Amino Acid Derangements in Patients With Sepsis:

Treatment With Branched Chain Amino Acid Rich Infusions

HERBERT R. FREUND, M.D., JOHN A. RYAN, JR., M.D., JOSEF E. FISCHER, M.D.

From the Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Sepsis is a major catabolic insult resulting in modifications in carbohydrate and fat energy metabolism, and leading to increased muscle breakdown and nitrogen loss. Insulin resistance, which develops in sepsis, decreases glucose utilization, but plasma insulin levels are sufficiently elevated to prevent lipolysis, resulting in a further energy deficit. The availability of fuels in sepsis is therefore limited, and the body resorts to muscle breakdown, gluconeogenesis, and amino acid oxidation for energy supply. Previous work has not defined, however, the exact alterations in amino acid metabolism. Therefore, the following studies were undertaken. Blood samples were drawn from fifteen patients in whom the diagnosis of sepsis was clinically established; the samples were analyzed for amino acid, β-hydroxyphenylethanolamines, glucose, insulin and glucagon concentrations. The plasma amino acid pattern observed was characterized by an increase in total amino acid content, due mainly to high levels of the aromatic amino acids (phenylalanine and tyrosine) and the sulfur-containing amino acids (taurine, cystine and methionine). Alanine, aspartic acid, glutamic acid and proline were also elevated, but to a lesser degree. The branched chain amino acids (valine, leucine and isoleucine) were within normal limits, as were glycine, serine, threonine, lysine, histidine and tryptophan. Those patients who did not survive sepsis had higher levels of aromatic and sulfur-containing amino acids as compared to those patients surviving sepsis. On the other hand, those patients surviving sepsis had higher levels of alanine and the branched chain amino acids. In a second group of five patients with overwhelming sepsis accompanied by a state of metabolic encephalopathy, a parenteral nutrition solution consisting of 23% dextrose, and an amino acid formulation enriched with branched chain amino acids was administered. In these five patients, normalization of the plasma amino acid pattern and reversal of encephalopathy was observed. The following sequence of events may be postulated: The septic patient develops insulin resistance in the peripheral tissues, primarily muscle, while the adipose tissue is much less affected. The insulin resistance and the inability to utilize fat leads to increased muscle proteolysis. Muscle breakdown results in release into the blood of enormous amounts of various amino acids; the muscle itself is able to oxidize the branched chain amino acids, supplying the muscles' own energy requirements and alanine for gluconeogenesis. The extensive muscle proteolysis coupled with relative hepatic insufficiency occurring early in sepsis results in the appearance in the plasma of high levels of most of the amino acids present in muscle, particularly the aromatic and the sulfur-containing amino acids. The outcome of patients with sepsis might be positively affected by combined therapy with glucose, insulin and branched chain amino acids.

THE METABOLIC CONSEQUENCES of infection have been the subject of increased interest in recent years, with particular attention being paid to deranged energy metabolism in sepsis and septic shock. Characteristically, in sepsis, proteolysis and negative nitrogen balance[2,4,16] are accompanied by the suppression of lipolysis[16] and a diabetic-type glucose tolerance curve with insulin resistance and decreased ability to oxidize glucose in the periphery,[3,10] These derangements in energy metabolism formed the theoretical basis for the treatment with hypertonic glucose, insulin and potassium.[3,9,13] However, although infection and sepsis are major catabolic stimuli, only limited insight into derangements in protein and amino acid metabolism in sepsis has been evident. Previous experiments from other laboratories has suggested that in overwhelming sepsis, a peripheral energy deficit is present; this deficit is generally made up by the increased breakdown of lean body mass and the oxidation of amino acids, particularly the branched chain amino acids.[16] However, the exact alterations in the other amino acids have not been fully investigated.

In the following studies, patients with established clinical sepsis were studied from the standpoint of amino acid metabolism, glucose, insulin and glucagon levels. The results reveal a deranged amino acid pattern in sepsis, generally consisting of elevated total

Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

Reprint requests: Josef E. Fischer, M.D., Department of Surgery, Hyperalimentation Unit, University of Cincinnati Medical Center, Cincinnati, Ohio 45267.

Supported in Part By U.S.P.H.S. Grants AM-15347 and AM-19124.

0003-4932/78/0900/0423 $00.85

TABLE 1. *Causes of Sepsis in 15 Patients*

Cause	Number of Patients
Abdominal sepsis	9
Perforated diverticulitis	
Perforated colonic cancer	
Postoperative intra-abdominal abscess	
Mesenteric occlusion—gangrenous bowel	
Cholangitis	
Urologic sepsis	2
Venous catheter sepsis (central)	2
Burn sepsis	2
	15

amino acids secondary to the elevation of aromatic and sulfur-containing amino acids. It appears that one can differentiate between those patients who may or may not survive their septic episode on the basis of a plasma amino acid pattern. In another group of patients with a similar yet more severely deranged amino acid pattern and a metabolic type of encephalopathy, an amino acid solution rich in branched chain amino acids and deficient in aromatic amino acids was infused, with resulting normalization of a plasma amino acid pattern and awakening from metabolic encephalopathy coincident with, of course, therapy of the septic episode. The results suggest that in patients with sepsis, muscle proteolysis and early hepatic function derangements conspire to produce a plasma amino acid pattern which is quite similar to that seen in hepatic failure and hepatic coma. Application of principles similar to those utilized in the treatment of hepatic encephalopathy, such as the infusion of glucose, insulin and the branched chain amino acids, appears to result in amelioration of the coma-like state and perhaps improvement in the overall metabolic status. Metabolic intervention in patients with sepsis may prove to be an important therapeutic modality.

Material and Methods

Fifteen patients hospitalized for various reasons at the Massachusetts General Hospital form the basis for this study. All patients suffered an episode of severe sepsis at some stage of their hospital stay. The causes of sepsis are specified in Table 1. Sepsis was defined clinically as a state of severe infection (fever, chills, prostration, leukocytosis) with widespread bacterial invasion sometimes resulting in a state of hypoperfusion and vascular collapse, and usually occurring as a result of an acute abdominal catastrophe, gangrenous bowel or as a direct result of bacterial introduction into the blood stream. Positive blood cultures were not *sine qua non* for establishing the diagnosis of sepsis, but were encountered in 10 of the 15 patients. Patients with bacteremia but without clinical symptomatology of sepsis were excluded.

Once the diagnosis of sepsis was clinically established, blood samples were drawn for amino acid analysis, B-hydroxyphenylethanolamines (octopamine, and phenylethanolamine), glucose, insulin and glucagon assay.

Amino acid determinations in plasma were carried out by a Beckman 121-MB amino acid analyzer, on plasma which was deproteinized with 4% sulfosalicylic acid. Octopamine and phenylethanolamine were measured simultaneously by a radioenzymatic method modified after Molinoff.[14] Plasma immunoreactive insulin was measured by combined radioimmunoassay[25] and plasma immunoreactive glucagon was measured by radioimmunoassay using a 30 K antibody.[20] Statistical analyses are based on Student's t-tests.

Treatment was also initiated in five additional patients with abdominal sepsis, similar to the first group of 15 patients, but in the presence of grade II–IV metabolic encephalopathy.[1] The patients were treated with an amino acid solution (F080) enriched with branched chain amino acids (35% branched chain amino acid compared to 22% in Freamine)[6,7] and decreased aromatic amino acids; amino acid pattern, β-hydroxyphenylethylamines, insulin and glucagon in the plasma were followed daily. A clinical assessment of encephalopathy grades was based on the criteria of Adams and Foley.[1]

Results

The amino acid pattern in the first group of 15 patients is summarized in Fig. 1. There was a significant increase in the plasma concentrations of the aromatic amino acids, phenylalanine and tyrosine. Phenylalanine levels increased to a mean of 340% of the norm, and tyrosine 194%. There were also marked increases in

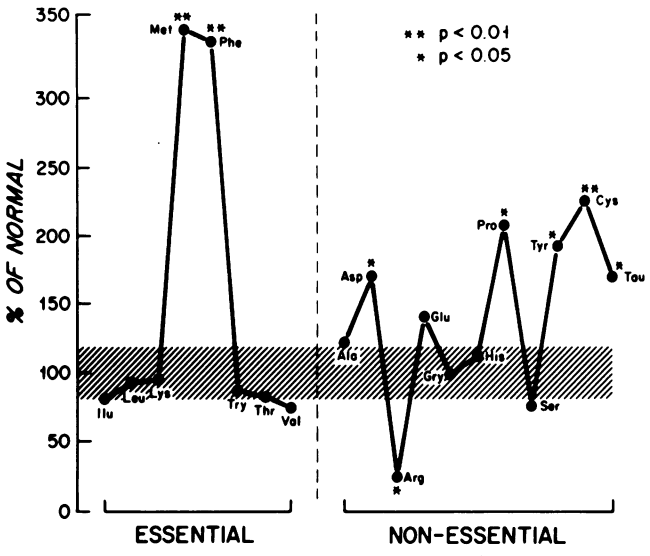

FIG. 1. Mean plasma levels of amino acids, represented as percentage of normal in 15 acutely septic patients. The shadowed area represents normal + S.E.M. values.

the sulfur-containing amino acids, with a mean rise of 170% for taurine, 225% for cystine and 351% for methionine. Lesser amino acids elevations include proline (207%), aspartic acid (171%), glutamic acid (141%) and alanine (123%). The branched chain amino acids (leucine, isoleucine and valine), lysine, threonine, serine, histidine, glycine and tryptophan were within normal limits. Arginine levels decreased to 24% of normal.

The mean total free amino acids was elevated from a norm of 2126.3 n mol/ml to 2511.6 n mol/ml, (118% of norm) while total branched chain amino acids remained within normal limits (397.88 n mol/ml vs. 324.6 n mol/ml). The ratio of branched chain amino acids to total amino acids decreased to 65% of its normal value. Octopamine and phenylethanolamine, β-hydroxyphenylethanolamine derivatives of phenylalanine and tyrosine, which may function as false or co-neurotransmitters (FNT),[6,7] were markedly elevated in six patients, all of whom also had markedly elevated levels of aromatic amino acids. In three additional patients, mild elevations in FNT levels were associated with small increases in plasma aromatic amino acid concentrations. Six patients with no change in FNT levels had low to markedly increased aromatic amino acid levels, so the association is not perfect.

Four patients out of the initial group of 15 patients were in a state of metabolic coma resulting from their septic state. No direct correlation could be found between the state or degree of coma and the plasma levels of FNT and amino acids to differentiate these four patients from the others.

Blood sugar levels ranged from 50 mg% to 459 mg% (mean 166 ± 45 mg%). Serum insulin levels ranged from

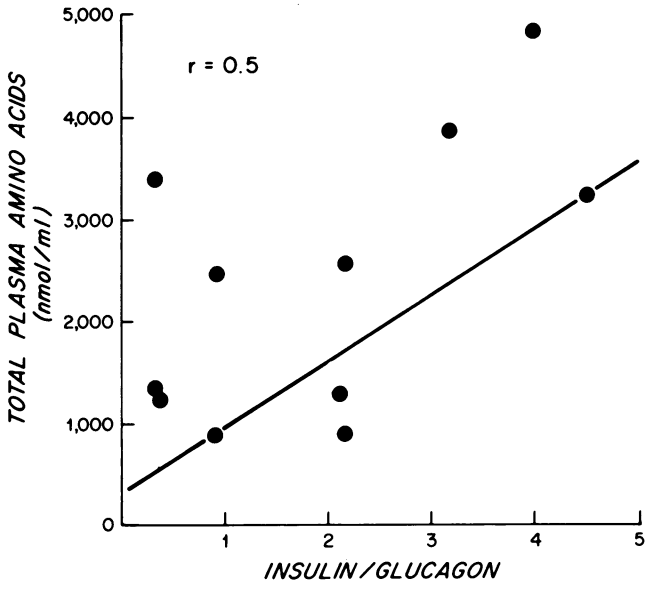

FIG. 2. Regression analysis of total plasma amino acid levels (nMol/ml) against insulin/glucagon ratio in 11 septic patients. There is no significant correlation between the two variables.

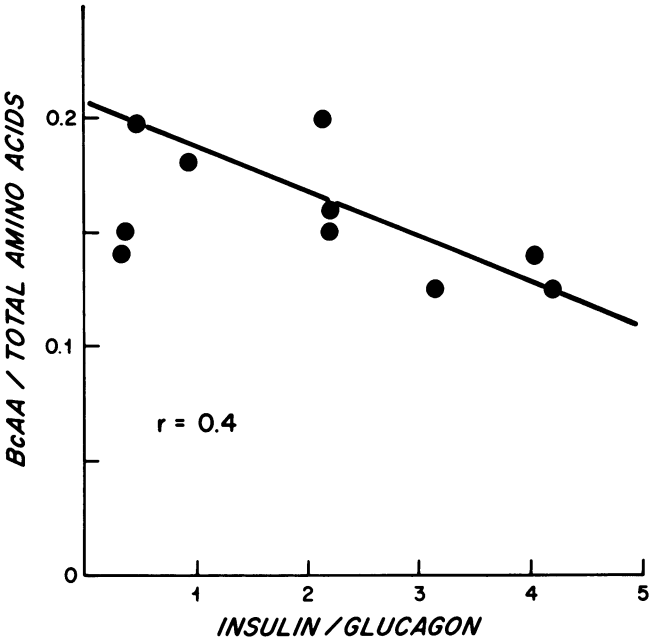

FIG. 3. Regression analysis of branched chain to total amino acid ratio against insulin/glucagon ratio in ten septic patients. There is no significant correlation between the two variables.

7.5 to 145 uu/ml (mean 37 ± 10 uu/ml). Serum glucagon levels ranged from 150–530 pg/ml (mean 361 ± 34). High glucagon levels were not necessarily associated with high levels of alanine, or low levels of insulin. The insulin to glucagon molar ratio (I/G × 23.33) was 3.61 ± 1.31, being 233% of normal. No correlation was found between glucose levels and the I/G ratio (10 patients). Increase in the I/G ratio was followed by an increase in total amino acid in the plasma; however, linear regression analysis of this relationship proved statistically nonsignificant (Fig. 2). The ratio between branched chain and total amino acids decreased with the increase in I/G ratio (Fig. 3) which also proved statistically nonsignificant. Similarly, the relationship between the branched chain amino acid level and I/G ratio (Fig. 4) was not statistically significant.

A correlation was found between certain amino acid levels and survival rates. Those patients who did not survive sepsis had higher levels of aromatic and sulfur-containing amino acids as compared with those patients surviving sepsis. On the other hand, those patients surviving sepsis had higher levels of alanine and the branched chain amino acids. Although statistically, only cystine, methionine, total branched chain and alanine levels were significantly different for differentiating survivors from nonsurvivors, we assume that with a larger population of patients, all amino acids would have been statistically significant (Table 2, Fig. 6). In order to express this mathematically, a ratio between phenylalanine plus methionine as numerator, and tyrosine plus total branched chain amino acids as denominator was calculated. This ratio, which in the nor-

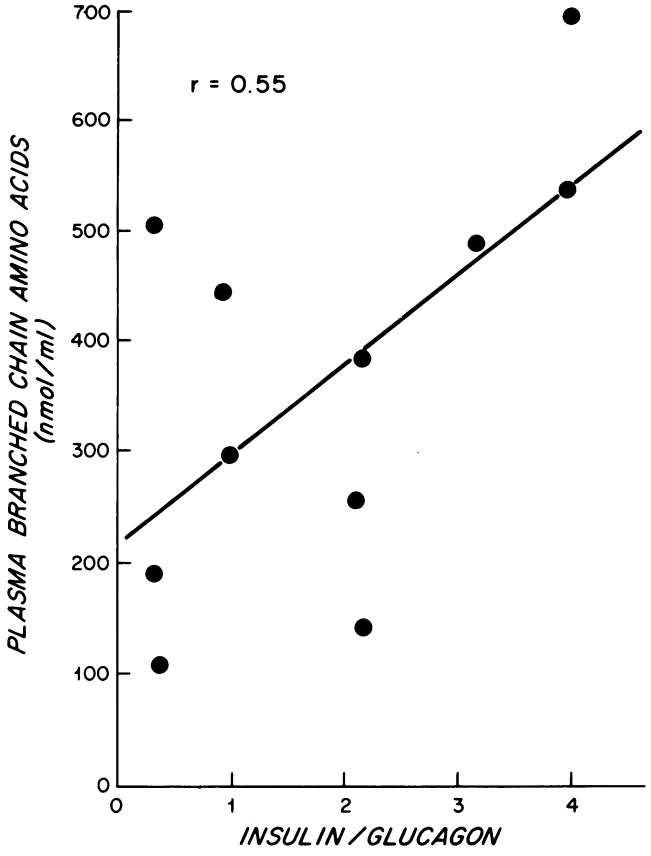

FIG. 4. Regression analysis of plasma total branched chain amino acid levels (nMol/ml) versus insulin/glucagon ratio in eleven septic patients. There is no significant correlation between the two variables.

mal patient is 0.16, was 0.43 ± 0.08 in the survivor group as opposed to 1.99 ± 0.65 in nonsurvivors ($p < .05$).

In a second group of five patients with overwhelming sepsis accompanied by a state of metabolic encephalopathy, grades II–IV,[1] a parenteral nutrition solution consisting of 23% dextrose, and an amino acid formulation (F080) enriched with branched chain amino acids (35% vs. the usual 22% in parenteral nutrition solution) was administered.[6,7] In these five patients, normalization of the plasma amino acid pattern (Table 3) and reversal of encephalopathy was observed. Phenylalanine and tyrosine which at the start of therapy were elevated to a mean of 255 and 198% respectively, and cystine and methionine which were increased to 336 and 321% respectively, returned to normal levels. Taurine levels which had been elevated to 154% normal at start of therapy, remained elevated. Alanine, valine, leucine and isoleucine levels which were within normal levels during sepsis, remained normal during the infusion of F080 (Fig. 6).

Comments

Sepsis is a major catabolic insult leading to increased muscle breakdown and nitrogen loss.[2,8,11,15,16] This progressive proteolysis is accompanied by modified carbohydrate and fat energy metabolism. The insulin resistance which develops in sepsis decreases glucose utilization and renders patients catabolic, very much as patients with low insulin levels. However, plasma insulin levels are sufficiently elevated to prevent lipolysis, resulting in further energy deficit.[3,18] The availability of fuels in sepsis is therefore limited and the body turns to muscle breakdown and amino acid oxidation (mainly BCAA) to supply energy needs.

The first group of 15 septic patients demonstrated an increase in total plasma amino acid concentrations due mainly to high levels of the aromatic amino acids (phenylalanine and tyrosine) and the sulfur-containing amino acids (taurine, cystine and methionine). Also elevated, but to a lesser degree, were alanine, aspartic acid, glutamic acid and proline. The branched chain amino acids (valine, leucine, and isoleucine) were within normal limits, as were glycine, serine, threonine, lysine, histidine and tryptophan. Arginine levels were exceptionally low. Wannemacher, et al. in a series of animal and human experiments demonstrated a decrease in total plasma free amino acids during various bacterial and viral infections.[22,26] Regarding individual amino acids, Wannemacher demonstrated a marked increase in plasma phenylalanine, tyrosine, and tryptophan levels with an increase in the phenylalanine

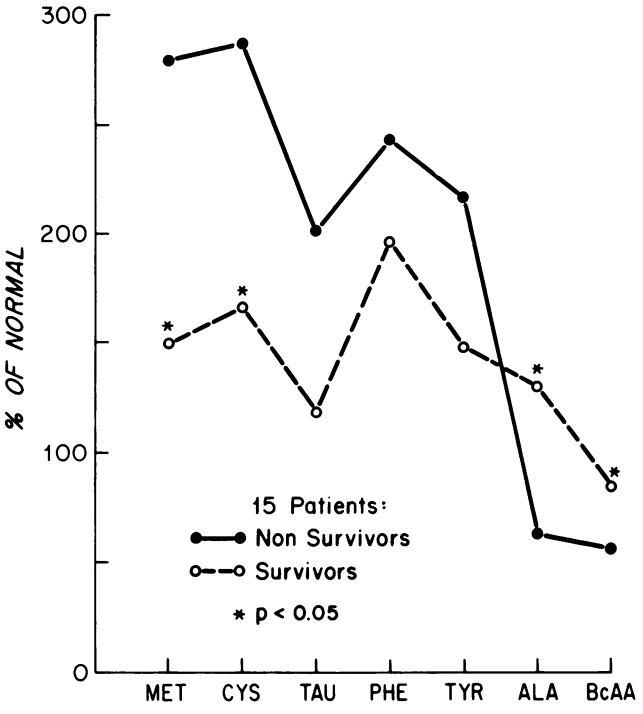

FIG. 5. Graphic display of differences in plasma amino acid patterns in patients who ultimately survived and those who did not survive an episode of sepsis. Those who survived had higher (more normal) levels of alanine and the branched chain amino acids and lower (more nearly normal) plasma concentrations of the aromatic amino acids (phenylalanine and tyrosine) and the sulfur containing amino acids methionine and cysteine.

to tyrosine ratio.[24] Others found high levels of phenylalanine and alanine in the blood of septic patients,[12] and an increased release of alanine and glutamine from skeletal muscle of infected rats[23] and septic patients[16] The plasma amino acid pattern of our patients is qualitatively similar to the one seen in patients with acute liver failure, namely a "breakdown" pattern resulting from extensive protein degradation, in this case, mainly muscle protein, without reutilization of the released amino acids. In our patients there was a significant increase in plasma amino acids usually metabolized by the liver (aromatic and sulfurcontaining amino acids). However, unlike hepatic failure, alanine levels were only mildly elevated and the branched chain amino acids were within normal levels, suggesting continued utilization of these amino acids, or relatively normal release from muscle.

In evaluating the results reported herein, and other reports in the literature, the following sequence of events may be postulated:

The septic patient develops a diabetic type of glucose tolerance curve which is due to insulin resistance in the peripheral tissues, primarily the muscle,[10,19] while the adipose tissue is much less affected.[16,18] The insulin resistance and the inability to utilize fat occurs, paradoxically at a time when the body is in desperate need of easily accessible energy, and leads to increased proteolysis.[4] The source of most of the mobilized protein is muscle tissue, while visceral protein is spared. As the muscle is insulin-resistant during sepsis and unable to utilize glucose, and as fatty acids and ketones are not available, the muscle turns to the use of its own amino acids. Muscle breakdown results in release into the circulation of large amounts of various amino acids, with the exception of the branched chain amino acids, which the muscle itself is able to oxidize. The oxidation of the branched chain amino acid serves to supply the muscles' own energy requirements, as well as the nitrogen and perhaps even the carbon skeleton for alanine synthesis in the muscle. The alanine so produced in the muscle is transferred to the liver where it is used for gluconeogenesis.[5] The utilization of BCAA for muscle energy and of alanine for gluconeogenesis explains the normal levels of BCAA and the only mildly

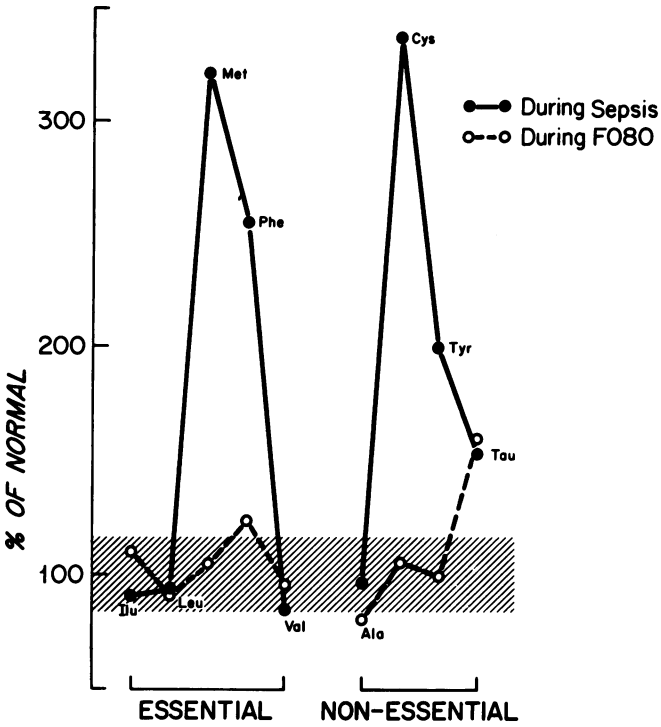

FIG. 6. Mean plasma levels of aromatic, sulfur containing, branched chain amino acid and alanine in five patients during acute sepsis and during treatment with a branched chain amino acid rich solution (F080). Note the normalization of the amino acid pattern during the infusion of F080 which also coincides in all five patients with reversal of metabolic encephalopathy.

elevated level of alanine in our patients. Of the remaining amino acids released into the circulation as a result of muscle proteolysis, the aromatic and sulfur-containing amino acids cannot be utilized by the muscle, but must be metabolized by the liver for the formation of new plasma and hepatic proteins or used for energy metabolism by liver or other visceral organs. During infection the liver is synthesizing acute phase plasma proteins.[24] However, except for these, protein synthesis by the liver is reduced because of early hepatic dysfunction occurring in sepsis,[21] or because of the lack of essential amino acids like the BCAA which are utilized to supply muscle energy requirements. The net end result of muscle breakdown with release of amino acids into the blood, coupled with relative

TABLE 2. *Plasma Amino Acid Levels in Surviving and Nonsurviving Septic Patients (n mol/ml)*

	Normal	Total (15 pts.)	Survivors	Nonsurvivors
Taurine	52 ± 6	88 ± 13	62 ± 14	105 ± 18
Cystine	42 ± 14	94 ± 20	70 ± 20*	121 ± 42
Methionine	24 ± 4	84 ± 16	36 ± 15*	73 ± 16
Tyrosine	46 ± 8	88 ± 17	68 ± 16	100 ± 35
Phenylalanine	47 ± 5	144 ± 24	92 ± 13	178 ± 22
Alanine	334 ± 34	410 ± 83	437 ± 57*	211 ± 87
Total BCAA	398 ± 40	325 ± 35	340 ± 89*	232 ± 70

* $p < 0.05$.

TABLE 3. *Amino Acid Levels (n mol/ml) in Five Patients During Sepsis and Coma Following Treatment with F080*

	Normal	Sepsis—Coma	F080-Postawakening
Taurine	52 ± 6	80 ± 19	83 ± 41
Cystine	42 ± 14	141 ± 17	44 ± 11
Methionine	24 ± 4	77 ± 20	25 ± 2
Phenylalanine	47 ± 5	121 ± 21	58 ± 6
Tyrosine	46 ± 8	91 ± 14	45 ± 5
Alanine	334 ± 34	325 ± 67	265 ± 32
Valine	218 ± 29	185 ± 25	207 ± 36
Leucine	117 ± 10	109 ± 14	108 ± 18
Isoleucine	63 ± 9	57 ± 8	69 ± 14

hepatic incompetence, is an excessive accumulation of all the unused amino acids in the patient's plasma, as demonstrated by a "catabolic" pattern of amino acids in our patients' plasma. Exceptional, of course, were the BCAA used by the muscle and alanine utilized for gluconeogenesis which were present at normal or near normal levels.

When comparing the plasma amino acid pattern of the surviving and nonsurviving patients a very clear distinction can be made (Table 2). Surviving patients had decreased levels of aromatic and sulfur-containing amino acids and higher levels of branched chain amino acids and alanine, as compared to the group of nonsurvivors. Whether these differences represent better preserved hepatic function in the survivors or maintenance of better overall energy metabolism is not clear. Better maintenance of hepatic function in survivors is plausible, as hepatic failure is a common mode of death in septic patients.

In the second group of five septic patients an attempt was made to restore the plasma amino acid pattern to normal hyperalimentation, using 23% glucose, insulin and an amino acid mixture rich in branched chain amino acids, but poor in tryptophan, methionine and phenylalanine. In these five patients the resulting normalization of the plasma amino acid pattern (Fig. 6) was probably due to decreased efflux of amino acids from the skeletal muscle, as suggested also *in vitro* experiments by Odessey, et al.[17] Thus, the role of the branched chain amino acids in correcting some of the metabolic problems in sepsis is to provide an exogenous source of energy to skeletal muscle and preventing skeletal muscle breakdown, and to control, independent of their energy satisfying needs, the efflux of various amino acids from skeletal muscle.

Simultaneously, with the normalization of plasma amino acid pattern (and the treatment of sepsis) metabolic coma thought to be secondary to sepsis cleared, and the patients improved to normal neurological status. Previous work from this laboratory has suggested that in hepatic failure in which a similar plasma amino acid pattern is present, normalization of plasma amino acid pattern results in improved neurotransmission, which is secondary to decreased brain toxic aromatic amino acids by principles of competition at the blood brain barrier and perhaps improvement in neurotransmitter profile.[6,7] The decrease in plasma aromatic amino acids as well as sulfur-containing amino acids may have had a causal relationship with awakening from metabolic encephalopathy. If this is the case, it raises the possibility of a common mechanism of all forms of metabolic encephalopathy, hepatic, septic and possibly uremic as well. Further investigations will be necessary to prove or disprove the accuracy of this suggestion.

Conclusions

Energy deficit in sepsis increases the utilization of the branched chain amino acids for energy metabolism. This selective use of the BCAA to satisfy energy requirements requires extensive muscle breakdown and proteolysis. The extensive muscle proteolysis coupled with a relative hepatic insufficiency results in the appearance in the plasma of high levels of most of the amino acids present in muscle, particularly the aromatic and the sulfur-containing amino acids. Plasma levels of the aromatic, the sulfur-containing, the branched chain amino acids, and alanine correlated well with survival. Those patients surviving sepsis had lower levels of aromatic and sulfur-containing amino acid with higher levels of the branched chain amino acids and alanine. This relationship might prove beneficial in predicting a patient's prognosis. Manipulation of the deranged plasma amino acid pattern of septic patients by the infusion of an amino acid mixture rich in branched chain amino acids and poor in aromatic amino acids resulted in the normalization of the plasma amino acid pattern, and awakening from septic-metabolic coma. The outcome of patients in sepsis might be positively affected by the combined treatment of glucose, insulin and branched chain amino acids.

References

1. Adams, R. D. and Foley, J. M.: Neurological Disorder Associated with Liver Disease in Metabolic and Toxic Diseases of the Nervous System. Res. Publ. Assoc. Nerv. Ment. Dis., 32:198, 1953.
2. Cuthbertson, D. and Tilstone, W. J.: Metabolism During the Post Injury Period. Adv. Clin. Chem., 12:1, 1969.
3. Clowes, G. H. A., O'Donnell, T. F., Ryan, N. T. and Blackburn, G. L.: Energy Metabolism in Sepsis: Treatment Based on Different Patterns in Shock and High Output Stage. Ann. Surg., 179:684, 1974.
4. Duke, J. H., Jorgensen, S. B. Long C. L. and Kinney, J. M.: Contribution of Protein to Caloric Expenditure Following Injury. Surgery, 68:168, 1970.
5. Felig, P: The Glucose Alanine Cycle. Metabolism, 22:179, 1973.
6. Fischer, J. E., Funovics, J. M., Aguirre, A., James, J. H., and Keane, J. M., Wesdorp, R. I. C., Yoshimura, N., Westman, T: The Role of Plasma Amino Acids in Hepatic Encephalopathy. Surgery, 78:276, 1975.
7. Fischer, J. E., Rosen, H. M., Ebeid, A. M., James, J. H., Keane, J. M. and Soeters, P. B.: The Effect of Normalization of Plasma Amino Acids on Hepatic Encephalopathy in Man. Surgery, 80:77, 1976.
8. Fleck, A. and Munro, H. N.: Protein Metabolism after Injury. Metabolism, 12:783, 1963.
9. Hinshaw, L. B., Peyton, M. D., Archer, L. T., Black, M. R., Coalson, J. J. and Greenfield, L. J.: Prevention of Death in Endotoxin Shock by Glucose Administration. Surg. Gynec. Obstet., 139:851, 1974.
10. Howard, J. M.: Studies of the Absorption of Glucose Following Injury. Ann. Surg., 141:321, 1955.
11. Kinney, J. A.: Energy Requirement of the Surgical Patient. In: Manual of Surgical Nutrition. Philadelphia, Saunders, 1975 p. 223.
12. Marchuk, J. B., Finley, R. J., Groves, A. C., Wolfe, L. I., Holliday, R. L. and Duff, J. H.: Catabolic Hormones and

Substrate Patterns in Septic Patients. J. Surg. Res., 23:177, 1977.
13. Manny, J., Schiller, M., Manny, N., Rabinovici, N. and Hechtman, H: Beneficial Effects of Glucose-Insulin Potassium Following Endotoxemia. Surg. Forum, 28:88, 1977.
14. Molinoff, P. B., Landsberg, L. and Axelrod, J: J. Pharm. Exp. Therapy, 170:253, 1969.
15. Moore, F. B., Olesen, K. H., McMorrey, J. D. and Parker, H. J.: The Body Cell Mass and its Supporting Environment. Philadelphia, W. B. Saunders, 1963, p
16. O'Donnell, T. F., Clowes, G. H. A., Blackburn, G. L., Ryan, N. T., Benotti, P. N. and Miller, J. D.: Proteolysis Associated with a Deficit of Peripheral Energy Fuel Substrate in Septic Man. Ann. Surg., 80:192, 1976.
17. Odessey, R., Khairallah, E. A. and Goldberg, A. L.: Origin and Possible Significance of Alanine Production by Skeletal Muscle. J. Biol. Chem., 249:7623, 1974.
18. Ryan, N. T., Blackburn, G. L. and Clowes, G. H. A.: Differential Tissue Sensitivity to Elevated Endogenous Insulin Levels During Experimental Peritonitis in Rats. Metabolism, 23:1081, 1974.
19. Ryan, N. T., George, B. C., Egdahl, D. H. and Egdahl, R. H.: Chronic Tissue Insulin Resistance Following Hemorrhagic Shock. Ann. Surg., 180:402, 1974.
20. Unger, R. H., Eisentrout, A. M., McCall, M. S. and Madison, L. L.: Glucagon Antibodies and an Immunoassay for Glucagon: J. Clin. Invest., 40:1280, 1961.
21. Vaidyamath, N., Oswald, G., Trietley, G., Weissenhoffer, W., Moritz, E., McMenamy, R. H., Birkhahn, R., Yuan, T. F. and Border, J. R.: Turnover of Amino Acids in Sepsis and Starvation: Effect of Glucose Infusion. J. Trauma, 16:125, 1976.
22. Wannemacher, R. W., Powanda, M. C. and Dienterman, R. E.: Amino Acid Flux and Protein Synthesis After Exposure of Rats to Either Diplococcus Pneumonia or Salmonella Typhimurium. Infect. Immun., 10:60, 1974.
23. Wannemacher, R. W., Klainer, A. S., Dinterman, R. E. and Beisel, W. R.: The Significance and Mechanism of an Increased Serum Phenylalanine-Tyrosine Ratio During Infection. Am. J. Clin. Nutr., 29:997, 1976.
24. Wannemacher, R. W.: Key Role of Various Individual Amino Acids in Host Response to Infection. Am. J. Clin. Nutr., 30:1269, 1977.

Discussion

Dr. George H. A. Clowes, Jr.: I think we've heard a most important paper this afternoon, in terms of taking care of the really sick patients who confront us on surgical services, namely, those that are grossly septic. I'd like to make three points. I want to show you some data from our own studies that confirm what Dr. Fischer has said, to talk briefly about the mechanism that probably produces this situation and, finally, I would like to point up the significance of his suggestion of using the branched chain amino acid solution.

(Slide) This diagram emphasizes that the blood levels that have been presented to you are the result of what happens to the amino acids in the central part of the system, in the liver and kidney and their production in the periphery.

Dr. Fischer has emphasized that the branched chains and certain others are oxidized, NH_3 is released and transaminated to pyruvate to make alanine, a glucogenic amino acid, along with glutamine. The other amino acids have to be released under those conditions, because everything isn't there for resynthesizing the protein in the muscle.

Now, with this in mind, we have examined the exchange of amino acids across the periphery. (Slide) Here we have the various groups that he's talked about. This is alanine, and the hatched bar represents our overnight normal fasting values. The white bar represents Fehlig's data from adaptive starvation.

You will notice that in every category the process is enhanced when liver failure is present. In other words, the branched chain amino acids are released in greater quantities, but at the same time the production of alanine glutamine from them is greatly enhanced. Here we have the sulfur-containing ones, methionine, which he mentioned and most important of all are the aromatics, tyrosine and phenylalanine.

Now, this represents approximately 40 cases, and I think that these values are significant.

(Slide) Looking at the values of the amino acid contents, or concentrations, in the blood, the branched chain amino acids actually are lower, but they're not as low as we see in adaptive starvation. There's something else going on. The important thing is that the phenylalanine, even in sepsis without liver failure, is elevated, and it's significantly elevated in those with liver failure.

(Slide) Other experimental and clinical work shows that the liver is frequently injured in the septic patient. To illustrate, this patient developed liver failure without a trace of it beforehand following a severe septic process in his abdomen. He's comatose, he's not healing his wound, and he's overwhelmed with infection and has pulmonary failure.

(Slide) Now, here's the record of that patient. You'll notice that his bilirubin progressively rose, and, importantly, whenever we infused enough amino acids, particularly thyronine, we got the alanine up and the isoleucine up, but the phenylalanine, that bad actor in terms of what happens to the central nervous system, also rose.

His plasma albumin fell in spite of infusing approximately three times the normal body content of albumin in the course of this disease. This, then, is the real trouble that leads to this difficulty.

I again would like to congratulate Dr. Fischer on having come up with the answer to this problem, as he has just demonstrated to you. I wish I had had the ability to use amino acid mixture, but the FDA gets in the way, and Dr. Fischer had the courage and persistence to overcome this roadblock. We now are seeing what I think is a tremendous step forward.

Dr. Thomas F. Nealon, Jr. (New York, New York): Drs. Cheng and Mills in our department have been following amino acids, as well as the usual biochemical parameters, in trying to evaluate the best nutritional routines for patients with advanced cancer, primarily, and they asked that I make two points concerning that.

In their experience, the lowered branched chain amino acids need not be limited to the patients with overwhelming sepsis. Patients with inadequate nutrition, particularly inadequate calories, have the same problems; so the basic concepts may be applicable to more than just the cases that they spoke about.

Secondly, when you are in a depleted situation in terms of the availability of these fine new solutions, we feel that the use of the TPN solution, and particularly if one uses an adequate amount of calories, is at least the best solution possible, until we do have these acids.

Dr. Francis D. Moore (Boston, Massachusetts): Joe Fischer and his group at the MGH have taken a remarkable leadership position in relating amino acid abnormalities in the blood to disease entities often encountered by the surgeon, and we are indebted to them for taking this particular tack in this complicated field and giving us this remarkably interesting and useful paper.

I would like to comment, and ask two questions, and I'm grateful for the chance to have seen the manuscript.

Drs. Schoenheimer, Sprinson, and Rittenberg, working in the late thirties at Columbia with the first stable and radioactive isotopes of common elements, summarized their work in the Dunham Lectures in a book entitled *The Dynamic State of Body Constituents*. This work was the milestone on which all modern understanding of protein metabolism is based. They stated, in approximately these words, that the metabolic fate of amino acids is most importantly determined not by the number or location of the amino and carboxyl groups, but by the shape of the carbon skeletons.

(Slide) Here are these three interesting characters, the branched chain amino acids, the only ones that have a branch in their skeleton. When messenger RNA rolls by and says, "We need to put a branch in