5. The anaemia can be rapidly cured, with marked improvement of general health, by the administration of iron salts.

6. The relation of these findings to preventive medicine is discussed.

REFERENCES

- ¹ Waddell, J., Hart, E. B., Steenbock, H., et al.: *Journ. Biol. Chem.*, 1928, lxxvii, 797.
- ² Mackay, Helen M. M.: Medical Research Council, Report No. 157, 1931.
- ³ McGowan, J. P., and Crichton, A.: *Biochem. Journ.*, 1923, xvii, 204; 1924, xviii, 265.
- ⁴ Aston, B. C.: *New Zealand Journ. Agric.*, 1924, xxix, 14 and 84.
- ⁵ Orr, J. B., et al.: Sixth Report, Committee on the Mineral Content of Natural Pastures, Economic Advisory Council.
- ⁶ Minot, G. R., and Murphy, W. P.: *Journ. Amer. Med. Assoc.*, 1926, lxxxvii, 470.
- ⁷ Castle, W. B., et al.: *Amer. Journ. Med. Sci.*, 1930, clxxx, 305.
- ⁸ Witts, L. J.: *Proc. Roy. Soc. Med.*, 1931, No. 24, ii, 543.
- ⁹ Davidson, L. S. P.: *Edinburgh Med. Journ.*, 1932, xxxix, Nos. 7 and 8.
- ¹⁰ Orr, J. B., and Clark, M. L.: *Lancet*, 1930, ii, 594.
- ¹¹ Royal Society, Food (War) Committee: *Report on the Food Requirements of Man*, 1919.
- ¹² Cathcart, E. P.: Vide Orr and Clark, loc. cit.
- ¹³ Sherman, H. C.: *Chemistry of Food and Nutrition*, New York, 1927.
- ¹⁴ Davidson, L. S. P.: *Proc. Roy. Soc. Med.*, March, 1933.
- ¹⁵ McLester, J. S.: *Nutrition and Diet in Health and Disease*, 1931, p. 116.

EXPERIMENTAL SHOCK

WITH SPECIAL REFERENCE TO ANAESTHESIA *

BY

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The problem of why persons subjected to physical trauma should pass into a condition of shock is one which has long been of interest to surgeons. Nowadays, indeed, shock rivals sepsis in its importance in surgical operations.

During the war the study of the subject received a great deal of attention, and many valuable conclusions were reached, but there still remains, especially on the clinical side, a state of great confusion. The present state may, I think, be indicated by the fact that the College last year divided one of its valuable prizes between two surgeons whose views on the treatment of so-called surgical shock were a direct contradiction one of the other.

Now it happens that shock can be produced with great ease in laboratory animals, and in the time at my disposal I propose to put forward evidence to you which will emphasize that shock is not a single entity, but may be produced experimentally and clinically from a variety of causes, and that any single remedy used without understanding of the case in hand is bound to give most contrary results.

DEFINITION OF SHOCK

We may define shock in an animal as the state which results from a fall of arterial blood pressure, which, if severe, may lead to death from oxygen want. Its onset may, however, be preceded by a compensated or even over-compensated stage in which the body succeeds in maintaining the blood pressure against the forces which would cause it to fall.

From our knowledge of the circulation, then, we must consider that shock may occur from cardiac failure, from loss of blood, from increased capacity of the circulation—that is, from an undue opening-up of vessels which are normally closed—or from a reduction of the peripheral resistance to the flow of blood from the arterial system. From the point of view of surgery, however, it is probably best to group the various experimental procedures under

headings which are indicative of the cause. In dealing with the detail I shall deliberately omit a large number of minor points, because I feel that if there was a clearer understanding of the principles involved the literature would not be in the confused state that we find it in to-day, for I am convinced that much of the excellent clinical literature appears discordant purely because those concerned are writing about a variety of different conditions, but all under the same title of "surgical shock." There is evidence which indicates that the patient who dies from gross tissue damage such as burning, the patient who dies from minor mechanical injuries, and those who die after prolonged surgical operations, may be deaths from distinctly different states. I hope you do not think I dwell too much on patients who die—many recover—but there are still thousands who die annually who might be saved if the subject was more systematically studied.

SHOCK FROM HAEMORRHAGE

I do not propose to spend much time in discussing this variety of shock, as its cause is obvious. I should, however, like to emphasize that many of the mechanisms by which the body attempts to compensate for haemorrhage are nervous and depend on the carriage of afferent impulses to the vasomotor centres, which in turn send out impulses to constrict the spleen and blood vessels generally. What is particularly important from a surgical point of view is that, being nervous, these mechanisms can be relatively easily anaesthetized, and the effect of the haemorrhage therefore becomes enhanced, and there is abundant evidence that a low blood pressure, say of 60 mm. of mercury, if allowed to persist for half an hour, is liable to bring about permanent changes, which may be fatal. Every attempt should therefore be made to restore the blood pressure before administering an anaesthetic.

DIRECT ACTION OF TOXINS ON PERIPHERAL VESSELS

Histamine or Toxic Shock.—Great attention has, since the war, been focused on this variety of shock since the discovery of the dramatic phenomenon of histamine shock by Dale and Laidlaw. By some it has been hailed as the complete solution of the shock problem, but it is only fair to say that the authors themselves have never made this claim. On the other hand, no one will deny that toxæmia is a most important factor in shock, and probably the most important factor when the onset of the shock is delayed.

The special importance of histamine lies in the fact that it is present in watery extracts of practically all tissues, as it is a simple derivative of the amino-acid histidine, and its effect when injected in minute quantities into the circulation of anaesthetized cats and dogs produces in a few minutes a condition of shock. The shock produced is comparable with that variety of shock in man in which the onset of the symptoms may have been delayed and have apparently depended on the absorption of toxins from damaged tissues.

The skin has been shown to contain relatively large amounts of histamine or its precursor; indeed, there is reason from the work of Lewis to believe that the production of this or a similar substance is a physiological method by which the skin is flushed subsequent to minor injuries. The delayed shock of severe burns is probably produced by the absorption of such a substance.

Dale and Richards showed that histamine acts by dilating the capillaries, and this has been since confirmed by many others. As a result of the capillary dilatation there is a relative insufficiency of blood—the animal, as it were, bleeding into its own capillaries, which have become opened up. The state is like that of haemorrhage, only the animal bleeds into its own vessels. But the

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capillaries are not necessarily congested, for in becoming dilated they apparently become more permeable, and the blood plasma rapidly passes into the tissues, leaving behind, as shown by many observers, a concentrated blood. The finding of a concentrated blood clinically is strongly suggestive that the case is one due to capillary dilatation.

Now we may ask ourselves, Does this variety of shock occur clinically? The matter was really settled for us by the Shock Committee of the Medical Research Council. There is abundant evidence that this is a common variety of shock, so common indeed that it has almost been allowed to overshadow the other varieties. I can best summarize the evidence that such chemical shock exists. The shock is delayed in its onset; the greater the tissue damage the more liable it is to occur. It may occur acutely if a tourniquet is removed from a severely damaged limb and the products of damaged tissue allowed to enter the circulation. The shock is enhanced by cold and anaesthesia with ether or chloroform. Typically we see this variety of shock after severe burns and when large masses of tissue are destroyed, the patients going into shock not immediately, but after several hours or even days, when there has been considerable absorption of the products of dead or dying tissues.

It has been pointed out, particularly by Zachary Cope, that clinically this variety of shock is commonly preceded by a rise of blood pressure, and by some this has been considered evidence against it being due to capillary dilatation. On the contrary, this is exactly what might be expected, for I have demonstrated that under suitable conditions this rise of blood pressure can be brought about by histamine exactly as in haemorrhage. It is indeed merely an over-compensation to a circumstance which tends to cause a fall of blood pressure. This over-compensation may be seen both in the response to haemorrhage and to posture, as pointed out by Leonard Hill. In the case of histamine Dale and Burn have shown that an increased secretion of adrenaline is called forth. The arterial constriction which has been noted clinically by Malcolm is part of the ordinary reaction to a loss of blood volume. I have shown that it occurs with small doses of histamine as with small haemorrhages. We see this in the progressive fall of venous pressure which occurs on the injection of non-shock doses of histamine, by the increased velocity of the pulse wave, the decreasing capability of the animal to withstand the maximum dose of histamine which may be recovered from, and the diminution in the volume of a limb which succeeds a histamine dilatation.

The importance of the suprarenals in relation to histamine shock has been now conclusively shown by Dale, and also by Kellaway and Cowell, in that if they are destroyed, histamine shock may be caused in unanaesthetized carnivora, which are otherwise very resistant. Herein no doubt lies the importance of cold in relation to shock, for subsequent experiments by Cramer and by Crowden have demonstrated that cold exhausts the suprarenal glands. The necessity for keeping a shocked patient warm is already so well recognized in surgical practice that I am surprised to learn that operating tables are no longer heated except by hot-water bottles.

The Effect of Anaesthetics.—That brings me to the relation of anaesthetics to histamine shock. Normally animals can withstand histamine in large doses, but carnivora become sensitive to histamine if anaesthetized, as was shown by Dale and Laidlaw. An anaesthetic such as ether probably acts by dilating vessels, by increasing their permeability, and by paralysing the normal mechanism of compensation. This is undoubtedly a point of enormous practical importance, the more so as the effect of the ether at the time of the operation may be

masked by the stimulating action which the ether exerts by irritating the respiratory tract. In a narcotized animal it is easy to demonstrate the vaso-dilator action of ether. We must therefore consider that the individual who administers ether or chloroform to a severely damaged patient is guilty of a crime, but he would probably escape censure as the patient may not die immediately. Probably the anaesthetic has been responsible for many fatal cases of obstruction or strangulated hernia which have been operated upon late. I don't think I am saying too much when I say that many such deaths could have been avoided. May I hope that modern surgeons will not be like their predecessors who continued to remove the thyroid gland for twenty years after physiologists had shown that its total removal led to death from myxoedema. We must not smile. It is already fourteen years since Dale and his colleagues did this work, but although it is mentioned in some surgical books its importance does not yet receive general recognition. If such patients must have a general anaesthetic then nitrous oxide is the anaesthetic of choice, since it has been shown by Dale that this anaesthetic does not render an animal so sensitive to histamine shock as ether. It is, however, not such an easy anaesthetic to administer, nor from the point of view of relaxation so satisfactory as ether or chloroform; indeed, we must frankly state that we are as yet without an ideal anaesthetic. Personally, I believe that we shall see a greatly extended and routine use of local anaesthetics for this class of case in surgery. It will be agreed that spinal anaesthesia does not meet the case, as it interferes with the nervous control of the vessels and also causes vaso-dilatation.

LOSS OF CENTRAL CONTROL OF BLOOD VESSELS

Damage to Vasomotor Paths.—All the blood vessels of the body are under the control of the vasomotor centre, and the majority are maintained in a state of partial contraction by its activity. It is evident, then, that interference with the pathway between these centres and the blood vessels must bring about vaso-dilatation and a fall of blood pressure. In this category must come the shock produced by injury to the spinal cord, also fat embolism in the medulla, which has been described as a sequel to fractures. The shock which is liable to occur in high spinal anaesthesia is somewhat similar in that the paths from the vasomotor centre to the abdomen and lower limbs are blocked and vaso-dilatation results.

I do not propose to spend time on such obvious causes of shock, but to pass on to the very interesting form of shock of nervous origin which results from operation or injury in which the tissue damage is negligible but the shock is profound.

Concussion of the Vasomotor Centre.—I should like, however, to mention that concussion as a cause of shock may be more common clinically than is commonly supposed. It may be produced experimentally by simply jarring the head. In accident cases there is obvious probability that it exists.

We now come to those varieties of shock which depend on afferent impulses.

Apapnic Shock.—The vasomotor centre may be thrown out of action by a loss of carbon dioxide. The fact that the carbon dioxide of the arterial blood was somehow responsible for the arterial blood pressure was first pointed out by Yandell Henderson. Unfortunately, Henderson postulated at the same time a somewhat remarkable veno-pressor mechanism, which made his theory an easy prey for critics, and his views even as late as 1923 received very little attention if we may judge by Cannon's book. Henderson showed that in etherized dogs, as a

result of the stimulation of afferent nerves, there might be over-breathing to an extent sufficient to lower blood pressure.

In 1923 the essential fact was confirmed by Dale and Evans, who also showed that the carbon dioxide of the arterial blood was responsible for maintaining the normal activity of the vasomotor centre in the medulla, and that a reduction of the carbon dioxide of the blood in an etherized animal led to a fall of blood pressure. I have since shown that the capability of an animal to adapt its circulation to changes in posture, such as being placed in a vertical position, depends on the presence of carbon dioxide. The fact that the vasomotor centre requires carbon dioxide must now be accepted, and we have to ask ourselves, Can this variety of shock occur clinically? The answer is again "Yes, certainly in etherized persons," for I have shown that in a limited number of animals under chloralose over-ventilation does not bring about a fall of blood pressure; a fall occurs if the animal is etherized. In man, over-breathing sufficient to cause apnoea (thus showing that the CO_2 has been washed out) does not necessarily cause a fall of blood pressure (Densham and Wells), because of compensatory constriction of vessels due to increased alkalinity. I do not, of course, deny that very violent over-breathing, which often is not followed by apnoea, does cause a fall, because this actually interferes with the circulation through the lungs. Mr. Wakeley has kindly allowed me to look over his records of operation cases, and among them I found many examples of increased respiration being associated with a fall of blood pressure. In further support of the existence of such washing out of carbon dioxide is the common practice for anaesthetists themselves now to administer carbon dioxide with their anaesthetics as advised by Henderson.

How far acapnia may be an important factor in shock in unanaesthetized patients is difficult to say, since any fall of blood pressure might cause over-breathing. The fall due to histamine, however, does not usually cause such breathing, because of the bronchial constriction. What I do want to emphasize, however, is that even if the acapnia is not a primary factor in shock, it cannot be ignored, for the evidence is complete that it reduces the activity of the vasomotor centre by which the body attempts to compensate for a fall of blood pressure. Every effort must be made, therefore, to reduce the effect of sensory stimulation during operation. It seems to me that herein lies the great value of morphine, which many surgeons still use in all accident cases. I shall return to the question of anaesthetics when I have dealt with depressor shock.

THE VASOMOTOR CENTRE MAY BE INHIBITED

Depressor Shock.—There is a class of case met with clinically which appears to fit into none of the categories already mentioned. I refer to severe shock from an apparently trivial injury, such as a bullet wound through the hand or, as I saw recorded recently, a snowball on the eye. The amount of tissue damage is negligible, and from what I have said of acapnia, it is difficult to see that acapnia is wholly responsible without the occurrence of obvious over-breathing. Here we must believe that there is definite inhibition of the vasomotor system by afferent impulses. The possibility of this occurrence was first put forward by Guthrie, but he did not have any clear idea where the inhibition took place; Meltzer apparently thought it peripheral and Guthrie thought it psychic.

The possibility that afferent impulses might be concerned in shock was first suggested by Crile, but unfortunately he claimed that all shock was produced in this way. His view was that the afferent impulses stimu-

lated the vasomotor centre, which became exhausted, and he bolstered up his view by so much erroneous argument that his theory fell into disrepute. The fact, however, is incontrovertible that certain afferent impulses cause shock. Anyone who reads the clinical literature of the subject will see quite easily that the shock which is so well described by Lockhart-Mummery is not the secondary wound shock on which the Wound Shock Committee worked. It is an entirely different entity. For example, Lockhart-Mummery, in his Hunterian Lectures in this place in 1905, emphasized the importance of the less destructive manipulations such as tractions in a pedicle or ligament and nerves. The Shock Committee emphasized the importance of gross destruction of tissue.

When men take the trouble to make observations these are usually true, but the deductions may be false. I think that on the whole Lockhart-Mummery supported Crile's view that the centre was exhausted, but his observations were none the less very valuable. We must, however, remember that the absence of any knowledge of histamine shock in 1905 made the whole problem much more difficult and confused. Actually the centre is remarkably resistant to exhaustion, and Porter and others have shown that the centre is not exhausted in shock, and could often be made to raise the blood pressure afferent by stimulation of an afferent nerve. This fact has caused the Crile-Mummery view to pass into abeyance, and what good there has remained of it has been taken over by the supporters of the acapnic theory. There is now, however, definite evidence that, apart from acapnia, shock may be produced not as a result of exhaustion, but by nervous inhibition of the vasomotor centre by certain afferent stimuli, especially mechanical stimuli. The occurrence of inhibition of the vasomotor centre is well known in physiology. The centre may be inhibited not only by special depressor nerves, but also by stimulation of many mixed nerves at a slow rate. This depression may be counteracted by stimulation of another region with a fast rate of stimulation, which stimulates pressor rather than depressor fibres in a mixed nerve because of the different excitability of the fibres. There is then no real conflict between Porter and Crile or Lockhart-Mummery, but merely a lack of full understanding on both sides. The question naturally arises, however, how far the results of Crile and Lockhart-Mummery might be due to loss of carbon dioxide due to over-ventilation, which commonly occurs at the same time.

It may be shown that this depression of the vasomotor mechanism produced by mechanical stimulation is not due primarily to acapnia, for it can be produced in an animal with the chest open and under artificial respiration. No doubt, however, acapnia does enhance the effect, so that from the point of view of prevention we can take acapnic and depressor shock together. They are both *preventable by deep anaesthesia*. This gives support to the view that the prevention of primary shock is possible by deep anaesthesia. This has long been claimed, but the claim did not rest on much experimental data. It is interesting to remark that in Beattie and Choyce's *Textbook of Surgery*, however, I find it stated that sometimes anaesthesia causes improvement in shock cases. Here we have, then, a great difference between shock produced by chemical and nervous stimuli, a difference which has an enormous importance in anaesthesia.

In an experiment under dial, the piercing of the forelimb with a sharp instrument caused a profound shock, which was recovered from under deep ether anaesthesia, during which no depression could be produced. Electrical stimulation of an afferent nerve at a fast rate brought about a temporary recovery of blood during a fall of blood pressure. I have also obtained a fall of blood pressure by merely tapping a tibia, while in other animals

shock has been produced by mere dissection of the sciatic nerve, which would be quite innocuous under deep ether anaesthesia. In my experiments I have found that cocainization of the carotid sinuses and the vagi enhances the depressor responses, but the exact significance of this point I have not yet made out.

This variety of shock, together with that produced by loss of carbon dioxide, is probably what has hitherto been known as primary shock—a state well recognized to be fundamentally different from secondary wound shocks by workers such as Cowell, Bayliss, Dale, and Wallace. But the experiments which I have just quoted suggest that this variety of shock may be more important in accident cases and in the operating theatre than is generally supposed. In relation to operations an interesting piece of work has recently been published by Richet and Dublineau, showing that the vaso-dilator centre seems to develop a preliminary higher excitability under anaesthetics. It seems likely that the pressor mechanisms become anaesthetized before the depressor mechanisms.

Now a very interesting point is that experimentally, under apparently similar states of anaesthesia, depressor shock cannot always be demonstrated. This time last year I had no difficulty in producing it; indeed, my attention was drawn to it by the fact that on many occasions I produced it accidentally by operations which are usually innocuous. On the ground of these experiments which appeared so certain I decided to give this lecture its present title, but when I began to prepare for it in detail in September and October I found myself totally unable to produce shock in this way. It was rather disconcerting. The results were so clear-cut in February and September that I decided to wait for a few months. Now I am relieved to find that I can produce the depressor shock easily again, but as yet I have not been able to define exactly the circumstances under which it arises. The difference may be due to the seasonal variability in the sympathetic system of cats or may be solely a question of exhaustion by cold. This is, however, by no means solely a purely experimental point, but one of clinical importance, because it is found that some patients are much more easily shocked than others, and that fear, emotion, and cold, which stimulate the sympathetic and may cause exhaustion of the suprarenals, are definitely looked upon as aggravating causes (Fraser).

Mixed Shock.—From what has been said it is almost obvious that in some instances the varieties of shock must overlap—for example, chemical shock may supervene on nervous shock; indeed, it may almost be assumed that it will if a nervous shock is allowed to persist, because oxygen want will of itself lead to tissue death and capillary dilatation.

CONCLUSION

The whole clinical problem now requires to be completely reinvestigated in the light of modern experimental facts, with a view to finding methods for diagnosis of the different varieties. A large amount of the existing literature is completely valueless. I do not pretend that what I have said is in any way final, and a large number of the facts are not new; all I hope is that it may serve as a simple basis from which systematic clinical study may be made. But I think you will agree that a fuller knowledge of the experimental facts makes the general approach to the subject easier.

I have omitted those methods of producing shock which I do not think are related to surgical practice, and (as I said at the beginning of the lecture) I have also deliberately omitted a large number of facts regarding shock. Many are secondary to the fall of blood pressure, acidosis, loss of muscle tone, lowered metabolism, etc. I have done so because I want to make it quite clear that a

number of clear-cut varieties of shock exist experimentally. Clinically they have not been differentiated except very crudely as primary and secondary, although, as I have indicated, there is every reason to believe that distinct varieties exist. To the physiologist and biochemist may be left the problem of how best to deal with histamine, a solution to which is one of the most important requirements of modern surgery. But meantime we also want in relation to shock a better clinical surgery capable of making a more adequate differential diagnosis—not the dramatic surgery of the operating theatre, but the unexciting and unremunerative study of the patient in bed, the work which is too often left to anybody willing to do it, the surgery which involves a careful study of available experimental data, which would be a stepping-stone to a new surgery. If more surgeons came into the physiological laboratories and saw the different varieties of shock for themselves, there would be a much better appreciation of the facts, and soon we should have the clinical investigations which are so desirable.

SUMMARY

Experimental shock may be divided into several distinct varieties which, apart from that produced by haemorrhage and cardiac failure, may be divided into chemical and nervous.

The chemical variety is typified by histamine shock experimentally and clinically by a delayed shock associated with gross destruction of tissue. This variety is enhanced by anaesthetics.

The nervous varieties may result from physical damage to the vasomotor centre or its efferent paths, from afferent impulses leading to loss of carbon dioxide (acapnia), or from inhibition of the centre. Acapnia and inhibition account for the shock which follows immediately on injury. Shock dependent on afferent impulses is prevented by deep anaesthesia and reduced by morphine. The chemical and nervous varieties may coexist and enhance each other.

INSULIN AND GLUCOSE IN THE TREATMENT OF HEART DISEASE

WITH SPECIAL REFERENCE TO ANGINA PECTORIS

BY

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The past twenty years have witnessed an increasing interest in the therapeutic nutrition of the heart. The fact that digitalis is the outstanding means of combating serious heart disease and failure is indisputable, but in certain types of heart failure, particularly those associated with normal rhythm, this drug confers but slight or transient benefit. Attention has therefore become focused upon intensive glucose administration as a supporting measure, or sometimes a last resort. Dangerous states of circulatory insufficiency often occur in the second half of life when arterial, and specially coronary, degenerations have frequently set in, and in such circumstances it is reasonable to suppose that an increased content of nutritive material in the blood should be beneficial. It may well be also that a relative failure of carbohydrate utilization from endocrine causes may constitute part of the disability in chronic myocardial disease. Furthermore, the continued overaction of the heart and the enhanced basal metabolic rate in congestive failure demand ample supplies of carbohydrate, which may not be forthcoming unless special provision be made.