EVALUATION OF RESTING ENERGY EXPENDITURE IN SARCOMA PATIENTS WITH LOCALIZED DISEASE

by

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(ABSTRACT)

Increased resting energy expenditure has been postulated to be one of the contributory factors in the development of cancer cachexia. Body composition and resting energy expenditure were evaluated in six male and seven female normal controls in order to validate methodology. Identical methods were then applied to seven male sarcoma patients with localized disease. Only the age and sex-matched group of controls were compared to the sarcoma patient group. All patients had received no prior cancer treatment. Body composition assessment included measurement of body fat using four-site skinfold measures, measurement of total body potassium (40K) as an indicator of body cell mass, and calculation of body surface area. Resting energy expenditure was measured by indirect calorimetry in an enclosed plexiglass hood and compared to predicted resting energy expenditure as determined by the Harris and Benedict formulae.

Measured resting energy expenditure per unit body surface area was significantly increased in the sarcoma group: 1610.7 +/- 369.2

(sarcoma) vs. 1290.3 +/- 74.3 kcal/m^2/day (controls), $p<.05$. Percent body cell mass was significantly decreased in the sarcoma group: 32.6 +/- 3.8% (sarcoma) vs. 39.8 +/- 3.7% (controls), $p<.05$. Predicted resting energy expenditure underestimated measured values by 42.1 +/-13.0% in the sarcoma group and 29.7 +/- 5.4% in the control group. Results of this study suggest that in otherwise asymptomatic cancer patients with metabolically active tumors, such as sarcomas, increased resting energy expenditure contributes to the onset of cancer cachexia prior to any signs of overt host depletion.

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INTRODUCTION

Awareness of the nutritionally debilitating effects of cancer has been enhanced over the past twenty years due to the progress made in diagnosis and treatment of malignant disease. Consequently, the role of nutritional support as an adjunct in the treatment of cancer patients has gained greater recognition. While early prospective, uncontrolled trials demonstrated improved survival in cancer patients treated with aggressive nutrition support (1,2), recent controlled studies have failed to show a uniform survival benefit in patients so treated (3). Thus, the exact role of nutritional intervention as an adjunct to cancer therapies remains to be determined.

Weight loss and accompanying host-tissue depletion is a common clinical finding in the patient with cancer. DeWys and coworkers noted a substantial decrease in body weight in 40% of patients with breast cancer and 80% of patients with carcinoma of the pancreas and stomach (4). Using standard methods of nutritional assessment, Nixon et al documented major losses of adipose tissue, visceral and skeletal muscle in a series of hospitalized cancer patients (5). Malnutrition may be more prevalent than the results of these studies suggest since standard methods of nutritional assessment may underestimate the extent of nutritional depletion (6,7).

The progressive wasting associated with malignant disease is called "cancer cachexia". Cachexia, while commonplace in patients with advanced metastatic malignant disease, may also affect patients with localized disease. Its relationship to tumor burden, disease stage, and cell type is inconsistent and no single theory satisfactorily explains all the abnormalities of the cachectic state (8). A variety of etiologic factors can occur simultaneously or sequentially to produce cachexia. The most widely recognized factors include anatomical alterations due to tumor site, decreased nutrient intake, malabsorption secondary to tumor or anti-tumor therapy, host-tumor competition for nutrients, and tumor-induced abnormalities in metabolism via humoral mediation (8,9).

It has been observed that some malnourished cancer patients continue to lose weight despite what appears to be an adequate dietary intake (10). Metabolic abnormalities resulting from remote effects of the tumor on host metabolism have been postulated to increase energy requirements in such cancer patients. Although the concept that cancer patients exhibit an elevated energy expenditure is popular, it has evolved from limited data and small studies utilizing widely varying methods to measure energy expenditure. Possibly of greater importance is the fact that the majority of these studies have been on heterogeneous groups of cancer patients and little attempt has been made to assess tumor burden. Increases in metabolic rate have been reported in recent studies of heterogeneous groups of cancer patients

with various types of malignant tumors (11-14,24). Other studies have indicated no change or decreases in the metabolic rate (13,14,15). It becomes obvious that existing literature lacks definitive clinical guidance for determining caloric requirements in cancer patients.

This study was undertaken to examine resting energy expenditure and body composition in pre-treatment sarcoma patients with localized disease as compared to a group of age/sex-matched controls. Validation of methods was sought by initial application to a group of age-matched female and male normal controls. Sarcomas are especially useful in studying the pathophysiology of cancer cachexia. In the initial stages, there are usually no overt signs of alterations in body composition or dietary intake, yet sarcomas have been documented to be metabolically active tumors (16). Non-cachectic, pre-treatment sarcoma patients offer a unique opportunity to examine alterations in energy metabolism solely as a result of the tumor-bearing state. A study of energy expenditure in these patients should lead to a better understanding of the mechanism of tumor-induced cachexia prior to obvious host depletion.

LITERATURE REVIEW

Despite the great deal of past and current investigation, inadequate understanding of the mechanisms of cancer cachexia has hampered the effective application of nutritional support techniques to malnourished cancer patients (17,18). The reasons why certain cancer patients fail to maintain or gain weight with levels of nutritional therapy that would cause weight gain in cancer-free malnourished patients remain unknown. It is known that maintenance of normal body composition in an individual requires that adequate quantities of energy and nutrient substrate be provided to and utilized by the host. Sarcomas have been associated with alterations in host metabolism of nutrients (16,19,20), yet few studies have documented their effect on energy metabolism. Evaluation of energy metabolism may provide a better understanding of the contributory factors in the development of cachexia in patients with metabolically active tumors.

ENERGY EXPENDITURE

The literature on energy expenditure studies in human sarcoma patients is limited. In a recent study, resting energy expenditure (REE) was measured in cancer patients with localized and diffuse disease as compared to matched controls; 11 of the 13 patients

assessed had a diagnosis of sarcoma. Both groups of cancer patients had significantly increased REE compared to controls (21). However, when REE was expressed as a function of metabolic body size, the significant difference persisted only in the patients with diffuse disease as compared to controls. In an animal study, freely fed sarcoma-bearing mice and pair-fed nontumor control mice were studied for body composition changes and energy expenditure changes in response to food intake (22). The sarcoma-bearing mice showed a significantly higher energy expenditure in relation to their food intake compared to that of pair-fed controls as tumor growth progressed. These results support the hypothesis that tumor-induced tissue depletion in experimental models may be due to an inability of the tumor-bearing host to adapt metabolically to the restricted food intake compared to healthy animals. In a second animal study, sarcoma-bearing rats were either free-fed or supported with TPN as compared to a nontumor control group (23). The free-fed group demonstrated marked hypophagia, weight loss and had a decreasing REE as the tumor enlarged. The TPN supported group maintained a positive nitrogen/energy balance and demonstrated a significantly increased REE throughout the study. The nutrient supply in the TPN group being adequate, the elevation in REE appears to be a consequence of the tumor-bearing state.

In an effort to determine the role that REE plays in the development of cancer cachexia, Hansell and co-workers recently

evaluated whether REE was increased in cancer patients who were losing weight (15). The study group included 42 patients with gastric, colorectal, nonsmall cell bronchial neoplasm, or other malignancies. They found that the weight-losing cancer patients had no detectable alteration in REE when compared to weight-stable cancer patients, weight-stable patients with non-malignant illness or weight-losing patients with non-malignant illness. They did find an elevation in REE when the combined weight-losing groups were compared to the combined weight-stable groups. They concluded that altered response to illness is the major determinant of increases in REE, rather than any factor associated with the tumor itself. Findings of Lindmark and colleagues, who compared 28 weight-losing heterogeneous cancer patients with noncancer weight-losing patients, indicated that a small but statistically significant elevation in energy expenditure occurred in a considerable number of cancer patients (24). Both groups of investigators related the weight-losing state of the cancer patient largely to anorexia and other processes seen in a state of non-malignant illness, rather than to tumor-induced alterations in energy expenditure. If anorexia and other processes seen in non-malignant illnesses were the major causes of cancer cachexia, total parenteral nutrition (TPN) would be effective in eliminating the malnutrition seen in cancer patients; this has not be shown to be the case (3,25,26). Hansell and Lindmark's studies evaluated cancer patients who were weight-losing, thus the variable of anorexia was superimposed which made delineation of tumor-induced effects on energy metabolism

more difficult. Both studies evaluated heterogeneous groups of cancer patients and there was no evidence that similar tumor type subsets were controlled for extent of tumor burden. As exemplified by this and previous work on energy expenditure in cancer patients, studies must be carefully controlled with particular attention to the homogeneity of the tumor types under investigation.

Whether or not alterations in REE would be observed was investigated in a recent study of cancer patients with localized and diffuse disease as compared to controls (27). All patients studied had gastrointestinal malignancies; REE was measured by indirect calorimetry and TBK was measured as an indicator of body cell mas (BCM). The results showed a close correlation between REE and BCM in all groups. The REE at a given BCM was greatest in those patients with diffuse disease, amounting to a mean elevation of 289 kcal/day as compared to control subjects. These findings suggest that the moderate elevation in REE seen in gastrointestinal malignancy patients with diffuse disease may be a contributory factor in the development of cancer cachexia in these patients. This study also helps to emphasize that not only is it important to evaluate energy expenditure in cancer patients of defined tumor type, but defined tumor burden as well.

RESTING ENERGY EXPENDITURE ESTIMATION

There is growing clinical emphasis on accurately predicting an individual's energy requirements since the success of nutritional support regimens depends upon the delivery of adequate calories and nutrients. Energy requirements are based upon a calculation of energy losses, the two main components of which are resting or basal energy expenditure and physical activity. The metabolic aspects of energy expenditure and utilization are reflected largely in the resting energy component (17). Two methods are commonly used to determine the caloric or energy requirements of an individual patient. The first method involves measurement of resting energy expenditure by indirect calorimetry, a widely accepted technique for continuous metabolic gas exchange measurement as initially designed by Kinney in 1964 (28). Indirect calorimetry is a sensitive, noninvasive technique which permits the gathering of sequential readings of metabolic gas exchange in the resting state. Recently, an indirect calorimetry system which combined the initial design by Kinney (28) with original technology was reported (21). This new system uses a plexiglass hood which significantly reduces artifacts introduced by the prior use of face masks and/or nose clips (28,29). The on-line capabilities of this new system include flexible computer hardware and software which allows rapid data collection with subsequent electronic data transfer to a mainframe computer for further manipulation (21). Indirect calorimetry is relatively simple to perform and results in a reliable measurement of resting energy expenditure (30).

The second method involves calculation of an individual's resting energy expenditure based on body weight, height, age and sex; the most widespread practice in hospitals in the U.S. is to use the equations of Harris and Benedict (31). In 1919, these pioneering workers developed multiple regression equations from indirect calorimetric determinations of energy expenditure in a large series of healthy individuals. From 1936-1952, other workers validated Harris and Benedict's results within +/- 5 percent (32-34).

Calculation of resting energy expenditure with the Harris and Benedict equations, produces a "predicted" resting energy expenditure estimation (p-REE). The continued widespread use of these equations in hospital settings has prompted a recent re-evaluation of the validity of these "predicted" estimations. Although, it is widely accepted that indirect calorimetry yields a more reliable measure of REE (m-REE), due to expense and practicality, indirect calorimeters are not in widespread clinical use. In a recent cooperative study, REE was measured in a group of healthy individuals (35). Using modern indirect calorimetry methods, the Harris-Benedict equation overestimated resting energy requirements by 10 to 15 percent in 201 healthy men and women. These results raise questions regarding the accuracy of the equations being used to "predict" REE. In a second study, indirect calorimetry and body composition measurements were performed in both normally nourished and malnourished patients to assess the accuracy of the Harris-Benedict equations in malnourished

patients (36). In the normally nourished patients, there was no significant difference in the measured and predicted oxygen consumption, whereas in the malnourished patients, the predicted mean oxygen consumption was 22 percent less than the measured mean oxygen consumption. The data in this study seriously questions the reliability of the Harris-Benedict equation in malnourished patients. In a third study, REE was both measured by indirect calorimetry and predicted using the Harris-Benedict equations in a group of clinically stable heterogeneous cancer patients (14). Out of 200 cancer patients, only 41% had measured REE within the normally accepted +/-10% range of the Harris-Benedict predicted REE. At the present time, the predictive formulae of Harris-Benedict are among the best available. Until predictive formulae of improved accuracy are developed, understanding the limitations of using the Harris-Benedict equations for specific patient populations is of clinical benefit.

BODY COMPOSITION

Total body weight is composed of two compartments: body fat (BF) and lean body mass (LBM). The LBM in turn can be divided into two major components: the body cell mass (BCM) and the extracellular mass (ECM).

The body fat (BF) compartment is relatively homogeneous; it

includes an anhydrous accumulation of neutral triglycerides. Body fat differs from LBM in that it contains practically zero water and potassium content, and does not contain work-performing tissue.

Body cell mass (BCM) represents the total mass of metabolically active cells in the body. Moore defines the BCM as "that component of the body composition containing the oxygen-exchanging, potassium-rich glucose-oxidizing, work-performing tissue" (37). In the normally nourished healthy individual, the muscle mass accounts for 60% of the BCM, while the viscera account for 20%, with the remaining 20% made up of red cells and the cells of the tissue with a sparce cellular population such as adipose tissue, tendon, bone, and cartilage (6). In contrast, the ECM represents that componenet of the LBM which is located outside the cellular compartment. It is not metabolically active, as it consumes no oxygen, produces no carbon dioxide and performs no work. It is composed of both fluids and solids, and its primary function is that of support and transport.

BODY COMPOSITION ASSESSMENT

Moore demonstrated that total exchangeable potassium (Ke), which is equivalent to total body potassium, is a measure of the BCM. Ke is linearly related to the size of the BCM as 98-99% of Ke is within the intracellular compartment of the BCM, and the potassium concentration

within this compartment varies within a narrow range (37). Since 0.012% of Ke consists of 40K which emits a gamma of 1.46MeV energy, Ke can be measured in vivo with low background whole body counters (38).

Since a large proportion of body fat lies in the subcutaneous layer, a measurement of the thickness of skinfolds picked up at various sites has been used to yield an estimate of total body fat. Investigators have demonstrated the improved accuracy in obtaining multiple skinfold measurements as opposed to single-site measures (39-42). The improved accuracy of multiple measurements was attributed to the fact that for occasional individuals, because of unusual fat distribution, there is the likelihood of large error when relying on single site measurements. The multiple skinfold sites most widely used are biceps, triceps, subscapular and suprailiac (39-42). Regression equations permit calculation of body fat content, corrected for age and sex, using these four sites (41). This method is very inexpensive, imposes minimal inconvenience to the subject, yet is highly dependent on investigator skill. The accuracy of skinfold measures has been reported to be highest in non-obese subjects (43). LBM can be determined from the difference between total body weight and body fat.

Factors such as age, sex, recent weight loss and level of physical activity can impact upon body composition in individuals (37,44).

METABOLIC REFERENCE STANDARDS

The problem of finding relationships between energy expenditure and various parameters of the body's shape, size and composition has intrigued scientists for many years. Relating basal or resting energy expenditure to such an easily measurable index of size as body weight has produced poor correlation (45). Body surface area (BSA) has been thought to be a preferable index for energy expenditure. DuBois developed extensive tables from which surface area could be derived from measured height and weight (46). The use of BSA requires the additional consideration of age and sex to improve the predictability of energy expenditure (45), thus, it is particularly useful in comparing groups of the same sex and similar age. Certain workers continue to feel that a fractional power of the total body weight represents a better index for resting energy metabolism than does surface area. Although fairly good correlations have been found when comparing the mean values for different animal species, in individuals of the same species no single fractional power of the body weight gives a reliable index of body size (47,48).

A strong correlation has been demonstrated between body cell mass (BCM) and REE in healthy adults, surgical patients with moderate to severe depletion, and patients with gastrointestinal malignancies (27,45). The BCM represents the total mass of metabolically active cells. Since the BCM is that component of body composition that is

responsible for all of the metabolic gas exchange within the body, it is the ideal metabolic reference standard for energy expenditure evaluation (27,36-37,49). The REE measures the energy turnover largely of the visceral component of the BCM, since the muscular components are at rest and thus, burning minimal fuel (the exceptions being the heart and diaphragm) (49).

Several groups studying body composition have noted that healthy adult population samples show close correlation between REE and measurements of LBM (50-54). REE and LBM have likewise shown a close correlation in a large group of heterogeneous cancer patients and healthy controls (15). Since the LBM compartment includes both the BCM and ECM, it has been demonstrated that the constancy of the LBM compartment may be expected to vary when studying heterogeneous populations or populations with significant tissue wastage due to disease state (49,6). In light of this, BCM appears to be a more universally reliable metabolic reference standard when studying energy expenditure (37,49).

SUMMARY

To date, the majority of studies evaluating energy expenditure in cancer patients have presented a confusing picture. Largely due to the heterogeneity of tumor types evaluated in the same study

population, inconclusive findings have resulted. Since different tumor types display varying levels of metabolic activity, it follows that evaluation of energy expenditure in patients of defined tumor type is necessary.

In the research setting, indirect calorimetry has provided an accurate means of measuring resting energy expenditure. Recently developed techniques have replaced the use of a face mask and/or nose clip with an enclosed plexiglass hood and have included the use of sophisticated on-line computer capabilities for data acquisition and manipulation. In the clinical setting, effective planning of nutrition support for cancer patients depends upon accurate prediction of caloric requirements. Currently the formulae of Harris and Benedict are receiving widespread use for that purpose. Major questions have been raised as to the validity of these formulae in accurately predicting resting energy expenditure for specific patient populations.

Other factors to consider in evaluation of energy metabolism are the changes in body composition which may accompany alterations in resting energy expenditure. Total body potassium (40K) is standardly measured as an index of body cell mass and multiple-site skinfold measures have provided a reliable method of body fat assessment. From measures of body cell mass and body fat, estimations of lean body mass can be inferred.

It is clear that energy expenditure studies in cancer patients require close control. Factors such as age, sex, body composition, use of metabolic reference standards, and tumor delineation (type, histology, extent of tumor burden) must be considered and/or controlled to produce a valid assessment. There have been few such studies conducted in sarcoma patients.

MATERIALS AND METHODS

SUBJECTS.

Seven white male patients with localized soft tissue sarcomas were evaluated. All patients had intact truncal or extremity tumors and showed no evidence of metastatic disease. The patients were otherwise healthy, had received no prior cancer therapy and were being admitted to the Clinical Center, National Institutes of Health (NIH) for surgical resection of their tumor. All measurements were performed prior to surgery. The control group included six white male and seven white female normal volunteers. The combined male/female control group was utilized for comparison to healthy subjects in previous studies as a means of validating methodology. Only age and sex-matched controls were compared to the sarcoma patient group.

TUMOR CLASSIFICATION.

Histological typing and grading of the tumor in each sarcoma patient was determined by microscopic examination of tissue samples in the NIH, Clinical Center Pathology Department. The location of the tumor was confirmed upon surgical resection. Tumor size was calculated, based on the three dimensional measurements of the resected mass, using the formula for volume of a sphere. In those

patients where only a uni-dimensional sample of the tissue was available, the assumption was made that the mass was spheroid in shape and the formula to calculate the volume of a sphere was then used to determine tumor size.

REE MEASUREMENT.

REE was determined by indirect calorimetry. Both sarcoma patients and controls were fasted from midnight. The patient's head was placed within a rigid lucite canopy, with an occlusive collar secured around the neck to provide an airtight seal. The patient was placed recumbent in a quiet room for the duration of each experimental run. A constant speed high volume blower was used to introduce room air into the canopy. Total flow into the system was measured with a pneumotach (Hewlett-Packard Model #210378) which was regularly calibrated with a flow-volume calibrator (Collins Model #21103). Total air flow into canopy was maintained between 45 and 52 liters per minute. These high flows prevented any rebreathing of carbon dioxide and the decrease in oxygen concentration remained large enough. The effluent gas stream (beyond the canopy) was directed into a baffle box to permit gas mixing and the final gas stream was sampled by a mass spectrometer (Perkin-Elmers 1100 Medical Gas Analyzer). The mass spectrometer was routinely calibrated with standardized mixtures of carbon dioxide balance oxygen as recommended by the manufacturer.

Data collection was managed by a microcomputer (MINC Model 11; Digital Equipment Corporation). The MINC sampled and stored the room air flow rate into the canopy. The Gas Analyzer constantly sampled fractional carbon dioxide and oxygen in the room air and canopy effluent fractional gas concentrations of carbon dioxide and oxygen. The MINC recorded that data every sixteen seconds. The range of patient runs in this study was 19.5 minutes to 40 minutes. After a patient run was complete, the raw data collected was transferred to a mainframe computer (Digital Electronics Model 10 mainframe). The mainframe computer calculated a trimmed mean from the raw data for oxygen consumption and carbon dioxide production. A trimmed mean eliminates any widely varying data points obtained during the subject's initial adjustment to the system. REE was then calculated for each subject from the trimmed mean using the modified Weir formula (57).

REE PREDICTION.

P-REE was calculated based on each subject's height in centimeters (H), weight in kilograms (W) and age in years (A), using the Harris and Benedict formulae (31):

MALES p-REE(kcal/day) = 5(H) + 13.7(W) + 66 - 6.8(A)

FEMALES p-REE(kcal/day) = 1.7(H) + 9.6(W) + 655 - 4.7(A)

BODY COMPOSITION ASSESSMENT.

Subjects were weighed in kilograms using a calibrated beam balance scale; all subjects were weighed in light clothing, without shoes. Height without shoes was measured in centimeters. Weight loss was assessed from the subject's recalled weight six months prior to evaluation. Body Surface Area (BSA) in meters squared was calculated using the formula of Dubois (56).

Body cell mass was determined from total body potassium (TBK). TBK was obtained by measuring the radioactivity of the naturally occurring radioisotope of potassium, 40K, with a whole body counter (38). TBK is measured in grams, then converted to mEq/liter and multiplied by a constant (8.33) to obtain BCM in kilograms (37). The BCM in kilograms was then divided by total body weight in kilograms to obtain %BCM.

Total body fat was determined from measurement of skinfolds thicknesses at the biceps, triceps, suprailiac and subscapular sites. Standard technique for measurement was used (40): 1) biceps: over the

anterior midpoint of the muscle belly with the arm resting supinated on the subject's thigh, 2) triceps: over the posterior mid-point of the muscle belly, mid-way between the olecranon and the tip of the acromion, with the upper arm hanging vertically, 3) subscapular: immediately below the tip of the inferior angle of the scapula, at an angle of about 45 degrees to the vertical, and 4) suprailiac: just above the iliac crest in the mid-axillary line. Skinfold thicknesses were measured to the nearest 0.5mm. All measurements were made on the right side of the body without the interference of clothing. The instrument used was the Lange caliper (Cambridge Scientific Industries, Inc.). Three sequential measurements were taken at each of the four sites with a brief rest period between each measurement. The skinfold thickness at each site was determined by the mean of the three sequential measurements made. The total skinfold measurement, in mm, was converted into its logarithmic value (X). Depending upon sex, one of the following regression equations was then used to determine body density (Y)(40):

$$\text{Men } Y = 1.1610 - 0.0632(X)$$

$$\text{Women } Y = 1.1581 - 0.0720(X)$$

Using the value for body density (Y) obtained above, the Siri equation was used to calculate percent body fat (57):

$$\%BF = [(4.95/Y) - 4.5] \times 100$$

Lean body mass (LBM) was determined as the difference between total body weight and body fat. The LBM in kilograms was then divided by total body weight in kilograms to obtain %LBM.

One investigator obtained all skinfold and height/weight measurements. All measures of body composition were obtained within three days of the REE measurement.

PHYSICAL ACTIVITY ASSESSMENT.

A history of usual activity during the six months prior to evaluation was elicited from each subject using the methods of the Framingham study (44). Four levels of activity were defined (Appendix I). Each subject was asked to identify the number of hours a day spent at each activity level using the form in Appendix II. A separate history was elicited for weekdays and weekends if subject identified a change of pattern due to work habits or other factors; the scores were weighted appropriately and averaged for the seven-day week. A composite score, the physical activity index (PAI), was then calculated by summing up the products of the hours at each level of activity times a weight based on the oxygen consumption required for that activity (Appendix III).

INCOME STATUS ASSESSMENT.

Relative income level was assessed from subject's recalled per capita income within their household during the year prior to evaluation. Per capita income levels were defined in $9,999 ranges with a total of eight ranges. Each range was assigned a number 1-8. Income status index (ISI) was determined by dividing the appropriate range level by the available ranges.

STATISTICAL ANALYSES.

All raw data are provided in Appendicies IV-VI. The mean +/- SD was calculated for each data set. In analyzing differences between the sarcoma and control group data, the Wilcoxon Rank Sum test was used. In evaluating the relationship between two variables, the pearson r correlation coefficient was used.

A summary of the data collection methods utilized in this study is as follows:

METHOD	INTENDED USE
Indirect Calorimetry	To directly measure resting energy expenditure.
Harris-Benedict Equation	To estimate resting energy expenditure using widely-accepted equation.
Height and Weight Measurement	For use in Harris-Benedict equation; to calculate body surface area; to derive lean body mass; to assess percent weight loss during six month period prior to evaluation.
Whole Body Counter	To directly measure naturally occurring radioactive potassium (40K) in body as index of the quantity of body cell mass.
Multiple Site Skinfold Measurement	To directly assess quantity of body fat; to derive lean body mass.
Subject Interview	To obtain data on recalled weight six months prior to evaluation, age, per capita income range.
PAI Questionnaire	To obtain data necessary for calculation of Physical Activity Index (PAI).

RESULTS

A. MALE vs. FEMALE CONTROLS

Thirteen normal controls, six male and seven female, were evaluated. In Table 1, general characteristics of the male and female controls are displayed. There were no significant differences between the two groups in age, percent weight loss, Physical Activity Index (PAI), or Income Status Index (ISI).

As displayed in Table 2, comparison of body composition parameters revealed that the body weight of the male group was significantly higher than that of the females ($p<.01$), as was the percent lean body mass ($p<.05$), and body surface area ($p<.005$). The percent body fat was significantly higher in the females as compared to the males ($p<.005$). The mean percent body cell mass was higher in the males as compared to the females, yet due to the large standard deviations, the differences were not statistically significant.

When looking at the control group as a whole, male and female combined, a statistically significant positive correlation was found between body cell mass and lean body mass ($r=0.9372$, $p<.001$) (Figure

TABLE 1

MEAN DATA: GENERAL CHARACTERISTICS
of FEMALE vs. MALE CONTROLS AND SARCOMA PATIENTS vs.
AGE/SEX-MATCHED CONTROLS

FEMALE vs. MALE CONTROLS

Group	Age (yrs)	% Wt Loss	PAI	ISI
Control-Female (n=7)	36.4 +/-11.8	0	34.2 +/-5.0	0.250 +/-0.125
Control-Male (n=6)	35.0 +/-16.6	0	33.6 +/-3.2	0.125 +/-0.000
p	NS	NS	NS	NS

SARCOMA PATIENTS vs. AGE/SEX-MATCHED CONTROLS

Group	Age (yrs)	% Wt Loss	PAI	ISI
Sarcoma-Male (n=7)	44.9 +/-16.5	3.8 +/-3.7	30.7 +/-3.4	0.229 +/-0.094
Control-Male (n=6)	35.0 +/-16.6	0	33.6 +/-3.2	0.125 +/-0.000
p	NS	NS	NS	<.05

TABLE 2

MEAN DATA: BODY COMPOSITION PARAMETERS
OF FEMALE vs. MALE CONTROLS AND SARCOMA PATIENTS
vs. AGE/SEX- MATCHED CONTROLS

FEMALE vs. MALE CONTROLS:

Group	Weight (kg)	%BF	%BCM	%LBM	BSA (m^2)
Control-Females (n=7)	58.4 +/-8.3	31.7 +/-6.0	34.5 +/-4.6	68.2 +/-6.0	1.63 +/-0.13
Control-Males (n=6)	78.3 +/-11.2	21.1 +/-5.2	39.8 +/-3.7	78.9 +/-5.2	1.99 +/-0.16
p	<.01	<.005	NS	<.05	<.005

SARCOMA PATIENTS VS. AGE/SEX-MATCHED CONTROLS

Group	Weight (kg)	%BF	%BCM	%LBM	BSA (m^2)
Sarcoma-Males (n=7)	86.3 +/-10.9	22.4 +/-4.6	32.6 +/-3.8	77.6 +/-4.6	2.05 +/-0.14
Control-Males (n=6)	78.3 +/-11.2	21.1 +/-5.2	39.8 +/-3.7	78.9 +/-5.2	1.99 +/-0.16
p	NS	NS	<.05	NS	NS

1), body cell mass and m-REE ($r=0.7702$, $p<.01$) (Figure 2) and lean body mass and m-REE ($r=0.7571$, $p<.01$) (Figure 3).

The m-REE was significantly higher in the males than in the females ($p<.05$). When m-REE was expressed per unit body surface area and per kg body cell mass, the significant difference between the two groups disappeared (Table 3).

The p-REE underpredicted the m-REE in the male group by a range of 23-36%. In the female group, p-REE overpredicted the m-REE in three out of seven subjects by a range of 3.6-4.4%. In the remaining four out of seven female subjects, p-REE underpredicted m-REE by a range of 13.2-46.1%. The mean percent underprediction was not significantly different between the male and female groups (Table 3).

B. SARCOMA PATIENTS vs. AGE/SEX-MATCHED CONTROLS

Seven male patients with localized sarcomas and six male controls were evaluated. Of the seven patients, four had low grade and three had high grade tumors (Table 4). Sarcoma patients exhibited a wide range of tumor size, varying from 100 - 18600cm^3 ($\bar{X}=4543$ +/-6732.7cm^3).

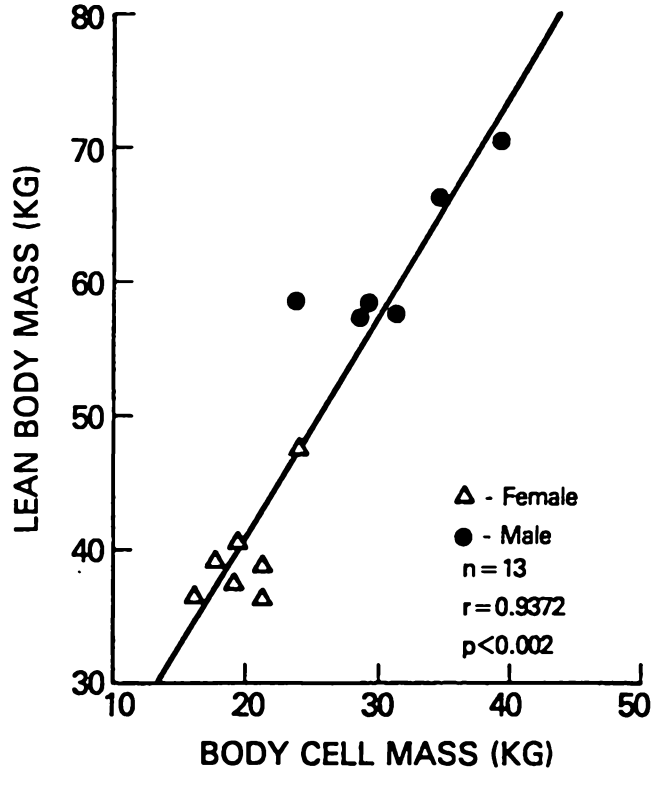

Figure 1. Correlation between body cell mass and lean body mass for the entire control group.

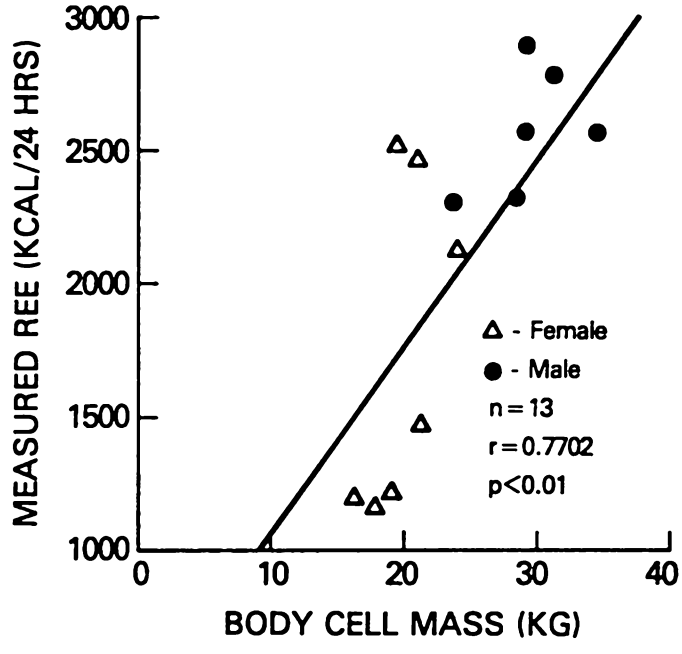

Figure 2. Correlation between body cell mass and measured REE for the entire control group.

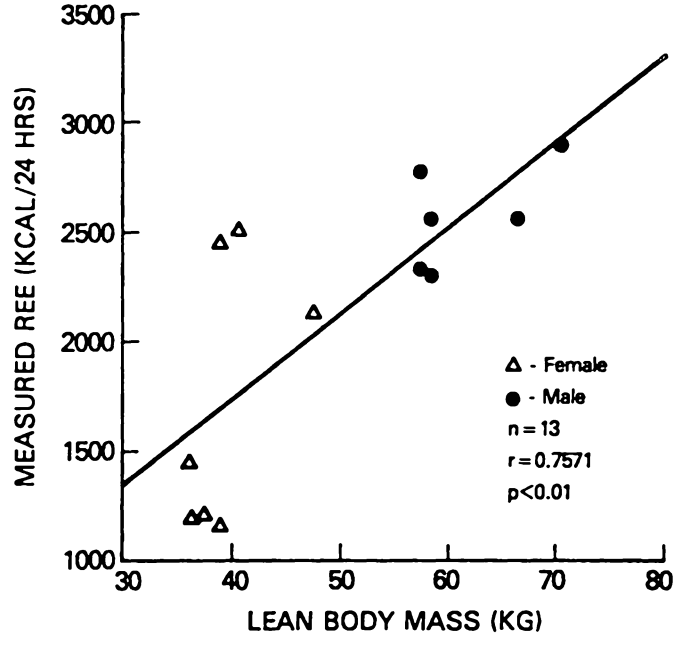

Figure 3. Correlation between lean body mass and measured REE for the entire control group.

TABLE 3

MEAN DATA: ENERGY EXPENDITURE
OF FEMALE vs. MALE CONTROLS AND SARCOMA PATIENTS
vs. AGE/SEX-MATCHED CONTROLS

FEMALE vs. MALE CONTROLS

Group	m-REE (kcal/d)	m-REE/BCM (kcal/d/kg)	m-REE/BSA (kcal/d/m^2)	p-REE (kcal/d)	%Under-prediction of m-REE
Control-Female (n=7)	1735.1 +/-617.7	86.1 +/-26.3	1055.3 +/-329.2	1323.9 +/-117.2	17.0 +/-22.3
Control-Male (n=6)	2571.3 +/-238.5	83.7 +/-9.0	1290.3 +/-74.3	1810.1 +/-231.2	29.7 +/-5.4
p	<.05	NS	NS	<.005	NS

SARCOMA PATIENTS vs. AGE/SEX-MATCHED CONTROLS

Group	m-REE (kcal/d)	m-REE/BSA (kcal/d/m^2)	p-REE (kcal/d)	%Under-prediction of m-REE
Sarcoma-Male (n=7)	3334.4 +/-949.0	1610.7 +/-369.2	1838.6 +/-172.3	42.1 +/-13.0
Control-Male (n=6)	2571.3 +/-238.5	1290.3 +/-74.3	1810.1 +/-231.2	29.7 +/-5.4
p	NS	<.05	NS	<.05

TABLE 4

TUMOR CHARACTERISTICS IN SARCOMA PATIENTS

Subject No.	Tumor Type	Location	Grade	Size (cm^3)
1	Synovial Cell Sarcoma	Thigh	High	700
2	Leiomyosarcoma	Pelvic	High	100
3	Liposarcoma	Retroperitoneum	Low	7700
4	Exoskeletal Osteo-sarcoma	Thigh	High	500
5	Liposarcoma	Retroperitoneum	Low	18600
6	Malignant Fibrous Histiocytoma	Retroperitoneum	Low	3000
7	Leiomyosarcoma	Retroperitoneum	Low	1200

Mean Tumor Size = 4543 +/- 6733 cm^3

Range of Tumor Size = 100 - 18600 cm^3

In Table 1, general characteristics of the subjects are displayed. There were no significant differences between the two groups in age, percent weight loss, or Physical Activity Index (PAI). The sarcoma group had a significantly higher Income Status Index (ISI) as compared to the control group.

Comparison of body composition parameters revealed that although there were no statistical differences in the body weight, body surface area (BSA), and percent body fat (%BF) between the two groups, percent BCM (%BCM) was significantly lower in the sarcoma group as compared to controls (Table 2).

The sarcoma group demonstrated a higher mean m-REE as compared to controls; however, due to the large standard deviations, these differences were not statistically significant (Table 3). When expressed per unit of body surface area (BSA), the increased m-REE observed in the sarcoma group became statistically significant. The difference between the two groups in p-REE was not significant.

In the control group, there were significant correlations found between BCM and LBM ($r=0.8537$, $p<.05$) and between BCM and m-REE ($r=0.8168$, $p<.05$) (Figures 4,5). Similar correlations were not found in the sarcoma group.

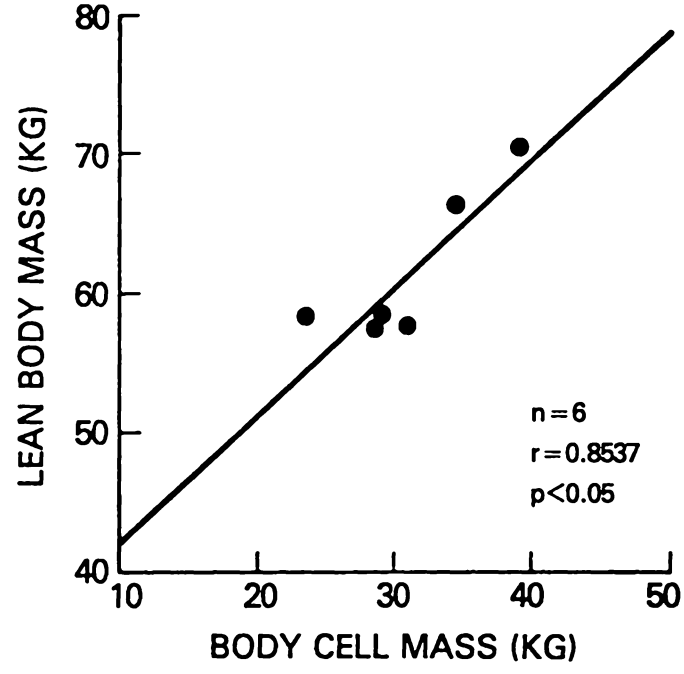

Figure 4. Correlation between body cell mass and lean body mass for the male control group.

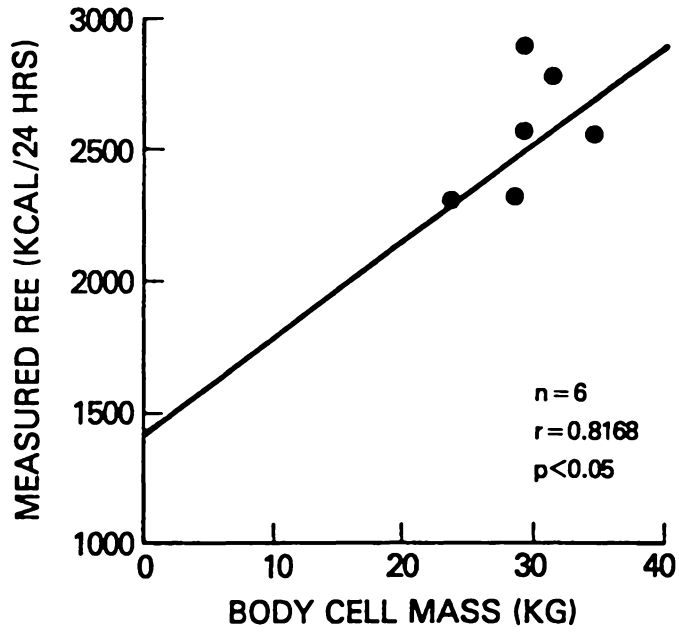

Figure 5. Correlation between body cell mass and measured REE for the male control group.

In the sarcoma group, there were significant correlations found between %BCM and LBM ($r=-0.8503$, $p<.05$), %BCM and m-REE ($r=-0.7755$, $p<.05$) and LBM and m-REE ($r=0.8399$, $p<.05$) (Figures 6-8). Similar correlations were not found in the control group.

The p-REE consistently underpredicted the m-REE in both groups. The mean percent underprediction was significantly greater in the sarcoma group compared to controls. The range of percent underprediction in the sarcoma group was 29-61% vs. 23-36% in the control group (Table 3).

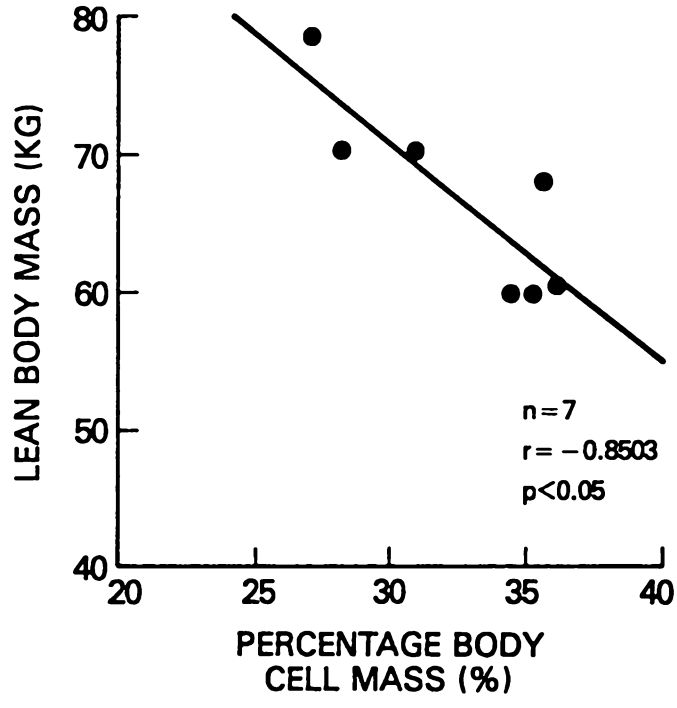

Figure 6. Correlation between % body cell mass and lean body mass for the sarcoma patient group.

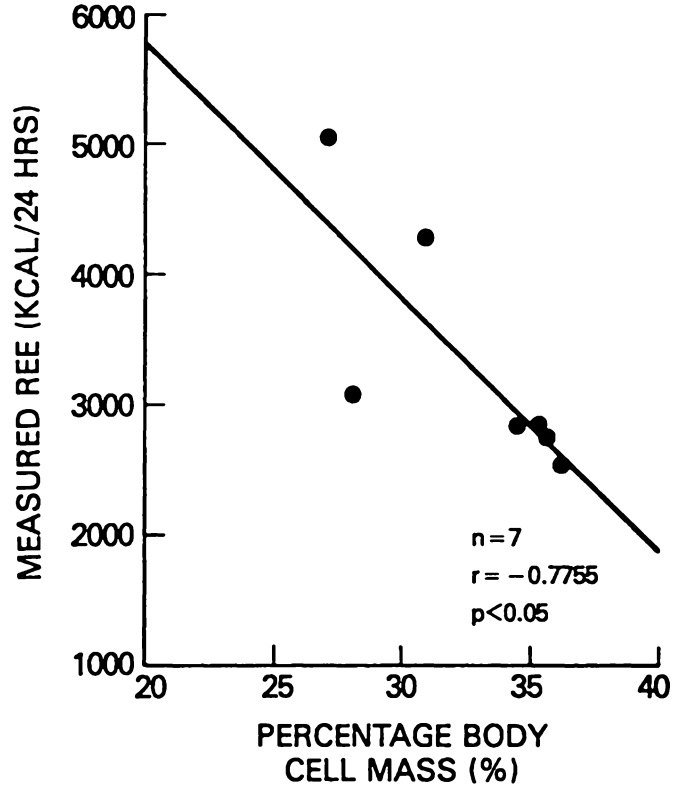

Figure 7. Correlation between % body cell mass and measured REE for the sarcoma patient group.

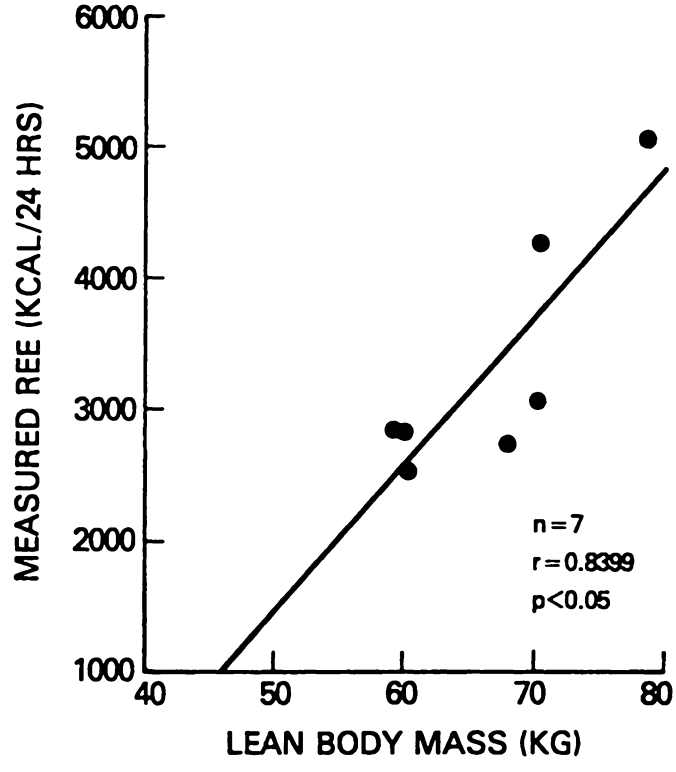

Figure 8. Correlation between lean body mass and measured REE in the sarcoma patient group.

DISCUSSION

A. MALE vs. FEMALE CONTROLS

Analysis of general characteristics revealed that the two groups were similar with respect to sample size, age, physical activity level during the six months prior to evaluation as indicated by the PAI, and income status level as reflected by the ISI. Neither group had experienced weight loss during the six months prior to evaluation. The major variable apparent between the groups was the difference in sex.

Analysis of body composition parameters reflected differences in body weight, % body fat, %lean body mass and body surface area between the male and female controls which are similar to the normal body composition variations seen in healthy adult males and females (37). In the control group of this study, females had a lower body weight, a greater % body fat, and a smaller % lean body mass than males. When compared to previous reports, the mean %LBM in both of the groups in this study were similar to that found in normal populations (37,40). Mean %BCM was higher in the male group as compared to the females, but due to the limited size of the sample, this difference was not statistically significant. BCM is approximately 30-38% of body weight in mixed normal populations (37); the mean %BCM for our mixed female and male control group was 37.2% which falls within this range.

Normal body composition as delineated for a reference 70kg male consists of 18% body fat and 82% lean body mass (37). The mean weight of the male group included in this study was 11.9% (8.3kg) higher than that of the reference male. If the reference male was corrected proportionally, the size of the body fat compartment would expand to 20%, thereby decreasing the LBM to 80%, which is very similar to the findings of a mean %BF of 21.1 +/- 5.2% and a mean %LBM of 78.9 +/-5.2% in the male control group of the present study. Normal body composition for a reference 60kg female reflects 32% body fat and 68% lean body mass (37); the mean weight, %BF, and %LBM in the present female control group show striking similarities with values of 58.4kg, 31.7%, 68.2% respectively. In 34 healthy males and 58 healthy females between the ages of 30 and 39, %BF as determined by the same four-site skinfold method used in this study, reflected a mean %BF of 23 +/-5.4 in the males and 33 +/- 9.5% in the females (40). Compared to findings in this study of 21.1 +/- 5.2% in the male controls and 31.7 +/- 6.0% in the females controls, there were essentially no differences. These strong similarities in the data support the validity of the methods used to obtain body fat measurements in this study.

In analyzing data for the control group as a whole, it was found that BCM and LBM were highly correlated. Variability in normal adult body composition is largely related to the fat content, and thus a constant relationship should be expected to exist between LBM and BCM

(45). It follows that a positive correlation in the control group was also found between LBM and m-REE as well as BCM and m-REE. It is well accepted that BCM is closely related to REE, as BCM is an ideal metabolic reference standard when evaluating energy expenditure (37). Several groups have noted that healthy adult population samples also show close correlation between REE and measurements of LBM (50-54). The close similarity between the findings of the present study and those previously reported further support the methodology used in this study.

The m-REE was higher in the male group as compared to the females due to the larger size of the BCM in males (37). As expected, when expressed per kg BCM and per unit BSA, the variable of body size was minimized and the m-REE between the two groups was similiar. The mean m-REE was higher for both groups than has been previously measured in controls using indirect calorimetry with a rigid hood (25,15,21). One of the few differences between the technique used by Arbeit and colleagues and the one used in the present study was a difference in frequency of readings per subject run from one every 10 minutes in Arbeit's study to one every sixteen seconds in the present study (21). The total length of patient runs were comparable, thus generating 160 more data points per 10 minute interval in the present study. Undoubtedly, the accuracy of the final result is enhanced by the additional data points, yet this adds in an additional variable when comparing our data to Arbeit's findings. The importance of a

controlled study when evaluating energy expenditure cannot be over emphasized. Due to a multitude of variables such as variations in equipment capability, and differences in calibration, frequencies of readings/run, and body composition of the subjects, it is difficult to compare m-REE values between studies which have been conducted independently.

The p-REE consistently underpredicted the m-REE in the male group by a larger percentage than previous reports (35). This would be expected since the mean m-REE was higher than that measured in the reports cited. In the females, p-REE underpredicted m-REE by a mean percent difference that was comparable to that reported previously (35).

B. SARCOMA PATIENTS vs. AGE/SEX-MATCHED CONTROLS

All methods used for data collection were first applied to the control group and validated by comparison between male and female controls. When appropriate, control group data was compared to normal data previously reported for further validation of methodology.

Review of tumor characteristics within the sarcoma group (Table 4) indicated that patients with low grade tumors all had tumors located in the retroperitoneum while those with high grade tumors had

locations both in the pelvic and thigh areas. The high grade tumors were consistently of smaller size (100-700cm3) as compared to the low grade tumors (1200-18600cm3). Tumor grade and size did not show any relationship with m-REE or m-REE/BSA, and thus were not considered interfering variables in this study.

Evaluation of general characteristics revealed that the sarcoma group and the male control group were comparable in age, percent weight loss and physical activity level during the six months prior to evaluation. Since sarcoma patients rarely present with outward signs of altered body composition or dietary intake, lack of significant weight loss or variation in activity level as compared to controls was as expected. Income level was higher in the sarcoma group as compared to controls, yet the difference did not appear to be large enough to be considered an interfering variable.

Analysis of group body composition parameters showed that both groups were similar with respect to weight, % body fat, % lean body mass and body surface area. The difference noted was a lower % body cell mass in the sarcoma group as compared to controls; this is of particular interest in light of the similarities between the two group in body weight, body fat, and lean body mass.

There was no correlation between m-REE and BCM in the sarcoma group. This differs from the findings in the control group and of a

previous study which found a positive relationship between m-REE and BCM in GI cancer patients with localized and metastatic disease (27). Since there was no positive relationship between m-REE and BCM in the sarcoma group, BCM would provide an unreliable metabolic reference standard for evaluation of energy expenditure in these patients. Due to this, REE was not evaluated per unit BCM in this study.

The mean m-REE was greater in the sarcoma group as compared to controls, however, due to the large individual variation among the sarcoma patients, the difference was not statistically significant. When m-REE was expressed as a function of BSA, a significant difference emerged between the two groups. A mean difference of 320.4 kcal/day/m^2 existed between the sarcoma group and the controls. Recent investigations have reported slight to moderate elevations in REE seen in patients of varying tumor types (24,27). It is difficult to make direct comparisons between those studies and this one. Many factors influence energy expenditure and must be controlled when interpreting data. A majority of the calorimetry studies present limited data about factors known to influence energy expenditure. Body composition, therapy factors, and disease factors such as tumor type, histology, and size are often not well defined. The inconsistent use of various measures of body size and/or metabolic mass as reference standards when evaluating energy expenditure also make comparison of data difficult between studies. It cannot be concluded from previous studies that energy expenditure is

consistently elevated in cancer patients since important potential determinants were either not considered or not controlled.

The control group exhibited a positive correlation between BCM and LBM which has been observed previously (27,45). BCM was positively correlated with m-REE in the controls which confirms findings of numerous other studies which have documented the relationship between energy expenditure and the mass of metabolically active tissue (BCM) in the body (27,45,36,37). Although LBM and m-REE were correlated in the control group, the relationship was not statistically significant. This is most likely due to the limited sample size, as when male and female control data were combined, a statistically significant relationship emerged. These findings would suggest that BCM is a more accurate metabolic reference standard than is LBM, particularly when evaluating energy expenditure in small samples.

In contrast, the sarcoma group exhibited a negative correlation between %BCM and LBM, indicating that when BCM is expressed as a proportion of body weight, a decrease is related to an increase in the total LBM compartment (Figure 6). A relationship was not observed between BCM and LBM, which suggests that the changes occurring in the LBM compartment were too small to detect when expressed in relation to the total BCM component. It was not until BCM was expressed as a proportion of body weight that a relationship with LBM emerged.

Upon further examination of the relationship between BCM and m-REE in the sarcoma group, a negative correlation was found between %BCM and m-REE (Figure 7). This suggests that sarcoma patients with elevated REEs are losing BCM as a proportion of total body weight. This is in severe contrast to findings in the control group where m-REE increased relative to increases in BCM. It has been reported that the principal endogenous energy and nitrogen sources during evolution of weight loss in cancer patients are primarily adipose tissue and skeletal muscle proteins (6,7). It is evident from our findings that although our sarcoma patients were not weight-losing and appeared outwardly similar to the control group (weight, %BF, %LBM, lack of significant weight loss), an underlying decline in BCM was occurring. In theory, if during the initial phases of the tumor-bearing state, REE is elevated and dietary intake is not increased proportionately, nutrient supply would then become inadequate. Previous studies have found that in sarcoma patients, when exogenous nutrient supply is low, the normal adaptive mechanisms of the host that result in body protein conservation are not functioning. The increased tumor demand for amino acids as precursors for gluconeogenesis suggest accelerated breakdown of the host muscle to supply substrate for glucose production by the liver (16). The nontumor-bearing host has well defined mechanisms to conserve body cell mass and to preserve total body protein. The tumor-bearing host seems less well able to utilize these lean tissue-conserving mechanisms and to decrease gluconeogenesis from protein stores in the presence of inadequate

dietary intake (20). This may in part explain the decreased BCM observed in the sarcoma patient.

The question remains as to why, in the face of decreasing BCM, does weight, %BF, and %LBM remain constant in this sarcoma patient group. The negative correlation between %BCM and LBM observed suggests that as body cell mass decreases, LBM increases proportionately. Recent data of Heymsfield and Shizgal support these findings (6,7). When compared to non-cancer semi-starved patients, Heymsfield found that weight-losing cancer patients with anorexia exhibited a far greater proportional reduction in fat and skeletal muscle than in overall LBM and body weight. Shizgal compared body composition data from 75 malnourished patients and 25 normal controls; the loss in BCM, which occurred with the development of the malnourished state, was accompanied by an expansion of the extracellular mass (ECM) (7). As a result of the expansion of the ECM, changes in LBM and body weight were minimized. Heymsfield found similar changes in body composition in anorexic cancer patients, with the expansion of the ECM consisting largely of increased tumor burden, fluid accumulation and visceral organ atrophy (6). The apparent constancy of body weight and LBM in the present sarcoma group, even in the face of decreasing BCM is consistent with these findings. A variable in the Heymsfield study which was not present in this study was that their patients exhibited anorexia. Thus, the body composition changes were a result of diminished intake as well as the

undefined metabolic effects of the tumor on the host. In contrast, the present study was designed to evaluate the metabolic effects of the tumor without superimposed anorexia. This difference explains why the sarcoma patients in this study did not exhibit the substantial loss in body fat as seen in Heymsfield's group.

The Harris-Benedict equations underpredicted m-REE by 23% to 36% in controls and 29% to 61% in the sarcoma group. As reviewed by another research group, the results of 16 other studies in which measured REE in healthy individuals were compared to a value predicted by the Harris-Benedict equation, showed a percent difference ranging from -14.1% to +19.1% (35). The findings in this study reflected a larger difference between p-REE and m-REE in both groups. This is undoubtedly related to the higher m-REEs obtained in both groups due to the methodology used in this study. Since the LBM compartment contributes more to REE than does fat mass, any attempt to predict REE related to body weight will tend to underestimate energy expenditure in patients with changing body composition (15). It follows that when formulas are used to predict energy expenditure in patients with altered body composition, they will underestimate REE if total body weight is part of the formula. Harris and Benedict formulas use body weight as a part of their formula and thus, this may explain the sizeable percent underprediction of m-REE in the sarcoma group since altered body composition was exhibited.

CONCLUSIONS

Based upon assessment of REE and body composition in a sample of seven male sarcoma patients with localized disease, a moderate elevation in resting energy expenditure concomitant with a decrease in BCM was observed. The strength of these findings is due to the demonstrated validity of methods used and to the homogeneous, well-defined nature of the patient group. The reproducibility of the techniques used for measuring body composition were demonstrated by comparison of control data to previous studies using the same or similar techniques, as well as by comparison to body composition standards for normal adults. The technique for measurement of REE was a unique combination of methods previously reported (21,45) and original technology. The major improvement on the technique reported by Arbeit (21) was the increased frequency of readings per patient run; other features of REE data acquisition and manipulation were essentially identical. All patients in this study were evaluated in the initial stages of their disease, prior to any treatment, and variables such as the size, location and histology of the tumor, body composition, age, physical activity, body weight changes and income level were considered. Furthermore, the sarcoma patient group was compared to a closely matched control group.

The limiting factor in this study was the small size of the

sarcoma patient group. In the study design, this factor was minimized by the consideration and/or control of interfering variables and the close match of the control group.

Patients with localized sarcomas offer a unique opportunity to assess the impact of the tumor-bearing state on energy metabolism without the interfering variables of anorexia and weight loss. Sarcomas have been documented to be metabolically active tumors which is an important baseline to establish when evaluating study results. The findings of the present study suggest that sarcoma patients with localized disease are exhibiting an moderate elevation in resting energy expenditure early on in the disease process, prior to any signs of obvious host depletion. There was variance in the magnitude of m-REE elevation within the patient group of this study , which was most likely a result of the limited sample size. Patients consistently exhibited a decrease in BCM, while maintaining a relatively constant body weight and distribution of body fat and lean body mass. The lack of a positive relationship between m-REE and BCM in the sarcoma patient is noteworthy. This finding is in significant contrast to the strong positive correlation between m-REE and BCM observed in healthy adult populations and non-cancer patients with moderate to severe tissue depletion (45).

The finding of a negative correlation between m-REE and %BCM relates the elevated REE to the loss of BCM in the sarcoma patient. Based on previous studies in sarcoma patients, a possible explanation may be that the elevated REE occurs without concurrent increases in dietary intake which superimposes a relative state of inadequate nutrient supply on the host; in response, the host is unable to utilize normal lean-tissue conserving mechanisms, and thus the tumor grows at the expense of the host cell mass. The result is ongoing body cell mass destruction (16,20). In the present study population, observation of decreased BCM was found early on in the disease process and thus, it would be expected that accelerated loss of BCM would occur as tumor growth progressed.

While decreased BCM was observed in the sarcoma group, body weight and LBM were seemingly unchanged. As found in both the work of Shizgal and Heymsfeild, inadequate nutrition results in a loss of body cell mass accompanied by an expansion of the extracellular mass (6,7). In cancer patients, the expansion of extracellular mass has been postulated to be a result of increasing tumor burden, fluid accumulation and visceral organ atrophy (6). As the decrease in BCM would become more pronounced in the sarcoma patient, it would be expected that weight loss and a decrease in LBM would be observed. The proportional reduction in fat and BCM would be expected to be far greater than the reduction in weight or LBM. Currently, in the clinical setting, evaluation of changes in body weight is a standard

practice in the nutritional assessment of cancer patients. Present findings would indicate that decreases in body weight underestimate the loss in body cell mass in cancer patients.

The Harris and Benedict formulae appear less than ideal in providing an accurate prediction of REE for sarcoma patients in the clinical setting. Since these formulae represent some of the best formulae presently available, it is important for the clinician to understand the limitations in their use when applying them to specific patient populations. Due to the wide range of percent underprediction in the sarcoma group, it would be inappropriate to suggest a standard percent increase be applied when using the Harris and Benedict formulae. Larger scale studies in sarcoma patients may produce a standard increase to use in the clinical assessment of energy needs of these patients.

SUMMARY

In order to isolate the effects of tumor-induced changes on host metabolism, studies must be closely controlled. Sarcoma patients offer a unique opportunity to observe alterations in host metabolism resulting from the tumor-bearing state without the interfering variables of weight loss and diminished intake due to anorexia.

A moderate elevation in resting energy expenditure was observed in this group of pre-treatment, weight-stable sarcoma patients with localized disease. While the mechanisms by which elevations in REE are associated with tumor-induced changes in host metabolism must remain speculative at present, it is apparent that aberrations in host energy metabolism occur early on in the disease process. Results of this study suggest that in otherwise asymptomatic cancer patients with metabolically active tumors, such as sarcomas, increased resting energy expenditure contributes to the onset of cancer cachexia prior to any overt host depletion.

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APPENDICIES

APPENDIX I

LEVELS OF PHYSICAL ACTIVITY

SEDENTARY	- time spent doing home or office work that requires little or no arm or leg movements.
SLIGHT ACTIVITY	- time spent walking slowly, doing housework, light activity or office work that requires upper or lower body movements.
MODERATE ACTIVITY	- time spent in activities requiring moderate upper and/or lower body movements. Heart rate may be elevated, but not for a sustained period of time.
HEAVY ACTIVITY	- time spent performing vigorous movements in which heart rate is elevated and sustained for a measureable period of time.

APPENDIX II

Name:_____
Date:_____

PHYSICAL ACTIVITY INDEX (PAI) QUESTIONNAIRE

Questionnaire Objective: To solicit information from patient to reflect level of physical activity during the six-month period immediately preceding interview.

I. Weekday:

Activity category	(a) average hrs/day	Interviewer comment	(b) weight factor	(a) X (b)
REST:				
Sleep				
Added Rest				
JOB:		Occupation:		
Sedentary				
Slight Activity				
Moderate Activity				
Heavy Activity				
EXTRACURRICULAR:				
Sedentary				
Slight Activity				
Moderate Activity				
Heavy Activity				
TOTAL	24		Weekday PAI=	

At any time during the past six months was there any weekday activity that you participated in that was not mentioned? If yes, describe the nature of activity and frequency:

II. Weekend:

Activity category	(a) average hrs/day	Interviewer comment	(b) weight factor	(a) X (b)
REST:				
Sleep				
Added Rest				
JOB:		Occupation:		
Sedentary				
Slight Activity				
Moderate Activity				
Heavy Activity				
EXTRACURRICULAR:				
Sedentary				
Slight Activity				
Moderate Activity				
Heavy Activity				
TOTAL	24		Weekend PAI=	

At any time during the past six months was there any weekend activity that you participated in that was not mentioned? If yes, describe the nature of activity and frequency:

APPENDIX III

PAI WORKSHEET

PAI WEIGHT FACTORS:

Physical Activity Level	Oxygen Consumption* (Liter/min)	Weight* Factor
Basal level (ie. sleep)	0.25	1.0
Sedentary	0.28	1.1
Slight activity	0.41	1.5
Moderate activity	0.60	2.4
Heavy activity	1.25	5.0

COMPOSITE SCORE FORMULA:

$$PAI = \frac{(\text{Weekday PAI} \times 5) + (\text{Weekend PAI} \times 2)}{7}$$

* Kannel & Sorlie, 1979 (44).

APPENDIX IV

RAW DATA: GENERAL CHARACTERISTICS

Subject No	Age (yrs)	%Wt Loss	PAI	ISI
A. CONTROL GROUP (FEMALES):				
1	23.7	0	32.0	.375
2	29.8	0	27.5	.375
3	23.9	0	32.4	.250
4	49.8	0	39.3	.125
5	41.4	0	34.3	.125
6	52.8	0	31.9	.125
7	33.2	0	42.3	.375
B. CONTROL GROUP (MALES):				
1	22.8	0	31.5	.125
2	27.5	0	32.9	.250
3	31.3	0	37.7	.250
4	34.2	0	36.7	.375
5	68.0	0	29.3	.125
6	27.1	0	33.4	.250
C. SARCOMA PATIENTS (MALES):				
1	21.3	8.0	33.1	.125
2	31.1	6.4	27.0	.125
3	31.1	5.0	31.6	.125
4	58.3	0	29.8	.125
5	53.3	7.5	26.7	.125
6	58.2	0	36.4	.125
7	61.2	0	30.3	.125

APPENDIX V

RAW DATA: BODY COMPOSITION PARAMETERS

Subject No.	Weight (kg)	%BF	%BCM	%LBM	BSA (m^2)
A. CONTROL GROUP (FEMALES):					
1	60.4	35.6	35.0	64.4	1.55
2	47.9	21.7	40.2	78.3	1.51
3	72.5	34.2	33.2	65.8	1.63
4	52.6	25.7	34.2	74.3	1.87
5	64.2	36.7	30.7	63.3	1.71
6	58.7	37.5	27.9	62.5	1.58
7	52.3	31.0	40.6	69.0	1.53
B. CONTROL GROUP (MALES):					
1	79.0	16.1	44.0	83.9	2.09
2	75.9	22.9	38.6	77.1	1.89
3	100.0	29.6	39.1	70.4	1.95
4	75.0	23.4	41.7	76.6	2.26
5	71.8	18.3	33.3	81.7	1.96
6	68.3	16.2	41.9	83.8	1.81
C. SARCOMA PATIENTS (MALES):					
1	84.1	28.6	34.5	71.4	1.95
2	76.7	21.2	36.3	78.8	2.21
3	85.0	20.0	35.6	80.0	2.08
4	97.3	27.8	31.0	72.2	1.84
5	84.0	16.4	28.1	83.6	2.21
6	104.0	24.4	27.2	75.6	2.08
7	72.9	18.6	35.3	81.4	2.00

APPENDIX VI

RAW DATA: ENERGY EXPENDITURE

Subject No.	m-REE (kcal/day)	m-REE/BSA (kcal/day/m^2)	p-REE (kcal/day)	%Under-prediction of m-REE
A. CONTROL GROUP (FEMALES):				
1	2464.8	746.2	1398.7	43.3
2	1205.0	797.9	1259.0	-4.4
3	2143.6	1512.0	1540.4	28.1
4	1157.3	1147.4	1201.7	-3.8
5	2516.8	1472.1	1357.4	46.1
6	1201.5	760.3	1244.4	-3.6
7	1457.2	952.2	1265.5	13.2
B. CONTROL GROUP (MALES):				
1	2551.3	1221.1	1963.7	23.0
2	2563.2	1216.8	1812.2	29.3
3	2899.0	1314.3	2150.2	25.8
4	2783.8	1283.0	1777.3	36.2
5	2300.9	1419.9	1477.3	35.8
6	2330.0	1287.1	1683.1	27.8
C. SARCOMA PATIENTS (MALES):				
1	2822.4	1296.1	1970.6	30.2
2	2527.9	1941.0	1801.0	28.8
3	2740.1	1356.8	1926.0	29.7
4	4290.3	1543.2	1930.0	55.0
5	3078.6	2281.0	1756.4	42.9
6	5041.7	1316.2	1986.4	60.6
7	2840.1	1540.4	1499.9	47.2

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