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ANALYSIS OF SHOCK

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During a period of 40 years shock has been the subject of extensive and intensive study, both clinical and experimental. This has resulted in a mass of well-attested factual evidence, but agreement on the pathophysiological mechanisms has not been reached. Writers differ widely in their views, and readers are bewildered by the evidence set forth in support of the conflicting opinions. It appears that a logical correlation of the known facts is needed now rather than a search for new facts. A realistic examination of the causes for disagreement may be illuminating.

What is Shock?

The broad and indefinite use of this term is not the least among several causes for disagreement. *Shock* has been applied to a number of unrelated conditions. Many regard it as a state of acute circulatory failure characterized clinically by prostration, apathy or stupor, tachycardia, feeble regular pulse, and diminished blood pressure. The peripheral temperature frequently is subnormal. When used in this sense shock includes several forms of circulatory disturbance having no other features in common; their pathogenesis and disorders of function are various. The effects of syncope, fright, exhaustion, anaesthesia, haemorrhage, primary shock, cardiac failure, or of secondary shock may produce the clinical signs mentioned. Each of these conditions may cause low blood pressure; hence it cannot be used as the criterion for differentiating them.

The attention of surgeons is focused chiefly upon shock seen in battle casualties and in those injured in accidents or air raids, and upon shock following extensive surgery. If, under these or other circumstances, a patient manifests the signs mentioned above, shock is regarded as present. Some writers recognize that at least *three unrelated mechanisms* may combine to cause weakness, pallor, feeble rapid pulse, and low blood pressure—interpreted clinically as shock—after traumatic injuries. Attention is invited to a brief consideration of each of these mechanisms.

Primary or Neurogenic Shock.—This is a neurovascular reaction like that of syncope or fainting. It may be excited by pain, fear, and the emotional effects of the injury, or by non-sensory nerve impulses arising in the damaged tissues. Primary shock comes on promptly, and is usually transient unless accompanied by extensive trauma or haemorrhage. In cases of severe abdominal injury, visceral perforations, pancreatitis, burns, or extensive damage to other parts, primary shock may merge gradually into secondary shock without an interval of partial recovery. This feature was emphasized by Cope (1928, 1935), Blalock (1940), and others.

Recent experiments (Phemister and associates, 1944) show that prolonged low arterial pressure can be produced in animals by continuous mild stimulation of afferent depressor nerves. Arterial pressures between 40 and 60 mm. Hg were maintained in some instances for several hours. The blood of such animals showed dilution regularly. This feature is opposite to that seen in secondary shock. It indicates that the mechanism of fluid balance is functioning normally and that the capillary walls are not abnormally permeable. Fluid balance and haemoconcentration will be discussed later. A decrease in total blood volume has not been shown in uncomplicated primary shock.

Haemorrhage.—The effects of haemorrhage are an obvious cause for low blood pressure and other signs of disturbed circulation after injuries. These signs may develop promptly from voluminous haemorrhage or gradually after slow or repeated small haemorrhages. The clinical signs of haemorrhage are like those of secondary shock, but they differ in other important particulars, as will appear presently. Haemorrhage directly lowers the total blood volume and is followed by a rapid dilution of the blood. This is accomplished by absorption of fluid from the tissues into the blood, tending to restore the blood volume. It is evident that the mechanism of fluid balance is operating physiologically. Low blood pressure developing shortly after trauma is due chiefly to neurogenic and haemorrhagic effects.

Secondary Shock.—This is the third mechanism by which circulatory deficiency may develop after extensive injuries. It is due to atony and abnormal permeability of capillary walls, and has been discussed (Moon, 1938a, 1942a, 1942b) as circulatory failure of capillary origin. Products of tissue autolysis or of infection, absorbed from damaged tissues, produce permeability of endothelium like the effects of histamine, peptone, venoms, and other capillary poisons. When this effect is produced in extensive areas it involves the mechanism of fluid balance. Osmosis requires the presence of a semi-permeable membrane—the endothelium. If the latter becomes so permeable that plasma colloids escape through it, osmotic attraction ceases to act and the mechanism of fluid balance is vitally deranged.

Leakage of fluid from the blood into the tissues lowers the blood volume and causes haemoconcentration, which is evidence in itself that the mechanism of fluid balance is not functioning adequately. Under normal conditions fluid lost from the blood is restored by absorption; haemoconcentration is thereby prevented.

Decreased blood volume, combined with increased volume capacity of the capillary bed, tends to cause circulatory deficiency, which is manifested by clinical signs like those of primary shock or the effects of haemorrhage. But the mechanism of capillary damage requires time for development; it is never seen immediately after injury, hence it is called *delayed* or *secondary* shock.

Confusion in Shock Analysis

Numerous reports, both from British and from American authors, indicate confusion in attempting to analyse the causes of shock resulting from injuries. Space does not permit detailed examination of each of these. Since the reports are similar in nature and in the conclusion drawn, one will be cited as an example.

Evans and his associates (1944) made haematocrit and blood-volume determinations in 143 cases of knife wounds, bullet wounds, and accidental injuries. Many of these developed shock, as indicated by low blood pressure and other clinical signs. Haemodilution was present in the majority; a few showed haemoconcentration. The authors concluded that low arterial pressure is the most useful criterion for shock and that haemorrhage is its most important cause. It was stated that the injured were seen *soon* after the wounds were received. Hence probably the time factor was not sufficient for the development of secondary shock. In many instances there was haemodilution, and evidence of extensive haemorrhage which averaged 38% of the estimated blood volume. It is probable that primary shock and haemorrhage were chiefly responsible for the low blood pressure.

However, among 63 cases of moderate or severe shock from skeletal, thoracic, and abdominal injuries there were 46 instances in which the haematocrit reading was 40 or above. Do the authors believe that haemorrhage was the major factor in *these cases*? A haematocrit reading of 40 indicates approximately 90% haemoglobin or 4,500,000 erythrocytes. Those who have lost 38% of their blood volume by haemorrhage should show haemodilution of greater degree than this. One suspects that some other mechanism was operating in this group of cases (see below: Haemoconcentration). Evident confusion is expressed in the authors' frank statement: "In his search for truth concerning traumatic toxæmia the reader may become bewildered by some of the writings on the subject."

The reasons for bewilderment are not far to seek. Conditions due to a combination of causes are not suitable for analysis of the mechanisms involved. By way of illustration:

Let X symbolize the effects of primary or neurogenic shock
 " Y " " " haemorrhages, " haemorrhagic " shock
 " Z " " " capillary damage, " toxæmic " shock
 Then $X + Y + Z$ = traumatic shock (as manifested clinically)

To propose conclusions as to the cause of shock upon data from cases of traumatic injuries is as unsafe as to propose the solution of a single equation containing three indeterminate variables.

Circulatory deficiency following trauma may be due to neurovascular reactions or to the effects of haemorrhages or to the absorption of toxic products, or it may be due in part to each. So-called *traumatic shock* is not a disease entity but a syndrome; it represents the summative effects of several factors. These vary in different cases and in the same case at different times. Obviously, the mechanisms involved in shock from trauma should be studied separately as neurovascular, haemorrhagic, and toxæmic factors.

Secondary Shock and Haemorrhage

Experimental studies on shock from trauma have been confused by the same combination of indeterminate variables as those present after injuries. Such experiments include also another item, the anaesthetic, which tends to lower the arterial pressure. A method commonly used experimentally is to narcotize an animal deeply with barbitol or some other anaesthetic agent. Shock is then induced by extensive trauma to the muscles, by intestinal manipulation, or by some other form of tissue abuse. Variations in the arterial blood pressure serve as the chief criterion of the animal's condition. Attention has been directed repeatedly (Moon and Kennedy, 1932; Moon, 1938a, 1942a, 1942b) to sources of error inherent in this mode of experimentation. Workers did not provide controls on the factors of anaesthesia and of haemorrhage. Narcosis with barbiturates and with other agents often causes low blood pressure.

Variable amounts of blood are lost owing to the trauma. In some reports the workers showed convincing evidence that they were dealing almost entirely with haemorrhage. Several hours' time is required for autolysis and absorption from damaged tissues to produce systemic effects. The animals often succumb to the effects of haemorrhage and anaesthesia before this occurs. Under such conditions the observed results may be due to narcosis or to haemorrhage or the absorption of toxic products, or they may be due in part to each. Manifestly it is unsafe to base conclusions as to the relative effects of haemorrhage and of secondary shock upon data obtained from experiments of this kind.

The necessity for studying each item separately is re-emphasized. Primary shock has been investigated clinically and experimentally by Phemister and his associates. A study of the effects of simple haemorrhage without anaesthesia or trauma presents no difficulties. We have reported such an investigation (Moon *et al.*, 1941). Circulatory failure due to capillary atony may be produced by injections of histamine, extracts of normal tissues, bile, cholic salts, peptone, bacterial toxins, venoms, or other capillary poisons. Several of these agents are concerned in the development of shock incident to intoxications and infections in man; but, excepting tissue extracts and bacterial toxins, they are not substances which usually result from autolysis and bacterial growth in traumatized tissues. The autolysis of tissues *in vivo* (Moon, 1942a) provides an experimental method for observing the effects of absorption, uncomplicated by anaesthesia and haemorrhage.

One method is to introduce a quantity of finely minced fresh normal tissue into the peritoneal cavity of a normal dog. Light ether anaesthesia is used while the abdomen is opened and the tissue, suspended in saline solution, is inserted. Recovery from the anaesthesia is prompt; the animal behaves normally for an hour or two, then progressive illness accompanied by vomiting develops. The blood becomes concentrated, the pulse rate increases, the peripheral parts become cold, urination is suppressed, and death by circulatory failure occurs 8 to 36 hours later. The severity of the illness and the speed of its progress depend upon the amount of tissue used. A dosage of 5 g. of liver or muscle pulp per kilogramme of body weight often results fatally in 8 to 10 hours; marked illness but eventual recovery may result from a dosage of 1 to 2 g./kg. The rapidity and severity of the illness are increased under anaesthesia as used for recording blood pressure.

The results described are highly significant for two reasons: they indicate that products derived from the autolysis of normal tissues will cause death by circulatory failure like that of secondary shock; also, the associated physiological disturbances and the changes seen in the viscera were identical with those resulting from the injection of capillary poisons and from anaphylactic shock.

A distinctive pattern of circulatory changes is seen when animals have died of shock caused either by autolysis *in vivo* or by the other agents mentioned above. This pattern consists of diffuse capillo-venous hyperaemia, oedema of soft tissues, capillary haemorrhages in mucous and serous surfaces, sometimes effusions of fluid in serous cavities, and parenchymal degeneration and necrosis. Such changes occur in the thoracic, abdominal, and cranial viscera; they are not seen in the external or somatic tissues.

The same pattern of visceral changes is seen when secondary shock has been the major cause for death in man. These changes are in sharp contrast to those resulting from haemorrhage. It appears that no one has compared carefully the physiological disturbances resulting from haemorrhage and those from secondary shock. My associates and I undertook such a comparison. We collected the recorded observations of different workers on various features seen in these conditions; then we verified each item experimentally (Moon *et al.*, 1941). The results of these comparisons follow:

Features Identical in Shock and Haemorrhage

Sympatho-adrenal activity
 Stimulation of myocardium
 Strong rapid pulse in early stages
 Peripheral vasoconstriction
 Reduced volume flow
 Peripheral ischaemia; pallor
 Loss of tissue turgor
 Discharge of reservoir blood into systemic circulation
 Contraction of spleen
 Increased blood sugar
 Dilatation of pupils; often perspiration
 Low basal metabolism
 Declining temperature
 Decreased alkaline reserve
 Increased respiratory rate; thirst
 Low arterial blood pressure (in late stages)
 Death due to inadequate circulatory function

Because of these similarities shock and the effects of haemorrhages have been regarded as identical. Other features which have been reported in secondary shock from wounds, burns, intestinal obstruction, anaphylaxis, and transfusion reactions are tabulated below and compared with the same items after simple haemorrhages.

We have attempted to produce the features recorded under the heading of Shock by haemorrhages of all degrees and varying duration, by successions of large haemorrhages ending fatally in 4 to 8 hours, and by repeated small haemorrhages with death in 1 to 4 days. In every instance the findings recorded under Haemorrhages resulted; in no case did the changes characteristic of secondary shock develop.

It seems remarkable that such numerous and important differences escaped the attention of those who have written voluminously on haemorrhages as the cause for shock. More remarkably, a few even advocate haemorrhages as the method of choice for producing shock experimentally. Let it be emphasized that haemorrhages, when present, are a highly important contributory factor; an animal or person in shock may not survive a minor

haemorrhage which under normal conditions would have insignificant effects. But haemorrhages alone, independent of trauma, anaesthesia, or toxic effects, will not produce the syndrome of secondary shock.

Contrasted Features

Items	Shock	Haemorrhages
Endothelium	Permeable to colloids	Impermeable
Flow of lymph	Increased	Decreased
Tissue fluid	Disturbed	Undisturbed
Fluid balance	Impaired	Unimpaired
Absorption	Persistent	No vomiting
Vomiting	Frequent	Absent
Diarrhoea	Ineffective	Often effective
Saline solutions, intravenous ..		
Renal:		
Excretion	Deficient	Unimpaired
Urine	Concentrated, low volume, albumin, erythrocytes, bile, debris	No characteristic changes
Blood:		
Coagulation time	Lengthened	Shortened
Concentration	Increased	Decreased
Non-protein nitrogen	"	Terminal increase
Potassium	"	Increased
Plasma chlorides	Decreased	
Necropsy findings:		
Oedema of soft tissues	Characteristic	None
Serous effusions	Present	Absent
Capillo-venous congestion	Characteristic	"
Petechiae	"	"
Visceral ischaemia	Absent	Present
Organ weight	Increased	Decreased
Gastro-intestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

Circulatory Dynamics

The principles of capillary physiology (Starling, 1909; Ebbecke, 1923; Lewis, 1927; Krogh, 1929) serve to explain how various noxious agents produce circulatory deficiency. A diversified group of substances which affect endothelium deleteriously are known as capillary poisons. These include extracts of normal tissues, products of tissue autolysis, foreign proteins and protein-split products, bacterial substances, histamine, bile, venoms, poisons, metabolic products, and even moderate lack of oxygen. It was established that any kind of injury to endothelium increases its permeability to the plasma colloids. Thereby other dysfunctions result as shown in the following table:

Agents or conditions injurious to endothelium	Pathological effects:
	Endothelial permeability
	Disturbance of fluid balance
	Oedema of soft tissues
	Serous effusions
	Increased flow of lymph
	Haemoconcentration
	Capillo-venous congestion
	Stasis
	Petechial haemorrhages

Permeability of capillary endothelium lowers both the actual and the effective blood volume. Leakage of plasma into the tissue spaces reduces the *actual* blood volume and causes haemoconcentration, while sequestration of blood by stasis in dilated capillaries and venules reduces the *effective* blood volume. This combination leads to a disparity between the volume of blood and the volume capacity of the vascular bed. Such a disparity produces a circulatory deficiency superficially resembling that resulting from haemorrhages. Physiological reactions compensate for minor degrees of such a deficiency. Activity of the sympatho-adrenal system causes arterial constriction, stimulates cardiac function, and causes the spleen to contract, discharging its reserve of blood into the circulation. Selective distribution of blood favours the vital organs at the expense of non-vital parts. Peripheral circulation is reduced, and the external parts become pale, cold, and almost pulseless.

So long as this compensation is effective there is no marked decline in the arterial blood pressure, but the latter is maintained at the expense of the volume flow. Stagnation of circulation in the dilated capillaries reduces the amount of venous blood returned to the heart. This lessens the cardiac output and decreases further the volume flow. A reduced delivery of oxygen to the tissues follows, with accompanying anoxia, which of itself causes further relaxation and permeability of capillary endothelium (Krogh, 1929; Landis, 1934, 1937). This feature introduces a self-perpetuating factor into the mechanism, causing it to progress in a vicious circle. When finally the compensatory reactions are no longer adequate the blood pressure declines progressively

and the complete syndrome of shock is manifested clinically. The items which constitute that syndrome were tabulated above in the comparison between shock and the effects of haemorrhages.

Circulatory deficiency originating in the capillaries produces the pattern of visible changes in the viscera described in a preceding section. The capillaries and venules become relaxed and distended with closely packed corpuscles, stagnation of circulation develops; stasis is the surest sign of increased capillary permeability (Landis, 1934, 1937). The leakage of plasma causes oedema of soft tissues and effusions into serous cavities. Dissolution of capillary walls causes minute haemorrhages in mucous and serous surfaces and in parenchymatous tissues. These changes are seen in varying degrees when secondary shock from any cause has been the major factor leading to death.

We have noted that marked hyperaemia and petechial haemorrhages predominate when severe shock has led to death in a few hours. Serous effusions and oedema are prominent when the deficiency has developed more gradually, leading to death after 24 hours or longer. We were able to produce pulmonary oedema experimentally (Moon and Morgan, 1936) by burns of moderate extent, by tissue autolysis *in vivo*, and by injections of various capillary poisons. To accomplish this it was only necessary to decrease the dosage of the agent so that fatal circulatory failure might develop more slowly. Partial circulatory stasis and oedema of the lungs predispose to pneumonia. We have reported (Moon, 1938b) on secondary pneumonia as a terminal event in shock of sublethal degree.

Half-truths

Erroneous beliefs persist longer when supported in part by truth than when entirely false. Propaganda is far more effective when based upon a modicum of fact; likewise in scientific matters. One example has been seen in the belief that shock from trauma is due entirely to haemorrhage. Another instance is the interpretation that leakage of plasma locally is the cause for low plasma volume.

The decreased plasma volume which develops after burns is attributed by many writers entirely to capillary leakage in and about the burned area. Scant attention is paid to the fact that capillo-venous hyperaemia and oedema develop in extensive visceral areas *remote from the burn*. Long ago it was shown (Schjerning, 1884; Bardeen, 1896-7, 1897; Pack, 1926) that the brain and meninges, the lungs, gastro-intestinal tract, liver, and kidneys are markedly hyperaemic, that the soft tissues are oedematous, and that petechial haemorrhages are found in the serous surfaces, mucous membranes, and parenchymatous tissues of the viscera.

These changes are the characteristic pathological finding after death from burns. Yet some ignore them, unwilling to admit the systemic effects of substances absorbed from burned tissues. It is true that local loss of fluid occurs about injured tissues; but it is equally true that such loss occurs also in visceral areas after extensive burns or trauma. Local fluid loss is only part of the mechanism by which plasma volume is reduced.

Some writers attribute the visceral hyperaemia and oedema to anoxia, and explain that they occur during the agonal period just before death. Clinicians who have listened to the breathing of severely burned patients testify to the presence of congestion and oedema when shock is present *before the agonal stage is reached*. It is true that anoxia will cause capillary atony accompanied by hyperaemia, stasis, and oedema. But this is not a complete picture of the relationship. Capillary atony and anoxia have reciprocal effects: either of them acting primarily will bring about the development of the other. This relationship gives the disturbance a self-perpetuating quality which operates in a vicious circle.

So long as the physiological mechanism of fluid balance is functioning, local fluid loss is compensated by the absorption of fluid from the tissues elsewhere. This maintains the blood volume and concentration within normal limits. For example, large amounts of fluid may be lost from the blood locally, as in hydrothorax or ascites, yet neither shock nor haemoconcentration follows. It is my belief that haemoconcentration is evidence of capillary permeability sufficient in extent and degree to disturb the mechanism of fluid balance. This may at times result from the *local* effects of burns or trauma of great extent. It probably will not develop from limited injuries.

Any loss of blood or fluid is of importance when secondary shock threatens to develop. The importance of the local loss is in proportion to the amount of fluid loss. The explanation of low plasma volume and haemoconcentration as resulting from local fluid loss is another instance of a part-truth.

Traumatic Toxaemia

During World War I the British Medical Research Committee organized a co-ordinated clinical and experimental investigation of shock following wounds. Eminent British, French, and American workers studied the manifestations seen in injured men and in experimental animals. These reports led to the theory known as *traumatic toxaemia*. It is summarized as follows:

"The theory of secondary shock which has the strongest support, both in clinical observations and in laboratory experiments, is that of a toxic factor, arising from damaged and dying tissue and operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the lymph spaces. Thus the concentration of the corpuscles is also readily explained. It is recognized that, after a sufficient time, infection may occur and be of such character in itself as to induce a persistent low blood pressure. According to this theory there may be no essential difference between the effects of toxins given off by damaged tissue and of toxins resulting from activity of bacteria." (Med. Dept. of U.S. Army in the World War, 1927.)

The chief objection to this explanation is negative in character, based on the fact that no toxic substances had been shown experimentally or identified chemically in the blood during shock. Digressing for a moment, let it be noted that the same objections and logic apply equally to the bites of venomous snakes. No toxic substance has been identified chemically in the bitten animal's blood; I have seen no report on transfusion of blood from a bitten animal to a normal one; it is highly improbable that the amount of venom so transferred would cause notable effects. The bitten limb swells enormously and its tissues are distended with blood and fluid. May not the effects of a snake-bite be due entirely to local loss of blood and fluid in the area affected? This explanation would make unnecessary the assumption that a toxic substance produces systemic effects after snake-bites.

Presumably the toxic substances which result from trauma are cleavage products of tissue autolysis or of bacterial action upon tissue proteins. Chemical methods are not yet perfected to identify such substances in the blood, except as non-protein nitrogen. The latter is markedly increased during shock, and is attributed (Whipple and van Slyke, 1918; Whipple *et al.*, 1920) to destruction of the body's proteins. The objection mentioned took no account of these facts nor of the mass of clinical and pharmacological evidence indicating toxic effects.

Recent reports indicate toxic effects in experimental traumatic shock. Best and Solandt (1940) instituted exchange transfusion of blood between pairs of dogs, in one of which shock was induced by trauma. The untraumatized dogs developed shock, as did those traumatized. These results were interpreted as indicating the effects of a toxic substance released from injured tissues and conveyed by the blood. Kendrick, Essex, and Helmholz (1940) performed a somewhat similar experiment by exchange transfusion, which likewise furnished evidence supporting the theory of toxaemia. Even those who have opposed vigorously the conception of a toxic factor have now relaxed their opposition. For example, Freeman and his collaborators (1941) reported experiments on traumatic shock which they interpreted as indicating the effects of a toxic factor absorbed from the traumatized region.

This view is in agreement with an enormous mass of clinical and experimental data. It is based upon sound physiological principles and it is supported by necropsy findings. The pattern of circulatory changes seen in the viscera after secondary shock is of unmistakable significance. These changes indicate the origin and nature of the circulatory deficiency. The recognition of a toxaemic factor in secondary shock will abolish the most important cause for disagreement. Investigations on other features can then go forward in an atmosphere cleared of controversial discussions.

The basic principles on which agreement may be expected are as follows: Surgical shock, like that resulting from extensive trauma, is not due to a single cause but to a combination of causes: the anaesthetic, the local loss of blood and fluid, emotional

reactions, infection, or intoxication which may have reduced the patient's physiological state; the disease itself, which necessitated operation; and the absorption of toxic products from traumatized tissues. The relative importance of these factors varies in each case, and they operate in varying combinations. Some of these factors are lacking in shock from other causes.

It is now recognized that the occurrence of shock is not limited to traumatic injuries, burns, and the aftermath of extensive surgery. I have emphasized repeatedly that the same mechanisms operate in severe infections, metabolic intoxications, abdominal emergencies such as intestinal strangulation, mesenteric thrombosis, perforation, peritonitis, and from the effects of poisons.

Renal Dysfunction

Deficiency of renal function is an item of importance in secondary shock from diverse causes. For example, extensive burns are followed promptly by oliguria or anuria, by a progressive accumulation of nitrogenous wastes in the blood, and by casts, red cells, pigment, debris, albumin, and other abnormal findings in the urine. This condition persists so long as the state of shock continues, and renal deficiency becomes prominent when patients survive for several days in a state of sublethal shock (Moon, 1942a). The excretion is inadequate, the non-protein nitrogen rises progressively, hyperazotaemia develops, and the clinical syndrome of uraemia often precedes death. Similar renal disturbance occurs in secondary shock from trauma, after extensive operative procedures, intestinal obstruction, metabolic intoxication as in diabetes, icterus gravis, toxaemia complicating pregnancy, anaphylactic reactions, transfusion with incompatible blood, poisoning with various drugs, and in severe infections.

An instance of sublethal shock leading to azotaemia is that of the crush syndrome which Bywaters (1942) and others have reported. Victims of air raids had been pinioned under masonry and debris for hours. When rescued they developed signs of shock, which were counteracted by modern treatment. Despite the fact that adequate systemic circulation was maintained, these cases developed the complete syndrome of uraemia, and many died from progressive renal deficiency. When recovery occurred oliguria gave place to polyuria rather suddenly, renal function was resumed, and the non-protein nitrogen declined to a normal level. The findings at necropsy in some instances included congestion and oedema of the lungs and other viscera, as seen in secondary shock; in other cases the visceral appearances were not described. The traumatized muscles were pale, friable, and necrotic. The kidneys were pale, swollen, streaked with red and brown. The convoluted tubules showed varying degrees of degeneration, necrosis, and desquamation. The lumina contained hyaline casts, debris, and masses of brown pigment. This was shown spectroscopically to be myoglobin: its source as derived from damaged muscle is *prima facie* evidence of absorption from the traumatized areas.

This type of renal disorder was known to Osler and his contemporaries as "acute parenchymatous nephritis." They recognized its occurrence under several of the conditions previously mentioned. The syndrome is usually discussed as "extrarenal uraemia" by clinicians. Its pathology is not adequately presented in treatises on renal disease. Some describe it under "tubular disease," others under "nephrosis."

The exact nature and pathogenesis of renal failure accompanied by parenchymatous degeneration and necrosis in otherwise normal kidneys, as a complication of sublethal shock, is a subject for future investigations. There is suggestive evidence that the same injurious agents, including toxins and anoxia, which cause circulatory failure by their effects upon endothelium, likewise cause renal failure by their effects upon the parenchyma of the kidneys.

Practical Considerations

"The best treatment for shock is prevention." To accomplish this it is essential to know the various conditions under which shock may develop. Hence not only after trauma, extensive surgery, or burns, but also in severe infections and intoxications, and in abdominal emergencies such as thrombosis, strangulation, perforation, and the like, the anticipation of shock may make its prevention possible.

Early amputation of mangled limbs, débridement of lacerated wounds, prompt local treatment of burns as by coagulation, surgical relief of an infarcted or strangulated loop of bowel, and the drainage of infected areas are procedures which may forestall the development of shock. Likewise the prevention of infection, by therapeutic or other means, removes a potent contributory factor. The careful surgeon reduces the danger of shock by reducing to the minimum both the depth and the duration of anaesthesia and by using regional or local anaesthesia when possible. General anaesthesia usually will not of itself cause shock, but it often leaves a narrow margin of safety when combined with other shock-producing conditions.

The successful management of secondary shock requires primarily that the conditions which caused it shall be obviated or removed; otherwise, efforts to restore the failing circulation are predestined to failure. For example, unlimited quantities of plasma probably would not prevent death from intestinal strangulation or from a crushed and mangled limb unless the causative condition could be obviated effectively.

Traumatic Shock

The clinical signs of shock often develop after injuries of various kinds and degrees. Weakness, pallor, circulatory deficiency, rapid pulse, and low blood pressure are prominent features, but unfortunately these do not aid in determining either the type of the circulatory disturbance or the mechanism by which it developed. Those in whom these features are marked, apparently indicating severe circulatory failure, often recover promptly under appropriate treatment while others whose apparent condition is not alarming—they may even be ambulatory—may develop circulatory deficiency which progresses to a fatal termination despite all counteractive measures.

Experiences of this kind are well known to those dealing with accidental injuries. They have been noted especially among civilian casualties from air raids. Much confusion arises from the fact that many surgeons regard so-called *traumatic shock* as a disease entity. In reality it is nothing more than a symptom-complex, which is not a dependable index either of the nature of the disturbance or of its severity. When this syndrome is seen after injuries it is essential to differentiate between three conditions which may be operating singly or in combination. These are:

1. Primary or neurogenic shock, which may appear extremely grave and yet lead to prompt recovery. If the victim is seen within an hour or two after the injury, if the character and location of the wounds do not indicate considerable haemorrhage, and if examination of the blood does not show notable dilution or concentration, it is safe to assume that primary shock is the major factor. Any wounds should receive appropriate care, and enough morphine should be given to allay pain and apprehension. After rest, warmth, and the ingestion of fluids, recovery from primary shock is usually prompt. The experiences of surgeons indicate that anaesthesia and operative procedures should be postponed, except emergency measures, until the patient reacts from the depressed circulation. In World War I special "shock teams" were employed in casualty clearing stations and field hospitals. They supplied dry clothing and administered stimulants, heat, warm drinks, and liquid nourishment. These measures were effective in the relief of primary shock and in preparing the wounded for operation.

2. When loss of blood has been considerable the clinical signs will be like those in other forms of circulatory failure. If the person is seen within a few hours after the injury these signs probably represent the combined effects of primary shock and of haemorrhage. Examination of the blood may show which of these is the major factor. Haemodilution occurs promptly after haemorrhages; the degree of this is an approximate index of the amount of blood lost. Reports on large numbers of accidental injuries and casualties from air raids show that haemodilution is usually present. The conclusion that haemorrhage is the major factor in such cases is not open to question. The local treatment of the wounds and the restoration of blood volume, preferably by transfusion of whole blood, do not require consideration here. Cases of primary shock plus haemorrhage, if not accompanied by extensive trauma, may show marked circulatory deficiency clinically, but they usually respond readily to treatment. A tendency to progress towards a fatal termination despite treatment is not a characteristic of such cases.

3. Delayed or secondary shock results from factors other than those which cause either primary or haemorrhagic shock. The fact that their clinical signs are the same is the chief source of confusion regarding shock following trauma. This condition requires time for development: except with cranial or abdominal injuries or extensive

burns, it is seldom seen until 4 or 5 hours after the injury. The chief cause for secondary shock is the absorption of toxic substances from damaged tissues. These substances originate in part from autolysis, in part from bacterial growth.

All accidental and battle wounds are grossly contaminated; bacteria, both pathogenic and saprophytic, multiply readily in the debris of damaged tissues. Probably the products of bacterial growth are more toxic than those of simple tissue autolysis. For example, shock developed more slowly and in less degree in crush injuries which were not accompanied by open wounds. When a similar amount of muscle tissue has been damaged and laid open, as by a shell fragment, the development of shock is more rapid and severe. Perhaps this is because products of bacterial growth are important factors in the latter instance.

It has been observed (Cope, 1928, 1935; Blalock, 1940) that a fall in blood pressure is not an adequate criterion for incipient secondary shock. Frequently, circulatory deficiency is developing while the blood pressure is well maintained or is even at its highest recorded point. So long as the mechanism of compensation is effective there is no marked decline of the arterial pressure; the latter indicates that the mechanism of compensation is failing and that the condition is becoming critical. An ominous fall in blood pressure is not a sign of incipient secondary shock; too often it is a sign of departed opportunity.

As stated earlier in this paper, secondary shock is accompanied by a disturbance of fluid balance which results from abnormal endothelial permeability. This disturbance affects the mechanism of absorption. Fluids given orally or subcutaneously are not absorbed. Thirst becomes incessant, but efforts to relieve it are followed by vomiting. The fluid vomited is often in excess of that swallowed, and the vomitus in this condition contains brown flecks—"coffee grounds" vomitus. These flecks contain haemoglobin; they result from capillary haemorrhages in the gastric mucosa.

Haemoconcentration

Abnormal endothelial permeability which disturbs fluid balance results in haemoconcentration—a distinguishing feature in this type of shock. This feature is valuable both in recognizing the type of circulatory deficiency and in noting its progress. Haemoconcentration may be shown by counts of erythrocytes, by haemoglobin readings, by haematocrit, or by the specific gravity of the whole blood. My personal preference is for erythrocyte counts. Whichever method is used, a reading should be made when the injured person is first seen. Subsequent readings at intervals of one to three hours will furnish valuable evidence as to the nature and progress of the condition.

Unfortunately haemoconcentration may be masked by the haemodilution resulting from associated haemorrhages. Also, the victim may have had some degree of anaemia before the injury. For example, an erythrocyte count of 5,000,000 appears normal, but in one whose previous count was 3,500,000 it would indicate more than 40% haemoconcentration.

If the first examination shows moderate haemodilution it is apparent that haemorrhage is the major factor; subsequent findings of the same degree or of lower dilution would likewise indicate haemorrhage. But in the same case a subsequent finding of a higher concentration some hours after the injury indicates that secondary shock is developing in one previously affected by haemorrhage or perhaps by anaemia. If a person seen for the first time four hours or longer after injury shows clinical signs of shock *not accompanied by haemodilution*, it suggests that neither primary shock nor haemorrhage is the cause. Inadequate circulation developing some hours after injury, with approximately a normal concentration of the blood, is strongly presumptive of secondary shock in one who has lost blood by haemorrhage, or perhaps in a previously anaemic person.

The incipient stage of secondary shock unaccompanied by haemorrhage may be detected by the presence of moderate haemoconcentration—10 to 20%—even before evidence of circulatory deficiency is manifested clinically. This is seen frequently within an hour or two after extensive burns because shock develops faster after burns than after other injuries. If a subsequent examination of the blood shows a higher degree of concentration it indicates progress in the development of shock even though the arterial pressure may not be ominously low.

In order to treat the patient intelligently it is of advantage to know which condition or combination of conditions is responsible for the circulatory deficiency. A consideration of the time factor plus observations on the concentration of the blood may be distinctly helpful.

Treatment

Several therapeutic misconceptions are prevalent concerning the treatment of secondary shock. There is no apparent basis for the belief that morphine is useful in counteraction or prevention. On the contrary, morphine is dangerous when given in full doses because it inhibits respiration and thereby increases anoxia, which is a major factor in this condition. Enough morphine should be given to allay pain and apprehension, but amounts sufficient to lower the respiratory rate will accelerate the development of secondary shock.

Experience has shown that stimulants, such as digitalis, strychnine, and adrenaline, not only are useless but may be distinctly harmful. Cardiac deficiency is not a factor in the development of secondary shock; the vasomotor system is active and the peripheral arteries are already contracted to the maximum. Under such conditions adrenaline cannot be expected to produce benefit, and it should be remembered that large or repeated doses will actually cause shock in experimental animals.

Another matter deserving thoughtful consideration is the application of heat in attempts to prevent or to counteract shock. It is natural that physicians should note the low peripheral circulation and temperature and should try to relieve them artificially. The application of heat is widely practised, perhaps without due consideration of the physiological principles involved. During shock and after haemorrhage the blood volume is reduced. There is not sufficient blood to fill the entire vascular bed and to support metabolism throughout the body. Physiological reactions compensate for this condition by a selective redistribution of blood, favouring vital organs at the expense of the external parts. The vascular channels in non-vital areas become collapsed and bloodless, but both circulation and metabolism are maintained where they are most needed.

It is possible to open up the peripheral vascular bed by the application of heat and stimulants. But this counteracts Nature's mechanism for conservation: the blood required to restore circulation in the external areas lowers needlessly the already depleted reserve of blood. Recent evidence, both experimental and clinical, indicates that the use of heat in the treatment of shock causes further circulatory deficiency and that the results are detrimental.

Those remedies which have proved useful are agents which tend to counteract one or another of the major items by which secondary shock develops or progresses; chief among these items are *anoxia*, *endothelial permeability*, and *reduced blood volume*. Lack of oxygen accelerates the development and progress of shock. The inhalation of oxygen aids in counteracting this and in preventing irreparable damage. It raises metabolic activity and tends to interrupt the action of the vicious circle even after shock has been initiated.

Physiological studies indicate that one function of the adrenal cortical hormone is to maintain the normal impermeability of endothelium. There is significant evidence, both experimental and clinical, that this substance is distinctly beneficial in the prevention and in the treatment of shock from burns (Wilson *et al.*, 1936; Rhoads *et al.*, 1941).

The successful treatment of shock requires, first, that the condition which caused it shall be removed; next, that the fluid which was lost from the blood be replaced by fluid which should approximate closely the composition of that lost. Thus after serious haemorrhages transfusions of whole blood provide the ideal remedy. But in shock accompanied by haemoconcentration whole blood is not so suitable; it does not relieve the haemoconcentration, which, because of viscosity, tends to impede circulation through the capillaries. The patient does not lack erythrocytes, but he sorely needs fluid to restore the blood to its normal composition and volume. These considerations indicate clearly that the ideal replacement fluid is either human plasma or serum.

These substances are now available in most hospitals and medical centres, either in the original form or concentrated or dehydrated. Plasma or serum, given in the normal or isotonic concentration, serves admirably as a replacement fluid to restore blood volume and to reduce haemoconcentration. But the same amount of plasma, concentrated to one-half or even to one-fifth of its original volume, is far more effective in counteracting both the low blood volume and the deranged equilibrium of fluids

which are prominent factors in the mechanism by which shock develops (Hill and Muirhead, 1942).

Concentrated plasma or serum, given intravenously, raises the osmotic pressure of the blood and thereby draws fluid from the tissues into the vascular system. This accomplishes several desirable results: it increases directly the total blood volume; it relieves the haemoconcentration, reduces the viscosity of the blood, and restores fluid balance; it tends to reduce the oedema of soft tissues; it also relieves the hypoproteinaemia which often is a notable feature. These effects increase the circulatory efficiency and the delivery of oxygen to the tissues. The relief of anoxia removes a most important factor from the vicious circle by which the deficiency progresses.

The foregoing considerations are not based upon personal experiences. They represent an analysis of the mechanisms involved and a comparison of these with the recorded experiences of physicians and surgeons.

Let it be emphasized that *early* recognition and treatment are of the highest importance if favourable results are to be hoped for. Treatment, to be effective, must anticipate the complicated interplay of the agencies whose combined effects culminate in the syndrome of shock. It must be administered before the failing circulation and the associated anoxia have produced irreversible changes in tissues whose functions are vital.

Summary

Confusion arises from the fact that three unrelated mechanisms may cause the clinical signs of shock following injuries. These are: primary or neurogenic shock, the effects of haemorrhage, and delayed or secondary shock. These may operate singly or in combination.

Traumatic shock is not a disease entity but a syndrome. It represents the summative effects of the three conditions mentioned. Each of these causes low arterial pressure, hence they cannot be distinguished by that criterion.

The physiological disturbances which accompany secondary shock are not the same as those of haemorrhage. Simple uncomplicated haemorrhages apparently will not produce this syndrome. But haemorrhage, when present, is a highly important contributory factor: a person in whom secondary shock is developing may not withstand the loss of an amount of blood which would be insignificant in an otherwise normal person.

Loss of capillary tonus and abnormal permeability of endothelium are important factors in *secondary* shock. These have not been shown to play a part either in primary shock or in the effects of haemorrhage. Abnormal permeability disturbs the mechanism of fluid balance, leading to oedema of the viscera and to haemoconcentration.

A serious derangement of renal function accompanies secondary shock. This is seen not only after injuries and burns but also from the effects of intestinal obstruction, mesenteric thrombosis, metabolic intoxications, anaphylaxis, transfusion reactions, severe infections, and from the effects of various poisons. Patients who survive several days in a state of sublethal shock frequently develop the syndrome of uraemia and die of renal dysfunction.

The clinical management of shock requires the recognition of the causative mechanism. Cases of primary or haemorrhagic shock, unless accompanied by extensive trauma, respond more readily to treatment than do those of advanced secondary shock.

Observations on the concentration of the blood and a consideration of the elapsed time since the injury are valuable aids in determining which mechanism is the major factor causing circulatory deficiency.

Loss of blood volume is an outstanding feature after haemorrhages and in secondary shock. The one is best treated by transfusion of whole blood; the other by plasma or serum.

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MENINGITIS DUE TO PITTMAN AND NON-PITTMAN STRAINS OF *H. INFLUENZAE*

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For the last few years treatment with sulphonamides has been extensively applied to cases of meningitis due to *H. influenzae*. In this country several cases treated successfully in this way have been recorded: Jones (1937), Teggart (1938), Roberts (1939), Sakula (1940), Harold (1941), Jacoby (1941), Archer and Singer (1943), Birch (1943), and Matthews (1943). None of these reports give any clue as to the serological type of the *H. influenzae* strains isolated. Two reports have been published in this country about unsuccessful treatment with sulphonamides of meningitis due to *H. influenzae*—Mackenzie, Page, and Ward (1940) and Jones and Sudds (1942). The latter paper is the only one in which a serological examination of the organism responsible was carried out; the culture was of the b type (Pittman, 1931).

A third group of papers give accounts of both successes and failures in *H. influenzae* meningitis (serological types not given) using the sulphonamides for treatment: Mutch (1941), Davies (1943), and Moir (1943). Davies and Moir, however, emphasize the importance of using large doses of these drugs at an early stage. Moir also stresses their continued use after meningeal symptoms have disappeared, in order to avoid relapses. Mutch has suggested that strains isolated in this country should be examined not only culturally but also serologically. Mutch and Davies are not very favourably impressed by the curative value of these drugs in this condition, particularly with infants.

American Views on Treatment

American publications on this subject are more numerous, and several reviews have been published: Bigler and Haralambie (1939), Aléman (1940), Neal, Appelbaum, and Jackson (1940), Lindsay, Rice, and Selinger (1940), Alexander (1941), Mitchell (1941), Neter (1942), Alexander, Ellis, and Leidy (1942), and Knouf, Mitchell, and Hamilton (1942). The general tone of the reviews is that sulphapyridine is more useful than sulphanilamide in the treatment of these cases, and some authors claim that the combination of an antiserum to *H. influenzae* and sulphapyridine provides the best form of treatment available at present. Neal, Appelbaum, and Jackson (1940) reported on 29 patients, 20 of whom were treated with this combination, 9 being given sulphapyridine alone. Of the 29 patients 14 recovered. The mortality rate was therefore 52%. Of the

14 patients recovered 5 had received the drug alone. Lindsay, Rice, and Selinger (1940), in reviewing 108 cases, showed that treatment with antisera reduced the mortality from 97% to 83%: by adding sulphanilamide and sulphapyridine the mortality for 13 cases was further reduced to 54%. Knouf, Mitchell, and Hamilton (1942) report altogether on four comparable series of 63 patients treated during the last 10 years. Group 1 consisted of 19 patients treated only symptomatically. In this group all patients died. Group 2 also had 19 patients. These were treated with anti-influenza serum. All died. In Group 3, which consisted of 13 sulphanilamide-treated patients, there was one survivor. Group 4 was made up of 12 patients, with 9 survivors, or a mortality of 25%. The patients in this group were treated with sulphapyridine.

Strains of *H. influenzae*

Pittman (1931) had shown that the majority of *H. influenzae* strains isolated from meningitis cases in the United States belonged to a special group of this organism, which is characterized by possessing a capsule consisting of carbohydrates. This capsule has antigenic properties. Six different types of capsular antigens can be differentiated, and the American meningitis strains belong mostly to Type b. According to Pittman capsulated strains have a smooth appearance, but the colonies are rough when the strains lose their capsules, whereas the strains usually isolated from the respiratory tract are non-type-specific and have a rough appearance when first isolated. Fothergill and Chandler (1936), on the strength of virulence and agglutination experiments on dissociated smooth strains, regarded all rough strains as avirulent variants of *H. influenzae*. Pittman (1939) could protect mice easily with sulphapyridine against infection with *H. influenzae* (non-type-specific). Pittman (1942), using *H. influenzae* (Type b) and confirming the findings of Povitzky (1937) with meningeal strains, showed that in experimental infections of mice the combination of antiserum and sulphapyridine gave a higher percentage of cures than either of these substances alone. Pittman (1942) also found sulphanilamide not very effective as compared with sulphapyridine, sulphathiazole, and sulphadiazine; furthermore, that several strains of *H. influenzae* (Type b) showed different sensitivity to the drugs. There are two fatal meningitis cases on record (Pittman, 1933; Mulder, 1939) in which rough strains (non-type-specific) were isolated from the cerebrospinal fluid. Neither of these two cases was treated with sulphanilamide or any of its compounds. Pittman (1931) has shown that rough strains, and Allison, Gordon, and Zinnemann (1943) have shown that respiratory strains not belonging to the Pittman types, are virulent for white mice, although this virulence is lower than that of strains of the Pittman types. In view, therefore, of the small number of cases reported as being due to non-capsulated strains of *H. influenzae*, and their theoretical importance, we are recording the following cases of meningitis, which responded very well to sulphapyridine and which could be shown not to belong to any of the Pittman types.

Non-Pittman Type of Meningitis treated with Sulphapyridine

Case 1.—G. R., aged 7. Fell from tricycle Aug. 14, 1942. Persistent headache and vomiting since. On admission, Aug. 21, T. 97.6°, P. 92, R. 20; appeared fairly well; quiet. Pupils equal, reacted briskly. Some neck rigidity. Abdominal reflexes equal and active. Knee-jerks—R. normal, L. almost absent. Triceps jerks equal. No Kernig, no Brudzinski, no Babinski. Tone of limbs normal. Swelling size of a walnut L. occipital region. Lumbar puncture: 10 c.cm. fluid removed; no increase of pressure; fluid slightly turbid. Aug. 22: Mentally very bright; no pain; neck rigidity marked; Brudzinski positive; Kernig negative, but test causes obvious pain; knee-jerks not obtained; T. 100°, P. 114, R. 22. Aug. 23: Neck rigidity less; T. normal, and never raised again. Aug. 24: Cyanosis (from sulphapyridine). Aug. 25: Neck rigidity almost gone. Aug. 27: No neck rigidity; no knee-jerks, otherwise appeared normal. Sept. 5: Discharged quite well. *Treatment.*—Aug. 21: Sulphapyridine 2 g. (4 tablets) stat.; 1.5 g. four-hourly for 24 hours; alkaline mixture (pot. cit. gr. 40, sod. bic. gr. 20) given four-hourly, along with sulphapyridine. Aug. 22: Sulphapyridine 1 g. four-hourly. Aug. 24: Sulphapyridine 0.5 g. four-hourly. Aug. 26: Sulphapyridine discontinued. Total dose of sulphapyridine, 26 g.

Case 2.—T. S., aged 5. Admitted March 3, 1943. Since March 1 had had headache and vomiting. On admission did not seem ill;