ON THE NATURE OF HISTAMINE ACTION.

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THE object of the experiments with which this investigation deals is to study in some detail the cause of the fall in systemic blood-pressure, which occurs when a small dose (·01 mg.) of histamine is injected intravenously.

In 1918, Dale and Richards(1) showed most conclusively that the action of histamine is on the capillaries, and later Dale and Laidlaw showed that the condition of histamine shock was due to increased capacity of the vascular system and lessened output of the heart. The early part of the fall in systemic blood-pressure produced by large doses of histamine they considered to be accelerated by pulmonary constriction which greatly diminished the flow of blood to the left side of the heart. With regard to the fall of blood-pressure which follows small doses, Dale and Richards (1, p. 163) state that "it is not a volume effect due simply to increased capacity of the system, but to a diminished peripheral resistance." This conclusion they based on a careful and elaborate series of perfusion experiments in which they found that there was a diminished peripheral resistance if histamine was added to the perfusion fluid (Ringer-Locke solution containing blood corpuscles and a trace of adrenalin). This evidence was supported by the result found by Dale and Laidlaw(2) that histamine produced larger excursions of the lever in cardiometer tracings; this was interpreted as indicating an increased output of the heart. From these experiments therefore it was assumed that more blood-pressure reached the heart during the action of histamine, a result which would be expected if the peripheral resistance was diminished.

The immediate impulse which led to the commencement of the present investigation came from finding that the venous pressure did not always rise as would be expected if there was a diminution of peripheral resistance and if more blood passed through to the veins. Moreover, when it rose, neither its onset nor its magnitude bore any constant relation to the systemic change, as might with reason be expected if they were due to the same cause.

Method. All experiments were made on cats anæsthetised in the first instance with ether; when deeper anæsthesia was required a chloroform-ether mixture, or chloroform alone, was used. Venous pressure was recorded by a method described elsewhere(3).

The question of dose was first considered. If under light anæsthesia a small dose such as ·01 mg. was given, there was a rise of venous pressure; as the dose was increased the rise became less and when the shock dose was approached there was usually a fall in venous pressure. These results appeared to support the conclusions of Dale and Richards and the results of Connet(4) who obtained a fall of venous pressure with relatively large doses (·5 mg.). But in view of the fact that Dale had called attention to the action of anæsthetic in making carnivora sensitive to the histamine, the depth of anæsthesia was varied. It was found that the venous response was markedly altered. Under light anæsthesia with a dose of ·01 mg. there was a rise of venous pressure as stated above, but under deep and prolonged anæsthesia there was a venous fall, although the systemic fall was about the same in both instances (Fig. 1). An explanation for this venous alteration was sought for. It might be said that the general sensitivity had increased and that the small dose was now having the effect of a large dose. This may readily be dismissed as the fall in arterial pressure does not necessarily change in magnitude although the venous response alters completely. An alteration in venous response without modification of the arterial suggests in itself that they are due to different causes.

It might also be said that deep and prolonged anæsthesia weakened the heart and that the histamine would then stimulate it, causing it to empty itself more effectively and so lower the venous pressure. While such anæsthesia is liable to cause high venous pressure through cardiac weakening, the same fall of venous pressure occurred in some cases when the venous pressure was not abnormally high (Fig. 2). Even if histamine stimulates the isolated heart, it does not follow that it stimulates the heart in the body. Dale and Laidlaw in their earlier paper came to the conclusion that the heart was weakened, and the occurrence of obvious cardiac failure on the injection of a small dose of histamine in an animal whose heart is already weak shows that the total effect of the histamine in the heart is to reduce rather than to improve cardiac efficiency. Further, when the pulmonary circulation is impaired or paralysed there is no evidence that the heart is benefited by histamine. Such benefit would show itself by a rise in pulmonary pressure, but at the stage just mentioned lessened efficiency of the heart may be evidenced

by irregularity of the heart's action and a fall in the pulmonary pressure (Fig. 2D). It is therefore concluded that cardiac effects following the

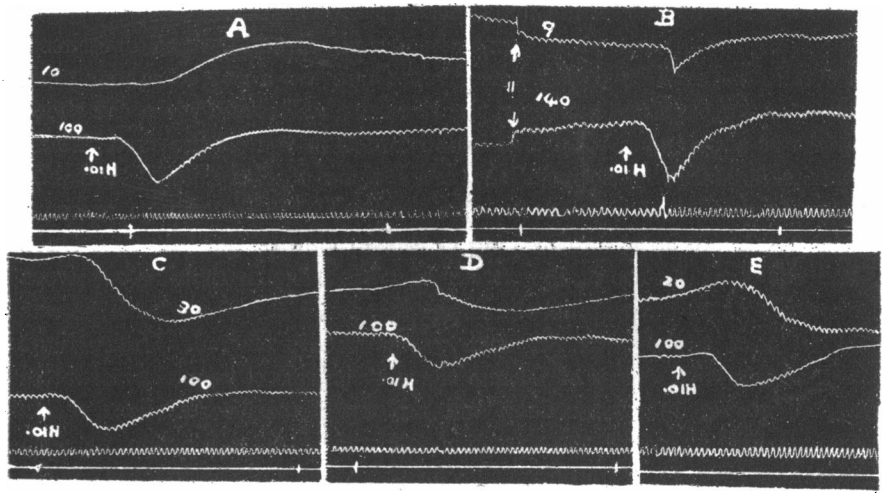

Fig. 1. Cat 3. 1 kg. C.E. mixture. Effect of varying anæsthesia on the change of venous blood-pressure caused by injecting ·01 mg. histamine. The upper tracing is the venous pressure in mm. H_2O; the lower tracing is the carotid pressure in mm. Hg. Natural respiration. Time in minutes. At each arrow ·01 mg. of histamine was injected.

A. Ordinary sufficient anæsthesia. Rise of venous pressure.

B. Later, anæsthesia throughout, corneal reflex still present, only slight rise of venous pressure. The primary venous fall is due to an inspiratory gasp seen in respiration tracing.

C. Anæsthesia increased. Venous pressure large fall.

D. Anæsthesia lessened. Venous pressure fall decreased.

E. A few minutes later, rise of venous pressure.

injection of histamine are insufficient to explain the change in the venous pressure response under deep anæsthesia.

The most satisfactory explanation appears to be that the rise of venous pressure which occurs under light anæsthesia is one due to backward pressure or obstruction in the pulmonary circulation, and that the anæsthetic removes the pulmonary obstruction. Histamine as first shown by Dale and Laidlaw(2) using the method of Bradford and Dean(5), constricts the pulmonary vessels to a marked degree (cp. Fig. 2A). They have shown in relation to large doses that the sharp initial fall in systemic arterial pressure is due to this cause, and it will be seen below that even with small doses this factor may make itself manifest. When it is remembered that the right ventricle is

already impaired by the lowered and falling aortic and coronary pressures, it is not difficult to imagine that it is no longer able to empty itself against the increased resistance in the pulmonary vessels.

Now it has been shown by Brodie and Dixon that the action of the vagus on the bronchial muscles may be greatly reduced or may be obliterated by deep anæsthesia. I have found that the action of adrenaline on the bronchioles may be similarly reduced and have brought forward evidence(8) that the action of amyl nitrite on the pulmonary vessels may be prevented by deep chloroform anæsthesia. This is presumed to be due to the local action of the anæsthetic on the lungs themselves. When the effects of anæsthetics on living tissue generally are considered it is indeed difficult to see how the lung tissues can escape serious impairment when exposed to anæsthetic vapour for prolonged periods.

As has been said above, the rise of venous pressure following a small dose of histamine disappears under deep and prolonged anæsthesia, and I have suggested that the rise is due to backward pressure from the lungs. Demonstration that the pulmonary constriction is reduced or abolished by such anæsthesia would be strong circumstantial evidence in favour of the suggestion. Experiments were therefore made to test this point. Pulmonary pressure was recorded by the method of Sharpey Schafer(9) and it was found that on varying the depth of anæsthesia a series of changes parallel to those in the venous pressure could be obtained when histamine was injected. At first under light anæsthesia there was the typical rise in pulmonary pressure (Fig. 2A), but as the anæsthetic was deepened there was a delay in the pulmonary rise (this point was first noted by my colleague Mr Winfield who witnessed the experiment) and later it lessened (Fig. 2B) and then it disappeared entirely (Fig. 2C). If the experiment be prolonged there may be an actual fall of pulmonary pressure (Fig. 2D) which may be considered to be due partly to cardiac weakness and partly to less blood reaching the right side of the heart.

The results just given lead me to consider that the fall of systemic blood-pressure caused by a small dose of histamine in an animal under light anæsthesia is due mainly, if not entirely, to pulmonary constriction causing decreased output of the left ventricle and not to decreased capillary resistance. Thus the histamine effect does not indicate that variation in capillary resistance plays an important part in the circulation as Dale and Richards suggest it does. Any increased flow into the veins is probably annulled by increased capillary capacity. The

experiments of Dale and Richards mentioned above were made on tissues removed or isolated from the body and the results are not

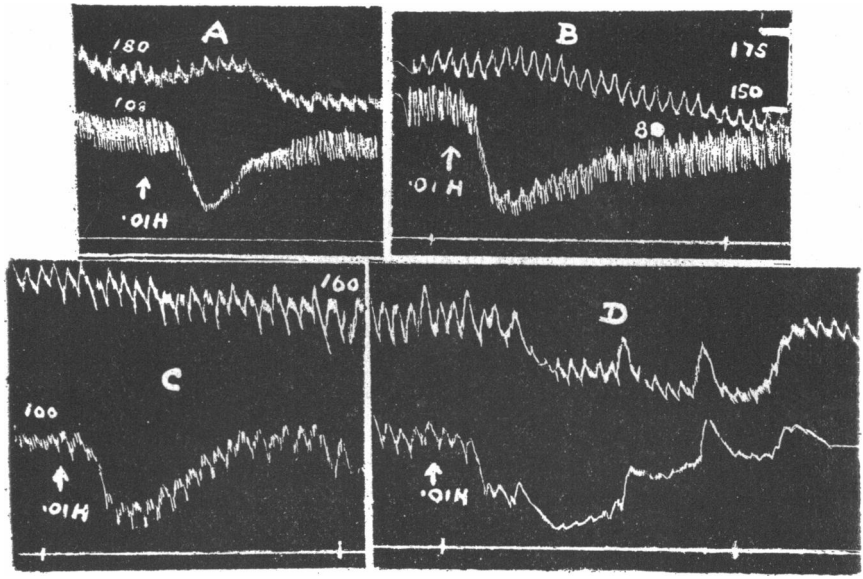

Fig. 2. Cat. C.E. mixture. Effect of varying anæsthesia on the blood-pressure in the pulmonary artery. Upper tracing, pulmonary blood-pressure in mm. H_2O. Lower tracing, carotid pressure in mm. Hg. At each arrow ·01 mg. of histamine injected. The anæsthetic was increased *A* to *D*.

A, rise of pulmonary artery blood-pressure. The rise is often much more marked. *B*, a slight rise; *C*, no rise; *D*, a fall.

necessarily applicable to the normal circulation. It is true the evidence is deficient on two points. (1) That the rise of venous pressure never occurs unless there is pulmonary constriction and (2) that the pulmonary constriction is always sufficient to prevent the heart emptying itself normally. Owing to other factors which arise these points do not seem to be capable of absolute experimental proof.

The increased pulmonary resistance caused by histamine accounts for some of the other effects which it produces or may produce.

(*a*) It was noted by Bayliss in some unpublished experiments privately communicated to me that the venous rise caused by a small dose of histamine sometimes did not occur until the systemic blood-pressure was beginning to return to its normal level. This delay can, I find, be brought about by the anæsthetic and it is the natural result of the decreasing excitability of the pulmonary tissue to histamine.

(*b*) Dale and Laidlaw noted that on the injection of a large dose of histamine, the systemic fall frequently took place in two stages. The first stage they considered was due to pulmonary constriction cutting off the blood from the left side of the heart, the second to increased capacity of the system. In one experiment I obtained a similar fall in two stages on injecting a small dose of histamine (Fig. 3). If the first

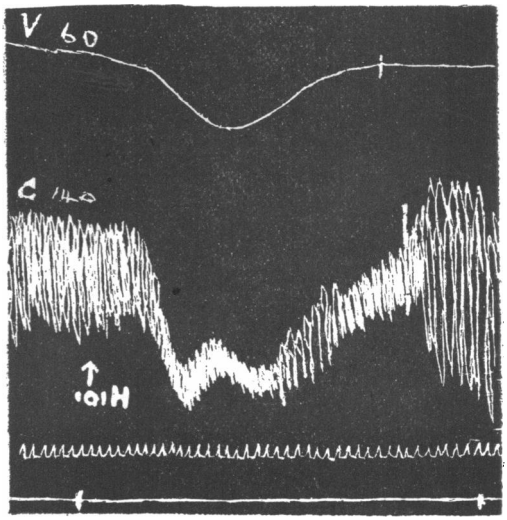

Fig. 3. Fall of systemic blood-pressure caused by a ·01 mg. histamine. (This was the only case under light anæsthesia observed in which ·01 mg. caused a fall of venous pressure.) Two stages seen.

stage in one case is due to pulmonary constriction, it may be assumed to be so in the other. In this experiment there was a fall in venous pressure (Fig. 3) so that in this experiment the effect of the pulmonary constriction was more than counterbalanced by the increased capacity of the capillaries just as ordinarily occurs on injecting a large dose of histamine.

(*c*) I have also found that in shock when the capillaries are already dilated, there is still a rise in venous pressure. Such a rise could not be due to more blood passing through to the veins as there was evidence of increased peripheral resistance, indicated by a rise of the systemic pressure from arteriole constriction. Investigation of the pulmonary circulation at this stage showed that the pulmonary rise could still be obtained, although the usual systemic arterial fall did not occur. It is

assumed then that the venous rise was due to the pulmonary constriction.

SUMMARY.

The parallelism between the disappearance under deep anæsthesia of the rise of pressure in the pulmonary artery and the rise of venous pressure which occurs as the result of the injection of a small dose of histamine suggests that they are both due to the same cause, namely, pulmonary constriction which is affected by the anæsthetic. Other results are given which support this view.

If the anæsthetic is increased so as to abolish the pulmonary effect, there is a fall of venous pressure although the systemic arterial fall may not have altered, nor the heart have been weakened.

The results indicate that the fall of arterial pressure which occurs on the injection of a small dose of histamine is the result of diminished output of the heart, due partly to pulmonary constriction, and partly to less blood reaching the heart as a result of increased capacity of the capillaries, and not, as Dale and Richards hold, to decreased capillary resistance.

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