were bled under local anaesthesia. Experiments were then planned to test the effect of anaesthetic ether on the histamine response of the lungs. Ether vapour was put into the lungs by introducing a bottle into the closed circuit between the trachea and the volume recorder. It was found that the pulmonary arterial pressure response was not much altered but the outflow response was changed from a rise to a fall (Fig.13). When the ether had been removed for ½ hour, histamine again caused an increase in outflow. It was noted that in the experiments where the animals were induced with a general anaesthetic, the preparations were less sensitive to histamine generally but gave a fall in outflow.

4./



P. A. p.

TIDAL AIR

V. R. vol.

Fig. 14.

EXPT 29.1.36. DOG ♂ 13·5 Kg. ISOLATED PERFUSED LUNGS. BLED UNDER LOCAL ANAESTHESIA. TOP TRACING PULMONARY ARTERIAL PRESSURE (MAREY TAMBOUR). 2ND TIDAL AIR, 3RD VOLUME OF VENOUS RESERVOIR. 4th TIME = 30 SECS, 5th SIGNAL. DRUGS INTO PUL. ARTERY.

1st Signal: (a) Histamine 50γ

2nd Signal: (b) Histamine 50γ with raised venous pressure

3rd Signal: (c) Histamine 50γ

4. Effect of increasing the venous pressure. It appeared over a series of experiments that a raised venous pressure increased the tendency of histamine to cause a rise in outflow. This was found to be the case on experiment, an increase in venous pressure causing the outflow decrease to become smaller or even to become an increase (Fig.14). Raising the venous pressure, however, holds back some blood in the lungs. There is, therefore, some change in dilution and further experiments are necessary to control this.

Discussion.

Two types of response have been seen from histamine, a rise of pulmonary arterial pressure with a rise of outflow with small doses, and a rise of pulmonary arterial pressure with a fall of outflow with large doses. This double effect on the outflow of histamine can be explained solely by its action on the veins, although by reference to the arguments relating to the action of adrenaline, there are other possible explanations. A small effect, as by small doses, on widely dilated veins will result in a large capacity and a low resistance response; that is, a rise in pulmonary arterial pressure due to arteriole constriction as well as venule constriction and a rise in outflow (capacity effect/

effect). But a stronger effect on partially constricted veins will result in a large venous resistance and a small capacity effect; blood then will be held back in the lungs and the response will be a rise of pulmonary arterial pressure and a fall in outflow.

The action of ether itself when introduced to the lungs was to cause a slight rise of pulmonary arterial pressure and a prolonged fall of lung blood volume (Fig. 9). This effect was unexpected. Burn and Bhatia (1933) found isolated perfused vessels of the hind limb to be unaffected by ether, the sympathetic effects in the whole animal being abolished by nicotine. It is possible the pulmonary vascular bed has a particular sensitivity to anaesthetics.

If the ether which appears to be causing some vasoconstriction is actually partially closing the veins, then it is clear that the same dose of histamine will now cause a fall in outflow, the diameter of the vein having reached the point where further closing will cause resistance rather than capacity effects.

As far as can be judged from the present experiments, the level of venous pressure determines the outflow response to histamine. Histamine injected into preparations with a high venous pressure causes a rise in outflow, with a low venous pressure, a fall

in/

in outflow. This may be explained on the assumption that well filled veins when constricted tend to produce a greater capacity than resistance effect, whereas depleted veins when constricted tend to cause a greater resistance than capacity effect.

GENERAL CONCLUSIONS.

It is seen that the actions of adrenaline and histamine on the isolated perfused lungs of the dog have a marked superficial resemblance. Both drugs cause a rise of pulmonary arterial pressure and both cause sometimes a rise in outflow and sometimes a fall. Some resemblance between the actions of adrenaline and histamine was observed by Dale and Richards (1918) in the hind limb vessels of the cat. To quote from their paper "... the conditions of vascular tone which favour the predominance of either vasoconstriction or vasodilatation in the normally enervated leg are the same for histamine as for adrenaline..." It appeared an attractive theory that adrenaline and histamine acted in these experiments on the pulmonary vessels at the same site, but most of the experimental evidence appears to favour the theory that the resemblance is chiefly superficial and entirely different vessels are contracting with the two drugs.

It is seen that with small doses of acetyl choline and adrenaline typically antagonistic actions are produced/

produced. In larger doses the two drugs also appear to excite the same portion of the peripheral apparatus as evidenced by the action of ergotoxine. The pressor response, however, given by acetyl choline shows this difference to the adrenaline rise that it can be abolished by atropine, therefore adrenaline and acetyl choline action in large doses are not similar in every respect.

SUMMARY.

The actions of adrenaline, acetyl choline and histamine on the isolated perfused lungs of the dog were found to be in general the same as those published by Alcock, Berry and Daly.

The pressor response of adrenaline was not greatly enhanced by cocaine.

The pressor responses of adrenaline and acetyl choline could be reversed by ergotoxine.

The effect of ether on adrenaline was negligible.

The effect of ether on histamine was to convert an increase in outflow to a decrease.

The effect of adrenaline, acetyl choline and histamine on the isolated perfused lungs of the dog were tried under varying conditions.

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REFERENCES.

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APPENDIX.

Action of drugs on the pulmonary circulation of the rat.

Action of drugs on the pulmonary circulation of the rat.

Introduction.

Tribe (1912) working on the rat, found that both vasoconstriction and vasodilatation could be obtained with adrenaline when injected into isolated perfused lungs. In these experiments vasodilatation was only obtained with Parke Davis adrenaline solutions, and it was concluded that the dilator response was due to the presence of chloretone in that preparation.

Hirakawa (1925), using doses of 100γ failed to obtain any response to adrenaline from the blood vessels of the isolated perfused lungs of the rat. Both Hirakawa and Tribe used a constant pressure method of perfusion and kept the perfusion fluid and the lungs at body temperature.

Smith and Bennett (1934) showed that in the whole animal the action of adrenaline on the pulmonary arterial pressure was to cause an abrupt rise of pressure but they did not produce any evidence that this rise was not due to increased cardiac activity.

The present investigation deals with the effects of adrenaline, acetyl choline and histamine on the perfused pulmonary vessels of the rat.

METHOD.

The method of perfusion of the isolated lungs of the rat was similar to that described by Daly, Peat and/

and Schild (1935) for the guinea-pig. The animal was killed by a blow on the head and cannulae were inserted into the trachea, pulmonary artery and left auricle. The animal was then placed in a tank, the temperature of which was kept at 34-37° C. The lungs were perfused with fluid at a temperature of 37-39° C., at constant pressure from a Mariotte bottle. With the constant pressure method changes in pulmonary vascular resistance are readily reflected in outflow alterations. A fall in outflow has been interpreted throughout as vasoconstriction, and conversely a rise in outflow as vasodilatation. The pressure in the Mariotte bottle system was 5-8.5 cm. saline. The outflow from the left auricular cannula was recorded by means of a Harris (1931) drop recorder.

The lungs were respired under positive pressure by means of the respiration pump described by Daly, Peat and Schild. This pump enables the pressure of inflation of the whole of both lungs to be recorded during any part of the inflation cycle, the lungs collapsing by virtue of their own elasticity. A rise in the level of the respiratory pressure (R.P.) curve indicates bronchoconstriction, a fall, bronchodilatation.

A glucose-free Tyrode fluid of the following composition/

composition was used for perfusion: NaCl 0.8 gm., KCl 0.02 gm., CaCl 0.02 gm., $MgCl_2$ 0.01 gm., $NaHCO_3$ 0.1 gm., NaH_2PO_4 0.005 gm. in 100 c.c. distilled water. All drugs for injection were made up in Tyrode fluid warmed to body temperature, and were never more than 0.1 c.c. in volume. The preparations used were for adrenaline, the crystalline base (B.D.H.); for acetyl choline, crystalline acetyl choline chloride (Hofmann La Roche and Co.); for histamine, crystalline histamine acid phosphate, the dosage being given in terms of the base.

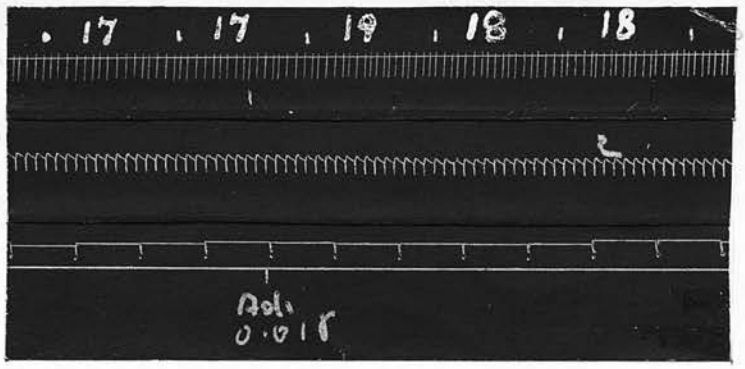
Results.

Dale and Narayana, working on the guinea-pig's lungs have shown that adrenaline may cause both dilatation and constriction of the pulmonary vessels. The vasomotor response to adrenaline appeared to depend in part on the condition of the bronchi. Injections of adrenaline always caused vasoconstriction when the respiratory pressure was low, but produced both vasodilatation and vasoconstriction when the respiratory pressure was high, the vasodilator effects being always accompanied by bronchodilatation. These workers suggest that this vasodilatation is a mechanical effect produced by the release of pressure on the blood vessels through bronchodilatation.

The response of the blood vessels and the bronchi in/

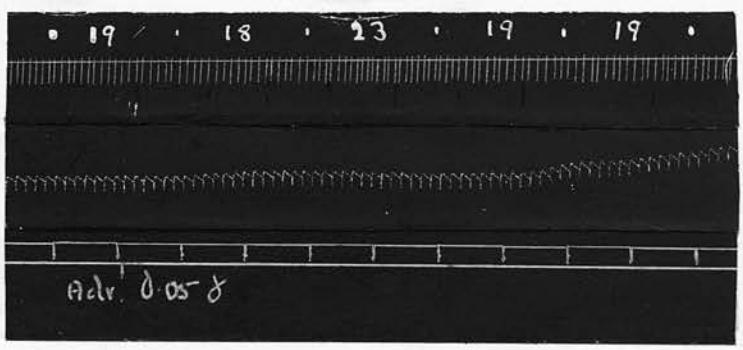
EFFECT OF SINGLE INJECTIONS OF ADRENALINE.

Fig 1.



EXPT 10 12 35. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, SECOND, RESPIRATORY PRESSURE, 3rd TIME = 30sec, 4th signal SIGNAL INJ. OF 0·01γ ADRENALINE

Fig 2.



EXPT 7 12 35. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, 2nd, RESPIRATORY PRESSURE, 3rd TIME = 30secs, 4th signal. SIGNAL INJ. OF 0·05γ ADRENALINE

Fig 3.

EXPT. 2.11.35 RAT. ISOLATED PERFUSED LUNGS TOP TRACING OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE, 3rd TIME = 30secs, 4th SIGNAL. SIGNAL INJ. OF 0·1γ ADRENALINE

in the isolated lungs of the rat to injections of adrenaline is shown in the following table:-

TABLE OF EFFECTS OF INJECTIONS OF ADRENALINE

Dose in γ	Vascular effect	Bronchial effect	No. of tests	No. of expts.
0.01	D	0	1	1
0.05	D	0	3	2
0.1	D	0	3	3
0.1	D then C	not recorded	1	1
0.1	C	0	2	2
0.25	C	0	4	2
0.5	C	0	11	9
0.5	C	sl.D, C-then D,sl.C	3	3
1.0	C	D	3	3
5.0	C	D	2	2

D = dilatation; C = constriction; 0 = no effect; sl. = slight.

The following points should be noted:

1. Small doses of adrenaline produce vasodilatation and larger vasoconstriction (Figs. 1-5, 12).

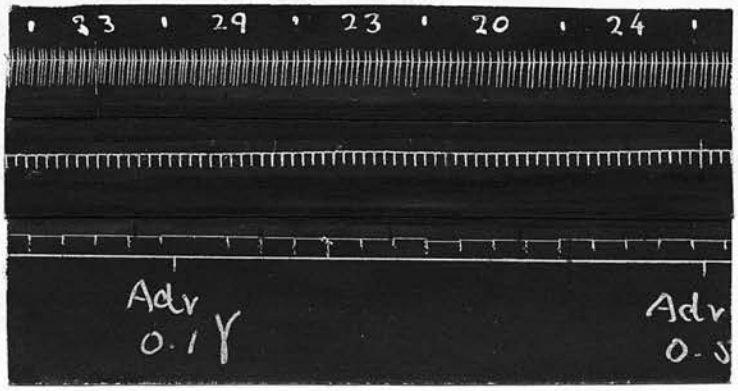
2. That there is no apparent relationship between the vascular and the bronchial effects.

3. That the bronchi appear to be less responsive to adrenaline than the blood vessels. Bronchodilatation was only seen when the bronchi were already partially constricted.

It appears from these experiments that in the pulmonary vascular system of the rat adrenaline may cause both vasodilatation and vasoconstriction in doses which do not affect the bronchial musculature. These results/

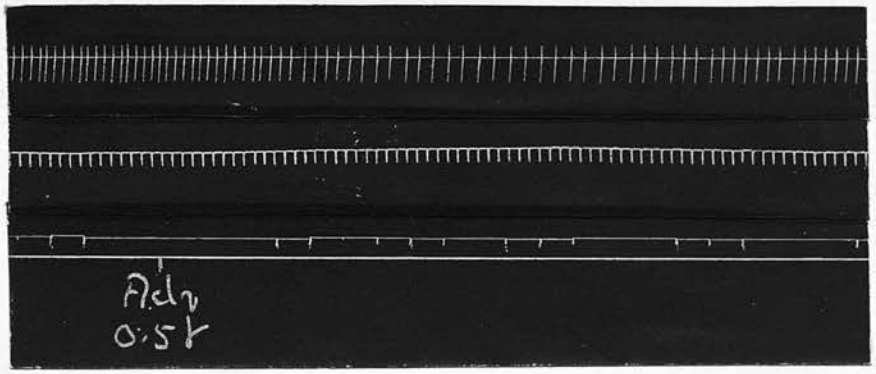
EFFECT OF SINGLE INJECTIONS OF ADRENALINE

Fig 4.



EXPT 5.10.35 RAT ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE, 3rd TIME = 30 secs, 4th signal. SIGNAL, Inj OF 0.1γ ADRENALINE

Fig 5.



EXPT 6.10.35. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE, 3rd TIME = 30secs, 4th signal. SIGNAL INJ. OF 0.5γ ADRENALINE

results are contributory evidence for the finding that vasomotor effects can take place independently of bronchomotor changes (Daly and Euler).

The effect of a constant infusion of adrenaline was investigated in view of the results obtained by Burn (1931) on perfusing the vessels of the hind limb of the dog. Burn found the presence of adrenaline in the perfusing fluid increased the vascular response of the limb vessels to sympathetic stimulation.

In the present experiments injections of adrenaline were given during a constant infusion of the same drug.

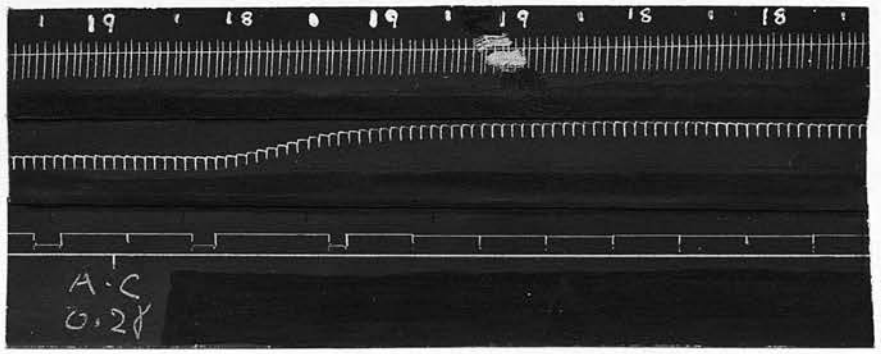
Equal doses were injected before and during the infusion with a view to finding out whether the presence of adrenaline in the perfusing fluid would alter the response. A control experiment in which three injections of 0.5 γ adrenaline were given at 15-20 minutes apart showed a slight decrease of the response (vasoconstriction) with each succeeding dose.

The effect of infusing adrenaline at a concentration of 0.2γ per minute was as a rule negligible, in some cases slight vasodilatation was observed.

In three experiments doses of 0.1-0.25γ of adrenaline were injected before and during infusion of adrenaline. The vasoconstrictor responses during the infusion obtained by the same dose of adrenaline were slightly more than twice the magnitude of the previous responses in each of the three experiments (Fig.9).

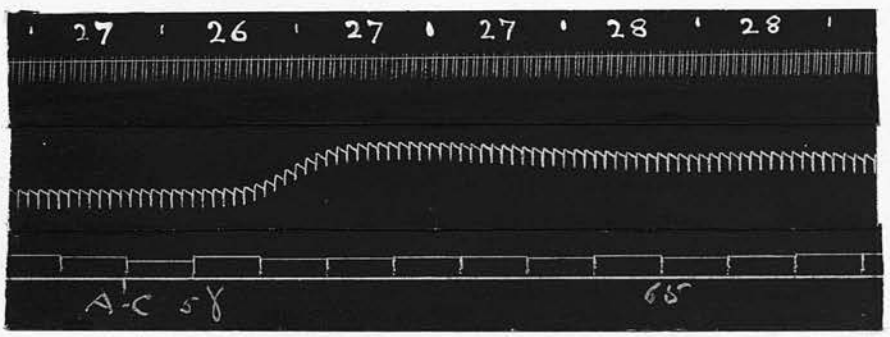
EFFECT OF SINGLE INJECTIONS OF ACETYL CHOLINE.

Fig 6



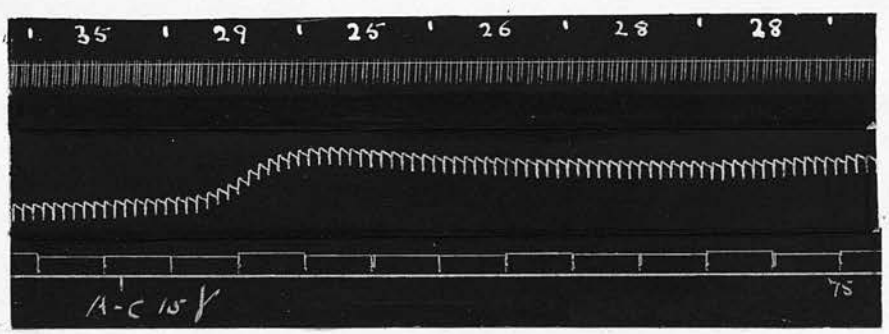
EXPT RAT. ISOLATED PERFUSED LUNGS. TOP TRACING, OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE. 3rd TIME (1ST PART MISSING) = 30secs, 4th signal SIGNAL 0·2γ ACETYL CHOLINE INJECTED.

Fig 7



EXPT. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING, OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE, 3rd TIME = 30secs, 4th signal. SIGNAL 5γ ACETYL CHOLINE INJECTED

Fig 8



EXPT. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING, OUTFLOW BY DROP RECORDER, 2ND RESPIRATORY PRESSURE, 3rd TIME = 30secs, 4TH SIGNAL. SIGNAL 15γ ACETYL CHOLINE INJECTED.

These experiments show that constant infusion of adrenaline causes an enhancement of the vasoconstrictor response to adrenaline injections similar to that observed by Burn on the response to stimulation of the sympathetic chain.

The effect of acetyl choline was more pronounced on the bronchial musculature than on the vascular system. Doses of 0.2-5.0γ showed no definite effect on the blood vessels but they produced some bronchoconstriction. (Figs. 6 and 7). Larger doses (10-50γ) caused vasoconstrictor effects in addition to the bronchial contraction (Fig.8).

It has not been possible with acetyl choline to obtain vascular effects without a concomitant bronchoconstriction. On the other hand, these experiments show that a bronchoconstriction can be obtained independently of vasoconstriction.

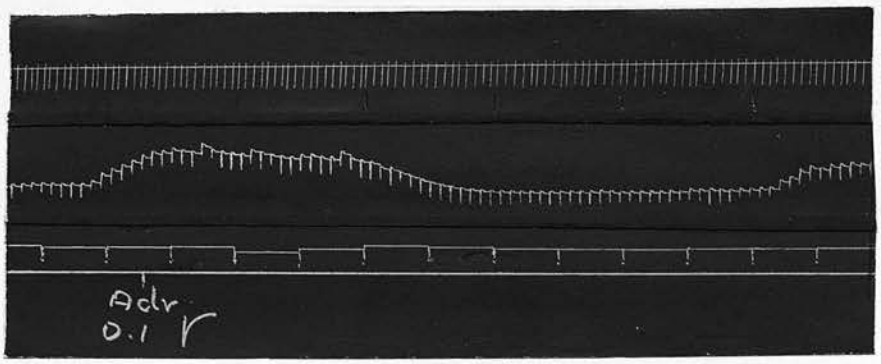
Daly, Peat and Schild have shown that the isolated perfused lungs of the guinea-pig are extremely sensitive to histamine. Doses of 0.1-0.2γ histamine produced a marked bronchial and vascular constriction.

Compared with the guinea-pig the isolated perfused lungs of the rat are insensitive to histamine, the smallest dose giving a response being 5γ, this response consisting/

FIG 9.

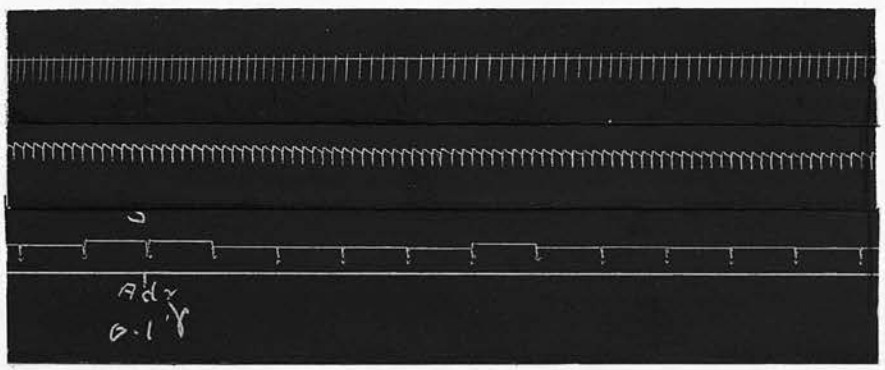
EFFECT OF AN ADRENALINE INFUSION ON INJECTIONS OF ADRENALINE

A



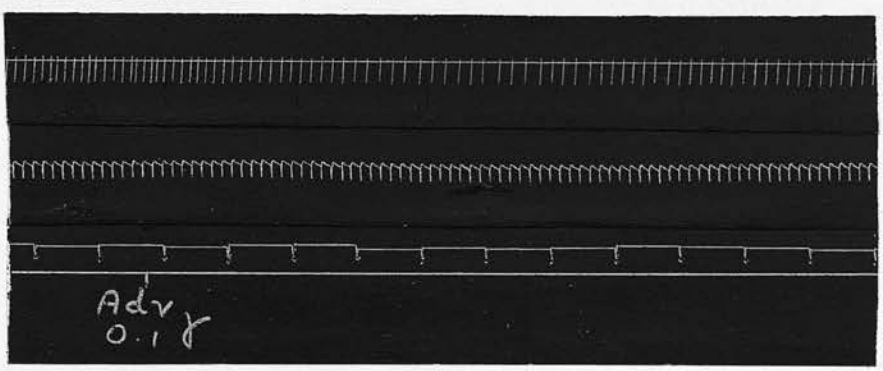
A. EXPT 10.12.36. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, SECOND RESPIRATORY PRESSURE, 3rd Time = 30secs, 4th signal. SIGNAL INJECTION OF 0.1 γ ADRENALINE BEFORE INFUSION

B



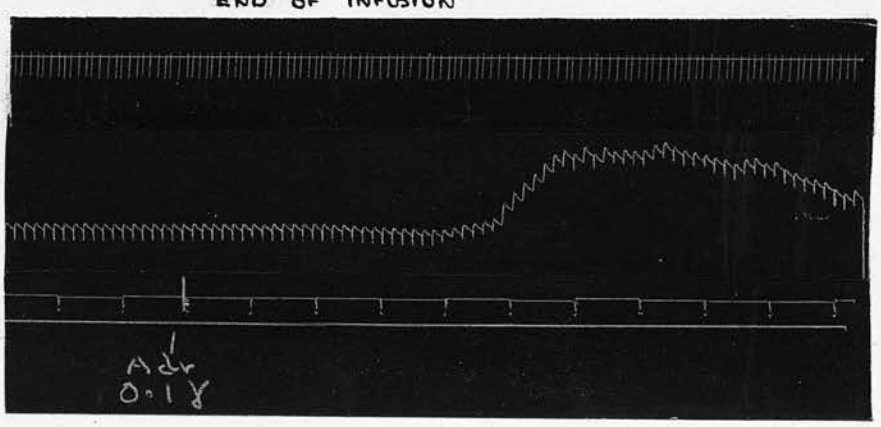
B. SAME ANIMAL. SIGNAL. INJECTION OF 0.1 γ ADRENALINE DURING CONSTANT ADRENALINE INFUSION, 0.2 γ PER MINUTE

C



C. SAME ANIMAL. SIGNAL INJECTION OF ADRENALINE 0.1 γ 8 MINUTES AFTER END OF INFUSION

D



D SAME ANIMAL. SIGNAL INJECTION OF 0.1 γ ADRENALINE 35 MINUTES AFTER END OF INFUSION

consisting of weak vasoconstriction. The effect of histamine both on the blood vessels and the bronchi was in every case constrictor. Doses of 10γ to 1 mg. histamine caused small bronchoconstrictor effects, in no case was complete lung rigidity seen, and the effects were not so large as those obtained with acetyl choline (Figs. 10 and 12). During a constant adrenaline infusion slight vasoconstriction was caused by histamine without a bronchomotor effect (Fig.11).

These experiments show the isolated perfused lungs of the rat are relatively insensitive to histamine, the blood vessels being under certain conditions more responsive than the bronchial system.

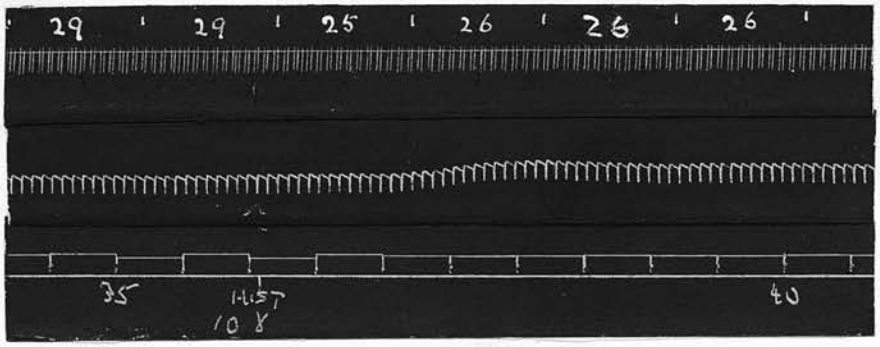
Discussion.

On the blood vessels of the isolated perfused lungs of the rat it was seen that adrenaline caused weak dilatation with small doses and vasoconstriction with large doses. The question of the mode of action of adrenaline in causing vasodilatation has been the subject of considerable discussion. Cannon and Rosenblueth (1935) found that vasodilatation caused by adrenaline (in the ergotoxinised animal) was not abolished by atropine, was augmented by cocaine, and these workers conclude that adrenaline in causing vasodilatation acts directly and not by liberation of acetyl choline.

In/

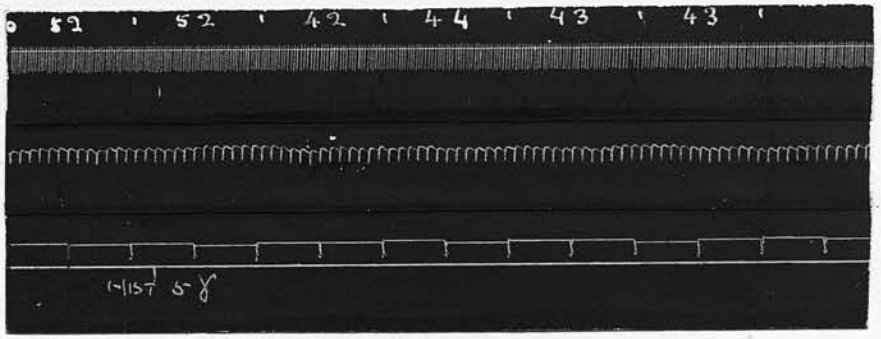
EFFECT OF SINGLE INJECTIONS OF HISTAMINE.

Fig 10



EXPT 2.11.35. RAT. TOP TRACING OUTFLOW BY DROP RECORDER, 2ND RESPIRATORY PRESSURE, 3RD, TIME = 30SECS, 4th SIGNAL. SIGNAL HISTAMINE 10γ INJECTED

Fig 11

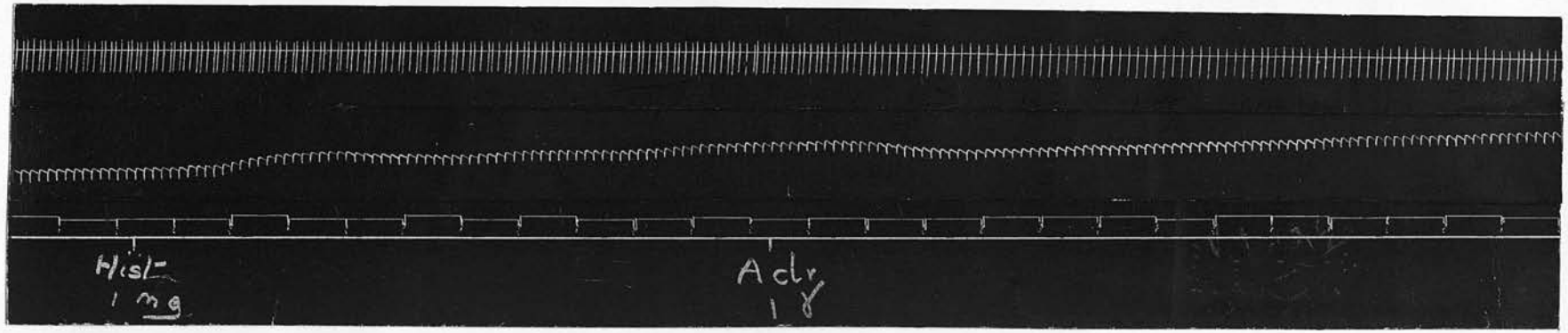


EXPT 2.11.35. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, 2ND RESPIRATORY PRESSORE, 3RD TIME = 30sec, 4th SIGNAL. CONSTANT INFUSION OF ADRENALINE TAKING PLACE, = 0·2γ PER MINUTE. SIGNAL HISTAMINE 5γ INJECTED

In these experiments on the pulmonary blood vessels of the rat, the vasodilator action of adrenaline was not tested out against atropine or eserine, but in view of the fact that acetyl choline caused either no effect or vasoconstriction it seems unlikely that adrenaline was acting by liberation of acetyl choline.

The effect of a constant infusion of adrenaline on the isolated perfused lungs of the rat was shown to increase to some extent the vasoconstrictor response to injections of adrenaline. Burn (1932) found an enhancement of sympathetic excitation effects by a constant adrenaline infusion. His experiments were on the perfused vessels of the hind limb of the dog, and it was shown that the effects of stimulation of the lumbar sympathetic chain were augmented by infusion of adrenaline. Burn puts forward the theory that sympathetic nerves possess a store of adrenaline at the nerve ending; this store may under certain conditions become depleted and stimulation of the sympathetic nerves now have little effect. The adrenaline infusion replenishes this store so that now a larger response is obtained. The experiments on the rat's pulmonary blood vessels show, however, that the presence of adrenaline may increase the response to injected adrenaline. This presents/

FIG 12. EFFECT OF INJECTIONS OF HISTAMINE AND ADRENALINE



EXPT. 5.10.35. RAT. ISOLATED PERFUSED LUNGS. TOP TRACING OUTFLOW BY DROP RECORDER, 2nd RESPIRATORY PRESSURE, 3RD TIME = 30 secs, 4th SIGNAL

1st SIGNAL. 1 MG HISTAMINE INJECTED. 2ND SIGNAL 1·0 γ ADRENALINE INJECTED.

presents another explanation of Burn's results that the presence of adrenaline actually sensitises the tissue to a sudden increase in the concentration of adrenaline.

SUMMARY.

1. The effects of adrenaline, acetyl choline and histamine on the blood vessels of the isolated perfused lungs of the rat were found to be as follows:-

Adrenaline caused both vasodilatation and vasoconstriction, dilatation being seen with smaller doses and constriction with larger.

Acetyl choline caused vasoconstriction only.

Histamine caused vasoconstriction only.

2. A constant infusion of adrenaline was found to increase the vasoconstrictor action of injections of the same drug.

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