OBSERVATIONS ON EXPERIMENTAL SHOCK

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Whilst the theory of traumatic toxæmia has been accepted in this country as providing the most reasonable explanation of the condition recognized by surgeons as secondary shock, a body of experimental research, which seems to discount this theory completely, has been produced in America during the past few years by a number of workers.^{5, 6, 9, 14} The still earlier theories have been generally discarded, since they fail to account for the diminution in the volume of the circulating blood, a diminution which Keith¹ emphasized and which is now generally admitted to be the outstanding feature of this type of shock. The theory of traumatic toxæmia arose from the observations of the Special Investigation Committee appointed by the Medical Research Council in 1917. Its reports were published officially,² and, later, Cannon summarized the work in his monograph,³ in which he also shows that the other theories of the aetiology of shock are untenable.

Shock was usually produced by traumatizing one of the posterior extremities of cats. The low blood pressure which resulted from such trauma was found to occur whether or not the nerves to the limb or the spinal cord had been severed prior to the damage. The amount of swelling due to loss of plasma or blood into the traumatized area was not believed to be sufficient in itself to account for the fall in the blood pressure. Further, it was found that by clamping the main artery and vein to the limb before trauma was applied collapse of the circulation was delayed until the clamps were removed. It was assumed that a depressor substance was liberated in the damaged tissues and that the fall in blood pressure was due to the absorption of this substance into the general circulation, on which it acted.

The Histamine Theory

About the same time Dale and Laidlaw⁴ described a shock-like condition produced in animals by the injection of histamine. This condition bore so close a resemblance to the shock produced by muscle trauma that it seemed reasonable to regard the two kinds of shock as closely related. Although the pure chemical substance has been separated from many tissues of the body this histamine theory has never been substantiated by the demonstration of a depressor or shock-inducing substance in the blood of the shocked animal. Furthermore, it is quite evident, as Smith⁵ points out,

"that the failure to produce shock by crushing the muscles of a limb, the main vessels of which have been clamped, is susceptible of an interpretation other than the prevention of the hypothetical capillary poison from reaching the general circulation. It might well be supposed that shock does not occur under these conditions because there is no actual loss of blood, whereas upon removal of the clamps shock does occur because of the extravasation of blood and transudation of plasma into the lacerated tissues."

Smith showed that when blood withdrawn from a branch of the distal end of the clamped femoral vein, after the muscles of the limb had been thoroughly crushed, was returned to the circulation there was not the slightest evidence for the presence of any depressor substance in this blood. On the contrary, the blood pressure was raised, being restored to the pre-bleeding level. The transfer of such blood to another animal which had been bled but not otherwise traumatized also raised the recipient's blood pressure, and never yielded any evidence

of containing histamine-like substances. If, however, histamine was injected intra-arterially into the limb the blood collected later from the clamped vein was easily shown to be depressor to the circulation of either the shocked animal or a bled recipient. Some mechanism other than the liberation of a histamine-like substance must then be responsible for the production of shock.

The Local Loss of Blood

Blalock⁶ repeated the experiments of Cannon and Bayliss⁷ on dogs. He found that trauma to the leg never reduced the blood pressure to a shock level without causing the loss of enough blood and plasma into the traumatized area to account for the fall. These results were opposed to the conclusions of Cannon and Bayliss, who stated: "In no case, however, was there sufficient bleeding into the wounds to account, by itself alone, for the effects observed." But Cannon and Bayliss determined the local loss of blood by weighing the extremities, traumatized and control, after amputation by symmetrical cuts across the upper ends of the thighs. Blalock soon discovered that trauma to a thigh results in extravasation into the loose tissues of the groin and flank. To include this in his comparative weighings he separated the hindquarters butcher-fashion, cutting across the body in the mid-abdominal region and splitting the lower part of the vertebral column. The difference in the weights of the limbs thus amputated in all experiments in which a low blood pressure was produced by trauma to one limb amounted to at least 4 per cent. of the body weight, or about half of the total calculated blood (taking the blood as one-thirteenth of the body weight). This work supplies such an impressive body of evidence and has received so little attention in this country that we decided to repeat, with such differences in technique as seemed advisable, the fundamental experiments of Smith⁵ and Blalock.⁶

EXPERIMENTS A

Depressor Substances in Blood from Damaged Limb

Dogs were anaesthetized with sodium barbitone (0.3 gram per kilo intravenously). Records of blood pressure and respiration were taken in the usual way: blood pressure, by means of a cannula in a carotid artery, connected to a mercury manometer; and respiration, by a tambour applied to the lower ribs. Shock was induced by striking the thigh muscles with the flat side of a 2 lb. hammer, applied so that neither the skin nor the bone was broken. For transfusion experiments clotting was prevented by the intravenous injection of chlorazol-fast pink (Boots), as recommended by Huggett,⁸ in a dosage of 200 mg. per kilo body weight. By inserting a three-way cannula into the common iliac vein it was possible to withdraw either the whole or part of the blood returning from the experimental limb during or after the trauma. This gave no trouble, probably because of the efficiency of the anticoagulant. In the light of Blalock's work it is obviously desirable to draw samples from and to clamp the common iliac vessels rather than the femorals, as practised by Smith.

Sixty c.cm. of blood collected during the latter part of a shock-producing trauma were reinjected as soon as the blood pressure became steady. This raised the blood pressure, although the sample was taken during a steep fall, when the likelihood of a spread of any depressor substance present was at its greatest. In no experiment of this kind, in which we have collected and reinjected blood from a traumatized limb, have we found any evidence for the presence in that blood of any histamine-like substance, taking the blood either during the trauma or at any interval afterwards. And the same conclusion is arrived at if the blood is transferred to another animal in which no trauma has been induced and which, with its higher blood pressure, is probably more sensitive to the action of depressor substances. If after clipping the vein we injected 1 mg. of histamine into the iliac artery of that leg and collected a small blood sample (5 to 10 c.cm.) from the vein even ten minutes later, such blood on reinjection produced a typical histamine response—a sharp fall in pressure with recovery in a few minutes.

These results are shown in the kymographic record here reproduced, and confirm Smith's claim that "direct methods have failed to demonstrate a depressor substance in the blood of the shocked animal."⁵

EXPERIMENTS B

Local Loss of Blood and Plasma

In this series of animals the same recording methods and the same technique for inducing anaesthesia and shock were used as in the previous experiment. When the blood pressure seemed to be established at a shock level the hindquarters were divided as recommended by Blalock, and weighed. The figures for ten dogs are set out in the accompanying table, which shows the blood pressure changes, the loss of blood and plasma into the traumatized area (indicated by the difference in weight between the limbs), and the proportion of the circulating blood which this loss represents. Great care was taken in dividing and weighing the limbs to ensure the reliability of these figures. The average percentage of blood volume lost into the traumatized area is calculated at 57 per cent., an ample confirmation of the observations of Blalock, who claims a corresponding figure of 50 per cent., whereas Cannon,¹⁵ amputating at a much lower level, found that the difference in weight only amounted to 11 per cent. of the blood volume. In a series of cats the corresponding figure was 43 per cent. Although lower than in dogs, this fluid loss is quite sufficient in itself to account for the collapse of the blood pressure, and makes it unnecessary to assume the absorption and general action of any histamine-like substance.

The nature of the fluid which produces the marked increase in the weight of the traumatized limb has been investigated by Blalock.¹⁰ He found that the local gain in weight was

developed, but in some experiments this usual increase in blood concentration was insignificant. Whilst agreeing that there is a general tendency towards concentration of the blood, we found that the figures obtained varied with the severity of the initial shock, with the repetition of the trauma, and with the ability of the animal to compensate, with tissue fluids, for its loss of plasma.

EXPERIMENTS C

The Initial Fall in Blood Pressure

In our earlier experiments we were surprised at the amount of trauma which was necessary to keep the blood pressure at a shock level. If no attempt was made to sustain the normal body temperature shock was maintained much more readily. We found that in healthy, well-nourished animals which were kept warm the blood pressure could often be brought down to a shock level by slight trauma, but on cessation of this the blood pressure tended to rise rapidly to normal. This fall in blood pressure came on so quickly as to suggest that it was of neurogenic origin.

It has been shown by several workers that denervation of a limb, even if it includes sympathectomy⁹ or transection of the cord,³ does not prevent the development of shock following trauma. These results were obtained from experiments in which shock was maintained. We determined to investigate the cause of the initial fall in blood pressure, believing that it might produce further evidence of the changes taking place in the traumatized tissues. The animals were anaesthetized and records taken as in Experiments A and B. We found that the fall in blood pressure after mild trauma occurred: (a) when all nerve impulses from the limb had been cut off by means of a spinal anaesthetic, the efficiency of which was tested by faradizing the central end of the sciatic nerve; and (b) when the common iliac vein was occluded, preventing the passage of blood from the traumatized tissues into the general circulation. The fall in blood pressure was prevented by occluding the iliac artery.

These findings suggested that even the initial fall in blood pressure is the result of a local change, presumably an opening up of the large vascular bed provided by the thigh muscles. Whether or not such a change is produced by the local action of a histamine-like substance as a result of the tissue injury we cannot say, but certainly, in our experiments, there is no evidence of the passage of such a substance into the general circulation.

Discussion

The old division of shock into primary and secondary types is misleading, since it does not take into account the pathological features of the two conditions. Primary shock is most reasonably explained on the basis of a disturbance of the nervous system. It is similar in origin to the fainting which not infrequently accompanies severe injuries. This variety of shock results from a reflex inhibition of the heart and a reflex relaxation of the vascular tone throughout the body. In the absence of gross injury to the nervous system there is a strong tendency to recover rapidly from this type of shock, for which the term "neurogenic" has been suggested. Secondary shock may develop several hours after injury, or in the presence of severe injuries it may follow so closely upon the primary shock that no temporary

Female, 9½ kg. Na barbitone, 2.85 grams, as anaesthetic; chlorazol-fast pink, 2 grams, as anticoagulant. (A) Effect of trauma on blood pressure: reduced from 105 to 60 mm. Hg; 60 c.cm. of blood collected from the iliac vein of the traumatized leg towards the end of trauma. (B) The return of this blood raised the blood pressure from 60 to 90 mm. Hg. Within half an hour the pressure had again fallen to 60 mm. Hg. (C) The iliac vein was clamped and 1 mg. histamine injected into the left common iliac artery. (D) Twelve minutes later 6 c.cm. blood was collected from the clamped vein and injected intravenously in the other leg, producing a brief fall in blood pressure because of the histamine present.

Experiment	Dog's Weight in Kilos	Initial Blood Pressure, mm. Hg	Shocked Blood Pressure, mm. Hg	Weight of Traumatized Limb in Grams	Weight of Control Limb in Grams	Difference in Limb Weights Calculated as Percentage of Animal's Total Blood
1	8	130	70	1,200	1,020	30
2	7½	140	85	1,240	990	43
3	6	180	50	920	580	74
4	9½	145	55	1,630	1,040	86
5	11	—	—	2,110	1,435	78
6	7	165	85	1,230	910	60
7	10½	175	55	1,910	1,450	57
8	7	150	65	1,360	1,020	63
9	9	160	40	1,570	1,250	45
10	9½	165	60	1,500	1,260	33

Average percentage of blood volume lost in traumatized area = 57 per cent.

due to the transudation of plasma rather than of whole blood, since the haemoglobin content of the fluid expressed from the traumatized limb was only 30 per cent. of that obtained from the control. This finding explains the result generally reported that the blood in traumatic shock is concentrated. We have attempted to follow the blood changes in these experiments by hourly cell counts and haemoglobin estimations. It was not unusual for the cell count and haemoglobin concentration to be increased by 25 per cent., or even more, as shock

recovery is demonstrable. Any satisfactory explanation of this type of shock, for which the term "haemogenic" has been suggested, must account for the diminution of the blood volume and the concentration of the blood which form the essential pathological features of this condition.

According to recent American work, which has been confirmed by us, the lowered blood volume is due to the loss of blood and plasma into the traumatized area. The immediate onset of this type of shock is characterized by a local vaso-dilatation of the vessels in the injured area, which is accompanied by an increased permeability of the vessel walls and a transudation of plasma into the tissue spaces. This is naturally accompanied in traumatic cases by some extravasation of blood from ruptured vessels, but, except in cases of severe haemorrhage, the loss of plasma is relatively greater than the loss of whole blood.¹⁰ In this way some concentration of the corpuscles in the circulating blood is accounted for. The cause of the increased permeability of the capillaries in the traumatized area is not definitely known. It is probably the result of a substance which is freed locally by the injured tissues, but no clue as to its nature is obtainable, since there is no evidence of its absorption into the general circulation.

This theory of secondary shock stresses the fact, which is supported by experimental evidence, that the lowered blood pressure and blood volume so typical of this condition are due primarily to local factors and not to a general increase in capillary permeability, as postulated by Cannon and Bayliss. This local factor, though the most important, is not working alone to bring about a state of shock, for, unless the blood volume is diminished so greatly as to cause death within a short time, there is a strong natural tendency to restore the blood volume to its normal level by drawing on the fluid reserves of the body. That such a change takes place was indicated in some of our experiments by the steady rise in the blood pressure and the accompanying dilution of the previously concentrated blood which took place after the cessation of trauma. The local factor may therefore be regarded as the initiating factor, but in order to maintain the state of shock others, which may be called sustaining factors, must be present. The loss of blood which frequently accompanies injuries directly lowers the blood volume. Sweating (common in severe shock), vomiting, and, under active service conditions, the prolonged lack of food and water reduce the reserves of body fluids which are necessary to restore the blood volume. Cold and exposure are also potent influences. In the presence of one or more of these sustaining factors the blood pressure is maintained at a level lower than is necessary to ensure an efficient circulation. Anoxaemia of the tissues, a lowered metabolic rate, increased permeability of the capillaries, and an increased viscosity of the blood are among the important changes which result from the low blood pressure. Cannon³ sums up the situation by saying: "A series of vicious circles may thus be started which, if not interrupted, lead to a still further aggravation of the already existent abnormal state, and which account for the progressive nature of fatal shock."

Clinical Considerations

The experimental work described in this paper has been concerned with trauma applied to one of the posterior extremities of anaesthetized animals, and any clinical application must therefore be made with some reserve. In civil practice severe burns and accidents are among the commoner causes of secondary shock. We believe that our experimental work is sufficiently similar to allow of comparison with the shock found in accidents, for

secondary shock is characteristically observed in connexion with extensive damage to muscles or with multiple wounds in which the sum of the damage is equivalent to considerable injury in one region. The secondary shock associated with severe burns has been somewhat overlooked as a result of the marked improvement which has followed the adoption of the tannic acid treatment. Underhill¹¹ claimed that the shock associated with burns was due to the marked concentration of the blood, and obtained excellent results from simply forcing fluids. Blalock¹² extended his experiments to the production of burns to wide areas of the body surface of dogs. Here again he found in the burnt and surrounding tissues an excess of fluid, akin to plasma, equivalent in amount to 40 or 50 per cent. of the total blood volume. This factor of loss of fluid after burns may be even more important in the human being than in the dog, since there is frequently a copious exudation from the injured skin in man which is not seen in dogs. It seems probable that the beneficial effect of tannic acid is largely dependent on the prevention of fluid loss as well as on lessening the absorption of toxins. Results obtained in the shock which results from intestinal manipulation¹³ also stress the importance of the local factor in producing secondary shock. In fact the present outlook would seem to relegate to a secondary position the toxic factors which have been regarded for the past fifteen years as of primary importance in the production of secondary shock.

The present theory of the pathology calls for no radical change in the treatment of secondary shock. Operations under ether, chloroform, or spinal anaesthesia, which all tend to produce in the presence of a low blood volume a pronounced fall in blood pressure, are contraindicated until adequate measures have been taken to restore the blood volume to normal limits. In secondary shock the restoration of the blood volume by the slow intravenous injection of compatible blood, or, failing that, of a gum-saline solution, the application of heat to the body, and the alleviation of pain and restlessness still form the cardinal features of the therapy, but further work on the treatment of shock is now in progress.

Summary

The evidence against the acceptance of the "traumatic toxæmia" or histamine theory of secondary shock is reviewed and accepted, since: (1) we have been unable to demonstrate the presence of any depressor substance in the blood from a traumatized area; and (2) in no experiment was the blood pressure reduced to a shock level without there being a loss of plasma and blood into the injured tissues, sufficient in itself to account for the effects observed.

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