THE ROLE OF FLUIDS, ELECTROLYTES AND PLASMA PROTEINS IN EXPERIMENTAL TRAUMATIC SHOCK AND HEMORRHAGE

SANFORD M. ROSENTHAL AND R. CARL MILLICAN

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Department of Health, Education, and Welfare, U. S. Public Health Service, Bethesda 14, Maryland

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This review will be limited to those forms of shock, experimentally produced, which are associated with large losses of fluid from the circulation either as a result of hemorrhage or as a result of swelling at the site of physical injury.

Animal investigations in the field of traumatic shock have yielded diversified and often contradictory results. An inquiry into the causes of this unsatisfactory situation might be helpful to future experimentation in this field.

One of the causes, which cannot be corrected in the present state of our knowledge, is that all of the basic mechanisms in the production of shock are not understood. This is reflected in the difficulty in precisely defining the shock state, and in the diverse methods and criteria which have been employed in

animal studies. Reviews covering various aspects of shock included in this publication have been compiled by Blalock (24), Harkins (118, 118a), Moon (186), Davis (54), Wiggers (276), Selye (241), Randall (217), Overman (202), Millican and Rosenthal (184), and Frank (88).

I. STANDARDIZATION OF EXPERIMENTAL PROCEDURES

An important source of discrepancy is the lack of standardization of experimental procedures. To obtain less variability of results the experience of bioassay might be profitably applied. This involves standardization in the following ways:

1. Uniformity of animals. Animals should be of one strain and sex, and of similar age and nutritional state. Much of the earlier work on shock has been carried out on the dog. While the dog is best suited for cardiovascular studies, this species presents several difficulties in meeting the requirements herewith outlined for standardization. Apart from the problem of obtaining homogeneity and adequate numbers, the dog has certain other drawbacks. The canine electrolyte pattern is quite different from that of man in that the erythrocyte cation is largely sodium instead of potassium (145). In some laboratories (10, 77, 85, 233) attempts to produce standardized burn shock without prolonged anesthesia have not been successful, as dogs are highly resistant. It is believed that this resistance may be related to the low erythrocyte K^+ in the dog (see also under anesthesia); thus Roos *et al.* (228) found toxic levels of serum K^+ in burned pigs, but not in burned dogs.

Another objection to the dog is the presence of bacteria in normal tissues, and the susceptibility of the shocked dog to bacterial invasion (79, 89, 210, 224, 249, 279). Much of the work on "irreversible" shock in dogs must be reevaluated in the light of this complication.

Small animals such as the mouse, rat, rabbit, or guinea pig offer many advantages for the study of shock. It is true that the mouse and rat are resistant to histamine intoxication (although not to certain metabolic effects) and do not afford good preparations for investigating the role of histamine in shock where mortality studies are employed.

The application of experimental results in shock to clinical practice, particularly in the field of therapy, has been viewed by many clinicians with considerable skepticism. The discordant results obtained in the laboratory have to some extent justified this skepticism, but experimental shortcomings have been due more to inadequate techniques than to differences between man and small laboratory animals, as is frequently stated. This is an important question, because progress in therapy without reliance upon the laboratory would be analogous to progress in bacterial chemotherapy without animal experimentation. There is at present no evidence that rodents differ from man in the fluid, electrolyte and protein disturbances that accompany trauma.

2. Environmental temperature. It has been shown that external temperature can profoundly affect the course of shock (54, 254). For this reason experiments should be carried out within a narrow range of temperature, preferably 25 to 28°C.

3. Anesthesia. The influence of anesthesia is controversial (78, 134, 186, 276), but deep and prolonged anesthesia reproduces many of the circulatory and metabolic manifestations of shock. In the reviewers' opinion prolonged anesthesia is best avoided. The ability of some investigators to produce standardized burn shock in dogs under barbiturate anesthesia (67) has not been achieved with brief ether anesthesia (77, 78, 85, 233), and the discrepancy has been attributed to the anesthetic. It would be well to establish this point more definitely by simultaneous experiments comparing ether with more prolonged barbiturate anesthesia, for the important question of the role of anesthesia on the course of shock cannot be answered with the evidence at hand.

4. Standardization of trauma. Many different types and conditions of trauma have been employed. Most of them bring about large fluid accumulations in the areas of injury, or fluid losses in the form of hemorrhage. Many instances of the importance of standardized trauma can be cited. Two types of burn injury can be produced; one brought about at a higher temperature is associated with little swelling and with a poor response to replacement therapy (214). It has also been observed (7, 91, 233) that when the amount of trauma is increased to two M.L.D. (such as tourniquet application to four legs instead of two) it is not possible with available therapy to bring about survival of most animals. The problem of assay of therapy is therefore at present complicated by its limited effectiveness. Trauma involving injury to the central nervous system, or other types of trauma not resulting in large fluid shifts (electric shock, certain bacterial toxins) results in a form of shock in many ways different from the type under discussion. The role of damage to the nervous system in "tumbling" shock has not been clarified (276). Likewise the possibility of bacterial invasion through the damaged mucous membranes has not been investigated in shock produced by intestinal trauma. A detailed survey of the various experimental methods for producing shock is not within the scope of this review.

Hemorrhage may bring about either acute death or prolonged hypotension with delayed death. The metabolic disturbances of the latter form are similar to those present in traumatic shock (54, 70, 278) and probably reflect generalized anoxic cell injury. The similarities of and differences between traumatic and hemorrhagic shock are reviewed by Moon (186) and Wiggers (276).

Irreversible shock.[1] This term is used to define a degree of shock that will not respond to therapy. Since this will vary with the therapy, and since it may be brought about by a variety of causes, including excessive amounts of trauma, certain types of trauma, or secondary bacterial infection, it would seem desirable to the reviewers to discourage the use of this term as an expression of the extent of shock.

5. The criteria of shock. The earlier experimental studies were chiefly related to changes in blood pressure, pulse, and hematocrit. These criteria have been found to be unreliable as an index of the severity of shock or of the survival of the animal (118, 276). Marked reduction in blood volume in experimental shock

[1] An article by Koletsky and Gustafson (150a) on therapy in the terminal phase of shock has currently appeared.

was originally observed by Mann (174), and later studies have shown a good but not complete correlation between blood volume and severity of shock (54, 108, 109). Attempts have also been made to employ certain biochemical changes in the blood, such as CO_2 (11) or amino nitrogen (234) as an index of shock.

All of these procedures measure important physiological and biochemical disturbances, but they do not necessarily correlate with mortality. This is best illustrated by the discrepancy between hemodynamic changes and survival which occur following various types of experimental therapy (141, 166, 167, 168, 183, 234, 249).

Erlanger and Gasser (71) were the first to recommend mortality as a criterion of therapy in shock, and they stressed the importance of statistical validity. This principle of employing mortality as a basis in the experimental evaluation of therapy has been generally adopted, as will be shown by the recent work presented later in this review.

6. Simultaneous comparisons in evaluation studies. In the evaluation of therapeutic procedures it is important to make comparisons of various experimental groups at the same time, preferably by rotation from one group to another. This may be difficult for large animals because of the limited numbers that can be used at one time, but in our experience considerable variations in mortality response may occur from one day to another in spite of efforts to standardize experimental conditions. These errors of sampling can only be reduced by simultaneous comparison of alternate groups of animals (119, 164, 167, 232).

7. Numbers of animals. Adequate numbers of animals must be employed to overcome the biological variations which occur even under standardized conditions. To illustrate this point, the following statistical analysis was made of the survival of 422 mice subjected to 1 MLD of burn injury and treated with 1 ml. of 0.9 per cent NaCl intraperitoneally. This amount of therapy was selected because it produces a survival response (approximately 50 per cent) which is favorable for statistical comparison. The experiments were carried out in our laboratory between August 1950 and August 1951 upon an inbred strain of albino mice under standardized conditions as outlined above. The object of this analysis is to show the range of variation that occurs in shocked animals receiving identical therapy, and the degree of reproducibility of our experimental results. From these data it is possible to define the number of animals and the percentage difference in survival response that will be required for statistical significance when two therapeutic agents are being compared under these standardized conditions.

In 27 individual experiments which averaged 16 animals in each experiment, shocked mice received 1 ml. of saline and the average survival was 45.2 per cent with a range of 15.4 per cent to 76.1 per cent. The average survival of the shocked untreated mice run alternately with the treated mice was 6.7 per cent. The distribution of the individual survivals of the treated mice, as indicated in Fig. 1, approximates a normal distribution. This is illustrated in the graph by the similarity of the experimental data to a theoretical distribution curve. This approach to a theoretical distribution indicates that the major factors influencing

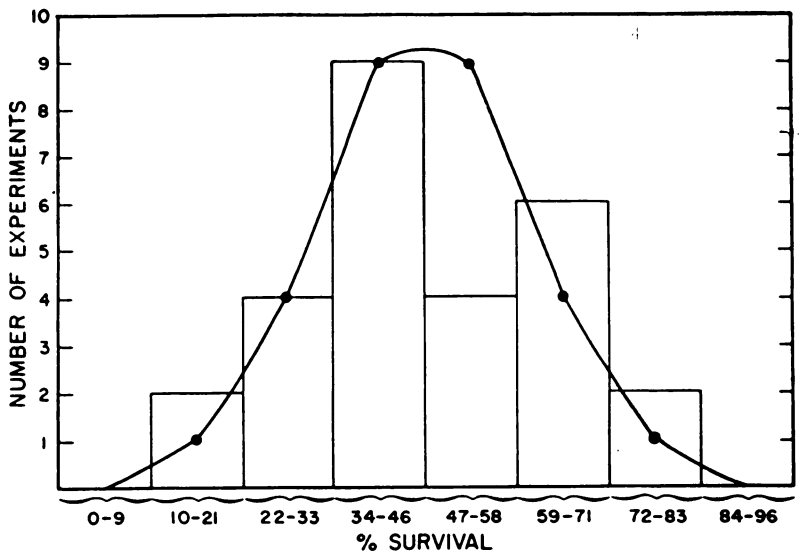

FIG. 1. Burn-shock in mice. Distribution of the 24 hr. survivals of burn-shocked mice treated with 1 ml. of saline intraperitoneally in 27 experiments comprising a total of 422 mice with an average of 16 mice per experiment. The solid curve line represents the theoretical distribution curve derived according to standard statistical procedures (208a).

mortality have been satisfactorily standardized in our procedure. For the treated mice the standard deviation was ± 17.3 per cent (for 16 mice per group). Standard deviations for groups of 32 and 48 animals were ± 12.3 per cent and ± 10.5 per cent respectively. When comparisons of therapeutic agents are made in the range of 50 per cent survival, it can be shown, on the basis of $\sqrt{\frac{p \times q}{n}}$, that when 15 animals per group are employed mortality differences greater than 35 per cent must be obtained in order to establish that one form of therapy is different from another ($P > 0.05$). If 30 or 45 animals per group are used, mortality differences greater than 25 and 20 per cent respectively are required.

With less exact standardization correspondingly greater differences will be needed for validity, and it is unfortunate that a large amount of the experimental work in this field will not meet the requirements of statistical validity (135).

8. Dosage and rate of administration of therapy. In the comparative evaluation of therapeutic agents, it is theoretically desirable to make comparisons at various dosage levels in order to obtain the statistical Survival $Dose_{50}$ of each compound. In the field of shock there is regrettably little quantitative data in this respect. With the use of small animals and simple techniques it is now feasible to accomplish this purpose (167, 182, 235).

Rate and also the route of administration must be considered when therapeutic comparisons are made, since it has been found that the administration of plasma is 50 per cent more effective when infused over a period of hours or given

intraperitoneally than when given in one intravenous injection (166, 181, 182, 249). A similar increase in effectiveness was not obtained with electrolyte solutions.

It must be pointed out that the study of certain biochemical or physiological changes in shock may be carried out under conditions of standardization much less rigid, since deviations from relatively constant normal values are of greater significance. The above requirements apply primarily to studies dealing with mortality.

II. FLUID DISTRIBUTION IN SHOCK

An historical review of this subject is given by Cannon (36) and Harkins (118). Following the demonstration of a reduced blood volume in shock unattended by hemorrhage (142, 194), explanations for the disappearance of this fluid were sought in the stagnation of blood in certain areas of the vascular bed, and in generalized tissue edema resulting from increased capillary permeability, later championed by Moon (186).

Accurate comparison of (a) the volume of blood removed by measured hemorrhage which would produce shock with (b) the amount of fluid which escapes locally into traumatized tissues, revealed a similarity which led Parsons and Phemister (206) and Blalock (22, 23, 136) to the view that fluid "loss" was a factor of major importance. It is now generally believed that these "losses" into the injured areas are sufficient to account for the decreases in blood volume which are characteristic of shock from trauma (108). Recent evidence, to be cited below, does not support the view that increased generalized capillary permeability is an important factor in shock.

The older experiments of Cannon and Bayliss (37) had underestimated the extent of fluid accumulation because their measurements did not include the entire area of swelling, which extends beyond the area of injury. More inclusive measurements of swelling following a fatal degree of leg trauma in untreated animals gave average values of "fluid loss", expressed as per cent of body weight, as follows: 4.17 per cent (206); 3.66 per cent, not necessarily fatal (22); 4.03 per cent (236); 5 per cent (137); 4.6 per cent (45); 4.5–5 per cent (146); 4.8 per cent (200); 4.8 per cent (149); 4.66 per cent (255).

A lack of correlation between fluid accumulation and mortality has been reported by some workers (106, 116, 173, 223, 236, 244). These results are interpreted in favor of additional "toxic factors", but the experimental errors involved in such a study would require a large series of animals to establish validity. The extensive literature on "toxic factors" will not be covered in this review.

The amount of whole blood that will produce death when removed within a period of a few hours has been found to be: 5.1 per cent (136); 4.5 per cent (227); 5.07 per cent (155); 4.5–5 per cent (146); 4.88–5.7 per cent (106); 4.8 per cent (200); 3.58 per cent (212); 5 per cent (252).

Studies upon 302 mice subjected to standardized acute hemorrhage revealed that the mortality response plotted against the volume of blood loss followed an almost linear curve beginning with 15 per cent mortality at a blood loss of

3.5 per cent body weight and ending with 95.5 per cent mortality at 5 per cent body weight. Thus, no sharply limited range of blood loss could be established which would represent a fatal or nonfatal hemorrhage (252).

Slightly lower values for removal of plasma alone have been reported: 4 per cent (120); 2.6 per cent (136); 4.4 per cent (227); 3.07 per cent (212). However, because comparisons have not been made simultaneously or under properly standardized conditions, it cannot be stated with certainty that the removal of plasma is more critical than the removal of whole blood. The similar degree of fluid loss in fatal hemorrhage and traumatic shock should not be emphasized to the neglect of some important differences between them (186, 276). While many of these differences tend to disappear in the later stages of shock, the possibility of toxic factors from local injury has not been excluded. Wang *et al.* (265) found that the LD_{50} from hemorrhage in the presence of muscle trauma occurs at a residual blood volume of 73 ml./kgm. as compared to 59 ml./kgm. in hemorrhage alone. Similar results were obtained by Fine *et al.* (78); this affords quantitative confirmation of the many earlier reports that traumatic shock reduces the tolerance to blood loss.

The local fluid accumulation in untreated shock must occur at the expense of the uninjured tissues. More than half of it is contributed from the blood, with the resultant decrease in plasma volume (77, 128, 200).

An over-all dehydration was observed in the viscera and in the uninjured upper half of the carcass of tourniquet shocked mice by Tabor *et al.* (255). No dehydration of uninjured legs was found after non-fatal trauma in mice (84). Measurement of the extent of dehydration of specific tissues has yielded inconsistent results (28, 51, 121, 152, 223, 259). Since a large part of the fluid is drawn from the blood, the losses in individual organs may be influenced by their vascularity, although no such correlation has been established. Underhill and Fisk (260) in hemorrhage and Holmes and Painter (128) in muscle trauma found that skin, and to a less extent muscle, lost water, and the former workers emphasized the great tenacity with which cells hold on to their water. The spleen has been shown to contribute a substantial amount of its blood in response to hemorrhage (55, 141, 156, 161, 201).

With a fatal degree of trauma in untreated animals, an amount of fluid equal to approximately half the plasma volume must be contributed from extravascular areas (77, 200, 223). Somewhat lower values have been obtained in trauma of less severity (13, 128). The source of this fluid has been the subject of considerable investigation. Earlier studies based on K^+ or N increases in the blood or excretion in the urine of animals subjected to hemorrhage led to the belief that part of the water was drawn from intracellular sources (94, 140, 144, 185, 248). Lands and Johnson (152) found a large increase in thiocyanate space 1 to 2 hours after hemorrhage in cats. Ashworth and Kregel (12) concluded that intracellular water increased after hemorrhage but decreased after muscle trauma.

On the other hand Brues *et al.* (28) using Na^{24} and thiocyanate found no increase in total extracellular space after hemorrhage, tourniquet or muscle trauma;

similar conclusions that no fluid was contributed from the intracellular space were reached by Holmes and Painter (128), and Danowski *et al.* (47). Some degree of intracellular hydration of uninjured tissues was postulated by Fox and Baer (84), similar to that reported in sodium depletion (50, 96). Lemley and Meneely (158) found a decrease of intracellular water associated with increases of total and extracellular water in anoxic heart muscle, but not in skeletal muscle.

Thus, while the movement of K^+ and nonprotein nitrogen might be associated with metabolic disturbances not involving commensurate water shifts, more direct measurements have not been in agreement. Although the most recent studies indicate no withdrawal of intracellular water it would appear to the reviewers that large depletion of the extracellular fluid might have an effect upon the intracellular fluid volume that is not revealed by the available techniques.

The behavior of fluids administered therapeutically in experimental traumatic shock reveals the remarkable avidity of injured tissues for fluid, additional to that which they can derive from the uninjured tissues; following certain types of injury, the capacity of traumatized tissues to swell appears to be limited chiefly by the amount of sodium containing fluid available to them. The experiments of Blalock *et al.* (25), Nickerson (200), Nathanson *et al.* (197), Langohr *et al.* (153), and Fox *et al.* (83, 84) indicated that administered fluids result in large accumulations in the areas of injury. The distribution of administered fluids in tourniquet-shocked mice was measured quantitatively by Tabor *et al.* (255) in the traumatized lower half of the carcass, in the nontraumatized upper half, and in the viscera. Two hours after intravenous injection of saline or mouse serum, three-fourths of the administered fluids could be recovered in the injured areas, even when amounts of therapy totaling 18 per cent body weight were given. No edema of the uninjured tissues (apart from some spreading by contiguity into tissues adjacent to the trauma) was observed after these large volumes of therapy; the amounts of administered fluid recovered in them did not exceed that which served to correct the dehydration which was present in the untreated controls. Comparable protein and electrolyte accumulations occur in the injured areas, and will be described below. It must be pointed out that these large accumulations were observed under conditions where therapy was administered during the period of swelling of the injured parts. Accumulations of less magnitude may be found when therapy is delayed beyond this period (see section V 3, p. 503).

Fogleman *et al.* (81) using deuterium measured the transcapillary movement of water following hemorrhage in dogs, and found it reduced from 72 per cent blood water per minute to 39 per cent. A similar study by Gellhorn *et al.* (95), using Na^{24} in traumatic shock showed a reduction to 50 per cent of normal, which was not influenced by therapy. These large changes are interpreted as due to decreased functional capillary area.

III. SODIUM DISTURBANCES IN SHOCK

The movement of extracellular fluid results in parallel shifts in electrolyte, and the earlier studies of Underhill *et al.* (258, 261) and Davidson (52) indicated

the magnitude of the changes in NaCl that occur following extensive burns. These authors advocated large volumes of saline in the therapy of burns, but general interest at that time was largely centered upon the role of plasma proteins in the cause and therapy of shock.

Manery and Solandt (173) analyzed traumatized muscle tissue and demonstrated a gain in Cl^- and a loss in K^+. A similar interchange had been found by Hastings and Eichelberger (114) with normal muscle placed in Ringer's solution. Tabor and Rosenthal (253) made quantitative measurements of the total changes in fluid, Na^+ and K^+ that occurred in the extremities of mice following tourniquet application. In untreated animals the gain in Na^+ was 33 per cent greater than could be accounted for by the fluid increase; a corresponding decrease in K^+ was found, indicating that the injured cells had lost K^+ and acquired Na^+ to this extent. The total Na^+ accumulation in the injured areas of untreated mice was equivalent to the entire sodium in the circulating blood, or one-fourth that in the total extracellular fluid. Changes of large magnitude were found independently by Fox and Keston in mice (83), employing Na^{24}, and comparable findings were later reported by Fuhrman and Crismon (92, 93) and by Walser and Bodenlos (264) in rats and rabbits, and by Holmes and Painter in dogs (128).

These changes are within the range of acute sodium depletion found by Darrow and Yannet (50) and by Elkinton *et al.* (64) to produce circulatory collapse in otherwise normal animals. These investigators produced salt depletion by the intraperitoneal injection into dogs of glucose solutions, followed by withdrawal of the solutions in 4 to 6 hours; water depletion was brought about by the intravenous injection of urea and glucose solutions. It was shown that with equal reduction of extracellular volume, circulatory collapse was manifest with salt depletion but not with water depletion. Similar results were obtained from intramuscular injections in dogs by Davis (53) and in goats and rabbits by Cameron *et al.* (33).

Following the demonstration that survival could be accomplished by large volumes of saline, it was possible to measure the extent of sodium retention that occurs in treated animals following a lethal degree of trauma (83, 253); 0.35 mM (of 0.38 mM administered) was retained during the first 24 hours, or approximately three times as much as could be accounted for in the injured area of untreated mice. It was later shown that the increased local swelling which follows treatment could explain the fate of this retained sodium (200, 255). A large retention of sodium has been confirmed clinically in burn cases (190).

The mechanism of this sodium retention might be attributed to decreased renal excretion (12, 189, 243a), as a result of circulatory or hormonal effects, but the evidence at hand indicates that the local accumulation in the injured areas is the most important factor (190, 255); however, the possible role of hormones in the production and regulation of swelling at the site of trauma has not been clarified.

Acute adrenal insufficiency bears a close resemblance to shock; the sodium loss occurs through renal excretion in the former and through the injured area in the latter. The urinary pictures are reversed, and it would not be expected that adrenal hormones could conserve sodium or significantly alter the course

of shock (132, 184, 189, 276). Pretreatment with DOCA can influence survival (43, 198, 219), but this can be explained by the sodium retention brought about prior to the onset of trauma.

The levels of plasma sodium (or chloride) in various forms of shock have been found within normal values (8, 12, 28, 128, 229) or slightly depressed (26, 50, 52, 165, 215, 248, 258, 264). The absence of large changes is not surprising since the replacement of blood volume occurs chiefly from extracellular fluids which have the same Na^+ content as plasma.

IV. THE ROLE OF POTASSIUM IN SHOCK

Earlier observations of Kerr (144), Thaler (256), Rabboni (215), Baetjer (15), and Fenn *et al.* (72) demonstrated the release of K^+ into the blood following hemorrhage, muscle trauma, or arterial occlusion. It was shown by Horton that an isolated frog muscle would lose K^+ as a result of physical or chemical trauma (130). Several reports followed on the increase of blood K^+ from asphyxia (38, 56, 57, 72, 131, 193, 286) (see Fenn (73) for review). Analyses of edema fluid at the site of trauma revealed higher concentrations of K^+ than in the plasma (173, 223, 257, 286). Zwemer and Scudder (285, 287) postulated an etiological role of K^+ in shock, based on blood levels in shocked animals as compared to normal animals intoxicated with K. Large increases in the blood were present in the terminal phases (for review see Scudder (238)). Although this was partially confirmed by Clarke and Cleghorn (40), later work upon dogs, rabbits, rats, and humans is in agreement that only small increases in the blood are present during the course of shock and concentrations sufficient to cause death are frequently, but not invariably, encountered shortly before death (12, 26, 28, 39, 59, 112, 127, 129, 173, 178, 211, 223, 225, 228, 229, 239, 253, 256, 282). It is of interest that some of these investigators reported concomitant rises in blood cellular K^+, indicating a storage function for excess K^+ (26, 144, 238), although this was not confirmed by Ricca (223).

Analyses of injured muscles have shown small (128, 223) or considerable losses of K^+ (28, 84, 92, 93, 173, 253, 280). Increases of Na^+ and Cl^- greater than the influx of water are present, indicating an intracellular exchange of cations previously described under sodium. The injured cells thus behave, to the extent of this exchange, as an extracellular compartment. These observations were confirmed upon rats and rabbits by Fuhrman and Crismon (92, 93) who further showed that the exchange was independent of the amount of swelling.

In an attempt to measure the magnitude of this liberation of K^+ the entire injured areas of mice subjected to a lethal amount of tourniquet trauma were analyzed for K^+ and Na^+ by Tabor and Rosenthal (253). 1.86 mM of K^+ per kgm. body weight disappeared from the injured area. In companion experiments upon mice where death was prevented by saline therapy, the excess K^+ excreted in the urine was approximately 3 times this amount, indicating liberation of K^+ from the uninjured parts of the body. Similar changes were reported independently by Fox and Baer (84). This could be attributed to the anoxia which accompanies shock. The magnitude of these changes was sufficient to incriminate

K^+ as a possible toxic factor. Increased K^+ excretion has also been reported following hemorrhage in dogs (12, 248). A considerable number of clinical reports have substantiated an increased K^+ excretion following trauma.

The adjustment of the uninjured tissues to these increased concentrations of K^+ has been given some study. Miller and Darrow (179) have reported increased concentrations of K^+ in muscle following KCl injection. Following hemorrhage or muscle trauma in dogs, rats and mice, similar elevations have been reported for uninjured muscle, liver, heart, pancreas, and erythrocytes (28, 30, 40, 51, 84, 86).

The blood levels of potassium in the terminal stages of shock seldom reach values that are attained when normal animals are killed by infusions of potassium. A further evaluation of the role of K^+ in death from shock rests upon a demonstration of the increased sensitivity of the shocked animal to K^+ intoxication, with the possibility that death will occur under these conditions at a lower level of plasma K^+ than in normal animals. Evidence in support of this was presented by Tabor and Rosenthal (253) for the mouse, where acute death of the shocked animal could be brought about by one-eighth of the amount of K^+ required to kill normal mice. A similar increased sensitivity has been reported for the dog by Davis (54).

Further evidence that in the shocked animal death from K^+ might occur at a lower blood level than in normal animals, was obtained in a comparison of the serum K^+ of (a) rabbits in the terminal stages of tourniquet shock, (b) shocked rabbits killed acutely by K^+ administration and (c) normal rabbits killed similarly by K^+ (253). Values were 12.08, 13.2, and 16.58 mM per liter for (a), (b) and (c) respectively. In view of the fact that the shocked animal behaves in many respects similarly to the adrenalectomized animal, it must be pointed out that the evidence of Winkler, Hoff and Smith (281) is not in agreement with the above observations; they found that adrenalectomized dogs behave similarly to normal dogs in response to plasma levels of K^+. However their animals were maintained on sodium, so that final evaluation must await further studies in untreated adrenalectomized animals, as well as in shock. It is pertinent that Kendall (143) states that in adrenal insufficiency untreated with cortical extract "the toxicity of K^+ cannot be expressed in terms of its concentration in the plasma", and that Hoff, Humm and Winkler (126) demonstrated that small elevations of serum K^+ greatly increased the activity of the vagus on the heart. It must also be borne in mind that potassium may exert toxic effects other than those revealed by electrocardiographic changes.[2]

Therefore, the evidence indicates that potassium may attain concentrations in the blood in the terminal phases of shock adequate to account for death in some instances. The possibility that potassium may exert some effects during the course of shock cannot be excluded on the basis of blood concentrations alone; this is suggested by the large and specific increases in sensitivity of the shocked animal to injections of potassium, and by the large amounts of potassium that appear in the urine as a sequence of trauma. While potassium death

[2] A current article by Ravin *et al.* (218a) has appeared on this subject.

in normal animals can be attributed to cardiac action, other loci of action have not been excluded. Three factors, fluid loss, sodium loss, and potassium liberation exist in shock, and are interdependent. While the magnitude of each change may not in itself be sufficient to produce death, their combined effects may augment one another, and may exert an important influence on mortality in shock.

V. PLASMA PROTEIN DISTURBANCES IN SHOCK

When it was demonstrated that a marked diminution of blood volume was present in most forms of shock (108, 118 for review), this was generally accepted as the cause of the circulatory collapse. Whole blood transfusions and the use of acacia and other colloid solutions were used during World War I as therapeutic measures to restore blood volume (36). Mann (174), who first demonstrated a reduction in blood volume in experimental shock, first used serum experimentally and reported its effect upon blood pressure to be equal to whole blood (175). As a result of clinical investigation during World War I little benefit was attributed to saline solutions (the amounts used were small) and the emphasis was centered upon colloid solutions. This was based on the transitory effects of electrolyte solutions on the circulation and upon the postulate of Starling (246, 247) on the important role of the plasma proteins in the transfer of fluids across capillary membranes.

1. Plasmapheresis experiments. While experimental production of circulatory collapse has been accomplished by water and NaCl deprivation (50, 64, 65), evidence that removal of plasma proteins will bring about shock is meager. Plasmapheresis experiments have been referred to as evidence for the importance of plasma proteins in the causation of shock, but a review of these experiments indicates that this evidence is not conclusive. Abel, Rowntree and Turner (4) devised the procedure of plasmapheresis, whereby erythrocytes in Locke's solution were returned to the circulation by intravenous infusion at the same time and at approximately the same rate at which blood was being withdrawn from an artery. They found that during the course of a day as much as twice the blood volume could be exchanged in this manner without serious consequences. This was later confirmed by Whipple and colleagues (243) who were able with 3 to 7 exchanges within a day to reduce the plasma proteins of dogs to as low as 1.1 gram per cent without causing death. (Stanbury *et al.* (245) by employing gum acacia in the replacement fluid were able to reduce the plasma proteins to 0.1 per cent without death.) Whipple *et al.* (275) observed that very rapid exchanges with Locke's solution could produce collapse, and later by carrying out the total exchange in 5 to 15 minutes they obtained symptoms of shock in 11 of 13 dogs, with 4 deaths, when the exchange amounted to 102 to 195 per cent of the estimated blood volume; when dialyzed serum instead of Locke's solution was returned with the erythrocytes no deaths occurred in 4 dogs. Similar results were obtained by Warren and Harkins (266). The unusual speed of removal, the large volumes removed, and the survival of the majority of the animals under these conditions suggest that more definitive evidence is needed to assay the role of plasma proteins in the production of shock.

It would seem that some degree of circulatory collapse can be attributed to extremely large and rapid plasmapheresis, and likewise in hemorrhage without replacement therapy the rate of bleeding as well as the amount removed determines whether shock will supervene (63, 69).

It has been demonstrated that the protein content of the edema fluid in various forms of trauma approaches that of plasma (13, 17, 42, 133, 149, 223, 257, 284). Following the demonstration that the volume of this plasma-like fluid which accumulates in injured areas in fatal trauma can equal that of the total plasma volume (see section II, p. 494), modified plasmapheresis experiments were carried out to establish the amount of plasma loss which would produce death (120, 136, 212, 227). In all of these experiments, however, the centrifuged erythrocytes were returned to the circulation without replacement of the removed plasma with any other fluid; this procedure therefore represents fluid and electrolyte as well as protein depletion. Death was produced by removal in this manner of an amount of plasma equal to 2.6 to 4.4 per cent of the body weight (see section II, p. 495), and it was assumed that the protein loss was the most critical factor in bringing about the reduction in blood volume and circulatory collapse (118). While this view had some justification at that time, the more recent data on the quantitative aspects of fluid and electrolyte disturbances in relation to shock (50, 64, 65, 253) would indicate that the fluid and electrolyte losses incurred in these modified plasmapheresis experiments were an important factor in causing death. This is further borne out by therapeutic experiments described below, where protein administered in the absence of electrolytes are less effective than saline solutions (182, 232).

2. Behavior of administered plasma proteins in normal and shocked animals. Recent work on the distribution of administered plasma proteins in the normal animal indicates that they equilibrate with the extracellular fluids and lymph with considerable rapidity. While Whipple and coworkers (80) demonstrated a dynamic equilibrium between plasma proteins and tissue proteins, the concept of a considerable degree of permeability of the normal capillary walls to plasma proteins had few supporters (58). The recent work of Wasserman and Mayerson (268), of Abdou *et al.* (1, 2, 3) and of Forker *et al.* (82) revealed that intravenously injected protein (labeled) attains concentrations in the lymph equal to those in plasma within 7 to 13 hours, indicating that every 20 hours the entire plasma albumin circulates through the extracellular spaces and lymph (268). Dextran solutions behaved similarly to plasma albumin (111, 270). Earlier observations on the rate of disappearance from the blood of infused plasma proteins (and fluid) in normal and shocked animals and man are consistent with these findings This has been determined either by isotopic labelling (41, 77, 97, 271) or by blood volume, hematocrit and plasma protein determination (20, 90, 176, 208, 226, 243). A novel finding that fluorescent dye-labeled albumin can be demonstrated intracellularly has been recently reported by Gitlin *et al.* (98).

The equilibration time of proteins between the vascular and extravascular fluids has been found to be prolonged following hemorrhage (272) or intestinal manipulation (80). However the quantitative aspects of this delay have not

been adequately established. Ravdin *et al.* (218) reviewed the recent evidence that the response of the blood volume to administered colloid solutions is more pronounced following hemorrhage than in normal subjects.

In normal man and animals Harroun *et al.* (122) and Calvin (31) presented evidence that saline infusions mobilize proteins from cellular sources but Wasserman and Mayerson (269) showed that this was a mobilization of "plasma" proteins from the extravascular spaces. This is pertinent to the older concept that saline infusions cause a "loss" of plasma proteins into the tissues, but the significance of this must be reevaluated in the light of the normally existing rapid circulation of these proteins.

Likewise, the older views on the role of the plasma proteins in the maintenance of plasma volume through their colloid-osmotic pressure were predicated on a relative impermeability of the capillary membrane to proteins. It would now seem that these views must be modified to encompass the extravascular circulation of the plasma proteins.

Plasma proteins labeled isotopically have been found to rapidly accumulate in the areas of injury, but no abnormal penetration into uninjured tissues has been found; this lends further support to the absence of generalized increased capillary permeability in shock (16, 41, 75, 77, 154, 180).

Electrophoretic analyses of the sera of injured animals indicated that the concentration of albumin is decreased while α- and β-globulins are increased (99, 100, 101, 162, 187, 209, 274). Similar analyses of extracts of injured tissues showed increases of the serum albumin component (187, 188, 284).

Following the demonstration that saline solutions administered in traumatic shock rapidly leave the blood stream and accumulate almost quantitatively in the injured area (200, 255), the behavior of infused protein solutions was studied because of the existing evidence that they remain longer in the blood stream. This was accomplished by measuring the rate of local fluid accumulation following the administration of plasma (183) and by measuring the distribution of I^{131} labeled (154) or S^{35} labeled (180) plasma proteins in shocked mice. When administered early in the course of shock, before swelling has reached a maximum, no retarding effect of homologous plasma proteins on the escape of fluids into the injured area was demonstrable. Approximately three-fourths of the administered fluid accumulated in the traumatized areas following the injection of plasma or of saline solutions (255). Likewise, more than three-fourths of the administered (S^{35} labeled) plasma proteins could be recovered in the injured area 2½ hours after administration (180). This is further confirmation of the plasma-like nature of the edema fluid; it also explains the transitory effects of plasma, administered under these conditions, on the restoration of blood volume (183).

From these data it is indicated that administration of plasma proteins does not significantly retard the escape of therapeutic fluids into the injured areas. Until a beneficial effect of the local accumulation of these proteins is established, it would seem illogical to employ plasma alone in the large amounts that would be required to meet the needs of local swelling, and to correct the dehydration

of the uninjured tissues. The supplemental use of large volumes of saline solution for these purposes is afforded a rational basis from the experimental evidence.

3. Static nature of plasma proteins accumulated in traumatized areas. The degree to which the proteins and electrolytes of the edema fluids participate in the general extravascular circulation was investigated by Millican (180) by injecting S^{35} labeled plasma to tourniquet shocked mice (adequately treated with saline) after the swelling had reached a maximum (3 hours). In contrast to experiments where labeled plasma was injected prior to the swelling (where rapid local accumulation occurred) equilibration was quite slow and did not reach completion in 18 hours. This indicates the sluggish character of the pool. Equilibration of Na^{22} administered in this way required only 1 to 2 hours, indicating that the pool is accessible to easily diffusible small molecules. These results suggest that the hemodynamic response to plasma therapy may vary with the time after injury, and they may explain the superiority of plasma administered over a prolonged period of time (see section VI, p. 507).

The results of Glenn, Muus and Drinker (103) and Cope *et al.* (42) are of interest in this connection; they found large increases above normal in the volume and protein content of lymph from the burned extremities of calves or dogs one to three hours after burn trauma. At later intervals the flow returned to a low level. This is consistent with a period of rapid local accumulation of fluid and protein, followed by a period of sealing off.

4. Plasma protein levels in shock. A review will be made of the plasma protein changes that occur in the various forms of shock, the changes that occur following therapy, and the relationship of these changes to mortality.

Beard, Blalock, *et al.* (18, 19) observed that in animals in shock saline therapy produced small increases in blood volume, minimal and transitory hemodynamic responses, and a marked lowering of the plasma protein concentration. These effects were considered harmful since the lower colloid osmotic pressure resulting from the reduced plasma protein concentration would increase the permeability of the capillaries to their contents. They were supported in their view by Starling's (246, 247) earlier observations of the role of the colloid osmotic pressure of the plasma proteins, and the observations of Leiter (157) and Darrow *et al.* (49) that generalized edema results from plasma protein levels below 3 g. per cent (also see Harkins (118) for review). Although the concept of an adverse effect of low plasma protein levels in shock has been accepted by many workers, the experimental data on this point are contradictory.

a. Plasma proteins in hemorrhage. In untreated hemorrhage the plasma protein level falls as a result of protein depletion and of the transfer of fluid from the tissues to the vascular system (5, 32, 63, 74). However, the magnitude of this fall is small compared to that observed after plasmapheresis. Following severe hemorrhage in dogs plasma protein levels decreased from 5.8–6.1 g. per cent to 5–5.5 g. per cent (19, 211, 262), or from 4.8 to 3.98 g. per cent (162). No difference was noted between survivors and nonsurvivors (262). The duration of the acute hypoproteinemia is 6 hrs. or longer and the A/G ratio is unaffected (66, 162). Within 24 hrs. of bleeding the rate of globulin replacement exceeds that of

albumin (68, 162, 171). Plasma protein levels of 4.1 g. per cent were observed in shock produced by single rapid bleeding of half the blood volume, while levels of 4.4 g. per cent were found in more prolonged hemorrhage where shock did not occur (63).

b. Plasma proteins following therapy in hemorrhage. Experiments are in agreement that plasma proteins are restored to values approaching normal when replacement therapy of whole blood or plasma is used, while values of 3.4 to 3.8 g. per cent were obtained after saline therapy in dogs (9, 160, 170, 203, 220).

When a comparison is made between plasma protein levels and effectiveness of therapy, the results are contradictory (see therapy in acute hemorrhagic death and in hemorrhagic shock, section VI C). Thus Levinson *et al.* (160) found saline ineffective while Parkins *et al.* (203) and Reynolds (220) found it effective in their experiments. McKee *et al.* (170) obtained survivals of 73, 100 and 20 per cent from plasma, erythrocytes in saline and saline respectively, while the corresponding plasma protein levels 3 hours after replacement were 5.5, 3.5, and 3.4 g. per cent.

c. Plasma proteins in burns. In burns in dogs plasma protein levels decreased (163) or remained unchanged (21, 141); in burns of small area they rose slightly in dogs (209), and decreased in calves (103). The albumin concentration and the A/G ratio of the plasma decreased. In the lymph collected from the burned area, the protein concentration increased and the A/G ratio approached the plasma ratio (42, 103, 209). These findings suggested that albumin leaves the plasma at a faster rate than globulin.

d. Plasma proteins after therapy in burns. In burned dogs Dunphy and Gibson (61) and Berman *et al.* (21) reported the plasma protein level was sustained after plasma and reduced after saline. In burn shocked mice protein levels afforded no index of survival (183). Without treatment the average plasma protein levels rose from a control value of 5.2 g. per cent to 7.5 g. per cent. Treatment with whole blood, plasma or serum albumin in saline did not influence this elevation while saline reduced the level to 4 to 4.5 g. per cent. With the volumes employed (5 per cent of body weight) approximately similar survivals were obtained from all of these forms of treatment. With 10 per cent of body weight of saline, plasma protein levels of 3.5 g. per cent were obtained although the survivals were increased. In contrast, plasma protein levels of 6.5 g. per cent were observed following serum albumin in glucose, although this therapy was ineffective upon survival (182) (see section VI B 2, p. 507).

e. Plasma proteins in muscle trauma. Following muscle trauma in dogs without treatment, plasma protein levels remained unchanged or increased slightly (18, 19, 80, 109, 147, 222, 223, 249, 250, 251). No difference was noted in the levels of survivors and nonsurvivors (222, 223). After plasma treatment plasma protein levels were unchanged (113, 147, 249). After saline administration plasma proteins were 5.9 g. per cent (147); 3.7 to 5.7 g. per cent (18, 19); and in another report they were 5.5 g. per cent in survivors and 4.6 g. per cent in nonsurvivors (113).

In rats 3 hrs. following tourniquet injury total protein, albumin and globulin

concentrations were unchanged from normals (149, 273, 274). After tourniquet injury in rabbits plasma protein levels decreased from 6.05 per cent to 4.99 g. per cent. Albumin decreased to a greater extent than globulin (274).

Warren, Merrill and Stead (267) suggested that in certain pathological states, *i.e.*, nephrosis, when plasma protein levels are reduced to 3 g. per cent plasma volume is maintained by means of an increased extracellular fluid space. The reduced plasma volume accompanying tourniquet shock in dogs was restored to pre-trauma levels by expanding the extracellular fluid space with massive saline infusions (50 to 100 per cent of body weight). Plasma protein levels after these large infusion volumes were 2.8 g. per cent (pre-shock values, 6.1 g. per cent), and all animals survived.

From the foregoing it is apparent that (a) plasma proteins fall moderately after hemorrhage but show no consistent changes in burn or tourniquet shock. (b) The level of plasma proteins show no correlation with survival; this is particularly true after therapy, where the variations produced bear no relation to effectiveness. (c) Low plasma proteins follow administration of large quantities of saline (d) the evidence does not support the view that decreases in plasma proteins observed in shock are deleterious to the outcome.

VI. EVALUATION OF COLLOIDS, SODIUM AND FLUID IN THE THERAPY OF SHOCK IN EXPERIMENTAL ANIMALS

The proper use of replacement therapy in shock requires a knowledge of the magnitude of the disturbance, which for fluid and electrolytes was not well defined until recently. It also involves problems of evaluation which have been outlined at the beginning of this review, and to which scant attention was paid in the earlier work.

Based upon the measurable fluid accumulation that occurs at the site of injury in untreated traumatic shock, fluid therapy approaching 5 per cent of body weight was until a few years ago considered adequate, and was rarely exceeded in laboratory or clinical trials. Prior to 1940 (for review see Harkins (118)) the experimental evidence with few exceptions (6, 127) as well as clinical experience, favored the use of blood, plasma, or other colloid preparations, while electrolyte solutions were considered of slight value or actually harmful.

Extensive reviews of the earlier literature have been compiled by Cannon (36), Blalock (24), Harkins (118), and this summary will include chiefly the experimental work since 1940.

A. Evaluation of therapy in shock resulting from local trauma

1. Muscle trauma in dogs by tourniquets. With tourniquet application (for 5 hours) fatal to the majority of untreated dogs, plasma or other colloid therapy in amounts of 4 to 6 per cent of body weight prevented death in 70 to 92 per cent of the dogs, while saline therapy (including sodium succinate) prevented death in 33 to 80 per cent (76, 117, 194, 195). Swingle *et al.* (147, 249) found single infusions of plasma (3.3 per cent of body weight) less effective (20 per cent survival) than infusion over 7 hours (77 per cent survival); a single infusion

of saline effected 58 per cent survival. Allen (6, 7) was an early advocate of large volumes of saline therapy but his reports include no comparative mortality data (see tourniquet shock, rats). Scott *et al.* (237), with a modified tourniquet technique, found equal effectiveness (50 to 70 per cent survival) with saline and various colloid solutions in amounts of 2.5 per cent of body weight. Local application of casts or other restrictive measures (60, 138, 150, 194, 240, 249) or cooling of the injured areas (6, 25, 240) was found to bring about a significant reduction in mortality; this is most likely due to the decrease in local swelling. Ashworth and Haist (14) found no benefit from application of casts to rats after swelling had reached a maximum, but it cannot be excluded that some further swelling occurred above the area of restriction.

2. Other forms of local trauma in dogs. With venous occlusion to the hind limbs of dogs Katz *et al.* (139, 177) found an average survival of 61 per cent in 3 series of experiments with the use of saline, while glucose was ineffective. With a Blalock press to the extremities Swingle *et al.* (250) obtained 70 per cent survival from prolonged administration of plasma or gelatin (4 per cent of body weight), 39 per cent from saline, and 9 per cent from gelatin given in a single infusion. In shock produced by gunshot wounds the same authors (251) obtained by the prolonged administration (3.3 per cent of body weight), 73 per cent survival from plasma, 62 per cent from gelatin and 50 per cent from saline. Trauma by dropping weights on the thighs was used by Guttman *et al.* (113). Serum (2.5 per cent of body weight) was much more effective than saline in prolonging survival time.

Winkler *et al.* (283) studied the effects of colloid and saline therapy upon the circulatory collapse which results from acute salt depletion in dogs. Plasma proteins were more efficacious than saline in hemodynamic responses, as shown by the use of serum or dialized serum. However saline solutions restored the circulation to normal in 2 hours, and brought about a return to the blood stream of proteins that had disappeared during salt depletion. Glucose solutions intravenously had little effect (48).

3. Muscle trauma in rats and mice. Allen (6) first employed tourniquet application to the extremities of rats and found that plasma, whole blood or saline would prevent death if administered early after tourniquet release, but only saline was effective at later stages. Dextrose was not effective. The importance of tissue dehydration was emphasized. He pointed out the limitations of therapy where more than a lethal amount of trauma was used, and also the influence of environmental temperature upon survival. Details of his experimental data were not submitted. Millican, Tabor and Rosenthal (182, 231) standardized tourniquet shock in mice, and with one MLD of trauma obtained 40–50 per cent survival with 5 per cent of body weight of saline, 77 per cent survival from 10 per cent of body weight and 91 to 98 per cent from 15 per cent of body weight. No significant differences were found between oral and parenteral administration.

This effect is characteristic of the sodium ion, since various sodium salts were equally effective, while related cations, potassium, rubidium, lithium and cesium were either inactive or of increased toxicity for the shocked animal (125, 177,

253). In simultaneous comparisons plasma (5 per cent of body weight) was equal to saline when administered in a single dose, but 50 per cent more effective when given over a 7 hour period. No difference in survival was found between equivalent doses of plasma and whole blood.

The efficacy of large volumes of saline in traumatic shock in small animals (see also burn shock and hemorrhage) was confirmed by Locke (164), Green and Stoner (107), Harkins (119) and Gray *et al.* (105). These findings were instrumental in the reintroduction into clinical use of large volumes of electrolyte solution, particularly by oral administration, in the treatment of various forms of shock.

B. Evaluation of therapy in experimental burn shock

1. Burn shock in dogs. The difficulty in obtaining standardized fatal burn shock in dogs, particularly in the absence of prolonged anesthesia (see section I 3, p. 491), is perhaps reflected in the paucity of experiments with this species. Parkins *et al.* (203) obtained survival of 3 of 4 dogs with plasma and 2 of 5 with saline (9 per cent of body weight). Moyer *et al.* (192) suggested that dogs without removal of the hair were more susceptible, and compared various agents on survival time. Electrolyte solutions and serum were less effective than whole blood plus electrolyte solutions. Berman *et al.* (21) obtained prolongation of survival time by injection of saline solutions into the burned areas. Application of plaster casts or restrictive bandaging has been found to favorably influence the course of burn shock, similarly to the results in muscle trauma (34, 35, 221).

2. Burn shock in small animals. a. Mice. Rosenthal, Tabor and Millican standardized burn shock in mice (192, 230) and obtained results similar to those in tourniquet shock. Fifteen per cent body weight of isotonic sodium solutions brought about survival of 92 per cent of the animals (916 mice). When the same *total amounts of sodium* were employed, isotonic solutions were superior to hypotonic or hypertonic; mouse plasma and saline were equal in survival response when administered in 1 or 2 doses, but plasma was 50 per cent superior with prolonged administration; water and 5 per cent glucose solutions were relatively ineffective; albumin or other colloids in glucose solutions (without Na^+) brought about acute circulatory responses similar to plasma, but their effects upon 24 hour survival were slight; saline (10 per cent of body weight) was effective when therapy was withheld for 6 hours after trauma, at a time when 25 per cent of the untreated animals were dead. No differences were observed in survival between whole blood and plasma, either with rapid or prolonged administration.

Prinzmetal *et al.* (213) (independently) and Hazán and Treadwell (124), Cullumbine (46), Neal *et al.* (198) and Reichman *et al.* (219) likewise reported the favorable effects of saline upon burn shock in mice and rats. Prinzmetal *et al.* (125) also obtained equal survival responses from plasma and saline administered in one dose to burned mice. Millican (181) found that plasma is as effective by intraperitoneal injection as by prolonged intravenous injection, in mice subjected to burn shock. This route of administration was suggested by the observation of Courtice and Steinbeck (44) that homologous plasma is effec-

tively absorbed into the blood stream, via the lymphatics, when introduced into the peritoneum of normal animals.

b. Rats. McCarthy *et al.* (167, 169) have done extensive evaluation studies upon burned rats. Plasma, other colloids in saline, and saline were equally effective when given shortly after the trauma. Eighty-six per cent survival was obtained with 10 per cent of body weight; where equal *volumes* of solution were administered, 1.4 per cent NaCl was more effective than 0.9 per cent; with an ingenious method of continuous infusion for 10 hours, survivals of 100 per cent at 24 hours were obtained with blood, plasma, and saline mixtures (18 per cent of body weight) as compared to approximately 50 per cent with sodium solutions with or without plasma (166).

C. Evaluation of therapy in hemorrhage and hemorrhagic shock

Although the line of demarcation is not sharp, attempts have been made to differentiate the condition produced by a single, massive hemorrhage from that produced by smaller bleedings repeated over a period of hours, and associated with prolonged hypotension. The hypotension following massive hemorrhage in dogs may result in delayed death similar to graded hemorrhage (135, 263), but some workers have encountered difficulties in standardizing this procedure (104, 160). In mice and rats massive hemorrhage results in either acute death or rapid recovery (235, 252). Both types of hemorrhage are distinguished from other forms of trauma by the diminished red cell mass and resultant impaired oxygen carrying capacity of the blood; this affords an additional source of tissue anoxia, and is reflected in the efficacy of erythrocytes in the replacement therapy of hemorrhage, generally confirmed by most observers.

1. Therapy against acute hemorrhagic death. a. Dogs. Massive exsanguination followed by immediate reinfusion of a volume of therapy equal to the blood withdrawn (3.8 to 7.4 per cent of body weight) was carried out in a large series of dogs by Ivy *et al.* (135). Heparinized plasma gave 96 per cent survival, serum 74 per cent, and saline 42 per cent. Almost identical results were obtained by Gropper *et al.* (110). Whole blood was not used in these comparisons. McKee *et al.* (170) obtained 100 per cent survival with red cells suspended in saline, 73 per cent with plasma, and 20 per cent with saline (4.4 to 5.5 per cent of body weight). Parkins *et al.* (115, 203, 204, 205) obtained 100 per cent survival with blood, colloid solutions in saline, and saline (4 to 6 per cent of body weight). Govier and Colovos (104) with a modified method obtained 25 per cent survival with plasma or gelatin and 6 per cent with saline (9 to 10 per cent of body weight). Reynolds (220), using Walcott's procedure (263), obtained 86 per cent survival with saline (in volumes of 18 per cent of body weight), while Allison *et al.* (9) report 62 per cent survival with blood, 81 per cent with plasma and no survivals with saline (3 to 4 per cent of body weight).

b. Cats. Buttle and Kekwick (29) reported 100 per cent survival with whole blood or plasma (2.5 to 3 per cent of body weight) and no survival with saline.

c. Guinea-pigs. Morrison *et al.* (191) obtained the following survivals with therapy of 1 per cent of body weight: whole blood and serum albumin, 100 per cent; plasma "substitutes", 50 to 80 per cent; saline, 10 per cent.

d. Mice and rats. Techniques for the production of acute hemorrhagic death in large numbers of mice, bled simultaneously, were developed by Tabor *et al.* (252). With one MLD of hemorrhage (5 per cent of body weight of blood loss) plasma or saline in one dose (3 to 5 per cent of body weight) were equally effective. Whole blood and red cells in saline also gave equal responses, which were two to three times as effective as plasma or saline. With large amounts of saline (8 to 19 per cent of body weight) 77 per cent survival was obtained. Water or isotonic KCl had little or no effect. Sayers *et al.* (235) standardized hemorrhagic death in rats by bleeding from the tail for 1 hour. Evaluation of therapy at various dosage levels gave results somewhat comparable to those described above for mice (252). Survival $Dose_{50}$ computed as per cent of body weight of therapy was as follows: whole blood 1.2, plasma 1.6, red cells in saline 2.3 and saline 3.9.

2. Hemorrhagic shock. a. Dogs. Several methods have been developed, based on bleeding in multiple stages (104, 160, 254) or upon maintaining a constant hypotension by means of a reservoir bottle (148, 151). The difficulty of obtaining standardized hemorrhagic shock in dogs is brought out by Glasser and Page in a study upon 244 dogs (102).

Magladery *et al.* (172) obtained equal survival (66 per cent) with whole blood and serum, when 40 per cent of the volume of hemorrhage was replaced. Levinson *et al.* (160, 199) obtained 75 to 100 per cent survival with both blood and serum, with 60 to 100 per cent replacement, and no survival from saline. Parkins *et al.* (115, 205) found 100 per cent survival from heparinized blood or colloid solutions and 40 per cent from saline (4 to 6 per cent of body weight) while in another report (204) saline (12 to 18 per cent of body weight) produced 60 per cent survivors. Morrison *et al.* (191), employing a bleeding volume index, listed the following order of effectiveness of therapy: whole blood, plasma, dextran, periston, saline. Govier and Colovos (104) and Hartman and Behrmann (123) obtained 60 to 100 per cent survival with colloid solutions and 0 to 6 per cent with saline (8 to 9 per cent of body weight). Dworkin (62) found that the effectiveness of saline was influenced by the duration of hypotension that preceded therapy. Sodium and glucose solutions, used as supplements to whole blood replacement in the later stages of hemorrhage shock, were found to have some beneficial effect on survival by Wiggers and Ingraham (277) and Levine *et al.* (159), but not by Frank *et al.* (87) or Nastuk and Beatty (196).

b. Rabbits. Raiz and Pulaski (216) with replacement equal to the blood withdrawn (3 per cent of body weight) obtained the following survivals: plasma 88 per cent, oxypolygelatin 94 per cent, dextran 80 per cent, and saline 50 per cent.

c. Rats. Sayers *et al.* (235) in hemorrhagic shock in rats obtained 100 per cent survival with whole blood (5 per cent of body weight) and 83 per cent with saline (10 per cent of body weight).

D. Comments on evaluation of therapy

From this review of the large and conflicting experimental evidence that has accumulated during the past 15 years, it is difficult to arrive at a clear evaluation of the relative merits of colloids, fluids, and electrolytes in the treatment of

shock. Although much progress has been made in the satisfactory standardization of trauma, much of the work falls short in other aspects of standardization previously outlined, particularly in respect to adequate numbers. The complicating factor of bacterial infection that occurs in prolonged tourniquet (89, 210, 224, 249, 279) or hemorrhagic shock (79)[3] in dogs may have considerable influence upon these evaluations, but this influence cannot be appraised with the evidence at hand. There is no clear evidence at present of a similar complication in other species.

In general the experimental work on evaluation supports the following conclusions:

Whole blood, plasma or other suitable colloids bring about a more pronounced and more sustained circulatory response than electrolyte solutions; they are more effective in combating the circulatory collapse of shock but in the amounts employed may be inadequate to correct the fluid and electrolyte disturbances.

Whole blood is the most effective therapy for severe hemorrhage. The superiority of whole blood over protein or other colloid solutions in shock not due to hemorrhage has not been demonstrated conclusively in experimental animals, although widely used clinically.

Plasma and related solutions are more effective than equal volumes of saline, particularly when administered over a period of hours. Within certain limitations larger volumes of saline can replace or reduce the need for colloid therapy.

The experimental evidence indicates that water and sodium free glucose solutions are distinctly inferior to saline in shock, while potassium solutions are toxic.

VII. GENERAL DISCUSSION

It would seem that one of the basic mechanisms of shock produced by trauma is the capacity of the injured tissues to swell, and the swelling may proceed to a depletion of fluid, electrolytes and proteins incompatible with life. This capacity to swell takes prior claim on administered therapy and most of it will accumulate in the injured area. It has been shown that the use of protein solutions will not lessen this swelling. Until remedies have been found (other than local cooling or other restrictive measures) which will curtail this swelling, the basis of "replacement" therapy must be (a) to satisfy this capacity to swell, and at the same time (b) to correct the depletions of fluids, electrolytes and proteins that has occurred in the undamaged tissues, and (c) to restore blood volume.

There are many other biochemical and physiological changes that occur in shock, and it is not intended to assign to fluids, electrolytes, and proteins an exclusive role in the etiology of shock. However, their importance rests on the evidence that circulatory collapse in normal animals can be produced by changes of similar magnitude to those observed in shock, and by the fact that administration of fluids, electrolytes and proteins can under certain conditions prevent the fatal outcome of shock.

[3] Beck, L., Vivaldi, E. and Nickerson, M. have been unable to confirm the effectiveness of antibiotics on survival of dogs in hemorrhagic shock. (Presented at meetings of Am. Society for Pharmacology, September, 1954.)

The individual role of fluids, electrolytes or proteins is more difficult to evaluate, since the changes occur simultaneously and their effects are interrelated. On a basis of depletion experiments in normal animals, circulatory collapse can be produced more readily by acute sodium deficiency than by fluid depletion alone. The available evidence indicates that a similar state can be produced by plasma protein removal (plasmapheresis) only if the depletion is very rapid and more extensive than usually present in shock. But when all three of them are removed simultaneously, as in plasma removal, circulatory collapse and death results from less extensive depletion of each factor.

The evidence from therapeutic experiments indicates that plasma proteins (or other colloids) play an important role in restoring the impaired circulation, but the addition of adequate fluid and electrolyte therapy is essential for optimum survival. Under experimental conditions the administration of large quantities of isotonic sodium solutions can reduce, and in certain instances replace the need for colloid therapy in bringing about survival. This effect can be obtained by oral as well as parenteral administration, and occurs even though early hemodynamic responses are considerably less marked than with plasma.

Potassium release has been implicated as a possible factor in the terminal phases of traumatic shock, but further investigation is required to evaluate its role in the development or fatal outcome of shock. The present evidence indicates that potassium is not an important factor in the development of shock.

An objective of future research should be to extend the effectiveness of therapeutic measures beyond the present limitations of one lethal degree of trauma.

Available evidence is not adequate to evaluate the role of plasma protein derangements in the causation of shock, nor can all phenomena of shock be explained on a basis of fluid and electrolyte disturbances.

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