AD-A043 018   ARMY MEDICAL RESEARCH INST OF INFECTIOUS DISEASES FR--ETC F/G 6/19
BASIC CHANGES IN PROTEIN METABOLISM DURING STRESS.(U)
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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Basic Changes in Protein Metabolism during Stress,		5. TYPE OF REPORT & PERIOD COVERED Interim rept.
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Robert W. Wannemacher, Jr.		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS U.S. Army Medical Research Institute of Infectious Diseases, SGRD-UIP-S Fort Detrick, Frederick, MD 21701		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102B 3M161102BS03 00 007
11. CONTROLLING OFFICE NAME AND ADDRESS U.S.Army Medical Research and Development Command, Office of the Surgeon General Department of the Army, Washington, DC 20314		12. REPORT DATE 21 July 1977
		13. NUMBER OF PAGES 19 + 2 figures
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release – distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

Reprints bearing assigned AD number will be forwarded upon receipt.
To be published in PROCEEDINGS OF FIFTH WESTERN HEMISPHERE NUTRITION CONGRESS.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Protein metabolism
Stress
Catabolism
Alanine production and utilization
Carbohydrate metabolism

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The wasting of body proteins during a stressful illness is the decreased synthesis and increased degradation of peripheral tissue such as skeletal muscle. The amino acids released from these tissues are used as an energy source by the peripheral tissue, substrate for gluconeogenesis, production of proteins associated with host defense against the stressful illness, tissue repair and abnormal growth, and synthesis of obligatory proteins. This results in a rapid depletion of protein in peripheral tissue and a decreased supply of amino acids to meet the metabolic insult of the stressful illness.

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Basic Changes in Protein Metabolism during Stress

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BASIC CHANGES IN PROTEIN METABOLISM DURING STRESS

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Since the classic work of Schoenheimer and co-workers, whose observations led to the concept that nearly all proteins in the body were in a state of flux,[1] a great deal of information has been obtained concerning protein metabolism in normal and various disease states. However, earlier workers[2,3] had reported that various types of trauma or inflammatory diseases resulted in an increased loss of body proteins. This wasting of body proteins has been characterized as a catabolic response to these stressful illnesses. As illustrated in Table 1, this protein wasting, which is noted by increased urinary nitrogen excretion, is seen during injury and/or various types of infectious disease.[4-9] The magnitude of the response appears to be related to the severity of the illness rather than the origin of the disease.[10,11] Since many of these illnesses are associated with anorexia, the increased excretory loss of nitrogen coupled with the reduced dietary intake results in marked negative balances. The inability to conserve body protein during periods of anorexia can, in part, explain the rapid wasting of protein stores during stressful illnesses.[10]

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Mechanism for Altered Protein Metabolism

A healthy, 70-kg man has a recommended protein intake of approximately 70 g of mixed protein which has a net utilization of 70%.[10] This protein is part of a diet that supplies a minimum of 2500 calories as well as adequate vitamin and mineral nutrients. Under these conditions the equivalent of 10 g of protein will be lost in the feces, 55 g in the urine, and 5 g from skin and flatus containing nitrogen gas. It can further be estimated that approximately 50 g of dietary protein are utilized to meet the so-called obligatory nitrogen loss, or that amount of body protein that that has to be replaced daily from dietary sources. In contrast, protein turnover in the 70-kg man is between 200 and 250 g/day.[12] Thus, daily protein synthesis is from 4 to 5 times in excess of the computed protein requirements, and illustrates the extensive re-utilization within the body of amino acids liberated from tissue breakdown. Body protein is in equilibrium with the metabolic pool of amino acids to which is added dietary protein. In addition, amino acids are lost from this pool by the group of nitrogenous compounds excreted in the urine. It is estimated that the free amino acid pool contains the equivalent of approximately 12.5 g of protein, which is distributed among the various tissues of the body. Since a 70-kg man contains approximately 13.3 kg of protein, the metabolic amino acid pool represents only about 0.1% of the total body protein. Further, while only 2% of the total body protein is turned over per day in adult man, individual tissue or cell populations vary greatly in their rates of protein turnover and can be markedly influenced by the protein economy of the host. For

example, skeletal muscle and connective tissue contain 70% total body
protein but represent 20 - 25% of the protein turned over per
day.[10,12] Thus, alterations in the protein metabolism of these
tissues could markedly influence the amino acid economy of the host.

As illustrated in Fig. 1, change over a given time period in the
concentration for the specific protein or cellular population with
time is a function of the rate of its synthesis versus its breakdown,
namely anabolism versus catabolism. Thus, a rather simple kinetic
model describing changes in body content of protein is a function of
the rate constant for synthesis minus the first order of rate
of degradation; the latter is a product of the concentration of
protein and first-order rate constant for degradation. For the adult
in nitrogen equilibrium the rate constant for synthesis equals that
for degradation (Fig. 1, group 1). As shown in this theoretical model,
an individual with 100 g of protein turnover per day can achieve a
50-g protein loss per day by either a 50% decrease in the rate of
synthesis (group 2) or a 50% increase in the rate of degradation
(group 3). In contrast, such a decrement in the rate of synthesis and
a 50% elevation in the rate of degradation will result in a 100-g
daily loss in body protein content (group 4).

Recent studies have demonstrated that a severe reduction in food
intake results in a marked decrement in the rate of protein synthesis,
with little change in the rate of degradation.[13-15] Prolonged fasting
in man or feeding a protein-free diet to rats results in a gradual
decrease in the rate of degradation. Since this is less than the
reduction of synthesis, the combined responses result in a slow wasting
of body proteins.[13-15] Pharmacological doses of glucocorticoids,

however, tended to increase rates of degradation with little change in synthesis.[13] Recently, it has been reported that total body protein breakdown is increased in severely burned children.[16] Thus, the magnitude of loss in body protein is a function of alteration in both the rate of synthesis and degradation. During prolonged fasting, man is able to conserve body protein by progressively decreasing the rates of degradation, while the opposite effect appears to be taking place during massive injury and/or sepsis.

Changes in total body protein metabolism appear to reflect the algebraic sum of what is happening in various tissues and the cellular compartment of the host. Therefore, recent studies have been concerned with the effect of stressful illnesses on protein metabolism of various tissues. Since skeletal muscle represents 40% of total body protein, it has been extensively studied in recent years. Studies in rodents suggest that acute infectious diseases result in a greater than 50% decrement in synthesis of proteins associated with skeletal muscle.[17-20] Over 90% of the total body content of 3-methylhistidine is associated with the peptide chains of actin in all muscles and myocin in white muscle fiber.[21] This amino acid is not reutilized when muscle protein is degraded and is excreted quantitatively in the urine; hence, it is a good in vivo index of the rate of myofibrillar protein breakdown.[22-23] In volunteers infected with sandfly fever virus, urinary 3-methylhistidine significantly increased during the febrile phase.[24] Recently, it has also been reported that the rate of excretion of this amino acid is elevated during the febrile phase of such stresses as major surgery and/or sepsis.[25] In addition, when the skeletal muscle of rats was pre-labeled with [^{14}C]phenylalanine and the rats were

subsequently infected, they expired more labeled CO_2 than those injected with heat-killed organisms; this is consistent with the concept of an increased rate of protein catabolism during infectious disease.[14] Thus, a stressful illness would conform to model 4 (Fig. 1), which is a combination of a decreased rate of synthesis and an increased rate of degradation of skeletal muscle, resulting in an elevated supply of endogenous amino acids, which could account for the catabolic response associated with stress. In contrast, during simple starvation, the degradation of skeletal muscle is unaffected or progressively decreases.[13-15,26]

Alterations in Amino Acid Metabolism

Once an amino acid is liberated as a result of protein degradation, it can enter a number of different metabolic pathways including: (a) reutilization of protein synthesis in the cells where degradation took place; (b) release into the extracellular fluids where it can be taken up by another cell of the body to be utilized for protein synthesis; (c) deaminated or transaminated and the carbon utilized as a gluconeogenic substrate or for oxidation as a source of energy; and (d) converted to other metabolites of the body, such as tyrosine to epinephrine or tryptophan to serotonin. Since injury and/or infection stimulate the wasting of skeletal muscle proteins, the amino acids released from this tissue could markedly influence the metabolism of other cells of the body. Recently a number of investigators[27] reported that alanine and glutamine are the major amino acids released from skeletal muscle. Since these amino acids are not prominent in the composition of the protein of skeletal muscle, it has been postulated that other amino acids contribute their

amino acid group and perhaps carbon skeleton for the synthesis of alanine and glutamine in skeletal muscle. Alanine has been shown to be the major gluconeogenic amino acid taken up by liver for the synthesis of glucose, which has led to the concept of an alanine-glucose cycle.[27] Further, glutamine can be taken up by intestinal cells and utilized for the synthesis of alanine or by kidney for ammonia production. Thus, under conditions of stress, skeletal muscle could be contributing increased amounts of substrates for glucose production.

During sepsis in man and experimental infection in monkeys and glucose production is significantly increased, resulting in slight hyperglycemia.[28,29] This increased rate of glucose production cannot be inhibited by the infusion of a 5% dextrose solution.[30] In infectious diseases increased glucose production is associated with elevated rates of glucose utilization, which may be related to elevation in phagocytic activity.[29] Infectious illness in the rhesus monkey also stimulates increased production and utilization of alanine, as well as accelerated rates of gluconeogenesis.[26,29] During gluconeogenesis the amino group of alanine contributes to the synthesis of urea. Recently, it has been demonstrated in the rhesus monkey that almost all of the increases in the excretion of urea nitrogen during the febrile response to infectious disease, can be accounted for by the contribution of amino nitrogen from the transamination of alanine during gluconeogenesis.[29] While this increased glucose production may in part represent functional wastage, it may be a necessary mechanism, especially in infectious disease, to supply an energy source to those cells involved in host defense mechanisms.

Since skeletal muscle is one of the major contributors of amino acids during stressful illness, a number of studies have been generated to determine what mechanisms stimulate the increased breakdown of this tissue. Skeletal muscle can use a number of substrates as energy, including ketones, free fatty acids, glucose, and branched-chain amino acids.[26] During sepsis in man and rhesus monkey, skeletal muscle increases the release of lactate, indicative of a decreased rate of aerobic glycolysis;[5,29] in addition, sepsis inhibits the development of starvation ketosis.[5,31] Thus, the reduced efficiency for utilization of glucose and the absence of elevated ketone concentrations forces skeletal muscle to utilize other substrates as a source of energy. One such source is the branched-chain amino acids, which indeed may be the preferred energy substrate of skeletal muscle.[26,32] Further, plasma concentration of the branched-chain amino acids significantly decreased during infectious disease.[24,26] Thus, a stressful illness may result in increased breakdown of skeletal muscle to supply branched-chain amino acids as a source of energy. Indeed it has been reported in fasting patients that the infusion of these acids will decrease urea nitrogen excretion.[32]

Certain aromatic amino acids, such as phenylalanine and tryptophan, cannot be metabolized by skeletal muscle and would be released in increased quantities as the result of elevated rates of protein breakdown. In the case of tryptophan, it has been demonstrated that infectious illness increases urinary excretion of its kynurenine-pathway metabolites, while phenylalanine, which is slowly metabolized, accumulates in the serum.[26]

Protein Anabolism during Stress

While stressful illness is characterized by marked wasting of body proteins, many anabolic responses are brought into focus. Almost all types of injury and infectious disease are characterized by marked increases in the production of acute-phase proteins, including α_1-antitrypsin, α_1-acid glycoprotein, haptoglobin, fibrinogen, C-reactive protein, ceruloplasmin, and C_3 complement.[11,33] The rate of synthesis and accumulation of the acute-phase proteins in the plasma depends upon the severity of the illness and the cause of the stress. Although the contribution that these acute-phase proteins make to the host defense mechanism has not been elucidated, some evidence has accumulated which suggests that they may play a role in minimizing tissue damage associated with phagocytes, amplifying the humoral and cell-mediated response of the host, aiding in tissue repair and in the removal of hemoglobin following red cell lysis.[10,11,33] Since the synthesis of these acute-phase globulins is increased even during periods of starvation or extreme protein-calorie malnutrition,[11,33] it would appear that they have a high priority for the utilization of endogenous amino acid supply during stress.

The presence of an infectious microorganism or necrotic cells can stimulate marked anabolic activity in many of the hemic cells of the host. This anabolic activity may include production of antibodies which are specific for the causative microorganism or they may constitute a nonspecific response which is characteristic of inflammatory disease. All these anabolic responses require the availability of added quantitites of cellular energy as well as intact protein-synthesizing mechanisms within the stimulated cells.[10,11]

The specific response requires the presence of cells in which the causal microorganism stimulates the release of factors which cause B-cells to synthesize specific immunoglobulins and T-cells to release the lymphokinins which are characteristic of cell-mediated immunity.[10,11] This process also stimulates the production of components of the complement system and interferon. Stimultaneously this process stimulates increased phagocytic activity in granulocytes and macrophages. During phagocytosis there is a burst of metabolic energy within the cell, formation of phagocytic vacuoles, and the activation and release of many lysosomal enzymes and mediators.

Injury, severe burn, and major surgery all stimulate protein anabolism associated with tissue repair. The magnitude of this response depends upon the severity of the injury and the amount of protein lost during hemorrhage and in exudate.[2] -

In another stress-related disease, cancer, the growth of neoplastic cells constitute an anabolic process which is taking place as a result of the wasting of host proteins. The amount of cell manipulation within tumors varies over a wide spectrum, from slow-growing, relatively benign neoplasms to rapidly multiplying, malignant tumors. Protein anabolism in neoplastic cells is considered a one-way street in that once an amino acid is utilized for protein synthesis in a neoplastic cell it is no longer available for utilization by other cells of the host.[10] Thus, a number of investigators have considered tumor growth as representing "a nitrogen trap." Another complication which can add to the wasting syndrome which usually accompanies malignant disease is the anorectic state which is often observed in the patients. The anorexia may be related

to both tumor-related alterations in amino acid metabolism and toxic effects of chemotherapy.[10] This results in a further deviation of amino acids away from tissues, such as skeletal muscle, and adds to the depletion of the host protein.

The presence of a stressful illness can also lead to increased synthesis of various enzymes which are associated with the visceral tissues of the host.[10,11,26] Thus, while stress is considered to be a catabolic disease, many tissues have stimulated rates of anabolic activity and elevated amino acid requirements.

Comments

Depending on the severity of the stressful illness, dietary protein intake may be reduced 50 - 100%. Thus, the alterations in protein metabolism during such illnesses are best compared to the effects of simple starvation. During periods of reduced food intake an individual must utilize his own body proteins to maintain both those cellular structures which are necessary for the homeostasis of the host and as a source of energy. Since skeletal muscle contains 40% of the body proteins, it represents an available reserve which an individual can utilize during periods of reduced nitrogen intake. This is accomplished by a rapid reduction in the rate of protein anabolism in skeletal muscle with minimal changes in the rate of breakdown of these proteins. During starvation of longer time periods the host becomes "ketone adapted" so that less of the amino acids are needed for synthesis of glucose. This results in a gradual decrease in the rate of breakdown of skeletal muscle and a reduction in the excretion of urinary nitrogen. Because of this ability to conserve body protein,

obese patients have been starved for up to 8 months without any clinical signs of severe protein depletion.[34] In contrast, a stressful illness, especially one associated with sepsis, inhibits "starvation-induced ketosis" which means that those tissues which cannot utilize fatty acids continue to burn glucose as a major source of energy. Further, in these patients amino acids are utilized at an increased rate for synthesis of proteins associated with tissue repair, humoral and cell-mediated immunity, phagocytosis, proteins associated with the "non-specific host defense mechanisms" (such as acute-phase globulins), and/or abnormal growth associated with malignant tissues. These anabolic processes require energy often in the form of glucose.

An estimate of the effects of a stressful illness on the rates of protein metabolism in various tissues of a patient who is fasted and excreting 25 g of nitrogen per day is illustrated in Fig. 2. As observed in a burned patient,[16] total body protein synthesis and degradation are both elevated in a stressed patient. However, the increase in the rate of degradation is greater than that of synthesis, resulting in a net loss of body protein. The proteins of skeletal muscle, skin, and intestinal mucosa (lower part of Fig. 2) are all contributing amino acids to the extracellular pool of the body. In skeletal muscle and skin the rate of protein synthesis is decreased and degradation is elevated, while in intestinal mucosa the rate of synthesis is reduced with little change in degradation. Amino acids are utilized for synthesis of obligatory proteins (those which are necessary for homeostasis) in various tissues but the rate of anabolism equals catabolism with no change in protein content. In the top part of Fig. 2, three tissue compartments are utilizing amino acids in

anabolic processes. The liver utilizes about 67% of the amino acids which are taken up for synthesis of glucose. This gluconeogenesis accounts for a large proportion of increased excretion of urea nitrogen. In liver, amino acids are also utilized in increased amounts for synthesis of acute-phase globulin and certain hepatic enzymes. There is an increased turnover and accumulation of proteins involved in humoral and cell-mediated immunity. Amino acids are incorporated into proteins produced for tissue repair and/or abnormal growth. This compartment contributes very little amino acid back to the extracellular pool and is considered a "nitrogen trap." The magnitude of this "nitrogen trap" depends on the severity of the illness and the extent of the tissue damage. While the values presented in Fig. 2 represent estimates of changes in protein metabolism of various tissues, they do illustrate several fundamental factors which are characteristic of stressful illness: (a) alteration in rates of total body protein synthesis and degradation represents the algebraic sum of changes in various tissue compartments; (b) certain tissues of the body are contributing amino acids to meet the anabolic requirements for homeostasis, gluconeogenesis, tissue repair, and host defense mechanisms; (c) changes in protein content of a tissue are a function of alteration in both the rate of synthesis and degradation; and (d) skeletal muscle is the major contributor of amino acids for anabolic activity in other tissues of the body.

A stressful illness places a marked drain on the protein reserves of the skeletal muscle. If the protein metabolic rates described in Fig. 2 continue for 7 days, skeletal muscle will lose 25 - 30% of its protein content. As illustrated in Fig. 1, protein

degradation follows first-order kinetics and is a function of both the rate constant for degradation and protein content.[10] Therefore, a 50% reduction in protein content and a 50% elevation in the rate constant for degradation (model 5) results in no more protein to be broken down than that observed in the host in nitrogen equilibrium (group 1) where a 50% lower rate constant for degradation would be observed. Thus, in the depleted patient with a stressful illness, skeletal muscle cannot supply sufficient amino acids to meet the anabolic and energy requirements of the visceral cells involved in homeostasis, tissue repair, and host defense mechanisms. It is this type of patient that must receive nutritional support to help in combatting stressful illness.

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TABLE 1 – Urinary Nitrogen Excretion in Normal and Fasted Subjects
during Various Stressful Illnesses.

Stress	Urinary Nitrogen g/day	Reference
Normal		
Fed[a]	13	4
Fasted 72 hr	7 – 11	5
Fasted 28 days	4	6
Bacterial infections	16 – 25	3,4,7
Malaria	20	8
Sandfly fever	16 – 18	4
Sepsis	12 – 22	5
Fracture of the leg	16 – 30	2
Muscle wound, severe	18 – 27	2
Major thermal injury	30 – 40	9

[a] Intake for 70-kg males was 14 – 15 g nitrogen and 2500 – 2800 cal/day.

Legends to Figures

Fig. 1. A theoretical model to illustrate how alterations in rate

of synthesis and/or degradation can affect the protein

content of a cellular population. $\dfrac{\Delta P}{\Delta T}$ = change in protein

content with time; K_S = rate of synthesis; k_D = first-order

rate constant for degradation; P = protein content.

Fig. 2. An estimation of the alterations in protein metabolism of

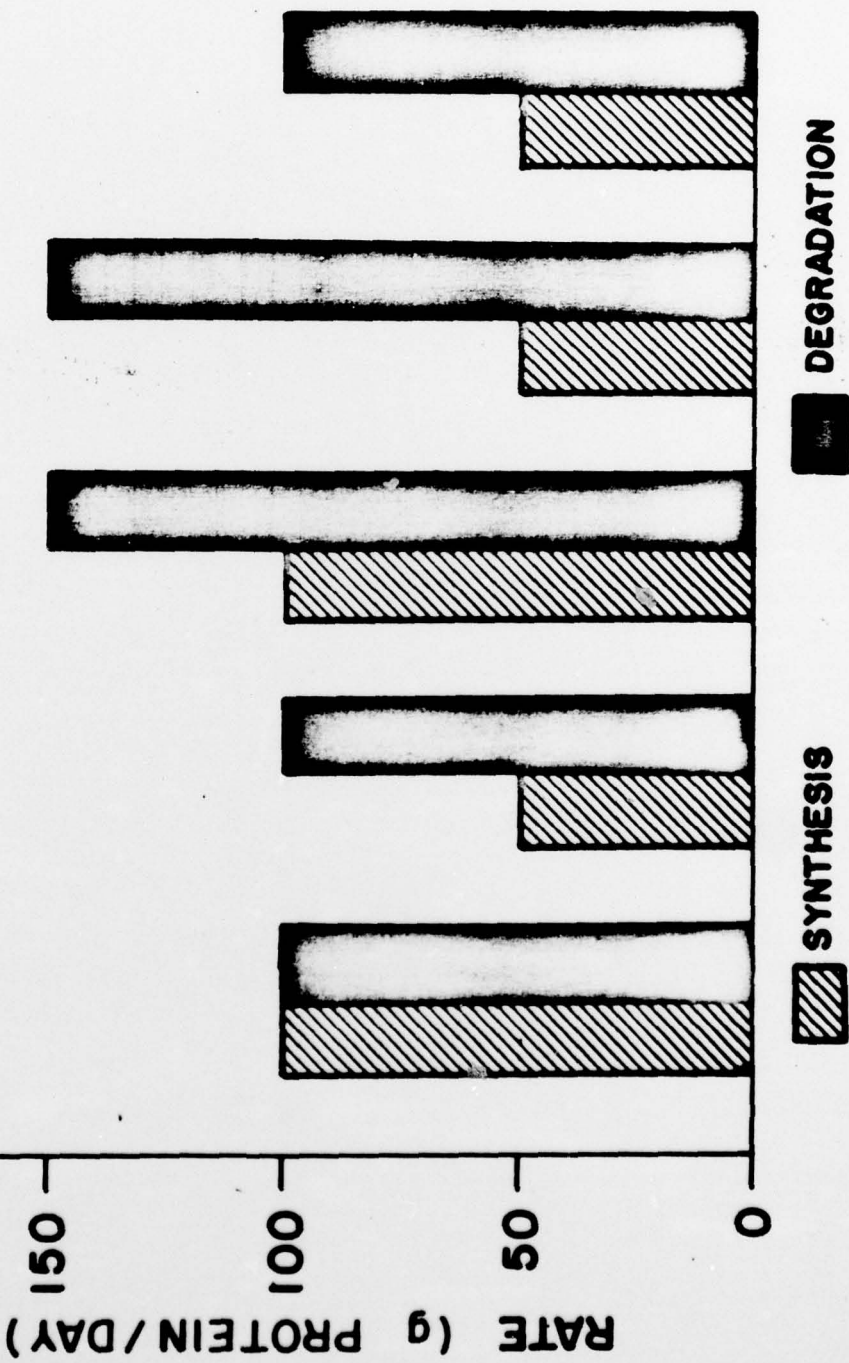stressed patients during a fast. Number next to the arrows

represents grams of protein per day.

Fig 2

PROTEIN METABOLISM (g/day) OF STRESSED PATIENT DURING A FAST

HEPATIC ACUTE-PHASE PROTEINS
GLOBULINS 38 15 ↓ ↑ 25
40 PLASMA PROT.
19 ↓ ↑ 20
AA ↑ 25 GLUCOSE

57

185

PROTEINS FOR HUMORAL & CELLULAR IMMUNITY
↓ ↑ AA

80

50 73

PROTEINS FOR TISSUE AND/OR ABNORMAL GROWTH ← AA

50

EXTRACELLULAR AMINO ACIDS (AA)

URINARY NITROGEN
155
(25 gN)

185

SKELETAL MUSCLE PROTEINS
AA

10

AA ↓ ↑ SKIN PROTEINS
5 ↓ ↑ 20

25 / 50
AA ↓ ↑ INTESTINAL MUCOSA

40
40

OBLIGATORY PROTEINS ⇌ AA

TOTAL BODY PROTEIN:

SYNTHESIS – 270 (35%) ↑

DEGRADATION – 425 (113%) ↑