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SERUM AMINO ACIDS IN STRESS

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Louis H. Stauss Surgical Research Laboratory

Richmond, Virginia

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INTRODUCTION

The first of the major amino acid constituents of protein was discovered in 1806 and the last in 1935, but knowledge concerning their involvement in various stages of protein degradation and synthesis is still incomplete. The available evidence suggests that each of the amino acid must exist, albeit fleetingly in some instances, in the free form in a dynamic total-body pool before it can be utilized in peptide and/or protein synthesis. However, the amino acids can be excreted in both the free and combined forms (12).

Most of the information about amino acid metabolism in man has been obtained by studying normal persons with specific metabolic diseases. The changes that occur following acute stress and/or disease have not been as well documented. Marked changes in protein metabolism occur in patients undergoing various types of trauma (1 and 2), and this study has been made to determine whether or not significant changes also occur in the free amino acid content of the serum of postoperative and burned patients.

ACKNOWLEDGMENT

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I. CLINICAL STUDIES

All of the analyses were made on a Technicon amino acid Autoanalyzer (R), using a slight modification of the methods described by Hamilton (6 and 7). Each sample was applied to a 127 cm. x 0.62 cm. glass column that was packed with Type A Chromobeads (R). The flow rate was 30 ml./hour, and all runs were made with a pH gradient of 2.875-5,00. The column temperature was maintained at 45^{0} C. for the first 2-1/2 hours, and then was raised to 60^{0} C. The initial column pressure was 310 p.s.i. Each chromatogram took 22 hours to complete. All of the components of this system have been previously described by the Technicon Corporation (R).

A. Control Values.

Six healthy adult males and females were used to obtain control values. The blood samples were drawn at 8 a.m. following an overnight fast.

The levels of the amino acids listed in (Table I) were measured in each sample. The standard control amino acid mixture consisted of 18 amino acids

TABLE I. NORMAL VALUES, SERUM FREE AMINO ACIDS.

Amino Acid	Values — micrograms /ml.		Values — micromoles /L.	
	Mean	Range ± 2 SD	Mean	Range ± 2 SD
1. Hydroxyproline	0		0	
2. Aspartic Acid	4.9	1.3 - 8.4	36.6	10.1 - 63.3
3. Threonine	31.2	10.3 - 52.0	261.7	87.1 -436.4
4. Serine	15.4	5.9 - 24.9	146.7	96.1 -236.9
5. Glutamic Acid	28.1	12.1 - 44.1	170.0	73.1 -266.9
6. Proline	25.5	3.3 - 47.8	221.7	28.5 -414.9
7. Glycine	17.7	8.3 - 27.0	235.0	110.6 -359.4
8. Alanine	34.2	4.3 - 64.0	383.4	48.3 -718.5
9. Valine	26.0	12.8 - 39.1	221.7	109.1 -334.2
10. Cystine	5.3	2.8 - 7.8	88.3	46.4 -130.3
11. Methionine	3.0	0.0 - 8.0	20.0	0.0 - 53.9
12. Isoleucine	9.3	0.6 - 18.0	70.8	4.3 -137.2
13. Leucine	16.3	3.4 - 29.3	124.5	25.9 -223.3
14. Tyrosine	10.9	0.8 - 20.9	60.0	4.6 -115.4
15. Phenylalanine	10.2	5.4 - 15.0	61.7	32.6 - 90.7
16. Lysine	35.9	12.3 - 59.6	196.7	67.0 -326.3
17. Tryptophan	10.2	3.3 - 17.1	50.0	16.1 - 83.9
18. Histidine	19.9	13.0 - 26.9	95.0	61.8 -128.2
19. Arginine	23.2	6.7 - 39.7	110.0	31.7 -188.9

(R) Technicon Corporation, Ardsley, New York furnished by the Technicon Corporation, with the addition of trytophan and hydroxyproline. An internal standard of 0.2 micromoles of isoleucine was used with each determination. A control measurement using the above amino acid mixture was made after every fourth patient sample or as needed if and when problems arose.

Blood samples were obtained from three groups of persons. Normal persons were sampled once in a fasting state, and patients undergoing elective surgical procedures were sampled on the day prior to surgery, the day of surgery, and then daily during their postoperative hospital stay. The patients that were studied after receiving thermal injuries were sampled on the day of admission (as soon as possible), daily for 2 weeks, then every other day until healing or death. All blood samples were allowed to clot immediately, centrifuged, and the serum was then removed. Two milliliters of the serum was added to 10 ml. of 3 percent sulfosalicylic, and the supernate was removed and freeze dried. Prior to chromatographing the freeze-dried sample was diluted with 2.0 ml. of 0.1N HCl and centrifuged clear, and 1.0 ml. was applied to the amino acid column with the internal standard. None of the serum samples were hydrolyzed.

B. Postoperative Patients.

Four patients were studied with different degrees of surgical stress. A brief case history is given for each of the patients.

Patient No. 1. A 21-year-old W.M. had suffered multiple abdominal and extremity injuries from gunshot wounds 1 year prior to this study. At this admission he had a residual neurological deficit in the right foot and leg, but no systemic abnormalities. One large and two smaller abdominal scars were removed using local anesthesia, and he was discharged on the fourth postoperative day. There were no complications during his postoperative stay.

Patient No. 2. A 49-year-old W.F. had been admitted 16 months prior to this admission with duodenal ulcer disease and treated surgically with an antrectomy, vagotomy, and a Billroth I anastromosis. Several admissions had been necessary since the initial operation because of failure to gain weight and the onset of a severe dumping syndrome. The physical examination was normal, and the abdominal scar was well-healed. The patient had lost no weight since her previous surgery. The laboratory examinations showed a hemoglobin of 10.3 gm. percent with a venous hematocrit of 34 percent. An upper gastrointestinal X-ray study showed a rapidly emptying gastric pouch with a dilated anastromosis and a rapid transit time of barium containing glucose from this anastromotic site to the cecum within 10 minutes. The patient was treated by interposing an isolated antiperistalic jejunal loop between the stomach and duodenum. She had a mild temperature elevation on the day following surgery (101^{o} F. rectal), but otherwise had no difficulties. She was on a regular diet without dumping symptoms by the eighth postoperative day.

Patient No. 3. A 31-year-old W.F. was admitted for treatment of exogenous obesity with a jejunocolic shunt. Her pertinent history revealed that she had previously had two anterior colporrhaphies with a recurrence each time, persistent stress incontinence and urinary infections, and two previous ventral herniorrhaphies followed by recurrence. Efforts had been made to control her weight with a diet alone, including a 1-month-long hospitalization, but there was no significant or persistent weight loss. Physical examination revealed that the patient was hypertensive, weighed 257 pounds, had ventral and umbilical herniae present, and had a cystocele with stress incontinence. Multiple laboratory determinations were within normal limits except for a low radioactive iodine uptake. The PBI was normal. The postoperative course following the performance of the jejunocolic shunt was completely benign, and a biopsy of the liver taken at the time of surgery showed moderate focal fatty changes.

Patient No. 4. A 31-year-old W.M. physician was admitted for surgical repair of bilateral inguinal herniae. The physical examination was otherwise within normal limits, and the laboratory tests were normal. The patient had a unilateral repair shortly after admission, and 5 days later the other side was repaired. His entire postoperative course was normal.

C. Burn Patients.

Four burn patients were studied, and their case histories are as follows:

Patient Sh. Sa. A 24-year-old C.F. was admitted with 20 percent third-degree burns of the right thorax and abdomen, right shoulder, and right arm. There were less severe burns of the right lateral and left anterior thighs. Upon admission, her BUN was 16; the hemoglobin was 14.6 gm. percent, and the leukocyte count was 13,050. The patient was treated using Evans formula and oral intake, and she was placed on penicillin and bedrest. She had daily temperature elevations of 103.4^{o} F., but blood cultures showed no bacterial growth. After the second week in the hospital she became essentially afebrile, but she had developed a chronic urinary tract infection. She was treated with appropriate antibiotics and became rapidly asymptomatic. On the 29th postburn day, the patient was skin grafted over the areas of third-degree burn; and she remained afebrile without complications until her discharge 11 days later.

Patient V. Cl. A 26-year-old C.F. was admitted with a 58 percent total body-surface-area burn (48 percent third degree) of the body and extremities. Her past medical history was essentially normal. Her initial hemoglobin was 15.6 gm. percent, and the leukocyte count was 19,000. The patient was placed on antibiotics and treated with the Evans formula. She became febrile on the third postburn day, and remained so. Eschar debridement was done 1 week after admission, but all of the blood cultures that were initially drawn during the temperature spikes occurring during this period were negative for bacterial growth. On the 21st day, the patient became lethargic, and on the 31st day she became semicomatose despite the eschar having been completely removed by this time. She then became afebrile. Cadaver skin was applied to two-thirds of the third-degree-burn area, and the "take" was 100 percent. The patient failed to respond to this procedure and only lived for 8 days after this. She developed marked bilateral pneumonitis and became completely comatose. She became hypotensive on her day of death; and despite the use of vasopressors and other supportive measures, she expired without any response. She received 16 units of whole blood and numerous units of albumin. Multiple organisms were cultured from her burn wound and urine. No blood cultures were positive for growth.

Patient W.P. This 43-year-old C.M. was admitted to the hospital with a 55 percent total body-surface-area burn (35 percent third degree). His past medical history was essentially normal, and the burns were found to involve the legs, arms, and hands. The initial urinalysis reported from 4 to 8 RBC/HPF, 2+ albumin, and a moderate number of casts. The hemoglobin on admission was 15.2 gm. percent, and the leukocyte count was normal. The patient was begun on intravenous fluids and antibiotics, but he began to spike a temperature to 102° daily by the fourth postburn day. The patient became disoriented with delirium tremens, but this cleared rapidly. The patient slowly developed bilateral brochopneumonia and remained slightly febrile. By the 28th postburn day, the patient was noted to have lost quite a bit of weight and was much weaker. The eschar was being debrided daily, but the patient's blood urea nitrogen slowly began to rise. On the 29th postburn day, this reached 62 mgms. percent; and 3 days later, it was 102 mgms. percent. The patient's temperature became essentially normal, although his leukocyte count reached 18,000. The patient went into sudden renal shutdown on the day prior to his death, became hypotensive, and died rapidly after he became hypothermic.

Patient J.H. This 90-year-old C.M. was admitted from another hospital approximately 12 hours after suffering a 95 percent total body-surface-area burn, over 70 percent being third degree. He had some evidence of a mild intraoral burn. No history was obtainable, and the physical examination was essentially normal for his age at the time of admission except for the large surface-area burn and coma. The hemoglobin was 11.5 gm. percent, the leukocyte count 11,800, the BUN 19 mg. percent, and the blood sugar showed a slight elevation. A urine specimen contained 1+ albumin and numerous RBC and WBC/HPF. The patient was treated with Evans formula, but his urine output was never adequate. The temperature remained low normal for the first 24 hours after admission. The patient gradually developed bilateral pneumonitis, remained comatose throughout, and died on the third postburn day without any previous clinical change. The studies on this patient were limited due to the short nature of his illness, but the results of the amino acid analyses will be mentioned where appropriate.

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II. RESULTS

The values that were obtained for the amino acid levels of the sera taken from normal persons are shown in both micrograms per milliliter per micromoles per liter in (Table I). A review of the literature (3, 4, 5, 8, 9, 10, and 14) reveals a wide range of normal values for many of the free amino acids that are found in human serum or plasma. In (Table II) those amino acids for which values outside the range given in (Table I) were found are listed, and the different values given in seven literature references are compared with those found in the small normal sample studied. In all instances there is agreement between the values found in this series and two or more reports in the literature; and, therefore, it was felt that no further studies of normal persons were necessary to determine the normal range of values. No hydroxyproline was found in serum samples obtained from the normal controls, the postoperative patients, or the burn patients.

TABLE II. VARIATIONS IN NORMAL VALUES FOR SERUM AND/OR PLASMA FREE AMINO ACIDS.

	Values (micromoles per liter)						
Amino Acid	Ref. No. 1	2	3	4	5	6	7
Aspartic Acid	67.7 - 90.2	.8 - 5.4	24 ± 10*			31*	3.7 ± 1.8
Threonine	94.0 - 245.2*	101.6 - 144.0*	131 ± 20*	72 - 144*	126 - 294*	78	117.9 ± 27.4*
Glutamic Acid	38.1 - 374.9*	26.1 - 100.0*	138 ± 60*	38 - 234*		105*	45.1 ± 13.4
Histidine	50.6 - 84.9*	37.7 - 70.6*	141 ± 10*	57 - 185*		27	65.8 ± 6.1*

* Agree with normal range this series

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1. Documenta, Geigy, 1956
2. Biological Handbook, FASEB., 1961
3. Levenson et al., 1965
4. Walker et al., 1962
5. McLaughlin et al., 1963
6. Gerritson et al., 1965
7. LaBrosse et al., 1967

Four of the serum-free amino acid levels studied in the patients undergoing surgery showed levels that were significantly abnormal at some time during the period of observation. Aspartic acid was elevated on the third day in patient No. 1 (mild surgical procedure), but it remained normal in all of the other patients. Cystine levels were decreased in patient No. 1 on the third postoperative day and in patient No. 2 on the second postoperative day. The level of phenylalanine was increased in patient No. 1 on the third postoperative day but otherwise remained normal. The greatest change was found in the levels of histidine. In patient No. 2, the serum levels were decreased slightly below normal values during the entire postoperative period. The level was also slightly decreased below normal limits in patient No. 3 on the first postoperative day.

All of these patients had good renal function. The least severe operative procedure was performed on patient No. 1, but three of the four amino acids that showed abnormal levels were abnormal on the first or third postoperative days in this patient. Patients No. 2 and No. 3 had fairly similar degrees of surgical stress, and they both showed decreased levels of histidine as noted above. This single change is consistent with that found in the burned patients. These findings can therefore be summarized to show that there were no consistent or characteristic changes in any of the other measured amino acids in all of these patients that could be related to operative stresses of these magnitudes.

Patient Sh. Sa. was the least seriously burned patient studied, and she survived a hospitalization of 37 days. Significantly abnormal changes occurred in four of the measured free amino acids, and the time and extent of the changes are shown in figure 1. Occasional and inconsistently abnormal values were found for three other amino acids. The serum levels of aspartic acid were increased during the second and third postburn weeks, while the levels of the other three amino acids showing changes were all below the normal range. Glutamic acid levels were decreased during the first postburn week, but they remained within normal range after that time. Histidine levels were decreased throughout the entire period of observation. The most marked change occurred with tryptophan, and only traces of this amino acid were found in any of the serum samples studies.

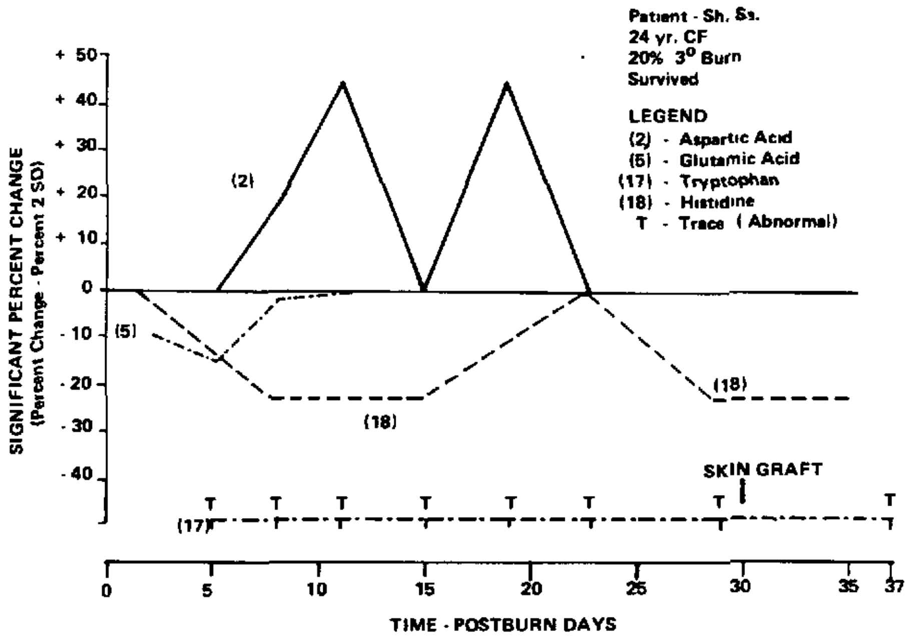

Figure 1. --Abnormal Serum Free Amino Acid Levels in Patient Sh. Sa. The 0 Line Represents Normal Range.

Patient V. Cl. was admitted with the most severe burn of all of these patients, and she died on postburn day 45. The serum levels of the same amino acids showed the abnormalities shown in figure 2 except for glutamic acid levels that remained normal. Otherwise, and despite the increased severity of the injury, the magnitude of these changes were similar to those occurring in the patient Sh. Sa.

Patient W. P. had a severe burn and died on the 34th day with septicemia and renal shutdown. Figure 3a and figure 3b depict the abnormal changes in the serum levels that occurred in several of the free amino acids. The number of amino acids levels that were abnormal and the degree to which they were abnormal were most marked in this patient. The greatest changes occurred in the serum levels of aspartic acid, and the degree of change was 16 times that shown in the other two long-surviving burned patients. The levels of tryptophan were again exceedingly low (or absent), and the abnormal depression of histidine levels was of the same order of magnitude as found in the previous patients.

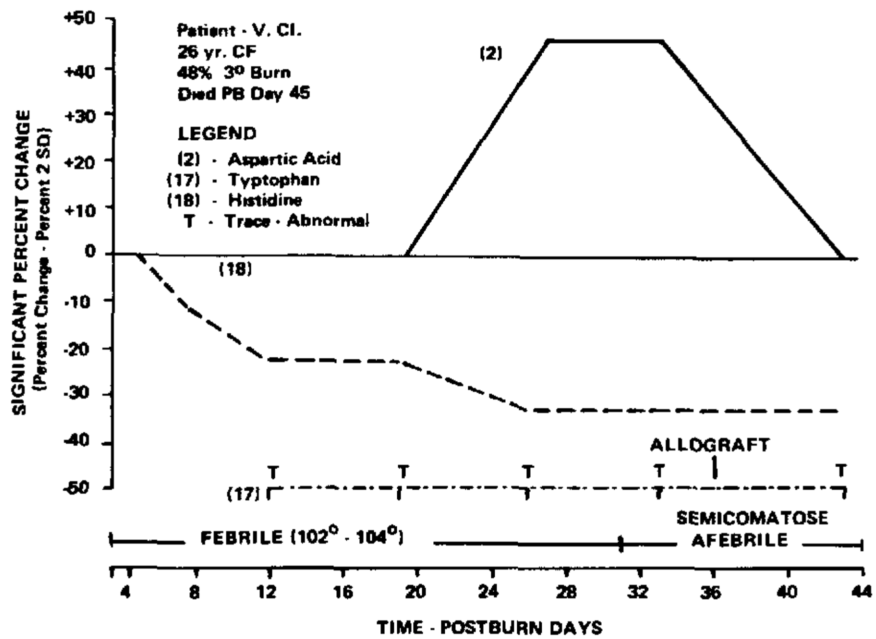

Figure 2. --Abnormal Serum Free Amino Acid Levels in Patient V.CI. The 0 Line Represents Normal Range.

The other amino acids that showed abnormal elevations were, in decreasing magnitudes of abnormal change, cystine, serine, phenylalanine, glutamic acid, and glycine. The peak levels of all of these amino acids occurred between the fifth and 15th days during his febrile course and prior to the onset of renal failure. Aspartic acid levels were the only ones to rise to abnormal levels the week prior to death.

The fourth burn patient lived only 2 days, but the levels of the serum free amino acids were all normal except for tryptophan, and only trace amounts of this amino acid were present each day.

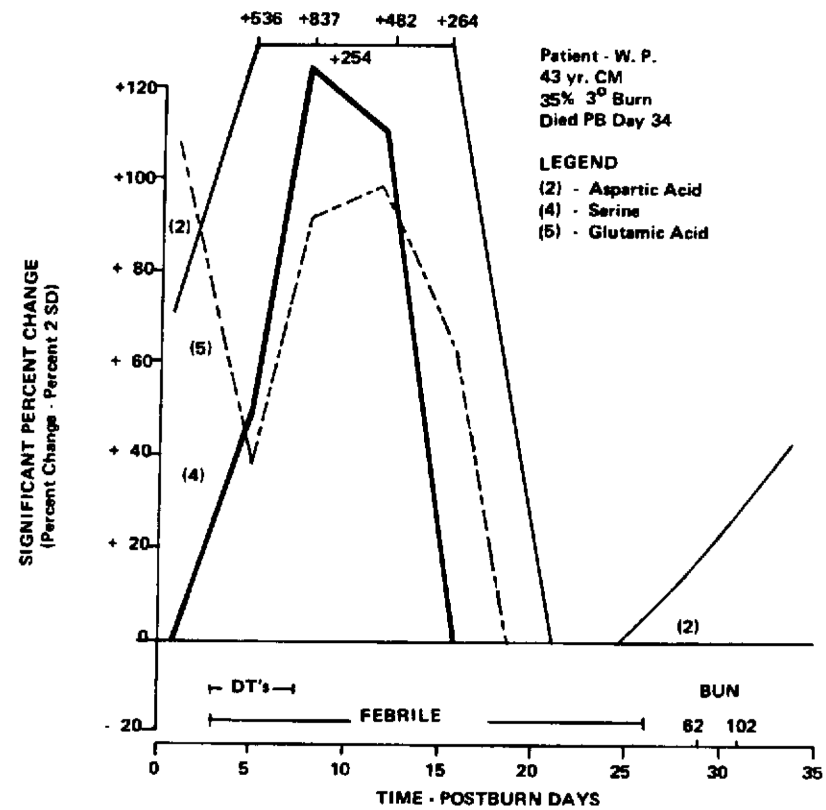

Figure 3a.--Abnormal Serum Free Amino Acid Levels in Patient W.P. The 0 Line Represents Normal Range.

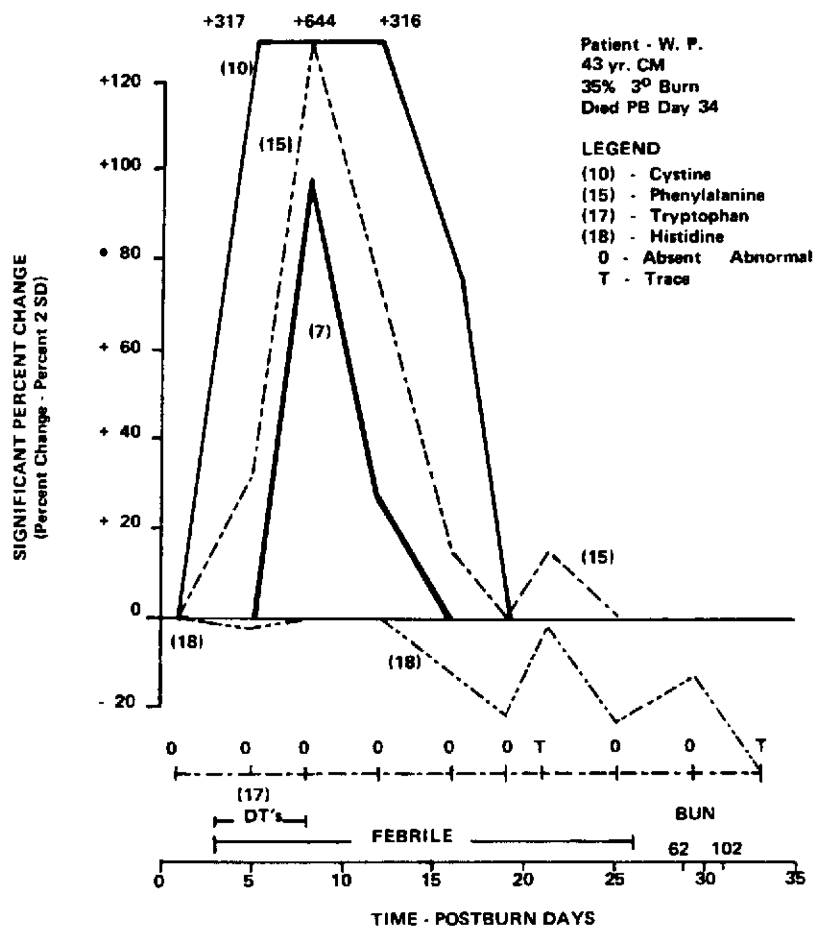

Figure 3b. --Abnormal Serum Free Amino Acid Levels in Patient W. P. The 0 Line Represents a Normal Range.

III. DISCUSSION

The abnormal values for the serum free amino acids that were obtained in these patients are, in all likelihood, due to the operative or thermal stresses suffered by each patient, but other factors could have affected the results. With the exception of patient W. P., all of these patients had adequate renal function; and, as noted earlier, the onset of his progressive renal failure was associated with an abnormal elevation of only one amino acid level. In addition there was no preterminal elevation of any other free serum amino acids in the other two patients that expired. This would not support the concept that these results could be due only to decreased renal function.

Variations in normal serum free amino acid levels have been found to occur in normal humans with and without superimposed dietary intake. Wurtman *et al.* (15) have measured normal diurnal variations in these levels, and tyrosine was the most affected of all. The range of values noted by those investigators agree with the normal values obtained in these studies; and since most of the serum samples in these patients were all drawn at approximately the same time each day, this factor is probably not effective.

McLaughlin *et al.* (10) studied the effect of various dietary intakes on the serum levels of free lysine, methionine, threonine, and tryptophan, and they varied in the postprandial period in direct relationship to the composition of the food that was eaten. The samples drawn from these patients were taken in a fasting state however, and this should nullify any dietary effect.

The only amino acid found to have consistently abnormally low levels in the sera of the burned patient was tryptophan, although histidine was low in all three of the patients that were followed for a significant time. These same three patients also had increased levels of aspartic acid in their sera, although the time of occurrence and the extent of the abnormal values varied.

Levenson *et al.* (9) studied the plasma-free amino acid levels in five severely wounded patients, four of whom died and all of whom had shock and renal failure. A wide patternless fluctuation occurred in the day-by-day values for each amino acid in each patient. These investigators did not measure tryptophan because the levels were too low, but they did not state whether or not these low levels could have been due to the techniques that were used. They divided the reactions of the plasma-free amino acids into three groups: group I (glycine, histidine, threonine, proline, and glutamic acid) remained near normal values; group II (leucine, isoleucine, lysine, valine, tyrosine, and alanine) rose moderately during the first week and then fell; and group III (phenylalanine, aspartic acid, and methionine) rose to a greater extent than the other acids.

LaBrosse *et al.* (8) reported on plasma amino acid in levels in 55 patients suffering from septic, hemorrhagic, or cardiogenic shock. They found that the amino acid levels in their surviving patients did not change in the manner noted by Levenson *et al.* ; but, in their nonsurviving group, 11 of the 14 amino acid levels did change significantly in a similar manner. Threonine (group I) and isoleucine and valine (group II) levels were not significantly changed. These authors did find that the levels of valine could be related to patient survival and the type of hypotension that was present, and that increased levels of glutamic acid, alpha-amino-n-butyric acid, cysteine, taurine, phenylalanine, tyrosine, and 3-methylhistidine and decreased levels of arginine and citrulline paralled the severity of the shock state. Tryptophan was not studied.

The results of this study are not in agreement with those reported above, but each of these had dealt with patients selected for study using different criteria. Therefore, this factor of selection may explain the different results that were obtained. The serum levels of aspartic acid were elevated in three of the adequately studied burn patients, but they were not consistently affected by less severe operative stress, these changes being similar to those noted in the above studies. In each of the burn patients in which the blood levels of this amino acid were abnormally elevated, an abnormal amount was also excreted in the urine; but there was relatively less excretion of this amino acid than of others for which the serum levels were normal (2 patients) or relatively less abnormal. Aspartic acid is a precursor of urea, purines, pyramidines, and other "non-essential" amino acids (13), and the increased levels in the serum could be due to the defective use of the increased amount of aspartic acid in the body "pool" resulting from increased protein catabolism. Although less likely, they could also be due to a renal defect that inhibits, but does not halt, its excretion.

The serum levels of free histidine were always abnormally depressed in both the long-surviving burned patients and the two patients with major operative stress. Both Levenson and LaBrosse found somewhat different results. Histidine is not essential for human growth, but the pathway by which it is synthesized is not yet completely known for man, although it is used to form other nonprotein and protein compounds (11, 13). The urinary excretion of this amino acid in the free form was only slightly abnormally high in the two most seriously burned patients, but it was normal in the postoperative and the less severely burned patients. This would suggest that the defect is endogenous and, in all probability, due to an actual decrease in biosynthesis, although these data do not rule out the fact that increased utilization could abnormally lower the values.

Tryptophan was present only in trace amounts in the sera from all four burned patients. It is the only heterocyclic amino acid that is essential for man and cannot be manufactured de novo; although it can be used to form various other substances, among them serotonin and 5-hydroxy-indole-acetic acid. It is interesting to note that the amount of free tryptophan excreted in the urine of all of these burned patients was elevated. A dietary lack or an increased rate of utilization would account for the trace amounts that were found in the sera of these patients. Stress alone would not account for the low serum levels of this amino acid because it was present in normal amounts in the postoperative patients. It was not possible to study the total urinary excretion of this amino acid because it is destroyed by hydrolysis.

Glutamic acid serum levels were abnormally high in one of the burned patients and abnormally low in the others. One patient (W. P.) had abnormal elevations of the levels of glycine, cysteine, and phenylalanine, but these changes were not present in any other patient.

The metabolic turnover of proteins is extremely rapid, and the wide fluctuations seen in the serum amino acid levels probably represent an interplay between utilization for protein synthesis, formation by protein breakdown, and excretion. Unfortunately these data do not furnish the direct information needed to explain the selective but significant changes that were found, but the elucidation of these changes furnished a guideline that can be used to study the metabolic phases of these specific amino acids.

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a. Levels of serum amino acids were determined in three groups of patients: normal; patients undergoing a surgical procedure; and patients that had received thermal injuries. (U)

b. The method of determining serum amino acid levels is presented. (U)

c. Brief case histories of patients involved in the study are given. (U)

d. A discussion of the results obtained is contained in the report. (U)

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