PROGRESS IN BURNS RESEARCH: A REVIEW OF ADVANCES IN BURN PATHOPHYSIOLOGY

LA RECHERCHE EN BRULOLOGIE: REVUE DES PROGRES EN PHYSIOPATHOLOGIE

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SUMMARY. Severe burns trigger a wide range of responses in the victim. Initial vascular changes are followed by hypermetabolic, inflammatory and immunologic changes. The prolonged hypermetabolic response is associated with an elevated resting rate of energy consumption, tissue wasting and altered substrate kinetics. There is increased blood glucose though insulin levels are above normal. The cortisol level is raised and, together with catecholamine, drives the metabolic response. The immune system is typically weakened. There is elevation in blood levels of a wide range of cytokines from activated cells. These agents drive a prolonged inflammatory response which can lead to tissue damage and multiple organ failure. Dynamic fluid resuscitation regimens have cut down mortality from shock in the early post-burn period. However, unbalanced activity of pro- and anti-inflammatory cytokines can leave patients in an immuno-suppressed state that affects outcomes. So far, many treatments, such as propranolol, a cardio-protector, and anabolic agents, such as oxandrolone and growth hormone, have been tried with mixed results. This review focuses on research that elucidated burn pathophysiology. Some clinical areas in which treatment centred on correcting altered physiology were also included. We have highlighted both the challenges and significant findings. Finally, this paper draws attention to the gaps between progress in basic research and clinical application and suggests areas where further research and funding could be focused.

Keywords: burn pathophysiology, fluid resuscitation, hypermetabolic response, immuno-suppression, smoke injury, multiple organ failure

RÉSUMÉ. *Les brûlures graves déclenchent un large éventail de réponses chez la victime. Après des modifications vasculaires initiales, on assiste a des changements hyper métaboliques, inflammatoires et immunologiques. La réponse hyper métabolique prolongée est associée à un taux élevé de consommation d'énergie au repos, d'élimination des déchets tissulaires et de la cinétique de substances altérées. Il y a une augmentation de glucose dans le sang même si les taux d'insuline sont supérieurs à la normale. Le niveau de cortisol est élevé ainsi que celui des catécholamines, et ils induisent la réponse métabolique. Le système immunitaire est généralement affaibli. Il y a aussi une élévation du taux d'un grand nombre de cytokines. Ces agents causent une réponse inflammatoire prolongée qui peut conduire à des lésions tissulaires et à une défaillance multi viscérale. Des nouveaux plans de réanimation liquidienne ont réduit la mortalité causée par le choc dans la période initiale après la brûlure. Cependant, l'activité déséquilibrée des cytokines pro- et anti-inflammatoires peut laisser les patients dans un état d'immunosuppression qui influe sur les résultats. Jusqu'à présent, de nombreux traitements, tel que le propranolol, un cardio-protecteur, et des agents anabolisants, tels que l'oxandrolone et l'hormone de croissance, ont été essayés avec des résultats mitigés. Cette revue se concentre sur la recherche qui a éclairci la physiopathologie des brûlures. Certains domaines cliniques centrés sur la correction des troubles physiologiques ont également été inclus. Au total,nous avons mis en évidence les défis et les résultats significatifs. Avec cet article, nous attirons l'attention sur les lacunes qui persistent entre les progrès de la recherche et son application. En plus, nous suggérons des domaines où la recherche et le financement pourraient être prioritaires.*

Mots-clés: *physiopathologie des brûlures, réanimation liquidienne, réponse hypermétabolique, immuno-suppression, inhalation de fumée, défaillance multiviscérale*

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Introduction

Despite a considerable decrease in the incidence of burns in the developed world, they remain one of the commonest forms of injury and account for a significant proportion of trauma cases in hospital emergencies worldwide. In the United States, up to 1.2 million people experience burn injuries each year, while there are 2 million fires reported.[1] Most cases (75%) are mild and are treated on an out-patient basis.[2-3] Severe burns, however, continue to cause devastating morbidity and significant mortality.[4-5]

Emphasis in research on burn pathophysiology has shifted considerably over the last few decades. Hypovolemic shock, followed by wound infection, accounted for the majority of deaths from burns in the early part of this period. Consequently, they were the main areas of burns research in the period leading up to the 1980s. Wound treatment, healing and scar problems were also prominent areas in the published literature at that time. The direct outcome of this earlier work was that various strategies to prevent hypovolaemic shock were developed and incorporated into clinical practice. These involved phased fluid/colloid replacement regimens.[6-8]

On the clinical side, a great deal of innovation occurred in the prevention and treatment of wound infection; strategies to control the healing process and reduce scarring were also developed. Novel wound covering materials and techniques were used to reduce access to invading microbes. Such was the explosion in the development of wound care products that wound dressings (synthetic, semi-synthetic and controlled delivery drug products) on the UK drug tariff increased from 4 in 1988 to 57 in 1998, and 256 in 2007.[9] Burn practitioners began to carry out bold debridement procedures which, by clearing wounds of devitalized tissue, reduced the fodder on which proliferating microbes thrived.[10-11] The war against wound infection also profited immensely from the development of new generations of increasingly potent broad-spectrum antibiotics. Though many measures have contributed to the great reduction in burn mortality, there is a consensus among investigators that early wound excision, followed by immediate restoration of the skin barrier through grafting has proved a significant benefit to overall patient well being and in reducing infection-related deaths. Of course, the war is yet to be completely won but much progress has been made.[1, 12-13]

In the last few decades, researchers have directed their attention towards new areas such as the metabolic,[14-15] inflammatory,[16-17] immunologic,[18-19] endocrine[20-21] and cytokine[22-23] responses to burns. Another new area in burn research is the effect of burns on male reproductive organs.[24-25] Consequently, a large body of studies has been published, especially by Herndon and his many collaborators, describing the metabolic response to burns and thus providing an expanded understanding of the variegated metabolic alterations taking place in the post-burn period. However, there is no evidence that rational interventions based on these findings have gained widespread application in patient care.

The objectives of our study were two-fold: to review significant developments in the study of burn pathophysiology over the last two decades; and to draw attention to the gap between research findings and clinical practice, including showing how the occurrence of unexpected and controversial findings may be encouraging this gulf.

To achieve our objectives, we reviewed summaries in English of the published literature on burns sequelae in humans and experimental animals in Medline and other web-based sources covering the years between 1992 and 2012. We used search terms such as: "severe burns," "metabolic changes'', "endocrine", and "cytokine changes." In order to improve depth of coverage, the focus was narrowed to issues relating to pathophysiology. Consequently, studies which emphasized purely clinical issues were excluded from this review. A summary of our key findings can be seen in *Table I.*

Table I - Summary of key findings

Topic	*Significant Finding*
– Fluids/Colloids:	No formula meets the needs of all patients; many patients are getting more fluids than predicted by formulas
– Hypermetabolic state:	Occurs for prolonged periods and is accompanied by increased energy and calorie demand
– Catabolic state:	Occurs along with nitrogen depletion and general tissue wastage
– Hyperlipidemia:	Can lead to fatty infiltration
– Endocrine changes:	Altered levels occur in several key hormonal axes, and include hypertestosteronemia
– Spermatogenesis:	Is impaired, possibly due to increased apoptosis and impaired spermiogenesis
– Smoke injury:	Increases fluid need and mortality; Carbon particles and toxic gases cause edema, slough lung mucosa and promote hypoxia
– Cytokine response:	A wide ranging response occurs sometimes involving groups with opposing effects on inflammation
– Immune suppression:	Is typical, with reduction in number and power of several subsets of the immune cell population

Resuscitation and respiratory care

A considerable number of fluid resuscitation formulas gained popularity in burn centers in the period under review. Although the Parkland formula, which is based on lactated Ringer's solution, has come to be adopted by the American Burn Association (ABA) as a consensus formula,[26] no single preparation meets the needs of all patients; a failure which explains, at least in part, the multiplicity of formulas. These formulas fall into three main groups:

i Isotonic crystalloid formulas, e.g. Parkland, are based on lactated Ringer's solution.
ii Hypertonic formulas, e.g. Monafo,[27] use Nacl or lactated Ringer's titrated to a UOP (urinary output) of 30-50ml/h.
iii Colloid formulas, e.g. Evans,[27] where fresh-frozen plasma is added to the electrolyte solution.

In these formulas, fluid requirement is calculated based on weight and TBSA, total body surface area burned a specific fraction is typically given in the first 8 hours post-burn and the rest is spread over the next 16 hours. Some centers have adapted these formulas in different ways to meet their own patient needs. However, practitioners are well advised to treat the burn patient like any critically ill person, and titrate resuscitation fluids in whatever formula is being used to clinical goals such as MAP (mean arterial pressure) of 60mm and urinary output (UOP) of 30ml/h, even though it has been shown that these parameters do not guarantee that all critical vascular beds have optimal perfusion pressures. These parameters must be considered suitable treatment targets while the search continues for better indicators of adequate perfusion because this is an important determinant of critical organ damage and mortality.[28]

It should also be noted that, while fluid treatment formulas are scientifically calculated, studies show that, in practice, burn patients generally end up receiving more fluids than predicted by most of these formulas. For example, in a multi-center survey, Engrav et al. found that up to 58% of patients were getting more fluids than indicated by the Baxter formula.[29] Patients taking more fluids have higher burn mortality, which would be expected because increased fluid intake is an indication of greater burn severity. Higher volumes can also promote fluid overload; a situation that carries a significant risk of further complications, especially compressed compartment syndromes.[30] Several approaches have been tried to reduce the fluid given to burn patients. They include the use of colloids and hypertonic fluids,[31] high-dose vitamin-C,[32] and albumin, as well as plasmapheresis.[33] Research on these treatments should be encouraged, though the use of albumin in the critically ill has generated controversial results.

It is well established that there is increased fluid requirement when burns are associated with inhalation injury. The figures vary but inhalation injury is present in anything from 15 to 35% of burn patients, especially with burns caused by flame fires in closed spaces.[34] The injury is mostly due to smoke but steam inhalation can also injure the lungs. Smoke damages the airways through several mechanisms. Dry heat damages the supra-glottic parts of the airways and can cause edema, and narrow the upper airways significantly. Carbon particles and combustion products generate an inflammatory reaction in the lower airways associated with edema and sloughing of respiratory mucosa.[35-36] Mucus, cell debris, netrophils and fibrin eventually form casts that block medium-sized airways, while plasma leak due to altered micro-vascular permeability, by increasing extra-vascular lung water can decrease lung compliance by as much as 50% within the first 24 hours post-burn.[35]

In addition, inhalation injury inactivates surfactant very quickly, causing micro-atelectasis and ventilation-perfusion mismatch. The resulting physiologic shunt in severe cases causes severe hypoxia, increased alveolar capillary permeability and alveolar flooding, and the clinical presentation of typical Acute Respiratory Distress Syndrome (ARDS).[35] Stasis in the terminal airways encourages bacterial growth and the development of pneumonia. Carbon monoxide and hydrogen cyanides are toxic gases found in smoke which have been shown to promote hypoxia and respiratory distress.[37-38] Carbon monoxide has an affinity for hemoglobin that is 200 to 250 times that of oxygen, and can therefore easily reduce arterial oxygen levels and cause death from hypoxia. Carbon monoxide is, for example, just one of up to 75 potentially toxic compounds released by burning polyvinylchloride (PVC). Smoke injury also causes the release of free radicals and inflammatory cytokines.[1]

Several approaches have been developed to deal with the respiratory and systemic consequences of smoke injury. Most of the specific therapies have achieved only limited success. Some of the treatments tried so far include: the use of bronchodilators, N-acetyl cysteine and high dose ascorbic acid. Ascorbic acid has been shown to significantly reduce fluid resuscitation volumes in burn patients with smoke injury.[32, 38-40] Nitric oxide has also been used to dilate the pulmonary arteriolar bed and does attenuate the ventilation-perfusion imbalance seen in many of these patients.[41-42]

There is agreement among investigators that after adjustment is made for age, weight and TBSA, the presence of inhalation injury is the single most important contributor to higher mortality in burns. Shirani and his colleagues have calculated that the combination of inhalation injury and pneumonia increases mortality by up to 60% when compared to people with only burns.[43] It would be interesting to see if there is a significant difference in the over-

all contribution of these two co-morbidities to mortality in patients in warmer climes, such as the tropics, compared to those in more temperate regions. This is because pneumonia is commoner in colder climates and it should be easier to achieve beneficial ambient temperatures for patients in the tropics.

The metabolic response

It had long been established that substrate metabolism is altered by major trauma. Increased demand for energy substrates, especially glucose, overwhelm supply, and non-carbohydrate substrates such as alanine get recruited into energy production. It is now clear that severe burns create a hyperdynamic, hypermetabolic state characterized by raised body temperature and increased oxygen consumption. There is increased glucose production too through glycogenolysis. We also know more about the biochemical and endocrine drivers of this hypermetabolic state.[14-15] Many believe that the first part of the metabolic response is driven by shock phase hormones such as cortisol and catecholamines.[17, 44-45]

Increased tissue degradation has been evaluated in terms of falling lean body mass (LBM), bone mineral content (BMC) and bone mineral density (BMD).[46-47] Serum levels of constitutive hepatic proteins, especially pre-albumin, transferin and retinol-binding protein, also fall after severe burns. In children, prolonged hypermetabolism has been seen in resting energy expenditure of up to 130-140% of predicted levels.[48-49] Tissue degradation and loss of essential body tissue have a serious effect on morbidity. There is a clear correlation between body tissue depletion and mortality. Chang et al. have shown that a 10% loss of LMB is associated with impaired immunity; a 20% loss with decreased wound healing; 30% loss with pressure sores; and a 40% loss with 50-100% mortality.[50] Several approaches have been made to counter catabolism and preserve protein and amino acid stores in burn patients. These include hyperalimentation and the use of biochemical and endocrine modulators such as: insulin,[51-53] growth hormone (GH),[54-55] insulin-like growth factor-1 (1GF-1),[56-57] oxandrolone[58-59] and propranolol.[60] Unfortunately, the results of controlled trials with these agents have not followed what theory predicted. This gap between predicted and observed findings may be one reason why many of these agents are yet to be widely used clinically. This is an area where further research is required.

Non-fasted glucose has been found in many studies to be markedly elevated in the acute post-burn period.[52, 61] This rise, which can reach 170-180 mg/dl, occurs in spite of raised insulin levels, suggesting insulin resistance.[17] This resistance may contribute to the discordant results in trials of insulin therapy in the post-burn period. The high circulating glucose is virtually directed to the burn wound where anerobic consumption of glucose is carried out by fibroblasts and endothelial cells.[62-63] Lactate produced from this anerobic process is recycled in the liver gluconeogenesis pathways into glucose. Futile substrate cycling is typical in fat and glucose metabolism in these patients. By using stable isotopes, Rolfe et al. have demonstrated up to 450% and 250% increase in glycolytic – gluconeogenic and triglyceride – fatty acid cycling respectively.[64]

Any attempts to meet the greatly increased energy needs of burn patients by supplementing oral feeding with parenteral ones must be made with caution. The reason is that, although up to 2200 kcals/m^2 of burned area needs to be added to the calculated basal metabolic need of the patient, in trials where patients received parenteral feeding combined with maximum tolerated enteral feeding, mortality increased when compared to those on only oral feeding.[65-66] It should only be applied when prolonged ileus makes enteral feeding impossible. However, the complications following the feeding processes have been largely overcome and early, adequate enteral nutrition is the standard practice in many centers now. The advantages of this practice are numerous. In a detailed review of experience with over 1,000 patients with burns of >40% TBSA, Williams and her colleagues report that, whereas patients fed solely orally with hospital food had lost up to 25% of pre-admission weight, within 21 days, those who had early aggressive and adequate enteral nutrition were able to maintain their weight. They also maintained better gut motility and had boosted immune systems.[67] To meet the challenges of supra-physiologic calorie needs and preserve body tissues when burns exceed 40% of TBSA, the Curreri formula is suggested to be more appropriate than the Harris-Benedict equation. In the former, the patients are given up to 25 kcal/kg of body weight plus 40 kcal/%TBSA of a diet low in fat and high in carbohydrates and proteins.[68] It is interesting to observe here, with respect to glucose metabolism, that even though hyperglycemia occurs, and insulin infusion improves outcomes in some situations, the best diet for burn patients have been shown to be ones that are low in fat and high in carbohydrates.[69]

Free fatty acids and total triglyceride levels have been shown to be elevated for weeks post-burn.[23] This elevation of total fats at a time when proteins required to transport fats from the liver are depleted partly accounts for the fatty infiltration and liver enlargement seen in acute burns. Fatty infiltration and the associated hepatomegally have been shown to increase sepsis and burn mortality.[70] Propranolol, a non-selective beta blocker that decreases peripheral lipolysis and reverses the liver changes, has been used with some benefits.[71] Nevertheless, research into therapeutic plans that deploy agents such as insulin, which can address the perturbations in fat and glucose kinetics, must be intensified because some studies suggest that the level of hyperglycemia in burn patients is a predictor of mortality.[72]

Overall, the evidence of studies from the past few decades shows that the metabolic changes in severely burned patients are extremely complex. This complexity in part explains why uniform results have not always followed therapeutic trials, even when they were based on otherwise sound theory. This in turn has meant that many of these interventions have hardly found their way into routine clinical use, even though they have the potential to improve patient outcome. Further research, and not resignation, is required to overcome this dilemma. Given the very real risks associated with hypermetabolism, we agree with Herndon and Tompkins that further investigation and innovation are required.[73]

The endocrine response

Burn injury represents a major trauma and elicits a widespread endocrine response. The survival effort in the burn patient produces a marked rise in stress hormones such as catecholamines, glucagon and cortisol.[74-75] Catecholamines are mostly responsible for the widespread changes in the cardiovascular system and the fluid shifts that follow these changes. The levels of these hormones may rise up to 10 times after burns, and they are believed to drive the initial stages of the hypermetabolic response to burns while cytokines sustain and prolong it.[76] Subsequent to the initial stress-related hormone response, however, alterations occur at several points in the hypothalamo-pituitary-organ axes. Jeschke et al. have demonstrated a temporary reduction in the production of TSH, T-3, T-4 and testosterone. They postulate that these changes may reflect a shift of emphasis from sex steroid production in favor of the stress-related hormones.[23]

Herndon and Tompkins have reviewed attempts to modulate the hormonal influence on metabolism by applying several hormones and their synthetic analogues: GH, insulin, IGF-1, oxandrolone and testosterone. The second approach they examined was the use of beta blockers, such as propranolol and metoprolol to block the effects of catecholamines.[73] Interesting findings emerged from these studies; recombinant human GH, for instance, cancelled out part of the severe growth retardation seen in burned children and improved cellular immune function. However, in non-burned critically ill adults, the hormone was seen to cause hyperglycemia and raise mortality.[77] A paradoxical action is observed with GH in that, though it raises blood glucose and most of its effects are mediated by IGF-1, rather than raising blood glucose IGF-1 causes hypoglycemia.

The use of a continuous infusion of insulin at levels that maintain hypoglycemia was shown to improve muscle synthesis and significantly reduce mortality in patients in surgical critical care units.[72] Similarly, long term use of propranolol reduced mortality partly because it reduced cardiac work load,[73] thermogenesis and peripheral lipolysis.[78] These hormones, however, only produced beneficial results in patients who were hypermetabolic.[73]

Testicular function after burns

Optimum function in human testis requires precise homeostasis in the physical, chemical and endocrine environment. Spermatogenesis is affected, for instance, by alterations in scrotal temperature, blood perfusion rate and testosterone levels.[79-80] Considerable germ cell apoptosis is a normal feature of spermatogenesis in mammals. It is probably a mechanism for controlling the relative quantities of specific members of the germ cell population, eliminating defective cells and ensuring the production of an adequate quantity of functional sperm cells. However, apoptosis can be accelerated by a number of testicular insults, including systemic trauma, heat stress and hormone depletion.[81-83] Lue and others have shown that heat stress from temperatures as mild as 42-43°C, can induce apoptotic and necrotic cell death when applied directly to the testis[84-85]

Testicular function is known to be abnormal in a variety of chronic illnesses. Conditions such as chronic renal and liver diseases have been associated with sub fertility, low testosterone and raised gonadotropin levels.[86-87] However, detailed studies of the effects of major burns on spermatogenesis and the testis in men are relatively recent.[88-89] The paucity of published studies in this area may stem from ethical issues involved in obtaining testicular tissue from burn survivors. One approach to overcoming this challenge has been to examine tissue from autopsy specimens.[90] We have also approached the matter by studying testicular histology and function in a rat model of severe burns. These studies have established the fact that thermal injuries cause widespread changes in the histology of seminiferous epithelium. Germ cell atrophy was the most typical finding followed by sloughing. In one study on animals with prolonged injury, only basal cells survived in the tubules.[91]

The precise mechanisms leading to testicular damage in burn patients are far from being established. There is evidence suggesting an endocrine pathway, especially testosterone depletion.[87, 92-93] It is also likely that increased germ cell destruction results from oxidative stress, possibly due to temporary under-perfusion. This hypothesis is supported by findings from a study of 20 burn survivors with a mean of 33% TBSA involvement where there was a positive correlation between suppression of sperm parameters and duration of time between injury and onset of any treatment.[88]

The deleterious effects of testicular toxicants are sometimes associated with reduction in serum testosterone levels, thus justifying attempts to ameliorate them by hor-

mone support.[94-95] Yet, in a study where testosterone was administered to severely burned rats, either alone or in combination with FSH, this did not provide significant protection from testicular damage. However, ascorbic acid, a broad spectrum free radical scavenger, reversed most of the changes in testicular histology and function in those animals.[89] Incidentally, as mentioned earlier in this review, high dose ascorbic acid administration has been reported to reduce resuscitation fluid needs and complications in burn patients.[32]

Thermal injury is common in children and young people. The evidence clearly suggests that male reproductive function is adversely affected by burns. Studies need to be intensified in this area. We know far too little at the moment about the fertility suppression that follows burns in males. It will be interesting, for instance, to find out the natural history of the observed hypospermia in burn survivors. However, as we have suggested elsewhere,[25] while efforts go on to improve our knowledge in this area, physicians caring for males with burns should bear in mind the fact that their patients may suffer damage to their reproductive function and consider adjunctive measures that can limit that damage in their therapeutic plans.

The cytokine response and immune alterations

Severe burns produce a widespread cytokine response characterized by markedly elevated levels of IL-6, Il-8, MCP-9, MIP-1B, and G-CSF, for example. In one multicentre study of over 250 children with major burns, 16 out of 17 cytokines assayed were found to be significantly elevated. In that study, in addition to the 5 cytokines listed above, significant elevations were recorded in IL-2, IL-13, Il-10, IL-17, IMF and INF-y, though the levels of the latter group returned to normal within six days post-burn.[23]

Studies suggest that complications from severe burns may be affected by a pro-inflammatory cascade induced by several mediators produced mostly from activated macrophages. This cascade involves IL-1, IL-6 and PGE-2, with TNF- as the major trigger.[96-97] In one study, the levels of anti-thrombin (AT) and several cytokines were measured in the plasma and peritoneal fluids of people who developed abdominal compartment syndrome from severe burns. It was found that while AT levels were lowered, there was an increase in levels of INF-y, IL-10, IL-6, IL-4 and IL-2 in both fluids. The levels were higher in those who died than in survivors.[98] INF, for example, is known to promote inhalational injury.[99-100]

These studies suggest that perturbations in the cytokine expression profile post-burn have a profound effect on clinical outcomes. In the study of children referred to earlier, only IL-5 level fell out of the 17 cytokines assayed. IL-5 is a pro-immunity agent which stimulates B-cell growth and immunoglobulin synthesis.[23] The depletion of this cytokine may play an important role in the widespread immune-suppression seen in burned animals and humans alike. The changes in cytokine profile are part of a widespread response involving the immune and endocrine systems which are designed to enhance survival.

Thermal injury exerts a considerable effect on the immune system, especially cellular immune responsiveness. Although the loss of skin and the mechanical barrier it provides contributes to infection in burn patients, it has long been established that impaired immune mechanisms are key factors in post-burn infection. Burns cause a reduction in the number and types of lymphocytes in peripheral blood. It is also associated with reduced expression of surface makers on lymphocytes. There is a reversal of the normal CD_3/CD_4 ratio after a few weeks. The response of the cellular immune system apparently follows a paradoxical pattern because there is initially an activation or pro-inflammatory phase characterized by the effort of the patient to restore homeostasis.[1] This is indicated by increased expression of cell surface makers and an elevation of IL-2 and soluble IL-2 receptors levels.[101-102] These cytokines account for the fever and several features of the acute phase clinical picture, including the hypermetabolic state.[103-104] They also elevate PGE and IL-6. The latter, together with TNF-α, are potent inducers of the acute phase state. However, this systemic inflammatory response, if severe enough, can induce a syndrome which ends in damage to critical tissues and end organs.[105-106]

This period of increased activity is followed by an anti-inflammatory phase in which there is significant reduction in numbers and functional power of critical members of the immune cell population: neutrophils,[107-108] macrophages and monocytes, T-helper[109] and natural killer cells.[110-111] For example, T-helper cell numbers fall in favor of Th-2 cells.[112] Significant research evidence suggests that even the mucosal barrier to bacterial invasion in the bowel wall is compromised after burns, a situation that predisposes to increased transfers of colonic microbes and toxins into the systemic circulation.[113]

Neutrophils, for instance, normally ingest bacteria and kill them by producing various cytotoxic oxygen radicals. Parment and others have shown that this oxidative burst is impaired for long periods if burns exceed 40% of body surface.[76, 114] Some success has been achieved in attempts to overcome functional defects in polymorphs and monocytes by using GM-CSF, an enhancer of cell function. This agent produced a series of pro-immune effects such as prolonged lifespan of macrophages and neutrophils, and enhanced expression of key complement receptors: CR-1, CR-3 and CD-118.[115]

Thermal injury, if severe enough, attacks several points in the immune defense system. For example, there are also reduced levels of circulating B-Lymphocytes and IgG, though the levels return to normal after about four weeks.

There is evidence that the ability of these cells to mount an immunoglobulin response is impaired after burns. Nevertheless, even though administration of exogenous IgG restores this immunoglobulin's serum levels to normal, it was not seen to affect mortality or morbidity in burn patients.[116] The search continues, of course, for effective modulators of the immune response. However, the hope – captured in Wiseman's exuberant declaration at the onset of the 1990s – that this problem would be solved using pharmaceutical agents, such as prostaglandin and adrenalin blockers, and synthesizing recombinant forms of various cytokines has been largely unfulfilled.[117]

Discussion

Over the last few decades, significant progress has been made in our understanding of the variegated processes involved in the reaction of a patient to thermal injury. Several factors have contributed to the great improvements seen in all aspects of treatment outcomes in burns during this time. Vigorous fluid resuscitation regimens have improved patient salvage during the early post-burn period when plasma leak is taking place, though in the low and medium income countries of this world, patients still arrive at burn centers in a state of advanced dehydration. Improved understanding of the metabolic demands in burns has also encouraged the application of several general support measures, including ambient temperature control and early and adequate enteral feeding based on scientifically calculated calorie needs. Better treatment of inhalation injury and application of respiratory support with intensive care has significantly reduced mortality from this comorbidity. Although inhalation injury is still a leading contributor to burn-related deaths, we have come a long way from 1981 when Birky and his colleagues estimated that a full 80% of the 8000 annual burn fatalities in the United States resulted from complications of this injury.[37]

On the strength of the evidence, one can only agree with Endorf and Gibran[26] that the strategy of early wound excision and grafting revolutionized survival outcomes in burn care. It reduced hospital stay and costs, and reduced mortality as well as the need for corrective surgery.[118-119] This treatment approach cuts down the flow of bio-active agents from the burned area into the general circulation, thus attenuating the effects of these drivers of inflammation and immune suppression. Beneficial results followed efforts to modify patient response to hypermetabolism with propranolol and many centers have begun the routine use of beta-blockers to reduce the cardiac workload and muscle catabolism, especially in pediatric patients.[120] Adequate nutrition not only supports body weight but also the immune system and, together with better wound care, reduces the tendency toward the development of sepsis and critical organ dysfunction. The latter are still key pathways to much burn-related mortality at the present time.[121]

Both basic and clinical research have contributed significantly, though perhaps not equally, to the massive improvement in burn survival achieved over the past few decades. This is true despite clinical application tending to lag well behind the evidence from basic research, even when the reports are published in clinically oriented journals. This is so, for instance, with regards to the use of ascorbic acid in the treatment of smoke injury and testicular damage. Published work by Tanaka et al.[32] and by Jewo et al.[89] have demonstrated the wide ranging benefits of this agent in the former and latter cases respectively. However, its use is yet to be generally adopted by burn physicians, despite being included as a treatment option in a recent review by Haberal and his colleagues.[122] A number of reasons probably account for this gap. The first is that clinicians are very busy and thus take quite a while to catch up with developments in research, and even more so if the studies convey a non-clinical outlook. Secondly, clinicians also tend to be wary of evidence derived from animal experiments, or from human experiments with too small sample sizes. A third issue is that some of this research, more often than not, throws up controversial results. This is true, for instance, with the attempts to stem tissue wastage by the application of testosterone, which proved to have too many complications, or the use of recombinant human growth hormone which increased mortality, as previously mentioned in this paper.[77]

On the strength of actual and potential contributions, therefore, all aspects of burn research deserve to be adequately funded. But the limitations described above need to be addressed. Multi-center studies can overcome the problems of sample sizes that are too small to represent the populations under review, and can more easily meet the requirements of grant givers, though they are more demanding in planning and execution. Further research may also need to focus on identifying new parameters and patient characteristics that can enable physicians to select patients who will benefit from specific interventions. Animal experiments are useful in practically all aspects of burn research but they will need to be better designed.

One of the least studied aspects of burn pathology is the effect of burns on the reproductive system. It has been largely overlooked. It would be unjustifiable to expect that the mammalian gonad, for example, with its highly active cells could be immune from damage in a condition where so many bio-active agents, including free radicals enter the systemic circulation and reach distant targets. As we have suggested elsewhere,[89] it may well have been overlooked for so long because it is not life-threatening and has no direct effect on treatment outcomes. Another probable reason is that much of the research, especially the basic type, occurs in the developed world where personal fertility may

not be regarded in the same way as it is in more traditional societies.

The availability of well developed assisted reproductive techniques to deal with male factor infertility may contribute to the paucity of interest in the subject seen in more advanced countries. After all, with intra-cytoplasmic sperm injection (ICSI), conception can be achieved in men with counts low enough to be classed as azoospermia. However, assisted reproductive procedures are expensive with no guarantees of producing babies, and concerns such as whether chromosomal abnormalities will be higher in ICSI babies are yet to be fully addressed.[123] There is evidence that severe burns cause disturbances in androgenesis and significant reduction in spermatogenesis. Though cultural differences exist in the way a sub-fertile male is viewed, virility is an important expectation of males in any society and failure in that area may cause psychological problems associated with feelings of inadequacy. Research ought to be encouraged to elucidate the mechanisms of reproductive damage in burns with a view to developing suitable treatments or preventive measures.

Finally, the evidence from studies over the last few decades shows that thermal injury produces extremely complex changes in metabolism and the immune system. An initial period of hemovascular fluid shifts is followed by another characterized by exaggerated and often unbalanced activity of pro- and anti-inflammatory cytokines. This leaves the victim in an immune-suppressed state with a profound impact on outcomes because it promotes sepsis, tissue damage and multiple organ failure. The complexity of the immune impairment induced by burns has made it difficult to design successful treatments against it. Moreover, as some have suggested, the failure of various therapeutic approaches, including vaccines, immune-modulators, and endocrine and serologic agents to fight infection and stop mortality in these patients, may highlight the inability of any single agent to correct the multiple defects generated by severe burns.[2]

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