Influence of Increasing Carbohydrate Intake on Glucose Kinetics in Injured Patients

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The metabolic and hormonal effect of glucose loads, ranging from 125 to 504 g/70 kg/day, were studied in severely injured patients. There was little or no correlation of glucose intake with nitrogen balance, plasma glucose, fatty acid concentrations, or epinephrine excretion. Increased norepinephrine excretion correlated with and may have resulted from increased glucose intake. Serum glucagon concentrations averaged 320 pg/ml and were not depressed by glucose intake. Insulin concentrations rose with glucose intake but were low for the level of plasma glucose. Glucose oxidation and non-oxidative metabolism, including glycogen deposition, correlated well with glucose intake. Gluconeogenesis from alanine was much higher than normal but was completely suppressed at very high intakes. The data imply that cycling of glucose, with glycerol, glycogen, or both, increased with increasing glucose intake.

THE PRIMARY SOURCE of calories in parenteral nutrition continues to be glucose. The ability to provide nutritional support for the severely injured patient is dependent upon the body's capacity to handle high glucose loads. The growing utilization of total parenteral nutrition (TPN) has now been extended by some to the immediate postinjury or postoperative period. The abnormal glucose metabolism that marks the early "flow" stage is therefore of increasing clinical interest.

This early flow stage after injury may be characterized as one in which a superabundant supply of nutrients is provided solely from body stores.[37] High levels of glucose are available which are needed and used by healing wounds.[42] Increased breakdown of muscle protein makes amino acids available for synthesis of visceral and blood proteins and for gluconeogenesis. Increased fat mobilization provides an adequate supply of fatty acids for those tissues which do not specifically require glucose. This state differs from fasting in that glucose concentrations are high, there is little or no ketosis, particularly in severe injury,[34] protein catabolism is much greater, and resting energy expenditure is above rather than below normal. These metabolic changes are associated with an hormonal pattern that includes abnormally high levels of catecholamines, glucagon, and glucocorticoids, and insulin levels that are low in light of the high glucose concentrations. Both the endocrine and metabolic changes appear to derive in large part from increased sympathetic activity.[37]

One feature of this state is that the normal effects of high glucose concentrations are attenuated or absent. Plasma fatty acid concentrations, which are markedly lowered by high glucose intakes in the normal state,[8,41] remain high. Gluconeogenesis, which is normally suppressed in the presence of high glucose concentration, persists in the traumatized or septic patient.[11,22] It seems reasonable to expect that this "glucose resistance," observed in the untreated patient or during infusion of 5% glucose solutions, would continue to express itself during higher rates of glucose administration.

The present study was undertaken to explore the effects of increasing glucose intakes to levels that are utilized for providing conventional TPN. Glucose kinetics were studied in severely injured patients. In addition, associated hormonal and substrate changes were determined in an effort to better identify the metabolic abnormalities responsible for glucose resistance in these patients.

Materials and Methods

Subjects

Nine men with severe accidental injuries were studied; one (HM) was infected; the others were not.

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Submitted for publication: October 10, 1978.

0003-4932/79/0700/0117 $01.05

TABLE 1. *Diagnosis, Degree of Trauma, Age, and Time of Study for 9 Men with Accidental Injuries*

Patient	Age	Height (cm)	Weight (kg)	Surface area (m^2)	Diagnosis	Degree of Trauma on Scale of 10	Start of Study (Days After Injury or Infection)
PR	24	180	104	2.14	Auto accident; fracture of right femur and pelvis, blunt abdominal trauma	9	13
RV	34	167	79	1.88	Gun shot, head and abdomen	8	6
HW	28	191	74	2.00	Gun shot, abdomen; left nephrectomy	8	1
VV	30	168	71	1.72	Gun shot, abdomen	7	3
AJ	36	175	82	1.99	Multiple stab wounds, abdomen	6	2
AC	47	178	76	1.90	Multiple contusions, pelvic fracture	6	3
HM	21	163	61	1.66	Infection of crush wound, right leg, with invasive sepsis	7	6
WC	56	170	85	1.96	Fracture of pelvis, left hip, femur and tibia (open)	9	2
BL	26	173	79	1.91	Multiple long bone fractures	8	7

All were physically healthy prior to the accident. In all but one case, studies were started within one week of the accident or onset of infection (Table 1). Five patients had multiple fractures, the others had extensive soft tissue damage. The severity of trauma, on the average was estimated to be 7.5 on a scale of 10. None of the subjects, with minor exceptions, were able to take oral nourishment. All were bedridden during the study. The details of this study and possible risks and benefits were discussed with each patient, members of his family, and his physician. Written consent was obtained in all cases.

Study Protocol

Eight patients were given continuous infusions of glucose at a constant rate for four days. In five instances 10% dextrose was infused peripherally without amino acid or vitamin supplements. In three patients, in whom a central catheter was already inserted for other purposes, total parenteral nutrition, including amino acids and vitamins, was provided. Fluid and electrolyte intakes were adjusted to individual requirements. Nitrogen and energy balances were measured during all four days. Blood samples were drawn daily at 08:00 for determination of serum insulin and glucagon, plasma glucose, free fatty acids (FFA), and blood urea nitrogen (BUN). U-^{14}C-alanine (20–30 μc.) was injected as a single bolus on the second day, and U-^{14}C-glucose (15–20 μc.) also as a single bolus, was injected on the third day. Ten blood samples were drawn just prior to, and at 5, 15, 30, 45, 60, 90, 120, 180, and 300 minutes after each injection for determination of the concentration and specific activity of blood glucose. The total amount and specific activity of expired CO_2 was measured at frequent intervals up to 12 hours after each injection.

One subject, HW, was maintained at two different levels of glucose intake, each for 3 days. On the third day of each period he was given an injection of glucose; no alanine was given.

Analyses

Balance measurements. All intake, whether oral or infused, was measured by differences in weights of the full and emptied containers. The amounts of each constituent (H_2O, N, etc.) were calculated from the manufacturer's specifications or by direct analysis in this laboratory according to established procedures.[2] Energy contents of diets were calculated from published values and, in the case of oral intake, were corrected for digestibility.[26] Urine, feces, and drainage were collected daily and analyzed for N, H_2O, Na^+ and K^+ content. In addition urea was determined in urine and drainage, creatinine was determined in urine, and glucose was determined in those urine samples in which qualitative tests (Ketodiastix®*) were positive. A manual, micro-Kjeldahl procedure was used for digesting samples for total N determination. Subsequent analysis of total N, and analyses of urea, creatinine, Na^+ and K^+ were carried out with single channel automated analyzers according to the manufacturer's procedures.†

Gas exchange. Oxygen consumption and CO_2 production were measured using a rigid lucite head canopy developed in this laboratory.[18,36] This permits frequent measurements of relatively long duration, three to five periods per day of 40–60 minutes each, with minimal discomfort to the patient.

Blood determinations. Plasma glucose was determined by an automated glucose oxidase procedure.‡ Blood urea nitrogen was measured by the clinical chemistry laboratory. Plasma FFA concentrations were

* Ames Company, Elkhart, Indiana.

† Auto Analyzer, Technicon Company, Tarrytown, New York.

‡ Glucose Analyzer, Beckman Instruments, Inc., Fullerton, California.

determined by the procedure of Dole and Meinertz.[4] Plasma insulin was measured by radioimmunoassay using Pharmacia kits. Glucagon measurements were kindly performed in the laboratory of Dr. J. B. Price, of this institution, using antiserums and methods supplied by Dr. Roger H. Unger, of the University of Texas Health Sciences Center, Dallas, Texas. Radioactivity in plasma glucose was measured by conversion to potassium gluconate,[21] recrystallization, and counting in a liquid scintillation counter.§ Urinary epinephrine and norepinephrine were measured by the trihydroxyindole method as adapted by Viktora et al.[39] with minor modifications.

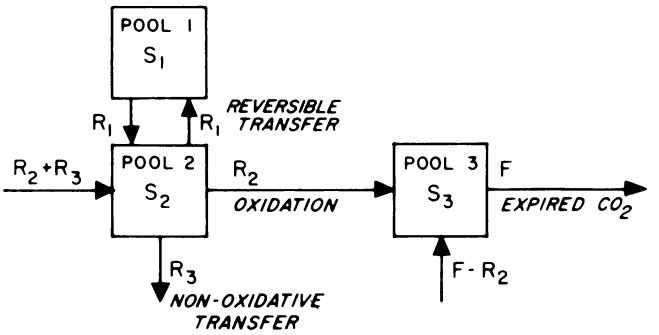

FIG. 1. Three-pool model of glucose metabolism. For explanation see text. Adapted from Long et al.[23]

Calculations

Glucose-^{14}C model. The method for calculating rates of glucose metabolism based on ^{14}C-glucose has been described in detail elsewhere[35] and will only be summarized here. The method involves injection of a single bolus of glucose U-^{14}C and repeated measurements, over the ensuing 6–12 hours, of the specific activity of blood glucose and the amount and radioactivity of expired CO_2. A computer model, schematized in Figure 1, is fitted to the data to derive the best values for three rates and the size of the glucose and CO_2 pools (S_2 and S_3). The rate of CO_2 production (rate F in Fig. 1) is measured directly. The physiologic significance of these rates may be explained with references to the simplified metabolic scheme shown in Figure 2. The rate R_1 (Fig. 1) refers to the rate of interchange of glucose with compounds, represented by pool 1 (Fig. 1), which return isotope to the glucose pool. The most important of these are glycogen, glycerol, and pyruvate and its derivatives, such as lactate and alanine. This corresponds to, but is not a quantitative measure of, glucose recycling. It is determined with poor precision by this method. The main function of R_1 in this model is to permit more accurate measurement of rates R_2 and R_3; the rate R_1, as measured here, has little or no physiologic significance.

Rate R_2 represents the rate of glucose oxidation and is equal to the sum of the contributions of glucose to the rates r_a, r_b, and r_c in Figure 2. Rate R_3 represents the rate of conversion of glucose to compounds from which there is negligible return of isotope and which, therefore, during the course of the experiment retain the isotope. This represents, essentially, the sum of the rates of conversion of glucose to glycogen, protein,

§ Amersham-Searle,

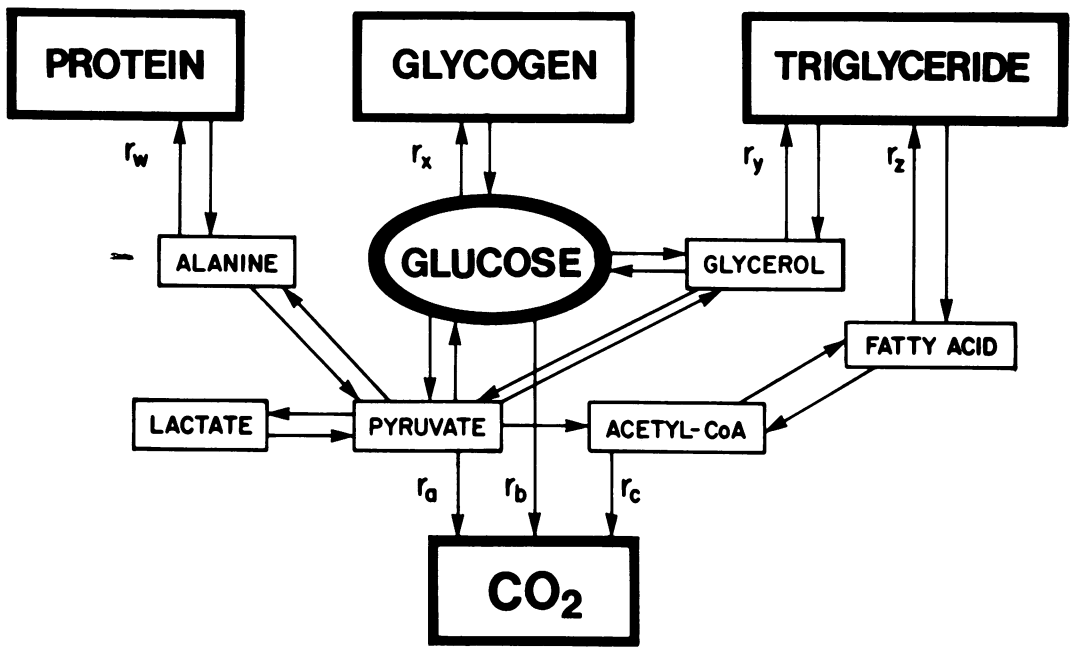

FIG. 2. Simplified scheme of glucose metabolism.

TABLE 2. *Metabolic Characteristics of Traumatized Patients*

	Mean*	SEM	Range
Energy intake (kcal/70 kg/day)	1258		496 to 2060
Nonprotein respiratory quotient (mole/mole)	0.86		0.79 to 1
Glucose intake (g/70 kg/day)	312		125 to 504
Resting energy expenditure (% of predicted)	118	6.6	91 to 159
Nitrogen balance (g/m^2/day)	−7.3	0.67	−4 to −9.7
Plasma glucose (mg/dl)	152	10	115 to 216
Plasma free fatty acids (mmole/l)	0.57	0.11	0.18 to 1.14
Serum insulin (μU/ml)	34	10	10 to 103
Serum glucagon (pg/ml)	324	142	47 to 1286
Insulin/glucagon ration (mole/mole)	4.2	1.3	0.7 to 12
Urinary norepinephrine (μg/day/70 kg)	297	76	15 to 682
Urinary epinephrine (μg/day/70 kg)	54	10	22 to 82
Glucose oxidation† (g/70 kg/day)			
Measured by indirect calorimetry	231	33	114 to 403
Measured with ^{14}C-glucose	250	31	133 to 468
Nonoxidative glucose metabolism† (g/70 kg/day), measured with ^{14}C-glucose	252	40	98 to 479
Total glucose turnover† (g/70 kg/day), measured with ^{14}C-glucose	502	70	221 to 947
Glucose balance† (g/70 kg/day), measured by indirect calorimetry	120	21	14 to 197
Alanine to glucose‡ (% dose ^{14}C)	10.4	2.6	1.9 to 21.4

* Mean daily values for 9 subjects each studied for 4–6 days.
† Day of glucose injection only.
‡ Day of alanine injection only.

and triglycerides, and corresponds to the contribution of glucose to rates r_w, r_x, r_y and r_z in Figure 2. Although the rates of conversion of glucose to other intermediates may be quite rapid, they are taken into account either as part of recycling (rate R_1) or as intermediates in the pathways to CO_2, protein and triglycerides (rates R_2 and R_3). Rate R_3 is referred to as the rate of nonoxidative glucose metabolism. The sum of R_2 and R_3 is taken as total glucose turnover, which by this definition does not include the Cori cycle or other recycling included in rate R_1. Rates R_2 and R_3, as measured here, are unidirectional rather than net rates. Since there is negligible conversion of CO_2 to glucose, the unidirectional rate R_2 is equal to net oxidation of glucose. By contrast, synthesis of glucose from unlabeled glycogen, protein, and fat is quantitatively significant, and can be greater than the reverse reactions. Therefore R_3 is strictly a unidirectional rate and this model does not measure net conversion of glucose to fat, protein, or glycogen, either singly or as their sum.

The accuracy of rates R_2 and R_3 depends on the assumption that the specific activity of glucose is the same, when measured in blood, as at the sites of reaction in various tissues. Since the glucose pool is largely extracellular, this appears to be a reasonable assumption.

Glucose oxidation and balance by indirect calorimetry. Calculation of resting energy expenditure and of the rates of glucose oxidation from measurements of N excretion, O_2 consumption, and CO_2 production was carried out by traditional methods of indirect calorimetry.[38] This method measures the net rate of glucose oxidation, which should be equal to that measured by the glucose ^{14}C model if the assumptions of both methods are valid.

Glucose balance is taken to be the difference between glucose intake and glucose expenditure as measured, at rest, by indirect calorimetry. Since in these experiments there was no *net* conversion of glucose to fat (nonprotein RQ $\leq$ 1), glucose expenditure was equal to glucose oxidation. Glucose balance is then equal to glycogen balance less any additional expenditure of glucose, during physical activity, over and above that measured at rest. Since, in this study, the patients were completely confined to bed, glucose balance may be presumed to approximate glycogen balance.

Conversion of alanine to glucose. The conversion of alanine to glucose is expressed as the percentage of the administered dose found in glucose when the specific activity of plasma glucose was at a maximum.[22] It is calculated by multiplying the maximum plasma glucose specific activity by the size of the glucose pool as measured with labeled glucose. Unlike the rates calculated from the glucose model and indirect calorimetry, this provides only a semiquantitative index of the rate of conversion of alanine to glucose. Intracellular concentrations of alanine are much higher than those in blood. The specific activities of amino acids differ markedly between blood and various tissues. In addition, the ratios of specific activities in tissues and blood vary under different conditions.[5,9] It seems unlikely, therefore, that more elaborate models or measurement of the specific activity of alanine in blood would significantly improve on the method used here.

Results

The metabolic characteristics of these patients (Table 2) indicate that they were severely traumatized, in agreement with the clinical estimates (Table 1). An increase of 18% above predicted values for resting energy expenditure is in the range previously observed for multiple long bone fractures.[16] Nitrogen balance of −7.3 g/m^2 was markedly negative, compared to

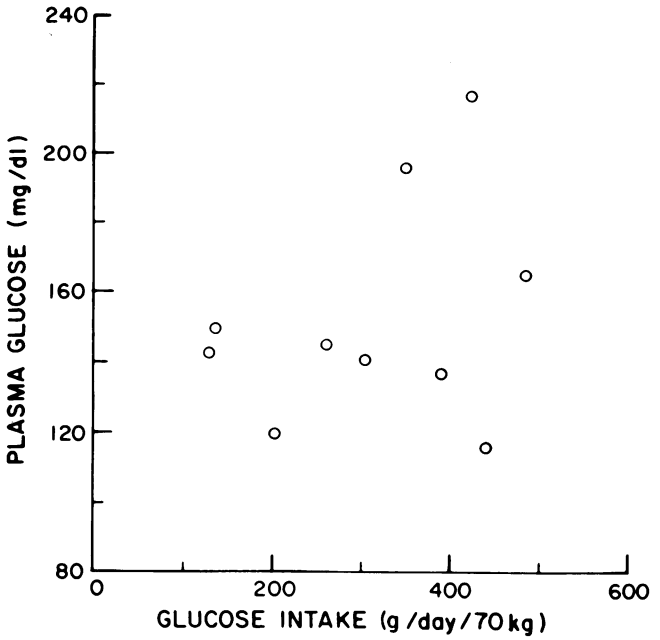

FIG. 3. Effect of glucose intake on plasma glucose concentation in injured patients.

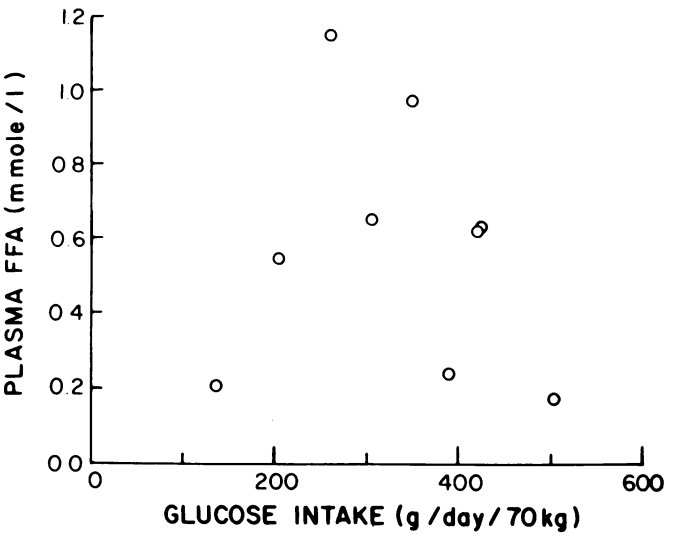

FIG. 4. Effect of glucose intake on plasma free fatty acid concentration in injured patients.

values of 0 to −3 for normal young men on similar intravenous diets.[45] Serum insulin concentrations were in the range of normal subjects receiving equal rates of glucose infusions,[45] but were abnormally low with respect to plasma glucose concentrations. Free fatty acids were in a normal postabsorptive range, but were higher than normal for the levels of glucose intake and concentration.[8,41,45] Urinary excretion of norepinephrine and epinephrine averaged seven and four times normal values (43 ± 20 and 14 ± 11 mg/day/70 kg respectively, as determined in our laboratory). Serum glucagon concentrations averaged 324 pg/ml, very much higher than values of 11–66 pg/ml observed in normal young men on similar glucose intakes.[45]

Metabolic Responses to Increasing Glucose Intake

Daily glucose intake (Table 2) ranged widely, from 125 g, provided by the customary administration of 5% dextrose, to 500 g/day, almost enough to meet resting energy expenditure. A number of the measured metabolic parameters correlated well with glucose intake, others did not. Plasma concentrations of glucose (Fig. 3) and FFA (Fig. 4), and N balance (Fig. 5) showed little correlation, when compared to glucose intake, as shown by slopes which did not differ significantly from zero, and small correlation coefficients (Table 3).

Serum insulin was positively correlated with glucose intake with a slope significantly above zero (Table 3, Fig. 6).

Serum pancreatic glucagon, somewhat surprisingly, increased with increasing glucose intake (Table 3, Fig. 7). Although this increase was not significantly different from zero (Table 3), it nevertheless suggests that there was no marked decrease in glucagon concentrations with increasing glucose intake, as occurs

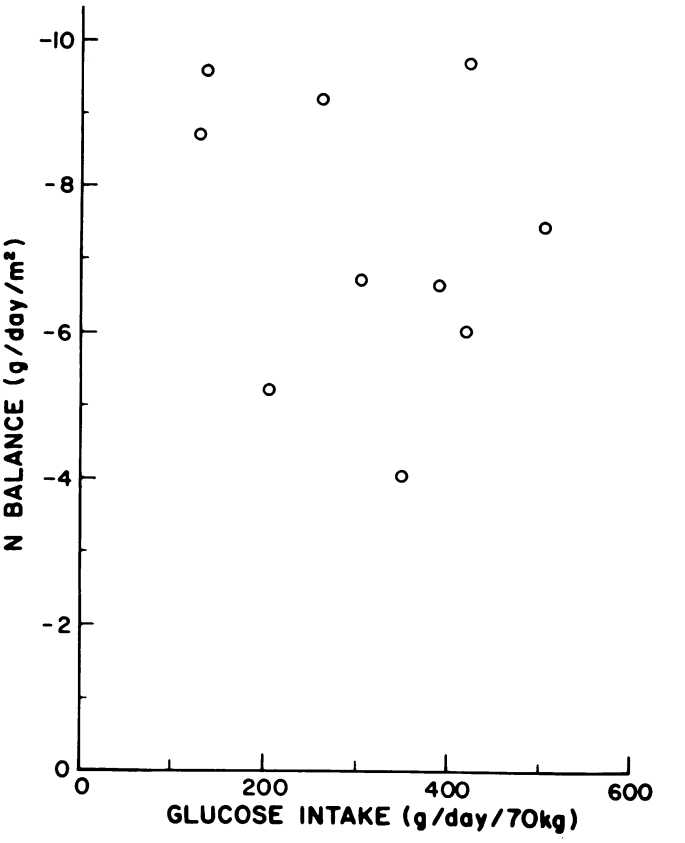

FIG. 5. Effect of glucose intake on nitrogen balance in injured patients.

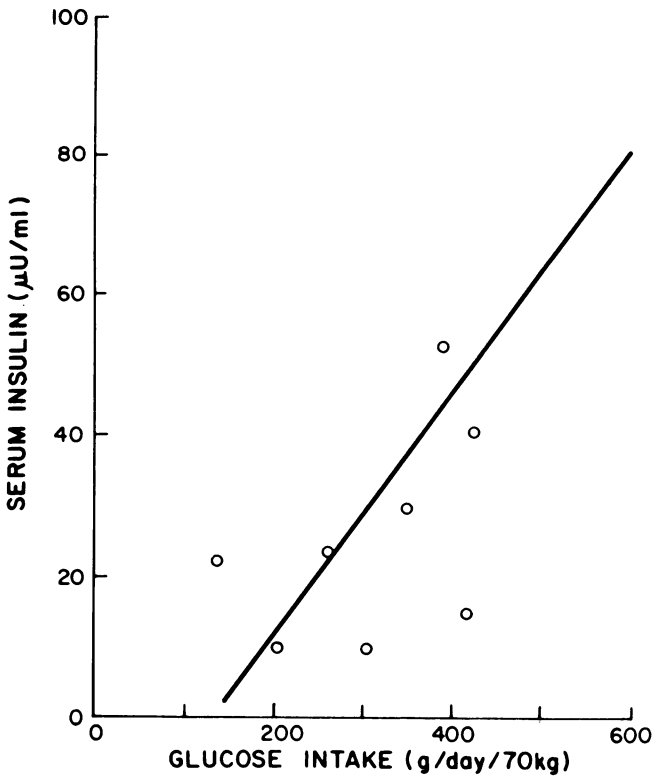

FIG. 6. Effect of glucose intake on serum insulin concentration in injured patients. Slope = 0.17 ± 0.07 (SEM).

in the normal individual.[45] The resulting insulin: glucagon rations were very low (Table 2) for the amounts of glucose infused and showed no significant change with glucose intake (Table 3).

Urinary norepinephrine showed a statistically significant increase with increasing glucose intake as shown for all nine patients in Figure 8 and Table 3. When the data on the three patients who were given amino acids

TABLE 3. *Correlation of Various Metabolic Parameters with the Rate of Glucose Intake**

	Slope	95% Confidence Limits of Slope	r
Plasma glucose	0.083	−0.083 to 0.166	0.33
Plasma FFA	−0.0004	−0.0026 to 0.0018	−0.13
Nitrogen balance	0.003	−0.007 to 0.013	0.22
Serum insulin	0.17	0.03 to 0.31	0.67
Serum pancreatic glucagon	1.4	−1 to 3.8	0.41
Insulin/glucagon ratio	0.007	−0.017 to 0.024	0.24
Urinary norepinephrine	1.2	0 to 2.3	0.6
Urinary epinephrine	0.02	−0.18 to 0.12	0.1
Glucose oxidation	0.54	0.32 to 0.76	0.86
Nonoxidative glucose metabolism	0.75	0.54 to 0.96	0.93
Total glucose turnover	1.29	0.88 to 1.70	0.91
Glucose balance	0.37	0.23 to 0.51	0.88
^{14}C-Alanine to glucose	−0.036	−0.057 to −0.015	0.82

* Units as given in Table 2.

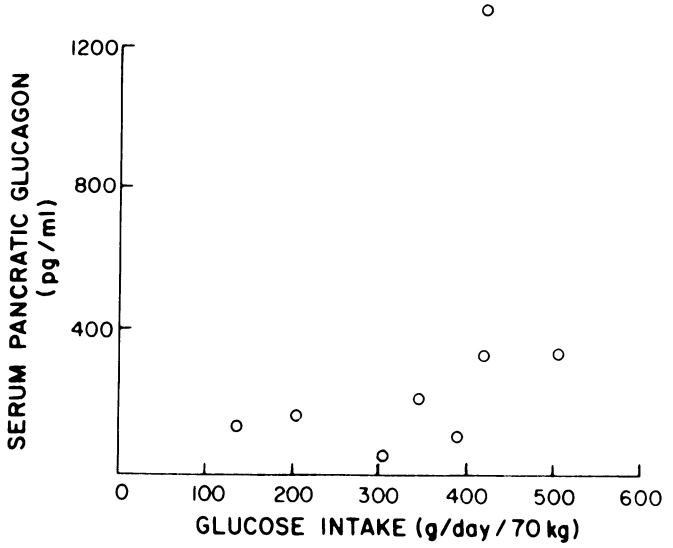

FIG. 7. Effect of glucose intake on serum concentration of pancreatic glucagon.

were omitted, the correlation between glucose intake and norepinephrine excretion improved as indicated by a correlation coefficient of 0.9. One patient was given two levels of glucose intake, 129 and 356 g/day/70 kg, for 3 days each. Mean values for norepinephrine excretion were 15 μg/day/70 kg on the low intake and 82 μg on the high intake.

Epinephrine excretion showed no correlation with glucose intake (Table 3).

Glucose metabolism as measured with ^{14}C. Glucose oxidation and non-oxidative glucose metabolism, as

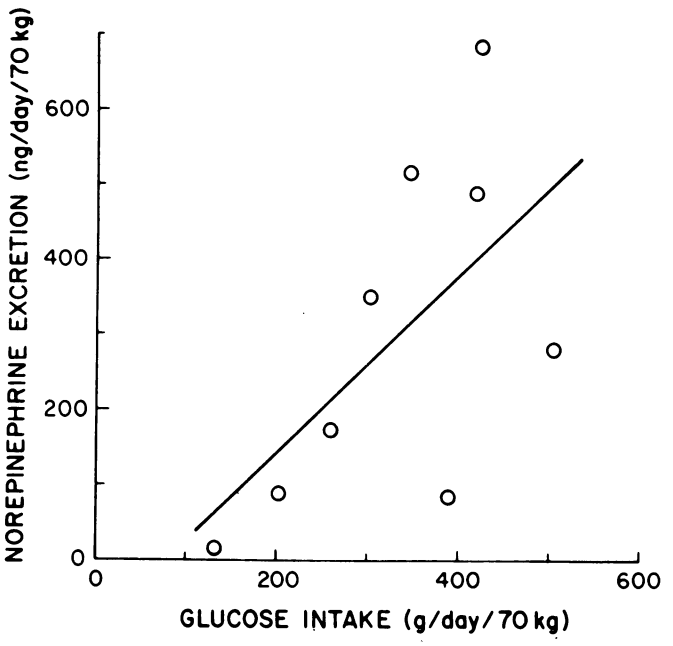

FIG. 8. Effect of glucose intake on daily norepinephrine excretion. Slope = 1.2 ± 0.6 (SEM).

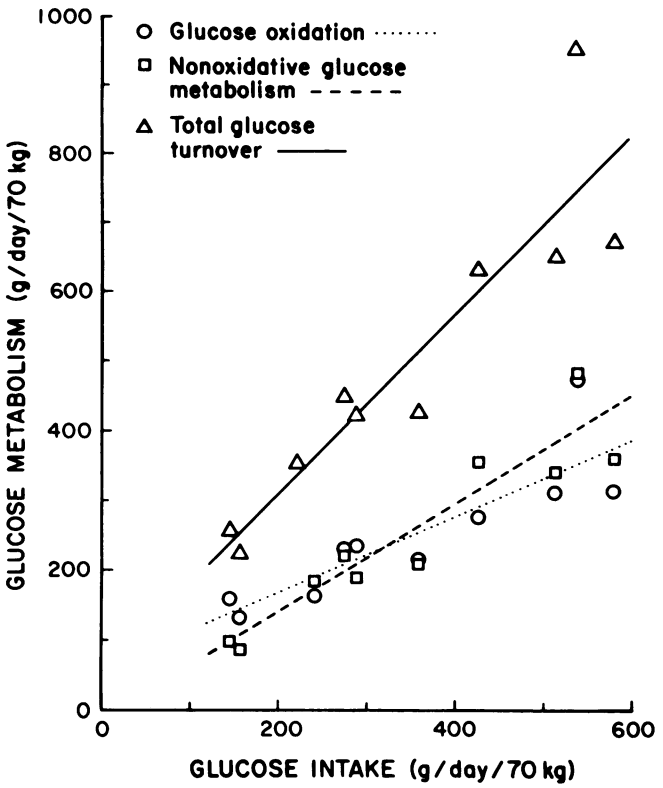

FIG. 9. Effect of glucose intake on glucose oxidation, nonoxidative glucose metabolism, and their sum, total glucose turnover, as measured by means of ^{14}C glucose. The slopes of the regression lines are 0.54 for glucose oxidation, 0.75 for nonoxidative glucose metabolism, and 1.29 for their sum.

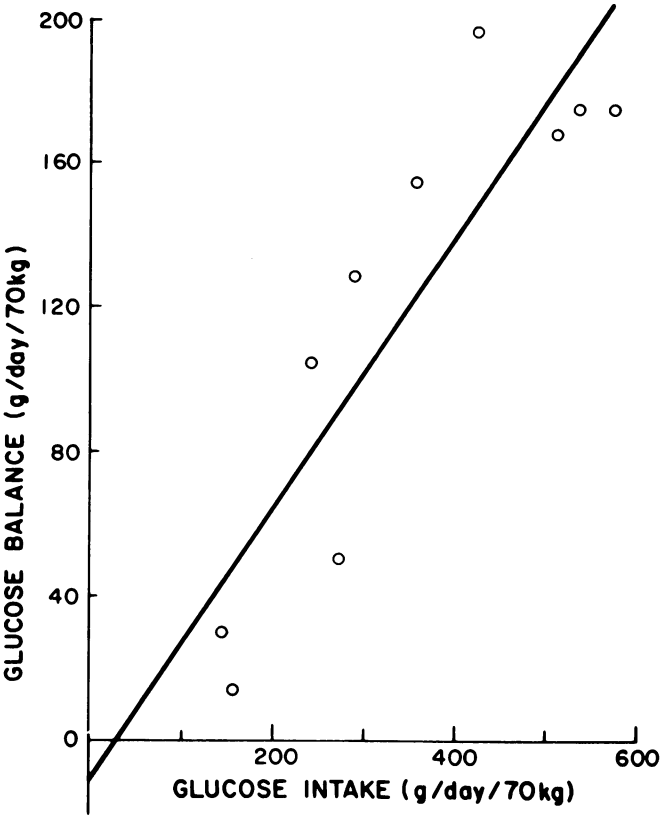

FIG. 10. Effect of glucose intake on glucose balance in injured patients. Slope = 0.37 ± 0.07 (SEM).

estimated with labeled glucose, both showed excellent correlation with glucose intake (Table 3, Fig. 9). Oxidative and nonoxidative metabolism were roughly equal to each other over the entire range of glucose intake. Total glucose turnover, the sum of oxidative and nonoxidative reactions, appeared to be somewhat higher (30–50%) than glucose intake over the entire range of intake.

Glucose balance measured by indirect calorimetry. Glucose balance correlated well with intake (Table 3, Fig. 10). It was positive in all instances and accounted for about one-third of intake, approximately 60 g at an intake of 200 g, and of 200 g at an intake of 600 g (Fig. 10). A positive glucose balance, as measured at rest, consists of two main components: (1) deposition of glycogen and (2) increased expenditure of glucose, above resting values, during physical activity. Since the patients in this study were confined to bed at all times, the major part of the observed positive glucose balance was probably due to glycogen deposition.

Comparison of glucose model and indirect calorimetry. The fraction of total CO_2 derived from glucose oxidation calculated from the ^{14}C-glucose model is compared in Figure 11 to that calculated by indirect

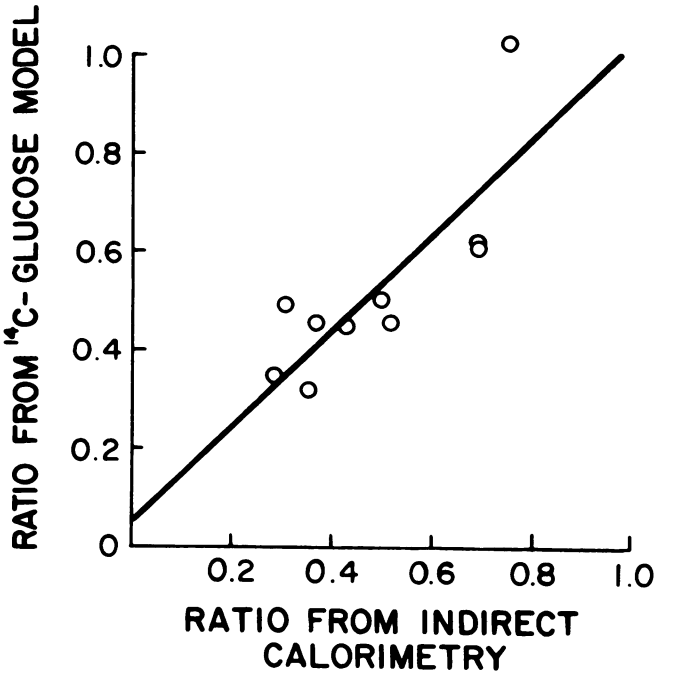

FIG. 11. Comparison of glucose oxidation in injured patients, expressed as a ratio to total CO_2 production, measured simultaneously by two different methods: (1) by injection of ^{14}C glucose; and (2) by indirect calorimetry. Slope = 0.95 ± 0.27 (SEM).

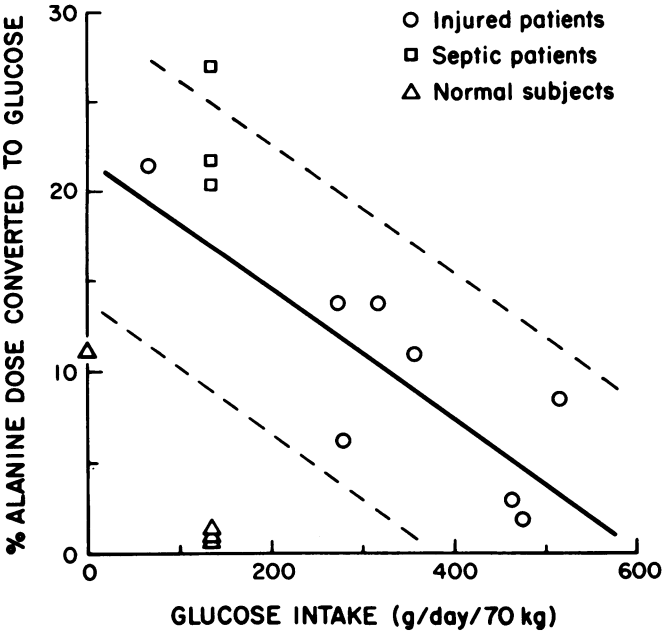

FIG. 12. Effect of glucose on gluconeogenesis in injured patients. Gluconeogenesis was measured as the percentage of alanine incorporation into glucose at the time of maximum glucose specific activity. The regression line and 95% confidence limits (*dotted lines*) are based solely on the data for the injured patients from the present study and do not include the septic patients or normal subjects, data for whom are taken from Long et al.[22] Slope = − 0.036 ± 0.11 (SEM).

calorimetry on the same day. There is good agreement between the two methods as shown by a slope of 0.95 ± 0.27 (theoretical = 1) and a correlation coefficient of 0.82.

Conversion of alanine to glucose. The percentage of the dose of ^{14}C-alanine converted to glucose showed an inverse linear correlation with glucose intake for the injured patients in this study (Table 3, Fig. 12). Values for three septic patients and four normal subjects from Long et al.[22] are also shown. It is clear that the injured and septic patients constitute a separate group from the normal subjects. Increasing glucose intake suppresses the conversion of alanine to glucose in both groups. However, zero conversion is reached at an intake of about 150 g/day in the normal and 600 g/day in the injured subjects.

Discussion

Hormonal Response to Glucose

These studies of traumatized patients indicate quite different reponses to hypocaloric glucose administration from those seen in normal subjects. Of particular significance are the rise in norepinephrine excretion and the lack of a decrease in glucagon concentration with increasing glucose intake. However, the finding that norepinephrine excretion is positively correlated with glucose intake does not necessarily mean that increased glucose intake is the cause of the increase in norepinephrine. An alternate explanation could be that the sicker patients were given greater amounts of glucose and that the amount of urinary catecholamines reflected only the severity of trauma. The purpose of the present experiment was primarily exploratory, to identify the significant metabolic and endocrine changes associated with increasing intakes of glucose. In eight patients, only a single level of glucose was given, and in general, the design of the study was not such as to provide definitive proof of one or another of these possible explanations. Nevertheless, there is suggestive evidence of a causal relation between glucose intake and norepinephrine excretion. There was no correlation (r = 0.03) between glucose intake and clinical estimates of the severity of trauma (Table 1). The patient studied at two different levels of glucose intake excreted more norepinephrine at the higher intake. Three additional trauma patients (studied by Y.A. Carpentier in this laboratory), given two different levels of glucose intake, also excreted more norepinephrine at the higher intake than at the lower intake. We may conclude, then, that it is quite likely that, in these patients representing the early "flow" stage of trauma, increasing glucose intake causes an increase in norepinephrine excretion. This is consistent with findings, in the rat, that increased dietary intake results in increased norepinephrine turnover and excretion.[19]

Catecholamines stimulate glucagon secretion and inhibit insulin production.[31] The high serum glucagon values in the present study, which were not suppressed by glucose infusion, can be at least partially explained by the high levels of norepinephrine. Likewise the low values for insulin, in consideration of the high plasma glucose concentrations, may be in large part due to inhibition of insulin release by norepinephrine.

Effect of Glucose Intake on Glucose Metabolism

There was, not surprisingly, a very close correlation between rates of glucose intake and glucose metabolism. This was true not only for glucose oxidation but also for non-oxidative glucose metabolism. These data are consistent with previous findings[11,22–24] that the hyperglycemia of trauma and sepsis is associated with increased glucose production rather than reduced glucose utilization.

The good agreement in estimating rates of glucose oxidation between indirect calorimetry and the glucose model, served to validate the assumptions of the latter method, and in particular the assumption that the specific activity of blood glucose is a valid measure

of that of the glucose pool. This assumption is of major importance in calculating both oxidative and non-oxidative rates of glucose metabolism. Therefore, the agreement between methods tends also to validate estimates of the rate of non-oxidative metabolism of glucose.

Gluconeogenesis

The conversion of alanine to glucose in injured patients was much greater than normal at a low glucose intake. Nevertheless, it was completely suppressed at high glucose intakes and the amount converted appears to be a linear function of the rate of glucose intake. In contrast, the rate of oxidation of alanine, as measured by appearance of radioactivity in expired CO_2, appears to be relatively constant, at about 30% of the dose, and to be independent of glucose intake or pathologic state.[22] Also there was little difference in specific activity of plasma alanine between normal and injured subjects.[22] Since pyruvate is an obligatory intermediate in conversion of alanine to both glucose and CO_2, these data suggest that inhibition of glucose synthesis is occurring between pyruvate and glucose rather than between alanine and pyruvate. This is in keeping with much evidence from other sources[6,28] that an important, if not the important, site of regulation of gluconeogenesis from pyruvate involves the enzyme phosphoenolpyruvate carboxykinase, which catalyzes the conversion of oxalacetate to phosphoenolpyruvate (PEP). These considerations suggest that incorporation of isotope from alanine into glucose serves as a semiquantitative index of the rate of glucogenesis, not just from alanine, but from all sources which must first be converted to PEP. These include all other glucogenic amino acids, as well as lactate.

Thus, the data presented here indicate that, in trauma, gluconeogenesis from both protein and lactate persists at abnormally high levels in the face of high rates of glucose intake. Nevertheless, at very high intakes (600 g/day) it is completely suppressed. The observed hormonal pattern is consistent with this. High and relatively unchanging values for glucagon should oppose inhibition, whereas insulin levels, which increase proportionately with glucose intake, are eventually high enough to overcome the glucagon effect and serve to suppress gluconeogenesis.

Total glucose turnover, as noted above, was more than 30% greater than glucose intake at all levels of intake (Fig. 9). This finding indicates that the unidirectional synthesis of glucose increased rather than decreased with increasing glucose intake. The isotopic alanine data, however, indicates complete suppression of gluconeogenesis from lactate and protein at high glucose intakes. This implies that there is increased unidirectional synthesis of glucose from other sources. The only two sources of quantitative significance are glycogen and glycerol. In the case of glycogen, as discussed more fully below, there was a marked increase in net glycogen deposition with increased glucose intake. It is possible that, simultaneously, there was a large increase in the unidirectional rates of glycogen synthesis and breakdown, leading to a high rate of interchange of isotopic glucose from the glucose pool with nonisotopic glucose from glycogen stores. There was no net conversion of glucose to fat in these studies, as indicated by nonprotein respiratory quotients, which never exceeded 1, and therefore no net conversion of glucose to glycerol. Nevertheless, there could have been an increase in the rate of triglyceride turnover in adipose tissue that would utilize labeled glucose to provide glycerolphosphate for triglyceride synthesis and release unlabeled glycerol, which would be resynthesized into glucose in the liver.

Thus, the finding of increased glucose turnover with decreased gluconeogenesis from alanine, implies that, in trauma, glucose administration causes an increased turnover of glycogen, triglycerides, or both. We would not expect to find such increases in normal subjects under glucose loading, although to our knowledge such studies have not been carried out.

Glycogen Deposition

The net rate of glycogen deposition, measured as glucose balance on the third day of glucose infusion, was approximately one-third the rate of glucose intake and reached values of more than 150 g/day/70 kg in some patients (Fig. 10). These rates seem very high when it is considered that: (1) the extreme range of diet-induced changes in glycogen storage in normal subjects can be calculated from data of Hultman et al.[12,13] to be about 400 g/70 kg; (2) that dietary intake was equal to or less than resting energy expenditure; and (3) that depleted patients on high carbohydrate diets have much lower rates of glycogen deposition (less than 50 g/day/70 kg) by the third day of a new dietary regimen than do these traumatized patients. Thus in these trauma patients there appears to be an abnormally high rate of glycogen deposition at all levels of glucose intake. This occurs despite very high concentrations of both norepinephrine and glucagon, which would be expected to stimulate breakdown of glycogen in both muscle and liver.

The effects of increasing glucose intake on glucose metabolism in trauma patients may be summarized as follows:

(1) Plasma glucose concentrations are maintained at

the already high level associated with trauma but are not significantly increased.

(2) Rates of glucose oxidation and non-oxidative metabolism increase proportionately with intake.

(3) There is an abnormally high rate of glycogen deposition which is proportional to glucose intake.

(4) Gluconeogenesis from protein is abnormally high but can be completely suppressed with an intake of approximately 600 g glucose per day.

(5) Glucose recycling with glycogen, glycerol, or both is increased with increasing intake.

Pathophysiologic Significance of Glucose Loads in Injured Patients

The patients in this study present a metabolic and hormonal pattern that is characteristic of the early flow phase of the response to severe injury.[1,17,37] This pattern includes increased resting energy expenditure, increased N excretion, hyperglycemia with increased glucose turnover, and increased fatty acid and glycerol turnover.[7,40] Elevated glucagon concentrations have been reported in burns[30,33,44] and in injury.[10,25,32] Increased plasma concentrations of catecholamines were seen in accidental trauma.[14] Increased urinary excretion of catecholamines was associated with high glucagon levels in burns.[43,44] Although not measured in this study, serum glucocorticoids are also elevated in trauma.[1] The characteristic pattern of glucose metabolism in trauma may be simulated in normal subjects by infusion of glucagon, cortisol, and epinephrine together, in amounts sufficient to raise serum concentration to levels seen in injured patients.* Since no two of these hormones can produce this effect, this suggests that a minimum condition for the metabolic response to trauma is increased production of all three of these hormones.

In a teleologic sense, this metabolic pattern may be viewed as a mobilization of the body's own stores of protein, fat and carbohydrate to provide normal or above normal levels of circulating substrates, glucose, FFA, and amino acids, without requiring any dietary intake. Thus gluconeogenesis is maintained despite high plasma glucose concentrations, and is able to meet normal requirements of the brain and other tissues as well as the increased requirements for glucose demonstrated for wound tissue.[42] Increased levels of amino acids are available for synthesis of viscera and blood proteins. High levels of fatty acid can meet the energy needs of heart and skeletal muscle sparing glucose for those tissues which specifically require it. In some respects this pattern is similar to that seen in fasting or acute starvation in normal subjects in whom there is also a dependence on the body's own stores of nutrients.[20] This includes increased plasma levels of glucagon and cortisol, increased excretion†[15] and plasma levels[3] of catecholamines, increased mobilization of protein, fat, and carbohydrate stores, and increased gluconeogenesis. However, there are differences between the two catabolic states. Trauma patients tend to be hyperglycemic, whereas fasted subjects become hypoglycmeic; ketosis develops rapidly in fasting normal subjects but is frequently absent in injured patients.[34]

The present studies indicate that the response to glucose loading is very different in the injured patient than in the normal fasted subjects. Infusion of glucose for 3–4 days after fasting resulted in a fall in glucagon concentrations and a decrease in catecholamine excretion to normal values.† In injured patients, by contrast, glucagon concentrations remained high (Fig. 7, Table 3) and catecholamine excretion was increased (Fig. 8, Table 3). It required much greater loads of glucose to suppress gluconeogenesis from protein in injured patients (Fig. 12) than in fasted subjects. Recycling of glucose with glycogen or glycerol is increased in injury. Nitrogen excretion is markedly reduced by giving glucose to fasted subjects†[27,29,45] but showed little change in the injured patients (Fig. 5).

These differences in response to glucose loading are consistent with the distinct etiologies of these two catabolic states. The abnormal metabolic pattern in fasting is of dietary origin and can be markedly affected or returned to normal by dietary means. The metabolic pattern in trauma appears to be highly resistant to dietary intervention, at least in the early phases of the flow stage as studied here. This raises, once again, the question as to the extent one should expect to correct the hypercatabolism of injury by dietary means. The term "nutritional stress" has been placed on inadequate nutrient intake in surgical patients. The present study indicates that providing carbohydrate may not always decrease this stress but in some conditions may add to it.

Acknowledgement

We are grateful to Oliver E. Owen, George A. Reichard and Douglas W. Wilmore for helpful comments during preparation of this manuscript.

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* Personal communication from Robert S. Sherwin, Department of Medicine, Yale University, New Haven, Connecticut.

† Unpublished observation from this laboratory.

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