creating a strong suspicion of a gas infection. His condition was so critical that a member of the shock team attached to our outfit, seeing him lifted out of the ambulance and recognizing the urgency of aid, had him carried directly to the operating room. Any kind of operation then would have meant death; so while he was being given 500 c.c. of blood, which were, fortunately, obtainable, I simply removed the foot with one stroke of the knife and put on a bandage—trusting to luck concerning later developments.

It was remarkable how that boy picked up. Within a few hours, aided by hot water bottles and some hot drinks, he had taken a new lease on life. Nor did he slip back in the slightest—even when, twenty-four hours later, the signs of gas infection were unmistakable. He withstood an amputation above the knee without a quiver and, a few days later, was evacuated to the rear, a well, happy boy, smoking the inevitable cigaret. I could cite other instances like this one, equally gratifying; but one example is as good as a dozen in the same class of cases.

So much, then, for the acute hemorrhage and shock of the battle casualties. The need for blood was great and urgent; the supply, pitifully small. Substitutes were tried and found wanting. Further to the rear, where conditions were a bit less strenuous than in the forward areas, it was possible to secure blood more often, and in greater quantities. Thus, in the base hospitals, a great light was shed on the value of blood transfusion in the anemias secondary to battle wounds. These were very common and most distressing. The men would lie pale, inert, unable to eat, nervous, day by day slipping back just a little, while their wounds not only failed to heal but became increasingly dirty, until all bodily resistance being finally overcome, septicemia ensued, and death resulted. Particularly was this true of bone and joint cases.

We transfused a number of these men, and in nearly every instance a prompt improvement followed. One of them had a huge wound of the buttocks with a great area of bone involvement—always a sad condition. He was having rough going until he got some blood, after which his improvement was rapid and continuous. Another man had a big thigh wound and a septicemia—staphylococcus, I think. He overcame the septicemia, as many did, but his anemia was so profound that he did not improve. With two or three doses of blood, however, he took on renewed life and finally recovered, though the leg had finally to be removed. Still a third, and a most remarkable demonstration of the efficacy of blood transfusion, was that of a young lieutenant of aviation who, being wounded through the chest, crashed to earth, sustaining a compound fracture of both bones of his right forearm, a similar condition of the bones of his left lower leg, and a compound fracure of the bones of his right foot. Two months later, when I saw him, he was a mere skeleton, and, in addition to his fractures, had three intractable bedsores and a knee joint involved in a metastatic infection necessitating the turning back of the patella. It was clearly a case of too much absorption from too many foci of infection. In all, this man received four transfusions. After the second, his right leg was removed just above the knee for, with the foot hopelessly crippled and the knee joint badly infected, it was simply pulling him down without offering him anything in case of his recovery. The last two started him on the road to recovery. He was far from a well man even when he reached America; but without those transfusions his chances for life would have been nil. These three cases, each one of a different type, are sufficiently illustrative to prove the efficacy of blood in aiding the recovery of the battle-wounded.

At my suggestion, the sodium citrate method was adopted by the Medical Department of the American Expeditionary Forces as the only method of blood transfusion to be used. The reasons for this are so obvious as hardly to need explanation. Its simplicity, its elasticity, the fact that it could be employed under circumstances that precluded the use of any other method, all combined to make it the one procedure of election. At my further suggestion, all transfusion work in France was turned over to the medical men. Thus it happens that many men have obtained a wide experience in blood transfusion who, in civil life, had had no opportunity to familiarize themselves with it. A brilliant page in the history of blood transfusion was written in France. Let the physicians who wrote it there expand the chapter here.

2313 Eutaw Place.

THE COURSE OF EVENTS IN SECONDARY WOUND SHOCK *

W. B. CANNON, M.D.
George Higginson Professor of Physiology, Medical School of Harvard University
BOSTON

In the issues of THE JOURNAL of February 23 and March 2, 1918, there was published a series of articles by Cowell, Fraser, Hooper and myself which described certain clinical observations that we had made on soldiers who suffered from shock and allied conditions. These observations confirmed earlier reports on the persistent low arterial pressure, the rapid pulse and respiration, and the lowered body temperature of the shock state; they also revealed a concentration of corpuscles in the capillaries, a reduction of the alkali reserve corresponding in general to the degree of lowering of arterial pressure, a marked sensitiveness to ether or chloroform anesthesia, and a tolerance of nitrous oxid and oxygen as an anesthetic. On the basis of these facts a definition of traumatic or wound shock might be offered; it is a general bodily state occurring after severe injury and characterized by persistent low arterial pressure, rapid pulse, pallor or slight cyanosis, sweating, superficial rapid respiration, and usually by a dulled mental condition.

EXEMIA AS A CAUSE OF LOW PRESSURE

Among the articles in the series above mentioned was a theoretical discussion of the nature of wound shock, in which the low blood pressure was regarded as the central fact of the fully developed complex.[1] Reasons were given for refusing acceptance of the acapnia theory and the nerve exhaustion theory of the low pressure. The factors determining arterial tension were then analyzed, with the result that the low pressure was ascribed to "exemia"; that is, a

* Read before the Section on Surgery, General and Abdominal, at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

1. Cannon, W. B.: A Consideration of the Nature of Wound Shock, J. A. M. A. **70**: 611 (March 2) 1918.

temporary lessening of the volume of circulating blood, though not a loss of blood from the body. The possibility that the acidosis of shock, if carried to a sufficient degree, might play a rôle in causing further exemia was considered, but the occasion for the primary fall of pressure was left unsettled.

Shortly after the foregoing articles were presented as a report to the Subcommittee on Shock of the English Medical Research Committee, opportunity was offered at University College, London, to cooperate with Prof. W. M. Bayliss in an experimental analysis of the phenomena which had been observed clinically. Unfortunately, that work was cut short by military necessities, and the possibility of resuming it did not arise until the establishment of the Laboratory of Surgical Research of the American Expeditionary Forces at Dijon, France. Much that appears later in this report has come from observations made in London and from observations made by the group working at Dijon.[2]

PROPER EVALUATION OF THE DIFFERENT AGENTS IN SHOCK

That the phenomena of shock require experimental analysis is clear from a consideration both of its inherent complexity and of its attendant conditions. Shock has long been one of the great mysteries in surgery, and because of associated hemorrhage and infection there is usually much difficulty in assigning proper values to the different agents which might produce the general state of depression. No doubt hemorrhage may have an important part in the development of this state, and infection likewise is important; but there are recorded cases in which both hemorrhage and infection were absent or slight and in which, nevertheless, shock was observed. These facts of observation have led to the view that, beside hemorrhage and infection, there is an unknown factor at work.

Various views have been advanced to account for the nature and operation of this unknown factor. It was early suggested that serious wounds exhaust the nerve centers controlling the blood flow and that in consequence arterial pressure falls. This view has been extended so as to include the idea that the shocked man is suffering from general exhaustion not only of nerve cells, but of other parts of the body as well. Another view which has been widely noticed is that excessive respiration, by reducing the carbon dioxid content of the blood, causes such vascular changes as to reduce the volume of circulating blood. And still another suggestion is that the low pressure follows accumulation of fat either in the lungs or in the nerve centers governing the circulation; in the former instance the low pressure would be due to mechanical obstruction in the pulmonary capillaries, and in the latter case it would be due to injury of the vasoconstrictor center by anemia. None of these views as to the unknown factor in shock has been generally accepted. Possibly, as will be seen later, certain of them may at some stage have significance in the production of shock. The fact that the condition of shock has long remained unexplained, however, indicated the need for further investigation. The question to be settled seemed to be a determination of what factor, naturally related to the onset of shock, may so operate in the body, when hemorrhage and infection are ruled out, as to induce the characteristic persistent low blood pressure of the shock state.

DUPLICATING IN EXPERIMENTS THE CONDITIONS SURROUNDING SHOCK

One of the fundamental principles of experimental research is that the phenomenon to be studied shall present, when experimentally reproduced, as much detailed similarity as possible to the phenomenon as it occurs naturally. This is a principle which has been largely neglected in experimental investigations of shock. There is no doubt that a persistent low blood pressure can be produced by a variety of means. Investigators have reported the duplication of certain aspects of shock by prolonged stimulation of nerves, by severe and long-continued manipulation of exposed intestines, by the application of acid to the abdominal viscera, by vigorous over-ventilation of the lungs, by repeated punching of the diaphragm, or by injecting into the circulation large amounts of cream. It is possible that such procedures induce changes similar to those which may occur naturally in shock; but no one can successfully argue that such procedures reproduce the circumstances which occasion shock after ordinary wounds or injury. Obviously, it is desirable to duplicate so far as possible the actual conditions which give rise to shock and then to analyze them to determine what factor among them is operative.

Shock occurs in warfare on an enormous scale. To find evidence of the interest which the subject of shock has aroused at times of fierce strife one needs only to look through any large catalogue of medical literature and observe the dates of publication of articles. In warfare the shock state occurs characteristically in association with extensive and severe wounds—wounds in which large tissue masses are shredded, torn or crushed; as, for example, when there has been rupture and mashing of muscle by shell fragments. Similarly in civil life, traumatic shock is seen characteristically after injuries under car wheels or in machinery, when limbs have been badly mangled.

As Cowell[3] pointed out, there are certain very severe wounds in which death is certain to occur soon because of the anatomic damage which has been done. The patient's condition may be seriously complicated by abundant hemorrhage. In such cases, symptoms of shock are seen immediately; and from the earliest moment there is low pressure. This may be called "primary wound shock." On the other hand, there is testimony from a variety of sources[4] that after large wounds the state of shock commonly does not appear at once, but develops in the course of a few hours. This is Cowell's "secondary wound shock." When shock thus develops it may be attended by little hemorrhage, and it may occur too soon to be due to infection. Since these facts have been actually observed by medical men and dressers working in front line relief stations, there is justification for looking for the development of a state of shock in which hemorrhage and infection are negligible factors.

2. Already reports of these observations have appeared: Cannon: Med. Bull. Med. Research Society of the American Red Cross, Paris, April, 1918, p. 426; Compt. rend. Soc. de biol. **81**: 850 (Oct. 19) 1918. Bayliss: Intravenous Injection in Wound Shock, London, 1918. Cannon and Bayliss: Note on Muscle Injury in Relation to Shock, Report of Special Committee on Surgical Shock, English Medical Research Committee, March 14, 1919, p. 19. Cannon: Some Characteristics of Shock Induced by Tissue Injury, ibid., p. 27; Mil. Surgeon **44**: 494 (May) 1918.

3. Cowell, E. M.: The Initiation of Wound Shock, J. A. M. A. **70**: 607 (March 2) 1918.

4. Archibald and McLean: Ann. Surg. **66**: 280 (Sept.) 1917. Sant: Bull. Mém. Soc. de Chir. **44**: 207 (Feb. 6) 1918. Quénu: Presse méd. **26**: 69 (Feb. 7) 1918.

EXPERIMENTAL PRODUCTION OF SHOCK

In order to duplicate in lower animals conditions which give rise to shock in man, the thigh muscles in the anesthetized cat were traumatized by means of a blunt wedge-shaped hammer. While being struck, the muscles were supported by an iron block. The trauma usually failed to break the skin, so that infection from without was impossible. Occasionally the femur was broken, but this had no important influence on the results which were seen. After this procedure the course of events was followed and the arterial pressure was recorded by means of a mercury manometer. In Figure 1 is presented a record of the blood pressure changes typically seen after such trauma.

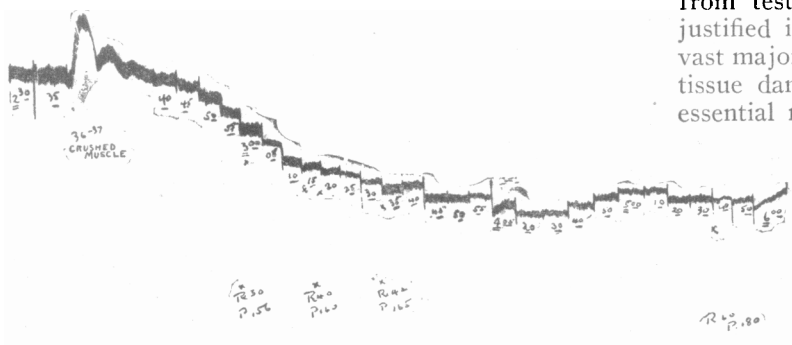

Fig. 1.—Typical fall of arterial blood pressure after crushing muscles of the thigh; *R*, respiration; *P*, pulse.

As Figure 1 indicates, the crushing of the muscles in the hind leg may have no immediate effect. After about twenty minutes, however, a fall of arterial pressure begins, and after about an hour the pressure has usually fallen to 80 or 90 mm. of mercury or even lower; that is, to a shock level. Pressure may persist at this level for several hours. Obviously, a general bodily condition resembling shock has been produced by duplication of circumstances which induce shock in man. The only variant from human conditions is the presence of anesthesia. That this is not a determining factor, however, is indicated by the use of a controllable anesthetic such as ether, which may be lightened as the animal goes into deeper and deeper stupor. The lessening of the ether concentration under these circumstances has no beneficial effect in improving the circulation.

THE PART PLAYED BY NERVOUS IMPULSES

The general bodily state which has been caused by the crushing of tissues in one hind leg naturally raises the question as to whether the widespread effect in the organism is due to nervous impulses roused by the trauma. These impulses on passing to the central nervous system might so affect it as to produce profound depression of nerve cells and the exhaustion which is apparent both in experimental animals and in human beings when shocked. Is that the case? The nature of the experiment permits the settlement of this question. It is only necessary to transect the spinal cord above the lumbar plexus or to sever all nerves of the limb which is to be injured in order to disconnect the region from the central nervous system. When this has been done and the denervated muscles are traumatized, events occur similar to those seen after trauma with the nerves intact (Fig. 2). There is common testimony from men who have been seriously injured that the wounds are not painful; in other words, afferent impulses are not arriving from the injured region in any such intensity as to affect deeply the central nervous system. It would be rash, however, to argue that nervous impulses play no part in the establishment of shock; indeed, there are cases in which a pure nervous shock from trivial wounds seems to be present. From personal experience and from testimony of other observers, however, I am justified in reporting that these cases are rare. The vast majority of shock cases are associated with severe tissue damage. As shown in Figure 2, there is no essential relation between the production of shock in such instances and excessive stimulation of the central nervous system.

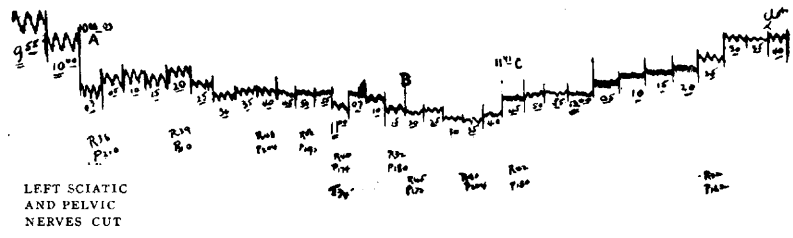

Fig. 2.—Fall of blood pressure after muscle injury though the nerves to the injured limb had been cut. Rise of blood pressure to the original level after tying (at 11:41) the blood vessels to and from the injured region. *A*, left leg muscles hammered; *B*, muscles hammered again; *C*, clip on vessels to left leg.

TOXIC MATERIAL PROCEEDING FROM WOUNDED TISSUES

If the general bodily state resulting from local trauma is not mainly the consequence of effects produced on the nervous system, the relation between the general and the local conditions may be looked for in the other great integrating system, namely, the circulatory. Quite possibly there is given off, from the injured tissue to the flowing blood or lymph, material which, when carried to the rest of the body, proves toxic and affects the vascular system in such a way as to lower arterial pressure. The idea can be readily tested. The blood vessels of the leg (the iliac artery and vein) are tied and the muscle then crushed. As stated above (Fig. 1), the arterial pressure usually begins to fall in the cat about twenty minutes after the injury. In Figure 3, the blood vessels of the leg were tied before the muscles were smashed, and ligatures were left in place for thirty-three minutes after the injury. The record shows that there was no dropping of blood pressure during this period; but as soon as the blood flow was restored, the pressure promptly fell to a low level.

The fall of pressure after restoration of blood flow in the traumatized limb might be regarded as due to loss of blood and lymph into the damaged tissues and not to the washing out of toxic material from these tissues into the rest of the body. This suggestion was put to test by removing with symmetrical cuts the two hind legs and weighing them. The difference in weight, which in some instances was only 10 per cent. of the estimated blood volume, would not represent enough extravasated blood to account for the fall of pressure.

The conclusion appears justified, therefore, that a pressure-lowering substance passes from the traumatized region to the rest of the body by way of the circulation. Extravasation of blood may augment the depressant effect.

The conclusion just stated receives support from an experiment in which the muscle was injured, and while the pressure in consequence was falling, the vessels of the leg (the iliac artery and vein) were clipped. As shown in Figure 2, the occlusion of the vessels was followed by a progressive rise of pressure to the normal level. This evidence indicates, therefore, that whatever may be the substance arising from the injured tissues, it is fairly promptly changed in the body so that its effect is not permanent.

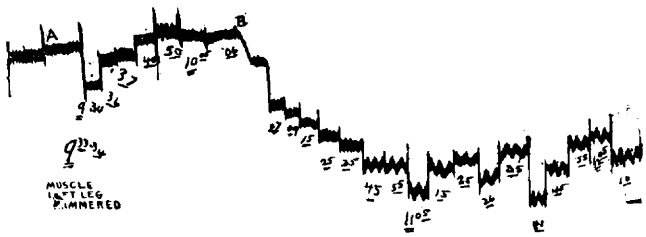

Fig. 3.—Failure of blood pressure to fall at the usual time after muscle injury if the blood vessels to the injured region have been tied. On restoration of the blood flow, the pressure promptly falls. *A*, vessels clamped; *B*, clamps off.

Experiments which have been performed by Cattell since returning to the United States indicate that the fall of blood pressure is not, at least in the early stages, associated with dilatation of the arterioles. This evidence is in agreement with that reported by Seelig and Lyon,[5] by Mann,[6] and also by Erlanger and Gasser.[7] It is further testimony against the view that shock is primarily due to nervous exhaustion.

Careful examination was made of the lungs in several of these cases by Col. L. B. Wilson and by Major Henry W. Cattell, and in no instance was there evidence of any accumulation of fat. Furthermore, there was no twitching or other disturbance which might indicate that fat had passed through the pulmonary capillaries and into the central nervous system. The fall of pressure, therefore, cannot be attributed to fat embolism.

Although there was usually a change of respiration in the direction of greater rapidity and lessened amplitude, this was not such as to cause a washing out of carbon dioxid and a consequent acapnia. The lowered blood pressure, therefore, cannot be ascribed to such a change in the blood.

For a long time it has been known that tissue extracts, when injected into the blood stream, will cause a temporary fall of pressure. In 1903, Vincent and Sheen[8] proved that watery extracts of a variety of tissues would produce this effect. Furthermore, Dale and Laidlaw have shown that a characteristic shock-like condition can be induced by the injection of extremely minute amounts of histamin, a substance which Barger and Dale proved present in the mucosa of the small intestine.[9] The low pressure caused by this substance is not due to dilatation of the arterioles but apparently to dilatation of the capillaries with escape of plasma into the tissue spaces.[10] This effect is in consonance with the evidence for diminished volume of circulating fluid and concentration of the corpuscles in capillaries in human cases. French surgeons with extensive experience in the war, Delbet[11] and Quénu,[12] have independently come to the conclusion that the phenomena of secondary shock are the consequence of absorption of proteolytic products arising from the region of the injury; and Turck[13] has expressed similar ideas. There is the possibility that this *traumatic toxemia* may be closely related to "peptone" shock and that the toxic agent is, like "peptone," capable of making the capillary wall more permeable to the fluid portion of the blood. These suggestions must be regarded, however, as purely hypothetic. It is clear that a large field for investigation is opened by the facts above described.

A SECONDARY DAMAGE

Besides the primary fall of blood pressure induced by substances given off by the injured tissues, there is a secondary damage, which may result from the low blood pressure itself. As stated above, there commonly appears in clinical cases of shock a reduction of the alkali reserve of the blood, or an "acidosis" in the sense defined by J. L. Henderson. The reduction of the reserve corresponds roughly to the degree of lowering of blood pressure. In forty-four cases of shock and hemorrhage which I investigated at Béthune in 1917, the relations between blood pressure and the alkali reserve were as shown in the accompanying table.

When we consider that 50 per cent. by volume of carbon dioxid capacity is close to the boundary between normality and acidosis, it is obvious that the maintenance of a blood pressure above 80 mm. causes little alteration in the blood, but that a reduction of the pressure below this level results in a marked diminution of the sodium bicarbonate as indicated by the carbon dioxid given off. These clinical observations have been confirmed by experiments. A cannula introduced through the chest wall and tied into the pericardium permits fluid to be introduced into the pericardial sac. By varying the pressure of this fluid, the output from the heart can be varied or held at any

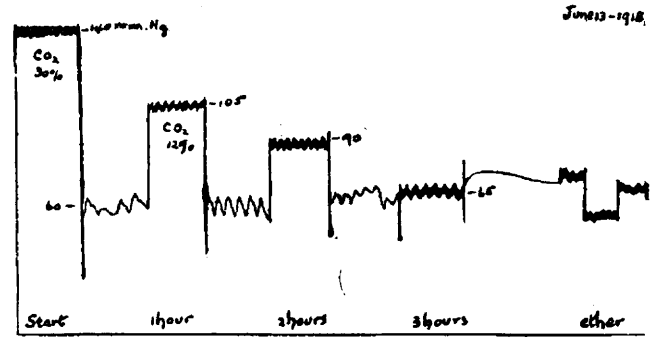

Fig. 4.—Record of an experiment showing the progressively harmful effects on the circulation of persistent low arterial pressure.

5. Seelig and Lyon: Surg., Gynec. & Obst. **11**: 146 (July) 1910.
6. Mann: Bull. Johns Hopkins Hosp. **25**: 208 (July) 1914.
7. Erlanger and Gasser: Ann. Surg. **69**: 391 (April) 1919.
8. Vincent and Sheen: J. Physiol. **29**: 264 (April) 1903.
9. Dale and Laidlaw: J. Physiol. **41**: 318 (Dec.) 1910 and 499 (Jan.) 1911; **43**: 182 (Oct.) 1911; **52**: 355 (March) 1919.
10. Dale and Richards: J. Physiol. **52**: 110 (July) 1918.
11. Delbet: Bull. de l'Acad. de méd., Paris **80**: 13 (July) 1918.
12. Quénu: Bull. et mém. Soc. de chir. de Paris **44**: 496, 1918; Presse méd. **26** (Feb. 7) 1918.
13. Turck: M. Rec. **89**: (June) 1918; **90**: 471 (March) 1919.

given level. When this is done, the interesting result is observed that unless there has been considerable hemorrhage, a blood pressure in the neighborhood of 80 mm. of mercury results in no diminution of the alkali reserve. On the other hand, a reduction of the pressure to 70, 60 or 50 mm. will cause, at the end of half an hour or an hour, a marked reduction of this reserve (Fig. 4), varying directly with the degree of lowering of the blood pressure. There appears to be, consequently, a critical level in the blood pressure below which it may not fall without bringing about a change in the character of the blood itself.

In the theoretical article previously referred to the suggestion was offered that the acidosis observed in shock may, when it becomes sufficiently developed, take part in a vicious circle of causation which might lead to still further reduction of blood pressure. This idea was put to experimental test, and it was found that if a volatile anesthetic, such as ether, is employed, the alkali reserve can be very greatly reduced by injection of

RELATION BETWEEN BLOOD PRESSURE AND ALKALI RESERVE

Systolic Blood Pressure, Mm.	Average Carbon Dioxid Capacity Vols. %
Above 80	49
70-80	43
60-70	35
Below 60	27

acid without any noteworthy fall of arterial pressure.[14] From these observations it appears clear that the reduction of the alkali reserve in the flowing blood has in itself no serious effect in the direction of augmenting the shock state.[15]

REDUCTION OF THE ALKALI RESERVE

The reduction of the alkali reserve may be accounted for on the basis of retarded blood flow. When the head of arterial pressure is lowered, the blood flow becomes slower. Observations by Gesell have revealed that a fall of arterial pressure from the normal to a low shock level (59 mm. of mercury) may be accompanied by the reduction of the flow to one fifth of its former speed.[16] Under such circumstances the number of trips which the corpuscles make between the lungs and the tissues will be reduced approximately to the same extent; thus, in such a case, though every corpuscle may leave the lungs fully laden with oxygen, the total amount of oxygen delivered to the tissues in unit time may be lowered, other things being equal, to one-fifth the usual amount.

It has been known for many years, chiefly from the work of Araki,[17] that any condition which diminishes the oxygen supply of the tissues, such as rebreathing expired air, or extreme slowing of respiration by morphin or by hemorrhage or poisoning with carbon monoxid, will lead to the production of lactic acid rather than carbonic acid as a tissue metabolite. Since lactic acid is nonvolatile, it will not be breathed away as is the case with carbonic acid. It will unite with the sodium of the sodium bicarbonate, forming sodium lactate, thus diminishing the alkali reserve. The carbon dioxid which is set free will, of course, be promptly eliminated.

DANGER FROM INSUFFICIENT OXYGEN SUPPLY

On the basis of the foregoing evidence, the acidosis which appears as the blood pressure is lowered, though not dangerous in itself, is an indication of a really serious danger, namely, the danger arising from insufficient oxygen supply.

The tissues of the body are known to vary greatly in their sensitiveness to oxygen want. Some muscles will endure total anemia for at least three hours without undergoing destructive alterations. On the other hand, certain nerve cells of the cerebral cortex cannot endure total anemia for more than seven or eight minutes without suffering changes so profound as to be irreversible. There is especial danger, consequently, that the nervous system will be damaged by persistence of the blood pressure below the critical level.

As shown in Figure 4, the blood pressure may be lowered to 60 mm. of mercury for an hour, and at the end of that time, if the pressure is allowed to rise, it will be nearly restored to its normal level. If now the pressure is again lowered to 60 mm. and held there for an hour, it does not rise so high; and when held to this low level for another hour, it may not rise at all. Examination of the blood under these circumstances indicates that there has been no material escape of fluid from the vessels. The failure of the pressure to rise after persistence at the low level is to be regarded, therefore, as dependent on the damage done to control of the circulation by the inadequacy of the circulation itself.

The facts just developed offer a basis for the similarity which has been repeatedly noted between the phenomena of shock and the phenomena of hemorrhage. After the blood pressure has once been lowered in shock, the effects on the organism are in all respects similar to those which are produced by a marked loss of blood. The dictum of the older surgeons that "shock is hemorrhage and hemorrhage is shock" is thus justified. The significance of this similarity in the treatment of both shock and hemorrhage will appear later.

SECONDARY SHOCK

A review of the evidence presented above permits us to follow the course of events in secondary shock. It may be thus summarized: Toxic material given off by smashed and dying tissue affects the circulation in such a way as to cause a lowering of the blood pressure; the low pressure involves a slowing of the circulation; the slow circulation involves damage because of diminished oxygen supply; and in consequence highly sensitive structures, especially nerve centers, become injured and lose their tonic activity. Thus, though in the early stages of shock the low blood

14. Acidosis and Shock, Report No. 9 of Special Committee on Shock and Allied Conditions, English Medical Research Committee, October, 1918.

15. In a discussion of theories of shock, Meltzer (Penn. M. J. **22**: 129 [Dec.] 1918) has stated that I became "converted to the theory that the most essential factor in the production of shock is acidosis." I have never published the idea that there was in the acidosis of shock a primary cause for the low pressure. At one time I did advocate the use of sodium bicarbonate as a means of avoiding the extreme acidosis which may follow surgical operation on shocked men. Men who were in great distress from air hunger after operation were made immediately comfortable by alkaline therapy. Because of this effect the suggestion was offered that the injection be made during the period when the pressure is likely to fall; that is, during operation. Thus the pressure was held up and the alkaline content of the blood increased. At that time it seemed possible that anesthesia and operation might in themselves produce a harmful acidosis. Later experimental work proved that the acidosis was probably purely secondary to the fall of pressure and that the main object should be to avoid the fall. Alkaline therapy thus became limited to the relief of symptoms of extreme acidosis. Because alkaline therapy was suggested is no warrant for assuming the conviction that shock is primarily due to acidosis.

16. Gesell: Am. J. Physiol. **47**: 491 (Jan.) 1919.

17. Araki: Ztschr. f. physiol. Chem. **15**: 335, 1891.

pressure may be associated with constriction of the arterioles, in the late stages the arterioles may be relaxed because of such damage to the vasoconstrictor center that it no longer holds the vessels in tonic contraction.

TREATMENT OF SHOCK

The principles of the treatment of shock are suggested by a consideration of the facts and inferences outlined above.

In the first place, if a part of the body has become shattered and useless through injury so that it is impossible to save it, the harmful toxic effect of the torn tissue on the rest of the body may be avoided by applying tightly, as near as possible to the injured region, a tourniquet. Extreme care should be taken *not to remove the tourniquet before operating at a point proximal to it.* The reason for this urgency is that when tissues are deprived of their blood supply they undergo at a slower rate the same changes which they undergo when mechanically traumatized. During the course of military operations last year, several cases were reported of the sudden production of shock on removal of a tourniquet which had been applied to stop bleeding and left in place for an indefinite period. These observations obviously support the view of shock which has been outlined above. If a tourniquet used to stop bleeding is to be left in place for a long period, it should be applied at the most distal effective location. The surgeon must be guided in his decision to save or sacrifice the part by questions of viability, of gross infection in the excluded region, and of danger to the rest of the body from its retention. The danger of the tourniquet should lead, whenever possible, to the substitution of other methods of controlling hemorrhage. If the injured tissue can be removed promptly either by amputation or débridement, that should be done in preference to the application of a tourniquet.

Observations by Lieutenant Aub in the Surgical Research Laboratory of the American Expeditionary Forces at Dijon proved that there is a marked diminution of the heat production as the blood pressure is lowered. Furthermore, the man in shock sweats and thus loses heat both by evaporation and by greater conduction of heat through wet clothing, especially when he is exposed in cold weather. These considerations give a rational basis for the treatment of shock by warmth, a procedure universally recognized as of great value. Every effort should be made to avoid loss of heat from the shocked man or to restore heat that has already been lost. These objects may be attained by avoiding unnecessary exposure of the body and by use of hot drinks, warm water bottles, and proper blanketing.

The facts regarding the damaging effects of low arterial pressure which have been emphasized above should be emphasized again. If the pressure is allowed to remain below the critical level for a sufficient length of time, the vasoconstrictor center may be so profoundly affected that no measure will restore it to its normal condition. The transfusion of blood, for example, then results in only a temporary rise of arterial pressure, just such a rise as may be seen after total destruction of the center. As shown in Figure 4, the time element in the damaging effect of low pressure is of the utmost importance. If simple measures, such as warmth and fluids by mouth, do not in half an hour raise the pressure above the critical level of 80 or 90 mm. of mercury, the case should be treated as if it were a case of hemorrhage; and the treatment should be *prompt* in order to avoid the progressive damage as time passes. There appears to be little doubt that the best method for raising the blood pressure is transfusion of properly matched blood; by such means not only is the pressure raised but oxygen carriers are added to the circulation. If blood is not available, Bayliss' gum salt solution,[18] made of selected pure gum in physiologic sodium chlorid solution, or Erlanger and Gasser's[7] modification of this solution, may be employed. These colloidal solutions, if used early, can permanently raise arterial pressure. They do so by increasing the circulating volume of fluid. The corpuscles which are present are made to circulate more rapidly and thus to be employed more efficiently as oxygen carriers. There is no evidence that either the subcutaneous or intravenous injection of physiologic sodium chlorid solution has more than temporary value, if it has any beneficial effect at all.

SENSITIVENESS OF THE SHOCKED TO OPERATIVE PROCEDURES

In the earlier series of articles the sensitiveness of the shocked man to operative procedures was emphasized. Work done in cooperation with Lieutenant Cattell at the Surgical Research Laboratory at Dijon revealed the fact that not the operation but the etherization was the chief reason for the fall of pressure. If shock is already present in an animal, etherization until the wink reflex disappears may cause the pressure to fall 30 or 40 mm. of mercury (Fig. 4). On the other hand, the same degree of anesthesia may be induced by using nitrous oxid and oxygen in a ratio not exceeding 3:1 without any fall of blood pressure. There is little difficulty in bringing about satisfactory anesthesia or analgesia in shock cases with this ratio of the gases if there has been a previous dose of morphin. From suggestions which have been given above, it should be clear that morphin should not be given in such amount as greatly to retard respiration; and it should be clear also that at all stages deep anesthesia, or cyanosis or such rebreathing as would diminish the oxygen supply in the respired air, should be scrupulously avoided.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. CANNON AND BERNHEIM

DR. GEORGE W. CRILE, Cleveland: During the campaign of 1917 the various teams of the Lakeside Unit with the British and in later campaigns, did nearly 1,000 transfusions of blood, the results of which confirm Dr. Bernheim's conclusions. Surgeons must feel gratified that physiologists have undertaken the solution of certain urgent practical problems. Dr. Cannon and many of his colleagues did most valuable work during the war. There are three practical reasons why we are unable to accept Dr. Cannon's work as conclusive: 1. Patients with extensive wounds of the extremities to which tourniquets had been applied so that the blood supply of the injured part was so completely blocked that no tissue poisons could have been introduced into the circulation, have passed into shock and have died from shock. Patients have died during operations from shock in which a tourniquet has completely controlled the circulation of the blood of the injured part. The tourniquet does not block nerve impulses; it does block circulation. 2. Nerve blocking does prevent shock. It is possible to kill animals by traumatizing nerve tissues without touching any other tissue. Indeed, if Cannon believes that the nervous system bears no part in shock, it would be

18. Bayliss: Intravenous Injections in Wound Shock, London, 1918.

an unfortunate conclusion from the surgical point of view. In this the work of men like Cabot, with low spinal anesthesia, is most illuminating. Cabot performed 180 amputations of the thigh—ninety under ether anesthesia in the usual way, ninety with low spinal anesthesia. The death rate of the latter series exactly reverses the death rate in the former series, that is, under ether anesthesia without blocking the spinal cord there were two deaths out of three; with the blocking of the spinal cord there was one death out of three. 3. Nitrous oxid is almost a specific preventive of shock. This action of nitrous oxid in the presence of toxins and proteins has been demonstrated conclusively in my laboratory as appearing from its influence on the nervous system. As a matter of fact, I believe that we must cling to the principle that a number of factors are concerned in the causation of shock. Of these various causative factors, Cannon's is one and in practical surgery one of the least important.

DR. OSWALD H. ROBERTSON, New York: While it is generally agreed that in cases of severe hemorrhage transfusion is the most effective method of treatment, I do not think that gum acacia solution, or gum saline as it is called, should be dismissed as having little value in this condition. The reports on the use of gum acacia solution in hemorrhage vary considerably. Some people are very enthusiastic, others say it has little or no effect. I think this diversity of opinion is due to several factors. I had an opportunity during the course of the war to investigate the subject in a number of our hospitals. Certain men reported very favorably from the clinical side; they got excellent results. Others are inclined to regard it as being the last resort if they could not get blood. It seems to me that the reason for this is that people, on the whole, are expecting gum acacia solution to act as a "cure-all." There were four classes of cases in which gum acacia solution was of very little use. In the first place, cases of shock or hemorrhage which had been in this condition for twenty-four to forty-eight hours responded very little to gum acacia, or to an injection of any substance, even blood. These patients had been in a condition of oxygen starvation so long that nothing would benefit them. Without morphin and rest any intravenous treatment is harmful if given before the patient has begun to recuperate. Third, in the case of those patients who had lost large quantities of blood, and who were very anemic, gum acacia solution increased the volume, the blood pressure rose temporarily, and then it dropped. What the patient needed was new blood. He did not get it, therefore, he died. In the fourth class, the patient often had a concealed gas gangrene and in these cases gum acacia solution was of no avail. Where gum acacia solution was used intelligently and with these considerations in view it had a very definite value and was successful in many instances. From intensive study of hemorrhage in the war we have learned the value of forced fluids in the treatment of hemorrhage. It is well known that considerable fluid is contained in the body tissues outside of the circulation. After hemorrhage this fluid is poured into the circulation in an attempt to make up the lost blood volume. If the hemorrhage has not been very severe sufficient fluid can be supplied by the tissues to make up for the lost volume and the pressure comes back to normal. If the hemorrhage is very severe the body tissues cannot supply sufficient fluid to make up the volume and outside assistance is needed. Even with moderate hemorrhage if the fluid reserves are low, before these can be made up fresh fluid must be given by forced fluids through the digestive tract. So that very soon the volume begins to rise and with it the blood pressure. Fluid may be given in very large quantities by mouth, as much as a liter, and by rectum. It is absorbed rapidly. In severe cases transfusion is needed. Forced fluids should be considered an essential part of the treatment of hemorrhage in all instances. Even in cases of severe hemorrhage transfusion makes up only a small part of the loss, the rest must be made up from the fluid of the tissues.

DR. HOWARD T. KARSNER, Cleveland: So far as the general proposition of the success of transfusion in cases of hemorrhage is concerned, I can support everything Dr. Bernheim said. From the point of view of a laboratory man, however, numerous points are to be considered and I feel that some exception must be taken to the statement of Dr. Bernheim that the citrate method has proved itself to be the best method of transfusion. Certain methods have been tried with certain degrees of success. I have been particularly impressed by a paper by Lindemann on the transfusion by the needle syringe method in which the blood is transferred from one individual to another almost directly, with a minimum of contact with foreign surfaces. It is unqualifiedly true that the longer the blood stays out of the body the more likely a change in the course of transfer. The more immediately the blood is changed from donor to recipient the better the results are likely to be. Of course, I am not taking into account the amount of blood transferred. The addition of chemicals, however, places in the blood a factor which otherwise would not have to be considered. It adds a variable and a considerable number of variants. As regards anaphylaxis and anaphylactic symptoms, I have seen nothing which would indicate that anaphylaxis plays any part in regard to transfusion. In the matching of blood we have a problem which affects the individual patient. I would like to put myself on record as favoring the grouping of donors and of patients. I am convinced that the safest method of matching donor and recipient is to have them in the same group. This matter has been the subject of investigation in my laboratory for the last year, with the collaboration of Dr. Reckert. The principle of serum for testing blood for transfusion is unsatisfactory if we are to preserve this serum for any length of time. After the lapse of five or six weeks the serum not only lost its potency but also its specificity. The final comment is on the matter of simply matching up the recipient's serum against the donor's corpuscles, maintaining that if in a test tube or slide it does not agglutinate the transfusion is safe. I believe in testing blood and in order to make this test the serum must be preserved in some other way than by drying.

DR. R. PICQUÉ, Bordeaux, France: During the last year of the war we experimented with thirty-six cases of blood transfusion: thirty-two were cases of hemorrhagic shock, with twenty-one successes; four were cases of operative shock, with two successes. As guides for transfusions we utilized, first, clinical examination of the patient, and second, the blood count. In two thirds of the cases the scale as per Depage and Govaertz (de la Panne) was proved correct. But in one third of the cases, when seen near the lines, we noted that in the recently wounded (first to sixth hour), though the men were almost bloodless from severe hemorrhage of a most serious type, the leukocytes were almost normal in number. Third, the blood pressure is a guide. The instrument of Pachon (of Bordeaux), which is ultrasensitive, allows us to follow the blood pressure from hour to hour and to seize the moment when loss from hemorrhage indicates instant transfusion. In such cases, either we transfuse first then operate; or we operate first and transfuse afterward. Either immediately after the venous injection, or later when serotherapy has proved unable to sustain the blood pressure, and at all times in order not to waste blood we only practice transfusion on those whom we judge able by a radical operation to protect from infection for transfusion itself has not a single action against infection. As to results, in these picked cases we have obtained, first, twenty-one "resurrections" among simple, severe hemorrhages. Second, two successes among serious cases of operative shock, where serotherapy had proved absolutely impotent. The wounded are constantly watched and studied in well warmed rooms, either in the divisional ambulance or the subterranean surgical stations. The study of the cases is made by trained, experienced surgeons or nurses. The blood pressure instrument permits the surgeon to keep in instant touch with the patient's condition before and after transfusion. Those giving blood for the transfusion are the surgeons, dressers, nurses of the ambulance who after administering 500 to 800 grams of their blood still continue to work at the bedside of the wounded. We have not studied the agglutination and we have not observed any bad effects among our cases, except for two cases of hemoglobinuria, with serious results. We endorse use of the ampule of Kinpton and the citrate method of Jonde.

DR. RICHARD LEWISOHN, New York: It is a great gratification to me that the sodium citrate method, which I first suggested in January, 1915, was adopted officially by the American Expeditionary Forces. The safety of the method is based on the atoxicity of the dose. The dose of sodium citrate is so small that it will not produce any toxic symptoms. Another important factor is that sodium citrate, though it prevents coagulation of the blood outside of the body, shortens the coagulation time temporarily when introduced into the body. This shortening is one of brief duration and the blood coagulation time falls back to pretransfusion time in about twenty-four hours. The advantages of the method are its simplicity, its flexibility, the possibility of the transfer of blood from one place to another, the very important factor that donor and recipient do not have to be together in the same room and do not have to be attached to each other by some form of apparatus, and that this transfusing can by simplicity of technic be repeated as frequently as we want to do it. The disadvantage of the method is the occurrence of chills. Chills occur in about 20 per cent. of the cases. The syringe methods and the Unger apparatus usually cause chills in 5 to 10 per cent. of the cases, so that the disadvantage is really not very great. A few points in the technic are very important, the proper insertion of the cannula into the vein and the use of very large cannulas for the donor so that the blood runs out very rapidly. My personal experience comprises about 300 cases. I have never seen any bad results. In another field of blood transfusion we have to make improvement and that is in cases of sepsis. This improvement will lie in the rapid immunization of the donor. At present it takes from two to three days to immunize the donor for a septic patient. If we can do this in a few hours, another field for transfusion will be opened up for us.

DR. WALTER B. CANNON, Boston: Dr. Bernheim suggested that efforts should have been made in France to assure transfusion of blood rather than injection of gum-salt solution. The resuscitation teams in the A. E. F. received about sixteen hours of instruction; about one hour was spent in considering gum-salt solution, and most of the rest of the time was spent in practicing blood transfusion. As long ago as last July we urged that gassed men be placed near the shock ward to provide blood for shock cases. And when later the badly wounded were found segregated, with the result that there was no possibility of getting blood for them, we called attention to the handicap they thus suffered, and again urged putting lightly wounded men near them to supply blood for transfusion.

Dr. Crile mentions lack of agreement regarding the toxic origin of shock. Possibly there is more agreement than he realizes. In the last report of the English Medical Research Committee on Shock, surgical, biochemical, physiologic and pathologic judgments all came to the support of "traumatic toxemia" as a highly important factor in the causation of shock. Furthermore, when the facts reported above were presented last October before the Société de biologie in Paris, Delbet, the well-known French surgeon, remarked that the meeting would be historic because biologists, physiologists and surgeons had for the first time agreed on the toxic origin of shock. Dr. Crile has argued that shock is of nervous origin because he has seen alterations in nerve cells in tissues taken from shocked animals. These alterations may be present in nerve cells, but one may disagree with Dr. Crile's interpretation of them. Dolley, the cytologist who worked with Dr. Crile, admitted that the same cellular alterations seen after shock are produced by hemorrhage. But the low blood pressure of shock is equivalent to hemorrhage. The changes in nerve cells taken from the shocked animal may be interpreted, therefore, not as the cause, but as the result of shock. As to the practical bearings of our views, Dr. Crile and I agree in being disturbed about the same thing, that is, rough surgery. He is fearful lest rough surgery affect nervous tissue, and I am fearful lest it may affect all tissues, including nervous. I do not wish to detract in the slightest from the moral effect of Dr. Crile's teachings; I would only insist that surgeons must not unnecessarily injure any tissues.

DR. BERTRAM M. BERNHEIM, Baltimore: Dr. Crile is interested in the nerve and Dr. Cannon in tissue; both are interested in surgery, and I am interested to see that they do not have any loss of blood. So that if we all get together by mixing a little blood with the tissue and nerves it will be all right. During the war we must consider the greatest good to the greatest number. Any man who maintains that the Kimpton-Brown method or the Pederson method is one twentieth as good as the citrate method has not been in France. I was rather surprised to hear Dr. Robertson make excuses for gum acacia solution. The advocates of gum acacia solution are always making excuses for it. That in itself should rule it out. They are always accusing the other fellow of not using it right. I have never found a man who had any good to say of it. There are men in this audience whose experience with it proved disastrous. Certain men here have seen deaths from it. It not only did not help, it killed men. While I was in France I did no transfusion. My sole object in reading this paper was to show that substitutes for blood are not of any help, and that we have a method of doing transfusion which any one can use. What I want to insist on is that the laboratory men find a method of preserving blood so that you can go to a corner drugstore and get half a liter just as you can anything else.

SCIENTIFIC MEDICINE—YESTERDAY AND TOMORROW *

GRAHAM LUSK
NEW YORK

Last winter I heard a talk by Galsworthy at the University Club in New York. His strain was that men who had fought in the war had become mentally addicted to the contemplation of their own past and that they could not look forward with hope or enthusiasm to the future. It seemed utter nonsense; and yet this theme has been so stressed that it has affected seemingly well balanced men. Only last Sunday a little girl visiting her grandfather told him that her mother was spending the morning studying pathology, while her father, home from France three months, was occupied in chasing butterflies. The young men of this country cannot become addicts of the pastime of butterfly chasing when the advance of the world is so largely in their hands.

The fathers of men now living, fathers who had been engaged in desperate fighting for four long years of civil war, returned after the war to their former occupations, some of them following medicine with joy and in careers of distinction. Galsworthy thoughtlessly disparaged the character of that war, the battles of which were much costlier in human life than those of the Franco-Prussian war of 1870, and a war in which one man out of every four living in the Confederate States was under arms: as large a proportion as served in Great Britain during the recent conflict. Do we, who are most of us the descendants of this race, propose to chase butterflies when the opportunity for carrying on the treasured learning of the world and for its future development is placed fairly and squarely on our shoulders? The meeting held today answers this in the negative.

Twenty years ago (June 16, 1899) Theodore Janeway, then 27 years old, wrote me that he would give up an idea he had had of going to New Haven to teach pharmacology at the Yale Medical School, and that he would conduct an "elementary clinic" for the benefit

* An address delivered before the American Society for Clinical Investigation.