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Discussion

Dr. Douglas W. Wilmore (Boston, Massachusetts): We heard this morning when the Medallion for Scientific Achievement was awarded the great contributions that Dr. Pruitt and individuals working at the Burn Unit in San Antonio have made for the reduction in morbidity and mortality in burn patients. This afternoon an outstanding paper was presented that shows a mortality rate of only 2% in a group of burned children with an average burn size of 60% total body surface injury. This confirms the tremendous translation of research that moves to the clinic from the laboratory. This group and others have shown improvement in wound healing, pulmonary mechanics, and muscle strength with the administration of growth hormone. A large series now reported from Europe has shown a decrease in length of stay and an improvement in convalescence in individuals receiving growth hormone following total hip replacement. And another large series from Italy has shown that growth hormone can reduce congestive heart failure in patients receiving the drug. The question that has surprised us all with additional data from Europe demonstrating increased mortality in critically ill patients receiving growth hormone: Is this selection of patients? Or is it individual physician or hospital effect? We heard this morning that physicians who have greater experience with an operation actually do a better job. And this same experience factor apply with the use of more complex and complicated drugs? In this regard, I would like to ask the authors: Is there data available from this series of increased production of cytokines or other pro-oxidants as a result of giving growth hormone? Growth hormone can in fact stimulate free radical production. Do you have evidence at all that that may be occurring in this group of patients? Is there any data available from your patient groups as to those who have responses with IGF-1 production? We demonstrated that those critically injured patients who could not increase serum concentrations of IGF-1 would in fact have a higher mortality rate than those who could. Is that data present in your data set? Finally, is there an increased mobilization of free fatty acids that occurs when growth hormone is administered to these patients? Fatty acids are deleterious to some cells, and indeed in these severe catabolic situations may affect cardiac function. We have learned from the European study that a very expensive and very potent drug may have toxic effects. But we have heard this afternoon that if used cautiously and correctly with appropriate guidelines, it may have real benefits to our patients. I think it throws up a flag of caution that certainly should encourage us all to proceed carefully and cautiously so we can reduce convalescence in many of our critically ill patients with the safe use of growth factors. Thank you.

Dr. David N. Herndon (Galveston, Texas): In answer to your specific questions, we have shown a decrease in Interleukin-6 production with recombinant human growth hormone in the same patient population. We have not seen increase in other cytokines. We have not seen an increase in other cytokines. We have not yet looked at antioxidant production; however, vitamin E levels are massively decreased in all of these patients. We have not seen differences between them, but are going to investigate just that. IGF-1 production is increased threefold in these patients. We were not able to see differences in IGF-1 levels in those that died versus those that lived. There is a marked increase in mobilization of free fatty acids caused by growth hormone. There is also an increase in cardiac work. In the future, the modulation of that response in certain patient groups by beta blocking agents such as propranolol might be indicated.

Dr. Basil A. Pruitt, Jr. (San Antonio, Texas): I rise to join Dr. Wilmore in complimenting Dr. Ramirez and Dr. Herndon on this impressive body of work. To help us evaluate their conclusions, we need some additional information. Dr. Herndon, you note that in the salvage group, that is those admitted 8 days postburn some of whom had infection, there was a lesser need for albumen supplementation. How do you account for that apparent paradox? Did the excess or deficit in calcium and phosphate relate to the time postburn? That is, were calcium and phosphorus high early postburn at the time of tissue destruction and low later when the lean body mass was being reconstituted? Since IGF-1 increases phosphate reabsorption by the proximal tubule, did the phosphorus levels correlate with IGF-1 levels?

Also, since IGF-1 stimulates osteoclastic activity, do those children to whom you have given growth hormone over the long term have a decrease in bone density? You excluded the beta blocked patients from the graphs of hemodynamic changes. Were those patients also excluded from the other tables? That is, were the calcium, phosphorus and glucose levels influenced by the propranolol beta blockade? Since testosterone increases IGF-1 levels, were the results in these patients who ranged in age from 1 to 18, influenced by circulating levels of testosterone? It is clear from this study that hGH is safe in extensively burned children who are not ill — that is, you excluded any that had organ failure. But for generic use, will it not be necessary to have a control group of untreated patients matched to the 82 "salvage" patients in whom mortality was actually, by chi square assay, statistically higher than in the randomized study patients? Finally, I believe that the growth and metabolic effects of growth hormone are strongly influenced by the amino acid configuration of the molecule. An obvious question then is, was the growth hormone administered in the adult and the childhood trials identical?

DR. DAVID N. HERNDON (Galveston, Texas): In my opinion, the lesser need for albumen supplementation in the salvage group is because they were in the hospital a shorter period of time overall. Looking at discreet time periods, albumen requirements were quite high in the salvage patients as well as in the untreated burn patients. Recombinant growth hormone had a similar salutory effect in both groups, decreasing albumin supplementation. IGF-1 does cause increased osteoclastic activity when given early, but it causes an increase in osteoblastic activity as time goes on. Bone mineral density was looked at in all of these patients, and there was no difference between the treatment group and the control group. That is, there was no improvement in bone density, but there was a decrease in bone density at the time of discharge in all patients. Unfortunately, at 6 months, 9 months postinjury follow-up studies, no improvement in bone density was apparent in either treated or untreated groups. We have looked at calcium and phosphorus balance over time, and as you have pointed out, calcium is released in a much higher fashion earlier and it is consumed later. We have separated out propranolol blockade versus those not receiving propranolol blockade. The most dramatic effects are on heart rate and lipolysis and not on the calcium balance that was discussed. Circulating levels of testosterone are uniformly quite low in these groups and to accurately respond to your question we are going to analyze testosterone levels. But given the levels are so low, I do not think that we are going to see any distinct difference between them. I agree with you that to better interpret the 10% mortality salvage group, a matched control salvage group will have to be looked at. (Included in revised manuscript.) The mortality difference was not significant by a three-way analysis of variance. Dr. Pruitt, I have never heard of you using a chi square without a Scheffe or Bonferoni's correction on three groups. But I am glad to see you did this day. Amino acid configuration is a significant issue. Our earliest randomized studies were done with two different Genentech recombinant products and our later studies were done with a Pharmacia recombinant product, and there is indeed a difference in the N-terminal amino acid between those three products. In fact, Genentech had two different products with distinct differences. But overall in regard to the issues discussed in this paper, there were no differences.

DR. CLEON GOODWIN, JR. (San Antonio, Texas): Dr. Pruitt has left me with two questions. First, your paper implied that the present study was carried out in response to the European studies demonstrating huge increases in mortality with growth hormone therapy. If this is so, how were you able to get your protocol through the IRB and how were you able to obtain informed consent? As a secondary question, how did you obtain consent from the children from Latin America? Second, I view the glass half empty, at least with regards to the growth hormone. Your paper has nicely demonstrated that human growth hormone does not improve major outcome criteria, including survival, quality of wound healing, or subsequent childhood development. So why do you still use growth hormone in light of the lack of any treatment effect? Was there any effect of age from 1 to 18 years in the outcomes?

DR. DAVID N. HERNDON (Galveston, Texas): The present study was actually done before the European study, and institutional review board approval was of course obtained. This study was a look back at our patient population, looking for clues that might explain the startling European findings. We were unable to support their findings in our patient population. Our permits are approved by our Institutional Review Board, and were obtained for all patients enrolled in the placebo blinded trial. We obtained permission from our Latin and South American patients by translating the permits into Spanish with fluent translators as patient advocates and witnesses. The question about developmental age between 1 and 18 years of age is an excellent one. We do not have a sufficient number of patients in any particular age group to look at developmental differences. However, when we looked at height and weight velocity, which is corrected for developmental age, we found that there was, as we would expect, about a 50% decrease in weight velocity within the first year postinjury in both groups which caught up to normal velocity at 1.5 to 2 years postinjury.

DR. RICHARD L. GAMELLI (Maywood, Illinois): Dr. Herndon, this is obviously an excellent study in terms of clinical outcome. To find that growth hormone is safe in children is very important. But as has been echoed by several of the other discussants, utility is key. In a small series of children that we treated at Loyola, we have found a reduction in length of stay, incidence of infectious episodes, not just septic events, improved wound healing, and also a somewhat greater likelihood of a child being discharged to home as opposed to the rehabilitation center. As you have outlined here today, in past publications you have found utility as it relates to donor site healing and length of stay. Shown in the slides and detailed in the manuscript was a reduced length of ventilatory support required in the children that were ventilated in the series treated with growth hormone. Your impression as to why that is true and the studies that support that would be intriguing. I think if we are going to take this to broad area use—the cost of this compound, at least as we have encountered, is not insignificant—and it is going to be important to know what the clear utility of this is and what the cost benefit ratio is on behalf of children and not just that it is safe.

DR. DAVID N. HERNDON (Galveston, Texas): We have shown that the cost of growth hormone throughout hospitalization for the average patient of this group was $12,000 for an 8-year-old with an 80% total body surface burn. The length of hospital stay for the same patient will decrease from 1 day per percent third degree burn if given placebo to 0.66 days for each percent total body surface burn. That will decrease overall hospital cost far out of proportion to the $12,000 cost. Overall hospital costs are decreased by about $40,000 for that individual, after paying for the drug. There is a decrease in ventilatory requirements that seemed to be apparent in the rhGH treated patients.

There is an improvement in wound healing. We have not been able to show long-term effects on growth; however, we do believe the patients return to strength much more rapidly, and that is a positive long-term outcome.

DR. WILLIAM CIOFFI (Providence, Rhode Island): I am down to one question. The real issue here is what is the difference between the European patients and your children? You show a very small risk-benefit ratio. They show very large risk-benefit ratio. So the question would be why and how did those patients die? What is the difference? You have shown in the past that there is an increase in catabolic hormones in patients who are administered growth hormone, specifically catechols cortisone and glucagon. Is there similar data in the European trials? How does that fit in in terms of the mortality? In terms of your patients, if these patients have increased catabolic hormones, especially catechols, why don't you see a difference in their heart pressure products, their metabolic rates, et cetera? If you examine the salvage group, there is a five-fold increase in mortality. And I agree with Dr. Pruitt, it is statistically different by chi square. That group is more similar to the European group in that they are treated late and they usually have organ failure at the time of treatment. Could you comment on how that then fits with the European data? Kids or adult patients that are referred to burn centers late after injury have usually undergone a bias toward survival, that is the most severely injured ones have already died, and yet you still had a five-fold increase in mortality.

DR. DAVID N. HERNDON (Galveston, Texas): Not to argue the statistics, a 10% mortality rate in an 8-year-old with a 60% total body surface burn is still quite low (control group added to revised manuscript). But I would agree that these patients were treated late in comparison to patients in our randomized studies. There was a cluster of people who died early after the administration of recombinant human growth hormone, perhaps from cardiovascular effects. We have shown an increase in production of catecholamines stimulated by rhGH administration. We would have expected that to increase cardiac output to increase cardiac work. Perhaps in those massively burned children, the level of baseline catecholamines was so great with these massive burns that the additional effect on catecholamine levels did not affect overall cardiac output and rate because their hearts were already maximally stimulated. In an older patient group of 61 years of age, that sort of catecholamine drive might cause an increase in cardiac output and cardiac rate. Growth hormone clearly causes an increase in lipolysis. In and of itself, increased free fatty acid levels can lead to cardiac arrhythmia. I would predict that the early cardiac effects are the area of greatest concern. As Dr. Wilmore alluded to, any drug that is used must be used with great caution. The use of growth hormone may cause increase in catecholamines, and it likely does. An increase in circulating lipids also likely occurs. The use of concomitant beta blockade can decrease those adverse responses. Growth hormone also causes an increase in insulin levels that persists when a patient is fasting, resulting in hypoglycemia. Growth hormone usually causes hyperglycemia, which can lead to increased infection if not adequately controlled. I believe any drug, when used, must be very closely monitored, with antidotes to its adverse effects instituted on an hour-to-hour basis in the critically ill.

DR. PALMER Q. BESSEY (Rochester, New York): Dr. Herndon, based on the prospective, randomized study of growth hormone in pediatric burns that you presented to this Association several years ago, many of us incorporated this anabolic agent into our treatment programs for adult burn victims, especially those with extensive or high risk injuries. Knox and Demling (*J Trauma* 1995;39:526) reported a survival advantage with growth hormone in such adult burns in a nonrandomized trial. Our own experience is also favorable. In a consecutive series of patients with high-risk burns all those who survived resuscitation and developed burn hypermetabolism received growth hormone daily. The unexpected mortality based on age, burn size, presence or absence of inhalation injury, and pneumonia was about 75%, but the observed mortality was only 23%. Thus, there is considerable experience in adults as well as children indicating that growth hormone is efficacious and safe. This morning President Spencer emphasized that a fundamental principle for a surgeon is to do what is best for the patient. How would you advise us about growth hormone? What is the best thing for us to do for burn patients? Many of us have found, as you have, that growth hormone is an efficacious adjunct to contemporary burn care, but the manufacturers now all advise us not to use it in catabolic patients. Do you still use growth hormone in your pediatric and/or adult patients? I would also like to ask your opinion about the worsened glucose tolerance seen with growth hormone. Do you have any information as to whether or not this might have been a factor in the European experience? If the blood glucose were not tightly controlled, that might have particularly deleterious, especially in cardiac patients, in whom hyperglycemia would have exacerbated the dehydrating effects of vigorous diuretic therapy, not to mention its associated hepatic and immunologic abnormalities. Finally, do you have an opinion as to whether or not any other anabolic agent, such as some of the testosterone derivatives or oxandrolone, might serve as a reasonable substitute for growth hormone in burns?

DR. DAVID N. HERNDON (Galveston, Texas): In over 300 adult burn patients in a meta-analysis of worldwide experience with rhGH administration, the findings of Demling and Wilmore and yourself are substantiated. There is no increased mortality with the use of recombinant growth hormone in adult burns or pediatric burns in all reported series that have so far come about. Why are burns different than the ICU patients? Perhaps they are already maximally stimulated with catecholamines and additional effects of up-regulation of catecholamine production are not significant, though growth hormone probably does lead to higher substrate cycling, particularly lipolysis, in this patient population. What is different about the adult ICU study and may very well be what you allude to, that hyperglycemia, tachycardia, and lipolysis was not tightly controlled. But I cannot answer that because I do not have privy to those data. I think that under tightly controlled circumstances we must push forward to try, in these desperately catabolic patients, to improve their anabolic lot. I think that this must be done with safety of the patients in mind. At the present, in lieu of this review, we have suspended our acute studies. We will reapply, and with the blessings of the FDA and our Institutional Review Board begin yet again, in children as well as adults to study the use of adjuvant therapy with recombinant human growth hormone. We are also investigating other anabolic agents—testosterone, that Dr. Levinson looked at so many years ago, oxandrolone, and those that you mentioned. No data are yet available. I think looking for safe and cheaper alternatives is appropriate, but we must look forward to the treating of the catabolic patient by new modalities based on prospective randomized trials.