Annu. Rev. Nutr. 1989. 9:445–73

THE EFFECTS OF INJURY AND SEPSIS ON FUEL UTILIZATION

Susan A. Goldstein

Department of Orthopedic Surgery, Columbia University, New York, NY 10032

David H. Elwyn

Department of Anesthesiology/Critical Care, The Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York 10467

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INTRODUCTION

Mechanical injury, both accidental and surgical, burn injury, and sepsis markedly alter metabolism and fuel utilization. The extent of alteration depends on the severity of the insult. It is relatively slight after a simple

0199-9885/0715-0445$02.00

elective operation, such as cholecystectomy, and very marked with extensive third-degree burns. The time course of changes varies from a few hours or days with surgical operations to weeks or months with extensive burns or chronic sepsis.

The pattern of these metabolic alterations undoubtedly varies with the type as well as the severity of injury or infection. Nevertheless, these alterations, whatever the cause, have many similarities, suggesting a common pattern of response. This common pattern is the subject of our review. Current knowledge in the field does not allow clear differentiation of separate patterns in the response to burns, mechanical injury, or sepsis, much less differentiation of different patterns within each area.

The problem of defining the metabolic response to stress (defined here to include injury, burns, and sepsis) is complicated by the frequent occurrence of malnutrition in stressed patients, since the metabolic consequences of malnutrition are different from, and often opposite to, those of stress.

This chapter focusses on human rather than animal studies. While animal experiments have been important in elucidating the mechanisms of the metabolic response, metabolism in humans differs quantitatively from that in all other animals. Most important is the difference in brain requirements for glucose. In humans the brain requires 20% of resting energy expenditure, while it requires 3% or less in all mammals other than primates (48). The brain obtains energy almost entirely from glucose and in humans uses 100–150 g per day (25). If this glucose is not provided by dietary carbohydrate, it must be synthesized, mainly from protein. Thus, below approximately 150 g protein per day, carbohydrate becomes an essential nutrient for humans but not for other mammals (23, 103).

D. P. Cuthbertson initiated the study of the metabolic response to injury in 1929. He showed that injury (mainly long-bone fractures) produced a general hypercatabolic state, in that excretion of N, S, and P increased in proportions characteristic of cellular tissue, much greater than could be accounted for by local tissue necrosis related to the wound (28). He also showed that injury produced a hypermetabolic state, in which resting energy expenditure was increased together with body temperature. Cuthbertson divided the metabolic response into an initial ebb, or shock, phase and a subsequent flow phase (28).

Many studies since 1929 have confirmed and extended these findings, as summarized below. The ebb phase is characterized by low blood pressure with or without a decrease in blood flow. It is caused by hypovolemia, cardiac failure, or sepsis and is usually accompanied by decreased oxygen consumption and energy expenditure and reduced body temperature, although increased temperature may occur in septic shock. Increased catecholamine excretion is associated with hyperglycemia until glycogen stores are ex-

hausted. This phase may not occur with mild or moderate injury. Therapy is mainly aimed at restoring hemodynamic and respiratory stability. Mortality rates, particularly for septic shock, are high, of the order of 50% (85).

The ebb phase of injury (for review see 44) lasts a few hours to a few days. It is succeeded either by a necrobiosis stage (112), which is usually accompanied by multiple system organ failure and from which the patient usually dies despite hemodynamic resuscitation, or by the flow phase of injury, from which most patients later recover and which can be divided into a catabolic and an anabolic stage (82). With elective surgery, there may be no ebb phase; peak effects of the flow phase occur within hours or up to 2 days, and recovery is complete within a week. With severe injury, burns, or sepsis, the time course is extended; peak effects usually occur within 3 days to a week, but complete return to normal may take weeks or even months to achieve.

The metabolic changes in the flow phase are the subject of the remainder of this chapter. After a brief overview, the topic is treated in depth.

Flow-phase changes include increased energy expenditure, increased body temperature, and a rise in the zone of thermoneutrality. Net catabolism of protein occurs primarily in muscle, resulting in increased flow of amino acids from muscle to visceral organs. These amino acids are used for synthesis of acute-phase proteins, for markedly increased gluconeogenesis, and–mainly as glutamine–to supply essential building blocks for rapidly dividing tissues such as intestinal mucosa, hemopoietic tissue, and the wound itself. The net catabolism of muscle protein is the result of increases in unidirectional rates of protein breakdown, at least in severe injury, that are greater than the increases in synthesis. Hyperglycemia develops, even in the fasting state, with increased substrate cycling of glucose to lactate and back, as well as increased synthesis from protein. Oxidation of glucose derived from all sources is increased; oxidation of preformed glucose—glycogen or dietary carbohydrate—is decreased; and there is both glucose and insulin resistance. Lipolysis is greatly increased, accompanied by increased plasma concentrations of glycerol but not of fatty acids. Fat oxidation is higher than normal at any dietary intake level, both absolutely and as a proportion of nonprotein-energy expenditure. The increase in lipolysis is much greater than that of fat oxidation and results in increased substrate cycling in which triglycerides are hydrolyzed to fatty acids and then resynthesized. The increased substrate cycling of protein, carbohydrate, and fat may account for much of the increase in energy expenditure.

Increases in glucagon, cortisol, and catecholamines, the latter mainly reflecting sympathetic activity, are largely responsible for the metabolic changes. There are two major mediators of these neuroendocrine changes: (*a*) the afferent nervous system, which receives signals from the wound itself and from pain, baro-, chemo-, and other receptors; and (*b*) cytokines, such as

interleukin-1 and tumor necrosis factor, which are released by white blood cells and act locally and systemically. These diverse signals are correlated and implemented mainly in the hypothalamus.

ENERGY EXPENDITURE AND BODY TEMPERATURE—HYPERMETABOLISM

Changes in resting energy expenditure vary markedly with the nature and degree of injury (Figure 1). Elective operations increase resting energy expenditure up to 10%; multiple fractures, stab wounds, or gunshot wounds cause increases to 30%; severe sepsis up to 60%; and extensive third-degree burns can cause a doubling of energy expenditure (66). By contrast, malnutrition may reduce energy expenditure as much as 40%. Since injured and septic patients are often malnourished, routine measurements of resting energy expenditure in intensive care unit (ICU) patients are variable and range from 40% below to 100% above predicted normal values, based on the Harris Benedict (53) or other formulas. Average values for ICU patients depend on the average severity of illness and degree of malnutrition of the particular patient population; reported values range from 5% to 40% above predicted (24, 40, 120, 123). Since resting energy expenditure in normal adults aver-

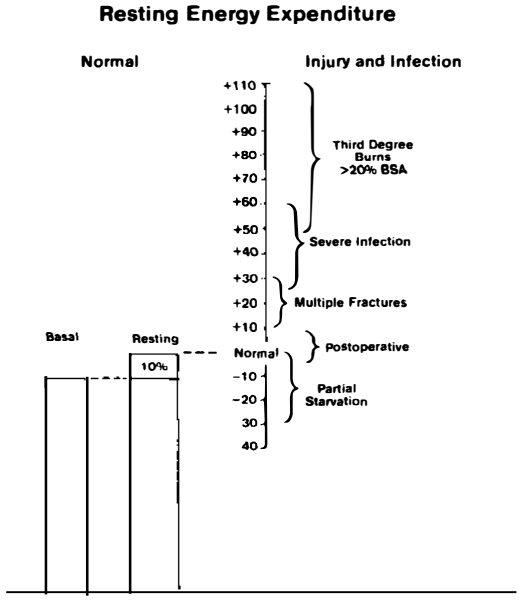

Figure 1 Effects of injury, sepsis, and starvation on resting energy expenditure. Adapted from Kinney et al (66). Reproduced from Kinney (65) with permission of Ross Laboratories.

ages approximately 1500 kcal/day, the range in severely ill patients is from approximately 900 to 3000 kcal/day, with very few values below or above this level.

The increased energy expenditure, or hypermetabolism, of injury is accompanied by an increase in core temperature and an increase in the zone of thermoneutrality (35). The zone of thermoneutrality is the ambient temperature at which energy expenditure (thermogenesis) is at a minimum and in which the subject feels neither too warm or too cold. For nude adults, this temperature is approximately 27–29°C. With injury or sepsis, this level may rise 2–3°C. This adjustment results from a resetting of the "thermostat" in the hypothalamus (110) that may be initiated by pyrogens such as interleukin-1 (29, 92) or possibly by other stimuli. Increasing the ambient temperature to the new thermoneutral zone decreases energy expenditure in patients with physical injury (119) or burns (8) but does not completely eliminate the thermic response. Thus, at normal temperature, a component of the increase in resting energy expenditure is due to resetting of the body's "thermostat," and this component can be eliminated by increasing the ambient temperature. Another component of the thermic response is due to increased substrate cycling, as discussed below.

PROTEIN METABOLISM—HYPERCATABOLISM

Extent of Catabolism and Severity of Injury

The effect of injury or sepsis is to cause net catabolism of body protein, the amount dependent on severity and type of insult and on dietary intake. Nitrogen excretion in various disease states and the normal state is shown in Figure 2 for subjects given 5% dextrose intravenously as sole nutrient support. Since there was no protein intake, the amount of N excreted is equal to negative N balance. Negative N balance would be higher in all instances if the subjects were completely fasted and much lower if given adequate nutrition. Nitrogen excretion for the burn patients was 27 g/day at 8 days after injury (127). Since N loss or gain in adults reflects intracellular protein almost exclusively (62, 68), this level represents a loss of 0.8 kg of body cell mass each day. Losses from the burn wound, not measured in this study, might add another 8 g N/day (122). These losses are more than five times those for normal subjects on the same diet (Figure 2). Protein losses in other conditions are less than for severe burns but substantially above normal values (Figure 2). Note, however, that each of these values represents one study taken from the literature and thus cannot be considered accurate averages for these conditions. Of interest is that the malnourished patients in Figure 2 excreted twice as much N as the normal subjects and three times that of fasted normals.

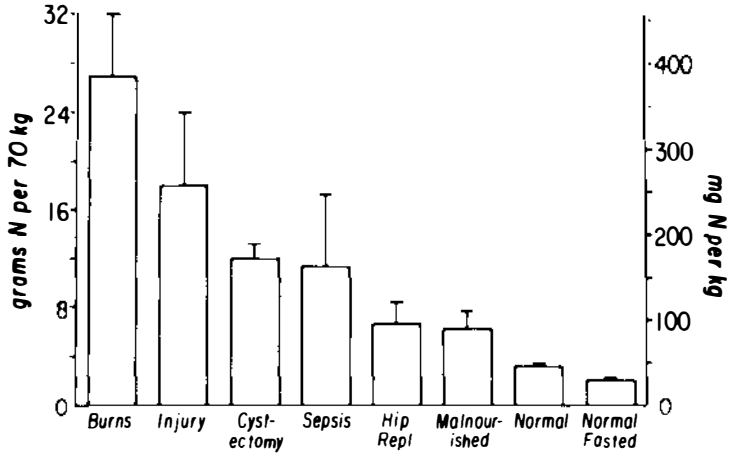

Figure 2 Total nitrogen excretion during 5% dextrose infusion in injured, septic, burned, or malnourished patients and normal subjects. Mean ± SD. Data from the literature for 47% whole-body burns (127), severe accidental injury (116), post–radical bladder cystectomy (57), sepsis (51), post–total hip replacement (5), malnourished patients (100), normal subjects (89), and normal subjects after a 10- to 14-day fast (37). Data for burn patients receiving 1426 kcal/day of glucose were corrected by the author's formula (127) to an intake of 525 kcal/day with no insulin supplementation. Data for severe injury, reported for urinary urea N only (220 ± 90 mg/kg/day), were corrected to total N excretion by adding 40 mg/kg per day for nonurea N. Reproduced from Elwyn (34) with permission of *Critical Care Clinics*.

This finding indicates considerable underlying disease in this particular group of patients, since uncomplicated malnutrition decreases N excretion. Studies of other malnourished patients show reduced excretion of N (101).

Nitrogen balance is improved in stressed patients in response to both N and energy intake, a response that is qualitatively similar to those of normal or malnourished subjects. At any given level of N and energy intake, however, N balance in stressed patients is less than in normal patients, and the size of the difference depends on the degree of stress. By contrast, malnourished patients not otherwise stressed are in more positive N balance than are normal patients. Even after moderate abdominal surgery (vagotomy, pyloroplasty, or cholecystectomy), an apparently obligatory N loss of 5 g per day occurs despite what would normally be considered adequate intake—11 g N and 2100 kcal per day—in the first 3 days after operation (95). By the fourth day, N balance returns to zero. These studies also indicated that N balance was somewhat better—4 to 7 g N per day in the first 4 days—with enteral than with parenteral feedings. Other studies, usually starting later, have found little difference between enteral and parenteral regimens (52). A number of reports show marked negative N balance immediately after severe burn, physical trauma, or septic shock despite high N and energy intakes; some of these

reports are summarized in Table 1. In the first five studies, N balance was negative despite daily energy intakes ranging from 1780 to 3450 kcal and N intake from 7 to 24 g. Although not measured, energy expenditure probably averaged approximately 2500 kcal per day. Therefore, in the study of Francois et al (43) energy intake was only 70% of expenditure. Data of Shenkin et al (102) and Larsson et al (70) indicate a big effect when N intake increased from 0 to about 14 g (200 mg/kg) per day. But data of Larsson et al (70) and Greig et al (51) suggest that above this level any further effect of N intake on balance is minimal unless accompanied by increased energy intake, as shown by the data of Bivins et al (15). The latter study indicates that increasing energy intake well above energy expenditure continues to exert a marked effect on N balance.

Nitrogen balance in the septic patients of Streat et al (114) is much more negative than would be expected from the other data. Streat et al measured total N content of the body at the start and end of their study by neutron activation analysis; N balance measurements were used in all other studies. Urinary urea excretion was reported by Streat et al (114) to be 17.7 g per day prior to the start of nutrition therapy; this level is consistent with data from N balance studies and much less than the −27g N balance measured during full nutrition. Why there should be such a disparity between the methods is not clear. With body composition methods, N balance is measured as the difference between two large numbers, and over short periods such measurement is less precise than balance methods (22, 131). Errors in neutron activation analysis should be of the order of 2%, but the change in N content reported by Streat et al (114) was 12.5%. This change is highly significant and unlikely to be due to random errors. Nitrogen balance measurements tend to be too positive and unduly influenced by large N intakes (56), but this problem seems too small to account for what appears to be a discrepancy of the order of 15 g N per day (22).

In contrast to the other studies, the burn patients of Wilmore et al (127) were in slightly positive balance (Table 1). These studies were started four weeks after injury; thus, these patients were beyond the acute catabolic stage. They had presumably lost substantial amounts of protein in the earlier stages and were malnourished. Nevertheless, this positive balance was achieved only at very high energy and N intakes.

With the less catabolic patients of Greig et al (51), zero N balance was achieved within a few days of initiation of sepsis (Table 1). Energy expenditure was only 1600 kcal in these patients, whose energy intake was 41% greater. Doubling N intake had only a small effect on N balance, and the effect lasted only 3 days. This brief effect is similar to the transient effect of increasing N intake in normal subjects, who cannot sustain a positive N balance for more than a few days at zero energy balance. The septic patients,

Table 1 Nitrogen balance and N and energy intake in severely injured or septic patients[a,b]

Type of patient	No.	Time after injury—length of study period (days)	Intake		Ratio CHO:fat (kcal:kcal)	N balance (g/day)	Reference
			N (g/day)	Total energy[c] (kcal/day)			
Sepsis, postseptic shock—APACHE score (69) 21.5	8	Immediate post-shock—9	23.5	3,300	1:1	−27	Streat et al (114)
Severe multiple trauma	?	Immediate post-injury—14	14	1,780	1:0	−11	Francois et al (43)
Multiple trauma and burns > 30%	7	Immediate post-injury—7	0	3,170	1:1	−13	Shenkin et al (102)
	7		24	3,530	1:1	− 6	
Brain injury—Glasgow Coma Score (117) 4–9		Not given—16					Bivins et al (15)
	17		13	2,300		−11	
	17		17	2,990		− 8	
	17		21	3,450		− 3	
Multiple trauma and burns	39	Immediate post-trauma—8	0	3,300		−14	Larsson et al (70)
			7	3,300		− 6	
			14	3,300		− 4	
			21	3,300		− 3.5	
Sepsis, moderate	9	3 to 5 days—5	12.7	2,290	1:1	− 0.7	Greig et al (51)
			24.3	2,220	1:1	0.5	
burns, average 56%	17	28 days—3–7	23	3,850	1:1	2	Wilmore et al (127)

[a] Multiple entries for each study are for different N or energy intakes.
[b] Data from several sources presented in different ways have been recalculated to units of g N or kcal energy/subject/day. In some instances, this recalculation has yielded approximate values.
[c] Includes protein intake.

however, were in markedly positive energy balance, a condition in which normal subjects would also be in positive N balance (22, 83).

The studies of burns (Table 1) did not measure N losses through the wound. Waxman et al (122) estimate that in the first week, protein is lost (in g N per day) at the rate of 0.19 × body surface area × percent burn, and at half that rate thereafter. Thus, in an adult man with a 50% burn, this loss would be 9 g per day in the first week and 4.5 g per day subsequently. Thus, the data for burns in Table 1 underestimate N balance by these amounts. Since this N loss is as protein rather than its oxidized end products, the loss does not indicate greater hypercatabolism. Thus, if the patients of Wilmore et al (127) excreted 5 g N per day through the wound, their N balance would be −3 g rather than +2 g per day. Still they would be synthesizing 12.5 (2 × 6.25) g protein per day in excess of breakdown, since the 5 g of N exuded by the wound would be in the form of 31.3 g of protein.

Thomsen & Sorensen (118) report on two patients, one with 60% and one with 70% full-thickness burns who achieved positive N balance in the first day after burn and maintained this throughout recovery. They attribute this achievement to their unit's practice "not to starve patients initially, but on the contrary to permit normal nourishment immediately after admission. As a consequence the patients are given large amounts to drink during the shock period, thus adding to the intravenously administered fluids and electrolytes in preventing hemoconcentration." That the beneficial results of this regimen may be due to the route of administration as well as the amount of nutrient intake is suggested by studies of burned guinea pigs. When given full-strength enteral feedings within 12 hours of burn injury, they had a minimal response to injury including minimal N losses (30, 81), as compared with the response with parenteral feeding or delayed enteral feeding. This effect was attributed to better maintenance of intestinal morphology, which prevented infiltration of colonic bacteria presumed to be the major cause of the metabolic response to injury. Similar results have been observed in human burn patients (J. W. Alexander, personal communication).

Thus, severe injury or sepsis produces an initial hypercatabolic response that can be ameliorated but not completely overcome by high levels of energy (50% above energy expenditure) and N intake given mainly by vein with enteral and oral supplementation (Table 1). With less severe stress, zero N balance can be achieved at these intakes. If energy were given at two to three times expenditure, zero N balance would likely be reached in all cases but only with enormous rates of fat and glycogen deposition and with large increases in energy expenditure because of diet-induced thermogenesis. Immediate, aggressive administration of oral nutrients may largely prevent this catabolic response, at least in burn injury, because it maintains intestinal

mucosal morphology and prevents infiltration of intestinal bacteria that may be responsible for much of the catabolic response.

Sites of Protein Breakdown—Role of Muscle

Autopsies of malnourished patients indicate that all organs contribute to protein loss except the brain and nervous tissue (49). Although critical organs such as the heart or diaphragm were formerly thought to be spared the effects of malnutrition, such sparing has been shown not to be the case (3, 49). These losses are almost entirely intracellular (67, 68). Since skeletal muscle comprises approximately 70% of body cell mass, the bulk of proteolysis during malnutrition occurs in muscle. Rates of protein loss after injury are much higher than in simple starvation (Figure 2), and most of this increase probably comes from muscle. That muscle is the major site of protein loss is supported by studies of interorgan flow of amino acids.

Pearl et al (91) measured arterial–femoral venous differences in amino acid concentration and leg blood flow to determine leg output of amino acids. Rat studies indicate that muscle accounts for more than 90% of amino acid output by the leg (1). Assuming the leg to be 20% of peripheral tissue permits estimation of total body peripheral output (Table 2). Lund et al (78) measured arterial–hepatic venous concentration difference and hepatic blood flow to calculate splanchnic uptake of amino acids in anesthetized preoperative and postoperative cholecystectomy patients. The values for splanchnic uptake in preoperative patients are very similar to those for peripheral output of normal subjects—7 to 8 g N per day (Table 2). This value reflects net proteolysis of muscle protein after an overnight fast and, since liver is a net exporter of plasma proteins, proteolysis of plasma proteins that occurs in large part outside the splanchnic region (33). This similarity between peripheral output and splanchnic uptake holds for most of the individual amino acids as well. That agreement is not closer is not surprising, since several organs and tissues including kidney, heart, lungs, and brain are not measured by either procedure.

The effect of severe trauma with or without sepsis is to greatly increase muscle amino acid output (Table 2). Peripheral output of 20 to 23 g N is roughly equivalent to the expected negative N balance of these patients. The increase in splanchnic uptake a few hours after cholecystectomy, somewhat smaller than with trauma, is in keeping with the lesser severity of the insult. There are other, less complete studies in general agreement with the data of Table 1 (9, 31, 105, 126). Glutamine and alanine are the largest carriers and account for 60 to 70% of splanchnic uptake and 35 to 46% of peripheral output.

While the liver is responsible for most of the splanchnic uptake, the intestinal tract is not inactive. In dogs, intestinal uptake accounts for most of

Table 2 Peripheral output[a] and splanchnic uptake[b] of amino acids in normal, injured, septic, and postoperative humans

Amino acid	Peripheral output (g N/day/subject)						Splanchnic uptake (g N/day/subject)	
	Normal fasting		Trauma		Trauma & sepsis		Preop.	Postop.
	(Muscle protein)[c]		(Muscle protein)		(Muscle protein)			
Gln	(0.67)	1.99	(2.14)	6.02	(1.86)	4.16	2.95	5.11
Ala	(0.49)	1.32	(1.57)	3.23	(1.36)	2.84	2.58	5.35
Arg	(1.02)	1.23	(3.26)	2.12	(2.83)	2.09	1.09	2.01
Lys	(0.79)	0.69	(2.50)	2.17	(2.18)	1.97	0.66	1.17
Glu	(0.34)	−0.60	(1.08)	−0.23	(0.94)	0.05	−2.23	−2.72
Gly	(0.45)	0.40	(1.43)	1.55	(1.24)	1.37	0.25	1.06
Asn	(0.40)	0.30	(1.29)	1.10	(1.12)	0.71	0.92	1.23
His	(0.37)	0.46	(1.17)	1.10	(1.02)	1.07	0.42	0.70
Pro	(0.29)	0.27	(0.94)	0.94	(0.82)	0.71	0.27	0.51
Ser	(0.33)	0.02	(1.04)	0.41	(0.91)	0.42	0.53	0.84
Thr	(0.26)	0.25	(0.83)	0.78	(0.72)	0.79	0.42	0.68
Val	(0.32)	0.30	(1.01)	0.80	(0.88)	0.91	0.12	0.26
Leu	(0.41)	0.04	(1.31)	0.84	(1.14)	0.73	0.06	0.31
Iso	(0.24)	0.07	(0.77)	0.57	(0.67)	0.38	0.01	0.11
Phe	(0.18)	0.10	(0.58)	0.37	(0.51)	0.44	0.09	0.23
Tyr	(0.12)	0.10	(0.37)	0.34	(0.32)	0.29	0.20	0.35
Met	(0.11)	0.06	(0.35)	0.37	(0.31)	0.37	0.02	0.14
Cys	(0.08)	0.02	(0.25)	0.04	(0.22)	0.14	0.01	0.12
Trp	(0.07)	0.10	(0.23)	0.20	(0.20)	0.28	−0.11	0.08
Asp	(0.20)	0.02	(0.65)	0.05	(0.56)	0.07	0.03	−0.00
Total	(7.14)	7.14	(22.77)	22.75	(19.81)	19.79	8.28	17.59

[a] Calculated from the study of Pearl et al (91) of normal fasted subjects and severely traumatized patients with or without sepsis who survived, and were measured within 4 days of injury.

[b] Calculated from study of Lund et al (78) of preoperative and 75-min postoperative patients.

[c] Muscle protein composition is presented for comparison to peripheral output at each level of total nitrogen. Derived from Block & Weiss (17), assuming 50% of glutamate and aspartate are actually present as glutamine and asparagine.

the splanchnic uptake of glutamine. Indeed, under some conditions there is a hepatic output of glutamine (108). The kidney also takes up large quantities of glutamine (108).

The increased flow of amino acids from muscle to viscera in injury is accompanied by decreased rather than increased plasma amino acid concentrations, with the notable exception of phenylalanine concentrations, which usually increase (6, 79, 91). This decreased plasma concentration means that there is an increase in splanchnic clearance of amino acids with injury, approximately fivefold (91), that occurs simultaneously with the increase in peripheral output. In the studies of Pearl et al (91) peripheral

output and splanchnic clearance of amino acids in trauma or septic patients who later died were only half those of values listed for survivors in Table 2. Thus, failure to mount an adequate catabolic response in muscle and an appropriate increase in splanchnic clearance of amino acids is a sign of a poor prognosis (91).

Acute-Phase Proteins

Injury, burn, and infection cause an increase in plasma concentrations of acute-phase proteins (41). These proteins include (*a*) C-reactive protein, which has several functions including activation of complement, enhancement of phagocytosis, and regulation of cell immunity; (*b*) alpha-1-acid glycoprotein, which inhibits platelet aggregation and phagocytosis and may be involved in spacing of collagen fibers; (*c*) haptoglobin, which binds to and clears free hemoglobin from plasma; (*d*) alpha-1-antitrypsin and alpha-2-macroglobulin, which regulate serine proteases; (*e*) ceruloplasmin, a copper-containing protein probably involved in copper transport; and (*f*) fibrinogen. These proteins are synthesized in the liver or in white blood cells. After a lag period of approximately 6 hours, plasma concentrations or the rate of turnover of these proteins increases because of increased rates of synthesis; the extent of increase is related to the severity of the injury (41, 109). The acute-phase protein response appears to be nonspecific and mediated at least in part by interleukin-1 (41).

The plasma concentrations of other proteins, including transferrin and albumin, fall with injury or sepsis (94). This decline is not a result of decreases in synthesis rate; indeed, the rates of both synthesis and degradation of transferrin increase (132). The fall in albumin levels results from an increase in the transcapillary escape rate, from a normal rate of 5% per hour up to 10 or 15% per hour (42). Since this increase is due to increased vascular permeability, it affects other low–molecular weight proteins as well. Sustained hypoalbuminemia in severe injury and sepsis is related to large, sustained increases in extracellular, extravascular water.

Utilization of amino acids for net plasma protein synthesis requires only a small fraction of the increased supply of amino acids from muscle in injury. Some evidence points toward a general increase in liver protein synthesis in sepsis, but this increase remains to be established conclusively (55). At any rate, the bulk of amino acids from muscle are eventually degraded to urea and CO_2. To a large extent the carbon skeletons are first converted to glucose, which is then oxidized, mainly by the brain. Much of the utilization of amino acids occurs in the liver, but other tissues including gut mucosa, white blood cells, and the regenerating wound play important roles.

Glutamine

The importance of glutamine as an essential nutrient for rapidly dividing cells, including lymphocytes, macrophages, and intestinal mucosa, has been emphasized by Newsholme and colleagues (2, 86, 87). In the dog, glutamine uptake provides a major portion of the energy requirements of the intestine in the postabsorptive state, and uptake is doubled with laparotomy (106–108). Glutamine provides a major part of the energy requirements of lymphocytes and macrophages, but more important it serves as a basic building block for synthesis of nucleic acids and other constituents required for cell division (2, 86, 87). The glutamine requirements of lymphocytes, macrophages, and the entire immune and hemopoietic system greatly increase with injury or sepsis as cells proliferate. In addition the healing wound, which also contains rapidly dividing cells, requires glutamine. Studies in the acidotic rat show that the increased glutamine requirements of the kidney for ammonia formation are matched by increased glutamine output by muscle (97). In an analogous manner, the increased glutamine requirements for host defense and wound healing are met by increased muscle glutamine output (Table 2).

Peripheral output of amino acids has been compared with the expected output if it all came from hydrolysis of mixed muscle proteins (Table 2). Such a comparison is only approximate, since it is not known if the protein hydrolyzed, whether of muscle or plasma origin, has the exact composition of mixed muscle proteins. Furthermore, although red blood cells also contribute to interorgan exchange of amino acids (79), the data of Table 2 is based only on plasma measurements. Nevertheless, there is very good agreement in both normal and injured subjects for most of the essential amino acids, including lysine, histidine, threonine, valine, phenylalanine, methionine, and tryptophan, and for the semiessential amino acid tyrosine. The amounts of N carried by glutamine and alanine are much greater than the amounts of these amino acids obtained from proteolysis. Outputs of serine, leucine, isoleucine, and aspartate, however, are much less than that derived from proteolysis, and in two instances an uptake rather than an output of glutamate occurred. Nitrogen from these amino acids appears to be converted to glutamine and alanine for transport purposes. It is generally considered that the branched chain amino acids make a major contribution to glutamine and alanine synthesis in muscle. Under the conditions of Pearl's studies (Table 2)—normal fasting, trauma, or trauma with sepsis—glutamate, serine, and aspartate seem to be the major contributors; leucine and isoleucine make a modest contribution; and valine makes none at all.

Synthesis of glutamine and alanine requires not only a source of nitrogen but also a source of the carbon skeletons, α-ketoglutarate and pyruvate, respectively. These skeletons can be supplied by the same amino acids that

donate N. Glutamate is converted directly to glutamine by addition of ammonia. The activity of glutamine synthetase, which catalyzes this reaction, is increased in rat muscle during injury (1). Since glutamate contains only 1 N atom, its N carrying capacity is doubled on conversion to glutamine, which contains two N atoms. Therefore, for normal fasted subjects, the glutamate released from proteolysis and taken up by muscles from plasma with an N content of 0.94 g, on conversion to glutamine, will have an N content of 1.88 g, more than the difference between glutamine output and that produced from proteolysis (Table 2). Serine on deamination and dehydration produces pyruvate, which can be used directly for alanine synthesis or can be converted via oxalacetate and the citric acid cycle to α-ketoglutarate. On transamination aspartate yields oxalacetate, which can be converted either to pyruvate or α-ketoglutarate. In the three examples shown in Table 2, glutamate, serine, and aspartate can provide 71% to 96% of the carbon skeletons needed for alanine and glutamine formation. The remainder probably comes from glucose by way of pyruvate, constituting what has been termed the glucose-alanine cycle.

The concentration of muscle glutamine decreases by one half or more with injury or sepsis (6) and in other catabolic states. Free glutamine in muscle contains about 25 g of N. Release of one half in the first few days after injury would supply adequate amounts of glutamine to other tissues before the peak rate of muscle protein breakdown occurs, usually in the third to fourth day.

Increased glutamine supply to host defense, wound, and possibly other tissues seems to be a beneficial aspect of the increased protein breakdown in muscle due to injury or sepsis.

Protein Turnover

With major injury, burns, or sepsis, whole-body protein-turnover studies indicate a marked increase in protein degradation, as much as twofold (13, 14, 63, 67, 75, 93). Synthesis rates also increased—not as much as degradation rates when patients were in negative N balance on hypocaloric diets (13, 14, 75) but more than degradation rates in burned children in positive N balance given adequate nutrition (63). Increases in both synthesis and degradation rates, which constitute a form of substrate cycle, will increase energy expenditure. Since a minimum of four high-energy phosphate bonds are required for incorporation of a single amino acid into protein, we can estimate that the minimal cost of synthesis of 100 g protein is 70 kcal. Normal protein turnover in the adult is estimated at approximately 300 g per day. If this turnover was doubled with injury, it would increase energy expenditure by 210 kcal, a substantial fraction of the increase in resting energy expenditure caused by severe injury or burn. Increased excretion of 3-methylhistidine, derived from breakdown of actin and myosin, indicates large increases

in muscle as well as whole-body protein degradation rates in severe injury or sepsis (12, 50, 74, 102, 128). That much of the increase in 3-methyl histidine comes from skeletal muscle in these conditions has been confirmed by measuring leg output (93).

With elective surgery, there may be a decrease or no change in both whole-body and muscle protein degradation that occurs with a greater decrease in synthesis, although part of these effects may be due to accompanying hypocaloric nutrition (67, 93). Under these conditions there would be no increase in energy expenditure from protein turnover.

CARBOHYDRATE METABOLISM

Hyperglycemia

The association of hyperglycemia with injury is well known. For severely injured patients upon hospital admission, plasma glucose concentrations (mmol/l) averaged 9.6 ± 4.8 (SD) in one report on 247 patients (121), and approximately 7.8 ± 2.8 in a report on 53 patients (111). Values ranged as high as 17. By contrast, control values were 4.5 ± 0.3 (121). In both series, glucose concentrations correlated positively with the severity of illness. As shown by the standard deviations, glucose concentrations are much more variable in injured than in normal subjects. Insulin concentrations were also highly variable, equal to or above normal values, and not related to the severity of injury. It follows that the concentration ratio of insulin to glucose decreased with severity (111). Hyperglycemia in injured patients is associated with increased insulin resistance. This association is illustrated by a study by Jeevanandam et al (60) of normal subjects and septic or injured patients maintained for 3 days on either a low (8 kcal/kg/day) or high (30 kcal/kg/day) infusion of glucose followed by the other. No other nutrients were given. Plasma glucose concentrations (mmol/liter) for the low and high intakes, respectively, were 5.7 and 6.7 for normal, 7.4 and 10.4 for injured, and 9.0 and 14.4 for septic patients. Corresponding insulin concentrations (mU/liter) were 18 and 54 for normal, 31 and 134 for injured, and 59 and 129 for septic patients. Thus, both insulin and glucose levels were higher in the patients than in the controls at the low intake and increased more for the patients than for the controls when glucose intake was increased.

Gluconeogenesis and Glucose Turnover

Long and colleagues demonstrated by use of isotopes that the hyperglycemia of injury and sepsis was due to increased production of glucose rather than decreased utilization (77). Associated with the increased production was an increased rate of oxidation and a greatly increased rate of turnover of glucose. Wolfe et al (129) had similar findings in burn patients studied at an average of

36 days after injury. In addition they found increased recycling of glucose to lactate and back and increased clearance of glucose with burns. Oxidation of glucose increased less than turnover, so that the fraction of glucose turnover oxidized was less in the burn patients. Long et al (76) showed also that, although administration of 5% dextrose completely suppressed gluconeogenesis (measured with isotopic alanine) in normal subjects, septic patients receiving 5% dextrose had rates of gluconeogenesis twice as high as normal fasted subjects. Complete suppression of gluconeogenesis was subsequently shown in injured or septic patients, but only when more than 600 g of glucose was given per day (38).

The rate of glucose utilization by the burn wound was studied by Wilmore et al (125) in patients with 40% whole body burns. Arterial–femoral vein differences in amino acid concentration and leg blood flow were measured in one group with small (less than 10%) leg burns and another group with large (greater than 50%) leg burns. Cardiac output and whole body and leg O_2 consumption were similar in the two groups. In legs with small or large burns, leg blood flows were 4.2 and 8.0 ml/min/100 ml leg; glucose consumption was 0.04 and 0.34, and lactate production was 0.06 and 0.30 mg/min/100 ml leg, respectively. Thus, the glucose was used almost entirely by the wound and was not oxidized but converted to lactate. The arterio-venous difference for glucose across the leg was 4.3 mg/dl. If we assume that 40% of the leg blood flow went to the wound, the arterio-venous difference across the wound would have been 11 mg/dl. Extrapolated to a whole-body burn of 40%, these data indicate daily consumption by the burn wound of 200–300 g glucose per day, which is glycolyzed, not oxidized, and with the lactate returning to the liver to be converted again to glucose. The energy derived from glycolysis of glucose is 0.2 kcal/g. Thus, although glucose consumption of the wound is very large, energy requirements are modest, about 60 kcal/day—only a fraction of the increase in whole-body energy expenditure of 500 to 1000 kcal/day due to a 40% burn. Wolfe et al (130) found glycolytic-gluconeogenesis cycling of glucose measured isotopically in severely burned patients to be a minimum of 170 g/day. Since this amount would be required mainly for the wound, it is in good agreement with the data of Wilmore et al (125). Wolfe et al (130) estimate that this increase in gluconeogenesis-glycolytic cycling can account for a minimum of 5% and possibly a much higher percentage of the increase in energy expenditure due to the burn.

Oxidation of Preformed Glucose—Glycogen and Dietary Carbohydrate

Although total oxidation of glucose is increased, oxidation of preformed glucose—glycogen or dietary carbohydrate—is decreased with injury or sepsis. Total glucose oxidation measured isotopically includes glucose formed

from protein and the glycerol moiety of fat. Oxidation of preformed glucose is measured by indirect calorimetry and does not include glucose derived by gluconeogenesis. Askanazi et al (4) compared the effects of administering glucose and amino acid–based TPN in excess of energy expenditure for 5-day periods to malnourished patients and to injured or septic-stressed patients previously receiving 5% dextrose as sole nutrient. In the malnourished patients O_2 consumption rose by 3%, CO_2 production by 32%, resting energy expenditure (calculated from O_2 and respiratory quotient data) by 9%, and the respiratory quotient rose from 0.85 to 1.03; the latter value corresponds to synthesis of 427 kcal fat/day. In the septic or injured patients, O_2 consumption rose by 29%, CO_2 production by 56%, and resting energy expenditure by 34%; the respiratory quotient increased from 0.75 to 0.90. In these patients, continued fat oxidation occurred at 474 kcal/day, although the rate of intake of carbohydrate and protein was 123% of the rate of energy expenditure. Similar findings, as compared with nonstress patients, have been found by Stoner and colleagues in severely injured patients shortly after injury (72) and in septic patients in whom the rate of glucose oxidation varied inversely with the severity of sepsis (113). Giovannini et al (47) found the same for septic patients whose O_2 consumption was increased above normal but not in more severely ill septic patients whose O_2 consumption was impaired. Nanni et al (84) have made similar findings.

Results with insulin and glucose clamp techniques have also shown decreased forearm and whole-body uptake of glucose in septic (124) or injured and burned patients (16, 18). This insulin resistance in peripheral tissues is consistent with a postreceptor defect (16). In the study by Jeevanandam et al (60), normal subjects and injured or septic patients were kept on exactly the same rate of continuous glucose infusions (8 or 30 kcal/kg day) for 3-day periods as sole source of nutrients. On the low and high intakes, respectively, glucose oxidation and conversion to fat (as percentage of resting energy expenditure) was 37 and 104% for normal subjects, 18 and 65% for injured patients, and 15 and 52% for septic patients. The corresponding values for fat oxidation were 55 and −9% (fat synthesis) for normal subjects, 63 and 22% for injured patients, and 74 and 40% for septic patients. Daily resting energy expenditure averaged 21.8 for normal subjects and 24.1 kcal/kg for patients and was not affected by diet. Thus, even after 3 days of glucose infusion at rates 24% above energy expenditure, fat oxidation was substantial—22 and 40% of resting energy expenditure—in both injured and septic patients, whereas there was net fat synthesis in the normal subjects.

A necessary consequence of decreased rates of glucose oxidation or lipogenesis, at comparable rates of intake, is that rates of glycogen storage must be increased, since the only quantitively important fates of glucose are oxidation, conversion to fat, and storage as glycogen. Accumulation of

glucose, lactate, and pyruvate in body water is too small to account for the large differences observed between septic or injured patients and depleted patients or normal subjects. In an extreme case, it was calculated that 2 kg of glycogen was deposited by a severely septic patient in 4 days (7). This amount is much greater than expected from studies of normal subjects on eucaloric diets, in whom maximal changes are approximately 400 g (58, 59). It is of the same order, however, as values of 900 g glycogen deposited in 7 days by normal young men on very high carbohydrate intakes (98). Stoner et al (113) and others have questioned whether increased glycogen storage is likely in patients with trauma and sepsis, in whom there is increased sympathetic activity and increased levels of glucagon and cortisol, all of which oppose glycogen synthesis. Unless the premises of indirect calorimetry are severely flawed, however, there is no other possible fate of the glucose that is infused but not oxidized or converted to fat (21). Thus, the increases in glucose and insulin concentrations in response to glucose administration, which are much greater in stressed patients than in normal subjects, would seem to more than compensate for the increased counterregulatory hormones and sympathetic activity with respect to glycogen deposition.

In the absence of disease, rates of glucose oxidation at rest are a function of the rate of carbohydrate intake and the amount of stored glycogen. Increasing fat intake at a constant rate of glucose infusion decreases the rate of glucose oxidation and increases the rate of glycogen deposition (36), but this effect is only transient. As glycogen stores increase, they increasingly inhibit the rate of glycogen synthesis until it and the rate of glucose oxidation have returned to their previous values, even with continued fat infusion. These factors—diet and amount of glycogen stores—must be taken into account when rates of glucose oxidation are compared in stressed and normal subjects. In fasting subjects, carbohydrate oxidation is close to zero, whatever the pathologic state. (This statement refers to preformed carbohydrate, not that generated from protein.) In Jeevanandam's study (60), at 3 days on the high-glucose diet, rates of glucose oxidation and glycogen storage were very different between patients and controls, but with time the faster rate of glycogen storage in the stressed patients would cause a large buildup in glycogen that would tend to return the rates of storage and oxidation in the stressed patients to normal values. The question of glycogen storage is particularly important in glucose and insulin clamp studies, which are of short duration. If, for instance, glycogen stores were much higher in the injured, burned, or septic patients than in the normal controls, it might have accounted at least in part for the decreased glucose uptake in the patients, either in the whole body or the forearm.

Despite these caveats, we consider the evidence convincing that injured, burned, or septic patients oxidize less glucose, convert less glucose to fat, and

oxidize more fat than do normal subjects or malnourished patients when dietary conditions are the same. Nevertheless, the stressed patients respond to diet, specifically carbohydrate intake, by increasing glucose and decreasing fat oxidation, and if intake is high enough, by converting glucose to fat. Long (73) has challenged some of the data indicating reduced glucose oxidation and increased fat oxidation in stressed patients. He cites no opposing data, however, except that isotopic studies indicate increased glucose oxidation and that septic patients are capable of converting glucose to fat. As discussed above, neither observation is in conflict with decreased oxidation of preformed glucose, and we find the evidence in favor of this hypothesis to be overwhelming.

FAT METABOLISM

Plasma Concentrations

Plasma free fatty acid (FFA) concentrations are close to the normal range in subjects with injury, burn, or sepsis when fasting or given 5% dextrose (26, 27, 45, 50, 54, 60, 80, 88, 96, 104, 111), but the concentrations show wide variability. While some studies report mean values as much as 40% above those of controls (27, 54, 96), others report mean values as much as 25% below (45, 60, 88). Concentrations of FFA appear to be higher with moderate than with minor injury (111), but lower with severe than with moderate injury (104, 111). Some evidence suggests that the decrease in FFA concentration with increasing carbohydrate intake is attenuated in injured or septic patients (26, 27, 60, 80). There was no change in FFA concentrations in burn patients up to 50 days (54).

Plasma glycerol concentrations are markedly increased, up to threefold with injury, burn, or sepsis, during fasting or 5% dextrose infusions (26, 27, 45, 54, 60, 111). They are decreased with increasing carbohydrate intake, as in normal or depleted subjects; but at any level of intake, they are substantially higher in the septic or injured patients (26, 27, 60). Glycerol concentrations are initially high and tend to decrease somewhat with time. Even so at days 30–50 after thermal injury, glycerol concentrations remained 50% above control values (54). Some evidence suggests that the increase in glycerol concentration is correlated with the severity of injury (111).

Severe injury suppresses ketone body concentrations in the fasting state (50, 54, 104, 111). In the absence of nutrients this suppression is observed up to 3 days after burn (50). Initial ketone body concentration has been used to differentiate severe (<200 μm/l) from moderate (>200 μm/1) injury (104). With carbohydrate intake even as low as 8 kcal/kg day, ketone body concentrations decrease so much that differences are no longer discernible (60).

Fat Mobilization and Oxidation

Glycerol turnover in plasma is increased by as much as fivefold in injured or septic (26, 27, 60) or burned (130) patients either fasting or given 5% dextrose over the turnover levels of malnourished patients or normal subjects. Injury and sepsis (88) or burns (45, 130) also increase turnover of FFA but to a smaller extent, by 25 to 100%. In a study of burns (130) in which both turnovers were measured in the same patients, FFA turnover increased from 6.7 to 14.5 and glycerol turnover from 2.4 to 8.2 μmole/kg/min. These increases occur almost immediately and also as late as 20 days after injury. The same effect of carbohydrate loads to suppress glycerol turnover is seen in injured or septic patients (27, 60) as occurs in depleted patients or normal subjects (26, 60). Carbohydrate intake has little if any effect in suppressing FFA turnover in injury or sepsis (60, 88).

Fat oxidation is also increased with injury, but with fasting or 5% dextrose administration, this increase is of the order of 20% (60)—much less than the increase in glycerol and FFA turnover. Glycerol appearance in plasma represents the unidirectional rate of lipolysis in adipose tissue and muscle; neither contains glycerol kinase and therefore neither can metabolize glycerol. Appearance of FFA in plasma represents release of FFA from adipose tissue. Since adipose tissue can reesterify fatty acids, plasma appearance of FFA represents the difference between the amount produced by lipolysis and the amount reesterified (or oxidized in muscle). The difference in plasma turnover of glycerol and FFA (3 FFA per glycerol in triglycerides) is then an approximation of the amount of FFA reesterified in adipose tissue. The difference in glycerol turnover and fat oxidation, as measured by indirect calorimetry, represents whole-body reesterification, presumably mainly in adipose tissue and liver. The effects of injury, sepsis, and burns are to increase triglyceride hydrolysis (fat mobilization) much more than fat oxidation. Reesterification of fatty acids, or substrate cycling of triglycerides, is increased as much as four times (27, 60, 130) and remains high even with sustained hypercaloric administration of glucose (26, 27, 60). Wolfe et al (130), by simultaneous measurements of glycerol and FFA turnover, found most of the increase in triglyceride cycling to occur in adipose tissue. The total increase accounted for a minimum of 10% of the increase in whole-body energy expenditure in these burn patients.

Injury and sepsis effect a large increase in fat mobilization, a large increase in triglyceride cycling, and a smaller increase in fat oxidation. This change occurs with little alteration in FFA concentrations. Ketone body concentrations and presumably, therefore, production are below normal. This decline is not due to decreased plasma FFA concentration but must reflect a diversion of FFA taken up by the liver to reesterification, instead of oxidation or ketone body synthesis. This diversion may be due to increases in both

glucose and insulin concentrations, uniformly observed in the flow phase of injury.

NEUROENDOCRINE MEDIATORS OF THE METABOLIC RESPONSE

The metabolic changes that occur with injury and sepsis are determined by corresponding neuroendocrine changes [for recent reviews, see (10, 19, 44, 115)]. In turn, the ability of injury and sepsis to cause these neuroendocrine changes is mediated by two major systems. One is the afferent nervous system, which is stimulated by a variety of receptors, including pain receptors near the injury and baroreceptors and chemoreceptors, that respond to changes in pressure and chemical content of blood. These signals are processed in the hypothalamus, which stimulates both the sympathetic system and increased pituitary hormone secretion (110, 115). The metabolic response to trauma in the operative and immediate postoperative periods can be prevented with spinal analgesia, which prevents transmission of these signals (61). The other mediating system consists of a number of polypeptide cytokines, which are elaborated by white blood cells at the site of injury or infection. These have, in addition to their local actions, general systemic effects and thus act as wound hormones. The best characterized and probably most important of these cytokines are interleukin-1 (29, 90, 92) and tumor necrosis factor, or cachectin (11a, 71). Interleukin-1 stimulates induction of fever, granulopoeisis, synthesis of acute-phase proteins, and hyperinsulinemia. It acts on the hypothalamus, supplementing and augmenting the effects of afferent nervous stimuli. Interleukin-1 also acts directly on a variety of tissues, including lymphocytes, granulocytes, macrophages, bone marrow, the reticuloendothelial system, liver, muscle, and endocrine organs. Its actions are mediated, at least in part, by production of prostaglandin E_2. There are at least two kinds of interleukin-1, α and β, with similar molecular weights (17,000 daltons) but different peptide sequences. A smaller (4000-dalton) peptide with similar activities is found in the blood of septic patients and is probably a breakdown product of interleukin-1. Tumor necrosis factor is elaborated in response to bacterial toxins but also to bacteria themselves and other stimuli. It appears to be the major factor mediating the effects of endotoxin. Its activities overlap with those of interleukin-1, and it can stimulate production of interleukin-1.

Both the cytokines and the afferent nervous system have observed properties that should enable either to cause the neuroendocrine changes resulting in the metabolic response to injury and sepsis. Both systems can probably cause the same qualitative pattern of response, which is regulated in large part by the hypothalamus. However, we have very little information as to the quan-

titative contribution of the two systems or their various components to the actual development of the metabolic response in human injury, sepsis and burn. Apparently, the afferent nervous system is the most important initially. The effect of spinal analgesia, which is to eliminate the metabolic response during and immediately after surgery, indicates that the cytokines do not yet have an effect. Studies of the acute effects of trauma in the isolated dog leg led Hume and Egdahl to conclude that there was no wound hormone (32). Most studies of the afferent nervous system, however, have been performed in the early acute phase of trauma or shock (10); in the ensuing flow phase of injury, the cytokines likely play an increasing, if not the dominant, role. Much more work is needed to define precisely the quantitative roles of the two systems.

The most important and best understood neuroendocrine changes in the flow phase consist of increases in plasma levels of insulin and the counterregulatory hormones, glucagon, cortisol, epinephrine, and norepinephrine. Increases in norepinephrine are considered to represent mainly spillover from increased sympathetic activity and have no general hormone functions until they reach concentrations well above 1000 ng/liter. Fairly typical values have been reported by Wolfe et al (130) for burn patients after an overnight fast and at an average of 20 days after injury. These values are, compared with those of normal subjects, as follows: insulin (μU/ml) 19.6 and 11.3; glucagon (pg/ml) 325 and 143; cortisol (μg/dl) 32 and 8; epinephrine (pg/ml) 376 and 35; and norepinephrine (pg/ml) 1558 and 184. For all these hormones, concentrations are variable, and reports range (in terms of increase above normal) from one tenth to ten times these values. The important roles of cortisol, glucagon, and epinephrine (representing sympathetic activity) were demonstrated by Shamoon et al (99), who infused them into normal subjects at a rate to give plasma concentrations similar to those seen in injury. The investigators were able to simulate the hyperglycemia, hyperinsulinemia, and insulin resistance of injured patients. Subsequent studies have shown an increase in energy expenditure and muscle protein catabolism as well (11, 46).

SUMMARY

The metabolic response to injury may be presumed to be adaptive, at least in terms of days to weeks. In the wild state where these patterns developed, the wounded organism has poor access to food and must live off its own stores of nutrients, mainly fat, and tissue proteins, mainly from muscle. In fasting, without injury, the organism conserves protein. In this condition there are reductions in blood glucose and insulin levels and increases in glucagon and fatty acid levels. Insulin-dependent tissues stop using glucose; the liver

converts fatty acids to ketone bodies, which increase about 100-fold in the fasting human; and the brain substitutes ketone bodies for more than one half of what would otherwise be an obligatory consumption of 100 to 150 g glucose per day in humans. This substitution spares the amount of muscle protein required for gluconeogenesis in liver and kidney, and net N losses can be reduced to less than 6 g per day (25). Energy expenditure decreases up to 30% (23).

The fasted, injured subject has additional nutritional requirements. Regeneration of the wound and rapidly proliferating white and red blood cells require a source of amino acids and other nutrients. Synthesis of acute-phase proteins required for host defense also needs amino acids. In addition, the wound, regenerating tissue, and white blood cells require large amounts of glucose for glycolysis. That the wound is poorly vascularized may be the major reason for hyperglycemia, which provides a glucose gradient between plasma and tissue high enough for extraction of sufficient glucose. The wound does not increase net consumption of glucose; rather, lactate returns to the liver to be converted again to glucose. Hyperglycemia due to the wound increases the requirements for gluconeogenesis from muscle protein, however. The high concentrations of counterregulatory hormones, cortisol, epinephrine, and glucagon will minimize glucose utilization by insulin-sensitive tissues, despite high concentrations of both glucose and insulin, but these hormones are not able to prevent suppression of ketone body synthesis in the liver. As a result, the brain continues to derive almost all its energy from oxidation of glucose. Synthesis of this glucose in liver is the biggest consumer of amino acids made available by net degradation of muscle protein.

The metabolic response to injury, initiated by afferent nerve impulses and cytokines and mediated by increases in counterregulatory hormones and sympathetic activity, is a well-coordinated, well-regulated process controlled largely by the hypothalamus. Increased consumption of nutrients occurs simultaneously with but is not caused by an increase in production. The increased amino acids made available by muscle protein breakdown are consumed by at least three important processes: (*a*) increased glutamine utilization by rapidly dividing cells for synthesis of nucleic acids and other key tissue components; (*b*) increased consumption of all amino acids for protein synthesis in regenerating, hemopoietic, and visceral tissues; and (*c*) increased gluconeogenesis in the liver. However, most amino acid concentrations decrease, indicating that the consuming tissues are pulling them in rather than that muscle is pushing them out. Indeed, increased plasma amino acid concentrations, indicating failure of the liver to remove them, is a sign of approaching death (39, 91). Likewise, increased fat oxidation occurs with greatly increased fat mobilization but little change in plasma FFA con-

centrations. This lack of change in FFA levels indicates that release of FFA from adipose tissue, controlled by rates of lipolysis and reesterification, is still sensitively tuned to FFA requirements in other tissues, despite the change in neuroendocrine milieu. Body temperature and the thermoneutral zone increase, presumably to provide more favorable conditions for host defense and wound regeneration. This increase, in turn, increases energy expenditure. Although the increased energy expenditure can be reduced by raising ambient temperature, it cannot be eliminated, since increased substrate cycles involving carbohydrate, lipid, and protein are obligatory and contribute substantially to the increase in energy expenditure.

These neuroendocrine changes, which favor survival in the fasting subject, cause increased nutrient resistance. Much more carbohydrate is needed to reduce gluconeogenesis and much more protein is needed to reduce muscle catabolism than is required for uninjured fasting subjects.

Furthermore, diet-induced thermogenesis of nutrients is higher in injured or septic patients than in normal or depleted subjects. Maintaining N balance in severely stressed subjects may not always be possible or desirable. Nevertheless, in time, the effects of severe N loss will themselves add significantly to mortality and morbidity. Thus, reasonably adequate nutrient intake should be maintained in stressed patients despite their resistance to nutrients (24).

The altered pattern of fuel utilization in injury and sepsis should not be viewed as an impairment to be overcome but rather as a successful adaptation of the fasted subject. Nutritional as well as other therapies should be aimed at maintaining the adaptive features of this pattern while preventing undue body wasting.

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