2000

SCUDDER ORATION

The Water of Life: A Century of Confusion

Charles E Lucas, MD, FACS

Each morning I give thanks for growing up in America, being a Fellow of the American College of Surgeons (ACS), and serving on the faculty at Wayne State University, the only school to be honored with three Scudder Orators who spent their entire careers at one institution. Their backgrounds say something about all three entities: Dr Alexander Walt, an immigrant who left his homeland because of apartheid to become my chairman and our president; Dr Anna Ledgerwood, a daughter of tenant farmers from the state of Washington, who became my longterm partner; and now, myself, the son of immigrant farmers—no kings or queens, just working bees.

Most Scudder Orations have dealt with philosophical, societal, or trauma system issues. Because my political acumen is lacking and my philosophical leanings are so far off the main stream that I believe that Adam and Eve came to earth on a spaceship, I have decided to discuss my favorite topic, namely, the pathophysiology of hemophagic shock and the resultant protein fluxes.

The Lucas clan emigrated from the West Coast of Ireland, where the "water of life" is known by the Gaelic term "uisce beatha." As one traveled across the Irish Sea to the East Coast of England, the "water of life" took on a new meaning one century ago when the great English physiologist, Ernest Starling, published his famous equation now known as the Law of the Capillary:

$$F_{H_2O} = KC \times SA\,[(Pc - Pi) - (OPi - OPc)]$$

where F_{H_2O} equals the flux of water across the capillary, KC equals capillary hydraulic conductivity, which is often mistaken for permeability, SA equals capillary surface area, Pc equals capillary hydraulic pressure, Pi equals interstitial hydraulic pressure, OPi equals interstitial oncotic pressure, and OPc equals capillary oncotic pressure.[1] Restated, this equation indicates that the extravascular flux of water is inversely related to capillary oncotic pressure as long as the other factors in the equation remain constant.

More than 100 years ago Starling emphasized that this is a two-compartment equation defining the relationship between plasma volume and interstitial space volume. Consequently, he emphasized that this equation could not be applied to man because man has a third space, namely, the intracellular compartment, and man also has an egress route from the second space, the interstitial fluid space, by way of the lymphatic system. Finally, Starling predicted one century ago that changes in one factor of the equation would affect the other factors, altering the rate of flux of water across the capillary membrane. This prescient prediction has since been confirmed.

Normal Physiology

Any serious discussion of the pathophysiology of hemorrhagic shock requires a brief review of normal physiology. A 70-kg person is composed of 60% total body water, or 42 L. This includes 28 L of intercellular water, which is divided into approximately 2 L of red cell volume and 26 L within muscles and organs. This same person has 14 L of extracellular water, which is contained within 3 L of plasma volume and 11 L of interstitial space fluid. The interstitial fluid, in turn, is primarily incorporated within the interstitial space matrix as part of the "gel" compartment, whereas a smaller portion of the interstitial fluid flows freely through the rivers and streams of the interstitial space matrix in the so-called "sol" component.

The capillary serves as the conduit for water, electrolyte, and protein delivery to the interstices, which, in turn, control the environment for optimal cellular homeostasis. Normally plasma contains 139 g of albumin. Contrary to a common misconception, the interstices contain 165 g of albumin. Each hour 7%, or 10 g, of albumin leaves the plasma and enters the interstitial space, where the albumin becomes attached to the interstitial space matrix. Concomitantly, in the balanced state, 10 g of albumin leave the interstitial space through the adjacent lymphatic channels and recirculate back into the plasma at a remote site. The differences in the

No competing interests declared.

Supported by the Interstitial Fluid Fund, Account 4-44966.

The Scudder Oration is delivered each year at the Clinical Congress of the American College of Surgeons. This lecture was delivered October 2000.

Received September 4, 2000; Accepted September 12, 2000.

From the Department of Surgery, Wayne State University, Detroit, MI.

Correspondence address: Charles E Lucas, MD, Department of Surgery, Detroit Receiving Hospital, 4201 St Antoine, Room 2V, Detroit, MI 48201.

ISSN 1072-7515/01/$21.00
PII S1072-7515(00)00761-4.

Table 1. Phases of Hemorrhagic Shock and Resuscitation

Phase I: Shock and active hemorrhage
Lasts from admission to end of operation for hemostasis
Phase II: Obligatory extravascular fluid sequestration
Lasts from end of operation to time of maximal weight gain
Phase III: Fluid mobilization and diuresis
Lasts from maximal weight gain to positive fluid balance

plasma-to-interstitial ratio of albumin (R_A) and the plasma-to-interstitial ratio of globulin (R_G) reflect a process known as capillary selectivity, whereby many small capillary pores and a few large pores favor the egress of lower molecular weight proteins.[2] These different sized pores have never been seen histologically, but have been envisaged from the mathematical derivation of fluid and protein contents in both the plasma and interstices. The matrix is composed of a coarse portion made up primarily of collagen and a fine portion composed of mucopolysaccharides, which, in turn, have ultrafine filaments known as proteoglycans.[2] Most of the interstitial water is attached to the "gel" matrix, where most of the sodium and albumin become attached to the proteoglycans. Interstitial matrix uncoiling or expansion favors this attachment by allowing the proteoglycans to lie free in the rivers and streams (sol) where sodium and albumin encounter and attach to the proteoglycans. This attachment parallels the increase in water content within the interstitial space. In contrast, matrix contraction, or coiling, causes the proteoglycans to be turned in toward the gel component of the matrix, thereby precluding sodium and albumin attachment.

The heart provides the hydrostatic forces that affect movement across the capillary wall; the kidneys serve as the main cardiovascular control organs for maintaining sodium and water balance.[3] This is done by way of the facultative hormones, aldosterone and antidiuretic hormone (ADH), which permit reabsorption of sodium and water from the distal nephron depending on the osmolar gradient within the inner medulla, or component three, of the kidney. This gradient, in turn, is regulated by the osmolar and oncotic forces within the inner medullary vessels and the loops of Henle.

The hemorrhagic shock insult

The hemorrhagic shock insult is triphasic and includes phase I, a period of shock and active hemorrhage that terminates at the end of the operation, which controls bleeding; phase II, a period of obligatory extravascular fluid sequestration, which averages 30 hours in patients receiving 15 blood transfusions for hemorrhagic shock during phase I; and phase III, a sequent mobilization period that averages 4 days in patients with the above severity of insult (Table 1). The patient presenting with an ACS class IV hemorrhagic shock insult has lost approximately 50% of his or her red cell mass and plasma volume.[4] Life is being sustained by the rapid movement of interstitial fluid into the plasma. Precapillary vasoconstriction reduces the hydrostatic egress of fluid, electrolytes, and protein into the interstitium, whereas interstitial matrix contraction replenishes plasma volume as electrolytes and protein are returned to the circulatory volume. Perioperative resuscitation with packed red cells and crystalloid solution restores both blood volume and interstitial space volume.

After intraoperative control of bleeding and restoration of blood volume, the patient often is oliguric. This is caused by the ongoing movement of fluid into the expanding interstitial and intercellular spaces. The resultant oliguria should be treated with additional crystalloid replacement. Diuresis, in this setting, will aggravate the trend toward hypovolemia, causing impairment organ perfusion, and threaten the development of acute renal failure.[5] A 500-mL bolus of balanced electrolyte solution infusion given over 15 minutes will promote a spontaneous diuresis and thereby guide subsequent therapy.

After successful operation, the patient enters into the obligatory sequestration phase, which is manifest by a modest rise in the intercellular fluid compartment and a marked expansion of the interstitial space. This leads to a reduction in plasma volume and plasma proteins with albumin relocation into the interstitial space.[6] Based on a multitude of clinical measurements, the typical total plasma albumin content will fall to about 70 g, while the rate of transcapillary albumin flux decreases to about 4 g per hour. These clinical observations totally destroy the misconception that phase II is caused by a capillary leak syndrome. Because the amount of albumin that enters the interstices is less than half of what normally exits the plasma, the only method by which hypoalbuminemia can develop must relate to the even slower movement of albumin out of the interstitial matrix into the lymphatics system. This can occur only if the interstitial space uncoils so that the proteoglycans lie free in the "sol" portion of the matrix and thereby attract and retain sodium and albumin.[7]

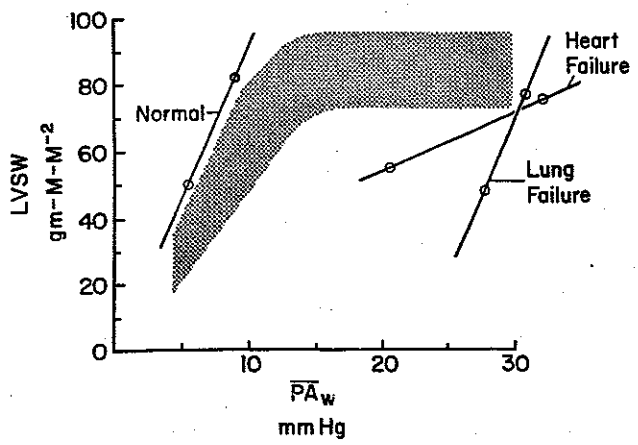

Figure 1. Francke-Starling curve showing relationship between left ventricular stroke work (LVSW) and pulmonary artery wedge pressure (PA_w).

An earlier misconception held that a loop diuretic given during phase II would prevent this fluid sequestration by increasing renal perfusion and filtration, mobilizing sodium and water from the plasma volume and, sequentially, the interstitial space, particularly the lung water component of the interstitial space.[6] This theory was assessed prospectively in 54 severely injured patients who had both renal artery and renal vein catheters in place to assess renal plasma flow, renal blood flow, renal flow distribution, filtration, and excretion.[8-10] These sophisticated studies showed that loop diuresis in the post-resuscitation sequestration phase simply causes sodium and water excretion without altering renal perfusion or interstitial space volume. So, diuresis in phase II worsens the hypovolemic insult and potentiates renal failure. Consequently, fluid therapy during the sequestration phase should be designed to maintain blood volume through the infusion of balanced electrolyte solution and red blood cells while accepting the obligatory expansion of the interstitial space.

During the transition from phase II to phase III, the period of fluid mobilization, there may be an acute increase in plasma volume with resultant hypertension and pulmonary dysfunction.[6] Fluid restriction and diuresis at this point may be life-saving. An earlier misconception held that the beginning of phase III represented the end of the so-called "capillary leak syndrome" so that there was no longer albumin efflux into the interstices. In reality, the amount of albumin that leaves the plasma is actually increased in phase III compared with phase II. More than 8% of the plasma albumin leaves the plasma each hour during phase III, compared with less than 6% that leaves during the period of extravascular fluid sequestration.[11] The differences between these two values are statistically significant with a p value <0.00005. Consequently, the progressive rise in the serum albumin during the mobilization phase reflects increased influx of albumin into the plasma by way of the lymphatic system. This phenomenon can occur only if the interstitial space matrix coils, forcing albumin off the proteoglycans for subsequent exit through the adjacent lymphatics.[7]

During the period of volume mobilization cardiopulmonary function is compromised. The distinction between fluid overload with heart failure as opposed to a pulmonary dysfunction from hemorrhagic shock insult without heart failure was also addressed by Starling. The Francke-Starling curve shows that patients with oliguria and hypotension who respond to a fluid bolus with a slope of left ventricular stroke work and pulmonary wedge pressure ratio that parallels the normal slope do not have heart failure, even though the wedge pressure may be markedly elevated (Fig. 1). Such patients need additional volume expansion.[12] In contrast, a precipitous rise in wedge pressure in response to this bolus infusion resulting in a flat slope indicates cardiac compromise and need for inotropic support (Fig. 1). After resuscitation from severe hemorrhagic shock, a patient with a high central pressure and low perfusion pressure who responds with a marked rise in perfusion pressure and little change in central pressure has lung failure and not fluid overload. Treatment of the low pressure and oliguria, in this setting, should be with additional fluid replacement.

The colloid/crystalloid controversy

The greatest confusion regarding the Starling equation led to the famed, or infamous, colloid/crystalloid controversy. Attempting to address this issue, a prospective randomized study was conducted over 2 years for patients requiring multiple transfusions for hemorrhagic shock after injury.[8-10,12] Ninety-four patients who received an average of 15 blood transfusions during phase I were randomized with 46 patients allocated to receive supplemental albumin during resuscitation. This study demonstrated that the albumin-supplemented patients had an increase in serum albumin, plasma volume, and effective renal plasma flow (Fig. 2). Despite the increase in renal perfusion there was a decrease in glomerular filtration, sodium clearance, osmolar clearance, and urine output. The decrease in filtration was caused by a

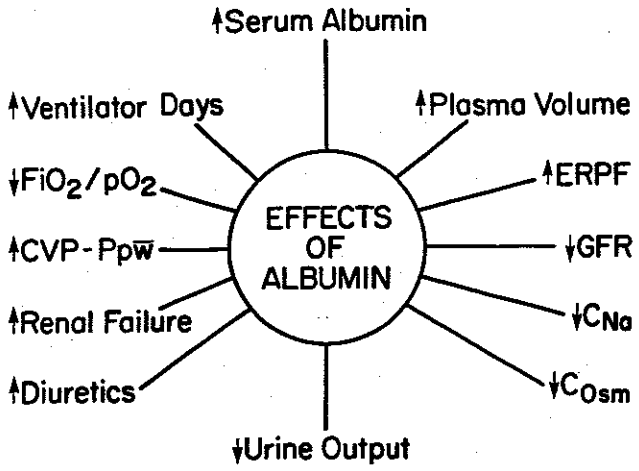

Figure 2. Effects of albumin. C_{Na}, sodium clearance; C_{Osm}, osmolar clearance; CVP-Ppw, central filling pressures; ERPF, renal plasma flow; FiO_2/pO_2, inspired oxygen/arterial oxygen pressure; GFR, flowtration rate. All arrows indicate significant differences in albumin-supplemented patients versus crystalloid patients.

rise in oncotic pressure within the glomerular tuft, which functions as a modified capillary. The decrease in sodium and osmolar clearances was from the increase in the oncotic pressure of the interstices of the inner medulla brought about by the increased oncotic pressure of the peritubular vessels and the loops of Henle. This resultant increase in the interstitial-tubular oncotic gradient augmented sodium and water reabsorption in response to the facultative hormones, aldosterone and antidiuretic hormone. The reduction in water and sodium excretion caused an increased need for diuretics, a higher incidence of renal failure, increased central filling pressures, impaired oxygenation, prolonged number of days on a ventilator, and an increased mortality rate. All of these effects were statistically significant.

Effects of nonalbumin protein fluxes

The most interesting byproduct of this study was the observation that albumin-supplemented patients had a decrease in all of the globulin fractions with the single exception of alpha-I globulin. The decrease in the globulin fraction included all of the immunoglobulins, alpha-II globulin, beta globulin, and gamma globulin.[8] This finding raised the question as to whether reductions in immunoglobulins altered the immune mechanism. Most patients had received tetanus toxoid. Analysis of deep frozen sera demonstrated that the reduction in the immune globulins was associated with a significant decrease in the response to tetanus toxoid in the albumin-supplemented patients.

Table 2. Albumin Supplementation and Coagulation Activity

Phase	Albumin patients*	Crystalloid patients
Phase II (U)	4.6	3.2
Phase III (U)	2.3	0.9
Phases II and III (U)	6.9	4.1
Patients matched for insult severity		
Phases I and II (U)	5.6	3.1

*<0.05.

Another interesting byproduct of this randomized clinical trial was the observation that albumin-supplemented patients required more units of blood transfused during both the sequestration phase and the subsequent mobilization phase.[9] During the first 5 postoperative days, albumin-supplemented patients required an average of 6.9 U blood transfusions compared with 4.1 U blood transfusions in the patients not receiving supplemental albumin (Table 2). These changes appeared to occur despite a comparable hemorrhagic shock insult. Patients matched for number of minutes in shock and number of blood transfusions given during phase I showed the same phenomenon (Table 1). Subsequent assessment of coagulation activity in these patients demonstrated a decrease in fibrinogen activity and a prolongation of prothrombin time associated with the supplemental albumin resuscitation. Measurement of deep frozen sera in these same patients confirmed that the actual protein contents of both fibrinogen and prothrombin were decreased in the albumin-supplemented patients.

Protein fluxes reproduced in canine shock model

Results demonstrated in a prospectively randomized clinical trial ought to be reproducible in a controlled experimental shock model. Using a modified Wiggers canine hemorrhagic shock model these observations were tested in animals receiving shed blood plus crystalloid solution, compared with animals who also received supplemental colloid. These experimental studies duplicated the clinical findings.[13] There was a significant decrease in the activities of fibrinogen, prothrombin, and factor-VIII in the albumin-supplemented animals compared with the crystalloid group (Table 3). This decrease in coagulation activity was associated with a decrease in factor-VIII content, which is the only canine coagulation factor for which one can measure the actual protein content (Table 3). All of these changes were statistically significant.

Table 3. Effects of Albumin on the Canine Coagulation Profile

Profile	Albumin supplementation*	Crystalloid
Coagulation activity		
Fg: C (mg/dL)	274	423
Factor II: C (%)	141	67
Coagulation content		
Factor VIII: Ag (%)	53	64

*$p < 0.05$.
C, coagulation; Fg, fibrinogen.

The fluxes of albumin and globulin after resuscitation from shock also duplicated those seen in the clinical setting.[14] The albumin-supplemented animals had a prompt rise in serum albumin, but a simultaneous fall in the globulin fraction immediately after resuscitation when compared with the crystalloid group.[14] This regimen of resuscitation was continued for two additional days and repeat measurements done on day 3 showed an even more striking increase in serum albumin and reduction in serum globulin in the albumin-supplemented animals.

These results prompted the question as to how a nonphysiologic colloid such as hydroxy ethyl starch (HES) would affect these protein fluxes.[15] The shocked animals receiving HES-supplemented resuscitation had a prompt decrease in both serum albumin and serum globulin fractions immediately after resuscitation when compared with the crystalloid group. These changes were more pronounced by postresuscitation day 3 (Table 4). Thoracic duct lymph measurements demonstrated that HES forced both the albumin and the globulin fractions into the interstitial space, as is reflected by the increase in thoracic duct protein concentrations. The thoracic duct lymph protein concentrations approached the serum concentrations by day 3 in the HES-supplemented animals (Table 3).

Table 5. Effects of Hydroxy Ethyl Starch on Coagulation

	Hydroxy ethyl starch (%)*	Crystalloid (%)
Posttherapy		
Fibrinogen: Coagulation	37	63
Factor II: Coagulation	73	76
Factor VIII: Coagulation	42	91
Day 3		
Fibrinogen: Coagulation	67	96
Factor II: Coagulation	42	83
Factor VIII: Coagulation	40	95

*$p = < 0.05$.

Table 4. Effects of Hydroxy Ethyl Starch Supplemented Resuscitation on Protein Fluxes

Protein fluxes	Hydroxy ethyl starch*	Crystalloid
Postresuscitation (g/dL)		
Albumin	1.5	2.8
Globulin	1.8	3.5
Day 3 (g/dL)		
Albumin	1.9	2.5
Globulin	2.0	3.1
Thoracic duct lymph: Day 3 (g/dL)		
Albumin	1.9	1.3
Globulin	1.9	1.38

*$p < 0.05$.

HES also adversely affected the coagulation profile.[15] The HES-supplemented animals had a significant decrease in fibrinogen activity and factor-VIII activity immediately after resuscitation. These decreases in fibrinogen and factor-VIII activity persisted through the postresuscitation period (Table 5).

Metaanalysis of clinical trials of albumin therapy

The Cochran Injuries Group of reviewers in Oxford, England, analyzed all prospective clinical studies regarding albumin resuscitation in critically injured patients. They performed a metaanalysis that showed a higher mortality rate in patients randomized for albumin supplementation.[16] They concluded, in 1998, that "albumin should not be used outside the context of a properly conceived and rigorously controlled trial with mortality as the endpoint." Based on these findings, the FDA has subsequently reached the same conclusion and made the same recommendation. One century after publishing the "Law of the Capillary," Starling can now rest in peace knowing that colloid supplementation will no longer be used on the basis of a misinterpretation of his fine work.

The Century of Enlightenment

Nobody presents a Scudder Oration without the support of many family and colleagues. My eldest, Dr Norene Lucas, a research physicist who departed this earth before her time from ovarian cancer, was a constant source of scientific and academic challenge. She would have encouraged me to no longer dwell on past history, but to reach out to the future during the 21st century, the Century of Enlightenment.

There will be an increasing interest in our trauma surgeons to be involved in all aspects of critical care. This interest will, in part, be stimulated by the addition of a

chapter on critical care in the Advanced Trauma Life Support course being offered by the ACS throughout the world. These trauma surgeons with special interest in the physiology of burns will demonstrate that the fluid sequestration phase after burn injury is from interstitial fluid space expansion with sodium and protein retention on the proteoglycans and has nothing to do with the so-called "capillary leak syndrome." The detrimental effects of the colloid-supplemented resuscitation of burn injury will be documented; the excellent paper presented by Dr Cleon Goodwin at the Western Surgical Association will see the light of day. Although there will be a flurry of industry-sponsored studies to look at the shortterm effects of colloid supplementation for hemorrhagic shock and burn injury, the trauma surgeon of the future will mandate that the endpoint of such studies include detailed organ function monitoring, fluid shift changes, length of stay, and mortality rate.

The most important advance that will happen in the Century of Enlightenment will be a reorientation toward the relationship between the capillary wall and total body homeostasis. Somehow, as we evolved from the Big Bang through one-celled animals to multicelled animals and finally to Man, we forgot that the cell is the control center for the organism, whereas the capillary is simply its servant. Starling's Law of the Capillary has been misinterpreted.[1] Too much emphasis has been placed on the teleologic importance of the capillary membrane in contradistinction to the interstitial space matrix and the cell.

The Century of Enlightenment will accept the Theory of Oncotic Balance, which defines the regulatory forces of the plasma and interstitial oncotic pressures. This plasma-to-interstitial oncotic ratio is rigidly maintained in the normal state. Insults such as hemorrhagic shock, sepsis, or burns lead to a new plasma-to-interstitial oncotic ratio, which is likewise rigidly maintained. The level of severity for each specific insult yields a ratio that changes only when the severity of insult changes.

The current concept that the capillary controls this oncotic ratio, as has been promulgated by the misinterpretation of Starling's Law, will be rejected. Trauma surgeons during the Century of Enlightenment will recognize that three-dimensional, or stearic, changes within the interstitial matrix are responsible for maintaining this ratio by a complex system of protein and sodium attachments or rejections, which, in turn, are regulated by these stearic changes.[16] When the matrix, like a hemp rope, contracts, the fine proteoglycans coil on themselves, thereby precluding sodium and protein adherence. In contrast, the uncoiled matrix promotes sodium and protein attachment, preventing reentry into the plasma by way of adjacent lymph channels. The results of future studies will demonstrate that the cell, through a complex system of release mechanisms, controls these three-dimensional structural changes within the interstitial matrix.

The current concept of capillary selectivity will be modified. The larger plasma-to-interstitial ratio of albumin compared with that of globulin is thought to reflect the presence of a few large pores interspersed with many small pores in the capillary wall, favoring the extravascular flux of smaller molecular weight proteins. These pores have never been seen histologically, but are simply mathematical ideations derived from observed protein fluxes. Future scientists will recognize that the geometric configuration of the interstitial matrix, allowing smaller proteins to enter all fluid channels in the "sol" portion while higher molecular weight proteins are confined to the larger rivers and streams, controls the process known as selectivity. In contrast to the elusive, putative capillary pores, these structural changes in the matrix can be identified microscopically.[17] Future physiologists will learn that artificial methodologies, such as venous hypertension, for studying the capillary membrane have little bearing on the surgical challenges of hemorrhagic shock and sepsis; they will shift their emphasis in studies of hemorrhagic shock and sepsis, and include analyses of the interstitial space in their protocols.

This Theory of Oncotic Balance does not contradict Starling's Law of the Capillary, but simply shifts the emphasis of control from the capillary wall to the interstices. These matrix changes, in turn, are controlled by the cellular release factors. Just as the Theory of General Relativity gave full meaning to Newton's Law of Gravity, so will the Theory of Oncotic Balance define how cellular release factors cause the matrix changes resulting in movements that have been attributed to the porous capillary wall. Future physiologists will teach medical students that these matrix changes, particularly the configuration of the proteoglycans, determine the extent of protein movement across the capillary wall and the extent of protein movement into the lymphatics for the journey back to the plasma.

The Theory of Oncotic Balance applies to other insults besides hemorrhagic shock. When a 37-year-old patient received radiation therapy and chemotherapy followed by an esophagectomy for esophageal cancer, he developed a thoracic duct fistula through which many proteins of all sizes were lost. This would be an example of postnodal lymph drainage.[18] By 10 postoperative days he had severe hypoalbuminemia (1,000 mg/dL) and hypoglobulinemia (1,100 mg/dL). His thoracic duct lymph concentrations of albumin (380 mg/dL) and globulin (190 mg/dL) were also very low. Within 60 minutes of starting an infusion of human serum albumin, the serum albumin concentration more than doubled (2,100 mg/dL) while the serum globulin concentration fell (850 mg/dL). Simultaneously, he had a marked rise in thoracic duct albumin (610 mg/dL) and globulin (310 mg/dL). These changes began within 15 minutes of initiating the infusion.

An elderly woman was operated on for a giant cyst adenocarcinoma of the ovary complicated by *Clostridia perfringens*-induced gangrene. After pelvic clean-out, she was extremely septic, sequestered a great deal of fluid, and developed skin blisters, one of which ruptured. She was severely hypoalbuminemic (700 mg/dL) and hypoglobulinemic (1,000 mg/dL). The blister fluid, which would be representative of prenodal lymph, showed that the concentration of albumin (190 mg/dL) and globulin (170 mg/dL) were also low.[18] During a human serum albumin infusion she had a prompt rise in serum albumin (1,300 mg/dL) and a fall in serum globulin (700 mg/dL); this was associated with a prompt rise in blister fluid albumin (380 mg/dL) and globulin (290 mg/dL). Both the serum and lymph protein concentrations in these patients returned to preinfusion levels within 4 hours of completing the infusion.

The rapid changes in protein fluxes identified in animal models and seen above in clinical measurements will provide data for the enlightened physiologist of the future to teach that the so-called period of "protein equilibration" in the interstitial space is not 24 hours or even 12 hours, but occurs much more rapidly in the seriously injured or septic patient.[2] This recognition will stimulate funding agencies to downgrade research projects that do not include analyses of interstitial space dynamics as part of their methodologies.[17] The measurements of serum cytokines, prealbumin, and other small peptides, or cellular release factors attached to protein moieties in isolation will no longer be funded because all these substances may relocate into the interstitial space and circulate through the lympathic system.[18,19] Isolated serum changes have absolutely no meaning. Stimulated by the advances made in our understanding of the control of oncotic balance, a Scudder Orator of the future will present the Theory of Osmotic Balance, which is likewise mediated by cellular release factors and is specific for the severity of insult whether the insult be hemorrhagic shock, sepsis, or burns.

The naysayers will challenge the teleologic purposes for these remarkable expansions of the interstitial space in association with albumin and sodium relocation. Future physiologists will teach that interstitial space expansion is associated with a reduction in interstitial space compliance. This, in turn, facilitates easier access of nutrients from the capillary wall to the cell and easier egress of cellular metabolites for subsequent excretion. These functions will be recognized as important for total cellular homeostasis. Balanced electrolyte solution will be accepted as the true water of life, "uisce beatha."

Acceptance of the Theory of Oncotic Balance as part of total homeostasis leads to inevitable conclusions about the ultimate benefit, or lack thereof, with other resuscitation fluids. Hypertonic saline resuscitation will be shown to delay interstitial space expansion, delaying cellular homeostasis. The current confusion that hypertonic saline resuscitation will reduce the release of harmful vasoactive cytokines will be identified as a myth. Clinical studies will demonstrate that early hypertonic saline resuscitation will inevitably be followed by a full crystalloid resuscitation in order to maintain perfusion pressures which, in turn, will be associated with the systematic release of the same cytokines once the interstitial space has become hydrated. The continued affection for colloid-supplemented resuscitations in some quarters will be blunted by the realization that colloid supplementation causes excessive plasma volume expansion at the expense of the heart and lungs, with delayed interstitial space filling, which is necessary for cellular homeostasis.[15,20] Movement of the colloid particles, whether they be albumin or artificial, will become enmeshed within the matrix, causing a prolongation in the fluid sequestration phase and all of the harmful organ effects associated with that phenomenon. Finally, the combination of hypertonic saline with colloid supplementation will lead to the detrimental effects of both solutions used independently. Physiologists in the Century of Enlightenment will reconfirm our salt-water or-

igins and the fact that optimal homeostasis is provided by hydration of the interstitial space.

The presentation of any new theory that challenges long-held beliefs will be attacked with great energy. Some of these attacks will be vicious and personal, just as they were when we reported the detrimental effects of resuscitation in those patients randomized for albumin supplementation. I look forward to these attacks, especially when they are reinforced by data.

REFERENCES

1. Starling EH. On the absorption of fluids from connective tissue spaces. J Physiol 1896;19:312–326.
2. Humphries MJ. Peptide sequences in matrix proteins recognized by adhesion receptors. In: Rohrbach DH, Timpl R, eds. Molecular and cellular aspects of basement membranes. San Diego: Academic Press; 1993;289–308.
3. Lucas CE, Harrigan C, Denis R, Ledgerwood AM. Impaired renal concentrating ability during resuscitation from shock. Arch Surg 1983;118:642–645.
4. Committee on Trauma of the American College of Surgeons. Advanced trauma life support course for doctors. 6th ed. American College of Surgeons: Chicago, IL: 1997;87–124.
5. Lucas CE, Zito JG, Carter KM, et al. Questionable value of furosemide in preventing renal failure. Surgery 1977;82:314–320.
6. Dawson CW, Lucas CE, Ledgerwood AM. Altered interstitial fluid space dynamics and postresuscitation hypertension. Arch Surg 1981;116:657–662.
7. Saxe JM, Ledgerwood AM, Lucas CE. Principles of resuscitation. In: Geller ER, ed. Shock and resuscitation. Cambridge, MA: McGraw-Hill Book Co; 1993;147–179.
8. Clift DR, Lucas CE, Ledgerwood AM, et al. The effect of albumin resuscitation for shock on the immune response to tetanus toxoid. J Surg Res 1982;32:449–452.
9. Lucas CE, Ledgerwood AM, Mammen EF. Altered coagulation protein content after albumin resuscitation. Ann Surg 1982; 196:198–202.
10. Lucas CE, Ledgerwood AM, Higgins RF, Weaver DW. Impaired pulmonary function after albumin resuscitation from shock. J Trauma 1980;20:446–451.
11. Lucas CE, Benishek DJ, Ledgerwood AM. Reduced oncotic pressure after shock. Arch Surg 1982;117:675–679.
12. Dahn MS, Lucas CE, Ledgerwood AM, Higgins RF. Negative inotropic effect of albumin resuscitation for shock. Surg 1979;86:235–241.
13. Leibold WC, Lucas CE, Ledgerwood AM, et al. Effect of albumin resuscitation on canine coagulation activity and content. Ann Surg 1983;198:630–633.
14. Denis R, Smith RW, Grabow D, et al. Relocation of nonalbumin proteins after albumin resuscitation. J Surg Res 1987;43:413–419.
15. Lucas CE, Denis R, Ledgerwood AM, Grabow D. The effects of hespan on serum and lymphatic albumin, globulin, and coagulant protein. Ann Surg 1988;54:434–437.
16. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: Systematic review of randomized controlled trials. BMJ 1998;317:235–240.
17. Saxe JM, Dombi GW, Lucas WF, et al. Hemodynamic, plasma volume, and prenodal skin lymphy responses to varied resuscitation regimens. J Trauma 1996;41:283–290.
18. Adair TH, Guyton AC. Modification of lymph by lymph nodes III effect of increased lymph hydrostatic pressure. Am J Physiol 1985;249:777–781.
19. Powers MR, Wallace JR, Bell DR. Initial equilibration of albumin in rabbit hind paw skin and lymph. Am J Physiol 1988;254:89–101.
20. Elliott LA, Ledgerwood AM, Lucas CE, et al. Role of Fluosol-DA 20% in prehospital resuscitation. Crit Care Med 1989;17:166–172.