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Improving Estimation of Resting Energy Expenditure in Seriously Injured Individuals

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Abstract

Although providing appropriate levels of energy and nutrients is essential for healing, there is no consensus in the literature regarding the optimal method to predict resting energy expenditure (REE) in seriously injured individuals, and no equation has previously been developed or validated solely with that population. This study sought to determine which of five previously developed equations provided the most accurate estimate of REE when compared to measurement by indirect calorimetry. In addition, the study attempted to adjust those existing equations to improve their adequacy, and to develop new equations specifically from and for seriously injured individuals.

Using a retrospective design, the data from 106 measurements on 83 subjects from a single trauma center in the Midwest were collected, and REE was estimated using the Harris-Benedict, Mifflin-St. Jeor, Ireton-Jones 1992, Ireton-Jones 2002, and Penn State equations. Bias, precision, and limits of agreement were determined using the method of Bland and Altman, and biases were compared using ANOVA by linear mixed model. The best performer was the Harris-Benedict equation, with a bias of -248.1 kcal; it predicted REE within 10% of the measured REE in 39.6% of the subjects and within 500 kcal/day of measured REE in 70.5% of the subjects. An omnibus F-test determined a significant difference in the Bland-Altman bias of the five equations, with $F (4, 328) = 603.77, p < 0.0001$. Post-hoc analysis using the Scheffé correction demonstrated all pairwise comparisons were significant at $p < 0.001$. Also using the linear mixed model, bias-predicting equations were developed for all five equations by multiple regression. Finally, two completely new equations were developed using the same data and regression method with one equation containing weight, height, age, sex, and an intercept, and the second equation containing BMI, age, sex, and an intercept.
Only one of the five terms in the first (weight/height) equation was statistically significant, but three of the four terms in the second (BMI) equation were significant.

Finding the Harris-Benedict equation most adequate in this population agrees with several previous studies, although none had previously used ANOVA to determine differences between the equations tested for adequacy. Using regression to predict Bland-Altman bias, and then using the equation generated as a correction factor to decrease bias in an existing estimation equation, also had not previously been attempted. The method of correction by bias estimation, as well as the two new equations generated by this study, need to be validated in independent samples.
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A project like this is never undertaken in a vacuum. So many people have helped along the way that I’m not quite sure where to begin, but here goes.

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Dedication

If we are lucky, life presents us a small glimmer of love, concern, and support to carry us through. I have been blessed with such, and dedicate this work to those without whom I would be and have so much less:

The love of my life, Ronni, who has accepted me and loved me unconditionally for the last thirty years. I cannot put my feelings for her into words but she knows what they are. Sweetheart, I love you – and I WILL cook for you now.

My father, Ralph Lee Hicks, who left us when I was seventeen, and never got to see me blossom. Dad, this is for you in many more ways than you know.

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And finally, baruch ha-Shem, in this Pesach season, my eternal awe and gratitude to El Elyon, G*d Almighty. Mi camocha ba’aelim Adonai?
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Chapter I

Problem and Significance

Traumatic injury and obesity are twin epidemics affecting American society in the 21st century. In 2000, more than 50 million Americans experienced a medically treated injury, with lifetime costs of $406 billion: $80 billion for treatment and $326 billion for lost productivity (Corso, Finkelstein, Miller, Fiebelkorn, & Zalooshnja, 2006). In the same year, approximately 1.7 million hospital discharges (or 620 per 100,000 population) had a primary diagnosis of such an injury (Greenspan, Coronado, MacKenzie, Schulman, Pierce, & Provenzano, 2006). According to the 2003-04 National Health and Nutrition Examination Survey (NHANES), a nationally representative survey of the US population, 17.1% of children and adolescents and 32.3% of adults are obese, having a body mass index (BMI) greater than or equal to 30, and morbid obesity (BMI ≥ 40) is present in 2.8% of males and 6.9% of females (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal, 2006).

When serious injury occurs to individuals with obesity, the problems of each are compounded. Obesity may be an independent risk factor for complications and death after a traumatic injury, with the highest increase in morbidity and mortality among those with BMIs ≥ 35 (Byrnes, McDaniel, Moore, Helmer, & Smith, 2005). Obese patients are more likely to need mechanical ventilation, and their length of stay in the ICU and in the hospital can be increased. A prospective study (Bochicchio, Joshi, Boccichio, Hemna, Tracy, & Scalea, 2006) identified obese patients in a level I trauma center as having twice as many infections as leaner ones, with significantly increased numbers of ventilator, Foley catheter, and central venous catheter days. Obese patients
can also be at greater risk of post-injury multiple organ failure than those of optimal weight (Ciesla, Moore, Johnson, Burch, Cothren, & Sauaia, 2006).

The focus of this inquiry is on the estimation of resting energy expenditure (REE) in seriously injured individuals, many of whom are also obese. Following is a discussion of the theoretical foundations pertinent to the study.

**Conceptual Framework**

The proposed study is grounded in physiological theories of injury and obesity. Both conditions have metabolic consequences: (1) injury causes a drastic increase in energy and protein requirements and can result in significant protein catabolism, and (2) obesity may result in a decrease in energy expenditure, possibly related to the greater proportion of fat mass relative to fat-free mass.

**Metabolic Consequences of Serious Injury**

For more than 20 years, serious injury has been understood to cause a systemic response in the human organism (Cerra, 1987). Classically, the response has been categorized into two phases, ebb and flow, with the ebb phase lasting approximately 24 hours, until normovolemia and skeletal stability are achieved (Smith & Mullen, 1991). Hyperglycemia then begins, corresponding with the initiation of maximal fuel mobilization in the body. Once the ebb phase passes, the flow phase begins, characterized by tachycardia, low-grade fever, and increased urinary nitrogen excretion. Hypermetabolism with catabolism ensues and lasts for five to seven days.

Recently, a different way of conceptualizing the response to stress and trauma has been suggested. This systemic response is triphasic, having three driving forces: neurologic stimulation, immunologic stimulation, and anabolic endocrine stimulation. The beginning of the neurologic period corresponds with the classical ebb phase,
demonstrating vascular response to neurological stimulation involving adrenomedullary discharge, vasoconstriction leading to ischemia, anaerobic glycolysis with lactate production, and decreased energy expenditure (Aller, Arias, Sanchez-Patan, & Arias, 2006). Subsequent vasodilation with reperfusion, along with the hypoxia-stimulated release of inflammatory mediators such as prostaglandins, thromboxanes, and leukotrienes, causes capillary leak and movement of intravascular fluid into the interstitial space (Rankin, 2004). The latter has previously been seen as the onset of the classical flow phase.

The second part of the triphasic response is immunologic in nature, involving infiltration of the damaged tissues by inflammatory cells and formation of a fibrin-vibronectin-fibronectin matrix (Aller et al., 2006). The resulting acute phase protein production by the liver requires a large increase in the circulating amino acid pool, which is met by skeletal muscle catabolism. This skeletal muscle catabolism is stimulated by pro-inflammatory cytokines such as tumor necrosis factor $\alpha$, which increase lysosomal breakdown and calcium release into the cytosol, and activate the ATP-dependent ubiquitin proteasome pathway (Langhans, 2002). In addition, the activation of hormone-sensitive lipase by circulating catecholamines increases the rate of lipolysis, and growth-hormone- and epinephrine-induced insulin antagonism hampers peripheral glucose uptake (Glasgow & Herrmann, 2006).

The third, anabolic phase of the response to injury does not occur until healing begins (Aller et al., 2006). Until that time, the hypermetabolic, hyperglycemic response described above requires specialized nutrition support that involves neither overfeeding nor underfeeding the patient (Pi-Sunyer, 2000).
Metabolic Consequences of Obesity

Obesity brings its own set of variations from typical energy needs. On the one hand, resting metabolic rate (RMR) may be higher in obese subjects than in thinner ones, both in total (Felig, Cunningham, Levitt, Hendler, & Nadel, 1983; Halliday, Hesp, Stalley, Warwick, Altman, & Garrow, 1979) and per kilogram of lean body mass (Hoffmans, Pfeifer, Gundlach, Nijkrake, Ophuis, & Hautvast, 1979). This increase in RMR has been demonstrated over the entire spectrum of body size, from 6% to 60% body fat (Garrow & Webster, 1985). On the other hand, postprandial thermogenesis (i.e., the caloric cost of eating) may be lower in obese individuals (Kaplan & Leveille, 1976), and some studies suggest that metabolic rate drops and remains lower after attempts at weight loss (Heshka, Yang, Wang, Burt, & Pi-Sunyer, 1990; Weigle, Iverus, Monsen, & Brunzell, 1988), although data are mixed (Wadden, Foster, Letizia, & Mullen, 1990; Wadden, Foster, Stunkard, & Conill, 1996). There are also data to suggest that obesity per se can cause a drop in metabolic rate (Martin et al., 2007).

Some of these changes may be artifactual, due to the relatively metabolically inert nature of adipose tissue, and since fat-free mass (FFM) is the best predictor of caloric needs (Wang, Heshka, Heymsfield, Shen & Gallagher, 2005). In fact, one study found that fat mass causes an increase in RMR of only 17% as much as an equivalent mass of FFM (Hodges, 2004). In contrast, a recent investigation examining changes in RMR after six months of caloric restriction found that a six-month sustained reduction of caloric intake, with or without an increase in physical activity, produced a statistically significant decrease in RMR (Martin et al., 2007).
Where Do Injury and Obesity Meet?

Unfortunately, there is no clear line of demarcation between optimal weight, overweight, and obese individuals. The National Institutes of Health definitions are based on Body Mass Index (weight in kilograms divided by height in meters squared); these definitions are commonly used in clinical practice and research. However, it is not known at what point in the continuum of weight status the metabolic effects of obesity begin. Therefore, one must study the changes along the entire spectrum from optimal weight to obesity.

Summary of Conceptual Framework

A review of the available theoretical models describing the physiologic changes in injury and obesity suggest that significant surgical or non-surgical trauma causes increased metabolic demands through neurologic activation resulting in increased sympathetic outflow; immunologic activation resulting in inflammation and release of cytokines that cause, among other manifestations, loss of thermoregulatory control and hyperpyrexia; and endocrine activation resulting in increased protein catabolism and urinary nitrogen loss. Obesity and increased proportion of fat mass may cause decreased metabolic demands by down-regulation of basal metabolic rate in response to multiple episodes of starvation by dieting and decreased metabolic activity of adipose tissue relative to other tissues, especially muscle, brain, heart, and kidney.

Although the metabolic effects of injury and increased proportion of fat mass are known, both physiologic stress of injury and metabolic changes due to adiposity are continuous phenomena. No firm line has been demonstrated indicating where either hypermetabolism of injury or metabolic changes of adiposity begin relative to the
normal state. Arbitrary distinctions between underweight, normal weight, overweight and obesity are not valid when examining changes occurring along such a continuum.

All of these theoretical considerations have an impact on nutrition support in seriously injured individuals who are overweight or obese. The potential for injury stress and increased adiposity to drive nutritional needs in opposing directions leaves the clinician with little guidance in predicting their combined effects.

Nutritional Support in Serious Injury and Obesity

Two factors create the need for specialized nutrition therapy in seriously injured patients: (1) the potential for nutritional depletion and/or muscle breakdown stemming from the need for large quantities of free amino acids for healing, and (2) the need for adequate calories to minimize the use of amino acids for hepatic gluconeogenesis (Frankenfield, 2006; Todd, Kozar, & Moore, 2006). Exogenous glucose does not completely suppress gluconeogenesis, so overfeeding of carbohydrate can result in hyperglycemia, and significant hyperglycemia correlates with greater morbidity and mortality (Cresci, Gottschlich, Mayes, & Mueller, 2007).

Underfeeding the injured patient can lead to progressive protein-calorie malnutrition, and cumulative energy deficit may increase hospital length of stay or complication rates. On the other hand, overfeeding calories exacerbates the hyperglycemic response to stress and can result in hepatic steatosis. Overfeeding may also delay weaning from mechanical ventilation because it causes increased carbon dioxide production. Hyperglycemia from overfeeding can also enhance proteolysis and protein depletion. In addition, overfeeding protein can result in azotemia (Plank & Hill, 2003).
When the injured individual is also overweight or obese, other factors come into play. Individuals who are both obese and injured have a relative decrease in blood flow to metabolically active tissue compared to those with lower BMIs, and slower recovery. One study demonstrated increased length of stay and heightened risks of sepsis, acute respiratory distress syndrome, and acute renal failure in severely injured obese patients (Balzberg, Wo, Demetriades, & Shoemaker, 2007). When underfed, obese individuals with serious injury mobilize more protein and less fat, and therefore are at higher risk for skeletal and visceral protein loss than thinner individuals (Jeevanandam, Young, & Schiller, 1991). This metabolic paradox may be due to the decreased insulin sensitivity associated with obesity, compounded by the insulin resistance related to injury (Plank & Hill, 2003). Thus, having an appropriate estimation of caloric demand, thereby avoiding both excessive and insufficient feeding, may be even more important in obese patients than in injured patients of lower weight.

Predicting Caloric Needs

In order to prevent both underfeeding and overfeeding, it is necessary to determine the individual patient’s caloric needs. However, to discuss caloric needs, some terms must be explained. Basal metabolic rate (BMR) reflects energy usage at rest and without food over a short measurement period, whereas basal energy expenditure (BEE) describes that energy usage over 24 hours. Resting metabolic rate (RMR) is energy usage at rest but not fasting, and REE is RMR extrapolated over 24 hours. Because BMR, RMR, and REE are all used in the literature to reflect energy needs, they can be considered approximately equivalent, especially in the target population for this study, who are frequently continuously fed by enteral or parenteral means. Further explanation can be found in Appendix A.
In the healthy, weight-stable person, caloric intake must equal total energy expenditure, which is a combination of BEE, energy required for digestion and absorption of food, and energy required for activity. Two methods are available for estimating caloric needs: measurement by indirect calorimetry, and prediction by equation.

**Measurement by indirect calorimetry.** The gold standard for determining RMR is indirect calorimetry: the collection of exhaled gases, and determination of the oxygen and carbon dioxide concentrations contained in them. The exhaled gas concentrations are then compared with the inhaled gas mixture, producing a measurement of oxygen consumption and carbon dioxide production by the test subject. Oxygen consumption and carbon dioxide production are directly related to metabolic rate, and can be converted to kJ/min or kcal/min by a simple equation contained in the memory of the indirect calorimeter (Lee & Nieman, 2007). With hospital inpatients, continuous nutrition is often present, but the metabolic cost of that nutrition is ignored because the metabolic increase can be considered negligible (Haugen, Chan, & Li, 2007). In such continually fed subjects, REE is considered equivalent to the total energy requirement, since any change in REE from stress or the absorption and digestion of food is continually present (da Rocha, Alves, & da Fonseca, 1996).

Indirect calorimetry is not without limitations. The apparatus is expensive (from $30,000 to $70,000 per unit), and a skilled operator is required. The calorimeter must be calibrated before every reading, and each reading can take up to 30 minutes (Ireton-Jones & Jones, 1998). Also, if the fraction of inspired oxygen the patient is receiving is over 60%, the calculation routine that computes REE in the calorimeter has unacceptable levels of error (Haugen et al., 2007). Some authorities mandate
concurrent collection of a 24-hour urine specimen for urine urea nitrogen, since estimating urinary nitrogen losses lends increased precision to the estimation, but others note that the difference is less than 10% and may not matter in a clinical setting (da Rocha et al., 1996).

*Estimation by equation.* When indirect calorimetry is unavailable, prediction equations are used to estimate caloric requirements. The first prediction equations were developed by Harris and Benedict in the early 1900’s (Harris & Benedict, 1919), and their use continues until today. The Harris-Benedict (H-B) equation was developed primarily on young, healthy individuals whose lifestyle was much more active than the typical person in the 21st century (Frankenfield, Muth, & Rowe, 1998). More than 150 other equations have subsequently been derived, in samples differing from Harris and Benedict’s subjects in age, weight, ethnicity, and state of health (Lee & Nieman, 2007; Reid, 2007). In a published systematic review, the Evidence Analysis Working Group of the American Dietetic Association (ADA) suggested the Mifflin-St. Jeor equation was the most accurate for healthy individuals of average and higher weights (Frankenfield, Roth-Yousey, & Compher, 2006). In their online practice guideline, however, the ADA specifically recommended *against* using the Mifflin-St. Jeor equation in the critically ill ("Critical illness evidence-based nutrition practice guideline," 2006). Equations, then, may be variably accurate in different states of health.

When developing predictive equations to estimate needs in illness, two strategies are possible. One strategy begins with the estimation of caloric needs in healthy subjects, then multiplies the estimate by a “stress factor” intended to reflect the increase in REE due to the illness or injury. The second strategy involves performing a regression analysis on the measurements obtained from subjects with the pathologic
processes of interest in order to develop an estimation equation specific to the corresponding population (Frankenfield et al., 2004).

A number of issues exist, however, with all predictive equations for use in illness (Reeves & Capra, 2003). Multipliers (stress factors) have been proposed to allow for increased energy needs in illness, but they are not standard, nor is there a consensus of when the multipliers are required. Also, there are so many equations available that clinicians have difficulty determining which equation is most appropriate in a specific patient group.

Various professional associations have made recommendations based on their own analyses. The American Society for Parenteral and Enteral Nutrition suggests using the 1990 Mifflin-St. Jeor equation (Wooley & Frankenfield, 2007), but the American College of Chest Physicians eschews equations altogether and recommends a simple 25 kcal/kg of current body weight (Cerra et al., 1997). The Eastern Association for the Surgery of Trauma, in their practice management guidelines for nutritional support in seriously injured patients, does not express a preference, and only mentions the Harris-Benedict equation in passing (Jacobs et al., 2003). A recent systematic review suggests that no equation adequately predicts energy needs in seriously ill individuals, but that the Harris-Benedict equation with a 1.1 stress multiplier is the most accurate (Boullata, Williams, Cottrell, Hudson, & Compher, 2007). The ADA Evidence Analysis Working Group disagrees, recommending the Penn State equation for both normal weight and obese patients who are critically ill (Frankenfield et al., 2007).

**Study Purpose and Research Questions**

Given the foregoing, the purpose of this study was to determine the optimal method for estimating caloric requirements in seriously injured, mechanically ventilated
patients, when compared to measurement by indirect calorimetry. The specific research questions are:

1) In mechanically ventilated, seriously injured subjects, do any of the following candidate equations yield an energy requirement within 500 kcal/day for individual subjects, when compared to measurement by indirect calorimetry:
   
   a. Harris-Benedict;
   
   b. Mifflin-St. Jeor;
   
   c. Ireton-Jones for obese patients;
   
   d. Ireton-Jones for ventilated patients;
   
   e. Penn State?

2) In mechanically ventilated, seriously injured patients, is it possible to modify any of the four candidate equations to increase precision and decrease bias with the addition of any or all of the following variables: mode of mechanical ventilation, use of sedatives, use of analgesics, use of vasopressors, severity of injury, or BMI?

3) Is it possible to construct an equation with greater precision and less bias using BMI, age, sex, and any of the candidate variables in question 2?

The literature review in the next chapter will help narrow the choices of prediction equations to test by describing previous attempts at validation, and will clarify some measurement issues.
Chapter II

Review of Pertinent Literature

Depending on the source, between 140 and 200 published equations are reported to exist for predicting non-protein caloric requirements when measurement is unavailable or impractical (Lee & Nieman, 2007; Reid, 2007). Even with the availability of bedside calorimetry, the expense of the instrument, the time required for measurement, and the training necessary for staff have made routine use difficult (Frankenfield, Roth-Yousey, & Compher, 2006). Prediction equations have remained the backbone of nutritional assessment, especially when specialized nutritional support is needed.

However, to discuss the existing studies comparing the gold standard, indirect calorimetry with predictive equations, some explanation of indirect calorimetry is necessary. The measurement of energy expenditure dates back to the 1700s, when Antoine Lavoisier was able to determine the amount of heat and carbon dioxide produced by a pig (Webb, 1991). The first studies were done by direct calorimetry, which measures the actual heat given off by the body, by enclosing the subject in a sealed room with heat sensor capability. By the beginning of the 1940s, direct calorimetry had given way to indirect calorimetry in which the heat of metabolism is derived mathematically from the amount of oxygen consumed and carbon dioxide produced by the subject.

Indirect Calorimetry

Indirect calorimetry became economically feasible on a wide scale in the late 1970’s with the development of portable and relatively affordable measuring devices. The proliferation of these devices, in turn, contributed to the explosion of development
Estimation by Prediction Equations

The use of equations to estimate energy expenditure carries its own group of assumptions and requisites. Implicit in the use of the parameters in the equation is the notion that these parameters have a static relationship to energy expenditure, unaffected by other variables that may influence energy requirements (McClave, Snider, & Ireton-Jones, 2002). Potential variables that may affect energy needs in the trauma population include:

1. time after injury (reflective of the phase of the metabolic response);
2. presence of infection;
3. glucose intolerance or frank diabetes;
4. degree of glucose control;
In addition, there are sources that suggest that the formulae for predictive equations may be incorrectly reported in some studies, in which case it is difficult to determine whether the investigators simply reported an incorrect equation or if they actually used an incorrect equation (McClave et al., 2002).

Statistical Tests Used to Compare Measurements

When an instrument and a predictive equation are compared for equivalence, ultimately the practitioner wants to know whether the equation gives an accurate estimate. This estimate must be free of bias (systematic error), and have maximal precision and minimal measurement error (Waltz, Strickland, & Lenz, 2005). The combination of minimum bias and maximum precision means that a given estimation has the greatest chance of being congruent with the measured value for that individual. However, predictive equations have commonly been constructed using multiple regression from data from a group of initial subjects, increasing the potential for error in each individual estimate (Bradfield, Huntzicker, & Fruehan, 1970). The importance of understanding the performance of a predictive equation in individual cases, rather than simply comparing group means, is so great that the American Dietetic Association’s recent systematic review of literature regarding these equations disqualified any study that did not report a measure of individual performance (Frankenfield et al., 2005).

In the following review of literature, the most frequently reported measure of predictive performance in individual cases is the limits of agreement procedure devised by Bland and Altman (1986). Bland-Altman analysis, developed specifically for
comparison between two methods of measurement of the same variable, provides definitions of bias and precision relative to that process. The mean of the individual differences between measured and predicted values is the bias. The standard deviation of the bias is termed precision, and the 95% confidence interval around the bias defines the limits of agreement.

These definitions are specific instances of more generalized concepts in the theory of measurement. In this theory, every measurement contains both the true value of the variable and some quantity of error, which can be broken down into systematic error and random error. Bias, in general terms, is equivalent to systematic error: a constant deviation between the true value and the measured value (Williams, 2008). Precision, in general terms, reflects the consistency between individual measurements; the more consistent the measurements, the greater the precision. Both ideas are subsumed in the concept of accuracy, which is the correspondence between the true value and the measured value (Stoker, 2008). Further clarification can be found in Appendix A.

The limits of agreement demonstrate how much potential inaccuracy the equation allows in individual determinations. If the limits of agreement do not contain zero, the bias is statistically significant. Using limits of agreement is more informative than using intraclass correlation, which was often reported previously as a measure of performance in individual predictions (Bland & Altman, 1990). The Bland-Altman procedure works best when REE determinations are multiple and simultaneous (Bland & Altman, 1999).
Structure and Criteria for Literature Review

This chapter integrates the findings of an extensive literature search using both MEDLINE and CINAHL; the Cochrane database and SCOPUS were consulted but did not contribute any additional references. Search parameters included “basal metabolic rate,” “calculated basal metabolic rate,” “resting energy expenditure,” “calculated resting energy expenditure,” “predictive equations,” and “indirect calorimetry.” Investigations having only subjects under 18 years of age, and works not published in English or French were excluded. The initial search produced only 40 pertinent studies, but examination of the bibliographies from those studies yielded more than 50 additional papers.

To be included, articles either reported the development of a prediction equation, or documented an attempt to validate one or more prediction equations in a sample differing from those from whom the equation was developed. For studies carried out on inpatients, at least a subset of subjects had to be mechanically ventilated and/or recovering from surgical or non-surgical injury. Studies with samples comprised solely of subjects with significant burn injuries (>20% of body surface area) were excluded. Sixty-seven studies met the inclusion criteria and will be discussed here.

The review is organized into four sections. The first section describes the work in developing predictive equations using subjects of optimal weight. It includes critiques of the Harris-Benedict (H-B) equation, and discusses the three additional equations that have been most frequently tested for accuracy in optimal-weight adults. The second section reviews the development and validation of equations using subjects having a body mass index (BMI) ≥ 30. The final section concentrates on the development and validation of equations using critically ill, seriously injured, and/or mechanically
ventilated subjects. Studies validating a given equation are reported along with the initial developmental work on that equation.

**Estimating REE in Individuals of Optimal Weight**

Harris and Benedict focused on optimal-weight individuals, as did a number of other investigators throughout the twentieth century. This section will discuss the pioneers in estimation of energy demands, and others whose investigations were limited to optimal-weight subjects.

*Harris and Benedict and other pioneers.* The seminal work of Harris and Benedict (1918) was originally an attempt to support or refute earlier studies relating basal metabolism to body surface area (duBois & duBois, 1916). Harris and Benedict measured ventilation by means of tubes inserted in the nose, or by the change in oxygen and carbon dioxide concentration in the air in a closed chamber, to determine normal metabolic rates. They then compared these rates with those of individuals with diseases and disorders such as diabetes, goiter, and fever (Frankenfield, Muth, & Rowe, 1998). The study sample consisted of 136 men, 103 women, and 94 newborns, and the two scientists found no relationship among minimum pulse rate, height, and body weight, but a “low but significant positive correlation” among minimum pulse rate, gas exchange, and heat production (Harris & Benedict, 1918, p. 371). Two equations, developed using multiple regression, related basal energy expenditure (BEE) to weight, height, and age, with separate coefficients and constants for men and women. Greater variance was explained by the equation for men ($R^2 = 0.75$) than by the equation for women ($R^2 = 0.53$).

The final equations (Harris & Benedict, 1919, p. 227) were
for men:
\[
\text{BEE (kcal/d)} = 66.4730 + 13.7516(\text{wt. in kg}) + 5.0033(\text{ht. in cm}) - 6.7550(\text{age})
\] (1)

for women:
\[
\text{BEE} = 655.0955 + 9.5634(\text{wt. in kg}) + 1.8496(\text{ht. in cm}) - 4.6756(\text{age}).
\] (2)

Publications using expanded databases (Benedict, 1928; Harris & Benedict, 1919) enabled modification of the equations to increase the explained variance to \(R^2 = 0.78\) for men and \(R^2 = 0.68\) for women, and expanded the age range of subjects. These modifications neither substantively changed the form of the equations nor significantly improved their accuracy.

Other early researchers produced guidelines for determining whether a measured metabolic rate was within normal limits. Not long after the appearance of Harris and Benedict’s monograph, two researchers from the Mayo Foundation published a study using 8,614 subjects measured between 1917 and 1922 (Boothby & Sandiford, 1922). Instead of reporting a formula for prediction, the 1922 article contained contrasts between measured BMR in their subjects and that estimated by the Harris – Benedict (H-B) equations. The researchers found that their measured values were approximately 5% higher than the H-B estimations. A few years later, the same Mayo Clinic laboratory produced a nomogram that could be used to estimate whether an individual’s measured BMR was within normal limits (Boothby, Berkson, & Dunn, 1936). Their definition of normality was based on a bell curve, and was expressed in kcal per square meter (m\(^2\)) of body surface area per hour.
The kcal/m²/hr form was maintained by some researchers as late as the 1950’s, when a Swiss investigator produced a mechanical device, called the Metabocalculator (Fleisch, 1951). Modeled after a slide rule, the Metabocalculator required the operator to line up the subject’s weight, height, and age. The operator could then read from the device either the subject’s estimated BMR, or the variation of the subject’s measured BMR from normal values.

A British study measuring 2,301 subjects from 3 to 80 years of age also reported BMR in terms of kcal/m²/hr. The researchers noted that this process implied a constant relationship between heat output and surface area, an implication that may not have been universally correct (Robertson & Reid, 1952). An attempt to fit the data to a curve yielded a fifth-power exponent, and even when reduced to natural logarithms the formula would have been very difficult to use before the era of the personal computer and personal digital assistant. Therefore, the researchers translated the formula values in kcal/m²/hr into a table, specific for gender and age.

Harris-Benedict validation in individuals of optimal weight. The H-B equations, the Mayo Foundation nomogram, the Metabocalculator, and the Robertson-Reid table were used in subsequent validation studies; in fact, the H-B equations were studied dozens of times against samples with widely varied compositions. This section discusses studies carried out to confirm the work of Harris and Benedict in healthy, non-obese subjects.

Early criticisms of Harris and Benedict’s work were conceptual in nature, contesting whether age, height, weight, and gender were appropriate parameters to use in the estimation of metabolic rate. Various investigators suggested that lean body mass (Cunningham, 1980), body cell mass (Roza & Shizgal, 1984), or a power function of
body weight (Kleiber, 1932) would be more appropriate bases for the calculation of estimated metabolic rate. In Kleiber’s equation, lean body mass and body cell mass were indirectly obtained (i.e., lean body mass from total body water, and body cell mass from exchangeable body potassium). In both cases, total body water was calculated, adding the potential for error with each conversion of terms.

Several critiques suggested other parameters that better estimated metabolic rate, especially fat-free mass (FFM) (Cunningham, 1991; Mifflin, St. Jeor, Hill, Scott, Daugherty, & Koh, 1990). More precise measurement technologies, such as underwater densitometry (Owen et al., 1987), made the determination of FFM easier and more accurate.

A number of studies retrospectively re-examined Harris & Benedict’s measurements in an attempt either to develop a better equation or to refine the original equation (Cunningham, 1980, 1991; Garrel, Jobin, & de Jonge, 1996; Henry, 2005; Livingston & Kohlstadt, 2005; Ramirez-Zea, 2005; Schofield, 1985). Most researchers, including those developing their own estimation equations, continued to find a lack of congruence between estimation of metabolic rate using the H-B equations and the results of metabolic rate measurement in their experimental populations. The subjects in these studies differed from the original H-B subjects in body size (Frankenfield, Rowe, & Smith, 2003; Ireton-Jones & Turner, 1991; Owen et al., 1987; Owen et al., 1986), age (Arciero et al., 1993a, 1993b; Taaffe, Thompson, Butterfield, & Marcus, 1995), and ethnicity (de Lorenzo et al., 2001). Variations in body size included BMIs indicative of significantly underweight persons (Muller et al., 2004; Roza & Shizgal, 1984).

Study findings were mixed. Several investigators determined that the H-B equations were more accurate than those developed later (de Lorenzo et al., 2001;
livingston & kohlstadt, 2005; siervo, boschi, & falconi, 2003), even in the older individual (taaffe et al., 1995), as long as the evaluation compared group means for measured and predicted values. others determined that the h-b equations significantly overestimated caloric requirements in diverse body sizes (mifflin et al., 1990; scalfi, coltorti, sapio, di biase, borelli, & contaldo, 1993) and ages (arciero et al., 1993a, 1993b). the overestimation was as great as 88% (daly et al., 1985). no investigator in this group reported that the h-b equations underestimated caloric requirements in any sample.

other equations developed for individuals of optimal weight. beginning in the mid-1980s, scores of investigators developed equations intended to be more precise than earlier methods. most of these equations were published but not validated, or validated in only one or two studies. this section focuses on three equations (or sets of equations), developed in 1985 or later, that have been validated eight or more times. the first is actually two groups of equations, initially developed by schofield (1985) in a meta-analysis of more than 7,000 subjects, and then modified at the request of the world health organization and published (fao/who/unu, 1985) in the modified form for worldwide use. another set of equations (owen et al., 1987; owen et al., 1986) was developed with men and women, with one-third of the female sample made up of trained athletes. separate equations were developed for men and for trained and untrained women. the last set of equations of this group (mifflin et al., 1990) was developed using data from 498 subjects, not separated by gender, but rather by the number of parameters to be included in the estimation.

the schofield/who equations (fao/who/unu, 1985; schofield, 1985) originated in a meta-analysis of 114 studies published between 1914 and 1980, with a
total of 7393 subjects (Table 1, p. 81). Approximately 2/3 of the sample was male. Of those men, the largest groups were Italian manual laborers or military recruits, and the increased RMR of these highly active subjects led to a bias toward overestimation of energy needs (Ramirez-Zea, 2005). This bias was not discovered until after the equations were adopted, in a modified form, by the World Health Organization (FAO/WHO/UNU). However, the WHO modification (Table 2, p. 82) added more than 3500 subjects to the study sample, so the effect of the individuals whose data skewed Schofield’s equations was diluted.

Neither the original Schofield publication, nor the subsequent WHO report, provided details of the regression analysis used to develop the equations, so the amount of variance explained by them was not known. Of subsequent validations, only one reported $R^2$, as 0.44 (Taafe et al., 1995).

Either Schofield’s equations, or the WHO modifications, or both, were validated in underweight (Muller et al., 2004), overweight, and obese populations (Luhrmann & Neuhauser-Berthold, 2004; Scalfi et al., 1993; Siervo et al., 2003; Taaffe et al., 2005). In addition, studies examined their accuracy in subjects from 30 to 91 years of age (Muller et al.; Scalfi et al.; Siervo et al.). Investigators rated these equations as most accurate (Arciero et al., 1993a, 1993b; Garrel et al., 1995; Luhrmann & Neuhauser-Berthold), or as one of two most accurate along with the H-B (de Lorenzo et al., 2001). Only one study reported systematic overestimation of energy needs with these equations (Alfonzo-Gonzales, Doucet, Almeras, Bouchard, & Tremblay, 2004).

Two studies reported limits of agreement, enabling estimation of how well the equations predicted REE for individual subjects, rather than simply comparing group means (Bland & Altman, 1986). When measured REE (MREE) was compared
separately to prediction by Schofield’s weight-only equation in a group of 74 lean and overweight young women, the equation demonstrated a bias of +520 kcal with limits of agreement from -468 to +1532 kcal (Scalfi et al., 1993). This means that on average, energy requirements were overestimated by 520 kcal, but that the limits of agreement ranged from underestimation by 468 kcal to overestimation by 1532 kcal. For the Schofield equation using both weight and height, in the same group of subjects, bias was +438 kcal, and the limits of agreement ranged from -515 to +1417 kcal. The WHO equation did not demonstrate much improvement, with a bias of +472 kcal and limits of agreement between -457 and +1429 kcal. In the same investigation, with separate analysis of data from the obese subgroup, the Schofield weight-only equation had a bias of +831 kcal with limits of agreement between -457 and +2119 kcal and the Schofield weight/height equation yielded a bias of +607 kcal with limits from -717 to +1930 kcal; the WHO equation showed bias of +752 kcal with limits between -608 and +2113 kcal.

A second pair of investigators (Livingston & Kohlstadt, 2005) did not report precise limits of agreement; however, using the Bland-Altman method, they determined that the bias of the Schofield equations were -635 kcal in men and -27 kcal in women. The specific equation that was applied (i.e., weight only or weight and height) was not reported. The WHO equation had a bias of +339 kcal in men and -47 kcal in women. The data set for the study included 239 subjects drawn from the original H-B data, 104 subjects from the two papers by Owen (Owen et al., 1987; Owen et al., 1986) and 327 new subjects presenting to a university-based weight management program. Energy expenditure was predicted within 10% of measured energy expenditure in 45% of men and 67% of women using the Schofield equation, and in 52% of men and 77% of women using the WHO equation.
In 1986 and 1987, two reports from Owen and colleagues described the development of new equations in separate groups of healthy men (Owen et al., 1987) and women (Owen et al., 1986). The women (n = 44) were from 18 to 65 years of age and weighed from 43 to 143 kg; eight subjects were trained athletes whose data were analyzed separately. The men (n = 60) ranged from 18 to 82 years of age and from 60 to 171 kg of weight. The equations were:

for the non-athletic women:

\[ RMR \text{ in kcal/day} = 795 + 7.18 \times \text{wt in kg} \]  

(3)

for men, either:

\[ RMR \text{ in kcal/day} = 879 + 10.2 \times \text{wt in kg} \]  

(4)

or

\[ RMR \text{ in kcal/day} = 290 + 22.3 \times \text{FFM}_D \]  

(5)

where \( \text{FFM}_D \) was fat-free mass measured by underwater densitometry.

Eight studies performed to validate these equations in other samples included subjects under 32 years of age (Scalfi et al., 1993; Siervo et al., 2003) and over 50 years (Arciero et al., 1993a, 1993b; de Lorenzo et al., 2001; Taaffe et al., 1995), as well as those with BMIs as high as 41.6 (Frankenfeld et al., 2003; Scalfi et al., 2003; Siervo et al., 2003; Taaffe et al., 1995). Of the eight studies, only one found the Owen equations to be the most accurate of those tested (Siervo et al., 2003). A second investigation reported that the Owen and H-B equations were both equally accurate, and more accurate than other equations studied (Taaffe et al., 1995). Three of the eight studies reported
significant overestimation using Owen’s equations (Arciero et al., 1993a, 1993b; Muller et al., 2004).

The original report of development of the Mifflin-St. Jeor equation (Mifflin et al., 1990) used a sample of 498 healthy individuals, approximately evenly divided by gender, aged 19 to 78 years, and BMIs from 17 to 42, with almost half having BMIs ≥30. The investigators found FFM to be the best single predictor of REE ($R^2 = 0.64$), but wanted a means of estimation that could be used readily at the bedside by clinicians with a minimum of technology. The difficulty of measuring FFM led them to look further. The following equation explained the highest proportion of variability in REE ($R^2 = 0.71$):

$$9.99 \text{ (wt)} + 6.25 \text{ (ht)} - 4.92 \text{ (age)} + 166 \text{ (sex)} - 161$$

where male sex = 1 and female = 0 (Mifflin et al., 1990).

The same eight validation studies mentioned for the Owen equations also compared measured RMR to RMR estimated by the Mifflin-St. Jeor equation. None of these studies reported overestimation of caloric needs by the Mifflin-St. Jeor equation. One study found the Mifflin-St. Jeor equation to be most accurate for both genders (Scalfi et al., 1993), while one found it to be so for men only (Livingston & Kohlstadt, 2005).

Conclusion. In spite of nearly 50 years of work attempting to identify the best single equation for the estimation of caloric needs in healthy individuals of optimal weight, no consensus was developed. The H-B was tested in adults of all ages, all sizes, and a number of ethnicities, and typically was found to overestimate measured REE.
slightly. The WHO equations were not used commonly in the U.S., even though they were simpler to use than the H-B. Newer equations, including the Owen and Mifflin-St. Jeor, were unable to achieve an $R^2$ greater than the H-B in men ($R^2 = 0.75$), leaving 25% of variability in REE unexplained.

Only two studies examined performance of equations in individuals rather than groups. In these studies, neither the Schofield nor the WHO equations predicted REE to within 10% of measured in more than 75% of subjects.

*Estimating REE in Obese Individuals*

The earliest study of subjects with higher than optimal body weight (Boothby & Sandiford, 1922) included 94 individuals diagnosed with “uncomplicated obesity” (p. 799), a term not further defined by the authors. Only 73 of the 94 had measured RMR that fell within 10% of predicted estimates using the H-B, but the mean difference between measured and predicted values was only 0.5%. No equation was developed from the gathered measurements; rather, the researchers constructed a nomogram, the “Mayo nomogram,” which was intended to identify the limits of normal RMR for individuals of a given height and weight.

*Validation of the Harris-Benedict equations in obese individuals.* Once portable indirect calorimetry was commercially available in the mid-1980s, a number of investigators tested the H-B equations in samples made up in whole or in part of healthy obese subjects with BMIs up to 77 (Das et al., 2004; Hirano, Heiss, Olson, Beerman, & Brahler, 2001; Ireton-Jones & Turner, 1991). In one investigation, the entire sample had BMIs over 40 (Lazzer, Agosti, Silvestri, Derumeaux-Burel, & Sartorio, 2007). In another study, the entire sample had BMIs between 25 and 40 (Weijs, 2008).
There were studies with all subjects under 35 years of age (Dobratz et al., 2007; Scalfi et al., 1993; Siervo et al., 2003), subjects as young as 16 years (Feurer, Crosby, Buzby, Rosato, & Mullen, 1983; Frankenfield et al., 2003; Hirano et al., 2001; Ireton-Jones & Turner, 1991), or as old as 80 years (Das et al., 2004; Frankenfield et al., 2003; Ireton-Jones & Turner, 1991; Pavlou, Hoefer, & Blackburn, 1986). Results of these studies were mixed. Several investigators found that the H-B overpredicted REE in obese subjects (Feurer et al., 1983; Foster et al., 1988; Heshka, Feld, Yang, Allison, & Heymsfield, 1993; Hirano et al., 2001; Pavlou et al., 1986; Weijs, 2007). In other investigations, the H-B underestimated REE (Das et al., 2004; de Luis, Aller, Izaola, & Romero, 2006; Feurer et al., 1983; Foster et al., 1988; Lazzer et al., 2007; Pavlou et al., 1986). Only one investigator rated the H-B as the best equation for estimation of REE in obese subjects, but only in females (Heshka et al., 1993). Another researcher (Weijs, 2007) found the H-B to be the least biased equation in Dutch subjects, but not in Americans. The Weijs study was also the only one that covered the entire gamut of overweight and obesity, with BMIs from 25 to 40.

New equations developed for obese individuals. Two equations discussed earlier – Owen and Mifflin-St. Jeor – were developed using samples containing some obese subjects (Mifflin et al., 1990; Owen et al., 1987; Owen et al., 1986). Investigators subsequently tried to validate these equations using samples made up entirely of obese subjects. One such study reported that the Owen equations overestimated REE (Scalfi et al., 1993); the rest reported that the Owen equations underestimated REE (de Luis et al., 2006; Dobratz et al., 2007; Frankenfield et al., 2003; Heshka et al., 1993; Lazzer et al., 2007; Siervo et al., 2003).
Two studies using multiple methods of estimation in all-obese samples reported the Mifflin-St. Jeor equations most closely approximated REE (Dobratz et al., 2007; Frankenfield et al., 2003). On the other hand, two investigators reported that the Mifflin-St. Jeor equations underestimated REE (Heshka et al., 1993; Lazzer et al., 2007), and one concluded that they overestimated REE (Scalfi et al., 1993). The single study using Bland-Altman measures of agreement showed that the Mifflin-St. Jeor potentially estimated REE within a 600 kcal margin (Siervo et al., 2003).

Some of these studies suffered from small sample size, especially those with samples made up only partly of obese subjects (Dobratz et al., 2007; Hirano et al., 2001). Owen’s studies (1987; 1986) used subjects with BMIs as high as 58.7, but only 16 obese subjects were in each sample. Almost half of the sample in the Mifflin, St. Jeor et al. study (1990) had BMIs ≥ 30, but no subgroup analyses were conducted. Likewise, some of the subjects studied by Cunningham (1991) had BMIs ≥ 30, but no subgroup analyses were done.

Two new equations were developed using only obese subjects during this time period and have been validated in a number of samples differing from the original. A large group from Columbia in the early 1980’s (Bernstein et al., 1983) measured RMR in 202 obese subjects weighing up to 204 kg and up to 231% of ideal body weight. Using multiple regression, Bernstein et al. developed three equations explaining up to 66% of the variance. Unfortunately all three Bernstein equations used total body potassium and total body water measurements by the costly isotope dilution method; therefore, these equations were of minimal clinical utility. Validation of the equations in other samples demonstrated both underestimation (Dobratz et al., 2007; Lazzer et al., 2007)
and overestimation (Das et al., 2004; de Luis et al., 2006) of energy needs. The highest $R^2$ achieved in validation was 0.66.

A second equation, the Ireton-Jones equation (Ireton-Jones, Turner, Liepa, & Baxter, 1992), was developed from two groups of obese subjects, 65 hospital inpatients and 65 persons from the community. All subjects were at least 30% above ideal body weight according to the 1959 Metropolitan Life tables, with BMIs ranging from 30 to 73. Approximately a third of the sample was hospitalized for burns, and half for trauma. Regression analysis produced two equations, the first appropriate for any obese patient:

$$REE = 606 \text{(sex)} + 9 \text{(weight in kg)} - 12 \text{(age)} + 400 \text{(ventilation)} + 1,444 \quad (7)$$

where sex was 1 for male and 0 for female, and ventilation was 1 for mechanical and 0 for spontaneous.

The second equation was only appropriate for non-hospitalized, spontaneously breathing obese adults:

$$REE = 294 \text{(sex)} + 11 \text{(weight in kg)} + 791 \quad (8)$$

where sex was scored as in equation 7. The new equations were not compared to any previously developed method of estimation.

Three investigators compared this set of Ireton-Jones equations to the H-B equations, with the highest $R^2$ being 0.52. In all cases, the Ireton-Jones equation overestimated measured REE. However, one study used both a handheld indirect calorimeter with disputed accuracy and a sample with a much smaller mean BMI (de
Luis et al., 2006). The second study had a small sample (n = 19) with an unknown range of BMIs (Hirano et al., 2001), and the third study included only 30 female subjects with BMIs ranging from 37.5 – 77 (Das et al., 2004). In the latter investigation, the Ireton-Jones equation overestimated REE by 40%.

**Conclusion.** In samples made up partially or entirely of obese subjects, there was no consensus on which equation was most accurate, except to say that the H-B was not. Only two studies recommended it as demonstrating best results, and one of those recommended it as superior only in women (Heshka et al., 1993). Newer equations that were developed using samples made up entirely of obese subjects were poorly validated, with fewer than six studies each. In addition, one of the new equations required measurements not available in clinical settings. More studies are needed, to determine which of the available equations works best with obese subjects. Studies that examine equations in samples extending across the continuum of adiposity are especially needed.

**Estimating REE in Seriously Ill or Injured Individuals**

Since most of the adequately-studied estimation equations were developed on healthy subjects, investigators sought to determine whether these equations gave adequate approximations of REE in the ill and injured. Once again, the most frequently tested estimation method was the H-B equations, with or without multipliers for increased stress and/or activity. Of seven new equations developed using samples of critically ill, seriously injured, or mechanically ventilated subjects, only two had three or more validation studies performed on them, namely the Penn State (Frankenfield et al., 1994) and the Ireton-Jones (Ireton-Jones & Jones, 2002) equations. The American College of Chest Physicians suggested, by consensus of expert opinion, that 25 kcal/kg be used as a baseline approximation of energy needs in mechanically ventilated and/or
critically ill patients (Cerra et al., 1997), and this recommendation was tested in seven of the studies discussed below.

**Harris-Benedict validation in illness and injury.** Twenty-three studies either validated the H-B equations against new samples or compared a newly-developed equation to the H-B. Ages of subjects ranged from 14 – 91 years (Ireton-Jones et al., 1992; Weissman, Kemper, Askanazi, Hyman, & Kinney, 1986), with 13 studies including subjects over 60 years of age. Body sizes also ranged widely, with one study having 13.9% of subjects underweight (BMI < 18.5) (Barak, Wall-Alonso, & Sitrin, 2002). Several investigators used samples with obese or morbidly obese subjects, with BMIs as high as 78 (Glynn, Greene, Winkler, & Albina, 1999). Mechanically ventilated subjects were all or part of the sample in 18 studies, and all or part of the sample in 18 studies were injured (see Table 3, p. 83). In addition to the injured samples, nine studies included subjects with elective or emergency surgical procedures, and four studies included subjects with burns.

Twelve of the investigators made use of stress or activity multipliers ranging from 1.1 to 2.5. Most frequently, *a priori* multipliers were taken from a reference (Long & Blakemore, 1979) that based them on expert opinion rather than clinical evidence. Some investigators attempted to verify stress multipliers by comparing calculated REE with measured REE to obtain a ratio.

Results of the studies were varied, with no clear consensus as to how the original H-B formulas should be modified to fit this patient population. Seven studies reported that the H-B without stress multipliers overestimated measured REE (Amato, Keating, Quercia, & Karbonic, 1995; Barco, Smith, Peerless, Plaisier, & Chima, 2002; Casati, Colombo, Leggieri, Muttini, Capocasa, & Gallioli, 1996; Ireton-Jones & Jones, 2002;
Savard, Faisy, Lerolle, Guerot, Diehl, & Fagon, 2008; Sherman, 1994; Stucky, Moncure, Hise, Gossage & Northrop, 2008), whereas only two found that it underestimated measured REE (Frankenfield, Coleman, Alam & Cooney, 2008; Swinamer, Grace, Hamilton, Jones, Roberts, & King, 1990). Four teams of investigators detected no significant difference between measured REE and calculated REE group means (Boulanger, Nayman, McLean, Phillips, & Rizoli, 1994; MacDonald & Hildebrandt, 2003; Paauw, McCamish, Dean, & Ouelette, 1984; Savino, Dawson, Agarwal, Moggio, & Scalea, 1985).

Six studies reported limits of agreement by Bland-Altman analysis, with five of them finding positive bias with varying degrees of precision. The lowest bias was +205 kcal/day (Amato et al., 1995), and the best precision was ± 65.4 kcal/day in postsurgical subjects and ± 62.9 kcal/day in injured subjects (Casati et al., 1996). One investigation reported underestimation, with a bias of -275 kcal/day (Frankenfield et al., 2008).

One study specifically investigated only obese burned and otherwise injured subjects, (Stucky et al., 2008) using an unbalanced repeated measures design. Subjects (n=28) were seriously injured, with a mean Injury Severity Score (ISS) of 22.18. The overall mean BMI was 35.39, with no range reported. Measured and estimated REE were compared using a paired t test, even though some of the observations were not independent, with several subjects measured more than once. Results showed the H-B without stress multipliers to be less biased (+254 kcal) than either Cunningham’s FFM-based equation (1991) or Huang’s equation developed for diabetic patients (Huang, Kormas, Steinbeck, Loughnan & Caterson, 2004).
New equations developed for ill and injured individuals. A number of new equations were created for ventilated, critically ill and/or injured individuals, but only two were validated against multiple samples.

The most frequently tested equations were those originally developed by Ireton-Jones and Turner (1991) using samples of hospitalized subjects. Subjects on whom the equations were developed comprised two groups, that is, one group for equation development (n = 200) and one group for validation (n = 100). Both groups had approximately equivalent demographics (including BMI), distribution of diagnoses, and proportion of mechanically ventilated subjects. Two separate equations were produced. One equation was for spontaneously breathing subjects:

\[ \text{REE} = 629 - 11\text{(age)} + 25\text{(wt in kg)} - 609\text{(obesity)} \]  

(9)

where obesity was defined as body weight at least 30% over ideal according to the 1959 Metropolitan Life tables, and valued as present = 1 and absent = 0. The second equation, for ventilator-dependent subjects, was

\[ \text{REE} = 1925 - 10\text{(age)} + 5\text{(wt in kg)} + 281\text{(sex)} + 292\text{(trauma)} + 851\text{(burn)} \]  

(10)

where sex was valued as male = 1, female = 0, and trauma and/or burn status was present = 1, absent = 0. The $R^2$ values for these equations were 0.50 and 0.43, respectively.

In 2002, the first author returned to re-analyze the original development and testing data, in an attempt to minimize error between calculated and measured REE,
without losing the correlation between them (Ireton-Jones & Jones, 2002). No improvement could be made for equation 9 for spontaneously breathing subjects, but refinement of equation 10 yielded

\[ \text{REE} = 1794 - 11(\text{age}) + 5(\text{wt in kg}) + 244(\text{sex}) + 239(\text{trauma}) + 804(\text{burn}) \]  

(11)

reducing the bias from -271 kcal/day to +8 kcal/day. The explained variance increased slightly to \( R^2 = 0.58 \).

Ten subsequent validation studies were carried out, using diverse samples. Ages ranged from 14 to 90 (Amato et al., 1995; Ireton-Jones & Jones, 2002), and BMIs from 16 to 78 (Frankenfield, Smith, & Cooney, 2004; Glynn et al., 1999). Six investigators used only subjects on mechanical ventilation (Flancbaum, Choban, Sambucco, Verducci, & Burge, 1999; Frankenfield et al., 2004; Frankenfield et al., 2008; MacDonald & Hildebrandt, 2003; Reid, 2007; Savard et al., 2008). One sample (Flancbaum et al.) was predominately postoperative subjects (83.3%) on ventilators; as many as one third of subjects were injured (Frankenfield et al., 2004).

Results were skewed toward underestimation. Only two researchers (Boullatta, Williams, Cottrell, Hudwon, & Compher, 2007; Glynn et al., 1999) found estimates too high, and one of those tested only the original 1991 version of the ventilator equation. Four studies identified systematic underprediction, with predicted REE as low as 85.1% of measured REE (MacDonald & Hildebrandt, 2003). One investigator determined that 89% of estimates were less than measured REE (Flancbaum et al., 1999). One of two Bland-Altman analyses (Amato et al., 1995) produced a bias of -120 kcal, precision of \( \pm 225.6 \) kcal, and limits of agreement from -350 to +570 kcal/day for the ventilator
equation, and a bias of -37 kcal, precision of ± 204 kcal, and limits of agreement of -378
to +456 kcal/day for the spontaneous breathing equation. The second Bland-Altman
analysis, using only the ventilator equation (Reid, 2007), demonstrated limits of
agreement from -759 to +1042 kcal/day. A test of both the original and revised
equations demonstrated that the revised equation consistently underestimated energy
needs, and was less precise than the original equation (Frankenfield et al., 2004).

A group from Pennsylvania State University in the early 1990s developed a
regression equation using only critically ill, mechanically ventilated subjects
(Frankenfield, 1988). The original study involved 26 injured subjects and 30 septic
subjects, with 423 total calorimetric measurements. BEE was calculated from the H-B,
with actual body weight compared to ideal body weight by the method of Hamwi (1964);
if actual body weight was more than 120% of ideal, body weight was adjusted by adding
25% of the excess weight to the ideal weight. All subjects were sedated, and 45% of
them were pharmacologically paralyzed.

Regression on the data yielded three equations, with varying parameters. One
equation used basal energy expenditure (BEE) calculated by the H-B, along with minute
ventilation (VE), dose of dobutamine infusing at the time of measurement (in
mcg/kg/min) and body temperature at the time of measurement:

\[
\text{REE} = -11000 + 100V_E + 1.5\text{REE (by H-B)} + 40(\text{dobutamine dose}) + 250(\text{temp}) +
300(\text{sepsis})
\]

(12)

where sepsis was scored 1 for yes and 0 for no. \( R^2 \) for this equation was 0.77.

The second equation had fewer of the same parameters:
REE = -1000 + 100V_E + 1.3REE (by H-B) + 300(sepsis)  \hspace{1cm} (13)

but the third equation used body weight (adjusted if over 125% of ideal) rather than BEE by the H-B, as follows:

REE = -200 + 100V_E + 25(adjusted body wt) + 350(sepsis). \hspace{1cm} (14)

\( R^2 \) for these equations was 0.71 in both cases.

In 2004, the same group published refinements of these equations based on the original data (Frankenfield et al., 2004), substituting maximum 24-hour temperature for current temperature at the time of testing, and using actual body weight in all cases:

\[
RMR = 0.85(H-B \text{ REE}) + 33 \text{ } V_E + 175(\text{temp}) - 6433 \hspace{1cm} (15)
\]

An alternative equation that used the Mifflin-St. Jeor equation with actual weight in place of the H-B was reported as:

\[
RMR = 0.96(\text{Mifflin REE}) + 31 \text{ } V_E + 167(\text{temp}) - 6212 \hspace{1cm} (16)
\]

The refinements actually decreased the explained variance, with \( R^2 \) of 0.67 and 0.69, respectively.

The 1994 equation was validated (MacDonald & Hildebrandt, 2003) using retrospective review of continuous 24-hour calorimetry in 76 clinical records of non-
obese subjects, whose average age was $59 \pm 16.7$ and 17.1% of whom were injured. The Penn State equations underpredicted measured REE by 85.1%. A second validation study used the 2004 equation in a sample of 395 subjects from 16 – 92 years old, with BMIs from 13 to 53 (Boullata, 2007). Most subjects (64.3%) were ventilating spontaneously, and 40% were postoperative surgical patients. The newer Penn State equations predicted accurately in only 43% of subjects, with individual values from 75% to 156% of predicted. Adjusted for age, sex, and ethnicity, the Penn State equation was four times as likely to be accurate in normal weight subjects as in obese ones. The H-B with a 1.1 stress factor predicted REE more accurately than the Penn State equations in ventilated subjects. Although the investigators state that the Bland-Altman method was used, no specific figures for bias or precision were reported. In addition, no description was given for how expiratory minute ventilation was measured in spontaneously breathing subjects.

The original developers of the Penn State equation compared it with the H-B, the 1992 Ireton-Jones, Mifflin-St. Jeor, Swinamer, and several other equations using 202 mechanically ventilated subjects of whom 47% were characterized as obese (Frankenfield et al., 2008). Twenty-six percent of the subjects were admitted after blunt trauma. They found underestimation by the H-B and Mifflin-St. Jeor equations, with the H-B predicting only 34% of subjects within 10% of MREE, and Mifflin-St. Jeor predicting only 25% of subjects within 10% of MREE. The Penn State equation, tested both in the form based on the H-B estimation and that based on the Mifflin-St. Jeor (equations 15 and 16 above), was unbiased with 64% and 67% predictive accuracy, respectively.
A systematic review of evidence regarding prediction of REE in critically ill adults recently emerged from the ADA Evidence Analysis Working Group (Frankenfield et al., 2007). Their scope was narrow, including only studies with sample sizes of at least 10 subjects per group, dropout rates of no more than 20%, and specific research designs (i.e., clinical trial, large observational, or case-control cohort methodologies). Their definition of acceptability was a prediction within 10% of the measured REE. The Harris-Benedict (with or without stress multipliers) and the Ireton-Jones (2002) received strong negative recommendations. On the positive side, the Ireton-Jones 1992 was found acceptable, along with the Swinamer (1990) and the Penn State (2003) equations. All positive recommendations were, however, weaker than the negative ones, based on the group’s estimation of the strength of the evidence.

**Conclusion.** The H-B equation was more frequently tested than any other in the critically ill and/or seriously injured patient. Frequently, stress multipliers were used to make the H-B more accurate, but the multipliers were not based on evidence, but rather on clinical opinion. Two other equations have been developed specifically for use in mechanically ventilated patients, but both are in need of further validation.

The equations to be tested in this study were verified less thoroughly than earlier equations such as the H-B, Owen, or FAO/WHO/UNU. The two Ireton-Jones equations (Ireton-Jones & Jones, 2002; Ireton-Jones et al., 1992) were developed using ventilated and obese subjects respectively, and were not adequately tested on the other group. The Penn State equation was not thoroughly tested in obese subjects; and the Mifflin-St. Jeor equation, although a part of the Penn State equation, was not well-tested on ventilated patients.
1. No consensus existed as to which prediction equation was most accurate in any subject population.

2. No well-studied prediction equation explained more than 78% of variance in any subject population.

3. Most development and validation studies compared group means, giving little guidance as to how prediction equations would perform in individual cases.

4. The most frequently used equations in clinical settings were the H-B, Owen, Mifflin-St. Jeor, and FAO/WHO/UNU (Frankenfield et al., 2005);

5. The Mifflin-St. Jeor, Ireton-Jones, and Penn State equations were the only ones that were developed in appropriate populations (obese, critically ill, or both) that have at least two supporting studies.

Appendix B describes all the validation studies reviewed in this chapter, divided according to the type of subjects in the sample: optimal-weight, obese, or seriously ill.
Chapter III

Methods

As discussed in chapter I, careful estimation of energy needs is necessary in hospitalized patients to prevent the effects of underfeeding and overfeeding. In Chapter II, results of studies that developed or verified equations for estimating REE in optimal weight, overweight, and obese individuals were discussed, showing that the data on overweight/obese injured patients were neither internally consistent nor adequate. Only a few small studies examined individuals who were both overweight/obese and injured. Chapter III outlines the methods employed in this study to determine relationships between measured and estimated REE in seriously injured, mechanically ventilated patients across a large range of BMIs.

Study Questions

Based on the preliminary questions presented at the end of chapter I and the literature discussed in chapter II, the following questions directed the current study:

1) In mechanically ventilated, seriously injured patients, do any of the following candidate equations yield an energy requirement within 500 kcal/day for individual patients, when compared to measurement by indirect calorimetry:

   a. Harris-Benedict (equations 1 & 2, 1919);
   b. Mifflin-St. Jeor (equation 6, 1990);
   c. Ireton-Jones for obese patients (equation 7; Ireton-Jones & Turner, 1992);
   d. Ireton-Jones for ventilated patients (equation 10, Ireton-Jones & Jones, 2002);
   e. Penn State (equation 14; Frankenfield, Smith, & Cooney, 2004)?
2) In mechanically ventilated, seriously injured patients, is it possible to modify any of the four candidate equations to increase precision and decrease bias with the addition of any of the following variables: mode of mechanical ventilation, use of sedatives, use of analgesics, use of vasopressors, severity of injury, or BMI?

3) Is it possible to construct an equation with greater precision and less bias using BMI, age, sex, and any of the candidate variables in question 2?

**Design**

The study design was cross-sectional and retrospective in nature, and examined differences between measurement and estimation of REE, as well as the relationships between the two methods. Retrospective studies have been commonly used to explore these relationships, especially in critically ill patients (Alexander, Susla, Burstein, Brown, & Ognibene, 2004; Barak, Wall-Alonso, & Sitrin, 2002; Boullata, Williams, Cottrell, Hudson, & Compher, 2007; Garrel, Jobin, & de Jonge, 1996; Ireton-Jones, Turner, Liepa, & Baxter, 1992; Livingston & Kohlstadt, 2005; MacDonald & Hildebrandt, 2003; Sunderland & Heilbrun, 1992).

The study utilized available indirect calorimetric data collected during the normal course of patient care in a level II trauma center in northern Illinois. The current calorimeter had been in use for five years, with the same procedures and the same personnel performing the measurements. Explicit inclusion and exclusion criteria are discussed below.

*Choice of Equations for Study*

Two prerequisites were used in selecting equations for this study: (1) all the chosen equations had to be experimentally validated, and (2) the equation had to be
developed using an appropriate sample, including overweight/obese, seriously injured, and/or mechanically ventilated individuals.

Of the 26 equations that were reviewed, 13 were developed for optimal-weight, healthy individuals. Of these 13 equations, the four with the highest number of published validation studies were considered for inclusion: Harris-Benedict, Schofield/WHO, Owen, and Mifflin-St. Jeor. Virtually every validation study examined for this project used the original Harris-Benedict equations as part of the evaluation process; therefore, the H-B was included here as well. The Mifflin-St. Jeor equation was selected because it was singled out by the ADA in a systematic review of available equations (Compher et al., 2006). The Owen and Schofield/WHO equations were not chosen because they neither had emerged as superior from a systematic review nor had as many validation studies in seriously ill and injured individuals as the H-B.

Seven equations developed specifically for use with obese individuals were evaluated for inclusion. Of those seven, the equation with the most validation work, the Ireton-Jones and Turner (1992), was chosen. Six equations were developed using hospitalized subjects but only two equations had both undergone more than one validation study and were developed on a sample containing ventilated and seriously injured subjects. Those two equations, namely the Ireton-Jones and Jones (2002) and Penn State (2004) equations, were chosen for this study. The Penn State equation had the added strength of having emerged as preferred from the ADA systematic review of equations for critically ill patients (Frankenfield et al., 2007).

For these reasons, the chosen equations were the Harris-Benedict (1918), the Mifflin-St. Jeor (1990), the Ireton-Jones (1992, 2002) and the Penn State (2004).
Methodological Limitations

One limitation of the study was the inclusion of only five candidate equations from the multitude of those available, since it is possible that one of the less adequately validated equations may actually be superior. Other limitations of the study method were the restriction to ventilated subjects, a single location, and a convenience sample. In addition, by relying on patient history for some of the exclusion criteria, and given the emergency nature of trauma patient admission, it is possible that some of the exclusion criteria may have been present without the knowledge of the treating physicians and nurses. In that case, the assumed relationship between variables used to predict REE may not hold. Admission weight may be falsely elevated by fluid resuscitation taking place in the field, the Emergency Department, and/or the operating suite.

When the indirect calorimetry reports were examined, no precise time for the measurement was found. Upon inquiry of the technicians, it was discovered that tests were always completed between 0700 and 1000; therefore, in retrieving vital signs and laboratory data, the 0800 numbers were retrieved. It is possible that, if tests were done later in the day, the Penn State estimate, which requires contemporaneous measurement of minute ventilation, may have been incorrect. Also, severity of illness (APACHE II) scores, which also require contemporaneous measurement of physiologic variables, may have been erroneous.

Population, Sample, and Sampling

The study population included individuals over 18 years of age admitted to a 250-bed Midwestern trauma center after an injury. The typical patient was male Caucasian,
over 50 years of age, with at least one orthopedic injury resulting from a motor vehicle crash.

**Inclusion Criteria**

As previously noted, only mechanically ventilated patients were eligible because only mechanically ventilated patients were tested by indirect calorimetry in this facility. If this were not true, it would still have been wise to limit the study to ventilated patients due to a potential effect of ventilatory mechanism on REE (Ireton-Jones et al., 1992; Paauw, McCamish, Dean, & Ouellette, 1984).

The initial intent was to obtain a list of patients admitted to the trauma service and billed for indirect calorimetry, from the billing department. However, using the billing code for indirect calorimetry (CPT 94690) yielded only 44 records from a five-year period, suggesting that the coding procedure was inaccurate. Therefore, a list was obtained of all patients admitted to the critical care units with a primary diagnosis of trauma (ICD-9 codes 800.0 to 960.0) for a five-year period. Those under 18 years of age were eliminated, as were those with length of stay less than 5 days, since the most common frequency of indirect calorimetry in the institution was weekly.

The original intent of the study was also to limit inclusion to patients with a BMI of 30 or more. However, once all charts had been screened, only 89 trauma patients had undergone indirect calorimetry during the study period, regardless of BMI. Therefore, the BMI criterion was dropped.

**Exclusion Criteria**

The use of a prediction equation assumes that the relationship it describes between REE and one or more physiologic parameters is constant. Exclusion criteria were based on those factors that could substantially alter this static relationship, and
therefore confound the relationship between measured and calculated REE. These factors included:

- pre-existing diseases, specifically chronic liver failure (Jhangiani, Agarwal, Holmes, Cayten, & Pitchumoni, 1986), chronic obstructive pulmonary disease (Baarends, Schols, Westerterp, & Wouters, 1997; Moore & Angelillo, 1988; Schols, Fredrix, Soeters, Westerterp, & Wouters, 1991), thyroid disease (Silva, 2003), active malignancy (Kulstad & Schoeller, 2007), NYHA Class III or Class IV heart failure (Obisesan, Toth, & Poehlman, 1997), renal failure on renal replacement therapy (Wang et al., 2004; Zarling, Grande, & Hano, 1997), or alcoholism (Mueller et al., 1999);
- use of certain medications prior to admission or during their hospital stay, specifically the antipsychotics risperidone or orlanzipine (Sharpe, Byrne, Stedman, & Hills, 2005), highly active antiretroviral therapy for HIV disease (Batterham, Morgan-Jones, Greenop, Garsia, Gold, & Caterson, 2003), or dopamine or epinephrine infusion (Chiolero, Flatt, Revelly, & Jequier, 1991);
- less than 30 minutes elapsed since the last nursing intervention (specifically suction, turning, bathing, or beginning-of-shift physical assessment) and the onset of REE testing (Weissman, Kemper, Askanazi, Hyman, & Kinney, 1984) or less than two hours since the last ventilator adjustment (Brandi, Bertolini, Santini, & Cavani, 1999);
- an air leak in patient-ventilator system (Brandi, Bertolini, & Calafa, 1997).

Standard protocols for indirect calorimetry ensured that (1) the measurement was not taken immediately after nursing interventions or less than two hours after the latest ventilator adjustment, (2) fraction of inspired oxygen did not exceed 60%, and (3)
no air leaks existed in the patient-ventilator system. As addressed in study questions 2 and 3, one of the criteria to be examined was the use of sympathomimetic drugs that affect energy requirements. Pre-existing chronic illnesses, including COPD, liver failure, renal failure, heart failure, malignancy, and HIV disease, are included in the APACHE II score, which was examined by study questions 2 and 3. In addition, a preliminary review of fifty patients treated by the critical care unit showed that no otherwise-eligible subjects would have been disqualified by any of the other factors in the preceding paragraph.

Therefore, exclusion criteria for this study were limited to:

1. agitation that persisted in spite of continuous or hourly intravenous administration of sedatives;
2. burn injury greater than 20% total body surface area (TBSA) (Demling & Seigne, 2000);
3. continuous barbiturate infusion to the point of documented EEG burst suppression (Dempsey, Guenter, & Mullen, 1985);
4. treatment with the atypical antipsychotic medications risperadone or olanzipine (Sharpe, Byrne, Stedman, & Hills, 2005);
5. continuous renal replacement therapy (Scheinkestel et al., 2003).

In the final study sample, two subjects were excluded for burn injury greater than 20% TBSA. One subject was on atypical antipsychotic medication other than the ones cited in the exclusion criteria. One patient was on continuous renal replacement therapy. Two additional screened subjects were excluded for clerical problems; the records contained reports of indirect calorimetry, but no notation of the date was found.
in the dietitians’ notes, and the subjects were no longer ventilated on the test days. In the final study sample, 106 tests were performed on 83 subjects.

**Human Subjects Protection**

The study was approved by the Institutional Review Boards (IRBs) of both the University of Cincinnati and OSF Saint Anthony Medical Center. Waiver of both informed consent and HIPAA authorization was granted by both IRBs. Identifiable health information was retained only until data collection was complete, at which time the document linking individual patient records and the data collection sheets was shredded.

**Instrumentation**

Some discussion of instrumentation was included in Chapter II. The supporting research and rationale for the use of each of the five equations chosen for the study have been discussed (i.e., the existence of more than a minimal number of validation studies with appropriate samples). Therefore, the following section elaborates on the limitations of indirect calorimetry. Then, the choice of variables tracked on the data collection instrument is discussed.

The limitations of indirect calorimetry were introduced at the beginning of Chapter II. Indirect calorimetry measures gas exchange, and estimates the degree of energy flux from the changes in oxygen consumption and carbon dioxide production. Through the First Law of Thermodynamics, the production of ATP (regardless of substrate) increases both free energy and entropy, and the free energy of combustion is trapped within the high-energy phosphate bonds at a rate of 12.5 kcal/mol of ATP under physiologic conditions (Ferrannini, 1988). Since ultimately the stoichiometry of complete nutrient combustion results in glucose and oxygen producing water, carbon
dioxide and approximately 30 moles of ATP per mole of glucose, the relationship between ATP produced and kilocalories produced is linear. Free fatty acids and amino acids enter the process at differing points, and produce different amounts of ATP per mole of substrate; however, the relationship between ATP and kilocalories remains constant. Therefore, the estimation of heat using measurements of changes in concentration of inspired and expired gases is accurate regardless of the substrate being burned.

The apparatus involved in measuring those changes in concentration is available in two types: mixing chamber and breath-to-breath. Most commercial devices use the mixing chamber technique. With this technique, gas from the intake lines and that exhaled by the subject travel to a baffled mixing chamber; a sample of the gas passes through separate analyzers for measurement of the concentrations of oxygen and carbon dioxide. In the breath-to-breath method, as the name implies, a measurement occurs with every breath, and gas sampling occurs at the proximal airway. A clinician-selected or machine-programmed number of samples are transformed into a moving average over time (Branson & Johannigman, 2004). The apparatus used at OSF Saint Anthony Medical Center during the study period was a SensorMedics open-circuit calorimeter using a mixing chamber technique.

For the available devices to accurately reflect the status inside the subject, certain conditions must exist. Since volumes of gas must be measured to determine oxygen loss and carbon dioxide increase, the volume sensor on the machine must be accurate. The SensorMedics unit was calibrated daily with a 3-liter syringe. Before each reading, a gas-concentration calibration procedure was done with 4% carbon dioxide and 16% and
26% oxygen. Other technical limitations were discussed above under Exclusions Criteria.

**Data Collection**

Data were abstracted from each patient’s medical record, with identification numbers assigned by the investigator. Variables were operationalized as follows:

1. *age* as the subject’s age in years as of the last birthday;
2. *weight* as the subject’s measured weight on admission, in kilograms;
3. *height* as the subject’s reported or measured height on admission, in centimeters;
4. *burn* as the presence or absence of burn injury on admission (body surface area burn greater than 20% was an exclusion criterion);
5. *sex* as the subject’s phenotypic sex, determined by the admission physical examination;
6. *minute ventilation* ($V_E$) as the volume in liters of expired gas per minute, measured by the ventilator, at the time of indirect calorimetry (equation 16);
7. *temperature* as maximum body temperature during the 23 hours preceding REE measurement, in degrees Celsius, by oral or tympanic membrane thermometer or by catheter thermistor (equation 16).

The other variables in equations 7, 11, and 16 were predetermined by the subject’s inclusion in the study: *ventilation* (equation 7) was always present since all subjects were mechanically ventilated; *trauma* (equations 11 & 16) was always present since all subjects were admitted for injury.

Chapter II pointed out that various investigators tested equations over differing genders, ages, and degrees of adiposity. Although opinions differ on whether ethnicity has a significant effect on REE. and because substantial work has compared REEs of
African-American and European-American populations (Foster, Wadden, Swain, Anderson, & Vogt, 1999; Jones et al., 2004; Valliant, 2005; Vander Weg, Watson, Klesges, Eck Clemens, Slawson, & McClanahan, 2004), the original study design called for collection of ethnicity information for inclusion as a candidate variable; however, since only 12 of 83 subjects (14%) were not Caucasian, the variable was dropped.

The variables in question 2 (Injury Severity Score, APACHE II Score, sedatives, pressors, ventilator mode) were also chosen for specific reasons. Authorities agree that sedation has a depressant effect on REE (Bruder, Lassegue, Pelissier, Graziani, & Francois, 1994; Bruder, Raynal, Pellissier, Courtinat, & Francois, 1998; Terao, Miura, Saito, Sekino, Fukusaki, & Sumikawa, 2003). However, data on the differential effects of various doses and agents are lacking. One commonly used sedative, propofol, is supplied as an emulsion of 10% lipid, which may significantly elevate the resting energy expenditure through increased energy required for the metabolism of the lipid. Vasopressors are acknowledged to cause an increase in REE via the direct effect of the catecholamines on uncoupling proteins (Chiolero et al., 1991; Ratheiser, Brillon, Campbell, & Matthews, 1998). Only dopamine and phenylephrine were used in the study sample. Originally, doses of sedatives, analgesics and vasopressors were to be retrieved, but the small sample size and lack of variability required transformation of all pharmaceutical variables into the dichotomous variables of present or absent.

Two markers of severity of injury were included in the variables: Acute Physiology and Chronic Health Evaluation (APACHE II) score, and Injury Severity Score (ISS). The APACHE II score (Knaus, Draper, Wagner, & Zimmerman, 1985) uses various laboratory and physical examination findings to quantify the severity of illness. The possible range of scores is from 0 to 36; severe illness is defined by the developers
(Knaus et al.) as a score exceeding 18. APACHE II scores are most prognostically useful when evaluated within the first 24 hours of admission. For purposes of the study, the APACHE II score was computed both at the time of admission and at the time of REE measurement, since the purpose of its use was not prognostic.

The Injury Severity Score is a measurement of the maximum tissue trauma by anatomic location (Baker, O’Neill, Haddon, & Long, 1974). Developed as a refinement of the Abbreviated Injury Score used by the Association for the Advancement of Automotive Medicine, the range of scores on the ISS is from 0 to 75. A score of 75 is automatic if any injury is not survivable. Serious injury is defined as an ISS ≥ 16. ISS was routinely calculated on admission to the trauma service, but those calculations were not available for retrieval due to a changeover in trauma registry data bases. ISS was therefore manually calculated by the investigator from clinical findings at discharge.

Although both APACHE II and ISS are accepted as reliable and valid measures of illness severity and/or injury, studies of the relationship between ISS, APACHE II and REE had mixed results. Some investigators found a relationship between REE and ISS (Hwang, Huang, & Chen, 1993; Swinamer et al., 1990), and some found a relationship between REE and APACHE II (Brown, McClave, Hoy, Short, Sexton, & Meyer, 1993; Swinamer, Phang, Jones, Grace, & King, 1987). Others found no relationships between REE and either scale (Brandi, Santini et al., 1999; Rodriguez, Sandoval, & Clevenger, 1995), but these studies used the H-B equation plus stress multipliers. Since stress multipliers increase with clinician-estimated severity of patient condition, the stress multipliers could co-vary with ISS and APACHE II. This would make any relationship between Harris-Benedict REE and either APACHE II or ISS a mathematical artifact of the stress multiplier.
Lastly, there were data to suggest that the mode of mechanical ventilation (i.e.,
the mechanism the ventilator uses to trigger delivery of gas to the patient) may cause
changes in REE, primarily through changes in the work of breathing (Casati et al., 1996;
Hoher, Teixeira, Hertz & Moreira, 2008; Savino et al., 1985; Weissman, Kemper,
Askanazi, Hyman, & Kinney, 1986). However, most of the available studies were
carried out years ago, and the newer generation of ventilators allow modification of the
work of breathing via changes in flow rate and sensitivity to inspiratory effort. For
purposes of this study, ventilator mode was defined as the mode being used at the time
of REE measurement. The variable was categorical and dummy-coded for purposes of
analysis into a separate dichotomous variable for each mode.

Information about the variables is summarized in Table 4 (p. 85). The data
analysis schema illustrates how each of these variables was used.

Data Analysis

The foundation for analysis for question 1 was the Bland-Altman method, as
briefly discussed in Chapter II. This method uses the mean difference between
measured and predicted REE as the bias of the prediction equation, the standard
deviation of the difference as precision and the 95% confidence intervals around the bias
as the limits of agreement (Bland & Altman, 1986). These limits of agreement also
inversely reflect the precision of the prediction equation; the narrower the limits of
agreement, the greater the precision of estimation.

Since the Bland-Altman bias is a mean, it can be treated as any other mean and
used in analyses of both differences and relationships. However, a simple ANOVA could
not be used for this study because some, but not all, of the subjects had more than one
REE measurement performed. For Question 1, the bias and limits of agreement for each
equation were determined, and then the differences between those biases were examined using a linear mixed-model analysis. The threshold for statistical significance was set at $p < 0.05$. Calculations were performed by SPSS MIXED and SAS PROC MIXED routines.

To evaluate the issue of clinical significance, weight loss or gain of one pound a week was chosen as the criterion, which would reflect over- or underfeeding of an average of 500 kcal/day. Therefore, if the limits of agreement extend farther than ± 500 kcal of measured REE, regardless of statistical significance, the difference was gauged as clinically significant. The percent of estimates for each equation that fell within this clinical criterion were reported. In previous literature, acceptability was commonly defined as ±10% of measured (Feurer et al., 1983; Frankenfield et al., 2008; Garrel et al., 1996); therefore, the proportion of estimates within 10% of measured values were also calculated.

Question 2 and 3 were addressed using multiple regression, incorporating the variables listed in the question. Variables were screened for linearity, and those passing the screen were entered or removed manually with tests for significance at each stage. Categorical variables were re-coded into dummy variables for purposes of the regression. The development of the new equation in question 3 took place by the same method.

**Conclusion**

The intent of this investigation was to determine a) which of five prediction equations most accurately estimated caloric needs in seriously injured patients, as measured by the method of Bland and Altman; b) whether the accuracy could be improved by consideration of variables not contained in the five original equations, such
as BMI, severity of illness, drugs administered, or mode of mechanical ventilation; and
c) whether a new equation developed specifically for this population could improve
accuracy.
Chapter IV

Results

The focus of this study was the estimation of caloric needs in injured subjects, by means of previously developed, new, and modified predictive equations. In the first study question, five previously developed equations were compared for bias and precision using the Bland-Altman method and unbalanced repeated measures analysis of variance under the linear mixed model. In the second and third study questions, a new equation was developed and the older ones were modified. Chapter IV includes a description of the sample and discussion of each study question in turn.

Sample Description

The study sample consisted of 83 individuals on whom 106 REE measurements were carried out. Of the 83 subjects, five had REE measured three times, and ten had REE measured twice. The typical subject was male (78%), white (91.6%), and 53 ± 19 years of age, with a BMI of 29 ± 7. The mean Injury Severity Score was 25; a score of 16 or greater is considered seriously injured. On the APACHE II severity of illness scale, the mean score was 17, with 18 or greater indicating serious illness. Full details are contained in Table 5 (p. 87).

Twenty-one (25.3%) subjects were characterized as having an optimal weight by the criteria established by the National Institutes of Health, with BMIs between 18.5 and 25. Thirty-two (38.6%) subjects were overweight, with BMIs of 25 – 29.9, and the remaining 30 (35.9%) subjects were obese with BMIs ≥ 30. Subjects’ ages ranged from 20 to 90 years, with 25 (30.1%) subjects being over 65 years of age.
Question 1

Question 1 asked which of five candidate equations (Harris-Benedict, Mifflin-St. Jeor, Ireton-Jones 1992, Ireton-Jones 2002, and Penn State) had the least bias and greatest precision by the Bland-Altman method. First, the Bland-Altman analysis of each equation is presented, followed by a repeated measures ANOVA by linear mixed model, to determine if there was a significant difference between the bias of the estimations.

Bland-Altman Analysis of Individual Equations

The intent of the Bland-Altman method is to determine whether two means of measurement are equivalent. To make this determination, the following steps were required. First, the two sets of measurements were plotted against one another to determine the line of equality (Figures 1 – 5, pp. 103 – 107). Then correlations were performed between the two measurements (Table 6, p. 88). Third, in what has been designated the “Bland-Altman plot”, the mean of each pair of measurements was displayed against the difference between them, and the plot was examined for the shape of the relationship (Figures 6 – 10, pp. 108 – 112).

Table 6 shows that all correlations between MREE and estimations, and between estimations, were significant at $p < 0.01$ (two-tailed). None of the correlations between MREE and an estimation exceeds 0.664; however, all but one of the correlations between estimations exceeds 0.900. The highest correlation between estimations occurred with the Harris-Benedict and Mifflin-St. Jeor equations ($r = 0.975$); the lowest correlation occurred between the Mifflin-St. Jeor and Ireton-Jones 2002 equations ($r = 0.864$). Examination of the equations demonstrated that the Harris-Benedict and Mifflin-St. Jeor equations used the same parameters for making the estimation (height,
weight, age, and sex), which may have explained the high $r$. The other three estimation equations used parameters such as presence of mechanical ventilation, presence of trauma, maximum temperature over 24 hours, and minute ventilation.

Once the relationships have been examined, the bias (mean difference), precision (standard deviation of differences), and limits of agreement (95% confidence interval around the mean difference) were calculated (Table 7, p. 89). Since the study definition for a clinically significant difference was ± 500 kcal/day, Table 7 additionally reports the percentage of individual estimations that lay within those parameters, for each equation. Other authors (most remarkably Frankenfeld’s group at Penn State) have used ± 10% as the limits of acceptability, and that calculation for each equation can also be found in Table 7.

Examination of Figures 1 – 5 demonstrated that four of the five comparisons between MREE and estimations lay mostly below the line of identity; this is validated in Table 7 by four of the five equations having positive bias, between 588.5 kcal/day and 1428.3 kcal/day. Only the Harris-Benedict comparison did not fall mostly on one side or the other of the line of identity. The bias for the Harris-Benedict estimations is -248.1 kcal/day, the smallest absolute difference among the group of five estimations.\(^1\)

The Harris-Benedict equation also provided the highest percentage of individual estimations within 500 kcal/day ($n = 74$, 70.5% of measurements) of measured values as well as the highest percentage of individual estimations within 10% of measured values ($n = 42$, 39.6% of measurements). The worst performer was the Ireton-Jones 1992 equation with only 2 [1.9%] individual estimations within 10% and 4 [3.8%] estimations within 500 kcal/day of measured values.

---

\(^1\) The Harris-Benedict equation was used without multipliers.
Limits of agreement, which is synonymous with the 95% confidence interval around the bias, were wide for all estimations, as shown in Table 7. Only two equations (Ireton-Jones 1992 and Penn State) had limits of agreement that did not contain zero; this indicates that the bias for each of these equations was statistically significant at \( p < 0.05 \).

The Bland-Altman plots for each equation are found in Figures 6 – 10. Note that the X-axis is the mean of one pair of measured and estimated values and the Y-axis is the difference between the same pair of measured and estimated values (Y axis). The dotted line indicates the mean difference (bias) and the solid lines indicate the limits of agreement. It is noteworthy that the Ireton-Jones 1992 plot showed no negative differences, and the Penn State plot showed only one. Both of these equations had bias that was significantly positive, and both biases exceeded 1000 kcal/day.

**Analysis of Variance**

To determine whether any equation had bias that was significantly different from any other, a one-way ANOVA was carried out by linear mixed model to allow for unbalanced repeated measures. The omnibus F-test was significant at \( p < 0.0001 \), with \( F (4,328) = 603.77 \). Post-hoc analysis using the Scheffé correction demonstrated all pairwise comparisons were significant at \( p < 0.001 \) (Table 8). The smallest difference was between the Ireton-Jones 2002 and Mifflin-St. Jeor equations (\( df = 328, t = -4.44, p = 0.0007 \)). The results mirrored the correlation matrix, where those two equations had the smallest correlation.

A post-hoc power calculation for the ANOVA showed that power reached 100% when the F-ratio reached 60. F for this analysis was 603.77.
Conclusion

Examination of the Bland-Altman analysis demonstrated that the Harris-Benedict equation, without multipliers, had the smallest bias (-248.1 kcal/day) and greatest precision (± 906.2). It predicted 39.6% of individuals within 10% of measured values, and 70.5% of individuals within clinically significant parameters (±500 kcal/day). The worst performer was the Ireton-Jones 1992 equation, with a bias of +1428.3 kcal/day and precision of ± 1090 kcal/day. This equation predicted only 1.9% of individuals within 10% of measured value and 3.8% within values of clinical significance.

Since all two-way comparisons within the ANOVA analysis were significant, all of the other equations were significantly different from (and therefore less accurate than) the Harris-Benedict equation.

Question 2

Question 2 asked whether any of the five estimation equations could be improved by the addition of other parameters, specifically ISS score (severity of injury), APACHE II score (severity of illness), BMI, use of medication (pressors, sedatives, or analgesics), or mode of ventilation. The severity indices and BMI are continuous variables, the drug-treatment variables are dichotomous and the ventilatory mode variable is categorical. Ventilatory mode was transformed into a family of dichotomous variables for purposes of the regressions.

Regression by Linear Mixed Model

In an attempt to improve on the five candidate equations, a regression was performed using the linear mixed model, incorporating all the aforementioned variables plus variables unique to each equation. The trauma dichotomous variable from the
Ireton-Jones 2002 equation was not included, nor was the *mechanical ventilation* variable from Ireton-Jones 1992 equation, since all the subjects in the study were both injured and mechanically ventilated.

When using the linear mixed model, regression equations are not refined by iteration in either a forward, stepwise, or backward fashion as they are in the general linear model. Variables must be forced individually into the equation and the probabilities examined manually to eliminate variables not contributing significantly to the regression. When all variables were forced into the study regression, the dichotomous dummy variables for ventilation type and drug treatment did not demonstrate sufficient variability to be included in the process; the calculation routine rejected them. Since height/weight and BMI are redundant variables, each was tested separately (Tables 9 & 10). Neither ISS nor APACHE II score contributed significantly. Therefore, the candidate variables were limited to height, weight, BMI, age, and sex, and using only these would not modify a specific older equation, but rather create a new one. The development of new equations will be addressed by Question 3.

*Correcting the Existing Equations*

Serendipitously, a missed communication between members of the research team resulted in a different set of regression equations that were produced using the linear mixed model. Instead of predicting measured REE, the initial set of equations produced for this question predicted the Bland-Altman bias, or the mean difference between predicted REE and measured REE for a particular estimation equation. The combination of the bias-predicting equations with the corresponding original equation could conceivably correct for some portion of the bias.
The bias-predicting equations (BPEs) were developed separately using either height/weight or BMI. In all cases sex is 1 for male and 0 for female; the sedation variable (sed) is 1 if the patient is receiving propofol or a benzodiazepine, and 0 if not receiving either medication.

For Harris-Benedict, the BPEs are:

\[
162.87 - 69.4684(\text{sex}) - 1.3495(\text{age}) - 2.9199(\text{ht/cm}) + 4.6355(\text{wt/kg}) - 157.83(\text{sed})
\]

or

\[
12.6331(\text{BMI}) - 1.7589(\text{age}) - 64.7467(\text{sex}) - 154.72(\text{sed}) - 317.73.
\]

Only sedation contributed significantly to either BPE \((p = 0.0206 \text{ and } p = 0.0190, \text{ respectively})\). Details regarding the H-B BPEs are found in Tables 11a and 11b (p. 93).

For Mifflin-St. Jeor, the BPEs are:

\[
0.7038(\text{age}) - 45.1523(\text{sex}) + 3.8904(\text{ht/cm}) + 9.7339(\text{wt/kg}) - 718.69
\]

or

\[
125.32(\text{sex}) + 41.4986(\text{BMI}) - 1.0038(\text{age}) - 140.5(\text{sed}) - 363.85.
\]
Only weight contributed significantly to the first BPE, \( p = 0.0122 \). BMI \( (p < 0.0001) \) and sedation \( (p = 0.0384) \) were significant contributors to the second. Details regarding the Mifflin BPEs are found in Tables 12a and 12b (p. 94).

For Ireton-Jones 1992, the BPEs are:

1441.60 + 397.19(sex) – 6.6198(age) - 3.4735(ht/cm) + 7.9684(wt/kg)

or

657.98 + 430.84(sex) – 7.7691(age) + 34.2091(BMI) – 149.35(sed).

In the first BPE, significant variables were sex \( (p = 0.0146) \), age \( (p = 0.0222) \), and weight \( (p = 0.0317) \). All parameters except the intercept (i.e., sex, age, BMI, and sedation) were significant in the second \( (p = 0.0002, p = 0.0025, p < 0.0001 \) and \( p = 0.0239 \), respectively). Details of the Ireton-Jones 1992 BPEs are found in Tables 13a and 13b (p. 95).

For Ireton-Jones 2002, the BPEs are:

2566.60 + 46.6377(sex) – 6.7144(age) – 9.9021(ht/cm) + 3.0399(wt/kg) – 162.89(sed)

or

977.08 – 73.1296(sex) – 6.5816(age) + 6.7413(BMI) – 166.35(sed).
Age \( (p = 0.0124 \text{ and } p = 0.0143, \text{ respectively}) \) and sedation \( (p = 0.0240 \text{ and } p = 0.0194, \text{ respectively}) \) were the only significant contributors to either BPE. Details of the Ireton-Jones 2002 BPEs are found in Tables 14a and 14b (p. 96).

For Penn State, the BPEs are:

\[
0.04248(\text{age}) - 81.6009(\text{sex}) + 6.7994(\text{ht/cm}) + 9.8535(\text{wt/kg}) - 757.62
\]

or

\[
55.6261 + 123.86(\text{sex}) + 38.7891(\text{BMI}) - 1.8866(\text{age}).
\]

Only weight contributed significantly to the first BPE \( (p = 0.0078) \). BMI was the only significant contributor to the second BPE \( (p < 0.0001) \). Details of the Penn State BPEs are found in Tables 15a and 15b.

**Conclusions**

A multiple regression using the linear mixed model for unbalanced repeated measures did not reveal any variables that consistently and significantly improved the candidate equations. However, a separate regression model produced a set of bias-predicting equations (BPEs) for each candidate equation, enabling prediction (and possible correction) of the bias of each candidate equation. These BPEs showed that the sedation of subjects sometimes could account for a significant portion of the bias, but the significance of sedation was not consistent across equations.

**Question 3**

Question 3 asked whether it was possible to construct an alternative equation to predict MREE in this population, specifically one with greater precision and less bias.
Since bias and precision cannot be estimated from the same population used to derive a regression equation, that part of the question cannot be answered until a second sample is gathered. However, the sample REE measurements were used, in linear mixed model regressions, to develop two new equations: one based on height and weight, and the other on BMI. Specifically, the new equations are:

predicted REE = 21.32 + 211.84(sex) – 3.94(age) + 9.97(weight) + 8.1(height)

and

predicted REE = 1446.23 + 499.01(sex) – 4.46(age) + 32.49(BMI).

In the first equation, only weight was a significant contributor ($p < 0.0001$). In the second equation, there were three predictors, namely BMI, sex, and the intercept with $p < 0.0001$. Further details about both equations are found in Tables 16 and 17 (pp. 98 – 99).

In conclusion, it was possible to construct new equations, using only the variables that remained in the mixed model regressions from Question 2. Two equations were developed, with one using weight and height, and one using BMI. However, it was not possible to evaluate the equations for bias and precision using the study data.

**Summary**

The specific questions involved in this investigation were all answered successfully. The Bland-Altman analysis and subsequent ANOVA by linear mixed model supported the Harris-Benedict equation, without multipliers, as the most accurate in the
subject population. Equations were developed to correct the five target equations for their bias, as that bias existed in this subject population. Finally, two new estimation equations, specifically for mechanically ventilated, seriously injured individuals, were developed. Both the corrected target equations and the new equations need to be validated.
Chapter V

Discussion

The study described in this dissertation was designed to answer three questions: (1) which of five classic prediction equations best estimated REE in seriously injured subjects; (2) whether the addition of other parameters could improve existing prediction equations; and (3) whether a new prediction equation could be designed specifically for seriously injured individuals. Retrospective chart review yielded 106 data points on 83 subjects. The data were analyzed using the linear mixed model for unbalanced repeated measures. Analysis of the data allowed substantive responses to all three study questions.

Implications of Findings

This final chapter will relate the findings from Chapter IV to the literature reviewed in Chapter II, discuss limitations of the methodology described in Chapter III, and suggest directions for future research. The relation of findings to the wider literature is addressed in regard to each study question; the limitations and directions for future research are discussed globally for all three questions. The chapter concludes with a discussion of implications for nursing science, practice, and education.

Question 1: Comparing the Accuracy of Candidate Equations

Three areas of discussion arise from the study results related to this question: (1) placing the results of question 1 in the context of the current state of the science; (2) proposing potential explanations of the findings; and (3) using ANOVA to compare the accuracy of the candidate equations. Each will be discussed in turn.

Placing findings in context. The literature reviewed in Chapter II yielded varied evaluations of the classic Harris-Benedict (H-B) equation. Six studies found that the H-
B equation estimated energy needs more accurately than the other equations that were studied; one of those studies was specifically carried out in trauma and burn patients (Stucky et al., 2008) and noted that using “stress factors” caused poorer accuracy. This notion agreed with our findings. Five other studies, one of which was in injured subjects (Paauw et al., 1984), found the H-B equation adequate but not superior. Three studies characterized the H-B equation as inaccurate, but were not specific as to its tendency to under- or over-predict energy needs. Seven studies concluded that the H-B equation systematically overpredicted REE, but only two investigations determined that it underpredicted REE. These findings are summarized in Table 18 (p. 100).

None of the cited studies, regardless of their conclusions, defined clinical significance, so bias of as little as 5% (e.g., 60 kcal/day of a 1200 kcal/day regimen) led to the equation being characterized as inadequate. Feurer et al. (1983) claimed that the H-B equation was inaccurate because fewer than 60% of patients were predicted within 10% of measured values, even though that 10% would equal only 120 kcal/day in a 1200 kcal/day regime. None of the equations tested in the current study was capable of predicting within 10% of measured values in more than 40% of subjects, so by the standards of Feurer and associates, every tested equation was inadequate. Our definition of clinical significance (i.e., a deficit or excess of 500 kcal/day) is more liberal than previous studies have allowed; the reason for the use of such stringent limits by other investigators is not clear.

Possible explanations for the results. What other factors could cause the H-B equation to perform so much better in this sample than in many past studies? Stucky et al. (2008) had a sample comprised of subjects with serious injuries and their results substantially agreed with our findings. Is there something about individuals with
serious injuries that causes an estimation equation to work well, when the same
equation works poorly in other patient groups?

One potential answer is derived from an examination of the sample Harris and
Benedict (1919) used to develop their equations. Their sample was made up of young,
healthy individuals from an era in which physical activity was more prevalent than today
(Frankenfield et al., 1998). Trauma, as the leading cause of death in the U.S. for
individuals under 44 years of age (Finkelstein, Corso, & Miller, 2006), is primarily a
disease of young, otherwise healthy people. Although the average age of the subjects in
the current study was 53, only 10.8% of the sample had a history of chronic disease.
Therefore, perhaps the similarity of the age and health of many trauma patients to the
original Harris-Benedict sample causes a greater degree of correspondence between the
Harris-Benedict estimates and measured REE.

*Using ANOVA to compare estimates.* Since the Bland-Altman bias is a mean, and
analysis of variance was designed to compare a group of means against one another, it
would seem that this method could be useful for comparing measures of accuracy.
However, to the limits of the Chapter II literature search, no other investigation had
previously used the Bland-Altman bias in such a manner, to compare accuracy of
estimation equations via analysis of variance.

Our analysis found that the biases were significantly different from one another,
and each pairwise comparison was likewise significant. If we accept the results of the
Bland-Altman analysis as evidence that the H-B equation is the most accurate equation
in this population, then significantly different biases equates to significantly worse
accuracy using other equations. Using ANOVA to compare equations enables
quantitative comparison across methods of estimation.
Question 2: Improving the Accuracy of the Candidate Equations

As described in Chapter III, the analysis method of Bland & Altman (1986) was developed expressly for the purpose of comparing methods of measurement. One method (i.e., indirect calorimetry) is designated as the reference method, and the second method (i.e., estimation by equation in our study) is compared to it. Since the Bland-Altman bias is a mean, it can be used in the same types of analyses as any other mean, enabling the analysis of variance in question 1. Because the Bland-Altman bias comes from a pair of numbers, the reference measurements and their differences can be used to develop a regression equation to predict the bias, as with any other pair of values.

Wider implications of bias prediction. The Bias-Prediction Equation (BPE) provides a method for compensating for bias. If the difference is predictable, it can be removed from the estimate by combining the original terms of the equation with the terms of the BPE. An example will clarify this concept.

The original Harris-Benedict equation for men is given in Chapter II as equation 1:

\[ 66.4730 + 13.7516(\text{wt}) + 5.0033(\text{ht}) - 6.7550(\text{age}) = \text{REE} \]

A regression performed using the Bland-Altman bias of the Harris-Benedict equation in this sample resulted in the following BPE:

\[ 162.87 + 4.6335(\text{wt}) - 2.9199(\text{ht}) - 1.3495(\text{age}) - 69.4684(\text{sex}) - 157.83(\text{sedation}) = \text{bias} \]
Since with men, \( \text{sex} = 1 \), the 69.4684 can be subtracted directly from 162.87 to simplify the BPE, yielding the following:

\[
92.3384 + 4.6335(\text{wt}) - 2.9199(\text{ht}) - 1.3495(\text{age}) - 157.83(\text{sedation}) = \text{bias}
\]

Since the bias of the Harris-Benedict equation is negative, the BPE is added to the original equation, producing the adjusted equation:

\[
158.8110 + 18.3871(\text{wt}) + 2.0834(\text{ht}) - 8.1045(\text{age}) - 157.83(\text{sedation}) = \text{adjusted REE}.
\]

The sedation term is 1 if the patient is on continuous or intermittent sedation, and 0 if not on sedation.

The importance of this method, if verified in practice, is that it could be used with any surrogate method of estimation when compared with a reference method, preferably a “gold standard,” to improve the accuracy of the surrogate. Clinical practice involves many different surrogate measures, and given the existence of a gold standard, our method could be used to minimize the systematic error of any surrogate.

The sedation term. The second remarkable finding about the correction equations relates to the recurrence of a new term, correcting the estimation for the effects of sedation. Previous studies had found a reduction in REE with sedation, most notably Terao and co-investigators (2003). In four of the five equations developed for the current study, a sedation term was part of the adjustment; only the Penn State equation did not require such adjustment (see Tables 11 – 15). To explain the unique results of the Penn State BPE, it is significant that Terao found that respiratory variables
decreased in sedated patients as well. Since the Penn State equation includes expired minute ventilation, a respiratory variable, it is possible that the change in ventilation is adequate to adjust for sedation.

The vast majority of patients in our sample were sedated, usually with propofol (Diprivan®), a drug developed for induction of anesthesia. This drug has widely been adopted for procedural sedation, as well as continuous sedation of those who struggle against mechanical ventilation. It is possible that the sedation term may be an artifact of such frequent use, but its lack of significance in an equation containing a ventilatory term argues against that possibility. In any case, the effects of sedation should be considered in any equation developed for patients on mechanical ventilation, even though our results for Question 3 discarded the term for lack of variability.

Question 3: Developing More Accurate Equations

BMI has been used for 30 years to characterize body fatness (Garrow & Webster, 1985b) and has been found to have a closer correspondence with adiposity than simple measurements of height and weight (Food and Nutrition Board, 2005). Adiposity is inversely related to fat-free mass, and fat-free mass directly impacts resting energy expenditure (Cunningham 1980, 1991; Mifflin et al., 1990).

In spite of the close relationship between fat-free mass and BMI, the literature search described in Chapter II found no REE-estimation equations using BMI as a parameter. When such an equation was developed as part of this study, along with one based on height and weight, the BMI equation yielded three of four terms with statistical significance. On the other hand, the equation using height and weight measurements had only one out of five terms reaching significance. BMI is easily available as part of the standard admission assessment, along with the other parameters in the equation
(i.e., age and gender). Use of a short, simple equation containing BMI could provide an easy and quick estimation of energy needs.

Conclusions

All three questions addressed by this investigation have been successfully answered. The determination that Harris and Benedict’s equation is the most accurate in a seriously injured sample agrees with previous investigations using similar samples, even though studies on other subject groups often found the H-B equation lacking in accuracy. The reason for increased accuracy of the H-B in this population could be the young age and otherwise healthy state of many injured patients, similar to the subjects used to develop the H-B.

The affirmative answer to the second question enables an attempt to correct for the systematic error in the equations. Moreover, the methodology devised to answer the question may have a wider function, by allowing determination and correction of systematic error in other estimation functions. Additionally, some of the newly developed equations incorporated a term for sedation, emphasizing the importance of drug therapy in the determination of energy needs in this population.

The differences in significance between the terms of the two equations developed to answer the third study question may be due to the use of BMI rather than height and weight measurements. The use of BMI to estimate energy needs is supported by previous findings that BMI is more predictive of adiposity (and therefore of fat-free mass) than height and weight measurements. Fat-free mass, a major influence on REE, is not easily measured at the bedside; therefore, a more precise surrogate measure of fat-free mass may predict REE more accurately.
Limitations of the Study

A discussion of the limitations of this study will address limitations of the sample, the method, and the analysis.

Limitations of Sample

The first limitation of the sample was its size. Although the absence of an established method for determining effect size in the linear mixed model made power calculations difficult, power was estimated using a general linear model calculation using only one measurement per subject. Using the G-Power program (Faul, Erdfelder, Lang, & Buchner, 2007), power was estimated to be greater than 0.90 for this sample size. Calculations based on the F ratio for the one-way ANOVA demonstrated power of 1.0 with an F-ratio of 60; the F-ratio for our ANOVA was > 600. Nevertheless, a larger sample would have made it possible to test for changes in bias across BMI classes or even to look at the continuous covariance of bias with BMI. Also, a sufficiently large sample could have been divided into groups with one group of subjects used to develop equations and the other to test those equations.

The small size of the sample also exacerbated other limitations, including lack of ethnic diversity and lack of variability across drug treatment and ventilatory modes. A larger sample would have allowed for comparison across the drug treatment and ventilatory mode subgroups.

Another limitation of the sample was its restriction to intubated patients. Unfortunately, at the facility where the study was conducted, the equipment needed to measure REE on subjects who are neither tracheostomized nor intubated was not available. Limiting measurement to those needing ventilatory support may be partially responsible for the severity of both illness and injury in the study sample.


**Limitations of Method**

Two limitations of the study methods were related to the time-dependency of certain parameters in the predictive equations. In the Penn State equation, a measurement of expired minute ventilation was required during the period of indirect calorimetry. Our calorimetry reports did not include the time of the test, and ventilator parameters were only recorded every 2 – 4 hours. Calorimetry was usually performed between 7 a.m. and 10 a.m.; therefore, the 8 a.m. measurement was chosen for use in this study. It is possible that there may have been a significant difference between expired minute ventilation at 8 a.m. and at the time of calorimetry. Nonetheless, calorimetry was not performed on patients who are physiologically unstable, so the chance that there was an important difference in the minute ventilation over a few hours’ time is small.

A second limitation of the methods was also related to timing, but in a different way. The APACHE II score is optimally calculated using the most abnormal value for each of the parameters of the score during the first 24 hours of hospitalization (Knaus et al., 1985). With some exceptions, the most abnormal value usually occurs on admission; therefore, it is likely that these values are assessed in the Emergency Department. In a few cases, the Emergency Department values were not available, and the first available inpatient measurements were used instead, which may have caused inaccuracy in APACHE II scores. However, Emergency Department values were missing for only 7 subjects in the study.

Finally, the APACHE II score required recoding of the Glasgow Coma Score (GCS) (Teasdale & Jennett, 1974), which introduced another possible limitation. One of the three variables included in the GCS is the patient’s best verbal response; however, no
verbal response is possible when subjects are intubated. It was the facility’s practice to include the minimum points for verbal response in an intubated patient, regardless of the subject’s other communication skills. However, APACHE II scoring requires that an estimate of the patient’s communication skill be made and a score for verbal response be given according to that estimate. Since the investigator did not see every subject and could not personally describe the communication ability of each, it is possible that recoding of the GCS could have underestimated the subject’s communication skills. An inaccurate APACHE II score would have been less likely to have a significant relationship with REE. On the other hand, the GCS is only a part of the APACHE II score, so the actual difference of the undercoding by facility standards compared to APACHE standards is unclear.

Limitations of Analysis

The limitations of the data analysis were related to the use of the linear mixed model, made necessary by the unbalanced repeated measures in the sample. Unlike the general linear model, available linear mixed model procedures do not automatically report an effect size; a number of methods for determining $r^2$ have been suggested, but no consensus of method has been reached. However, estimation of power (1.0) was possible using the F-ratio, as reported above.

Likewise, the linear mixed model in SPSS did not provide for automatic insertion of variables or groups of variables into the regression equation; therefore, variables had to be forced into the equation individually and the adjusted $p$ examined for each. When using only the first measurement on each subject, as above, the results of a forward stepwise regression approximated the final results from the linear mixed model.
Conclusion

Limitations existed in this study based on the sample, study methods, and data analyses. In summary, the most notable limitations involved the small sample size, the lack of a precise time at which indirect calorimetry took place, and the lack of a consensus method for estimating effect size in the linear mixed model. The extent of inaccuracy each limitation would cause is unclear. In addition, using the (smaller) sample of one measurement for each subject suggests that power was adequate.

Implications for Nursing

Since this study was performed in partial fulfillment of the requirements for a doctorate in nursing, it is appropriate to examine implications of the findings for nursing science, education, and practice. The greatest implication for nursing science is found in the development of the bias-predicting equation; this method has implications for measurement that reach beyond the strict limits of resting energy expenditure, or nutrition assessment in general. Both physiologic and psychometric measurements are subject to bias, although the means for correcting them differ, and correction is impossible unless the degree of error can be estimated. A method for predicting that error by means of regression could be useful across a wide range of quantitative investigations.

Implications for nursing education and practice are parallel. Estimation of energy needs is part of the nutritional assessment of any individual, ill or well, and part of the nutritional prescription that is a collaborative responsibility of medical, nursing and dietetic personnel. Therefore, indirect calorimetry should be a component of interdisciplinary health care education, as should other methods of determining energy
requirements. Moreover, a quick, simple equation that adequately estimates caloric needs can ensure that the process of energy assessment is carried out for every patient.

**Recommendations for Future Research**

Suggestions for further research can be drawn both from the limitations of the current study and from its implications.

**Recommendations Based on Study Limitations**

To ensure an adequate sample size and simultaneous, accurate measurements, a prospective study with adequate power to compare accuracy of estimation across BMI categories should be conducted. As noted in Chapter I, there is no current evidence as to when changes in resting energy expenditure associated with adiposity begin, so an examination of all classes of BMI could lend valuable information about the onset of those changes. Concurrent prospective data collection will ensure that Emergency Department clinical values are available and that GCS recoding is appropriate. Ensuring balanced repeated measures (or eliminating repeated measures altogether) will enable the use of the general linear model with its effect size estimates and iterative variable entry or removal from regression equations.

Additionally, an optimal replication and extension of the current study would include non-ventilated trauma patients, allowing for investigation of the relationship between severity of illness or injury and REE in a more varied sample, since the limitation of this study sample to those receiving mechanical ventilation positively skewed the severity of illness and injury.

The literature reviewed in Chapter II strongly suggested the possible variation of REE between Caucasians and African Americans, a relationship that deserves investigation across methods of estimation. In addition, smaller bodies of evidence
suggest possible differences of REE in other groups, including natives of China (Liu, Lu, & Chen, 1995), the Indian subcontinent (Soares, Francis, & Shetty, 1993), and Japan (Okura, Koda, Ando, Niino, & Shimokata, 2003). One investigator postulated a relationship between geographic origin and REE (Hayter & Henry, 1994).

A larger sample at one location, however, will guarantee neither increased ethnic diversity nor increased variability in drug administration or ventilator mode utilization. The best possible study would involve more than one facility, so that a broader range of ethnicities, as well as sedatives, analgesics, and weaning modality of choice may be represented.

Recommendations from Study Implications

The first recommendation from study implications involves the discovery of the significance of sedation in systematic error from the prediction equations. It is possible that a dose-response relationship exists between sedation and REE. Use of a larger sample with information about drugs and dosages could clarify such a relationship, if it exists.

Also, validation of the equations developed in this study is needed. Is the new equation with BMI really more accurate than the equation with weight/height in this subject population? Do the Bias-Predicting Equations significantly increase accuracy of REE estimation?

The widest and possibly most important suggestion stemming from the study findings is the validation of the Bias-Predicting Equation methodology. As discussed earlier, the Bland-Altman bias reflects systematic error; a method for estimating and minimizing that error using predictive equations could be used in many instances when research or patient care requires estimation of a physical parameter. If found to be
useful, the Bias-Predicting Equation method has implications for minimizing inaccuracy in many kinds of estimation methods. For instance, the Bias-Predicting Equation method could be tested in algorithms used in instruments that estimate cardiac output non-invasively.

Conclusion

The preceding five chapters described and discussed an investigation of equations for predicting REE in the seriously injured. Three questions were posed and answered, and the implications of those answers may carry over into other programs of research.

The study findings agreed with previous investigators who found that in the seriously injured, unlike many other patient groups, the Harris-Benedict equation corresponded more closely to measured REE than the other candidate equations. Further studies could uncover the precise characteristics of injured patients that cause that close correspondence. Additionally, an easy-to-remember, simple-to-calculate new prediction equation was generated specifically for seriously injured individuals. Future investigations need to validate the accuracy of the new equation, and explore its accuracy in other critically ill populations.

Finally, this study developed a new and unique method for deriving Bias-Predicting Equations that could be used to minimize error in existing equations for estimating REE. If the bias-predicting method successfully improves accuracy in REE estimation, the method could be tried in equations for the estimation of other physiological parameters. Eventually, bias-prediction could increase the validity of many methods of calculating physiologic values from directly or indirectly measured parameters.
This work has opened doors, not only in nutrition support of seriously injured individuals, but possibly into the wider world of physiologic instrumentation. It is hoped that this effort will yield theoretical and practical knowledge to improve patient care.
Table 1

*Schofield (1985) Equations for Estimation of Resting Energy Expenditure According to Age and Sex*

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Sex</th>
<th>Equation 1</th>
<th>Equation 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 30 years of age</td>
<td>Male</td>
<td>0.063 (wt) + 2.896</td>
<td>0.063 (wt) – 0.42 (ht) + 2.953</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.062 (wt) + 2.036</td>
<td>0.057 (wt) + 1.184 (ht) + 0.411</td>
</tr>
<tr>
<td>30 – 60 years of age</td>
<td>Male</td>
<td>0.048 (wt) + 3.653</td>
<td>0.048 (wt) – 0.011 (ht) + 3.670</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.034 (wt) + 3.538</td>
<td>0.034 (wt) + 0.006 (ht) + 3.530</td>
</tr>
<tr>
<td>&gt; 60 years of age</td>
<td>Male</td>
<td>0.049 (wt) + 2.459</td>
<td>0.038 (wt) + 4.068 (ht) – 3.491</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.038 (wt) + 2.755</td>
<td>0.033 (wt) + 1.917 (ht) + 0.074</td>
</tr>
</tbody>
</table>

*Note.* Weight is measured in kg. Height is measured in cm. Resting energy expenditure is measured in kcal/day.
Table 2

*FAO/WHO/UNU (1985) equations for estimation of resting energy expenditure in kilocalories (kcal)/day and megajoules (MJ)/day*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Gender</th>
<th>Formula for kcal</th>
<th>Formula for MJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 30 years of age</td>
<td>Male</td>
<td>15.3 (wt) + 679</td>
<td>0.0640 (wt) + 2.94</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>14.7 (wt) + 496</td>
<td>0.0615 (wt) + 2.08</td>
</tr>
<tr>
<td>30 – 60 years of age</td>
<td>Male</td>
<td>11.6 (wt) + 879</td>
<td>0.0485 (wt) + 3.67</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8.7 (wt) + 829</td>
<td>0.0364 (wt) + 3.47</td>
</tr>
<tr>
<td>&gt; 60 years of age</td>
<td>Male</td>
<td>13.5 (wt) + 487</td>
<td>0.0565 (wt) + 2.04</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10.5 (wt) + 596</td>
<td>0.0439 (wt) + 2.49</td>
</tr>
</tbody>
</table>

*Note.* Weight is measured in kg.
Table 3

*Composition of Samples of Critically Ill Subjects in Studies for Validation of Resting Energy Expenditure Estimation Methods*

<table>
<thead>
<tr>
<th>Study</th>
<th>% subjects trauma</th>
<th>% subjects surgery</th>
<th>% subjects ventilated</th>
<th>% subjects burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al., 1995</td>
<td>15%</td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Barak et al., 2002</td>
<td></td>
<td>26.1%</td>
<td>43%</td>
<td>5%</td>
</tr>
<tr>
<td>Barco, Smith, Peerless,</td>
<td>100%</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Plaisier, &amp; Chima, 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boulanger, Nayman, McLean,</td>
<td>100%</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Phillips, &amp; Rizoli, 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boullata et al., 2007</td>
<td></td>
<td>40%</td>
<td>35.7%</td>
<td></td>
</tr>
<tr>
<td>Casati et al., 1996</td>
<td>44%</td>
<td>38%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Flancbaum et al., 1999</td>
<td>11%</td>
<td>83%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Frankenfield, Coleman, Alam</td>
<td>26%</td>
<td>32%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&amp; Cooney, 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frankenfield et al., 2004</td>
<td>30%</td>
<td>57%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Glynn et al., 1999</td>
<td>12%</td>
<td></td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Ireton-Jones &amp; Jones, 2002</td>
<td>24%</td>
<td>56%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>MacDonald &amp; Hildebrandt, 2003</td>
<td>17%</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>% subjects</td>
<td>% subjects</td>
<td>% subjects</td>
<td>% subjects</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>trauma</td>
<td>surgery</td>
<td>ventilated</td>
<td>burns</td>
</tr>
<tr>
<td>Savino, Dawson, Agarwal, Moggio, &amp; Scalea, 1985</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sherman, 1994</td>
<td>4%</td>
<td>4%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Stucky, Moncure, Hise, Gossage &amp; Northrop, 2008</td>
<td>68%</td>
<td></td>
<td>100%</td>
<td>32%</td>
</tr>
<tr>
<td>Sunderland &amp; Heilbrun, 1992</td>
<td>100%</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Swinamer et al., 1990</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swinamer, Phang, Jones, Grace, &amp; King, 1987</td>
<td>30%</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Grace, &amp; King, 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Lanschot, Feenstra, Vermeu, &amp; Bruining, 1986</td>
<td>16%</td>
<td>32%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Weissman et al., 1996</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4

*Summary of Study Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>at subject’s last birthday</td>
</tr>
<tr>
<td>analgesia</td>
<td>administration of opioids, continuously or intermittently</td>
</tr>
<tr>
<td>APACHE II</td>
<td>an estimation of severity of illness drawn from physiological parameters on the day of admission; severe illness is APACHE II &gt; 17</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index, subject weight in kilograms divided by the square of the height in meters</td>
</tr>
<tr>
<td>burn</td>
<td>presence or absence of burn injury on admission; burn injury greater than 20% total body surface area is an exclusion criterion</td>
</tr>
<tr>
<td>gender</td>
<td>male or female</td>
</tr>
<tr>
<td>Harris-Benedict</td>
<td>energy expenditure estimated via equation 1 or 2</td>
</tr>
<tr>
<td>Ireton-Jones 1992</td>
<td>energy expenditure estimated via equation 7</td>
</tr>
<tr>
<td>Ireton-Jones 2002</td>
<td>energy expenditure estimated via equation 11</td>
</tr>
<tr>
<td>ISS</td>
<td>an estimation of severity of injury, incorporating the three most seriously-injured areas of the body; serious injury is ISS &gt; 16</td>
</tr>
<tr>
<td>Mifflin-St. Jeor</td>
<td>energy expenditure estimated via equation 6</td>
</tr>
<tr>
<td>minute ventilation</td>
<td>liters per minute of exhaled gases, measured by the ventilator</td>
</tr>
<tr>
<td>MREE</td>
<td>energy expenditure measured via indirect calorimetry</td>
</tr>
<tr>
<td>Penn State</td>
<td>energy expenditure estimated via equation 16</td>
</tr>
</tbody>
</table>

85
| pressors | administration of intravenous dopamine or epinephrine |
| sedation | administration of intravenous benzodiazepine or propofol |
| temperature | body temperature measured orally or via thermistor catheter |
| ventilator mode | assist/control, IMV, or pressure-supported |
Table 5:

*Descriptive Characteristics of Study Sample (N = 83; 18 females; 85 males)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>175.2 (10.41)</td>
<td>145 - 198</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90.0 (23.9)</td>
<td>49.9 – 194.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 (19)</td>
<td>20 – 90</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>29 (7)</td>
<td>18.3 – 58.2</td>
</tr>
<tr>
<td>ISS</td>
<td>25 (11)</td>
<td>4 – 50</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17 (7)</td>
<td>3 – 35</td>
</tr>
</tbody>
</table>

*Note.* ISS = Injury Severity Score; APACHE II = Acute Physiology and Chronic Health Evaluation, a measure of severity of illness.
Table 6

*Correlation Matrix between Measured Resting Energy Expenditure and Estimates of Resting Energy Expenditure Using the Five Candidate Equations*

<table>
<thead>
<tr>
<th></th>
<th>MREE</th>
<th>Mifflin</th>
<th>IJ 1992</th>
<th>IJ 2002</th>
<th>Penn St.</th>
<th>H-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>MREE</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mifflin</td>
<td>0.623*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IJ 1992</td>
<td>0.632*</td>
<td>0.947*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IJ 2002</td>
<td>0.568*</td>
<td>0.864*</td>
<td>0.941*</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penn St.</td>
<td>0.664*</td>
<td>0.968*</td>
<td>0.910*</td>
<td>0.834*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>H-B</td>
<td>0.607*</td>
<td>0.975*</td>
<td>0.956*</td>
<td>0.901*</td>
<td>0.944*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note. MREE = measured resting energy expenditure; Mifflin = Mifflin-St. Jeor Equation; IJ 1992 = 1992 Ireton-Jones Equation; IJ 2002 = 2002 Ireton-Jones Equation; Penn St. = Penn State Equation; H-B = Harris-Benedict Equation. *p < 0.05*
Table 7:

*Bland-Altman Bias, Limits of Agreement, and Accuracy (i.e., the Number of Subjects within 10% and within 500 kcal/day of Measured Resting Energy Expenditure) for the Five Candidate Equations*

<table>
<thead>
<tr>
<th>Equation</th>
<th>Bias</th>
<th>Limits of agreement</th>
<th>Subjects within 10%</th>
<th>Subjects within 500 kcal/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris-Benedict</td>
<td>-248.1</td>
<td>-1136.2 – +640.0</td>
<td>42 (39.6%)</td>
<td>74 (70.5%)</td>
</tr>
<tr>
<td>Mifflin-St. Jeor</td>
<td>+748.6</td>
<td>-277.9 – +1775.1</td>
<td>22 (20.8%)</td>
<td>34 (32.1%)</td>
</tr>
<tr>
<td>Ireton-Jones 1992</td>
<td>+1428.3</td>
<td>+360.1 – +2496.5</td>
<td>2 (1.9%)</td>
<td>4 (3.8%)</td>
</tr>
<tr>
<td>Ireton-Jones 2002</td>
<td>+588.5</td>
<td>-339.6 – +1516.6</td>
<td>20 (18.9%)</td>
<td>37 (34.9%)</td>
</tr>
<tr>
<td>Penn State</td>
<td>+1143.8</td>
<td>+77.61 – +2209.9</td>
<td>3 (2.8%)</td>
<td>8 (7.5%)</td>
</tr>
</tbody>
</table>
Table 8

**Scheffé Pairwise Post-Hoc Comparisons Between Candidate Equations**

<table>
<thead>
<tr>
<th>equation 1</th>
<th>equation 2</th>
<th>estimate</th>
<th>SE</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireton-Jones 2002</td>
<td>Ireton-Jones 1992</td>
<td>-841.59</td>
<td>37.4204</td>
<td>328</td>
<td>-22.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ireton-Jones 2002</td>
<td>Harris-Benedict</td>
<td>840.58</td>
<td>37.4204</td>
<td>328</td>
<td>22.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ireton-Jones 2002</td>
<td>Penn State</td>
<td>-606.84</td>
<td>37.4204</td>
<td>328</td>
<td>-16.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ireton-Jones 2002</td>
<td>Mifflin-St. Jeor</td>
<td>-166.27</td>
<td>37.4204</td>
<td>328</td>
<td>-4.44</td>
<td>0.0007</td>
</tr>
<tr>
<td>Ireton-Jones 1992</td>
<td>Harris-Benedict</td>
<td>1682.17</td>
<td>37.4204</td>
<td>328</td>
<td>44.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ireton-Jones 1992</td>
<td>Penn State</td>
<td>234.75</td>
<td>37.4204</td>
<td>328</td>
<td>6.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ireton-Jones 1992</td>
<td>Mifflin-St. Jeor</td>
<td>675.32</td>
<td>37.4204</td>
<td>328</td>
<td>18.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Harris-Benedict</td>
<td>Penn State</td>
<td>-1447.42</td>
<td>37.4204</td>
<td>328</td>
<td>-38.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Harris-Benedict</td>
<td>Mifflin-St. Jeor</td>
<td>-1006.85</td>
<td>37.4204</td>
<td>328</td>
<td>-26.92</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Note.* The p value is adjusted.
Table 9

*Regression Test of Fixed Effects Using Sex, Age, Weight and Height With Variables Added in Attempt to Improve Accuracy*

<table>
<thead>
<tr>
<th>Source</th>
<th>Numerator df</th>
<th>Denominator df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>1</td>
<td>93.960</td>
<td>0.198</td>
<td>0.658</td>
</tr>
<tr>
<td>sex</td>
<td>1</td>
<td>97.484</td>
<td>2.276</td>
<td>0.135</td>
</tr>
<tr>
<td>age</td>
<td>1</td>
<td>90.093</td>
<td>1.072</td>
<td>0.303</td>
</tr>
<tr>
<td>ISS</td>
<td>1</td>
<td>94.278</td>
<td>0.638</td>
<td>0.427</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1</td>
<td>92.107</td>
<td>0.291</td>
<td>0.591</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>1</td>
<td>97.627</td>
<td>26.508</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>height (cm)</td>
<td>1</td>
<td>97.285</td>
<td>2.175</td>
<td>0.144</td>
</tr>
</tbody>
</table>

*Note.* In the linear mixed model, denominator degrees of freedom are calculated rather than fixed. They may not be integers, and may not be equal across the same regression.

ISS = Injury Severity Score; APACHE II = Acute Physiology and Chronic Health Evaluation, a measure of severity of illness.
Table 10

Regression Tests of Fixed Effects Using Sex, Age, and Body Mass Index with Variables Added to Attempt to Improve Accuracy

<table>
<thead>
<tr>
<th>source</th>
<th>Numerator df</th>
<th>Denominator df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>1</td>
<td>96.562</td>
<td>11.30</td>
<td>0.001</td>
</tr>
<tr>
<td>sex</td>
<td>1</td>
<td>99.910</td>
<td>20.214</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>age</td>
<td>1</td>
<td>92.892</td>
<td>1.858</td>
<td>0.176</td>
</tr>
<tr>
<td>BMI</td>
<td>1</td>
<td>97.844</td>
<td>26.116</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ISS</td>
<td>1</td>
<td>98.428</td>
<td>0.153</td>
<td>0.696</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1</td>
<td>91.562</td>
<td>0.033</td>
<td>0.857</td>
</tr>
</tbody>
</table>

Note. In the linear mixed model, denominator degrees of freedom are calculated rather than fixed. They may not be integers, and may not be equal across the same regression.

ISS = Injury Severity Score; APACHE II = Acute Physiology and Chronic Health Evaluation, a measure of severity of illness.
### Table 11a

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Harris-Benedict Equation, Including Weight and Height*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>162.87</td>
<td>958.91</td>
<td>77</td>
<td>0.17</td>
<td>0.8656</td>
</tr>
<tr>
<td>sex</td>
<td>-69.4684</td>
<td>140.87</td>
<td>77</td>
<td>-0.49</td>
<td>0.6233</td>
</tr>
<tr>
<td>age</td>
<td>-1.3495</td>
<td>2.5180</td>
<td>77</td>
<td>-0.54</td>
<td>0.5935</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>4.6335</td>
<td>3.3005</td>
<td>77</td>
<td>1.40</td>
<td>0.1644</td>
</tr>
<tr>
<td>height (cm)</td>
<td>-2.9199</td>
<td>6.1738</td>
<td>77</td>
<td>-0.47</td>
<td>0.6376</td>
</tr>
<tr>
<td>sedation</td>
<td>-157.83</td>
<td>66.7695</td>
<td>77</td>
<td>-2.36</td>
<td>0.0206</td>
</tr>
</tbody>
</table>

### Table 11b

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Harris-Benedict Equation, Including Body Mass Index*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>-317.73</td>
<td>253.85</td>
<td>78</td>
<td>-1.25</td>
<td>0.2144</td>
</tr>
<tr>
<td>sex</td>
<td>-64.7467</td>
<td>109.16</td>
<td>78</td>
<td>-0.59</td>
<td>0.5548</td>
</tr>
<tr>
<td>age</td>
<td>-1.7589</td>
<td>2.4761</td>
<td>78</td>
<td>-0.71</td>
<td>0.4795</td>
</tr>
<tr>
<td>BMI</td>
<td>12.6331</td>
<td>6.3943</td>
<td>78</td>
<td>1.98</td>
<td>0.0517</td>
</tr>
<tr>
<td>sedation</td>
<td>-154.72</td>
<td>64.5998</td>
<td>78</td>
<td>-2.40</td>
<td>0.0190</td>
</tr>
</tbody>
</table>
Table 12a

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Mifflin-St. Jeor Equation, Including Weight and Height*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>-718.69</td>
<td>1128.10</td>
<td>78</td>
<td>-0.64</td>
<td>0.5259</td>
</tr>
<tr>
<td>sex</td>
<td>-45.1523</td>
<td>165.53</td>
<td>78</td>
<td>-0.27</td>
<td>0.7858</td>
</tr>
<tr>
<td>age</td>
<td>0.7038</td>
<td>2.9512</td>
<td>78</td>
<td>0.24</td>
<td>0.8121</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>9.7339</td>
<td>3.7939</td>
<td>78</td>
<td>2.57</td>
<td>0.0122</td>
</tr>
<tr>
<td>height (cm)</td>
<td>3.8904</td>
<td>7.2643</td>
<td>78</td>
<td>0.54</td>
<td>0.5938</td>
</tr>
</tbody>
</table>

Table 12b.

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Mifflin-St. Jeor Equation, Including Body Mass Index*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>-363.85</td>
<td>261.11</td>
<td>78</td>
<td>-1.39</td>
<td>0.1674</td>
</tr>
<tr>
<td>sex</td>
<td>125.32</td>
<td>112.31</td>
<td>78</td>
<td>1.12</td>
<td>0.2679</td>
</tr>
<tr>
<td>age</td>
<td>-1.0038</td>
<td>2.5429</td>
<td>78</td>
<td>-0.39</td>
<td>0.6941</td>
</tr>
<tr>
<td>BMI</td>
<td>41.4986</td>
<td>6.5835</td>
<td>78</td>
<td>6.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sedation</td>
<td>-140.50</td>
<td>66.7154</td>
<td>78</td>
<td>-2.11</td>
<td>0.0384</td>
</tr>
</tbody>
</table>
### Table 13a

**Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the 1992 Ireton-Jones Equation, Including Weight and Height**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>1441.60</td>
<td>1083.92</td>
<td>78</td>
<td>1.33</td>
<td>0.1874</td>
</tr>
<tr>
<td>sex</td>
<td>397.19</td>
<td>159.04</td>
<td>78</td>
<td>2.50</td>
<td>0.0146</td>
</tr>
<tr>
<td>age</td>
<td>-6.6198</td>
<td>2.8377</td>
<td>78</td>
<td>-2.33</td>
<td>0.0222</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>7.9684</td>
<td>3.6419</td>
<td>78</td>
<td>2.19</td>
<td>0.0317</td>
</tr>
<tr>
<td>height (cm)</td>
<td>-3.4735</td>
<td>6.9797</td>
<td>78</td>
<td>-0.50</td>
<td>0.6201</td>
</tr>
</tbody>
</table>

### Table 13b

**Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the 1992 Ireton-Jones Equation, Including Body Mass Index**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>657.98</td>
<td>254.73</td>
<td>78</td>
<td>2.58</td>
<td>0.0117</td>
</tr>
<tr>
<td>sex</td>
<td>430.84</td>
<td>109.55</td>
<td>78</td>
<td>3.93</td>
<td>0.0002</td>
</tr>
<tr>
<td>age</td>
<td>-7.7691</td>
<td>2.4845</td>
<td>78</td>
<td>-3.13</td>
<td>0.0025</td>
</tr>
<tr>
<td>BMI</td>
<td>34.2091</td>
<td>6.4172</td>
<td>78</td>
<td>5.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sedation</td>
<td>-149.35</td>
<td>64.8468</td>
<td>78</td>
<td>-2.30</td>
<td>0.0239</td>
</tr>
</tbody>
</table>
Table 14a

Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the 2002 Ireton-Jones Equation, Including Weight and Height

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>2566.60</td>
<td>1001.51</td>
<td>77</td>
<td>2.56</td>
<td>0.0123</td>
</tr>
<tr>
<td>sex</td>
<td>46.6377</td>
<td>147.12</td>
<td>77</td>
<td>0.32</td>
<td>0.7531</td>
</tr>
<tr>
<td>age</td>
<td>-6.7144</td>
<td>2.6234</td>
<td>77</td>
<td>-2.56</td>
<td>0.0124</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>3.0399</td>
<td>3.4592</td>
<td>77</td>
<td>0.88</td>
<td>0.3822</td>
</tr>
<tr>
<td>height (cm)</td>
<td>-9.9021</td>
<td>6.4486</td>
<td>77</td>
<td>-1.54</td>
<td>0.1287</td>
</tr>
<tr>
<td>sedation</td>
<td>-162.89</td>
<td>70.7618</td>
<td>77</td>
<td>-2.30</td>
<td>0.0240</td>
</tr>
</tbody>
</table>

Table 14b

Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the 2002 Ireton-Jones Equation, Including Body Mass Index

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>977.08</td>
<td>270.50</td>
<td>78</td>
<td>3.61</td>
<td>0.0005</td>
</tr>
<tr>
<td>sex</td>
<td>-73.1296</td>
<td>116.38</td>
<td>78</td>
<td>-0.63</td>
<td>0.5316</td>
</tr>
<tr>
<td>age</td>
<td>-6.5816</td>
<td>2.6253</td>
<td>78</td>
<td>-2.51</td>
<td>0.0143</td>
</tr>
<tr>
<td>BMI</td>
<td>6.7413</td>
<td>6.8340</td>
<td>78</td>
<td>0.99</td>
<td>0.3270</td>
</tr>
<tr>
<td>sedation</td>
<td>-166.35</td>
<td>69.7115</td>
<td>78</td>
<td>-2.39</td>
<td>0.0194</td>
</tr>
</tbody>
</table>
Table 15a

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Penn State Equation, Including Weight and Height*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>-757.62</td>
<td>1091.53</td>
<td>78</td>
<td>-0.69</td>
<td>0.4897</td>
</tr>
<tr>
<td>sex</td>
<td>-81.6009</td>
<td>159.82</td>
<td>78</td>
<td>-0.51</td>
<td>0.6111</td>
</tr>
<tr>
<td>age</td>
<td>0.04248</td>
<td>2.8877</td>
<td>78</td>
<td>0.01</td>
<td>0.9883</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>9.8535</td>
<td>3.6049</td>
<td>78</td>
<td>2.73</td>
<td>0.0078</td>
</tr>
<tr>
<td>height (cm)</td>
<td>6.7994</td>
<td>7.0254</td>
<td>78</td>
<td>0.97</td>
<td>0.3361</td>
</tr>
</tbody>
</table>

Table 15b

*Regression Test of Fixed Effects, Bias-Predicting Equations to Correct Systematic Error in the Penn State Equation, Including Body Mass Index*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>55.6261</td>
<td>255.88</td>
<td>79</td>
<td>0.22</td>
<td>0.8285</td>
</tr>
<tr>
<td>sex</td>
<td>123.86</td>
<td>110.81</td>
<td>79</td>
<td>1.12</td>
<td>0.2671</td>
</tr>
<tr>
<td>age</td>
<td>-1.8866</td>
<td>2.5763</td>
<td>79</td>
<td>-0.73</td>
<td>0.4662</td>
</tr>
<tr>
<td>BMI</td>
<td>38.7891</td>
<td>6.3639</td>
<td>79</td>
<td>6.10</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 16

Regression Test of Fixed Effects, New Equation Based on Study Sample, Using Weight/Height

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>-21.319</td>
<td>1005.34</td>
<td>99.894</td>
<td>-0.021</td>
<td>0.983</td>
</tr>
<tr>
<td>sex</td>
<td>-211.84</td>
<td>133.40</td>
<td>99.511</td>
<td>-1.588</td>
<td>0.115</td>
</tr>
<tr>
<td>age</td>
<td>-3.9374</td>
<td>2.4512</td>
<td>99.448</td>
<td>-1.606</td>
<td>0.111</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>9.9701</td>
<td>1.9539</td>
<td>99.475</td>
<td>5.103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>height (cm)</td>
<td>8.1004</td>
<td>5.8534</td>
<td>99.971</td>
<td>1.384</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Note. In the linear mixed model, denominator degrees of freedom are calculated rather than fixed. They may not be integers, and may not be equal across the same regression.
Table 17

*Regression Test of Fixed Effects, New Equation Based on Study Sample, Using Body Mass Index*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>1446.22</td>
<td>224.95</td>
<td>100.301</td>
<td>6.429</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sex</td>
<td>-499.02</td>
<td>110.63</td>
<td>101.88</td>
<td>-4.511</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>age</td>
<td>-4.4574</td>
<td>2.5761</td>
<td>98.493</td>
<td>-1.730</td>
<td>0.087</td>
</tr>
<tr>
<td>BMI</td>
<td>32.493</td>
<td>6.3364</td>
<td>99.080</td>
<td>5.128</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Note.* In the linear mixed model, denominator degrees of freedom are calculated rather than fixed. They may not be integers, and may not be equal across the same regression. BMI = body mass index.
### Table 18

**Summary of Findings of Prior Validation Studies of the Harris-Benedict Equation**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Findings</th>
<th>Sample</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al., 1995</td>
<td>best</td>
<td>obese, ICU, ventilated</td>
<td>high bias, low precision</td>
</tr>
<tr>
<td>Boullata et al.,</td>
<td>best</td>
<td>ICU, ventilated</td>
<td>low bias, high precision</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glynn et al., 1999</td>
<td>best</td>
<td>obese, ICU, ventilated</td>
<td>best bias</td>
</tr>
<tr>
<td>Lazzer et al., 2007</td>
<td>best</td>
<td>obese healthy, all female</td>
<td></td>
</tr>
<tr>
<td>Stucky, 2008</td>
<td>best</td>
<td>all trauma and burn</td>
<td>worse with “stress factors”</td>
</tr>
<tr>
<td>Taaffe et al., 1995</td>
<td>best</td>
<td>healthy, all female</td>
<td>within 116 kcal/day</td>
</tr>
<tr>
<td>de Lorenzo et al.,</td>
<td>adequate</td>
<td>healthy</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livingston &amp; Kohlstadt, 2005</td>
<td>adequate</td>
<td>healthy</td>
<td></td>
</tr>
<tr>
<td>Paauw et al., 1984</td>
<td>adequate</td>
<td>ICU, ventilated</td>
<td>no significant difference from REE</td>
</tr>
<tr>
<td>Reference</td>
<td>Findings</td>
<td>Sample</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Reid, 2007</td>
<td>adequate</td>
<td>ICU, ventilated</td>
<td>mean bias of 111 kcal/day</td>
</tr>
<tr>
<td>Roza &amp; Shisgal, 1984</td>
<td>adequate</td>
<td>“normals”</td>
<td>within 14% of REE</td>
</tr>
<tr>
<td>Feurer</td>
<td>poor</td>
<td>obese healthy</td>
<td>&lt;60% of REE values predicted within 10%</td>
</tr>
<tr>
<td>Frankenfeld et al., 1984</td>
<td>poor</td>
<td>ICU, ventilated</td>
<td>only 30% of variance explained</td>
</tr>
<tr>
<td>Sunderland &amp; Heilbrun, 1992</td>
<td>poor</td>
<td>ICU, ventilated</td>
<td>only 22% of variance explained</td>
</tr>
<tr>
<td>Das et al., 2004</td>
<td>underpredicted</td>
<td>ICU, ventilated</td>
<td></td>
</tr>
<tr>
<td>Swinamer et al., 1987</td>
<td>underpredicted</td>
<td>ICU, ventilated</td>
<td>underpredicted by 20%</td>
</tr>
<tr>
<td>Boothby &amp; Sandiford, 1922</td>
<td>overpredicted</td>
<td>healthy</td>
<td>overpredicted by 42%</td>
</tr>
<tr>
<td>Daly et al., 1985</td>
<td>overpredicted</td>
<td>healthy</td>
<td>in 88% of patients</td>
</tr>
<tr>
<td>Dobratz et al., 2007</td>
<td>overpredicted</td>
<td>obese healthy</td>
<td></td>
</tr>
<tr>
<td>Garrel et al., 1996</td>
<td>overpredicted</td>
<td>healthy</td>
<td>overprediction proportional to REE</td>
</tr>
<tr>
<td>Reference</td>
<td>Findings</td>
<td>Sample</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Mifflin et al., 1990</td>
<td>overpredicted</td>
<td>healthy</td>
<td>Overpredicted by 5%</td>
</tr>
<tr>
<td>Owen et al., 1986 &amp; 1987</td>
<td>overpredicted</td>
<td>healthy</td>
<td></td>
</tr>
<tr>
<td>Scalfi et al., 1993</td>
<td>overpredicted</td>
<td>healthy</td>
<td>all over 40 years of age</td>
</tr>
</tbody>
</table>

*Note.* Findings are those of the study authors. Best = met authors’ criteria for adequacy better than other studied equations. Adequate = met authors’ criteria for adequacy. Poor = did not meet authors’ criteria for adequacy.
Figure 1. Scatterplot of measured resting energy expenditure (MREE) vs. resting energy expenditure (REE) estimated by the Harris-Benedict equation.
Figure 2. Scatterplot of measured resting energy expenditure (MREE) vs. resting energy expenditure (REE) estimated by the Mifflin-St. Jeor equation.
Figure 3. Scatterplot of measured resting energy expenditure (MREE) vs. resting energy expenditure (REE) estimated by the 1992 Ireton-Jones equation.
Figure 4. Scatterplot of measured resting energy expenditure (MREE) vs. resting energy expenditure (REE) estimated by the 2002 Ireton-Jones equation.
Figure 5. Scatterplot of measured resting energy expenditure (MREE) vs. resting energy expenditure estimated (REE) by the Penn State equation.
Figure 6. Scatterplot of the difference between measured and calculated resting energy expenditure vs. the mean of measured and calculated resting energy expenditure, using the Harris-Benedict equation. Dotted line marks the mean difference between measured and calculated resting energy expenditure (Bland-Altman bias). Solid lines mark the limits of agreement between measured and calculated resting energy expenditure. MREE = Measured Resting Energy Expenditure. REE = Resting Energy Expenditure. H-B = Harris-Benedict Equation.
Figure 7. Scatterplot of the difference between measured and calculated resting energy expenditure vs. the mean of measured and calculated resting energy expenditure, using the Mifflin-St. Jeor equation. Dotted line marks the mean difference between measured and calculated resting energy expenditure (Bland-Altman bias). Solid lines mark the limits of agreement between measured and calculated resting energy expenditure. MREE = Measured Resting Energy Expenditure. REE = Resting Energy Expenditure. Mifflin = Mifflin-St. Jeor Equation.
Figure 8. Scatterplot of the difference between measured and calculated resting energy expenditure vs. the mean of measured and calculated resting energy expenditure, using the 1992 Ireton-Jones equation. Dotted line marks the mean difference between measured and calculated resting energy expenditure (Bland-Altman bias). Solid lines mark the limits of agreement between measured and calculated resting energy expenditure. MREE = Measured Resting Energy Expenditure. REE = Resting Energy Expenditure. I-J92 = 1992 Ireton-Jones Equation.
Figure 9. Scatterplot of the difference between measured and calculated resting energy expenditure vs. the mean of measured and calculated resting energy expenditure, using the 2002 Ireton-Jones equation. Dotted line marks the mean difference between measured and calculated resting energy expenditure (Bland-Altman bias). Solid lines mark the limits of agreement between measured and calculated resting energy expenditure. MREE = Measured Resting Energy Expenditure. REE = Resting Energy Expenditure. I-J 02 = 2002 Ireton-Jones Equation.
Figure 10. Scatterplot of the difference between measured and calculated resting energy expenditure vs. the mean of measured and calculated resting energy expenditure, using the Penn State equation. Dotted line marks the mean difference between measured and calculated resting energy expenditure (Bland-Altman bias). Solid lines mark the limits of agreement between measured and calculated resting energy expenditure. MREE = Measured Resting Energy Expenditure. REE = Resting Energy Expenditure.
References


Score, Septic Severity Score, and APACHE II Score. *Journal of Trauma, 34,* 247-251.


## Appendix A

### Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>accuracy</td>
<td>correspondence between a measured value and a true value</td>
</tr>
<tr>
<td>basal energy expenditure (BEE)</td>
<td>basal metabolic rate extrapolated over 24 hours</td>
</tr>
<tr>
<td>basal metabolic rate (BMR)</td>
<td>energy burned by a fasting individual while awake but resting in a thermally neutral environment</td>
</tr>
<tr>
<td>bias</td>
<td>systematic error</td>
</tr>
<tr>
<td>measurement error precision</td>
<td>degree of variability between measurements of the same thing using the same instrument</td>
</tr>
<tr>
<td>resting energy expenditure (REE)</td>
<td>RMR extrapolated over 24 hours</td>
</tr>
<tr>
<td>resting metabolic rate (RMR)</td>
<td>energy burned by a resting but not fasting individual</td>
</tr>
<tr>
<td>systematic error</td>
<td>error maintained across the range of measurement</td>
</tr>
</tbody>
</table>
Appendix B
Tables of Studies

Table A1

Validation Studies in Optimal Weight, Healthy Subjects.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equations Tested</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arciero et al., 1993a</td>
<td>H-B, Owen,</td>
<td>All overestimated</td>
<td>Subjects all elderly females</td>
</tr>
<tr>
<td></td>
<td>Mifflin-St. Jeor</td>
<td>by at least 3%</td>
<td></td>
</tr>
<tr>
<td>Arciero et al., 1993b</td>
<td>H-B, Mifflin-St.</td>
<td>Estimates ranged</td>
<td>Subjects all elderly, both genders</td>
</tr>
<tr>
<td></td>
<td>Jeor</td>
<td>from -19% to +14% of MREE</td>
<td></td>
</tr>
<tr>
<td>Daly et al., 1985</td>
<td>H-B</td>
<td>Overpredicted in</td>
<td>Two study locations, three different calorimeters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88% of subjects</td>
<td></td>
</tr>
<tr>
<td>de Lorenzo et al., 2001</td>
<td>H-B, Owen,</td>
<td>H-B valid using</td>
<td>Population included healthy obese</td>
</tr>
<tr>
<td></td>
<td>Mifflin-St. Jeor</td>
<td>group means</td>
<td></td>
</tr>
<tr>
<td>Frankenfield, Rowe &amp; Smith, 2003</td>
<td>H-B, Owen,</td>
<td>No equation predicted within</td>
<td>Used individual estimations</td>
</tr>
<tr>
<td></td>
<td>Mifflin-St. Jeor</td>
<td>10% of MREE in more than 74% of subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Garrel, Jobin, &amp; de Jonge, 1996</td>
<td>H-B, Owen,</td>
<td>None predicted within 10% of MREE in all cases</td>
<td>Overestimation by H-B was inversely related to REE</td>
</tr>
<tr>
<td>Livingston &amp; Kohlstadt, 2005</td>
<td>H-B, Owen,</td>
<td>H-B results characterized as “reasonable”</td>
<td>Methodology poorly described</td>
</tr>
<tr>
<td>Mifflin et al., 1990</td>
<td>H-B only</td>
<td>H-B overestimated by 5%</td>
<td>FFM was the best predictor of REE</td>
</tr>
<tr>
<td>Muller et al., 2004</td>
<td>H-B, Owen,</td>
<td>Relation between REE and weight, and REE and FFM were nonlinear; therefore, all linear prediction methods inaccurate.</td>
<td>Tested only group means</td>
</tr>
<tr>
<td>Owen et al., 1987</td>
<td>H-B</td>
<td>H-B overestimated</td>
<td>All subjects male</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Owen et al., 1986</td>
<td>H-B</td>
<td>H-B</td>
<td>All subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>overestimated</td>
<td>female, 1/3 of sample were trained athletes</td>
</tr>
<tr>
<td>Ramirez-Zea, 2005</td>
<td>H-B</td>
<td>H-B</td>
<td>Log</td>
</tr>
<tr>
<td></td>
<td></td>
<td>overestimated</td>
<td>transformation did not increase accuracy</td>
</tr>
<tr>
<td>Roza &amp; Shizgal, 1984</td>
<td>H-B</td>
<td>H-B estimated</td>
<td>Tested only group means</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MREE in normal weight</td>
<td>within 14%</td>
</tr>
<tr>
<td>Scalfi et al., 1993</td>
<td>H-B, Owen,</td>
<td>H-B and Mifflin</td>
<td>Evaluated</td>
</tr>
<tr>
<td></td>
<td>Mifflin-St. Jeor</td>
<td>overestimated, &gt;</td>
<td>individual estimations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1700 kcal/day in normal</td>
<td>normal weight</td>
</tr>
<tr>
<td>Siervo, Boschi, &amp; Falconi, 2003</td>
<td>H-B, Owen,</td>
<td>Best fit was Owen</td>
<td>Examined only group means</td>
</tr>
<tr>
<td></td>
<td>Mifflin-St. Jeor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taaffe, Thompson, Butterfield &amp;</td>
<td>H-B, Owen,</td>
<td>Owen and H-B</td>
<td>Evaluated</td>
</tr>
<tr>
<td>Marcus, 1995</td>
<td>Mifflin-St. Jeor</td>
<td>estimated within</td>
<td>Individual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>116 kcal/day</td>
<td>estimations</td>
</tr>
</tbody>
</table>
### Table A2

*Validation Studies in Obese Individuals.*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equations Tested</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato, Keating, Quercia &amp; Karbonic, 1995</td>
<td>H-B, Ireton-Jones for obese, Ireton-Jones for ventilated, Owen</td>
<td>Use of simple 21 kcal/kg had smallest bias but poor precision; H-B had best precision but high bias.</td>
<td>Bland-Altman method used</td>
</tr>
<tr>
<td>Das et al., 2004</td>
<td>H-B, Ireton-Jones</td>
<td>H-B underpredicted; Ireton-Jones overpredicted</td>
<td>BMI of 37.5 = “extremely obese”</td>
</tr>
<tr>
<td>de Lorenzo et al., 2001</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>H-B valid for both normal weight and obese</td>
<td>Only group means evaluated</td>
</tr>
<tr>
<td>de Luis, Aller, Izaola &amp; Romero, 2006</td>
<td>H-B, Owen, Ireton-Jones</td>
<td>Ireton-Jones overpredicted; H-B and Owen underpredicted</td>
<td>Used MedGem calorimeter, that only measures oxygen consumption</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Dobratz et al., 2007</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>H-B and Mifflin overestimated; Owen underestimated. Mifflin most accurate.</td>
<td>Individual estimations evaluated; alpha set at 0.10</td>
</tr>
<tr>
<td>Feurer, Crosby, Buzby, Rosato &amp; Mullen, 1983</td>
<td>H-B</td>
<td>H-B inaccurate Individual variation in REE variation of 57 – 135%</td>
<td></td>
</tr>
<tr>
<td>Foster et al., 1988</td>
<td>H-B</td>
<td>Measured REEs varied from 73 – 123% of predicted</td>
<td>Tested only group means</td>
</tr>
<tr>
<td>Frankenfield, Rose &amp; Smith, 2003</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>No equation predicted more than 74% of subjects within 10% of measured</td>
<td>Statistics weak</td>
</tr>
<tr>
<td>Heshka et al., 1993</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>Poor results for all three equations tested</td>
<td></td>
</tr>
<tr>
<td>Hirano et al., 2001</td>
<td>H-B, Ireton-Jones</td>
<td>Neither adequate N = 19; individual estimations evaluated</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lazzer et al., 2007</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>H-B estimated best; Owen grossly underestimated</td>
<td>Individual estimations evaluated</td>
</tr>
<tr>
<td>Livingston % Kohlstadt, 2005</td>
<td>H-B, Owen, Mifflin-St. Jeor, Ireton-Jones</td>
<td>H-B results &quot;reasonable&quot;</td>
<td>Obese subsample not analyzed separately</td>
</tr>
<tr>
<td>Mifflin et al., 1990</td>
<td>H-B</td>
<td>H-B overestimated by 5%</td>
<td>Obese subsample not analyzed separately</td>
</tr>
<tr>
<td>Muller et al., 2004</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>All linear prediction methods inaccurate</td>
<td>Only group means evaluated</td>
</tr>
<tr>
<td>Owen et al., 1987</td>
<td>H-B</td>
<td>H-B overestimated</td>
<td>Sample entirely male; only group means evaluated.</td>
</tr>
<tr>
<td>Owen et al., 1986</td>
<td>H-B</td>
<td>H-B overestimated</td>
<td>Sample entirely female; only group means evaluated.</td>
</tr>
<tr>
<td>Pavlou, Hoefer &amp; Blackborn, 1986</td>
<td>H-B</td>
<td>H-B unsatisfactory</td>
<td>Only group means evaluated</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------</td>
<td>--------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Ramirez-Zea, 2005</td>
<td>H-B</td>
<td>H-B overestimated</td>
<td>Only group means evaluated</td>
</tr>
<tr>
<td>Scalfi et al., 1993</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>All except Owen overestimated</td>
<td>Individual estimations evaluated</td>
</tr>
<tr>
<td>Siervo, Boschi &amp; Falconi, 2003</td>
<td>H-B, Owen, Mifflin-St. Jeor</td>
<td>Best fit was Owen</td>
<td>Relationship curvilinear in obese subgroup</td>
</tr>
<tr>
<td>Weijs, 2008</td>
<td>H-B, Bernstein, Owen, Mifflin-St. Jeor</td>
<td>Mifflin clearly superior in US subjects but not in Dutch subjects</td>
<td>Bland-Altman analysis used</td>
</tr>
</tbody>
</table>
Table A3

*Validation Studies in Ill and Injured Individuals.*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equations Tested</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato, Keating, Quercia &amp; Karbonic. 1995</td>
<td>H-B, Ireton-Jones obese, Ireton-Jones ventilator, Owen</td>
<td>H-B had best precision but high bias</td>
<td>Bland-Altman method used</td>
</tr>
<tr>
<td>Barak, Wall-Alonso &amp; Sitrin, 2002</td>
<td>H-B</td>
<td>Evaluated only for stress factors</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td>Barco et al., 2002</td>
<td>H-B</td>
<td>Used stress factors; H-B + 30% predicted within 2% of MREE</td>
<td>Group means only evaluated; all subjects (n=11) with spinal cord injury</td>
</tr>
<tr>
<td>Boulanger et al., 1994</td>
<td>H-B</td>
<td>H-B underpredicted even with stress factors</td>
<td>Measured REE correlated with temperature</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Boullata et al., 2007</td>
<td>H-B, Mifflin-St. Jeor, Ireton-Jones Penn State</td>
<td>Mifflin worked twice as well in men; H-B had lowest bias, but</td>
<td>Individual estimations evaluated poor precision</td>
</tr>
<tr>
<td>Casati et al., 1996</td>
<td>H-B</td>
<td>H-B overestimated by 10 – 20% if stress factors used</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td>Flancbaum et al., 1999</td>
<td>H-B, Ireton-Jones</td>
<td>Ireton-Jones not significantly different from predicted</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td>Frankenfield et al., 2008</td>
<td>H-B, Mifflin-St. Jeor, Ireton-Jones 1992, Penn State</td>
<td>H-B, Mifflin-St. Jeor underpredicted; Penn had smallest bias and greatest precision</td>
<td>Bland-Altman method used</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Glynn et al., 1999</td>
<td>H-B, Ireton-Jones</td>
<td>H-B had lowest bias; Ireton-Jones had highest precision</td>
<td>Bland-Altman method used</td>
</tr>
<tr>
<td>MacDonald &amp; Hildebrandt, 2003</td>
<td>H-B, Ireton-Jones, Penn State 1998</td>
<td>Penn State most accurate</td>
<td>Group means only used</td>
</tr>
<tr>
<td>Paauw et al., 1984</td>
<td>H-B</td>
<td>No significant difference</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>between H-B and measured REE in trauma.</td>
<td></td>
</tr>
<tr>
<td>Reid, 2007</td>
<td>H-B, Ireton-Jones</td>
<td>H-B bias 111 kcal; Ireton-Jones bias 141 kcal</td>
<td>No subgroup analysis; Bland-Altman used</td>
</tr>
<tr>
<td>Savino et al., 1985</td>
<td>H-B</td>
<td>Evaluated only stress factors</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td>Reference</td>
<td>Equations Tested</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Sherman, 1994</td>
<td>H-B</td>
<td>H-B unacceptable</td>
<td>Individual estimations evaluated.</td>
</tr>
<tr>
<td>Stucky et al., 2008</td>
<td>H-B</td>
<td>H-B most accurate</td>
<td>Individual estimations evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unless stress factors added</td>
</tr>
<tr>
<td>Swinamer et al.,</td>
<td>H-B</td>
<td>H-B unacceptable</td>
<td>Group means only evaluated</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weissman et al.,</td>
<td>H-B</td>
<td>H-B acceptable</td>
<td>Little correlation between measured REE</td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td></td>
<td>and any factor other than weight</td>
</tr>
</tbody>
</table>