line according to published guidelines for safe and effective use of these solutions. Despite appropriate use of HSS, the expected benefit of reduced fluid volume was not observed. Hypertonic sodium solutions had an adverse effect on patient outcome; the observed mortality was much greater than predicted and greater than that of a similar group resuscitated with LR several years earlier. Both the incidence of renal failure and patient mortality decreased markedly after reinstitution of LR resuscitation.

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Discussion

DR. DAVID N. HERNDON (Galveston, Texas): Dr. Williams, Dr. Copeland, Members, and Guests. The authors are to be congratulated on an arduous review of an extensive clinical population. Most large series reviewing the cause of death in burn patients have noted a marked decrease in the incidence of acute renal failure, particularly in the first week postburn.

Three decades ago, an incidence of acute renal failure in large burns of 30% to 50% was commonplace. Today, a less than 10% incidence of this complication is usually reported. The authors were understandably concerned when they noted a 40% incidence of renal failure in their burn patients treated in their intensive care unit between July of 1991 and June of 1993. Particularly disturbing was that 13 of these 65 patients developed renal failure during the first week postburn. The most common cause of early renal failure in burns has in the past been thought to be due to failure to maintain central venous pressure, arterial pressure and urine output at sometime during the early resuscitation, most frequently prior to hospitalization, a delay in re-

suscitation or an inadequate resuscitation before entrance into an intensive care unit. It's interesting that the 13 patients who developed acute renal failure in the hypertonic salt treatment group received larger salt and fluid loads than did those at the same time who did not develop renal failure. The authors infer that that larger salt and fluid load caused the renal failure rather than being from renal failure. Wouldn't it also be possible that increased salt and fluid load requirements were required by these patients because of the delay in resuscitation, a period of shock, a period of hypoperfusion to the kidney which resulted in a permeability edema consequent to the period of underresuscitation? The manuscript gives no data about resuscitation or time intervals prior to admission to the intensive care unit in any of the groups.

I'd like to ask the authors if they examined the records of these patients to see if there were delays or failures to maintain adequate resuscitation in the pre-admission period. Such factors would be expected to affect renal failure far more than the type of resuscitation fluid administered after admission to the ICU. Differences in transport and triage systems to the treatment unit could quite conceivably be different between the widely divergent time periods studied. The attending surgeons of the intensive care unit were different. Did they have different admission criteria? A prospective randomized study could have addressed variations that might have occurred over time. Barring that, an account of the primary contributor to renal failure should be documented in detail on all patients who developed it in both groups.

It would also be of interest to know when renal failure did first become apparent in the hypertonic saline patients, those 13 who developed it. How was this recognized early on? Were creatinine clearances available? Were early creatinines elevated? It would be surprising if salt loading would continue in patients showing early signs of renal failure.

Finally, the authors compare their mortality incidence during the different time period study with a predictor defined by Sherant et al., from an extensive series of patients treated at the Brooke Army Institute of Surgical Research between 1980 and 1984. The mortality of the patients seen during these authors' studies in 1986 and 1988, 1993, and 1994 were not different from Sherant's predictor. I don't really find that surprising; however, most subsequent series of patient studies have shown a decrease in mortality for major burns over time. Admittedly, large numbers of patients are required to substantiate variations in mortality from predicted as being other than statistical variation. But one would expect an improvement over time. A prospective randomized design might show a treatment effect on mortality in regards to the type of resuscitation instrument utilized with the numbers reported in this study. But the variation in time and the variations in early resuscitation techniques between the patient series decrease the statistical power of the study.

The authors' speculations remain extremely provocative and intriguing and I congratulate them on their extremely arduous effort.

DR. BENJAMIN F. RUSH (Newark, New Jersey): Dr. Williams, Dr. Copeland, Members, and Guests. I suspect one of the main values of my comments may be to give the authors an opportunity to think up answers to Dr. Herndon's battery of questions. I'd like to take everyone back some 42 or 43 years to an era when the young physicians in the MASHs of Korea were treating patients according to the recipe of the times, which was 1500 cc of glucose and water a day and all other resuscitation for hypotension was with blood. And the fact, of course, that the incidence of renal failure in those troops was actually the main cause of death in the soldiers who managed to reach the MASHs alive.

Now as Dr. Carey and others who were present in Viet Nam know, the Army set up dialysis stations all over Viet Nam, but the treatment had changed—they were dousing patients with Ringer's lactate freely—and renal failure was rarely seen. I guess what that comes down to is the kidney really needs a lot of free water to excrete and, of course, high sodium solutions don't have much free water present.

However, there is another aspect of this observation that is of special interest and, perhaps, an implication that needs to be looked at seriously. And that is that the kidney was not the only organ that seems to have suffered, at least according to this report. Going back again to the 1960s, Larry Finburg, pediatrician at Hopkins, invested a good deal of time looking into the effect of hyperosmolarity on the cell and concocted a hypothesis that under the stress of hyperosmolarity that the cell actually responds by creating what he called ediogenic osmoles produced by the breakdown of some of the proteins within the cell itself leading to cellular damage. I don't know if that explains the process that we have witnessed today, but it certainly may be an aspect that deserves further study, and I would be interested in hearing the comments of the authors on this point. Thank you very much for the privilege of the floor.

DR. WILLIAM W. MONAFO (St. Louis, Missouri): I sustained mild hypovolemic shock when I opened the abstract book and read this proposal. I do not think there is any argument that the results were very poor with the hypertonic saline in this study. The manuscript, which I received in ample time, implies that delayed onset of *de novo* renal failure—as late as 21 days after the resuscitation period—was somehow associated with the hypertonic resuscitation and that, perhaps, other organ dysfunction also was a late problem.

I interpret the data quite differently from the way the authors did. It seems clear that there were 13 patients, as Dr. David Herndon mentioned, who were resuscitation failures and who developed acute renal failure within the first week, as would be expected under resuscitation. Excluding these 13 patients, the mortality becomes 22 or almost identical to the predicted mortality of 23 by their step-wise logistic regression analysis. The question then becomes what occurred in these 13 patients. And—unfortunately, from my point of view—the manuscript gives the data combined on all 25 patients treated with the hypertonic saline, no matter when the renal failure developed, which was more than 21 days in five or six of the patients. In addition, beyond the sodium and water loads, there is no other hemodynamic or metabolic data that would permit one to assess what was going on; I think that this is a major difficulty with the paper.

I think it is important to point out that the fluids these authors used and the criteria that were used for the rate of their administration were quite different from those, to my knowledge, others who have used this method have employed. Specifically, they used a fluid containing 290 mEq/L of sodium, 160 mEq/L of

acetate, 28 of lactate and 89 of chloride, and this was given initially based on an arbitrary calculated sodium load. And that fluid then was discontinued if serum bicarbonate exceeded 30 mEq/L at which time a 3% sodium chloride solution that contains over 500 mEq/L of sodium was administered, again, at a rate determined by arbitrary calculated sodium load. Now this approach, I think, fails to account for the wide variability in response of patients with apparently similar injuries (which always has complicated the study of burn shock) and would also seem to invite a vicious circle of unnecessary large initial sodium loads with diuresis induced and progressive hypovolemia followed by the administration of very small volumes of 3% sodium chloride inadequate to maintain or restore circulating volume, which would then further decline.

Since the early 1970s, we and others have used, as was mentioned, a solution containing 250 mEq of sodium balanced with 100 mEq of lactate, containing also 154 mEq of chloride. No one, to my knowledge, has used 3% sodium chloride, in burn shock resuscitation. Finally, we use no predetermined criteria for the rate of fluid administration, but instead, have been extremely attentive to driving the urine flow rates only at or a little above 0.5 mL per kilo per hour in adults. And, also, to the best of my knowledge, others have not observed an inordinate incidence of renal failure, nor, certainly, have we. Further, our published early and late mortality data using this flexible and individualized—perhaps that's the problem—use of hypertonic sodium solutions has been in the expected range or even better, with the benefit being—unlike what was shown in this paper—a 30% to 40% reduction in the water load without an increase in the sodium load—again, contrary to what this paper shows. It's obvious that the therapeutic margin is narrow with this sort of treatment and, unfortunately, I think this paper demonstrates that.

I have a couple of questions. Did the patients with acute renal failure evidence severe alkalosis or elevations of the bicarbonate and/or was the 3% sodium chloride solution infused for prolonged periods in those patients? And, finally, how do you explain the more than adequate urine volumes in the renal failure patients? It seems paradoxical that they were secreting over a milliliter per hour, yet had renal failure. I thank the organization for the privilege of the floor.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): Dr. Williams, Dr. Copeland, Members, and Guests. Dr. Rush took us back to the Korean conflict, but we should go back one more conflict to World War II. The Board for the Study of the Severely Wounded evaluated hypertonic salt back then and found that it had no diuretic effect on patients whom they considered to be at risk of renal failure. I don't know where the concept of diuresis caused by hypertonic salt comes from, but there is a half-century of documentation that it doesn't work in hypovolemic patients.

Dr. Dimick and his associates have presented data which help define the clinical usefulness of hypertonic salt solutions. Their findings confirm that there is no diuretic effect associated with the use of hypertonic salt and indicate that in a setting of increased evaporative water loss and increased circulating levels of salt conserving hormones which characterizes the postresuscitation burn patient, the use of HSS appears to be deleterious and associated with an increased occurrence of renal failure.

Studies done by Dr. John Hunt at our burn center several years ago demonstrated that exchangeable sodium mass was elevated even at the 12th postburn day. That salt retention was accompanied by a proportional increase in extravascular water, which can complicate postresuscitation fluid management. The authors noted an increase in pulmonary complications in their hypertonic salt group, and I wonder how many of those patients developed evidence of pulmonary edema?

I have always thought that if there were a place for hypertonic salt in the resuscitation of burn patients, it would be in the elderly burn patient with limited cardiopulmonary reserve. However, Dr. Dimick and Dr. Rue note that the HSS patients who developed renal failure tended to be older, a very discouraging association. The HSS patients who did develop renal failure had a greater average sodium intake, 1.08 mEq per kilo per percent burn in the first 24 hours *versus* 0.7 mEq per kilo per percent burn in those who didn't develop renal failure. In light of that, I ask the authors whether they have identified a sodium intake which, when reached, necessitates administration of less concentrated solutions.

If one limits the acceptable serum sodium level to 165 mEq/L (these investigators used 160 mEq as their limit) the ECF expansion is progressively limited as the sodium concentration of the infusate increases. Since the volume contributed by the intracellular compartment is fixed by fixing the serum sodium concentration, the volume expansion affected by the fluid containing the infused salt also is reduced as the sodium concentration increases. In light of that, I ask why you chose a sodium concentration of 290 mEq/L and whether you have used more dilute but still hypertonic solutions, for example, the 250 mEq/L solution mentioned by Dr. Monafo.

Because renal failure can occur as a consequence of cardiovascular failure, were all of the renal failure patients contained in the group of patients who had cardiovascular failure? If so, was the magnitude or duration of cardiovascular failure related to the risk of renal failure? In that same vein, did you have occasion to measure blood volume in circulating levels of antidiuretic hormone to confirm the adequacy or inadequacy of blood volume restoration in the patients who received hypertonic salt?

I think this is an important paper with broad application. One of the signal accomplishments on our evolutionary trek was to heave ourselves out of the heated brine of the primordial ooze. Dr. Dimick and Dr. Rue have indicated that hypertonic salt is a fluid in search of a receptacle. They are telling us that life without brine is better and that the burn patient is not an appropriate receptacle for hypertonic salt solution. I thank the Association for the privilege of the floor.

DR. CHARLES G. WARD (Miami, Florida): Dr. Williams, Dr. Copeland, Members, and Guests. This work by my colleagues from Alabama is provocative because I use hypertonic solutions for burn patient resuscitation and I have not recognized an increased incidence in renal failure or death, both difficult to deny, and I have used it in both adults and children for the past 15± years. Why such a difference in experience?

Perhaps it is a difference in the kitchen from which these recipes come and, thus, the genesis for my questions. What is happening with the patient's urine output during resuscitation? Though sodium resuscitates the cell, as so aptly shown by Dr. Baxter and others, there is a minimum volume needed to carry

the sodium, and this must be met or renal failure is the result. During hypertonic resuscitation, additional volume is best met with standard Ringer's lactate to provide an adequate urine production, not more hypertonic solution. Electrolyte difficulties are best controlled during hypertonic solution resuscitation by stopping the hypertonic solutions when the serum sodium reaches 150 mEq or at 24 hours, whichever comes first. Have you considered stopping the hypertonic solutions earlier than 24 hours?

Lastly—and if can add anything additional to the group that has so aptly preceded me—for hypertonic solution resuscitation, has it been used in children? I have used it in such groups and found it to be useful in this patient population because it abrogates large fluid volumes when they may in fact create problems in this patient population. Hypertonic solutions are not useful in all patients, but they do become more universally applicable in larger and larger burns which have large surface area injuries and in patients with inhalation injuries. I thank the Association for the opportunity to offer my comments at this afternoon's session.

DR. L. W. RUE (Closing Discussion): I am very appreciative of all the discussants for their comments.

I guess we should start with Dr. Herndon's questions, and I will attempt to answer these in the order that they were provided to us. You mentioned the fact that some of the patients perhaps had a delay in resuscitation as being an explanation for the fluid requirements. Now basically, from the second and third time intervals we studied, there certainly was no difference in time from initial injury to when we received the patients. Most of them were transported within 12 to 24 hours following their burn injury. We did not have any differing admission criteria by attending surgeons. And, again, in the second lactated Ringer's group, as compared to the hypertonic resuscitation group, the same attending physicians were involved in the management of those patients.

You asked what we did when renal failure was recognized. I think it's important to stress that this was not a pure failure of resuscitation in the sense that the patients were profoundly hypotensive and did not really manifest the renal failure for about 4 to 5 days postresuscitation, so this wasn't like an acute event occurring within the first 48 hours. And what did we do when we recognized the renal failure? We attempted to optimize the patient's fluid status and undertake the usual maneuvers one would employ in an intensive care unit for renal dysfunction.

You asked why we didn't see a decrease in mortality over the time period when we used the Shirani predictor which was from patient data from 1980 to 1984. I'm not aware of any reports in the literature which would support dramatic improvements in outcome in a 10-year span. I would say that we did not use some of the newer treatment modalities, for example, high frequency ventilation for inhalation injury which has been demonstrated at the ISR to be beneficial in improving outcome. And that may explain the lack of an improvement, as our patients were managed with conventional ventilation much like the earlier Shirani patients.

Dr. Rusk, I appreciate your historic perspective on this problem. You mentioned that the kidney was not the only organ that suffered. And, indeed, I think that's true. I think the thing that was most impressive to us was that half of the patients that developed renal failure did so in the first week, and that the subsequent organ failures that occurred, I think, were partially driven by the initial renal failure. Many of the other organ failures that occurred, particularly the ones in which the patients developed renal failure in the 21-day period probably was a manifestation of multiple organ failure.

Dr. Monafo, you also took issue with renal failure occurring at 21 days and our association of that phenomenon with the resuscitation strategy. I would only point out that renal failure was encountered in both groups of patients and it was not necessarily our implication to say that the 21-day renal failure patients were a direct result of the resuscitation. But the disturbing factor, again, comes back to the fact that half of the renal failure occurring in the HSS patients developed within the first week, and the distribution of renal failure in our lactated Ringer's group, typically, was toward the latter part of their hospital stay. Now you asked what potentially occurred in these patients as a cause of their renal failure, and I think it relates somewhat, again, to the slide we demonstrated that these patients received large sodium loads and the fact that these patients tended to more avidly retain sodium and maintain this elevation and osmolarity for more prolonged periods of time. We chose 290 mEq *versus* 250 mainly to facilitate the ease in making this solution. Granted, it is 40 mEq more sodium than your original recommendation. You also questioned the use of acetate. If I recall correctly, the original recommendations of using hypertonic sodium lactate was as a theoretic source of bicarbonate. I would say that acetate is an equally effective one and perhaps somewhat better in that it can be metabolized by more organs than just the liver. The 3% sodium chloride was very rarely employed, as most of these patients never had bicarbs in excess of 30.

Dr. Pruitt, you mentioned the increase in pulmonary complications seen with hypertonic saline. Most of these were a consequence of infection and not pulmonary edema. You also mentioned or asked about the use of lower sodium content fluids. We did not employ any of those, and we have not measured any blood flow studies such as those done at the ISR, but that would be an intriguing thing to pursue.

And, finally, Dr. Ward, I compliment your success on using this resuscitation strategy for 15 years. Some of the advocates of this approach have noted that they have not seen the same findings we have. Unfortunately, the literature has no outcome data besides this one that compares these two resuscitation stratagems in any fashion. You have apparently used a sodium concentration of 150 as your upper limit. The published recommendations have been 160 mEq/L. You also asked if we should consider stopping the hypertonic saline before 24 hours. I would suggest that its major use would be perhaps at best in the first 8 hours postburn, as many centers are using.

I want to thank the discussants, again, for their comments. Many of you have been mentors and role models, and I am appreciative. And on behalf of my co-authors, I'd like to thank the Association for the privilege of presenting the data and allowing me to close the discussion. Thank you.