A RETROSPECTIVE, EXPLORATORY ANALYSIS OF PREDICTIVE AND STRUCTURAL VARIABLES RELATED TO METABOLIC ENERGY EXPENDITURE IN TRAUMATIC BRAIN INJURY

by

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SUPERVISORY COMMITTEE APPROVAL

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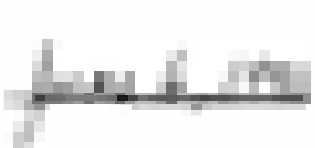
This dissertation has been read by each member of the following supervisory committee and by majority vote has been found to be satisfactory.



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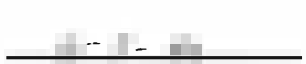

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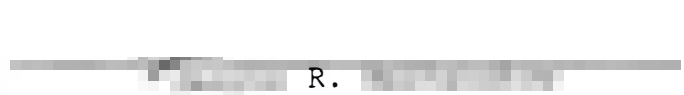

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FINAL READING APPROVAL

To the Graduate Council of the University of Utah:

I have read the dissertation of Peter Martin Sunderland in its final form and have found that (1) its format, citations and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the supervisory committee and is ready for submission to The Graduate School.

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ABSTRACT

Traumatic brain injury (TBI) produces severe derangements in metabolic and physiologic function with significant ramifications for determining nutritional therapy. The ability to understand the nature of current metabolic indicators is essential to improving the outcome from TBI. This study is a retrospective exploratory analysis of the predictive value and structural nature of current variables related to metabolic energy expenditure.

The variables evaluated in this study address pertinent processes of nutritional metabolism including injury classification, indices of metabolic expenditure advocated in the literature, concurrent treatments in TBI, clinical vital signs, neurological responses, glucose synthesis, protein synthesis and nitrogen excretion, and immune responses.

Analysis of the data included descriptive, correlational, predictive (regression), and factor modeling. Significant results include the lack of precision of current methods for estimating caloric expenditure in this population. Further, only 31% of this sample energy expenditure values as measured by indirect calorimetry were in the normal metabolic range as predicted by the Harris-Benedict Equation. Cost effectiveness of indirect calorimetry was further analyzed and found to be less expensive than alternative methods. Factor analysis of the metabolic variables provided a unique structure for conceptualizing the dimensions the metabolic variables represent.

Patients with TBI display unique metabolic patterns with significant implications for monitoring and supplementation. An integrated management model for nutrition in TBI is proposed with recommendations for timing of initiation, caloric supplementation, and delivery methods. Research implications are discussed.

To Sherry, who has made it all worthwhile. Without her support and caring this endeavor would not have been possible.

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CHAPTER I

NATURE OF THE STUDY

Introduction

Traumatic Brain Injury (TBI) produces severe derangements in metabolic and physiologic function with significant ramifications for the determination of nutritional requirements and subsequent therapy. Evidence promoting aggressive metabolic monitoring and optimal nutritional support as a method to improve the outcome from TBI continues to accrue. This nutritional support, however, has yet to receive general acceptance in the complex critical phases of injury in TBI. The realization of integrated nutritional management in the acute phase of TBI is hampered by a lack of understanding of the relationships among metabolic and physiologic processes, reliable indicators of these processes, and their direct impact on nutritional therapy. Increasing our knowledge of these processes holds the potential for improved nutritional management and patient outcome.

Significance of the Problem

The Interagency Head Injury Task Force (Department of Health and Human Services [DHHS], 1989, p. 7), recently reported on the devastating incidence and sequelae of Traumatic Brain Injury (TBI):

> Every fifteen seconds someone receives a head injury in the United States; every five minutes, one of those people will die and another will become permanently disabled. Each year, head injuries claim the lives of 75,000 to 100,000 Americans, with most of the deaths occurring at the time of the injury or within the first two hours of hospitalization. Of those who survive,

> each year approximately 70,000 to 90,000 will endure life-long debilitating loss of function, 5,000 new cases of epilepsy will result, and 2,000 will exist in a persistent vegetative state.

The reported yearly costs were estimated at 25 billion dollars per year. The DHHS Task Force (1989) recommended the primary emphasis for reduction of the incidence and severity of TBI (and rightfully so) to be in the realm of primary prevention. There is, however, a great need for increased understanding of the nature and treatment in the tertiary health setting, especially during the acute phase of injury.

In the acute phase, vast resources are utilized in terms of human resources and critical care facilities. Improved understanding of TBI by all clinicians responsible for the care of these individuals will help to save life, restore precious function, and help to reduce a formidable economic and emotional toll. The DHHS Task Force (1989) further identified a number of research priorities, three of which are particularly pertinent to the issues addressed by this dissertation: 1) "Integrating clinical brain injury research into clinical care settings" (p. 27); 2) "Developing new methods and modalities for more effective measurement of diagnosis, degree of injury, postinjury monitoring, and prognostic assessment of head injury for the acute and prolonged phases of care" (p. 26); and 3) "Developing, modifying and evaluating therapies that retard, prevent, or reverse brain damage after acute head injury: arrest further deterioration during the subacute phase; and provide for restitution of function for patients with long-term injury" (p. 26).

Metabolic and nutritional management in TBI has direct implications for contribution to these research goals. Improved understanding of postinjury metabolic sequelae, measurement methods, and appropriate clinical methodology holds promising potential for improving nursing assessment, management, and subsequent patient outcome.

Health promotion has been an important conceptual basis of nursing practice since its beginning. In the intensive care setting, however, nursing has assumed a more disease-oriented approach. Management of nutrition, as a uniquely human response, is one of many areas in the critical care setting where nurses can assert themselves as health promoters. Nutrition is not a disease and should not be conceptualized as such. The sequelae of malnutrition, however, can and most likely will lead to disease. If nurses value the principles of disease prevention, the provision of optimal nutrition must receive more emphasis. An understanding of metabolic alterations and the consequences for nutritional management is highly significant to the body of nursing knowledge at many levels. To the staff nurse specializing in intensive care, the understanding of the alterations they may encounter can lead to a greater awareness of the potential adverse sequelae created by insufficient or excess amounts of nutrients or improper quantities or proportions of substrate.

Through heightened awareness of these problems the intensive care nurse working with victims of TBI can assert himself or herself to insure that appropriate nutrition is made a priority. To the nurse specialist or practitioner, the ability to diagnose alterations in metabolism and provide appropriate nutrition represents a realization of the importance of nutrition as a valued health promoting function. It is insufficient for nursing to value a goal and not to take an active part in realizing that goal. This study represents a significant contribution to nursing by the effort taken to appreciate more fully the physiologic and metabolic alterations of TBI and the subsequent effects of nutritional needs as a health promoting activity in the intensive care setting.

Metabolism and Nutrition in TBI

Metabolic changes and the resulting nutritional sequelae have been well-characterized in TBI. Consensus, however, has not been reached as to the magnitude and the exact nature of the mechanisms and sequelae involved. Neuroendocrine response with the production of increased levels of catecholamine (norepinephrine, epinephrine, and cortisol) are believed to be the primary mediators of hypermetabolism and catabolism in response to injury (Clifton, Ziegler, & Grossman, 1981; Robertson, Clifton, & Grossman, 1984). More recently, the role of the acute phase response has been added to this list of mediators (McClain, Cohen, Ott, Dinarello, & Young, 1987). A summary of metabolic responses to injury from the pioneering work of Cuthbertson (1979) is illustrated in Figure 1. The differential effects of epinephrine and norepinephrine are depicted in Table 1.

The hypermetabolic response produced by these mechanisms is distinguished by an increased demand and utilization of the body's energy stores, primarily glycogen in the initial phases. When these glycogen stores are depleted, alternate endogenous sources of energy are supplied by the breakdown of protein from muscle and fat from adipose tissue. This protein and fat breakdown constitutes the hypercatabolic response (utilization of the body's tissues for primary energy production at the expense of less crucial physiologic functions).

In light of the metabolic changes in TBI, inadequate nutritional support has been implicated in a number of adverse sequelae including delayed wound healing, compromise of the immunological systems, loss of muscle mass (vital organs, including the heart and diaphragm, being most consequential), delayed gastric emptying, coagulation disorders, anemia, and loss of portions of the intestinal lining (Anderson, 1987). These consequences can be delayed or prevented by early, aggressive nutritional support.

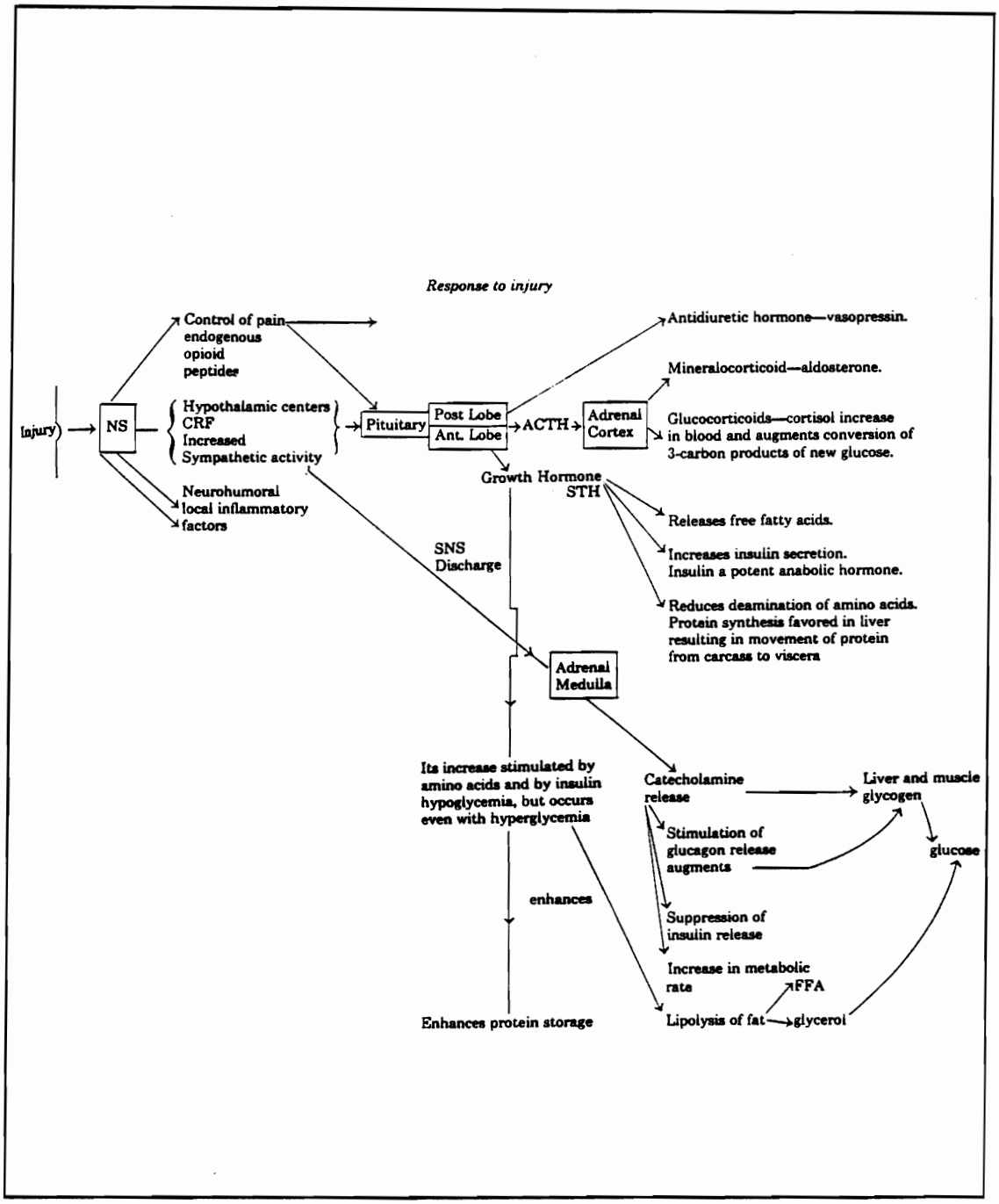

Figure 1. Metabolic response to injury. Note. From "The Second Annual Jonathon E. Rhoads Lecture. The metabolic response to injury and its nutritional implications: Retrospect and prospect" by D. P. Cuthbertson, 1979, Journal of Parenteral and Enteral Nutrition, 79(3), p. 111. Copyright 1979 by the American Society for Parenteral and Enteral Nutrition. Reprinted by permission.

Table 1

Effects of Epinephrine and Norepinephrine Infusion in Man

	Epinephrine[a]	Norepinephrine[a]
Cardiac		
Heart rate	+	-
Stroke volume	++	++
Cardiac output	+++	0,-
Arrythmias	++++	++++
Coronary blood flow	++	++
Blood pressure		
Systolic arterial	+++	+++
Mean arterial	+	++
Diastolic arterial	+,0,-	++
Mean pulmonary	++	++
Peripheral circulation		
Total peripheral resistance	-	++
Cerebral blood flow	+	0.-
Muscle blood flow	+++	0,-
Cutaneous blood flow	--	--
Renal blood flow	-	-
Splanchnic blood flow	+++	0,
Metabolic effects		
Oxygen consumption	++	0,+
Blood sugar	+++	0,+
Blood lactic acid	+++	0,+
Eosinopenic response	+	0
Central nervous system		
Respiration	+	+
Subjective sensations	+	+

Note. [a] + = increase, 0 = no change, - = decrease.

Note. From The Metabolic Management of the Critically Ill (p. 111) by D. W. Wilmore, 1977, New York: Plenum. Copyright 1977 by Plenum Publishing Co. Reprinted by permission.

Aggressive nutritional support, however, if not provided prudently and cautiously, can have serious untoward effects. Overfeeding can result in increased CO_2 production with significantly increased work of breathing, hyperglycemia, hyperlipidemia, hepatic dysfunction, and characteristics of prerenal azotemia all of which increase the energy demand on an already taxed system. The provision of nutrition is also complicated by working within therapeutic fluid restrictions (for the control of cerebral edema) and high incidence of electrolyte imbalances. The placement of central venous catheters to administer total parenteral nutrition (TPN), further increases the incidence of secondary complications including infection and pneumothorax.

Basis for the Study

This study is based on the experiences and observations obtained from the development and implementation of a nutritional protocol for patients with acute neurological disorders as the Neurosurgical Clinical Nurse Specialist, Division of Neurosurgery, University of Utah Health Sciences Center. During development and implementation of this protocol, discrepancies were found between current recommendations in the literature for caloric requirements compared with measurements obtained from performing energy expenditure measurements using indirect calorimetry (MGM II, Metabolic Gas Monitor). Although current caloric recommendations may be adequate for the majority of these patients, a significant number of the patients on the nutritional protocol had caloric requirements that fell markedly higher or lower than these recommendations (see Appendix A, Sunderland and Heilbrun, 1987, for a more complete discussion of these findings). The nutritional protocol also includes a highly developed framework for monitoring specific metabolic parameters to detect levels of metabolic stress developed at the University of Minnesota (Cerra, 1982; Konstantinidis, Teasley, Lysne, Shronts, Olson,

& Cerra, 1984). The level of metabolic stress in this framework is used as an indicator for specific nutritional supplementation.

These determinations of metabolic stress have not consistently correlated with clinical metabolic monitoring performed under the nutritional protocol. The inconsistencies observed, may in part, be due to the reality that the nutritional support framework developed at the University of Minnesota was not designed specifically for acutely neurologically compromised patients.

Statement of the Problem and Research Questions

The ability to decipher the meaning of metabolic indicators and make rational, informed decisions as to specific individual nutritional needs is a necessary ingredient to a favorable outcome in TBI. In order for the understanding of these metabolic indicators to be meaningful they must also be viewed in the context of the whole therapeutic scheme. This perspective is crucial for integration of this knowledge into practice.

Our present understanding of nutritional management of TBI is in the early stages. Although the critical first steps in understanding alterations in metabolic processes have been taken, there is a need for further exploration and replication of the present research findings in a variety of clinical settings. All too often, research investigations are carried out under rigorously controlled conditions despite variation in individual requirements. Justifiably, efforts are made to control for extraneous variables. Marked individual variation and needs, however, must be recognized to achieve the goal of optimal nutrition. Research findings must also be reproducible in a variety of different clinical settings to justify implementation and full integration into clinical practice.

Current studies of specific metabolic stress indicators, and their relationship to energy expenditure in TBI have been meager as well as varying markedly in their

recommendations. A total of six articles addressed variables that affect metabolic rate and only one of these made specific recommendations (see Appendix C, ARKS Variate Database Listing and Chapter II). These metabolic estimates vary to an extent that may result in clinically significant overfeeding or underfeeding in victims of TBI. Often the clinician must also rely on nutritional guidelines not specific to TBI with the subsequent potential for less than optimal nutritional management. The accurate prediction of energy expenditure within this context is a pivotal and essential piece of information on which all subsequent therapeutics rely. Most facilities treating TBI do not possess sophisticated monitoring capabilities such as indirect calorimetry, and thus rely on the ability to determine energy requirements from the outcome of research correlating sophisticated measurement tools such as indirect calorimetry with other more readily obtained physiologic and metabolic observations. For those facilities that do possess the capability of obtaining sophisticated metabolic analysis, the exploration of these concurrent metabolic phenomenon may be used to provide a more accurate understanding of metabolic processes leading to fewer adverse sequelae from inadequate nutrition and an understanding of clinical management principles that aid other clinicians with enhancing nutrient assimilation in their patients.

The following research questions were identified and provide the basis for this exploratory analysis among a population of patients with TBI:

1. Which metabolic indices are most predictive of metabolic expenditure and the catabolic response?
2. Can a clinically efficient method for predicting energy expenditure be derived from the relationship between indirect calorimetry and more easily acquired, clinically observable, metabolic indicators in TBI?

3. Is there sufficient variation in metabolic rate in TBI, among and within individuals to warrant routine use of indirect calorimetry for nutritional assessment and monitoring?
4. What are the patterns and dimensions of the relationships among metabolic indices (including laboratory measurements of carbohydrate and protein metabolism and physiologic indicators such as heart rate, and temperature) and calculations of energy expenditure by indirect calorimetry in TBI?
5. Are there theoretical factors that explain the relationships among observable data?
6. Can a structure of the relationships between metabolic parameters and theoretical factors be identified using multiple regression and exploratory factor analysis?
7. Once identified, can this structure be confirmed?

CHAPTER II

REVIEW OF THE LITERATURE

A general overview of nutrition in TBI, using a computerized knowledge development system [A Research Knowledge System (ARKS); Graves, 1989] will be presented first. The focus will be on frequency and definition of domain findings. Second, issues in the literature relating to the metabolic response in TBI will be reviewed. Third, specific indices of metabolic rate identified in the literature and their relationship to metabolic events occurring in TBI will be addressed. Fourth, strategies for clinical management will be presented.

Information from the literature addressing nutritional aspects in head injury from 1979 to 1989 was extracted using ARKS (information prior to 1979 was judged to be outdated): ARKS is a computer software program and methodology used for storing, structuring, and retrieving research data (see Appendix B). Out of 50 manuscripts specifically addressing nutrition and TBI, 29 were identified as original research in adult human subjects. Only these manuscripts were used for information extraction. The other citations identified were found to be primarily review articles, duplication of previous research, and research on non-human subjects. The pertinent information from animal studies was found to be included in the human subjects research cited. Information collected from the 29 citations included independent and dependent variable pairs, statistical findings and significance, relationships of the variables, and research conditions under which the variables occurred (i.e., time frame or specific information about the subjects or setting and research controls).

Variables were then given a broader abstract variable category for future structuring and summarization of the data, i.e., the abstract variable for the disease process head injury was classified as type of injury. Type of injury may, for future use, be extended to include all trauma and disease of the brain and surrounding structures or further generalized to other populations of disease or injury. Variables extracted from the literature were also assigned a to a category for modeling and analysis of domain findings. These categories include diagnosis, person (demographic and personal attributes), intervention/treatment, environment, and outcome. The outcome measures constituted both treatment outcome and disease outcome.

Overview of Nutrition in TBI: ARKS Analysis

One hundred ninety-four variable pairs were identified in the literature. All independent and dependent variables fell within four of the five categories; diagnosis, person, intervention/treatment, and outcome. No variables related to the environment category could be identified. A listing of these metastructure classifications (categories) and abstract variables is illustrated in Figure 2. Research variables derived from the literature review specifically relating to metabolic rate are shown in Table 2. The complete ARKS variate database listing of metastructure classifications (categories) with the corresponding abstract variables and author specified variables can be found in Appendix C. The citation database corresponding to the variate listings can be found in Appendix D.

Disease/Population

All research variables within the Disease/Population category were condensed into three abstract variables; type of injury, extent of injury, and temporal response. The type of injury in this review was confined to those manuscripts addressing TBI in adult human subjects. Extent of injury in the literature primarily consists of the

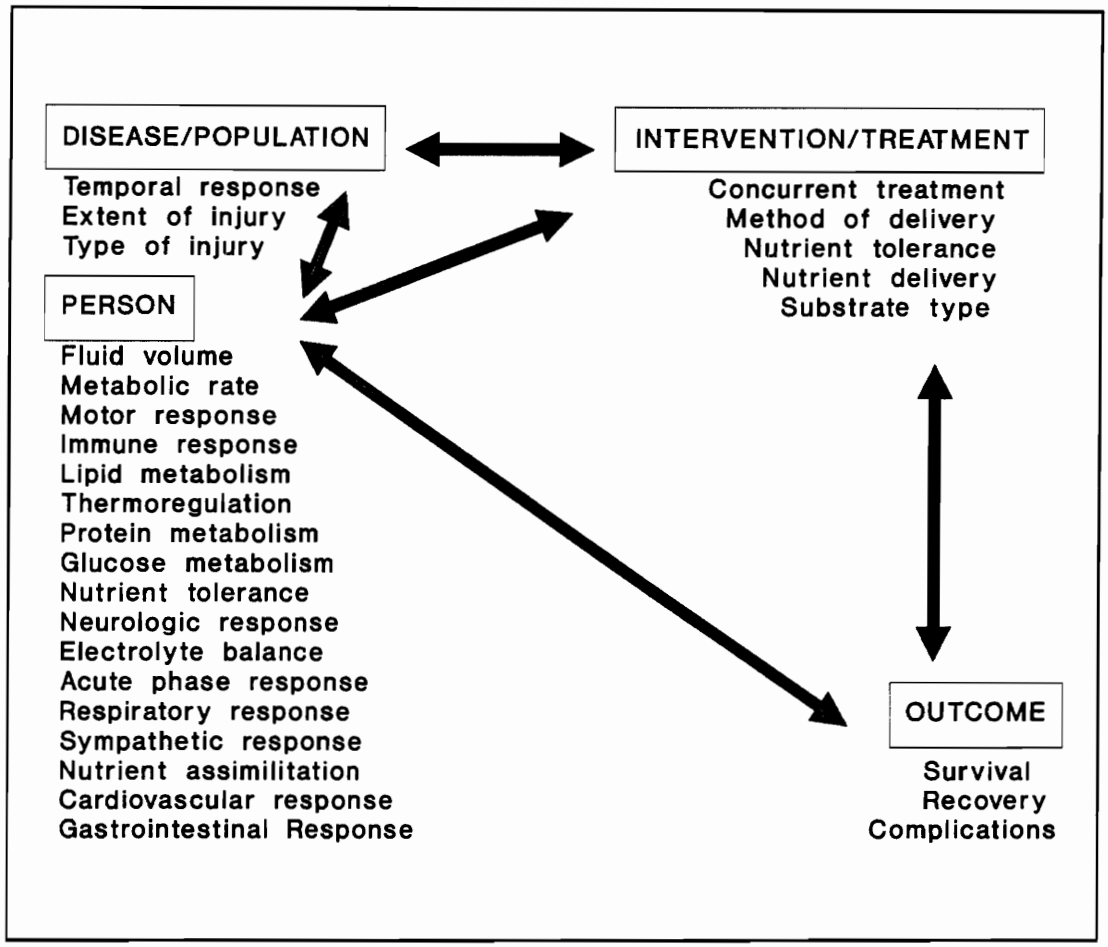

Figure 2. ARKS Categories and Abstracted Variables. Note. Abstractions of variables related to nutrition in TBI arranged by category. Arrows represent the presence of relationships between categories. Causal relationships are not implied.

differential effects of two concepts on metabolic response: 1) the severity of the primary brain injury; and 2) the presence of concurrent injuries, i.e., multiple system trauma. The greatest proportion of variables included within this classification are related to temporal response. Further discussion of specific findings will follow in the next section.

Temporal response can be defined as the time frame under which the variables or their magnitude occurred. Two issues have particular importance within this category. First, is the hypermetabolic response to TBI, as a direct result of

Table 2

ARKS Derived Research Variables Directly Related to Metabolic Rate

Category	Abstraction	Researcher Specified
Disease	Type of injury	Head Injury
	Temporal Response	Days since injury
Intervention	Concurrent Treatment	Steroids
		Barbiturate Coma
		Paralytic Agents
		Sedation
	Sympathetic Response	Beta-Blockade
	Nutrient Delivery	Caloric Intake
Person	Cardiovascular Response	Heart Rate
		$AV0_2D$
	Motor Response	Spontaneous Activity
		Glasgow Coma Scale
	Sympathetic Outflow	Arterial Epinephrine
		Arterial Norepinephrine
	Thermoregulation	Body Temperature
	Neurological Response	Glasgow Coma Scale

Note. Variables sorted by metastructure code (category), abstract variable representation, then researcher specified name. $AV0_2D$ = Arteriovenous oxygen difference.

persistent brain dysfunction, present over a prolonged period of time, or are there other plausible hypotheses explaining the appearance of a sustained hypermetabolic state? Second, if the hypermetabolic response to TBI is sustained, can this response be predicted using metabolic or physiological observations?

Person

The Person category demonstrates the greatest proportion of research emphasis. Seventeen abstract variable classifications contain all specific research variables extracted from the literature. This classification can be defined as containing individuals' observable attributes in response to injury or intervention as well as their inverse effects upon injury, intervention, and outcome. These variables represent the data upon which assessment and intervention rely. Interestingly, the investigations of these variables have been limited to bivariate correlational analysis (small sample sizes) with one exception (Clifton, Robertson, & Choi, 1986). The only variables related to outcome have been indices of protein metabolism (primarily nitrogen balance). The complexity of the relationships among these individual attributes comment on the highly interconnected nature and sheer quantity of metabolic responses in TBI. These relationships further illustrate that effective clinical nutritional management must be conducted with due regard for potential adverse consequences on physiological function. Three predominant examples of adverse consequences exist in TBI; problems associated with concurrent management of fluid and electrolyte balance and nutritional support, glucose metabolism (predominantly hyperglycemia), and respiratory response (increased CO2 production). Further analysis of individual, observable responses constitutes the major portion of this review and will follow later in this chapter.

Intervention/Treatment

The Intervention/Treatment category was condensed to five abstract variables. The predominant research emphasis and significant findings involve method of nutrient administration, specifically, groups of subjects receiving TPN (total parenteral nutrition) versus TEN (total enteral nutrition). These findings also constitute the only nutritional intervention strategies that have repeatedly demonstrated a favorable effect on the outcome from TBI. The specific method of delivery is not the issue however. Instead, the difference between these groups is believed to be the effect of receiving nutrition without delay or not withholding nutrition until gastrointestinal function is reestablished (Rapp, Young, Twyman, Bivins, Haack, Tibbs, & Bean, 1983).

Variables related to nutrient tolerance have been primarily limited to the quantity of calories received, usually as a secondary finding to the primary research variables. Nutrient tolerance has been mostly concerned with the time frame within which enteral feedings could be initiated as well as the relationship to the level of neurological function. Substrate type refers to the therapeutic manipulation of different concentrations of specific nutrients. This area of inquiry has not received near the emphasis that has been given to other categories of injury and disease. This lack of information has made it necessary for the clinician providing nutritional management to this population to rely on guidelines not specifically related to TBI (as is the case in our institution).

Concurrent treatment has also been the subject of controversy. The principle issue has been the use of glucocorticoids and subsequent hypotheses of their impact on metabolic alterations. The results of these studies have been conflicting in approximately equivalent proportions. The questionable efficacy of steroids, however, in the treatment of TBI has all but made this issue moot. The most

significant issue for nutritional management concerns the concurrent use of four classes of pharmacologic agents; narcotics (i.e., morphine), paralytic's (i.e., pancuronium bromide), sedatives (i.e., midazolam and diazepam), and beta-blockers (i.e., propranolol). The first three of these agents influence metabolic rate primarily by reducing or eliminating the influence of activity or motor response. Beta blockade is believed to reduce the metabolic influence as a result of reducing sympathetic response. These agents together or individually can have a profound effect on metabolic rate. The consequential effects on nutritional requirements have not been adequately addressed in the literature and need further examination.

Outcome

The outcome category consists of variables related to clinical complications, recovery from the injury, and survival (mortality). Variables addressed in the literature have been related primarily to the method of delivery and time frame, specifically TPN versus TEN. Rapp, Young, Twyman, Bivins, Haack, Tibbs, and Bean (1983) and Young, Ott, Twyman, Norton, Rapp, Tibbs, Haack, Brivins [sic], and Dempsey (1987) have shown significant influences of early TPN on reducing mortality. These results, however, were not confirmed in two additional independent studies possibly due to smaller sample sizes and shorter time of follow-up (Hadley, Grahm, Harrington, Schiller, McDermott, & Posillico, 1986; Hausmann, Mosebach, Caspari, & Rommelsheim, 1985). High renal nitrogen loss has been associated with poor recovery and mortality by Piek, Lumenta, and Bock (1985).

Hypermetabolic and Catabolic Responses to TBI

To aid the appreciation of the following discussion, basic terminology used in the metabolic literature will be reviewed. Basal metabolic rate (BMR) refers to the amount of fuel or substrate, generally expressed in kilocalories (Cal), required

for synthetic, chemical and osmotic processes, and mechanical work, i.e., respiration, digestion, and cardiac contraction (Gadisseux, Ward, Young, & Becker, 1984). Energy expenditure is a term used to denote fuel utilization from a combination of the BMR plus physical activity. Another term commonly used in the literature is resting metabolic or energy expenditure (RME/REE respectively). This term reflects the combination of the BMR plus the energy requirement from physical activity with the subject at rest. REE, as expressed in the current literature, is most commonly derived by a relatively new technique of metabolic gas monitoring known as indirect calorimetry. Measurements of oxygen consumption ($V0_2$), carbon dioxide production ($VC0_2$) and their ratio expressed as the respiratory quotient (RQ) are obtained. This information can be used to calculate energy expenditure as well as alterations in the ratio of substrate utilization when combined with measurements of nitrogen excretion (Westenskow, Cutler, & Wallace, 1984). Measured energy expenditure (MEE) implies that varying degrees of activity may exist or are uncontrolled during measurements of metabolic rate. Predicted energy expenditure (PEE) generally refers to calculations using the Harris-Benedict equation (basal energy expenditure, see Table 3). The value derived for BMR is then multiplied by a somewhat arbitrary factor to account for additional activity and metabolic stress. Generally 1.25 to 2 times the BMR is used as the basis for calculating caloric supplementation (depending on illness severity).

Duration and Severity of Responses

The extent and actual presence of a sustained hypermetabolic and catabolic response in TBI has, itself, been the subject of controversy. This issue has important implications for risk assessment and aggressiveness of clinical management. The physiological and metabolic response to isolated closed head injury (absence of other significant injuries) was evaluated by Deutschman, Konstantinides, Raup, Thienprasit,

Table 3

Harris-Benedict Equation

Males: BMR = 66.5 + (13.8 X weight [Kg.]) + (5 X height [cm.]) - (6.8 X age).
Females: BMR = 655 + (9.6 X weight) + (1.8 X height) - (4.7 X age).

Note. Adapted from Nutritional Medicine: A Case Management Approach (p. 175) by G. L. Blackburn, S. J. Bell, & J. L. Mullen, 1989, Philadelphia: Saunders.

and Cerra (1986); and Deutschman, Konstantinides, Raup, and Cerra (1986). Ten patients with mean GCS scores of 4.4 + or - 1.5 were studied with the goal of determining the longitudinal changes in metabolic parameters relative to level of stress. Metabolic parameters were compared to fasting (overnight-fasted preoperative patients) and stressed (post-operative general surgery or trauma) control groups from retrospective data (preexisting data banks). Initial elevations in arterial-venous oxygen difference ($AV0_2D$), $C0_2$ production, and lactate/pyruvate ratio were noted on day one after injury, and total peripheral resistance and cardiac index on day 3 after injury (all indicators of metabolic stress). These stress responses were found to subsequently decline over the following seven day study period. Amino acid profiles (including 3-methyl histidine) were comparable to stress controls on the first day after injury, whereas by day 7 a pattern more consistent with the fasting control group was noted. The authors concluded a resolution of the hypermetabolic state by day 7 after head injury in their sample. Persistent nitrogen excretion found in their group was hypothesized to be the result of obligatory nitrogen breakdown in response to reduced levels of activity and not catabolic in nature. Elevation of CO_2, induced by intravenous glucose administration, was presented as the explanation for elevated energy expenditure estimates from previous

research, (the research of Robertson et al. [1984] was specifically addressed). RME measurements of up to 350% of PEE cited by Robertson, however, cannot be explained by endogenous glucose supplementation. The issue of increased CO_2 production has also been primarily related to intravenous dextrose infusions, whereas Robertson's subjects received a mixed substrate enteral formula.

In contrast, Clifton, et al. (1981) demonstrated persistent increases in metabolic expenditure up to 3 weeks after injury. These increases were further found to correlate with neurologic function as measured by the Glasgow Coma Scale (GCS). Negative nitrogen balance persisted throughout the three week study period, although gradually improving by the end of the study period. The findings of a persistent hypermetabolic state have been subsequently confirmed: Young, Ott, Norton, Tibbs, Rapp, McClain, and Dempsey (1985) reported a mean increase in MEE over PEE of 1.4 at 21 days ($\underline{n}=16$); McClain et al. (1987) reported MEE as 1.6 times the PEE during the first 3 days after injury, slowly declining to 1.12 times the PEE at 16-19 days ($\underline{n}=12$). In my experience with the nutritional protocol at the University of Utah, caloric supplementation in excess of 20% over RME has been associated with RQs in excess of 0.95. These elevated RQs have further been associated with hyperglycemia and elevated hepatic enzymes, indicating fat synthesis and deposition in the liver.

The differential metabolic response between isolated TBI and TBI with concurrent trauma has also been characterized. Fell, Benner, Billings, Siemens, Harbison, and Newmark (1984) evaluated indices of protein metabolism (serum albumin, and thyroxin binding prealbumin [TBPA]), serum CO_2, and electrolyte profiles over 5 days in isolated TBI ($\underline{n}=23$), TBI with multisystem injury ($\underline{n}=27$), and multisystem injury without TBI ($\underline{n}=10$). The combined TBI and multisystem injury group demonstrated significantly lower albumin and TBPA levels compared to

isolated TBI. The combined injury group showed significantly higher negative nitrogen balances compared to the isolated TBI group. Although not reported, nitrogen balance between isolated TBI and isolated multisystem injury appeared comparable. Measurements of energy expenditure were not reported. The author's conclusion of the absence of a hypermetabolic state in isolated TBI based on the data presented is weak. Given the study period (5 days), high variability of serum proteins and CO_2 over this short period does not substantiate a normal metabolic state in isolated TBI. In contrast, Chiolero, Schutz, Lemarchand, Felber, DeTribolet, Freeman, and Jequier (1989) studied 3 groups comparable to Fell et al. (1984). The three groups failed to differ significantly on measures of plasma cortisol, glucagon, insulin, nitrogen excretion, catecholamine, and free fatty acids over a 5 day period after injury.

The issue of duration and severity of catabolism addressed by Deutschman et al. (1986) is far more complex in nature. Amino acid profiles in stress show a decline in response to increased hepatic extraction to support gluconeogenesis and increased cellular clearance for use as an energy substrate. Differentiating the longitudinal effect between increased protein mobilization in response to stress and obligatory nitrogen loss from inactivity is difficult. The only comparable research to Deutschman et al. (1986) is Hausmann et al. (1985) whose estimates of the amino acid 3-methyl histidine showed consistent elevation over an 8 day study period. This amino acid is, further, produced solely by muscle, indicating endogenous protein mobilization for use as energy substrate versus excretion of exogenous supplementation (Long, Birkhahn, Geiger, Betts, Schiller, & Blakemore, 1981).

Additional indicators of protein synthesis and utilization addressed in the literature have included serum proteins (albumin, transferrin, TBPA, and retinol binding protein [RBP]), creatinine-height index, urine 3-Methyl histidine, and urinary

urea nitrogen (UUN) excretion. Measures of serum proteins vary markedly over time and are especially subject to variation in the critically ill, primarily in response to shifts in fluid balance and trans-vascular protein shifts. The differing half lives of serum proteins must also be taken into account; albumin-21 days, transferrin-7 days, TBPA-2 to 3 days, and RBP-1 day. The most often cited serum protein in the literature has been albumin. The half-life of 21 days, however, makes albumin a poor indicator of protein synthesis in response to nutritional therapy in critically ill patients. Results from studies of proteins with shorter half lives, also, do little to illuminate the nature of protein synthesis over time. Kaufman, Bretaudiere, Rowlands, Stein, Bernstein, Wagner, and Gildenberg (1987) studied transferrin levels at 10 days after TBI. Taking into consideration the seven day half-life of transferrin, the levels at day 10 may be questionable. Young et al. (1985), reported weekly RBP levels consistently in the normal range over a 22 day study period. Piek et al. (1985) reported similar results for RBP and TBPA over an 8 day period. The primary emphasis placed on measures of serum proteins, in the literature, has been to differentiate between nutritional regimens and not to illustrate the severity or duration of the catabolic response. Additional indicators of protein synthesis reported in the literature include creatinine-height index and urine urea nitrogen. These are useful indicators of protein excretory products and nitrogen loss. Reports of nitrogen balance have consistently reported severe negative values. Nitrogen and creatinine secretion, however, have been difficult to interpret in differentiating obligatory nitrogen loss from catabolism secondary to stress.

This discussion of the issues and research in nutritional therapy points out that a consensus on the nature of the hypermetabolic and catabolic phenomenon, in TBI, is far from complete. Although the literature favors the presence of a hypermetabolic state, there continues to be disagreement on extent, causation, manifestations, and ultimate effects of the metabolic derangements in TBI.

Consensus on measurement methods and standardization of metabolic indicators is also lacking. Small sample sizes and short study durations have hampered the understanding of these issues. The lack of consensus further points out inherent metabolic variability in this population. This variability makes a good argument of the need for accurate and efficient assessment techniques.

Indicators of Metabolic Rate

Indicators directly associated with metabolic rate in TBI have been related to neurologic response, sympathetic activity, cardiodynamics, and thermoregulation. The ability to meaningfully interpret these indirect indices of physiological and metabolic function is an important key to successful nutritional management. Only one predictive analysis, however, combining variables in a multiple regression analysis has been reported in TBI (Clifton et al., 1986, Table 4). Days since injury (DSI), GCS, and heart rate (HR) were reported to have good predictive value (comatose patients with isolated closed head injury, n = 57). Individuals with a GCS equal to or less than eight were analyzed separately and regression analysis resulted in the equation in Table 4. DSI did not account for a significant proportion of the variance in a separate analysis of individuals with a GCS above eight (see Table 4).

Table 4

Clifton's Regression Equation

GCS < 8: RME = 152 - 14(GCS) + 0-.4(HR) + 7 (DSI).
GCS > 7: RME = 90 - 3(GCS) +0.9(HR).

Note. 1. RME = resting metabolic expenditure, GCS = Glasgow Coma Scale, HR = heart rate, DSI days since injury. 2. Clifton et al. (1986).

One limitation evident in this study is the time frame. Individuals were studied over 14 days. Extrapolation of this method, outside of that period, could have questionable results. Multiple regression analysis is a robust procedure; however, certain violations of basic assumptions in this analysis have not been addressed. These assumptions and additional characteristics of the specific indices will be addressed in the following sections.

Neurological Function and Metabolic Rate

The Glasgow Coma Scale has been the exclusive measure of neurologic function associated with metabolic rate in the TBI literature. Within the GCS is the observation of flexor or extensor posturing which has, by itself, been related to metabolic rate (see Table 5). The GCS has also been associated with measures of protein metabolism, neuroendocrine response, tolerance of nutrition, and cardiovascular response (see appendix C). Two reports specifically address GCS and metabolic rate, Clifton et al. (1986) noted above and Robertson et al. (1984). The latter evaluated RME by indirect calorimetry and found the highest values in individuals with GCS scores of 4-5, lowest values associated with scores of 6-7, and intermediate values with scores greater than 7.

Two seemingly different patterns are presented by these two reports. These patterns are especially perplexing considering the presence of a shared author/co-author. One of the basic assumptions of linear regression analysis is the presence of a linear relationship between variable pairs (Lewis-Beck, 1980). The regression analysis reported above assumes a linear relationship between GCS and metabolic rate whereas the results of the latter bivariate analysis report data more consistent with a curvilinear relationship. Curvilinear relationships can often be managed in multiple regression analysis with transformation procedures, but none was performed on these data. The parameter of days since injury must also be curvilinear.

Table 5

Glasgow Coma Scale

Neurological Response	Grade
Eye Opening Response	
Spontaneous	4
To Speech	3
To Pain	2
No Response	1
Best Verbal Response	
Oriented to time, place, and person	5
Confused/Disoriented	4
Verbalization inappropriate	3
Verbalization incomprehensible	2
No Verbalization	1
Best Motor Response	
Follows Commands	6
Localizes to Pain	5
Withdraws to Pain	4
Abnormal Flexor Response	3
Abnormal Extensor Response	2
No Motor Response	1

Note. The total score is derived by adding the scores from the three categories.

Note: Adapted from the Manual of Patient Care in Neurosurgery (p. 219) by J. R. Howe, 1983, Boston: Little Brown.

The value, at some point, must resort to a negative sign in the relationship, assuming a return to baseline metabolic expenditure. The clinical significance of the magnitude of error this relationship represents needs further examination.

The effects of paralysis and sedation on metabolic rate have also reported; patients at rest, who were nonsedated and nonparalyzed, were compared to those who were sedated, paralyzed, or in barbiturate coma. Daily variation in caloric expenditure of 99% to 250% in nonsedated patients was noted (as measured by indirect calorimetry). In spontaneously posturing patients, daily caloric consumption ranged from 5,000 to 12,000 calories per day (Robertson et al. 1984). Metabolic rate was reported to decline to 100-125% of predicted energy expenditure with the use of paralytic and sedative agents (Clifton et al. 1986).

Cardiovascular and Sympathetic Responses

The association between cardiovascular responses and metabolic rate in TBI have been identified in four papers. Clifton et al. (1981) demonstrated significant positive correlations of serum norepinephrine and dopamine beta-hydroxylase (serum catecholamine) with blood pressure and heart rate (HR). Robertson et al. (1984) reported significant positive correlations of arterial norepinephrine and epinephrine with REE; decreased REE with beta-blockade (propranolol); and correlations of the GCS, oxygen consumption, and plasma volume with cardiac index (cardiac index is the cardiac output divided by body surface area, a function of stroke volume and HR). Arterial epinephrine levels (as an indicator of increased sympathetic activity) were further reported to be significantly related to HR and arterial blood pressure. REE and HR were reported as demonstrating no relationship. This conflicts with the later finding of one of three variables showing good prediction by multiple regression analysis discussed earlier (Clifton et al. 1986). Deutschman et al. (1986)

also showed a significant elevation of cardiac index in TBI in the first three days after injury.

The data presented here conceptually demonstrate the linkages between sympathetic response with observable cardiodynamic changes and the presence of concurrent metabolic effects. The association of sympathetic activity as a mediator of hypermetabolism and catabolic responses has been well established in other patient populations (i.e., burn and trauma). These conceptions are also consistent with the mediation of the hypermetabolic response as originally described by Cuthbertson (1976, see Figure 1).

Thermoregulation

Altered thermoregulation is a common finding in head injury. Elevated body temperature, further, has been shown to increase metabolic rate. Mechanisms accounting for an increased incidence of fever in TBI include increased susceptibility to infection, altered hypothalamic function, the effect of increased catecholamine, and to a lesser degree the effect of endogenous nutritional supplementation. Clifton et al. (1981) demonstrated elevations in norepinephrine (NE) and dopamine beta-hydroxylase (DBH) that positively correlated with elevated body temperature. Robertson et al. (1984) reported positive correlations of temperature with REE when subjects were separated into groups based on severity of injury as determined by GCS (45% increase for each degree centigrade (C) with a GCS of 4-5 and a 15% increase for each degree C with a GCS of 6-7). Endogenous supplementation of nutrients, in both normal and injured subjects, increases heat production through a process termed specific dynamic action (SDA): SDA is the effect that food sources have on increasing heat production (Silberman, 1989). Under normal circumstances ten % is added to calculations of energy expenditure. According to Wilmore (1977),

however, the SDA under conditions of hypermetabolism only accounts for a small error in energy expenditure calculations, approximately 10%.

It is evident from the preceding discussion that direct correlates of observable clinical attributes, directly related to metabolic expenditure estimates, are small in number. It is also noteworthy that they have evolved from the pursuits of a limited number of researchers and clinical studies. Clifton and associates of the Baylor College of Medicine are the most exemplary.

Nutritional Management Models

Nutritional monitoring guidelines specific to head injury are few in number and incomplete. No references were found in the literature that address when to initiate feedings; what differential protein, lipid, and carbohydrate ratios to provide; the caloric quantity; and necessary assessment parameters. Regardless of these inadequacies, specific conventions are evolving from the present research. Accepted conventions for nutritional management in TBI now include early initiation of TPN or TEN, supplementation consistent with the expectation of a hypermetabolic and catabolic state (although estimates vary), and monitoring to recognize protein or calorie deficiencies and complications of nutritional therapy. The most comprehensive management approach noted has been described by Twyman and Bivins (1989). Twyman and Bivin's essay includes all of the conventions noted above with the exception of assessment guidelines for protein synthesis. They also recommend supplying 75% of PEE derived from the Harris-Benedict Equation. The consequences of routine supplementation at this rate is unknown. From my experience, it is unlikely to meet the specific needs of a significant number of individuals.

A model for categorizing metabolic stress and recommendations for subsequent nutritional supplementation (see Table 6) was reported by Cerra (1982)

Table 6

Metabolic Stress Framework

Categories of Metabolic Stress				
Stress Level	0	1	2	3
Clinical Example	Starvation	Elective Surgery	Multiple Trauma	Sepsis
Urinary Urea Nitrogen Excretion Gms./Day	<5	5-10	10-15	>15
Serum Lactate MMOL/L	0.01+/-.005	1.2+/-.2	1.2+/-2	3+/-5
Serum Glucose Mg%	100+/-20	150+/-25	150+/-25	250+/-50
Insulin Resistance	-	-	+	+
Oxygen Consumption ml./M^2	90+/-10	130+/-6	140+/-6	160+/-10
Nutritional Requirement by Level of Stress				
Estimated Caloric Need	BEE	BEE x 1.3	BEE x 1.5	BEE x 2.0
Total Calories KCal/Kg/day	28	32	40	50
Amino Acids Gms/Kg/day	1	1.5	2	3

Note. Adapted from "Nutritional Requirements of the Hypermetabolic Patient" by N. N. Konstantinides et al., 1984, Nutritional Support Services, 4, p. 42 and 43.

and Konstantinides et al. (1984). Metabolic stress in this model is determined from urinary urea nitrogen excretion, urinary 3-methyl histidine secretion, plasma lactate, plasma amino acids, plasma glucose, detection of insulin resistance, and glucagon levels. Once categorized, individualized nutritional recommendations are given and include the appropriate stress factor over BEE, amino acid supplementation in Gms./Kg./day, total non-protein calories, total calories, and percentage of total daily caloric supplementation from fat, protein, and carbohydrate. Guidelines for serial evaluation include complete electrolyte profile, evaluation of coagulation, hepatic function, triglyceride levels, short half life serum protein levels, serum amino acid determinations, vitamin and trace elements, and nitrogen excretion. Realistically, acquisition of many of these parameters is beyond the ability of most institutions, however, a significant number are easily and routinely obtained. This nutritional management model is intriguing. Evaluation of the model, however, has yet to be reported. Should these indices provide an accurate reflection of individual requirements the model would be an invaluable tool.

Summary

This review has summarized the present understanding of the metabolic and nutritional characteristics in TBI. A structural representation was offered to condense and simplify a complex domain of inquiry (Figure 2). The conceptual relationships of induction, process, and consequences of a hypermetabolic and catabolic state in TBI were demonstrated. Literature available on specific indices of metabolic rate were reviewed and the lack of a comprehensive management model addressed.

The overwhelming message this review points out is the population of TBI is at high risk for significant malnutrition. Once malnourished, all aspects of therapeutic management are affected. The subsequent cost in terms of loss of

function and health care resources cannot be underestimated. The accumulation of knowledge and methods to prevent malnutrition in this population is a worthwhile goal and deserving of rigorous academic and clinical pursuit.

CHAPTER III

METHODOLOGY

Metabolic phenomena in Traumatic Brain Injury (TBI) and their clinical implications will be studied with a retrospective, correlational/descriptive, exploratory design with predictive and factor modeling (Brink & Wood, 1989; and Polit & Hungler, 1987). This chapter will provide a description of the sampling plan, subjects, and protocol used for nutritional management in this sample, data collection procedures, and data analysis strategies.

Sampling Plan and Subject Description

Following Institutional Review Board approval, medical records of patients admitted to the Neuro Critical Care Unit (NCC) on the Neurosurgery Service at the University of Utah Health Sciences Center, from the years 1986 and 1989, was reviewed. Information from the records of patients admitted with the diagnosis of TBI and placed on a nutritional protocol was included in this study.

Treatment of TBI in this institution, during the sampling period, was standardized. These treatment standards address control of airway and ventilation, fluid and electrolyte balance, and increased intracranial pressure. Patients with a Glasgow Coma Scale (GCS) score of 8 or less were routinely intubated and mechanically ventilated. Hypocarbia was induced with mechanical hyperventilation to a $pC0_2$ of 25-30 mm. Hg. to reduce cerebral blood flow and subsequent cerebral edema. Sedatives, narcotics, and/or paralytic agents were concurrently administered

for agitation during mechanical ventilation. Fluid management consisted of mild dehydration by replacement of approximately 70-80% of maintenance fluid requirements. To inhibit progressive cerebral edema, intravenous fluid electrolyte solutions used in this group consist of either Ringer's Lactate or normal saline and dextrose prior to initiation of TPN or TEN. Dextrose is eliminated from intravenous solutions after TPN or TEN is initiated to prevent worsening hyperglycemia. Intracranial pressure (ICP) monitoring was utilized in the majority of these patients either by subarachnoid screw or ventriculostomy. Fiberoptic transducers for ICP monitoring were routinely used. ICP's greater than 20 mm. Hg., uncontrolled by mechanical ventilation alone, were treated by osmotic diuresis using mannitol and/or furosemide. Persistent ICP of 20 mm. Hg. or greater was treated by the administration of lidocaine HCl (1 mg./Kg. every 20 minutes). Barbiturate coma, for the treatment of increased ICP refractory to other measures, was not used in any of these subjects. Beta-blockade, for the control of hypertension, was also not routinely used.

Nutritional Protocol

The inclusion criteria for placement of patients on the nutritional protocol consisted of a GCS score of 8 or less on admission and/or the subjective prediction that the neurological injury would preclude oral intake within 3 days after injury, necessitating the initiation of total parenteral or enteral nutrition. The goal for initiating TPN or TEN was within 48 hours of admission. This criteria, further, included both open and closed head injury, the presence of neurovascular disruption (intracranial hemorrhage), and the presence of other non-neurological injury (including multiple trauma).

Baseline nutritional/metabolic parameters were obtained as soon as possible after admission and consisted of serum Sequential Multiple Analysis Computer

assessment (SMA-20); serum: osmolality, magnesium, lactate, TBPA, and transferrin; partial thromboplastin time and prothrombin time; complete blood count with differential; UUN excretion; and metabolic gas measurements (indirect calorimetry).

The goal of the protocol was to initiate TPN or TEN within 72 hours of admission. Caloric supplementation was based on REE derived from indirect calorimetry (IC). When IC could not be obtained, supplementation was based on the Harris-Benedict equation in combination with the nomogram developed by Clifton, et al. (1986, reviewed in Chapter 2). Substrate composition was based on the recommendations of Cerra's (1982) and Konstantinides' (1984) stress stratification framework (see Table 6). This framework uses measures of protein excretion (urinary urea nitrogen and urinary 3-Methyl histidine), degree of insulin resistance and gluconeogenesis (serum blood glucose, serum lactate, glucagon to insulin ratio, and insulin requirements), and oxygen consumption to classify the individual's level of metabolic stress in four categories. Measures of Serum 3-Methyl histidine and glucagon levels were not available at this institution and thus not used as indices for the interpretation. Based on the parameters the corresponding percentages of substrate were administered according to stress categorization (Table 6).

The nutritional management, on this service, varied from the recommendations of the stress categorization framework when fluid restriction precluded the administration of these quantities of substrate. In these situations, the use of increased amounts of lipid emulsions were substituted (up to 60% of non-protein calorie intake) to achieve the goal of caloric balance. Triglyceride levels were obtained in these situations to detect significantly elevated levels indicating poor lipid assimilation. Nutritional supplementation and monitoring continued until neurological status improved and oral intake was adequate, or until the patient's

condition deteriorated to the degree that further aggressive support would be futile and extraordinary life support measures were withdrawn.

Laboratory parameters were repeated at weekly intervals to evaluate the efficacy of nutritional therapy. The goal for obtaining Indirect Calorimetry was one to three times weekly depending on variation in REE in reference to previous measurements or change in patient condition.

Data Collection Procedures and Instrumentation

Specific data collected from this sample were contained within seven categories. These categories included injury classification, indices of metabolic expenditure, concurrent treatments, vital signs, neurologic and motor responses, measures of gluconeogenesis, and protein excretion and synthesis. All laboratory measurements are standardized and were performed by the Associated Regional and University Pathologists laboratory (ARUP). Certification for ARUP is provided by the American Society of Pathologists.

Injury Classification

Severity of injury and the effect of metabolism in the TBI literature has been solely addressed by rank categorization in one of two categories: isolated neurological trauma or neurological plus non-neurological trauma. In an effort to more fully appreciate the effect of severity of injury on metabolic rate, a severity of injury index was computed on patient variables at the time of admission. The APACHE II scale was specifically utilized (Knaus, Draper, Wagner, & Zimmerman, 1987). This scale uses the combined scores from acute physiological parameters, chronic health states, and age to produce a score reflecting a general assessment of disease or injury severity (see Table 7). This score has been closely correlated with mortality risk in a large group of intensive care patients. Patient data routinely

Table 7

Apache II: Acute Physiology Score

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥ 41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤ 29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
HEART RATE (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
OXYGENATION: A-aDO$_2$ or PaO$_2$ (mm Hg) a. FIO$_2$ ≥ 0.5 record A-aDO$_2$	≥ 500	350-499	200-349		< 200				
b. FIO$_2$ < 0.5 record only PaO$_2$					PO$_2$ > 70	PO$_2$ 61-70		PO$_2$ 55-60	PO$_2$ < 55
ARTERIAL pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
SERUM POTASSIUM (mMol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥ 3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
GLASGOW COMA SCORE (GCS) Score = 15 minus actual GCS									
(A) Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 individual variable points									
Serum HCO$_3$ (venous mMol/L) [Not preferred, use if no ABGs]	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

Table 7 (continued)

B = AGE POINTS

Assign points to age as follows

AGE (yrs.)	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

C = CHRONIC HEALTH POINTS

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows

a. for nonoperative or emergency postoperative patients - 5 points

or

b. for elective postoperative patients - 2 points

Definitions

Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission an conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR: New York Heart Association Class IV

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resuslting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respiratory dependency

RENAL: Receiving chronic dialysis

IMMUNOCOMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS

APACHE II SCORE

Sum of A + B + C:

A = APS points _____

B = Age point _____

C = Chronic Health points _____

Total APACHE II _____

Note. From "APACHE II: A severity of disease classification system" by W. A. Knaus, E. A. Draper, D. P. Wagner, and J. E. Zimmerman, 1985, Critical Care Medicine, 13, p. 820. Copyright by the Williams & Wilkins Co. Reprinted by permission.

collected in the emergency room contains the necessary information to calculate the APACHE II score. The score represents a potential method for analyzing the relationship between severity of injury and changes in metabolism. Severity of injury, in the past, has only been related to type of injury as previously noted. Data on the mechanism and nature of the injury collected included extent of cranial disruption, presence of hematoma, and non-neurologic injuries. Outcome evaluation was reflected by the Glascow Coma Scale at the time of discharge from the Intensive Care Unit and Glascow Outcome Scale (Pal, Brown, & Fleiszer, 1989) at the time of hospital discharge (see Table 8).

Indices of Metabolic Expenditure

All data on metabolic expenditure measurements (indirect calorimetry) were collected. Concurrently, calculations of metabolic expenditure using the Harris-Benedict equation (Table 3), the nomogram developed by Clifton et al. (1986, Table 4), and the stress stratification framework by Cerra (1982) and Konstantinides (1984) were collected for comparison (see Table 6).

Indirect calorimetry was performed by two technicians highly skilled in the use of the metabolic cart during this sampling period. Calibration procedures were strictly followed. Patients were measured following the manufacturers recommended warm up period. Measurements were taken at four minute intervals until stable readings were obtained (generally about 20 minutes) and accomplished between one to three times weekly. Patient stimulation or procedures were avoided during the measurement period. Instrument validity and reliability for the MGM II Metabolic Gas Monitor can be found in Appendix E. A sample printout of the MGM II data sheet is shown in Appendix F.

Table 8

Glasgow Outcome Scale

Functional Outcome	Score
Good Recovery	4
Moderate Disability	3
Severe Disability	2
Persistent Vegetative State	1
Death	0

Note. Adapted from "The value of the glasgow coma scale and injury severity score: Predicting outcome in multiple trauma patients with head injury" by J. Pal, R. Browm, and D. Fleiszer, 1989, The Journal of Trauma, 29, p. 747.

Concurrent Treatment

Therapeutic paralysis and sedation have been demonstrated to significantly affect metabolic rate. Drug administration records were reviewed and information collected on all sedatives, paralytic agents, and narcotics administered within a 1 hour interval prior to the metabolic gas measurement (half life by the I.V. route). Caloric supplementation and protein intake for 24 hours prior to the metabolic gas measurements was compiled.

Vital signs

Measurements of heart rate and temperature were collected at the intervals corresponding to the metabolic gas measurement. Heart rates are routinely obtained by reliable cardiac monitoring apparatus in conjunction with a 1 minute timing of the

apical pulse in the NCC. Three methods are utilized for measurement of temperature in the NCC: Core temperature from a thermal transducer integral with a central venous catheter, digital rectal thermometer, and core temperature from a thermal transducer integral with an indwelling urethral catheter. Personal experience with these devices has shown minimal variation and excellent clinical reliability.

Neurological and Motor Responses

The GCS (see Table 5) comprised the evaluation of neurological function in this study. The results of prior studies, however, have shown a curvilinear relationship between metabolic rate and this scale. A plausible explanation is the concurrent measurement of two sources of variation: neurological function and motor response (measures of spontaneous activity or resting muscle tone). To examine these sources of variation, categories of the GCS representative of patients with decorticate and decerebrate posturing were compared with categories representative of normal muscle tone.

Measures of Gluconeogenesis, Protein synthesis/excretion

The following narrative describes the variables collected and the rationale for their use. Support of gluconeogenesis is derived in part by the conversion of glucose in muscle to pyruvate and finally lactate. The lactate is then transported via the circulatory system to the liver where it is reconverted to glucose and released into the general circulation. This measure has been advocated to evaluate levels of metabolic stress (Cerra, 1982). Specific ranges of lactate levels corresponding with stress level are shown in Table 6.

Evaluation of protein synthesis is best derived from short half-life plasma proteins including TBPA, RBP, and transferrin. These plasma proteins have been

reported as valuable indicators of protein synthesis and response to nutritional therapy (Fletcher, Little, & Guest, 1987; Winkler, Gerior, Pomp, & Albina, 1987). TBPA and transferrin were routinely collected as part of the nutritional protocol.

Urinary urea nitrogen (UUN) excretion was also performed as part of the nutritional protocol. Total nitrogen excretion was calculated using a standard formula to account for nonurinary losses: UUN X 1.2 + 2 (Wilmore, 1977). Nitrogen balance is derived from Protein intake converted to equivalent nitrogen content minus total nitrogen output: Protein intake (Gms.) / 6.25 - total nitrogen output.

Total lymphocyte counts (TLC) were used as measures of cellular immune status and subsequent visceral protein exhaustion in response to inadequate nutritional supplementation (Silberman, 1989). Lymphocyte counts, however, have been shown to vary widely from day to day.

Data Analysis

Analysis of data collected in this study proceeded through three phases. The emphasis of the first phase was exploratory/descriptive. The goal of the second phase was to test the ability of three existing model's to accurately predict metabolic expenditure (Cerra, 1982; Clifton et al., 1986; Konstantinides, 1984; and the Harris-Benedict equation). The analysis continued further to determine if a model could be developed to improve on existing prediction of metabolic expenditure by using the variables obtained in this study. The third phase will use factor analytic techniques in the attempt to reduce the large set of variables and complex inter-relationships, addressed by this study, into a more understandable and practical set of theoretical constructs.

Descriptive/Exploratory Analysis

First, descriptive univariate statistics were compiled on all repeated measures identified in the previous section. These statistics were derived from a computerized software program (SPSSPC+, 1990). Examples of these measures include count, minimum, maximum, range, mean, median, sum, sums of squares of each variable, variance, standard deviation, and standard error of mean. This information was used to provide a framework for sample characteristics and distribution patterns. Emphasis was placed on visual representations of data characteristics. The goal in this portion of the analysis, in addition to pattern and dimension, was to identify clinically significant variations in the data set.

Regression Analysis and Predictive Modeling

Second, regression analyses was performed to provide the basis for the goal of predictive modeling. Initially, bivariate analyses were used to identify significant Pearson correlations of all nutritional parameters with metabolic expenditure. The results of bivariate analysis of heart rate, days since injury, and GCS on metabolic expenditure derived from indirect calorimetry (Clifton et al. 1986) were examined for possible violations of the assumptions of linear regression. The assumptions of primary concern, in this data set, was to insure the presence of a linear relationship between variable pairs, and minimal heteroscedascity (Lewis-Beck, 1988). These assumptions are further discussed in Chapter 4. Multiple regression analysis was performed and compared to the results of Clifton et al. (1986). The next step was to subject the parameters developed by Cerra (1982) to multiple regression on metabolic expenditure using the steps noted above. Bivariate relationships for all of the remaining variables were examined for possible contribution to explain remaining variance of metabolic expenditure by multiple regression analysis.

Factor Analysis and Modeling

Prior to the factor modeling phase of this analysis, the decision was made whether or not to pursue techniques appropriate to either exploratory or confirmatory factor analysis. The decision was based on the examination of underlying dimensions present in the data from the exploratory and regression phases. Exploratory techniques are more appropriate if the number of underlying dimensions are unknown, whereas, confirmatory techniques are more appropriate for testing of a preconceived theoretical model. The goal in using either the exploratory or confirmatory factor analytic technique was to: 1) determine the presence of a smaller number of theoretical factors with the potential for data reduction; 2) improve conceptual understanding; and 3) determine the underlying dimensions of metabolic stress (Kim & Mueller, 1978).

Summary

The methodology proposed in this chapter addresses the rationale for exploring pertinent issues present in the clinical management of nutrition in TBI. Exploratory and descriptive designs in the scientific literature have been characterized as less powerful than purely experimental approaches by virtue of a loss of control over confounding factors, inability to assure equivalent groups, and inability to manipulate the variables of interest. As research has shown, however, use of these methods are not an assurance of reliable, unbiased results. The rationale for this design entailed a number of considerations. First, the information this series of data represents is larger than has been previously reported, representing a wealth of potential knowledge. To abandon this potential knowledge source for a prospective study would have little impact on the results, given the specific research questions of interest. The variables of interest addressed in this study are not subject to significant variation. The procedures used for determining

the variables are also highly standardized. A summary of the data collected in this study is provided for the reader in Table 9.

Second, ethical considerations often preclude designs which manipulate treatment variables. The clinician is obligated to provide the best possible treatment using the best available assessment tools. The third consideration involves theory development. Many of the limitations of present research are directly related to a lack of understanding of the basic conceptual relationships and the associated observable variables. This understanding can be best obtained by returning to the fundamental exploration of these conceptual relationships. The last consideration concerns evaluation of treatment programs: This methodology also represents a method for determining the effectiveness of the current nutritional protocol.

Table 9

Summary of Data Collected

Category of Data	Type of Data
Injury Classification	APACHE II (severity of injury index)
	Multiple trauma versus Isolated Neurological Trauma
	Glasgow Coma Scale
	Glasgow Outcome Scale
Indices of Metabolic Expenditure	Harris-Benedict Equation: Age, Height, Weight, and Gender
	Clifton's Equation: Heart Rate, Days Since Injury, and GCS
	Stress Stratification Framework: UUN, Serum Lactate and Glucose
	Indirect Calorimetry
Concurrent Treatment	Sedatives, Narcotics, Paralytic Agents, and Caloric Supplementation
Vital Signs	Heart Rate and Body Temperature
Neurological and motor responses	Glasgow Coma Scale
Gluconeogenesis, glucose synthesis, and insulin resistance	Serum glucose and Lactate, and 24 Hour Insulin Dose
Protein synthesis	TBPA, Transferrin
Nitrogen excretion	Urinary Nitrogen Excretion, and Calculated Nitrogen Balance
Immune response	WBC count, Percent Lymphocytes, and Total Lymphocyte Count

CHAPTER IV

RESULTS

Medical records of patients admitted to the Neurosurgery Service at the University of Utah Health Sciences Center from 1987 to 1989 were reviewed. A total of 182 patients, with a variety of neurological injuries, was placed on the Nutritional protocol. One hundred thirty-two out of the total of 182 patients were traumatic brain injury. Thirty patients with TBI were excluded from the analysis because of incomplete, unavailable, or missing medical records resulting in a total sample size of 102 patients for this analysis. Examination of the information available on the 30 missing patients did not reveal any characteristics that would represent a bias in the study.

Three hundred eighty-six metabolic measurements (indirect calorimetry) were available for analysis. This number represents just under four metabolic measurements on the average per patient. Three hundred twenty-nine of these measurements were performed in the Intensive Care Unit and were used for analysis and comparison to the nomogram of Clifton et al. (1986) which describes the measures of days since injury, Glasgow Coma Scale (GCS), and heart rate as highly predictive for energy expenditure (Caloric expenditure, see Table 4). Two hundred sixty-seven sets of complete laboratory measurements including serum lactic acid, serum glucose, and urinary nitrogen excretion with concurrent indirect calorimetry were recorded. These measurements were used for the comparison to the stress framework of Cerra (1982) and Konstantinides (1984).

The Stress Stratification Framework provides a means for estimating Caloric expenditure based on the values of the above mentioned laboratory measurements. The reader may wish to review the Stress Stratification Framework on page 29, Table 6. Age, gender, height, and weight were recorded on each individual for calculation of Basal energy expenditure by the Harris-Benedict equation.

The strategy used for the analysis proceeded in specific phases using a variety of statistical techniques. The predominant theme in this chapter is exploration of the variables for discovery of new insights along similar lines proposed by Hartwig and Dearing (1979). Their approach is characterized by visual representations, skepticism tempered with openness, and a search for subtle patterns and meaning. In this perspective no statistical techniques are particularly more powerful. Often the simplest statistical techniques provide the greatest insights for subsequent analyses.

Sample characteristics, demographics and outcomes of the nutritional protocol were analyzed first. Nutritional protocol outcomes included pertinent aspects relating to energy and protein balance, and metabolic measurement. Second, univariate statistics and simple correlations on variables related to energy expenditure, based on the current models found in the review of literature, were analyzed for emerging patterns and strength of association. Third, the values for specific metabolic indicators obtained in this sample were used to derive estimates using the model's mentioned above (Clifton's estimate, 1986, the Stress Stratification Framework), as well as the Harris-Benedict Equation. These estimates were compared to each patient's actual REE obtained by indirect calorimetry to evaluate the accuracy of these models. The fourth step in the analysis strategy subjected all variables collected (related to metabolic expenditure) to multiple regression analysis in an attempt to improve on estimations of energy expenditure as measured by indirect calorimetry. The last step subjected indices of metabolic expenditure to factor analysis in order to define underlying dimensions in the data (see Table 10).

Table 10

Summary of the Data Analysis Strategy

Phases in the Analysis
1. Sample characteristics, demographics, and evaluation of the nutritional protocol.
2. Univariate statistics and and Pearson correlations for variables believed to be associated with energy expenditure based on current models.
3. Comparison of the estimates for caloric requirements by the Harris-Benedict Equation, Clifton's Equation, and the Stress Stratification Framework with Indirect Calorimetry.
4. Regression analysis for metabolic variables collected in this study to attempt to improve on current estimates.
5. Factor analysis on variables related to metabolic rate for the purpose of identifying the underlying dimensions in the data.

Subject Characteristics

Table 11 lists the percent of patients by time to feeding in hours. Table 12 lists the variety of injuries found in the sample along with age, sex, type of injury and admission (GCS). Forty-nine (48%) of the subjects diagnoses were designated as isolated TBI, whereas 53 (52%) of the subjects injuries were classified as multiple trauma. Multiple trauma was defined by the presence of major disruption of two or more organ systems.

The distribution and statistics for age are demonstrated further by histogram in Figure 3. As might be expected, the age of individuals with the cause of injury attributed to falls was considerably higher than the mean, whereas motorcycle

Table 11

Time Elapsed to the Initiation of Feeding

Time Elapsed in Hours	Percent of Patients
< 24 hours	20
24-48 hours	40
49-72 hours	23
73-96 hours	14
> 96 hours	3

accidents were noted in a younger age group. Table 13 shows the breakdown of injuries by cause. Analysis of demographic data showed the distribution by gender to be 24 females and 78 males.

Statistics were collected showing descriptions of the extent or severity of injury, length of hospitalization, and outcome. A severity of injury index (Apache II score, Knaus et al., 1987) was obtained from Emergency Medical Services (EMS) records when available. Body temperature measurement was not routinely performed in the field and this variable for the Apache II score was obtained from Emergency Room records. Similarly, laboratory values and blood gas analysis were obtained from the first recorded values after hospitalization. A small number of scores for patients admitted without EMS involvement were derived from the Emergency Room records. Table 14 illustrates the breakdown of these variables. In regards to length of hospitalization, it could have been considerably longer had the services of the Rehabilitation Service not been available for these patients.

The time elapsed to the initiation of parenteral, enteral or self-nutrition is also shown in Table 14. The mean value of 60 hours is somewhat skewed due to a delay in several patients who improved sufficiently in the early post injury phase as to not require TPN or TEN (median time to initiation of feeding was 48 hours).

Table 12

Subject Characteristics

AGE	SEX	DIAGNOSIS	TYPE OF INJURY	ADMIT GCS
18	M	CHI	1	3
22	M	CHI	1	4
23	M	CHI-AIRPLANE MISHAP/DSF	1	12
31	M	CHI-ASSAULT	1	14
86	F	CHI-ASSAULT/BIPARIETAL CONTUSIONS/SAH	2	10
25	M	CHI-ASSAULT/EDH	1	4
34	M	CHI-ASSAULT/SDH/BASILAR SKULL FRACTURE	1	4
45	M	CHI-ASSAULT/SDH/PARENCHYMAL CONTUSION	1	8
34	M	CHI-AUTO-PEDESTRIAN/BASAL GANGLIA HEMATOMA	1	4
16	M	CHI-AUTO-PEDESTRIAN/EDH	1	5
55	F	CHI-AUTO-PEDESTRIAN/SAH/PNEUMOTHORAX	2	6
23	M	CHI-AUTO-PEDESTRIAN/PELVIC FX/LIGAMENTOUS KNEE INJURY	2	3
26	F	CHI-AUTO-PEDESTRIAN/SDH/EDH/SKULL FRACTURE	1	5
40	M	CHI-BICYCLE ACCIDENT/ICH/CLAVICLE FX/ELBOW FX	2	8
37	M	CHI-FALL-ETOH/FRONTAL ICH AND SDH/CEREBELLAR CONTUSION	1	6
42	F	CHI-FALL-ETOH/FRONTO-PARIETAL SDH/CERVICAL FX	2	3
83	M	CHI-FALL/BI-PARIETAL SDH/SKULL FX	1	14
77	M	CHI-FALL/CONTUSION/SAH	1	10
43	M	CHI-FALL-ETOH	1	3
36	M	CHI-FALL/ICH/EDH	1	7
40	M	CHI-FALL/SDH	1	4
62	M	CHI-FALL/SDH	1	13
76	F	CHI-FALL/SDH	1	10
84	M	CHI-FALL/SDH	1	14
30	M	CHI-HELICOPTER CRASH/LUMBAR FX'S/TIBIA FX	2	8
18	M	CHI-MCA	1	3
30	M	CHI-MCA	1	7
36	M	CHI-MCA	1	9
17	M	CHI-MCA/SDH/DSF	1	7
23	M	CHI-MCA/DIFFUSE CORTICAL CONTUSION/ABDOMINAL TRAUMA	2	6
34	M	CHI-MCA/EDH/PNEUMO-CRANIUM/PNEUMOTHORAX	2	13
28	F	CHI-MCA/HEAD AND SCALP LAC'S/MULTIPLE FX'S	2	7
18	M	CHI-MCA/MULTIPLE ICH'S/SAH/CLAVICLE FX'S	2	5
29	M	CHI-MCA/MULTIPLE TRAUMA	2	13
17	M	CHI-MCA/PARIETAL CONTUSION	1	4
25	M	CHI-MCA/R FEMUR FX	2	4
21	M	CHI-MCA/RIGHT SDH/SKULL FX/CLAVICLE FX	2	4
21	M	CHI-MCA/SAH/ABDOMINAL TRAUMA	2	3
45	M	CHI-MCA/SDH/FACIAL FX'S/RIB FX	2	8
31	M	CHI-MCA/SMALL INTRAPARENCHYMAL HEMORRHAGES	1	12
32	M	CHI-MCA/TEMPORAL CONTUSION/FACIAL LACERATIONS/ELBOW FX	2	6
17	M	CHI-MVA	1	4

Table 12 (continued)

AGE	SEX	DIAGNOSIS	TYPE OF INJURY	ADMIT GCS
19	M	CHI-MVA	1	8
22	M	CHI-MVA	1	7
33	M	CHI-MVA	1	4
52	M	CHI-MVA	1	4
71	M	CHI-MVA	1	6
21	F	CHI-MVA/CERVICAL FX/HEMOPNEUMOTHORAX	2	4
37	M	CHI-MVA/ABDOMINAL TRAUMA	2	4
40	F	CHI-MVA/ABDOMINAL TRAUMA/PNEUMOTHORAX/PELVIC FX	2	5
21	M	CHI-MVA/ANKLE FX/SHOULDER FX/PULM CONTUSION	2	8
18	F	CHI-MVA/BASILAR SKULL FRACTURE/ABDOMINAL TRAUMA	2	6
33	F	CHI-MVA/CERVICAL FX/MULTIPLE FX'S	2	14
19	M	CHI-MVA/CHEST TRAUMA/THORACIC FX'S	2	9
76	F	CHI-MVA/CLAVICLE FX/RIB FX/PNEUMOTHORAX	2	8
23	M	CHI-MCA/EDH/CERVICAL FX/TIBIA-FIBULA FX	2	12
7	M	CHI-MVA/EDH	1	7
23	F	CHI-MVA/EDH/RIB FX'S	2	6
31	M	CHI-MVA/FACIAL FX'S/BASILAR SKULL FX/PULMONARY CONTUSION	2	7
59	M	CHI-MVA/CEREBRAL CONTUSION/CERVICAL SUBLUXATION/SKULL FX	2	15
20	F	CHI-MVA/FRONTAL CONTUSION/OCCIPITAL FX/PNEUMOTHORAX	2	7
27	M	CHI-MVA/FRONTAL CONTUSION/PULM CONTUSION	2	7
21	F	CHI-MVA/SDH	1	5
16	F	CHI-MVA/MULTIPLE SMALL CEREBRAL CONTUSIONS/PELVIC FX	2	6
20	M	CHI-MVA/PNEUMOTHORAX/PERITONEAL HEMORRHAGE	2	5
20	M	CHI-MVA/PNEUMOTHORAX/KNEE WOUND/ABDOMINAL TRAUMA	2	5
24	M	CHI-MVA/PULMONARY CONTUSION/RIB FX'S/CLAVICLE FX	2	10
17	F	CHI-MVA/PULMONARY CONTUSION	2	9
32	F	CHI-MVA/EDH/FRONTOTEMPORAL CONTUSION	1	4
52	F	CHI-MVA/SAH/RIB FX/LUMBAR FX	2	7
49	M	CHI-MVA/SAH/SKULL FRACTURE	1	6
36	M	CHI-MVA/SCALP LACERATION/BILATERAL PNEUMOTHORAX	2	11
31	F	CHI-MVA/SDH	1	3
19	M	CHI-MVA/SDH/SCALP LACERATION/PULM CONTUSION	2	4
14	M	CHI-MVA/SDH/ULNA AND RADIUS FX'S/HEMOPNEUMOTHORAX	2	6
26	M	CHI-MVA/SHOULDER DISLOCATION/SKULL FX	2	4
37	M	CHI-MVA/SMALL RIGHT FRONTAL SDH	1	6
55	F	CHI-MVA/TEMPORAL CONTUSION/CERVICAL FX'S/EXTREMITY FX'S	2	3
37	M	CHI-MVA/ODONTOID FX/SCALP LACERATION	2	10
22	M	CHI-MVA/ZYGOMA FX	1	7
19	M	CHI-ROCK CLIMBING FALL/SKULL FX/MULTIPLE EXTREMITY FX'S	2	3
16	M	CHI-ROCK CLIMBING/MULTIPLE PUNCTATE HEMORRHAGES	2	4
41	M	CHI-SKIING/CAROTID ARTERY DISSECTION/RIGHT CVA	2	15
20	M	CHI-SKIING/MULTIPLE EXTREMITY FX'S	2	5
16	M	CHI-SNOW-BOARDING/LEFT PARIETAL SDH	1	8
57	M	DSF-FALL/SDH/MULTIPLE RIB FX'S/TIBIA-FIBULA FX	2	13
16	M	DSF-MCA/FACIAL FX	1	4
16	M	DSF-MVA	1	4

Table 12 (continued)

AGE	SEX	DIAGNOSIS	TYPE OF INJURY	ADMIT GCS
18	M	DSF-MVA-ETOH/SAH	1	13
31	M	DSF-ASSAULT	1	3
22	M	DSF-MINING/TEMPORAL LOBE CONTUSION	1	4
31	M	GSW TO HEAD	1	15
26	M	CHI-MVA/FRONTOTEMPORAL CONTUSION	1	4
30	M	OPEN DSF-FALL/BILATERAL WRIST FX'S/ELBOW FX	2	5
26	M	CHI-MCA/SDH	1	4
18	M	CHI-MCA/SDH	1	4
30	M	CHI-MVA/MIDBRAIN AND RIGHT BASAL GANGLIA HEMORRHAGE	1	3
12	F	CHI-MVA/MULTIPLE SKULL FX'S/ICH/PELVIC FX	2	12
24	F	CHI-MVA/MULTIPLE TRAUMA	2	5
35	F	CHI-MVA/MULTIPLE TRAUMA	2	6
59	F	CHI-MVA/MULTIPLE TRAUMA	2	5
37	M	CHI-MVA/MULTIPLE TRAUMA	2	5

Note. Diagnoses: CHI=Closed head injury; DSF=Depressed skull fracture; EDH=Epidural hematoma; SDH=Subdural hematoma; SAH=Subarachnoid hemorrhage; ICH=Intracerebral hemorrhage; ETOH=alcoholic beverages involved. FX=Fracture. TYPE OF INJURY; 1=head injury only; 2=Multiple trauma.

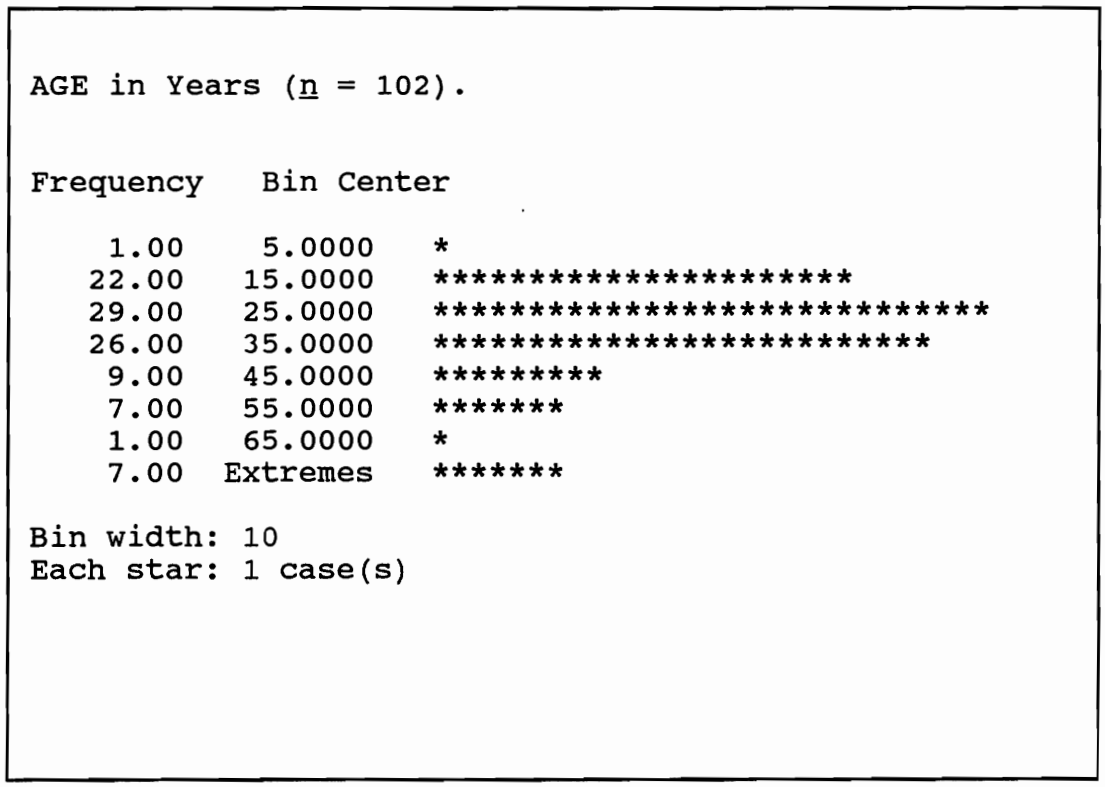

Figure 3. Distribution of Age: Histogram. Note. Mean 32.5; Std. Err. 1.7; Min. 7; Skewness 1.5; Median 28.5; Variance 295.5; Max. 86.

Table 13

Mechanism of Injury

Motor Vehicle Accidents	48%
Motorcycle Accidents	17%
Falls	12%
Auto Pedestrian Accidents	5%
Assaults	5%
Miscellaneous	13%

Table 14

Severity of Injury and Hospitalization Data

Variable	Mean	Std. Dev.	Minimum	Maximum	N
APACHE II	17.39	6.3	1	31	99
GCS on admission	7	3.52	3	15	102
Time to initial feeding (hours)	59.76	30.21	24	168	102
GCS on ICU discharge	9.73	4.52	0	15	102
Number of ICU days	17.03	10.91	2	59	102
Glasgow Outcome Scale	1.82	1.11	0	4	102
Glasgow Outcome Scale (time of measure-days after admission)	26.92	22.24	4	122	102
Length of acute hospitalization	28.07	20.82	5	122	102

The Apache II scores and the admission GCS were subjected to regression analysis with the Glasgow Outcome Scale (GOS). The APACHE II scores demonstrated higher correlation than the GCS alone (see Figure 4). Given this finding the APACHE II score was subjected to analysis with other metabolic factors in addition to the GCS.

In retrospect, higher accuracy may have been obtained between the APACHE II scale and the GOS if the best parameters within a 12 hour period after admission

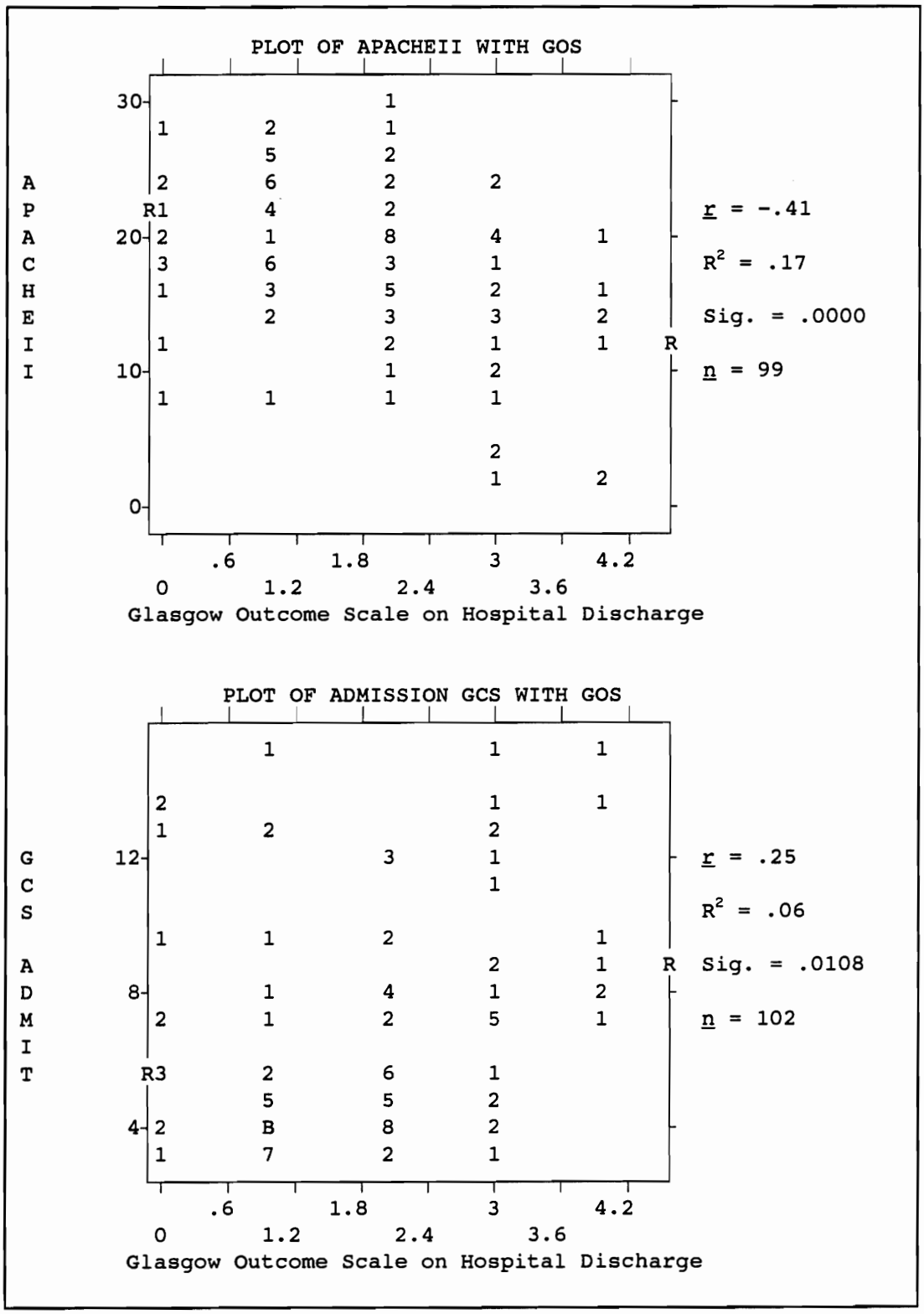

Figure 4. Bivariate Regression Plots of the APACHE II and Glascow Coma Scale with the Glasgow Outcome Scale.

had been used instead of the EMS records. The method used in this study to select variables for this analysis likely represented the worst state of the patients early injury phase and did not consider the effects of early resuscitation efforts in improving the overall condition of the patient. This delay in evaluation of the APACHE II score would also allow for the variables to be collected at a single point in time. This alternative strategy may improve the reliability of the measure (see Table 7 for a review of the APACHE II scale). Pearson correlation coefficients were also calculated for the severity of injury index and total number of ICU days (n = 99, r = 0.30, p < 0.01) and severity of injury index and total number of hospital days (n = 99, r = 0.02, p = NS). Indicating increased length of hospitalization in conjunction with increased severity of injury as measured.

The greater proportion of surviving patients were discharged to the rehabilitation unit (66%). Disposition of the other patients is as follows; deceased as a result of injuries (12%); placement in extended care facilities (10%); discharged to home (10%); discharged to home with home based nursing care (1%); and transferred to another hospital (1%). Overall mortality was 12%.

Nutritional Support

Energy balance

Repeated observations for concurrent Caloric intake and energy expenditure measurements were evaluated (n = 321). Energy balance at these times of measurement was calculated by subtracting the energy output (based on two sources of energy expenditure estimation, indirect calorimetry and the Harris-Benedict Equation) from the total daily Calories provided. The difference between the two calculations provided a gross estimation of the enhancement that indirect calorimetry provided in terms of numbers of Calories more closely approximating actual need. The total difference between energy balance calculations on the average accounts

for 202 Calories per day. What this estimation does not take into consideration, however, is that over half of the indirect calorimetry measurements reveal actual energy consumption below that calculated by the Harris-Benedict equation (Calc. BEE). If only those observations that demonstrate actual energy expenditure exceeding calculated energy expenditure had been used, the value for the average Calories this group was fed, as a result of having indirect calorimetry performed, goes up to 500 Calories per day, on the average. Concurrently, the indirect calorimetry was also successful in identifying those individuals with low Caloric needs who may otherwise have been overfed. The estimate of the difference between Calories that would have been given had the Calc. BEE been used instead of indirect calorimetry also included all cases prior to the initiation of nutritional support ($\underline{n}$ = 53) where Caloric intake was limited to IV dextrose further underestimating the benefit.

Nitrogen balance

One hundred sixty-eight nitrogen balance computations were made on repeated measures within the sample of 102 patients. Nitrogen balance was computed by the equation (protein intake / 6.25 = nitrogen intake) - (urine urea nitrogen x 1.2 + 2 = urinary nitrogen loss) = nitrogen balance (Wilmore, 1977). The mean nitrogen balance over all observations was -11.03 (+/- S.D. = 10.63). A box plot demonstrating the distribution of values for nitrogen balance and concurrent measurement of protein synthesis are shown in Figure 5. The boxplot shows the 25th to 75th percentile within the box. The upper T and lower inverted T denote the extreme values which are not outliers. Outliers are values more than 1.5 box lengths from the upper or lower quarter percentiles. Extreme values are more than 3 box lengths from the upper or lower quarter percentiles. Extreme values and outliers are marked by an E and O respectively. An asterisk marks the median.

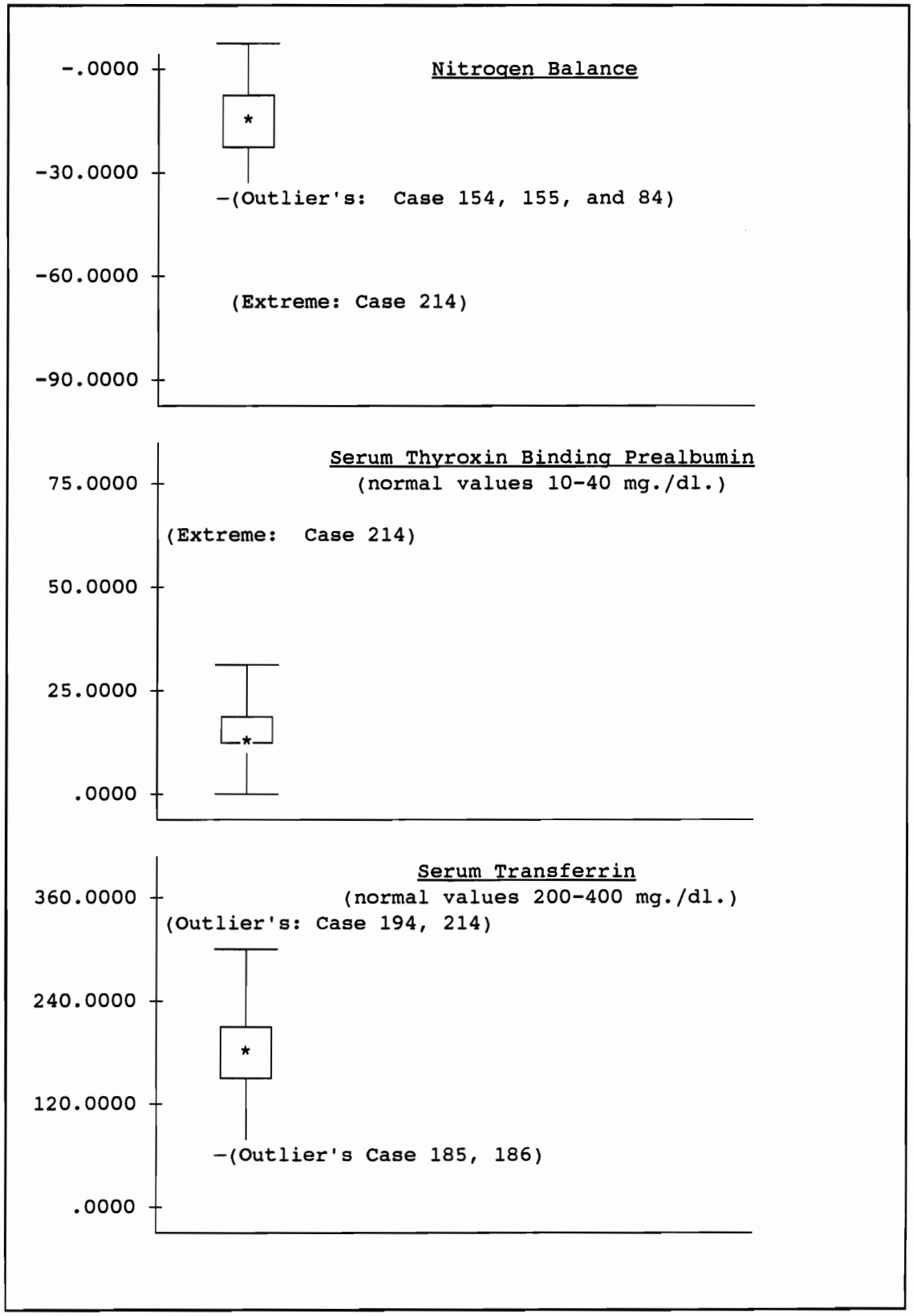

Figure 5. Box Plots of Nitrogen Balance and Protein Synthesis.

Despite a predominance of negative nitrogen balance scores, measures of visceral protein stores were not comparably affected. Transferrin (half life 7 days) and thyroxine binding prealbumin (TBPA, half life 2-3 days) are sensitive indicators of protein but also caloric deficit. This observation of noncomparable effect reflects the nature of what has been termed obligatory nitrogen loss. Any individual on bedrest will tend to lose lean muscle mass due to disuse. This obligatory loss will reveal itself in increased urinary nitrogen excretion without a concurrent decrease in protein synthesis.

Three outliers were detected in the nitrogen balance scores. Two of these cases (154 and 155) were the same patient with a UUN (urine urea nitrogen) repeated 5 days later equivalent values. This patient's concurrent measures of protein synthesis (transferrin and prealbumin) were well into the normal range. The third outlier (case 84) was severely fluid restricted because of increased intracranial pressure with subsequent Calorie and protein restrictions imposed. One extreme case (214) was noted which represents a patient transferred from another institution who was receiving extreme amounts of protein via TPN (over 2 Gms./Kg./day).

Analysis of serum TBPA levels (Figure 5) demonstrated a narrow range for the middle 50% of values (Mean = 18.7 +/- S.D. = 8.3). Only 13% of the values were below normal. The extreme case here (elevated) represents the same case noted above (214). Serum transferrin levels demonstrated somewhat reduced protein synthesis in the majority of patients (Mean = 200.9 +/- S.D. = 56.1). Because of the relatively longer half life of transferrin, these values represent protein changes farther in the past, and hence, somewhat less reliable than TBPA. The outliers above the norm are again as noted above (case 214) and case 194 who was measured the day after injury. Case 194's transferrin level of 348 mg./dl. was still within the normal range for this protein. Cases 185 and 186 represent the same

individual with a severe and protracted illness (days since injury 27 and 29) and could be expected to have reduced visceral protein stores.

Body weight

Daily weights were only available on a small number of patients, primarily because of concerns with intracranial pressure. For those values present (n = 220) the observations represent a mean weight loss of 2 kg. +/- S.D. = 5.75 over the time of acute hospitalization. Two predominant factors enter into the value of body weight as an anthropometric measure of nutrition: First, body water changes dramatically in the critically ill population, making determinations difficult. Second, measurements are often inaccurate because of the mechanical logistics of the ICU environment.

Summary

The purpose of this section was to provide insight into the demographic and sample characteristics pertaining to severity of injury as well as a descriptive evaluation of the nutritional protocol. Evaluation of the demographic data and sample characteristics demonstrates patient profiles consistent with the mechanism of injury in TBI including age, gender, and type of injury. The age distribution represents a predominantly younger population. Gender reflects a predominantly male population. Inferences from this sample will be limited in the respect that these groups are under-represented. Severity of injury data, as discussed, demonstrated consistency among the various measures (i.e., length of hospitalization, and severity of injury indices). These measures support the proposition that TPN and TEN are necessary given the extent of injury and prolonged hospitalization.

Repeated measures for the metabolic variables addressed do not appear to reflect any systematic bias in the data. Further, for the purposes of prediction, implied by the use of a nutritional assessment model, repeated measures must be consistent in variations within subjects across time. The repeated measures as

analyzed, however, are limited in the ability to detect trends among individuals. The inferences for this study are confined to strength of association at specific time intervals consistent with repeated clinical evaluations. The implications of the analysis of protein synthesis and nitrogen excretion are discussed further in the following sections and Chapter 5.

Pattern and Strength of Association for Variables Related to Energy Expenditure

Severity and Type of Injury

Four variables were collected related to severity of injury to identify the association between initial level of injury in the 102 patients and their subsequent repeated measures of energy expenditure: the severity of injury index on admission (APACHE II), type of injury (isolated closed head injury versus multiple trauma), the GOS, and the GCS on admission and concurrent with each Indirect Calorimetry (I.C.) measurement. These variables represent magnitude of injury. Further, magnitude of injury has been associated with the stress response and subsequent alterations in metabolic profiles and nutritional requirements (see Chapter 2). The literature also infers the association between magnitude of injury and hypermetabolic response.

Correlations of these variables with the exception of concurrent GCS scores and energy expenditure by indirect calorimetry are shown in Table 15. No significant correlations were found between I.C. and severity of injury measurements. Type of injury, also, did not correlate significantly with the GOS.

Temporal Response

Energy measurements (I.C.) were analyzed over a period of up to 34 days since injury. Subgroups were devised to elicit changes in the mean value of energy by I.C. As shown in Table 16, there is an uneven distribution with peaks in the mean on days 10 to 14 and again on days 25 to 29. This observation will have

Table 15

Correlations for Severity of Injury Scores and Energy Expenditure

Correlations:	REE	TYPE OF INJURY	APACHEII	ADMIT GCS	GOS
REE:	1.0000	-.0814*	.0574*	.0212*	-.0223*

Note. * = NS (n = 375 measures/102 patients). REE = Resting energy expenditure by I.C.

Table 16

Comparison of Means for Energy Expenditure by Days Since Injury

Variable	Value Label	Mean	Std Dev	Cases
For Entire Population		1836.14045	627.545900	356
DSI	0-4	1567.30612	510.181035	98
DSI	5-9	1947.33708	621.512158	89
DSI	10-14	2065.39394	717.184793	66
DSI	15-19	1955.08889	589.386192	45
DSI	20-24	1691.10000	570.806649	30
DSI	25-29	1948.63158	595.727679	19
DSI	30-34	1633.88889	556.916835	9

Note. Summaries of ENERGY (I.C.) by levels of Days since injury. Total Cases analyzed = 403

implications for later regression analyses. The curvilinear distribution of the energy variable by days since injury reduces its efficiency in linear tests of association. A bivariate regression was also analyzed showing severe heteroskedascity (repeated measures showing a wide variance in the first 2 weeks and narrowing thereafter) and minimal correlation ($\underline{r}$ = .07).

Person Attributes

Clinical characteristics of the subjects are analyzed in the subsequent section. Person attributes are those unique, clinically observable, characteristics that define the condition of the patient at any given point in time (see Figure 2 for a review of the ARKS Domain Analysis for Nutrition in TBI).

Thermoregulation

Three hundred forty-four observations of energy expenditure (I.C.) with body temperature were available for analysis. Figure 6 illustrates the distribution of values obtained. Extreme values were detected and analyzed. Extreme low values ($\underline{n}$ = 7) were in the range of 34-35 degrees centigrade and represented true clinical hypothermia. One extreme high value of 39.8 was representative of a patient with a severe pulmonary infection. Regression analysis for the effects of temperature on energy expenditure (Figure 7) reported statistics of: $\underline{r}$ = .25, R^2 = .06, S.E. of Est. = 0.68, Sig. = 0.0000. The reported slope coefficient (B): for temperature was reported as 222 Calories representing an approximate increase in metabolic expenditure by each degree centigrade on a linear scale. The values for the regression statistics are further detailed later in the chapter.

Cardiodynamics

Heart rate values were obtained paired with energy ($\underline{n}$ = 352). Figure 8 shows the distribution. Distribution statistics are reported in the figure box +/- S.D.

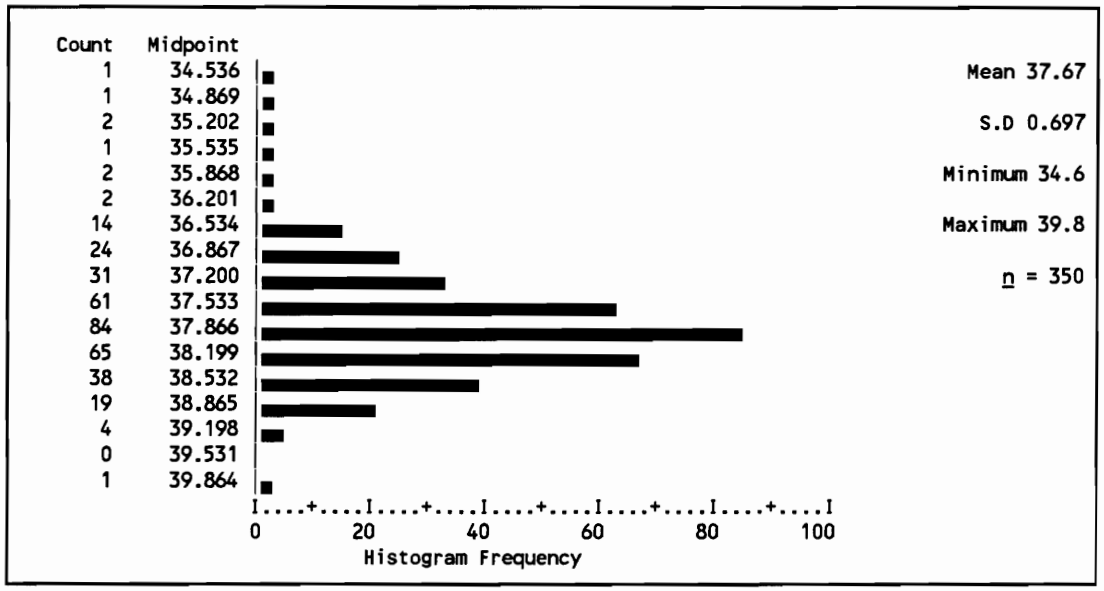

Figure 6. Distribution of Temperature Observations.

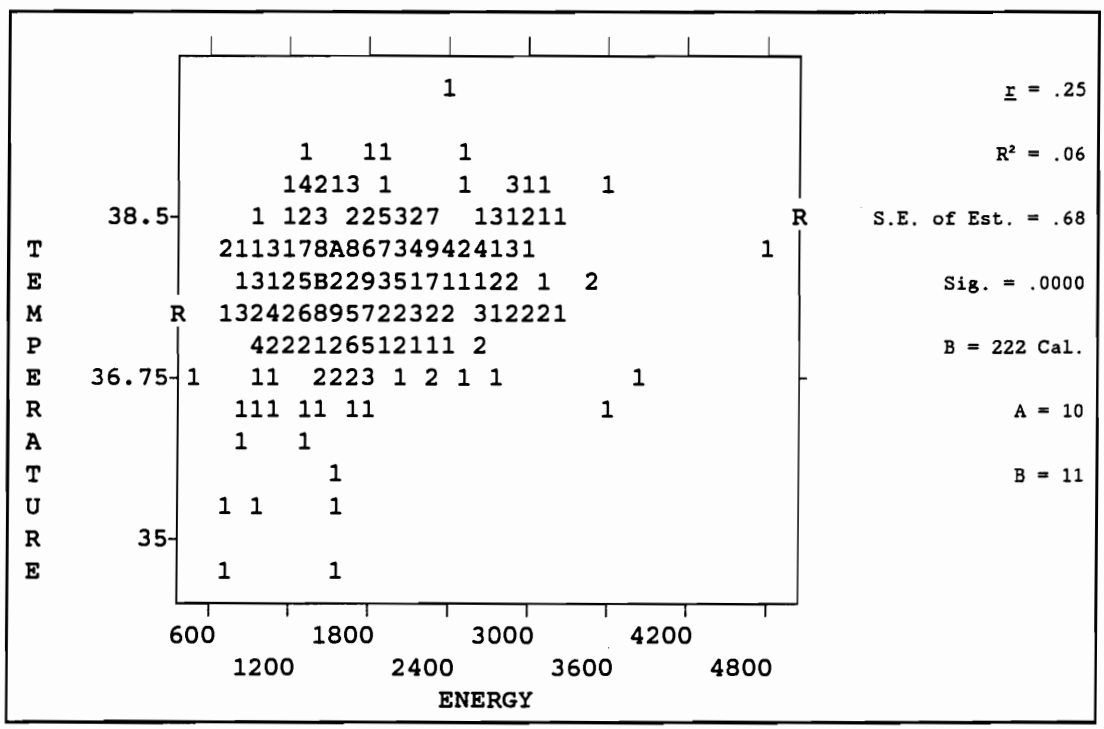

Figure 7. Regression Plot of Temperature with Energy Expenditure. Note.

R = regression line point on Y axes.

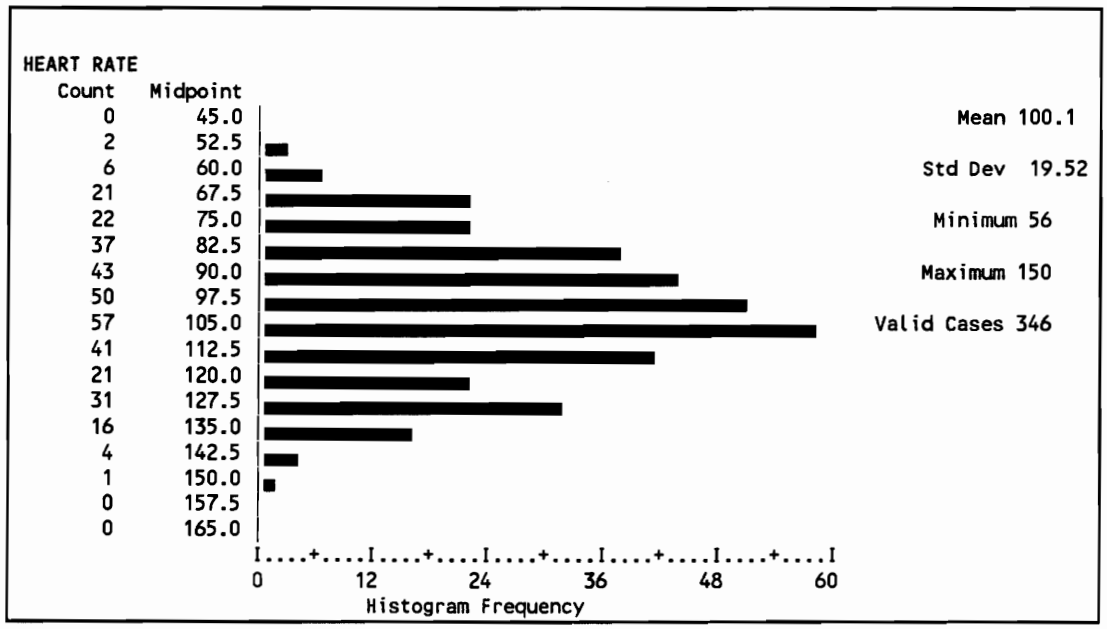

Figure 8. Distribution of Heart Rate Observations.

No extreme values or outliers were detected in the analysis. A plot for bivariate regression of heart rate with energy is illustrated in Figure 9. Regression statistics are reported as r = .23, R^2 = .05, S.E. of Est = 19.04, Sig. = 0.0000. B = 7.31 (Heart rate).

Neurologic responses

The GCS was used as the primary method for evaluation of neurologic responses to injury. The individual scores of the GCS were not available from the medical records (scores were only reported as the sum). Therefore, relationships of energy expenditure with the individual characteristics of the GCS, i.e., eye opening response, verbal response, and motor response were not possible to estimate. Figures 10 and 11 illustrate distribution characteristics of the GCS and bivariate regression with energy expenditure (n = 329). Examination of the distribution shows an expected skew of the distribution to the right characteristic of the poor neurologic

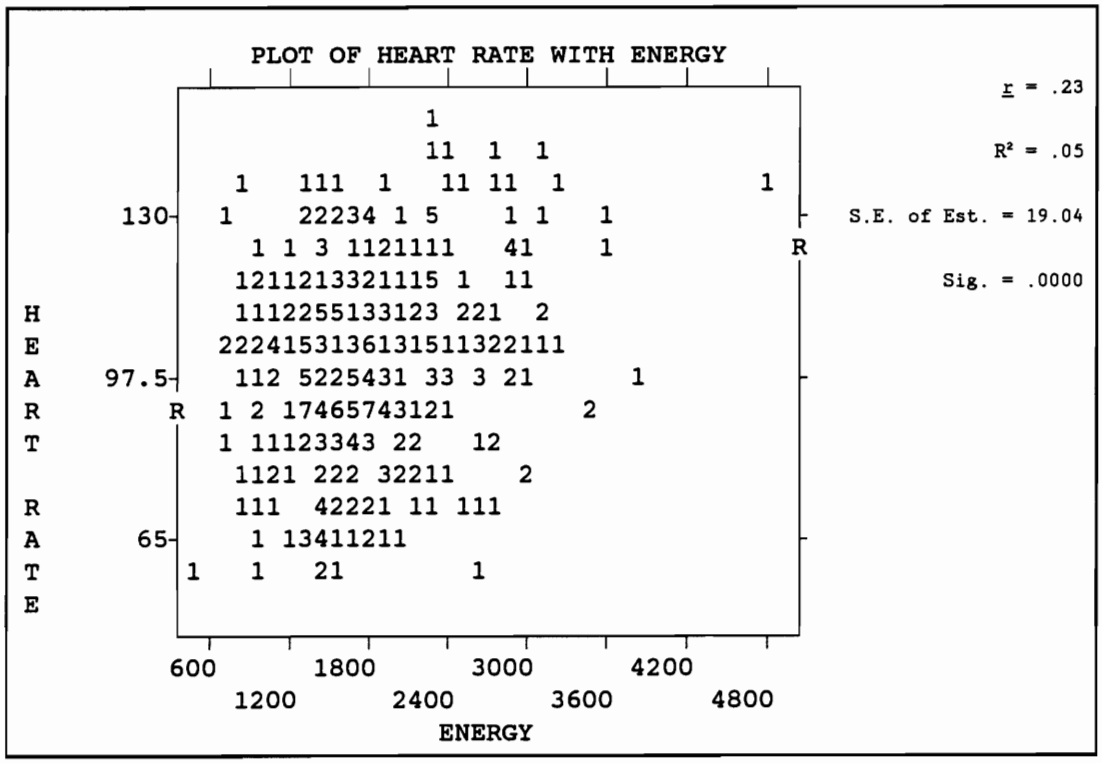

Figure 9. Regression Plot of Heart Rate with Energy. Note. R = regression line point.

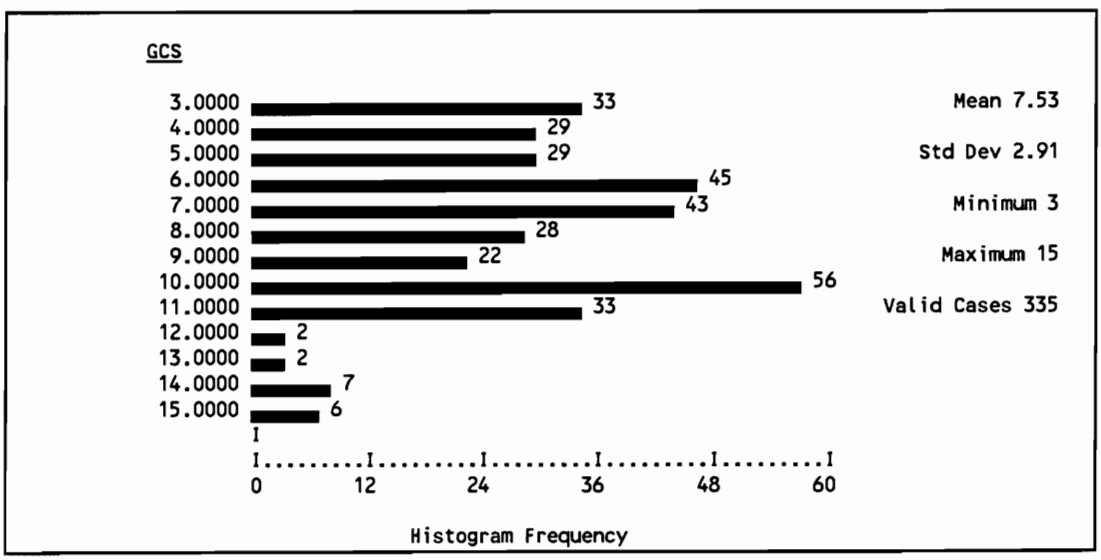

Figure 10. Distribution of the GCS.

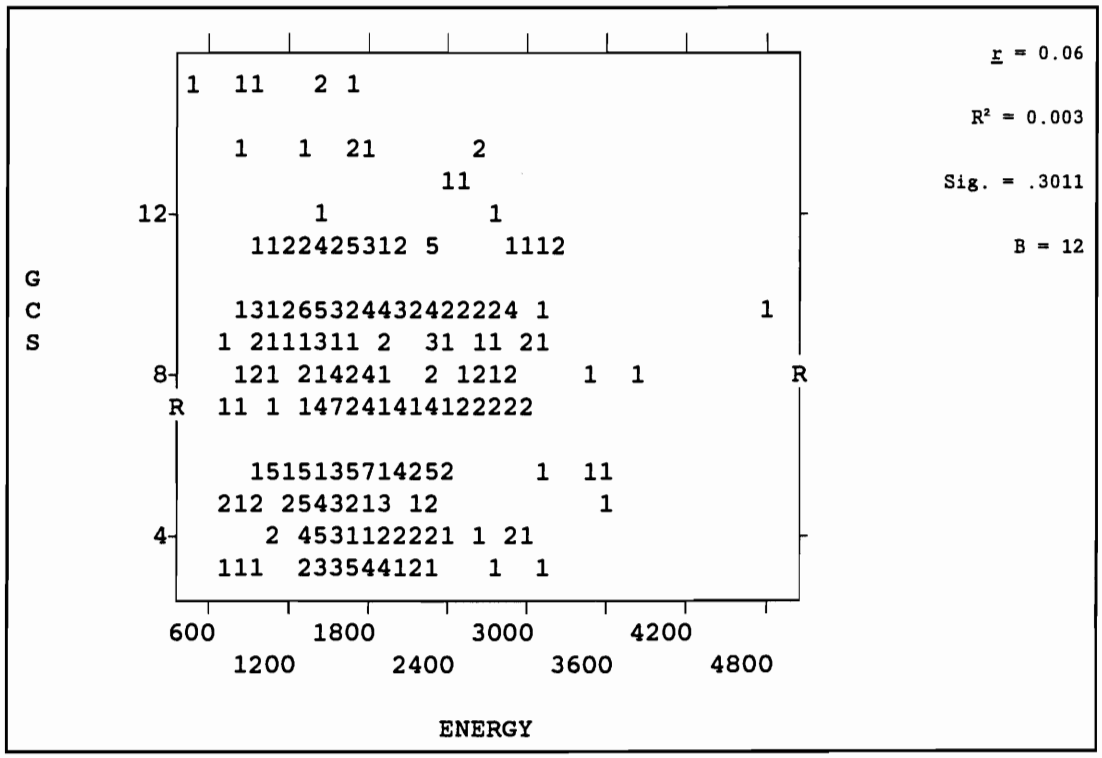

Figure 11. Regression Plot of GCS with energy expenditure by indirect calorimetry.

condition of the subjects. The GCS scores showed poor correlation and regression values relative to energy expenditure (r = 0.06, R^2 = 0.003, Sig. = 0.3011).

Glucose metabolism

Glucose metabolism was analyzed by observations of serum glucose and serum lactic acid (lactate). Lactate is the principle mediator of glucose precursors in gluconeogenesis. Distributions are shown in Figures 12 and 13. Analysis of extreme values and outliers were all within clinically reasonable values. Measures of correlation with energy expenditure were not statistically significant.

The interrelationships between other factors associated with serum glucose were explored with regression analysis. Using serum glucose as a marker of metabolic stress can be difficult with concurrent interactions of the amount of caloric

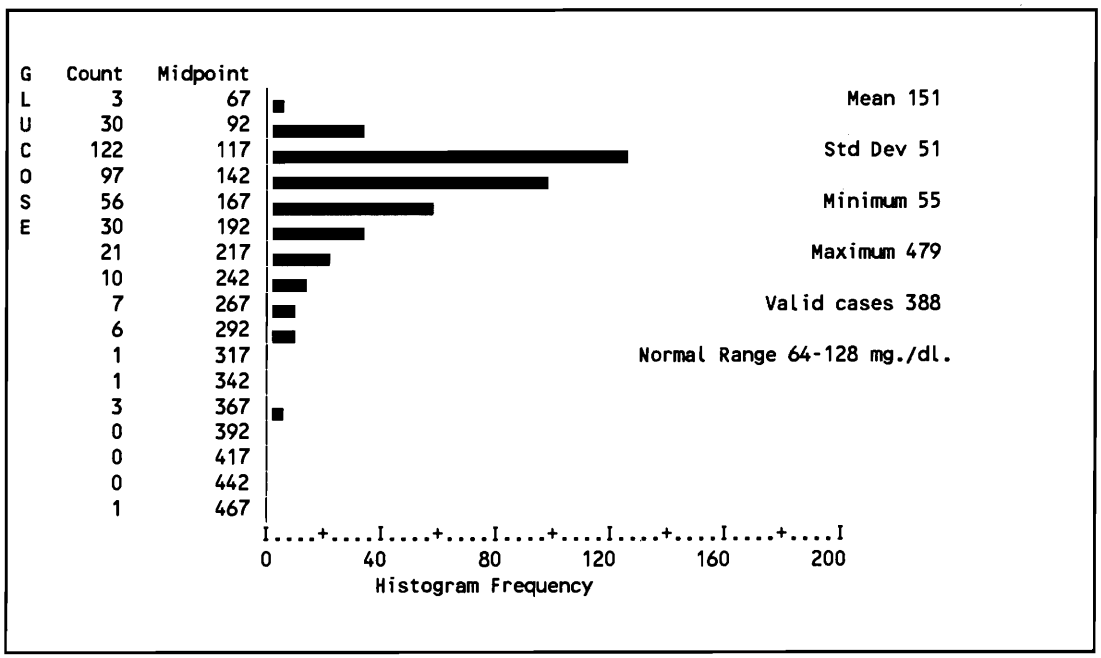

Figure 12. Distribution of Serum Glucose Values.

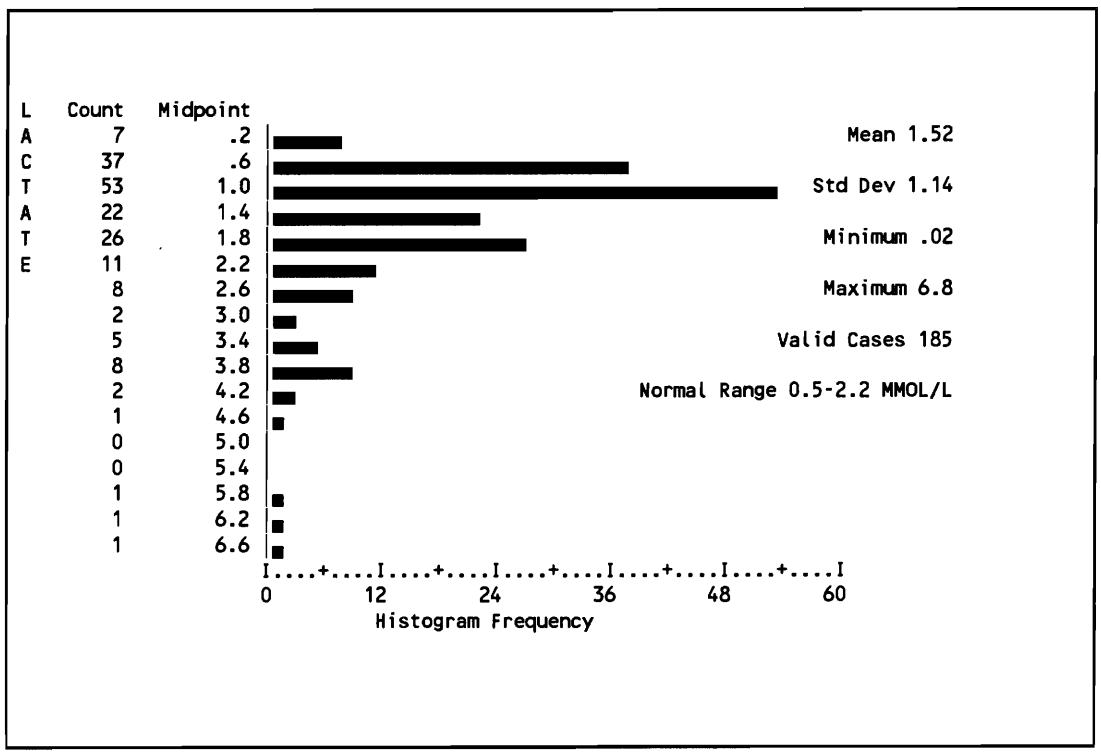

Figure 13. Distribution of Serum Lactate Levels.

replacement and insulin doses as well as the interaction between serum lactate and serum glucose. Figure 14 demonstrates the correlations and regression statistics of serum lactate and Insulin Dose with serum glucose. The extreme values of serum lactate values (upper portion of the first plot) do not appear to correlate with higher glucose levels. These values also corresponded with individuals in the first few days after injury, all with multiple trauma. The values may represent an exaggerated effect of incomplete oxidation as a result of extensive soft tissue trauma or hypoxia in the early acute stages of injury and not concurrent hypermetabolism.

Analysis of the effects of insulin dose show a moderate correlation with serum glucose values (Figure 14). The therapeutic goal in the nutritional protocol was to keep serum glucose values below 180 mg./dl. Approximately 40% of the values for serum glucose are beyond that goal. This observation demonstrates a difficulty managing hyperglycemia in this population of patients. A negative correlation was also identified between glucose and days since injury ($r = -0.16$, $p < 0.01$) indicating a resolution of hyperglycemia in the ICU period.

Table 17 gives regression statistics for the exploration of the effects of Caloric Intake, serum lactate levels, and insulin dose on concurrent serum glucose levels. In the first analysis approximately 16% (coefficient of determination, R^2) of the variance in serum glucose levels can be explained by the combination of these three factors. In the second analysis, when Caloric intake is excluded, the explained variance drops to only 14%. This observation would tend to support the premise that the amount of calories replaced does not account for a large proportion of the hyperglycemia found in these subjects.

The positive sign for insulin dose in the slope coefficient (B) in Table 17 and the positive slope in plot 2 of Figure 14, may be, in part, explained by the effect of insulin resistance. The other portion of the explanation may be the unsuccessful

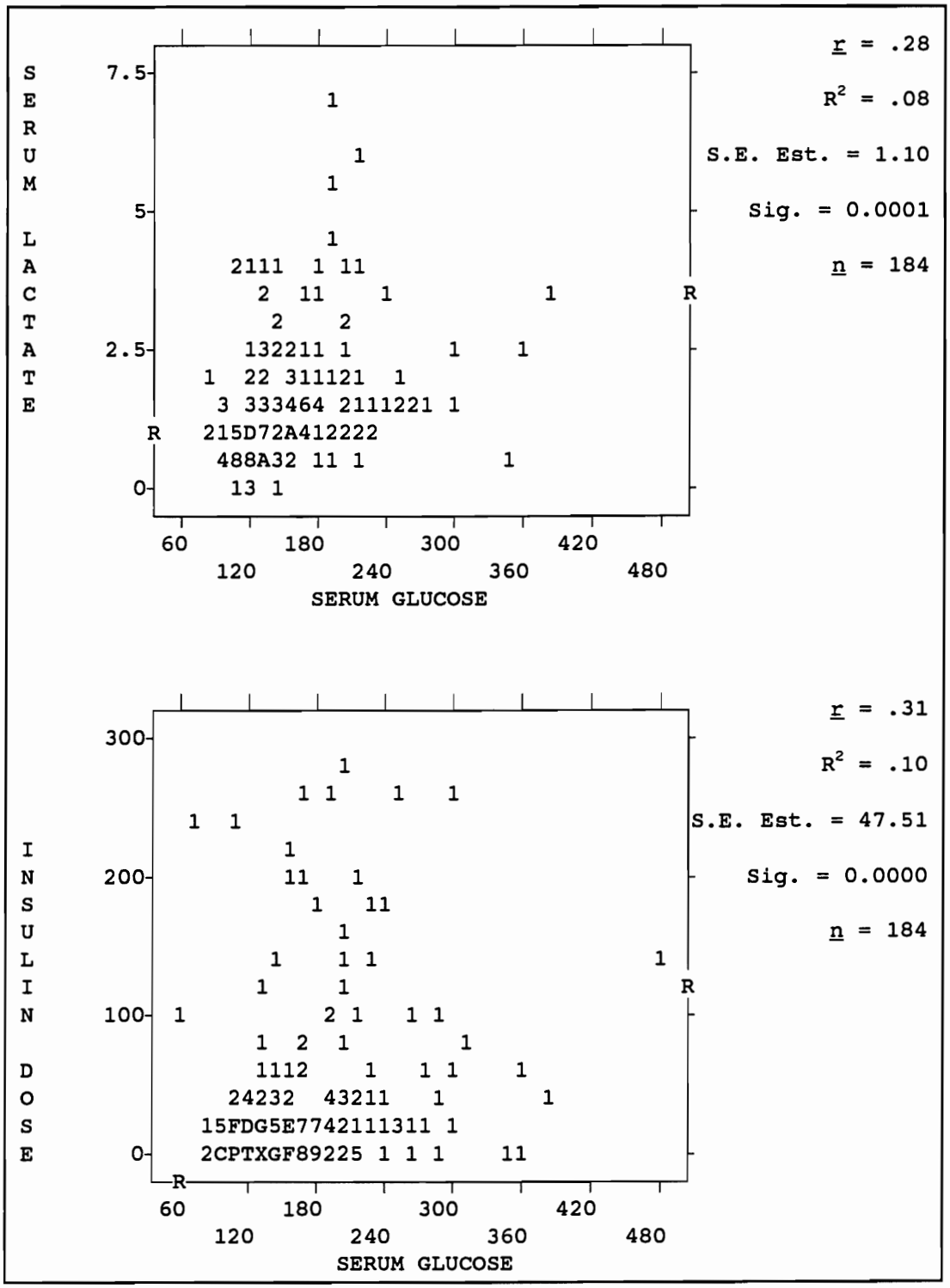

Figure 14. Bivariate Regression Plots of Serum Lactate and Insulin Dose on Serum Glucose.

Table 17

Multiple Regression of Caloric Intake, Insulin dose, and Serum Lactate on Serum Glucose Levels

Descriptive Statistics

(n = 163)	Mean	Std. Dev.
Caloric Intake	1674.609	1049.731
Serum Lactate	1.512	1.159
Serum Glucose	156.974	52.861
Insulin dose	26.162	52.321

Correlation Matrix

	Caloric Intake	Serum Lactate	Serum Glucose	Insulin Dose
Caloric Intake	1.000	-.258	-.116	.250
Serum Lactate	-.258	1.000	.265	.075
Serum Glucose	-.116	.265	1.000	.292
Insulin Dose	.250	.075	.292	1.000

Regression Statistics

Multiple R	.40209	R Square	.16167
Adjusted R Square	.14491	Standard Error	48.88133

Analysis of Variance

	DF	Sum of Squares	Mean Square
Regression	3	69120.17987	23040.05996
Residual	150	358407.71623	2389.38477

F = 9.64267 Sig. F = .0000

Variables in the Equation

Variable	B	SE B	Beta	T	Sig T
Insulin Dose	.31467	.07888	.31146	3.989	.0001
Serum Lactate	9.36720	3.56697	.20546	2.626	.0095
Caloric Intake	-7.10293E-03	4.05735E-03	-.14105	-1.751	.0821
(Constant)	146.47639	10.23904		14.306	.0000

Table 17 (continued)

Regression Statistics (note)			
Multiple R	.37400	R Square	.13988
Adjusted R Square	.12913	Standard Error	49.00914

Analysis of Variance

	DF	Sum of Squares	Mean Square
Regression	2	62498.22824	31249.11412
Residual	160	384303.40366	2401.89627

F = 13.01018 Sig. F = .0000

Variables in the Equation

Variable	B	SE B	Beta	T	Sig T
Insulin Dose	.27987	.07460	.27556	3.752	.0002
Serum Lactate	10.69846	3.31578	.23699	3.227	.0015
(Constant)	133.98993	6.56201		20.419	.0000

Note. Excluding caloric intake for comparison, n = 154.

therapeutic attempt to gain control over increasing serum glucose levels by increasing the insulin dosage.

Immune response

White blood cell count (WBC), percent of lymphocytes from the differential, and total lymphocyte were recorded for analysis. Total lymphocyte count was calculated by WBC x percent of lymphocytes. Distributions are illustrated in Figure 15. Three extreme values were noted in the distribution of WBC counts. Two of the values at midpoints 41 and 44 represent two individuals with severe pulmonary infections. The extreme case at midpoint 69 represents a case of severe leukocytosis

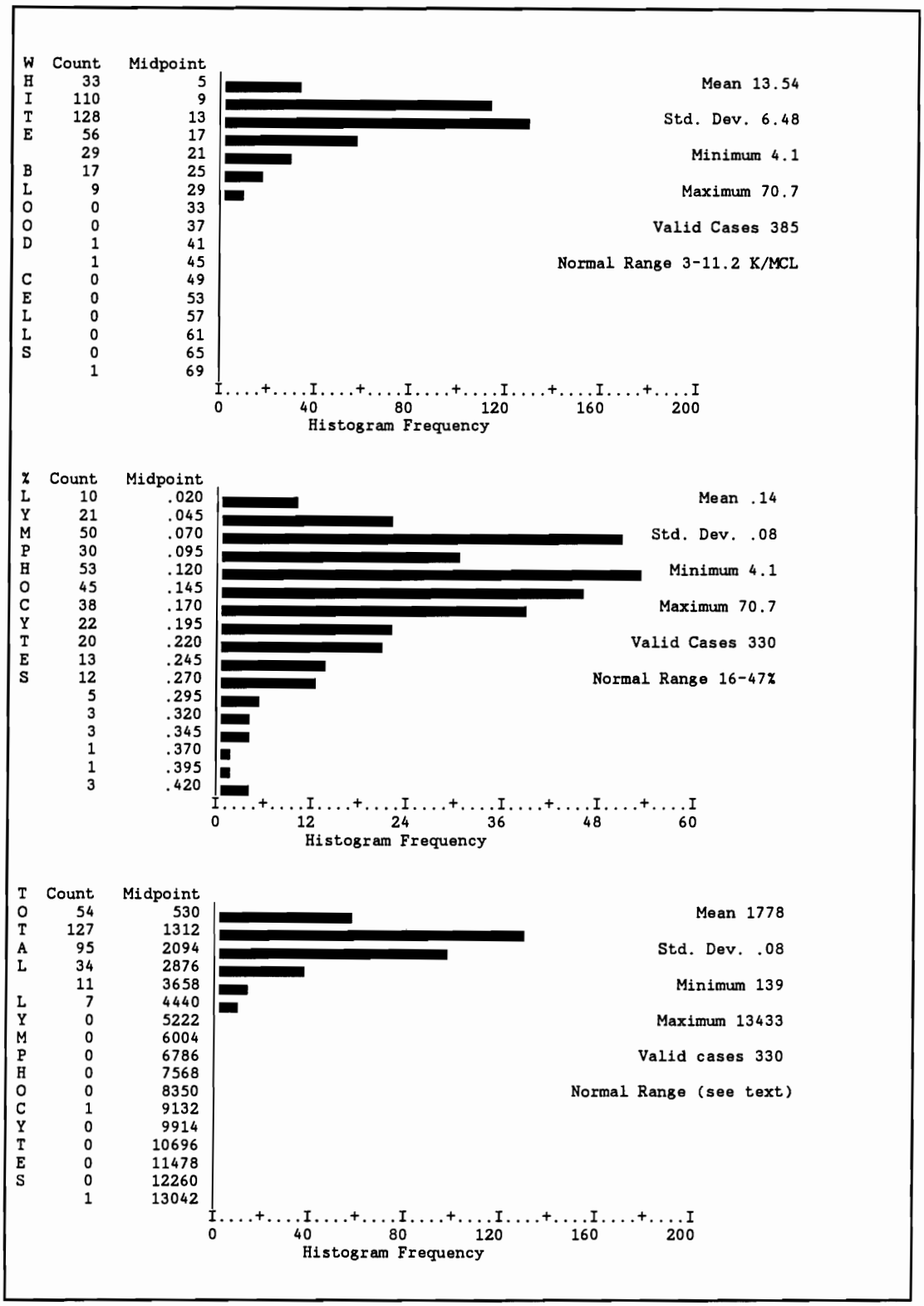

Figure 15. Distribution of White Blood Cell Count, Lymphocytes and Total Lymphocyte Counts.

likely secondary to pulmonary embolus. These cases are also reflected in two extreme values for the total lymphocyte count.

Total lymphocyte counts (TLC) are advocated as a sensitive measure for the effects of nutrition on immunity (Blackburn, Bell, & Mullen, 1989). Lymphocyte counts of 800-1200 are indicative of moderate malnutrition whereas counts of less than 800 are indicative of severe malnutrition. Thirty-two cases or approximately 10% of the sample displayed TLC's below 800. Fifty-eight cases or approximately 18% of the sample values fell between 800-1200 (TLC).

No significant correlations between actual REE and hematologic studies were identified. Correlation of days since injury and increasing lymphocyte count ($r = .18$, $p < .001$) demonstrated resolution of relative lymphocytopenia in the ICU period. As might be expected, WBC count, percent lymphocytes, and total lymphocyte count correlated well with each other.

Gastrointestinal response

The earliest time of the initiation of enteral nutrition in this sample was day 6 after injury. The most common time for the initiation of enteral nutrition was between 10 and 14 days after injury. The ability to feed enterally was hampered primarily by ability to place enteral feeding tubes, high residual feeding aspirated from the feeding tubes, high risk for aspiration, and abdominal distention.

Protein metabolism

Nutrient assimilation is measured by a variety of variables. These aspects have already been addressed, in part, in the discussions of glucose tolerance, insulin resistance, and hematologic values. The remaining portion is the distribution and characteristics of protein synthesis and their relationship to actual REE. Two variables are particularly good measures of protein synthesis: thyroxin binding

prealbumin (TBPA) and transferrin. Figure 5 showed the distribution of these variables, in this sample, under the discussion of nutritional support. Measures of these plasma proteins did not correlate significantly with actual REE, protein intake, or Caloric intake in this sample. The relative number of cases of concurrent measurement, however, was relatively small (n = 133). High correlations between TBPA and transferrin were noted (0.603, $p < 0.001$).

Summary

The goal of this section was to explore and analyze the distributions, characteristics and correlations of variables grouped under the category termed person variables (see Figure 2). This analysis serves to provide the basis for subsequent analysis. Metabolic rate in the analysis so far is notably missing: The distribution of actual REE measured by indirect calorimetry. This variable was analyzed more completely in the next section comparing different methods of deriving estimates of caloric requirement.

Intervention/Treatment

Intervention and treatment is a category under the domain for nutrition in TBI that addresses nutritional practices, patient tolerance, and concurrent treatment. Aspects of this category have already been explored under the discussion of nutritional support and in the previous section on person variables and their relationship to actual REE. The remaining variables to be considered are sedatives, narcotic analgesics, and paralytic agents with their subsequent relationship to energy expenditure.

Three hundred twenty-eight concurrent observations of energy expenditure with doses of midazolam (sedative), morphine sulfate, and pancuronium bromide were made. Seventy-nine (24%) of these observations had concurrent sedative,

narcotic, or paralytic's within 1 hour (half-life of all three drugs by the intravenous route) of the REE measurement. For purposes of analyzing the effect of the drugs, doses were divided by the time elapsed from the time of administration to the measurement of REE. The paralytic agents were dummy coded for the equivalent of a full dose of narcotic and sedative agent or 8 mg. given at the time of the REE measurement. No significant differences in actual REE were found from concurrent doses of sedative, narcotic, or paralytic agents in this sample. Note, however, the relative number of cases of concurrent sedation or paralysis with the indirect calorimetry was small (24%).

Estimation of Caloric Requirements

The purpose of this section is to explore the differences between four methods of determining energy expenditure and subsequent caloric needs. The first method, also the oldest, is the Harris-Benedict Equation (see Table 3 for an example of the equation). The result of the equation will be termed calculated basal energy expenditure (calc. BEE). The second method will use the Stress Stratification Framework (see Table 5) of Cerra (1982) and Konstantinides et al. (1984) . The third method will use the regression equation of Clifton et al. (1986) to calculate percent of REE which was converted to REE for comparison (see Table 4). The regression equation of Clifton et al. (1986) was qualified by the authors as only pertaining to the first 2 weeks after injury: Scores were, therefore, limited to that time frame. The fourth method for comparison was actual REE obtained from indirect calorimetry (IC). Actual REE measurements used for comparison were limited to those obtained while the patients were cared for in the NCC.

Actual REE and calculated BEE

Actual REE was compared to Calc. BEE. To obtain similar units for comparison, actual REE was multiplied by 1.4 to give the actual Caloric replacement to maintain weight. An equivalent Caloric replacement for Calc. BEE would be Calc. BEE x activity factor (10 %) x weight maintenance factor (140%). The end product is 1.5 times the BEE to equal 1.4 times the actual REE. Figure 16 compares the distribution for values of Caloric replacement by these two methods. Interestingly, the median for the two methods is approximately equal. Note, however, the variability of the distributions is quite different. The actual REE covered a much broader range of values.

One extreme value is noted for actual RME. This value represents a 16 year old with an APACHE score of 15 on admission (below the Mean). His GCS at the time of this measurement was 10, heart rate 132, temperature 38.2 C., WBC count 25.5, and serum lactate of 1.4. A review of the indirect calorimetry reading showed a remarkably stable analysis. The indirect calorimetry readings for the outliers in the actual REE group ($\underline{n}$ = 4) were also reviewed and only one of the readings was unstable. A review of other metabolic parameters (severity of injury, laboratory values, vital signs, and neurologic status) show no patterns to explain the unusually high REE's. The outlier ($\underline{n}$ = 1) for the Calc. BEE group was a 6 foot tall, 263 lb. individual.

A bivariate regression analysis was performed between Caloric replacement by actual REE and Calc. BEE and is shown in Figure 17. By the results only about 15% of the variance in actual RME was explained by the Calc. BEE. A portion of this nonlinear pattern can be seen by the outliers and extreme values for Calc. BEE seen in the upper part of Figure 18. Although the Calc. BEE was high the corresponding actual REE for these cases was moderate.

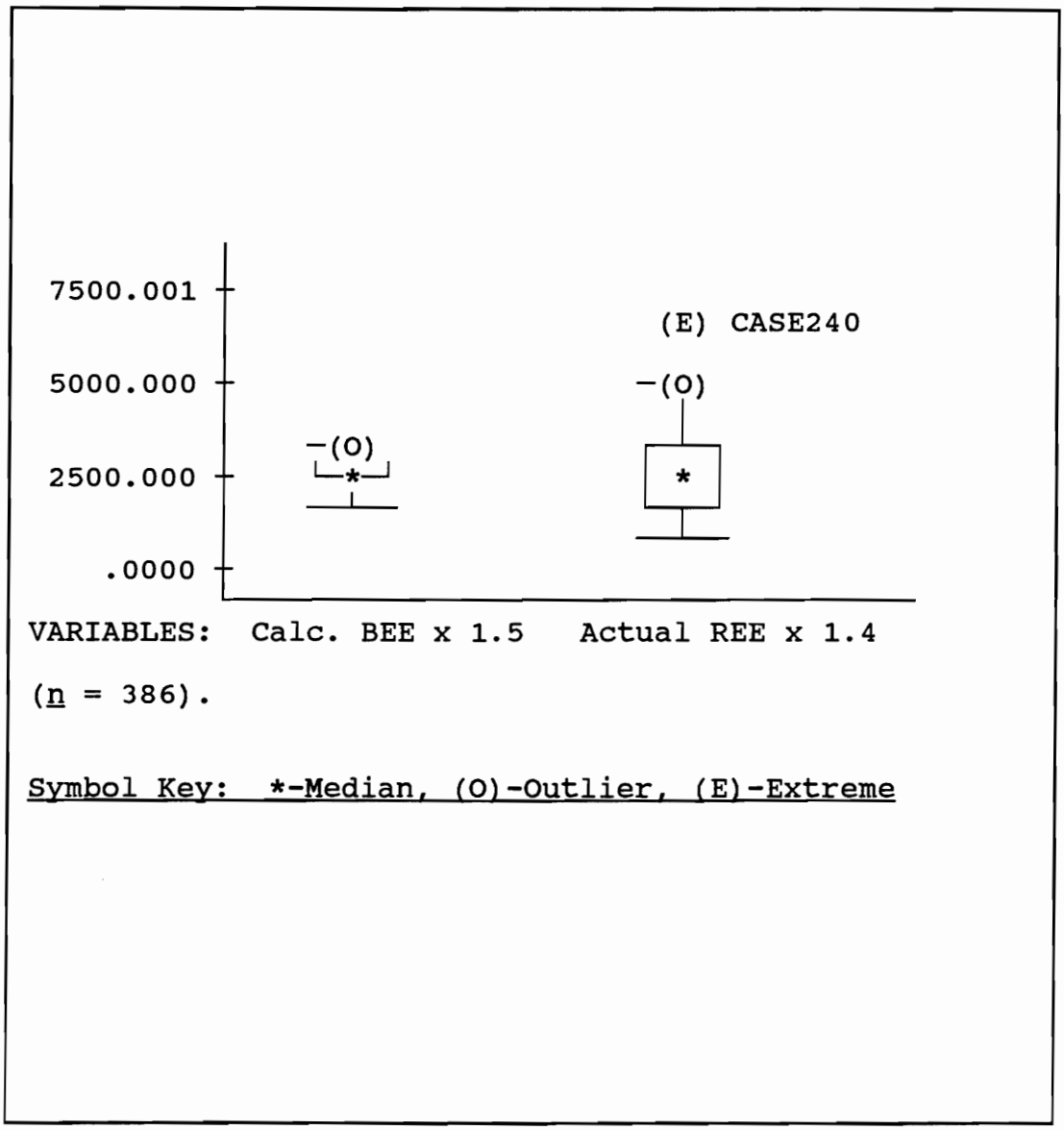

Figure 16. Plots of Actual REE with Calculated BEE. Note. Calculated Bee x 1.5 (complete statistics): Mean 2475; Std. Err. 19.32; Min. 1645; Median 2512; Variance 144075; Max. 3586. S.D. 379.57. Actual REE x 1.4 (complete statistics): Mean 2580; Std.Err. 44.35; Min. 744; Median 2454; Variance 759095; Max. 6752; S.D. 871.26;

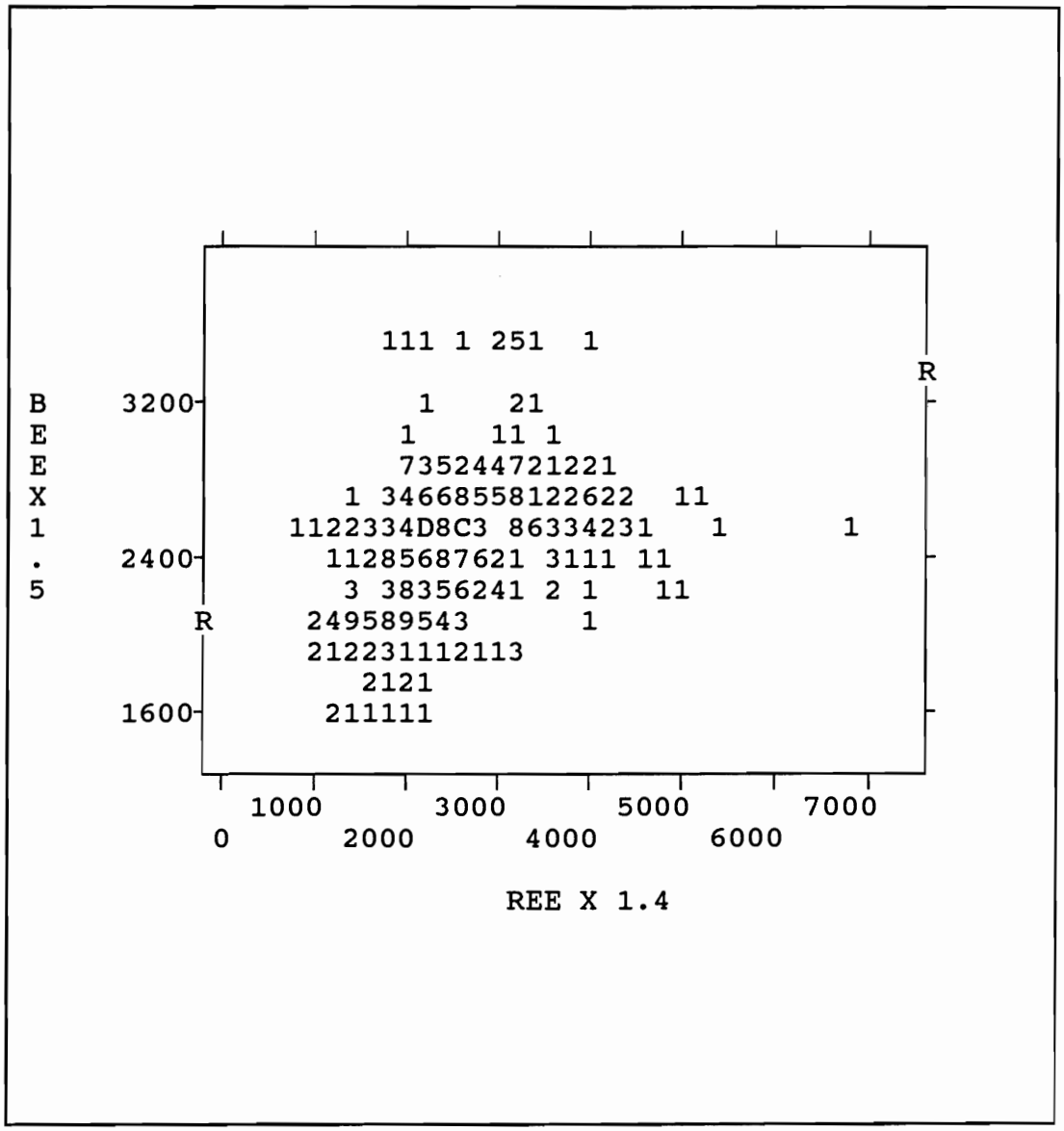

Figure 17. Caloric replacement by calculated BEE and actual REE. Note. Regression statistics of CALC. BEE X 1.5 on ACTUAL REE X 1.4: r = 38; R^2 = .15; S.E. of Est. = 350.81; Sig. = .0000; Intercept (S.E.) = 2042 (55.89); Slope (S.E.) = .16761 (.02052)

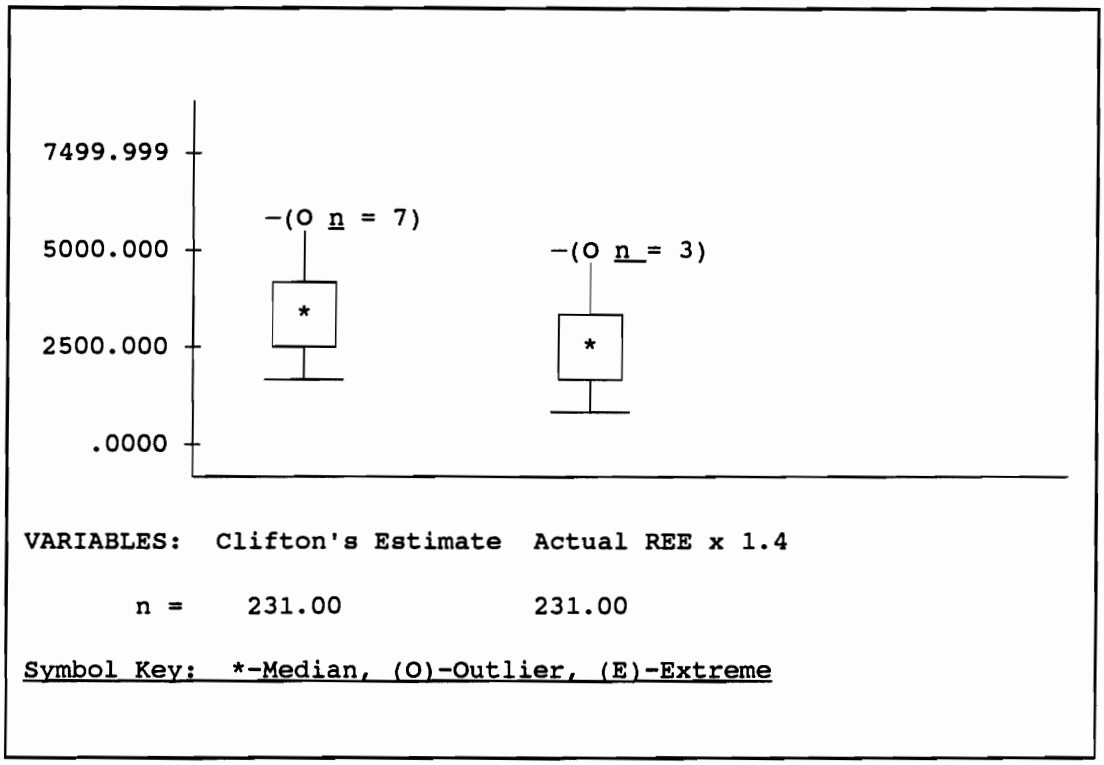

Figure 18. Box Plots of Actual REE with the estimates of Clifton et al. 1986. Note. Clifton's estimate (complete statistics): Mean 3513; Std. Err. 59.77; Min. 1701; Median 3363; Variance 825277; Max. 6186; S.D. 908.45; Range 4485. Actual RME x 1.4 (complete statistics): Mean 2519; Std. Err. 56.16; Min. 745; Median 2335; Variance 728521; Max. 5377; S.D. 853.53; Range 4633.

Actual REE and Clifton's equation

The second method to be compared to actual REE is the regression equation based on heart rate, days since injury, and GCS for the first 2 weeks of injury for comatose individuals (GCS < 8) and heart rate and days since injury for semicomatose or noncomatose individuals with TBI (Clifton et al. 1986, Table 4, for a review of the regression equations). Individuals with concurrent indirect calorimetry and values for heart rate, days since injury, and GCS were extracted. Estimates of the percent of REE were then obtained from the regression equation.

The percent of REE was then converted to actual Calories replaced by multiplying the value by the Calc. BEE to obtain an equivalent value to compare to the actual REE. Note that the estimates obtained by the equations of Clifton et al. (1986) only represent individuals within 14 days of injury and therefore a subset of the sample population. Distributions are shown in Figure 18. The most prominent aspect of this comparison is the extent of overestimation. The outliers noted, represent individuals who are close to the end of two weeks and have correspondingly high estimates: by the regression equation of Clifton et al. (1986) approximately 7% of the Calc. BEE for every day since injury (slope coefficient).

Figure 19 shows an analysis of the bivariate regression of the values obtained from the regression equation of Clifton et al. (1986) with actual REE. In this observation approximately 16% of the variance in actual REE can be explained by the value of regression equation. This represents an approximate percentage of variance explained increase over the Harris Benedict Equation by 1%. The plot also demonstrates a departure away from the regression lines at high values.

The box plots and regression plots, however, do not fully portray the extent of departure of estimates of Clifton et al. (1986) from the Actual REE derived from indirect calorimetry. Figure 20 directly compares each calculation from the formula of Clifton et al. (1986) with the Actual REE. It is readily apparent that basing clinical Caloric supplementation on these estimates would result in overestimation and underestimation of individual needs the majority of the time.

Actual REE and stress stratification estimates

The third method to be compared with actual REE is by the Stress Stratification Framework (Cerra, 1982; Konstantinides et al., 1984). The Framework uses urinary nitrogen loss, serum glucose, and serum lactate as metabolic markers to predict a Caloric replacement (see Table 6). These metabolic markers were

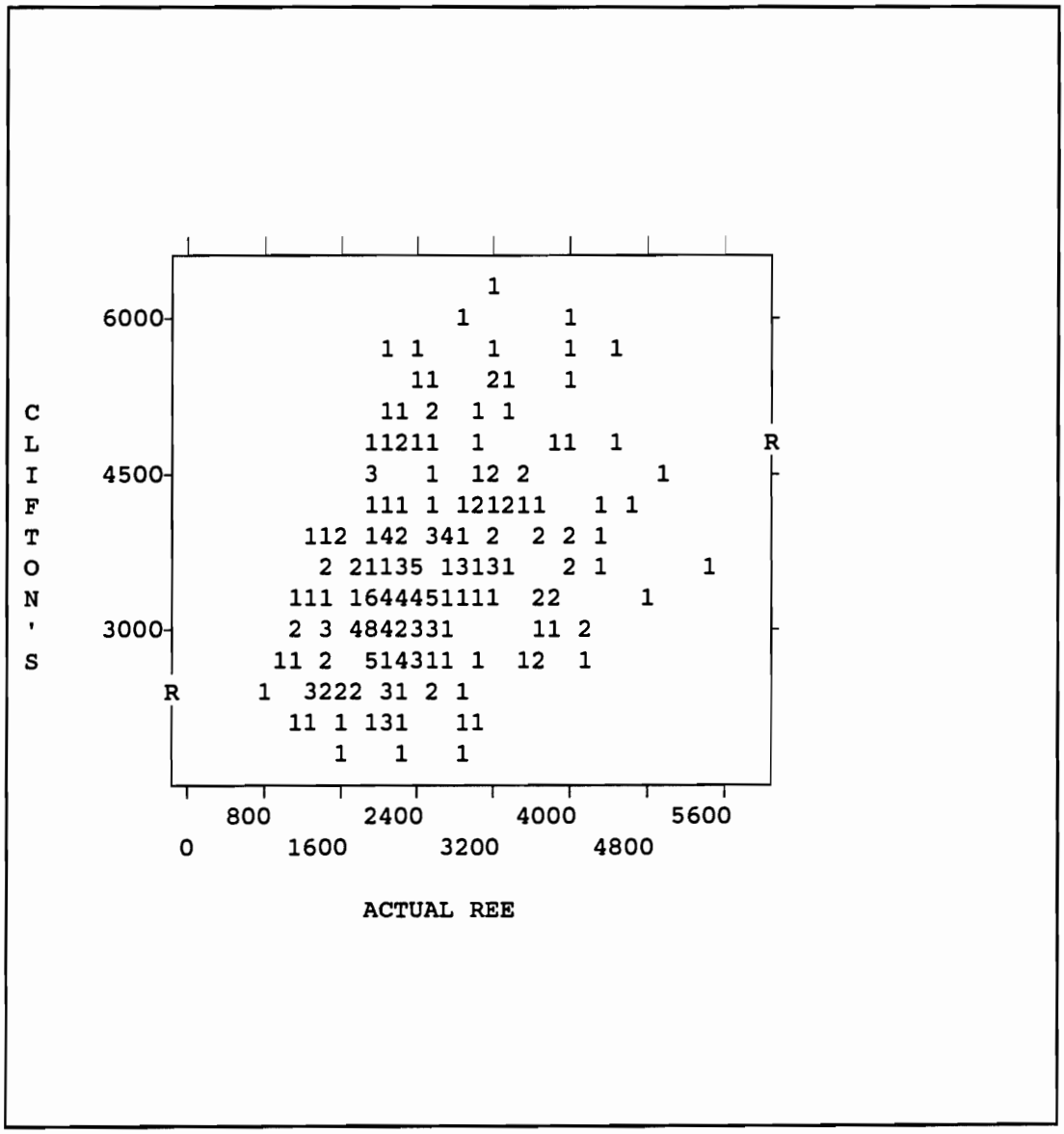

Figure 19. Bivariate Regression Plot of Actual REE with estimates of Clifton et al. 1986. Note. Regression statistics of CLIFTON'S ESTIMATE on REE X 1.4: r = .39 R^2 .16; S.E. of Est. = 836.58; Sig. = 0.0000; Intercept (S.E.) = 2456 (171.86); Slope (S.E.) = 0.42 (0.06); n = 231.

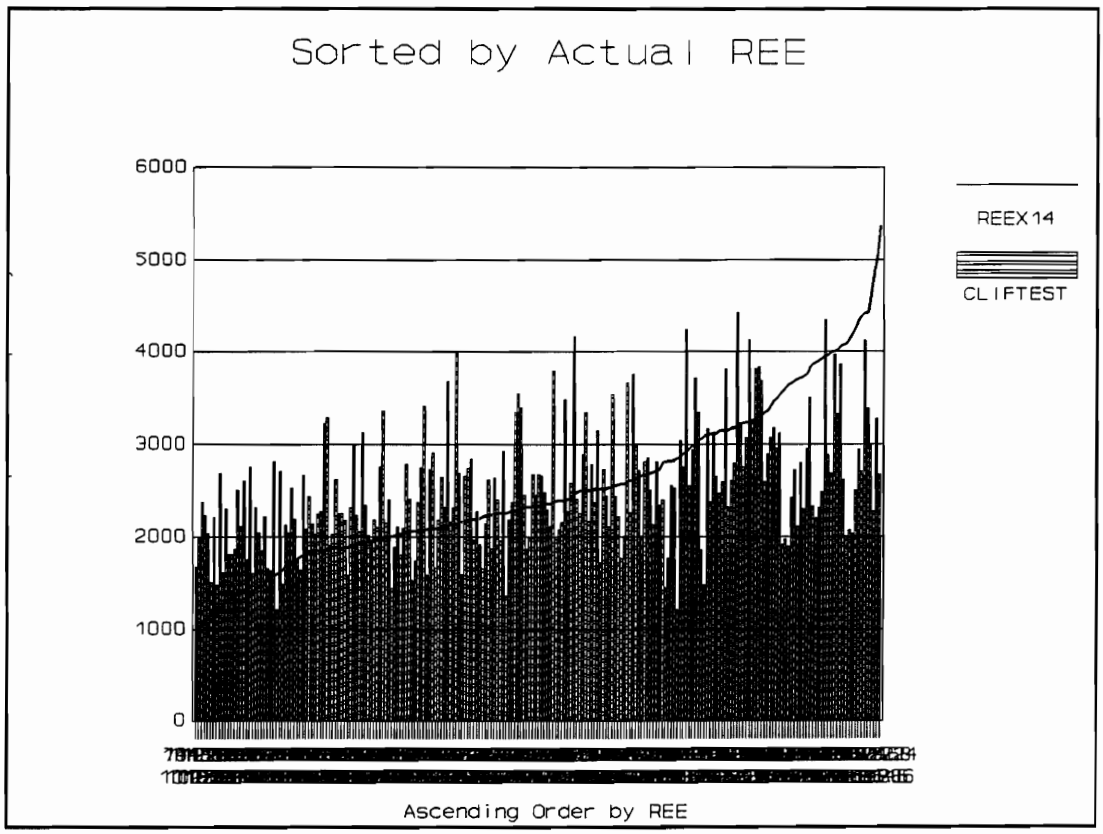

Figure 20. Comparison of estimates of Clifton et al. (1986) with Actual Resting Energy Expenditure. Note. REEX14 = Actual Resting Energy Expenditure multiplied by 1.4. Cliftest = Calculated REE (see Table 4 for a review of the metabolic equation by Clifton et al. [1986]).

evaluated and a Caloric replacement calculated for the sample. Two hundred sixty-seven measures of laboratory values and concurrent measures of REE by IC were available for analysis. A plot comparing estimates from the stress stratification framework (SSF) and actual REE is shown in Figure 21. Note the narrow range of values encompassed by the SSF compared to the actual REE values.

Bivariate regression analysis was performed for the relation of the SSF scores and actual REE. These representations are depicted in Figure 22. By the analysis the percentage of variance explained drops to 5 showing minimal ability to predict actual REE.

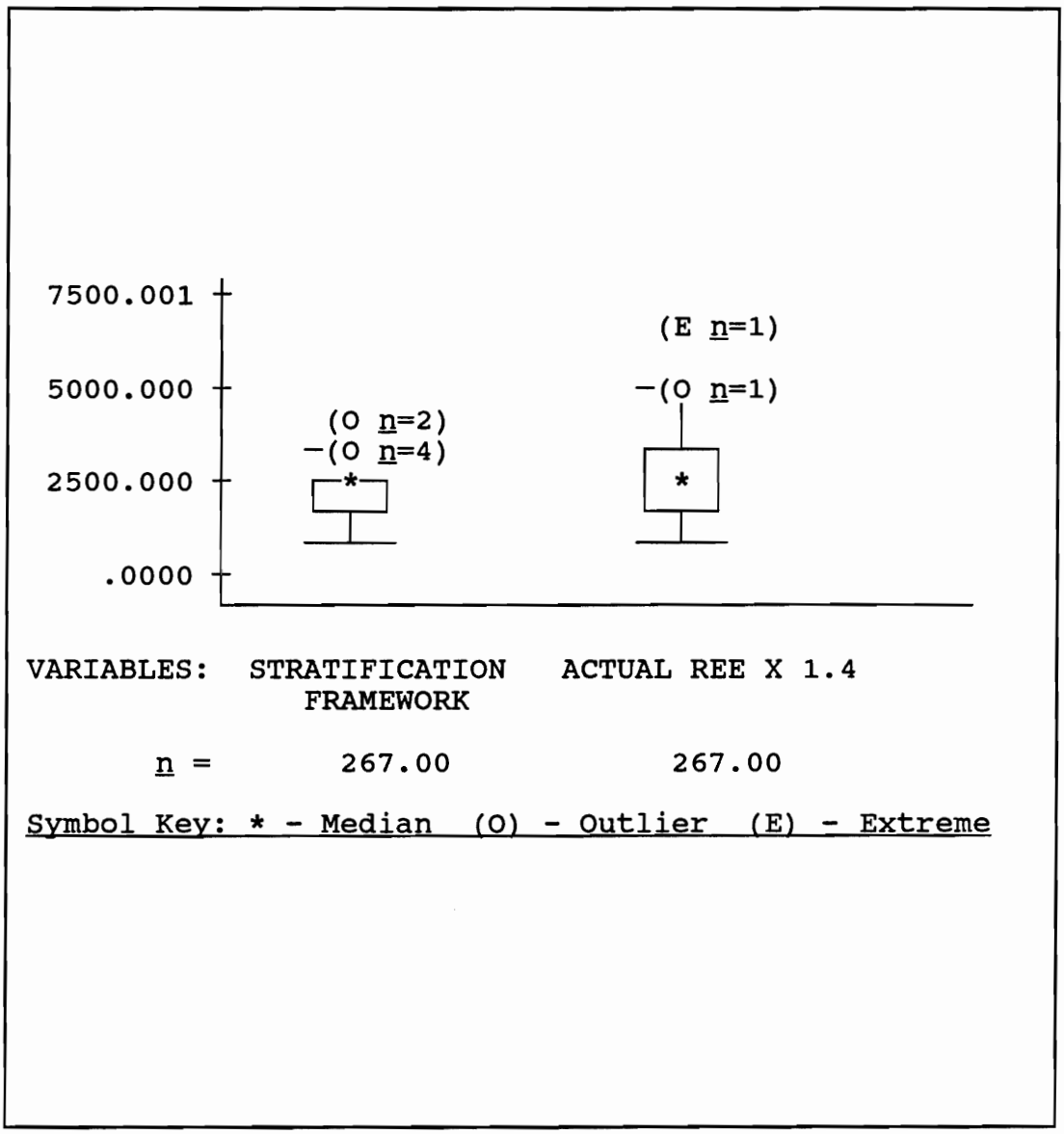

Figure 21. Plot of Actual REE with Stress Stratification Estimate. Note. SSF: Mean 2236; Std. Err. 31.75; Min. 1230; Median 2205; Variance 269164; Max 3934; S.D. 518.8; Range 2703. Actual REE x 1.4: Mean 2571; Std. Err. 53.12; Min. 745; Median 2405; Variance 753459; Max. 6752; S.D. 868.02; Range 6007.

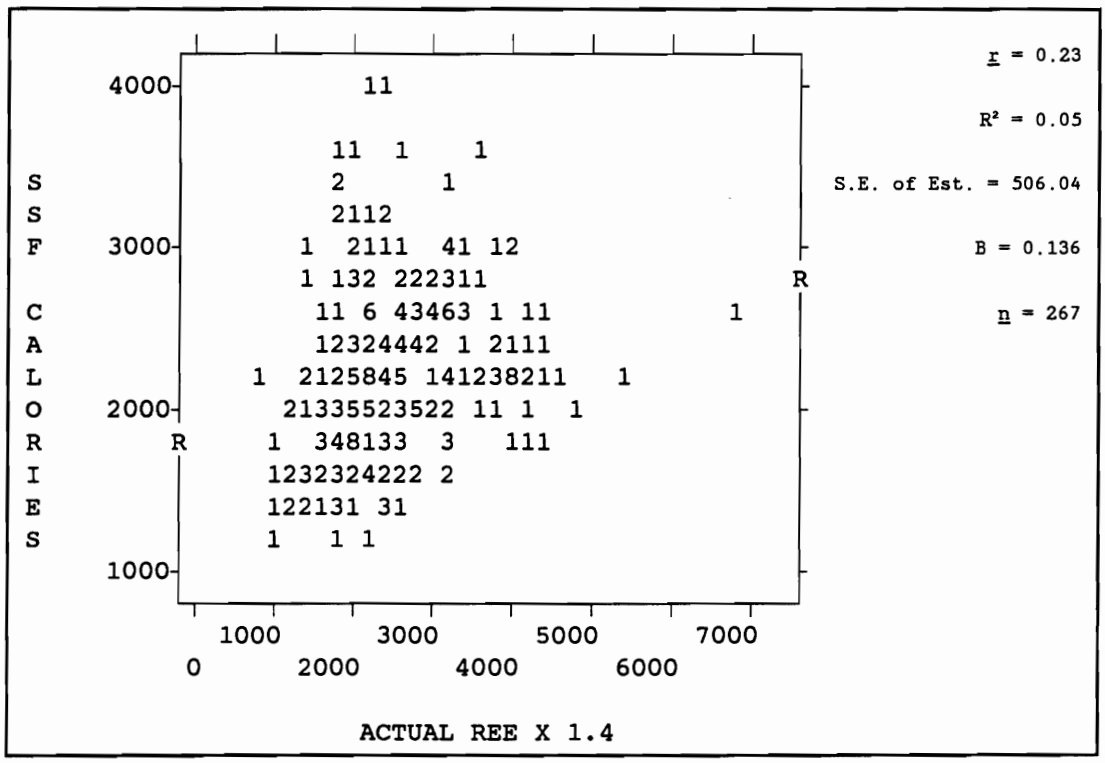

Figure 22. Plot of Actual REE with Caloric Replacement from the Stress Stratification Framework.

Scores from the four methods, demonstrated in terms of percentile ranks, are shown in Table 18. Haverage is a weighted percentile with the corresponding rank noted whereas Tukey's hinges denote the ranks at the 25th, 50th, and 75th percentile. This illustration is useful in pointing out the extent of variance in the distribution in terms of actual Calories delivered. Examination of the distributions indicates that the sample of repeated measures in this study have a broadened distribution compared to the Harris-Benedict equation. The regression equation of Clifton et al, (1986) appeared to show a movement of the whole distribution to higher values. The distribution of the Stress Stratification Framework is more consistent with a broader variation, similar to the indirect calorimetry values.

Table 18

Percentile Ranks for Four Methods of Determining Caloric Requirement

Percentiles	5.0000	10.0000	25.0000	50.0000	75.0000	90.0000	95.0000
CALORIC REPLACEMENT BY INDIRECT CALORIMETRY:							
HAVERAGE	1325.520	1568.000	1974.700	2454.900	3150.000	3863.300	4175.710
Tukey's Hinges			1975.400	2454.900	3150.000		
CALORIC REPLACEMENT BY CALCULATION OF HARRIS-BENEDICT EQUATION:							
HAVERAGE	1858.232	2006.025	2202.735	2512.890	2754.405	2898.330	3028.394
Tukey's Hinges			2202.735	2512.890	2754.405		
CALORIC REPLACEMENT BY CLIFTON'S ESTIMATE:							
HAVERAGE	2223.867	2445.776	2877.019	3363.212	3973.321	4779.007	5336.038
Tukey's Hinges			2887.231	3363.212	3959.559		
CALORIC REPLACEMENT BY THE STRESS STRATIFICATION FRAMEWORK:							
HAVERAGE	1400.605	1630.980	1858.550	2205.242	2534.835	2926.636	3198.288
Tukey's Hinges			1858.550	2205.242	2534.835		

Metabolic distribution of actual REE

The discussion of Caloric estimation would be incomplete without illustrating the extent of actual metabolic expenditure by definition. The terms commonly used to define normal, hypermetabolic, and hypometabolic rate are derived from the Harris-Benedict Equation (Blackburn et al, 1989). Hypometabolic is actual REE that is less than 90% of the Calc. BEE. A normal metabolic rate (actual REE) falls between 90% and 110% of Calc. BEE. A hypermetabolic rate is defined as actual REE above 110% of Calc. BEE. Figure 23 shows the percentage of cases in each category (n = 386). Over two-thirds of all indirect calorimetry measurements made in this population over a three year period, by current definitions, fell outside the range of normal energy expenditure. The clinical significance of this observation translated to the realization that the clinician who administers nutrition based on the most commonly used standards of nutritional evaluation will only be meeting the unique needs of the TBI population less than one third of the time. Although the specific benefits of precise nutritional repletion have yet to be proven, the extent of this error would not be tolerated in other areas of human nutrition.

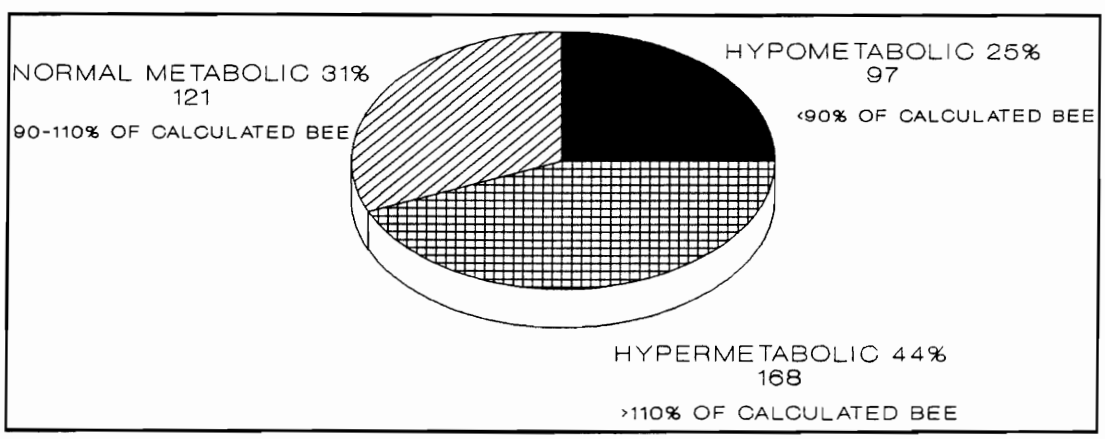

Figure 23. Distribution of Indirect Calorimetry Measurements by Category of Metabolic Rate. Note. Listed by number and percent of all cases.

Multiple Regression Analyses of Metabolic Indicators

The purpose of this section is to further examine the metabolic indices obtained in this study to determine the concordance with the current literature and the parameters in this specific population and attempt to improve on current predictions. The analysis will proceed using the most abundant metabolic indices, in this case physiological measures including heart rate, GCS, temperature, and their temporal relationship defined as days since injury. Less abundant measures, for example laboratory measurements, will then be added to evaluate their usefulness in the regression analyses.

Prediction of Actual Resting Energy Expenditure

Easily obtainable clinical parameters (obtained in this sample) for estimation of energy expenditure were subjected to multiple regression analysis using the method of forward entry. Forward entry consists of taking each successive variable in order of specific entry criteria. The criteria used in this analysis included a probability of F to enter the variable into the equation of < 0.05 and a minimum tolerance of 0.01 to prevent highly intercorrelated independent variables from entering the equation (multicollinearity). Multicollinearity, however, was not anticipated because of relatively low correlation coefficients.

To control for age, height, weight, sex, and expected values of basal energy expenditure in the equation, the percent of resting energy expenditure (REE) was used as the dependent variable. The percent REE was derived for each case by the following equation (Actual REE by indirect calorimetry / Calculated BEE x 100 = %REE). This transformation of the dependent variable allowed for ease of comparing results with the current literature and providing a common frame of reference. Variables in the initial analysis were not, otherwise, manipulated in any way.

Table 19 shows the results of the initial regression analysis. Figure 24 displays plots of observed with expected values and residuals with predicted values resulting from the regression analysis. Figures 25, 26, and 27 are plots of the independent variables (IVs) with the regression residuals. No identifiable relationships between the IVs and residuals were found.

By step number, heart rate was found most influential in the regression equation followed by body temperature and days since injury respectively. Although the values for the coefficient of determination (R^2) vary dramatically from the results of Clifton et al. (1986), the coefficient for heart rate is practically identical (0.4). When body temperature was entered alone in the regression analysis, the value closely matched the estimates from extensive studies of fever in illness reported by Kinney, Jeejeebhoy, Hill, and Owen (1988). The estimate reported was a 13% increase in REE for every degree centigrade, whereas the estimate on this sample was an 11% increase.

Examination of the beta values (Independent variables expressed as z scores, Table 19) suggests that temperature in the equation accounts for the highest degree of influence in the regression equation followed by days since injury then heart rate. This observation is most consistent with the current literature. The report by Clifton et al. (1986) that temperature was not statistically significant in their regression equation may, in part, be explained by the restriction of their analysis to the first 2 weeks after injury. When the analysis in the present example was restricted to 2 weeks, temperature was also not found to be statistically significant. It may be postulated that in the first 2 weeks after injury the intercorrelation between heart rate and temperature is greater than after 2 weeks. Examination of the correlations between heart rate and temperature in this sample do not verify this observation ($\underline{r}$ = .2773 (DSI < 14, $\underline{n}$ = 231), $\underline{r}$ = .4335) (DSI > 14, $\underline{n}$ = 98). Examination of the

Table 19

Regression Analysis of Heart Rate, Body Temperature, and Days Since Injury on Percent of Resting Energy Expenditure

Multiple Regression

Dependent Variable: Percent of REE. Independent Variable(s) Entered on Step Number: 1. Heart Rate; 2. Temperature; 3. Days Since Injury.

Multiple R: .32309

R Square: .10439

Adjusted R Square: .09612

Standard Error: 34.04412

Analysis of Variance

	DF	Sum of Squares	Mean Square
Regression	3	43902.49362	14634.16454
Residual	325	376675.72180	1159.00222

F = 12.62652 Sig. F = .0000

Variables in the Equation

Variable	B	SE B	Beta	T	Sig T
HR	.25604	.10401	.14032	2.462	.0144
TEMP	10.25537	2.84610	.20148	3.603	.0004
DSI	.62202	.20960	.16441	2.968	.0032
(Constant)	-307.71007	105.17589		-2.926	.0037

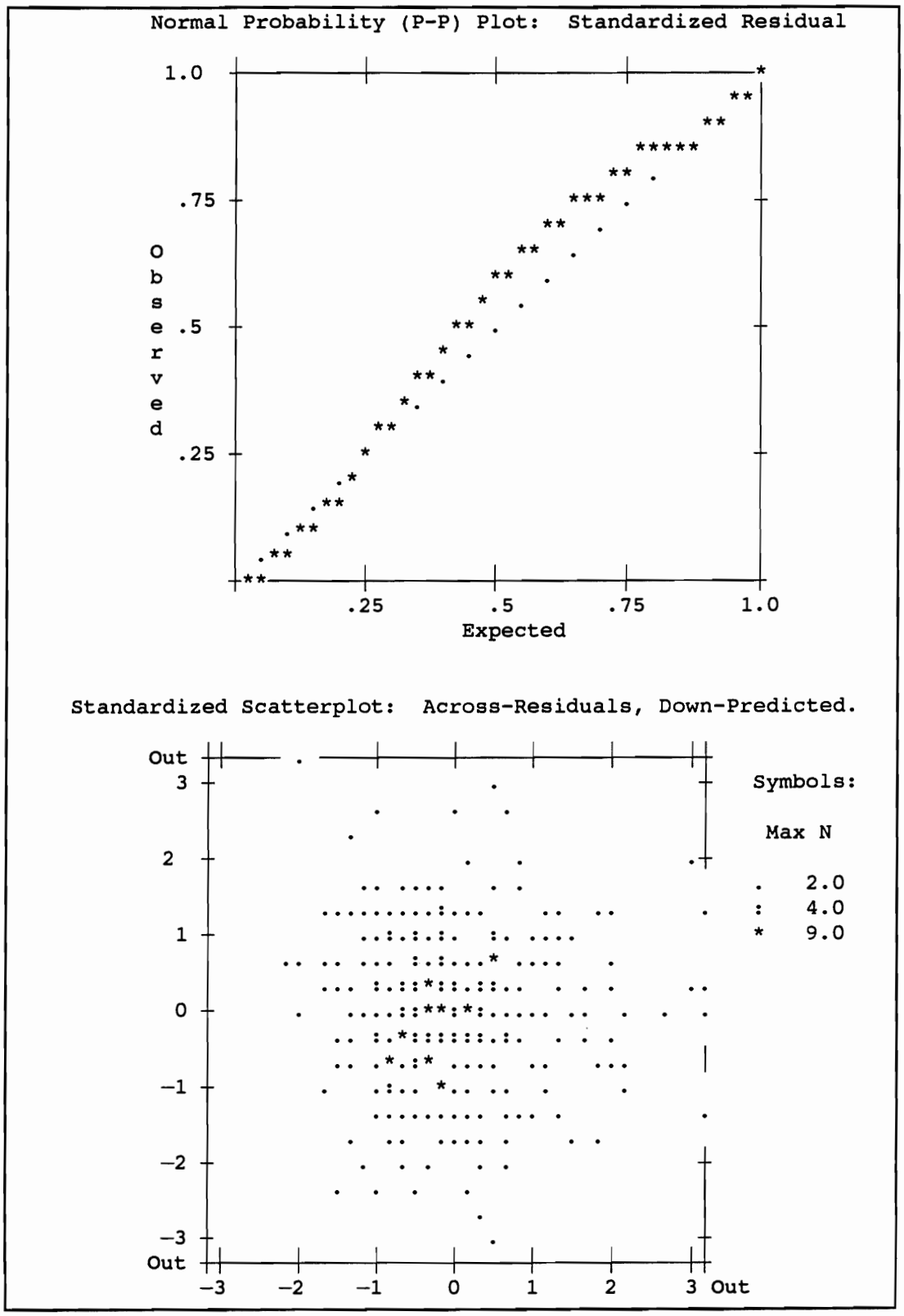

Figure 24. Plot of Expected and Observed Values for Percent REE.

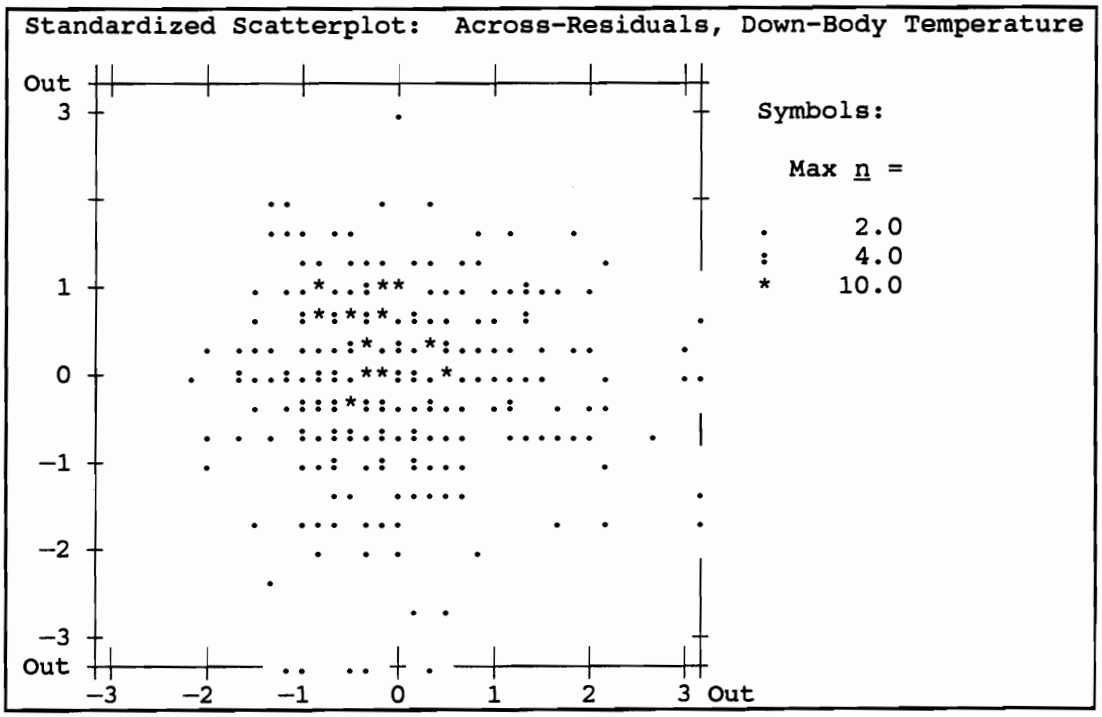

Figure 25. Plot of Body Temperature against Residuals.

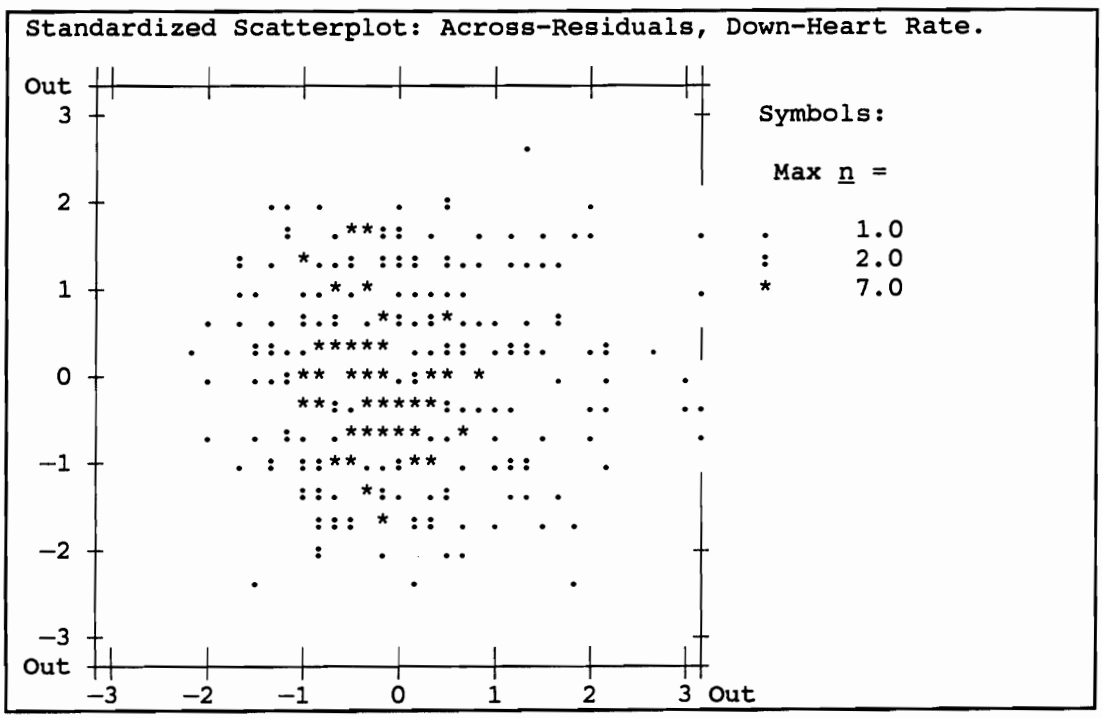

Figure 26. Plot of Heart Rate against Residuals.

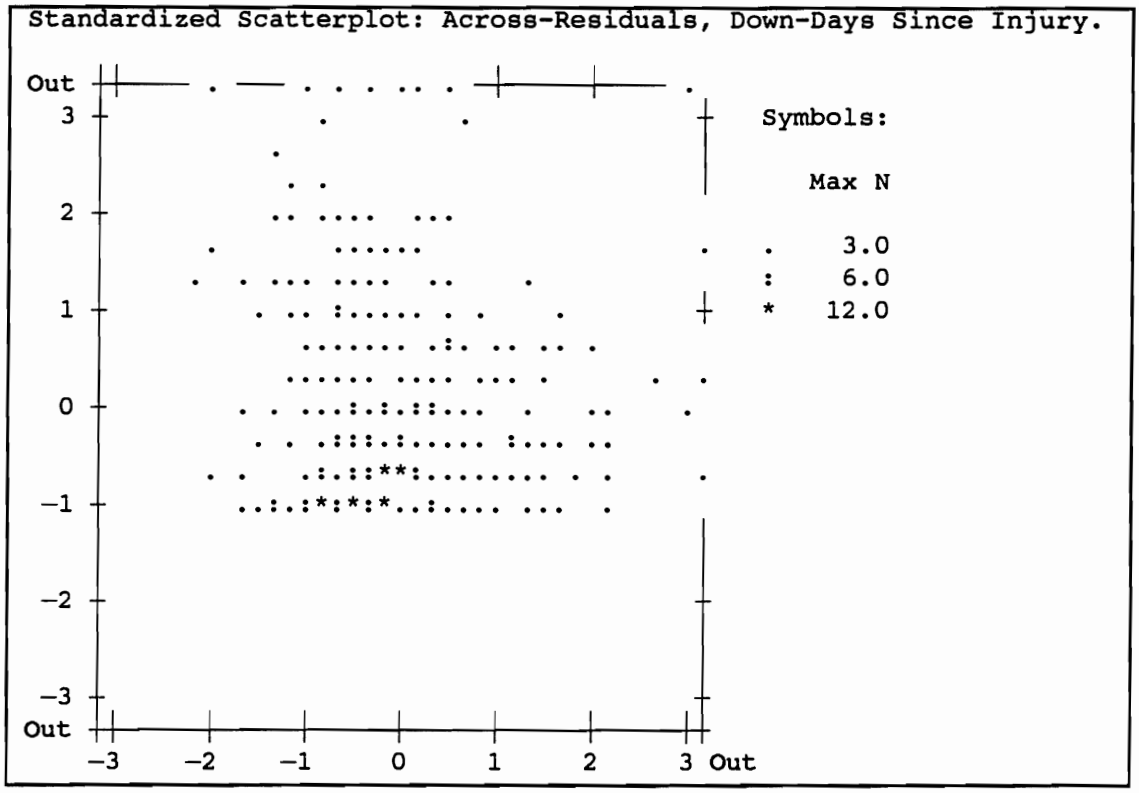

Figure 27. Plot of Days Since Injury against Residuals.

distributions for the variables and statistics, by time, did not offer any further explanation for this phenomenon.

Days since injury represents a conceptually puzzling variable in prediction of energy expenditure. Theoretically one may hypothesize that the variable must be curvilinear: In the early periods after injury, a gradual rise in energy expenditure would be anticipated followed by a gradual decrease as the influence of the injury subsides. If the two variables were to be plotted, it would be expected to resemble a parabola and represent the presence of quadratic regression. In this sample, plots of energy expenditure over time (Table 16) suggested that this was not the case. Instead, the plot is more characteristic of an S shaped curve or cubic regression. Attempts to coax the days since injury variable distribution to a more linear relationship was attempted by transforming variables to the natural log. The

transformation could be beneficial in improving the goodness of fit and improve the prediction estimates. The transformation appeared to improve the normality of the distribution as evidenced by viewing the new plot of the residuals, but did not significantly change the degree of variance explained in the regression model. The presence of the curvilinear distribution of energy plotted over ranks of days since injury may also represent a change in causal relationships to energy expenditure. It is conceivable that over time the causal factors for variation in energy expenditure change. In the first 1 to 2 weeks, for example, the variation in REE may result from physiologic influences from brain trauma, whereas, after this period the causal variables may be increasingly related to immune factors in response to infection.

The departure of the described regression model from that of Clifton et al. in terms of the Glasgow Coma Scale is also of interest. From the initial bivariate analysis in this population (see Figure 10, p. 62) little predictive value appeared to be associated with this assessment parameter. Attempts were made to more closely approximate the model to match their estimates by analyzing comatose (GCS <8) and noncomatose (GCS > 7) individuals separately. Restriction of the observation periods were made to the first 2 weeks after injury. No improvement in predictability was found.

An examination of the distributions of energy expenditure by ranks of Glasgow Coma Score from 3 to 11 (most common patient groups requiring TPN or TEN) demonstrated a number of interesting relationships (Figure 28). First, the median value for energy expenditure was remarkably stable across these levels of GCS scores. This stable median, in part, explains the low explanatory value of the GCS in prediction of energy expenditure. Second, there is marked variability of the shape and characteristics of the distribution across all levels of GCS scores. These

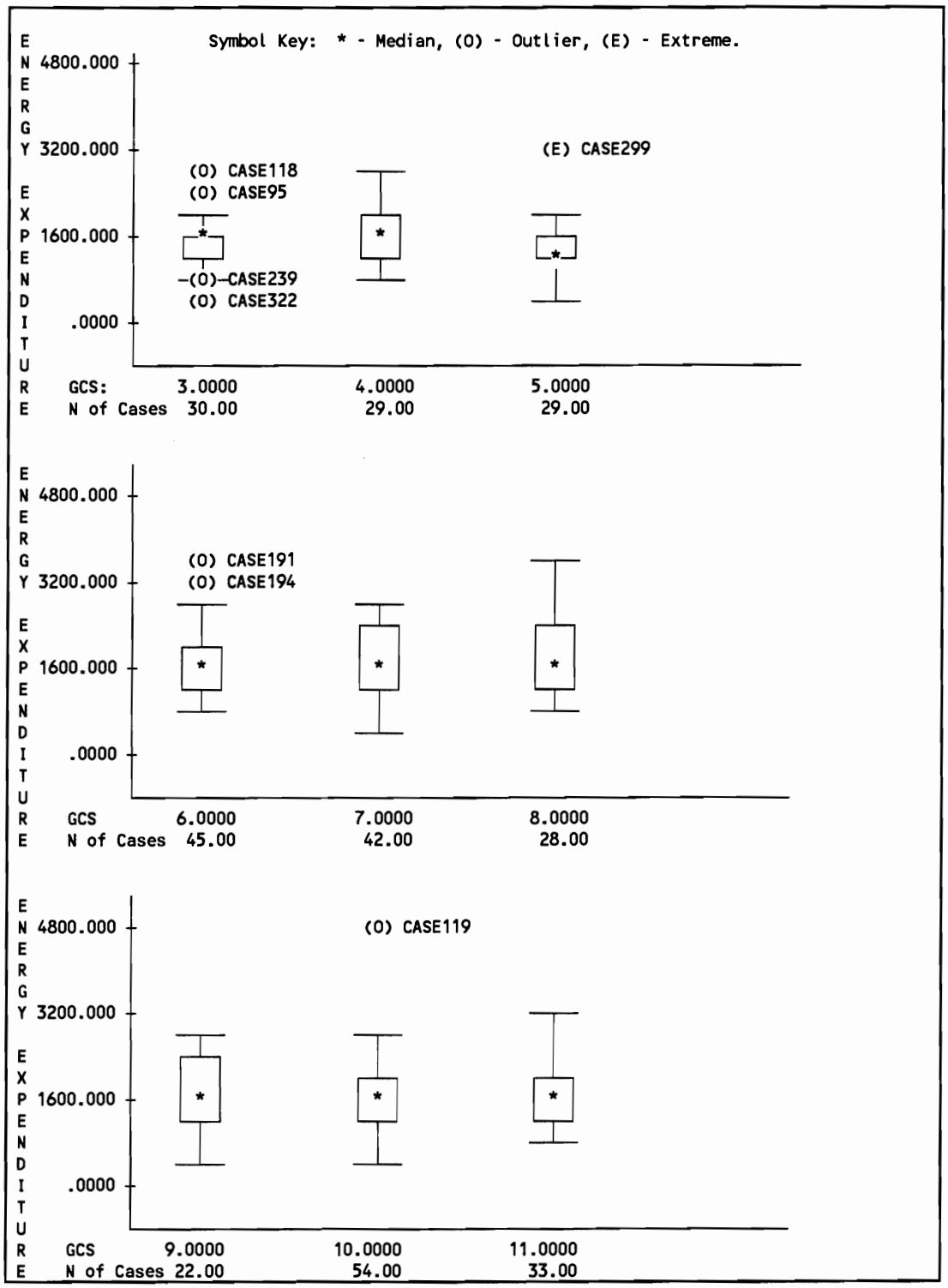

Figure 28. Distribution of Energy Expenditure by Glasgow Coma Scale Score.

changing levels of variance decrease the value of the GCS as a predictive measure of concurrent energy expenditure.

The distribution of outliers in Figure 28 also appears to follow a trend from more to less as GCS increases (no outliers are demonstrated in the rank distributions of GCS above 6). Theoretically, this would be consistent with the proposition of greater variance in energy expenditure with increased severity of injury. The increased number of outliers in the lower GCS groups may also lend support to the proposition that the GCS can identify a subpopulation at increased risk for deviation from normal energy expenditure.

Summary

The regression analysis and comparison to postulated models have shown a number of intriguing relationships. Although the relative value of explained variance in energy expenditure is minimal, the necessity for caution in application of unrepeated research results is exemplified. There may be variation in the methods of managing TBI that greatly influence energy expenditure and reduce predictability by statistical methods in actual clinical practice. For example, the use of beta blockers for blood pressure control also reduces metabolic rate.

Exploratory Factor Analysis for Metabolic Indicators

The task of further identifying the structure of metabolic indicators in TBI was accomplished using exploratory factor analysis. Exploratory factor analysis is a technique that expedites the process of discovering an underlying structure between variables for the purpose of defining dimensions within the data and allowing for subsequent data reduction. The basic principle involved in factor analysis is the assumption that variables are linear combinations of theoretical constructs or hypothetical factors (Kim & Mueller, 1978). The derivation of these theoretical

factors can be helpful in gaining greater insight into the nature of nutrition in TBI. The variables used in the analysis were chosen by two criteria: 1. Representation of major concepts and 2. plentiful in number in the clinical setting as well as the sample presented here.

Representation of extent or severity of injury was provided by the use of the APACHE II scale on admission, the GCS at the time of the metabolic measurement, and the Glasgow outcome scale at hospital discharge. The representation of normal metabolic rate was furnished by the ingredients of the Harris-Benedict Equation; age, height, and weight. The additional variable in the Harris-Benedict equation (gender) was not included because of its dichotomous nature and inability for statistical expression in the factor analytic model (Kim & Mueller, 1978). Heart rate and body temperature represent the influence of cardiodynamics and thermoregulation on energy expenditure. Days since injury will represent temporal response. Serum glucose and daily insulin dosage represent relative carbohydrate synthesis and response to exogenous nutrients.

Steps in the Factor Analysis

Preparation of the correlation matrix

The initial step in factor analysis is the preparation of a correlation matrix to be used for further analysis. Separate correlation matrices were also prepared using subsets of the data to include both men and women, women alone, and men alone. A concern in the factor analysis was that the inclusion of both genders would not adequately represent the two groups (or the factors representing the variables would change significantly by gender). The scrutiny of these correlation matrices (see Table 20) revealed sufficient differences in crucial parameters to warrant separate factor analyses by gender in addition to a combined groups analysis. A limitation imposed by this approach is the small sampling of females. It is anticipated that this

Table 20

Correlation Matrices for Factor Analysis:

By Gender and Combined

	GLUC	ENERGY	DSI	GCS	HR	TEMP	AGE	ADMWT	HTCM	INSULIN	APACHEII	GOS
GLUC	1.00000											
ENERGY	.00519	1.00000										
DSI	-.12312	.10906	1.00000									
GCS	-.05739	.09470	.04176	1.00000								
HR	-.10339	.32977	.20890	-.05159	1.00000							
TEMP	.09037	.31948	-.12138	-.03674	.30853	1.00000						
AGE	.34143	.07487	.24778	.15830	-.09669	.04356	1.00000					
ADMWT	.23556	.22225	.09168	.22506	.07834	.23888	.48698	1.00000				
HTCM	.07691	.18310	-.09850	.05104	-.11607	.21595	.09573	.25383	1.00000			
INSULIN	.34535	.10667	.34871	.07731	.07116	.13323	.59337	.43046	.00619	1.00000		
APACHEII	.01221	.07824	.14672	-.28015	.10639	.06470	.00307	.11139	.08739	.12186	1.00000	
GOS	-.19649	-.00139	-.26481	.27800	-.07352	-.04185	-.43923	-.35473	-.18164	-.39988	-.43312	1.00000

Males only (n = 223).

GLUC	1.00000											
ENERGY	.04643	1.00000										
DSI	-.15757	.31251	1.00000									
GCS	-.04827	.13938	.16633	1.00000								
HR	-.29148	.21013	.38442	.08647	1.00000							
TEMP	.00260	.21910	-.19619	-.21316	.01734	1.00000						
AGE	.30351	-.05997	-.09847	.07507	-.18395	-.08280	1.00000					
ADMWT	.37715	.18348	.38540	-.08887	-.08650	-.12668	.16639	1.00000				
HTCM	-.03130	.00482	-.05406	.31607	-.21972	-.12288	.14532	.03926	1.00000			
INSULIN	.23602	.23299	.25840	-.19226	.08149	.07199	.24673	.70065	-.35886	1.00000		
APACHEII	.43036	.27671	.24286	-.13952	-.17094	.15274	.36175	.43538	.11823	.22062	1.00000	
GOS	-.30572	.02038	-.12634	.46450	-.04251	.00900	-.31396	-.52160	.43372	-.55798	-.40727	1.00000

Females only (n = 65).

Table 20 (continued)

	GLUC	ENERGY	DSI	GCS	HR	TEMP	AGE	ADMWT	HTCM	INSULIN	APACHEII	GOS
GLUC	1.00000											
ENERGY	-.02246	1.00000										
DSI	-.13476	.15388	1.00000									
GCS	-.04515	.06581	.05141	1.00000								
HR	-.14206	.26472	.22736	-.01546	1.00000							
TEMP	.07499	.27597	-.13383	-.06411	.25078	1.00000						
AGE	.34104	-.01264	.15586	.14891	-.10662	.01994	1.00000					
ADMWT	.20966	.30795	.15769	.11855	.01292	.14647	.30601					
HTCM	-.01067	.29825	-.03133	.03591	-.15318	.11507	-.00144	.36152	1.00000			
INSULIN	.31312	.08413	.29412	.00985	.08060	.11531	.47409	.41888	-.13846	1.00000		
APACHEII	.11874	.09303	.15653	-.24557	.04269	.08293	.10590	.15612	.05942	.15354	1.00000	
GOS	-.21585	-.02083	-.24045	.32283	-.06030	-.02826	-.38312	-.39073	-.07849	-.43495	-.42239	1.00000

Males and Females (n = 288).

Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

small sampling will impose significant limitations to the interpretation of the factor analysis for females.

The computer program used for the factor analysis (SPSSPC+, 1990) also provides a number of test statistics (see Table 21). The determinant of the correlation matrix provides an estimation of the relative redundancy of the variables in the equation. As the value for the determinant of the correlation becomes smaller the greater the redundancy (K. Smith, personal communication, April 26, 1990). The Kaiser-Meyer-Olkin Measure of Sampling Adequacy is an index that compares the size of the observed correlation coefficients to their partial correlation coefficients. This produces a measure that reflects the extent that the variables are interrelated. The values obtained in this sample are tolerable. Values below 0.5 are considered unacceptable for factor analysis. The Bartlett Test of Sphericity test the hypothesis that the sample correlation matrix is an identity matrix, i.e., the independent variables are unrelated to each other. Relatively high values and low significance are required for the factor analysis.

Extraction of initial factors

Principal components analysis was the method used to extract the initial factors. Principal components have two major characteristics. First, the components represent uncorrelated linear combinations of the variables with the first principal component accounting for the largest amount of variance, the second principal component accounts for the second largest amount of variance and so on until the last principal component accounts for the least variance. The second characteristic lies in the derivation of the axis. The axis is formed from minimizing the perpendicular distance to the axis from the data points, whereas in least squares regression the distance from the data point perpendicular to the Y axis is minimized to form the regression axis. The criteria for the minimum number of factors was

Table 21

Test Statistics for the Factor Analysis

Test	Men	Women	Combined
Determinant of Correlation Matrix:	0.060	0.009	0.078
Kaiser-Meyer-Olkin Measure of Sampling Adequacy:	0.65	0.50	0.62
Bartlett Test of Sphericity (BTOS):	611.26	281.84	719.56
Significance (BTOS):	0.0000	0.0000	0.0000

based on using factors whose eigenvalues exceeded 1 in magnitude (default criteria, SPSSPC+, 1990).

Table 22 illustrates the initial statistics for the principal components analysis. In principal components analysis the communality of a variable or the proportion of variance explained by the common factors, in standardized form, is 1. The total variance of the sample equals the number of variables, in this case 12. The communality to the right of the variable reports the magnitude of the total variance explained by that variable. The factors and their associated statistics, reported in the last four columns, and the first two columns describing the variables, are unrelated to each other.

Two criteria for determining the number of factors to retain for further analysis were used. First, only those factors with an eigenvalue greater than 1 were to be selected (eigenvalues less than 1 do not provide less explanatory value than a single variable). Second, the scree plots were examined for a clear differentiation between the axis defining the higher magnitude eigenvalues and the axis defining the factors with a more horizontal appearance (Kim & Mueller, 1989). Figure 29 shows the scree plot for each of the three analyses performed. An artificial axis is

Table 22

Initial Variable and Factor Statistics:
Principal Components Analysis

Variable	Communality	*	Factor	Eigenvalue	Percent of Variance	Cumulative Percent
GLUC	1.00000	*	1	2.86970	23.9	23.9
ENERGY	1.00000	*	2	1.65768	13.8	37.7
DSI	1.00000	*	3	1.59109	13.3	51.0
GCS	1.00000	*	4	1.38385	11.5	62.5
HR	1.00000	*	5	1.02335	8.5	71.0
TEMP	1.00000	*	6	.68034	5.7	76.7
AGE	1.00000	*	7	.65509	5.5	82.2
ADMWT	1.00000	*	8	.54671	4.6	86.7
HTCM	1.00000	*	9	.53188	4.4	91.2
INSULIN	1.00000	*	10	.39796	3.3	94.5
APACHEII	1.00000	*	11	.36696	3.1	97.5
GOS	1.00000	*	12	.29539	2.5	100.0
Note. Males only (n = 223).						
GLUC	1.00000	*	1	3.13692	26.1	26.1
ENERGY	1.00000	*	2	1.92885	16.1	42.2
DSI	1.00000	*	3	1.74754	14.6	56.8
GCS	1.00000	*	4	1.29312	10.8	67.6
HR	1.00000	*	5	.85619	7.1	74.7
TEMP	1.00000	*	6	.79418	6.6	81.3
AGE	1.00000	*	7	.67427	5.6	86.9
ADMWT	1.00000	*	8	.50765	4.2	91.2
HTCM	1.00000	*	9	.47914	4.0	95.1
INSULIN	1.00000	*	10	.28281	2.4	97.5
APACHEII	1.00000	*	11	.20073	1.7	99.2
GOS	1.00000	*	12	.09861	.8	100.0
Note. Females only (n = 65).						
GLUC	1.00000	*	1	2.71831	22.7	22.7
ENERGY	1.00000	*	2	1.67271	13.9	36.6
DSI	1.00000	*	3	1.46976	12.2	48.8
GCS	1.00000	*	4	1.36891	11.4	60.2
HR	1.00000	*	5	1.16756	9.7	70.0
TEMP	1.00000	*	6	.69698	5.8	75.8
AGE	1.00000	*	7	.65728	5.5	81.3
ADMWT	1.00000	*	8	.56281	4.7	86.0
HTCM	1.00000	*	9	.53756	4.5	90.4
INSULIN	1.00000	*	10	.49455	4.1	94.6
APACHEII	1.00000	*	11	.33925	2.8	97.4
GOS	1.00000	*	12	.31433	2.6	100.0
Note. Combined-males and females (n = 288).						

Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

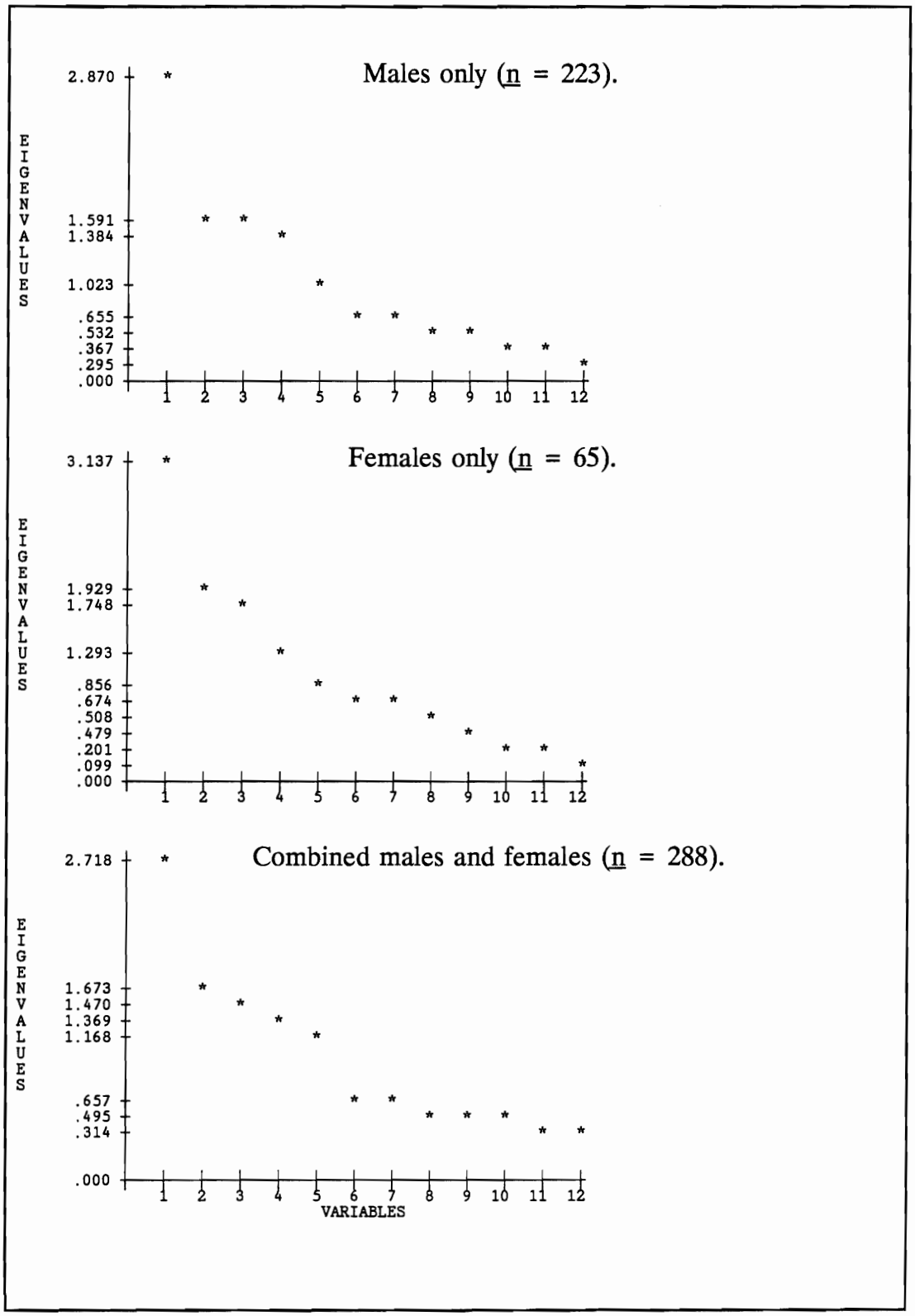

Figure 29. Factor Scree Plots.

superimposed on the plots to visually demonstrate the distribution of the eigenvalues for the retained factors (axis 1). The combined groups scree plot shows the clearest differentiation between the axis for the higher eigenvalues and those not retained. The scree plots for males alone and females alone, however, can be differentiated reasonably well. The principal components method extracted five factors for the male and combined group, and four factors for the female group based on the criteria mentioned above.

Once the number of factors to retain has been determined, statistics can be once again computed for the extracted factors and associated variables. Table 23 shows these statistics. The communality of the variables in this table now reflect the contribution of each variable in explaining the variance in the retained factors. For example, if the communalities shown in Table 23 are totaled they will equal the total variance accounted for by factors (reported as eigenvalues). The eigenvalues in turn represent the total variance explained as reported in the cumulative percent column. In the case of the combined groups analysis, the total percentage of variance in the sample, accounted for by five factors, is 70%. The sum of the eigenvalues is approximately 8.4 (70% of the total number of variables-12). The sum of the communalities for each variable can also be shown to equal approximately 8.4.

Factor rotation

Factor rotation simplifies the structure, easing interpretation of the factor loadings. By transforming the factor matrix by rotation, patterns among the factor loadings become clearer and more distinct. The method chosen for the rotation in this case is termed varimax (SPSSPC+, 1990). Varimax limits the number of variables with high loadings on a single factor, allowing differentiation between the factors by a knowledge of the variables with the highest loadings. Varimax also uses orthogonal rotation which presents the factors as uncorrelated to each other which

Table 23

Final Factor and Variable Statistics:

Factor Analysis

Variable	Communality	*	Factor	Eigenvalue	Percent of Variance	Cumulative Percent
GLUC	.72609	*	1	2.86970	23.9	23.9
ENERGY	.58572	*	2	1.65768	13.8	37.7
DSI	.74765	*	3	1.59109	13.3	51.0
GCS	.74987	*	4	1.38385	11.5	62.5
HR	.73924	*	5	1.02335	8.5	71.0
TEMP	.68080	*				
AGE	.74363	*				
ADMWT	.63706	*				
HTCM	.78595	*				
INSULIN	.72411	*				
APACHEII	.64632	*				
GOS	.75923	*				
Note. Males only (n = 223).						
GLUC	.54326	*	1	3.13692	26.1	26.1
ENERGY	.72827	*	2	1.92885	16.1	42.2
DSI	.74689	*	3	1.74754	14.6	56.8
GCS	.62430	*	4	1.29312	10.8	67.6
HR	.59678	*				
TEMP	.79748	*				
AGE	.45623	*				
ADMWT	.74460	*				
HTCM	.68377	*				
INSULIN	.69335	*				
APACHEII	.68433	*				
GOS	.80716	*				
Note. Females only (n = 65).						
GLUC	.62816	*	1	2.71831	22.7	22.7
ENERGY	.64530	*	2	1.67271	13.9	36.6
DSI	.75907	*	3	1.46976	12.2	48.8
GCS	.73402	*	4	1.36891	11.4	60.2
HR	.73689	*	5	1.16756	9.7	70.0
TEMP	.73507	*				
AGE	.65181	*				
ADMWT	.69028	*				
HTCM	.81057	*				
INSULIN	.71455	*				
APACHEII	.54994	*				
GOS	.74160	*				
Note. Combined-males and females (n = 288).						

Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

simplifies the identification of variables which load on a specific factor. Table 24 shows a complete listing of all loadings on each factor. For ease of interpretation, Table 25 shows the factor loadings sorted by magnitude and factor loading below 0.5 blanked out. The sorting and blanking eases the identification of which variables are most highly associated with each factor. Visual analysis of the factor solution was also provided by rotation plots shown in Figure 30. Only the combined group plots are shown. The interpretation of the factor loading plots involves identifying clusters of variables. If the terminal factor analysis solution has been successful in achieving a simpler structure, groupings of variables with high loadings on one factor should occur at the ends of axes. Variables occurring between axes are explained by both factors. Variables near the origin of the plot have low factor loadings. In the case of the first plot (Figure 29), a clustering of variables is occurring at the end of the axis for Factor 1. This clustering includes serum glucose, age, weight, and daily insulin doses and is shown to have high factor loadings on Factor 1. Another clustering of variables occurs near the intersection of the plot consisting of energy expenditure, days since injury, heart rate, temperature, and height indicating minimal loading on either factor represented.

Interpretation of the Terminal Factor Solution

Examination of the Rotated Factor Matrices demonstrates a number of interesting dimensions appearing in the data. Because of the tentative nature of the female group, as a function of the small sampling, little can be said with any certainty about the dimensions of this group. It can be said, however, that the differences in characteristics among the factor loadings support the notion that metabolic patterns may vary among gender. This observation supports the need for further research in metabolic gender differences.

Table 24

Rotated Factor Matrices (Varimax): Complete Listings

	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
GLUC	.55768	-.03369	-.07491	-.63036	-.10483
ENERGY	.07970	.71124	.08387	.13116	.22196
DSI	.34553	.06493	-.12937	.75319	-.20004
GCS	.19254	.01956	.77072	.25501	.23103
HR	-.03114	.76037	-.12813	.21935	-.30916
TEMP	.07795	.72533	-.05562	-.34067	.17167
AGE	.85235	-.07511	.04001	.04141	.09035
ADMWT	.64792	.24323	.05020	.01204	.39426
HTCM	.04788	.08264	-.08931	-.09577	.87160
INSULIN	.82812	.11037	-.07784	.07832	-.11814
APACHEII	.04702	.08727	-.75218	.19396	.18195
GOS	-.52787	.03592	.65733	-.13620	-.16930
Note. Males only (n = 223).					
GLUC	.71501	-.09376	-.13890	.06274	
ENERGY	.09821	.16459	.55202	.62194	
DSI	-.00540	.04177	.85940	-.08092	
GCS	-.05468	.72270	.26952	-.16241	
HR	-.48418	-.14645	.58122	.05561	
TEMP	-.04867	-.18469	-.18997	.85142	
AGE	.64509	.04430	-.09353	-.17141	
ADMWT	.64790	-.23451	.50556	-.11933	
HTCM	.23746	.78480	-.10099	-.03557	
INSULIN	.41924	-.54613	.46829	.00542	
APACHEII	.73072	-.00991	.19471	.33521	
GOS	-.46967	.73622	-.18545	.10075	
Note. Females only (n = 65).					
GLUC	.62968	-.10315	-.02255	-.02690	-.46882
ENERGY	-.01135	.04514	.55225	.55732	.16595
DSI	.17915	-.09155	.03196	.04427	.84594
GCS	.18076	.80316	.15907	-.03564	.17237
HR	-.07266	-.03603	-.19654	.74890	.36170
TEMP	.09585	-.06845	.14077	.74992	-.37282
AGE	.79404	.03629	.04606	-.12185	.05496
ADMWT	.52194	-.05733	.62205	.11399	.12094
HTCM	-.11557	-.05404	.88190	-.08255	-.09863
INSULIN	.79049	-.10799	-.06467	.16919	.21263
APACHEII	.12864	-.70550	.13739	.04197	.12258
GOS	-.49919	.65970	-.12752	.02882	-.20030
Note. Combined-Males and Females (n = 288).					

Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

Table 25

Rotated Factor Matrices: Blanked and Sorted

	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
AGE	.85235				
INSULIN	.82812				
ADMWT	.64792				
HR		.76037			
TEMP		.72533			
ENERGY		.71124			
GCS			.77072		
APACHEII			-.75218		
GOS	-.52787		.65733		
DSI				.75319	
GLUC	.55768			-.63036	
HTCM					.87160
Note. Males only (n = 288).					
APACHEII	.73072				
GLUC	.71501				
ADMWT	.64790		.50556		
AGE	.64509				
HTCM		.78480			
GOS		.73622			
GCS		.72270			
INSULIN		-.54613			
DSI			.85940		
HR			.58122		
TEMP				.85142	
ENERGY			.55202	.62194	
Note. Females only (n = 65).					
AGE	.79404				
INSULIN	.79049				
GLUC	.62968				
GCS		.80316			
APACHEII		-.70550			
GOS		.65970			
HTCM			.88190		
ADMWT	.52194		.62205		
TEMP				.74992	
HR				.74890	
ENERGY			.55225	.55732	
DSI					.84594
Note. Combined-Males and Females (n = 288).					

Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

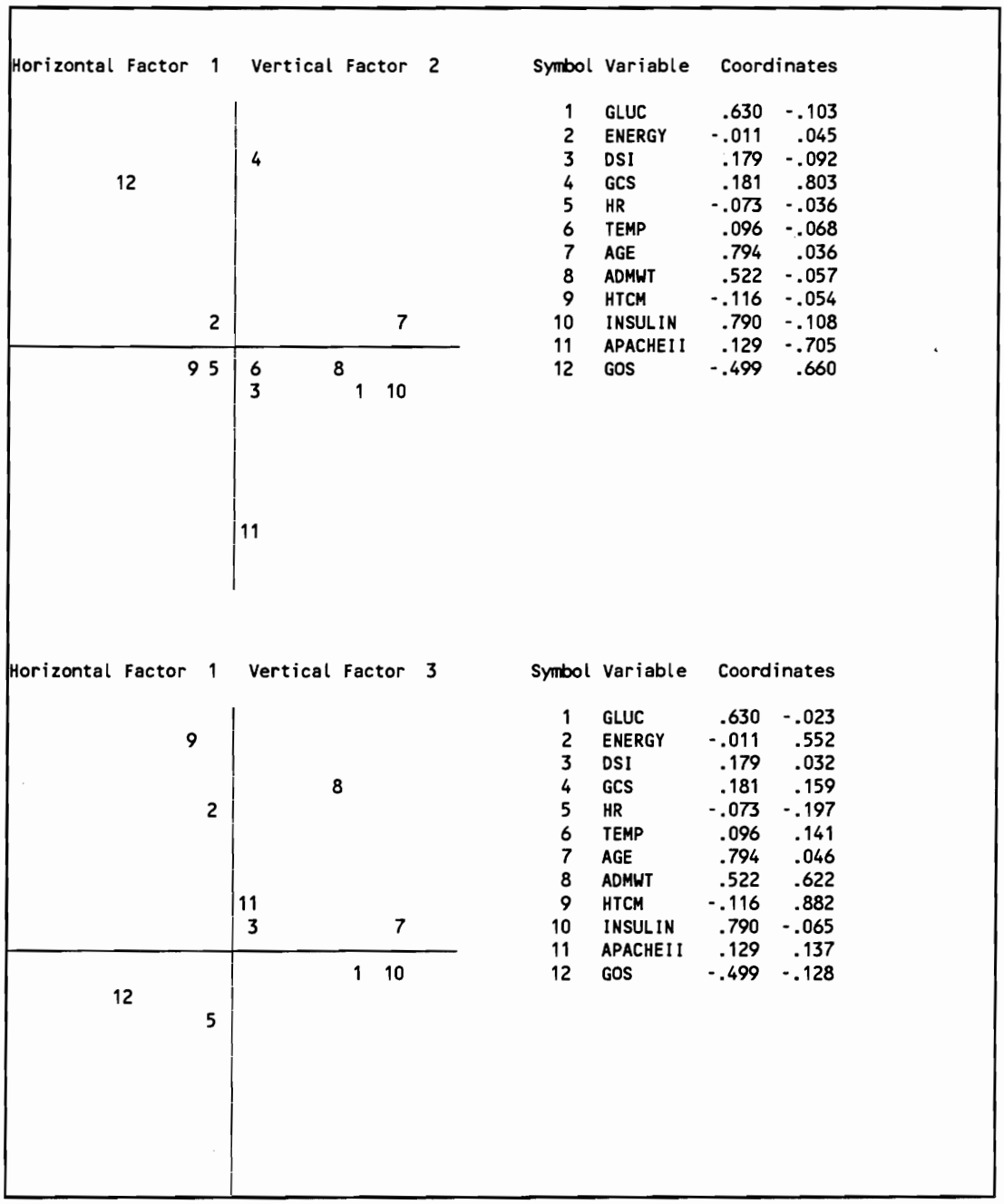

Figure 30. Factor Loading Plots: Combined Groups (Males and Females). Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

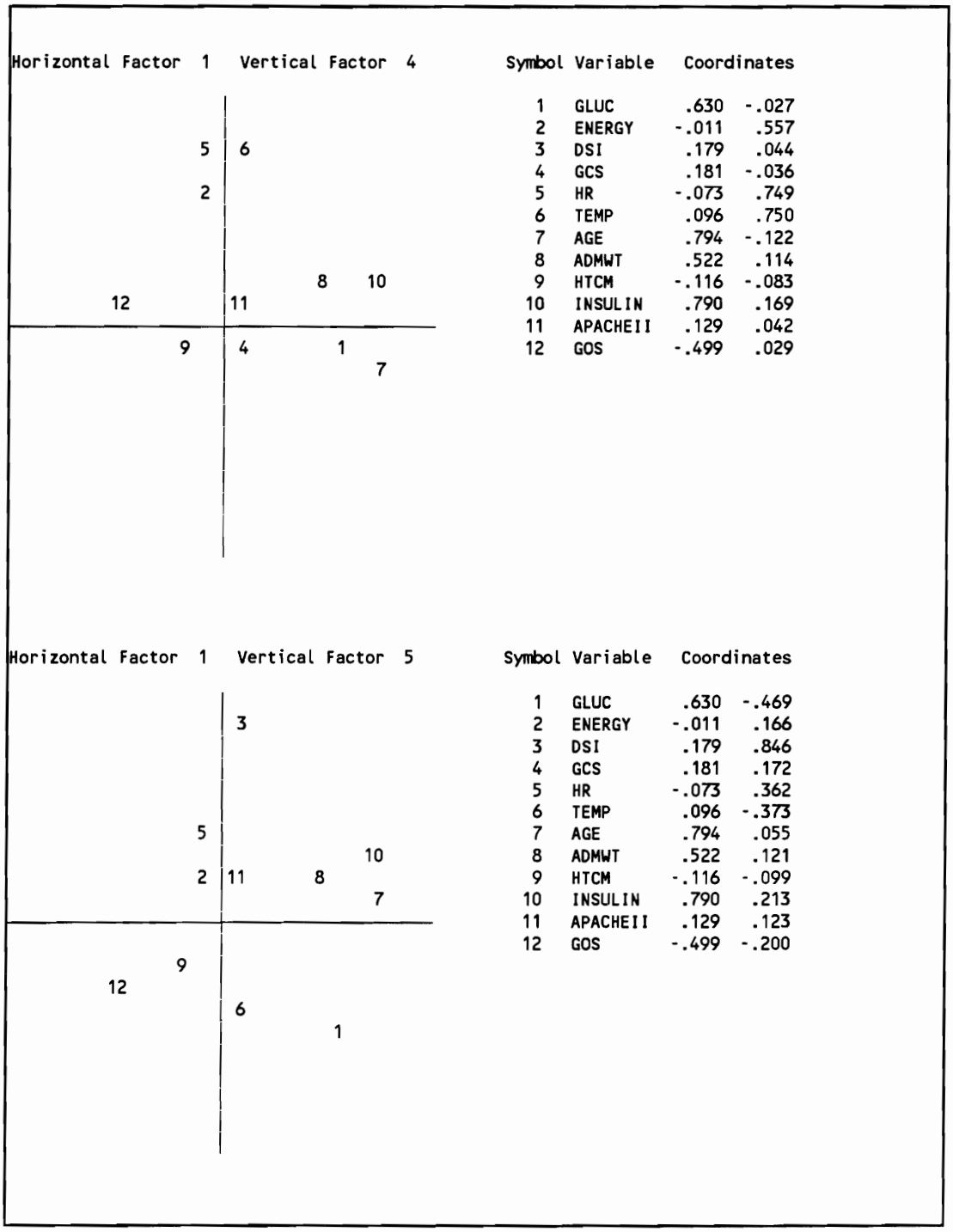

Figure 30 (continued). Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

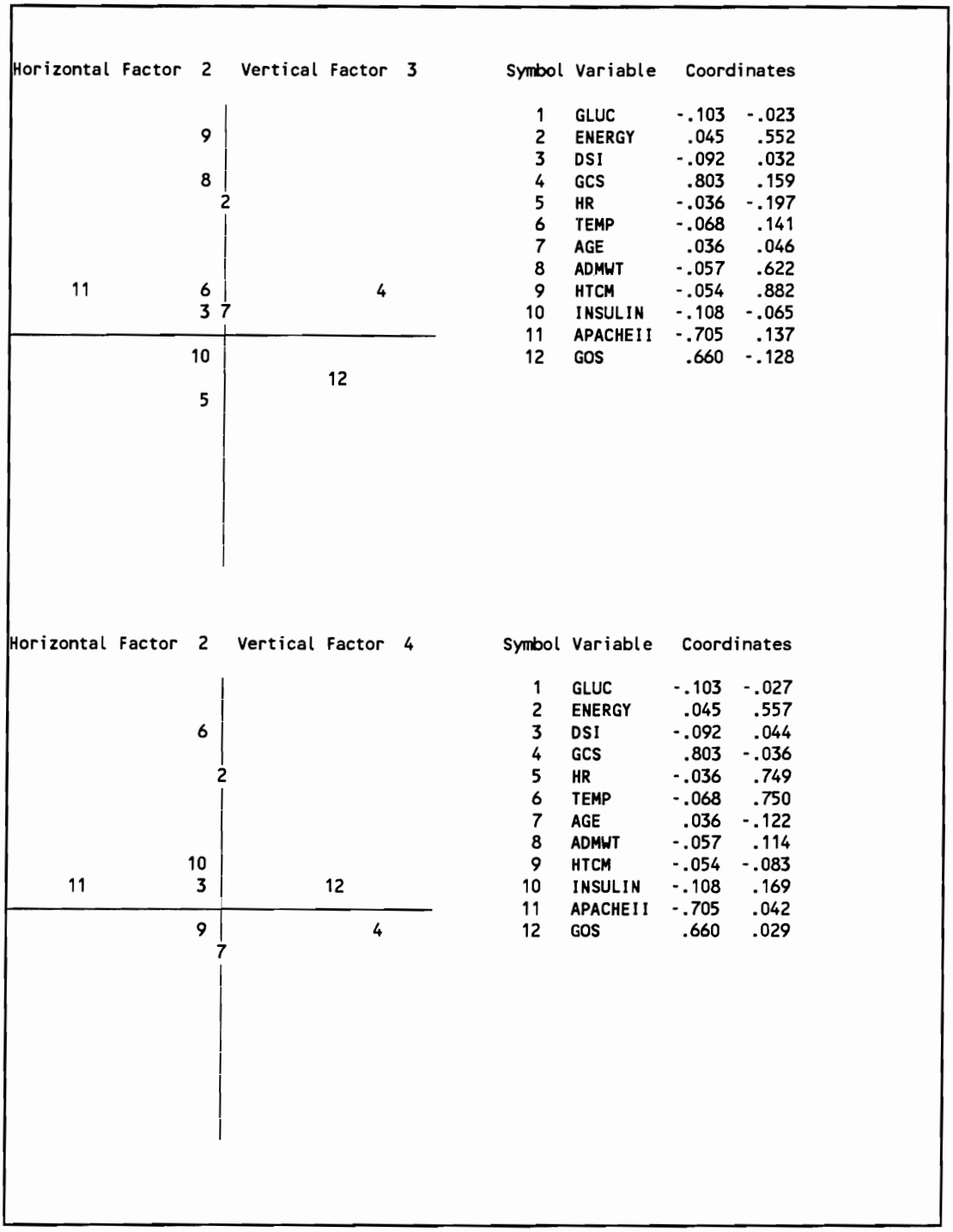

Figure 30 (continued). Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

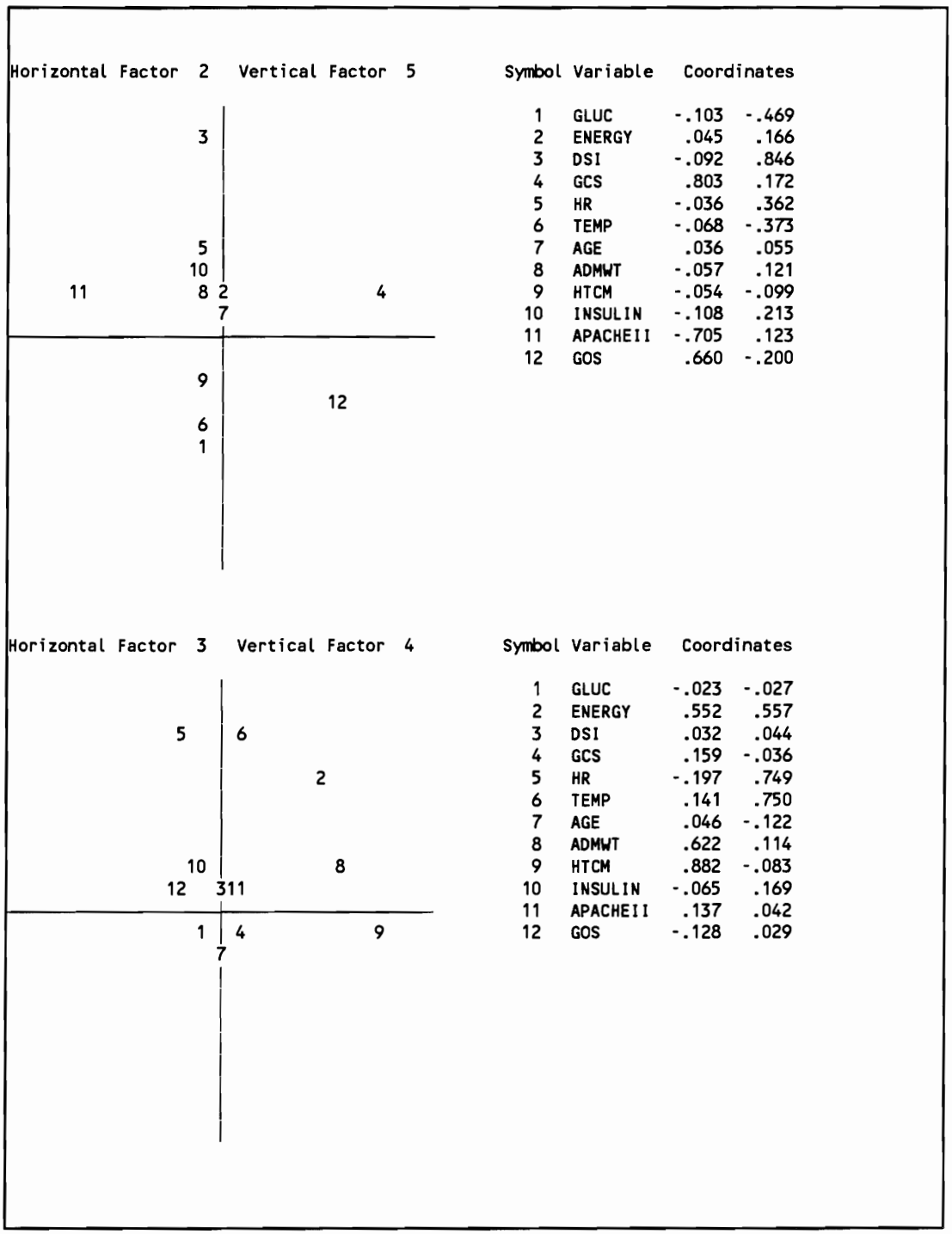

Figure 30 (continued). Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

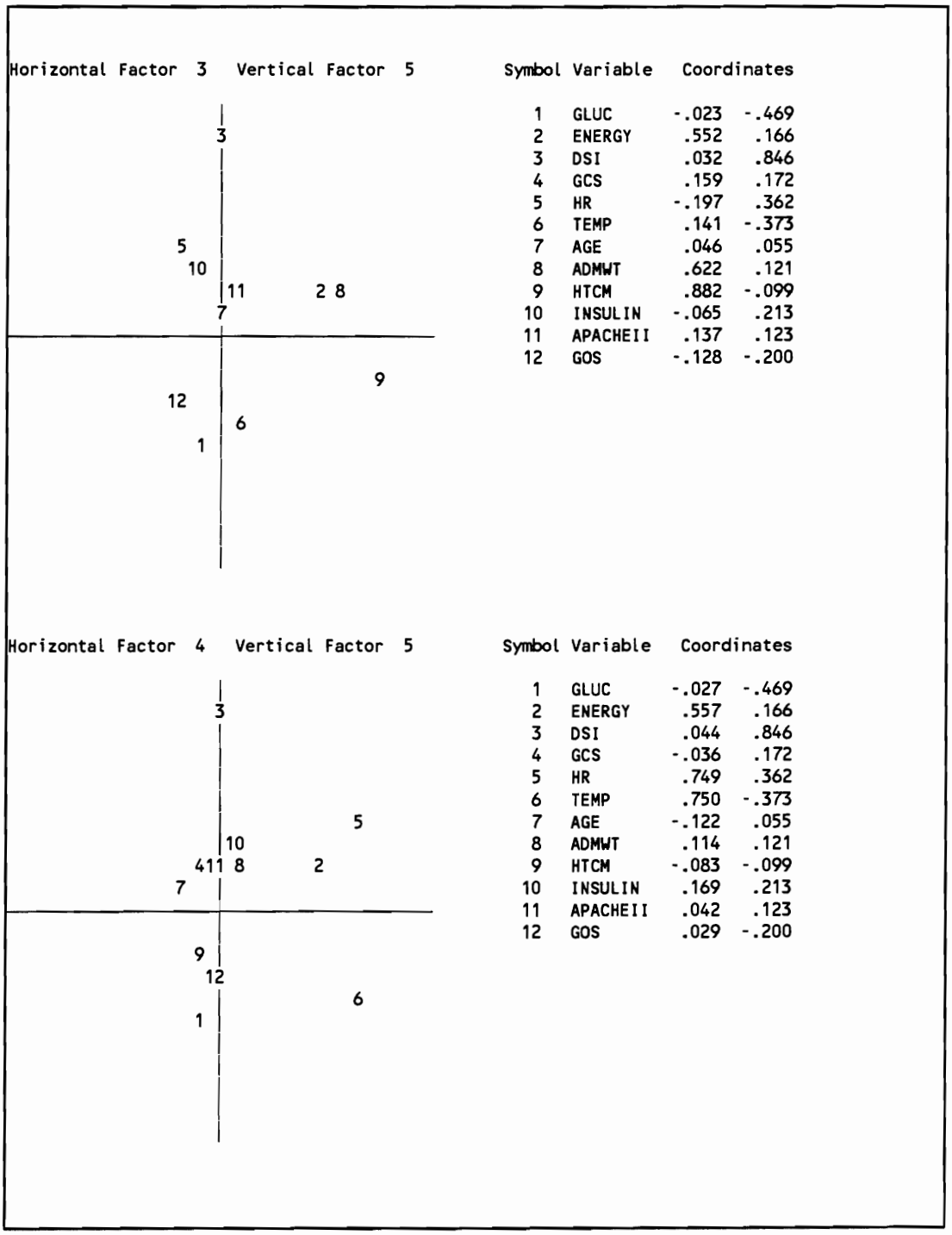

Figure 30 (continued). Note. GLUC = serum glucose, Energy = REE, DSI = days since injury, HR = heart rate, TEMP = body temperature, ADMWT = admission weight (Kg.), HTCM = height (cm.), INSULIN = insulin dosage/24 hours, APACHEII = severity of injury score on admission.

Factor 1 (explaining the most variance among the sample) for the combined groups shares a common high factor loading for age. Serum glucose levels, daily insulin doses, and admission weight also load heavily on Factor 1. Factor 1 appears to represent a dimension related to carbohydrate synthesis and insulin resistance. Physiologically the effects of age, weight, serum glucose, and insulin doses can be expected to be related to each other. As age increases glucose tolerance is known to decrease. The characteristics of weight as a significant factor in this dimension, however, are not entirely clear. It may be postulated that total body weight may have effects on glucose synthesis and production much in the same way that obesity has been linked with the development of Type II diabetes mellitus.

Factor 2 in the combined groups and Factor 3 in the males only group clearly demonstrate the dimension of severity of injury. The GCS, APACHEII, and GOS all have substantial loadings on this factor. The low loading of energy on this dimension supports the findings of the regression analyses: Measures of severity of injury do not account for a substantial amount of the variation in metabolic expenditure. The ability of the factor analysis to identify this dimension of severity of injury, by related variables, is substantial evidence in support of the validity of this statistical procedure.

In the combined groups analysis, Factor 3 and Factor 4 show practically equivocal factor loadings for energy. The other substantial loadings for Factor 3 include height and weight. The dimension expressed by this factor may be hypothesized as pertaining to the anthropometric (size and proportions of the body) relationship to energy expenditure. Factor 4, showing considerable loadings from heart rate, temperature, and REE, could reflect the dimension of metabolic work. The observation of equivocal factor loadings from the energy variable in this case would support the contention, at least in part, that anthropometrics and metabolic

work are both functions that result in and explain differential energy expenditure. In essence, the size and proportion of the human body result in a range of typical energy expenditure values. Heart rate and body temperature, on the other hand, are also functions of body size in that the amount of mechanical work and subsequent energy expenditure is dictated, in part, by the size of the body. The results of the regression analyses also support this premise by the observation that these variables were not substantially additive in their explanatory power for concurrent energy expenditures. The conclusion formed by the relationships demonstrated between mechanical work and anthropometrics is that direct measurements of metabolic work potentially have the ability to more accurately represent concurrent energy expenditure. As we have already seen in the regression analyses, however, the ability of measurements of heart rate and temperature to account for concurrent energy expenditure is poor. Theoretically, if mechanical work could be measured more precisely, as in cardiac outputs, the explanatory power may be improved substantially. The clinical reality, however, would not support this alternative as an efficacious method for measuring energy expenditure.

Days since injury represents the only highly loading variable in the combined group for factor 5 and grouped with a negative loading of serum glucose in the males only group. As we have seen in the previous analyses for serum glucose, levels abate over time, explaining the factor as a temporal glucose response in the males only group. In the combined group no data reduction occurred and the factor represents temporal response only.

Summary

A variety of techniques have been used to analyze the metabolic indicators measured in this sample of patients with TBI. The subject characteristics support the premise of a typical population for this type of injury: predominantly younger

and male with almost half resulting from motor vehicle accidents. The extent of correlation between the APACHEII and Glasgow Outcome Scale is an exciting finding representing a method to more accurately determine outcome from injury with implications for family education and anticipatory guidance.

The analysis of the nutritional support offered to these patients indicates that indirect calorimetry substantially influenced the prescription of total caloric intake. The analysis of indices of protein metabolism resulted in a clearer representation of the construct of obligatory nitrogen loss. Measures of nitrogen loss (urinary urea nitrogen) may not be an accurate indicator of deficient protein synthesis because of the inability to accurately determine the differential contributions from obligatory nitrogen loss from bedrest versus the utilization of visceral protein stores to support gluconeogenesis (catabolism). Short half life plasma proteins offer much higher accuracy in reflecting response to nutritional therapy.

The analysis of variables related to energy expenditure was shown using an exploratory approach followed by regression analyses, and finally factor analysis. This exploratory data analysis approach was beneficial from the perspective that in any statistical analysis the researcher must have a basic understanding of the variables being studied. To proceed with more sophisticated analyses, before having a clear picture of the attributes of the individual variables, makes results tenuous and less interpretable. In this case the exploratory analysis provided crucial information for the behavior of variables in subsequent analyses. For example, the relationship between days since injury and energy expenditure was shown to be unstable and a poor theoretical and statistical candidate for regression analysis. The measures of GCS scores and energy expenditure showed marked fluctuation in variance although median values were remarkably stable.

Three models for estimation of energy expenditure were evaluated using metabolic indices from this study sample: The Harris-Benedict Equation, the Stress Stratification Framework (Cerra, 1982; Konstantinides, 1984), and the regression analysis proposed by Clifton et al. (1986). All three models were found to be inadequate in explaining the measured energy expenditure by indirect calorimetry. The estimation of energy expenditure section concluded with possibly the most important finding in this study-69% of all indirect calorimetry measurements were outside of the normal metabolic range as defined by 90-110% of the calculated basal energy expenditure by the Harris-Benedict equation.

Multiple regression analyses of all metabolic indicators were performed next. The results indicate that at best only 11% of variance between the calculated BEE and actual Resting Energy Expenditure could be explained. This result leads to the conclusion that estimation of energy expenditure from clinical variables is extremely tenuous.

Exploratory factor analysis was the concluding statistical procedure providing new insights into the nature of metabolic indices in this sample. The hypotheses suggested by this analysis were helpful in explaining the interactions in a very complex area of inquiry. Possibly the most notable of these discoveries was the differential loadings of energy expenditure on anthropometrics and metabolic work. The implications for these observations on clinical nutrition are addressed in the next chapter along with conclusions and ramifications pertaining to all results obtained in this chapter.

CHAPTER V

DISCUSSION

The discussion will begin by addressing the original research questions. The primary focus of these questions revolved about patterns and prediction of energy expenditure. The section "Dimensions and Patterns of Metabolic Indices" will address the fourth, fifth, sixth, and seventh research questions. The following section "Energy Expenditure and Caloric Supplementation" will address the first, second and third research questions. Next, based on the conclusions resulting from the answers to these research questions, a discussion of what method is the most accurate, cost effective, and efficient for calculating nutritional supplementation will be presented.

The goal of this chapter, further, is to delineate in detail these implications and make pertinent recommendations in the form of a clinical nutritional management model in the Traumatic Brain Injury (TBI) patient. This model will address the actual goals and mechanics of nutritional supplementation integrated into the clinical management of TBI. The nutritional management model will, further, offer specific recommendations for nutritional assessment and data collection, methods and timing of delivery, calculation of supplement proportions, and evaluation of the effectiveness of therapy.

The fourth area to be addressed involves overcoming barriers to optimal nutrition. Central issues related to nursing education and specialization as well as nursing roles regarding nutrition in critical care will be discussed. Crucial questions

regarding responsibility and accountability for optimal nutrition among members of the allied health sciences team will also be addressed.

Finally, the findings of this study have resulted in numerous implications for future research. The most pertinent of these implication will be addressed.

Dimensions and Pattern of Metabolic Indices

The concluding factor analysis in Chapter IV provides a more global view of the nature of the metabolic variables and thus a good starting point in the discussion of the fourth, fifth, sixth, and seventh research questions: 4) What are the patterns and dimensions of the relationships among metabolic indices and calculations of energy expenditure by indirect calorimetry in TBI, 5) Are there theoretical factors that explain the relationships among observable data, and 6) Can a structure of the relationships between metabolic parameters and theoretical factors be identified be identified using regression and factor analyses? A discussion of the ramifications of the multiple regression analysis will be saved for the section on prediction of energy expenditure. The seventh research question as noted in Chapter 4 is unanswerable at the present time.

The factor analysis resulted in a five dimension solution for the 12 most abundant variables in this sample. These five factors were further hypothesized to represent: 1) glucose synthesis, 2) severity of injury, 3) anthropometrics, 4) indices of metabolic work, and 5) temporal response in the combined male and female population. The top half of Figure 31 is a representation of the higher factor loadings on each of these dimensions. Significant correlations between these variables and actual energy expenditure, however, were few. Only the variables comprising the dimensions of anthropometrics and metabolic work had concurrent appreciable actual energy expenditure loadings.

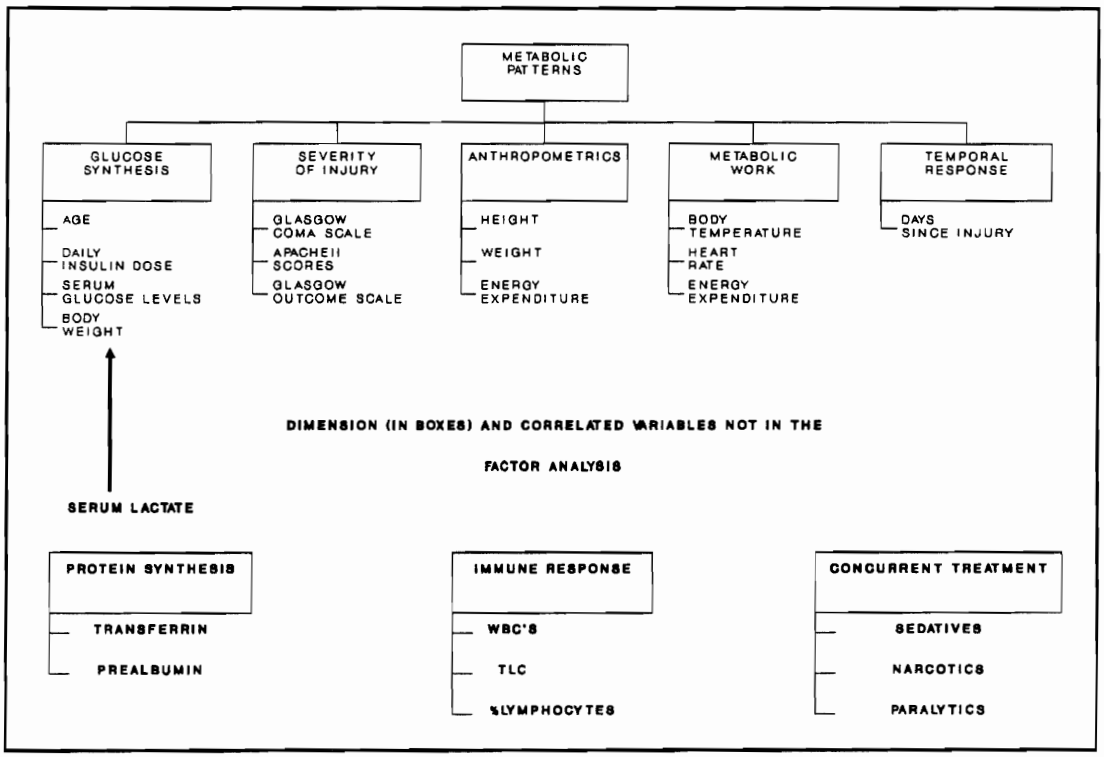

Figure 31. Patterns and dimensions of metabolic indices in traumatic brain injury. Note. The organizational structure (top) is derived directly from the factor analysis. Dimensions and associated variables, not in the factor analysis, with significant correlations are noted in bold print in the bottom half of the figure. Serum lactate is shown as correlated with glucose synthesis (arrow).

The major differences between the combined groups factor analysis (male and female) and the males only group involved the variables of the Glasgow Outcome Scale, serum glucose levels, height, and days since injury. In the male group the Glasgow Outcome Scale scores have high loadings on the first factor. This loading may represent an outcome perspective in the factor dimension of glucose synthesis and predominance in the male population. While days since injury loaded alone on factor 5 in the combined group, days since injury and serum glucose level loaded together on factor 4 in the male group. This observation would support the proposition of factor 4 in the male group representing a time limited hyperglycemic

state. Height alone loaded on factor 5 in the male group. Among a more homogenous group such as males, height could play a much smaller role in the dimension of anthropometrics.

The dimensions of protein synthesis, immune response, and concurrent treatment were also included in the lower half of the model (Figure 31). Although they could not be used in the factor analysis because of sampling insufficiency, they represent important constructs in the metabolic model.

Additional characteristics of the variables discussed here will have further implications related to evaluation of nutritional therapy, prediction of energy expenditure, and the ability to identify subgroups at higher risk for malnutrition. These issues will be discussed in the appropriate preceding sections.

The seventh research question (Once a structure is identified can it be confirmed?) was answered from the measures of sampling adequacy in the factor analysis in Chapter 4 (Table 21). Had the measures of sampling adequacy been higher in magnitude, it may have been feasible to randomly assign all variables to two groups. The first group could have provided the substance for the initial factor analysis solution, whereas the second group could be subjected to a confirmatory factor analysis. The marginal sampling adequacy displayed by this population, however, precluded the use of this procedure.

Energy Expenditure and Caloric Supplementation

Three of the original research questions related to the prediction of energy expenditure (numbers 1, 2, and 3). The first of these (Which metabolic indices are most predictive of metabolic expenditure and the catabolic response?) was addressed in the multiple regression analyses of Chapter 4. It was found that of all metabolic data gathered in this study, only heart rate, body temperature, and days since injury were significant predictors of the differences between calculated basal energy expenditure (Harris-Benedict Equation) and actual resting energy expenditure (REE) by indirect calorimetry. These variables were also found to explain a cumulative

total of only 10% of the variance in the REE, which leads to the research question number 2. Can a clinically efficient method for predicting energy expenditure be derived from the relationship between indirect calorimetry and more easily acquired, clinically observable, metabolic indicators in TBI? Table 26 shows a summary of predictive analyses from Chapter 4.

We have seen from the last chapter the results of calculating energy expenditure from two nutritional management models (Cerra, 1982; Clifton, et al., 1986; Konstantinides, 1984). Of these two methods, the estimate of Clifton et al. (1986) is the closest to actual REE. As was shown, however, the exactness of fit results in clinically significant errors in estimation. On this basis, their routine use in energy expenditure estimation is not supported. The regression analyses reported in Chapter 4, using indirect calorimetry, support using the measures of heart rate and temperature. These measures may be useful, however, only as clinical clues to the presence of a hypermetabolic state. Their precision in daily estimation of Caloric needs is grossly lacking. Based on these observations the answer to research question number 2 must be negative! This statement leads us to research question number 3: Is there sufficient variation in metabolic rate in TBI to warrant routine use of indirect calorimetry for nutritional assessment and monitoring? The answer to this question is yes. Under these circumstances the routine use of indirect calorimetry can also be shown to be more cost effective. If insufficient resources and lack of dedication are apparent, it is unlikely, however, that indirect calorimetry will result in significant changes in nutritional management.

A recent report by Campbell and Kudsk (1988) indicated that 40% of 101 nutritional support services surveyed, who had metabolic carts for conducting indirect calorimetry, actually used them. A more detailed discussion of these issues will be presented in the section on barriers to optimal nutrition.

Table 26

Summary of Predictive (Regression) Analyses for Metabolic Markers of Resting Energy Expenditure

Metabolic Marker	Multiple R or correlation	R^2	S.E. of Est.
Stress Stratification Framework: Serum Lactate, Serum Glucose, and Nitrogen Excretion	0.23	0.05	506.04
Clifton's Estimate: Heart rate, Days since injury, and GCS.	0.39	0.16	836.58
Harris-Benedict Equation: Sex, Height, Weight, and Age	0.38	0.15	350.81
University of Utah Sample: Heart rate, Temperature, and Days since injury	0.32	0.10	34.04

Note. The University of Utah sample's dependent variable is "percent of predicted REE" by the Harris-Benedict equation. In bivariate regressions the Pearson correlation is reported (all except University of Utah Sample).

Recommendations for Caloric Supplementation

The recommendations proposed in this section take a number of criteria into consideration. First, what type of treatment facilities predominantly care for TBI? Second, what are the cost considerations in an effective nutritional support program? Third, what health care personnel are required?

The treatment of TBI often involves prolonged and complex care in the intensive care unit (ICU). Those institutions accepting these individuals for admission must be capable of providing a sufficient level of expertise. This level of expertise is increasingly being tasked to level 1 trauma centers. Given this type of center, it is estimated from experience that approximately one-third of all ICU patients (not only TBI) would require enteral or parenteral nutrition. These patients would be potential recipients of metabolic monitoring (indirect calorimetry). Given this criterion, would indirect calorimetry be cost effective?

The primary criterion for establishing the cost effectiveness of routine metabolic monitoring is a consideration of, not only expense, but effectiveness of the alternatives. The best alternative to indirect calorimetry in this population was demonstrated to be the Harris-Benedict equation. If this method is used to predict Caloric supplementation, we may expect from the results of this analysis that a considerable portion of the TBI population would be either underfed or overfed. Overfeeding or underfeeding could be detected in a number of ways: monitoring of hepatic enzymes, protein synthesis, serum glucose levels, coagulation studies, nitrogen balance studies, and hematologic studies. Electrolyte and serum glucose levels as well as hematologic studies are generally monitored on a daily basis; therefore, they would be monitored regardless of the method of metabolic monitoring. We have found from experience that weekly monitoring of the additional laboratory studies is adequate in detecting abnormalities if Caloric supplementation is based on indirect

calorimetry measured two to three times weekly. In the absence of indirect calorimetry, laboratory evaluation would have to be increased in frequency to accommodate the greater chance of complications from overfeeding or underfeeding. The current recommendations are twice per week (Konstantinides, 1984).

Given the increased frequency of laboratory measurements, the effectiveness of the metabolic monitoring would also be considerably hampered by the laboratory measurements. For example, if a trend in rising hepatic enzymes is detected the correction in caloric supplementation may be delayed by 3 to 4 days (interval between laboratory measurements). There are also no current published criteria from which to make these corrections. The specificity for making nutritional adjustments is therefore considerably decreased in comparison to indirect calorimetry. On the other hand, for a metabolic monitoring program to be effective, dedicated personnel must be acquired who are completely familiar with operation and calibration procedures. In my experience with this nutritional program, respiratory therapists have been found to be the most adept at these procedures.

The cost comparison will therefore consider the differences between the increased frequency of monitoring laboratory measurements versus the cost of dedicated personnel, equipment, and supplies involved in indirect calorimetry. Table 27 shows the breakdown of the cost estimates for indirect calorimetry. Table 28 shows the comparison between the two methods of metabolic monitoring.

It is clearly evident from Table 27 that a metabolic monitoring program is clearly feasible, even for a moderate size hospital. It is also evident that at $60.00 per measurement, metabolic monitoring is not as expensive as one might assume. The estimated profit in this example gives ample latitude for unpaid fees, accounting and repairs. The profit realized may very easily and appropriately be placed in a fund to support further research.

Table 27

Costs of Metabolic Monitoring by Indirect Calorimetry

Description of item	Weekly
Hardware: Metabolic Cart @ $30,000. Based on 3 year note @ 12% interest.	$230.00
Personnel: Respiratory Therapist @ 20 hours per week ($15,000 per year).	$288.00
Subtotal:	$518.00
Current Medicare Reimbursement (limited to 2 metabolic measurements per week) for a projected need of 1/3 out of 30 total ICU patients (10 patients x 2 measurements per week):	$1200.00
Supplies and Calibration gas (per measurement @ $5.00 each):	$100.00
Net profit not considering repairs and accounting:	$582.00

Note. 1. Estimates are extremely conservative. Thirty ICU beds represents a moderate size hospital. The University of Utah Health Sciences Center currently has over 50 ICU beds. 2. The cost of $60.00 per metabolic measurement is roughly equivalent to one arterial blood gas.

Table 28

Comparison of Two Methods for Metabolic Monitoring

Method and Cost	Weekly
With Indirect Calorimetry:	
SMA-20 (1 per week)	$46.80
Coagulation Studies (PT/PTT-1 per week):	$46.60
Thyroxin Binding Prealbumin (1 per week):	$51.80
24 hour Urine Urea Nitrogen (1 per week):	$23.80
Indirect Calorimetry (2 per week):	$120.00
Total:	$194.60
Without Indirect Calorimetry:	
SMA-20 (2 per week):	$93.60
Coagulation Studies (PT/PTT-2 per week):	$93.20
Thyroxin Binding Prealbumin (2 per week):	$103.60
24 hour Urine Urea Nitrogen (2 per week):	$47.60
Total:	$337.60
Difference:	$143.00

The calculations in Table 27 give an even better picture. In this example the method using indirect calorimetry accounts for a cost saving of $143.00 per week over metabolic monitoring without indirect calorimetry. There are also a numberof considerations that these figures do not take into account. The analysis of laboratory reports and calculation of caloric supplement other than with indirect calorimetry is time consuming for the clinician. It is too tempting to make rough estimates and knowledgeable guesses under these circumstances. One may also postulate that patient complications will likely be greater with nutritional support that does not utilize indirect calorimetry, further increasing costs and effort.

In summary this section has demonstrated reasonable cost effectiveness of indirect calorimetry, greater ease of estimating caloric supplementation for the health care practitioner, and greater efficacy for individualizing caloric supplementation. Chapter 4 identified the marked variation in individualized needs and identified the population of TBI as highly at risk for complications resulting from over and underfeeding. It is also clear from the demographic data presented in Table 14 that parenteral and enteral nutrition is necessary in this patient population, i.e., average number of days in the ICU = 17, average GCS score on admission = 7, average GCS on discharge from the ICU = 9, and total length of hospitalization = 28 days. In other institutions, patients may go for weeks without adequate nutritional support.

An Integrated Nutritional Management Model

The results of this study have given necessary information for the construction of a nutritional management model specific to TBI. The last section clearly identified indirect calorimetry as the method of choice in caloric supplementation. However, other aspects concerning nutrition and integration of a nutritional methodology along with other goals of therapy must be addressed. The most important aspects to consider when devising a nutritional management plan in TBI

include providing optimal Calories and substrate, maintenance of fluid and electrolyte balance, management of increased intracranial pressure, selection of a method of delivery, prevention of infection, and promotion of gastrointestinal function. These aspects will be considered in the format of a four step process outlined in Figure 32.

Assessment

Assessment is the first step in this model. Examination of Figure 32 shows the constituent activities. Note that the first five of these constituents have been derived from the factor analysis of Chapter 4.

Glucose synthesis

The evaluation of glucose synthesis serves a number of purposes. The most crucial of these is reduction of hyperglycemia. As stated earlier, the goals of

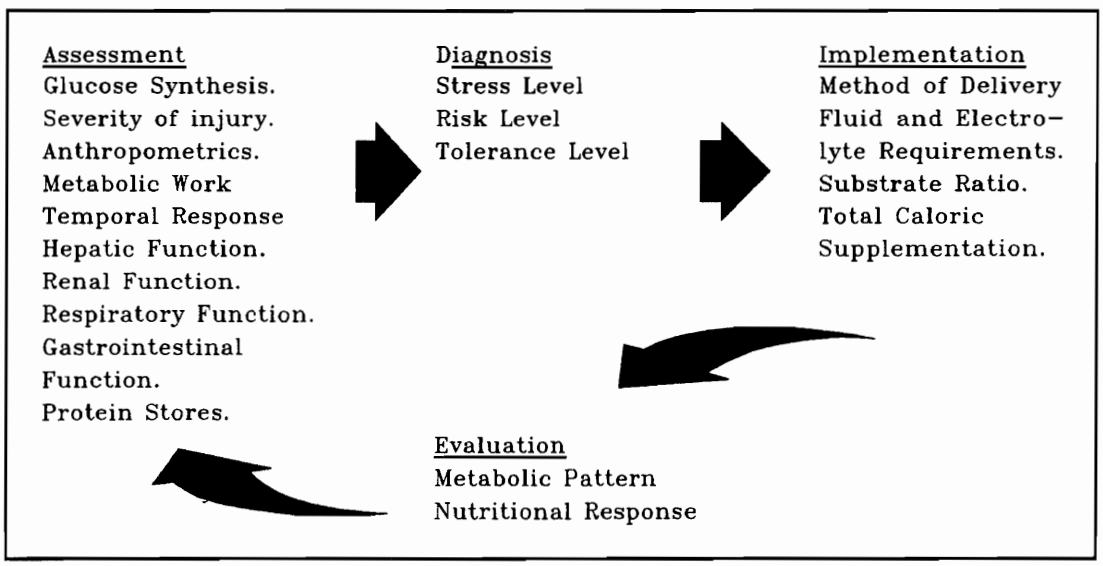

Figure 32. Process and Constituents of Nutritional Management in Traumatic Brain Injury.

management in TBI are to maintain serum glucose levels below 180 mg./dl. Serum glucose levels over this value have been associated with increasing intracranial pressure. The results of the analyses indicate that a significant number of observations in this sample exceeded this value (see Figure 12) with concurrent insulin resistance as evidenced by a positive regression sign for insulin (Table 17). These observations indicate that more aggressive dosing of insulin is required in thispopulation to achieve reduction in hyperglycemia. The analysis (Chapter 4) also revealed good correlation between serum glucose and lactate levels and poor correlation with levels of energy expenditure. Serum lactate from this standpoint does not appear to provide additional information useful in assessing stress levels. Their routine use in metabolic profiles is, therefore, unjustified at the present time.

The analysis shown in Table 17 also indicated that the amount of supplementation did not significantly affect serum glucose levels. Therefore given early nutritional initiation, abrupt changes in glucose levels are not expected as a result of initiating parenteral or enteral nutrition. From my experience with this particular nutritional protocol, worsening of hyperglycemia, in response to exogenous nutrition, is a clinical myth in this population of patients. It is very likely, however, that hyperglycemia may be problematic when Caloric supplementation is not based on specific individualized needs. High serum glucose values, further, may very well indicate overfeeding and should be further evaluated with indirect calorimetry. The temporal response was not shown to extend much beyond the ICU period indicating that the intensity of monitoring may be reduced in the post-ICU period.

Severity of injury

The results of the analysis on severity of injury measures in Chapter 4 indicated the presence of an important assessment parameter. Although the presence of good correlation with energy expenditure was not found, it was observed

that all outliers and extreme values for energy expenditure were found in subjects with GCS scores below 7. It was also found that the variability in energy expenditure measurements was much greater in these groups compared to patients with GCS scores of 7 or greater. Prudent management of patients in the lower GCS groups or a patient's assessment changing to a lower GCS would include increasing the frequency of metabolic monitoring and/or reevaluating energy expenditure.

Anthropometrics

Anthropometrics and indices of metabolic expenditure discussed in the last section have not shown the level of precision required for energy expenditure measurements; however, anthropometrics may be extremely valuable in other areas of assessment. The most important of these assessment parameters include determination of fluid and protein requirements. Experience with the nutritional protocol has revealed that often fluid requirements are set at a predetermined level despite body size and proportion of the individual patient. Prior to initiation of the nutritional protocol the standard fluid regimen consisted of dextrose in Ringer's Lactate solution at 85 cc. per hour despite body size. Because dosing of protein is contingent upon the combination of body weight and fluid volume, assessment of anthropometric indices is vital. These assessment parameters include body weight, ideal body weight, and body surface area. The utilization of these parameters will be discussed further in the coming section on the implementation process.

Energy expenditure

Indirect calorimetry supplies a number of indices other than caloric consumption. For the purposes of this discussion, however, oxygen consumption (VO_2), carbon dioxide production ($VC0_2$), and the respiratory quotient (RQ) are the

principle indices. The RQ is the primary assessment parameter denoting the principle substrate for fuel utilization. The goal of therapy is to keep the RQ between 0.85 and 0.95 denoting mixed substrate (carbohydrate, fat, and protein) utilization. RQs above this value have been implicated in overfeeding syndromes, below this value increased gluconeogenesis and catabolism. Evaluation of the RQ and subsequent corrections must take into consideration both total level of Caloric supplementation and substrate ratios: there will be combined influences.

Respiratory function

Increased $C0_2$ production in response to excessive glucose production was not felt to be problematic in this sample with caloric supplementation based on indirect calorimetry (minimal correlation between $C0_2$ production and serum glucose levels). However, increased $VC0_2$ should raise suspicion for excessive glucose intake. Under conditions of increased $VC0_2$ work of respiration is substantially increased.

Time frame

Time frame is the assessment category addressing temporal responses. A number of relationships have been found in the analyses relative to this parameter. The time limited response of alterations in glucose synthesis and insulin resistance has already been discussed. It has been observed from analysis of this sample that energy expenditure measurements peak at 2 to 3 weeks, then decline (Table 16). Anticipation of this peak energy period and making appropriate corrections will enhance energy balances in this population of patients. The assessment of time frame may also be expanded to include the timing of initiation of nutrition. The analysis of severity of the neurologic injury as measured by the GCS indicates that the overwhelming majority of patients entered into the nutritional protocol had scores of 11 or less. This majority also required TPN or TEN for an extended

period of time. On the basis of these findings, patients with GCS scores of 11 or less or those known to be unable to take adequate nutrition by mouth at the earliest possible time should be started on TPN or TEN. Experience with the nutritional protocol has suggested that indices of adequate nutrition deteriorate rapidly. Further, maintenance of these indices is much easier than restoration. The median timing for initiating nutrition shown in this study has been exclusively related to the presence of the investigator in conjunction with the admission of the patient. In many instances feeding has been initiated on the day of admission (n = 20). No adverse effects from early initiation have been encountered in this population.

Hepatic function

Measures of hepatic function were not addressed in the analysis of this study. However this function requires thorough evaluation during nutritional support, especially when TPN is the method of delivery. Elevated hepatic enzymes very often represent the first indication of excessive glucose administration. Hepatic failure may represent one of the most serious complications of nutritional management (Kinney, et al., 1988, p. 315).

Renal function

Baseline renal function values offer an index to evaluate responses to nutritional management and mild fluid restriction. Elevated blood urea nitrogen (BUN) in response to high protein administration is rare but has been known to occur (Blackburn, et al., 1989). Elevated BUNs may indicate a decreased ability to utilize exogenous proteins and the need to decrease protein supplementation. The fluid restrictions imposed on TBI patients in order to limit cerebral edema can also impair renal function. Abnormal renal function values may indicate the need to reevaluate fluid therapy with concurrent adjustments required in the Caloric

supplementation. All too often fluid adjustments are made without concurrent adjustment of the quantity of Caloric substrate often resulting in marked deviation from nutritional needs.

Gastrointestinal function

The earliest initiation of TEN was day 6 with the most common time between 10-14 days. Evidence for the beneficial effect of TEN over TPN is accumulating dramatically. In a recent report Grahm, Zadrozny, and Harrington (1989) demonstrated the ability to feed TBI patients via a fluoroscopically placed jejunal feeding tube within 36 hours of injury. Unfortunately, what the citation failed to mention was the ability for portable fluoroscopy at these author's institution (personal communication, Thomas Grahm, February 9, 1990). The most pertinent considerations based on this study is the stability of the patient's condition. Although I have had good success with blind intubation of the duodenum, tolerance of duodenal hyperalimentation in the early periods after injury has been poor.

Protein stores

Based on the findings, visceral protein stores, on the average, have been maintained with early nutrition and approximately 1.5 Gms. per Kg. of IBW per day. Assessment parameters included weekly measurements of urinary nitrogen excretion, serum transferrin, and serum thyroxin binding prealbumin. As discussed earlier, the inability to separate obligatory nitrogen loss from catabolism greatly limits measures of nitrogen excretion as a useful assessment tool in the prescription of protein supplementation. Its primary usefulness in this sample has been to determine levels of stress and type of protein to be administered. High branched chain amino acids with potential protein sparing effects have been used when urinary nitrogen excretion

is 10 Gms. per day or greater (Brennan, M. F., Cerra, F., Daly, J. M., Fischer, J. E., Moldawer, L. L., Smith, T.J., Vinnars, E., Wannemacher, R., & Young, V. R., 1986).

In the beginning years of the nutritional protocol at the University of Utah, the availability of TBPA was limited. Transferrin levels, therefore, were used as the principal measure of visceral protein stores. Since that time the availability of TBPA has exceeded that of transferrin. As described in Chapter 4, the TBPA with its shorter half-life is believed to be a more efficient indicator of response to nutritional supplementation: declining TBPA levels indicate the need to increase protein supplementation, and if this is ineffective, an increase in total Calories is indicated.

Diagnosis

Diagnostic categories related to nutritional management in TBI were devised and were shown in Figure 32. These categories include stress level, risk level, and tolerance level. Stress level refers to two metabolic characteristics: level of metabolic energy expenditure and presence or absence of a catabolic state. Risk level addresses the issues of benefit versus adverse sequelae directly related to nutritional supplementation. Tolerance level identifies the patient's ability to absorb and assimilate nutrients. Absorption and assimilation, further, are functions related to both method of delivery as well as quantity and proportions of substrate.

Stress level

The analysis of metabolic energy expenditure levels from indirect calorimetry supports previous research findings demonstrating a high proportion of patients (41%) with TBI who are hypermetabolic by current definition (see Figure 23). The findings also suggest a significant proportion of patients with hypometabolic levels of energy expenditure (25%). Classification of metabolic state is often helpful in decisions related to type and quantity of substrate replacement.

The presence of a catabolic state is determined principally from levels of visceral protein stores. Nitrogen balance, as discussed earlier, is lacking in specificity for catabolic processes versus obligatory nitrogen loss. For the purposes of nutritional management, catabolism may be identified by visceral protein levels requiring greater than 1 mg./Kg./day (normal protein utilization) to maintain levels and/or fasting nitrogen excretion in excess of 10 Gms. per day. In this sample, the greater majority of patients (87%) maintained adequate protein synthesis as measured by TBPA levels. This level of protein synthesis, further, was maintained despite mean nitrogen losses of approximately 11 Gms. per day. These levels were maintained, however, with an average of 1.5 Gms./Kg./day (150% of normal maintenance). These data indicate that this TBI population is predominantly catabolic.

Risk level

The predominant risks associated with nutritional support in the TBI population are related to total parenteral nutrition. The area of greatest risk is associated with the placement of central lines. In this sample, no prolonged or permanent adverse sequelae has been attributed to nutritional support including TPN. Central line infection, for example, has been consistently below the average compared to other ICUs at the University of Utah (personal communication, Critical Care Committee, 1987-1989, monthly meetings). A large proportion of this finding may be related to the nutritional protocol, which utilizes peripherally introduced central venous catheters for administration of TPN. In over 200 of these catheter placements, no subsequent catheter related infection has been detected. Had traditional methods been utilized, including jugular and subclavian line placement, the morbidity associated with parenteral nutrition may have been substantially

higher. In addition, no adverse sequelae has been attributed to the placement of duodenal feeding tubes.

Other risks associated with aggressive nutritional support have included unretractable hyperglycemia, respiratory failure, renal failure, hepatic failure, hypomagnesemia, hypophosphatemia, and increased intracranial pressure. Individualized nutritional support and aggressive monitoring provided by this protocol has resulted in no occurrence of these risks. The latter two, hypomagnesemia and hypophosphatemia, may have been prevented by early nutritional support: they are generally associated with refeeding syndromes in individuals who have not received nourishment for an extended period of time. The findings in this sample indicate a low risk to high benefit ratio for early, aggressive nutritional support given this specific nutritional protocol.

Tolerance level.

The findings of this study, in relation to method of delivery, suggest that enteral feedings given by duodenal feeding tube are poorly tolerated in the first two weeks after injury. The tolerance of enteral feedings, however, has been shown to be superior to TPN in the literature (Norton, et al., 1988). The recommendation for method of delivery in the TBI population is to place a jejunal feeding tube at the earliest possible time. The welfare of the patient, however, in regard to transport to the X-ray department should be evaluated carefully. In lieu of a jejunal feeding tube, TPN via peripherally introduced central venous catheter should be initiated. Upon resumption of gastrointestinal function, a duodenal feeding tube should be placed in the ICU (negating the risks of transport) and enteral feedings initiated. Absorption of the enteral feedings requires close monitoring. Patients placed on this protocol have demonstrated low risk of aspiration of gastric contents with monitoring

of gastric residuals and placement checks by auscultating air injected into the tube at two hour intervals.

No adverse sequelae has been found in this sample attributable to ratios of substrate. Initial TPN substrate ratios consisting of 1.5 Gms./Kg./IBW with approximately 40-50% of the nonprotein calorie contribution as lipids and 50-60% as carbohydrate have been well-tolerated. Enteral substrate of comparable ratios has also been well-tolerated.

In summary, three diagnostic categories for nutritional management have been proposed to classify metabolic characteristics in TBI. Pertinent findings of the study, in relation to these categories, have further been discussed. The next section on implementation will address execution of nutritional support in a step-wise approach given individual patient assessment parameters and diagnostic attributes.

Implementation

Implementation of TPN or TEN in TBI, to be successful, requires an understanding of the complex interplay between clinical management of TBI, physiological processes encountered in TBI, and the physiological effects of nutritional supplementation. These relationships must be given due consideration if complications are to be prevented. Figure 33 illustrates the initial decision trail and constituents for initiating nutritional supplementation. The optimal time for nutritional evaluation, to prevent excessive delays, is the day of admission.

Fluid and electrolyte requirements

The best tolerated fluid solution in the early acute phase of TBI has been found to be ringers lactate. A formulation closely approximating this solution with the added electrolytes of magnesium, phosphate, and calcium has been devised, with the assistance of staff pharmacists, for use in this institution (personal

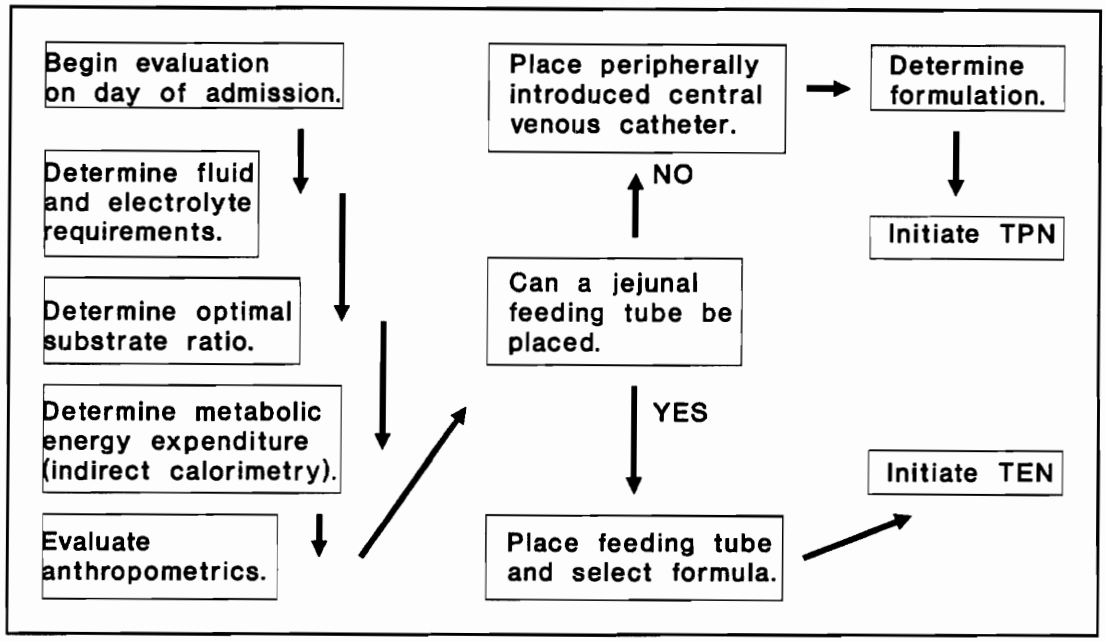

Figure 33. An Algorithm for Initiating Nutrition in TBI.

communication, William Rusho, January 1987). A sample TPN order sheet with this formulation is shown in Appendix J.

Adjustment of electrolytes in TEN, to the best of my knowledge, has never been addressed in the published literature. A methodology derived from experience with the nutrition protocol consists of the use of normal saline for irrigation to fulfill sodium requirements. The normal saline is mixed with powdered formulas to achieve the desired sodium replacement.

Substrate ratio

The ratio of carbohydrate, protein, and lipids is based on evaluation of stress level previously discussed. Selection of protein type is based on the Stress Stratification Model (see Table 6). Patients falling into the stress category of 2 or higher (the majority) are given high concentrations of the branched chain amino acids. The branched chain amino acids are hypothesized to exhibit a protein sparing effect (Brennan et al. 1986). The initial quantity of proteins best tolerated in this

effect (Brennan et al. 1986). The initial quantity of proteins best tolerated in this population has been found to be 1.5 Gms./Kg./day (Blackburn et al. 1989). Non-stressed patients (stress category 0 or 1) appear to tolerate the less expensive standard amino acid solutions. The initial quantity administered is the same.

The ratio of nonprotein caloric contribution is also based on stress level. Patients displaying hypermetabolic rates of energy consumption, elevated serum glucose levels, and catabolic rates of protein consumption best tolerate an approximate ratio of 50-60% carbohydrate and 40-50% lipids. Patients who are normal metabolic and noncatabolic tolerate a more normal ratio of 80% carbohydrate and 20% lipid.

TPN formulations allow precise formulation of specific nutrients. Several TEN solutions currently available, however, closely approximate the ratios noted above.

Total caloric supplementation

Energy expenditure estimates derived from indirect calorimetry supply the final data required to complete the supplementation calculations. In lieu of indirect calorimetry, the best recommendation for caloric expenditure estimation, based on the findings of the study, would be 120% of the calculated BEE by the Harris-Benedict equation. This estimation, however, is not sufficient for routine use.

An example of the calculations required for the final TPN supplement is shown in Table 29. These calculations are based on a 130 lb., 5 foot 6 inch female. This example will also serve to illustrate the differences between individualized and standard formulas. Note that the traditional 85 cc. per hour rate normally given to TBI patients is closely matched to the female in this example. Remember, however, that the more common TBI patient is male with a greater body surface area, indicating fluid supplement more severe than required. If the standard formulation

Table 29

Calculations for TPN Formulations

Step	Components	Result
1. Calculate Ideal wt	Computerized	61.3 Kg.
2. Calculate protein supplement.	IBW X 1.5 Gms. (pro)	92 Gms./24 hours
3. Protein calorie contribution.	92 Gms. X 4 Cal/Gm.	368 Cal./24 hours
4. Fluid quantity	46 Gms./L.	2L./24 hours
5. Maintenance Fluid	1500 cc. X BSA (1.66 M2)	2490 cc/24 hours
6. % of maintenance from TPN	Step 4/Step 5	80% of maintenance (ideal for TBI).
7. Calculate non-protein calories	REE-protein calories	2032 Cal.
8. Lipid supplement	40% of NPCC	Approx. 875 Cal.
9. Carbohydrate supp.	60% of NPCC	70% Dext. 1150 Cal.

Note. 1. REE = resting energy expenditure. 2. BSA = body surface area in M^2 = weight in Kg. to the .73 power X 1.73. 3. IBW = ideal body weight: Males = 50 KG. + (2.3 X Height in inches over 5 feet). Females = 45.5 + (2.3 X Height in inches over 5 feet). 4. Based on a female, 130 lbs., 5 feet 6 inches tall.

less than 1.5 Gms. of standard amino acids. The nonprotein calorie contribution would total 2250 Cal.; 76% carbohydrate and 24% lipid (the standard lipid supplement = 550 Cal.). Note also (Appendix J) that the standard electrolyte solution is approximately equivalent to 1/4 normal saline, a solution not tolerated well in TBI because of worsening of cerebral edema. This worsening of cerebral edema results from decreasing intravascular osmotic pressure and fluid shifts to the central nervous system. The lower the sodium replacement, the lower the osmotic gradient.

Method of delivery

As previously discussed, the enteral route is the method of choice for nutritional supplementation in TBI. This route, however, is limited to those patients who are physiologically stable enough for transport to the radiology department. The majority of patients will be unable to do so. Based of the findings of this study, TPN would likely be the predominant method of delivery in the initial nutritional process. From experience, placement of peripherally introduced central venous catheters is also dependent on the time frame. The catheters are more easily placed before multiple venapunctures have occurred. In most situations, if peripheral catheters cannot be initiated, other methods of central venous access (i.e., subclavian) are warranted for patients with a GCS of 11 or less. The implementation process, in summary, consists of an integrated approach to metabolic management based on clinical experiences with the TBI population. The crucial aspects of this approach include; 1) selection of the best method of delivery given individual evaluation, and 2) optimization of fluids and electrolytes, nutritional substrate, and total Calories. The next section will address the issues of evaluation and routine metabolic monitoring.

Evaluation of Nutritional Management

The evaluation process is essential in detecting nutritional complications and changes in metabolic state from the baseline evaluation. Table 30 outlines recommendations of serial monitoring of TBI patients receiving parenteral or enteral nutrition in the ICU. These recommendations are based on the findings of the study and experiences with the nutritional protocol. This scheme directly relates to those areas of initial assessment already mentioned.

As discussed earlier, temporal response is also a crucial assessment parameter. The findings of the study suggest that the period of highest risk for

Table 30

Recommendation for Serial Nutritional Monitoring in Traumatic Brain Injury

Evaluation Measure	Frequency	Function Evaluated
SMA-7	Daily	Glucose synthesis Insulin resistance Renal function Electrolyte balance Fluid balance
CBC with differential	Daily	Immune response
Physical Assessment	Daily	G.I. function Metabolic work Respiratory function
Indirect Calorimetry	Twice weekly	Respiratory response Energy Expenditure
SMA-20/magnesium(TPN)	Weekly	Hepatic function Electrolyte balance
TBPA/24 hour UUN	Weekly	Visceral protein

Note. In the acute care setting for patients receiving parenteral or enteral nutrition.

hypermetabolism occurs at approximately 2 weeks after injury. The findings also indicate that protracted illness results in depletion of visceral protein stores. This depletion suggests the need for continued close monitoring for patients requiring TPN or TEN for extended periods of time.

The determination of changes in metabolic pattern and nutritional responsedisplayed by evaluation of the assessment parameters is the key to reducing risks from nutritional support. The discussion has also eluded to a number of situations in the conceptualization of nutrition that act as barriers to its realization.

The health care team in its entirety must be devoted and informed if optimal nutrition is to be achieved.

Barriers to Optimal Nutrition

Despite the accumulation of overwhelming evidence in support of aggressive nutritional practices, the realization of commitment to these ideals has not been achieved. A large number of nurses, physicians, and dieticians continue to conceptualize aggressive nutrition as a non-necessity. A large part of this conceptualization most likely stems from a lack of understanding. Nursing curriculum, in regards to nutritional practices, is notably deficient in content addressing the alternative sources of nutrition for critically ill patients. Medical education is also notably deficient. Dietetics has also demonstrated inadequacies in understanding of intervening factors such as fluid and electrolyte balance, management goals of specific disease states, and familiarity with critically ill patients.

From a nursing perspective, curriculum in both undergraduate and graduate programs must address nutritional and metabolic physiology as well as the processes of parenteral and enteral nutrition. The ultimate goal is achieving a minimum knowledge base for nutritional supplementation consistent with, for example, knowledge of pharmacologic agents or a component part of physical assessment.

Nurse specialists and practitioners must also be tasked with gaining increased familiarity for specific patient groups in their particular area of specialization. In many community based nursing groups, for example, nutrition is a fundamental part of the educational process. This process has yet to extend to tertiary care. These nurse specialists could play a crucial role in the provision of nutritional therapy.

The fundamental barrier to nutrition in critically ill patients is the lack of accountability and responsibility among members of the health care team. The

delivery of nutrition, to be successful, is a team effort. All groups must be equally dedicated. When other priorities of clinical management are considered higher priority, however, the responsibility and accountability cannot be found. In essence everyone is responsible but no one is responsible.

This lack of enthusiasm with nutritional support is somewhat understandable. It is time consuming and complex. Next to education, the most important promotion aspect is developing methods to simplify the assessment and prescription process for clinicians. A number of changes in nutritional methods could, however, make critical differences in achieving the goal of optimizing nutrition. The TPN order sheet noted in Appendix J is a good example. The time required to make these calculation requires an extraordinary quantity of human resources. Standard formulations, in addition, rarely meet a specific patients' individual needs. A more effective practice would include specifying the goals of therapy instead of the specific components. Instead of, for example, specifying the quantity and concentration of specific nutrients, the total caloric supplementation and ratios could be prescribed. These goals of therapy could then be placed in a computer algorithm for determination of specific quantity and concentration. Standard formulations from this perspective should be discontinued. Many nutritional support services for neonatal nurseries have effectively adopted this methodology.

Implications for Further Research

The most notable ramification for future research found in this study involves the potential relationship between evaluating nutritional supplementation strategies and methods for determining caloric expenditure. Predominantly, clinical research trials have used "isonitrogenous" and "isocaloric" regimens in the evaluation of, for example, differing nutritional formulations or specific substrate. The terms "isonitrogenous" and "isocaloric" refer to standard quantities of nutrients generally

based on anthropometric measures. Although the findings in this sample suggest that isonitrogenous supplementation is adequate, isocaloric supplementation is grossly inadequate. When evaluating nutritional supplementation in this way, the difference between what the patient needs and what the patient receives has the potential for influencing the amount of statistical error introduced into the study, especially Type II error. This methodology has implications for the next area in need of further research.

Current clinical research has supported the use of high concentration of branched chain amino acids (HBCAA) to improve nitrogen retention and decrease the catabolic response in highly stressed patients. A number of studies, however, have not been effective in replicating the results (Brennan, et al., 1986). All studies involving the differences between HBCAA and standard amino acids have used the isocaloric approach mentioned above. It would appear plausible to hypothesize that significant statistical error and reduction in statistical power may be attributed to this Caloric replacement methodology. The conduct of a clinical trial for the efficacy of HBCAA using an approach where supplementation be based on actual REE based on indirect calorimetry has exciting potential.

Further research is also indicated for a number of recommendations made in this study. It has been advocated that supplementation be prescribed based on level of stress. A controlled, prospective trial comparing outcomes on nutritional measures between stressed and nonstressed groups would certainly be prudent and warranted.

Possibly the area in the greatest need for research is the lack of efficient outcome measures. Clinicians advocating aggressive nutrition are often tasked with proving benefit. Ethical considerations, however, preclude the use of many methods used in the past, for example, delayed TEN versus early TPN. One area noticeably

lacking in nutritional research in TBI is trends analysis of specific, individual metabolic profiles. A great deal may be learned from analyses of which patients demonstrate favorable outcomes based on metabolic indices.

The findings of this study in regard to the APACHEII scale (Knaus, et al., 1987), also have potential for controlling for severity of injury in the evaluation of randomized nutritional trials. It is often difficult to evaluate between groups treatment effects when severity of injury cannot be shown to be equivalent.

As mentioned earlier, analysis of gender differences in terms of nutritional requirements and metabolic indices holds great potential for expansion of the understanding of metabolic processes. As the mean age of our societies population increases, the evaluation of age difference and metabolic profiles also holds the promise for fruitful research endeavors.

Summary

The implications derived from a better understanding of metabolic and nutritional processes in TBI have been discussed from a number of vantage points. These vantage points have included the theoretical perspectives in terms of structure and pattern as well as clinical perspectives related to day to day patient management. These results have been stimulating and identify areas in need of reevaluation. The analysis of metabolic indicators and evaluation of current nutritional management models have significant practical clinical and research implications. The singular message portrayed in this study is the realization that we have the potential for reducing the tragic waste incurred by traumatic brain injury in our society.

APPENDIX A

PRELIMINARY REEVALUATION OF A NUTRITIONAL PROTOCOL IN HEAD INJURY

By Peter M. Sunderland and M. Peter Heilbrun

Introduction

Nutritional management of the critically ill patient has received a great deal of attention over the past decade, primarily in general surgery, multiple trauma, and burn populations. Only in the past few years, however, have the unique nutritional needs of the head injured population been addressed (most notably by Clifton and associates of the Baylor College of Medicine and Medical College of Virginia). As a result of current research, a greater number of management options are now available to the practitioner. To date, however, few reports on the effectiveness of these options in other clinical settings have been reported.

This paper is a preliminary retrospective analysis of currently recommended methodologies for nutritional management of the critically ill and adapted for use with patients sustaining neurologic injuries. The specific methodologies include to be investigated include: 1) timing of initiation of parenteral or enteral nutrition, 2) determination of caloric expenditure and subsequent supplementation, and 3) a comparison of the effectiveness of high concentrations of branched chain amino acids compared with standard amino acid solutions. The rationale for the early initiation of feeding is based on the recommendations of a study conducted by Rapp, Young, Twyman, Bivins, Haack, Tibbs, and Bean (1983) at the University of Kentucky. This study compared the effects of early initiation of parenteral nutrition with delayed enteral nutrition in 38 head injured patients. Results of this study indicated a significantly higher mortality rate in patients receiving delayed enteral nutrition.

In regards to determining caloric expenditure, numerous methodologies in a variety of pathologic processes have been proposed making clinical management

decisions difficult. Four methods for determining energy expenditure will be addressed by this paper. The traditional method has been to rely on the Harris-Benedict equation, which estimates basal energy expenditure using the parameters of height, weight, and sex. The determination of nutritional requirement from the Harris-Benedict equation requires multiplication by a somewhat arbitrary factor, usually 50%. This formula is also based on observations of normal individuals and does not take into consideration the effects of injury or changes over time. Wilmore (1977) combined the determination of basal energy expenditure with a stratification scheme for differential injuries in critically ill patients, however, the scheme does not specifically address head injury. Clifton et al. (1986) reported a study of energy expenditure in 57 head injured patients. Using multiple regression analysis on metabolic measurements of 312 days of observations it was determined that energy expenditure could be predicted using a formula that uses the parameters of days since injury, heart rate, and Glascow Coma Score. This regression score is then used as a multiple in conjunction with standard methods (Harris-Benedict Equation) for determining basal energy expenditure to determine caloric requirement. The last method to be discussed for determining energy expenditure is the individual measurement of gas exchange using indirect calorimetry, which, incidentally, is the method used to derive the previous formulas. Indirect calorimetry measures oxygen consumption and carbon dioxide production. These measurements are then subjected to a standardized formula to derive an accurate and reliable prediction of resting metabolic expenditure, in the case of our metabolic cart (metabolic gas monitor MGM II, Medicor Inc. Salt Lake City, Utah) it is Weir's formula. Adaption to volume ventilators is easily made by appropriate connectors and oxygen blender.

The respiratory quotient or the ratio of oxygen consumption to carbon dioxide production is also determined and provides useful information concerning the predominant substrate being utilized (i.e., <.75 lipid oxidation, .75 to .95 mixed utilization, and >.95 predominantly lipid production. The greatest limitation of metabolic measurements is the relative nonavailability of this tool (indirect calorimetry) to most practitioners, therefore, creating the need for the standard formulas described earlier. Unstable readings from high respiratory flow rates associated with hyperventilation is another common difficulty encountered with indirect calorimetry measurements in head injured patients. High concentrations of oxygen may also adversely affect the reliability of the measurements.

Parenterally or enterally administered modified amino acid formulas, in particular, high concentrations of the branched chain amino acids isoleucine, leucine, and valine has been recently advocated as an effective method to reduce extreme protein losses and enhance visceral protein synthesis in hypercatabolic states. Increased reliance on the branched chain amino acids as carbon sources for oxidative metabolism in skeletal muscle and the differential extraction by the liver for protein synthesis during high stress states has been reported as possible mechanisms for their effectiveness.

Methods

Thirty patients with closed head injury and Glascow Coma Scale of eight or less were admitted to the University of Utah Neurosurgery Service and placed on a nutritional protocol. The primary components of the protocol were: first, initiation of parenteral or enteral nutrition within 24 to 72 hours; second, monitoring of oxygen consumption and carbon dioxide production by indirect calorimetry to determine

resting energy expenditure and subsequent caloric supplementation. These measurements were then compared to the formulas proposed by Wilmore (1977) and Clifton (1982). When metabolic measurements could not be obtained, caloric supplementation was based on approximately one 140 percent of predicted basal energy expenditure (Harris-Benedict Equation). This estimation was based on previous experience with indirect calorimetry and neurosurgical patients. Third, during the time period analyzed (1986-1987) the nutritional protocol was modified to include the use of high branched chain amino acids versus our previous use of standard amino acids. The use of the high branched chained amino acids was based on stress parameters proposed by Cerra, Mazuski, Teasley, Nuwer, Lysne, Shronts, and Konstantinides (1983). These parameters include degree of hyperglycemia, nitrogen excretion and lactic acid levels.

One of our greatest concerns with the use of early parenteral nutrition was probable electrolyte imbalance when using "standard solutions." Electrolyte composition of standard solutions is approximately equivalent to 1/4 normal saline. For this reason, parenteral formulations were modified to provide a salt solution equivalent to Ringer's lactate to minimize the effect of hypotonic electrolyte solutions on increasing cerebral edema. Another concern was the ability to provide adequate nutrition while maintaining fluid restriction. In most cases, increasing the ratio of fats to carbohydrate was required to deliver the appropriate calories and still maintain fluid intake at approximately 2 liters. Routine nutritional monitoring consisted of baseline and weekly evaluation of; indirect calorimetry measurements, lab values including SMA-20, serum osmolality, CBC with differential, total lymphocyte count, serum transferrin, and 24 hour urine urea nitrogen determinations.

Urinary nitrogen excretion was then subjected to a standard formula suggested by Wilmore (1977) to determine total body nitrogen excretion. Daily weights were obtained unless contraindicated by increased intracranial pressure.

Results

To date, results have been tabulated on 23 of the 30 patients placed on the protocol. Data on three patients were excluded because of concurrent spinal cord injury with quadriparesis. Medical records for the other four patients were unavailable at the time of analysis. The parenteral solution modified to approximate Ringers Lactate was found to be an effective method of controlling common electrolyte disturbances encountered in these patients (primarily hyponatremia secondary to the Syndrome of Inappropriate Antidiuretic Hormone). Mild fluid restriction was also maintained without compromising the level of nutrients administered. By preliminary analysis, nutritional parameters, routinely evaluated, were found to be consistently maintained or improved over the course of the protocol. Weight losses were calculated at a mean of six-tenths of 1% of total body weight per day +/- a standard deviation of two-tenths of 1%. Evaluation of the three methods of determining caloric requirement showed a consistent overestimation of caloric expenditure by the two currently recommended formulas/nomogram that can be used at the bedside. The degree of overestimation shown by the mean values for this group of patients is approximately 600 to 700 Calories between indirect calorimetry and the Clifton and Wilmore formulas. This degree of difference can be significant in the clinical setting.

Nitrogen balance between patients receiving high-branched chain amino acids and standard amino acid formulations showed a slightly higher nitrogen retention in

the high branched chain group. These results are similar to a study reported by Rowlands and associates from the University of Texas Medical School (1987). The degree of difference between Rowland's and our group is most likely due to the method of determination of nitrogen balance. The equation used to determine total nitrogen excretion under our nutritional protocol produces higher nitrogen excretion results than most methods currently published in the literature.

Conclusions

As a result of this preliminary analysis several conclusions have been reached. First, early nutrition can be safely initiated using electrolyte and substrate modifications with currently recommended nutritional monitoring. In addition, these practices reduce common reasons for delaying therapy. Monitoring of thyroxin-binding prealbumin (TBPA) levels was also added to our protocol as a result of current findings. These levels aid in rapid detection of the effectiveness of alterations in therapy. The half life of TBPA is 2-3 days, whereas transferrin is 7-10 days, and albumin is approximately 20 days. Monitoring of triglycerides was also added because of the necessity to increase the overall ratio of the lipid component to provide adequate Calories. Second, currently recommended methods for bedside estimation of Caloric requirement may result in overfeeding. Overfeeding can worsen hyperglycemia, increase carbon dioxide production, and adversely effect liver function. These methods, however, are still the most reliable in lieu of the capability of indirect calorimetry and should be relatively safe if combined with caution and attention to signs of overfeeding. Third, modified amino acid formulas in the head injured population show a slight advantage over standard amino acids. A more definitive conclusion depends on the conduct of more stringent study designs.

Another concern with the use of modified amino acids is the lack of clearly defined parameters to determine the appropriate timing for returning to standard amino acid formulations. Continuation of the current line of research is supported by the present findings and concerns for adequate nutritional support in the head injured population.

APPENDIX B

A RESEARCH KNOWLEDGE SYSTEM (ARKS):

NARRATIVE DESCRIPTION

ARKS©

There is a great increase in the number of research studies with a concomitant increase in new knowledge. Storage and management of all the new knowledge is as much a problem as the storage and management of the massive amounts of data and information in the sciences. Just as we need methods of transforming data into meaningful information and information into knowledge, we need ways of aggregating, summarizing, organizing knowledge so it is meaningful and useful to students, clinicians, and researchers. Just as we have developed methods for storing and managing data, i.e., *databases*, we need new methods for storing and managing knowledge, i.e., *knowledge-bases*..

ARKS© is a knowledgebase management system that provides menu-selected tools for extracting, storing, managing, and modelling research knowledge from the scientific literature in an **MS-DOS** environment. Once the research knowledgebase is built, using the **Knowledgebase Builder**, the **Knowledge Manager** assists in the management of the knowledge of generating several types of indexes and offering menu-driven search strategies. The **Knowledge Modeller** can generate two types of models of the knowledge it contains. One is a causal/associational model of relationships between selected variables. The second is a density map of all the research represented and arranged by clinical metastructure categories: person, environment, population, treatment, treatment outcome, diagnostic classification (nursing, medical, etc.)

ARKS© was built to manage knowledge in the health sciences, especially nursing; however, ARKS© is useful for managing relational knowledge in any field.

APPENDIX C

ARKS VARIATE DATABASE LISTING

REFID	IMC	AIV	IV	DMC	ADV	DV
9.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	ACUTE PHASE RESPONSE	WBC COUNT
9.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	METABOLIC RATE	MEE
46.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	METABOLIC RATE	RME
9.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	NUTRIENT ASSIMILATION	BODY WEIGHT
34.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	PROTEIN METABOLISM	NITROGEN BALANCE
35.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	PROTEIN METABOLISM	NITROGEN BALANCE
21.00	D	INTRACRANIAL INSULT	HEAD INJURY	P	PROTEIN METABOLISM	NITROGEN EXCRETION
9.00	D	INTRACRANIAL INSULT	TBI VS MYELOGRAM	P	ACUTE PHASE RESPONSE	INTERLEUKIN I
22.00	D	TEMPORAL RESPONSE	DSI	I	NUTRIENT DELIVERY	CALORIES RECEIVED/MEE
9.00	D	TEMPORAL RESPONSE	DSI	I	NUTRIENT DELIVERY	TOTAL KCAL/MEE
9.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	BODY TEMPERATURE
5.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	C-REACTIVE PROTEIN
9.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	SERUM C-REACTIVE PROTEIN
5.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	SERUM COPPER
9.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	SERUM COPPER
5.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	SERUM ZINC
9.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	SERUM ZINC
5.00	D	TEMPORAL RESPONSE	DSI	P	ACUTE PHASE RESPONSE	URINE ZINC
21.00	D	TEMPORAL RESPONSE	DSI	P	CARDIOVASCULAR RESPONSE	CARDIAC INDEX
21.00	D	TEMPORAL RESPONSE	DSI	P	FAT METABOLISM	SERUM TRIGLYCERIDES
21.00	D	TEMPORAL RESPONSE	DSI	P	GLUCOSE METABOLISM	SERUM GLUCOSE
9.00	D	TEMPORAL RESPONSE	DSI	P	METABOLIC RATE	MEE/PEE
22.00	D	TEMPORAL RESPONSE	DSI	P	METABOLIC RATE	MEE/PEE
16.00	D	TEMPORAL RESPONSE	DSI	P	METABOLIC RATE	METABOLIC RATE
22.00	D	TEMPORAL RESPONSE	DSI	P	METABOLIC RATE	SUBSTRATE INTAKE AND OXIDATION
22.00	D	TEMPORAL RESPONSE	DSI	P	NUTRIENT ASSIMILATION	WEIGHT
28.00	D	TEMPORAL RESPONSE	DSI	P	NUTRIENT ASSIMILATION	WEIGHT
21.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	3-METHYL HISTIDINE
22.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	ALBUMIN
28.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	ALBUMIN
21.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	AMINO ACID LEVELS
28.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	CREATININE-HEIGHT INDEX
28.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	CUMULATIVE NITROGEN BALANCE
13.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	NITROGEN BALANCE
9.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	NITROGEN BALANCE
13.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	NITROGEN INTAKE AND LOSS

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REFID	IMC	AIV	IV	DMC	ADV	DV
15.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	NITROGEN INTAKE AND LOSS
22.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	RBP
34.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	RBP AND PREALBUMIN
9.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	SERUM ALBUMIN
34.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	TOTAL SERUM PROTEIN
10.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	TRANSFERRIN AND ALBUMIN
10.00	D	TEMPORAL RESPONSE	DSI	P	PROTEIN METABOLISM	TRANSFERRIN AND ALBUMIN
21.00	D	TEMPORAL RESPONSE	DSI	P	RESPIRATORY RESPONSE	AV02D
21.00	D	TEMPORAL RESPONSE	DSI	P	RESPIRATORY RESPONSE	CO2 PRODUCTION
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	GLUCOSE METABOLISM	SERUM GLUCOSE
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	LIPID METABOLISM	FREE FATTY ACIDS
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	SYMPATHETIC RESPONSE	SERUM ADRENALINE
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	SYMPATHETIC RESPONSE	SERUM CORTISOL
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	SYMPATHETIC RESPONSE	SERUM GLUCAGON
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	SYMPATHETIC RESPONSE	SERUM INSULIN
50.00	D	TYPE OF INJURY	CRANIAL VS NON-CRANIAL INJURY	P	SYMPATHETIC RESPONSE	SERUM NORADRENALINE
30.00	D	TYPE OF INJURY	MULTI VS NEURO INJURY	P	RESPIRATORY RESPONSE	SERUM CO2
30.00	D	TYPE OF INJURY	NEURO AND MULTI INJURY	P	PROTEIN METABOLISM	NITROGEN BALANCE
30.00	D	TYPE OF INJURY	NEURO VS MULTI	P	ELECTROLYTE BALANCE	SERUM CALCIUM
30.00	D	TYPE OF INJURY	NEURO VS MULTI	P	GLUCOSE METABOLISM	SERUM GLUCOSE
30.00	D	TYPE OF INJURY	NEURO VS MULTI	P	PROTEIN METABOLISM	SERUM ALBUMIN
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	ELECTROLYTE BALANCE	SERUM CL-
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	ELECTROLYTE BALANCE	SERUM K+
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	ELECTROLYTE BALANCE	SERUM MG++
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	ELECTROLYTE BALANCE	SERUM NA+
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	ELECTROLYTE BALANCE	SERUM PO4
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	PROTEIN METABOLISM	PREALBUMIN
30.00	D	TYPE OF INJURY	NEURO VS MULTI INJURY	P	PROTEIN METABOLISM	RBP
34.00	I	CONCURRENT TREATMENT	HEMATOMA REMOVAL	P	PROTEIN METABOLISM	NITROGEN EXCRETION
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	IMMUNE RESPONSE	SKIN TEST REACTIVITY
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	IMMUNE RESPONSE	TOTAL LYMPHOCYTE COUNT
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	METABOLIC RATE	RME
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	NUTRIENT ASSIMILATION	WEIGHT
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	PROTEIN METABOLISM	ALBUMIN
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	PROTEIN METABOLISM	CREATININE HEIGHT INDEX
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	PROTEIN METABOLISM	CUMULATIVE NITROGEN BALANCE
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	PROTEIN METABOLISM	NITROGEN LOSS

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REFID	IMC	AIV	IV	DMC	ADV	DV
49.00	I	CONCURRENT TREATMENT	STEROIDS	P	PROTEIN METABOLISM	SERUM TOTAL PROTEIN
46.00	I	FLUID VOLUME	PLASMA VOLUME	P	CARDIOVASCULAR RESPONSE	CARDIAC INDEX
1.00	I	GASTROINTESTINAL RESPONSE	BOWEL SOUNDS	P	METHOD OF DELIVERY	DAYS TO FSFR TEN
3.00	I	METHOD OF ADMINISTRATION	TPN VERSUS TEN	I	NUTRIENT DELIVERY	CALORIC BALANCE
3.00	I	METHOD OF ADMINISTRATION	TPN VERSUS TEN	I	NUTRIENT DELIVERY	PROTEIN INTAKE
3.00	I	METHOD OF ADMINISTRATION	TPN VERSUS TEN	O	RECOVERY AND SURVIVAL	NEUROLOGICAL OUTCOME AT 1 YEAR
1.00	I	METHOD OF DELIVERY	TOLERANCE OF TEN	P	PROTEIN METABOLISM	SERUM ALBUMIN
27.00	I	METHOD OF DELIVERY	TPN VERSUS CN	P	GASTROINTESTINAL RESPONSE	LOSS OF GASTRIC FLUID
27.00	I	METHOD OF DELIVERY	TPN VERSUS CN	P	GASTROINTESTINAL RESPONSE	PROTEIN CONC. OF GASTRIC FLUID
27.00	I	METHOD OF DELIVERY	TPN VERSUS CN	P	PROTEIN METABOLISM	3-METHYL HISTIDINE
27.00	I	METHOD OF DELIVERY	TPN VERSUS CN	P	PROTEIN METABOLISM	NITROGEN BALANCE
8.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	I	NUTRIENT DELIVERY	CALORIC INTAKE
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	I	NUTRIENT DELIVERY	NITROGEN INTAKE
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	I	NUTRITIONAL DELIVERY	CALORIC BALANCE
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	IMMUNE RESPONSE	BACTERIAL INFECTION
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	IMMUNE RESPONSE	INFECTION
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	IMMUNE RESPONSE	PNEUMONIA
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	IMMUNE RESPONSE	SEPSIS
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	IMMUNE RESPONSE	URINARY TRACT INFECTION
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	MOTOR RESPONSE	GCS
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	RECOVERY AND SURVIVAL	NEUROLOGICAL OUTCOME AT 3 MONTHS
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	SURVIVAL	DEATHS DAYS 18-83
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	SURVIVAL	TOTAL DEATHS
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	COMPLICATIONS	COMPLICATIONS OF NUTRITIONAL RX
8.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	ELECTROLYTE BALANCE	SERUM OSMOLALITY
8.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	GLUCOSE METABOLISM	SERUM GLUCOSE
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	IMMUNE RESPONSE	SKIN TEST REACTIONS
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	IMMUNE RESPONSE	TLC
8.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	NEUROLOGICAL RESPONSE	ICP
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	NUTRIENT ASSIMILATION	BODY WEIGHT
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	% CHANGE IN SERUM TRANSFERRIN
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	%CHANGE SERUM ALBUMIN
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	MEAN SERUM TRANSFERRIN
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	NITROGEN BALANCE
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	NITROGEN BALANCE
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	NITROGEN BALANCE
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	NITROGEN LOSS

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REFID	IMC	AIV	IV	DMC	ADV	DV
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	NITROGEN LOSS
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	PEAK CREATININE EXCRETION
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	SERUM ALBUMIN
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	SERUM ALBUMIN
43.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	SERUM ALBUMIN
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	P	PROTEIN METABOLISM	SERUM RBP
43.00	I	METHOD OF DELIVERY	TPN VS TEN	P	PROTEIN METABOLISM	NITROGEN BALANCE
13.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	I	NUTRIENT DELIVERY	CALORIE/NITROGEN RATIO
3.00	I	METHOD OF DELIVERY	TPN VERSUS TEN	O	RECOVERY AND SURVIVAL	NEUROLOGICAL OUTCOME AT 6 MONTHS
46.00	I	MOTOR RESPONSE	BARBITURATE COMA	P	METABOLIC RATE	RME
46.00	I	MOTOR RESPONSE	PARALYSIS	P	METABOLIC RATE	RME
35.00	I	MOTOR RESPONSE	PARALYSIS/SEDATION	P	METABOLIC RATE	RME
43.00	I	MOTOR RESPONSE	TPN VERSUS TEN	P	METHOD OF DELIVERY	GCS
1.00	I	NEUROLOGIC RESPONSE	DAYS OF ICP MNTR	I	METHOD OF DELIVERY	DAYS TO FSFR TEN
1.00	I	NEUROLOGIC RESPONSE	ICP	P	METHOD OF DELIVERY	DAYS TO FSFR TEN
35.00	I	NUTRIENT DELIVERY	CALORIC INTAKE	P	METABOLIC RATE	RME
46.00	I	NUTRIENT DELIVERY	CALORIC INTAKE	P	METABOLIC RATE	RME
27.00	I	NUTRIENT DELIVERY	METHOD OF ADMINISTRATION	O	OUTCOME	MORTALITY
50.00	I	NUTRIENT DELIVERY	NITROGEN INTAKE	P	PROTEIN METABOLISM	CUMULATIVE N+ BALANCE
16.00	I	NUTRIENT DELIVERY	NITROGEN INTAKE	P	PROTEIN METABOLISM	NITROGEN BALANCE
43.00	I	NUTRIENT DELIVERY	TPN VERSUS TEN	I	METHOD OF DELIVERY	CALORIC INTAKE
43.00	I	RECOVERY AND SURVIVAL	TPN VERSUS TEN	O	METHOD OF DELIVERY	GLASCOW OUTCOME SCALE
26.00	I	RESPIRATORY RESPONSE	FAT ADMINISTRATION	P	FAT METABOLISM	RESPIRATORY QUOTIENT
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	GASTROINTESTINAL RESPONSE	BOWEL MOVEMENTS
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	BUN
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN BALANCE
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN BALANCE
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN BALANCE
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN BALANCE
28.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN BALANCE
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN EXCRETION
23.00	I	SUBSTRATE TYPE	PROTEIN CONCENTRATION	P	PROTEIN METABOLISM	NITROGEN INTAKE
47.00	I	SUBSTRATE TYPE	PROTEIN TYPE	P	PROTEIN METABOLISM	NITROGEN BALANCE
42.00	I	SUBSTRATE TYPE	TUBE FEEDING COMPOSITION	P	GASTROINTESTINAL FUNCTION	GASTRIC ACID SECRETIONS
43.00	I	SURVIVAL	TPN VERSUS TEN	O	METHOD OF DELIVERY	DEATH WITHIN 18 DSI
46.00	I	SYMPATHETIC RESPONSE	BETA BLOCKADE	P	METABOLIC RATE	RME
16.00	P	CARDIOVASCULAR RESPONSE	HEART RATE	P	METABOLIC RATE	RME

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REFID	IMC	AIV	IV	DMC	ADV	DV
46.00	P	CARDIOVASCULAR RESPONSE	HEART RATE	P	METABOLIC RATE	RME
27.00	P	GASTROINTESTINAL RESPONSE	GASTRIC OUTPUT	P	PROTEIN METABOLISM	NITROGEN BALANCE
46.00	P	METABOLIC RATE	AVDO2	P	METABOLIC RATE	RME
46.00	P	METABOLIC RATE	V02	P	CARDIOVASCULAR RESPONSE	CARDIAC INDEX
16.00	P	MOTOR RESPONSE	ACTIVITY	P	METABOLIC RATE	RME
1.00	P	MOTOR RESPONSE	GCS	I	METHOD OF DELIVERY	DAYS TO FSFR TEN
10.00	P	MOTOR RESPONSE	GCS	I	NUTRIENT DELIVERY	CALORIC INTAKE
10.00	P	MOTOR RESPONSE	GCS	I	NUTRIENT DELIVERY	PROTEIN INTAKE
10.00	P	MOTOR RESPONSE	GCS	O	IMMUNE RESPONSE	INFECTION
46.00	P	MOTOR RESPONSE	GCS	P	CARDIOVASCULAR RESPONSE	CARDIAC INDEX
16.00	P	MOTOR RESPONSE	GCS	P	METABOLIC RATE	RME
46.00	P	MOTOR RESPONSE	GCS	P	METABOLIC RATE	RME
46.00	P	MOTOR RESPONSE	GCS	P	METABOLIC RATE	RME
46.00	P	MOTOR RESPONSE	GCS	P	METABOLIC RATE	RME
10.00	P	MOTOR RESPONSE	GCS	P	NUTRIENT ASSIMILATION	WEIGHT
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	CREATININE HEIGHT INDEX
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	NITROGEN BALANCE
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	NITROGEN BALANCE
26.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	NITROGEN EXCRETION
34.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	NITROGEN EXCRETION
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	SERUM ALBUMIN
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	SERUM ALBUMIN
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	SERUM TRANSFERRIN
10.00	P	MOTOR RESPONSE	GCS	P	PROTEIN METABOLISM	SERUM TRANSFERRIN
46.00	P	MOTOR RESPONSE	GCS	P	SYMPATHETIC RESPONSE	ARTERIAL EPINEPHRINE
46.00	P	MOTOR RESPONSE	GCS	P	SYMPATHETIC RESPONSE	ARTERIAL NOREPI AND EPI
46.00	P	MOTOR RESPONSE	GCS	P	SYMPATHETIC RESPONSE	ARTERIAL NOREPINEPHRINE
48.00	P	MOTOR RESPONSE	GCS	P	SYMPATHETIC RESPONSE	NOREPINEPHRINE
48.00	P	MOTOR RESPONSE	GLASCOW COMA SCALE	P	SYMPATHETIC RESPONSE	NOREPINEPHRINE
16.00	P	MOTOR RESPONSE	PARALYSIS	P	METABOLIC RATE	RME
10.00	P	PROTEIN METABOLISM	CREATININE HEIGHT INDEX	O	IMMUNE RESPONSE	INFECTION
34.00	P	PROTEIN METABOLISM	NITROGEN EXCRETION	O	RECOVERY AND SURVIVAL	NEUROLOGIC RECOVERY AT 3 MONTHS
46.00	P	SYMPATHETIC RESPONSE	ARTERIAL EPINEPHRINE	P	CARDIOVASCULAR RESPONSE	ARTERIAL PRESSURE
46.00	P	SYMPATHETIC RESPONSE	ARTERIAL EPINEPHRINE	P	METABOLIC RATE	OXYGEN CONSUMPTION
46.00	P	SYMPATHETIC RESPONSE	ARTERIAL EPINEPHRINE	P	METABOLIC RATE	RME
46.00	P	SYMPATHETIC RESPONSE	ARTERIAL EPINIPHRINE	P	CARDIOVASCULAR RESPONSE	HEART RATE
46.00	P	SYMPATHETIC RESPONSE	ARTERIAL NOREPINEPHRINE	P	METABOLIC RATE	RME

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REFID	IMC	AIV	IV	DMC	ADV	DV
48.00	P	SYMPATHETIC RESPONSE	DOPAMINE BETA-HYDOXYLASE	P	CARDIOVASCULAR RESPONSE	BLOOD PRESSURE
46.00	P	SYMPATHETIC RESPONSE	METABOLIC RATE	P	ARTERIAL EPINEPHRINE	OXYGEN CONSUMPTION
48.00	P	SYMPATHETIC RESPONSE	NOREPINEPHRINE	P	CARDIOVASCULAR RESPONSE	HEART RATE
50.00	P	SYMPATHETIC RESPONSE	SERUM GLUCAGON	P	PROTEIN METABOLISM	NITROGEN BALANCE
50.00	P	SYMPATHETIC RESPONSE	URINARY ADRENALINE	P	PROTEIN METABOLISM	NITROGEN BALANCE
50.00	P	SYMPATHETIC RESPONSE	URINARY NORADRENALINE	P	PROTEIN METABOLISM	NITROGEN BALANCE
46.00	P	THERMOREGULATION	BODY TEMPERATURE	P	METABOLIC RATE	RME
46.00	P	THERMOREGULATION	BODY TEMPERATURE	P	METABOLIC RATE	RME
50.00	P	THERMOREGULATION	BODY TEMPERATURE	P	PROTEIN METABOLISM	CUMULATIVE N+ BALANCE
46.00	P	THERMOREGULATION	BODY TEMPERATURE	P	METABOLIC RATE	RME

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APPENDIX D

ARKS CITATION DATABASE

Reference ID: 1

Authors: Norton-J-A. Ott-L-G. McClain-C. Adams-L. Dempsey-R-J. Haack-D. Tibbs-P-A. Young-A-B.

Title: Intolerance to enteral feeding in the brain-injured patient.

Citation: J-Neurosurg. 1988 Jan. 68(1). P 62-6.

Reference ID: 2

Authors: Phillips-R. Ott-L. Young-B. Walsh-J.

Title: Nutritional support and measured energy expenditure of the child and adolescent with head injury.

Citation: J-Neurosurg. 1987 Dec. 67(6). P 846-51.

Reference ID: 3

Authors: Young-B. Ott-L. Twyman-D. Norton-J. Rapp-R. Tibbs-P. Haack-D. Brivins-B. Dempsey-R.

Title: The effect of nutritional support on outcome from severe head injury.

Citation: J-Neurosurg. 1987 Nov. 67(5). P 668-76.

Reference ID: 4

Authors: Ford-E-G. Jennings-L-M. Andrassy-R-J.

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Citation: Curr-Surg. 1987 Jul-Aug. 44(4). P 311-3.

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Citation: JPEN-J-Parenter-Enteral-Nutr. 1987 Sep-Oct. 11(5). P 488-93. (Review).

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Reference ID: 7

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Citation: J-Neurosci-Nurs. 1987 Aug. 19(4). P 211-5.

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Authors: Gardner-D.

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Authors: Young-B. Ott-L. Norton-J. Tibbs-P. Rapp-R. McClain-C. Dempsey-R.

Title: Metabolic and nutritional sequelae in the non-steroid treated head injury patient.

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Reference ID: 32

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Citation: J-Neurosurg. 1984 Jun. 60(6). P 1334-5.

Reference ID: 33

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Citation: Dig-Dis-Sci. 1984 Jun. 29(6). P 577-88. (Review).

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Title: Parenteral nutrition in head injury [letter].

Citation: J-Neurosurg. 1984 Apr. 60(4). P 874-6.

Reference ID: 35

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Citation: J-Neurosurg. 1984 Apr. 60(4). P 687-96.

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Citation: J-Neurosurg-Nurs. 1982 Oct. 14(5). P 262-7.

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Citation: Neurosurgery, (15)3, p. 307-14, (1984)

Reference ID: 47

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Citation: Neurosurgery, 8(1), (1981), p. 10-14.

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APPENDIX E

VALIDITY ASSESSMENT OF INDIRECT CALORIMETRY IN THE ACUTE SETTING

Introduction

The ability to maintain adequate nutrition has been a concern of nursing since its inception. Nursing expertise in this area, however, has fallen behind the technological advancements made in other fields, e.g., the determination of Caloric requirements reported in most nursing texts refer to the Harris-Benedict Equation established in 1919. Numerous reports in the fields of physiology, dietetics, and medicine have refuted this method for years.

The concern with metabolic predictions and subsequent nutritional therapy has been primarily the result of the realization that nutritional requirements cannot be accurately predicted not only from equations developed outside of the clinical setting on mostly healthy individuals but equations developed for specific hospitalized groups (Cortes & Nelson, 1989; Kinney, 1987; Jequier, 1987; Lanschot, Feenstra, Vermeij, & Bruining, 1987; Mann, Westenskow, & Houtchens, 1985; Saffle, Medina, Raymond, Westenskow, Kravitz, & Warden, 1985). Further, the consequences of these inaccurate predictions can severely compromise patient outcome in situations of underfeeding and overfeeding. Effects of underfeeding have been known for quite some time. These include, but are not limited to: immune compromise, loss of lean muscle mass with concomitant loss of muscle function (primarily pulmonary and cardiac), poor wound healing, and fatigue.

The ability to more accurately predict nutritional requirements has been primarily a result of development of indirect calorimetry. Instrumentation required for indirect calorimetry is now portable and efficient enough to afford measurements at the bedside. The current instrumentation and methods have reported capabilities of accurately determining Caloric requirements, and optimal substrate ratios. This information is vitally important to nursing concerns of optimal nutritional delivery

and evaluation; and the effects of nutrition on other nutritionally dependent physiologic functions, e.g., wound healing, respiratory performance, and immune function. A method with the ability to accurately measure Caloric expenditure and substrate utilization in a non-invasive manner at the bedside represents an instrument with a wide variety of nursing research and clinical applications.

This validity assessment of clinical indirect calorimetry will be focused on the metabolic gas monitor MGM II (Medicor Inc. Salt Lake City, Utah). The issues of reliability and validity of applicable measurements, constructs, and the efficacy of this device as well as the conceptual components of indirect calorimetry in the acute care setting will be addressed.

Proposed Construct

Theoretical Implications of Indirect Calorimetry

The fundamental purpose of I.C. is the extrapolation of a numerical value representative of resting energy expenditure (REE) in KCal per 24 hours and subsequent determination of appropriate Caloric supplementation. REE is defined as the basal metabolic rate plus energy expenditure from activity. Substrate utilization is also determined as a function of the respiratory quotient (RQ) after analysis by standardized formulas. In terms of the REE, the fundamental reaction that is extrapolated is:

$$C_6H_{12}O_6 + 6H_20 \text{ --- } 6CO_2 + 36 \text{ ATP} + \text{Heat.}$$

The basic premise underlying indirect calorimetry is that by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2) at the whole body level, the rate of cellular oxidation can be indirectly measured. VO_2 and VCO_2 are determined by measuring the difference between inspired and expired oxygen and

carbon dioxide. The difference between these two values represents gas extraction and elimination over time. Further, by taking the ratio of VO_2 to VCO_2, the RQ can be determined and differential substrate calculated from the three indices (VO_2, VCO_2, and RQ). Differential substrate utilization essentially refers to the ratio of protein, fat, and carbohydrate being utilized by the subject at the time of the measurement. In addition to gaseous measurement, urine nitrogen excretion must also be determined to complete the equation since protein is not fully oxidized and urea nitrogen determinations represent the quantity of the metabolic end product of protein metabolism. Measured RQ's in the region of 0.7 are indicative of fat oxidation whereas RQ's around 1.0 are primarily indicative of glucose oxidation and fat synthesis (Ireton-Jones, 1987).

The measurements derived from indirect calorimetry can be used to evaluate current Caloric intake and sufficiency of substrate ratio of the nutrients being administered. The MGM reports, via paper hard-copy, metabolic energy utilization in KCal./24 hours, RQ, and the ratio of protein, carbohydrate and fat utilization as well as a graphic display of the stability of the measurements.

System Description and Function

The MGM samples inspired oxygen from the inspiratory limb of the patients breathing circuit, either the inspiratory circuit of the ventilator or supply side of a tightly fitting face mask. Exhaled gases are sampled from the expiratory circuit of the ventilator or exhaust tubing of the face mask and passed through a 2.8 L. mixing chamber. The sample is then drawn from the outlet port. Gases are passed through zirconium oxide and infrared sensors and measured for O_2 and CO_2 concentrations respectively. Expired flow is measured by an ultrasonic vortex-shedding transducer.

The O_2 sensor has a 120-msec. response time, resolution of .02% O_2, and an accuracy of 1% of reading. The CO_2 sensor has a 100-msec. response time, accuracy of 1% full scale, and a stability better than 1% full scale over 8 hours. The flow meter has an accuracy of 2.5% of full scale, expired flow is displayed at standard temperature, pressure, and density. Barometric pressure is entered via keypad. Auto-calibration cycles are carried out via microprocessor at 1 min. to 1 hour intervals, depending on stability of the sensors, using an established calibration gas (Westenskow, Cutler, & Wallace, 1984).

The resulting measurements (VO_2, VCO_2, and RQ) are subjected to analysis by standardized formulas (Bursztein, Glazer, & Trichet, 1980) to determine percent of carbohydrate, fat and protein contributions.

Counterhypotheses

The reliability and validity of indirect calorimetry can be undermined from a number of sources. Three areas are particularly damaging: first, erroneous interpretation of the concept of REE and measured expenditure; second, subject reactivity; third, deficiency of standards for interpreting data.

Misinterpretation of the concept of resting energy expenditure versus metabolic expenditure is common place in the literature. These two concepts have very distinct meanings and underlying assumptions. Resting energy expenditure assumes just that, a stable resting state in the patient. In the clinical setting patients are often either agitated, restless, sedated, or have decreased levels of consciousness with concurrent consequences for the metabolic measurements. In other words, there are a multitude of factors at play that would make one believe anything but a resting state in a large majority of these patients. Most reports in the literature,

however, refer to this concept as the measurement produced by indirect calorimetry. In reality, indirect calorimetry produces what is termed measured energy expenditure. This term implies no control over factors that may effect metabolic rate at that specific period of time at which the gas measurement is being taken. This point has significant implications for the interpretation and predictability of the energy expenditure values to nutritional requirements, especially in the critically ill population.

The second source that has the potential to decrease validity is subject reactivity. In order to sample gases from a ventilator circuit a number of alterations are required. These alterations include disconnections and reconnections with resultant ventilator alarms, and changes in ventilation patterns for the patient. Although these processes are short in duration and not harmful to the patient, the possibility of apprehension or unwanted stimulation and subsequent effect on measurements cannot be dismissed. In the case of the MGM, reliability measurements may still be produced but what is being measured? Is the measurement a reflection of a stable state that varies to a minor degree over time or a measure of a metabolic rate influenced by short-lived apprehension which will subside over time? In another scenario where measurements are taken by a tightly fitting face mask the consequences of the discomfort of this device are obvious and the validity of concurrent measurements threatened.

The third threat to validity that will be addressed is the lack of standards and knowledge of intervening factors (criterion) required to appropriately interpret the data produced by indirect calorimetry. The first issue in this instance is that interpretation (prediction) of an indirect calorimetry reading involves extrapolating the results of a single measurement of energy expenditure to the Caloric requirement

over a much greater period of time (the interval between subsequent measurements). The second issue is the lack of established standards for a multiple over the measured expenditure that would quantify an appropriate Caloric supply. For example, take the situation of a patient who is stimulated or exercised during a certain amount of time over a days period. An indirect calorimetry measurement is then made at rest. How does one quantify that proportion of the daily metabolic rate that is influenced by activity and subsequently derive an accurate prediction of energy supplementation. Finally, knowledge of factors contributing to a change in metabolic rate and their quantity is as yet unknown and rarely discussed in the literature.

Summary of Existing Evidence for the Construct and Counterhypotheses

Evidence in Support of the Construct

In vitro evaluation of the MGM was performed by Westenskow, Cutler, and Wallace (1984) using a lung model consisting of a pressure ventilator and anesthesia bag coupled with entrained nitrogen and CO_2. Simulation included variations of intermittent mandatory ventilation, positive end expiratory pressure, and fractions of inspired oxygen. The highest errors reported were for VO_2 and the RQ in conjunction with FiO_2's of .80 and were reported at 11.7% and 12.5% respectively. Simulations with PEEP and IMV were conducted at room air concentrations. Theoretically, errors present at higher oxygen concentrations in conjunction with PEEP and IMV would be greater than those noted above. However, in clinical use with oxygen concentrations of 50% or less, error would be confined within 5% (Westenskow, personal communication). Factors present under intensive care

conditions that were not simulated were reported and include, but are not limited to, a patient fighting the ventilator, a leaky endotracheal tube, or an unstable oxygen blender. These are significant considerations when interpreting the meaning of the measurements.

The question of the validity of the equations for derived values of metabolic expenditure and substrate utilization was recently addressed by Westenskow, Schipke, Raymond, Saffle, Becker, Young, and Cutler (1987). Equations from nine different sources were compared using metabolic measurements in 30 ICU patients. Differences produced from these equations averaged 0.8-96 KCal per day suggesting a clinically insignificant difference.

Several questions of the validity of the MGM under clinical conditions were addressed by Nelson, Anderson, and Garcia (1987). A study of 12 patients in an intensive care setting was conducted to quantify validity of the MGM. Three questions were asked: first, what is the correlation between values obtained at the bedside by the MGM as compared with the proven reliability of mass spectrometry? Second, what is the difference in measurement at different levels of FiO_2? Third, what variation in measurements is due to the use of an oxygen blender versus a premixed cylinder of gas? Differences between values obtained from the MGM and mass spectrometry were analyzed by linear regression; p values of $<.05$ were considered significant. No significant differences were detected in minute volume determinations, FiO_2 values, VCO_2, VCO_2, or premixed gas versus blender. Slight but significant variations were noted in $FeCO_2$ (higher in the MGM) and the difference in VO_2 at FiO_2's of .45 versus .21.

Evidence in Support of the Counter-hypotheses

Robertson, Clifton, and Grossman (1984) addressed the issue of the discrepancy of the use of the term REE in indirect calorimetry measurements. In their estimation, reports in the literature commonly used this term when instead they were measuring "measured energy expenditure" (p. 310). This discrepancy may at first seem to be a minor point; however, the interpretation and subsequent clinical use for gas measurements rely on the assumptions implicit in the concept of REE. If a measured energy expenditure is substituted for REE subsequent clinical decisions may be invalid.

Damask, Askanazi, Weissman, Elwyn, and Kinney (1983) studied the relationship between the effects of a relatively minor procedure (muscle biopsy) and concurrent measurements of gas exchange in four patients. Maximum increases of 93% and 103% were found in VCO_2 and VO_2 respectively following the procedure. Mean duration of gas measurement was 10.6 +/- 7.8 (VCO_2) and 11.4 +/- 5.9 (VO_2) minutes. Damask et al. (1983) further remarked on the influence of patient stability by remarking that during a one hour measurement 10-20 L. of O_2 and CO_2 are exchanged. They estimate total body CO_2 stores and O_2 stores at 20 L. and 1 L. respectively. Therefore, they estimate an error factor of 10% for VO_2 and 1% error for VCO_2. Further, most measurements are probably closer to 20 min. in duration and in light of the above statement represent the possibility of a larger degree of error.

The effects of other metabolic depressants, e.g., narcotics or sedatives, are also believed to represent artifact in gas exchange measurements. In many populations of patients these drugs may be administered continuously. Head, McManus, Seitz, Grossman, Staton, and Heymsfield (1984) also commented on

apprehension during the measurement period and subsequent potential for unstable measurement from hyperventilation. They further commented that patient education and practice decreased this incidence. In the critically ill, however, patient cooperation is rarely an attainable goal. Durnin (1978) estimated at least a 7% overestimation of energy expenditure when hyperventilation is present, the attained value for the RQ is greater than 1.0, and Weir's formula is used.

In the clinical validation report of the MGM (Nelson, et al., 1987) it was pointed out that although single isolated measurements may assist in making clinical decisions, multiple measurements are more indicative of the patients true metabolic state. It was also stated that critical illness is a nonsteady state.

Factors in Interpretation

The authors of both reports on the MGM II (Nelson, et al., 1987; Westenskow, et al., 1984) report excellent reliability and validity of this instrument for determining metabolic state. In respect to the accuracy, stability, and reliability, their claims are well documented with only a few, probably clinically insignificant, faults (assuming proper set up and operation). However, the validity of the measurements in terms of the conceptual underpinnings of what exactly is measured and how it is interpreted is questionable. A great deal of effort has been expended to create a state of the art gas measuring device, but little effort has been taken to resolve the critical issues of concurrent and predictive validity of the measurements for use in nutritional management.

Construct Validation Strategies

In order to improve the validity of metabolic measurements for determining current nutritional status and predicting future needs, several points need to be

resolved. First, the measurements must be coupled with quantified factors that would provide the clinician with the guidance to determine the variances in the patient from the measured state over time. Clinical studies of continuous measurements on homogenous groups of patients with concurrent documentation on effects of activity, pharmacologic agents, nursing procedures, and other extraneous stimuli would serve to clarify interpretation of the data. The relatively new advent of factor analytic procedures is a promising method that may be used in this particular instance. By predicting those factors that play a proportionately greater role in their effect on metabolic rate, algorithms can then be deduced by multiple regression analysis and coupled with metabolic readings to enhance prediction.

Methods to reduce subject reactivity must also be devised to minimize effects on metabolic measurements. Such a device has been recently developed but evaluation is still pending. This device consists of a sealed head canopy which is reported to decrease noxious stimuli to the patient. The language of metabolic measurement must also be refined. Deriving useful knowledge from clinical studies using concepts such as REE is tenuous at best, especially considering that critical clinical decisions are based on the findings.

Although all questions of validity and reliability have not been resolved, current instrumentation for indirect calorimetry is capable of precise gas measurements at the bedside and represents a significant advancement in the ability to improve patient outcome through improved nutrition. In comparison to other available methods for determining nutritional needs, indirect calorimetry, even with it faults, is far more precise.

APPENDIX F

MGM II: METABOLIC GAS MONITOR DATA SHEET

MGM/TWO MONITORING RECORD

PATIENT NAME: _____ 07/05/89
PATIENT ID: _____ 9:51
Barometric Pressure 637 mmHg

OXYGEN CONSUMPTION (o) & CO2 PRODUCTION (.) ml/min (STPD)

TIME	V̇O2	V̇CO2	RQ	V̇E	ME C/d	ET CO2 mmHg
9:55	113	289	2.54	9.88	2665	

	gm/d	Cal/d	%
CHO	0	0	0
Fat	216	2043	77
Pro	144	622	23

(UUN = 23.0 gm/d)

9:59	146	350	2.39	11.6	1359	

	gm/d	Cal/d	%
CHO	35	146	11
F S	542	591	43
Pro	144	622	46

(UUN = 23.0 gm/d)

10:03	273	331	1.21	10.9	2039	

	gm/d	Cal/d	%
CHO	289	1208	59
F S	187	204	10
Pro	144	622	31

(UUN = 23.0 gm/d)

10:07	309	329	1.06	10.7	2231	

	gm/d	Cal/d	%
CHO	360	1505	67
F S	95	104	5
Pro	144	622	28

(UUN = 23.0 gm/d)

10:11	344	317	0.92	10.4	2403	

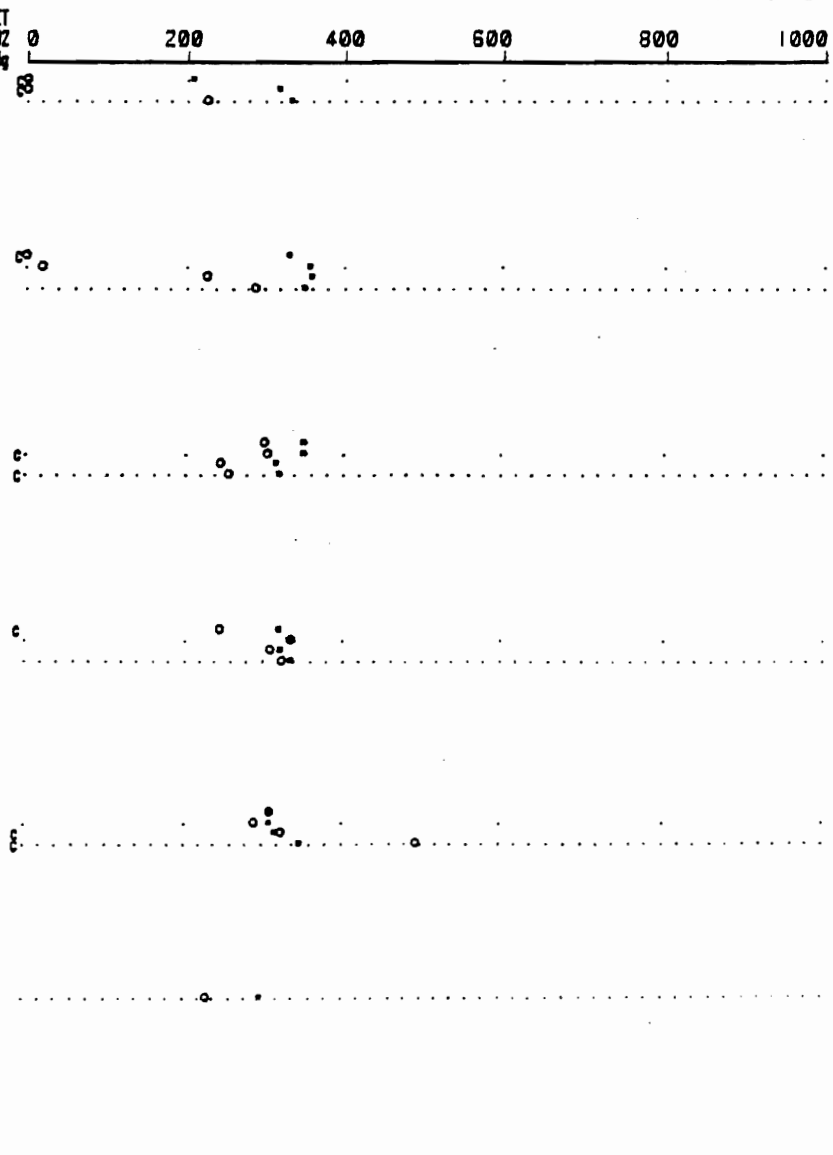
	gm/d	Cal/d	%
CHO	383	1601	67
Fat	19	180	7
Pro	144	622	26

(UUN = 23.0 gm/d)

10:11	231	298	1.28	9.86	1745	

	gm/d	Cal/d	%
CHO	214	895	51
F S	209	228	13
Pro	144	622	36

(UUN = 23.0 gm/d)



APPENDIX G

LISTING OF DEMOGRAPHIC DATA, SEVERITY OF INJURY SCALES AND HOSPITALIZATION STATISTICS

AGE IN YEARS	SEX	APACHEII	ADMIT GCS	FDNGINIT	GCS: ICU DISCHARGE	DAYS IN THE ICU	GCS: DISCHARGE	GOS	HOSPITAL STAY	BEE CALC.
35	F	NO DATA	6	48	6	11	9	1	18	1389
36	M	NO DATA	9	120	11	17	11	3	25	1848
59	F	NO DATA	5	24	9	12	14	2	20	1185
31	M	1	15	72	15	10	15	4	17	1776
31	M	2	14	72	15	3	15	4	5	1722
41	M	2	15	120	15	8	15	3	14	1730
18	M	4	13	168	14	10	15	3	32	1911
23	M	4	12	48	14	4	15	3	10	2225
23	F	7	15	24	15	7	15	3	17	1341
34	M	7	13	96	15	8	15	3	10	2391
59	M	7	15	144	15	6	15	1	10	1758
37	M	8	10	48	11	13	14	2	27	1681
84	M	8	14	48	0	18	0	0	18	1440
12	F	9	12	48	13	13	13	2	17	1255
33	F	9	14	72	15	16	15	3	21	1401
20	F	10	7	48	14	8	14	3	15	1341
17	F	11	9	48	14	10	15	4	11	1397
23	M	11	12	48	14	14	15	2	18	1712
29	M	11	13	72	0	16	0	0	16	2041
19	M	12	8	36	13	4	4	2	7	1675
19	M	12	9	72	15	6	15	3	10	2057
16	F	13	6	24	5	18	9	1	25	1400
16	M	13	8	72	15	4	15	4	8	1674
22	M	13	7	48	11	19	15	3	30	1705
36	M	13	11	48	11	19	14	3	44	1591
45	M	13	8	48	15	7	15	4	12	1439
22	M	14	7	96	14	5	14	3	10	1601
25	M	14	4	24	12	22	14	2	25	1708
31	M	14	12	48	14	15	14	2	19	1936
40	M	14	8	96	13	13	13	2	17	1872
62	M	14	13	96	7	59	13	1	122	1836
7	M	15	7	96	14	13	3	1	64	1722
16	M	15	5	96	10	51	14	2	66	1693
20	M	15	5	24	9	26	9	1	26	1804
27	M	15	7	24	14	13	14	3	14	1741
30	M	15	7	96	14	4	15	4	6	1457
31	M	15	7	48	11	12	14	3	30	1642

FDNGINIT: Time in hours from hospital admission to initiation of feeding. HOSPITAL STAY: Total number of days hospitalized. BEE CALC: Calculated BEE by the Harris-Benedict Equation.

AGE IN YEARS	SEX	APACHEII	ADMIT GCS	FDNGINIT	GCS: ICU DISCHARGE	DAYS IN THE ICU	GCS: DISCHARGE	GOS	HOSPITAL STAY	BEE CALC.
34	M	15	4	24	10	11	10	2	31	1616
37	M	15	6	48	14	15	14	2	23	1549
52	M	15	4	48	0	8	0	0	8	1631
16	M	16	4	72	15	37	15	2	53	1337
18	F	16	6	72	10	21	10	2	24	1529
76	F	16	10	24	11	14	9	1	17	1097
17	M	17	7	24	14	11	2	2	45	1712
18	M	17	5	48	10	30	14	2	36	1957
23	M	17	6	72	10	18	10	2	26	1698
40	F	17	5	48	6	19	6	1	31	1344
14	M	18	6	24	11	8	14	3	15	1688
20	M	18	5	48	11	10	11	1	16	1697
23	M	18	3	72	4	20	7	1	25	1931
30	M	18	3	24	3	14	7	1	28	1801
36	M	18	7	48	6	22	0	0	104	1889
37	M	18	6	48	0	5	0	0	5	1673
43	M	18	3	24	5	19	8	1	24	1546
55	F	18	6	96	0	7	0	0	7	1462
57	M	18	13	144	6	51	6	1	111	1468
21	F	19	4	96	15	25	15	3	27	1351
21	M	19	8	48	10	33	14	2	34	1914
32	M	19	6	48	9	25	9	2	32	1557
37	M	19	5	36	8	6	14	2	23	1675
45	M	19	8	48	8	20	8	1	20	1696
77	M	19	10	24	10	4	0	0	36	1427
83	M	19	14	96	0	9	0	0	9	1447
23	F	20	6	24	14	26	15	2	52	1318
24	F	20	5	60	7	15	15	3	25	1407
24	M	20	10	120	14	6	15	4	8	1792
30	M	20	5	24	14	6	15	3	13	1549
30	M	20	8	48	14	9	15	2	9	2330
31	M	20	3	24	11	17	15	2	37	1694
40	M	20	4	72	11	11	15	2	47	1592
76	F	20	8	96	14	24	15	3	28	1141
86	F	20	10	72	9	12	9	2	19	1107
21	M	21	4	24	10	17	10	2	28	1597
19	M	22	3	48	9	34	10	1	46	2027

FDNGINIT: Time in hours from hospital admission to initiation of feeding. HOSPITAL STAY: Total number of days hospitalized. BEE CALC: Calculated BEE by the Harris-Benedict Equation.

AGE IN YEARS	SEX	APACHEII	ADMIT GCS	FDNGINIT	GCS: ICU DISCHARGE	DAYS IN THE ICU	GCS: DISCHARGE	GOS	HOSPITAL STAY	BEE CALC.
32	F	22	4	24	11	2	15	2	38	1261
34	M	22	4	48	5	23	8	1	31	1665
52	F	22	7	24	0	30	0	0	30	1573
16	M	23	4	48	7	14	7	1	74	1690
19	M	23	4	96	11	18	15	2	27	1896
21	F	23	5	48	11	30	11	1	45	1464
21	M	23	3	48	10	18	15	1	23	2115
22	M	23	4	48	0	11	0	0	11	1822
26	M	23	4	96	14	19	15	3	23	1611
28	F	23	7	96	11	21	14	2	29	1599
71	M	23	6	72	0	45	0	0	45	1844
22	M	24	4	48	7	29	7	1	41	1667
25	M	24	4	48	8	30	8	1	32	1630
26	F	24	5	48	9	22	5	1	34	1518
42	F	24	3	48	14	17	15	3	22	1354
17	M	25	4	24	10	5	10	1	8	1683
18	M	25	3	72	6	30	9	1	35	1745
26	M	25	4	72	8	30	8	1	30	1859
33	M	25	4	48	6	20	6	1	30	1967
18	M	26	3	72	14	8	14	2	14	1930
37	M	26	4	24	6	28	6	1	71	1979
49	M	26	6	72	9	17	14	2	45	1767
17	M	27	4	48	12	10	12	2	10	1699
55	F	27	3	72	7	26	7	1	32	1230
16	M	28	4	72	4	32	11	1	45	1919
31	F	28	3	72	0	8	0	0	8	1502
20	M	31	5	72	8	24	14	2	24	1707

FDNGINIT: Time in hours from hospital admission to initiation of feeding. HOSPITAL STAY: Total number of days hospitalized. BEE CALC: Calculated BEE by the Harris-Benedict Equation.

APPENDIX I

SAMPLE TPN ORDER SHEET

ADULT PARENTERAL NUTRITION ORDERS

MUST BE WRITTEN DAILY — CHECK DESIRED ORDERS

SAMPLE

A. COMPOSITION (for valid order, address each component, limit volume to 1150 ml/bottle):

1. PROTEIN component options (each bottle):

____a. **Standard amino acid solution: 500 ml 8.5% crystalline amino acids = 42 g prot (6.7 g N).**

____b. Renal failure: 300 ml renal failure formula, essential amino acids, 15.7 g prot (2.5 g N).

____c. Custom solution: brand_____; volume_____ml; Concentration _____% AA.

2. CARBOHYDRATE component options (each bottle):

____a. **Standard dextrose solution: 500 ml 50% dextrose monohydrate = 850 non-prot cal., 250 g CHO.**

____b. Standard fluid restricted (e.g., renal failure) solutions: 500 ml 70% dextrose monohydrate = 1190 non-prot cal. 350 g CHO.

____c Custom dextose solution: volume_____ml; dextrose concentration (circle one) 10%, 20%, 50%, 70%.

3. INSULIN component: regular insulin_____units/bottle (if none, so indicate).

4. ELECTROLYTE component options (each bottle):

____a. **Standard electrolyte solution:**

		Usual adult daily infusion:
NaCl:	**35 mEq Na, 35 mEq Cl**	60-180 mEq Na
KH_2PO_4:	**30 mEq K, 15 mM P**	60-180 mEq K, 15-45 mM P
$MgCl_2$:	**5 mEq Mg, 5 mEq Cl**	8-24 mEq Mg
Ca:	**5mEq Ca Gluconate**	4.5-15 mEq Ca

XX____b. Custom electrolyte solution (alone, or in addition to standard). Each bottle:

NaCl	89 mEq	K Acetate	_____mEq
Na Acetate	28 mEq	KH_2PO_4	_____m mole
Na Lactate	_____mEq	$MgSO_4$	10 mEq
NaH_2PO_4	10 m mole	Ca Gluconate	5 mEq
KCl	45 mEq	Ca Chloride	_____mEq

5. VITAMIN component:

____a. **Standard: Multiple Vitamin Solution in first bottle of series.**

____b. Custom preparation (specify):_____

6. TRACE ELEMENT component:

____a. **Standard: Zn 2 mg, Cu 1 mg, Cr 10 mcg, Mn 1 mg, Iodine 75 mcg in ONE bottle daily.**

____b. Supplementary to standard: To a single bottle add:_____

7. OTHER (Cimetidine, heparin, free water, etc.)

B. INFUSION RATE AND START TIME:

1. Infuse at rate of _____ml/hr or _____bottles/day.

2. Route of infusion:____ central, ____ peripheral

C. FAT EMULSION (usual administration 1-7 bottles/week):

____1. No fat.

____2. Infuse 200 ml, 250 ml, or 500 ml (circle) bottle of fat emulsion 10%, 20% (circle) over _____hours (max infusion rate 500 ml of 10% emulsion/4 hrs; min rate 500 ml/12 hrs). Check: _____ 2 bottles same day. (500 ml 10% lipid = 56 g fat, 550 kcal)

D. **TIME, DATE, SIGNATURE: hour _____; date _____; signature _____, M.D.**

IV ADMIXTURE CENTER TELE. EXT. 2244

UNIVERSITY OF UTAH HOSPITAL

PHYSICIAN'S ORDER SHEET

UUH 1011/6-88

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