THE 1994 PRESIDENTIAL ADDRESS
Accepting the Challenge

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The challenge facing burn care today is the union of the natural development of research advances and burn care pioneered by our predecessors within the exigencies of imminent health care reform. Broadly stated, the objectives of health care reform are to provide all Americans with quality care while simultaneously reducing the percentage of the gross national product expended in these efforts.

Many concerns about reform have been raised among burn care workers, the most salient of which is an implied rationing of overall health care resources that would restrict the performance of certain high-risk interventions. As an example some have suggested that organ transplants be limited to low-risk groups or, in our area, that very large burns should not be resuscitated. A further concern is that emphasis on cost reductions might inhibit the development of new drugs such as antibiotics to treat ever-evolving resistant organisms, recombinant genetic products to modulate the host immune or metabolic response to burns, or to improve wound healing.

In this type of environment our challenge is to demonstrate unequivocally which patients will benefit from particular therapies by performing long-term studies that focus on improvement of quality of life, to critically examine treatments accepted in the past and those newly developed treatments that demonstrate efficacy and cost savings through prospective clinical trials, and to develop studies and programs that lead to prevention and early diagnosis of disease, which could offset health care costs.

During the history of the American Burn Association, there has been a marked decrease in burn-related mortality, particularly in patients younger than the age of 35 years. From 1942 to 1952 a 50% total body surface area burn killed nearly half the young people, whereas now a 98% total body surface area burn kills only half the young people who receive it. The advances that have led to this decrease in burn-related mortality in young patients are due to a better understanding of how to resuscitate burns, control infection, support the hypermetabolic response, early closure of the burn wound, and prevention. I would like to discuss the advances that have occurred and give examples of the challenges that face us in each of these particular areas.

RESUSCITATION

In terms of resuscitation, formulas developed by our predecessors, the Evans formula, the Brooke for-
mula, and the Parkland formula, all differ in the amount of colloid given, but all adequately resuscitate patients so that renal failure has ceased to be a major cause of death in burns. Variations in these resuscitation formulas were pioneered by Monarco and Larson. These variations include a hypertonic salt resuscitation that is most appropriate for the elderly and a body surface area formula for children.

In the next decade our challenge goes beyond modifying the components of fluid resuscitation to pharmacologic modulation of the vascular response to burn and smoke inhalation injury. For example burn injury can be adequately volume-repleted and yet perfusion to vital organs such as the gut not adequately restored.

Burn injury causes a decrease in mesenteric blood flow despite normalization of central venous pressure and cardiac output, which leads to bacterial translocation across the gut wall. A decrease in gut mucosal integrity causes an increase in gut permeability, allowing bacteria to cross into the mesenteric lymph nodes and seed distant organs. In experimental burn models blood flow to the gut decreases by approximately 40% despite adequate urinary output, cardiac output, and perfusion of the rest of the body. In experimental models, decreases in mesenteric blood flow caused by burn or mesenteric arterial occlusion can cause bacterial translocation to lymph nodes and systemic organs. The decreases in blood flow seen after burn and increases in bacterial transit across the gut wall may be reversed by pharmacologic modulation of the response. Nonspecific vasodilators such as nitroprusside can restore blood flow and decrease bacterial translocation. Resuscitation formulas using hypertonic saline solution and dextran, agents that block prostanooids or vasopressin production can also restore blood flow and attenuate bacterial translocation. The challenge is to institute prospective randomized clinical trials of agents that preserve vital organ blood flow during burn shock.

Currently the primary determinant of burn mortality is smoke inhalation injury. In patients with large burns the additional mortality caused by the presence of an inhalation injury is approximately 50%. Burn and smoke inhalation-injured patients demand a much larger resuscitation volume than patients who do not sustain such combined injury. More fluid (2 ml/kg/percent burn) is required in these patients, and when withheld they paradoxically experience an increase in microvascular permeability. An initial increase in extravascular lung water and a fall in arterial oxygenation occurs in the first 10 to 20 hours after injury, but between 20 and 100 hours after injury, extravascular lung water is essentially normal. It is during this latent period that pharmacologic modulation of the smoke inhalation injury response should occur.

The initial response to smoke is destruction of the ciliated epithelium, which in combination with transudated plasma forms casts that can block the tracheobronchial tree during the first 24 to 48 hours after injury. Pathophysiologic effects include a fall in arterial oxygenation, atelectasis, and emphysema in the distal lung behind bronchi that are obstructed with these inspissated casts.

Forty-eight hours after injury pulmonary edema from increased microvascular permeability begins flooding the alveoli, resulting in an end-stage lung showing areas of atelectasis and flooded pulmonary parenchyma. During the initial exposure to smoke there is a release of thromboxane that causes an increase in pulmonary artery pressure in combination with airway cast formation. These two phenomena cause a fall in arterial oxygenation. There is an activation of pulmonary macrophages, which recruit polymorphonuclear leukocytes to the lung. These polymorphonuclear leukocytes are markedly increased in number at 24 and 48 hours after injury. In parallel with their appearance in the lung is the production of proteolytic enzymes such as elastase or trypsin. It is these substances that cause an increase in microvascular fluid formation, an increase in lymph flow, and lung water appearance. Animals that have been depleted of polymorphonuclear leukocytes do not have this endstage pulmonary edema after smoke injury. It is not practical to deplete patients of polymorphonuclear leukocytes, but randomized prospective studies using antiadherence antibodies are currently underway in an attempt to decrease pulmonary edema after lung injury.

Trials using agents that block thromboxane production and substances which interfere with proteolytic enzyme production have decreased lung fluid formation after smoke injury. Free oxygen scavenging agents such as dimethylsulfoxide or n-acetylcysteine can be given as aerosols to decrease lung fluid formation. In one series of experiments a dose of smoke that uniformly killed 100% of the animals was made 50% lethal by given aerosolized dimethylsulfoxide or by giving aerosolized heparin. A combination of the two, which scavenges free radicals and prevents cast formation, converted a 100% lethal injury to one that was uniformly survived. The challenge of the coming decade is not just in providing adequate amounts of fluid in the first 24 to 48 hours after injury, but it is in reversing the release of mediators that lead to increased mesenteric vascular resistance, peripheral edema after burn injury, and pro-
gressive destruction of the lung after smoke inhalation injury.

We believe that chemicals in smoke directly damage epithelial cells, causing a release of chemotactic factors that prime neutrophils. Their release of oxygen radicals and proteolytic enzymes in combination with prostanooids leads to vasoconstriction and the formation of airway casts, which leads to progressive pulmonary failure. All of these steps can be inhibited or modulated pharmacologically as a part of burn resuscitation. Our challenge is to organize multicenter, randomized, prospective trials of such therapies. Because of the high mortality of smoke injury, the number of patients required to demonstrate a treatment effect cannot be easily obtained by a single unit.

CONTROL OF INFECTION

The second major contributor to the decrease in mortality for patients with thermal injuries has been advances in control of infection. Our predecessors devised topical antimicrobial agents such as silver sulfadiazine, developed by Dr. Charles Fox in New York,\textsuperscript{21} mafenide acetate,\textsuperscript{22} developed by Doctors Lindberg, Moncrief, and Pruitt at the Institute of Surgical Research in San Antonio, and silver nitrate, developed by Dr. Moyer in St. Louis. All these agents decreased the incidence of mortality from sepsis in major burns.

More recently the use of oral prophylaxis and topical use of mycostatin as described by Desai have been of great utility in decreasing the rate of candida infection.\textsuperscript{23,24} Frequent use of biopsies to vary the use of topical antimicrobials and to guide administration of systemic antimicrobials was popularized by Doctors Robson and Krizek.\textsuperscript{25} Unfortunately the development of new antimicrobials has not kept pace with the development of resistant organisms.

In the next decade multiply resistant organisms will develop unless new drugs are formulated. Immune deficiency after major burn injury is an area of major interest with prospective studies of such agents as isoprinosine, interleukin-5, and interleukin-2\textsuperscript{26} geared toward improving immune responsiveness are currently underway.

SUPPORT OF THE HYPERMETABOLIC RESPONSE

A third area that has contributed to decreased mortality from burns has been the support of the hypermetabolic response to trauma. After burn injury metabolic rate increases up to 100% above normal. This is paralleled by a marked increase in glucose flow as described by past presidents Pruitt and Mason.\textsuperscript{27} The increase of glucose flow is paralleled by increased production of glucagon, catecholamines, and corticosteroids with low to near normal insulin levels. The catabolic hormones cause a loss of nitrogen from the body, and before the era of maximal caloric supplementation, a total body weight loss of 25% over time was typical. Catecholamines, glucagon, and gluco- corticosteroids cause an erosion of peripheral muscle mass to supply the large amounts of energy required of the voracious anaerobic burn wound.

In the early 1970s, Dr. P. William Curreri devised a formula for adults to maintain total body weight during hospitalization,\textsuperscript{29} and Dr. Duane Larson devised one that maintained total weight in children.\textsuperscript{30} With these formulas enteral feeding for maximal caloric intake was accepted; however, patients had difficulty tolerating the volumes and rates of feeding, and catabolic weight loss continued.

During the beginning of the last decade, it was demonstrated that juvenile dogs could grow and function normally with no other food than provided by total parenteral nutrition. A randomized prospective study was not done, but the burn community embraced this new therapy, and widespread implementation of this mode of caloric supplementation proceeded. Unfortunately, when a controlled randomized prospective study was done comparing enteral feeding with total parenteral nutrition, those who were supplemented with total parenteral nutrition had a profound immune suppression with elevated suppresser to helper cell ratios relative to those fed only what they could tolerate enterally. Mortality was markedly elevated in patients receiving total parenteral nutrition compared with those who were fed enterally.\textsuperscript{31,32} Our challenge is to critically evaluate our current accepted therapies and new modalities with the use of randomized prospective clinical trials. Standard of care is now continuous enteral feeding beginning within hours of the time of injury and proceeding through operative procedures, but the composition of diet and additives such as glutamine, fish oil, vitamin E, and arginine must be examined.

Maintenance of temperature decreases metabolic expenditure, and use of antianxiety agents, pain medicines, and agents that decrease cardiac work such as propranolol\textsuperscript{23} or metoprolol have been advocated,\textsuperscript{34} but patients still lose peripheral protein. In a chronic study that examined children with greater than 40% total body surface area burns, there was a true growth arrest. Weight velocity was massively decreased below the 5th percentile for boys and girls at 1 year after injury. Height velocity was retarded for up to
2 years after the time of injury in both boys and girls.\textsuperscript{35} The children were small in stature and peripherally thin.

The growth arrest in large burns stimulated a prospective randomized study that gave an anabolic agent, recombinant human growth hormone, to combat the catabolic response of the hypermetabolic response. A randomized prospective trial was done that compared placebo with 0.2 mg/kg/day recombinant human growth hormone injected subcutaneously in matched patients with a burn size of approximately 60% total body surface area and a mean age of approximately 8 years. There was a decrease in donor site healing time from 8.5 days to 6.4 days in the treated individuals. This translates into a decrease in length of hospital stay from 0.97 day per percent full-thickness burn to 0.66 day per percent full-thickness burn. The decrease in length of hospital stay was even more dramatic when calculated on the basis of third-degree burns. Hospital stay was decreased from 1 day per percent full-thickness burn in the placebo treated individuals to 0.66 day per percent full-thickness burns in those treated with recombinant human growth hormone.\textsuperscript{56}

Our challenge is to demonstrate that new therapies are not only chemically or biologically effective but that they are fiscally responsible and improve long-term outcomes. In this example not only did the recombinant human growth hormone decrease length of hospital stay and improve donor site healing time, but it improved peripheral nitrogen balance, taking patients who were previously catabolic and making them anabolic.\textsuperscript{37} The average patient of this group would be an 8-year-old, 39 kg child with an 80% total body surface area burn. The cost of recombinant human growth hormone would be $12,000 for such a patient. The shortened hospital stay, however, would decrease the overall cost for a patient not receiving recombinant human growth hormone from $120,000 to $93,000 for the treated patient, a savings of 23%. In the future we must examine the use of anabolic agents such as recombinant human growth hormone in children or in adults and the use of insulin-like growth factor to modulate the hypermetabolic responses. Anabolic steroids, which may potentially be cheaper and have fewer complications than the recombinant human growth hormone, are of promise.

**Early Burn Wound Closure.** The area that has probably decreased mortality more than any other particular area has been the early closure of the burn wound. Burns that heretofore would have been treated by twice-a-day application of topical anti-microbial agents and would have taken 3 to 5 weeks to heal with daily tubbing characterized by excruciating pain and sepsis can now be taken to the operating room the day of the injury and covered with cadaver skin, pigskin, or artificial substances and be completely healed within 2 weeks. Exquisitely painful second-degree wounds of the hands can be closed the day of the injury with Biobrane gloves, with the pain markedly reduced and patients returning to work relatively quickly.

Janzekovic and later Heimbach showed that third-degree burns or deep second-degree burns involving functional areas can be excised early after injury, the skin grafts can be applied, and the patient can return to work within 2 to 3 weeks after the accident. It is in the massive burns, that is, burns covering more than 60% total body surface area, that early excision has reduced mortality.

Because of the availability of cadaver skin, blood banks, and advanced anesthesia techniques, it is now possible to remove all the burn wound within 24 hours and cover the area with autografts and cadaver skin. These techniques, defined by Dr. Jack Burke\textsuperscript{38} and refined by Dr. J. Wesley Alexander,\textsuperscript{39} have led to a marked decrease in mortality in younger patients. But few randomized prospective studies have been done to demonstrate the limits of excision. One study of patients between the ages of 17 and 30 with large burns showed a 45% mortality with conservative techniques and a 9% mortality with early excision. Older patients and those with inhalation injury, however, showed no major benefit.\textsuperscript{40} Other studies have shown that the earlier the excision, the less the blood loss. If excision is performed within the first 24 hours after injury, a blood loss of 0.4 cc/cm\(^2\) is expected, whereas if the excision is delayed for 48 hours, blood loss can be twice that amount.\textsuperscript{41} No randomized study on the timing of excisions is available.

The decrease in mortality seen with excision of massive third-degree burns should not be translated to excision of all deep second-degree burns. In a prospective randomized study it was demonstrated that the pendulum in some cases has swung too far in the patients with deep scald burns. Those patients who had burns excised early suffered more blood loss, more operating time, and twice as many required surgeries as patients who were treated with conservative techniques.\textsuperscript{42} During the next decade there is a need to be able to define the depth of a burn injury better so that we can clearly demonstrate which patients are going to benefit by early excision and which patients will do better with delayed excision. Further prospective randomized studies are required with
larger patient populations to precisely define what age categories and types of patients will benefit from aggressive early surgical therapy and in which patients this approach might be harmful.

Another major contribution made during the last 5 years has been the availability of tissue culture grown skin, which can be applied to massive burns as a temporary cover. Patients, however, need to be suspended in traction or nursed on air beds, because vigorous nursing activity or physical therapy may result in large amounts of skin loss from friction. The problem that needs to be addressed in the coming years is how to prevent tissue-cultured epithelial skin from forming blisters and sloughing off.\textsuperscript{42} It appears there is a lack of formation of anchoring fibrils between epithelial cells and the underlying dermis.

Another issue is one of cost. The allograft overlay technique for closing major burns costs approximately $600/sq ft of coverage or $14,000 to cover a 60% total body surface area burn. Cultured epithelial autograft techniques cost approximately $25,000/sq ft or up to $200,000 for a 60% total body surface area burn and graft takes are variable even at this prohibitive cost.\textsuperscript{43}

Prevention. In the area of prevention our predecessors, Doctors Truman Blocker, Duane Larson, and Sally Abston found that 80% of all childhood burn injuries occurred in the home and that 80% of those were caused by combustible materials.\textsuperscript{44} They undertook campaigns to legislate for fire-safe clothing. This effort probably decreased mortality from burns more than any particular surgical therapy undertaken.

In the current decade 16% of all residential fires are the result of flammable liquids being ignited by water heater pilot lights. These cause $32 million worth of damage, injure nearly 240 persons, and kill 40 persons annually. Current standards do not address the hazards presented by the open pilot light, which can easily ignite spilled flammable liquids or dense vapors. This is particularly dangerous when the water heater is placed at floor level within a confined space, where such items as gasoline, kerosene, or paint thinner may be used.

Over the past 25 years we have seen 64 children injured as a result of water heaters spontaneously igniting flammable liquids or gases. These children sustained large burn injuries, most around half their body surface area, resulting in hospital stays of about 45 days. Twelve of these children died as a result of their injuries.\textsuperscript{45}

Another preventable injury is bathtub scalds. Water heaters are frequently set at temperatures of 140\degree F or greater. Water at these temperatures can cause a significant burn within seconds of contact.\textsuperscript{46} If water heater temperatures were reduced to 110\degree F, the occurrence of hot water scalds would be significantly reduced. The challenge is clearly to expand our efforts in prevention to decrease overall health care costs.

As rationing of health care becomes a social and economic issue in our society, what size burn should be resuscitated has become a major question. In comparing survivors versus nonsurvivors of burns covering more than 80% total body surface area, we cannot tell at the time of admission on the basis of burn size, who should live or who will die.\textsuperscript{47} Survivors who had a mean burn size of 90% were indistinguishable from nonsurvivors. Although 70% of the nonsurvivors had an additional smoke inhalation injury, 42% of the survivors also had significant smoke inhalation injury such that the additional presence of smoke injury does not define futility in treatment. Later in the hospital course the development of organ failure requiring ventilatory support or gut failure requiring total parenteral nutrition were harbingers of poor outcome. Dialysis for total renal failure, however, was the only absolute indicator of who would not survive in this massive burn category. Unfortunately we cannot predict who is going to survive by prehospitalization or acute hospitalization phenomena. In the future we have to look beyond burn size, inhalation injury, and multiple organ failure and look more at the quality of life or long-term outcome to justify our interventions.

If we examine patients with burns covering more than 80% of their total body surface area at 1 year after injury, outside observers would think their quality of life is poor and that overall scarring and facial scarring would limit their future employability.\textsuperscript{48} But 5 years after discharge objective psychologic tests such as the Child Behavior Checklist, Teacher Report Form, and Youth Self Report form revealed no differences in the survivors of these massive injuries from healthy individuals. Psychologic evaluations by the Piers-Harris assessment found boys to exhibit a more positive self-concept in areas of behavior, intelligence, and physical appearance than their normative groups, and girls demonstrated no significant differences from healthy individuals.\textsuperscript{48}

Our major emphasis in the next 10 years must be to reduce scar. In the next 5 years we must learn the chemical signals that stimulate the fibroblast to form scar. But all of our studies must focus on long-term outcomes rather than short-term results.

In summary we must take the next step in moving from basic research to clinical trials to modulate the
responses to burn injury of skin, lung, gut, and other systemic responses. Our colleagues in other parts of the world such as the People’s Republic of China routinely practice in much less supportive environments and for less monetary compensation than we receive in North America. Despite this they are able to produce remarkable results with their innovative surgical techniques perfected through numerous prospective trials. Their postage stamp grafting procedure, for example, has demonstrated that they can achieve grafting results rivaling any of our techniques. These same colleagues have overcome much more catalyticm reform that we face today. Their experience should surely allow us to place the current climate of health care reform in some global perspective.

We must simply accept the challenge presented to us. Quite clearly, health care for all, which would continue to improve quality within the means of society, is an important objective for us to achieve. It is incumbent upon burn care practitioners to take a proactive approach in demonstrating through prospective studies the benefits of our interventions. Health care reform provides us with an opportunity to focus our efforts on clinical research, which can unequivocally demonstrate the efficacy and quality of our treatments. This can help us in pursuing those therapies that could be expected to improve the long-term outcomes of our patients and will in fact stand up to rigorous scrutiny over time. By focusing on prevention, lessening overall cost of human health care, and improving long-term quality, we can provide the best possible care for the patients we treat.

REFERENCES

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