HISTAMINE SHOCK. By O. INCHLEY.

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It is generally accepted that histamine is a direct poison to capillaries, leading to their dilatation. Dale and Richards(1), and Dale and Laidlaw(2) have shown that in histamine shock the capillaries are dilated, and that this is associated with a fall of blood-pressure and a state of collapse. Krogh(3) has shown that capillaries constantly perform active changes in calibre and suggests that there are "arteriomotor and capillariomotor systems which are able to act in opposite directions."

The contractile power of the veins had been observed as early as 1863 by Goltz(4). Rouget(5) discovered certain cells on the capillaries which have been studied by Vimtrup(6) who ascribes to them the function of constricting capillaries, though no active dilator mechanism has been described. Krogh thinks that the constrictor cells of Rouget are traceable to, and gradually merge into the plain muscle fibres of the veins and arteries. Gunn and Chevasse(7) have demonstrated the constriction of the veins by adrenaline. In the case of arterioles, dilatation when it occurs is obviously passive, the dilating force being derived from the heart. It is conceivable that, even in an excised organ, portions of capillaries, actively constricting, might squeeze their contents into adjacent capillaries, giving appearances under the microscope suggesting active dilatation. Microscopical observations, therefore, become difficult to interpret, and Krogh(8) describes, from observations on the frog, constriction occurring in certain capillaries at a time when dilatation is obtaining in adjacent ones.

Capillary dilatation is the characteristic phenomenon of histamine shock as well as of shock by other substances. Dale's view, which is generally accepted, is that histamine acts directly on the capillaries. The present experiments suggest another and simpler explanation to account for the effect, namely, that the dilatation of the capillaries is passive, and due to constriction of the veins. In a circulation through intact arteries, capillaries and veins, where a variable resistance may be imposed in any one of the three, it is difficult to draw conclusions as to which is affected in altered circulatory conditions. Each of these three factors of the circulation must be examined separately.

Experimental.

I. *Perfusion of arteries and capillaries without veins. Perfusion of veins and capillaries without arteries.* The first experiments were made by using isolated organs artificially perfused and excluding either arteries or veins. The organs of cats and rabbits were employed. The animals were killed by pithing. Cannulæ were placed in the main artery and vein of the isolated organ and the organ was then freely incised so that, during a perfusion through either the artery or the vein the fluid would escape, in the main, through the capillaries when the vein or artery respectively had been previously occluded. The methods of doing this necessarily varied with the organ employed. Thus, in the case of the intestine, the intestinal loop was opened up along the side distant from the mesentery: in the liver, the viscus was scarified with a hard wire brush: in the limb, the muscle tissue was similarly scarified after removing the fascia lata. Valves are absent or rudimentary in the mesenteric veins so that the perfusion backwards is easy under low pressure: in the limbs the pressure must be increased sufficiently to render the valves in these veins incompetent. The following protocol is typical:

Cat. Loop of small intestine 15 cm. long, removed. Mesenteric artery clamped. Mesenteric vein perfused with oxygenated Ringer under a pressure of 25 cm. Small intestine incised.

Number of drops in outflow in consecutive 30 sec.: 17, 25, 25, 24, 27, 26, 25.

After injection of 2 c.c. histamine phosphate 0·1 p.c. into tube supplying the vein the drops registered 15, 15, 14, 15, 14, 14, 13, 13, 14, 15, 14.

It is known (2) that the rabbit responds to histamine differently from the cat. It is a suggestive fact that this unusual reaction of rabbits to histamine should be associated with the fact that histamine has little constriction effect on the mesenteric veins.

As the flow through a pipe varies directly as the difference of pressure between the two ends, and inversely as the resistance in the pipe, and as in each of my experiments the pressure was kept constant, the resistance interposed as the result of histamine may be expressed as a ratio, namely, the outflow before histamine, divided by the lowest outflow obtained during histamine perfusion; these resistances, for the vessels of the cat, may be thus tabulated:

Organ	Vessel	Outflow before hist.	Outflow during hist.	Resistance
Intestine	Vein	25	13	2
	Artery	15	5	3
Liver	Portal vein	75	10	7·5
		6·5	1·6	4
	Hepatic vein	12	9·5	1
Hind limbs	Vein	2·2	0·9	2·4
	Artery	5	1·5	3

Mautner and Pick(10) also observed marked obstruction of the hepato-portal circulation after histamine.

These experiments show that histamine phosphate causes powerful constriction of both veins and arteries in the concentrations used. Ringer solution adjusted to the same *p*H causes slight relaxation. It becomes necessary to explain why histamine causes a fall of blood-pressure with dilated capillaries, while adrenaline does the opposite. To obtain an answer to this it was suggested to me that the preparation be perfused with very dilute solutions of histamine in oxygenated Ringer, using veins and arteries alternately, to determine whether the one were more sensitive than the other in such dilutions. A preparation was made of the small intestine of the cat; one cannula was placed in the mesenteric vein supplying oxygenated Ringer at a low pressure from one funnel; another cannula was placed in the mesenteric artery supplying similar Ringer from a second funnel at a higher level. After the outflow had been provided for by the longitudinal incision in the gut, by the occlusion of one cannula, the perfusion could be obtained by the other. Perfusion by each channel was made alternately; the heights of the funnels were adjusted so that an approximately equal outflow was obtained in both cases. Perfusions with different concentrations of histamine were then made through the vein and artery. Fig. 1 is the record of a typical experiment under these conditions, and it shows that the veins are more sensitive than the arteries to histamine and constrict before the arteries are appreciably affected.

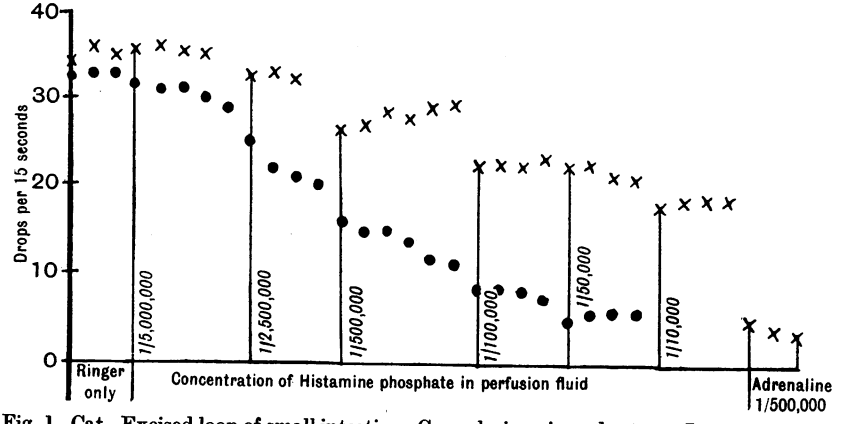

Fig. 1. Cat. Excised loop of small intestine. Cannulæ in vein and artery. Intestine incised. Outflow recorded in drops during intervals of 15 seconds. The perfusion fluid was supplied to the vein under a pressure of 28 cm. Ringer, to the artery under 80 cm.

× = artery. • = vein.

II. *Perfusion of arteries or veins without capillaries.* A preparation of the small intestine of the cat was made as described above, except that instead of an incision in the gut the intestine was cut away along the line of the mesenteric attachment, the vascular loops which course along the edge of the mesentery being retained in the preparation. As before, the height of the funnels was adjusted to give approximately equal outflows from either vein or artery. The following experiment is typical:

Cat. Excised loop of small intestine. Cannulæ in vein and artery. Small intestine removed. Outflow recorded in c.c. during intervals of 1 minute. Perfusion fluid supplied to vein under pressure of 10 cm. to artery under 51 cm.

	Outflow: c.c. per min.						
Fluid	Perfusion of vein			Perfusion of artery			
Oxygenated Ringer	34	34		35	36		
Hist. phosph. 1/5,000,000	15	17		37	37		
Hist. phosph. 1/500,000	10	11	11	36	34	35	33
Adrenaline 1/500,000	6·5	7	7·5	5	6		

These experiments show, in so far as perfusion experiments are valid for the purpose, that histamine acts in the same way whether a simple arterial system is used or whether an arterio-capillary system: and that histamine acts identically on a venous and on a veno-capillary system. One is forced to the conclusion that the capillaries play an insignificant part in the phenomenon.

If the isolated organ with the vessels in their natural sequence is considered there is reason to believe that histamine when perfused should here also exert effects on the veins and arteries such as I have shown in the separated vessels. If this be so, increased resistance in the veins with unaltered arterial resistance must cause (1) increased capillary pressure, (2) distention of capillaries, (3) diminished flow. If adrenaline increases the resistance in the artery more than it does that in the veins, then there should follow, (1) diminished capillary pressure, (2) diminished distention of capillaries, (3) diminished flow. If the normal animal has an efficient controlling mechanism on each of these resistances, the capillary pressure and the rate of flow could each be separately adjusted to requirements.

III. *Ring preparations.* These results were confirmed by using a different method. Ring preparations of the mesenteric artery and vein of the pig (from the slaughter house) were suspended in the same bath of oxygenated Ringer; simultaneous records of their movements obtained, and the effects on them of different concentrations of histamine recorded. It was found that small concentrations, such as 1/1,700,000 caused

constriction of the vein only, much stronger concentrations, such as 1/100,000 being required to affect the artery (see Fig. 2). That the artery

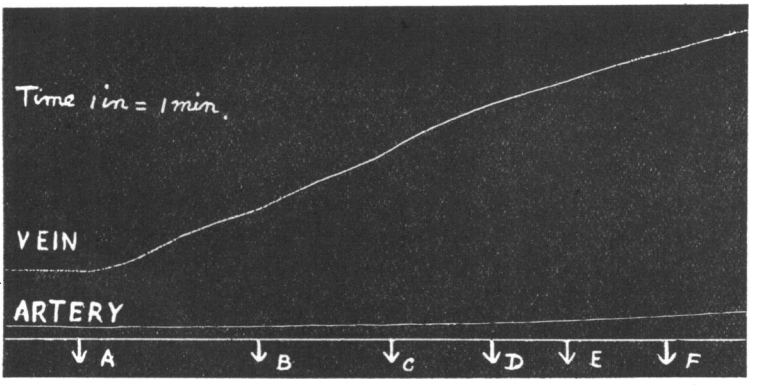

Fig. 2. Isolated mesenteric artery and vein of pig suspended in a bath of oxygenated Ringer 250 c.c. capacity. Histamine phosphate 0·1 p.c. was added by pipette, 20 drops from which equals 1 c.c. In the figure $A=3$, $B=6$, $C=20$, $D=20$, $E=20$, $F=20$ drops. The tensions on the thread attached to vein and artery were in the proportion of 1 : 3 respectively.

was responsive to drugs was shown by the fact that it entered into maximal contraction on the addition of adrenaline. This method was also used with the pulmonary artery and vein of the pig. Here the smaller pulmonary veins, about 1·5 mm. diameter, constrict with histamine while the corresponding arteries do not; on the other hand, the larger arteries constrict under histamine while the corresponding veins do not. Cow(9) found that the pulmonary artery may be divided into two portions, that without the lung reacting to adrenaline like other arteries, that within the lung either not affected or actually dilated. Fig. 3 shows

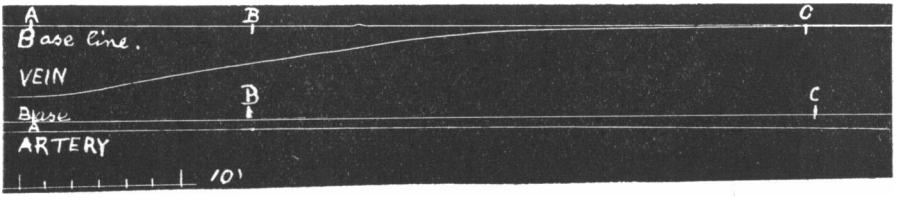

Fig. 3. Isolated pulmonary artery and vein of pig suspended as in Fig. 2. In this experiment the tension on the thread attached to the ring was 0·6 grm. in each case. At *A*, 2 drops of 0·1 p.c. histamine phosphate were added to the bath, at *B*, 20 drops and at *C*, 10 drops of adrenaline 0·1 p.c.: the vein constricts but not the artery.

the effect of histamine on these small vessels. Vessels of this calibre are found branching off at right angles from the main stems in the body of the lung. Fig. 4 shows the effect on larger vessels, about 5 mm.

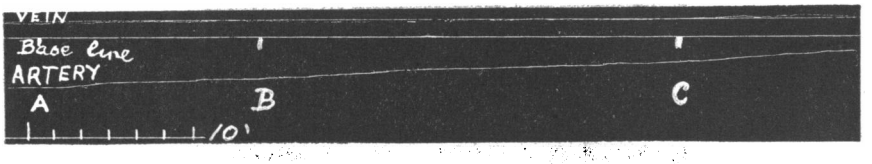

Fig. 4. (See text.)

diameter. At *A*, two drops of the histamine solution were added, at *B*, two drops more, at *C*, eight drops: the artery contracts but not the vein.

These experiments suggest that vascular constriction under histamine is mainly venous.

IV. *Experimental occlusion of veins in anæsthetised animals.* If the preceding experiments give a valid interpretation of histamine action then experimental obstruction of veins by mechanical means should also produce histamine-like effects. Occlusion of certain large veins was made by applying pressure. The veins used were, (1) the inferior vena cava above the entrance of the renal veins, and (2) the portal vein. Cats anæsthetised with urethane were employed and the effects were found to differ according to whether the occlusion period was short or long. Occlusion for one minute of either the inferior vena cava or of the portal vein caused a slight fall in blood-pressure with rapid recovery to normal on releasing the vein. Occlusion of the portal vein for 14 minutes caused marked fall in blood-pressure with sometimes failure of respiration. On release the blood-pressure showed only a partial recovery.

Occlusion of portal vein and vena cava together for 30 minutes caused a profound fall of blood-pressure which on release did not recover, the animal remaining permanently collapsed (Fig. 5). At this stage intravenous injection of Ringer, 50 c.c. slowly administered, did not appreciably improve the condition. Adrenaline injections caused a marked but temporary rise in blood-pressure which, however, rapidly returned to the previous level of collapse. *Post mortem*, the intestinal mucous membrane is practically normal, in colour salmon pink rather than yellow; the surface shows the normal velvety appearance, not the glassy uniform surface of œdema. This absence of congestion and œdema is

explained by the low blood-pressure, for if a short loop of intestine in a normal anæsthetised cat be ligatured at either end and its vein occluded

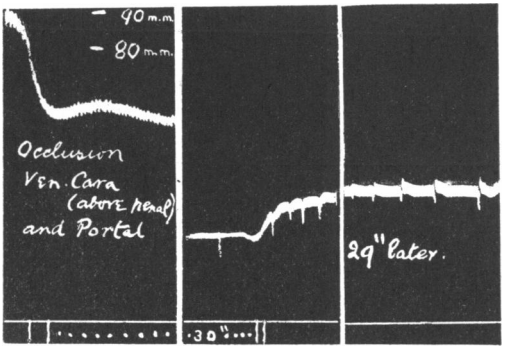

Fig. 5. Cat. Urethane. Shows the effect on the blood-pressure of occluding by pressure for 30 minutes the inf. vena cava and portal vein.

for 30 minutes, no great alteration of general blood-pressure occurs, but *post mortem* the intestine is plum coloured, œdema of the mucous membrane is obvious, and punctate hæmorrhages are seen under the peritoneal surface of the gut: here the sustained general blood-pressure accounts for the high capillary pressure and consequent œdema.

The fall of blood-pressure during occlusion of large veins is easily explained. Krogh(8) has emphasised the great capacity of distended capillaries. The animal "bleeds into its own capillaries" and the effective volume of circulating fluid is so diminished as to cause the fall in blood-pressure observed. The permanent low blood-pressure and collapse following after release from prolonged obstruction of great veins is also easy to explain. Here resiliency of vascular tissue, which is effective in returning the pent-up blood after obstruction of short duration, becomes ineffective. Such resiliency would appear to be in the capillary region and may be the effect of the tonus, either of Rouget cells or of the capillary wall itself. Perhaps, under prolonged distention, such tissues may lose their tone. If this be so the condition is analogous to that which obtains during digital dilatation of the anus and other sphincters. Such response to abnormal and continued distention may be inherent in plain muscle. Many explanations of the collapse following mechanical obstruction of veins might be offered; it deserves further investigation. The action is peripheral since the same result occurs in the pithed animal under efficient artificial respiration.

V. *Painting vessels with histamine solutions.* If a large vein is painted with a strong solution of histamine in an anæsthetised animal sufficient is absorbed to produce general systemic effects almost immediately; but when an artery is similarly treated only local effects are observed in the tissues supplied by it.

The hind limb of the cat, anæsthetised with urethane, was placed in an oncometer. The rectum was excised and the iliac vessels exposed in the pelvis. The iliac vein and artery were consecutively painted with a 3 p.c. solution of histamine phosphate (= 1 p.c. hist. base). Blood-pressure and limb volume were recorded.

After either the iliac vein or the inferior vena cava was painted there was a fall in the general blood-pressure and a simultaneous moderate increase in limb volume. After painting the iliac artery an immediate marked increase in limb volume occurred but no appreciable effect on blood-pressure. After painting the vein there is a general shock with fall of blood-pressure. After painting the artery there is constriction only of the veins of the limb supplied by that vessel with resulting vaso-dilatation and the animal is protected in some way from shock. How this protection is produced has not been further investigated.

VI. *The effect of large doses of histamine.* Dale has shown that after intravenous doses of 1–2 mgrm. histamine base per kilo typical shock with failure of respiration and death occurs after 10 or 15 minutes. Such doses probably cause venous but not arterial constriction; with larger doses arterial constriction might preponderate. If this hypothesis is true then the injection of a large dose of histamine should contract arterioles as well as veins and cause a rise in blood-pressure. It has been shown that with high concentrations of histamine the arterial resistance is equal to or greater than the increased resistance in the veins, so that "bleeding into capillaries" with consequent fall in blood-pressure is to that extent diminished. Fig. 6 is a record of such an experiment. As the histamine concentration in the circulation gradually diminishes so collapse symptoms become evident. The experiment shows that the important factor in this collapse is the ratio of the arterial inflow to the venous drainaway, not the absolute amount of either factor, venous or arterial, in the resistances interposed.

Dale has described the wheal produced on the surface of the pancreas after painting with histamine solution. This phenomenon in the light of these experiments may be ascribed to constriction of venules in the presence of an adequate blood-pressure. In confirmation of this view I find that the simultaneous administration of papaverine, a drug

which paralyses plain muscle, delays the onset and checks the amount of wheal formation on the skin.

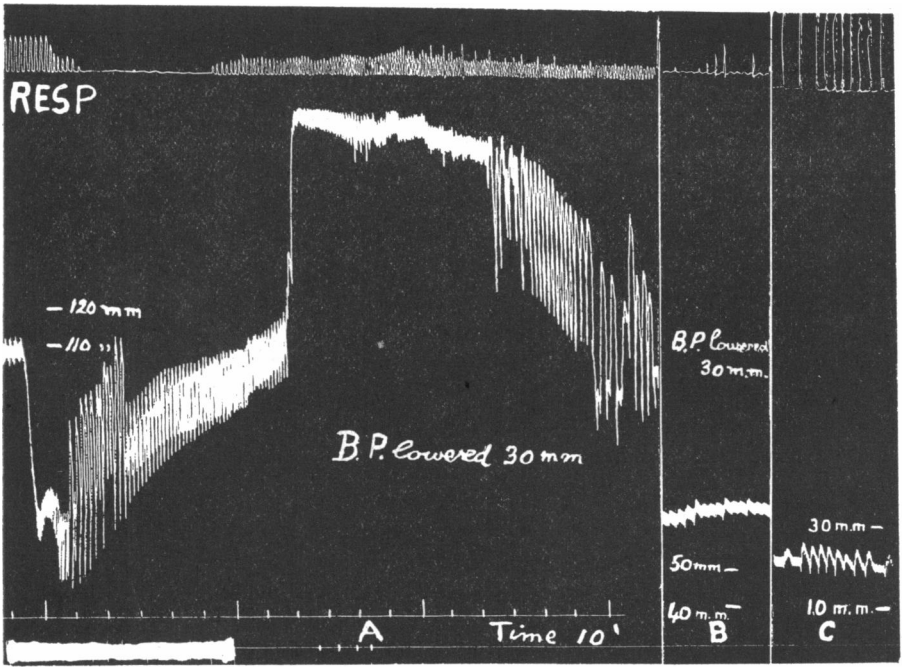

Fig. 6. Cat. Urethane. Blood-pressure, lower curve; respiration, upper curve. Shows the effect of an intravenous injection of 150 mgrm. hist. phosph. in 15 c.c. Ringer. After a preliminary fall in blood-pressure and temporary failure in respiration the blood-pressure rises. The condition of the animal 45 minutes later is shown in *B*. Shortly after this artificial respiration was required. *C* shows the condition 1¾ hours after the injection, natural respiration had returned. Fifteen minutes later respiration finally failed and the animal died, under artificial respiration, 2¼ hours after the injection, in a state of profound collapse.

One difficulty in accepting this simple explanation of histamine action is that in the experiments of Dale and his collaborators on the limb of the cat artificially perfused with fluid containing adrenaline, histamine was shown to cause increase in the limb volume and in the venous outflow.

The following experiments differing in certain details from those under discussion throw some light upon them. A cat was pithed and its defibrinated blood diluted with oxygenated Ringer, and arenaline added to a concentration of 1 in 1,000,000. A loop of bowel was perfused with

this fluid and 2 mgrm. of histamine phosphate dissolved in 1 c.c. of the same fluid was injected into the arterial tubing. Under these conditions the first effect of the histamine was to diminish the flow by a half; this phase was followed by a greatly increased flow: the higher the perfusion pressure at the commencement of the experiment the greater was this increase.

The following experiment illustrates these effects:

Cat. Pithed, bled. Perfusion fluid 1 part defibrinated blood, 2 parts oxygenated Ringer, adrenaline 1 in 1,000,000. Loop of bowel perfused, flow recorded in drops during consecutive 30 seconds.

1. Perfusion pressure, 60 mm. of mercury:

Before histamine	13		12		12							
After hist. phosph. 2 mgrm.	8	6	6	6	8	11	13	14	17	18	18	

2. Perfusion pressure raised to 100 mm. of mercury:

Before histamine	18		18		18	
After hist. phosph. 2 mgrm.	13	10	18	32	40	53

It thus appears that with doses of histamine much larger than those used by Dale there is a first phase of diminished outflow followed by a second with great increase of outflow. It is reasonable to think that under the conditions of Dale's experiments, viz. a perfusion pressure of 165 mm. of mercury and such a small dose as 0·01 mgrm. of histamine, the first phase might be less obvious, in fact only represented by the preliminary phase of increased volume, the increased outflow showing itself after a preliminary latent period.

My preceding observations suggest that this first phase is a venous obstruction. It now becomes necessary to determine if mechanical obstruction of veins, under the conditions of Dale's experiments, might lead to an increased flow of perfusion fluid.

The following experiment resembled the preceding in all respects except that a perfusion pressure of 140 mm. of mercury was employed and histamine was not used, but the apparatus was arranged so that the rubber tubing on the vein cannula could be gradually occluded by a screw clamp. After a number of trials it was found that a certain degree of obstruction increased the flow. Recording drops per minute with the outflow tube fully open, the readings were 10, 10, 10. After slightly screwing down the clamp the readings remained 10, 10, 10. On further slight increase of obstruction the readings became 12, 12, 12. The clamp was now screwed down until a momentary stoppage of flow occurred, the clamp was immediately released sufficiently to allow a flow of 9, 9, 10, 10, 10. The obstruction was again increased by screwing the clamp down until the readings were 5, 5. No further alteration of the

clamp was made. After 5 minutes the outflow was 7, 8, 10, 9, and after a further 5 minutes it became 16, 16, 19, 28, 34. From this it appears that under these special conditions mechanical obstruction of veins may lead after a sufficient latent period to increased flow, and that within limits the greater the obstruction the greater the increase of flow, but also the longer the latent period. The significance of the favouring conditions, high perfusion pressure, preliminary treatment with adrenaline and the use of a corpuscular fluid needs further comment. The resistance to the circulation of the blood through a system of capillaries is determined by the friction of the fluid and its contents against the capillary walls.

Moderate constriction of the venous outflow, whilst placing a further and direct resistance to the outflow also by mild damming back, diminishes the internal resistance of the capillaries by dilating them. It is conceivable, with a high arterial pressure under the conditions enunciated, that the venous constriction may be the means of diminishing the resistance of the veno-capillary system taken as a whole. Such an effect is necessarily enhanced by the red corpuscles in the perfusion fluid and a good arterial pressure is an essential factor. Further, if this explanation be valid, it implies that in any capillary there should be what may be described as two critical pressures not far apart; with the lower critical pressure as well as with all pressures below it the corpuscles are gripped by the capillary wall, with a consequent high resistance to the flow through them; with the higher critical pressure and those above it the corpuscles are free to pass easily, resulting in a low resistance to flow. It follows from this that additional resistance in the veins will increase flow when the capillary pressure is in the region of these critical pressures. Further, when the capillary pressure is far below or above these critical pressures, then increased resistance in the veins will diminish flow. These considerations account for the erratic behaviour in perfusion experiments, where in the same preparation sometimes the Dale phenomenon is obtained, while at other times the opposite effect occurs.

It is a pleasure to acknowledge the advice and help of Dr W. E. Dixon throughout this research.

Conclusions.

1. Histamine in low concentrations constricts the veins, leaving the arteries unaffected. Such constriction leads to passive dilatation of capillaries.

2. Long continued occlusion of great veins leads to permanent relaxation of capillaries.

3. Evidence is produced to show that histamine shock is best explained by venous constriction.

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