Etiology and Control of Postburn Hypermetabolism: The 1991 Presidential Address to the American Burn Association

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EARLY STUDIES

The unraveling of the metabolic response to burns and trauma began in the 1930s and has continued with increasing intensity to the present. I will explore with you one facet of this overall mosaic, the hypermetabolic response (HMR) that follows burn injury. Oliver Cope’s article in 1953 entitled “Metabolic Rate and Thyroid Function Following Acute Thermal Trauma in Man,” first described the phenomena of sustained hypermetabolism after burn injury. Dr. Cope’s description and discussion of this response excludes a thyroidal origin and is both prescient and sagacious in suggesting possible mechanisms of etiology including increased adrenaline release, Q10 effect of fever, and specific dynamic action of protein. Furthermore, Dr. Cope related the HMR to the wasting and cachexia that is observed after burn injury. Morgan et al., in 1956, described the effect of burn injury on insensible weight loss in rats, and were followed by Lieberman and Lansche (1957), whose studies of heat production (H) and evaporative heat loss led them to suggest increased evaporative heat loss through burned skin and/or an open wound “as the most important factor in the genesis of the increased metabolism and mortality of burned animals.”

Shortly thereafter, Hume and Egdahl (1959), reported a series of experiments with dogs under anesthesia with pentobarbital sodium, which demonstrated that peripheral innervation and intact spinal cord were essential for a corticotropin-cortisol re-

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response to a burn injury of an extremity that was isolated except for vein, nerve, and artery. This eliminates a possible humoral messenger from the site of injury as the afferent limb of this classical response to injury.

In 1959, we demonstrated a cause and effect relationship between increased evaporative heat loss and hypermetabolism in rats with burn injury and confirmed that this response was not dependent on increased thyroid function. At this point, a new variable, environmental temperature, was added to the
Figure 1. Representative animals from the four experimental groups at the time of sacrifice. A, Burn at 30°C; B, control at 30°C; C, burn at 20°C; D, control at 20°C. From Caldwell. Ann Surg 1962;155:124. Reprinted with permission.

research paradigm. For over 25 years now, we have tracked this variable in order to demonstrate how and to what extent, directly and as a moderator of other variables, it influences the metabolic response to thermal injury. In small burns with a mean size of 18% of the body surface area (BSA), the HMR could be eliminated by exposure of the animals to an ambient temperature of 32°C. In 1962 we reported the beneficial nutritional effects on body weight gain, nitrogen balance, and mortality rate for rats with burn injury to 29% BSA that were housed at an ambient temperature of 30°C, as compared with rats with similar burns that were housed at a temperature of 20°C with the calorie intake fixed at preburn levels. The mean body fat content of burned rats that were housed at 20°C was 3.4% versus 11.8% for similarly burned animals that were housed at 30°C (Table 1 and Figure 1).
Figure 2. Heat balance for burned and control rats on postburn days 15, 22, 36, and 43 at ambient temperatures of 27.5°C and 30°C, before and after separation of the wound eschar.

Figure 4. Average body temperature (obtained from an 80:20 weighted ratio of rectal and average skin temperatures) for burned and control rats with and without adrenal medullectomies and with wounds open or covered at ambient temperatures of 28° C and 20° C. From Caldwell. Arch Surg 1976;111:182. "Copyright 1976, American Medical Association." Reprinted with permission.

Table 1. Mean values for terminal (eviscerated) body fat content for the four groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Body fat as percent of body weight</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn 20° C (n = 5)</td>
<td></td>
<td>3.38</td>
<td>2.20</td>
</tr>
<tr>
<td>Control 20° C (n = 4)</td>
<td></td>
<td>13.90</td>
<td>1.65</td>
</tr>
<tr>
<td>Burn 30° C (n = 7)</td>
<td></td>
<td>11.84</td>
<td>2.79</td>
</tr>
<tr>
<td>Control 30° C (n = 5)</td>
<td></td>
<td>14.24</td>
<td>1.56</td>
</tr>
</tbody>
</table>

SD, Standard deviation.
Percent fat = 100 · [(5.362/specific gravity) − 4.880].

*One animal died on postburn day 36 and one on postburn day 44.

THE SIXTIES

The study of energy metabolism of humans with burns by Harrison et al. in 19647 included as coauthors two past presidents of the American Burn As-

sociation, John A. Moncrief and Arthur D. Mason, and demonstrated during a 4-hour study period at a temperature of 24° C to 26° C a strong positive correlation between evaporative heat loss and the area of burn wound and between evaporative heat loss and rate of heat production. Six of nine patients demonstrated a drop in rectal temperature, and vigorous shivering was common. It is not stated, but it is presumed that these patients were studied without dressings, since the patients with the largest injuries demonstrated approximately a 100% increase in their rate of Hp7.

In 1966, we reported the results of a simultaneous direct and indirect calorimetry that was performed on burned rats at ambient temperatures of 27.5° C and 30° C. These studies balanced the heat balance equation within 5% and showed that increased evaporative heat loss accounted for most of the increment in rate of Hp, with a small part that resulted from increased radiational loss. The HMR peaked with eschar separation and progressively decreased there-
Figure 5. Heat balance and body temperature data for burned and control rats, with and without adrenal medullectomies and burn wounds covered and open at an ambient temperature of 20°C. Note that with or without the burn wound covered, with adrenal medullectomies, the burned rats are hypothermic.

after as the burn wounds closed by contraction and as evaporative heat loss from the wound progressively decreased. The decrement in the HMR to burn injury in rats at 30°C versus 27.5°C was demonstrated to be secondary to decreased radiational heat loss with little or no effect on evaporative heat loss. We suggested in this article, that in the rat, the zone of thermal neutrality was shifted upward after burn injury8 (Figure 2).

Barr et al. reported in 1967 and 1968,10 the beneficial effect of treating patients with burns with warm, dry air (40°C and 20% relative humidity [RH]). These patients were presumably treated without dressings. Although warm, dry-air treatment increased evaporative heat loss, the rate of Hp decreased by approximately one half.

Harrison et al.,11 in 1967, reported good linear correlation between the urinary excretion rates of epinephrine (E) and norepinephrine (NE) and percent increase in Hp for nine patients with burns. Percent increase above normal in oxygen consump-
tion was plotted on the x axis as the independent variable, and the logarithm of the 24-hour excretion rates of E and NE was plotted on the y axis as the dependent variable. Without transformation, the data (Hp vs E and NE) resulted in a nonlinear relationship.

In 1969 Davies12 reported the results of treatment of 19 patients with burns with warm, dry air (air temperature, 32°C; RH, 20% to 30%) compared with the results that were obtained by treating 41 patients with air at 22°C and 30% to 90% RH. The conclusions were that patients who were treated with warm, dry air lost less weight and had significantly lower rates of Hp. Whether the patients were treated with or without dressings was not stated.12

Also in 1969 Barr et al.13 reported on the results of treatment of patients with severe burns with warm, dry air compared with treatment of patients with similar burns with cool moist air (32°C and 20% RH vs 22°C and 45% RH). Those patients who
Figure 6. Linear regressions results when the increment in rectal temperature is used as the independent variable and the percent increase in the rate of Hp is used as the dependent variable. None of these lines has a slope that is significantly different from the others.

THE INFLUENCE OF BURN DRESSINGS ON HEAT PRODUCTION AND COMPARTMENTED HEAT LOSS

n 16 PATIENTS
x 38 ± 15% BURN

(BANDAGED)

NON-FEVER CORRECTED HEAT PRODUCTION
66%

FEVER CORRECTED HEAT PRODUCTION
P<.001

PREDICTED NORMAL HEAT PRODUCTION
30%

Evaporative Heat Loss
Dry Heat Loss

(23.2° F)

P: NS
(7.3° F)

were treated with warm, dry air lost less body weight (average 5% of admission weight), had lower rates of Hp, and had a mortality rate that was lower than predicted. The rate of Hp (% above normal) had an excellent positive linear correlation with the rate of evaporative heat loss through the first 3 weeks after burn injury. These authors were the first to demonstrate in patients that burn wound closure decreased evaporative heat loss and rate of Hp.13

THE SEVENTIES

Zawacki et al.14 reported in 1970 the results of covering the burn wounds of 12 patients with Saran wrap for 12 hours, after which evaporative heat loss and rate of Hp were measured. Evaporative heat loss decreased significantly with no change in Hp and only a 0.5°C increment in body temperature. With evaporative heat loss cut to less than half by Saran wrap, only a 0.5°C increment in body temperature, and no change in rate of Hp, no explanation was offered as to where all the heat went. Certainly, a 0.5°C increase in rectal temperature cannot produce increments in radiational, convective, and conductive heat losses to account for the added heat that would require removal by these routes.14

In the last 20 years, Birke et al. (1972),15 in an elaborate study on the metabolic effects of warm, dry-air treatment, confirmed an earlier report and added data on urinary excretion rates for E and NE. They demonstrated that in patients who received warm, dry-air treatment, E excretion returned to the normal range by the fifth postburn day and did not correlate with the rate of Hp. Norepinephrine excretion rates correlated positively with Hp, even though NE is probably not calorigenic at the plasma concentrations that have been observed in patients with burn injuries15 (Figure 3).

Wilmore et al. (1974)16 studied 20 patients with noninfected burns at ambient temperatures of 33°C, 29°C, 25°C, 21°C, and 19°C. For most of the patients, equilibration time at an ambient temperature was 4 hours. Urinary catecholamine excretion rates did not demonstrate a positive linear correlation with Hp. Furthermore, α-blockage and β-blockage produced only a 40% decrease in the HMR. Short exposure to an ambient temperature of 33°C for these patients, whose wounds were left open and treated with topical Sulfamylon (Winthrop Pharmaceuticals, New York, N.Y.) while they were in an open ward that was kept at a temperature of 24°C to 26°C, did not consistently or significantly decrease the HMR. Wilmore concluded that evaporative heat

Figure 8. Plasma E concentrations do not correlate with the rate of Hp of bandaged patients at an ambient temperature of 28°C. From Caldwell, Bowser, Crabtree. Ann Surg 1981;193:587. Reprinted with permission.

THE INFLUENCE OF EXPOSURE ON HEAT PRODUCTION AND COMPARTMENTED HEAT LOSS

n=16 PATIENTS
X=38±15% BURN

![Graph showing heat production and heat loss](image)

Figure 10. Compartmented heat loss and rate of Hp for 16 patients with burns with their dressings removed 4 hours previously. From Caldwell, Bowser, Crabtree. Ann Surg 1981;193:579-91. Reconstructed from data included in Table 2, page 581.

Figure 11. Plasma E (adrenaline) concentrations do not correlate with the rate of heat production when the burn wounds are exposed at 28°C. From Caldwell, Bowser, Crabtree. Ann Surg 1981;193:587. Reprinted with permission.

Figure 12. Plasma NE (noradrenaline) concentrations have a positive linear correlation with the rate of Hp when the burn wounds are exposed. From Caldwell, Bowser, Crabtree. Ann Surg 1981;193:588. Reprinted with permission.

loss and surface cooling in the patient with burns is not the primary stimulus for the hypermetabolic state; rather he proposed that the HMR is related to an endogenous reset in “metabolic activity,” vaporizational heat loss serving only as a convenient
Figure 13. This figure demonstrates the effect of occlusive dressings on the percent increase in the rate of Hp after burn injury. The slope of the regression for patients who were treated with occlusive dressings at 28°C is significantly less than the slope for these patients when wounds were exposed at 28°C and the slope for Wilmore's patients who were treated by the exposure method at 25°C. The slope when patients' wounds were transiently exposed at 28°C is also significantly less than the slope for Wilmore's patients, whose wounds were exposed at 25°C.

route for transfer of this large heat load from the body.¹⁶

Neely et al. (1974)¹⁷ covered the burn wounds of several patients with plastic and measured Hp and body temperature with and without the plastic covering. Contrary to Zawacki's results,¹⁶ the rate of Hp of Neely's patients was uniformly decreased when wounds were covered with plastic as compared with wounds in the open state. Except for one normothermic patient, Neely's patients were febrile by as much as 2°C. When one accounts for the Q₁₀₁0 effect of increased body temperature, most of these patients, when their wounds were covered, had Hp within the normal range for Neely's controls (45.5 ± 4.2 W/m²).¹⁷

In 1976, we investigated the effect of bilateral adrenal medullectomy on energy metabolism after burn injury in the rat. (Adrenal medullectomy in the rat lowers plasma E to undetectable levels). At an ambient temperature of 20°C, burned rats that had adrenal medullectomies were hypothermic, with less elevation in the rates of heat loss and Hp than in burned rats that did not have medullectomies. Thus in the rat, the adrenal medulla is essential for near maximal rates of Hp but is not responsible for the primary drive for the HMR (Figures 4 and 5). Much later, in 1989, Chance et al.¹⁹ reported work that supported this conclusion. Covering the burn wound with polyethylene eliminated the HMR in rats with or without adrenal medullectomy.²⁰

Danielsson et al. (1976)²⁰ reported on the elimination of the HMR with the use of patient-regulated infrared heaters and “fever correcting” the rate of Hp. This report focused attention on the increase in body temperature after burn injury. The etiology of the response in body temperature after burn injury is complex. There may be several components—hyperthermia secondary to hypermetabolism, fever caused by circulating pyrogens, or effects secondary to other circulating or noncirculating cytokines. The net result is that the nonseptic patient with burns appears to be regulating body temperature at a new set temperature, which is shifted up in direct proportion to the size of the burn injury.²¹
Figure 14. The POAH was implanted with two thermodes and a reentrant tube constructed as a single unit. From Caldwell et al. J Burn Care Rehabil. 1989;10:487. Reprinted with permission.

Awareness of the relationship between an increase in body temperature and increased Hp goes back a long way. In 1921 DuBois showed that an increase in body temperature produces an increase in rate of Hp of 13% to 16% per 1°C increase in body temperature: this is the so-called "Q₁₀ effect," a real biologic phenomena even in noncellular systems. The correction for increased body temperature by Danielsson was arbitrary, but by doing so he demonstrated that increased body temperature in nonseptic patients with burns may need to be dealt with, along with Hp, as a separate but interrelated phenomenon.

Comparisons of Danielsson's patients with those of Wilmore's, who were treated with wounds exposed at an ambient temperature of 28°C (with rectal temperature as the independent variable and metabolic rate uncorrected for fever as the dependent variable) demonstrate very little overlap of the data points (data points for two patients overlapped). Figure 6 shows the regressions that result when increase in rectal temperature is used as the independent variable and percent increase in the rate of Hp above predicted normal values is used as the dependent variable for Danielsson and Arturson's patients, who were treated with infrared heaters when they were either falling asleep or resting quietly compared with data for our cohort of patients who were treated the occlusive dressings and whose wounds were transiently exposed. The slopes of the regressions are shown in Figure 6. The slopes of these lines are not significantly different. The conclusion to be reached is that adequate energy from external infrared heaters or the use of occlusive dressings reduces the HMR to burn injury to a manageable level (without fever correction). It does not, however, eliminate the HMR response.

Arturson, in the Everett Idris Evans Memorial Lecture for the American Burn Association in 1976, reviewed the Swedish experience. It had become obvious that the HMR in humans with burns could be significantly decreased but not eliminated by control of the ambient temperature. The residual increment in Hp demonstrates a positive linear correlation with body temperature.

In 1978 Arturson summarized the results of treatment of patients with major burn injuries with the use of patient-controlled infrared heaters. A key phrase in the summary was "... nonseptic patients with thermal injury respond to elevation of their ambient temperature above the zone of thermal neutrality with a decrease in rate of heat production and dry heat loss, no change or slight increase in evaporative heat loss, and a marked decrease in H MR. However, H MR is not eliminated by this approach.

Figure 15. Steady-state heat loss for rats with full-thickness burns over 30% of BSA. Compared with controls, burned rats lost significantly more heat at ambient temperatures of 28°C and 20°C, but rates of heat loss were no different than those of control animals at an ambient temperature of 32°C. From Caldwell et al. J Burn Care Rehabil. 1989;10:489. Reprinted with permission.
The response suggests that the zone of thermal neutrality after thermal injury is increased. I agree with this statement.

THE EIGHTIES

In the last decade, in 1981 we reported partitioned calorimetry studies for 23 children with burns with and without occlusive dressings. These studies demonstrated that, while patients were lying quietly in bed with occlusive dressings in place overnight (having food withheld since midnight) at an ambient temperature of 28°C, the average rate of Hp of 66 W/m² for 16 patients with large burn injuries was only 23% above the predicted normal value. Sixty-eight percent of the total Hp was transferred to the environment by a 237% increment in evaporative heat loss equal to 45 W/m², whereas only 33% (22 W/m²) of the heat was lost by the dry route (Figure 7). Epinephrine and NE plasma values were not significantly different from values for patients with healed burns: $E = 99\pm73$ pg/ml versus $67\pm39$ pg/ml (healed) and $NE = 598\pm273$ pg/ml versus $483\pm237$ pg/ml (healed) and did not correlate in any way with Hp (Figures 8 and 9). After only 4 hours without dressings, the patients with exposed burns demonstrated a further increase in their average rate of Hp to 81.4 W/m² (52% above predicted normal for the group [$p < 0.001$]). The corresponding increase in the rate of heat loss was approximately equally divided between evaporative and radiational heat losses (Figure 10). Mean plasma $E$ concentration increased to 251 pg/ml and NE to 1171...
pg/ml; both values are significantly higher than values for the same patients with occlusive dressings and average values for patients with healed burns. Only NE plasma levels showed positive correlation with the rate of Hp (Figures 11 and 12).

These data demonstrate that the severity of the hypermetabolic state after burn injury can be greatly decreased by the use of dressings (Figure 13). They confirm the work of Arturson, which showed that the portion of the hypermetabolism following burn injury, unrelated to fever, can be controlled by effective long-term use of an external heat source such as an infrared heater. These data are qualitatively similar to the results that were obtained in studies by Necly in which acute burn wounds were covered with plastic, which resulted in decreases in evaporative heat loss and rate of Hp. However, it should be noted that neither Necly's nor Arturson's patients returned to a normal rate of Hp. Arturson corrected Hp for elevated body temperature, whereas Necly did not. All of these studies demonstrate a residual increase in the rate of Hp, which shows a positive linear correlation with body temperature.

With either infrared heaters or occlusive dressings and a comfortable ambient temperature, the postburn HMR can be eliminated or reduced to a manageable level.

Thus far, the problem of fever and central set-point for body temperature and the interrelationship with the HMR to burn injury has been impossible to resolve in humans, and few, if any animal models are credible for the study of this problem.

Regulation of body temperature in health and disease is a complex problem, which is made increasingly difficult by the discovery of new cytokines such as interleukin-1, which is believed to be the internal pyrogen that acts directly on the preoptic anterior hypothalamus (POAH).

Almost certainly, as first demonstrated by Hume and EGDAH, the central nervous system controls and orchestrates the entire response to burn injury as well
Figure 18. Plasma E levels demonstrate a negative linear correlation with the rate of Hp for burned rats with bilateral POAH lesions at an ambient temperature of 28° C.

Figure 19. Plasma E levels demonstrate a positive linear correlation with the rate of Hp for control rats without POAH lesions.

as to injury in a generic sense. The question as to whether the long-term elevation of body temperature (directly proportional to the size of the burn injury) that accompanies burns is fever and/or hyperthermia is moot. It has some elements of both; as with fever it is defended and the thermopreferendum is increased. It is directly proportional to the size of burn injury as with the hyperthermia of exercise, in which sustained regulated elevation of the body temperature is directly proportional to the work load even in a cool environment.25

The etiology of increased body temperature after
burn injury is probably multifactorial. Pyrogens from wound or gut may partially account for increased body temperature; however, nonseptic patients with burns have increased body temperatures, and ibuprofen that is administered to nonseptic patients with burns decreases body temperature and metabolic rate in proportion to the decrement in body temperature.\textsuperscript{38} Ibuprofen blocks the arachidonic acid cascade and production of prostaglandin E\textsubscript{2}, which is the final step in fever production in the POAH and which is triggered by interleukin-1.

We have examined temperature regulation after burn injury in awake burned and control rats at three ambient temperatures by serial displacement of the POAH temperature by perfusion of chronically implanted thermodes (Figure 14).

Figure 15 demonstrates the effect of ambient temperature on the HMR after burn injury. At an ambient temperature of 32° C, the HMR is eliminated, mainly as a result of a reduction in dry heat loss. The data show that burn injury produces an upward shift of the set-point temperature for body temperature in the POAH as well as in the reference temperature. In practical terms, this means that the burned animals should respond more efficiently to the increased energy demands of burn injury. The sensitivity or slope of the response in rate of Hp to downward displacement of POAH temperature is, however, not altered by burn injury in the rat. As with most small animals, however, the slope of the response in rate of Hp of both burned and control animals is equally increased at a cool, ambient temperature of 22° C\textsuperscript{37} (Figures 16 and 17).

Because of the persistent scientific conundrum as to the role of the catecholamines in the pathophysiology of the HMR to burn injury, we have recently studied the role of the central nervous system in the production of E and NE after burn injury in the rat. Bilateral electrolytic lesions were produced in the POAH of rats. Failure of rats with lesions to regulate body temperature was established by cold stress of 5° C for 90 minutes. Serial arterial blood samples for E and NE analysis were drawn from burned and control rats with lesions during calorimetry performed at 22° C and 28° C. Appropriate controls without lesions were also examined. Not so surprisingly, rats with lesions tolerated burn injury poorly, so that the average size of burn wounds studied had to be reduced to 23% of the BSA. Burned rats with lesions were chronically hypothermic at an ambient temperature of 22° C, similar to rats with burn injury after adrenal medullectomy.
There was a total lack of positive relationship between E and NE plasma levels and the rate of Hp in both burned and control animals with lesions. There was actually an inverse relationship between the rate of Hp, E and NE values, which produced a negative linear correlation, (i.e., the higher the rate of Hp the lower the values for E and NE for burned rats with lesions). Only control rats without lesions, which were studied at an ambient temperature of 28°C, showed a positive linear correlation between plasma E and the rate of Hp (Figures 18 and 19). These rat studies, as considered with earlier human studies, make it quite unlikely that catecholamines initiate and/or sustain, in a primary sense, the HMR to burn injury. It is just as clear that some level of catecholamines is essential for full expression of the HMR in rats, and probably in humans as well.

Advances in our understanding of the general nutritional requirements after burn injury and trauma have been very great. The importance of glutamine for the gut, arginine, vitamin A, vitamin C, adequate amounts and types of carbohydrates, protein, and fats for wound healing have been the subjects of extensive research. In addition, delivery systems that use the gut have been developed to allow early (first 48 hours after burn injury) resumption of enteral feeding. Prolonged intravenous feeding, although possible, is associated with an inordinate incidence of bacterial, yeast, and fungal infections when used in patients with burn injury.

Mochizuki et al. (1984), with the use of a guinea pig burn model, concluded that resumption of enteral feeding within 2 hours after burn injury eliminated the HMR to burn injury and prevented atrophy of the gut mucosa and bacterial translocation from the gut.

Wood et al. (1986), working in our laboratory, however, repeated this experiment at the same calorie level and general diet composition with a rat burn model and could not show any effect of early feeding on the HMR in a rat burn injury model (Figure 20). As a matter of fact, burned rats that were allowed rat chow ad libitum gained weight at a significantly faster rate than any group that was fed by gastrostomy.

At present Mochizuki’s hypothesis that the HMR after burn injury is secondary to the systemic effects of endotoxin that is translocated from the gut is untenable as a general statement, since measurable circulating endotoxin in nonseptic patients with burns after the first postburn week is difficult to document, whereas hypermetabolism that is directly proportional to burn wound size is the usual state. Cytokines other than interleukin 1 may participate in the pathophysiology of the HMR at a cell-to-cell level including interleukin 6 and tumor necrosis factor, but there
is little extant evidence that they do so as systemic humoral agents.

**IMPLICATIONS FOR PATIENT MANAGEMENT**

Where does all this leave us in the current management of the energy and nutritional requirements of the patient with burns?

First, we should sequentially monitor the oxygen consumption rate of individual high-risk patients to determine their energy needs. They are not the same from patient to patient with apparently similar injuries. Equipment is readily available to make reliable estimates of the oxygen consumption rate and respiratory quotient at the bedside. Ambient conditions for these measurements must be standard.

Second, the HMR must be minimized by one of two methods. The first involves the establishment of a warm ambient temperature or the provision of supplemental infrared heaters. In either instance, the positive heat load must be regulated by the patient's expression of comfort. The second procedure involves use of occlusive dressings with insulative value.

Either method produces similar effects on energy metabolism, that is, a major reduction in, but not elimination of, the HMR. In the absence of other complications, patients who are managed by either method can reach stable body weight within the first two weeks after burn injury.

Third, wound closure of full-thickness injuries should begin as soon as the patient is hemodynamically stable—usually within the first postburn week. There is as yet no critical evidence that massive excision of burn wounds within the first 48 hours after injury lowers the mortality rate or improves function.

Prompt wound closure ends the stress of burn injury and the associated HMR. Sequential burn wound closure that decreases heat loss from the patient with burns is associated with a corresponding decrement in Hp31 (Figure 21). Thus by means of aggressive early planned permanent burn wound closure, one can convert a potentially lethal injury into a survivable one.

The stress of burn injury on the host is a complex mosaic with the HMR, in my judgment, playing the central role. It is the engine that drives and sustains the fantastic mega-responses that follow burn injury. Control of the HMR by prompt closure of wounds avoids the ugly complications of prolonged stress and malnutrition (i.e., wound colonization; immunosuppression; bacterial, yeast, and fungal invasive wound infection; systemic sepsis; and death).

At present, however, inhalation injury has supplanted the triad of hypermetabolism, malnutrition, and sepsis as the leading cause of death after burn injury. It has emerged as the Gordian knot that must be untangled in the next decade. May the members of the American Burn Association lead the way in this new decade toward an understanding of and treatment for inhalation injury associated with burn injury.

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