Glucose Requirements Following Burn Injury

Parameters of Optimal Glucose Infusion and Possible Hepatic and Respiratory Abnormalities Following Excessive Glucose Intake

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Glucose and leucine metabolism in 18 severely burned patients were studied using the primed constant infusion of U-^{13}C-glucose and 1-^{13}C-leucine, respectively. The leucine data were used to calculate rates of whole-body protein synthesis. In four additional burn patients and seven normal controls, the effects of exogenously infused insulin on the metabolism of infused glucose were evaluated. Also, the effect on leucine metabolism of adding insulin to infused glucose was tested and rates of protein synthesis were calculated. The protein studies were divided into two groups depending on the rate of glucose infusion. Protein synthesis was 4.3 + 0.54 g protein/kg/day during the lower infusion rates (1.4–4.5 mg/kg/min) and 5.17 + 0.19 g protein/kg/day during the higher infusion rates (4.7–9.3 mg/kg/min) (statistically different, $p < 0.05$). However, when the high infusion rate group was divided into two subgroups (high, 4.7–6.8 mg/kg/min, and very high, 7.03–9.31 mg/kg/min), there was no difference in the rate of protein synthesis. When U-^{13}C-glucose was infused during varying rates of unlabeled glucose infusion, we found that the per cent of CO_2 coming from the direct oxidation of glucose rose rapidly at the lower infusion rates but reached a plateau at approximately 55% as the infusion rates exceeded 5 mg/kg/min. Addition of insulin did not affect the rate of glucose oxidation but did seem to exert a stimulatory effect on protein synthesis. It was concluded that there appears to be a maximal rate of glucose infusion, beyond which physiologically significant increases in protein synthesis and direct oxidation of glucose cannot be expected. Furthermore, there appears to be a physiological cost of exceeding the optimal glucose infusion rate, as indicated by increased rates of CO_2 production during infusion as well as large fat deposits in the liver at autopsy in patients infused with large amounts of glucose.

A NEGATIVE NITROGEN BALANCE and hyperglycemia point to the extensive changes in protein and carbohydrate metabolism in response to injury. This reaction, although possibly effective in the short term, requires that a substantial amount of exogenous substrate be given following injury and resuscitation to reverse catabolism. Thus, intravenous delivery of substrate—usually glucose and amino acids—is used extensively to provide energy and protein precursors in an attempt to bring about anabolism. However, the exact amount of each that will provide sufficient energy and protein precursors to ensure an optimal level of protein synthesis over catabolism is an important but unsettled issue. In addition, although the long-term importance of undernutrition is recognized, the consequences of overnutrition (made possible by the ease of central venous delivery of extensive quantities of glucose), particularly the metabolic and respiratory consequences, have not been thoroughly examined.

In order to obtain information concerning the rate of exogenous glucose delivery required to provide optimal protein synthesis over catabolism following injury, as well as obtain information on the possible consequences of glucose overload, we have studied the effects of graded increases in intravenous glucose delivery with a fixed amino acid delivery on seriously burned patients in the acute phase of their injury following resuscitation and before complete wound closure. The techniques used gave kinetic information concerning whole body glucose and leucine metabolism. From these data rates of protein synthesis in relation to nitrogen balance are calculated. These studies addressed the following problems: 1) the effect of increasing rates of delivery of exogenous glucose on energy production from glucose as monitored by the proportion of total CO_2 excretion coming directly from glucose; 2) the effect of increasing rates of exogenous delivery of glucose on the rate of protein synthesis; 3) the effect on protein synthesis

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brought about by the addition of sufficient exogenous insulin to return the blood glucose toward a normal range during glucose infusion; and 4) to explore the metabolic and respiratory consequences of providing glucose at rates well above the level of energy requirements over long periods of time.

Materials and Methods

Patients and Study Designs

These studies were carried out in burned patients at the Massachusetts General Hospital and Shriners Burns Institute and in normal volunteers. The studies themselves are divided into studies of glucose metabolism and leucine metabolism, including calculated rates of protein synthesis, the effect of exogenous insulin infusions of glucose oxidation and protein synthesis and the respiratory and hepatic effects of providing intravenous glucose at a rate above the level of energy requirement.

Glucose Kinetics and Rate of Oxidation

Twenty-seven studies were carried out in nine burned patients whose ages ranged from 16 to 80 years, average 43 years, and whose burn size averaged 31% body surface area (BSA), ranging from 20 to 61% BSA. Glucose kinetics were studied using the primed constant infusion of trace amounts of sterile, pyrogen-free U-^{13}C-glucose. The isotope infusion rate was approximately 0.0018 mg/kg/min, and the prime-to-infusion ratio was 80:1. All isotope infusions were delivered with a Harvard infusion pump at 0.191 ml/min. All measurements were made during the quasi-equilibrium of tracer enrichment in the plasma (between 9 and 120 min following prime and onset of infusion).

The determination of oxidation of glucose requires the determination of the quasi-equilibrium value for the per cent enrichment of CO_2 in the expired air. In humans, this necessitates a constant infusion of tracer for many hours. In order to complete each study period in two hours, we applied existing tracer theory to priming the bicarbonate pool, thereby achieving equilibrium within this pool within 90 min. We have recently described the theory and validation of this technique.[2] For the U-^{13}C-glucose and ^{13}C-leucine studies we administered approximately 400 μmol of $NaH^{13}CO_3$ at the start of the experiment in order to prime the bicarbonate pool. In all studies a plateau in CO_2 enrichment in expired air was achieved in 90 min. Measurements were made between 90 and 120 min.

In all glucose kinetic and oxidation studies, the subject also received a constant infusion (via Harvard pump at 1.91 ml/min) of unlabeled glucose together with a constant amino acid mixture (Freamine II®). The amount of glucose given changed in a stepwise way with use of a low (1.4–4.5 mg/kg/min), a high (4.7–6.8 mg/kg/min) and a very high (7–9.3 mg/kg/min) glucose infusion rate. The glucose steps were varied at random in order to avoid systematic error, and although the patient had been receiving the approximate level of glucose to be studied for 24 hours, the exact rate of infusion was begun at least 12 hours before the sampling period. During the entire period of studies for each patient, he/she received a constant amino acid infusion (Freamine II®) which delivered the equivalent of 1.33 g protein/kg/day. As far as possible, each patient was studied at each glucose infusion level on successive days to insure as constant a clinical state as possible.

Leucine Kinetics—Protein Synthesis

Forty-seven studies were carried out in nine burned patients whose average age was 28 years (range, 8–72 years) and whose mean burn size was 41% (8–85%) BSA. Leucine kinetics and oxidation were determined using the primed constant infusion of sterile pyrogen-free 1-^{13}C-leucine in trace amounts. The isotope infusion rate was approximately 0.0094 mg/kg/min and the prime-to-infusion ratio was 100:1. All isotope infusions were delivered with a Harvard infusion pump at 0.191 ml/min. All measurements were made during the quasi-equilibrium of ^{13}C-leucine enrichment in the plasma and $^{13}CO_2$ in the expired air achieved between 90 and 150 min following leucine and bicarbonate prime and onset of trace infusion (please see section on glucose kinetics for details of bicarbonate prime). Protein synthesis was calculated from the leucine kinetics and oxidation (see Calculations).

In determining leucine turnover, each subject was studied at least three times at randomly varied glucose infusion rates using the same steps in glucose infusion used to study glucose kinetics, so that the influence of different infusion rates of glucose on leucine turnover and protein synthesis could be determined. The unlabeled glucose and amino acid mixtures (Freamine II) solutions were infused using a Harvard pump at 1.91 ml/min. The unlabeled glucose and amino acid solutions were infused in exactly the same manner as in the glucose kinetic studies. The amino acid mixture was delivered at approximately the equivalent of 1.33 g protein/kg/day over the entire period covered by the studies. Glucose infusion rates were varied randomly for each study using the same steps as in the glucose kinetic studies (low, high and very high). The studies were repeated three to six times in each patient at random levels of glucose intake on successive days as far as clinically possible. The exact glucose and

amino acid delivery rate was established at least 12 hours prior to measurement.

Exogenous Insulin Effects on Glucose Oxidation and Protein Synthesis

The effect of added insulin on glucose oxidation was tested in five burned patients (burn size 30–85% BSA) and on protein synthesis in three burned patients (burn size 30–85% BSA). The glucose kinetic and oxidation studies and protein synthesis in studies were done exactly as described above, except a level of unlabeled glucose infusion was chosen for each patient to give moderate hyperglycemia, and a study was done with infused insulin and another was done without on successive days. The studies with and without insulin were alternated.

Autopsy Studies

All of the patients (nine) who died at the Shriners Burns Institute between 1974 and 1978 and who died more than 30 days after injury were evaluated. All had autopsies, and the liver weight, presence of fatty infiltrations of the liver, as well as glucose intake over the 3 weeks before death were evaluated.

Collection of Expired Air: Measurement of Gas Exchange

Oxygen consumption (V_{O_2}) and CO_2 production (V_{CO_2}) were determined in all subjects three times during each study period. Expired air was collected over 6-min intervals in Douglas bags with the use of a two-way Rudolph valve. The O_2 and CO_2 concentration of the expired gas was measured on a Perkin Elmer Model 1100 Medical Gas Analyzer, and the total volume of expired air was measured with use of a Gasometer (Warren E. Collins Co., Braintree, Mass.). Respiratory quotient (RQ) was calculated in the conventional manner.

In order to analyze the enrichment of carbon in expired CO_2, expired air was collected in 3-liter anesthesia bags. The collected air was then bubbled through 0.1 NaOH to absorb the expired CO_2, and the ^{13}C atoms per cent excess in the trapped CO_2 was determined with use of a Nuclide Model 3-60-RMS dual inlet, dual collector, isotope-ratio mass spectrometer and corrected for the background value of ^{13}C in a CO_2 sample collected prior to tracer infusion. From 90 to 150 min after commencement of the study, five collections of expired CO_2 were made for such isotopic analysis.

Blood Sampling

When either U-^{13}C-glucose or l-^{13}C-leucine was infused, a 5-cc blood sample was drawn before the commencement of the study in order to measure the naturally occurring background enrichment of either glucose or leucine in the blood. Subsequent blood samples (5 cc) were then drawn at 90–120 or 150 min into sterile, heparinized syringes. These blood samples coincided exactly with the obtaining of a matched expired air sample for determination of $^{13}CO_2$ enrichment.

Analytical Procedures

Blood samples were kept on ice until centrifuged at 4° to separate the plasma.[15] A duplicate determination of glucose concentration was made on all plasma samples with a glucose AutoAnalyzer® (Beckman, Inc., Fullerton, Calif.).

U-^{13}C-glucose Analysis

When U-^{13}C-glucose was infused the analysis of glucose for its isotopic enrichment (^{13}C) first involved the removal of labeled products of glucose metabolism, such as lactate. The extraction was performed by first precipitating the plasma proteins and passing the supernatant sequentially through anion (Dowex AGi-X8) and cation (Dowex AG50W-X8) exchange columns. The eluate was combusted in a vacuum oven at 1000° and the resulting CO_2 was analyzed for per cent enrichment of carbon on the isotope-ratio mass spectrometer. We have validated this technique of measuring rate of appearance of glucose into the plasma in dogs.[1] In all studies the exact concentration in the unlabeled glucose infusion was determined by diluting the infusate and measuring the glucose concentration on the Beckman glucose analyzer.

l-^{13}C-Leucine Analysis

Each plasma sample was analyzed for l-^{13}C-leucine enrichments, expressed as molecules per cent excess. The enrichments in plasma are determined by combined gas chromatograph-mass spectrometry (GCMS) with selected ion monitoring on one of two systems: a PDP-12 computer-controlled ion monitor on a LKB-900 GC-MS or a voltage sweeping circuit designed for an AEI MS 12 GC-MS.[8,9] With each system, stable isotopic enrichment of glucose or alanine within the range of 0.2–10% can be measured with a coefficient of variation less than 5% of the observed ratio.[5] Isotopic enrichment values for leucine are determined using the *N*-acetyl, *n*-propyl ester (NAP) derivative and represent the mean of duplicate determinations. The ^{13}C enrichments of leucine have been measured in the range of 0.9–2.5 molecules per cent excess, with a coefficient of variation less than 5% of the observed ratio.[12]

The leucine content of both the combined glucose and Freamine II infusate and of the l-^{13}C-leucine infusate was measured on a Beckman 121 Automatic Amino Acid Analyzer.

Plasma Insulin

Plasma insulin was determined by the radioimmunoassay method described by Albano *et al.*[3] utilizing insulin-binding reagent (Wellcome Research Laboratories, Beckman, England) and a human insulin standard (Eli Lilly and Co., Indianapolis, Ind.).

Estimated Nitrogen Balance

During the entire study period complete 24 hour food intake records and urine output collections were made. Because almost all nutrition was given intravenously, feces were scant during the study period and were not collected. Urine was analyzed for creatinine, urea and total nitrogen. A careful intake record was made of all oral and intravenously delivered substrate, including blood, plasma and albumin solutions. The nitrogen content of intake was determined on a 24 hour basis. Nitrogen balance was estimated by subtracting output from intake. All values are expressed as protein equivalent/kg/day. Measurements of urinary creatinines were used to help judge the completeness of 24 hour urine collections. Wound nitrogen loss was not accounted for.

Calculations

Glucose turnover. For the calculation of rate of production of glucose the equation derived from Steele was used.[16] In a steady state the rate of appearance of glucose into the plasma equals its rate of disappearance (or uptake). All our calculations were made at an isotopic steady state.

$$Ra_{gl} = \frac{F(mg/kg/min)}{\%\ \text{enrichment of plasma glucose}}$$

where Ra_{gl} = rate of glucose production (mg/kg/min), F = constant isotopic infusion rate of ^{13}C-glucose (mg/kg/min).

Leucine turnover. Because the leucine infusate contributes 1.5% of the total leucine flux, a correction needs to be made for the contribution that the infusate makes to the total flux. The leucine turnover (or rate of appearance into the plasma) (Ra_{leuc}) was therefore calculated by the following equation:[14]

$$Ra_{leuc} = \left(\frac{\%\ \text{enrichment of the infusate}}{\%\ \text{enrichment of plasma leucine}} - 1\right) \times F$$

where F = rate of isotopic infusion of I-^{13}C-leucine (μmol/kg/min).

Oxidation. The per cent of CO_2 from glucose and the rate of glucose oxidation were calculated by the following equations:[10]

$$\%\ CO_2\ \text{due to glucose oxidation} = \frac{\%\ \text{enrichment of } CO_2/0.81}{\%\ \text{enrichment of plasma glucose}}$$

Glucose oxidation (mg/kg/min) = (% CO_2 due to glucose oxidation × V_{CO_2} × 0.18)/6 where V_{CO_2} is the rate of carbon dioxide production (μmol/kg/min),

$$\text{Leucine oxidation} = \frac{\%\ \text{enrichment of } CO_2}{\%\ \text{enrichment of plasma leucine}} \times \frac{V_{CO_2}}{0.81}$$

Two equations involve division by 0.81 to account for labeled CO_2 retained in the body as determined by $NaH^{13}CO_3$ infusions into burned patients.[2] When determining glucose oxidation, since oxidation of 1 mol of labeled glucose gives rise to 6 mol of labeled CO_2, the right side of the equation is also divided by 6. The figure is multiplied by 0.18 to convert the units to mg/kg/min.

The per cent of the uptake oxidized was determined by dividing the oxidation rate by the total production rate.

Protein synthesis. The model for calculation of protein synthesis is based on the model proposed by Golden and Waterlow.[7] This model assumes that the l-^{13}C of leucine is either oxidized or incorporated into protein. Thus, by measuring leucine uptake (from kinetic data) and leucine oxidization, protein synthesis can be indirectly calculated.

The rate of appearance of leucine (Ra_{leuc}) into the amino acid or metabolic pool is described by the following equation: $Ra_{leuc} = \dot{I} + \dot{B}$, where $\dot{I}$ is the rate of intake of leucine and $\dot{B}$ is the rate at which leucine appears in the metabolic pool from protein breakdown. The rate of leucine uptake (Rd_{leuc}) is $Rd_{leuc} = \dot{S} + \dot{E} + \dot{M}$. When the plasma concentration of leucine is constant (as in our experiment), $Ra_{leuc} = Rd_{leuc}$, and thus $Ra_{leuc} = \dot{I} + \dot{B} = \dot{S} + \dot{E} + \dot{M}$. $\dot{S}$ is the rate at which leucine is taken up for protein synthesis, $\dot{E}$ is the rate of leucine oxidation and $\dot{M}$ is the rate of metabolism of leucine in other pathways. Assuming $\dot{M}$ is zero, then $\dot{S} = Ra_{leuc} - \dot{E}$.

Hence the rate of protein synthesis is determined by calculating the total turnover of leucine and then subtracting the oxidation rate from the total turnover. This value ($\dot{S}$) gives the rate at which leucine is being directed toward protein synthesis. Since it has been estimated

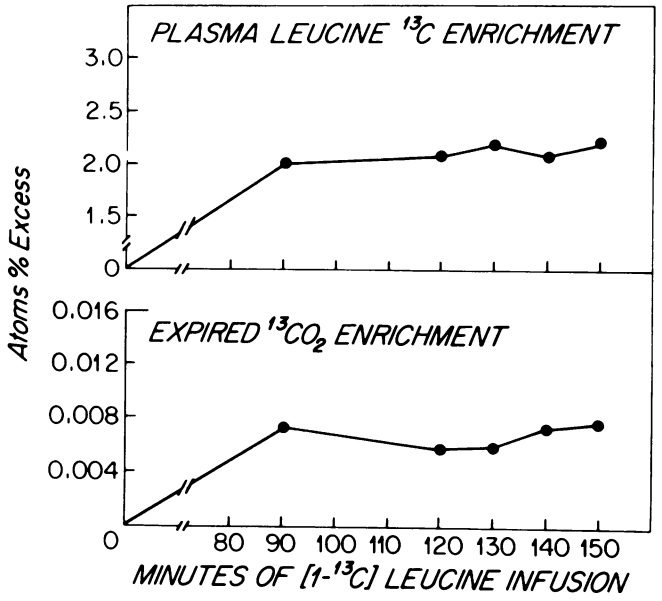

FIG. 1. A representative example of ^{13}C enrichment of plasma leucine and expired CO_2 at 90 min after initiation of primed constant l-^{13}C Leucine infusion.

that total body protein is made up of 8% leucine, then the protein synthesis rate can be calculated from the following equation:

$$\text{Protein synthesis (g/kg day)} = S\ (\mu\text{mol/kg/min}) \times \frac{131.2}{0.08 \times 10^6} \times \frac{24\text{ hr} \times 60\text{ min}}{1}$$

Statistics

All values are expressed as means plus or minus the standard error of the means. Curve fitting was carried out using the statistical program available for the Texas Instrument SR-60A computer. Comparisons between two groups of values are made using the Student's t-test.

Results

Nitrogen Balance

All patients were in positive nitrogen balance during the study period, ranging from 7.4 to 0.2 g protein/kg/day, with a mean of 1.7 ± g protein/kg/day, save one who had a negative nitrogen balance of 1 g protein/kg/day on 1 day, although this patient's nitrogen balance was positive for 2 days before and for the remainder of the study period of 7 days. Nitrogen balance remains positive even if the estimated nitrogen loss via the wound is included.[11] The mean nitrogen intake of all patients was 2.75 ± 0.35 g protein/kg/day, and the mean excretion was 1.36 ± 0.11 g protein/kg/day.

Whole Body Leucine Flux and Protein Synthesis

In all subjects an apparent plateau in plasma l-^{13}C-leucine enrichment (atoms per cent excess) had been reached by 90 min after prime and onset of infusion (*e.g.*, Figure 1). Estimation of whole body leucine rate of appearance (Ra) in μmol/kg/min are shown in Table 1. These studies are divided into two groups, depending on the rate of intravenous infusion of glucose in mg/kg/min. Patients studied while receiving the lower levels of glucose had a small change in the total amount of glucose appearing in the plasma (exogenous infusion and endogenous production of glucose), because the amount of glucose given intravenously tended to be balanced by a similar reduction in rate of gluconeogenesis. In the patients receiving higher exogenous glucose levels, the glucose was delivered in excess of the rate of endogenous gluconeogenesis, so that even with suppression of gluconeogenesis the rate of delivery of exogenous glucose caused a marked increase in the total delivery of glucose into the plasma. The rate of appearance of leucine in Group 1 (1.4–4.5 mg/kg/min glucose) and Group 2 (2.7–9.3 mg/kg/min) was similar (3.42 ± 0.17 μmol/kg/min and 3.25 ± 0.15 μmol/kg/min ($p > 0.05$). Despite the lack of difference in the rate of appearance of leucine, the rate of leucine oxidation was lower in Group 2, so that the calculated rate of protein synthesis was higher in Group 2

TABLE 1. *Whole-Body Leucine Rate of Appearance and Protein Synthesis as a Function of Varying Glucose Infusion Rates*

IV Glucose Infusion Rate (mg/kg/min)	Whole Body Leucine Rate of Appearance ("Flux")* (μmol/kg/min)		Whole Body Protein Synthesis† (gm protein/kg/day)	
Group 1: 1.4–4.5	3.55		4.31	
	2.56		3.79	
	3.37		5.84	
	3.18	$\bar{X} = 3.42 \pm 0.17$	5.87	$\bar{X} = 4.3 \pm 0.54$
	3.60		5.04	
	4.51		3.96	
	3.30		1.34	
	3.28			
Group 2: 4.7–9.3				
Group 2a, 4.7–6.8	2.77		5.44	
	3.10		5.11	
	3.18		5.21	
	3.11		4.69	
	2.58	$\bar{X} = 3.12 \pm 0.14$	5.14	$\bar{X} = 5.2 \pm 0.28$
	3.46		6.20	
	3.29		4.71	
	2.60		3.72	
	4.02		6.90	
Group 2b, 7.03–9.31	2.89		4.76	
	4.00		4.61	
	2.59	$\bar{X} = 3.47 \pm 0.38$	5.04	$\bar{X} = 5.05 \pm 0.183$
	2.90		5.80	
	3.01		5.07	
	$\bar{X} = 3.25 \pm 0.15$ equals mean for combined groups 2a and b		$\bar{X} = 5.17 \pm 0.19$ equals mean for combined Groups 2a and b	

* Leucine flux $p > 0.05$ for all groups.

† Protein synthesis: Group 1 vs. Group 2, $p < 0.05$; Group 2a vs. Group 2b, $p > 0.05$.

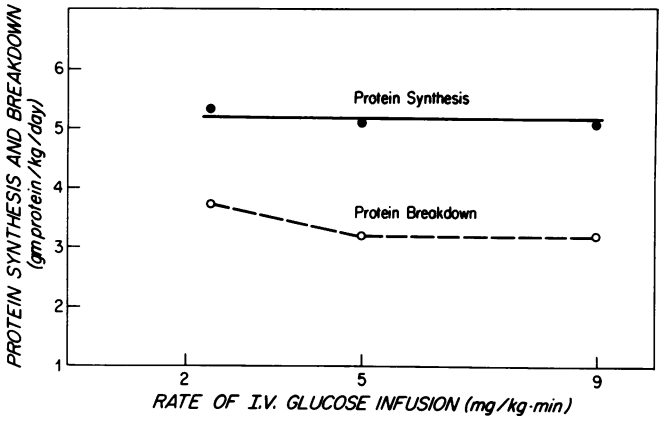

FIG. 2. Rates of protein synthesis and breakdown in an 8-year-old boy with 65% BSA burn during three rates of glucose infusion (2, 5 and 9 mg/kg/min).

(Table 1). The mean rate of protein synthesis in the lower glucose group was 4.3 ± 0.54 g protein/kg/day and for the higher group, 5.17 ± 0.19 g protein/kg/day ($p < 0.05$). However, when the group receiving a higher glucose infusion was broken down into two subgroups (high, 4.7–6.8 mg/kg/min, and very high, 7.03–9.31 mg/kg/min), there was no difference in the rate of protein synthesis in patients receiving high or very high glucose infusion rates. The mean synthesis rate for patients in the high group was 5.2 ± 0.28 and for the very high, 5.05 ± 0.19 g protein/kg/day ($p > 0.05$). All patients in all groups received nitrogen in the form of intravenous amino acids at the rate of 1.33 g protein/kg/day during the study period.

Figure 2 demonstrates the relationships in an 8-year-old patient who had suffered a 65% body surface burn. In addition, for this patient the rate of protein breakdown is also given. Studies were carried out on 3 successive days in the recovery phase following injury. On the three levels of intravenous glucose provided, the synthesis rate was unchanged. The protein catabolic rate, however, decreased between a glucose intake of 2.32 and 5.03 mg/kg/min. There was no further drop in catabolic rate when the glucose intake was increased to 9.31 mg/kg/min. Exogenous leucine intake on these 3 days was identical at 1.21 μmol/kg/min.

The Effect of Exogenous Insulin on Protein Synthesis

The effect of exogenous insulin on whole body leucine rate of appearance and protein synthesis in the young adults studied is demonstrated in Table 2. The patients studied received glucose infusions at a rate which created moderate hyperglycemia. On the day of insulin infusion, the insulin was infused at a rate sufficient to bring the blood sugar toward normal. The mean leucine rate of appearance was 3.10 ± 0.23 μmol/kg/min without insulin and with insulin was 3.20 ± 0.23 μmol/kg/min ($p > 0.05$). However, there was an increase in protein synthesis with insulin. The mean for protein synthesis without insulin was 4.23 ± 0.23 g/kg/day and with insulin was 5.68 ± 0.49 g/kg/day ($p > 0.05$). Although there is an increase in the protein synthesis rate measured, this change is not significant. An additional study was done in an elderly patient who did not fit the pattern seen in the young patients. Because of the known changes in glucose metabolism and insulin sensitivity seen with age[4] and the insufficient number of studies, these data are not included.

Changes in CO_2 from Glucose with Increases in Intravenous Glucose Infusion Rate

The change in the proportion of excreted CO_2 directly derived from glucose oxidation, which results

TABLE 2. *Effect of Insulin Infusion on Rate of Protein Synthesis*

Study	Leucine Flux (μmol/kg/min)	Protein Synthesis (g/kg/day)	Rate of Glucose Infusion (mg/kg/min)	Blood Glucose During Study (mg/dl)	Serum Insulin During Study
Patient #1					
No insulin	3.55	4.31	4.76	127	61.5
Insulin	3.85	6.90	4.96	144	72
Patient #2					
No insulin	3.29	4.71	5.22	186	74
Insulin	2.99	5.14	5.16	180	69
Patient #3					
No insulin	2.60	3.72	6.31	139	65
Insulin	3.01	5.02	7.03	126	75
Means					
No insulin	3.15 ± 0.23	4.25 ± 0.23	5.99 ± 0.32		
Insulin	3.28 ± 0.23	5.69 ± 0.50	6.31 ± 0.47		
	$p > 0.05$	$p > 0.05$			

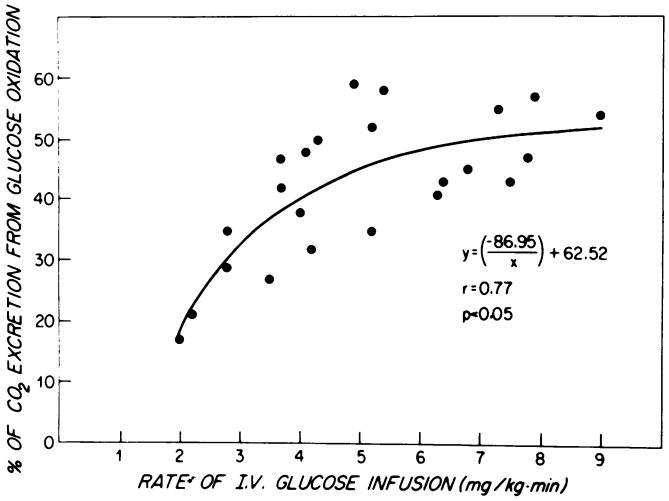

FIG. 3. Correlation between per cent CO_2 production from glucose oxidation and rate of intravenous glucose infusion (mg/kg/min). At infusion rates of less than 2 mg/kg/min the curve would be expected to plateau at about 18%.[18]

from graded increases in the rate of intravenous glucose infusion, is demonstrated in Figure 3. The proportion of CO_2 derived from glucose rises rapidly at low glucose infusion levels and levels off at the higher levels in a statistically significant manner, $R = 0.77$ ($p < 0.05$). At the low levels of glucose infusion the estimated rate of increase in direct glucose oxidation is greater than 10% for each 1 mg/kg/min increase of glucose infusion, while at the high levels there is only about a 2% increase for each 1 mg/kg/min infusion. As a result, there is little increase in direct glucose oxidation from increases in glucose infusion above about 5 mg/kg/min in the patients studied.

The Effect of Exogenous Insulin on the Proportion of CO_2 Derived from Glucose

The effect of intravenously delivered insulin on the rate of glucose oxidation was studied by examining the proportion of the total CO_2 excreted that was directly derived from glucose in both normal volunteers and seriously burned patients. Table 3 demonstrates these findings. In the normal volunteers the addition of insulin to a glucose infusion which had produced moderate hyperglycemia reduced the blood sugar to normal but did not increase glucose oxidation as assessed by the proportion of the total CO_2 from glucose. The mean per cent CO_2 from glucose was 40 ± 2.42 without glucose and 39.4 ± 4.84 with insulin infusion ($p > 0.05$). This was also true in the seriously burned patients studied. In these patients the addition of insulin to the glucose infusion was sufficient to lower the blood sugar concentration but did not increase the rate of glucose oxidation. In the burned patients with a glucose infusion alone the per cent CO_2 from glucose was 47.8 ± 5.2. When a glucose plus insulin infusion was given, the mean per cent CO_2 from glucose was 42.9 ± 2.4 ($p > 0.15$).

Respiratory Quotient as Related to Rate of Glucose Infusion

The relationship of respiratory quotient (RQ) to rate of glucose infusion is demonstrated in Figure 4. The RQ slowly increases as the rate of glucose infusion increases to an RQ of about 1, due to a slow increase in CO_2 production as the level of intravenous glucose delivered increases. However, beyond an RQ of 1, a relatively small increase in the intravenous glucose delivery rate creates a marked increase in RQ and a marked increase in CO_2 production in relation to oxygen consumption. As a result, there is a considerable increase in the volume of CO_2 that the respiratory system is required to excrete.

Fatty Infiltration of the Liver and Very High Glucose Infusion Rates

Between 1974 and 1978 there were nine patients who died more than 1 month following injury who were treated at the Shriners Burns Institute. All patients had an autopsy examination, and all had received glucose infusions in the form of various volumes of Hypercal (glucose + Freamine II) for 3 weeks or more immediately before death. These patients are described

TABLE 3. *The Effect of Added Insulin on CO_2 Production from Glucose*

Means	Rate of IV Glucose (mg/kg/min)	Glucose Oxidation (mg/kg/min)	Per Cent Uptake Oxidized	Per Cent CO_2 from Glucose	Plasma Glucose at Time of Study	Plasma Insulin During Study
7 Healthy volunteers						
No insulin	3.91 ± 0.14	1.49 ± 0.08	32.5 ± 4.31	40.0 ± 2.42	150 ± 6.41	38.1 ± 6.5
Insulin	3.96 ± 0.08	1.47 ± 0.11	33.7 ± 3.82	39.4 ± 4.84	86 ± 2.32	63.2 ± 12.3
5 Burned patients						
No insulin	6.88 ± 0.72	3.89 ± 0.87	53.6 ± 12.8	47.8 ± 5.2	192 ± 37	67 ± 30
Insulin	6.21 ± 0.57	2.95 ± 0.48	51.6 ± 8.0	42.9 ± 2.4	137 ± 26	121 ± 29

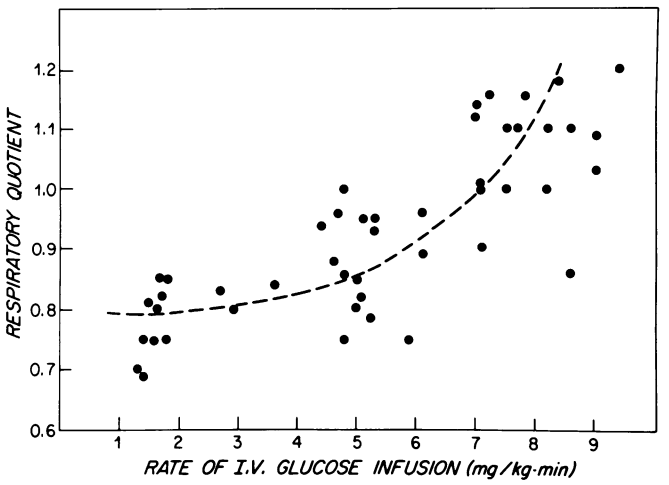

FIG. 4. Respiratory quotient as a function of glucose infusion rate (mg/kg/min) in 47 observations on 18 severely burned patients. The *dotted line* is fitted by eye.

in Table 4. Their average age was seven years, with a range from ten months to 14 years. There were four boys and four girls, and their average burn size was 66% BSA, ranging from 39–86%. No autopsy note was made of muscle wasting in any patient. The rate of glucose infusion for these patients averaged 13.7 mg/kg/min, ranging from 9.3–17 mg/kg/min. At autopsy all showed fatty infiltration of the liver, and their liver weights averaged 273% above normal, with a range of 164–440% above normal.

Discussion

Although the complex metabolic reactions to trauma are not accurately understood, the broad nature of the response with its negative nitrogen balance and the at least partial reversibility of this nitrogen loss with glucose administration have led to treatment regimens which have greatly improved the patient's metabolic state following injury. There is clear evidence that treatment improves nitrogen balance[17] and increases rates of protein synthesis.[11] This success has led to the use of extensive intravenous delivery of amino acids, fat and especially glucose without the establishment of an exact end point. Although the minimum level of glucose delivery required to substantially spare protein was established by Gamble[6] at about 100 g/day (approximately 1 mg/kg/min) in fasting man, there is limited information on the maximum level beyond which further increases in glucose administration would not produce physiological cost-effective increments of energy production and protein sparing in burned patients. The studies reported here provide evidence that there is a maximum physiological cost-effective rate of glucose administration in severely burned patients who were not starving or in the depleted state at the time of injury and whose protein intake was fixed following injury at approximately 1.33 g protein/kg/day. It is probable that patients who are severely depleted or starving would demonstrate a maximum effective rate of glucose administration at a different level. It is also possible that the optimal level of glucose intake identified in this study would shift if a higher or lower level of amino acid intake were used.

The data presented here strongly support the concept that there is a maximum level of glucose intake in relation to energy production and protein synthesis when viewed from the concept of physiological cost effectiveness. The rapid rise in CO_2 produced directly from the glucose at low rates of glucose infusion and the leveling off of glucose oxidation at high rates support this idea. It is of interest to note that even at the highest rate of glucose delivery the per cent of CO_2 derived directly from glucose continues to increase slowly. However, at the highest rates of glucose infusion studied, only approximately 40% of the glucose administered was oxidized, leaving 60% of the administered glucose to be handled via other metabolic pathways. Although we have no direct evidence, we believe that it is probable that the metabolic fate of this unoxidized glucose in this circumstance (*i.e.*, nonstarving or depleted patients receiving very high

TABLE 4. *Autopsy Findings of Patients Treated with Very High Glucose Infections*

Patient	Sex	Age	Per Cent BSA Burned	Muscle Atrophy	Hypercal for 3 Weeks Before Death	Rate of IV Glucose (mg/kg/min)	Liver Weight at Autopsy (Per Cent Above Normal)
1	M	11	80	0	yes	13.5	254
2	F	14	66	0	yes	14.8	246
3	F	10	86	0	yes	9.3	164
4	M	13	54	0	yes	10.8	309
5	F	16 mo	47	0	yes	17	291
6	M	10 mo	39	0	yes	17	324
7	M	3	85	0	yes	13.1	440
8	F	4	70	0	yes	14.3	331

levels of glucose infusion for periods longer than one to two weeks) is an adenosine triphosphate (ATP) requiring conversion to fat and the production of CO_2 in excess of oxygen consumed.

The fact that the RQ is above 1 indicates that in a net sense all CO_2 production is coming directly or indirectly from glucose. Thus, some of the infused glucose directed to fat must then be oxidized as fat. Although we have no direct proof of this scheme, it is the only plausible explanation for the existence of a quasi-plateau in expired CO_2 enrichment. This is because the ^{13}C molecules must be going into a large enough pool so that they will be diluted to such an extent that subsequent oxidation of molecules containing those labeled carbons will not lead to a progressive rise in expired CO_2 enrichment over the time span of the experiment. Fat would seem to be the only likely candidate, although isotopic exchange with glycogen cannot be excluded entirely. Furthermore, glucose is a known stimulator of fat synthesis in the liver.[13] The presence of fat in the liver at autopsy is consistent with the concept of an increased fat synthesis during the glucose infusion. It is not clear why the normal transport mechanisms that are responsible for the translocation of triglyceride from the liver to the periphery were not adequate, but the fact that they were not (at least to the extent that the fat deposits accumulated) suggests a negative effect of extremely high glucose infusion rates.

The concept of physiological cost effectiveness is important here, for although increasing glucose loads do, in fact, increase CO_2 production directly from glucose, the increased net ATP production is small and outweighed by the increased respiratory work required to excrete the excess CO_2 and the energy required for lipogenesis, as well as the space requirements for fat storage in the liver. Furthermore, the administration of pharmacologic levels of glucose disrupts the normal hormonal and substrate profile of the blood, and this may have many subtle effects as yet unrecognized.[19]

Studies carried out relating the rate of protein synthesis to the rate of glucose infusion also support the concept of an optimal level of glucose infusion when examined on a physiological cost-effective basis. There is a statistically significant increase in protein synthesis with the higher levels of glucose infusion as compared to lower levels. However, when the higher levels of glucose infusion are divided into high and very high levels, no difference is present. The number of studies carried out to examine leucine rate of appearance and protein synthesis is not sufficient to allow evaluation of protein synthesis rates at small increases in rate of glucose infusion. It is probable, however, that as in CO_2 production from glucose, the protein synthesis rate at high levels continues to increase as the glucose infusion rate is increased. However, even if present, we believe that this small increase is offset by the above-mentioned problems caused by the conversion to fat of that portion of the infused glucose which is unoxidized.

The addition of exogenous insulin to a glucose infusion which had caused moderate hyperglycemia alone, although successful in returning the blood sugar toward normal, did not raise the rate of CO_2 production directly from glucose in the healthy male volunteers or in the burn patients studied (Table 3). Thus, any beneficial effect of insulin is not mediated through an enhancement of the direct oxidation of glucose.

The addition of insulin to the glucose infusion appeared to have affected protein synthesis differently from the way it affected glucose oxidation. Although the number of studies is small, the addition of insulin to glucose infusions sufficient to reverse the mild hyperglycemia toward a normal level of glucose produced a consistent increase in protein synthesis in patients 8–38 years of age; however, the increase was not statistically significant. The available data are insufficient to comment on the older age groups. It is known that sensitivity to insulin is altered in the elderly,[4] so that the response may be different from that seen in the young.

The possible increase in rate of protein synthesis in young patients when insulin is infused with glucose is not a surprising finding. However, it is of interest to note that the increased rate of protein synthesis does not appear to be mediated through an increase in glucose oxidation but perhaps is mediated directly through protein synthesis mechanisms.

Striking findings of this study were the two untoward effects, hepatomegaly produced by fatty infiltration and increases in the respiratory work load secondary to an elevated CO_2 production. Both of these effects we believe are directly related to very high glucose infusion rates over periods of several weeks in patients who were not in depleted nutritional state or starving at the beginning of the period of glucose infusion. These two problems, hepatomegaly and the increased respiratory work load, are both involved in producing degrees of respiratory failure, although mild liver function tests and abnormalities such as small elevations in the serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and alkaline phosphatase indicate a degree of hepatic dysfunction, possibly secondary to a degree of intrahepatic obstruction. The respiratory abnormalities were more prominent in children, probably because the increase in liver size secondary to fatty infiltration produced a more marked elevation and fixation of the diaphragm and thus a more pronounced reduction in tidal volume than in the adult. However, we have noted degrees of respiratory

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?