CONDITION OF THE CAPILLARIES IN HISTAMINE SHOCK.

BY ARNOLD RICE RICH, M.D.

(From the Department of Pathology of the Johns Hopkins University, Baltimore.)

PLATES 13 TO 17

(Received for publication, November 5, 1920.)

The recent work of Dale, Laidlaw, and Richards has brought into prominence the idea that the phenomena observed in shock may have their origin in a primary peripheral circulatory failure. These investigators have used the discovery that histamine (β-iminazolylethylamine) injected intravenously in minute quantities brings about promptly, in certain animals, a condition which is strikingly similar to and apparently identical with the clinical condition designated by the term shock. The blood pressure falls to a very low level and remains there; the pulse becomes small and feeble; the respirations are shallow, irregular, or gasping; the superficial reflexes are active, but a dulling of the sensibility permits the discontinuance of the anesthetic without discomfort to the animal which lies quietly in an apathetic state. Further points of resemblance between histamine shock and clinical shock can be found in detail in the papers by these workers.

The amino-acid histidine enters into the composition of practically every body protein. Since histamine is derived from this amino-acid by decarboxylation, there arises immediately the idea that histamine, or similar substances, may be formed in the body under certain conditions, especially following extensive destruction of tissues by trauma or by widespread inflammatory processes, and that the entry of such substances into the blood stream may be the fundamental cause of the shock which accompanies these conditions. At present, however, in spite of certain suggestive experimental evidence such ideas are entirely speculative, and the present work is not concerned with the question whether histamine and allied substances cause clinical shock. We are interested here rather in a study of the mode of action of histamine which confers upon its shock-producing potentialities.

The action of histamine has been studied by Dale and his coworkers\(^1\) who concluded that the base exerts upon all capillary endothelium a poisonous local effect which results in a dilatation of the lumen of the capillary and an increased permeability of the endothelial wall. The first of these effects is assumed to


CAPILLARIES IN HISTAMINE SHOCK

bring about an accumulation of blood within the capillary system and a con-
sequent inadequate venous return to the heart ("... the shock-like failure of
the circulation is due to accumulation of the blood in relaxed capillaries ...,
the flow through the capillaries becomes ever slower and the tendency to stagna-
tion greater, till ultimately only a relatively small part of the available blood is
effectively circulating."

The increased permeability of the capillary walls is
assumed to favor the escape of plasma from the vessels and so to impose an actual
oligemia upon the already enfeebled circulation. While Dale and Laidlaw 2 are
"convinced that general dilatation of the capillaries and loss of plasma from the
blood are main factors in the production of the shock," they were unable to
observe directly the reactions of capillaries subjected to the influence of histamine,
but deduced their conclusions from other considerations, stating: "Several
attempts were made to observe changes in the calibre of capillaries under a moderate
power of the microscope, without any result to which we could attribute
importance." Dale and Richards 1 had written previously: "We made several
attempts to measure changes in the calibre of blood vessels—arterioles and capil-
laries—in the mesentery by direct observation with the microscope, histamine
solution being directly applied to the area under observation. The results were
not sufficiently convincing to ourselves to make it desirable to record them.
Later experience of the ease with which this vasodilator action is impaired, by
temporary interference with the circulation through an organ or exposure to
cold, made it clear that satisfactory observations of this kind would need a speci-
cially elaborated technique."

Since this important theory of shock has as its basis the assumption
of accumulation of the blood within a capillary system dilated by the
action of an endothelial poison, the present work was begun, at the
suggestion of Dr. W. G. MacCallum, in an attempt to study directly
the effect of histamine upon the capillary system in order to deter-
mine (1) whether histamine is actually an endothelial poison acting
locally upon capillaries to produce a dilatation of their lumina, (2)
whether the capillary bed during histamine shock undergoes a general
dilatation of a degree sufficient to endanger the circulation, and (3)
whether such a dilatation precedes or follows the circulatory failure
occurring in shock.

EXPERIMENTAL.

The omentum was chosen as the site most suitable for observation
because its transparency favors microscopic study in fresh and fixed
preparations and especially because the local action of histamine was
to be studied. Since the capillaries of the omentum are for the most part practically surface capillaries, they can easily be brought into contact with locally applied histamine solutions.

**Effect of Histamine Studied Microscopically in Vivo.**

An attempt was first made to study microscopically, *in vivo*, the effect of histamine upon the capillary circulation of the omentum. Any satisfactory technique for such a study must safeguard the capillary bed under observation from at least four sources of error—trauma, mechanical interference with the circulation, temperature changes, and evaporation of moisture. In order to protect the field from abnormal temperature changes a box large enough to accommodate an anesthetized cat was constructed of wood, lined with asbestos, and equipped with a thermostat. The chamber was fitted with a glass window, a movable opening for the barrel of a microscope, and felt arm sleeves through which work could be carried on within the box while it was entirely closed to maintain a constant temperature. A microscope, from which the base and substage had been removed, was attached to a horizontal bar clamped to an upright rod so that it could be raised or lowered, advanced or retracted to the desired position. The stage was covered with a thick glass plate, and a minute electric globe taken from a small pocket flash-light was fitted beneath the stage and served for illumination; the amount of heat given off by this tiny lamp was too slight to be measured by an ordinary thermometer placed on the glass plate above it.

Dale and his coworkers found cats especially susceptible to the action of histamine. This was the animal used, therefore, in all the present experiments. A cat was anesthetized with ether, tracheotomized, and connection established with an ether respiration bottle by means of a tracheal cannula. The animal was then placed within the box in which the atmospheric temperature was maintained at about 37°C. The abdomen was opened along a midline incision, the edges of which were held apart by small Balfour retractors. The intestines were covered with pads soaked in normal saline solution; the glass stage was warmed to 37°C C. by immersion in normal saline.

*All operations were performed under ether anesthesia.*
solution kept at that temperature. The microscope was now advanced and lowered so that the stage occupied a position within the abdominal opening on a level with the intestines. The omentum was then gently lifted onto the stage of the microscope, care being taken to avoid unnecessary stretching, twisting, pulling, or any manipulation which might traumatize the omentum or disturb its circulation even momentarily. The stage of the microscope was made to occupy such a position that the omentum could be lifted upon it with a minimal displacement from the normal situation. During the period of observation the omentum was continually kept moist by means of capillary pipettes from which normal saline solution flowed, warmed to body temperature. Thus the omentum lay upon the glass stage of the microscope scarcely disturbed from its normal position, was protected against the effects of drying, and its normal temperature was maintained. Throughout all the observations the omentum was handled as little as possible and always with extreme care.

With the low power objective the blood can be watched coursing through the capillaries and the smaller arterioles and venules of the omentum. Capillaries may easily be seen which have diameters so small that they permit the passage of only one red corpuscle at a time. The omentum may be shifted gently upon the stage until a capillary bed which is suitable for study comes into the field. A field which contained a small arteriole and venule, as well as a rich anastomosis of capillaries of different diameters, was usually chosen. Any individual vessel selected for observation was measured at intervals with an eyepiece micrometer in order that any variations in diameter might be detected. While the omentum lay undisturbed upon the stage of the microscope, capillaries were observed as long as 30 minutes, during which time there occurred no measurable changes in their diameters.

Local Application of Histamine.—After a field had been chosen for observation, the vessels were watched for several minutes in order to acquire an impression of the rate of flow through them, and the diameters of several selected capillaries were measured. Then, while the observer kept a careful watch over these measured capillaries and the blood stream flowing through them, an assistant, using a capillary pipette, flooded the field with a solution composed of his-
histamine dissolved in normal saline solution warmed to body temperature. Solutions of histamine ranging in strength from 1:500,000 to 1:500 were in this manner applied locally to the capillaries of the omentum in a large number of experiments. Careful inspection and measurement disclosed no change whatever in the diameters of the capillaries or in the rate of flow through them, nor were any capillaries opened up which were not visible before the application of histamine. Under the conditions of these experiments histamine locally applied produced no detectable change in the appearance of the capillary circulation.

Histamine Shock.—In another series of experiments, while a field of capillaries was kept under observation, the animal was thrown into shock by an intravenous injection of 4 mg. of histamine, blood pressure tracings being taken from the carotid artery. As the blood pressure fell the rate of flow through the capillaries became slower, until the stream was moving in a strikingly sluggish manner; but again, as with local applications of histamine, no widening of the capillaries could be detected.

These experiments demonstrated that a pronounced slowing of the capillary stream accompanies the fall in blood pressure which histamine produces when injected intravenously. Two possibilities were suggested in explanation of the fact that the local application of histamine did not affect the size of the capillaries in these experiments. Either histamine exerts no effect upon the diameters of capillaries, or else the handling of the omentum necessary to bring it under the microscope, in spite of the care with which this was done, inflicted sufficient trauma to bring about either a capillary paralysis and dilatation or a loss of capillary irritability, with the result that the vessels could not be dilated further by the action of histamine or any other agent. Experiments were, therefore, carried out in which

---

4 The histamine preparation used was the dihydrochloride of the base supplied by the Hoffmann La Roche Chemical Works of New York. The activity of the stock supply was tested from time to time upon the virgin uterus of the guinea pig and was found to produce the characteristic contractions at each test. The potency of this preparation was also exhibited in the numerous animal experiments performed during this study, in which it was used to induce shock. Fresh solutions were always prepared before every experiment.
irritants and alleged capillary dilators were applied locally to omenta under microscopic observation.

Local Application of Inflammatory Agents.—Among the substances used were cantharides, turpentine, croton oil, gold and sodium chloride, amyl nitrite, and chloroform. It is well known that irritants locally applied to the web of the frog's foot bring about a marked dilatation of the capillaries, and that in mammals the intraperitoneal injection of these substances produces a dilatation of the peritoneal capillaries during the resulting inflammatory reaction. It was assumed, therefore, that, if the normal reactivity of the capillaries under observation in these experiments was undisturbed, the local application of such substances would be followed by definite changes in the capillary diameters. Some of the irritants brought about a stasis of blood in the capillary area to which they were applied—apparently a result of osmotic disturbances. In no instance was there seen any definite dilatation of the capillaries which, in some experiments, were observed as long as 30 minutes following the application.

Effect of Histamine Studied in Fixed and Stained Preparations.

Since the local application of such inflammatory agents failed to produce a detectable capillary dilatation, it seemed that the conditions of the experiment must have brought about some alteration of capillary irritability, and an attempt was made to determine what effect the handling of the omentum in these observations exerts upon the capillaries. In a series of experiments a midline incision was made in the abdomen of normal cats under anesthesia, and the abdominal cavity was immediately flooded with a fixative. The fixative used in all experiments was a modification of Zenker's fluid, formaldehyde being substituted for glacial acetic acid. The omentum was then quickly cut along the line of attachment and transferred to a dish of the fixative where it was left for 24 hours. It was washed, spread over large glass slides, and stained with hematoxylin

5 The web of the frog's foot, while offering ordinarily a standard and convenient field for capillary observation, was unsuited for study in these experiments, because the frog is extremely resistant to the shock-producing effects of histamine.
and Van Gieson's stain. In such a preparation the arterioles, venules, and capillaries are distinguished in minute detail. Since the omentum was, in this manner, fixed before being subjected to any manipulation or exposure, these slides were assumed to reveal the normal appearance of the omental capillaries. In another series of experiments, after the abdomen had been opened, the omentum was lifted to the stage of the microscope with all the care and precautions described above. It was at once fixed by flooding with the fixative, and was then treated in the same manner as the normal control specimens.

Microscopic comparison of the capillaries in the omenta of these two series at once revealed striking differences in appearance. The capillaries and the smaller arterioles and venules of the manipulated omenta were distinctly dilated, tortuous, and engorged with blood; furthermore, there was an actual increase in the number of visible capillaries in the handled omenta. It is clear from a study of these slides that many of the fat cells within the fat streaks are bounded by capillaries, that at any given time, under normal conditions, only a relatively small number of these capillaries are open channels for the blood stream, many lying collapsed and closed, and that handling the omentum opens up the collapsed capillaries either by causing a loss of tone through paralysis or by stimulating them to dilate.

The opening up of occult capillaries is seen with especial distinctness along the arterioles and venules which run through the connective tissue between the fat streaks. Clumps of mononuclear cells lie along the course of many of these vessels and form cellular sheaths about them. In the normal omenta these cellular areas are apparently avascular. It is only occasionally that a delicate capillary loop can be seen outlined between the cells. But in the handled omenta these cell clumps are invariably traversed by rich, engorged capillary plexuses, so that the arteriole and venule are bordered by a network of capillaries which can easily be traced to their origins from the arteriole and venule. This appearance is so striking that the handled omenta can be quickly distinguished from the normal omenta by an inspection of these areas.

These observations are entirely in accord with Krogh's demonstration that normally, at any given time, only a relatively small

---

portion of the entire capillary bed is an open channel for the bloodstream, many capillaries remaining collapsed and microscopically invisible; and that these collapsed capillaries open up under conditions which excite their dilatation.

It was evident from a study of these slides that the capillaries were dilated by the manipulation necessary for the placing of the omentum upon the microscope stage; and this fact made it clear that no trustworthy conclusions concerning the effect of histamine upon capillaries could be drawn from such microscopic observations in vivo.

**Local Application of Histamine.**—Since the method of fixation of the omentum had yielded such distinctive results, it was utilized in an attempt to study the reaction of the capillaries under the influence of histamine. Two series of experiments were carried out. The animals in the first series were treated as follows: After 20 minutes anesthesia the abdomen was opened along the midline and 10 cc. of normal saline solution warmed to 37°C. were immediately poured over the omentum. The edges of the incision were quickly drawn together and held closed. The omentum was not handled in any way. 1½ minutes after the saline solution had been applied, the edges of the incision were retracted and the omentum was fixed by flooding with the fixing solution. It was quickly removed and permanent stained preparations were made as in the previous experiments.

Microscopic study of these omenta showed that the capillaries, arterioles, and venules presented an appearance in no way distinguishable from those of the previous experiments in which the omenta were immediately fixed upon opening the abdomens. It was apparent, then, that the application of saline solution had not affected the capillaries in any way, and the blood vessels in omenta of this series were considered to exhibit the normal vascular appearance (Figs. 1 and 2).

In the second series of experiments the technique was the same as in the first, except in one respect. The period of anesthetization was the same, the solutions, the temperatures, and the length of time between the saline applications and fixation were identical, but in these experiments histamine was dissolved in the saline solutions, so that the histamine proportion in various experiments ranged from 1:1,000 to 1:20,000. The omenta from these two series of experi-
ments thus afforded for study capillaries which had been subjected to local applications of histamine, and controls in which, under the same conditions, normal saline solution had been applied locally instead of histamine. Microscopic study of these preparations showed that the capillaries of the omenta which had been brought in contact with histamine were very markedly dilated, tortuous, and engorged with blood (Fig. 3) in comparison with the capillaries in the normal controls. There was also seen a distinct increase in the number of visible capillaries. The dilatation was not confined to the capillaries but included the smallest arterioles and venules at the periphery of the capillary bed. The local application of histamine clearly brings about a marked dilatation of both the visible and occult capillaries. That this effect is local was demonstrated by blood pressure tracings taken during the experiments. The pressure was maintained, with the usual slight fluctuations, at a constant normal level, indicating that during the period of contact of the capillaries with histamine not enough of the base had been absorbed to exert the slightest depressor action upon the circulation. When strong histamine solutions were used in the local applications a fall of blood pressure occurred, indicating sufficient absorption to produce the characteristic depressor effect, but the series examined for the purely local effects of the base comprised the omenta only from animals which had exhibited no blood pressure disturbance during the application.

**Histamine Shock.**—In another series of experiments the animals were thrown into shock by intravenous injections of histamine dissolved in 2 cc. of normal saline solution, 2 mg. of the base being used per kilo of body weight. When the blood pressure had fallen to the shock level the abdomen was opened and the omentum immediately fixed as described above. As controls, the omenta of animals which had been given an intravenous injection of 2 cc. of normal saline solution instead of histamine were fixed, the time between the injection and the fixation of the omentum being the same in the two series. The omenta of these controls exhibited a vascular picture differing in no way from that of the normal controls previously described. The capillaries and smaller arterioles and venules of the shocked animals, on the other hand, were definitely dilated and
engorged with blood; and here again it was clear that many occult capillaries had been opened up (Figs. 4 and 5). A study of these slides made it evident that a widespread peripheral vascular dilatation of such a degree could easily accommodate an amount of blood large enough seriously to impair the circulation.

These experiments demonstrated that histamine exerts a local dilating effect upon capillaries and that during histamine shock the blood stream moves sluggishly through a dilated, engorged capillary bed. It was now of importance to determine the relation of the capillary dilatation to the fall in blood pressure which occurs during shock.

Relation of Capillary Dilatation to Blood Pressure Fall in Shock.—Experiments were made in which the abdomens were opened and the omenta fixed at various intervals following the injection of histamine. It was found from a study of these preparations that the capillary dilatation had begun in the omentum taken 15 seconds after the injection, before the blood pressure had fallen to the shock level. The progression of the dilatation to a maximum could be followed by a study of the omenta taken at intervals of 15 seconds. No recovery from this peripheral vascular dilatation has been encountered; omenta fixed as late as an hour after the onset of shock have shown the persistence of the dilatation, which apparently must be looked upon as a paralytic loss of capillary tone. The dilatation was uninfluenced by the brief secondary rise in blood pressure which characteristically follows the injection of histamine, and which Dale and Laidlaw have attributed to a constriction of the pulmonary arteries. Omenta fixed at the summit of this rise exhibit the vascular dilatation. This fact makes it clear that the capillary dilatation and engorgement occurring during shock are not a mere result of low blood pressure; the fall of blood pressure is more properly to be attributed to the peripheral vascular relaxation.

There has been ample opportunity during this study to confirm the observations of Dale and Laidlaw regarding the excellent functional condition of the heart in histamine shock. The fall in blood pressure cannot be attributed to cardiac failure. It has frequently been observed, in the present experiments, that during unrecuperable shock the heart efficiently discharges relatively large amounts of
saline solution injected into the jugular vein. In a number of
instances repeated intravenous injections of adrenalin have been
administered to animals in deep shock, and the heart has always
worked with remarkable efficiency during the height of the blood
pressure rise. Death during shock has always resulted from respira-
tory rather than cardiac failure.

The inadequate venous return to the heart has also been observed,
and an inspection of the great veins makes it clear that the blood is
not accumulating in that portion of the vascular system. The pres-
et experiments demonstrate that histamine exerts a local dilator
effect upon capillaries and that during histamine shock there are
marked widening and engorgement of the capillary bed. The capil-
lar dilatation during shock is accompanied by a fall in blood pres-
sure, but persists independently of subsequent blood pressure varia-
tions. These facts are entirely in accord with the view of Dale and
Laidlaw that the fall of blood pressure during histamine shock is
due to a general loss of capillary tone produced by the poisonous
local action of the base.

CONCLUSIONS.

1. Histamine exerts a local dilator effect upon capillaries and upon
the smallest arterioles and venules which border the capillary system.
There occurs also an opening up of large numbers of capillaries of
which no trace can be seen before the application of histamine.

2. When injected intravenously in amounts sufficient to produce
shock, histamine causes a quickly progressive dilatation of both the
visible and the occult capillaries and of their immediately adjacent
arterioles and venules, all of which become engorged with blood that
moves through them in a strikingly sluggish manner. The circula-
tory failure which characterizes histamine shock results from the
dilatation of the peripheral vascular bed.
EXPLANATION OF PLATES.

The five photomicrographs were taken with the same magnification.

PLATE 13.

Fig. 1. Fat streak in the omentum. Local application of normal saline solution.

PLATE 14.

Fig. 2. Arteriole and venule in the normal omentum showing the apparently avascular cell sheath.

PLATE 15.

Fig. 3. Fat streak in the omentum. Local application of histamine. Blood pressure normal.

PLATE 16.

Fig. 4. Fat streak in the omentum during histamine shock.

PLATE 17.

Fig. 5. Arteriole and venule in the omentum during histamine shock, showing capillary network throughout the cell sheath.
Fig. 1.
(Rich: Capillaries in histamine shock.)
Fig. 2.
(Rich: Capillaries in histamine shock.)
Fig. 3.
(Rich: Capillaries in histamine shock.)
Fig. 4.

(Rich: Capillaries in histamine shock.)
Fig. 5.

(Rich: Capillaries in histamine shock.)