lactic reactions. This danger is greatly increased if the patient is seriously debilitated or is suffering from cardiovascular disease. A potent solution of adrenaline hydrochloride and a sterile syringe must always be at hand; and 0.5 c.cm. should be given immediately any signs of an allergic reaction occur.

Summary

The nature and frequency of reactions to parenteral liver therapy and the significance and technique of skin tests for sensitivity are discussed.

The successful desensitization of 15 cases with severe reactions is reported, with a description of the method employed.

We wish to express our thanks to those of our colleagues on the staff of the Royal Infirmary, Edinburgh, who have permitted us to investigate cases of sensitivity under their charge. One of us (J. G. M.) was in receipt of a Bursary in Medicine from the National University of Ireland during part of this investigation.

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EXPERIMENTAL TRAUMATIC SHOCK

BY

J. CHARNLEY, M.B., F.R.C.S.

Major, R.A.M.C.

The aetiology of traumatic shock still eludes final proof. All are agreed that a reduction of blood volume underlies the state of shock, but the mechanism whereby this reduction occurs is still obscure.

Traumatic shock has been investigated by clinicians and experimentalists, and many important facts have been established. There is, however, a fatal tendency to mix indiscriminately the facts of clinical shock with the facts of experimental shock, and a tendency to mix deductions from one type of experimental shock with shock produced by quite unrelated means. As a result of loose inference the problem of shock is to-day more difficult than it has ever been, and as much time must be spent in "debunking" the literature as in tackling the facts of the problem itself. Before the gaps between the various aspects and manifestations of shock can be bridged by a single theory the truth of each aspect must be firmly established. It is the purpose of this paper to concentrate exclusively on experimental traumatic shock produced by mechanical trauma to a limb.

Despite the fact that experimental traumatic shock might be considered a threadbare field for research, there is no unanimous answer to the question, "Why does an animal under anaesthesia pass into shock when severe mechanical trauma is applied to the limb muscles?" This problem is purposely kept within narrow and artificial limits. Until the complete answer is known it is fatal to make analogies with the causes of shock after burns, of surgical shock in the presence of superadded disease, or of the complex mixture of oligæmic, neurogenic, psychogenic, and metabolic factors which contribute to the state of shock in the wounded soldier.

An attempt is made here to present an old experiment in a new light, and to emphasize the need to regard this artificial

problem as one which should be capable of complete experimental proof; then, and then only, can it be viewed in relation to the problem of shock in general.

The History of Traumatic Shock

Traumatic shock first aroused interest during the war of 1914-18 by the fact that it often supervened some time after the patient was wounded and after a mysterious latent interval during which he appeared quite normal. It was the nature of this latent interval which focused attention on shock. It was this which gave rise to the clinical entities described as "primary" and "secondary" shock.

By what was no more than a remarkable coincidence physiologists, notably Dale and Laidlaw (1918) and Dale and Richards (1918), were interested at this time in the pharmacological reactions of the comparatively new substance histamine, which seemed likely to open up new vistas in physiology. In a hurried piece of research undertaken during the war, when a solution was urgently needed, Cannon and Bayliss (1919) appeared to establish as a fact that so-called "secondary" shock was due to the action of a tissue toxin akin to histamine.

About ten years later Blalock (1930, 1934) started to publish the results of further investigations on the Cannon-Bayliss experiment, undertaken with a degree of patience probably unequalled in the history of experimental surgery. He failed entirely to find any toxic cause for shock, and produced many reasons explaining the death of the Cannon-Bayliss animal as the result of local fluid loss at the site of trauma. But many of the forms of shock encountered in clinical practice—i.e., after surgical operations, after head injuries, burns, etc.—seemed so obviously unrelated to haemorrhage that there was a tendency to reject Blalock's theories even for the conditions of his own experiments. This refusal to believe led to a determination to find some other explanation with a dangerous over-elaboration of experimental technique.

As regards the toxæmic theory of shock few new facts have emerged. The capillary phenomena following toxæmia produced by the introduction of crushed muscle into the peritoneum have been extensively studied by Moon (1938) and his collaborators, though it is doubtful whether this bears any relation to the conditions of the original Cannon-Bayliss experiment. Practically all recent variations of this latter classical experiment—notably the dialysis experiment of O'Shaughnessy and Slome—have failed to reveal any toxic substance in the blood stream.

There remained only the nervous pathway for secondary shock, and O'Shaughnessy and Slome (1935) believed that they were able to demonstrate such a condition in the absence of blood loss and toxæmia. It is to be noted in this connexion that at the time when Cannon and Bayliss did their original experiment neurogenic factors were in the public mind one of the most likely causes of delayed shock. But these workers, and later Blalock in a more extensive research, were entirely satisfied that this very obvious source was not a cause of experimental traumatic shock. It was only after excluding this possibility that there was any justification for assuming a toxic theory of shock. The experiments of O'Shaughnessy and Slome were extremely elaborate, and there could be but little surprise that shock resulted.

Finally, clinical experience now casts doubt upon the existence of "secondary" shock as a clear-cut entity. Modern battle and air-raid casualties tend to be shocked progressively from the time of reception of the wound. It is the exception rather than the rule for a patient to appear initially quite fit and later to pass into a state of shock for no apparent reason. The disappearance of the mysterious latent interval removes the original condition for which toxic theories were first invoked. The latent interval seen in 1914-18 might have been due to exposure to wet and cold for many hours after wounding—a state of affairs not commonly seen in this war, but one often commented on in the Special Reports of the Medical Research Council of 1917-18.

Cannon and Bayliss (1919) established as a definite fact that shock did not result if the femoral artery and vein were ligated before applying trauma to the thigh. This fact has never been questioned since, and Blalock carried the experiment a little

further by showing that shock did not result even if the artery alone were tied; the vein being left patent. He explained this absence of shock on the grounds that the local blood loss was reduced by the ligature, and felt that there was here strong evidence against the toxæmic theory.

The Present Experiment

It is my purpose to attempt to show that this simple experiment of femoral artery ligature is capable of a very much wider interpretation than has generally been ascribed to it. The research pursues the following scheme: (1) control series without ligature of the vessels; (2) effects of ligature of the femoral artery before trauma; (3) investigation of the collateral circulation after ligature.

Series 1

Trauma without Ligature of Vessels; 25 Cat Experiments

The anaesthetic was intravenous chloralose 0.09 g. per kg. of body weight, after preliminary ether induction. All animals were kept at 39° C. on an electrically heated table and controlled by rectal thermometer. A kymographic record of carotid blood pressure was made, using saturated sodium bicarbonate solution in the cannula. Trauma was applied to the thigh with a 5-lb. padded mallet, and a standard number of 50 blows were applied and the femur fractured in all cases. Shock level of blood pressure was taken as 70 mm. Hg, and was reached in times varying from 20 minutes to 6 hours after trauma. Shock did not develop in 3 of these cases even after 6 hours. It was invariably noticed that the crushed thigh was visibly and palpably swollen even before the end of the trauma was reached, and this speed of the initial swelling left absolutely no doubt that a brisk internal haemorrhage into the muscle planes was the immediate sequel to trauma under these conditions.

At the conclusion of the experiment the animal was killed, if it had not already succumbed to the shock, and the increase in weight of the traumatized limb was estimated as described by Blalock—i.e., the tail was removed, the trunk severed at the level of the lowest lumbar vertebra, and the pelvis sectioned through the midline. The weights of the two hind quarters thus separated could then be compared. Control attempts to divide untraumatized hind quarters showed that this manoeuvre could not be done with an error of less than 10 g., but even this inaccuracy did not invalidate general comparisons. The original blood volume of the animal was deduced from the figures quoted by Holt and MacDonald (1934) as being 5.75% of the body weight in the cat. The increase in limb weight was thus converted into percentage loss of total blood volume.

In these 25 experiments the proportion of the total blood volume lost into the traumatized thigh averaged 37%. This agreed closely with the 35% found by Holt and MacDonald in the same experiment.

Series 2

Trauma after Ligature of the Femoral Artery; 10 Cats

Anaesthesia as before. The carotid blood pressure was not recorded in this series until the conclusion of the experiment. The femoral artery was tied through a small incision in the groin. A similar amount of trauma was then applied to the thigh—i.e., 50 blows with the same mallet, and the femur fractured in all cases. The absence of rapid swelling of the thigh after trauma in these cases was very noticeable.

Clinical examination revealed no evidence of the onset of shock, and after 6 hours the carotid blood pressure was recorded by tying in a cannula and connecting to the kymograph. The pressures recorded after 6 hours were: 140, 120, 160, 95, 160, 100, 100, 90, 100, 100 mm. Hg. The three high pressures might have been due to the pressor effects of small additional doses of chloralose which had to be given in some cases towards the end of the experiment. In no case was shock level even approached. The average loss of total blood volume into the thigh in this series was 19%.

Series 3

Examination of Collateral Circulation after Ligature of Femoral Artery and Trauma to Limb; 4 Cats

(a) After 6 hours 4 of the preceding animals traumatized after ligation of the femoral artery showed the following carotid blood pressures: 120, 140, 100, 100 mm. Hg. A second arterial cannula was now taken and tied into the femoral artery distal to the previously applied ligature, and directed with its lumen open towards the foot. The cannula thus recorded the pressure of the anastomotic circulation existing in the femoral artery distal to the ligature. This arrangement is shown diagrammatically in the accompanying illustration. The pressures recorded in this second cannula were

respectively 40, 50, 40, 35 mm. Hg. These pressures are thus roughly one-third of the respective systemic arterial pressures. Such anastomotic pressures should be capable of maintaining a considerable anastomotic circulation through the limb.

(b) In the same 4 cats the great saphenous veins were exposed in both legs just below the knees. Into the normal limb an intravenous injection of 0.1 c.cm. of a weak solution of histamine was given. The usual transient fall of arterial pressure was recorded on the kymographic tracing of the carotid blood pressure. This fall started 10 to 15 seconds after the injection was made. When the carotid blood pressure was restored to normal level 0.1 c.cm. of a solution of histamine was injected at the same level into the saphenous vein on the traumatized side. It was found that the arterial depression resulted from 30 to 40 seconds after the injection. This volume of solution—0.1 c.cm.—could not have reached the general circulation by virtue of its bulk, and must have been washed in by the venous return from the limb resulting from the anastomotic circulation. Ligation of the femoral artery delayed this return from about 15 seconds to about 40 seconds.

Diagram showing the method adopted in Series 3.

Discussion

In making deductions from this femoral ligature experiment, four factors deserve special attention:

1. That ligation of the femoral artery prevents the onset of shock on subsequent trauma to the limb.
2. That local blood loss is reduced from about 35% of the total blood volume to about 19%.
3. That rough qualitative tests indicate the existence of an active collateral circulation after trauma to the limb in the presence of the femoral ligature.
4. That the rate of swelling of the traumatized limb is much slower in the presence of a ligature on the femoral artery.

The absence of shock after trauma in the presence of a ligature on the femoral artery could be explained according to the current theories of shock in three ways, thus:

1. By the reduction of local fluid loss (oligaemic theory).
2. By a reduction of venous return from the limb (toxæmic theory).
3. By anaemia affecting sensory-nerve endings (neurogenic theory).

The crux of the femoral ligature experiment lies in the explanation of how the ligature can reduce the amount of local fluid loss and yet leave an effective collateral circulation. These two matters might at first sight appear incompatible; indeed, it could be argued that, though observations might indicate an active collateral circulation, the fact that local haemorrhage is reduced after the ligature must prove that these observations were fallacious.

There is, however, a simple explanation for this apparent paradox. When a limb is heavily traumatized without a ligature on the main artery the initial swelling of the limb proceeds at such a visible and palpable rate as to leave no doubt that a great part of this initial swelling is due to a rapid extravasation of blood under high arterial tension. Now, the

amount of arterial blood lost into the tissues during and immediately after the trauma depends on (a) the height of the arterial pressure in the ruptured vessel, and (b) the time elapsed before the haemostatic factors of arterial retraction and coagulation stem the initial extravasation.

After ligation of the main artery, and though the collateral circulation is quite effective for ordinary purposes of nutrition, etc., trauma to the limb results in extravasation of blood at only one-third of full arterial pressure (for this was the pressure discovered by direct measurement in the preceding experiments). During the time interval before haemostatic mechanisms come into action there is thus a smaller effusion of blood into the traumatized part. This, then, explains how the femoral ligature can reduce local blood loss after trauma without necessarily implying a defective collateral circulation through the limb.

As regards the toxæmic theory of shock, these observations agree with the deductions of Blalock—that shock does not result if all venous channels are open to the systemic circulation, provided that local blood loss into the limb is restricted.

These results are also consistent with those of all observers since the original Cannon-Bayliss experiment who have failed to find shock resulting from sensory-nerve stimulation under experimental conditions. How do these observations compare with those of O'Shaughnessy and Slome? It will be recalled that these workers severed all vascular connexions to the hind limb of an animal, A, and kept this limb alive by cross-circulation from a second animal, B. (It is interesting to note in parenthesis that to isolate this limb from the general circulation needed an extremely extensive multiple ligation of all collateral channels.) On traumatizing the perfused limb of animal A they were able to produce late shock in the systemic circulation of animal B. The limb was in connexion with the systemic circulation by only nervous channels. The nature of this shock must, however, be regarded with suspicion, as the necropsy appearances of the tissues which they describe are in no way consistent with their own excellent description of the typical appearances in traumatic shock. The great criticism of this elaborate experiment is that incidental trauma (which is extensive) is biased towards the production of the desired result—i.e., to produce shock. Compare this with the femoral ligature experiment, in which experimental factors are biased against the desired result—i.e., for a positive result the animal must *not* pass into shock during an experiment which is in itself very likely to result in shock. This is a very stringent experimental criterion.

In interpreting the results of the femoral ligature experiment it is possible to go a step further. There is always the theoretical possibility that traumatic shock might not be the result of only one factor, but of the combined action of several factors. Most experiments on traumatic shock have been ingeniously designed to study the action of only one factor at a time. In the experiment of femoral ligation described here all factors are capable of acting at one and the same time. Thus after losing 19% of its blood volume and being open to neurogenic and toxic shock channels, the blood pressure was still high after six hours.

Conclusions

In the cat, under chloralose anaesthesia and for periods up to six hours after severe trauma to a limb, no evidence could be found for the existence of any shock-producing factors, or combination of factors, other than that of local fluid loss.

This work was done in the physiological laboratories of King's College, London, in 1939, through the kindness of Prof. R. J. S. McDowall, to whom I am deeply indebted. The costs of the research were defrayed by a grant from the Medical Research Council.

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DICOUMARIN IN THE TREATMENT OF PUERPERAL THROMBOSIS

BY

ALBERT DAVIS, M.D., Ch.M., F.R.C.S.

Consultant Obstetric Surgeon, London County Council

AND

MARGARET PORTER, B.Sc.

Biochemist, Dulwich Hospital (L.C.C.)

3:3-methylene-bis-(4-hydroxy-coumarin)—“dicoumarin” for short—is the anticoagulant principle of spoiled sweet clover, ingestion of which causes haemorrhagic disease in cattle. Since its introduction by Link in 1941 the drug has been employed experimentally in a variety of conditions, notably post-operative thrombosis, and the present paper embodies the results of an investigation into its possible value in obstetrics. In all, 43 cases of post-partum thrombosis were treated. They were of every degree of severity, from small saphenous lesions to bilateral femoral blockage; but, in view of their common origin, the general action of the drug, and the homogeneity of its results, they are here grouped together without further classification.

Properties

Dicoumarin is a powerful anticoagulant, the action taking place at the prothrombin level. Given by mouth the drug takes approximately 24 hours to act, but with continued administration the result is a steady rise in the clotting time, the effect lasting for several days after the dicoumarin is discontinued. It greatly reduces the incidence and degree of thrombus formation after the intravenous injection of ethanolamine in dogs (Richard and Cortell, 1942), and is apparently similarly effective in preventing post-operative thrombophlebitis and pulmonary embolism in man (Baker, Allen, and Waugh, 1943). It also appears to limit the extension of an already established thrombosis and to produce symptomatic improvement in cases of thrombo-angiitis obliterans (Bingham *et al.*, 1943). Most observers state that although dicoumarin is an anti-prothrombin its effects are not antagonized by vitamin K. Our own results, however, show that when both preparations are administered simultaneously the coagulation-time curve rises more slowly and less steeply than when dicoumarin is given alone. This confirms Townshend and Mills's (1942) clinical observation that, while blood transfusion failed to produce any perceptible decrease in the prolonged prothrombin time of a case in which dicoumarin had induced haemorrhage, a second transfusion plus vitamin K therapy resulted in an immediate drop of the prothrombin and coagulation times to normal levels, and these normal values were maintained. It would indeed be surprising if this view of the antagonism of the two drugs were incorrect; for, theoretically, vitamin K is primarily concerned with the physiological elaboration of prothrombin in the liver. One must assume that its reported impotence in some cases of established dicoumarin haemorrhage is due to secondary changes produced by the anaemia.

Dicoumarin differs from heparin in method of administration, speed of initial response, and mode of action. The latter must be given by intravenous injection; but its action is instantaneous, the effect being produced by inhibition of platelet agglutination. Otherwise the clinical effects are similar, except that heparin haemorrhage reacts well to simple blood transfusion.

Dosage

Experimental overdosage with dicoumarin in animals produces multiple haemorrhages. In fatal cases there is central necrosis of the liver (Rose, Harris, and Chen, 1942), with widespread haemorrhage indiscriminately throughout the body. There is a considerable difference in tolerance between various species of animals, and also among individuals of the same species. This latter is of much significance, for it applies equally to man, and calls for extreme care in therapeutic administration; in fact, few of the earlier clinical reports are without a description of one or more cases of idiosyncrasy. The optimum dose is that which will reduce prothrombin to 30% of normal (Davidson and MacDonald, 1943), and this has been calculated at 200–300 mg. a day. We have taken the