Reflection
Evolution of the Field over Seven Decades

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KEYWORDS
- Burns
- Fluid resuscitation
- Inhalation injury
- Burn wound care
- Metabolic response to injury
- Organization of burn care and research

KEY POINTS
- Fluid resuscitation has moved from inadequate to excessive and is now returning to adequate.
- Reliable diagnosis and improved ventilatory management have reduced the comorbid effect of inhalation injury.
- The microbial ecology of the burn wound is constantly changing, with fungi now prominent and viruses emerging.
- Clinically effective biologic dressings require a bilaminate construction.
- Burn patients are internally warm, and the hypermetabolic response is wound directed.
- Multidisciplinary integrated clinical/laboratory research programs have provided the data that have improved burn care and significantly increased burn patient survival.

Both evolutionary and revolutionary changes have advanced the organization and delivery of burn care over the past 7 decades. Those changes have refined resuscitation, improved the diagnosis and treatment of smoke inhalation injury, virtually eliminated invasive bacterial burn wound sepsis, validated burn wound excision, defined full service metabolic support, expanded the goals of rehabilitation, and led to the development of a regionalized hierarchical system of burn treatment facilities.

In 1959, I was drafted after the second year of my surgical residency and reported to the US Army Surgical Research Unit (USASRU) to begin my 2 years of obligated military service as a member of the surgical staff of the Army Burn Center. I was impressed by the standard of care the burn patients received, which consisted of formulaic fluid resuscitation, prophylactic antibiotics, daily hydrotherapy and burn wound debridement, use of canine cutaneous xenografts for temporary wound...
coverage, and infusion of fat emulsions to supplement the diet of the extensively
burned. The patients were nursed on rotating beds, and physical therapy consisting
of functional splinting and both active and passive exercise was carried out daily.
Physician-led aeromedical evacuation teams were also used to transfer patients
from other military facilities and civilian hospitals.

FLUID RESUSCITATION

The historically high incidence of acute renal failure in patients with extensive burns or
high-voltage electric injuries was recognized by the inclusion of a renal section within
the USASRU and the presence of a Brigham-Kolff dialysis machine in that section.
Even then, a greater understanding of the pathophysiology of burn injury, acquired
in the first half of the twentieth century, had decreased the need for hemodialysis in
burn patients. The clinical studies of Haldor Sneve\(^1\) at the turn of the nineteenth cen-
tury, the studies of Frank Underhill in patients from the Rialto Theater fire of November
1921 and in the laboratory, the clinical experience of the surgeons at the Boston City
Hospital and the Massachusetts General Hospital with the patients from the Coconut
Grove nightclub fire in November 1941, and earlier clinical experience at the USASRU,
combined with the results of the animal studies of Henry Harkins, Alfred Blalock, and
E.I. Evans had rationalized the fluid resuscitation of burn patients.\(^2\) The analysis of
those study results identified the biphasic omni-system response to burn injury (Table 1)
and the sigmoid dose-response relationship of those changes to the extent
of the burn injury (Fig. 1). An understanding of those relationships provided the scient-
ific infrastructure for the research programs that have generated the data used to
develop present-day burn care.

Appreciation of the relationships between the extent of burn and the volume
of resuscitation fluid needed led to the development of formulae to predict burn patient
resuscitation fluid needs. Arguably the first formula, based only on the extent of the
burn, was recommended by the National Research Council at a meeting chaired by
I. S. Ravdin in January 1942 for members of the military with burns sustained in com-
batt in WWII.\(^3\) Subsequently, formulae based on the extent of the burn and body weight
were proposed and used as the Burn Budget Formula of Cope and Moore (1947), the
Evans Formula (1952), and the Brooke Formula (1953).\(^2\) Use of those formulae essen-
tially eliminated burn shock and acute renal failure; but success led to excess, and the
earlier complications of inadequate resuscitation were replaced by an increasing
occurrence of acute pulmonary edema and compartment syndromes (Box 1).\(^4\)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Early Change</th>
<th>Later Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Shock</td>
<td>Hyperdynamic</td>
</tr>
<tr>
<td>Urinary</td>
<td>Oliguria</td>
<td>Diuresis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Ileus</td>
<td>Hypermotility</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Hypoperfusion</td>
<td>Hyperperfusion</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Hypoventilation</td>
<td>Hypermotility</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Catabolism</td>
<td>Anabolism</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Inflammation (SIRS)</td>
<td>Suppression (CARS)</td>
</tr>
<tr>
<td>CNS</td>
<td>Agitation</td>
<td>Obtundation</td>
</tr>
</tbody>
</table>

Abbreviations: CARS, compensatory antiinflammatory response syndrome; CNS, central nervous
system; SIRS, systemic inflammatory response syndrome.
As recently as 1994, Sheridan and colleagues\(^6\) reported 5 cases of intracompartmental sepsis as a consequence of prolonged unrecognized elevation of compartment pressure. Those investigators recommended frequent examination of burned limbs during resuscitation, prompt decompression as indicated, and evaluation of muscle compartments during the excision or debridement of burn wounds.

**Reduction of Resuscitation Volume**

A program of integrated clinical/laboratory research conducted at the US Army Institute of Surgical Research (USAISR) (the USASRU had been renamed the USAISR), identified the hazards of colloid solutions and excessive crystalloid infusion and the limitations of hypertonic resuscitation.\(^6\) Those findings led to the development of a Modified Brooke Formula as detailed in **Box 2** to reduce both the protein content and volume of the infused resuscitation fluid. That formula recognizes the findings of studies showing that in the first 3 hours after injury, burn wound edema is most strongly affected by intravascular pressure and later most strongly by capillary permeability.\(^7\) The initially increased capillary permeability decreases across time and establishes a new transcapillary equilibrium 24 hours after the burn at which time water and protein content of the burn wound peak.\(^8\) The use of the Modified Brooke Formula, with careful attention to preventing fluid overload, reduced the occurrence of acute renal failure to a level whereby only 10 (0.3%) of 3266 burn patients treated at the USAISR between 1994 and 2004 required dialysis for early or late-onset renal failure. Recently, investigators at the USAISR have developed a computerized burn patient

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**Box 1**

**Complications of excessive resuscitation**

1. Pulmonary compromise
   a. Airway edema
   b. Pulmonary edema
2. Compartment syndromes
   a. Muscle compartments of burned and unburned limbs
   b. Cerebral edema
   c. Anterior ischemic optic neuropathy
   d. Abdominal compartment syndrome
resuscitation program in which the necessary adjustment of the fluid infusion rate is
related to urinary output measured at 10-minute or lesser intervals. In early studies,
the use of that program has further refined resuscitation as indexed by decreased infu-
sion volume and resuscitation volume variability with maintenance of organ function.

### HIGH-VOLTAGE ELECTRIC INJURY

The management of high-voltage electric injury has been another area in which inte-
grated research has clarified the understanding of the pathogenesis of deep-tissue
injury and led to improved management. Much had been made of differences in tissue
resistance to current flow and susceptibility to injury at low voltage, but studies by
Hunt and colleagues revealed those differences to have little or no impact on
high-voltage tissue injury. When in contact with a current of more than 1000 V, body
parts act as volume conductors in which current density and heat production are
inversely proportional to the cross-sectional area of each body part. When the current
flow ceases, the body parts act as volume radiators, with heat more slowly lost from
the deeper tissues. These characteristics explain why tissue injury in digits and limbs is
typically severe and less severe in the trunk and mandate exposure and evaluation of
the periosseous tissues even if the overlying tissue appears to be viable at the time of
debridement or fasciotomy (Fig. 2). Other studies by Zelt and colleagues refuted the
belief that there is progressive extension of tissue injury after a high-voltage injury,
meaning that at the initial surgical debridement, tissue viability should be carefully

### Box 2: Modified Brooke Formula

<table>
<thead>
<tr>
<th>1. First 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Adult: lactated Ringer's solution: 2 mL per kilogram of body weight per percent TBSA burned</td>
</tr>
<tr>
<td>b. Child: lactated Ringer's solution: 3 mL per kilogram of body weight per percent TBSA burned</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Second 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Colloid-containing fluid (albumin diluted to physiologic concentration in normal saline in relation to extent of burn):</td>
</tr>
<tr>
<td>i. 30%–49% TBSA: 0.3 mL per kilogram of body weight per percent TBSA burned</td>
</tr>
<tr>
<td>ii. 50%–69% TBSA: 0.4 mL per kilogram of body weight per percent TBSA burned</td>
</tr>
<tr>
<td>iii. 70% and greater TBSA: 0.5 mL per kilogram of body weight per percent TBSA burned</td>
</tr>
<tr>
<td>b. Electrolyte-free water to maintain urinary output</td>
</tr>
<tr>
<td>c. Patients with delayed resuscitation and those with high-voltage electric injury may require more than estimated volume.</td>
</tr>
</tbody>
</table>

**Abbreviation:** TBSA, total body surface area.

*One-half of estimated volume should be infused in the first 8 hours after burn.*

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evaluated and all nonviable tissue excised. Other than a trivial amount of necrotic tissue present in the wound at the time of reoperation for wound closure indicates inadequate initial debridement, not progressive tissue damage.

**ACUTE GASTROINTESTINAL STRESS ULCERS**

Yet another program of integrated research elucidated the natural history of acute ulcerations of the gastrointestinal tract (Curling ulcers) and identified the effectiveness of antacid prophylaxis. The clinical use of either antacids or the histamine H$_2$ receptor antagonist cimetidine reduced the incidence of Curling ulcer to only 9 (0.3%) of 3266 burn patients treated in an 11-year period.

**INHALATION INJURY**

As is always the case in medicine, the solution of one problem, that of inadequate resuscitation, revealed a previously unapparent problem (ie, the strong comorbid effect of smoke inhalation injuries). Another program of integrated clinical/laboratory research defined the clinical impact of inhalation injury and developed an animal model of inhalation injury in which the pulmonary pathophysiology induced by that injury could be characterized and the effects and effectiveness of therapeutic interventions evaluated.

**Diagnosis**

The clinical arm of the inhalation injury research program characterized the relationship between the comorbid effect of that injury and mortality as predicted from patient age and the extent of the burn and found it to be greatest (increased by a maximum of 20%) in the region of the LA$_{50}$ for all age groups. The comorbid effect of pneumonia, a common complication in patients with inhalation injury, was found to be independent but additive to that of the inhalation injury. In burn patients with inhalation injury who develop pneumonia, mortality increases by a maximum of 60% more than that predicted from age and the extent of the burn when the burns are in the region of the LA$_{50}$ and by a lesser percentage on either side of the LA$_{50}$. Clinical studies further evaluated the usefulness of diagnostic modalities and identified fiberoptic bronchoscopy of both the supraglottic and infraglottic airway as being readily available and having an accuracy of 86% with no false-positive diagnoses. The $^{133}$xenon
A ventilation-perfusion lung scan was of comparable accuracy alone but, when used along with bronchoscopy, increased the diagnostic accuracy to 93%, with a 7% false-positive rate and a difficult-to-justify increase in cost for that modest increase in accuracy (Table 2).

**Use of Animal Model**

The laboratory component of the inhalation injury research program focused on the development of an ovine model and the use of the 6–inert gas technique to characterize alterations of lung air flow and blood flow in response to the injury. In that model, the principal pathogenetic change was found to occur in the airways as reflected by the appearance of a low air flow–high blood flow compartment in proportion to the dose of smoke administered. Only a modest increase in true shunt was observed. Those findings identifying the primacy of airway injury prompted the evaluation of modes of ventilation and pharmacologic interventions to reduce the incidence of pneumonia and prevent, or at least limit, mismatching of ventilation and perfusion. The use of high-frequency interrupted-flow positive pressure ventilation has been associated with a decrease in pneumonia and mortality in patients with inhalation injury. Laboratory studies have also documented that a platelet-activating factor antagonist CV-3988 and pentoxifylline, given either before or after the injury, significantly reduce blood flow mismatching to the true shunt and low airflow compartments, reduce the decrease in PaO₂, and limit the histologic and pulmonary function changes induced by inhalation injury. The clinical management of burn patients with inhalation injury has essentially eliminated the comorbid effect of mild

**Table 2**

<table>
<thead>
<tr>
<th>Diagnostic Modality</th>
<th>Diagnostic Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiberoptic bronchoscopy</td>
<td>86</td>
</tr>
<tr>
<td>133Xenon lung scan</td>
<td>87</td>
</tr>
<tr>
<td>133Xenon lung scan + fiberoptic bronchoscopy</td>
<td>93</td>
</tr>
</tbody>
</table>

**Fig. 3.** Bronchoscopic view of the airways in a patient with burns and smoke inhalation injury. Note the endobronchial inflammation, the debris at 12 o’clock near the center of the field, and the variably sized areas of carbonaceous material adherent to the mucosa at 2 o’clock and 5 o’clock near the periphery of the field and elsewhere.
injury; but the comorbidity of moderate/severe inhalation injury, though reduced, persists at a level that supports clinical trials of promising pharmacologic agents (Table 3).19

BURN WOUND CARE

Background

The predominant organisms causing infections in burn wounds have changed across time, preceding by several years those causing infections in patients in other intensive care units (ICUs) in the hospital. In a real sense, burn patients have been the canary in the coal mine of surgical ICU infections. Before the availability of the sulfonamides and penicillin, β-hemolytic streptococci were the organisms most commonly causing fatal infections in burn patients. Dressings soaked with 5% sulfathiazole oil in water emulsion used by Fraser Gurd in Canada (1942) and a penicillin cream advocated by Leonard Colebrook in England (1954) were early attempts to forestall burn wound infections, but the toxicity associated with the former and the emergence of Staphylococcus aureus resistant to penicillin compromised those early topical agents and led to their abandonment and the use of prophylactic systemic antibiotics for the first 5 to 10 postburn days. The development of the semisynthetic penicillins controlled staphylococcal infections; but their use was associated with the emergence of gram-negative opportunists, especially Pseudomonas aeruginosa, as prominent members of the flora colonizing and infecting burn patients in the latter half of the 1950s.20

Exposure Treatment

The use of occlusive dressings applied in the vain hope of preventing contamination of the burn, which often accelerated subeschar suppuration and induced systemic sepsis, was abandoned after A. B. Wallace21 of Edinburgh reintroduced the exposure technique. After an evaluation at the USASRU by Artz and colleagues confirmed the beneficial effects of the exposure technique, it became the favored method of wound care at the USASRU. The burn wounds were examined during daily hydrotherapy when the debridement of nonviable eschar was carried out to the point of bleeding or pain. The treatment was continued until a majority or the entirety of an anatomic area could be closed by skin grafting. Unfortunately, and all too frequently, in patients with burns of more than 30% of the body surface, the burn wound underwent degeneration with the formation of a neoeschar and the appearance of nodular necrotic lesions in unburned skin (ecthyma gangrenosum characteristic of pseudomonas septicemia) and systemic sepsis with an ultimate demise before wound closure could be obtained (Fig. 4). In the 1950s, that trajectory was the fate of 60% of the patients treated at the USASRU and other burn centers who died.22 The reported autopsy cause of death was typically died of burns, a diagnosis that did little to advance pathophysiologic understanding.

Table 3

Characteristics and outcomes of patients with moderate/severe inhalation injury

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Number of Patients</th>
<th>Age (y)</th>
<th>TBSA (%)</th>
<th>Pneumonia (%)</th>
<th>Mortality (%)</th>
<th>Predicted Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1984</td>
<td>260</td>
<td>39.0</td>
<td>50.0</td>
<td>48.5</td>
<td>57.7</td>
<td>—</td>
</tr>
<tr>
<td>1985–1990</td>
<td>245</td>
<td>35.6</td>
<td>46.1</td>
<td>46.9</td>
<td>38.3*</td>
<td>50.4</td>
</tr>
</tbody>
</table>

Abbreviation: TBSA, total body surface area.

* p<.05.
Multidisciplinary Studies and Model Development

The genesis of the subsequent revolution in burn wound care was a fortuitous exchange between Dr Artz, Commander of the USASRU, and Dr Averill Liebow, Professor of Pathology at Yale University, at a National Research Council meeting. Dr Artz described the clinical characteristics of moribund burn patients, and Dr Liebow suggested that a detailed pathologic examination of the burned tissue and the ecthyma might provide pathogenic insight into the problem. Dr Liebow further suggested that Dr Artz request that Dr Liebow’s chief resident, who was about to be drafted into the Army, be assigned as a pathologist at the Army Burn Center to conduct burn-specific autopsies. Such was done, and the detailed pathologic examinations by that pathologist and his successors, in conjunction with the clinical observations of the surgical staff, identified the pathogenesis of invasive burn wound sepsis. Proliferation of colonizing microorganisms with eschar penetration led to suppuration in the subeschar space, invasion of underlying viable tissue with microvascular involvement resulting in hematogenous dissemination to remote organs and tissue, and sepsis. The clinical condition was then simulated in a reproducible murine model in which the wound changes and systemic signs mimicked those observed clinically (Fig. 5).

Fig. 4. Invasive pseudomonas burn wound sepsis caused the necrosis of the meshed cutaneous autografts placed on these wounds and the formation of a neoeschar of nonviable tissue. Note the 5 circular ecthyma gangrenosum lesions with dark brown to black peripheral discoloration and a pallid central area in unburned skin near the infected wound.

Fig. 5. The “Rat that Roared and Changed Burn Care.” This model of invasive pseudomonas burn wound sepsis, which replicates the focal wound discolorations seen clinically and shows ruffling of the hair and serosanguinous nasal discharge indicative of the septic state, was used to identify the effectiveness of topical antimicrobial chemotherapy.
Clinical Use of Topical Antimicrobial Therapy

The model was then used to evaluate the effectiveness of topical antimicrobial agents. The sulfonamides were reintroduced as an 11.1% suspension of mafenide acetate (Sulfamylon) in a vanishing cream base. That agent converted the universal mortality of the murine model of invasive pseudomonas burn wound sepsis to universal survival when tested against several Pseudomonas strains of variable virulence. Transfer of the laboratory findings to the clinic ensued. Twice-daily topical application of the Sulfamylon burn cream was associated with a 50% reduction in invasive pseudomonas burn wound sepsis as the cause of death in the burn patients (Fig. 6). Contemporaneous studies at other burn centers documented the effectiveness of the topical application of 0.5% silver nitrate soaks and a 1% suspension of silver sulfadiazine (Silvadene) in a water-miscible base (Silvadene burn cream) for the control of microbial density on the burn wound. In recent years, a variety of silver-impregnated membranes have been added to the armamentarium of antimicrobial agents available for topical use on burn wounds.

Burn Wound Excision

Control of the microbial density in the burn wound by effective topical antimicrobial chemotherapy also permitted the surgical excision of the nonviable eschar without inducing profound endotoxemia, which had previously limited the usefulness of the

Fig. 6. Sulfamylon burn cream applied to the burn wounds twice a day as shown here controls the microbial density on the surface of the burn wound, limits microbial penetration of the eschar, and prevents hematogenous dissemination.
excision of necrotic eschar with a heavy microbial burden. Burn wound excision by scalpel at the level of the investing fascia or more commonly by the use of the tangential excision technique developed by Dr Zora Janzekovic in Maribor, Yugoslavia, further reduced the incidence of invasive burn wound sepsis as a cause of death to 6% (ie, a 10-fold overall reduction).

**Biologic Dressings**

Excision of the burned tissue in extensively burned patients generated the problem of closure of that surgical wound in patients with extensive burns and a paucity of donor sites. To fill that void, canine xenografts were often used as temporary biologic dressings in the 1950s; but porcine xenografts became commercially available and displaced the canine tissue. It was clearly recognized that cutaneous allografts were the ideal biologic dressing, but they were associated with the same risk of infection as a unit of blood and ultimately had to be replaced by cutaneous autografts. The problems associated with allogeneic and xenogeneic cutaneous tissue led to studies of unilamellar synthetic membranes, such as amino acid films. Unfortunately, no biologic union occurred between the host, and such material and suppuration commonly developed beneath the films.

It was found that an effective skin substitute should be bilaminate, consisting of an inner layer (dermal analogue) with sufficient thickness and pore size to permit ingrowth of fibrovascular tissue from the wound to effect firm biologic union with the host, and an outer layer (epidermal analogue) that served as a barrier to microbial invasion, yet permitted the transmission of water vapor to prevent subgraft fluid collection. The first clinically effective bilaminate membrane was Biobrane, which consists of a dermal analogue of collagen-impregnated nylon mesh and a thin sheet of silastic as the epidermal analogue. The second-generation collagen-based skin substitute, Integra, consists of a dermal analogue of collagen fibrils enriched with the glycosaminoglycan 6-chondroitin sulfate and a thin sheet of silastic as the epidermal analogue. In clinical studies, it was noted that the dermal analogue of Integra was readily vascularized by the ingrowth of vascular and connective tissue from the wound bed following which the silastic membrane could be removed and the neodermis covered with an ultrathin cutaneous autograft (Fig. 7).26

![Fig. 7](image)

**Fig. 7.** The burns on the anterior trunk of this burn patient were excised; cutaneous autografts were applied to the right chest wall; Integra was applied to the left chest wall. (A) The bright red coloration of the left chest wall visible through the silastic epidermal analogue of the Integra indicates vascularization of the dermal analogue by ingrowth of host fibrovascular tissue. (B) Following removal of the silastic epidermal analogue, the vascularized dermal analogue was covered with thin cutaneous autografts that provided durable closure of the left chest wall burns comparable with that of the right chest wall.
Because the naturally occurring biologic dressings and the collagen-based skin substitutes have to be replaced by split-thickness cutaneous autografts, attention in recent years has focused on the development of autogenous culture-derived tissue with which the excised burn wound could be definitively closed making subsequent cutaneous autografting unnecessary. Cultured autogenous keratinocytes enjoyed an initial enthusiastic reception. That enthusiasm was tempered by persistent fragility and recurrent ulceration of the engrafted keratinocytes. A review of the experience with cultured keratinocytes at the USAISR indicated that such tissue persisted to the greatest extent in patients with small burns and showed progressively less engraftment as the extent of the burn injury increased with little permanent replacement noted in patients with the largest burns.27 That report and the comparable clinical experience of others has shifted attention to the development of composite cultured tissue preparations, such as the coculture of fibroblasts, endothelial cells, and keratinocytes described by Augier and colleagues, in which a vascular network seemed to form in the collagen matrix after 28 days, which presents the possibility of definitive wound closure with the connection of that neovascular tissue with host vessels by inosculation to constitute a dermal analogue underlying the coalescent keratinocytes on the outer surface of the membrane.28 Disappointingly, after the initial laboratory reports, no studies have confirmed the clinical potential of that cultured tissue.

**Emergence of Other Microbial Opportunists**

In short, a revolution in burn wound care has occurred over the past 7 decades marked by the development of effective topical antimicrobial chemotherapy to control intraeschar microbial penetration and proliferation, prompt excision of the burned tissue, and the use of biologic dressings to provide early temporary wound closure. In the aggregate, those advances and current ICU care have decreased the occurrence of bacterial invasive burn wound sepsis as the cause of death in burn patients and delayed the occurrence of those infections that do occur. The occurrence of invasive burn wound infections has continued to decline and is now the cause of death in only 2.3% of fatal burns at the USAISR (an overall almost 30-fold reduction), but those invasive burn wound infections that did occur were associated with a 61% mortality (Table 4). Slightly more than two-thirds (72%) of the cases of invasive burn wound infection are caused by opportunistic fungi; the occurrence of fungal infection, which has a comorbid effect equal to that of a burn involving an additional 33% of the total body surface, may explain, at least in part, the present-day mortality in patients who develop invasive burn wound infections.29 Herpetic viral infections have made a recent appearance as the causative agents of burn wound infections, confirming the constant evolution of causative organisms and the fact that, in severely burned patients, there are no benign opportunistic organisms.30

### Table 4

<table>
<thead>
<tr>
<th>Wound Treatment</th>
<th>Incidence as Autopsy Cause of Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No topical therapy</td>
<td>60.0</td>
</tr>
<tr>
<td>Topical antimicrobial therapy</td>
<td>28.0</td>
</tr>
<tr>
<td>Topical antimicrobial therapy Early excision</td>
<td>6.0</td>
</tr>
<tr>
<td>Topical antimicrobial therapy Early excision plus current ICU care</td>
<td>2.3</td>
</tr>
</tbody>
</table>
**Burn Wound Biopsy for Diagnosis of Infection**

In order to monitor the microbial status of the burn wound and diagnose invasive burn wound infection in a timely manner and institute treatment promptly, collaborative studies involving surgeons and pathologists established burn wound biopsy as the most accurate means of assessing the microbial status of the burn wound. The histologic examination of a biopsy specimen including eschar and underlying unburned tissue, processed by either a rapid section or a frozen section technique, enables one to distinguish microbial colonization from microbial invasion, determine the depth of invasion, and identify involvement of the microvasculature as a predictor of hematogenous dissemination to remote organs and tissues (Fig. 8). A biopsy staging system was developed in which microbial proliferation, microbial density, and involvement of unburned tissue were related to the diagnosis of invasive infection, the likelihood of systemic spread, and survival (Table 5). In addition to the reliable diagnosis and staging of infection in the burn wound, biopsies are also useful in assessing the adequacy of excision and the absence of infection in the wound bed following excision of an infected wound.31

**POSTBURN HYPERMETABOLISM**

Another area of revolutionary change has been in the nutritional and overall metabolic support of burn patients. The studies of patients with long bone fractures by Sir David Pruitt Jr...
Cuthbertson\textsuperscript{32} in the 1920s and 1930s established that injury induced an increase in the metabolic rate. In burn patients, the increase in metabolic rate, which was proportional to the extent of the burn, was considered to be exaggerated by increased evaporative heat loss from the burn wound. Attempts to reduce evaporative water loss included bulky occlusive dressings and external heating by the use of heat lamps and an increase in ambient temperature, but those measures had little effect on the elevated metabolic rate and promoted proliferation of bacteria in the burn wound. Studies conducted by Wilmore and colleagues\textsuperscript{33} in a specially constructed metabolic study room in which the temperature could be varied, the relative humidity maintained at a uniform and constant 50% and the wind velocity maintained below a level (50 linear feet per minute) that exaggerated evaporative water loss clarified the pathophysiology of burn patient hypermetabolism (Fig. 9). In essence, burn patients were found to be internally warm, not externally cold. The elevated metabolic rate is temperature sensitive but not temperature dependent, decreasing by only a modest 10% at an environmental temperature of 33°C versus 25°C in patients with burns involving more than 40% of the body surface. Additional studies demonstrated an elevation of the hypothalamic thermoregulatory set point as manifested by burn patients selecting an ambient temperature of comfort above that of unburned man (ie, a mean of 30.4°C [range 28°C–35°C]).\textsuperscript{34} It was found that the thermoregulatory changes were accompanied by endocrine changes characterized by early prominence of the

<table>
<thead>
<tr>
<th>Histologic Classification</th>
<th>Mortality Rate (%)</th>
</tr>
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<tbody>
<tr>
<td>Stage</td>
<td>—</td>
</tr>
<tr>
<td>1. Colonization</td>
<td></td>
</tr>
<tr>
<td>a. Microorganisms on surface of eschar</td>
<td></td>
</tr>
<tr>
<td>b. Variable depth of microbial penetration of eschar</td>
<td></td>
</tr>
<tr>
<td>c. Proliferation of microorganisms in the subeschar space</td>
<td></td>
</tr>
<tr>
<td>2. Invasion</td>
<td></td>
</tr>
<tr>
<td>a. Microinvasion of viable tissue</td>
<td>65</td>
</tr>
<tr>
<td>b. Generalized involvement of viable tissue</td>
<td></td>
</tr>
<tr>
<td>c. Microvascular involvement</td>
<td>83</td>
</tr>
</tbody>
</table>

\textbf{Table 5}

Histologic assessment of microbial status of the burn wound

\textbf{Fig. 9.} This special room in which environmental conditions could be controlled was used to conduct studies characterizing postburn hypermetabolism.
catabolic hormones (catechols and glucagon) and later predominance of the anabolic hormone, insulin with restoration of the preinjury insulin-glucagon molar ratio across time, and increased levels of thyroid hormones.\textsuperscript{35,36}

Further studies demonstrated that the elevated metabolic rate in burn patients could be reduced by β-adrenergic blockade (propranolol) or by pharmacologic doses of morphine sulfate; but hemodynamic instability or respiratory depression, respectively, severely limited the clinical usefulness of those agents. Additional studies using a full-limb venous plethysmograph revealed the wound directedness of the metabolic response to burn injury. During the peak hypermetabolic period (6th to 21st postburn days), leg blood flow to an unburned limb in a burn patient was similar to that in a limb of an unburned control, whereas the blood flow to the patient’s burned limb significantly increased in curvilinear proportion to the extent of the burn wound on the limb (Fig. 10).\textsuperscript{37}

**METABOLIC SUPPORT**

Integrated clinical/laboratory research focused on postinjury hypermetabolism has defined the components of full-spectrum metabolic support (Box 3). That support includes measures to prevent exaggeration of postinjury hypermetabolism by maintaining a warm environment to eliminate cold stress, adequate analgesia and anxiolytic therapy to eliminate or at least reduce the pain-related increase in catecholamine secretion, and maintenance of muscle activity by progressive physical therapy beginning on admission and exercise long after discharge to minimize muscle atrophy from disuse. The use of effective topical antimicrobial chemotherapy and early burn wound excision and grafting eliminate or reduce the increase in the metabolic rate secondary to microbial colonization and proliferation in the burn wound and decrease circulating levels of inflammatory cytokines and chemokines to curtail the intensity and duration of the systemic inflammatory response syndrome by closing the wound. An effective program of infection surveillance is essential to facilitate early diagnosis and prompt

![Fig. 10. Blood flow to a leg is increased in proportion to the percentage of the leg’s surface area involved in the burn as is consistent with the concept that the hemodynamic response is wound directed to support healing.](image-url)
treatment of all infections, which can cause reversion of the normalizing neuro-hormonal milieu to that of the early postburn catabolic state.

Nutrition

Nutrition should be provided that matches the metabolic rate as measured by indirect calorimetry or by the use of a formula such as that developed at the USAISR to estimate the energy requirement of a burn patient: 

\[
EER = \frac{[BMR \times (0.89142 + 10.01335 \times TBS)] \times m^2 \times 24 \times AF}{AF},
\]

where \(EER\) is estimated energy requirement, \(BMR\) is basal metabolic rate, \(TBS\) is total burn size, \(m^2\) is total body surface area in square meters, and \(AF\) is activity factor of 1.25. Studies of nutrient utilization under controlled conditions have shown that urinary nitrogen loss is lowest when the carbohydrate intake/metallic rate ratio approaches 1 and that nitrogen balance is a function of nitrogen intake, dietary nonprotein calories, and basal insulin levels. To avoid hepatic steatosis and increased carbon dioxide production, the infusion rate of the nutrients, if given parenterally, should not provide more than 5 mg of glucose per kilogram of body weight per minute. The calorie/nitrogen ratio of the diet should range between 100 and 150 calories per gram of nitrogen and 1.5 to 3.0 g of protein per kilogram of body weight per day. To prevent essential fatty acid deficiencies, lipids should be included in the diet but should not exceed more than 3 g per kilogram of body weight per day or supply more than 40% of total calories.
Whenever possible, the enteral route should be used for nutritional support. When properly monitored to prevent aspiration, enteral feedings can be continued during excision and grafting procedures to attain nutritional goals.

**Pharmacologic Agents**

In recent years, pharmacologic intervention has been used to minimize erosion of lean body mass and accelerate convalescence. It has been reported that the metabolic response to burn injury in children is reduced by β-adrenergic blockade, the long-term effects of which are currently being evaluated in a multi-institutional study.42 Other hormonal interventions that have been reported to enhance nutritional support include growth hormone, insulinlike growth factor 1 either alone or in combination with insulinlike growth factor 1 binding protein-3, low-dose insulin, and the androgenic steroid oxandrolone.43–45 In a recent study in children of the effects of the daily administration of recombinant human growth hormone during the first year following a burn injury, accelerated reconstitution of lean body mass, skeletal growth, and body weight gain were observed with a reduction in metabolic rate, percent body fat content, and, somewhat surprisingly, a decrease in hypertrophic scarring.46

**ORGANIZATION OF BURN CARE**

A national hierarchical regionalized system of burn care facilities has developed since 1949 that supports the referral and transfer of burn patients to a facility where the necessary personnel and equipment are available to provide the level of care required. The system has expanded from the small number of units and centers represented by the founders of the American Burn Association (ABA) in 1968 to the 123 self-designated burn care facilities (54 verified as burn centers by the ABA), which are distributed in close relation to population density.47

The transfer of burn patients to burn centers from remote locations is often carried out as an aeromedical evacuation procedure by either fixed-wing or rotary-wing aircraft. The staffing, equipment, and supplies initially described for the burn flight teams at the USASRU in the 1950s have been expanded, refined, and modified as needed for the present-day intercontinental transport of not only critically ill, severely injured burn patients but, in recent conflicts, the transport of other combat casualties.

**ABA**

The ABA, which designed and now maintains the National Burn Repository (NBR), has over the past 45 years matured as a professional organization that sponsors an impressive array of activities to benefit its members, burn care facilities, and burn patients. The ABA’s educational activities for members and other burn care providers are highly focused on the publication of the *Journal of Burn Care and Research*, its annual scientific meeting, and the Advanced Burn Life Support Program. The ABA’s support for burn care facilities includes its Burn Center Verification Program, the previously noted NBR, and its annual National Burn Leadership Conference during which interactions and information exchange between the ABA members and their federal legislators are facilitated. In 2013, the NBR published its annual report noting that it has expanded to include more than 175,000 entries from 91 burn centers in the United States, 4 in Canada, and 2 in Sweden. The NBR reports epidemiologic data on inpatient burns treated at the contributing burn centers in the most recent 10 years.48 The ABA’s research initiatives include multi-institutional trials and the administration and oversight of research studies receiving competitively awarded federal funding, all of which benefit the burn care universe and burn patients.
ORGANIZATION OF RESEARCH

With few exceptions, the advances described earlier have resulted from integrated clinical/laboratory research conducted at burn centers wherein experienced burn surgeons have collaborated with physicians representing other disciplines and laboratory scientists. Those investigative teams consisting of various combinations of the disciplines listed for the investigators at the USAISR (Table 6) have identified clinical problems of importance, taken the problems to the laboratory to apply state-of-the-art measurement and assay techniques or develop a relevant model to identify effective interventions, and returned those to the bedside to improve burn patient outcomes.

IMPROVED SURVIVAL AND NEW OUTCOME GOALS

As noted in this reflection, the results of those team efforts at burn centers in the United States and elsewhere have been applied to virtually eliminate burn shock and acute renal failure, tame inhalation injury, control invasive bacterial burn wound sepsis, prevent acute gastrointestinal ulceration, reduce postburn catabolism, and accelerate convalescence. In the aggregate, those advances have improved, at statistically significant levels, the survival of burn patients. The hallmark of an improved outcome has traditionally been an increase in survival as measured by the LA50 (i.e., the extent of burn fatal to 50% of those patients having a burn of that extent). The LA50 of burn patients of all ages has significantly improved over the past 7 decades as the manifestation of the advances cited in this reflection (Table 7).49 That success is tempered by an intrinsic frustration of biomedical research, that is, the solution of any pathophysiologic problem, particularly those in injured man, invariably reveals a previously unapparent problem or problems that present new clinical and research challenges to which the investigators can apply their intellect and skills.

The survival of burn patients has improved to such a degree since the midpoint of the twentieth century that attention has been refocused on scar prevention and control and the psychosocial reintegration of burn patients as the new indices of outcomes success.50 To that end, studies are in progress at many burn centers evaluating the effectiveness of laser therapy in the control and amelioration of hypertrophic scarring.51,52 In the realm of whole-person reintegration, the ABA and the Shriners

<table>
<thead>
<tr>
<th>Disciplines of investigators: USAISR</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td>General surgery</td>
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<td>Cardiotoracic surgery</td>
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<td>Plastic surgery</td>
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<td>Pathology</td>
</tr>
<tr>
<td>Veterinary medicine</td>
</tr>
<tr>
<td>Master machinist</td>
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Hospitals for Children have developed age-specific questionnaires to assess the status of the burn survivor’s recovery in multiple quality-of-life domains. Serial administration of the questionnaires now permits the development of domain-specific recovery trajectories. If a trajectory is found to be at variance with the anticipated recovery curve, corrective interventions can be applied to improve outcomes and enhance the success of burn survivors as productive members of society.

All of the advances in our understanding of burn injury have contributed to the development of the current best evidence-based treatment of burn patients. That treatment is presented in detail by the authors included in this issue of the *Surgical Clinics of North America* who were selected by Dr Sheridan because of their experience and expertise.

### REFERENCES


<table>
<thead>
<tr>
<th>Age Group</th>
<th>LA_{50}^{a}</th>
<th>LA_{50}^{b}</th>
<th>LA_{50}^{c}</th>
<th>LA_{50}^{d}</th>
<th>LA_{50}^{e}</th>
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<tr>
<td>Pediatric (0–14 y)</td>
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<td>71^{b}</td>
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<td>Young adult (15–40 y)</td>
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<td>Older adult (&gt;40 y)</td>
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<td></td>
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<td>65^{d}</td>
</tr>
</tbody>
</table>

^{a} Percentage of total body surface area burned associated with 50% mortality.

^{b} Representative age: 5 years.

^{c} Representative age: 21 years.

^{d} Representative age: 40 years.

^{e} Representative age: 60 years.