Proline Metabolism in Sepsis, Cirrhosis and General Surgery

The Peripheral Energy Deficit

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Proline metabolism was prospectively evaluated in patients with surgical sepsis, cirrhosis, and elective surgical procedures. Significant correlations were found in the septic patients. Proline levels were an excellent indicator of mortality and correlated positively with lactate levels. Lactate and proline were inversely related to total peripheral resistance and oxygen consumption. In septic patients who expired: the metabolites involved in the hepatic pathways of proline degradation were elevated in proportion to proline; lactate, glutamate and proline were directly related to pyruvate; lactate/pyruvate ratios were constant; proline, glutamate, ammonia, ornithine, lactate and pyruvate levels were inversely proportional to oxygen consumption and total peripheral resistance. The primary defects in sepsis seem to be metabolic; there are very strong correlations in time between physiology and metabolism; the metabolic abnormality seems to be a progressive energy-fuel deficit, possibly from a progressive inhibition of substrate entry into the Krebs cycle.

THE METABOLISM of septic man seems to be distinctly different from that of fasting man.[3-5,10,14,19] In the fasting state, the economic utilization of fatty acids and ketone acids occurs as the blood glucose level declines so that protein may be spared.[14] The metabolic course of the seriously septic patient, however, is marked by derangements of glucose, fat and amino acid metabolism.[3-5,10-13,19,20] The plasma amino acid pattern of the septic patient has characteristic alterations in the levels of aromatic, branch chain, and sulfur containing amino acids.[4,12] Recent reports have also indicated that proline is elevated during sepsis.[4] A detailed study of proline metabolism in septic man, however, has not been done.

This present study prospectively explores the relationship of serum proline to survival and mortality, and to metabolic and physiologic processes in patients with serious surgical sepsis, cirrhosis, or who are undergoing major elective surgery. Evidence presented indicates that the serum proline level is a key marker in the deranged metabolic response to sepsis and can be closely correlated in time to concurrent physiologic and metabolic changes and mortality.

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Materials and Methods

Thirty-seven patients admitted to the Intensive Care Unit of the Buffalo General Hospital were prospectively studied with simultaneous physiologic-hormonometabolic profiles. These patients were divided into three groups: septic (12 patients), cirrhotic (nine patients), and those who had neither sepsis nor cirrhosis but were undergoing major surgery (16 patients).

All patients classified as septic had clinical signs of severe infection and presented in septic shock with gram negative bacteremia. Septic sources were fecal peritonitis from colonic perforation (seven patients), intra-abdominal abscesses (three patients), and biliary sepsis from extrahepatic calculous biliary obstruction (three patients).

All nine cirrhotic patients had an alcoholic history and biopsy proven micronodular cirrhosis. They all were encephalopathic at the time they were studied. Five were postoperative for protocaval decompression; two had placement of LeVeen shunts; one had repair of a Mallory-Weiss tear; and one had no surgery but was being treated conservatively for bleeding esophageal varices.

All patients in the nonseptic noncirrhotic control group were studied preoperatively and were admitted

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TABLE 1. *Patient Demographic Data*

	Septics	Cirrhotics	Nonseptic, Non-cirrhotics	All Patients
Age (years)	60.1 ± 2.5	53.8 ± 1.4	53.2 ± 2.4	55.8 ± 2.1
male	7	6	9	22
female	5	3	7	15
Survived	3	7	14	24
Number died	9	2	2	13
ICU stay (days)	17.5 ± 5.1	10.8 ± 2.5	7.5 ± 1.9	11.5 ± 2.0

All values expressed as mean ± SEM.

to the Intensive Care Unit for postoperative monitoring and care. A wide variety of surgical procedures were performed, including: distal pancreatectomy, colectomy, cholecystectomy, gastrectomy, splenectomy, coronary artery grafting, and mitral valve replacement.

All patients in all groups received appropriate medical and surgical treatment. All received similar nutritional support in the form of intravenous solutions of glucose and amino acids (Freamine II) with a glucose calorie to nitrogen ratio of 100 to 1. The solution was given at a rate of 1 g protein/kg/24 hours. Exogenous colloid was limited to 30–40 g/day as albumin and/or plasma protein fraction. The group of inotropic agents used was the same in all patients and consisted of digoxin, dopamine (3–5 μg/kg/min) and isoproterenol (0.25–0.75 μg/min). All patients had adequate renal function at the time of their study, with GFR's greater than 25 ml/min. No exogenous steroids, insulin or intravenous fat were used throughout the study period. All patients were NPO during the study period. No patients were known to have diabetes mellitus.

The physiologic–hormonometabolic profiles were performed preoperatively when feasible and daily postoperatively on each patient until the patient expired or became well enough to leave the Intensive Care Unit. All patients who left the Intensive Care Unit were subsequently discharged from the hospital. The physiologic profile was accomplished using cardiogreen dye according to the method described by Siegel et al.[16,17] The parameters determined were cardiac index (CI), pulmonary dispersive blood volume, cardiac mixing time (tm, a measure of cardiac contractility), systolic ejection time, arterial blood pressure, stroke volume, total peripheral resistence (TPR), arteriovenous oxygen content difference (A-VO_2) and oxygen consumption index (O_2C/M^2). Concurrently, a metabolic profile was performed on a sample of arterial blood. Thirty minutes prior to sampling, the infusion of all nutritional solutions was stopped in order to achieve a steady state of plasma substrate concentrations. Glucose, pyruvate, lactate, triglycerides, acetoacetate, beta-hydroxybutyrate, glycerol and total free fatty acid concentrations were determined by standard laboratory techniques. Branch chain, aromatic, proline, basic and sulfur containing amino acids were analyzed using a Jeol amino acid analyzer with a one colume technique.

Prior profile studies seemed to indicate that a high and/or rising plasma proline concentration might be correlated with mortality in sepsis. The metabolic–physiologic data, therefore, were correlated in time with the plasma proline values. In so doing, the best correlations were between the highest plasma concentration in the postoperative course for each patient and the concurrently determined values for cardiac index, total peripheral resistance, oxygen consumption and the plasma concentrations of lactate, pyruvate, glutamate, ornithine, and ammonia. It is the results of this later analysis that are to be reported.

Values of individual parameters were analyzed using the Student's t-test. Analysis of the correlation between variables was accomplished using linear and curvilinear functions for best fit with calculation of the correlation coefficient, r. Probability values calculated for each r indicate that $r = 0$. Mean values are expressed as the mean ± SEM.

Results

Patient demographic data are listed in Table 1 for the septic, cirrhotic, and nonseptic, noncirrhotic groups. The mean age of all patients was 55.8 ± 2.1 years and the mean Intensive Care Unit stay was 11.5 ± 2.0 days. The septic patients were older than the cirrhotics ($p > .05$) and had a longer intensive care unit stay than the nonseptic control group ($p > .05$).

All Patients

The relationship between the highest plasma proline levels and survival for the various patient groups is shown in Figure 1. The septic group clearly had higher proline levels than the nonseptic, noncirrhotic control group ($p < .005$) and the cirrhotic group ($p < .010$). The mean value was not significantly different between the cirrhotics and the control although it was slightly elevated in the cirrhotics. When all patients were considered, the proline levels were much higher in those who expired ($p < .0005$); no patient with a proline level greater than 700 micromol/l survived. The relationship between plasma proline level and mortality was also evident when the septics and the cirrhotics were considered separately ($p < .05$, $p < .01$, respectively). The cirrhotic group, however, contained only two patients who died, and even though statis-

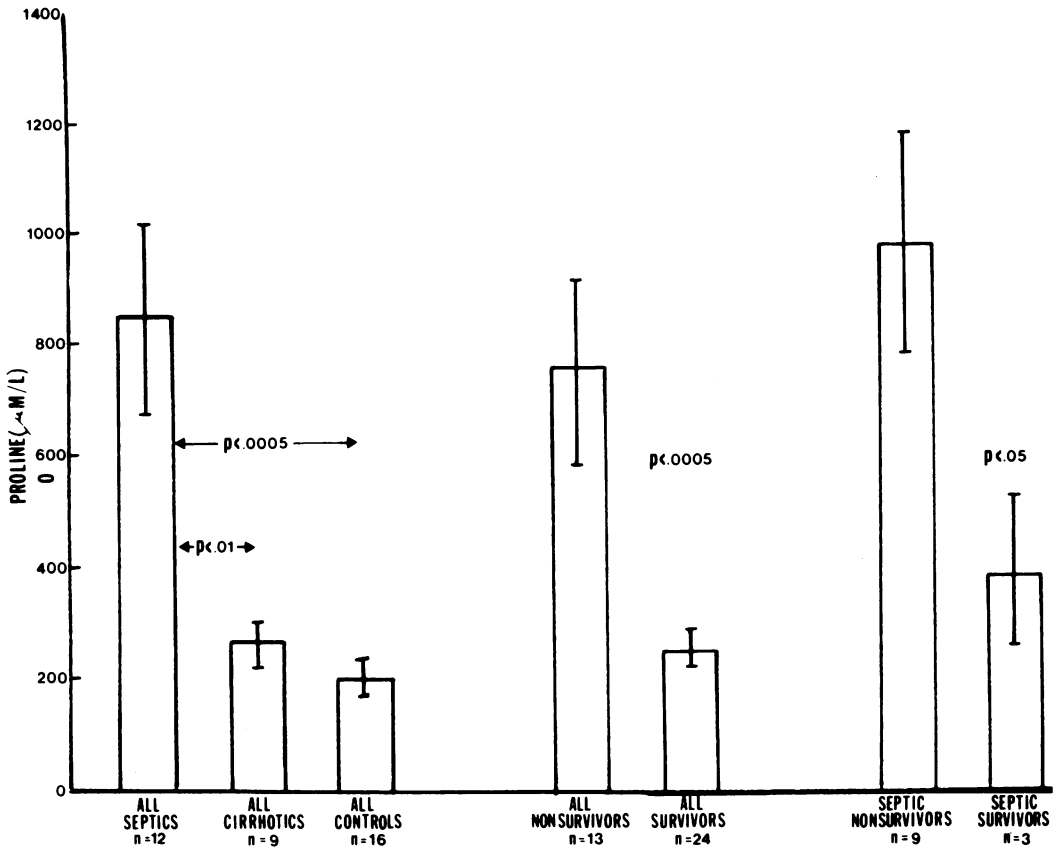

FIG. 1. Histogram of plasma proline level relative to disease state and survival. Proline level is elevated in sepsis and strongly correlated with survival or mortality.

tically significant, the result must be interpreted with caution. The difference between the survivors and the nonsurvivors in the control nonseptic, noncirrhotic group was not significant, although proline levels tended to be low in those who died.

Compared to the nonseptic, noncirrhotic control group, the septics had significantly higher lactate (4307 ± 737 μM/l vs. 2016 ± 395 μM/l; $p < .01$) and significantly lower oxygen consumption (110 ± 11 ml/min/M^2 vs 143 ± 10 ml/min/M^2; $p < .05$) at the time of highest proline concentration. No septic patients with serum lactate levels greater than 4000 μmol/l survived. In those patients who died, the highest proline levels correlated with the time to death. Patients who were closest to death exhibited the highest proline values, and no patient with levels greater than 1200 μmol/l survived longer than four days. (Fig. 2)

In the septic patients, correlations between the highest recorded proline and simultaneous lactate values were found to exist, as well as between lactate and TPR and proline and TPR. Plasma proline increased in an exponential fashion with rising lactate (Fig. 3). The correlation of TPR with proline was linear, with higher proline levels being associated with a lower TPR (Fig. 4). A similar relationship was found between lactate and TPR (Fig. 5).

The correlation between proline and lactate was also evident in the cirrhotic patients (Fig. 3). It was not statistically, significantly different from that in the septic group. No other relationships among the variables were statistically significant in the cirrhotic group, however.

In the nonseptic, noncirrhotic control group no statistically significant correlations were found to exist among the same parameters discussed for the septic and cirrhotic groups. It should also be noted that no statistically sound correlations were found in any of the patient groups when the above parameters were analyzed at times of the highest recorded lactate levels.

Nonsurviving Septic Patients

The metabolism of proline and pyruvate were investigated in nonsurviving septic patients by an analysis of the plasma level of substrates involved in the metabolism of these two substances. The seven patients studied represented a group of terminally ill septic patients with an increasingly deranged metabolism terminating in death within seven days of the highest recorded proline levels. The plasma substrate relationships that were statistically significant are shown in Figures 6 and 7.

Figure 6 shows the relationship between glutamate concentrations and time to death; and between the

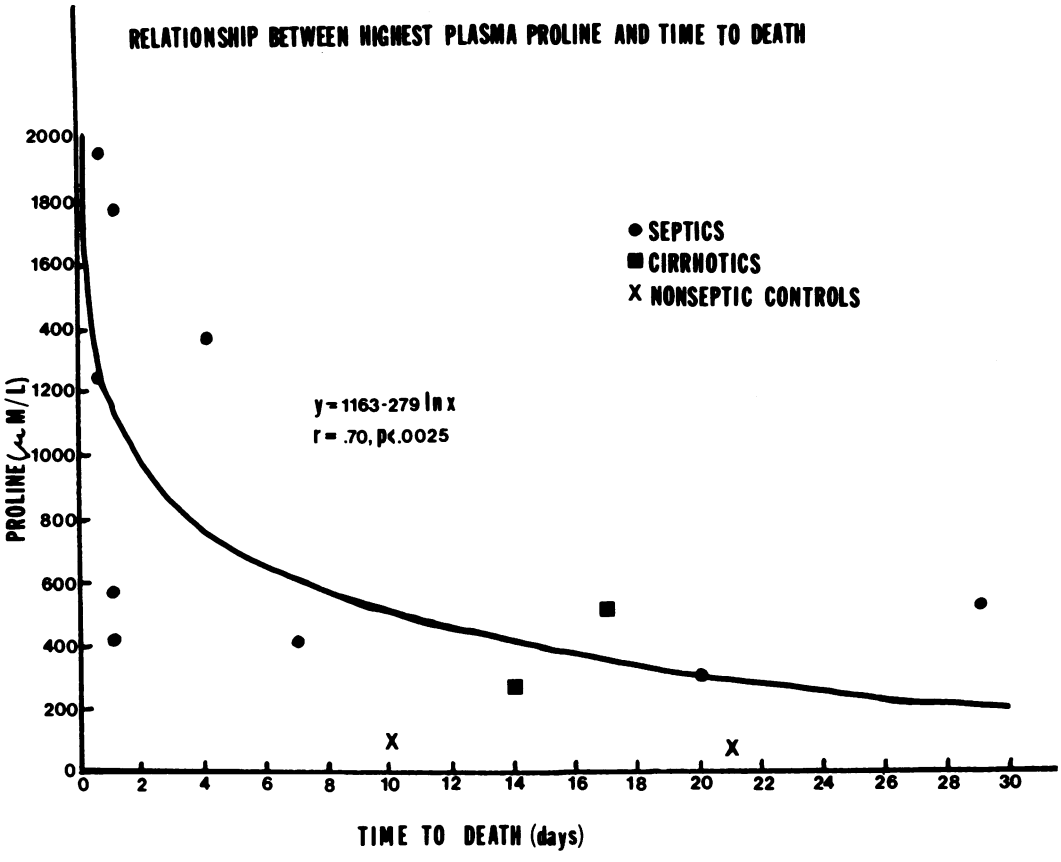

FIG. 2. Plasma proline concentration rises as death approaches in patients with fatal sepsis or cirrhosis. No patient with a plasma proline ≥700 μM/l survived.

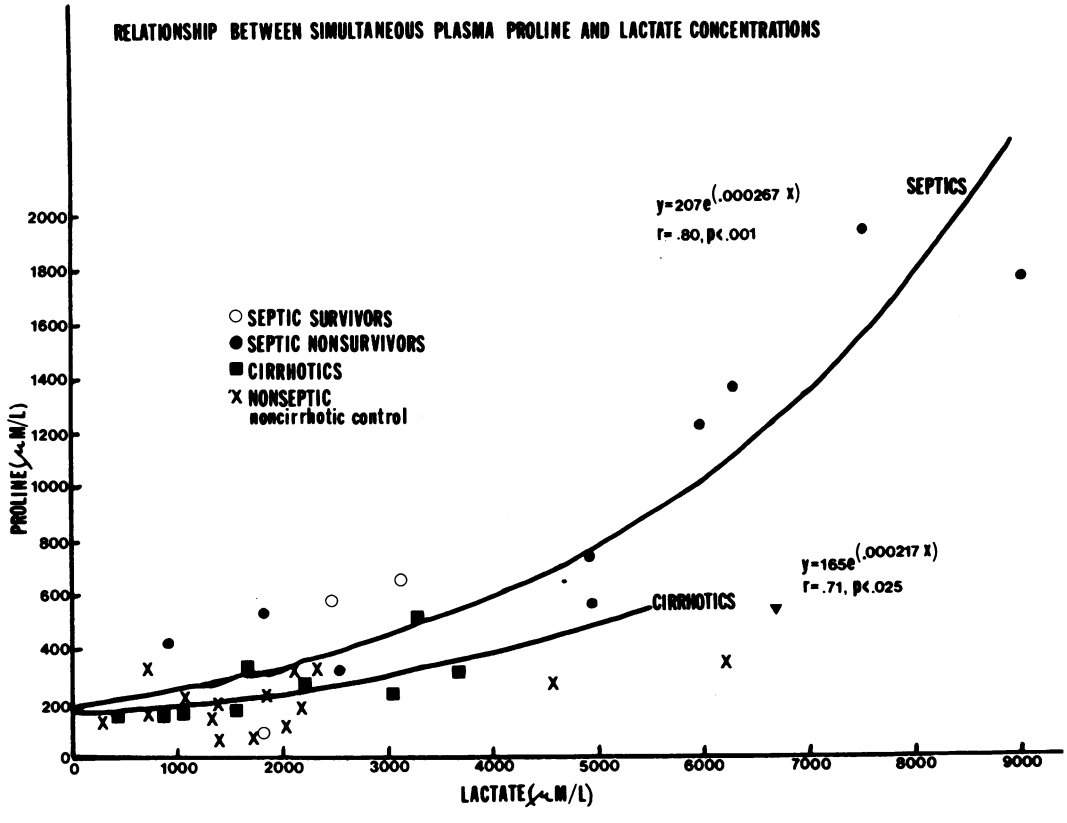

FIG. 3. Plasma proline and lactate levels are tightly related in patients with sepsis or cirrhosis. No such correlations were found in the nonseptic, noncirrhotic patients undergoing elective surgery.

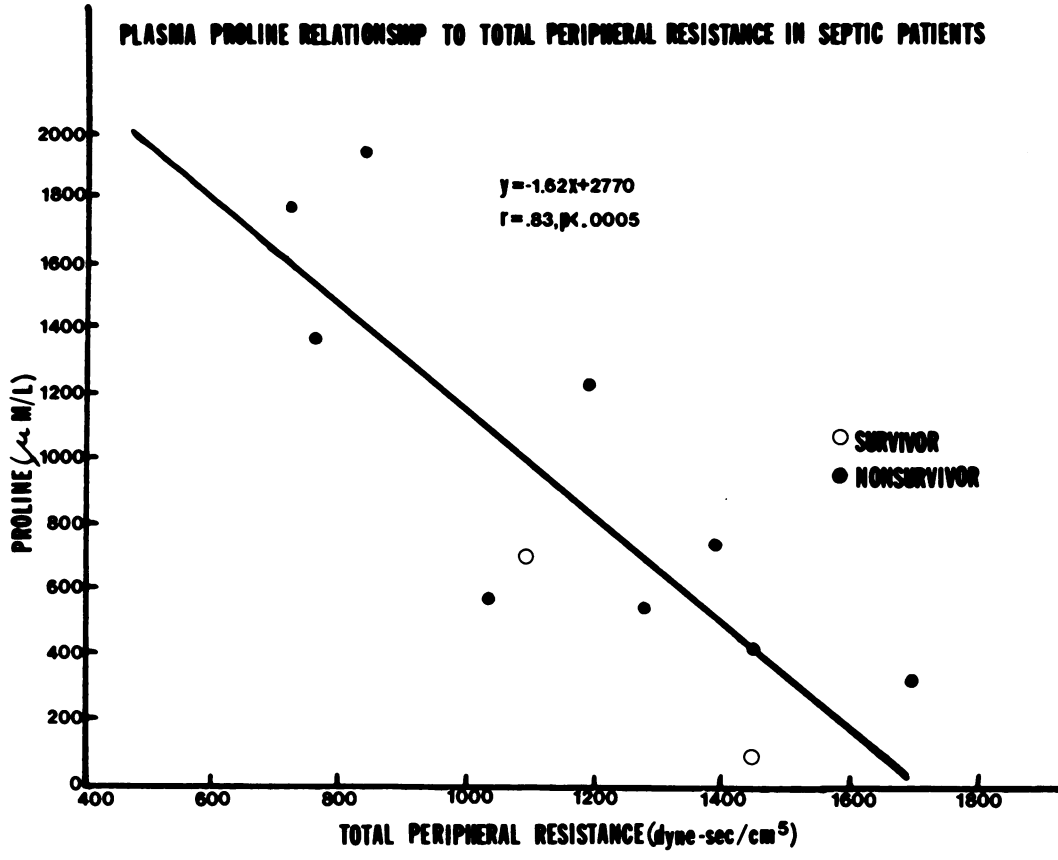

FIG. 4. As total peripheral resistance falls in septic patients, proline level rises. Physiology and metabolism are correlated in time.

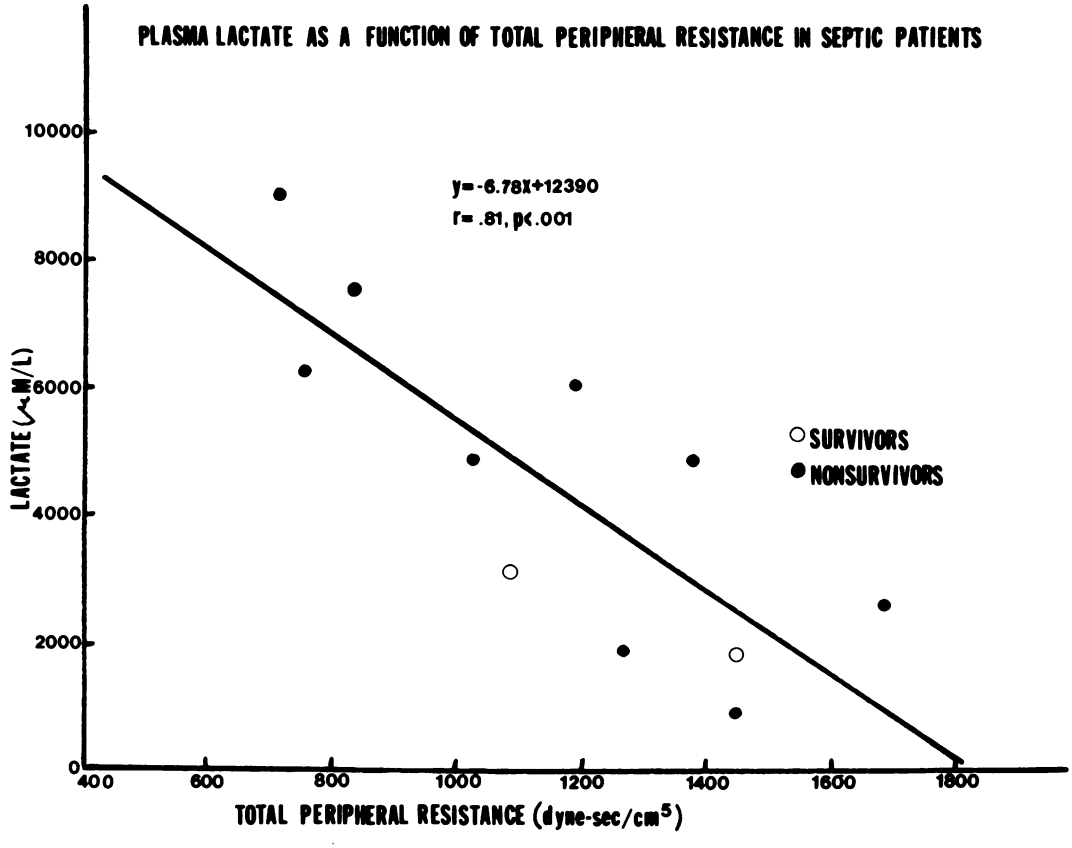

FIG. 5. Lactate level was inversely related to total peripheral resistance. The lactate/pyruvate ratio, however, remained constant.

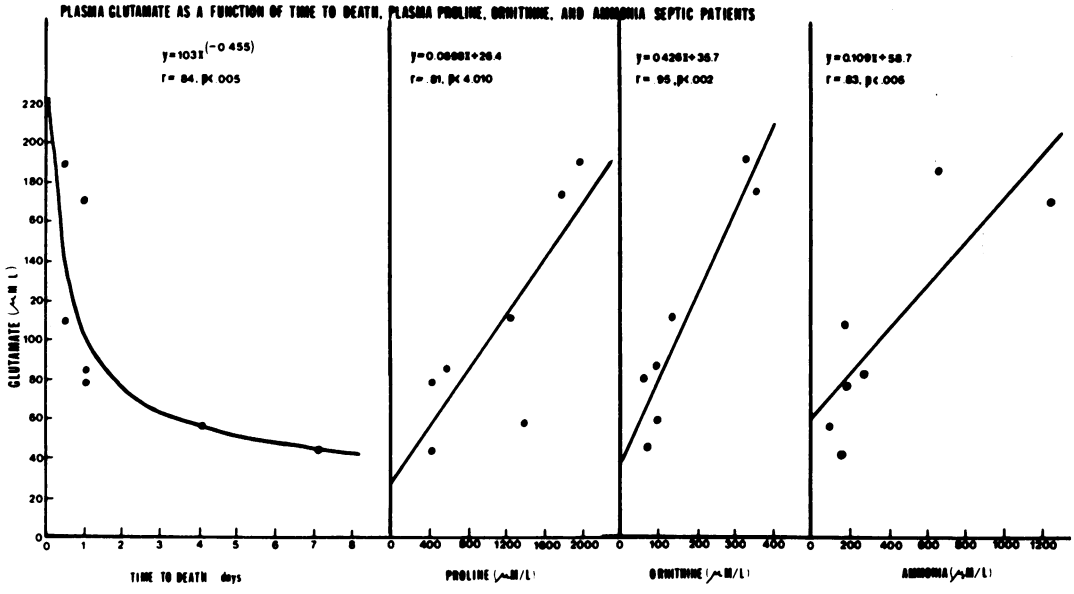

FIG. 6. In septic patients who expired, glutamate levels closely correlated with time to death. As the glutamate level rose, there were parallel rises in proline, ornithine and ammonia, all substrates involved in the hepatic pathway of proline metabolism. A relative inhibition of glutamate dehydrogenase is indicated.

glutamate level and the concentrations of proline, ornithine, and ammonia that existed at the same point in time. All correlations were highly significant. It is evident that septic patients closer to death manifested increasingly higher plasma levels of glutamate, ammonia, ornithine and proline, substances all involved in the hepatic pathway of proline metabolism.

The relationship between the plasma pyruvate concentration and the plasma levels of lactate, glutamate, and proline are shown in Figure 7. Increasing pyruvate levels correlated very strongly with increasing levels of lactate, glutamate and proline. It is also noteworthy that the lactate/pyruvate ratio remained constant throughout.

Plasma concentrations of lactate, pyruvate, and proline are all similarly related to TPR and oxygen consumption as shown in Figures 8 and 9, respectively. Increasing levels of these substrates are associated with decreasing TPR and decreasing oxygen consumption. The same relationships also held for glutamate, ornithine, and ammonia.

It is, therefore, apparent in nonsurviving septic patients that increasing plasma concentrations of the substances involved in the metabolism of both proline and pyruvate are associated in time with each other and with both TPR and oxygen consumption. None of these relationships were of statistical significance in the cirrhotic patients or in the nonseptic, noncirrhotic control group.

Discussion

The serum proline levels were clearly elevated in septic patients compared to cirrhotics and nonseptic, noncirrhotic controls; and were a good indicator of mortality in septic and perhaps cirrhotic patients. Analyzing patient data at times of highest plasma proline levels served to synchronize the course of the septic patients in such a way as to make other metabolic–physiologic correlations apparent. Proline levels correlated well with lactate levels in septics and cirrhotics but not in the controls. Lactate and proline levels were both inversely related to total peripheral resistance and oxygen consumption in septic patients but no relationship was apparent in cirrhotic or control patients. The plasma levels of the amino acids involved in the hepatic pathways of proline metabolism were found to be elevated in proportion to proline in terminally ill septic patients; these substances were highest in patients closest to death. In this same group of severely septic patients, all studied at times of highest proline, plasma concentrations of lactate, glutamate, and proline were directly related to the plasma concentration of pyruvate, and were inversely proportional to TPR and oxygen consumption.

Plasma proline levels have been reported to be increased in septic patients as compared to nonseptic controls.[3,4,12] This increase in proline is coincident with increases in the aromatic and sulfur containing amino acids, and appears to come at a time when peripheral muscle catabolism is marked.[4] Proline is primarily catabolized in the liver. McMenamy et al. studied the splanchnic substrate balances in a severely septic patient who subsequently expired. In this patient, rising plasma proline levels were associated with increasing splanchnic clearance of proline; the hydroxyproline concentrations were not elevated and had no

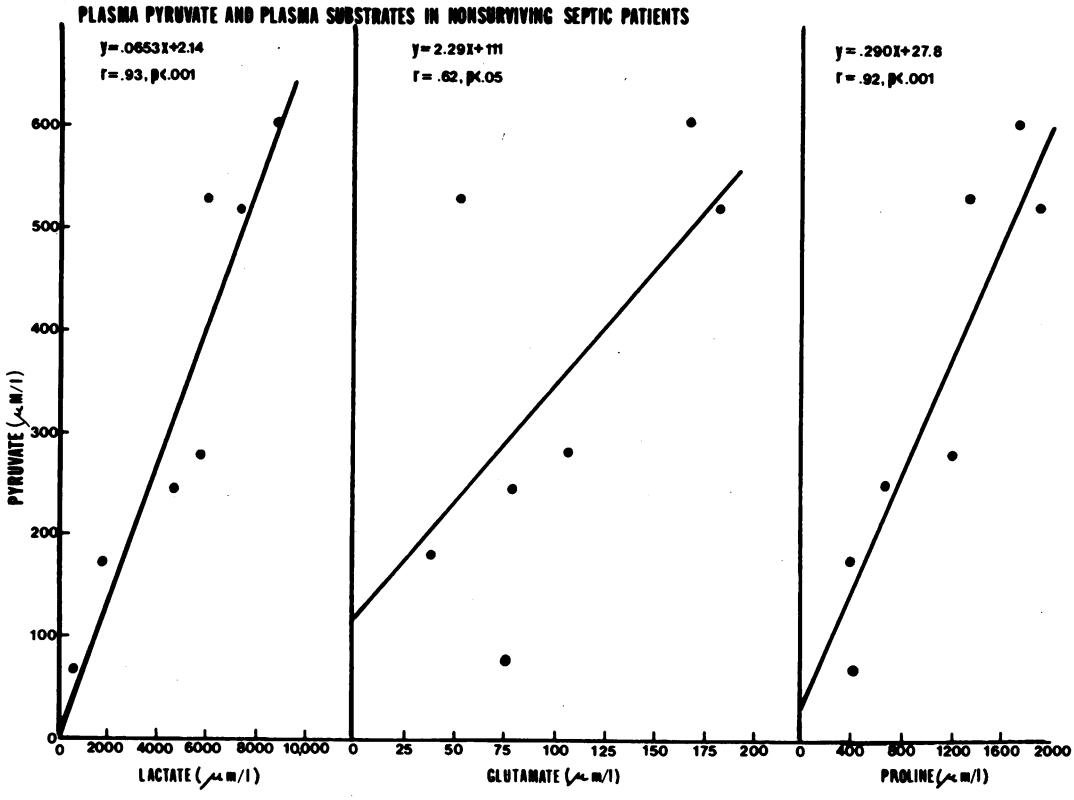

FIG. 7. There is a positive linear relationship among levels of pyruvate, lactate, glutamate and proline. With the constant lactate/pyruvate ratio, a relative inhibition of pyruvate dehydrogenase is indicated.

relationship to proline or other substrate concentrations.[12] It appears, then, that proline was being released from the periphery and that the source was most likely muscle.

Studies of metabolism in septic man who expires indicate marked, progressive derangements of glucose, fat, and protein metabolism. The alterations in glucose metabolism include: hyperglycemia that increases with

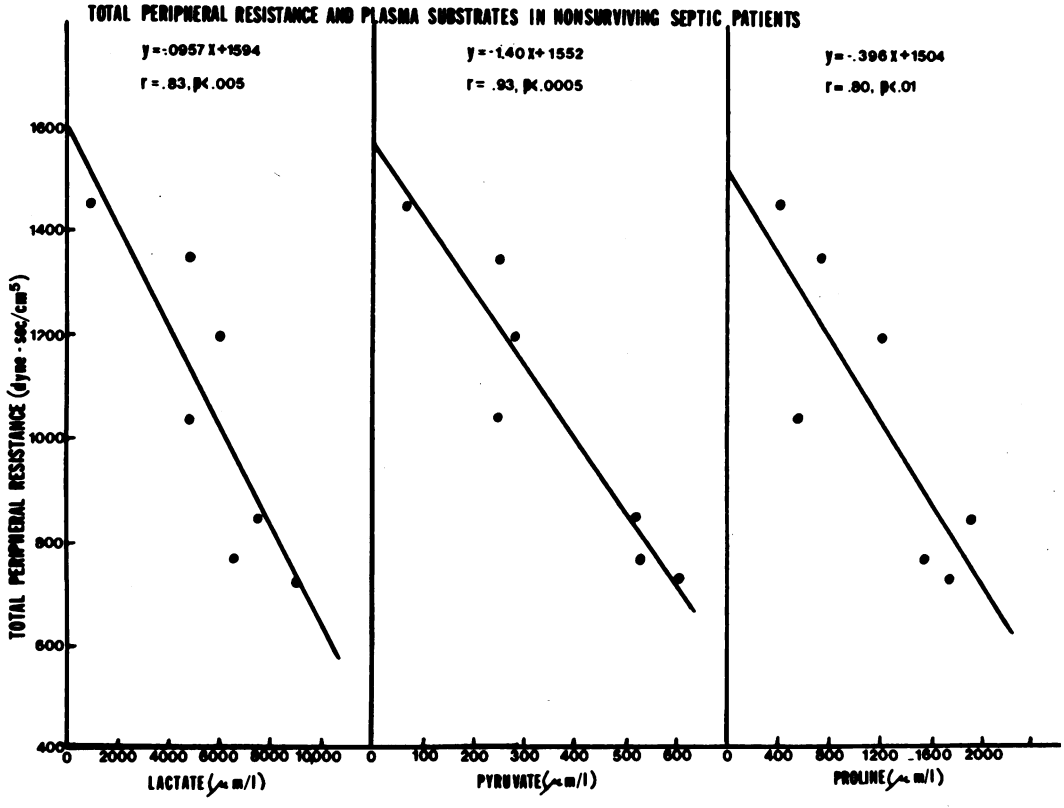

FIG. 8. The substrate levels of lactate, pyruvate and proline were inversely correlated to total peripheral resistance. The relationship in time between physiology and metabolism is evident.

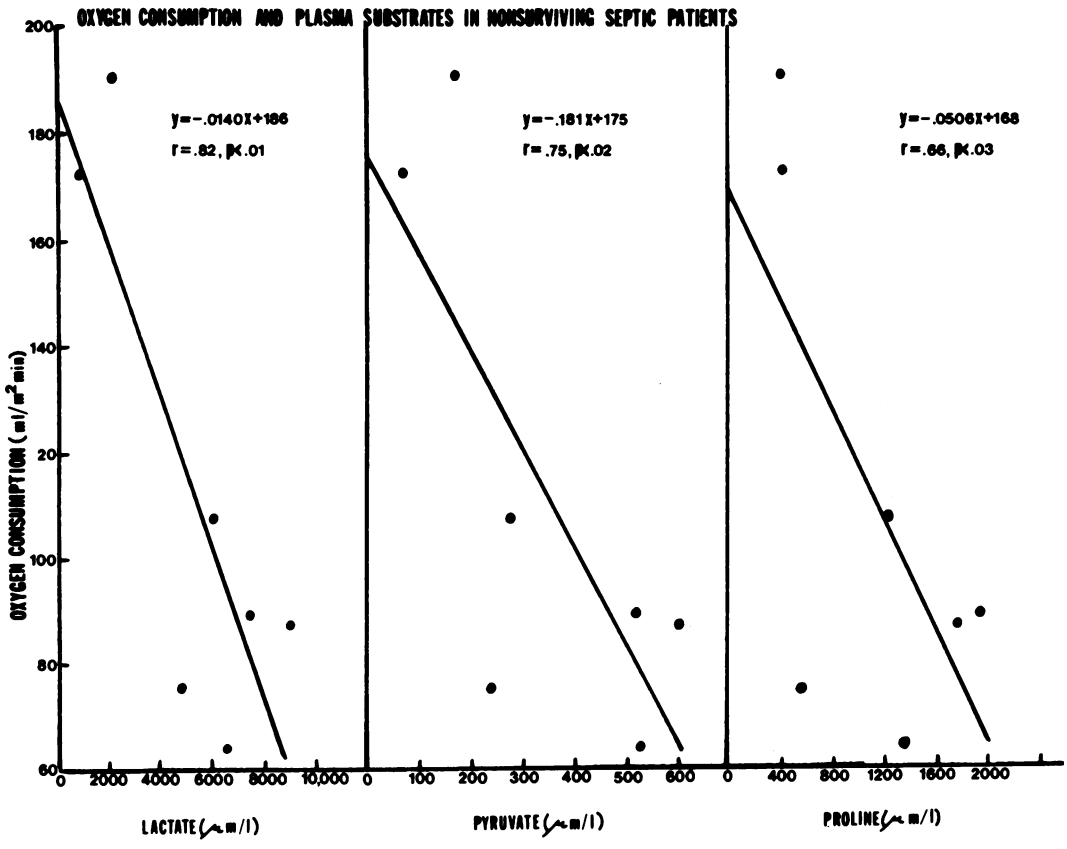

FIG. 9. Lactate, pyruvate and proline inversely correlated to oxygen consumption. With the other evidence presented, the fall in oxygen consumption seems to be one of nonutilization rather than being related to inadequate delivery.

increasing glucose loads; is resistant to insulin administration; is associated with an increased rate of gluconeogenesis that is nonsuppressable by exogenous glucose.[5,10,11,20] Lactate and pyruvate levels progressively rise, while the lactate/pyruvate ratio remains constant. Free fatty acid levels are normal relative to overnight fasting man but are inappropriately high for the existing glucose level.[4,13] Early on, ketone bodies are present. As death approaches, B-OH butyrate levels remain elevated while acetoacetate levels fall, with a progressive increase in butyrate/acetoacetate ratio.[4,13] Triglyceride levels are high and progressively rise as death approaches.[4] Other studies indicate a decreased utilization of fat and an energy economy that is based primarily on protein.[5,9,13] Animal and human investigations strongly support the increased peripheral utilization of branch chain amino acid in sepsis.[3,5,12,19] Branch chain and glutamate levels are initially low, while levels of proline and aromatic amino acids are high. As death approaches, however, the levels of branch chain increase, as do those for glutamate, ornithine, ammonia, proline and aromatic amino acids. These data are quite consistent with the development of a progressive peripheral energy deficit, most likely in muscle. The end result of the metabolic deficit seems to be the multiple organ failure syndrome. The proline data described indicate that proline levels serve as an identifiable marker of the presence, progression, and severity of this metabolic process in patients who expire from sepsis.

The correlation between oxygen consumption and prognosis in the septic patient has been pointed out by Siegel et al.[18] Patients in a low oxygen consumption state do much more poorly than those in a high oxygen consumption state, even though both are hemodynamically compensated by a high cardiac output. More recent data indicate a strong correlation between physiology and metabolism in sepsis.[4] The development of the metabolic alterations described is coincident in time with the progressive unbalanced physiologic response that occurs in septic patients who expire. This response is characterized by rising cardiac output with an inappropriately low TPR, narrowing A-VO_2, and falling O_2C/M^2.[16,17] The correlations described in the present study between O_2C/M^2 and TPR and the plasma levels of proline, lactate, pyruvate, glutamate, ammonia an ornithine represent another demonstration of this correlation between physiology and metabolism. The pathophysiology does not seem to entirely one of shunting as has been previously thought. The metabolic alterations, such as the constant lactate/pyruvate ratio, are not what is observed or expected for a state of decreased oxygen delivery to the periphery. Indeed, increased muscle blood flow has been demon-

strated during sepsis.[6] Whether or not the peripheral distribution of this blood flow is uniform, however, has not been determined. Rather it seems as if the primary defects in sepsis are metabolic and are subsequently reflected in the physiology. At this point, the metabolic derangements seem to appear first in muscle with the development of an energy deficit; the process in patients who expire eventually seems to appear in other organs such as liver and heart.

The origin of the fuel deficit is still uncertain. Clowes et al. have suggested that this deficit occurs as a result of insulin resistance, preferentially in muscle.[5] Border, et al. have implicated a deficiency of carnitine, a peptide necessary for the transport of fatty acids across mitochondria for oxidation.[3] Another possibility is the presence of intracellular metabolic blocks which lead to decreased substrate utilization and low oxygen consumption from nonutilization. In order to evaluate the possibility of multiple metabolic blocks playing a role in the genesis of a fuel deficit, the pattern of plasma substrates involved in both proline and glucose metabolism were analyzed in a group of severely septic patients.

Proline is an amino acid which can neither be interconverted nor oxidized by muscle, but is metabolized in the liver.[1,15] The hepatic pathways of proline metabolism are shown in Figure 10. The first step of proline degradation results in the formation the intermediate Δ'-pyrolline-5-carboxylate. This compound may be further oxidized to glutamate, or may be converted to ornithine. These substrates gain access to the Kreb cycle and the gluconeogenic pathway via the oxidation of glutamate to α-ketoglutarate by glutamate dehydrogenase. In the group of severely septic patients (all of whom died within seven days) glutamate levels were found to be higher in those patients nearer to death. Also, increases in plasma glutamate were paralleled by increases in plasma proline, ornithine, and ammonia. This appears to be happening secondarily to hepatic proline loading, and could be due to saturation of the enzyme glutamate dehydrogenase. The K_m of this enzyme, however, is relatively large and it would appear that the intracellular saturation of this enzyme with glutamate is not likely.[18] Rather, a state of relative enzyme inhibition seems to be present.

It is evident in the septic patient that glucose metabolism is deranged. Part of this is from increased gluconeogenesis presumably resulting from the high levels of glucagon, the increased supply to the liver of nonbranch chain amino acids, and the large influx of lactate in the Cori cycle. These phenomena, together with the rising levels of lactate and pyruvate and a con-

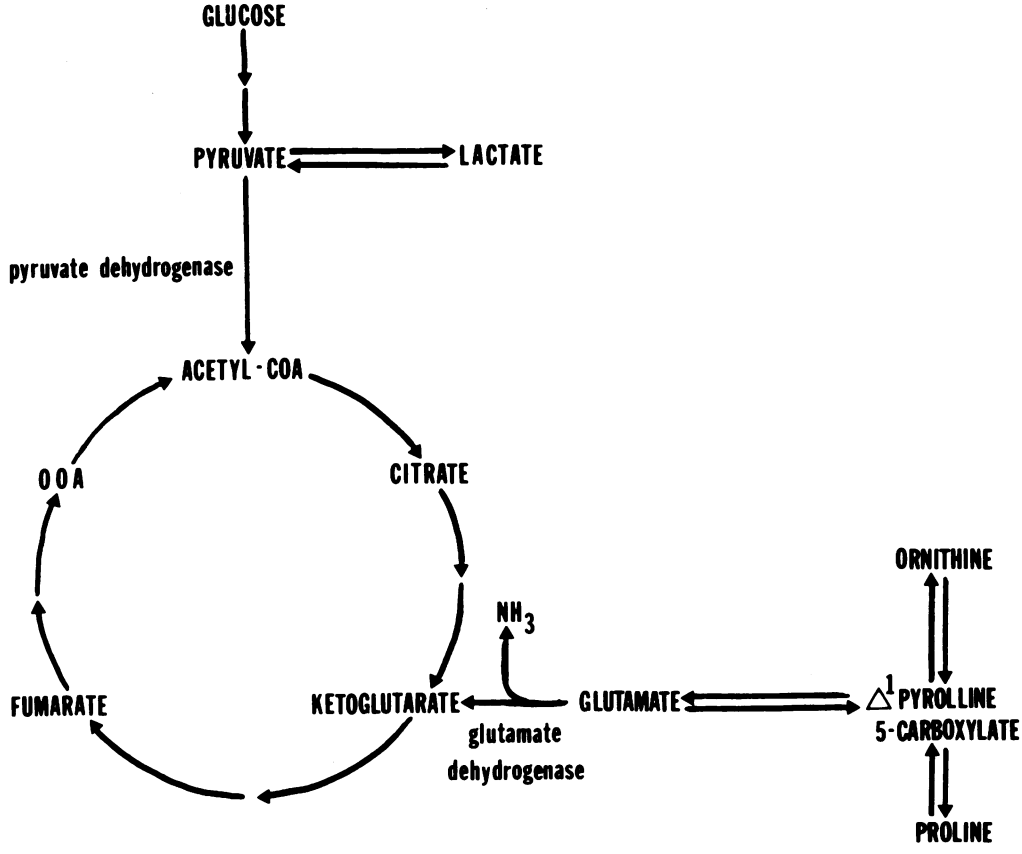

FIG 10. Diagrammatic representation of the pathways of pyruvate and proline metabolism. Two possible sites of inhibition of substrate entry into the Krebs cycle are indicated. The enzymes pyruvate dehydrogenase and glutamate dehydrogenase are implicated.

stant lactate/pyruvate ratio are consistent with a relative inability for pyruvate to be converted to acetyl-Co-A by pyruvate dehyrogenase (Fig. 10).

The rising B-OH butyrate/acetoacetate ratio in septics who expire together with the progressively falling acetoacetate level are consistent with a progressive reduction in intramitochondrial redox potential and a decreased utilization of B-OH butyrate. Muscle biopsy studies in septic patients have documented decreased levels of ATP, with increased levels of ADP and AMP.[2] Metabolically, therefore, the overall picture is consistent with a progressive inhibition of substrate entry into the Krebs cycle at multiple points as the septic process evolves toward death. This would produce a decreased oxygen consumption from nonutilization with the resultant physiologic abnormalities described.

The concept of multiple metabolic blocks occurring at the mitochondrial level, especially in those processes requiring NAD+, would be particularly appealing in explaining many of the septic metabolic abberations. Indeed, a reduced mitochondrial state with a decreased NAD+ to NADH ratio would impair fatty acid and ketone oxidation. The functions of pyruvate dehydrogenase and glutamate dehydrogenase are both dependent on the presence of adequate amounts of NAD+. Reduced intramitochondrial levels on NAD+ would logically impede the entrance of pyruvate into the Krebs cycle, and would result in elevated pyruvate levels. The production of lactate from pyruvate would be facilitated by high concentrations of NADH. Glutamate dehydrogenase is known to be limited by a reduced mitochondrial state, and would explain the apparent inhibition of this enzyme as previously discussed. The progressive nature of these defects would also help to explain other observed alterations in amino acid plasma profiles. As the redox potential of the mitochondria decreases, the ability to utilize branch chain amino acid for energy production via the Krebs cycle would also be interfered with, producing a resultant rise in branch chain plasma levels.

Clearly, definitive treatment of the defects underlying the energy fuel deficit must await the clarification of the fundamental mechanisms and prime mover(s) involved. In the meantime, it would appear that rational metabolic support would consist of the normalization of the blood amino acid pattern so that a balanced mixture may be presented to the liver for protein synthesis. Such treatment might consist of an infusion of an amino acid solution fortified with those amino acids which are deficient in the blood, particularly the branched chain amino acids. Investigations reported by Fisher et al. indicate that this approach is quite feasible.[7,8] Infusion of branch chain rich amino acid mixtures have been shown to improve nitrogen balance and reduce weight loss in post trauma man and rats.[8] Other fuels, such as acetoacetate, are as yet uninvestigated in septic man. Metabolic manipulation and appropriate fuel support should help to reduce the morbidity and mortality from the systemic septic response.

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