INTRODUCTION

Burn care has significantly advanced in the past decades, commencing with the work of Gilles, Wallace, and McIndoe, who developed specific centers for burn care during World War II (Box 1, Figs. 1 and 2).\(^1\) The response to key burn-related disasters in Boston, Massachusetts, and Texas City, Texas,\(^2\) and the threat of nuclear war further drove the development of prominent burn centers dedicated to research and improving outcomes in severely burned patients. Advances in the 1950s, 1960s, and 1970s were rapid and wide ranging in response, most importantly the development of topical antimicrobials to decrease the threat of wound infection and...
resuscitation protocols to significantly decrease the incidence and ramifications of burn shock.³

In the late 1970s through the 1990s, advances in operative care took the forefront with the growing acceptance of early excision and grafting of burn wounds, ushering in another era of burn care and greatly diminishing wound care complications.⁴,⁵ Further, enhanced attention to the effects of nutrition and control of the hypermetabolic response decreased not only effects on mortality, but improvements in quality of life; thus, morbidity also became more of a focus. All of this took place during codification of multidisciplinary burn teams to enhance outcomes and recovery.⁶ The teams included not only surgeons and nurses with specialty in wound care,
but also specialists in critical care, rehabilitation, mental health, and nutrition. With the improvements in mortality, the margin for rapid recovery has diminished in this area, and thus quality of life after injury is now a larger target for future research. We are all indebted to the many pioneers who led the way to these tremendous advances that have dramatically decreased mortality and suffering in those with severe burns.7

Consequent to these major advances, we now see more clearly the problems left in their wake. Survivors of massive burns have significant wound and metabolic burden that could be addressed more comprehensively and rapidly. Further, the complication of burn wound healing is pain and scarring, which could be mitigated through novel treatments and techniques during acute care and convalescence. Last, survivors of significant burns are left with psychological scars that also should be addressed. It is in these areas that we expect to see advances in the coming years, and we hope that we will be able to maintain the pace set by those before us. In this article, we present some “preliminary” work that may be pointing to the direction of these advances, although time will tell in the end.

Current Standard Is Insufficient

- We cannot be satisfied with the status quo

Fig. 1. Major burn care advancements in the 20th century (and the future...).

Fig. 2. Ultimate goals of burn care.
CONTROLLING INFLAMMATION AND REGULATING HYPERMETABOLISM

In the past 10 to 15 years, significant advances have occurred from a greater understanding of the response to injury, and in particular burn injury, led by the findings of the Glue grant from the National Institutes of Health (www.gluegrant.org). Xiao and colleagues found that after injury, massive changes occur in almost every sphere of the genome of circulating cells, and that these are persistent with a response shape not related to subsequent clinical condition. Instead, the severity of the initial injury induces the massive genetic response without discrimination of those with good and bad outcomes. This was the first wide-scale and comprehensive study of the genomic response to injury in circulating cells, and showed that responses associated with innate immunity are radically upregulated, whereas those associated with the adaptive immune system were likewise massively downregulated. Perhaps most importantly, the responses for severe burn were 95% congruent with severe blunt trauma, providing support for the notion that severe burn is “the universal trauma model,” as espoused by Basil Pruitt many years ago, at least for the genomic response. The advantage of severe burn as a model of injury is that severity can be easily quantitated by total body surface area burned, and the clinical recovery phase can be reasonably predicted making it easier to research causes and the effects of treatment because of diminished variability. Further, solutions found for inflammatory and metabolic derangements in severe burn are likely directly applicable to severe injury and illness as well.

Surprisingly, complications such as nosocomial infections and organ failure were not associated with clear genomic evidence in these studies, as the responses differed only in magnitude and duration; the patterns of injury were indistinguishable between those with good and bad outcomes. Thus, investigations into differences in the genomic response patterns are not likely to yield much fruit in predicting outcomes after injury; perhaps differences in downstream events and interactions depicted in the epigenome or proteome may be an answer for prediction of outcomes, and thus targets for therapy. However, we thought this before with the genome... Regardless, only more investigation will give the answer. What this does tell us, from a general point of view, is that the responses to injury and their interactions are quite complex, and perhaps reductionist approaches from controlled bench research and rigid clinical trials will not yield blockbuster definitive answers. Instead, a piecemeal approach through empiric observation that has served us so well for millennia will continue to be the right approach. This large-scale study from the Glue grant has demonstrated that complexity rules the day, and no easy answers are forthcoming. For the future of burn research, this means that the study of the inflammatory and immune responses will need to be comprehensive. Further, these investigators showed that the shape of genetic responses in humans and preclinical models are not closely associated; thus, any findings in animal models must be confirmed in patients, as trans-species responses to severe burn may be quite different.

These series of studies showed us that in the human response to severe burn, the innate immune responses, such as those common in neutrophils and macrophages, are massively increased while the T-cell adaptive responses are downregulated. These give us some targets for treatment; the massive metabolic changes after severe burn are likely related to prolonged upregulation of innate immunity, and thus mitigation of this response may be effective with the use of such agents as propranolol and other anabolic agents. On the other side of the equation, relatively late effects of severe burn, such as viral and fungal infections, may be due to decreased adaptive
responses, and stimulation of this system with interleukin-2 or some other effector may be an answer to these specific problems.

Massive inflammation is generally related to the most severe burns, which are treated in critical care units because of the risk of complications, including organ dysfunction and frank failure. Future research will be related to identification of differential early responses between those who recover without incident, and those who go on to organ failure and death with the caveats mentioned previously. When these are identified, prospective treatments can be developed. Biomarker research has been a recent emphasis with interest in procalcitonin and urinary neutrophil gelatinase–associated lipocalin as early markers of sepsis and poorer outcomes; however, these have not as yet proven fruitful. What might be on the horizon is the use of nonlinear approaches considering dynamic contribution of many indicators and biomarkers depending on the particular clinical condition at a particular time. This information can then be collated and new signals unearthed; this is likely to be associated with the use of information technologies.

With the development of faster data processors, interconnectivity of platforms, and greater availability of data from computerized medical records, we are primed for further work in development of computerized support for decisions made in the burn intensive care unit (ICU). Currently, we have such systems for support of early resuscitation and glucose management. Almost any of the activities that occur in the burn ICU are amenable to such support systems, and it is conceivable that these also could be extended to less acute care and even outpatient management; we look forward to the development of such clinically applicable systems. Also, a significant by-product and feature of such systems is a systematized collection of data, which will likely contribute to even further advances.

As was recently espoused in a presidential address from the Shock Society by Robert Cooney, many of the “advances” in care of the critically ill, including burns, have occurred by discontinuing harmful practices. Examples in burns include barotrauma with high ventilator pressures, and waiting for separation of eschar before grafting. It is probable that some of our current standard-of-care methods will be questioned with the development of new technologies or changes in practice that will be eliminated. Potential targets for this will be the overuse of sedative medications and potentially topical medications. For instance, recent data suggest that opioid overuse contributes to adaptive immune suppression, which may be associated with poorer outcomes, and some topical antimicrobials actually may be counterproductive in terms of wound healing. Of course such changes must be preceded by novel treatments to address and treat the symptoms and outcomes for which these treatments are prescribed.

**ACCELERATING HEALING**

Burn wounds close naturally through extirpation of wound necrotic tissue in the first stage, and then coverage of the defect through contraction of adjacent normal skin or generation of new skin through epithelialization. Currently, we accelerate these processes through excision of eschar rather than spontaneous separation, and closure through local suturing techniques or the much more commonly used technique of skin grafting. With the development of early excision and grafting, healing times have decreased, as well as hospitalization times, but we seem to have plateaued in this regard. In this case, we are limited by the time for skin graft adherence and donor site healing, which has not seen any shifts since the inception of the technique almost 100 years ago. We previously showed that donor site healing might be
accelerated through the use of anabolic hormones, such as growth hormone and insulin, to stimulate proliferation of skin cells; however, this has not been widely accepted, perhaps because of cost and perceived side effects of the medications. It may be time to revisit the notion of whether healing times can be accelerated. This will benefit not only health care resource utilization, but also perhaps shorten the “inflammatory” stage and improve outcomes by decreasing subsequent complications.

Another potential avenue to accelerate healing might be through the use of cell-based therapies to vastly expand donor sites and thus decrease wound area. This might be accomplished through sprayed autologous keratinocytes. These might be used independently or in combination with allograft or allogeneic cells in hybrid techniques. This type of therapy was developed in Australia by Fiona Wood and her colleagues, with some initial success. Independent investigators in Italy showed that use of this technique was associated with significantly reduced donor site area and coincident pain. We are aware of current trials under way in the United States seeking Food and Drug Administration approval for the technology. Once this technology becomes available for use, we expect that many innovations will take place that might show an acceleration in healing, as demonstrated by the original investigators. This might occur in 2 ways, first by expanding the reach of cells while radically decreasing donor site area.

Another method by which healing time might be accelerated is through the use of skin substitutes that mimic a healed wound until autologous healing is secured. We currently use allograft or xenograft skin for wound closure, but the effect is only temporary. We need a technology that is longer lasting and that has other potential advantages, including improved scarring. This notion was first tested with a product termed Integra developed originally by Jack Burke and his colleagues in Boston. Many publications have shown that this and other materials like it can indeed mimic skin temporarily, and will incorporate into tissue with some advantage for wound closure time in massive burns. But, these still have to be associated with autologous skin grafts applied later in the course. These might be supplemented with some of the technologies mentioned previously that may be either immediate, as in Integra mentioned above, or with the use of cultured epithelial autografts.

Of course the problem of wound closure could be most thoroughly addressed by development of a skin substitute with the following specifications:

- Abundant and easy to store
- Handles easily and is not difficult to apply to a viable wound bed
- Adheres and does not separate with time; no rejection and no additional grafting needed
- Provides stable and long-lasting epithelial coverage once adherent

As a by-product, such a material would be optimal if no scarring were to occur either. Such a product is far into the future in all likelihood, but represents the “Holy Grail” of burn surgery. If this were available, then all that would be needed is excision of nonviable tissue and application of the product (without autogenous donor sites), and then immediate rehabilitation.

SCAR MITIGATION

Burn wound healing is associated with scarring, leaving both cosmetic and functional defects; these are the principal problems that plague burn survivors throughout their lives. At present, we address these scars through choosing techniques for initial
wound closure associated with less scarring, such as skin grafts in sheets or full-thickness grafts if available, and reconstruction with local or distant flaps or resurfacing. Although these are tried and true, new technologies are likely to further improve these outcomes; eventually we hope to secure healing without any scarring. There were initial hopes for this possibility with the development of Integra® and later acellular human dermis, as these substitute for the missing dermis thought to be the principal problem associated with scarring. However, these dermal substitutes have been in use for more than 30 years, and only a few reports have demonstrated objective benefit in terms of scar. Indeed, it seems as if a full-scale well-controlled multicenter trial is clearly indicated to demonstrate whether this is indeed an effective strategy for scar mitigation. This will show whether a dermal substitute is in fact beneficial in long-term scarring in those with significant open wounds, and will have great impact inside and outside the burn world.

Other potential treatments to mitigate scar include the use of localized therapies. Currently, some of the most commonly used are pressure garments with and without silicone, either in sheets or as a spray, and injected corticosteroids and antimitotic medications. Many have shown benefit for these therapies, whereas others have shown either modest or no improvement, including recent meta-analyses and review. Most of the effect appears to be on scar height with minimal effect on vascularization and pigmentation. Other potential agents in this sphere include intrallesional verapamil, and antimitotic agents, such as 5-fluorouracil, mitomycin C, and bleomycin. These too have shown some effect, again mostly on scar height, but the effects remain modest. All of these therapies are not easy to administer, as it takes months of treatment or repeated injections to have these effects. What is optimal is an easy-to-administer treatment either at the time of repair or thereafter that has beneficial effects to decrease or even eliminate scar. Ideally, this would be a local treatment to minimize systemic side effects.

Along the lines mentioned previously, the use of lasers to mitigate scar has gained significant momentum. This therapy is thought to activate more normal healing through “reinjuring” the tissue at intervals in a controlled way that “reorients” the healing process to proceed more normally. This treatment holds some promise, and may be effective, as would be demonstrated through well-controlled trials. Scar improvement is difficult to measure because all scars improve with time, even those that are “mature,” thus testing with well-matched controls should be done to demonstrate benefit; such a trial should be done in the near future.

Systemic treatments for scarring have not been tested methodically, but there is hope here. Hypertrophic scarring is typically associated with prolonged local inflammation (thus the steroid and antimitotic agent local therapies). Theoretically, prolonged inflammation should be associated with continued activation of a T-cell clone or group of clones that drive the inflammatory response that is quenched only with the development of tolerance. This most often occurs in 9 to 12 months, which is consistent with such a mechanism. Therefore, we wonder whether targeting activated T cells systemically, or even better the particular T-cell clones(s) driving the response might be an answer to scar mitigation. The act of scarring might be due to a self-antigen that keeps such a set of cells activated, and a search for such a potential mechanism should be considered. However, the finding from the Glue grant of decreased adaptive immunity argues against this theory, and perhaps it is an as-yet not understood manifestation of an innate immune response that is long lasting (?). These possibilities should be investigated in the future with a potentially systemic solution for those with massive burns, or perhaps a local solution for those with small injuries.
Last, from clinical observation, we know that scarring is worse in some than others, which appears to be partially related to genetic background. Such an observation suggests a predisposition for scarring that can be targeted for treatment. This would inhibit hypertrophic scarring in these persons, but would also identify a central mechanism for all scarring. Approaches to address this would be to first identify the population at risk, and then comparative differences between the affected and nonaffected populations. These differences will likely be related to the genome, but may be genetic or epigenetic and thus will be difficult to work through. It should be noted that the system is likely to be quite complex, with a number of stimulators and inhibitors interweaving across time (see an example in transforming growth factor-β as described by Arno and colleagues). The first step is that above, we need more descriptive research in this area to illuminate the target better which will allow for a more rational approach.

ELIMINATING PAIN

One of the principal consequences of burns is pain, which can be from minor to severe in the acute phase depending on the depth of injury. Paradoxically, deeper burns have less pain because of associated destruction of nerve endings acutely; however, treatment of these injuries with skin grafts induces intense pain from the donor sites. Then, as the wound heals and the scar matures, contracture and reinnervation lead to classical pain sensation as well as neuropathic pain, which can be extremely debilitating. Treatments for pain related to burns have been with the use of opioids, which are time-honored and generally effective. However, some have recently shown that the use of exogenous opioids is associated with immunosuppression, and may have other downsides. At times, opioids alone may be insufficient for pain relief, and so adjuncts will be used, such as anxiolytics, nonsteroidal anti-inflammatory agents, gabapentin and its derivatives, and even nontraditional methods, such as hypnosis and distraction techniques. The last of these has attracted the most attention of late, with virtual reality and other technologies.

Research into pain control suffers from a “lumping approach” it seems; burn pain in the acute phase is likely to be different from that related to scarring and rehabilitation, yet these are treated similarly. Inflammatory mediators and other inducers of pain differ radically between these periods, thus it seems that to move research in this area forward, we should be seeking to categorize pain and thus its likely effective treatments as a major effort. This will involve efforts in clinical research as well as basic bench research to elaborate the potential known and novel mechanisms and treatments to alleviate the associated suffering of patients. This should include an assessment of variability in pain throughout the day as well as across days to weeks. For instance, background pain is often not severe in the first few days of treatment once the pain of the initial injury has subsided, but procedural and movement-related pain can be excruciating. Research into how to address pain at the right time is sorely needed. Further, as the wound heals and scarring starts, pain seems to shift to more of a background nature, and other treatments may be of benefit. We hope that through investigation of mechanisms and temporal-related effects, we will be able to address pain in a more proactive manner to decrease these sensations. Further, we hope that new techniques can be developed to decrease wound burden to decrease the afferent signals causing the pain in the first place.

Neuropathic pain is typically difficult to treat, and is thought to occur in 7% to 70% of those with severe burns, which is related to burn size and skin grafting. It commonly develops at 4 months after injury, and is characterized by complaints of
“pins and needles,” stabbing, burning, or shooting sensations. Hypertrophic scarring is a common associating factor. The pain is defined by its variability, and thus treatment is often hit-and-miss and therefore commonly ineffective. Medications in use include gabapentin and its derivatives, as well as methadone, local lidocaine, and even hyperbaric oxygen. Neuropathic pain is common in our patients, but we do not have any defined answers. Research efforts then should be focused on clearly defining the condition in the severely burned, including its characteristics, both acute and prolonged, long-term effects, and any resolution from a clinical standpoint from many viewpoints. These efforts should then direct the development of models to determine mechanisms and therefore focus on potential solutions. This problem, like so many of those already mentioned, is complex, with many contributors having dynamic temporal effects and nonlinear impacts; this must be appreciated to realize truly beneficial treatments.

In this section, we must mention the problem of itch as another target for future research. This is a quite debilitating issue that is encountered by almost every burned patient, and like the problem of neuropathic pain, is incompletely understood and thus incompletely treated. In fact, the two are likely related. Further research should be directed in a manner similar to that of neuropathic pain.

REHABILITATION IMPLICATIONS

Rehabilitation to facilitate return of function during and after burn wound healing is a central part of treatment, and persons dedicated to this problem comprise a large part of the burn treatment team. Then, from its near universal adoption, including a significant amount of funding, the empiric benefits of directed rehabilitation efforts in the severely burned are clear. Interestingly, this benefit has never been well described in the literature with only a few showing objective benefit. Therefore, one of the first tasks in burn rehabilitation research is to demonstrate benefit at all. Then, questions about dosing (time spent in rehabilitation) and particular techniques should be tested objectively to show whether these are worthwhile. It would seem that the burned patient would be a great population to demonstrate the effects of rehabilitation, as these persons are significantly debilitated and then return to normal function in most cases, thus providing a great model to demonstrate utility of changes in practice.

We need to know exactly how we should be treating burned patients, which is mostly based on experience and expert opinion with a paucity of data. Questions that should be addressed include description of expected recovery trajectories, depending on the initial injury and other contributors that can be measured. This has been shown to some extent in children, where it was found that many rehabilitation outcomes, such as gross motor skills, rapidly recover after injury but then plateau at 3 to 6 months. All of these children received active rehabilitation from dedicated professionals, but was this beneficial (which we believe is quite likely), and if so which types were most effective objectively? This type of analysis should be expanded further in children, and then extended to address these particular findings in adults (and the elderly in particular). With this information, we can show that established and novel treatments have beneficial effect, and whether these should be generally adopted. Specific questions to be addressed include early versus late treatments? Does the state of evolution of the wound/scar matter in terms of rehabilitation techniques? What about the role of routine exercise? Are there pharmacologic adjuncts that should be explored? Should patients be pushed to some threshold to maximize benefit, or is any effort sufficient? These are pressing questions that should be answered in the coming years.
PSYCHOLOGICAL RECOVERY

Finally, as described previously, mortality has given way to long-term outcomes as a primary target for modern research. Of these, psychological outcomes are clearly among those that could be improved, and should be further addressed. A significant amount of published work is extant on such topics as acute stress disorder, post-traumatic stress disorder (PTSD), adjustment disorder/depression, and anxiety. Many have shown that those who sustain burns are more likely to have preexisting mental health issues. Further, the incidence of PTSD is 10% to 30% in those treated for burns, regardless of severity, and is associated with the development of serious depression and other psychiatric disorders; this is a striking figure that is not well understood or appreciated. Reasons for this may be the lack of data to support effective treatments, although this is changing, with recent studies showing some benefit for pharmacologic treatments. Regardless, this is an area ripe for the development of effective therapies.

Therapies for psychologic and psychiatric outcomes for the severely burned may be pharmacologic, or may come from other measures, such as adaptive techniques, nontraditional methods, such as acupuncture or aromatherapy, or from some other method that has yet to be discovered. What we do appreciate is that symptoms and effects of treatment are likely to be highly variable because of the diversity of backgrounds, effects of injury, extenuating circumstances, and the environment of treatment and home life after injury. This amount of variability intimates that there are very many unappreciated contributors that effect the course of disease development, the effects of treatment, and the eventual outcomes of affected patients across the spectrum of time after injury. We need more information about these contributors and when the contribution is greatest (and least) to maximize outcomes.

SUMMARY

This review demonstrates that many advances have been made in burn care that have made dramatic differences in mortality, clinical outcomes, and quality of life in burn survivors; however, much work remains. In reality, the current standard of care is insufficient and we cannot be satisfied with the status quo. We must strive for the following goals:

- No deaths due to burn
- No scarring
- No pain

These particular goals have only begun to be confronted.

To address these issues, continued work using established methods, such as clinical observation and assessment, clinical trials, and translation from the bench, will continue to be effective, and must be fully supported and encouraged. However, new insights and new techniques, such as the use of information technology to investigate and understand dynamic and temporal effects, should come more to the forefront. Many of these techniques are well established in such fields as economics and business strategy, and some of these should be borrowed to better understand the role of scalable events and interactions among significant contributors in the development of findings and recovery from severe burns. This will involve a shift from reductionist (classical mechanics) to dynamic contribution/probabilities (quantum mechanics) and thus will be unfamiliar to many. However, in clinical care, weighing a number of findings at a particular time and background, and reaching a decision for treatment is something that burn care providers do every day; it is inherent and
often not recognized as such. Experts in any field examine the interactions of various contributors, both known and unknown, and reach decisions that are more often than not beneficial. In the future, this should be recognized and defined, and then promulgated. Further, these known and unknown contributors are likely specific to the species of interest, the human. This statement is not meant to detract from investigations in other species; biologic truths are likely to extend past these boundaries; however, the interactions of these truths will most likely be species specific. So, the best model of human disease is in fact the human...

REFERENCES


