Modulation of the Post-Burn Hypermetabolic State

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Physiologic Basis of the Hypermetabolic Response in Burn Patients

Burn patients have the highest metabolic rate of all critically ill or injured patients. The metabolic response to a severe burn injury is characterized by a hyperdynamic cardiovascular response, increased energy expenditure, accelerated glycogen and protein breakdown, lipolysis, loss of lean body mass and body weight, delayed wound healing, and immune depression [1, 2]. This response is mediated by increases in circulating levels of the catabolic hormones, catecholamines, cortisol, and glucagon [3]. Catecholamines increase up to 10 times normal. Catabolism after major burn injury begins on the 5th day after injury and continues up to 9 months later [4]. Increasing age, weight, and delay in definitive surgical treatment predict increased catabolism in children. In adults, the response increases up to age 50 where it plateaus [5]. The body surface area burned increases catabolism until a 40% body burn is reached. The magnitude of metabolic expenditure is 1.5 to twice normal in burns of greater than 40% total body surface area (TBSA). Catabolism is further increased by 50% with environmental cooling or the development of sepsis.

Hypermetabolism and muscle protein catabolism continue long after completion of wound closure [4]. Protein breakdown continues 6 and 9 months after severe burn. There is almost complete lack of bone growth for 2 years after injury resulting in long-term osteopenia which may adversely affect peak bone mass accumulation [6, 7]. Severely burned children with a burn size of >80% have a linear growth delay for years after injury [8].
Therapeutic attempts to manipulate the hypermetabolic response to severe burn injury should be sustained for at least 9 months after burn.

**Nutritional and Environmental Support of Burn Patients**

There is a change in the hypothalamic temperature set point after major burns such that patients are striving for a core temperature 2 °C above normal [9]. Warming rooms from 20 °C to 33 °C decreases the metabolic rate from 100% above normal to 40% above normal in burns over 40% of the body.

Despite nutritional manipulation, weight loss of up to 30% of body mass was common in burn patients prior to the use of continuous feeding [10]. Nutritional support of the hypermetabolic response in severely burned patients is best accomplished by early enteral feeding. Burn-induced intestinal ileus is not nearly as pervasive a problem as once commonly believed. Early enteral feeding with whole milk or complete elemental formulas (100% free amino acids) preserves gut mucosal integrity and improves intestinal blood flow and motility.

Caloric needs are estimated using formula created by the retrospective analysis of the calories required to maintain body weight in large patient series or by direct measurement of metabolic rate using indirect calorimetry. Overfeeding causes increases in carbon dioxide production, fatty infiltration of liver, and blood urea nitrogen. Underfeeding results in increased loss of lean body mass, muscle wasting, poor wound healing, and increased susceptibility to infection. Indirect calorimetry is performed using a mobile metabolic cart measuring the concentration of oxygen and carbon dioxide in the inspired and expired gas to determine oxygen consumption and carbon dioxide production. This can be performed at the bedside.

Total energy expenditure measured over the hospital course by stable isotope techniques is 1.2 times the resting energy expenditure (REE) measured by a metabolic chart [11]. Caloric delivery beyond 1.2 × REE results in increased fat mass without attenuation of loss of lean body mass [12]. REE/predicted basal metabolic rate correlates directly with burn size, time of surgical grafting, sepsis, ventilator dependence, and muscle protein catabolism [12].

One of the most commonly used formulas for calculating caloric needs in burn patients estimates caloric needs to be 25 kcal/kg/day plus 40 kcal/% TBSA burn/day in adults; there are separate formulas for children of different ages (table 1) [13–16].

Enteral nutrition, supplied predominantly as carbohydrate and protein rather than as fat-based formula such as milk and the majority of available hospital diets, improves the net balance of skeletal muscle protein in severely burned children [17]. Muscle protein degradation is decreased with a high-carbohydrate protein diet due to increased endogenous insulin production.
Burn patients may require exogenous insulin to control hyperglycemia. Tight euglycemic control with insulin improves wound healing and decreases infection and mortality [18, 19].

Protein breakdown is elevated in the acute, flow, and convalescent phases of burn injury [20]. Increasing protein delivery from 1.5 to 3 g nitrogen/kg/day, however, shows little benefit on whole-body protein breakdown and muscle protein synthesis rates [21].

Arginine and glutamine are not considered essential amino acids, but under severe stress they become essential dietary nutrients. Arginine is known to stimulate T lymphocytes and enhance natural killer cell function, and to stimulate synthesis of nitric oxide, which is important in communication and host resistance to infection. Arginine appears to improve immune responsiveness and promote wound healing when given as a supplement. Glutamine is a primary fuel for enterocytes. It appears to play an integral role in wound healing as well. Muscle glutamine formation is suppressed in severely hypercatabolic burned patients. There is increasing evidence that supplementation of arginine and glutamine is of benefit in critically ill patients [22].

A small quantity of fat is an essential component of nutritional support. A substantial proportion of calories delivered as fat improves glucose tolerance and decreases CO₂ production, but the hormonal environment of the burn patient causes such a great degree of endogenous lipolysis that the extent to which lipid can be utilized in the burned patient is limited.

Increased peripheral lipolysis, a principal component of the metabolic response to injury, results in fatty infiltration of the liver. This can be exacerbated by overfeeding and the use of total parenteral nutrition. Released free fatty acids are oxidized for energy and re-esterified to triglyceride in the liver. They are either deposited in the liver or further packaged for transport to other tissues. The liver weight of burn children is increased up to 2 times the liver weight of age- and sex-matched controls [23]. Mochizuki et al. [24] demonstrated an adverse effect on immune function in burned guinea pigs when diets contained more than 15% lipids. n-6 fatty acids, from vegetable and animal oils, are metabolized to yield PGE₁ and PGE₂ which have immunosuppressive properties. n-3 fatty acids from fish oil are metabolized
to yield PGE₃, which is immunologically inert. Post-burn immunosuppression might be improved by replacing n-6 fatty acids with n-3 fatty acids. Alexander et al. [25] showed that burned guinea pigs fed a diet high in fish oil compared to safflower oil had better cell-mediated immune responses.

Electrolyte disturbances are common in burn patients and must be corrected frequently, particularly calcium and potassium. Albumin supplementation may also be necessary during the acute phase since protein loss is extensive and hepatic synthesis of constitutive proteins is decreased as the liver accelerates its production of acute-phase proteins.

Prevention of Infection, Excision and Closure of the Burn Wound

Prevention of infection and sepsis are critical therapeutic maneuvers to decrease the hypermetabolic response. The patients who develop sepsis, as defined either by a burn-specific score or one modified from the American Academy of Chest Physicians and the Society of Critical Care Medicine, have an increased metabolic rate determined by metabolic chart and an increase in protein catabolism determined by stable isotope techniques of 40% greater than that of like-sized burns throughout the hospital course and well into the time of rehabilitation [5]. The other major therapeutic modulation that has been shown to have a marked effect on metabolic rate is early excision and closure of the burn wound. Early burn wound excision with coverage using a widely meshed autograft covered with cadaver skin, and cadaver skin being used to cover all other remaining areas, results in decreased operative blood loss, decreased length of stay, fewer septic complications and decreased mortality in children and young burned adults relative to patients treated by serial debridement [5, 26–28]. Comparing patients who had total burn wound excision and coverage within 72 h of injury (early group) to a group in whom excision and coverage of wound was performed within 3–10 days after injury (middle group) and to a group whose excision was performed 10–21 days after the time of injury (late group), the net protein loss across the patients’ legs increased from 0.03 (early) to 0.05 (middle) to 0.07 (late) μmol phenylalanine/min/100 cm³ of leg blood volume, a doubling of catabolism results from delay in wound excision. It was also demonstrated that bacterial log counts in quantitative tissue cultures increased from 3 in the early treatment group to 3.5 in the middle treatment group to 4.2 in the late treatment group. The incidence of burn wound sepsis also increased during the hospital course from 20% in those excised early to 35% in those excised in a middle period and to 50% in those excised late [29].

The metabolic rate markedly increases with activity, pain and anxiety. Burn care (debridement, range of motion exercises, dressing changes and application of topical antimicrobials) increases already nearly unbearable
pain levels. Maximum utilization of narcotics, sedatives, and supportive psychology help reduce these effects.

**Pharmacologic Modulation of the Hypermetabolic Response in Burn Patients**

Pharmacological agents have been used to attenuate catabolism and to stimulate growth in burn injury. Growth hormone, insulin, insulin-like growth hormone (IGF)/IGF-binding protein-3 (IGFBP-3), testosterone, and oxandrolone improve nitrogen balance and promote wound healing [30–34]. Tachycardia is sustained for many weeks in massively burned patients even after they are covered with autografts. The use of propranolol decreases cardiac work, myocardial oxygen consumption, resting energy consumption, lipolysis and also contributes to the maintenance of lean body mass [35].

**Recombinant Human Growth Hormone**

Recombinant human growth hormone (rhGH) has shown efficacy in improving muscle protein kinetics and wound healing [3, 30]. In adults, plasma growth hormone levels have been shown to decrease after severe burn [30]. rhGH administration leads to an increase in catecholamines, glucagon, and free fatty acids [3]. Administration of 0.2 mg/kg/day of rhGH accelerates donor site healing by up to 30% by increasing epithelial mitosis and synthesis of structural proteins such as collagen [36]. Accelerated healing leads to earlier burn wound coverage, decreased length of hospital stay, and decreased septic morbidity and death. Growth hormone has also been shown to increase type-1 T-helper cytokine production and decrease type-2 T-helper cytokine production [37].

Questions have been raised about the safety of administration of rhGH to adults in intensive care units by European trials that reported a significant increase in mortality among catabolic patients (exclusive of burns) treated with rhGH compared to a control group [38]. However, Ramirez et al. [39] demonstrated that rhGH treatment of severely burned children is safe and efficacious. A 2% mortality was observed in both rhGH and placebo groups, with no differences in complications or mortality. The requirements for albumin supplementation to maintain serum albumin levels above 25 g/l was reduced by more than 50% in the group receiving rhGH. Growth hormone given during acute hospitalization maintains growth in severely burned children who would otherwise experience a significant growth delay [40]. There is a significant improvement in height velocity during the first 2 years after burn in growth hormone-treated groups compared to controls [40], rhGH stimulates bone formation and muscle protein synthesis via insulin-like growth factor-I [7] successfully abating muscle catabolism and osteopenia [7, 40].
Insulin

Submaximal insulin administration produces muscle anabolism by stimulating net muscle protein synthesis in severely burned patients [18]. Insulin also improves skin graft donor site healing and improves wound matrix formation [31]. Clinical studies are underway using exogenous insulin infusions to produce euglycemic hyperinsulinemia for the duration of hospital stay in an attempt to reduce muscle breakdown and improve outcomes.

IGF-1/IGFBP-3

Administration of IGF-1/IGFBP-3 attenuates catabolism [28] and results in a decrease in interleukin-1β, tumor necrosis factor-α, and type-I acute phase protein (C-reactive protein, α1-acid glycoprotein, and complement C-3) production in burned patients [32, 41].

Other anabolic agents are being investigated, such as testosterone and oxandrolone, in a search for safe and less expensive alternatives to recombinant growth hormone, IGF-I/IGFBP-3, or insulin for the treatment of burn patients.

Testosterone

Testosterone production is greatly decreased after severe burn injury, which can last for several months afterwards. Testosterone administration has been shown to ameliorate the catabolism of fasting by increasing net protein synthesis in normal men. Increased protein synthesis with testosterone is accompanied by a more efficient utilization of intracellular amino acids derived from protein breakdown and an increase in inward transport of amino acids [33]. An increase in net protein synthesis is attainable in adult men with large burns by restoring testosterone concentrations to the physiologic range [33]. Total testosterone increases significantly from baseline to the low normal range after 1 week of testosterone administration, protein synthetic efficiency increases 2-fold and protein breakdown decreases almost 2-fold resulting in an improvement in net amino acid balance [33].

Oxandrolone

Oxandrolone, an analogue of testosterone (with less androgenic effect), has been used therapeutically in Turner's syndrome and other constitutional delays of growth, in cachectic alcoholic hepatitis patients, and AIDS patients [42]. It also has been used in acute and rehabilitating adult burn patients with promising results in terms of weight gain [42]. Oxandrolone improves muscle
protein metabolism in severely burned children through enhanced protein synthetic efficiency [34].

Adrenergic blockade has been used with success in pathologic hypercatecholamine states and thyrotoxicosis by decreasing myocardial workload, whole-body irritability, and tremulousness. Herndon [1] showed in 1980 that total catecholamine absence in 60% burned rats, induced by either adrenalectomy or chronic reserpine administration decreased hypermetabolism. Wilmore et al. [43] were able to show significant decreases in metabolic rate with combined $\alpha$- and $\beta$-blockade and with $\beta$-blockade alone in burned patients. This decrease in metabolic rate is associated with a decrease in pulse rate, blood pressure, minute ventilation, and free fatty acids. Several studies have demonstrated that limited $\beta$-blockade can be safely used in severely burned patients throughout the hospital course [35, 44]. No significant side effects or complications were noted in these studies. Maggi et al. [45] showed that selective $\beta_1$-blockade decreased cardiac work without adverse side effects using intravenous metoprolol administration. Five days of metoprolol administration ($2.0 \pm 1.1 \text{ mg/kg/day}$) significantly reduced heart rate and the rate-pressure product in large burns without affecting protein metabolism or lipolysis.

**Nonselective $\beta_1$ and $\beta_2$ Antagonist**

The most frequently used antiadrenergic agent is propranolol. Studies have shown that propranolol administered in doses of 1–2 mg/kg/day can produce a reduction in heart rate and left ventricular work of approximately 20%. In addition to decreasing heart rate and left ventricular work, propranolol administration causes decreased peripheral lipolysis, decreased tremulousness, and irritability. Propranolol treatment is a safe and effective means for mitigating the hyperdynamic cardiovascular and catabolic response to thermal injury [44].

In children with severe burns, treatment with propranolol during hospitalization attenuates hypermetabolism and reverses muscle-protein catabolism [35]. $\beta$-Blockade decreases heart rates and REE. In propranolol-treated patients muscle protein net balance improved by 82% compared to pretreatment baseline values, where it decreased by 27% in untreated controls [35]. Lean body mass was maintained by propranolol treatment compared to a 9% loss in controls [35].

Increases in metabolic rate and core temperature are characteristic responses to severe injury. Increased substrate cycling contributes to the increased thermogenesis and energy expenditure following severe burns. Increased triglyceride-fatty acid cycling is due to $\beta$-adrenergic stimulation [46]. Administration of propranolol decreases peripheral lipolysis and decreases fat deposition in the liver of burn patients [8, 47].
Insulin, β-blockade with propranolol and use of the synthetic testosterone analog oxandrolone are the most cost-effective and least toxic pharmacotherapies for the treatment of the hypercatabolic responses to trauma (table 2, 3) [48].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Complication</th>
<th>Incidence %</th>
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<tbody>
<tr>
<td>rhGH</td>
<td>Hyperglycemia</td>
<td>50a</td>
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<tr>
<td></td>
<td>Growth arrest</td>
<td>0</td>
</tr>
<tr>
<td>Insulin</td>
<td>Hypoglycemia</td>
<td>50a</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Hypoglycemia</td>
<td>25a</td>
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<tr>
<td></td>
<td>Neuropathy</td>
<td>23</td>
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<tr>
<td>Oxandrolone</td>
<td>Hirsuitism</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hepatic dysfunction</td>
<td>0</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Bronchospasm</td>
<td>0a</td>
</tr>
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<td></td>
<td>CV collapse</td>
<td>0a</td>
</tr>
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Table 3. Potential complications and identified incidence of anabolic agents

In the table, rhGH, 0.2 mg/kg/day costs 490 USD, Oxandrolone, 15 mg/day costs 21.42 USD, Insulin, 240 units/day i.v. costs 83.28 USD, Propranolol, 200 mg/day costs 2.56 USD. The rate of hyperglycemia with insulin is 50% and with IGF-1 is 25%. Growth hormone can cause hyperglycemia and growth arrest.

Conclusion

Hypermetabolism is a characteristic response to severe burn which lasts up to 1-year after injury. Persistent catabolism slows rehabilitative efforts, which in turn slows meaningful return of individuals to society. Hypermetabolism can be attenuated by nutritional treatments that include enteral feeding with high-carbohydrate, high-protein feeding, possibly supplemented with n-3 fatty acids, arginine and glutamine, calcium and specific vitamins [49]. Early excision and grafting, prevention of sepsis, maintenance of a warm environment, and pain and anxiety reduction also attenuate hypermetabolism [26–29]. Growth hormone is an anabolic treatment which has been used for the last 15 years in burns and has been shown to improve wound and donor site healing, to increase growth in growth-stunted pediatric burn survivors and to increase accretion of lean body mass and bone mineral content. It can cause
hyperglycemia due to peripheral insulin resistance. But these problems have been shown to be easily manageable by most groups reporting their experience with growth hormone. Recently questions have been raised about the safety of growth hormone in adult patients in the intensive care unit. A significant increase in the mortality rate of critically ill patients who were given growth hormone has been reported from two large prospective randomized trials from Europe. These results were in direct contrast to the results of many studies carried out in burn populations. While the cause of increased mortality in these European studies has not been identified, clinicians have sought other possibly safer adjunctive anabolic therapies such as insulin, IGF-1, alone or in combination with IGFBP-3, testosterone, oxandrolone and propranolol. The simplest effective anabolic strategies for severe burn injuries are early excision and grafting of the burn wound, maintenance of environmental temperature at 30–32 °C and continuous enteral feeding of a high carbohydrate, high protein diet. To further minimize erosion of lean body mass, administration of rhGH, insulin, oxandrolone or propranolol is a reasonable approach. Exogenous continuous insulin infusion, β-blockade with propranolol, and administration of the synthetic testosterone analog, oxandrolone, are the most cost-effective and least toxic pharmacotherapies to date [48].

References

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Discussion

*Dr. Moldawer:* You made the statement earlier on that a 40% full-thickness burn was your threshold for intervention. Is that all right, is that across all comers depending upon age, prior initial nutritional status, co-existing morbidity, does that 40% hold up?

*Dr. Herndon:* Certainly not, the answer to your question is that co-morbidity, pre-existing starvation, pre-existing sepsis or other traumas will increase or change that threshold. I meant to say that only in pure burn is the threshold around 40%. With other pre-existing diseases or co-morbidities or co-traumas that threshold changes greatly. What I would suggest practically is to determine the resting energy expenditure after the first 5 days after injury to determine whether a patient is hypermetabolic, then you should introduce therapy or you should get genetic profiles and see what the single nucleotide variation is.

*Dr. Moldawer:* What is it about 40%? Is it the resting energy expenditure, is that the inflexion point, is that the criteria then that you use?

*Dr. Herndon:* Over the many burns that we have studied, it takes this size of injury alone to cause the increase in resting energy expenditure and the protein catabolism which have been our phenotypic markers in the past, and we can't correct upon the endogenous responses in smaller burns. However, a 30% burn with a fracture we can; a 30% burn with a small keenolation injury we can, and a 30% burn with delay in
resuscitation which causes a perfusion-reperfusion injury, like aortic aneurysm for example, we can.

**Dr. Moore:** I spoke to you a bit earlier about the study by van den Berghe et al. [1] in the *New England Journal of Medicine* on the use of intensive insulin therapy in critically ill patients. They randomized about 1,500 patients and showed reductions in sepsis, mortality, and poly-neuropathy of critical illness. They propose that by keeping the glucose low that they are somehow modulating the immune response. I don't know if this is true, what are your thoughts? And the second question, is just how aggressive do you need to be? We are placing people on continuous insulin drips of roughly 7 to 10 units of insulin an hour, and there have been some problems with hypoglycemia.

**Dr. Herndon:** Yes, I think the continuous use of insulin throughout the hospital course in appropriately monitored ICUs is a very potentially useful therapy. Its primary effect, as I have measured it, has been general improvement in protein synthesis and an improvement in protein synthesis in healing wounds. The needed dose for these effects is much lower than we originally had found. We studied hyper-insulinemic euglycemic clamps in which we were initially giving 10–20 units/h throughout the hospital course and this was efficacious. But if, for instance, the nurse turned off the enteral feeding for some reason, if you use total parenteral nutrition (TPN) and somebody shut that off, then you get a hyperglycemic person developing sepsis and ileus and becoming hyperglycemic unless continuously monitored. We have recently found that in burn patients just to maintain type euglycemia, their plasma glucose should be 8.4–9.0 mmol/l throughout the hospital course, presumably because of the increase in glucose flow and not necessarily insulin resistance. But if you give them 2–4 units of insulin/h throughout the hospital course they don't become hyperglycemic, their plasma glucose is around 5.6 mmol/l type euglycemic control considering that they are continuously getting 1,500 kcal/m² plus 1,500 kcal/m² burn they get a high carbohydrate protein diet. The difficulties come with ileus or therapeutic mistakes or turning the feeding off during operation, then you can have disastrous hyperglycemic episodes. So it is only under purely control conditions that I think this is a psiatory effect and I do think that looking at immune responsiveness in this setting is also required. I think there are psiatory effects.

**Dr. Martindale:** I am interested in your comments about hypercaloric feeding when you are monitoring the patient so they have more adipose tissue. What about hypocaloric feeding in the burn population in the critical care setting? We feed our obese population hypocalorically, and we are now leading towards feeding normal-sized patients hypocalorically. What about in the burn population?

**Dr. Herndon:** How do you define hypocaloric? I think you need to feed sufficiently to maintain lean body mass, to have sufficient protein delivery and glucose delivery to maximize the host-defense mechanism. What that threshold is, in any particular disease state, remains to be seen. Hypocaloric relative to what we use to think was appropriate certainly, absolutely hypocaloric definitively not.

**Dr. Cynober:** You got very impressive results with different anabolic agents. From a practical point of view I would like to know which ones you are using routinely in your clinical practice.

**Dr. Herndon:** I don't really have a routine clinical practice in that everybody who comes to our institute is involved in some sort of clinical trial. But if I would recommend what I would routinely use today on other people, it would be oxandrolone and propranolol in combination during the acute hospital stay, except in ICUs where insulin can be given safely in low monitored doses, then perhaps that would be a more psiatory agent than oxandrolone. Insulin also causes epithelial mitosis and production of proteins that are psiatory by the epithelium and are important to me. It may well be
that both oxandrolone and propranolol will have immunological effects, but if you believe that we do worse with oxandrolone and go the wrong way, insulin would be the better and preferred agent in combination with propranolol in units that can handle it.

**Dr. Cynober:** I think this is an important issue because this type of research is in principle to improve the care of the patient and if, for example, you have a 40% improvement in protein synthesis with IGF-1, logically we should try to further improve and provide IGF-1 to all the patients and to look at what happens even, for example, in addition to propranolol.

**Dr. Herndon:** I think that those are psiatory benefits in the data I did not have time to show today. I believe that we have to treat our patients not just during the acute hospital course but we must look hard at their convalescence, 6, 9 and 12 months after injury, the use of exercise and anabolic agents can markedly improve protein mass, lean body mass and growth in children if we refocus our efforts away from just the ICU towards convalescence.

**Dr. Cynober:** Of course to make anabolism you need anabolic agents but you also need amino acids to make proteins. Have you some special view and recommendation about amino acids in burn patients and the potential synergistic effect between amino acids and anabolic agents?

**Dr. Herndon:** I don’t have a lot to say about that scientifically. The studies that we have performed show that 1 g/kg/day of protein is as efficacious as 3 g/kg/day of amino acids, that you can only handle so much amino acid before it just flows over, similar to glucose. As far as which amino acid is best, I do have some papers on that but it goes a little bit out of the scope. But glutamine and arginine do have a place as supplements but I don’t want to plug that too much right now.

**Dr. Berger:** Two questions, one about the timing of oxandrolone. Clearly our patients change with time and there is worry about hepatic function with early oxandrolone. While insulin is currently used early on, would you use an early time point for initiating oxandrolone? What would your criteria be?

**Dr. Herndon:** We have not been instituting any of these anabolic agents until the 5th day after the first operation which would be about day 5 after ICU admission, and day 7 after admission, bearing in mind that my patients are in hospital for a month or so. Oxandrolone is an agent that we are using for long-term treatment to try to improve muscle mass over time, insulin is a better ICU agent theoretically.

**Dr. Berger:** So you would agree with starting with insulin and, when the acute phase response fails, to introduce oxandrolone or something like that.

**Dr. Herndon:** That is probably a reasonable strategy.

**Dr. Berger:** The second question is about growth hormone in children and the difference with adults. It is known that in children there is a depression in growth hormone and so on. Would you think this could be an explanation for the better response to growth hormone in children than in the adults who are not obviously deficient?

**Dr. Herndon:** There are probably many reasons for differences with age and response to this. Quite clearly children who are growth hormone-deficient an bringing their levels back up improve their growth, improve their albumin synthesis, decrease the acute phase response, improve the wound healing.

Those results, not being been translatable to adults, may have any number of reasons. Clearly adults get more hyperglycemic, they get more hyperlipidemic, their cardiac output effects of growth hormone may actually be deleterious to an older population whereas children love it. They already have a fixed tachycardia and growth hormone helps the cardiac output and improves oxygen and substrate delivery. Those things can’t happen in adults.

**Dr. Berger:** When would you start them on it, just timing?
Dr. Herndon: In children again I don’t start any anabolic agent until Dr. Cuthbertson has said the ebb phase is over. So about 5 days; his findings have guided me for a long time.

Dr. Kudsk: I should comment on studies that we did when I was in Tennessee. I think that the findings you have are relevant. They have to be tested in individual populations. We tried growth hormone and IGF-1 and oxandrolone in our trauma population. Growth hormone had a real effect upon constitutive proteins but did not have much of an effect on nitrogen balance. Hyperglycemia was only a problem when the patients developed an infection. IGF-1 also had an effect on constitutive proteins. We did a study with the University of Kentucky. The patients had positive nitrogen balance at least until the binding proteins were inhibited. Oxandrolone had no effect. These findings were recently published [2]. This has to be tested in individual patient populations.

Dr. Chioléro: I have an additional question concerning anabolic therapy since you have nicely shown that there are a lot of possibilities. But when you combine drugs there is the possibility of interaction, for example insulin and β-blockade. Have you done any studies on combined therapy?

Dr. Herndon: I have many currently running studies on combined therapy. In the last one that was published in the Annals of Surgery, I gave growth hormone and propranolol and found that when I gave propranolol the growth hormone effects were inhibited, but conversely the growth hormone effects did not inhibit the propranolol effects. So your comment is well taken that combination therapies need to be studied for interactions and this alphametric technique also helps you a lot in seeing what genes are regulated and not regulated by each individual therapy, and how the combination therapies can affect it. You can then go on and look at the proteins that were varied in those experiments and that might help us come to grips more quickly with the drug interactions.

Dr. McClain: Many of your patients had fatty liver. Do you think this is analogous to the fatty liver that you see with obesity where an over-production of cytokines is seen and the patients are insulin-resistant?

Dr. Herndon: I think that there may be major corollaries between those. The fatty infiltration in liver seen after major injuries has been seen as a non-phenomenon or something that really does not cause morbidity. I think it is a very significant and a huge phenomenon. Most people have said it is due to TPN or overfeeding, but I am not sure that this bears out either. I think it is more a catecholamine effect which causes profound peripheral lipolysis and the liver cannot export fat in the form of very low density lipoproteins. We recently published a paper in the Annals of Surgery showing that there is too much fat coming into the liver and you can’t get rid of it under these circumstances. Whether you hypocalorically feed or not, this phenomenon occurs: just feeding pure protein and sugar and no fat it still occurs, and it is something that needs to be addressed by specific purpose. I don’t think it is a non-phenomenon, I think it leads to liver failure and to multiple organ failure in the debts of disease.

Dr. McClain: It is a critical phenomenon because when you try to transplant those livers, the patients die because those are dysfunctional or ‘bad’ livers.

Dr. Herndon: Our thoughts for the last 40 years that the livers were alright are wrong, I think there are bad livers.

Dr. McClave: The comment you made about the effects of these hormonal therapies on protein metabolism and propranolol reducing the phenotypic expression of the response: the question is are these really surrogated end points, how many of these hormonal therapies actually affected outcome parameters? Oxandrolone for alcoholic hepatitis did all of the things on proteins that you mentioned but really had almost no effect on outcome.
**Dr. Herndon:** I think that is an absolutely key sort of question. Of course my outcome parameters are very long-term. Short-term enhanced acute outcome parameters, there is virtually no effect in these small studies that I am describing. There have been huge effects on growth and huge effects on strength when you look at people at 6, 9, 12 and 24 months. So my outcome parameters, unlike many in the literature on trauma, go beyond this charge and well into the convalescence. I think we need to do that when we are looking at an inflammatory hypermetabolic response that sets up when an acute insult establishes itself, and maintains itself for very prolonged periods of time. So all of these have had profound effects on long-term outcome indicators, they have had very little effect on short-term mortality infectious disease-type indicators, though there are many biochemical indicators that show that it is doing something in the acute phase.

**Dr. Nitenberg:** Just to make a point, you are specially dealing with burn patients?

**Dr. Herndon:** Children with burns.

**Dr. Nitenberg:** We are talking about critical care in this meeting, so I want to be sure that there is no confusion because I have some experience with beta-blockade in ICU patients and I can say that I have killed patients with this practice. We tried that with Bekins 20 years ago and that was the result. We have had the same experience with growth hormone and, as Dr. Kudsk said, I think we have to modulate our experience with this type of hormone and hormone manipulation in acutely ill patients depending on the level of trace. Do you agree with that?

**Dr. Herndon:** I certainly agree that you need to be very careful translating results in children to adults. I do think the burn patients are definitely critically ill individuals and are a superb example of critically ill individuals. I am very sorry that you killed people with propranolol, I would point out that this is due to a little lack of attention to details, and I would also say that killing people with growth hormone is due to a lack of attention to detail. So I would advise in any study to be very conscious about utilizing these profound modulators of the response.

**Dr. Cynober:** To react to Dr. Nitenberg’s statement. You were abrupt in saying that human growth hormone killed adult patients in the ICU because, among various reasons I have read, the Takala et al. [3] study showed that the nitrogen support of the patients was very low, 0.15 mg/kg/day, and there are some speculations open for discussion. Of course the speculation about the fact that by blocking muscle the amino acid was an insult for the patient because there was no sufficient amount of amino acids to synthesize in the liver some of the proteins which are required in response to injury. Those results were published 2 years.

**Dr. Nitenberg:** I agree with you. I don’t say that growth hormone is especially lethal in every patient. I said that in this type of patients in this type of experiment it killed patients. My point was we must be careful in using this type of hormone in patients. That is the only thing I want to say because, for example, to use beta-blockade in septic patients is clearly dangerous. Dr. Herndon is dealing with children who are in a stable situation over a long time. In this type of patient you can probably manipulate the hormones very easily. In acutely ill patients with one hint, a second hint, a third hint, you can’t do that very easily and you are probably being harmful. That is the point.

**Dr. Herndon:** I would like to respond just briefly to the comment. Many evidence-based articles, including a very large one in the New England Journal of Medicine showing the decreased mortality with beta-blockade, not only during acute hospitalization but with a long-term outcome, have shown that the use of beta-blocking agents in individuals undergoing major operative trauma, pre- and peri-operatively, causes the overall decrease in myocardial advance with the utilization of that agent over time. So I am not arguing with you that a drug was certainly misused causing
difficulties with it, but I think that careful utilization can be safe and done for great benefit to patients.

*Dr. Zazzo:* A few years ago, in major surgery Kelhet and Kolics demonstrated a positive metabolic effect of epidural analgesia and early nutrition. Have you any data on the strict use of analgesia without other drugs and do you think that good analgesia could be added to your list?

*Dr. Herndon:* Absolutely, I think that the apherin stimulators that cause the central hyperdynamic response, the stress response, are greatly augmented and modulated by pain and any technique that can ameliorate the pain response will down-regulate the apherin stimulator, and it should be studied and tried and encouraged.

*Dr. Moore:* Your data on TPN being harmful supports my bias. You are dealing with very hypermetabolic patients and, if you are not using TPN, how do you meet their caloric goals and is that important early in their hospital course or do you just feed them high protein enteral diets and as time goes on you are able to get up to a reasonable rate?

*Dr. Herndon:* Actually in burn patients if you start feeding them immediately after the burn injury you can get to full caloric maintenance within 24 or 36 h at the time of injury. The ileus that has been described in the past immediately after injury is, I believe, generally an edema problem that can be greatly reduced by using the gut, stimulating it with food earlier on and increasing blood flow, and perhaps by not giving as much lactate as you are known to do in the other parts of Texas.

*Dr. Moore:* Do you feed into the stomach or post-pyloric?

*Dr. Herndon:* I feed into the stomach initially because it takes a while to get post-pylorically. I used to feed entirely just the stomach and not post-pylorically, and it has become a fad to feed post-pylorically and I do it sort of 50/50.

*Dr. Moore:* So you try to get people on positive caloric balance as soon as possible.

*Dr. Herndon:* That is correct.

*Dr. Allison:* It is sort of reassuring that if you stick around long enough you come back into fashion again. We started using insulin in the 1960s and 1970s and published data [4], and I want to echo Dr. Cynober's point that one of the effects of insulin is that you are limiting the endogenous amino acid supply, so you should not only give enough glucose to prevent hyperglycemia, and as a diabetologist I would suggest that if you are getting hyperglycemia you may not be managing the situation very well, you should also give adequate protein or amino acid with your insulin. The other thing we showed was that one of the major responses to injury which has not been mentioned is that you get salt and water retention, and you just mentioned the edema problem. One of the things we showed with insulin was that not only maintaining an adequate intravascular volume was important in enabling patients to excrete an excess salt and water load but, in contrast to the effect of insulin in obesity which causes the salt and water retention, these people had massive diuresis of salt and water following the insulin, and so that is another way in which insulin might be effective in this situation. I don't know whether with modern management you get much problem in that direction but I would be interested to know if you have any observations on this.

*Dr. Herndon:* Our earlier studies are still right on and we appreciate them.

*Dr. Ngwu:* From a dietetic point of view we know that patients have some factors affecting their nutrient intake, something like appetite, something like stress. Should we target giving them diets that are recommended dietary allowances, especially in areas where TPN is not very active, or do you have other standards to measure their nutrient intake?

*Dr. Herndon:* This is a very important comment. I think that you can give continuous enteral feeding to populations with great efficacy but you need to be very careful about measuring how much that is because it is often exaggerated, from
self reporting and reporting of others. I think we are going to have a debate about TPN versus other feedings later. Maybe we can expand on them.

Dr. Baracos: I would like to ask you, with so much success with therapies that are both anti-catabolic and hyper-anabolic, where do you have any catabolic patients left? I don't mean to be cynical, what I want to ask really is do you have any patients that you believe are intractable to those things that you do? Are you presently aware of and what do you think might be going on in those instances? What fraction of your patients do you believe have an anabolic or catabolic problem that you don't presently have the means to manage?

Dr. Herndon: Quite clearly those individuals who become septic are more catabolic than patients just catabolic from the injury itself, and we and others in this room have read extensively about such patients making it hard to handle glucose and protein and other regular nutrients. So a septic patient is very difficult to handle with anabolic agents and is more intransient to anabolic agents though insulin seems to be the one to use particularly in septic individuals, you get another inter-current stress and it remains problematic. I did not mean to say we have conquered the mountain here. We cannot maintain lean body mass except by assiduous utilization of anabolic agents in those patients who cannot tolerate enteral feeding and require TPN. We still develop exacerbation of immune suppression and do not reach anabolic goals.

Dr. Baracos: In addition to that you have your benchmark at a reasonable expectation of promoting the lean body mass, i.e. skeletal muscles in instances where the patients are completely bedridden.

Dr. Herndon: I have put up this slide just to point out that exercise and physical therapy are absolutely required to maintain lean body mass, early institution of physical therapy and exercise are critical in that effort. You can maintain nitrogen balance with anabolic agents but I would say not without some form of physical therapy.

Dr. Allison: Boulder in Buffalo was eccentric, he used to exercise his patients in the ICU, bag them as they walked up and down.

Dr. Herndon: He was eccentric but smart.

Dr. Rosenfeld: Welhara and Hill almost 2 years ago demonstrated that septic and trauma patients increased their metabolic rate about 2-fold after the first week. Have you observed this in burn patients and have you observed a necessity to change the anti-catabolic strategy you planned?

Dr. Herndon: Yes, our time course for seeing the increase in metabolic rates in the data of Dr. Cuthbertson shows an ebb phase for about a week or so after injury then it reaches a maximum at 7–15 days after injury and remains elevated, at least I hope I have shown here not just throughout the hospital course but well into the 1st year or 2 after injury. I generally do not begin anti-catabolic or anabolic agents until the ebb phase or the relatively hypermetabolic phase has been completed. Some of the studies by Dr. Moldawer and others show that the genetic evidence, the genetic effects that may set up this inflammatory response, may occur in the first minutes or hours after injury and the typical endocrinologic phenotypic response is maximized in your studies at 1–2 weeks after injury.

Dr. Chioléro: An additional comment on the route of feeding since we all agree that enteral feeding should be implemented in burn patients, there is no question about that. However, concerning the statement that TPN is a poison in such patients, I am not sure it is supported by the literature, since most of the papers that were published on the bad effect of TPN are old papers, the patients received hyper-alimentation, and they had too much fat with all solutions. So, at least in adults, when enteral nutritional support is difficult in our units, we sometimes add TPN to patients and they do well.
Dr. Herndon: I certainly don’t want to be dogmatic about the paper, when I tried TPN augmentation and maximal enteral feeding that was 10–15 years ago, and clearly more reason than superior techniques may modify those results and don’t have to be repeated. We fortunately have been able to get away with just enteral feeding in the last 20 years in the treatment of burns without TPN, but there is no question and no disrespect intended to current practices elsewhere.

Dr. Allison: Could you speculate on something that has always been a mystery to me. As you just said, how this inflammatory store perpetuates this metabolic response for such a period of time long beyond the point where the neuroendocrine and the inflammatory storm is over is unknown. Maybe there is some persistent neuroendocrine effect. Why do you, particularly in burns, get this very prolonged effect?

Dr. Herndon: I am currently stupefied by that question and terribly interested in trying to gain some insight into it. It might be the persistent development of hypertrophic care in this patient population providing persistent inflammatory foci, sufficient to cause an already revved up engine to rise, but that is hypothesis and certainly not a fact, which continues to intrigue me and I will continue to look.

References