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Discussion

DR. CLEON W. GOODWIN, JR. (New York, New York): This paper is an especially outstanding example of the long line of

investigations of the metabolic response to injury by the Army Institute of Surgical Research. I have three short questions.

If glucose oxidation and fat oxidation remain unchanged and protein oxidation decreases after IGF-1 treatment, what nutrient fills the gap as a fuel source to maintain the elevated energy expenditure described in the treated patients?

Second, the measurements in this group of patients were made while enteral feedings of a high calorie-high nitrogen diet were being administered. As you know, many studies of the metabolic response to injury were carried out after at least an overnight fast by the study subjects. Do you feel that your findings would have been different if derived during fasting? And if so, how?

Third, and along the same lines, do you feel that IGF-1 administration might be dangerous if given in the absence of exogenously administered substrate in that what is at least an early survival metabolic response could be diminished? For example, could patients become dangerously hypoglycemic?

Finally, I would like to thank the Association for the privilege of membership.

DR. DAVID N. HERNDON (Galveston, Texas): I would like to join Dr. Goodwin in congratulating the authors on an excellent clinical research study that clearly demonstrates that this newly available recombinant product has a small but significant effect of decreasing lysine oxidation in hypermetabolic burn patients over a 3-day infusion period.

This study titillates us in its conclusion to speculate that this agent might have clinical utility. The introduction of any modulator of the host response should address risk benefits, including discussions of potential alternatives. And in that regard I would like to ask three questions.

As to clinical efficacy, I would like to ask the authors to comment on recent reports that demonstrate that when IGF-1 is given for chronic periods to AIDS patients there is an initial anabolic effect on protein metabolism but this effect disappears in the second and third week of treatment, presumably due to reciprocal increase in binding proteins which limits free IGF-1 availability. How would you prevent binding protein production from negating the effects of IGF-1 over time?

In terms of risk, could you comment on the decision of the major pharmaceutical suppliers of IGF-1 to suspend the availability for clinical trials of the agent because of five cases of Bell's palsy and three cardiac arrests in patients being studied?

Finally, insulin and insulin-like growth factor-1 exert their anabolic effects through related if not in some cases identical membrane receptors. One of the co-authors of this paper has shown a twofold improvement in protein synthesis, in fact a more dramatic improvement than shown with IGF-1, with insulin infusions in patients that are quite similar to those studied here. Might the authors be able to subserve the same therapeutic anabolic function at a lower risk and a lower price with insulin than the newly available recombinant product?

DR. PALMER Q. BESSEY (Rochester, New York): I, too, would like to rise to congratulate Dr. Cioffi and his associates for completing these sophisticated metabolic studies in a group of very difficult, complex, critically ill patients.

This presentation and its manuscript will join many of the other superb reports from the ISR under Dr. Pruitt's direction that have revolutionized burn care and markedly improved the outlook for victims of perhaps the most horrendous and challenging injury we face.

Dr. Cioffi and his associates tried to shift the balance between anabolism and catabolism in recovering burn patients by infusing IGF-1, an anabolic hormone. The good news is that—amazingly—it looks as though maybe they did it.

IGF-1 infusion appeared to inhibit the erosion of body protein by reducing the use of protein as a fuel for oxidation and, as Dr. Cioffi indicated, over the course of recovery from a major burn this might spare several kilograms of lean body mass and thus reduce the debility associated with recovery.

But before we rush to adopt IGF-1 as a routine therapy in our ICUs, we should consider some of the possible limitations of the study.

First, the isotopic dilution techniques are most reliable when a variety of fairly strict conditions are met. The size of the compartments or pools in which the isotope is distributed should be constant during both studies; the isotopic distribution should be in a steady state; and recycling should be negligible or certainly constant. The metabolic state of a recovering burn patient is certainly a dynamic one as he or she progresses toward recovery, so that the conditions under which these two studies were accomplished might well be different.

Dr. Cioffi, could the differences you observed in lysine kinetics be due in part to progression of the patient's convalescence? In other words, if the patients did not receive IGF-1 would the results of isotopic dilution studies done in 3-day intervals be constant or would they show similar changes?

Secondly, when you look at how all these parameters are derived or calculated through the formulas in the manuscript, you realize that the parameters here, protein oxidation and protein breakdown, are really derived from just a few primary measurements. In addition to measurements of isotopic enrichment, the calculations of the parameters depend heavily on the values of the intake of the unlabeled lysine and also on the output of urea nitrogen. Lysine intake came from absorption of lysine from the enteral feeding in the GI tract. This was assumed to be constant during these studies. Although the measurements of urea nitrogen and total nitrogen is standard, there was enough variability in the system that nitrogen balance was not statistically different before and after IGF-1.

When there are significant differences in the derived parameters but not in the primary data on which they are based, we must be cautious in our interpretation of the data. Dr. Cioffi, would you comment further on this?

But nonetheless, the burn patient is certainly the biggest metabolic challenge we face and the fact that Dr. Cioffi and his associates detected improvement in protein metabolism with IGF-1 is an exciting finding and offers the possibility of further reducing the catabolic cost of critical illness.

DR. JOSEF E. FISCHER (Cincinnati, Ohio): Those of us who have struggled in the area of proteolysis have probably reluctantly begun to come to the conclusion that one of the problems in the proteolytic situation is not the presence of positive factors that increase proteolysis but the absence of positive fac-

tors such as IGF-1. My simpleminded way of looking at this is that perhaps what IGF-1 does is decrease transport of amino acids from the periphery to the center.

If data are correct, and assuming that you have a 70-kilogram man, I calculated from the differences in protein, fat, and glucose oxidation that there is a difference over 24 hours of about 69 calories expended in a 70-kilogram man. So it is not surprising that a resting energy expenditure did not detect the difference in this particular group of patients.

On the other hand, I wonder—and Cleon Goodwin has already referred to this—whether you stack the deck against yourselves by giving these people and continuing 5 milligrams per kilogram a minute of carbohydrate by enteral feeding, which remained stable throughout the experiment, and whether the difference between the animal experiments, which show efficacy of IGF-1 under these circumstances, and humans, is the fact that the animals were fasted, or at least were not fed to excess, and here you had no alternative but to continue the feeding.

One possible way around this, since it would be unethical and you wouldn't want to decrease the feedings for a prolonged period of time in patients with these extensive burns, is perhaps to go back to an old technique which I know is available in the laboratory—amino acid fluxes in the unburned extremities, if such existed—in which if you fasted the patients maybe for 6 hours you probably would see the effect of IGF-1 on muscle amino acid flux and perhaps prove your point.

I do have another problem, and that's with the calculation of glucose oxidation. Since you obviously have the capacity for isotopic dilution, wouldn't it be better to derive the glucose oxidation figures from a direct test of glucose oxidation enrichment than an indirect calculation? I think it would make a very nice paper and a very nice series of studies even nicer.

It's a very nice manuscript and it was an excellent presentation.

DR. STANLEY M. LEVENSON (Bronx, New York): Just one brief comment. The data presented by Dr. Cioffi are very suggestive, but from the point of view of experimental design of the study, I would have liked to have seen an equal group of similar patients studied concurrently but prospectively randomized in a double-blind study to have received only the vehicle in which the insulin-like growth factor-1 was solubilized.

The reason for my suggestion is that these patients were studied at a time when their clinical and metabolic states may well be changing. I am not saying that what has been demonstrated by Dr. Cioffi and his colleagues is not the case, but their conclusion regarding the effects of the insulin-like growth factor-1 would be significantly more solid had there been an appropriate control group of patients studied concurrently.

DR. WILLIAM G. CIOFFI (Closing discussion): I would like to thank the discussants for their questions, and I will answer them in the order that they were asked.

Dr. Goodwin asked three questions, the first concerning the changes in glucose, fat, and protein oxidation, and why there was no observed change in resting energy expenditure. I think that Dr. Fischer answered that question, in that the decrease in protein oxidation equates to a very small number of calories, and thus I would not expect to find a difference in resting energy expenditure.

Dr. Goodwin also asked about the use of fasting *versus* fed patients. Indeed, it is preferable to perform metabolic studies in a fasting state. However, the hypoglycemic response that you would anticipate at the infusion of 20 micrograms per kilogram per hour of IGF-1 would be prohibitive. Thus, similar to the insulin studies that Dr. Herndon alluded to, you need to supply a constant glucose infusion.

The safety of the compound, IGF-1, was questioned by both Dr. Herndon and Dr. Goodwin. Indeed, there have been several incidences of Bell's palsy and cardiac arrest in other patient populations that have been studied using IGF-1. We did not note any untoward effects in our patients. The majority of complications that have been documented, that Dr. Herndon noted, occurred in a group of AIDS patients and a group of severe insulin-dependent diabetics that were receiving much higher doses of IGF-1 than we administered.

Dr. Herndon asked about the size of the protein-sparing effect, and was it enough to really make a clinical difference. He also asked if we could obtain the same effect as Dr. Gore had previously published using higher doses of insulin. I think that the size of the effect that we documented is substantial if we take the lysine data and extrapolate it to whole body protein kinetics and then look at what would happen over the initial 30 days postburn period.

The purpose of the IGF-1 infusion was not to decrease resting energy expenditure of the patients, but to decrease the autocannibalism of lean body mass and attempt to keep protein stores, both functional and structural, intact.

If we wanted to use insulin instead of IGF-1, I think there are several problems with that approach. The study that Dr. Herndon alluded to pointed out some of those problems. In order to halve the protein oxidation rates with insulin, it required 52 units of insulin per hour and the administration of 12 milligrams per kilogram per minute of glucose to those patients.

I would hesitate to use that as a standard therapy in any intensive care unit where I would think the complications associated with hypoglycemia would be immense, and certainly much worse than they were noted to be in this study.

An additional effect of insulin is that very small infusion rates result in essentially shutting off hepatic gluconeogenesis. IGF-1 has been noted to have a similar effect, but at much higher doses, and I would hope that at the dose we employed in this study we would not observe this effect.

Dr. Bessey alluded to some of the limitations of using isotopic techniques to do these studies. I can only say that during the time period the patients were studied, their weights were stable, they were on a stable nutritional diet, and they received no exogenous nutrition other than the enteral feedings. As he noted, however, we cannot be sure they absorbed all the enteral lysine which we presented to them.

In terms of the stability of the resting energy expenditure and nitrogen metabolism in these patients, we previously reported that from postburn day 4 or 5 until at least the 30th postburn

day, resting energy expenditure and nitrogen wasting is essentially stable in this kind of burn patient.

Dr. Bessey also asked about the nitrogen balance data not being statistically different between the two groups. That data was calculated using 24-hour urine collections, while the isotope data was calculated over a 3-hour time period of the isotope infusion. I think the urine collections during the 3-hour study are much more accurate than the 24-hour urine collections in the intensive care unit.

Dr. Fischer asked why we did not use glucose isotopes rather than the metabolic cart data. I agree with him that it would be a much better study if we were able to use the glucose isotopes. We started this as a pilot and we were hoping to see if we could document a protein-sparing effect of the IGF-1 and then go on to look at its effects on glucose oxidation in a much more precise way. As Dr. Herndon commented, both Genentech and Ciba Geigy have withdrawn the compound from the market for the present time and we are going to have to wait and see if we can get more compound.

Again, I think the most important point of the study is that we were not looking to decrease resting energy expenditure, but we were hoping to preserve lean body mass. I think we demonstrated that we can do that with IGF-1 in thermally injured patients.

Dr. Herndon, I think, had the most critical comment, and that is "Could we do the same with insulin?" Indeed, the two compounds work in a very similar fashion. IGF-1 does bind insulin receptors, and many of its effects are then modulated by the insulin receptor. However, I think in terms of clinical utility, IGF-1 would be a much safer drug to use in an intensive care unit in terms of symptomatic hypoglycemia. As I noted, it takes exceptionally high doses of insulin to get the same kind of effect that we noted with relatively modest doses of IGF-1.