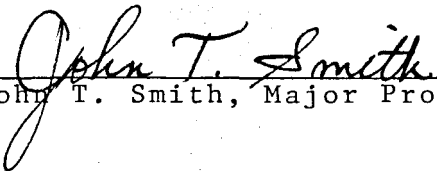
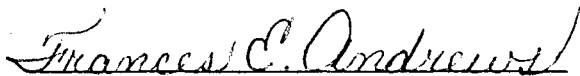


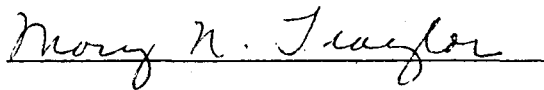
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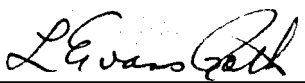

John T. Smith, Major Professor

We have read this thesis
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Graduate Studies and Research

Prognostic Nutritional Index:
Its Usefulness as a Predictor
of Clinical Course

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Elizabeth Fenn Lowe

June 1982

DEDICATION

The author wishes to dedicate this thesis to her husband and son whose unending patience, encouragement, and support were responsible for its completion.

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ABSTRACT

It is of great consequence to be able to predict an individual's risk of clinical complication during hospitalization. The Prognostic Nutritional Index (PNI), which is based upon one's nutritional status, is a method that has been developed for this purpose. The PNI equation is comprised of the following indicators of nutritional status: serum albumin level, serum transferrin level, triceps skinfold thickness, and delayed hypersensitivity. This study was designed to evaluate the usefulness of PNI in predicting clinical course.

The sample was composed of 328 subjects who had been admitted to medical or surgical services of the Veterans Administration Medical Center, Johnson City, Tennessee. The criterion for inclusion in the study was complete nutritional assessment between 1978 and 1981. A PNI was calculated for each subject. Using a retrospective review of subjects' medical records, extent and type of complications was determined. The measure of complication score used in the study could range from 0 - 28.

The mean for the PNI was approximately 45%, indicating that, on average, the risk of clinical complications in this sample was 45% or in the intermediate (40-50%) category. This was the equivalent of a complication score of 8. There was a significant ($p < 0.05$), positive correlation between

PNI and complication score. A positive multiple correlation was found between complication score and the block of variables upon which PNI is based, specifically serum albumin level, serum transferrin level, triceps skinfold thickness, and delayed hypersensitivity. These results support a direct relationship between nutritional status and clinical course. This provides documentation for the usefulness of PNI as a technique for predicting clinical complications based upon nutritional assessment.

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CHAPTER I

INTRODUCTION

In the past decade medical professionals have become increasingly aware of the importance of nutrition in the hospitalized patient. Protein-calorie malnutrition has been observed and documented in patients with various disease entities from every socioeconomic background. Much research has been directed toward a relationship between nutritional status and morbidity and mortality in large series of patients. There is a need for further documentation of correlation between the nutritional status of individuals and suboptimal clinical course. There has been little attempt to predict an individual patient's risk of nutritionally related complications. Such evidence would justify nutritional therapy for those patients at predicted risk of developing complications.

This study was designed to document the usefulness of the Prognostic Nutritional Index (PNI) as a predictor of clinical course in a specific population.

The objectives of the study were:

1. To determine if a correlation exists between nutritional status and clinical complications.
2. To determine if a patient's risk of developing complications can be predicted based upon nutritional assessment.

CHAPTER II

REVIEW OF LITERATURE

I. DEFINING MALNUTRITION

Malnutrition was at one time synonymous with classical vitamin deficiencies which are encountered very occasionally in hospitals. In assessing the nutritional status of the hospitalized patient, one is attempting to identify protein-calorie malnutrition (PCM). This term indicates a diagnostic category that encompasses two specific disease processes: marasmus and kwashiorkor. Marasmus is characterized by severe fat and muscle wastage due to a chronic inadequate intake of calories. The diagnosis is based on a diminished triceps skin-fold thickness, reflecting loss of calorie reserves as fat, and reduced mid-arm muscle circumference, which reflects muscle wasting and protein resorption. The laboratory profile is essentially within normal limits except for an occasional depressed serum albumin. (1)

The diagnosis of kwashiorkor, in contrast, is based largely on laboratory data. Children in underdeveloped countries are often the victims of this disease, but in the United States it is found primarily in adults who are hospitalized by the stress of an acute illness or major surgery and are unable to eat. Fat reserves and muscle mass are usually normal, thus the

deceiving appearance of adequate nutrition. Significant laboratory data include depressed levels of albumin and transferrin with an associated decrease in cellular immunity. Without early correction these symptoms progress to easily pluckable hair, edema, delayed wound healing, and an inadequate defense against infection. A combination of the two forms of PCM, marasmic kwashiorkor, can occur when poor nutrition is superimposed with the stress of surgery or severe illness. Without vigorous nutritional intervention, the results are usually catastrophic (1).

II. PREVALENCE OF MALNUTRITION

Only recently has the prevalence of malnutrition in the hospitalized patient been recognized. Scarcely a decade ago, Butterworth (2) charged that one of the largest areas of unrecognized malnutrition in the United States and Canada could be found in hospitals rather than slums and ghettos. At that time little attention was paid to the nutritionally depleting effect of hospitalization, stress, trauma, and infection. These shocking case histories and accusations led to findings (3) which indicate that one-fourth to one-half of medical and surgical patients who are hospitalized for more than two weeks develop protein-calorie malnutrition at some level. These studies provided the impetus for

instituting nutritional assessment, thus identifying those patients suffering from malnutrition and initiating therapies for its reversal.

The use of accepted standards (3-5) for assessing nutritional status has indicated malnutrition occurs at a rate of approximately 50% in general surgical patients (6). This alarming frequency was found to be true preoperatively and in those patients still hospitalized more than one week after major surgery (7). General medical patients also experienced a high rate of malnutrition, approximately 44% or greater (8). It was found that the indicators of malnutrition varied somewhat between medical and surgical patients. The medical patients exhibited more calorie depletion as indicated by measures of weight/height and triceps skinfold, whereas surgical patients had depleted protein stores as measured by arm-muscle circumference and serum albumin.

A study by Weinsier, et al., (9) which evaluated the nutritional status of medical patients throughout hospitalization, suggests some interesting implications. Using eight nutrition-related parameters, they determined the likelihood of malnutrition. On admission 48% of patients had a high likelihood of malnutrition, which was positively correlated with a longer hospital

stay and an increased mortality rate. A large percentage (75%) of those patients who had normal values for the nutrition-related parameters upon admission, were found to become nutritionally depleted during hospitalization. A greater proportion of patients fell into the depleted range for several of the parameters at final follow-up, as compared to admission. These findings indicate an association between nutritional status and hospital course, with a trend toward declining nutritional status during hospitalization. This process is further complicated if surgery is performed. A mild case of protein-calorie malnutrition can be easily and quickly transformed into a clinically significant state by elective or semi-elective surgery in which there is a delay in wound healing, impairment of immune-defense systems, and a prolonged recovery (10).

III. THE EFFECT OF MALNUTRITION ON MORBIDITY AND MORTALITY

In both medical and surgical patients, malnutrition is well recognized as a substantial factor in increasing morbidity and mortality (11-16). This is most often due to an inadequate intake of nutrients needed to meet excessive demands incurred by stress and injury. Mullen, et al. (11) performed preoperative nutritional and immunological assessment on 64 surgical patients, and then

monitored their hospital course for complications. Of the sixteen factors studied, only serum albumin, serum transferrin, and delayed hypersensitivity were significant predictive indicators of postoperative morbidity and mortality. Patients with a serum albumin level less than 3 g/dl had a two and one-half fold increase in the complication rate. There was a five-fold increase in complications in those patients with transferrin levels below 220 mg/dl. A complication rate of 33% was found in anergic patients, who also had a two and one-half fold increase over patients who were skin test responsive.

In 1977, Meakins and co-workers (12) showed that anergy is a positive factor which can be used to identify surgical patients at risk for developing sepsis and related mortality. The anergic and relatively anergic patients who never exhibited a positive response to skin testing had a mortality rate of 74.4%, whereas those who converted to a positive response had a mortality rate of 5.1% ($p < 0.001$). In another measure of host defense mechanisms, Seltzer, et al. (13) found that an abnormal lymphocyte count denoted a four-fold increase in deaths. They also found a four-fold increase in complications and a six-fold increase in deaths with an abnormal serum albumin. This study, based on admission serum albumin levels and total lymphocyte counts of 500 subjects, reveals that the depression of both albumin and lymphocytes results

in a four-fold increase in complications and a twenty-fold increase in deaths. In surgical patients with abnormal albumin levels the number of complications increased, whereas medical patients with a low serum albumin exhibited an increase in number of deaths. This would suggest that these two parameters be reviewed in all patients upon admission and appropriate therapy initiated for those at risk of developing complications and/or dying.

Using a population of veterans, Reinhardt, et al. (14) demonstrated a linear correlation between the degree of hypoalbuminemia and the subsequent 30-day mortality rate. For all patients the 30-day mortality rate was 24.6%, yet those whose albumin level fell to 2.0 g/dl or below had a mortality rate of 62%.

Mullen and co-workers at the University of Pennsylvania (15) developed a Prognostic Nutritional Index (PNI) using four parameters which had substantial predictive value. The PNI provided a predictive model relating the risk of a postoperative morbid event to a patient's preoperative nutritional status. The assessment was based on serum albumin level, serum transferrin level, triceps skinfold thickness, and reactivity to skin test recall antigens. They found that substantial malnutrition existed in surgical patients and was positively correlated with subsequent morbidity and mortality. As the patient's

predicted risk increased there were significant increases in all classes of complications.

Buzby, et al. (16) evaluated the applicability and validity of the PNI using 100 patients undergoing major gastrointestinal surgery. In a prospective study they compared the predicted risk of complications with their actual occurrence and found that as PNI increased, actual incidence of death, complications, and sepsis increased.

IV. RELEVANCE OF ASSESSING NUTRITIONAL PARAMETERS

There are numerous biochemical, clinical, anthropometric, and immunologic indicators of one's nutritional status. It is necessary to be aware of the value and clinical relevance which each measure portrays. Mullen, et al. (17) attempted to determine those nutritional parameters which would be useful in identifying clinically relevant malnutrition and have significant value in predicting clinical course. Of the 16 nutritional and immunologic variables evaluated, only three correlated with ultimate outcome: a serum transferrin level (TFN) < 220 mg/dl, a serum albumin level (ALB) < 3.0 gm/dl, and delayed hypersensitivity reactivity (DH). These variables, plus triceps skinfold (TSF), were weighted according to their impact on clinical outcome and resulted in the Prognostic Nutritional Index:

$$\text{PNI}\% = 158 - 16.6(\text{ALB}) - 0.78(\text{TSF}) - 0.20(\text{TFN}) - 5.8(\text{DH}).$$

Serum Proteins

The serum proteins, albumin and transferrin, are well recognized as indicators of protein status. These proteins are especially dependent on exogenous intakes of calories and amino acids. A deficiency of these constituents results in depressed synthesis of albumin and transferrin (18). The serum proteins are reduced further as the body loses its protein stores during a semi-starvation state (19). The half-life of transferrin is shorter (6-8 days) than that of albumin (16-18 days), thus transferrin is a more sensitive early indicator of marginal protein depletion (20). Although hypoalbuminemia is not an early indicator of protein-calorie malnutrition, it is the primary factor in its diagnosis and is always a prominent feature in kwashiorkor (21).

In a study (22) of Ugandan children suffering from kwashiorkor, Hay, et al. showed that the serum albumin concentration at admission was closely related to mortality rates. In 1955 Rhoads and Alexander (23) analyzed 102 surgical patients for a correlation between post-operative infection and hypoproteinemia. They determined a correlation between postoperative infectious complications and serum protein concentrations below 6.3 g/100 ml. Almost three decades ago these authors were charging medical professionals to provide appropriate nutritional therapy to meet the "unusual needs" of surgical patients.

In a recent study by Harvey and her co-workers (24) serum albumin was found to be the best indicator of concurrent sepsis and anergy and the best predictor of mortality. Routine assessment parameters were evaluated with respect to ultimate outcome in 282 hospitalized patients. An initial albumin of 2.2 g/dl was associated with a greater than 75% chance of having concurrent anergy and sepsis and dying. It was also demonstrated that the most accurate predictor of improved prognosis was an improvement in delayed hypersensitivity response to recall skin antigens. Young, et al. (25) found preoperative and postoperative patients to have low levels of serum and somatic proteins. In their study of 54 surgical patients and 19 normal individuals, prealbumin and transferrin were highly correlated with most of the 10 parameters used for assessment, and patients with low mean values for these proteins also had low levels for most of the other variables.

Delayed Hypersensitivity

Cellular immunity or cell-mediated immunity is one branch of the very complex immune system. It is an important host defense system against all types of infection. The T-lymphocytes attack specific bacteria and are especially prominent in defense against viruses. A simple, yet reliable test for measuring immunocompetence is delayed hypersensitivity. Standard procedures for skin testing

involve the intradermal injection of a commonly encountered antigen on the inner surface of the forearm. Readings are made from 24-72 hours later, and an induration of 5 mm or more indicates a positive response and normal cellular immune function (26). If the response is negative, the individual is considered to have anergy or a failure of the immune system to function properly. The induration at the site of injection is the result of T-cells mounting a response by reacting to the antigen.

The association between malnutrition and pestilence has been recognized for thousands of years. Malnourished individuals are not only more susceptible to infectious diseases, but the diseases are much more severe than in well-nourished individuals. Infections result in catabolism, thus, further compromising nutritional status and leaving the person even more susceptible to infection (26).

In 1974 Law, Dudrick, and Abdou (27) studied the relationship between nutritional status and host defense mechanisms. Their data strongly suggest an impairment of humoral and cell-mediated immunity in the malnourished individual. They emphasize the importance of repleting malnourished surgical patients prior to surgery in order to restore adequate nutrition and improve depressed immune parameters. In an earlier study by the same authors (28) the thymus dependent immune system (cell-mediated immunity) was impaired in patients with protein-calorie malnutrition, and nutritional repletion

improved their immunocompetence. Chandra (29) found cutaneous hypersensitivity to be distinctly impaired in malnourished children. These data confirm the clinical and epidemiologic belief that malnutrition alters the immune response of the host.

A study of 21 hospitalized patients with adult protein-calorie malnutrition (30), determined by reduced levels of serum albumin and transferrin, found them to have depressed total lymphocytes and a loss of cell-mediated immunity after being maintained on 5% dextrose and water for seven days or more. Spanier, et al. (31) determined that anergy is associated with an erosion of the body cell mass and a relative expansion of the extracellular mass, characteristics typical of malnutrition. This correlation between malnutrition and the presence of anergy led the authors to support the use of total parenteral nutrition (TPN) in anergic patients.

Bistrian and his co-workers (32) assessed cellular immunity in adults with marasmus and determined that skin test responsiveness was impaired in the presence of recent weight loss to less than 85% of the standard weight/height ratio and a serum albumin > 3 gm/dl. Their findings confirmed the sparing effect of marasmus on vital functions dependent on protein metabolism. This form of adaptation was not present in hypoalbuminemic malnutrition, i.e. kwashiorkor-like syndrome. A study (33) was performed on laboratory animals to determine the effect of protein nutrition on cell-mediated

immunity. In normal rats neither a synthetic amino acid diet, nor a pure carbohydrate diet was found to maintain immunocompetence. The synthetic amino acid diet did not restore depressed cell-mediated immunity in protein depleted animals. The protein sparing effect of calories from carbohydrate and fat was substantiated by data from this study.

Data from separate studies (12,34) indicated a correlation between anergy and mortality and sepsis. When serial skin tests remained abnormal or worsened, mortality rate increased. These results showed that failure of the delayed hypersensitivity response can identify patients who are at risk for developing sepsis and related mortality.

Many studies have been performed on patients with cancer to determine its relationship to anergy. In 1974, Hersh and co-workers (35) performed serial studies of immunocompetence in adult patients with acute leukemia. They showed a strong correlation between immunocompetence at the start of treatment and a good prognosis. They concluded that therapeutic modalities which restore immunocompetence or prevent its decline will improve both the remission rate and the duration of remission of patients with acute leukemia. In this disease, immunocompetence related to a good prognosis, while anergy related to a poor prognosis.

Cancer patients who are undergoing chemotherapy, surgery, or radiation for the malignancy are usually found to be immunologically incompetent since these procedures are

immunosuppressive. Anergy in these patients may be secondary to malnutrition, which often characterizes the cancer patient (36). Copeland, et al. (37) suggested that nutritional repletion may restore cell-mediated immunity. They found that response to chemotherapy and adequate nutritional status were correlated. There were fewer surgical complications and no mortality in those patients who received hyperalimentation both preoperatively and postoperatively, yet tumor growth was not measurably enhanced by the nutritional solutions. Another study by the same authors (38) indicated a better response to chemotherapy and fewer surgical complications in immunocompetent patients than in those patients who were immunosuppressed. They also found a positive, significant ($p < 0.05$) correlation between skin test reactivity and the other parameters used in nutritional assessment, specifically weight loss, serum albumin, and total lymphocyte count.

Harvey and her co-workers (39) found similar results in 161 cancer patients who were nutritionally assessed prior to receiving therapy for their malignancies. Those patients whose immune function was preserved or improved had a lower mortality rate than those who remained anergic or become anergic during therapy. They concluded that detection and treatment of protein-calorie malnutrition prior to or in conjunction with oncological treatment was associated with a decrease in mortality rate. Dominion, et al. (40) investigated other causes of anergy in 111 cancer patients with solid tumors.

Their results indicated that impaired immune function appeared to be mainly caused by aging and by malnutrition due to progression of the cancer.

Triceps Skinfold Thickness

Triceps skinfold thickness is a commonly used anthropometric measure of nutritional assessment (4). This parameter reflects total body fat by measuring the thickness of the subcutaneous fat ring, and is a good indicator of body fat since approximately 50% of the adipose tissue is located in the subcutaneous area (41-42). As fat is the main storage form of energy in the body, triceps skinfold can be considered a valid index of the body's energy stores (43).

Diminished triceps skinfold does not reflect protein nutriture or adult kwashiorkor but is a constant characteristic of marasmus (21). Faintuch, et al. (44) determined that triceps skinfold as well as other anthropometric measurements show striking decreases after operative injury. The measurements showed more dramatic changes as the degree of surgical trauma increased.

V. PURPOSE OF THE STUDY

It has been documented by the foregoing review of literature that abnormal measures of serum albumin, serum transferrin, and delayed hypersensitivity are statistically related to increased morbidity and mortality in large series of patients. Mullen, et al. (11, 15, 17) developed the Prognostic

Nutritional Index (PNI) as a reliable method for predicting one's risk of clinical complications by using the four parameters of nutritional assessment which have predictive value, specifically serum albumin level, serum transferrin level, delayed hypersensitivity, and triceps skinfold thickness. The purpose of this study is to replicate the work of Mullen and his co-workers and to determine the usefulness of the PNI in predicting clinical outcome in a specific population.

VI. SCOPE AND LIMITATIONS OF THE STUDY

This retrospective study was undertaken to determine a correlation between nutritional status (as reflected by the PNI) and clinical complications, and to determine if a patient's risk of developing complications can be predicted based upon nutritional assessment. The effects of nutritional support were not analyzed in a serial fashion in this study. The subjects had been admitted to the surgical and medical services of the Veterans Administration Medical Center, Johnson City, Tennessee, and had complete nutritional assessments performed at some point during hospitalization(s) between 1978 and 1981. Although there was no standardization as to the time of assessment, clinical course was reviewed only subsequent to the date of nutritional assessment until follow-up assessment, discharge, or death. There was no analysis by type of therapy received or by the disease process of the subjects.

The relationship between nutritional status, primary disease process, and morbidity and mortality is complex, multifactorial, and analytically difficult. The author recognizes the influence of nonnutritional factors on the variables used in the PNI, as well as in the development of complications. The study does not intend to ignore this relationship, but will investigate only the association between the four nutrition-related parameters and clinical course.

CHAPTER III

METHODS

I. GENERAL PLAN

The sample was composed of 328 nutritional assessments from 240 patients who were admitted between 1978 and 1981 to the medical and/or surgical services of the Veterans Administration Medical Center, Johnson City, Tennessee. Many of the patients had multiple nutritional assessments performed over the course of one admission or several different admissions to the hospital. A physician's written order in the medical record was the established protocol for initiating nutritional assessment, thus there was no uniformity as to the point(s) during hospitalization that the patient's nutritional status was assessed. Those patients who were assessed more than once had at least four weeks between assessments. Henceforth, reference made to subjects will pertain to the 328 nutritional assessments, since each is treated as a separate entity. There were 324 males and 4 females ranging in age from 32-86, mean age of 59.

The subjects who were on the surgical service were undergoing various types of surgical procedures, both major and minor. Some were receiving medical therapies or oncological therapy in the form of radiation and/or chemotherapy prior to, following, or in place of surgery.

The criterion for inclusion in the study was a complete nutritional assessment. The subjects had been referred to the Nutrition Support Team for assessment and recommendations, and this team with assistance from laboratory and nursing personnel was responsible for performing all nutritional assessments.

A retrospective review of each medical record was performed by the author, who had no other patient responsibilities, to determine the extent and type of complications encountered during hospitalization. Clinical course and complications were evaluated and categorized as follows: recovery, response to therapy, septic, thromboembolic, healing, hemorrhagic, respiratory, cardiac, psychiatric, gastrointestinal, renal, central nervous system, hepatic, and miscellaneous, eg. anemia, mucositis, edema, etc. Confirmation of complications was based upon written evidence in the chart, such as laboratory studies, positive cultures, radiographic confirmation, or clinical assessment. Each category of complication was subdivided for scores: 0 = no evidence of complication; 1 = minor complication; 2 = major complication (Appendix A). Thus, more complications incurred, the greater the score, with the maximum total score being 28.

II. PROCEDURES AND EQUIPMENT

Serum Albumin (ALB)

Ten ml of fasting blood were drawn into a vacutainer tube for determining serum albumin level. The standard

method for albumin is based on the binding of the dye brom-cresol green (BCG). It is one of eighteen values reported by the SMA-18 procedure using the Technicon SMA II System,¹ and is measured in terms of g/dl.

Serum Transferrin (TFN)

Serum transferrin is calculated by the following formula:

$$\text{TFN} = (\text{TIBC} \times 0.8) - 43$$

TIBC (total iron-binding capacity) is the sum of serum iron and saturated iron-binding capacity, therefore both of these values must be determined prior to obtaining the value for TIBC. Ten ml of fasting blood were drawn into a vacuum-tainer for this test.

The procedure was performed using the Ferro-Chek II Test² which is a rapid Colorimetric test for serum iron and iron-binding capacity. Once the TIBC is obtained by laboratory personnel, the Nutrition Support Team dietitian calculated the transferrin for use in the nutritional assessment. Transferrin is measured in terms of mg/dl.

Delayed Hypersensitivity (DH)

Skin testing was performed using an injection of each of four recall antigens: mumps skin-test antigen³ (undiluted),

¹Technicon SMA II System, Technicon Instruments Corp., Tarrytown, NY 10591.

²Ferro-Chek II Test, Hyland Diagnostics, Division of Travenol Labs, Inc., Deerfield, IL 60015.

³Eli Lilly and Company, Norcross, GA 30091

Candida⁴ (1:100 dilution), Streptokinase-Streptodornase (Varidase⁵ 1:100 dilution), Tuberculin Purified Protein Derivative⁶ intradermal strength (PPD, 5 test units/dosage). Varidase recall antigen was found to produce severe reactions in many patients. Its use for skin testing was discontinued as of October, 1980, at the facility where this research was undertaken. It has since been removed from the market.

Syringes were prepared containing 0.1 ml of each antigen solution immediately prior to injection. The antigens were injected intradermally into the volar surface of the forearm of each subject in the study. The skin tests were administered by the Nutrition Support Team nurse (R.N.), but were measured and recorded at 24, 48, and 72 hour intervals by ward nurses (R.N.). Using the same scale for reading the skin-tests as did Mullen, et al. (17), no reaction at the site of injection was recorded as 0, indicating anergy; reactivity of < 5 mm = 1, indicating relative anergy; reactivity of ≥ 5 mm = 2, or normal immune function.

⁴Hollister-Stier Laboratories, P. O. Box 19957, Atlanta, GA 30325.

⁵Lederle Laboratories, Chamblee, GA 30341.

⁶Parke-Davis, P. O. Box 4928, Atlanta, GA 30302.

Triceps Skinfold Thickness (TSF)

The triceps skinfold thickness was measured by standard techniques using the Ross caliper⁷ and the Lange caliper⁸. The measurement was made at the midpoint of the upper arm between the tip of the olecranon process of the ulna and the acromion process of the scapula. The caliper measures in mm the thickness of the subcutaneous layer of fat while the arm is hanging freely. Two readings were made and the mean value was reported.

III. PROGNOSTIC NUTRITIONAL INDEX CALCULATION

The values of these four clinically relevant indicators of nutritional status were applied to the formula as developed by Mullen, et al. (11, 17) for the Prognostic Nutritional Index (PNI), thus deriving a PNI for each subject:

$$\text{PNI} = 158 - 16.6(\text{ALB}) - 0.78(\text{TSF}) - 0.20(\text{TFN}) - 5.8(\text{DH}).$$

IV. STATISTICAL ANALYSES

Data collected were analyzed at the East Tennessee State University Computing Center using the Statistical Package for Social Sciences (SPSS) (45), release 9. The subroutines within SPSS that were used were frequencies, crosstabs, new regression, and scattergram.

⁷Ross Laboratories, Inc., 625 Cleveland Ave., Columbus, OH 43216.

⁸Cambridge Scientific Industries, Inc., P. O. Box 265, Cambridge, MD 21613.

CHAPTER IV

RESULTS

I. REPORT OF DATA

The mean value for each variable is reported in table 1. The mean age of the 328 subjects was 59, ranging between 32 and 86 years of age. The mean serum albumin was 3.7 g/dl, and ranged between 2.0 and 4.9 g/dl. The mean value for triceps skinfold thickness was 9.2 mm, and ranged between 1.4 and 29.0 mm. The mean value for serum transferrin level was 193.0 mg/dl, and ranged between 61.80 and 354.0 mg/dl. The mean for the Prognostic Nutritional Index (PNI) was 44.63 and ranged between 2.14 and 102.54. This indicates that the average risk of developing clinical complications in this population was 44.63%. The mean complication score for the subjects was 8 and ranged between 0 and 25. Thus, on average, the subjects in this sample had a 45% risk of clinical complications. This translates to an 8 on the measure of complications used in the study.

There were 134 subjects (40.9%) of the sample who were anergic when evaluated for delayed hypersensitivity, as shown in table 2. Forty-three subjects, or 13.1% of the population, had a reactivity level of 1, indicating < 5 mm of induration at any skin test site. A reactivity level of 2, indicating ≥ 5 mm of induration at any skin test site, was observed in 151 subjects or 46% of the sample. There were 194 subjects

TABLE 1
DESCRIPTION OF VARIABLES

Variable	Mean	$\pm$	Standard Deviation	Minimum	Maximum	Norms ¹
Age (yrs.)	59	$\pm$	9	32	86	-
Albumin (g/dl)	3.70	$\pm$	0.57	2.0	4.9	>3.5
Triceps Skinfold Thickness (mm)	9.27	$\pm$	4.94	1.4	29.0	12.5 male 16.5 female
Transferrin (mg/dl)	192.85	$\pm$	52.16	61.80	354.00	>200.00
PNI (%)	44.63	$\pm$	21.36	2.14	102.54	-
Complication Score	8.24	$\pm$	6.35	0	25	-

¹Kaminsky, M. V. and Winborn, A. L. (1978) Nutritional Assessment Guide. Midwest Nutrition Education and Research Foundation, Inc., pp. 1-21, Abbott Laboratories, North Chicago, IL.

TABLE 2
FREQUENCY OF DELAYED HYPERSENSITIVITY

Degree of Reactivity	Absolute Frequency (n = 328)	Relative Frequency (%)
0	134	40.9
1	43	13.1
2	151	46.0

(59.1%) who mounted a response to skin test antigens of some degree, compared to 134 subjects (40.9%) whose immune systems were found to be incompetent or anergic.

II. CORRELATIONS AMONG VARIABLES

Pearson Product-Moment (PPM) Correlation Coefficients (46) were calculated to determine if a linear relationship existed between the following: PNI and age; complication score and PNI; complication score and age; complication score and serum albumin level; complication score and triceps skinfold thickness; and, complication score and serum transferrin level. These correlations are reported in table 3. As PNI is a function of albumin, transferrin, triceps skinfold, and delayed hypersensitivity, determining a correlation between these is not meaningful. It was not important to measure age with each variable, since age and PNI were measured. There was no significant correlation between PNI and age or between complication score and age. This indicates that there is no linear relationship between age and nutritional status or age and clinical course.

There was a significant ($p < 0.05$) positive correlation between complication score and PNI which indicates that as PNI increases complications also increase. Significant ($p < 0.05$) negative correlations exist between complication score and serum albumin and between score and serum transferrin, indicating an inverse relationship, i.e. as serum

TABLE 3
PEARSON PRODUCT-MOMENT CORRELATION COEFFICIENTS AMONG VARIABLES

Variable	PNI	Age	Serum Albumin	Triceps Skinfold Thickness	Serum Transferrin Level
Complication Score	0.36*	0.03	-0.40*	-0.08	-0.25*
PNI		0.04			

* (p < 0.05)

proteins decrease, complications increase. There was no significant correlation between complication score and triceps skinfold thickness.

Since delayed hypersensitivity is categorical in nature, calculation of Pearson's correlation coefficient is not meaningful. Therefore a Chi-square test was performed to determine if a relationship existed between complication score and delayed hypersensitivity, as shown in table 4. This test indicates a significant ($\chi^2 = 10.60$, $df = 4$, $p < 0.05$) relationship between complication score and delayed hypersensitivity. The findings demonstrate that the majority (50.6%) of the subjects who had a low score or few complications were immunocompetent as indicated by reactivity of 2. Of those subjects with a high score or many complications, the greatest percentage (63.2%) showed anergy or failure to respond to skin testing, indicated by 0 reaction.

Table 4 also reveals that 174 subjects (53%) had complication scores in the 0 - 8 (low) range; 116 subjects (35.4%) had complication scores in the 9 -16 (intermediate) range; 38 subjects (11.6%) had complication scores in the 17 - 25 (high) range. In the intermediate range of complication scores 57.8% of the 116 subjects showed some immune function by reacting to skin tests to some degree. Of the 38 subjects in the high range of complication scores, only 36.8% mounted any immune response, while 63.2% were anergic. Of the 134 subjects who were anergic, 45.5% were in the low range of

TABLE 4
Chi-Square Contingency Table for Categorized
Complication Scores Versus Reactivity Categories

Categorized Complication Scores							
		0 - 8 (LOW)	9 - 16 (INTERMEDIATE)	17 - 25 (HIGH)			
Skin Test Reactivity Categories	0	Count	61	49	24	134	Row Total
		Row %	35.1	42.2	63.2		
		Column %	45.5	36.6	17.9	(40.9)	(Row %)
		Total	18.6	14.9	7.3		
	1	Count	25	14	4	43	Row Total
		Row %	14.4	12.1	10.5		
		Column %	58.1	32.6	9.3	(13.1)	(Row %)
		Total %	7.6	4.3	1.2		
	2	Count	88	53	10	151	Row Total
		Row %	50.6	45.7	26.3		
		Column %	58.3	35.1	6.6	(46.0)	(Row %)
		Total %	26.8	16.2	3.0		
		Column Total	174	116	38	328	Row Total
		(Column %)	(53.0)	(35.4)	(11.6)	(100.0)	(Row %)

scores, 36.6% in the intermediate range of complication scores, and 17.9% in the high range of complication scores.

The variables which comprise the PNI were entered into a forced entry multiple regression procedure to determine whether a multiple correlation existed between complication score and the block of four variables. It was found that there was a positive multiple correlation ($R = 0.41$) between complication score and the PNI variables. By calculating R^2 , it was determined that this correlation accounts for 17% of the variability among the complication scores. Another interpretation of this is that PNI provides 17% of the information needed to be able to predict complication scores perfectly. Therefore, 83% of the variability in predicting complications is not accounted for by these nutritional parameters.

III. DEVELOPMENT OF PNI EQUATION BASED ON SAMPLE DATA

Based on these data and the procedures described by Mullen (11,17), it seemed meaningful to generate an equation for PNI which was specifically based upon this sample of observations. The regression coefficients for the equation generated by the multiple regression procedure are as follows:

$$\text{PNI} = 86.80 - 14.68(\text{ALB}) + 0.18(\text{TSF}) - 0.02(\text{TFN}) - 1.66(\text{DH}).$$

CHAPTER V

DISCUSSION

I. ANALYSES OF DATA

Compared to accepted standards reported by Kaminsky, et al. (47), the mean value for serum albumin of the patients in the study was within the normal range, while the mean values for serum transferrin and triceps skinfold thickness were below normal (table 1, page 24). Some authors (11, 41, 48, 49) have found that discrepancies exist among some of the "accepted standards" for nutritional assessment norms. Although the norm for serum transferrin is reported as > 200 mg/dl, Mullen and associates (11) observed a five-fold increase in complications when serum transferrin levels were < 220 mg/dl. Based upon his findings, the subjects in the present study, on average, could be expected to incur clinical complications in light of the depressed mean serum transferrin level.

There is an on-going controversy (41, 48, 49) in the literature concerning the validity of anthropometric norms in the nutritional assessment of hospitalized patients. The norms for triceps skinfold are based upon Jelliffe's standards (5) which were designed for use in developing countries. The reference population for deriving these standards is not indicated. In 1974 Frisancho (41) developed percentiles for triceps skinfold based on a cross-sectional sample of over

12,000 white subjects from the Ten State Nutrition Survey (50). In 1979 Gray & Gray (48) compared Jelliffe's standards to those measurements obtained from 5000 adults in the Ten State Nutrition Survey. The existence of marked discrepancies between the two sets of data has led the authors to recommend the use of the more recent standards for the United States. In a letter to the editor of the American Journal of Clinical Nutrition Bistrian (49) reiterates the importance of general agreement on standards for anthropometry. He also recommends using the 5th percentile from the Ten State Nutrition Survey rather than the median value to identify the abnormal.

Mullen and Buzby (17) classified PNI in the following manner: high risk = $\text{PNI} \geq 50\%$; intermediate risk = $\text{PNI} = 40 - 49\%$; low risk = $\text{PNI} < 40\%$. Using this same classification, the subjects in this sample, on average, were in the intermediate risk group (table 1, page 24). A mean PNI of approximately 45% would seem reasonable for this sample of veterans. One may anticipate a lower mean PNI in a community hospital setting where the cases are rather simple in nature. A research facility or teaching hospital would likely have a higher mean PNI, as the majority of patients would be referrals due to the complex nature of a disease process or its treatment. This Veterans Administration hospital would be on a level between the two afore-mentioned settings. Cases and treatment would range from the simplest in nature

to the most difficult and complex. Due to various socioeconomic factors of this veteran population, the nutritional status, as measured by PNI, would have likely deteriorated to a greater degree than would be expected in the general population. Thus, it is not surprising to have the data indicate that these subjects have an intermediate risk of clinical complications. This 45% risk is translated into a complication score of 8, based upon the scale for measuring complications within this study (Appendix A).

II. CORRELATIONS AMONG VARIABLES

The data collected from this sample indicate that a linear relationship does not exist between age and nutritional status, as measured by PNI, or between age and clinical complications (table 3, page 27). One would expect no significant correlation between age and PNI, as nutritional status is in no way related to an individual's age. It is very plausible to have a poorly-nourished young person, as well as a well-nourished older person and vice versa. However, it is generally accepted that advanced age is accompanied by an increased risk of clinical complications. The lack of significant correlation between age and complications in this sample does not support this statement.

The data reported in table 3 reveal significant ($p < 0.05$) positive correlations between complication score and serum albumin and between score and serum transferrin.

These correlations support the results of many other studies which indicate that as serum protein stores are diminished, clinical complications increase (11-14, 22-24, 51). Although serum transferrin has a shorter half-life than does serum albumin, the latter protein has been found to be the best single indicator of the incidence of morbidity and mortality (24). Ching, et al. (51) found that response of serum albumin to nutritional support is a good indicator of ultimate outcome in critically ill surgical patients. However, evaluation of the serum proteins as well as the cellular immune function is the most accurate measure of predicted postoperative morbidity and mortality (11).

Approximately 41% of the subjects in this sample were anergic when evaluated for delayed hypersensitivity (table 2, page 25). The Chi-square test (table 4, page 29) indicated that a significant ($p < 0.05$) relationship existed between delayed hypersensitivity and complication score. These data support existing evidence which indicates a positive correlation between protein-calorie malnutrition and immune competence (27-32, 37).

Serum protein depletion is a result of inadequate intake of protein and calories to meet the increased requirements placed by stress and injury. In a study by Meakins, et al. (12), it was found that when serum albumin was depressed less than 3.0 g/dl, there was concurrent depression of cell-mediated immunity which resulted in impaired host

defense mechanisms. This branch of the immune system is thought to relate to tumor resistance, transplantation immunity, and resistance to fungal, viral, and intracellular bacterial infections. Anergy is associated with an increased incidence of morbidity and mortality from infectious diseases (18-20).

Table 3 (page 27) also reveals a positive significant ($p < 0.05$) correlation between PNI and complication score. Since PNI is based upon nutritional parameters, this indicates a correlation between clinical course and nutritional status. The direction of the correlation is such that as nutritional status worsens or PNI increases, complications also increase. Those individuals who are determined to be at risk of clinical complications based upon nutritional assessment, should be provided therapy to improve their nutritional status.

It is well recognized and accepted that nutritional rehabilitation reverses protein-calorie malnutrition and replenishes diminished body stores. Thus, many studies (27, 28, 30, 31, 37, 51, 52) support the use of nutritional therapy, either by enteral or parenteral routes, in order to restore adequate nutrition, which will in turn improve the serum proteins and the cellular immune function. This is particularly vital prior to major therapeutic regimens, such as surgery, chemotherapy, or radiation. These procedures are very debilitating to one's nutritional status and immune competence, unless measures are taken to provide adequate

nutrition prior to, during, and following therapy. Mullen, et al. (52) determined that adequate preoperative nutritional repletion significantly ($p < 0.05$) reduced postoperative complications, major sepsis, and mortality.

III. MULTIPLE CORRELATION

By using a forced entry multiple regression procedure, a positive multiple correlation ($R = 0.41$) was found to exist between complication score and the block of four variables, specifically serum albumin, serum transferrin, triceps skinfold, and delayed hypersensitivity. The procedure was comprised of the data collected in this study for each of the variables. By calculating multiple correlation squared ($R^2 = 0.17$), it was found that this correlation accounts for 17% of the variability among the complication scores. The square of the correlation between complication score and PNI ($r^2 = 0.13$) reveals that 13% of the variability among the complication scores is accounted for by this correlation.

The variation between these two percentages is explained in part by the difference in the data upon which they were based. The PNI, as developed by Mullen, et al. (11, 17), was derived from data collected from a specific population. Thus, the PNI, as calculated for each subject in this sample, was actually designed for another group of individuals. Therefore, the square of the correlation between complication score and PNI ($r^2 = 0.13$) is a reflection of the correlation

between the nutritional status and clinical complications of subjects in this study, based on a formula derived from data from another sample. The multiple correlation squared ($R^2 = 0.17$) reflects the correlation between clinical complications and the data collected specifically from this sample. It is reasonable that the correlation which uses only data generated by this study will account for more of the variability among complication scores of these subjects. That is, 17% of the information needed to perfectly predict complication score is accounted for by data generated by this study, but 83% of the variability is not accounted for by these four nutritional parameters. This would be related to the myriad of nutritional and nonnutritional factors which influence nutritional status and clinical course.

D. DEVELOPMENT OF PNI EQUATION BASED ON SAMPLE DATA

The multiple regression procedure was also utilized to produce a PNI based upon this sample of observations. Using these data and procedures described by Mullen, et al. (11, 17), an equation was generated which is designed uniquely for this sample. The new equation is as follows:

$$\text{PNI}(\%) = 86.80 - 14.68(\text{ALB}) + 0.18(\text{TSF}) - 0.02(\text{TFN}) - 1.66(\text{DH}).$$

Although the constant and regression coefficients vary somewhat from those developed by Mullen (page 22), there are also similarities between the two equations. The magnitude of the coefficients varies, but their relative weights are the same.

Mullen, et al. (11) demonstrated the relative impact of the four predictive variables in influencing ultimate outcome by calculating PNI for a hypothetical, well-nourished individual using normal values for the variables. The calculation is as follows:

$$\text{PNI (\%)} = 158 - 16.6(\text{ALB}) - 0.78(\text{TSF}) - 0.20(\text{TFN}) - 5.8(\text{DH})$$

$$\text{Serum albumin (ALB): } 4.8 \text{ g/dl} \times 16.6 \quad 79.7$$

$$\text{Triceps skinfold (TSF): } 14 \text{ mm} \times 0.78 \quad 10.9$$

$$\text{Serum transferrin (TFN): } 250 \text{ mg/dl} \times 0.20 \quad 50.0$$

$$\text{Delayed hypersensitivity (DH): } 2 \times 5.8 \quad \underline{11.6}$$

$$\text{Total} \quad \sim 152.0$$

$$\text{Hence, PNI} = 158 - 152 = 6\%$$

That is, a well-nourished individual with normal values for the four variables still has a predicted risk of 6% that complications will be encountered during hospitalization.

The same normal values were applied to the new equation developed from this sample in order to determine if the predicted risk is similar.

$$\text{PNI (\%)} = 86.80 - 14.68(\text{ALB}) + 0.18(\text{TSF}) - 0.02(\text{TFN}) - 1.66(\text{DH})$$

$$\text{Serum albumin (ALB): } 4.8 \text{ g/dl} \times 14.68 \quad 70.5$$

$$\text{Triceps skinfold (TSF): } 14 \text{ mm} \times 0.18 \quad 2.5$$

$$\text{Serum transferrin (TFN): } 250 \text{ mg/dl} \times 0.02 \quad 5.0$$

$$\text{Delayed hypersensitivity (DH): } 2 \times 1.66 \quad \underline{3.3}$$

$$\text{Total} \quad 76.3$$

$$\text{Hence, PNI} = 86.60 - 76.3 = 10.5\%$$

That is, a well-nourished individual in this sample, who had normal values for the variables, has a predicted risk of 10.5% that complications will be encountered during hospitalization.

The PNI equation as developed by Mullen, et al. (11, 17) has been shown to be consistent across populations, as the same relationships held true under replication. These results indicate that the PNI is a useful tool for predicting the percentage of complications that would likely occur during a clinical course. Thus, it is possible to identify those patients at predicted risk of complications based upon the four nutritional parameters which comprise the Prognostic Nutritional Index.

CHAPTER VI

SUMMARY

The primary purpose of the study was to evaluate the usefulness of the Prognostic Nutritional Index (PNI) in predicting clinical course in a specific population. This was accomplished by determining the relationship between nutritional status and clinical complications.

There was a positive, significant ($p < 0.05$) correlation between PNI and complication score. The four parameters which comprise PNI are recognized and accepted as standard measures of nutritional status. Therefore, this correlation, in effect, supports a direct relationship between nutritional status and clinical course. That is, as one's nutritional status worsens, more complications would be encountered clinically, whereas, a well-nourished individual could expect to incur fewer complications.

A positive multiple correlation ($R = 0.41$) was found to exist between complication score and the block of four variables upon which the PNI is based. By calculating R^2 , it was determined that this correlation provided 17% of the information needed to perfectly predict complication scores. Considering the many nutritional and nonnutritional factors which influence nutritional status and clinical course, it is meaningful to have accounted for 17% of the variability among complication scores. Thus, results of the study

indicate that it is possible to adequately predict a patient's risk of developing clinical complications by way of nutritional assessment.

These findings were also utilized to generate an equation for PNI, based upon the data, which is designed uniquely for this population. The relative weights of the coefficients within the equation are very similar and the relationships hold true under replication. This supports the work of Mullen and associates (11, 17) in that the PNI was found to be a useful tool for predicting the rate of complications based upon individual nutritional status.

The results of this study indicate that nutritional status had a direct relationship to clinical course as measured by complication score. This evidence lends support and justification for the use of nutritional therapy, via enteral or parenteral routes, in those patients who are at predicted risk of complications as determined by nutritional status. Nutritional support will improve their nutritional status and return nutritional assessment parameters toward normal levels. However, it cannot be inferred from this that morbidity and mortality will be reduced solely by reversing protein depletion and restoring immune competence. This question remains to be answered by ongoing studies which would provide objective data as to the effectiveness of nutritional support. Although quantifiable data are lacking in this area, clinical experience with total

parenteral nutrition has generated the consensus of opinion that perioperative nutritional support is effective and often indicated.

It would be meaningful to design a prospective study using this population to evaluate the applicability and validity of the PNI equation which was generated by this data. It would also be of interest to conduct serial measurements of nutritional assessment and determine the relationship(s) between response to nutritional repletion and clinical course. The effect of total parenteral nutrition on ultimate outcome could also be evaluated in such a study.

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LITERATURE CITED

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APPENDIX

APPENDIX A
COMPLICATION SCORING SHEET

NAME _____ SS# _____ Primary DX _____
DATE _____ ALB _____ TSF _____ SKIN TEST _____ PNI _____

_____ 0 Recovered
_____ 2 Died

RESPONSE TO THERAPY (SURGERY, DRUG, RADIATION)

_____ 0 None
_____ 1 Minor (Wound, UTI)
_____ 2 Major (Wound, Septicemia, Pneumonia)

THROMBOEMBOLIC COMPLICATIONS

_____ 0 None
_____ 1 Minor (Phlebitis)
_____ 2 Major (Phlebitis, Pulm. Emboli, Periph. Emboli, Graft Thrombosis)

HEALING COMPLICATIONS

_____ 0 None
_____ 1 Minor (Wound seroma)
_____ 2 Major (Wound dehiscence, Fistula, Anastomosis, Decubiti, Fx)

HEMORRHAGIC COMPLICATIONS

_____ 0 None
_____ 1 Minor (Wound, Ecchymosis)
_____ 2 Major (Wound, Op-site, DIC)

RESPIRATORY COMPLICATIONS

_____ 0 None
_____ 1 Minor (Atelectasis, Pneumonitis)
_____ 2 Major (Atelectasis, Pneumonia, Insufficiency, ARD, Edema)

CARDIAC COMPLICATIONS

_____ 0 None
_____ 1 Minor (Arrhythmia)
_____ 2 Major (Arrhythmia, MI, Failure)

PSYCHIATRIC COMPLICATIONS

_____ 0 None
_____ 1 Minor (Personality, Confusion)
_____ 2 Major (Combative, Psychotic)

GASTROINTESTINAL COMPLICATIONS

_____ 0 None
_____ 1 Minor (Prolonged Ileus, Impaction, Emesis, Diarrhea)
_____ 2 Major (Bleeding, Obstruction, Fistula, Anastomosis)

RENAL COMPLICATIONS

_____ 0 None
_____ 1 Minor (UTI)
_____ 2 Major (Failure or Insufficiency)

CNS COMPLICATIONS

_____ 0 None
_____ 1 Minor (Delirium)
_____ 2 Major (CVA, Coma)

HEPATIC COMPLICATIONS

_____ 0 None
_____ 1 Minor (Mild Jaundice)
_____ 2 Major (Failure)

MISCELLANEOUS COMPLICATIONS

_____ 0 None
_____ 1 Minor (Parotitis, Pancreatitis)
_____ 2 Major (Pancreatitis, Hepatitis)

_____ TOTAL SCORE

VITA

Elizabeth Fenn Lowe was born in Johnson City, Tennessee, on December 25, 1951. She attended public schools in that city and graduated from Science Hill High School in June, 1970.

She received the Bachelor of Science degree in Home Economics from The University of Tennessee in June, 1974, majoring in Food Science, Nutrition, and Food Systems Administration and completing the Coordinated Undergraduate Program in Dietetics. She became a Registered Dietitian in 1975.

From June, 1974 to May, 1976, the author worked as a clinical dietitian at Johnson City Memorial Hospital. She was a Nutritionist II with the Tennessee Department of Public Health from May, 1976 to July, 1980. She accepted a part-time position as Nutritionist with the University Physicians' Practice Group in August, 1980, which she held until the birth of a son in December, 1980. She is a member of the American Dietetic Association and the Tennessee Dietetic Association. She is married to Kenneth S. Lowe, and they reside in Johnson City, Tennessee.

She enrolled in the Graduate School of The University of Tennessee in January, 1979, via the off-campus program. She received the Master of Science degree from The University of Tennessee with a major in nutrition in June, 1982.