What's New in General Surgery: Burns and Metabolism

Jeffrey R Saffle, MD, FACS

"What's New in Surgery" evolves from the contributions of leaders in each of the fields of surgery. In every instance the author has been designated by the appropriate Council from the American College of Surgeons' Advisory Councils for the Surgical Specialties. This feature is now presented in issues of the Journal throughout the year.

This review will focus on notable clinical and scientific contributions in the areas of burns and metabolism over the past 12 months and will attempt to place them in perspective for surgeons in practice. In preparation, a Medline search was conducted among English-language publications for the subject heading “burns,” covering the period from October 1, 2001 to October 15, 2002. More than 500 citations were identified, 15 of which were randomized, controlled clinical trials. Several additional articles that appear clearly relevant to clinical burn treatment are also discussed.

BURN INJURIES AND SEPTEMBER 11

The terrorist attacks of September 11, 2001 focused unprecedented public attention on burn injuries. Eighteen burn victims from the World Trade Center were treated at the New York Hospital Burn Center and nine victims of the Pentagon attack were treated at the Washington Hospital Center. The care of this relatively small group of patients was followed closely throughout the world, and their stories—dramatic in themselves—were made even more newsworthy as symbols of the disaster. To the public, these patients came to personify both the stunning tragedy and losses caused by the attacks, and the inspiring resilience and fortitude of the American people. From a medical perspective, these cases exemplified the current status of burn treatment at the end of the 20th century, and illustrated some of the problems burn care is likely to face in the decades to come.

These 27 patients suffered burns ranging from 9% to 100% total body surface area (% TBSA) (personal communications: Dr Marion Jordan, Washington Hospital Center, September 2002; Dr Roger Yurt, New York Hospital Burn Center, September 2002). Mean burn size was approximately 43% TBSA (54% TBSA for New York Hospital; 34% TBSA for Washington). Mean age of the New York patients was 43 years. Eight patients ultimately died, making the mortality rate 29.6%. This low mortality itself demonstrates the remarkable success achieved by burn treatment in the last several decades. In addition, the fact that all patients were moved quickly to major burn centers demonstrates the widespread acceptance—on a federal and a local level—of the concept of burn centers as regional resources. All patients had immediate access to comprehensive, team-oriented programs of care. In these respects, the system worked well.

Other aspects of this experience illustrate the resource-intensive nature of modern burn care and underscore potential limitations of our ability to provide for mass casualties. These patients all required “routine” modern treatment, which included aggressive fluid resuscitation, ICU and ventilator care (13 of 18 New York patients were intubated on arrival), topical and parenteral antibiotics, nutritional support, laborious daily dressing changes, immediate and repeated surgery for burn wound coverage (the nine patients at Washington Hospital Center underwent 116 operative procedures!) (Dr Marion Jordan, personal communication, September 2002), and prolonged, intensive rehabilitation.

Not surprisingly the most limited and critical resource proved to be skilled nursing. The Federal Emergency Management Agency (FEMA) provided nursing assistance to both institutions, initially by mobilizing Disaster Management Assistance Team (DMAT) nurses; subsequently, nurses from several burn centers through-
out the US were recruited to work 2-week shifts as temporary federal workers. This assistance was required for a long time. Although burn care has become more efficient and more successful, patients with major injuries still average about 1 day of inpatient treatment for each percentage of TBSA burned. As a result, on October 20, more than 5 weeks after the disasters, seven patients remained hospitalized in New York, and eight DMAT “float” nurses were still employed.\(^1\) Mean length of stay for the 11 survivors at New York Hospital was 58.7 days (Dr Roger Yurt; personal communication, September 2002); the last patient discharged from the Washington Hospital Center, with a 68% TBSA burn, went home 96 days after September 11.\(^1\)

Even more sobering is the realization of just how much greater the magnitude of this disaster could have been. If one or both World Trade Center towers had not collapsed, surviving burn victims could easily have numbered in the hundreds. During the past three decades, the number of burn centers in North America has decreased by 25%. Only 139 burn centers are currently listed by the American Burn Association (ABA), with a total capacity of perhaps 1,700 beds,\(^2\) most of which are occupied at all times by domestic burn patients. So even a relatively “limited” disaster of the magnitude of the recent Volendam night club fire in the Netherlands (200 burn patients)\(^3\) could easily overwhelm the resources of many of our best burn centers for months. Obviously, in such circumstances “float” nurses would not be available from other busy centers. The ongoing downsizing of the Brooke Army Burn Center removes another “failsafe” from our network of burn care facilities. As we enter the new millennium, our country’s ability to respond to a major burn-related disaster remains precariously limited.

The events of September 11 have been widely discussed in the burn care community, and will be a major focus for the 2003 meeting of the ABA, under President Marion Jordan. In the face of this experience, and of the potential for additional terrorist activity in the US, it is critical that the trauma and burn care communities of the US, with support of the federal government, work to create a realistic, workable, and adequately supported system of disaster management for the future.

### ORGANIZATION AND DELIVERY OF BURN CARE

#### Activities of the ABA
In the past 5 years, the ABA has expanded its scope of activities dramatically. In addition to the duties of a typical professional society (annual meeting, publications, etc.), the ABA has taken on major projects in professional and public education, advocacy, and support for burn care’s “infrastructure.”\(^4\) These include development of a coding manual (and accompanying instructional course) for burn surgeons, the Practice Guidelines for Burn Care, and a number of efforts to encourage and promote burn prevention legislation and practices. Other projects include the following: burn center verification, the TRACS/ABA burn registry, Advanced Burn Life Support (ABLS), and advocacy and public policy.

#### Burn center verification
The program of verification developed jointly by the ABA and the American College of Surgeons (ACS) Committee on Trauma has been reviewed in previous versions of this annual report.\(^5\) The program continues to thrive, with more than 60 burn centers verified (and reverified) to date. Burn centers that participate in this process uniformly find it helpful in improving quality of patient care, morale among staff, and visibility both within the hospital and in the greater community. As discussed, widespread acceptance of the burn center concept was demonstrated after September 11, 2001.

#### The TRACS/ABA burn registry
In another joint project with the ACS, the ABA has designed, developed, and distributed a sophisticated computerized database program to record information on admissions to burn center hospitals. The software,
called TRACS—including free training—is available to ABA member institutions; so far, more than 90 burn centers have received software. Two important advances in this project have recently been completed. First, the ACS and ABA have released version 3.0 of the registry, a Microsoft Windows-based program containing many upgrades and improvements, including a database for outpatient burns. Second, under a grant from FEMA, the ABA has created a National Burn Repository (NBR), and solicited data from ABA member institutions. At this year’s annual meeting in Chicago, the first annual report, containing data on more than 50,000 patients, was presented, and will soon be published. The ABA is committed to continuing and expanding these efforts in the future.

**Advanced Burn Life Support**
The ABA has taken over and revised the ABLS course initially developed in 1985 by the Nebraska Burns Institute. New provider and first-responder courses have been created, and CD-based instructional material distributed through the ABA central office. Courses are organized locally through ABA member institutions, and the number of courses being held is at an all-time high, stimulated, perhaps again in part, by the recent terrorist attacks.

**Advocacy and public policy**
Recognizing the uniquely close relationship the burn “team” has with hospitals, the ABA has created an Institutional Affairs Council, comprised of hospital administrators and burn care professionals. Last year, the Council met for their first annual leadership conference in Washington, DC, in an effort to contact and educate lawmakers regarding the critical role that burn centers play in national health. A second such retreat is planned for the spring of 2003.

Professionals interested in these and other programs of the ABA are encouraged to contact the association through their web site: http://www.ameriburn.org.

**“Extending” the burn center**
The decline in the number of North American burn centers is caused by several factors. The incidence of burn injuries has decreased through product and home safety efforts. Economic pressures to maximize bed usage have reduced “surge” capacity and shifted emphasis toward outpatient burn treatment. A number of hospitals have elected to discontinue financially nonviable services, and simply closed their burn centers. One consequence of this decline is that patients can have difficulty obtaining initial or followup burn care, especially when they live long distances from a burn center. Because burns are cutaneous, visible injuries, they should be ideal for evaluation through video photography. Redlick and colleagues have established a telemedicine network for followup care of their remotely located patients. In a pilot study, both patients and physicians found the system satisfactory; travel costs saved by patients helped to offset the expenses of setting up the system. Similar systems are now being developed in the US. In the future, as burn care adheres increasingly to national standards and technology becomes more available, telemedicine will likely become widely used for acute care of patients, consultation, and patient followup.

**Computerizing burn care**
Many aspects of burn treatment rely on assessment of burn extent and depth, including fluid resuscitation, nutritional requirements, and timing and type of surgery. But although burn wounds should be uniquely “quantifiable,” earlier studies have shown that individual practitioners estimate burn size and depth very differently, and that inexperienced clinicians are particularly inaccurate. As burn care moves more toward data-sharing and practice guidelines, the need to standardize burn wound estimates is obvious. To address this need, several computerized systems for estimating burn size have been developed. Neuwalder and associates evaluated two commercially available systems. Sage II (available at http://www.sagediagram.com) provides an age-specific, reproducible burn diagram, and also calculates fluid resuscitation requirements. 3-D Burn Vision (available on CD-ROM from Electric Power Research Institute, Concord, CA, 1-800-313-3774) provides a three-dimensional, rotating model. Both were judged usable in Neuwalder’s review. Programs for calculating fluid resuscitation, adapted for “palm top” computers, have also been described.

Assessment of burn depth is equally a problem. Holland and coworkers compared clinical assessment with laser Doppler imaging in the evaluation of partial-thickness wounds in 57 pediatric patients, who were then followed until healed or grafted. Clinical evaluation correctly predicted healing of 66% of deep-partial thickness burns, compared with 90% accuracy of laser Doppler imaging. Several previous studies have confirmed the
accuracy of laser Doppler imaging in evaluating partial-thickness wounds, though it remains debatable whether this modality is really superior to the assessment of an experienced surgeon. A new technology, “high-speed fiber-based polarization sensitive optical coherence tomography” was used to measure reduction of collagen birefringence in rat burn wounds, and correlated with burn depth assessed histologically. This and other technologies might be clinically useful in the future.

FLUID RESUSCITATION

Resuscitation volumes and endpoints

For some years, a common trend in burn care has been the use of increasingly generous amounts of fluid for burn resuscitation. Cartotto and colleagues reviewed 31 burn patients with mean burns of 27% TBSA (inhalation injuries and electrical burns were excluded) and found that they received a mean of $6.7 \pm 2.8$ mL/kg/6% TBSA burned for adequate resuscitation, with a mean urine output of $1.2 \pm 0.6$ mL/kg/hr. This finding illustrates the frequently made observation that resuscitating patients to a given level of urine output (as opposed to averaging urine output at the end of the resuscitation) very often results in administration of more fluid than called for by standard formulas.

In addition to departing more frequently from established formulas, burn care providers are questioning the appropriate endpoints for fluid resuscitation in burn patients. Jeng and coauthors performed a retrospective review of patients resuscitated using the Parkland formula, and found that only serum lactate and patient age, but not base deficit, correlated with mortality.

One argument in favor of “restrictive” resuscitation has been that lung water sequestration complicates fluid resuscitation, particularly in patients with inhalation injury. But Holm and associates studied lung water accumulation in a group of 35 adult patients resuscitated with crystalloid. Lung water and other cardiac parameters were measured using a thermal dilution, fiberoptic monitoring system, and patients were resuscitated with the goals of endpoints of normal circulating blood volume and cardiac index of 3.5 L/min/m². Authors found elevated lung water in only 3 of 140 measurements in these patients; no correlation was found between lung water content and resuscitation volume, or presence of inhalation injury. Of note is that all patients received more fluid in the first 24 hours than they would have using Parkland formula calculations, and individual patients received as much as four times Parkland estimates. Similarly, a study in sheep found that the addition of a cutaneous burn injury to smoke inhalation did not adversely affect oxygenation; Kuntscher and coworkers demonstrated no correlation between $\text{PaO}_2/\text{FiO}_2$ ratios and lung water measurements in a group of burned patients. Related studies found that circulating blood volume was low in patients with burns or inhalation injury despite the provision of Parkland resuscitation, and reconfirmed several previous findings that the presence of inhalation injury considerably increased fluid requirements for successful resuscitation in adult burn patients. Shimizu and colleagues demonstrated in a rat model that changes in oxygen radical production played a more important role than interstitial fluid hydrostatic pressure in causing postburn edema. Kim and associates demonstrated that enhanced perfusion of the “zone of stasis” of experimental burns occurred with resuscitation volumes in excess of the Parkland formula.

Taken together, these studies support the concept that Parkland resuscitation, though historically a “generous” resuscitation formula, in fact does not restore normal circulating volume during the first 24 hours postburn. Earlier work has shown that resuscitation to endpoints of cardiovascular function, oxygen delivery, or both will require substantially more fluid than is called for by standard formulas.

Do patients who receive increased resuscitation volumes fare better than those resuscitated with more restrictive, traditional regimens? No conclusive data support this premise; mortality rates for patients with even very large burns are now very low in many US burn centers despite lack of consensus regarding the best method of fluid resuscitation. Although the optimal method of resuscitation is yet to be determined, these recent studies would appear to argue that at least there is no reason to intentionally “run patients dry” during fluid resuscitation.

Abdominal compartment syndrome

In light of the trend toward more aggressive fluid resuscitation, it might not be coincidental that the abdominal compartment syndrome is being documented with increasing frequency in burn patients. But the relationship between development of abdominal compartment syndrome and “excessive” resuscitation is unclear. Regardless, patients who develop abdominal compartment syndrome often require decompressive laparotomy, with
additional procedures to attempt abdominal closure, or skin grafting of the abdominal contents with resultant hernia formation. In attempts to avoid some of this morbidity, two reports have evaluated the efficacy of percutaneous drainage of free abdominal fluid as an alternative to laparotomy. Latenser and associates treated nine patients with peritoneal dialysis catheters and were successful in avoiding laparotomy in five patients. Three additional cases were reported by Corcos and Sherman. This simple procedure might well be worth attempting in patients with threatened abdominal compartment syndrome, though these experiences underscore the need for continued vigilance and aggressive treatment if percutaneous drainage fails. It would also be interesting to know if quantifying free intraperitoneal fluid with ultrasonography would predict success for this procedure.

Myocardial depression in burns
The role of myocardial dysfunction in the pathogenesis of burn shock and resuscitation has been examined and debated for decades and has been the subject of several recent laboratory studies, mainly from the University of Texas Southwestern Medical Center in Dallas. The possibility that postburn myocardial depression could be partly from transient endotoxemia was investigated in an animal model in which mice lacking the gene for Toll-like receptor 4 (a necessary component of endotoxin response), or rats given an endotoxin-neutralizing protein, were protected from the impaired myocardial contractility usually seen after burn injury. This response appears to be mediated at least partly through interleukin (IL)-1 receptor-associated kinase activity because mice deficient in this enzyme are also protected against myocardial dysfunction postburn. In addition, plasma from burned animals induced cardiac myocyte apoptosis through a mechanism thought to be mediated by endotoxin. Indirect support for at least the presence of endotoxin in the immediate postburn period was provided by Steinstraesser and colleagues, who demonstrated increased expression of endotoxin receptor CD-14 in the skin of burn patients within 24 hours of injury. These findings suggest that endotoxin blockade might ameliorate the myocardial depression seen after clinical burn injury.

Other studies suggest equally important alternative—or complementary—mechanisms. In another study from University of Texas Southwestern, the activation of P38 mitogen-activated protein kinase, which participates in postburn myocardial depression, was shown to be stimulated by exogenous phenylephrine administration (though not by isoproterenol), and blocked by administration of prazosin or propranolol. Myocytes also elaborate both necrosis factor (NF)-kappa-B and tumor necrosis factor (TNF)-alpha after burn injury, without an obvious influence of endotoxin. This appears to be mediated partially through increased concentrations of ionized calcium in the myocyte. Ruthenium red, which blocks mitochondrial calcium uptake, ameliorates myocyte dysfunction. Administration of calcium channel blockers in a rat model also ablated burn-mediated TNF-alpha production by myocytes and improved myocardial function. Finally, myocyte contractile dysfunction is associated with a parallel increase in myocyte sodium concentration, without accompanying change in either cardiac ATP/plasma creatinine, or in intracellular pH. Clearly, the mechanism for this phenomenon is complex and undoubtedly multifactorial. Until the relative contributions of various components of postburn myocardial dysfunction are understood more clearly, clinical implications of these findings are limited.

Deep venous thrombosis in burn patients
Although prospective surveillance studies have demonstrated that trauma patients have a high incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE), limited data suggest that burn patients are at low risk. Recently published practice guidelines for burn patients did not find evidence to recommend routine prophylaxis against DVT, although burn patients theoretically have many of the same risk factors for DVT (tissue injury, hypercoagulability, bed rest, etc) as trauma victims. In a small prospective study from Michigan, Wahl and colleagues found DVT/PE in 11 of 30 burn patients (23%) followed with weekly duplex ultrasonographic examinations. This intriguing finding should be evaluated further in a large, multicenter study. Because clinically significant DVT/PE seems to be uncommon in burn patients, such a study would, ideally, also be able to define the therapeutic implications of asymptomatic DVT found on duplex examination in this population.

CARBON MONOXIDE AND CYANIDE INJURY
In what will likely become a landmark randomized controlled clinical trial, Weaver and associates demonstrated...
strated improved cognitive outcomes in victims of carbon monoxide (CO) poisoning treated with hyperbaric oxygen (HBO) therapy. Patients with CO toxicity were given three “dives” in HBO chambers totaling 7 hours in duration. Cognitive impairments were less frequent in the HBO group than in control patients at 6 weeks after treatment (25% versus 46%, p < 0.007). Because this influential study is likely to elevate HBO therapy to the level of a medical and legal standard of care for this condition, it might be worthwhile to discuss why these findings should not necessarily change the treatment of burn patients.

Weaver's group studied “isolated” CO poisoning, from automobile exhaust or malfunctioning furnaces, not smoke inhalation, which—by producing asphyxia, exposure to cyanide and other toxins, generalized inflammation, and airway and alveolar damage—is different and more severe than CO toxicity alone, with a multiplicity of pathologic consequences. Before that, Chou and coworkers found that children with smoke inhalation injury suffered more frequent loss of consciousness and cardiorespiratory arrest, required intubation more frequently, and had lower Glasgow Coma Scores and more severe acidosis than children with isolated CO exposure. Mortality from smoke inhalation was 23%, compared with zero for children exposed to CO alone. Weaver's group apparently studied no burn victims; only 8% of patients required intubation, few were hospitalized, and none died. In short, Weaver's group studied a distinctly different spectrum of illness than that of typical burn victims. In addition, the endpoints of their treatment—cognitive outcomes that were sometimes subtle and transient—were likewise very different from the goals of therapy for critically injured burn patients, for whom survival is itself a major challenge. In addition, burn patients must often recover from the effects of lengthy sedation, mechanical ventilation, major surgery, metabolic stress, and prolonged critical illness. These factors might well nullify the potential benefits of HBO therapy; certainly they make subsequent assessment of cognitive function and assignment of cause and effect far more difficult, and perhaps irrelevant.

Perhaps most importantly, the logistic problems of delivering HBO therapy to victims with major burns and inhalation injuries are formidable. Fluid resuscitation is perhaps the most critical component of early burn treatment. As mentioned previously, inhalation injury increases fluid requirements, but successful resuscitation might be impossible when patients are enclosed in HBO chambers for 7 of their first 24 hours. Transporting critically ill patients to HBO facilities is also dangerous and labor intensive: A previous study from Seattle documented a substantial incidence of complications among a small group of burn victims referred for HBO therapy, including hypovolemia, aspiration, hypoventilation, and cardiac arrest. These risks can frequently outweigh the modest improvements in cognition documented by Weaver's group. Partly for these reasons, recently published Practice Guidelines for Burn Care do not recommend HBO treatment to patients with major burns, critical pulmonary injury, or for whom interfacility transport is required.

Thom and coauthors demonstrated in a rat model that administration of HBO after smoke exposure resulted in diminished neutrophil accumulation in the lung, suggesting that HBO can benefit inhalation injury victims in ways other than by removal of carbon monoxide. Clearly, additional studies need to be conducted to elucidate the correct role of HBO in clinical management of smoke inhalation. Until a study demonstrates unequivocal benefits of HBO in critically ill burn patients, management should continue to be individualized by burn care practitioners.

INHALATION INJURY
Murakami and colleagues reported development of an animal model of smoke inhalation and respiratory sepsis by bronchoscopic instillation of *Pseudomonas aeruginosa* into the lungs of sheep after creation of an inhalation injury by cotton smoke. The animals treated in this manner developed a picture of hyperdynamic sepsis and acute respiratory failure considerably worse than sheep given inhalation injury alone. In commentary, Dries pointed out that, although this model provides valuable pathophysiologic insights, clinical inhalation injury can be capricious and unpredictable.

Pathophysiology of inhalation injury
In sheep, Cox and coworkers examined expression of endothelin-1, a potent vasoconstrictor with a variety of other inflammatory mediating properties. Endothelin-1 activity was pronounced in the upper airways but absent in the lung parenchyma. This peptide might play a major role in the upper airway spasm and inflammation seen in acute smoke exposure.
The local and systemic effects of smoke inhalation are known to be mediated in part by oxygen-free radicals. In a rat model, smoke inhalation was shown to increase oxidant stress for the first 48 hours after injury, independent of associated burn injury.\(^{41}\) In dogs, smoke inhalation produced decreased levels of cyclic guanosine monophosphate in blood and lung tissue.\(^{42}\) Treatment with inhaled NO attenuated pulmonary vasoconstriction, and was associated with notable increases in cyclic guanosine monophosphate, suggesting that NO might exert some of its effects through modulation of smooth muscle cyclic guanosine monophosphate levels.

But intrinsic NO appears to play a role in the cardiac dysfunction associated with inhalation injury. In a sheep model, inhibition of inducible NO synthetase (iNOS) prevented the appearance of NO metabolites in plasma after burn injury and the cardiac dysfunction and hemoconcentration seen in control animals.\(^{43}\)

Two recent studies have documented notable reductions in serum cholinesterase activity in patients with burns that correlated with both burn size and survival, and was even more pronounced in the presence of accompanying inhalation injury.\(^{44,45}\) The importance of this is unknown; cholinesterase levels are sometimes used as markers of hepatic function after organophosphate insecticide exposure. But they have also been shown to correlate with survival in septic patients. This chemical might be a marker for acute hepatic dysfunction occurring immediately after burns or smoke inhalation.

**Therapies for inhalation injury**

Previously, pretreatment of experimental animals with manganese superoxide dismutase has markedly reduced the hypoxic and hypotensive effects of inhalation injury. The efficacy of this treatment after inhalation injury was evaluated by Bone and associates.\(^{46}\) Ewes given inhalation injuries were randomized to receive various doses of manganese superoxide dismutase one hour after injury. No major differences were observed between control animals and those given three different doses of manganese superoxide dismutase (1,000, 3,000, or 9,000 units) in cardiac output, pulmonary artery pressure, pulmonary vascular resistance, or lung lymph flow. Bone and associates concluded that this therapy is substantially less effective than pretreatment.

Tasaki and coauthors\(^{47}\) evaluated the effectiveness of aerosolized heparin with and without the addition of intravenous lisofylline, which inhibits a number of inflammatory mediators, in a sheep model of inhalation injury. Only animals treated with both heparin and lisofylline demonstrated notable improvements in alveolar-arterial oxygen gradient and shunt fraction, and a reduced need for ventilator support. This study questions earlier studies demonstrating improvements in clinical parameters of pulmonary function after treatment with either aerosolized or intravenous heparin alone.

**Tracheostomy in burn management**

Possible advantages of tracheostomy in burn patients include the provision of a secure and comfortable airway, improved pulmonary toilet, and possible improvements in oxygenation. Palmieri and associates\(^{48}\) evaluated parameters of mechanical ventilation and sedation in a group of 38 pediatric patients before and after undergoing elective tracheostomy. Patients had mean burns of 54 ± 4% TBSA and underwent tracheostomy a mean of 3.9 ± 0.7 days after injury. After tracheostomy, patients had improved ventilatory volumes, lower compliance, and improved ratios of PaO\(_2\)/FiO\(_2\). There were no complications associated with tracheostomy in these patients.

**Complications of inhalation injury**

Ward and coworkers\(^{50}\) evaluated swallowing difficulties among 30 patients with major burns who had required prolonged mechanical ventilation (mean 24 days). Most had some problems on initial evaluation, but 90% of patients were able to tolerate a normal diet safely by the time of discharge. Dysphagia is probably quite frequent among patients being weaned from mechanical ventilation and can be a cause of major morbidity unless evaluated appropriately.

In an interesting long-term followup study, Casper and colleagues\(^{51}\) evaluated 10 patients, who had suffered burns and inhalation injury between 16 and 25 years earlier, for speech abnormalities. Seven of the patients were thought to have some degree of dysphonia, and all had abnormal laryngeal mucosa on direct examination. The authors speculated that earlier surgical or behavioral treatment could have corrected these problems. As more patients with severe burns and inhalation injuries survive their acute care, problems like this will doubtless become more widely recognized.
EXCISION AND SKIN GRAFTING
A number of previous studies have investigated the possible benefits of early burn wound excision and skin grafting in patients with major burns. Wu and colleagues,\textsuperscript{35} from the Galveston Shriner’s Hospital, examined their experience with what many surgeons would call very early surgical treatment. Among 157 children with major burns whom they reviewed, patients who had their first surgical procedure within 48 hours of injury experienced notably shorter lengths of hospital stay, less wound contamination, and fewer invasive wound infections than patients who underwent surgery from 3 to 6 days, or from 7 to 14 days postburn. They concluded that excision within 48 hours was optimal for children with extensive burns. There is no question that early surgical excision is widely accepted for burns of all sizes, and that surgeons are excising large burn wounds earlier and more aggressively than ever. But most burn surgeons wait to perform initial excision and grafting after patients are stabilized after fluid resuscitation, before wounds can become contaminated with bacteria. There might be no need to rush unresuscitated patients to surgery, but neither is there a benefit to waiting beyond 2 or 3 days postburn.

A number of burn care facilities use subdermal infiltration of salt solutions, often with the addition of epinephrine or neosynephrine, to facilitate donor-site harvesting and reduce blood loss—the so-called tumescent technique. Robertson and colleagues\textsuperscript{36} reconfirmed the efficacy of this technique in a small, retrospective study in their unit. Fort and associates\textsuperscript{37} documented that even very large doses of epinephrine (3 to 7 mg) given subcutaneously are usually well tolerated, with a minority of patients demonstrating modest increases in heart rate and blood pressure.

Ongoing disagreement (and, by implication, a paucity of data) surrounds the use of thick versus thin split thickness skin grafts. As pointed out by Mann and associates,\textsuperscript{38} most burn surgeons are taught that thick grafts have superior cosmetic results and less contracture; thin grafts have superior “take” and improved donor-site healing. In an attempt to resolve this issue, Mann’s group randomized adult patients to receive thick (0.025 inches) versus standard (0.015 inches) sheet grafts to the hands after burn wound excision. Both groups exhibited near-total “take,” normal range of motion, and acceptable appearance. Worthy of note is that donor sites in the standard group took more than 40 days to heal, while those in the thick group were themselves grafted with thin (0.008 inches) skin grafts. Authors concluded that standard grafts were as good as thick grafts in this setting.

This article deserves some comment. Donor site morbidity is an often-overlooked, but major source of concern to burn patients. Certainly a donor site that requires secondary grafting is unacceptable because it doubles the size of the wound, the discomfort of surgery, and the areas of cosmetic deformity. But donors who take as long to heal as those described in the standard group by Mann and coauthors are equally problematic. Many surgeons attempt to compromise by using moderately thick (0.010 to 0.012 inch) skin grafts, which give acceptable cosmetic appearance (especially on hands and feet, where “take” is usually excellent) with minimal donor site complications. Also, we have found that most dermatomes do not measure skin graft thickness accurately, and that the amount of pressure used while harvesting, the site harvested, and the use of subcutaneous clysis (the “tumescent” or “Pitkin” technique) all influence donor thickness. Often, the surgeon must “eyeball” the graft to assesses thickness. In short, this aspect of skin grafting, like many others, remains an art rather than a science.

Another study of donor site healing compared donor sites in adult burn patients treated with a moist silver-delivery system (Acticoat, Smith & Nephew, Inc, Largo, FL) with donors dressed with antibiotic-soaked gauze dressings.\textsuperscript{39} Silver-treated donors healed approximately 40% faster. Because donor sites are readily available wounds of defined thickness, they are often selected for trials of various topical wound-care methods. This study, like others, raises questions about the factors that really affect donor-site healing. Many gauze-type dressings facilitate growth of epithelial tissue into the gauze, retarding complete healing: nonadherent, moist dressings (NOT changed daily) facilitate healing. These details affect epithelialization markedly; the increment of improved healing provided by silver could have been assessed more directly if half the patients had been treated with Acticoat on top of the gauze dressings.

Skin grafting the burned face presents particular problems in both function and cosmesis. Cole and associates\textsuperscript{40} reviewed the experience of the Harborview Burn Center in Seattle with early excision and grafting of face burns in approximately 100 patients over 20 years. This group has popularized this technique; in this report, they
present 45 sets of complete photographs (including 1-year followup) of patients treated since 1979.

SKIN SUBSTITUTES
Although the use of cultured epidermal autografts (CEAs) can achieve closure of near-total burn wounds, the fragility and susceptibility to infection of this product severely limit its practical usefulness. In an animal model, addition of proinflammatory cytokines IL-α1 and IL-6 to keratinocyte cultures enhanced the expression of antimicrobial proteins and increased resistance to a variety of bacteria. This technique could facilitate durability of CEAs, though these cytokines could have a number of unpredictable or adverse effects on burn patients.

In a study from Japan, cryopreserved CEAs from other patients (“cultured allografts”) were applied to partial-thickness burn wounds and to split-thickness donor sites in a group of pediatric patients. The CEA-treated patients achieved closure of both types of wounds in less than half the time needed for untreated wounds, and scar formation was reduced in both situations. This use of “leftover” CEAs for these purposes has been reported before; though intriguing, the great expense of producing CEAs, and the legal and ethical problems associated with using them as allografts probably prevent the widespread use of this technique at present.

A bewildering array of synthetic and biologic dressings now exist for burn care. Although many products probably have some legitimate role in burn treatment, their optimal uses are often obscured by imprecise terminology (cadaver allograft, for example, can be either a biological dressing or a skin substitute), and considerable expertise is required for success with any of them. An illustration is found in the report by Peck and colleagues. They studied their initial usage of artificial dermis marketed as Integra (Integra LifeSciences, Plainsboro, NJ) in a randomized controlled clinical trial among adult patients with 45% TBSA, who had one of a pair of “mirror image” areas of excised burn wound (eg, bilateral arms of bilateral legs) randomized to receive artificial dermis, while the opposite area was covered with another available skin substitute, either human allograft, or Biobrane (Bertek Pharmaceuticals, Research Triangle Park, NC). In five of seven patients enrolled, and two additional pediatric patients, serious infections developed beneath the artificial dermis that required its removal. Four of these patients died. The authors point out that a considerable learning curve exists for artificial dermis. This experience is probably similar to that of other burn centers, and as a general principle, can be applied to other available products as well. Successful use of Integra has been reported from numerous other burn centers. It would obviously be beneficial to both providers and patients for surgeons to gain initial expertise in the use of such new products at experienced centers with established track records and protocols. In addition, the occasional use of such products outside of dedicated burn centers should be discouraged. This is one of the many areas of unique expertise that need to be concentrated in a few specialized “centers of excellence.”

Longterm results of a European skin substitute described as a “collagen Type I and elastin hydrolysate” were evaluated in two studies in the Netherlands. Patients had paired wounds covered with either conventional split-thickness skin grafts, or the collagen/elastin synthetic, plus a split-thickness graft. Patients were evaluated by physical examination and wound biopsy 12 months after surgery; no major differences were found between conventional and synthetic-enhanced skin grafts in a variety of parameters of scarring or wound healing assessed by blinded observers. The authors point out that the superiority of dermal substitutes to conventional skin grafting has never been demonstrated. At present, the most important potential usage for such products is to replace conventional grafting by temporarily covering excised wounds (and “buy time” to await the healing of donor sites), by permitting coverage with alternative techniques, such as ultrathin skin grafts or cultured epidermis, or by providing complete and permanent coverage without grafting.

This approach was attempted by Nanchahal and co-workers, who reported preliminary clinical use of an allogeneic composite allograft consisting of rat collagen and human fibroblasts and keratinocytes. This substance was used to graft three burn patients in a one-stage procedure, and compared with other areas covered with traditional split-thickness autograft. Cultured allografts showed modest amounts of “take” at 1 week, but were clearly inferior to autografts; one patient required regrafting.

As these reports illustrate, momentum is growing in the search to find an ideal skin substitute. At present, the most promising results have been those from the Cincinnati Shriners’ Hospital using a collagen-
glycosaminoglycan substrate covered with autologous keratinocytes to form a cultured skin substitute. This substance has achieved near-total “take” in a small number of patients with major burns. It is far more durable than CEs alone and has the advantage of being usable over Integra synthetic dermis. A review of 45 patients treated with either the cultured skin substitute or standard split-thickness autografts showed equivalent qualitative outcomes at 12 months. In the most recent subgroup of 12 patients, cultured skin substitute “take” exceeded 75%, and coverage was obtained with considerably smaller donor sites than for coverage with widely meshed autograft. The process still requires skin biopsy, and some time is needed to grow autologous keratinocytes, but the major limitation of this promising product is that it has not been able to be manufactured for widespread use. The next few years will likely see continued progress as investigators continue to move closer to perfecting a practical skin substitute.

INFECTION AND IMMUNOLOGY

Clinical studies
Burn units have historically concentrated effort on effective protocols to prevent spread of infection between patients, and units are often designed to optimize patient isolation and infection control. When their burn unit was remodeled, Thompson and associates moved their patients to either private ward rooms or ICU rooms, and noted a marked decrease in infectious complications, compared with before and after renovation, when patients were cared for in the burn center. Though the authors claim their data support the concept of patient isolation, in fact, isolation precautions appear to have been in effect at all times, and patients were cared for by the same staff; the most obvious variable seems to be that burn unit rooms were positive pressure isolation rooms. Previous studies have questioned the effectiveness of isolation precautions; this report does little to clarify this issue. Some unmeasured or uncontrollable variables, such as frequency of hand washing, traffic by visitors and other providers, and use of staff unfamiliar with burn care, could all have had a marked effect on infection rates in this report.

Central line infections have been a recurring source of complications in burns. Though routine catheter changes are performed in many units, the efficacy of this treatment remains largely unproved; also, the exact indications for this practice are unclear. In an interesting study from Argentina, Ramos and coworkers studied central venous catheters located near open wounds (NOW catheters, defined if an area of 25 cm² surrounding the insertion site overlapped the wound), compared with those located far from wounds. NOW catheters had almost twice the rate of colonization (84% versus 47%, p < 0.001), and almost five times the rate of bacteremia (27% versus 6%, p < 0.004). But the rates of colonization and bacteremia in both sets of patients seem high enough to justify caution, and perhaps routine catheter changes, in either case.

Urinary tract infections are also a problem in burn patients. Newton and coauthors compared standard latex to silver-impregnated Foley catheters in a group of burn patients. Standard catheters were associated with a higher incidence of urinary tract infections (7.2 per 1,000 patient-days) than silver-impregnated catheters (4.4 per 1,000 catheter-days; p < 0.029). But, it should be pointed out that the policy of changing the catheters in the silver-impregnated group might have been responsible for some (or all) of the reduction in infection rates.

Myelopoiesis in burn injury
One contributor to the immune dysfunction seen in burn injury is a reduction in circulating lymphocytes and neutrophils. In a rat burn model, both B and T lymphocytes underwent marked apoptosis and almost disappeared from the spleen, with some recovery beginning at 48 hours. Similarly, burn injury in rats resulted in reduced T-cell proliferation and IL-2 production in both Peyer’s patches and spleen. Changes in lymphocyte numbers, and in specific subpopulations, might be regulated partly by expression of the Fas antigen, which is decreased after burn injury.

In a mouse model of burn wound infection, Gamelli and colleagues demonstrated considerably increased production of granulocyte colony-stimulating factor in bone marrow and spleen, despite reduced peripheral blood leukocyte counts. This paradox appears to have several explanations, including a shift toward monocyte production, reduced receptor activity on granulocyte colony-forming cells, and suppression of myelopoiesis that is partially regulated by prostaglandin E-2. Similarly, Noel and associates demonstrated that bone marrow from burned rats exhibited a shift toward production of eosinophils when exposed to colony-stimulating factor. In a mouse study, serum prolactin deficiency in-
increased the formation of granulocyte-macrophage colony-forming units after burn injury.\textsuperscript{75}

**Cytokines and inflammatory mediators**

Active investigations continue into the extremely complex mechanisms that control the inflammatory response after burn injury. The availability of oligonucleotide arrays to assess for multiple changes in gene expression simultaneously was reported in animals, and demonstrated a variable of specific genetic responses affecting cell survival, metabolism, inflammation, and immune function, both in burn wounds\textsuperscript{76} and in intestinal cell cultures.\textsuperscript{77} Similarly, both burn injury and infection with *Pseudomonas* caused upregulation of expression of multiple proinflammatory and hematopoietic cytokines.\textsuperscript{78}

Although TNF-\(\alpha\) and IL-1 appear to mediate many aspects of endotoxin toxicity, the fact that specific antagonists of these agents have not been clinically effective illustrates the complexity of the many interactions involved in this process. In a study in patients, receptors to TNF-1 and -2 were increased and were higher in non-surviving patients than in survivors, although burn size was not different between groups.\textsuperscript{79} Levels of TNF-\(\alpha\) and endothelin-1 were also not different between survivors and nonsurvivors. Is the exaggerated expression of TNF receptors genetically predetermined? If so, it might provide one explanation for the failure of TNF blockade as a therapeutic intervention.

Fang and coworkers\textsuperscript{80} examined the role of high mobility group-1 (HMG-1) proteins, which have been implicated as another mediator of endotoxin. In a rat model, after burn injury, they found notably enhanced gene expression for HMG-1 in blood, lung, and liver that persisted up to 72 hours after injury and correlated with elevations of hepatic transcranes. Fazal and colleagues\textsuperscript{81} found that administration of a platelet-activating factor antagonist prevented Ca\((2+)-\) mediated elaboration of reactive oxygen intermediates, indicating the major role of platelet-activating factor and modulation of platelet-activating factor receptor activity in burn-related neutrophil function.

Schwacha and associates\textsuperscript{82} studied macrophage response to IL-10, an antiinflammatory cytokine, in burned mice, and found that IL-10’s ability to ameliorate inflammation was reduced, presumably because of diminished IL-10 receptor activity. In the same model,\textsuperscript{83} this group demonstrated increased macrophage produc-

tion of prostaglandin E(2) and COX-2, and suppression of IL-12. Treatment with a COX-2 inhibitor reversed these effects, but had no effect on IL-10 production. The authors concluded that COX-2 might have a major role in the immunosuppression seen after burn injury.

Pratt and coauthors\textsuperscript{84} identified changes in the phospholipid content of cell membranes of circulating lymphocytes from burn patients; 20:4\(\omega-6\) fatty acid content decreased initially after injury, but increased notably during the third week postinjury, while \(\omega-3\) fatty acids decreased. Simultaneously, natural killer cell cytotoxicity increased. This was true despite provision of an \(\omega-3\) fatty acid-supplemented “stress” formula to the patients evaluated. Though the authors speculate that dietary fatty acids might influence these observations, no direct evidence for this is provided in their study.

In mice, production of monocye chemoattractant protein-1 occurs quickly after injury and initiates type 2 T-cell responses that include elaboration of IL-4. These responses appear to increase susceptibility to some viral and fungal infections.\textsuperscript{85-87} Burn injury also appears to facilitate transcription of murine AIDS virus DNA, which has implications for other viral infections and immune dysfunction in burns.\textsuperscript{88}

In a randomized controlled clinical trial from India, Ravikumar and colleagues\textsuperscript{89} administered oral trypsin-chymotrypsin compound to 15 burn patients, and demonstrated reduced levels of serum IL-6 and IL-1\(\beta\) over the next 10 days. Patients with large injuries and patients suffering from sepsis had higher levels of these cytokines, but still appeared to respond to treatment. The authors also reported decreased edema formation in the treated patients, but provided no data to support this. If true, the fact that enterally administered proteolytic enzymes produced these effects is surprising. Does this agent affect hepatic synthesis of inflammatory mediators, or gut release from enterocytes or both? This intriguing finding deserves further study because it offers a potentially simple and noninvasive way to ameliorate inflammation after burn injury.

Antimicrobial peptides are being investigated as therapeutic modalities for infection control. Steinstraesser and associates\textsuperscript{90} investigated the efficacy of a “designer” peptide, novispirin G10, against resistant strains of *Pseudomonas aeruginosa* in vitro, and in a rat model of burn wound infection, and found marked bacterial killing in both situations. This peptide is thought to work by causing a massive efflux of potassium from *Pseudomo-
nas cells. In a similar study, the synthetic peptide D2A21 was effective in eliminating burn wound infection, and improving survival in burn-infected rats. Such innovative approaches can offer considerable hope for improved control of bacterial infections that are becoming increasingly resistant to traditional antibiotics.

**NUTRITIONAL SUPPORT**

**Selecting the route of enteral nutrition**

Although the superiority of enteral over parenteral nutrition for burn patients appears well established, controversy continues over the optimal route of delivery for enteral nutritional support. Some experts believe that intragastric feeding is more difficult than feeding with enteral tubes, and others deny that a difference exists. For example, Sefton and coworkers\(^9\) were able to use gastric feeding successfully in only 7 of 17 burn patients; jejunal feeds were successful in 10 of 12 patients (the 10 who failed gastric feeds plus an additional 2 patients).

The success of nasojejunal versus nasogastric feeding was evaluated in a randomized controlled clinical trial from Australia.\(^9\) Seventy-three surgical ICU patients were randomized to nasojejunal or nasogastric feedings. Patients fed into the intestine had smaller gastric residuals and a tendency toward improved tolerance of feedings. In contrast, Kreis and colleagues\(^4\) placed percutaneous endoscopic gastrostomy tubes in 12 burn patients (including 2 children), and found them more comfortable and trouble-free than nasogastric tubes, even when percutaneous endoscopic gastrostomy tubes were placed through burn wounds.

Some studies have also used prokinetic agents, such as erythromycin or metoclopramide to enhance gastric tolerance of enteral nutrition. At present, however, successful administration of enteral feedings of any type, especially in critically ill patients, remains complex and labor intensive. Surgeons who manage these patients need to individualize route, rate, and the use of adjunctive methods, and continue to monitor patients carefully to ensure success and avoid complications.

**Quantity and composition of nutritional support**

As clinicians have become more successful at feeding critically ill patients, recognition of the adverse effects of overfeeding have stimulated an effort to tailor nutritional support to the precise needs of patients. Hart and associates\(^9\) evaluated lean and fat body mass in a group of 42 patients with burns of 60% TBSA. Patients were fed enterally according to a standard formula, but also had routine determination of resting energy expenditure (REE) by indirect calorimetry. Increasing caloric intake above 1.2 × REE did not improve lean body mass, but was associated with an increase in fat mass. It should be noted that this study confirmed early observations that decreasing REE was correlated with mortality in this setting. Although maintenance of body weight is a common goal of nutritional support in other situations, burn victims suffer obligatory loss of lean body mass that feeding or overfeeding will not prevent.

Numerous earlier reports have documented that the high degree of variability in energy requirements for hypermetabolic burn patients render standardized formulas of limited value in estimating individual nutritional needs. In comparing several such formulas to indirect calorimetry in 24 adult patients, Dickerson and colleagues\(^9\) found none that were consistently within 15% of REE. They noted that older (before 1980) formulas tended to systematically overestimate energy needs, possibly because requirements actually were higher in the era of frequent sepsis and delayed wound coverage. This underscores the relative inaccuracy of using any static formula to predict the dynamic energy needs of burn patients, the superiority of indirect calorimetry, and the need for frequent reassessment of patient nutritional requirements and response.

**The gut and glutamine**

Considerable interest persists in the issue of gut-derived inflammation and bacterial translocation as contributors to the inflammatory response in infection seen in burn patients. In rats, Xia and coauthors\(^7\) demonstrated that burn injury produced major increases in portal vein concentrations of endotoxin, which were associated with enhanced lymphocyte apoptosis in mesenteric lymph nodes and splenic tissue. In a rat model, the addition of acute alcohol exposure was shown to enhance burn-induced intestinal permeability to bacteria without producing visible changes in gut mucosal morphology.\(^8\) Alcohol and burn injury also appear to have an additive effect in decreasing T-cell production of IL-4, which downregulates inflammation. Addition of exogenous IL-4 in this model restored delayed-type hypersensitivity responses and reduced IL-6 production.

Provision of the amino acid glutamine (GLN) is widely thought to be important as a specific nutrient for both enterocytes and lymphocytes, to reduce mucosal
atrophy, and ameliorate bacterial translocation. Wischmeyer and colleagues\(^9\) evaluated the effect of parenteral GLN supplementation in randomized controlled clinical trial among 26 patients with severe burns. The use of GLN was associated with a significant decrease in gram-negative bacteremia (8% versus 43%, \(p < 0.04\)), increases in transferrin and prealbumin, and reduction in C-reactive protein, compared with values in control patients. Mortality was not notably reduced. This interesting paper warrants several comments. First, this is a very small study; its results will need to be validated in larger trials before being accepted. Second, most studies of GLN efficacy have used enteral GLN to supplement parenteral nutrition (standard total parenteral nutrition formulas contain no GLN, which is relatively insoluble). These authors did the opposite and used large doses of GLN (0.57 g/kg/day). Their patients were fed a standard enteral formula containing no supplementary GLN. In contrast, most trauma and burn surgeons use specially designed stress formulas supplemented with arginine, \(\omega-3\) fatty acids, and GLN (in doses roughly equivalent to those used here). These formulas have been shown to enhance protein synthesis, and reduce infectious complications and oxidative stress in a variety of settings, including recent studies in burns.\(^{100-102}\) Although the study by Wischmeyer’s group appears to validate the benefit of GLN as a nutrient for burn patients, it would be helpful to know if specific GLN supplementation adds anything to the use of commercially available stress formulas.

Gut mucosal atrophy is observed after burn injury. In a mouse study, administration of antibody to TNF-\(\alpha\) reduced burn-associated loss of mucosal height and cell number and diminished the number of apoptotic cells,\(^{103}\) suggesting that gut mucosal changes are regulated by inflammatory cytokines and local nutritional effects. In a rat burn model,\(^{104}\) administration of a variety of COX inhibitors was associated with improved gut motility, restoration of gut and liver glutathione levels, and improved liver histology. Importantly, both COX-1 and COX-2 inhibitors were required to produce maximum improvements. These findings might give some insight into the clinical problems with intestinal mortality sometimes seen in burn patients.

**Mediation of hypermetabolism**

The past year has seen continued interest in the manipulation of burn-related hypermetabolism. Improved understanding of the hormonal influences on postburn catabolism and muscle wasting have stimulated therapeutic trials to reduce and control these phenomena. The foremost group in this area continues to be led by Dr David Herndon at the Shriners’ Burns Institute in Galveston, TX. They have evaluated a number of modalities for ameliorating hypermetabolism, including reduction of metabolic rate using propranolol, administration of counter-regulatory hormones such as insulin and insulin-like growth factor (IGF), and stimulating anabolism using growth hormone, natural steroids, and synthetic products such as oxandrolone.

**Propranolol**

A study from Galveston randomized 56 children with major burns to receive supplemental growth hormone, propranolol, or both.\(^{105}\) Propranolol markedly reduced resting heart rate and energy expenditure, measured by indirect calorimetry, and improved net muscle protein synthesis. Interestingly, the addition of growth hormone did not increase these effects. Muscle protein wasting appears to be caused primarily by accelerated protein breakdown; protein synthesis is also increased, but it fails to keep pace with proteolysis and amino acid mobilization in this setting.\(^{106}\) These benefits of propranolol treatment were confirmed in another prominent study by this group.\(^{107}\)

Propranolol also appears to reduce the rate of hepatic fat accumulation.\(^{108}\) This might be important because of the frequent finding of fatty infiltration of the liver—sometimes to massive proportions—in an autopsy study of children dying from major burns.\(^{109}\) There was a clear association between fatty liver and systemic sepsis, suggesting hepatic dysfunction, not overfeeding, as the cause of this finding. Hepatic triglyceride synthesis was enhanced in an animal model of burn injury;\(^{110}\) impaired peripheral use of nutrients in sepsis might enhance this effect.

**Insulin**

Thomas and coworkers\(^{111}\) evaluated the effect of continuous infusions of insulin (to maintain blood glucose between 100 and 140 mg/dL) on preservation of muscle mass in a randomized controlled clinical trial in 18 children with major burns. Evaluation of each patient when 95% healed showed that insulin-treated patients had improved lean body mass, less muscle wasting, and reduced length of hospital stay, compared with controls.
In an animal study, daily administration of subcutaneous insulin to burned rats resulted in reduced protein degradation in both skeletal muscles and immune cells. In a review of diabetic burn patients, McCampbell and associates found that patients with diabetes with uncontrolled blood glucose levels (defined as values greater than 180 mg/dL on more than 50% of determinations) had higher rates of infection and longer lengths of hospitalization than patients with diabetes with controlled blood glucose levels, confirming the clinical importance of careful control of blood sugar in burn patients.

**Insulin-like growth factor**

Gianotti and colleagues studied temporal fluctuations in IGF-1 and its binding protein in a group of burn patients, and demonstrated that both proteins declined for the first 14 days postburn, paralleling decreases in prealbumin and transferrin; plasma levels of growth hormone remained unchanged. In a small trial in children, administration of IGF-1 and IGF binding protein appeared to exert widespread effects in ameliorating acute inflammation by reducing the synthesis of type I and II acute phase proteins, and IL-6, and increasing synthesis of constitutive proteins, such as prealbumin and transferrin.

Alterations in IGF-1 seen after burn injury appear to be mediated at least partially by glucocorticoids. Lang and coauthors demonstrated that administration of a glucocorticoid antagonist prevented burn-induced decreases in plasma IGF-1, and associated muscle wasting. Antagonists to TNF-α had no effect on these measurements.

**Sex hormones**

The effect of male and female sex hormones in burn injury was investigated in several studies. In male mice, administration of 17β-estradiol after burn injury restored delayed-type hypersensitivity, reduced macrophage production of IL-6, and increased survival after bacterial challenge.

The ability of testosterone and of synthetic male hormone analogs such as oxandrolone to promote muscle anabolism and wound healing has previously been examined in a number of studies. Ferrando and coworkers administered intramuscular testosterone to six severely burned male patients, and evaluated testosterone levels and protein synthetic activity before, during, and after hormone administration. They found no change in protein synthesis, but there was a twofold decrease in protein breakdown, resulting in a net improvement in protein balance. Napolitano pointed out that there is some evidence that males have increased mortality and risk of infection after injury and that testosterone appears to have an immunosuppressive effect, including suppression of IL-2 and IL-3 release. This suggests that clinical use of testosterone will need to be evaluated extremely carefully.

How should practicing clinicians apply the results of these multiple trials of metabolic mediators? At present, the most immediately useful and probably least controversial intervention would be careful control of serum glucose. A recent large multicenter randomized controlled clinical trial in intensive care unit patients confirmed that careful regulation of blood sugar reduces infectious complications and overall mortality. It is unclear whether the benefit of this intensive regimen derives from the administration of exogenous insulin, or simply from reducing blood sugar to normal levels. Regardless, hyperglycemia is seen, and often tolerated, in many patients with major burns. The results reviewed here suggest that clinicians should be aggressive in treating this abnormality and in monitoring the effects of insulin administration.

In addition, propranolol is being used more and more for a variety of indications in surgical patients—it also reduces tremors and anxiety in surgeons. It appears to be a reasonably safe intervention, though the effects of β-blockade on protein metabolism have not resulted in major clinical improvements. Tachycardia and dynamic cardiac function are often apparent in burn patients, and use of this agent to reduce these findings seems reasonable. But this drug, like insulin, can have major side effects; practitioners will need to remain vigilant when administering β-blockers to critically ill burn patients.

Anabolic steroids, including testosterone and analogs like oxandrolone, are also widely used to ameliorate muscle wasting in patients with cancer and AIDS. Previous studies have suggested limited benefits associated with the use in burn patients. But before any of these modalities should be regarded as proved therapies, they will need to be confirmed in large, preferably multicenter, randomized clinical trials. Such a trial is currently
underway within the ABA. Hopefully, the next few years will see more such trials.

**Bone metabolism**

Previous studies have documented accelerated rates of bone resorption and clinically significant demineralization in burn patients. Akcay and colleagues demonstrated that administration of calcitonin in a group of burn patients was associated with reduced urinary excretion of deoxypyridinoline, a marker of collagen breakdown activity; growth hormone administration did not have this effect. Klein and coworkers studied levels of vitamin D and parathormone in a group of 12 children burned 2 to 13 years previously. They found abnormally low levels of 25 (OH) vitamin D in 10 of 11 patients, which correlated with bone mineral density and inversely with intact parathormone levels. The authors speculate that avoiding sun exposure, which burn patients are often advised to do, can contribute to chronic demineralization in these patients.

**WOUND HEALING**

**Immediate cooling of burns**

The practical benefit of immediate cooling in the treatment of burn injuries continues to be debated. An interesting large retrospective review from Vietnam examined this issue. Authors evaluated 695 children referred for burn treatment and grouped them according to whether they had been given immediate cold-water treatment as a first aid measure. They found that children given immediate cooling had a smaller proportion of full-thickness burns (33% versus 49%); relative risk for deep burns was 0.68 in the immediate-cooling group (95% confidence limits, 0.55–0.85). Authors concluded that immediate cooling should be advertised as a public health measure. The obviously uncontrolled and retrospective nature of this study calls its conclusions into question, but the methodology is unique, and data are rendered more notable by the realization that a randomized trial can never be performed.

Immediate cooling has been postulated to improve wound healing by reducing the zone of stasis surrounding the central burn wound. Baskaran and associates evaluated intravenous administration of the surfactant Poloxamer-188 (P-188), a common component of blood substitutes, in an experimental burn model. They found improved perfusion to the area surrounding the burn wound, and a smaller area of central necrosis, after treatment with P-188, suggesting that red cell “sludging” contributes to the extent of full-thickness injury after burns.

**Growth factors**

Circulating growth factors are widely recognized to affect many aspects of burn wound healing. Cribs and colleagues documented increased production of heparin-binding epidermal growth factor-like growth factor, and transforming growth factor-alpha (TGF-α) in epidermal cells after burn injury in mice. Levels of circulating TGF-β, a potent immunosuppressive cytokine, increased progressively for 8 days after burn injury in a rat model, but levels of IL-4, which is thought to regulate TGF-β secretion, remained undetected. TGF-β1 was also shown to increase in thymic tissue after burns in mice, with associated increased apoptosis and loss of thymic cell mass, while levels of smad-2 and 3, transcription factors that ameliorate the effects of TGF-β1, were reduced. This suggests a change in the balance and regulation of TGF-β1 activity and a mechanism for some of its immunosuppressive effects.

Yang and coauthors found elevated numbers of circulating fibroblasts, a newly described type of cell, in the blood of burn patients for up to a year after injury. These cells can play an important role in wound healing and scarring after burn injury. Numbers of cells correlated with burn injury size, and with levels of TGF-β1, suggesting systemic activation of this cell population.

The potential might now exist to deliver growth factors more effectively through gene transfer technology. Keratinocyte growth factor stimulates epidermal proliferation, but has been ineffective when applied topically, presumably because of enzymatic inactivation. Jeschké and colleagues delivered liposomal keratinocyte growth factor-cDNA to burned rats, and demonstrated dramatically accelerated epidermal proliferation and increased collagen deposition and neovascularization. In another experiment, liposomal cDNA for both keratinocyte growth factor and IGF-I were delivered to rats, and resulted in accelerated dermal and epidermal regeneration similar to that seen with administration of growth factor proteins. In a study of transgenic mice that overexpress the latent form of TGF-β, wound reepithelialization was notably inhibited in both heterozygous and homozygous animals.

Treatment of burn wounds by nonscientific methods is common in many parts of the world. A study from
Brazil examined the efficacy of propolis cream, a traditional remedy derived from bees' wax, in comparison with silver sulfadiazene cream in outpatient burns. The authors found no differences in microbial contamination, and believed that propolis-treated wounds showed less inflammation and more rapid scarring. It should be pointed out that patients' dressings were changed only every 3 days, considerably longer than the recognized efficacy of silver sulfadiazene. The infection rate in minor burns is low; any protective dressing is likely to be acceptable in this setting. The study does not permit the inference that propolis is an effective antimicrobial for use in patients with large or infected burn wounds.

**Hypertrophic scarring**

Application of topical silicone gel has reduced hypertrophic scarring in many patients, though its mechanism of action is not understood. Musgrave and associates measured cutaneous perfusion (by laser Doppler), and skin temperature in a series of 16 patients treated with silicone gel. Although the perfusion of scar tissue exceeded that of adjacent normal skin, there was no change in perfusion after 30 minutes of gel application. But skin surface temperature increased by almost 2°C. They postulated that change in local temperature might play a role in the mechanism by which silicone gel reduces scarring.

Nedelec and colleagues evaluated the number and function of myofibroblasts in normal skin, hypertrophic scars, and normotrophic scars from burn patients. They found a high number of myofibroblasts in hypertrophic scars that decreased over time as wounds healed. Treatment with interferon-α was associated with a reduction in total fibroblast number and increased numbers of apoptotic fibroblasts. The authors suggest that interferon can improve the clinical appearance of hypertrophic scars.

Altun and coauthors evaluated nerve regeneration into healing partial-thickness burn wounds in 22 patients. They found progressive increases in nerve fibers in both the dermis and epidermis over time, which did not reach normal levels. Of interest, they found notably fewer nerve fibers in hypertrophic scars, which appears to dispute the clinical observations that hypertrophic scars are painful. They postulated that nerve growth helps regulate scar formation in healing wounds.

Bioengineering technology in an animal model was used to assess the effectiveness of several types of treatment for full-thickness sulfur mustard burns in pigs. Full-thickness burn debridement using a CO₂ laser, followed by skin grafting, produced results equivalent to those of standard surgical excision and skin grafting. The authors believed that use of evaporation to detect vapor barrier function was the best indicator of wound healing.

**PSYCHOLOGIC SUPPORT AND PAIN CONTROL**

Burn centers are now devoting increased attention to the issue of pain control after burn injury, at least partly in response to mandates from the Joint Commission on Accreditation of Healthcare Organization that pain assessment (the fifth vital sign) and treatment be priorities in all hospitals. This focus on pain control, and ongoing efforts to discover innovative techniques to provide it, have doubtlessly been a tremendous boon to burn patients. This has been the subject of recent reviews.

The quantities of analgesics required by burn patients often exceed those of other disease states, and the pharmacokinetics of many drugs are altered after burn injury, because of increased volume of distribution and increased renal excretion and hepatic clearance of drugs. The pharmacokinetics of morphine and its metabolites was studied by Perreault and colleagues. They studied five patients on continuous morphine infusions at rates ranging from 4 to 40 mg/hour; although the clearance of morphine and morphine metabolites exhibited marked individual variation, values were within the range reported for other populations. Importantly, they noted no change in morphine kinetics during the 3 weeks the study lasted. Among burn patients, requirements for adequate pain relief are both variable and unpredictable; close monitoring and individualization of dosing are essential for successful pain control.

The use of oral analgesics for pain control in burn patients is preferred in many settings, particularly in children. Sharar and associates studied the use of oral transmucosal fentanyl in providing pain relief for 22 pediatric patients undergoing outpatient wound care procedures. They found that the fentanyl (10 μg/kg) was as effective as equivalent doses of oral oxycodone (0.2 mg/kg).

Three European randomized clinical trials have evaluated modalities for treatment of pain and inflammation after superficial burns. These studies are unusual in that they all use volunteers—for obvious reasons, a rarity.
in burn research. Werner and colleagues created first-degree (epidermal) burns on the legs of volunteers by exposure to a heated electrode. In two separate experiments (46 patients total), neither the topical application of cooling (8°C for 30 minutes, also by electrode) nor intravenous dexamethasone administered preburn produced any major reduction in erythema, pain, or secondary hyperalgesia. The finding of lack of utility for cooling is of interest, though the authors were obviously unable to assess the effect on depth of injury.

In contrast, a similar study from France evaluated the use of topical corticosteroids in a radiation-induced model of acute sunburn in 24 volunteers. Both steroid products improved erythema, edema, itching, and time to heal when compared with controls.

Nonpharmacologic methods of pain control are increasingly popular in burn centers. A recent randomized clinical trial found that hypnosis was more effective than other stress-reducing strategies in reducing anxiety associated with dressing changes, though pain scores were not affected. But Landolt and coworkers found that the more simple distraction provided by a cartoon movie did not appear to reduce pain associated with dressing change in a group of burned children.

Psychiatric dysfunction in burn patients
A series of studies have documented the frequent occurrence of psychological and psychiatric problems in burn patients. reviewed the psychiatric problems likely to be encountered in burn care, including disorders that contribute to burn injuries (psychoses, impaired judgment, self-harm), those resulting from the burn that affect the patient, and the psychiatric stresses encountered by family members (bystander stress). Two studies from the University of Washington tracked patient-reported levels of depression before, during, and after hospitalization for acute burn treatment. In the first study, moderate to severe depression was reported in 43% of patients. In the second, severe depression was uncommon, but depression scores correlated with burn size. Authors advise that patients should be screened for depression because it can seriously impair rehabilitation and quality of life for patients.

REHABILITATION
The effectiveness of a strict, supervised exercise regimen on pulmonary function after burn treatment was evaluated by Suman and associates in a group of children recovering from major burns. Children were randomized to receive a 12-week, in-hospital program supplemented with exercise, or a home-based program without exercise. Not surprisingly, the children in the inpatient group exhibited major improvement in pulmonary function compared with their home-based controls. Although it is obvious that few burn centers (or patients) could afford such a lengthy inpatient rehabilitation program, it is likely that the real improvement in these patients came from their exercise program, which could certainly be implemented on an outpatient basis.

Returning to work is a major goal of burn rehabilitation, but it has been studied relatively infrequently. Bych and colleagues reviewed the recent literature on this topic, and compiled return-to-work statistics for a group of 363 adults. Previous studies have documented return-to-work rates of 66% to 90%, but these authors noted that only 37% of their patients returned to their preburn jobs. Time to return to work correlated with burn size and was increased in patients with a preburn psychiatric history. As burn treatment becomes more successful, more attention should be focused on this and other important measures of functional outcomes.

A continual problem in the rehabilitation of burn patients is the calculation of impairment, which can have tremendous effect on compensation and return to work. Published American Medical Association guidelines are not completely applicable to burn injuries, and calculations are tedious and somewhat subjective. A new computerized program, the Dexter Evaluation and Therapy System (Cedaron Medical), connects directly to standard instruments, measures strength and range of motion, calculates impairments from them, and generates standardized reports. In a comparison to manual techniques, the Dexter system was almost twice as fast. Though the system is expensive ($27,000), it might be worthwhile for burn centers besieged with requests for these tedious but important procedures.

Relatively little research has been published dealing with the quality of life for survivors of burn injury, but interest in this field is growing as more patients survive massive injuries that would have been fatal just a few years ago. A major concern in this area is the arbitrary and subjective nature of the psychological tools used to measure outcomes. In a major, multicenter study funded partly by the ABA, a health outcomes questionnaire for children was developed at the Shriners Burn Institutes and reported this year. The 55-item questionnaire
(much shorter than many of the multistest panels frequently used in outcomes research) was tested in a group of 184 infants and children (and their parents) and 285 nonburned children, and found to have high internal consistency, clinical validity, and sensitivity to change over time. This valuable tool will almost certainly be widely used in the expanding field of outcomes research for burn patients; additional tools for older children are in preparation. In Sweden, Kilda and colleagues reported improvements of the “Burn Specific Health Scale,” also an abbreviated (40-item) tool for evaluating postburn functional outcomes.

RECONSTRUCTION

There are few controlled studies, or even large series, in the area of reconstructive surgery for burn patients. Nisanci and colleagues reported results in treating 32 patients with axillary contractures after acute skin grafting. They prefer the use of a scapular fasciocutaneous island flap, and report enhanced improvement in range of motion in 16 patients, compared with 16 patients treated by skin grafting or local flaps. This was a retrospective study, and selection of patients was not randomized. This type of flap would not be available in many patients whose torso burns extend to the back. Finally, the authors’ comment that axillary contractures develop after “inappropriate treatment of axillary burns” is probably misleading; contracture development is often more a consequence of postsurgical therapy and, importantly, of patient compliance, than of the operation itself.

Both tissue expansion and free tissue transfer are techniques regularly used in burn reconstruction. Takushima and colleagues described a unique combination of the two, creating an expanded latissimus dorsi flap for coverage of neck and face injuries. Yang and coworkers used thin (suprafascial) anterolateral thigh flaps for successful reconstruction of neck deformities in seven patients. Yildirim and colleagues reported use of distally based neurofasciocutaneous flaps for reconstruction of the lower extremity in 14 patients after electrical injury. Viability of the flap was thought to require a wide (5-cm) pedicle. Finally, El-Khatib and coauthors described an adipofascial flap based on the ulnar artery to reconstruct elbow contractures in 13 burned patients.

Synthetic skin replacement has also been used as a reconstructive technique. Danzer and Braye reported their results in using Integra synthetic dermis in 39 reconstructive procedures. Technical complications occurred in 9 patients, but results were considered good in 28 patients, average in 6 patients, and poor in 3 patients (2 patients were lost to followup). The use of Integra for reconstruction has been previously reported from several centers. Advantages include its “off the shelf” availability, simplicity of use, and the good functional and cosmetic results often obtained; disadvantages include technical problems (detachment of the silicone membrane, infection, hemorrhage) and the need for two operations over a 3- to 4-week period.

BURN UNIT TREATMENT OF NONBURN CONDITIONS

Over the past decade, the advantages of burn unit treatment for a number of nonburn conditions has become widely recognized. Foremost among these is toxic epidermal necrolysis (TENS), a severe variant of Stevens-Johnson syndrome. Because this disorder produces widespread epidermal loss in association with immune dysfunction and predisposition to infection, meticulous wound care and systemic support are key components of successful treatment.

Several publications have documented improving results for patients with TENS treated in burn units. Palmieri and colleagues conducted a multicenter review of 199 TENS patients treated at 15 US burn centers, the largest series in the literature. Overall mortality was 32%, but was increased in patients transferred to a burn center more than a week after the onset of symptoms. Other series from individual burn centers have documented similar excellent results for this extremely severe condition. In particular, mortality rates in children with TENS were below 10% in several recent series. Although a number of adjunctive treatments for TENS, including the use of intravenous immune globulin, therapeutic plasmapheresis, or both have been reported to improve survival from TENS in small, uncontrolled trials, it should be pointed out that mortality with conventional treatment is now so low that the incremental benefit of these measures is difficult to assess. Sorting out the relative benefits of these therapies will require a larger, multicenter trial. Until then, early burn center referral for patients with TENS should remain a standard of care.

Patients with necrotizing fasciitis and related soft-tissue infections are also frequently managed in burn centers. Faucher and colleagues reviewed their experience with 57 patients with necrotizing fasciitis or
Fournier's gangrene over a 10-year period. Survival for these patients was 88%, despite the frequent presence of diabetes, obesity, and other comorbidities. In the future, as burn centers struggle to exist in an era of cost containment, their ability to function as “wound” centers, and to attract supplementary patients with major wound-related problems, will likely be important elements of their survival.

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