failure in adult burn patients, particularly in those patients who had pre-existing respiratory disease. In these patients oxygenation was not a problem even on room air, but the arterial P_{CO_2} was elevated, and occasionally correction demanded mechanical respiratory support. We believe that patients on room air who have hepatomegaly and mild liver function abnormalities together with a normal P_{O_2} and an elevated P_{CO_2} and who have been receiving a high glucose infusion over a period of weeks should be evaluated for metabolic as well as respiratory and hepatocellular abnormalities.

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Discussion

DR. WILLIAM R. DRUCKER (Rochester, New York): As Dr. Burke pointed out, we are now in an era of cost containment and concern about costs, and this is not just a socioeconomic problem it's a biological problem and that, in essence, is the theme of his paper, as I heard it.

As he also mentioned, Dr. Gamble gave us the minimum standards for the administration of glucose. The 100 g/day keeps a normal, nonstressed individual out of ketosis. Dr. Burke is now looking at the other end of the scale: Can we overdo it? Is there such a thing as overnutrition?

Many in this audience know that Dr. Robert Alman, somewhere during the war and shortly thereafter, demonstrated that the administration of glucose can protect against protein loss up to a level of about 800 calories; after that it has very little effectiveness.

Later, Drs. William Abbott and William Holden in Cleveland demonstrated very clearly that patients can be kept in nitrogen balance if they receive essentially the same caloric, nitrogen and carbohydrate intake postoperatively as they received preoperatively.

Some time ago, Dr. Wilmar showed us that the size of the injury has a very direct effect on the demand for nutrition following injury.

The question here is: Just what is overnutrition? The technology used is very interesting, and I admit, frankly, I'm not really in a position to understand it fully, and that is something that I think in time will have to be looked at: Is this technique that was employed valid for the conclusions that are drawn?

I have two comments, and three questions. My comment is that, as far as insulin is concerned, the data obtained are exactly what I think one would expect. I doubt very much if insulin would have an effect on the oxidation, but it does have an effect on glucose uptake. Insulin is a banker hormone; it stores all the foodstuffs, fat, protein, and carbohydrate. In this instance, insulin allowed the glucose to enter the cell, and, in fact, there is a decrease in the level of blood glucose in the manuscript. What happens to the glucose inside the cell—I suspect, here it was more available to promote protein synthesis, rather than going in other pathways.

The next comment is that I would be concerned about the production of CO_2, and the conversion of glucose to fat, in terms of the consequences physiologically. To me, this is one of the most interesting aspects of the paper. Dr. Burke and his associates have shown that there may be very detrimental biological consequences by overnutrition in addition to the hyperosmolality that we all know about; that there can be an increased production of CO_2 which produces a respiratory demand on a patient that potentially is already overburdened because of the burn and other problems they have.

In addition, the glucose going to fat can cause an increased size of the liver, and cause respiratory embarrassment from that.

My questions, Dr. Burke, are these. Did you, as Dr. Wilmar has shown previously, demonstrate a relationship to your glucose tolerance, in effect, to the size of the wound? Does the wound constitute a demand for glucose—a primary demand for glucose—so that, in fact, your tolerance will go up as the burn size increases?

What is the source of this increased CO_2? Where does it come from, and what is its effect on energy metabolism?

I have enjoyed this paper very much. It's very well done. It's well written; and my only concern is that someone look at this technology carefully.

DR. JOHN H. SIEGEL (Buffalo, New York): I do have a couple of questions and comments.

The first is that Dr. Burke used the amino acid leucine which was labeled with C^{13}—that is, labeled on a carbon atom—and has attempted to infer from the fact that there is a reduced amount of labeled CO_2 produced from the labeled leucine in the presence of high glucose loads, that there was more protein synthesis under these conditions. However, he has also shown us that fat, derived from labeled glucose through acetyl CoA, may be the consequence of the increased metabolism of glucose, rather than CO_2 production through oxidation.

I wonder whether the leucine may also be going to fat, since it also has access to the 2-carbon fat synthetic pool through acetyl CoA, and perhaps what he is interpreting as protein synthesis may, in fact, simply be the diversion of ketogenic amino acid substrates into pools that are not really related to protein synthesis but to lipogenesis.

The second comment is that I think a lot of the data one sees under these substrate loading conditions depends on the kind of patient that one is studying, that is to say their physiologic state. Dr. Burke's group of burned patients look much like nonseptic trauma patients in terms of their physiologic parameters, and although they have some burn wound infection, they would appear to have minimal true sepsis. In this regard, I noticed by looking at his CO_2 data that they probably have very high oxygen consumption, since their RQ's are fairly high and their CO_2 production seems to be large. Also they are already in near or positive nitrogen balance, which puts them in the best group of septic patients on metabolic grounds.

This is the group of patients in whom I think one would expect to see the findings that Dr. Burke has shown. However, there is a group of patients who become severely septic, in whom oxygen consumption falls, and in this group of septic patients with inadequate oxidative metabolism it would appear that there is an enormous amount of gluconeogenesis. If one looks at these low oxygen consumption septic patients, there are large amounts of circulating alanine, which is the carrier amino acid for muscle NH_3 derived from branch chain amino acid catabolism. This suggests that there are other kinds of septic patients with large amounts of tissue breakdown and unrestricted gluconeogenesis, since glucose also rises in this type of patient.

In contrast to the patients described by Dr. Burke, this group of severely septic patients, with low oxygen consumption, cannot effectively have their circulating glucose levels reduced by insulin. In fact, these people show an exaggerated gluconeogenesis syndrome in spite of insulin.

The final comment is to note the fact that if one uses labeled leucine as a marker, the leucine which is important is the leucine which one does not see. The unseen leucine is the structural leucine in peripheral muscle tissues which is liberated by catabolism. It is metabolized first by transamination with pyruvate, and large amounts of carrier amino acids like alanine, glycine, and glutamine are produced, and yet one would not see this amino acid as leucine, in terms of enlarging the leucine pool, and yet the three carbon fragment originally from leucine is, of course, a major source for glyconeogenesis, and via hepatic metabolism of alanine an oxidative or lipogenic substrate.

I wonder if Dr. Burke would comment on these issues.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): I'd like to present some confirmatory data recently generated by Dr. Wilmore, (slide) indicating that the glucose needs of the burn patient and the effect of glucose infusion relate directly to metabolic rate and burn size. You can see that the infusion of glucose at a rate of 2 mg/kg/min reduces hepatic gluconeogenesis in the control patients, while there is still a significant hepatic vein/arterial difference in the burn patients. Although a definite decrease in hepatic glucose production occurs with glucose infusion in hypermetabolic patients it is not to the same extent as in the control patients with lower metabolic rates.

(slide) Since the metabolic rate of patients with burns is related to the size of the burn, as depicted here, I would ask Dr. Burke how glucose utilization in his patients was related to burn size.

(slide) Lastly, I would take issue with the comment that what the authors call cost-effectiveness is a superior assessment of nutritional adequacy as compared with simple nitrogen excretion rate. Dr. James Long, some years ago, showed that in patients with burns nitrogen excretion plateaued at a minimum when the carbohydrate intake/metabolic rate ratio approached 1. A glucose infusion rate of 6 mg/kg/min, as in Dr. Burke's patients, represents about 0.8 of the resting metabolic needs of a 70 kg man with a 50% burn. That data point would be located on this nitrogen excretion curve near the inflection point and such is reflected in Dr. Burke's data. I therefore, think that one can come up with the same assessment of nutritional adequacy using just nitrogen excretion data in burn-injured patients.

DR. STANLEY M. LEVENSON (Bronx, New York): The questions asked by Burke and his colleagues are straightforward, but the techniques required to answer the questions are far from straightforward. There are a number of assumptions which must be made in the tracer methodology employed, and Burke and his associates have gone to great lengths in their prior work to establish the validity of the assumptions.

I would like to comment briefly on their observations regarding the occurrence of hepatomegaly caused by fat accumulation, seemingly associated with the infusion of large amounts of glucose. Their observations were in children, but presumably the same would hold for adults.

In their paper the authors state: "It is not clear why the normal transport mechanisms that are responsible for the transfer, or translocation, of triglyceride from the liver to the periphery were not adequate." I would like to offer two speculative suggestions.

1) It is known experimentally that large amounts of glucose will interfere with the action of the lipid mobilizing factor produced by the pituitary gland.

2) It occurs to me that it is possible, though the data are not given in Burke's paper for me to determine this, that there may have been an inadequate choline intake by these individuals. When patients are fed parenterally, the only significant source of choline would be from intravenous fat emulsion and the chances are that the amount the patients receive may be inadequate. We know that if there is inadequate choline intake, fat begins to accumulate rapidly in the liver. This is an area which we really do not know enough about how much choline to put into the intravenous mixture to make it optimal for seriously ill and injured patients. Burke's patients received no intravenous fat emulsion during the study periods. It is not stated whether they received fat emulsion or choline in some other form in the periods preceding the study periods.

I would like to now pass briefly to ask Dr. Burke how the data regarding protein synthesis as related to the amount of glucose infused correlated with the measured caloric expenditure by the patients. As I calculated the intakes given during the various study periods, the caloric intake was roughly 25 calories per kilogram body weight during the period of low level glucose infused, 50 calories per kilogram body weight during the midlevel period and 70 calories per kilogram body weight at the high level of glucose infusion. I suspect that in terms of the measured caloric expenditure, it would turn out that 25 calories per kilogram body weight was much too low to meet the caloric expenditure, and therefore one would anticipate that as one increased the glucose infused, one would get an increase in protein synthesis until the caloric intake was significantly greater than the caloric expenditure, a point which was probably reached at a level below the 70 calories per kilogram intake, the highest level infused by Burke and his colleagues. This point was likely not too far above the midlevel of caloric intake.

Finally, in the full written paper Dr. Burke mentions that the data regarding the optimal amounts of glucose infused would probably vary depending on the amount of amino acids infused with it; I am sure that is correct. I would like to point out that the level used by Burke and his associates during the study periods, 1.33 gm of pro-

tein per kilogram body weight, is substantially less than what has been found in a large number of studies to be required by the burn patient at a reasonable caloric intake for maximal long-term positive nitrogen balance, which, when corrected for urea accumulation, reflects protein synthesis.

I noted that Burke's patients, except for during the study periods, had protein intakes about twice as high as were given during the study period.

The last question that I would like to ask Dr. Burke is whether he noted any differences in caloric expenditure as the amounts of glucose infused were increased. I mention this because about 50 years ago DuBos, Schaeffer and Coleman in their studies of patients with serious infections with oral diets noticed that the amounts of calories that had to be given for near maximal protein utilization were significantly higher than the resting caloric expenditure measured at lower caloric intakes.

DR. FRANCIS D. MOORE (Boston, Massachusetts): There was an old saying that "fat burns in the flame of carbohydrate"; tiny amounts of sugar prevent ketosis. We have come to realize in the last few years that "peptide bonds are forged in the furnace of carbohydrate," and that that metabolic heat, ATP, is essential for protein synthesis. The fuel in the furnace must be regulated pretty carefully.

It might be helpful to calculate the data that Dr. Burke has shown us, to help our everyday clinical thinking. Approximately 1.33 mg/kg/min of amino acids, about 100 g/day in a 70 kg adult, which is about 3.1 of the regular central vein mix that most of us use is, fundamentally, that originally used by Dr. Dudrick. Giving the glucose at the rate of his Group II, it figures out to about 600 g of glucose/day, which is about 3.1 of the 400/600 central vein mix that we usually use.

That equals out to a calorie/nitrogen ratio of 180 nonprotein calories per gram of nitrogen, which is a little bit lower than we had thought was ideal. We had been shooting for 200–220.

He has shown us the satiety syndrome, or fatty liver. I think everyone who has worked in this field has shown that you can give too much rich intravenous food and get all sorts of effects. We found that humans given too much glucose (*i.e.*, supracaloric amounts) had pain in the right upper quadrant and disordered liver functional tests; obviously, we stopped the study then.

It is interesting in this connection that fatty livers can be produced by excessive fat oxidation from within the body. An example is weight loss after jejunoileal bypass, in which no glucose is given whatsoever. Fatty livers can come from other sources involving unbalanced caloric availability, and I would wonder, and ask Dr. Burke, if that could not enter into some of their calculations.

On the insulin added, it is interesting to compare Dr. Burke's data with those of Hinton and Allison, the British workers who did so much work with huge amounts of insulin. Dr. Burke used very small amounts of insulin. The plasma insulin concentrations in these subjects were already 50–60 microunits, which is what we would expect in persons given this much carbohydrates. The normal pancreas produces plenty of insulin, and if you give small additional amounts, you are probably not going to get a big additional effect. The British workers gave huge amounts.

Dietitians and nutritionists have been saying that we need to give people a balanced diet for years. This paper strengthens the view that when diet is given intravenously it should also be balanced regarding carbohydrate and protein precursors, perhaps fat also.

DR. JOHN F. BURKE (Closing discussion): To answer at least some questions, I will begin with glucose tolerance. The relation of the glucose tolerance test to glucose turnover and to burn size is an interesting problem. In our evaluation of the glucose tolerance test we have demonstrated that it does not give reliable information on the exact level of glucose turnover. Although these patients would have an abnormal glucose tolerance test it would not necessarily mean that they had an abnormal rate of glucose clearance from the blood. We have therefore chosen to measure glucose kinetics directly using tracer methodology in the isotopic steady state. None of our calculations include glucose tolerance test data.

The source of the CO_2 raising the RQ, at least in our mind, is related to lipogenesis from glucose. This metabolic pathway produces CO_2 without a comparative production of ATP. The excess CO_2 generated must be excreted at an energy cost for the additional respiratory work.

We used leucine in our studies because it not only was useful for a number of other studies but also for technical isotope reasons. Although there is probably a small amount of the leucine carbon skeleton converted to fat it does so after decarboxylation and is therefore assumed to be oxidized because the label appears as CO_2. It does not raise the estimation of protein synthesis. I say this with some certainty because our N^{15} data in these patients gives us the same protein synthetic rate. I believe that within the errors of the system we are observing protein synthesis when 1 ^{13}C leucine is used as a tracer molecule.

It is important to recognize that the studies reported are whole body leucine turnover, CO_2 production and protein synthesis rates. These are not studies of an organ, or any organ system. Internal cycles such as conversion of glucose to alanine and alanine back to glucose would not be seen in this type of study. In other studies we have demonstrated that these patients have a large lactate turnover, but this metabolic reaction is not seen using uniformly labeled C^{13} glucose because none of the carbons are oxidized during the recycling.

The rate of suppression of gluconeogenesis in the liver produced by exogenous glucose is variable in burned patients but on the whole we have found it not markedly different from normal volunteers. It is our feeling that the normal regulation of the blood glucose level is obtained by modulating glucose production in the liver. In the burned, nonseptic patient this regulation is present, but it is decreased. For example, in a normal person near maximum suppression of gluconeogenesis can be obtained at a glucose infusion rate of, say, 2 mg/kg/min. In the burned, nonseptic patient, in our experience, it is somewhere around 5 mg/kg/min.

Concerning choline production I cannot comment specifically except to say that in the patients in whom it was measured the level was normal. Fat does occur in the liver in at least some patients who die of injury or sepsis, but I do not think it is seen at the extensive level seen here, unless the patient has received extensive levels of glucose infusion.