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Ringer's Lactate Solution and Extracellular Fluid Volume in the Surgical Patient:

A Critical Analysis

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SEVERAL decades ago the care of the surgical patient was greatly improved with the introduction of parenteral salt and water for sustenance during and following surgical operations. In subsequent studies, principally the classic work of Moore,[12] it was demonstrated that the metabolic and hormonal responses of the body to surgical stress profoundly altered the need for salt and water in the postoperative period. As a result of these studies, it has been customary for some years to limit the amounts of water and sodium administered in the operative and early postoperative period. Most surgeons believe that such limitation has reduced the incidence of edema, dilutional hyponatremia, and water intoxication, problems which had been noted to occur in the postoperative patient. A number of recent reports, however, have indicated that there is an acute deficit in the volume of the extracellular fluid space in animals during shock and in man during surgical trauma.[2, 10, 19, 22] It has been recommended on the basis of these studies that large amounts of Ringer's lactate solution be administered during operation and for the treatment of hemorrhagic shock. In recent months patients have been receiving in the operating room four times as great amounts of fluid than those previously recommended and amounts of sodium which were previously considered adequate for the first 4 to 10 postoperative days. This study was stimulated by the clinical observation that patients receiving massive amounts of sodium and water occasionally developed pulmonary edema, a complication which had been rare in all but cardiac surgical patients. The present investigation was designed to evaluate changes in extracellular fluid (ECF) vol-

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ume during hemorrhagic shock in dogs and during major surgical operations in man.

The current interest in the use of large volumes of Ringer's lactate solution originated with the experimental work of Shires and associates.[20] These studies demonstrated that in dogs bled into a state of profound shock by a modified Wiggers technic, the ECF space diminished greatly (as much as 43%), as measured by ^{35}S-tagged sodium sulfate. The administration of large amounts of isotonic sodium lactate solution resulted in the restoration of ECF to normal. Subsequent studies[19] performed in man during hemorrhagic shock also showed a loss in ECF of approximately 31%. Moreover, the disappearance of fluid from the ECF space was reported to occur not only in clinical shock, but also in patients undergoing major operative procedures.[22] Deficits in ECF of up to 28% occurring with conventional fluid therapy during operation could be corrected by the administration of sodium lactate solution.[7] These observations on the ECF space have been confirmed independently by other investigators.[2, 10] On the basis of these clinical and experimental studies, it has been recommended that patients receive during an operation from 500 to 1,000 ml./hour of isotonic Ringer's lactate solution up to a total of 4 liters.[18]

Not all investigators agree that a deficit in ECF occurs under the foregoing circumstances. Serkes and Lang[16] reported that in rats a deficit in ECF after hemorrhage could be accounted for by the plasma volume lost during hemorrhage. Virtue, LeVine and Aikawa[25] were unable to demonstrate a deficit in ECF in a study of 25 patients undergoing cholecystectomy. Cleland and associates,[8] using radiobromine and radiosulfate, studied ECF volume in 30 patients undergoing open-heart operations. In contrast to all other investigators, they found an increase in ECF after operation.

The study of Cleland and associates deserves special comment because it pinpoints specific methodological problems which might serve to explain conflicting experimental results. These investigators identified a difference in the period of time needed for equilibration of the injected isotope with the ECF space preoperatively and postoperatively. By inference, they suggest that the method of measuring ECF employed by many investigators contains an inherent error.

The motivation for initiating the present study arises from several sources. Significant differences of opinion are expressed in our clinical practice among the various consulting surgeons, anesthesiologists, and internists concerning the fluid therapy of specific patients. Some consultants, who have practiced for many years without concern for the magnitude of the ECF, fear for the safety of their patients who are given volumes of fluid two to four times the usual daily requirement on the day of operation. They are even more concerned when their patients receive during a brief operation sufficient sodium ion to satisfy the body requirements for the first postoperative week. The general trend in sodium and water administration at the UCLA Hospital over the past 5 years is illustrated in Figure 1. Although there has been no change in the type of patient or in the operation performed, the amount of crystalloid solution administered by the anesthesiologist during operation has more than doubled. The amount of sodium ion given shows an elevenfold increase.

It has been stated that the postoperative patient requires no sodium on the first two postoperative days and 75 mEq. per day thereafter.[12] Accordingly, the average amount of sodium administered in 1967 to a UCLA surgical patient was sufficient to supply the body's metabolic needs for 4 to 5 days. These average data conceal the fact that some patients received a two-week supply of sodium during an operation.

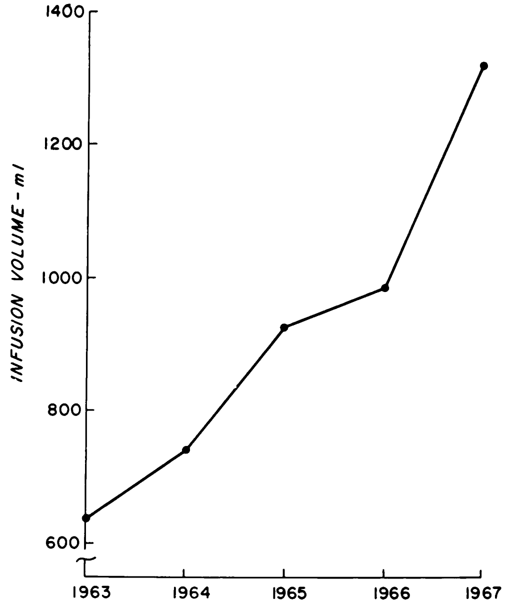

FIG. 1A. The volume of crystalloid solution administered to 50 patients undergoing cholecystectomy from 1963 to 1967 is illustrated. Ten patients were randomly selected by computer for each year of the study. To facilitate interpretation, volumes (measured in ml./Kg. body weight) are expressed as total volume administered per "standard" 60-Kg. man. There is a striking increase in fluid loading each year with no plateau in sight.

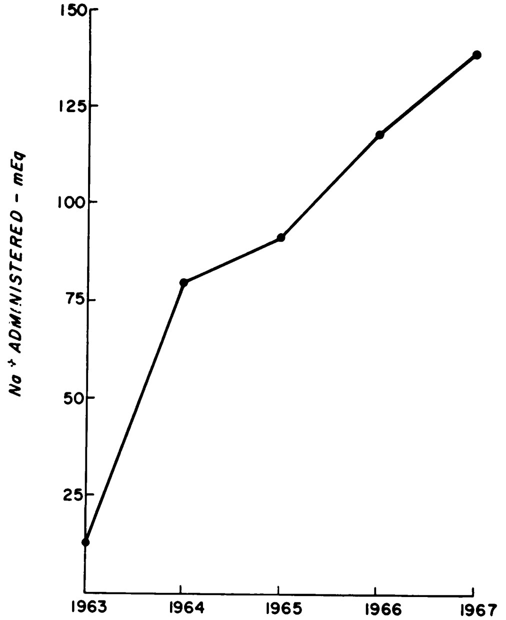

FIG. 1B. The amount of sodium ion administered to the same group of patients as in Figure 1A is illustrated. There has been an elevenfold increase in the amount of sodium administered to the patient by the anesthesiologist over a 5-year period.

Figures 1A and 1B do not include additional water and sodium administered after termination of anesthesia.

There is no leveling-off of the rising curves in 1967. That we are right to fear for the safety of the patient is given some support by the fact that occasional episodes of massive pulmonary edema have been witnessed in noncardiac patients on the night of operation, a complication which until recently had been rare. The fact that this experience is not unique is illustrated by the report of Mills, McFee and Baisch[11] who found a 50% mortality in Vietnam battle casualties who developed pulmonary edema following the treatment of battlefield shock with massive amounts of Ringer's lactate solution.

Although our experience with the administration of large amounts of Ringer's lactate solution during the intraoperative period suggests that the majority of patients who have normal cardiovascular and renal systems tolerates water and sodium loads without difficulty. It is, nevertheless, becoming increasingly clear that some patients pay dearly for the physician's attempt to maintain ECF by such treatment. The conflicting nature of the data cited induced us to initiate our own study of the behavior of the ECF space in dogs in shock and in man undergoing operation.

Experimental Design

Preliminary investigations showed that the isotope technics employed in the measurement of ECF were of critical importance. Three tracers currently employed in our laboratory for this purpose are ^{82}Br-sodium bromide, ^{14}C-sucrose, and ^{35}S-sodium sulfate. Each of these tagged materials has both theoretical and technological advantages and disadvantages. Furthermore, each isotope has a somewhat different volume of distribution within the body. Most investigators concerned with the problem have employed ^{35}S and this was chosen for the present study so that our results could be compared with those obtained by others.

Dog Studies: Group I

Eight dogs were anesthetized, bled into a state of hemorrhagic shock and maintained in that state for a period of 90 minutes. ECF and erythrocyte volumes were measured before induction of shock and again after 90 minutes of hypotension. In each dog both femoral arteries and one femoral vein were ligated and cannulated centripetally to allow withdrawal of samples and the injection of tracers. Analysis of the results of these experiments suggested that the femoral cannulation introduced a serious technical error into the study. A second group of dogs was therefore investigated.

Dog Studies: Group II

The same general procedure was followed with this group of dogs as with Group I. Instead of femoral cannulations, however, a catheter introduced into a ligated carotid artery was passed into the aortic arch, and a single venous catheter was introduced into the superior vena cava through a jugular vein. It is to be noted that ligation of a carotid artery in a dog does not produce cerebral ischemia because of the dog's excellent collateral circulation via the internal and external carotid arteries.

Group I studies indicated that femoral ligation produced quite different results from those of Group II. The animals of Group I clearly showed ischemia and delayed mixing of tracer throughout the legs, phenomena which did not occur in Group II. Consequently, the results of the Group II experiments are considered more reliable than those from Group I.

Patient Studies: Cardiac Surgery

Nine adult patients undergoing major cardiac operations with extracorporeal circulation were studied. Seven patients required valve replacement and two underwent correction of congenital malformations. This group of patients was selected because of the extensive surgical trauma to which they were subjected. ECF was measured in these patients 16 hours prior to operation and 6 hours postoperatively.

Patient Studies: General Surgery

Eight patients undergoing major general surgical operations were studied by the same methods and schedule used for the cardiac patients. Of the eight patients, four had colon operations, two had cholecystectomies, one a partial liver resection, and one an aortofemoral bypass graft.

Methods

Sixteen dogs with an average weight of 23.5 Kg. were used. Splenectomy was carried out 8 days before the experiment. After a fasting period of 12 hours, the dogs were anesthetized with pentobarbital in a dose of 30 mg./Kg. body weight. Additional small amounts of pentobarbital were administered during the 9-hour experiment when necessary. The dogs were intubated but no respirator was used. The eight dogs of Group I had catheters in both femoral arteries and in one femoral vein; the eight dogs in Group II had catheters placed in one carotid artery and in one jugular vein. Arterial blood pressure was recorded with a strain gauge and direct-writing oscillograph.

After a normotensive period of 180 minutes during which control measurements were made, the dogs were injected with heparin (4 mg./Kg. body weight) and bled through an arterial catheter at a rate of 50 ml./minute until a mean arterial pressure of 50 mm. Hg was obtained. The two-step hypotension method (90 minutes at 50 mm. Hg and 45 minutes at 30 mm. Hg) employed by others was not used because pilot experiments demonstrated that the dogs did not survive long enough to permit uniform mixing of the tracer throughout the ECF space. Mean arterial pressure was maintained for 5 hours at 50 mm. Hg by a method described by Braasch *et al.*[3] somewhat modified for our purposes. Blood was collected in a graduated bottle immersed in a 37° C. water bath and fitted with a magnetic stirrer. The bottle, open to the arterial system, represented a potential source of error in the isotope dilution technic. If equilibration of the contents of the bottle with the whole blood volume of the dog were to take place slowly, a large error would be introduced. To avoid this difficulty, a small roller pump exchanged the blood in the bottle with the dog's vascular system at a rapid rate (70 ml./minute). Since the volume of blood outside the dog was rarely more than 800 ml., it was renewed rapidly. The time taken for renewal was seldom more than 12 minutes and usually much less. Thus, equilibration errors were avoided while arterial pressure was maintained constant. Constancy of arterial pressure was assured by regulating air pressure in the bleeding-bottle.

Tracer Methods

The red cell volume (RCV) was measured with ^{51}Cr-tagged red cells and ECF space with ^{35}S-tagged sodium sulfate. The first isotope injections were made to measure the RCV and ECF in a normotensive control period. The second isotope injections were made after 90 minutes of hypotension at a mean arterial pressure of 50 mm. Hg. A sample was drawn immediately before the second injections so that suitable corrections could be made for traces of isotope still present from the control period.

The erythrocyte-chromium tagging method of Read[15] was employed, and tagged cells were resuspended in uncontaminated plasma to reduce the correction factor for excess ^{51}Cr remaining in the plasma of the tagged blood. Each injection of 10–15 μc. ^{51}Cr in 1 ml. of tagged blood cells was made into the venous catheter, which was then flushed to clear it of any residual tracer material. Suitable standards were made in volumetric flasks from 1 ml. of tagged blood and 1 ml. of the injected plasma. Arterial blood samples (6 ml.) for ^{51}Cr were drawn at 30 and 60 minutes after the first injection and at 120, 150, and 180 minutes after the second injection. Blood sampling in the shock period was extended over a longer time than for the control period, since pilot experiments showed a delay in uniform mixing of the tracer throughout the ECF space in shock. For each of these samples both whole blood and plasma were counted. Correction was made for counts present in the plasma of the drawn samples, although the level of such counts was generally only about 1½ times background. Whole blood and plasma samples were counted for ^{51}Cr content in a automatic gamma-counting system equipped with a thallium-activated sodium iodide crystal three inches in diameter and an ultrascalar. Quantitative transfer of 1.0 ml. aliquots of whole blood and 0.5 ml. of plasma was ensured by rinsing the pipettes used to effect the transfer with distilled water. Duplicates were prepared of all samples drawn and these were made up to uniform volume so that the geometry with respect to the detecting crystal would be constant. The plasma standard was counted along with the whole-blood standard. The total counts injected by means of ^{51}Cr-tagged red cells were determined by subtracting the total counts in the injected plasma from those in the whole blood. The total counts in the injected plasma were determined from the counts/ml. of this material and the microhematocrit in the injected whole blood corrected for 2% trapped plasma.[1] The final calculation for the RCV was made by using the formula:

$$\mathrm{RCV} = \frac{\text{total counts in injected RC}}{\text{counts/ml. drawn RC}}$$

For calculations of the plasma volume (PV) the microhematocrit was corrected by the factor 0.98 for trapped plasma and by a factor of 0.88 to derive total body hematocrit from large-vessel hematocrit.

Twenty μc. of ^{35}S-tagged Na_2SO_4 in 1 ml. isotonic saline were injected at the beginning of the control period and again after 90 minutes of hypotension. A suitable standard with the same amount of tracer was prepared in a volumetric flask. Arterial blood samples were drawn after the tracer injection at 10, 20, and 30 minutes, and then every 15 minutes thereafter for 180 minutes in the control period and for 210 minutes in the shock period.

For the assay of ^{35}S, a 0.25-ml. aliquot of each plasma sample was taken with a micropipette and placed in a clear glass liquid scintillation screw-capped counting vial. To this was added 1.0 ml. of a 1.0 M solution of hyamine hydroxide in methanol. The contents were mixed and allowed to stand for 5 to 10 minutes until all protein material which had coagulated was sufficiently hydrolyzed to produce a clear fluid. Scintillant reagent (17 ml.) was then added to each aliquot and mixed. All samples were prepared in duplicate. To correct for quenching, unlabeled plasma taken from the dog prior to injection of any tracer was added to known amounts of ^{14}C-hexadecane in toluene. The fractional decrease in the counts brought about by the added plasma was applied as a general correction factor of the ^{35}S counts. This method of internal standardization was the most practical because of the complex nature and quenching characteristics of whole plasma and the similarity of the beta emission spectra of ^{14}C and ^{35}S. The ^{35}S-tagged sodium sulfate standard was counted in the presence of the same amount of scintillant reagent and hyamine as the plasma samples. Quenching due to the water content of the standard was found to be negligible. ^{35}S was assayed in an automatic liquid scintillation spectrometer.

A mathematical time function consisting of the sum of two exponential terms represented adequately the observed counts on the series of plasma samples drawn in both control and shock periods in the dogs, or preoperatively and postoperatively in patients. Prior to hemorrhage or operation 13 samples were drawn over a period of 180 minutes; 17 samples were drawn after hemorrhage or operation over a period of 240 minutes. A multiexponential time function was fitted to the data for each period of each study with the aid of a computer program previously described.[29-31] With each set of data points, a set of trial values, which served as approximations for the parameters in the exponential time function to be fitted, was presented to the computer. These trial values were first obtained by semilogarithmic hand-analysis and later by simple inspection of the data. By use of a series of successive approximations, the program enabled the computer to improve on these trial values by applying corrections obtained by solving a matrix determined from a set of linear differential equations. The best possible fit was obtained when the total sum of the squares of the differences between all of the observed values and those predicted by the fitted function was a minimum. The second exponential term of lesser magnitude was regarded as being indicative of the disappearance of radiosulfate from a space of distribution representative of the functional ECF space. The value of this term at zero time yielded the counts in plasma that were used to calculate the ECF space.

The foregoing method of analysis is not open to the criticism that data points may have been selected over a time range during which radiosulfate had not yet equilibrated throughout the functional ECF space. Whether or not equilibration took place after a longer time period following hemorrhage or operation is also of no consequence as far as the mathematical method of analysis is concerned. In fact, the exact point in time at which such equilibration does take place need not be known to analyze the data.

No correction was made for radiosulfate excreted by the kidneys during the equilibration period, since the sampling of bladder urine or ligation of ureters may introduce other errors. Rather, it was assumed that the rate of sulfate loss through the kidneys was constant during the equilibration period.

The final calculation for the interstitial fluid (ISF) was made by using the formula:

$$\mathrm{ISF} = \frac{A - B}{CD}$$

where, A = total counts injected;
B = total counts in plasma at zero time: (counts/ml.) PV;
C = counts/ml. plasma water at zero time;
D = Gibbs-Donnan correction factor of $(1.05)^2$ for divalent SO_4 ion.

Water content of plasma was measured in duplicate in each experiment in the control and shock or preoperative and postoperative periods by weighing 1.0 ml. plasma, drying it for 24 hours at 105° C., and reweighing the solid residue. The ECF was determined from the sum of ISF and PV.

The same methods were used in patients. Control measurements were made 16 hours before operation, and again within 6 hours after operation. Blood samples for RCV determination were drawn during both periods at 30, 60 and 90 minutes after injection of tracer. Blood samples for ECF determination were taken at 10, 20 and 30 minutes after injection of tracer and then every 15 minutes for 180 minutes before operation and for 240 minutes after operation. Infusions administered and urine produced during the operation and the early postoperative period were measured.

Results

The data on dogs in hemorrhagic shock showed that a 30 to 40% deficit in ECF could be found if the single-sample isotope dilution method of Shires, Williams and Brown[21] was used as the basis for the calculation. This method for estimating ECF depends upon measurement of the concentration of radiosulfate in a single sample drawn 20 or 30 minutes following injection. The method is a modification of a technic described by Walser, Seldin and Grollman,[26] and is dependent upon the assumption that 30 minutes represents an adequate period for the injected ^{35}S to be distributed uniformly throughout the ECF space in dogs and that 20 minutes is adequate in man. Measurement of the volume of a body compartment by the distribution of a tracer substance within it is dependent upon the following general equation:

$$V = \frac{Q}{C}$$

where, V = volume of the body compartment;
Q = quantity of the tracer injected;
C = concentration of tracer at a time when the isotope is uniformly mixed within its volume of distribution.

Clearly, if sufficient time is not permitted for the tracer to be distributed uniformly throughout the space, C will be erroneously high, and the apparent volume of the compartment will be less than its actual volume. All investigators who have reported a deficit in ECF in man or in animals have used the single-sample isotope dilution method. The following data demonstrate that this method contains an inherent error when used following shock or operation.

It can be seen from Figure 2 that prior to operation 75 minutes are required before the radiosulfate is uniformly distributed throughout the ECF space. This is indicated by the appearance at 75 minutes of a second exponential component, which reflects the disappearance of the tracer from the ECF space. In this case, when the

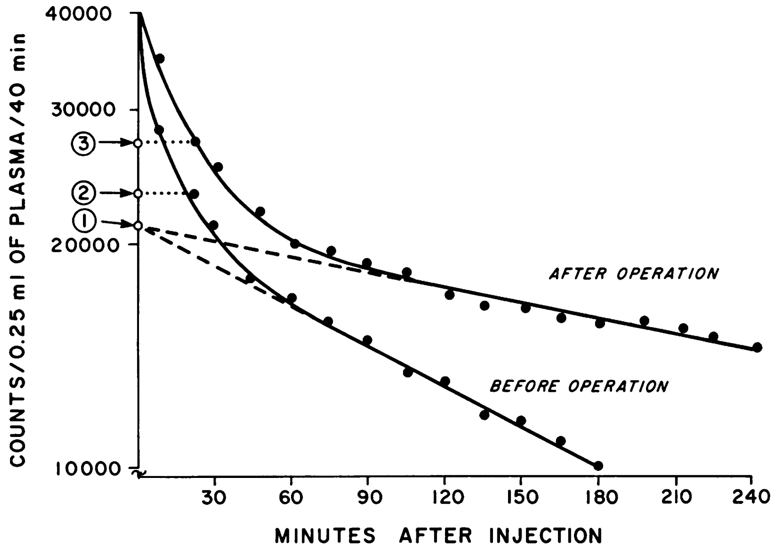

FIG. 2. A semilogarithmic plot demonstrates the difference in disappearance of radiosulfate from the plasma in a patient before and after a cardiac operation. Each data point represents measured isotope concentration in plasma. Smooth lines are computer-fitted curves represented by a sum of two exponential terms. Dashed lines represent the computer-determined exponential component of lesser magnitude, extrapolated to zero time to calculate ECF space. Arrow 1 indicates that the extrapolated isotope concentration, and therefore ECF, is the same before and after surgery. Arrow 2 shows that before operation the single-sample isotope dilution method (dotted line) gives a higher count and therefore a slightly smaller value for ECF than the extrapolation method in this case. After operation, however, the altered disappearance curve causes the single-sample method to show an apparent, but erroneous, ECF deficit (Arrow 3).

single-sample method is used as a basis for the analysis, a lower estimate of ECF is obtained than by the extrapolation of the exponential component which begins at 75 minutes. In general, however, the single-sample and extrapolation methods gave similar results in the control period. Figure 2 demonstrates that after operation the dilution curve is altered in a distinct manner, such that the single-sample isotope dilution method consistently underestimates the volume of the measured space. The same error is introduced after hemorrhage in the dog by the single-sample method. This observation was made previously and its significance clearly appreciated by Cleland and associates.[8] These investigators found an increase rather than a decrease in ECF following surgical operations.

In view of the foregoing, in all experiments reported in this paper plasma sampling was extended over a 3-hour period before hemorrhage or operation, and over a 4-hour period afterward. The data were analyzed by the mathematical methods already described.

Dog Studies: Group I

Table 1 shows that there was a deficit of 19.8% in ECF following hemorrhage in dogs in which both femoral arteries and one femoral vein were cannulated. This is considerably less than a deficit of approximately 40% which can be found from the same data if the basis for the analysis is the single-sample isotope dilution technic. The volume of plasma removed as part of the shed blood during hemorrhage was found to be 7.7% of the ECF determined in the control period. Thus, the combined volume of the ECF following hemorrhage and of plasma removed as part of the shed blood was only 12.1% less than that of the ECF in the control period. During the course of these studies an observation was made which invalidated not only the results of the foregoing experiments, but probably also the results of many investigators who have studied changes in ECF during hemorrhagic shock in animals. After several hours of profound hemorrhagic shock, the dogs developed a rigidity in the lower extremities suggestive of rigor mortis. Because of the possibility that obstruction of the femoral artery by cannulation in an animal with profound hypotension might cause this rigor, two additional experiments were performed in which only one leg was cannulated. In these experiments only the cannulated leg developed rigidity suggestive of rigor mortis. It was immediately apparent that part of the deficit in ECF noted in the Group I animals following hemorrhage might be due to failure of the injected tracer to mix uniformly throughout the ECF space of the cannulated legs. This suspicion was confirmed by examination of muscle biopsies taken from the thigh muscles in the cannulated and noncannulated legs prior to and after five hours of hypotension. Following the hypotensive period the ^{35}S content per gram of muscle in the cannulated leg was consistently less than in the noncannulated leg. Apparently, the collateral circulation of the leg, which nourished the limb during the normotensive phase, failed to do so in the presence of profound hemorrhagic shock. A second group of dogs was therefore studied.

Dog Studies: Group II

In these dogs cannulae were introduced into a carotid artery and a jugular vein. One or both carotids may be occluded in the dog without producing cerebral ischemia because of collateral circulation characteristic of the canine species. In this group of dogs three types of common error in measurement of ECF following hemorrhagic shock were avoided by ensuring that:

(1) uniform mixing of the isotope in its volume of distribution was demonstrated in each case;
(2) results were corrected for plasma removed by hemorrhage;
(3) the "dead-leg syndrome" was not encountered.

TABLE 1. *Changes in Body Composition after Hemorrhage in Dogs*

Group I: Femoral Cannulation
(average BW: 24.6kg ±3.8)

	Control ml / Kg	Shock ml / Kg	% Change	p-value
RCV	31.4 ± 6.2	18.5 ± 5.9	-42.2 ± 9.1	< 0.001
PV	41.6 ± 4.1	30.1 ± 5.3	-27.8 ± 9.6	< 0.001
ISF	159.4 ± 15.4	131.3 ± 18.8	-17.9 ± 6.6	< 0.001
ECF	201.0 ± 16.8	161.4 ± 17.8	-19.8 ± 4.2	< 0.001
corr. ECF	201.0 ± 16.8	176.9 ± 18.9	-12.1 ± 5.0	< 0.001
Group II: Carotid Cannulation (average BW: 22.3kg ±3.1)				
RCV	29.3 ± 6.9	16.2 ± 4.1	-46.8 ± 5.3	< 0.001
PV	39.8 ± 4.1	25.8 ± 2.8	-35.1 ± 4.4	< 0.001
ISF	166.0 ± 9.6	150.5 ± 14.1	- 9.4 ± 6.6	< 0.01
ECF	205.8 ± 10.9	176.3 ± 15.0	-14.4 ± 5.3	< 0.001
corr. ECF	205.8 ± 10.9	194.2 ± 14.6	- 5.7 ± 5.1	< 0.02

RCV = red cell volume
PV = plasma volume
ISF = interstitial fluid
ECF = extracellular fluid
Corr. ECF = corrected ECF (see text)

Table 1 shows that there was a 5.7% deficit in ECF in these dogs following a 90-minute hypotensive period at a mean arterial pressure of 50 mm. Hg. This amounted to 267 ml. in dogs of 23 Kg. average body weight (equivalent to 696 ml. in a 60 Kg. man). This deficit, although statistically significant in degree, may not be of real importance. No correction was made for the ECF lost during the course of the study in the 13 blood samples removed for analysis of radioactivity in the control period; nor was any allowance made for respiratory or urinary water loss during the 4.5 hours between the first and second tracer injections. It is therefore probable that no real ECF deficit was demonstrated in these dogs.

These experiments are slightly different from those performed by other investigators, who subjected animals to 90 minutes of hypotension at a mean arterial pressure of 50 mm. Hg followed by 45 minutes of hypotension at 30 mm. Hg.[6] Animals subjected to the second period by hypotension at a mean arterial pressure of 30 mm. Hg did not survive long enough to permit uniform distribution of the isotope throughout the ECF space.

The results in Table 1 show an expected decrease in RCV of 42 and 46%, and a decrease in PV of 28 and 35% in Group I (femoral cannulated) and Group II (carotid cannulated) animals, respectively.

TABLE 2. *Changes in Body Composition with Operation in Surgical Patients*

	Before operation ml / Kg	After operation ml / Kg	% Change	p-value
CARDIAC SURGERY				
RCV	26.0 ± 3.0	22.9 ± 5.1	-13.9 ± 12.9	< 0.01
PV	42.0 ± 5.8	37.3 ± 7.5	-11.4 ± 10.2	< 0.01
ISF	182.5 ± 20.3	208.7 ± 36.7	+13.5 ± 12.0	< 0.01
ECF	225.5 ± 23.8	246.0 ± 37.1	+ 9.0 ± 9.9	< 0.05
corr. ECF	225.5 ± 23.8	224.4 ± 33.5	- 0.6 ± 9.3	N.S.
GENERAL SURGERY				
RCV	21.1 ± 2.4	20.2 ± 2.7	- 3.4 ± 7.5	N.S.
PV	45.2 ± 5.3	38.1 ± 6.6	-15.9 ± 6.8	< 0.005
ISF	188.8 ± 26.7	230.9 ± 26.0	+22.8 ± 7.2	< 0.001
ECF	234.2 ± 29.5	269.7 ± 29.1	+15.5 ± 5.9	< 0.001
corr. ECF	234.2 ± 29.5	234.8 ± 32.8	+ 0.2 ± 3.8	N.S.

Symbols as in Table I

The decrease in the PV is less than that in the RCV, partly because of the compensating movement of fluid and protein from ISF into PV in an attempt by the body to maintain the intravascular volume. The loss of ISF is proportionally less than the loss of PV because both protein and its accompanying water are removed directly from the PV in the course of hemorrhage (ISF = – 9% *vs.* PV = – 35%).

Patient Studies: Cardiac Surgery

In a group of nine patients undergoing an extreme degree of surgical trauma, the ECF shortly after the operative procedure was found to be increased by 9.0% (Table 2). ISF was increased by 13.5%. Patients, unlike the dogs, received intravenous fluids and excreted significantly larger amounts of urine during the longer time between the preoperative and postoperative measurements. When the values for ECF were corrected for intravenous fluids administered and for urinary excretion during operation and the early postoperative period, there was no significant difference between preoperative and postoperative measurements of ECF (–0.6%).

It is noteworthy that ECF increased in these patients (+9.0%) whereas PV diminished (–11.4%). It is acknowledged that fluid alterations in PV and ECF will be similar when a steady-state equilibrium condition exists, except for differences between the two compartments attributable to the Gibbs-Donnan relationship. After hemorrhage, however, the two compartments are not in equilibrium. The direct loss of protein from PV during the course of an operation is more than adequate to explain the discrepant directional alterations in PV and ECF.[13]

Patient Studies: General Surgery

In patients undergoing general surgical operations ECF was increased postoperatively by an average of 15.5%, and ISF by an average of 22.8% (Table 2). When this change in ECF was corrected for the intravenous fluids administered to the patient and for the urinary excretion during the period of observation, there was no significant difference between the preoperative and postoperative determinations for ECF (+0.2%).

It is clear that in dogs in profound hemorrhagic shock there is no substantial deficit in ECF, provided the common sources of experimental error are avoided. Moreover, surgical patients undergoing both cardiac and general surgical operations showed an increase in ECF shortly after the operative period. This increase can be accounted for *in toto* by the crystalloid solutions administered in the intraoperative period.

Although the value for ECF, corrected for intravenous fluids and urinary excretion, is the same for the general surgical and cardiac surgical patients, the two groups differ. The treatment of the general surgical patients has been influenced by the current tendency among anesthesiologists to load patients heavily with salt and water during the intraoperative period at the rate of 500 to 1,000 ml. of Ringer's lactate solution per hour. These patients received an average of 48.9 ml./Kg. of crystalloid solution between the time of induction of anesthesia and the second isotope injection. As might be expected, there was an increase in ECF of 15.5%, which is totally accounted for by the large amounts of fluid administered. In contrast to this, cardiac patients received only 24.3 ml./Kg. Ten years ago at this institution, cardiac surgeons demonstrated a significant reduction in the incidence of postoperative pulmonary edema in their patients when daily fluid intake in the first two postoperative days was reduced from 1,500 ml./m^2 of body surface area to 50% of that value on the first postoperative day, and to 75% of that value on the second postoperative day. Because of this clinical experience, cardiac patients were vigorously defended against the administration of a large salt and water load. The effect is reflected by the fact that in cardiac surgical patients the increment in ECF following operation was not as great as in the general surgical patients who were given large amounts of fluid, particularly Ringer's lactate solution (Table 2).

Discussion

There is an established current trend in both surgical and anesthetic practice to load patients with large amounts of water and sodium during operation. This trend is based upon the demonstration of deficits in the volume of ECF in man and animals by several groups of investigators. A study of 50 computer-selected, randomized patients undergoing cholecystectomy over a 5-year period at the UCLA Hospital indicates that the water load to which the patient is currently subjected during operation has doubled since 1963, and the sodium load has increased elevenfold. Some appreciation of the magnitude of the change is gained from the observation that in 1967 during an average 2-hour period of operation patients were given a sodium load which until recently was considered adequate for metabolic needs for the first five postoperative days. This therapeutic trend represents a radical departure from the recommendations of Moore,[12] who advises restriction of both water and salt in the immediate operative and postoperative period. These recommendations are based upon study of a large number of patients over many years, and reflect the alterations in salt and water metabolism brought about by hormonal responses to the stress of surgical trauma. It is the clinical experience of most surgeons that the course of the surgical patient has been greatly improved in the past 15 years as a result of moderate water and salt restriction. Consequently, water intoxication, dilutional hyponatremia, and cardiovascular complications secondary to salt and water loading have been less frequent.

As knowledge of surgical physiology increases, including altered concepts of water and salt metabolism, radical departures from past practices are to be expected. Nevertheless, before general principles of therapy based on scientific studies which have passed the test of practice are abandoned, convincing scientific evidence that a change in regimen will be beneficial must be presented. The present investigation was designed to examine critically the evidence on the basis of which we are currently being asked to increase fluid therapy of surgical patients. On close scrutiny, the evidence appears to be deficient.

The present change in viewpoint concerning administration of crystalloid solutions to surgical patients is based on studies demonstrating large deficits in ECF occurring in experimental animals following hemorrhage and in man following surgical operation. The accurate measurement of ECF is therefore the crucial point upon which therapy depends. The present study demonstrates that in dogs subjected to hemorrhagic shock the deficit in ECF (if any exists) is 5.7%. Both in a series of general surgical patients, and patients undergoing cardiac surgical procedures, a significant increase in ECF was demonstrated. This increment in ECF can be entirely accounted for by the volume of fluid administered intravenously during the operative procedure less the amount excreted in the urine. When ECF was corrected for intravenous fluid administered and urine excreted, there was no change in postoperative compared to preoperative ECF in either group of patients (cardiac surgery −0.6%, general surgery +0.2%).

What benefit arises from the current fad of administering large water and sodium loads to the patient during operation? The intended good is to prevent a deficit in ECF. Little benefit can be expected on this basis, since the present study demonstrates that there is an increase rather than a deficit in ECF in patients undergoing major surgical procedures. There is evidence from several sources that survival rates in dogs subjected to severe prolonged hemorrhagic shock are improved if Ringer's lactate is used instead of reinfusing the shed blood.[5, 9, 28] It occurs to the present authors that two possible beneficial effects might accrue from the use of Ringer's lactate solution. The buffering effect of the lactate has a beneficial effect in an experimental preparation in which plasma pH is frequently in the range of 6.9 to 7.1. A second possible advantage is that hemodilution may reduce intravascular sludging and sequestration of erythrocytes which occur in the microcirculation of some animals. Previous work in this[17, 23] and other laboratories demonstrated that this phenomenon is particularly important in the dog. In addition, water and salt loading may help maintain a high urine flow during the operative and postoperative periods. Continuous excretion of large amounts of urine during operation has a reassuring effect on the surgeon because of the presumption that renal shut-down is being prevented. Unfortunately, there is controversy concerning the effect of high urine flow in the prevention of acute tubular necrosis. Many investigators believe tubular necrosis is more related to circulation in capillaries of the distal tubule than to the flow of urine in the renal collecting system. The question remains moot and awaits objective data based on controlled observations.

What harm may come from the infusion of massive amounts of Ringer's lactate solution? It seems probable that in the majority of cases there are no adverse effects. Even very ill cardiac patients tolerated modest expansions of ECF by 9.0% and ISF by 13.5% without difficulty. Nevertheless, during this study otherwise healthy noncardiac patients undergoing simple general surgical procedures developed massive pulmonary edema on the evening of operation. This complication in the past decade or two has been exceedingly rare. Two such patients under observation by the authors recovered after vigorous therapy and passage of quantities of urine. One 50-Kg. patient received 4.8 liters of crystalloids during operation. Battle casualties in Vietnam have been treated with massive amounts of crystalloid solution to replace blood loss. This therapy has been greatly favored by those employing it, presumably on the basis that they were treating a deficit in ECF. Nevertheless, some disquieting reports[11] indicate a 50% mortality among patients who developed pulmonary edema following this treatment. Harmful effects must be infrequent and subtle, or many observers would have recognized adverse effects.

General surgical patients who received Ringer's lactate in the present study tolerated the increase in ECF without difficulty. If the ECF volume were corrected for intravenous fluids administered and for urine volume excreted during a study, the postoperative value for ECF was precisely what it had been on the evening before operation. Homeostatic defenses of the body seem capable of maintaining body composition in the face of a large salt and water load. Apparently the ECF accommodates to the extra load as a transient storage space between the intravenous bottle and the urinal. The exception is the occasional patient who, perhaps because of inappropriate secretion of antidiuretic or adrenal hormones, fails to excrete the load.

It may be true that the administration of sodium and water during the operative period needs to be liberalized. Before discarding conventional therapeutic methods, however, we need scientific evidence in support of the need for change. The present studies suggest that inherent errors in the methods of measurement of ECF serve as the basis for the present enthusiasm for the administration of Ringer's lactate solution.

Enthusiasm for Ringer's lactate therapy has led to the use of this crystalloid solution as a blood substitute. It has been recommended that volumes of Ringer's lactate equivalent to twice the normal blood volume be administered instead of blood for the treatment of hemorrhage involving 50% of the blood volume.[2] All surgeons of experience have successfully resuscitated terminal patients in hemorrhagic shock by administering a liter or two of crystalloid solution rapidly until such time as blood or colloid was available. There seems to be little rationale for routine administration of a crystalloid as a blood substitute, since noncolloid solutions are distributed within a matter of minutes to the extravascular space. The distribution between the intravascular and the ISF space is in proportion to the existing volumes of these spaces. Thus, since ISF is approximately four times as large as PV (15% *vs.* 4% of body weight), five liters of Ringer's lactate solution will distribute in the proportion of four liters to ECF and one liter to PV. Although appropriately crossmatched blood may not be available for 15 or 30 minutes in a modern hospital, the ready availability of dextran, plasma, and other colloids seem to make inappropriate routine use of crystalloids for maintenance of intravascular volume.

In metabolic acidosis, the response of the heart to both endogenous and exogenous catecholamines is deficient. Buffering may therefore beneficially affect a cardiogenic element in shock. When sodium lactate is metabolized by the liver, a desirable buffering effect is achieved. Metabolism of lactate ion unfortunately takes significant time, especially with impaired hepatic blood flow which characterizes shock. Sodium bicarbonate is a more effective buffer since it need not be metabolized to be effective, and its effect in restoring pH toward normal is immediate. The defective metabolism of lactate in shock is well illustrated by the high plasma lactate levels in this condition. In recent years cardiac surgeons have taken advantage of the rapid buffering action of bicarbonate in metabolic acidosis and deficient cardiac activity. Bicarbonate is frequently injected directly into the heart. The positive inotropic effect is apparent within seconds. The buffering action of lactate is, therefore, not an entirely appropriate reason for recommending Ringer's lactate solution when better buffers are available. Trudnowski, Goll, and Lam[24] recently provided valuable objective data on this subject.

The former practice of labeling commercially prepared Ringer's lactate solution as containing 26 mEq./l. of bicarbonate ion is to be deplored. This custom apparently originated many years ago with the concept that equimolar amounts of sodium bicarbonate, sodium lactate, and sodium citrate had equivalent buffering capacity. So indeed they do, but in the latter two compounds, metabolism of the anion is required before an effect is achieved. The misleading labeling on commercial Ringer's lactate solution has caused many physicians to believe erroneously that they were administering a buffer, bicarbonate, which was immediately effective in the treatment of acidosis.

Broido, Butcher and Moyer[6] recently proposed what we considered an interesting possibility. "It is possible that changes in the inorganic chemical composition and pH of ground substance secondary to cellular metabolic abnormalities attendant upon hemorrhage and prolonged severe hypotension could be the causes of the functional salt and water deficits that attend hemorrhagic shock." Although we cannot agree that there is a deficit in ECF, we respond to this general thesis. We have independently come to the same conclusion. Work in our laboratory over several years has led us to the conclusion that alterations in the reactivity of long-chain protein molecules of the extravascular space with changes in hydrogen ion concentration could result in fluid shifts within the ECF and ISF. The work of Wolf[27] in this laboratory gives substance to this speculation. Evidence comes from both the laboratory and from a large-scale mathematical model of the body fluid and electrolyte system described elsewhere.[4] It was by mathematical model that we first investigated the shifts in fluid within ECF and ISF which were postulated to occur in metabolic acidosis which characterizes hemorrhagic shock. It had been our impression that alteration in cation binding by collagen-like material in the extracellular fluid in acidosis might explain the large ECF deficit reported by many investigators. The mathematical model predicted that an infusion of hydrochloric acid sufficient to reduce plasma pH to 7.1 should produce a slight increase rather than a decrease in ECF. In laboratory studies on dogs performed by Wolf, the predictions of the model were validated. Although we agree that the behavior of long-chain proteins in the extracellular space may affect intercompartmental fluid shifts, both laboratory data and the mathematical model suggest that the shift due to metabolic acidosis is too small to be of clinical significance.

Summary and Conclusions

Since the classic work of Moore and associates, salt and water therapy has been based upon the recognized hormonal and metabolic responses of the body to the stress of surgical operation. On the basis of that work, moderate restriction of water and sodium has been recommended, and this had been followed by most surgeons. Recently, several groups of investigators have recommended that large amounts of Ringer's lactate solution be administered to patients during operation and for the treatment of hemorrhagic shock. This recommendation is based upon the finding of a deficit in extracellular fluid volume in animals in shock and in man following operation. An experimental and clinical study was therefore carried out to determine if this radical alteration in therapeutic principles was justified on the basis of available evidence.

1. A series of 50 patients undergoing cholecystectomy in the years 1963–1967 was studied with regard to the administration of salt and water during operation. During this 5-year period, there has been a progressive increase in the salt and water loading of patients, so that those operated upon in 1967 received twice the amount of water and eleven times the amount of sodium ion as those operated upon in 1963. It is our clinical impression that, although most patients tolerated this treatment well, even healthy noncardiac patients occasionally developed massive pulmonary edema without apparent cause other than the water and sodium loading.

2. Extracellular fluid volume was measured with radiosulfate in a series of dogs prior to and after subjection to hemorrhagic shock. There was a mean decrease in extracellular fluid volume of 5.7% after 1½ hours of profound shock following hemorrhage, with the animals maintained at a mean arterial pressure of 50 mm. Hg. This small deficit (equivalent to 696 ml. in a 60 Kg. man) is probably not a real deficit, but is accounted for by removal of blood samples, transpiration, and urine formation during the experiment. The discrepancy between this finding and the reports of others, can be explained by: (a) the single-sample radiosulfate dilution method used by other investigators, which contains

an inherent error and leads to the determination of an apparent, but erroneous, ECF deficit; (b) the failure of some investigators to account for the volume of extracellular fluid lost in the shed blood; and (c) errors introduced in the measurement of extracellular fluid because of incomplete mixing of the tracer owing to the "dead-leg syndrome," which follows cannulation of the femoral artery in dogs in hemorrhagic shock.

3. Extracellular fluid volume was measured in a series of nine patients undergoing open-heart surgical procedures and eight patients undergoing major general surgical operations. An increase in extracellular fluid volume was demonstrated. In the cardiac patients extracellular fluid volume increased by 9.0%, and interstitial fluid volume increased by 13.5%. In the general surgical patients extracellular fluid volume increased by 15.5%, and interstitial fluid volume increased by 22.8%. When correction was made for intravenous fluids administered and for urinary excretion of fluid during the course of the study, there was no change in postoperative extracellular fluid volume in either the cardiac patients (−0.6%) or the general surgical patients (+0.2%).

4. Ringer's lactate solution may be of theoretical benefit in treatment of the metabolic acidosis that accompanies profound hemorrhagic shock. The restoration of plasma pH to normal permits the myocardium to respond to the positive inotropic effects of endogenous catecholamines and may improve the circulation. Unfortunately, Ringer's lactate is a poor choice as buffer, since it is not effective until lactate ion has been metabolized in the liver. The high level of plasma lactate which characterizes hemorrhagic shock is evidence of the inability of the liver to metabolize lactate in the presence of a deficient blood flow. Clinical experience suggests that buffering ions which are immediately effective, such as bicarbonate, are superior to lactate in correcting the metabolic acidosis of shock.

5. The study of intercompartmental fluid shifts in the body during shock and during surgical operations provides an interesting and valuable avenue of investigation in the effort to improve the care of surgical patients. In particular, further study of the effect of altered hydrogen ion concentration on the chemical reactivity of long-chain protein molecules in the extracellular space seems promising. Both theoretical considerations and laboratory data, however, suggest that the size of the intercompartmental fluid shift, which accompanies the metabolic acidosis of shock, may be neither as large in magnitude nor as significant as that reported by other investigators. It is upon such reports that the current therapeutic use of massive amounts of Ringer's lactate solution is based.

It is concluded that until such time as scientifically acceptable evidence of a deficit in extracellular fluid volume in shock and during operation is presented, consideration of the extracellular fluid volume should not serve as the basis for loading patients with salt and water. It is our impression that the current interest in Ringer's lactate solution will have served as a valuable stimulus to the re-evaluation of present methods of fluid therapy. We support fully the view expressed by Moore and Shires[14]: ". . . the surgeon should carry on with his established habits of careful assessment of the patient's situation, the losses incurred, and the physiologic needs in replacement. The objective of care is restoration to normal physiology and normal function of organs, with a normal blood volume, functional body water, and electrolytes. This can never be accomplished by inundation."

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