Energy Expenditure in Malnourished Cancer Patients

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It is widely believed that the presence of a malignancy causes increased energy expenditure in the cancer patient. To test this hypothesis, resting energy expenditure (REE) was measured by bedside indirect calorimetry in 200 heterogeneous hospitalized cancer patients. Measured resting energy expenditure (REE-M) was compared with expected energy expenditure (REE-P) as defined by the Harris–Benedict formula. The study population consisted of 77 males and 123 females with a variety of tumor types: 44% with gastrointestinal malignancy, 29% with gynecologic malignancy, and 19% with a malignancy of genitourinary origin. Patients were classified as hypometabolic (REE < 90% of predicted), normometabolic (90–110% of predicted) or hypermetabolic (>110% of predicted). Fifty-nine per cent of patients exhibited aberrant energy expenditure outside the normal range. Thirty-three per cent were hypometabolic (79.2% REE-P), 41% were normometabolic (99.5% REE-P), and 26% were hypermetabolic (121.9% REE-P) ($p < 0.001$). Aberrations in REE were not due to age, height, weight, sex, nutritional status (% weight loss, visceral protein status), tumor burden (no gross tumor, local, or disseminated disease), or presence of liver metastasis. Hypermetabolic patients had significantly longer duration of disease ($p < 0.04$) than normometabolic patients (32.8 *vs.* 12.8 months), indicating that the duration of a malignancy may have a major impact upon energy metabolism. Cancer patients exhibit major aberrations in energy metabolism, but are not uniformly hypermetabolic. Energy expenditure cannot be accurately predicted in cancer patients using standard predictive formulae.

WEIGHT LOSS is a common clinical finding in the patient with cancer. In many instances, it is seen late in the course of the disease, while in other cases it is the first symptom that induces the patient to seek medical attention. Many factors contribute to loss of weight and progressive cachexia. No direct correlation between the size, site, extent, stage, or cell type of the neoplasm and the incidence and severity of the cachexia has been documented.[1] Regardless of etiology, severe tissue wasting in the cancer patient is of major clinical significance. Warren, reporting in 1932 on the autopsies of 500 cancer patients, observed that the most frequent single cause of death was cachexia.[2] The common underlying explanation for cachexia is a negative balance between caloric intake and expenditure.[3] In some instances, the etiology of decreased intake and/or increased requirement is obvious. Factors such as anorexia, nausea, mechanical obstruction of the gastrointestinal tract, chronic blood loss, proteinuria, and gastrointestinal loss of albumin contribute to the development of cachexia. However, in many instances the etiology of cachexia is less obvious. Proposed mechanisms include host tumor competition for nutrients and tumor-induced host abnormalities in carbohydrate, lipid, and protein metabolism.

One factor often cited as contributing to the development of cachexia is an increase in the metabolic rate. Frequently cited studies performed on small numbers of cancer patients have reported increases in the metabolic rate,[4–8] while other studies indicate no change or decreases in the metabolic rate.[6,9,10] It has become widely presumed that the presence of a tumor causes an increase in the basal metabolic rate and total energy expenditure of the cancer patient.

The development of total parenteral nutrition (TPN) by Dudrick, Rhoads, Wilmore, and Vars has made it possible to force-feed cancer patients. In many instances TPN is able to prevent, retard or reverse the development of cachexia. However, the nutritional requirements for the cancer patient are not well defined. Clinical experience shows TPN to be effective in many patients, but controlled clinical trials have produced mixed results. In certain studies, TPN has been ineffective in promoting significant tissue weight gain and positive nitrogen balance.[11–14] Perhaps the patients studied were hypermetabolic and energy and nitrogen supply too low.

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In the case of a hypometabolic patient, standard estimates of energy and nitrogen requirements may be too high. The adverse effects of overfeeding have been well documented.[15-17] With the increased use of adjuvant TPN, it becomes imperative that the nutrient and energy requirements of the cancer patient are clearly defined.

The development of portable accurate reliable equipment for indirect calorimetry has facilitated the study of energy expenditure in a large number of heterogeneous cancer patients. The study objectives were to measure and evaluate resting energy expenditure in a large series of cancer patients and to evaluate the possible determinants of energy expenditure in this patient population.

Materials and Methods

The study population consisted of 200 clinically stable heterogeneous cancer patients, referred to the Nutrition Support Service of the Hospital of the University of Pennsylvania for nutritional assessment and possible nutritional support. Septic, febrile, and recent postoperative (<5 days) patients were excluded. All patients were spontaneously breathing without mechanical ventilation. Patients were entered into the study at time of referral.

All patients underwent nutritional assessment including anthropometric assessment and evaluation of immunologic and secretory protein status.[18] Nutrient intake data for day of study was grossly quantitated: including oral intake (NPO *vs.* oral intake *ad lib*), presence or absence of TPN, and quantification of intravenous intake (kcal/day and grams amino acid/day).

Resting energy expenditure (REE) was both measured (REE-M) and predicted (REE-P) for all subjects. REE is the metabolic rate in kcal/day of an individual in a thermoneutral environment, lying at rest for a minimum of 30 minutes with skeletal muscles completely supported and greater than two hours after a meal.[19] Under these conditions, REE-M was determined by bedside indirect calorimetry[20,21] (Metabolic Measurement Cart, Beckman Instruments, Inc., Schiller Park, IL). This instrument has been independently validated by other workers.[22] This instrument employs a polarographic oxygen sensor and infrared carbon dioxide sensor which are calibrated to gases of known composition (16.0% O_2, 4.0% CO_2) every three hours. The MMC was also checked for drift before each measurement; excessive drift was corrected by recalibration against gases of known composition. In addition, the instrument contains a barometer, temperature sensor, and volume transducer which are calibrated to independent instruments. A programmable calculator integrates data, performs calculations, and prints the measured and calculated values at predetermined time intervals. The patient breathes room air through a mouthpiece connected to a nonrebreathing valve. Expired air is passed through tubing to a gas collection drum from which a continuous aliquot (500 cc/min) is withdrawn and passed through the gas analyzers, volume transducer, and temperature sensor. Data were calculated and printed at one-minute intervals. Monitoring of expired air continued until equilibration, as evidenced by five consecutive stable $\dot{V}O_2$ and $\dot{V}CO_2$ measurements. Patients unable to equilibrate were excluded from the study. One minute $\dot{V}O_2$ and $\dot{V}CO_2$ measurements from the equilibrated data points were averaged and used to calculate respiratory quotient and resting energy expenditure. Respiratory quotient is the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ ($RQ = \dot{V}CO_2/\dot{V}O_2$).

The abbreviated Weir formula[23] was used for the calculation of REE.

Abbreviated Weir Formula

$$\text{REE-M (kcal/day)} = (3.9\dot{V}O_2 + 1.1\dot{V}CO_2)1440 \text{ min/day}$$

$$\dot{V}O_2 = O_2 \text{ consumption (L/min)}$$

$$\dot{V}CO_2 = CO_2 \text{ production (L/min)}$$

Studies performed at this institution have demonstrated that REE may be measured at any time during the day (greater than two hours postprandial).[24] In ten patients, resting energy expenditure was measured at midmorning and midafternoon. A mean difference of $1 \pm 2\%$ between measurements was observed. These data illustrate the stability of resting energy expenditure and repeatability of measurements under resting conditions during the day.

Expected energy expenditure as predicted by Harris–Benedict was used as the control standard for purposes of statistical comparison. Expected resting energy expenditure (REE-P) was calculated using the anthropometric based formula of Harris and Benedict.[25]

$$\text{REE-P (kcal/day in males)} = 5(H) + 13.7(W) + 66 - 6.8(A)$$

$$\text{REE-P (kcal/day in females)} = 1.7(H) + 9.6(W) + 665 - 4.7(A)$$

Where: H is height in centimeters, W is weight in kilograms and A is age in years.

These anthropometric based formulae were statistically derived from indirect calorimetric determinations of energy expenditure in a large series of healthy volunteers. In a population of normal individuals, these formulae have been demonstrated to be valid for pre-

TABLE 1. *Site of Primary Tumor*

	Number
Gastrointestinal	
Colon	28
Pancreas	17
GI (miscellaneous)	15
Rectum	11
Esophagus	9
Stomach	8
Gynecologic	
Cervix	33
Ovary	11
Endometrium	8
Vulva	4
Genitourinary	
Bladder	17
Urethra	2
Other	37

diction of REE.[26,27] Long et al.[26] demonstrated a mean difference of 2% when REE-M and REE-P were compared in 20 normal controls.

Energy expenditure data (measured and predicted) were normalized to kilogram of body weight, metabolic body size ($kg^{0.75}$), and body surface area (BSA). Kleiber's metabolic body size is body weight to the 0.75 power.[28] BSA in m^2 was calculated using the formula of Dubois and Dubois.[9]

Characteristics of the malignancy included site, duration of disease, tumor burden and presence or absence of liver metastasis. Duration of disease was defined as the length of time in months from histologic diagnosis to study entry. Tumor burden was classified: no gross tumor, localized tumor, local recurrent tumor or disseminated disease. Tumor data were collected by one investigator (LK) through a review of operative records, medical records, pathology and radiology reports.

Data were analyzed by multiple statistical procedures using a computerized statistical package (Statistical Package for the Social Sciences, SPSS, Inc). The primary procedure was one-way analysis of variance with differences between groups established by the Scheffe's test.[29,30] When appropriate, chi square analysis and unpaired t-tests were employed.[31]

TABLE 2. *Summary of Energy Expenditure Data for Study Population*

	Measured	Predicted
Parameter	$\bar{X}$ (S.D.)	$\bar{X}$ (S.D.)
REE-M (kcal/day)	1287 (291)*	1314 (232)*
REE-M (kcal/kg/day)	21.2 (5.0)*	21.5 (2.9)*
% of REE-P	98.6 (18.3)	90–110%
$\dot{V}O_2$ (ml/min)	184.6 (42.0)	
$\dot{V}O_2$/kg (ml/min/kg)	3.0 (0.7)	
$\dot{V}CO_2$ (ml/min)	162.0 (40.2)	
$\dot{V}CO_2$/kg (ml/min/kg)	2.7 (0.7)	
RQ	0.88 (0.11)	

* Means are not statistically different by unpaired Student's *t*-test.

Results

Two hundred patients (77 males and 123 females), with a mean age of 59.5 ± 13.8 years, were studied. Their mean height was 166.0 ± 10.0 centimeters, and mean weight was 62.5 ± 15.7 kg. The patients were 89.9 ± 10.6% of usual body weight (UBW) and 106.4 ± 28.0% of ideal body weight (IBW). Serum protein status was compromised as evidenced by a serum albumin of 3.09 ± 0.71 gm/dl (normal range: 3.70–5.20 gm/dl) and a serum total iron binding capacity (TIBC) of 235 ± 61 μg/dl (normal range: 245–430 μg/dl).

All patients had documented malignancy with a mean duration of disease of 20.7 ± 44.8 months. Forty-three (21.5%) subjects had no residual gross tumor, 45 (22%) had localized disease, eight (4%) had recurrent local disease, and 104 (52%) had disseminated disease. Eighty-eight (44%) patients had tumors of gastrointestinal origin, 56 (28%) had gynecologic tumors, and 19 (9%) had tumors of the genitourinary tract (Table 1). Cervical and colon malignancies accounted for 30% of all patients. The "other" group included lymphomas and leukemias, and primary tumors of the brain, breast, larynx, tonsil, and tongue. The distribution of primary tumor site in this study population differs from that of all new cancer patients seen in a year at this institution.[32] This institution's major tumor types are breast (13.1%), lung (13.0%), female genital (12.5%), and colorectal (8.4%). Lung and breast cancer account for only 4.5% of the study population but 26.1% of the institution's cancer population. In contrast, primary tumors of gastrointestinal origin account for 44% of the study population but only 17% of the hospital's cancer patient population.

Measured resting energy expenditures (REE-M) derived from indirect calorimetry data (Table 2) were compared with Harris–Benedict predictions (REE-P). For the study population, mean measured resting energy expenditure was 98.6% of predicted with no significant differences. No differences were observed when REE-M and REE-P were normalized to kilogram body weight (Table 2). Although population means of expected and measured resting energy expenditure show no difference, the distribution of individual patients is rather striking (Fig. 1). Boothby has demonstrated that 95% of normal individuals will have a measured resting energy expenditure within 10% of that predicted by the Harris–Benedict formulae.[33–35] The data depict a general flattening of the normal bell-shaped distribution curve with

only 41% of study patients within Boothby's normal range of ±10% of predicted.

Energy data were further evaluated by classifying patients (Table 3) according to the standards of Boothby[33–35] with measured resting energy expenditures within 10% of Harris–Benedict predictions (90–100% REE-P) considered normometabolic, those <90% REE-P considered hypometabolic, and those >110% of REE-P considered hypermetabolic. Thirty-three per cent (N = 66) were hypometabolic, 41% (N = 82) normometabolic, and 26% (N = 52) were hypermetabolic. Hypermetabolic patients were older, and had a lower absolute body weight and per cent IBW than hypometabolic or normometabolic patients. As patients in each metabolic group experienced weight loss of the same magnitude (11.8% *vs.* 8.0% *vs.* 11.1%), the premorbid absolute (UBW) and relative (% IBW) weight of the hypermetabolic patients was lower. There was no significant correlation between per cent weight loss and resting energy expenditure expressed as per cent of expected energy expenditure for the population (Fig. 2). No differences were observed between groups for serum TIBC. One-way analysis of variance of serum albumin values indicates significant difference ($p < 0.04$) exists between groups. However, further analysis via Scheffe's test[39] fails to confirm statistical significance. The hypermetabolic group clearly had a significantly lower serum albumin (2.92 gm/dl) than the normometabolic group (3.23 gm/dl).

Hypometabolic subjects had measured resting energy expenditures of 79.2% of predicted (REE-P), normometabolic subjects were 99.5% REE-P, and hypermetabolic subjects were 121.9% REE-P (Table 4). Significant differences ($p < 0.05$) were observed between all groups for REE-M in kcal/day, and for REE-M normalized to kilogram body weight (kcal/kg/day) and body surface area (kcal/m^2/day).

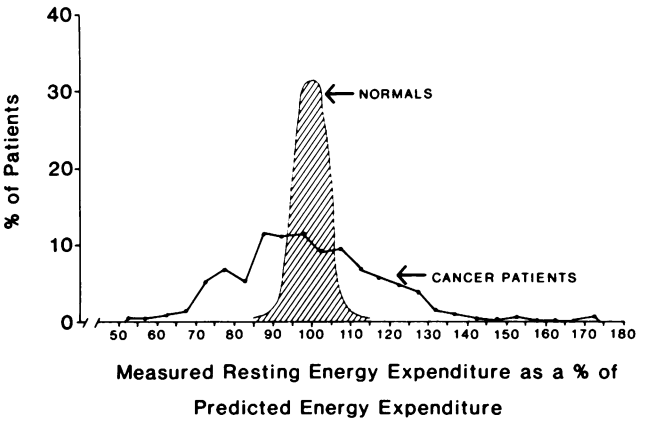

FIG. 1. The distribution of measured resting energy expenditure in "normals" and in cancer patients.

The hypermetabolic group had a smaller mean body surface area and a lower predicted energy expenditure per m^2 than the other groups, but had a significantly higher measured energy expenditure per m^2. Despite differences in REE-M, $\dot{V}O_2$ and $\dot{V}CO_2$, no differences were observed for respiratory quotients (0.87 *vs.* 0.88 *vs.* 0.88).

With Kleiber's assumption of normal body composition, analysis of selected parameters normalized to "metabolic body size" (Table 5) showed hypermetabolic patients to have a smaller metabolic body size than normometabolic or hypometabolic patients. REE and $\dot{V}O_2$ normalized to metabolic body size showed marked differences between all groups. No differences were observed for REE-P normalized to this standard (Table 6).

Fifty-one per cent of study patients (N = 101) were

TABLE 3. *Metabolic Group Characteristics*

Parameter	Hypometabolic	Normal	Hypermetabolic	
% REE-P	<90% REE-P X̄ (S.D.)	90–110% REE-P X̄ (S.D.)	>110% REE-P X̄ (S.D.)	p <
N	66	82	52	
Age (years)	57.2 (15.2)[a]	58.6 (12.8)	63.7 (12.7)[a]	0.03*
Sex (male/female)	25/41	31/51	21/31	NS†
Height (cm)	166.6 (9.2)	166.6 (10.2)	164.2 (10.7)	NS*
Weight (kg)	63.8 (17.2)[a]	65.9 (15.4)[b]	55.5 (11.7)[a,b]	0.0005*
% Usual body weight	88.2 (10.7)	92.0 (10.9)	88.9 (9.5)	NS*
% Ideal body weight	108.3 (28.8)[a]	111.7 (30.9)[b]	95.6 (17.8)[a,b]	0.004*
Serum albumin (gm/dl)	3.05 (0.74)	3.23 (0.65)	2.92 (0.75)	0.04*
TIBC (μg/dl)	231 (64)	242 (62)	229 (53)	NS*
% Receiving TPN	48	54	48	NS†
TPN (kcal/hr)	79.9 (32.1)	85.6 (36.1)	79.7 (23.2)	NS*
TPN (gm amino acid/hr)	2.99 (0.89)	3.11 (0.87)	3.14 (0.28)	NS*

* One-way analysis of variance.
† Chi square analysis.
a *vs.* a, b *vs.* b, $p < 0.05$.

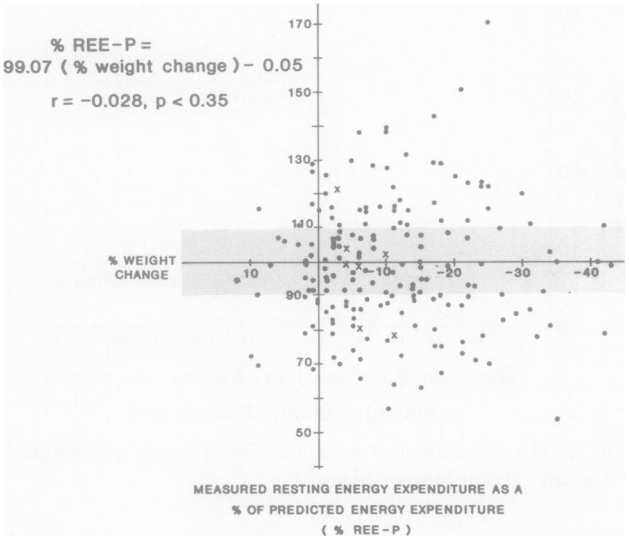

FIG. 2. The relationship between per cent weight change and measured resting energy expenditure. The shaded area represents the normal range of 90 to 110% of expected energy expenditure.

receiving TPN. No significant differences were observed between the TPN and the non-TPN groups for mean resting energy expenditure (1287 *vs.* 1287 kcal/day). No differences were observed between metabolic groups for per cent of patients receiving TPN or the quantity of nutrients (kcal/hr and grams amino acid/hr) (Table 3).

Tumor data of the metabolic groups is presented in Table 6. Normometabolic patients had a significantly shorter duration of disease than hypermetabolic patients. However, there was no significant correlation between duration of disease and resting energy expenditure expressed as per cent of expected for this study population (Fig. 3). No differences were found between groups for the per cent of patients with liver metastasis. Chi square analysis of tumor burden by metabolic group showed no significant differences between groups.

Discussion—Previous Studies

At present it is widely held that cancer patients exhibit an elevated energy expenditure, and this increased energy consumption by host and tumor is a major determinant in the pathogenesis of cancer cachexia. Though popular, this concept has evolved from limited data of small studies with a variety of undefined and/or uncontrolled variables.

Many early studies[33,36-38] were performed on adult subjects with acute leukemia demonstrating an increase in basal metabolic rate (BMR) of 6 to 100%, parallel to the severity of the disease.[33,36,37] Metabolic rate was high with elevated leukocyte counts, and if treatment was successful, the metabolic rate returned to normal limits. These series studied limited numbers[16-33] of patients.

Streick and Mulholland[10] reported a series of 52 heterogeneous patients with 80% having energy expenditures of greater than 110% of "normal." Wallersteiner[6] measured REE in 33 afebrile primarily gastric cancer patients with advanced disease and only 50% were normometabolic, the remainder being hypermetabolic.

Waterhouse[39] serially studied nitrogen exchange and caloric expenditure in eight patients with metastatic tumors, concluding that a rapidly growing neoplasm appears to increase the energy expenditure of the host. Patients were found to be in caloric deficit when kept on diets considered to be liberal for conditions of the study and which had been observed to be adequate for maintaining positive caloric balances for similar individuals without malignancy. Net caloric deficits were most pronounced in the two patients with the most rapidly growing tumors.

Warnold[4] studied body composition and energy balance in ten heterogeneous cancer patients and nine controls to investigate the relationship between energy expenditure and energy intake in the development of cancer cachexia. Energy intake was not significantly different

TABLE 4. *Resting Energy Expenditure by Metabolic Group*

Parameter	Hypometabolic X̄ (S.D.)	Normal X̄ (S.D.)	Hypermetabolic X̄ (S.D.)	p <*	Predicted
REE-M (% REE-P)	79.2 (8.3)	99.5 (5.6)	121.9 (11.4)		90–110
REE-M (kcal/day)	1062 (233)[a,b]	1355 (2.39)[a,c]	1466 (255)[b,c]	0.0001	1314 (232)
REE-M (kcal/kg/day)	17.1 (3.2)[a,b]	21.0 (2.8)[a,c]	26.9 (4.1)[b,c]	0.0001	21.5 (2.9)
REE-M (kcal/m^2/day)	620.0 (86.9)[a,b]	781.1 (75.3)[a,c]	918.3 (96.9)[b,c]	0.0001	763.6 (142.8)
$\dot{V}O_2$ (ml/min)	152.2 (33.9)[a,b]	195.2 (34.9)[a]	209.1 (36.3)[b]	0.0001	
$\dot{V}O_2$ (ml/min/kg)	2.4 (0.5)[a,b]	3.0 (0.5)[a,c]	3.8 (0.6)[b,c]	0.0001	
$\dot{V}CO_2$ (ml/min)	132.4 (30.2)[a,b]	172.2 (343)[a]	183.7 (38.7)[b]	0.0001	
$\dot{V}CO_2$ (ml/min/kg)	2.1 (0.5)[a,b]	2.7 (0.6)[a,c]	3.4 (0.7)[b,c]	0.0001	
RQ	0.87 (0.11)	0.88 (0.11)	0.88 (0.11)	NS	

* One-way analysis of variance.

a *vs.* a, b *vs.* b, c *vs.* c, $p < 0.05$.

TABLE 5. *Energy Expenditure Normalizations*

Parameter	Hypometabolic X̄ (S.D.)	Normal X̄ (S.D.)	Hypermetabolic X̄ (S.D.)	p <*
Current Weight$^{.75}$ (kg$^{.75}$)	22.4 (4.5)[a]	23.0 (4.0)[b]	20.3 (3.2)[a,b]	0.0004
REE-M (kcal/kg$^{.75}$/day)	47.7 (7.8)[a,b]	59.2 (6.6)[a,c]	72.8 (9.4)[b,c]	0.0001
REE-P (kcal/kg$^{.75}$)	60.2 (6.8)	59.5 (6.1)	59.7 (5.3)	NS
$\dot{V}O_2$ (ml/min/kg$^{.75}$)	6.8 (1.2)[a,b]	8.5 (1.1)[a,c]	10.4 (1.3)[b,c]	0.0001
$\dot{V}CO_2$ (ml/min/kg$^{.75}$)	6.0 (1.1)	7.6 (1.3)	9.1 (1.7)	0.0001

* One-way analysis of variance.
a *vs.* a, b *vs.* b, c *vs.* c, $p < 0.05$.

between groups, while energy expenditure was elevated in the cancer patients, but not in controls. The investigators concluded that an increase in resting metabolic rate is one of the major factors responsible for the development of cachexia.

Arbeit[40] studied 22 subjects: ten controls, nine with localized tumors, and three with metastatic disease. A 20% and 26% elevation in REE were observed for patients with local and metastatic disease, respectively, as compared with control subjects.

Recent investigations, assuming that energy expenditure is elevated in cancer patients, have explored the pathophysiologic basis. Alterations in substrate utilization with excessive mobilization of lipid, alteration in glucose metabolism, and reduction in the efficiency of energy metabolism have been demonstrated.[41] It has been suggested that various abnormal metabolic pathways are responsible for increased energy expenditure in the cancer patient. Holroyde[42] has reported increased Cori cycle activity in patients with advanced cancer. The highest Cori cycle activity was observed in patients with the greatest total energy expenditure and greatest weight loss. Gold[43] has proposed that the increased rate of gluconeogenesis from lactate produced by the tumor acts as a significant metabolic drain on the host. Young[41] has suggested that increased rates of protein turnover, synthesis, and breakdown are responsible for increased energy expenditure in the depleted host.

Few studies report normal or decreased REE in cancer patients, yet all of the aforementioned studies must be interpreted with caution. 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. In these studies, the techniques of indirect calorimetry are well defined as are the factors of age, sex, height, and weight. Nutritional status, therapy factors, and disease factors such as tumor stage, duration, and treatment are not well defined. The lack of such information in early calorimetry studies makes a direct comparison between those studies and this one impossible. It is difficult to logically conclude from previous studies that energy expenditure is consistently elevated in cancer patients since important potential determinants were either not considered or not controlled.

At present, the authors are unable to prospectively identify individuals who will later develop a malignancy. If this were possible, serial energy expenditures could be measured before and after the development of the malignancy and the precise "tumor effect" upon energy expenditure could be determined. As this serial observational study is impossible, a thorough understanding and consideration of factors known to influence energy expenditure is necessary if the effect of the malignancy upon the patient's resting energy expenditure from a spot measurement is to be defined.

TABLE 6. *Tumor Characteristics*

Parameter	Hypometabolic	Normal	Hypermetabolic	p <
Duration of disease (months)	21.0 (46.0)	12.8 (30.0)[a]	32.8 (58.8)[a]	0.04*
% With liver metastasis	29	24	23	NS†
Tumor burden (N)				
No gross tumor	16	16	11	NS†
Local tumor	13	22	10	
Recurrent local tumor	1	5	2	
Disseminated tumor	36	39	29	

* One-way analysis of variance.
† Chi square analysis.
a *vs.* a, $p < 0.05$.

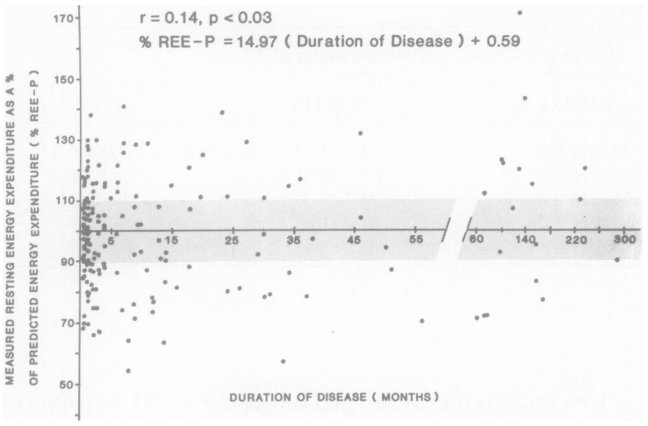

FIG. 3. Relationship between duration of disease and measured resting energy expenditure. The shaded area represents the normal range of 90 to 110% of expected energy expenditure.

Determinants of Resting Energy Expenditure

The major determinants of resting energy expenditure are age, sex, height, and weight. Metabolic rate decreases as an individual ages. A steady decrease is seen between birth and sexual maturity, from a rate of 53.0 kcal/m^2/hr at the age of one year to a rate of 35.3 to 38.6 kcal/m^2/hr at the age of 20. Throughout the remainder of the life span, the decrease in metabolic rate is more gradual, occurring at a rate of 1 to 2% per decade. The metabolic rates of a 30-year-old male and a 70-year-old male are approximately 36.8 kcal/m^2/hr and 33.8 kcal/m^2/hr.[19,44,45] The majority of subjects in this study were middle age, with a mean age of 59.5 years and a range of 33 to 87 years. Although the age differences between groups were small, the hypometabolic subjects were significantly younger (57.2 *vs.* 63.7 years) than hypermetabolic subjects (Table 3). The highest resting energy expenditure was observed in the oldest subjects which is directly opposite of the age effect in normal subjects. The differences in REE between the three metabolic groups are not due to an age effect.

Sex affects metabolic rate with females having a slightly lower metabolic rate than males. A 50-year-old normal male has a metabolic rate of 35.8 kcal/m^2/hr as opposed to a rate of 33.9 kcal/m^2/hr for a woman of comparable age.[45] This most likely reflects differences in body composition with women having a higher proportion of body fat than men. The distribution of males and females in each metabolic group in this study was not significantly different (Table 3) discounting a sex effect in the measured REE between the three metabolic groups.

Body size, as defined by height and weight, is the single most important determinant of energy expenditure although it is difficult to separate the individual specific effects of height and weight. In general, a tall person has a higher REE than a short person of equal weight, and when two people are of equal height, the heavier person will have the higher REE.[9] Metabolic rate is directly proportional to body size.[28] REE represents the energy necessary for all metabolic activity of oxygen-consuming tissues necessary for maintenance of life. The larger the organism, the larger the metabolically active tissues, the greater the oxygen consumption and the greater the resting energy expenditure.[46,47] Metabolic rate is a reflection of both the intensity and the size of the metabolically active cells.[46,47]

To compare energy expenditure measurements between individuals, data must be normalized. Normalization corrects for the primary confounding variables of height and weight. In a population of normal subjects, normalization will eliminate differences in REE due to height and weight. A commonly used method is to normalize REE to body weight (kcal/kg/day). Two other standards of normalization are body surface area (kcal/m^2/day) and metabolic body size (kcal/$kg^{0.75}$/day) described by Kleiber[28] as the power of body weight to which metabolic rate is proportional. The use of metabolic body size for data normalization is the preferable method as body $weight^{0.75}$ is thought to reflect the metabolically active portion of the body, *assuming normal body composition.* A linear relationship in normals has been demonstrated between metabolic rate and both body surface area and metabolic body size.[28] When metabolic rate is normalized to weight, this linear relationship no longer exists.[19] The above standards of normalization assume a normal body composition and control for differences in body size only. No linear relationship exists when REE is normalized to body weight due to differences in body composition, *i.e.*, a varying proportion of relatively inactive body fat.

A wide range of weights (28.2 kg–127.3 kg) were observed in these subjects. Hypermetabolic group subjects weighed significantly less than hypometabolic and normometabolic subjects with no differences observed for height. The hypermetabolic group also had a smaller metabolic body size. Subjects with the smallest absolute body size and metabolic body size had the highest energy expenditure, which is directly opposite of observations in normals.

In this study both measured and predicted energy expenditure were normalized to control for influences of body size. As expected, normalization of *predicted* energy expenditures to kcal/kg/day and kcal/$kg^{0.75}$/day eliminated differences in REE-P between groups due to primary height and weight effects. Normalization of *measured* resting energy expenditure did not eliminate or reduce differences between groups but in fact showed them to be more dramatic (Table 5). The dramatic dif-

ferences in measured REE between metabolic groups are not due to height and weight effects.

Despite differences in current body weight, per cent weight loss was essentially the same in all three metabolic groups and cannot be a marker for differences in measured energy expenditure between groups. This finding contradicts other studies,[8,42] and is further supported by the lack of significant correlation between per cent weight loss and per cent of predicted energy expenditure (Fig. 2).

Normal Standards

Early work in clinical calorimetry was directed at the establishment of normal standards and derived predictive formulae. The establishment of normal standards was necessary so that aberrations in energy expenditure could be identified in future studies. The Harris–Benedict formulae, developed from the study of energy expenditure in a series (N = 239) of healthy volunteers, is a multiparameter linear regression formula for prediction of REE. It is composed of the four factors that most influence energy expenditure in the healthy, normal individual: age, sex, height, and weight. Boothby compared this linear formula with the surface area predictive formula of DuBois and found that both were able to predict resting energy expenditure with "practically no difference in the precision of the two formulas."[48] The validation and final development of normal standards can be credited to Boothby's work at the Mayo Clinic. Boothby clearly showed that 95% of normal individuals have a measured resting energy expenditure within ±10% of predicted.[33–35] Ninety-nine per cent of normals are within ±15% of predicted. Boothby's definition of ±10% of predicted was used as the range for the normometabolic patients, since the indirect calorimetry methods in normals closely approximates the above limits.

These clinically accepted predictive formulae were developed in a healthy, normal population. Preliminary data from this institution indicate that hospitalized individuals, including noncancer patients, show wider and more frequent deviations from the normal range than do normal individuals. The Harris–Benedict formula has been demonstrated to be accurate in predicting energy expenditure for a *population* of hospitalized patients,[49] but not for predictions in individuals. Feurer et al. showed that 40% of 200 hospitalized clinical stable patients exhibited measured REE above or below the normal range predicted by the Harris–Benedict formula. In this study of 200 patients, the population mean of measured REE was not statistically different from the population mean of predicted REE. However, in our 200 cancer patients only 41% had measured REE within the normally accepted ±10% range.

At the present time, the predictive formulae and normal standards of Harris and Benedict and of Boothby are the best available. The analysis of measured REE data expressed as a per cent of predicted or expected REE serves to normalize the data for the four most important determinants of resting energy expenditure: age, sex, height, and weight. The influence of each factor is quantified in the Harris–Benedict formula which is being used as a reference standard.

Additional Determinants of REE

Other factors influence resting energy expenditure: sepsis, trauma, major surgery, and nutritional status. Elevations in measured REE of 36 to 79%[26] above predicted by Harris–Benedict have been observed in patients with trauma and sepsis. In this study, patients with sepsis and blunt trauma were excluded to remove these possible influences. The influence of major surgery on resting energy expenditure is variable. In one study by Long et al., patients undergoing major elective general surgical procedures (appendectomy, colon resection, inguinal hernioraphy) had elevations of 24% above predicted energy expenditure.[26] Elevations in REE were demonstrated to persist long into the postoperative period (1–2 weeks). In a study of Askanazi et al., REE was shown to remain within ±10% of preoperative values.[50] As the influence of major surgery on REE is not well defined, patients in the immediate postoperative period (<5 days) were excluded from the study.

Nutritional status and Body Composition

Nutritional status profoundly effects resting energy expenditure. Resting energy expenditures as low as 54% of predicted (unpublished observations) have been observed in patients with anorexia nervosa. Grande[51] observed a decrease in BMR of as much as 21.4% in experimental male subjects receiving a hypocaloric diet while maintaining a high level of physical activity. In normal individuals, the basal metabolic rate will progressively decrease as duration of starvation increases. Benedict[52] studied a professional faster allowed only distilled water for a period of 31 days, observing a 16.7% decrease in body weight and a 30% reduction of the BMR. Keys et al.[53] observed a 25% reduction in weight and a 40% reduction in BMR in 32 subjects during a 24-week study of semistarvation. This normal compensatory decrease in REE seen in starvation may not always occur in the starved or semistarved cancer patients.[54–56]

In this study, an attempt was made to quantify the effects of nutritional status. Since all subjects were previously referred to this Nutrition Support Service, one would expect a high incidence of malnutrition. Study

patients were malnourished as evidenced by a mean 10% weight loss and depletion of visceral protein stores. Patients in each metabolic group were equally malnourished by these measures. Thirty-nine per cent of the study population were truly hypometabolic. The decrease in resting energy expenditure (21%) may have been a normal response to chronic starvation. However, two thirds of the study population had normal or elevated energy expenditures, and were as equally malnourished as the hypometabolic group but obviously did not exhibit the normal expected decline in energy expenditure. It can be hypothesized that this nutritional influence on REE may have occurred in some of the subjects but was not observed due to confounding effects of other factors. The effects of the tumor cannot be separated from the effect of malnutrition, but the presence of malnutrition in the tumor-bearing state does not uniformly effect the energy metabolism of the host.

Refeeding

Refeeding also influences resting energy expenditure. Askanazi,[57] in a study of septic hypermetabolic patients, demonstrated that the infusion of TPN led to increased urinary excretion of norepinephrine and an increase in resting energy expenditure. In one patient, the increase in REE was almost 50% greater than the pre-TPN value. Barot et al.[58] studied the effect of fat-free TPN (25% dextrose, 4.25% amino acids) on REE in 20 unstressed clinically stable, malnourished patients. REE increased 12% on a repletion regimen that provided caloric replacement equal to 1.5 times the pre-TPN REE. Askanazi,[50] in a study of patients undergoing elective total hip replacement, demonstrated that the postoperative infusion of 5% dextrose and 3.5% amino acids led to a 13% to 17% rise in resting energy expenditure. In this study there were no abnormal distributions of patients receiving TPN between metabolic groups (Table 5). Since refeeding has been demonstrated to increase REE, the authors wanted to control for this effect. Data analysis of only non-TPN patients (N = 50) essentially was no different than the population as a whole. Again, the complex interactions between refeeding, malnutrition, and tumor effect are difficult to separate. The effects of malnutrition and refeeding upon energy expenditure cannot alone explain the dramatic aberrations in REE seen in these 200 subjects. Since the data was normalized to control for the influence of the aforementioned primary factors, it must be concluded that the presence of a tumor has considerable direct and indirect influences upon a cancer patient's REE.

Tumor Effects

The analysis of tumor data between the three metabolic groups showed significant differences in duration of disease between normometabolic and hypermetabolic subjects with the normometabolic group having the shortest duration of disease. Although the duration of disease of hypometabolic subjects was not significantly different from normometabolic subjects, the mean months of disease was greater (21 *vs.* 12 months). This suggests the tumor-bearing state may influence energy metabolism differently during different phases of the tumor life cycle. However, the specific influences cannot be elucidated due to the lack of significant correlation between duration of disease and per cent of expected REE.

Gross classifications of tumor burden did not explain differences in REE. Chi square analysis by tumor burden revealed equal distribution between the three metabolic groups. This finding contradicts the general conclusion of other studies that REE increases[39,42] with increasing tumor burden. Although not true for this population as a whole, this proposed hypothesis may well be operational within specific tumor types.

The only specific site of metastasis evaluated was the liver. Under normal circumstances the liver accounts for 27% of the total resting energy expenditure.[59] Major liver involvement might substantially influence REE. No differences were observed for the mean resting energy expenditure between the patients with liver metastasis (1297 kcal/day) and those without liver metastasis (1290 kcal/day). The percentage of patients with liver metastasis was equal in each metabolic group, indicating that liver metastases were not a major determinant of the resting energy expenditure differences between groups.

Cancer patients present with varying degrees of weight loss depending on the site of the primary tumor. Patients with lung and pancreatic cancer often present with a substantial weight loss, whereas patients with cervical cancer often have experienced no weight loss. Although many factors can account for these differences, it can be hypothesized that all tumors do not effect the energy metabolism of the host in the same way. At present, the authors are unable to do a site-specific analysis due to the limited number of patients within each site. Patients were grouped by organ system of tumor origin: gynecologic, gastrointestinal; and genitourinary. Analysis showed no differences between these gross groups. This does not prove that different effects do not emanate from tumors of varying origin. These groupings had a great deal of heterogenicity and thereby may have masked any real differences between specific sites.

Further characterization of energy expenditure in more homogenous cancer groups will more clearly elucidate the relative importance of various markers. One can hypothesize a number of potentially important determinants of energy expenditure in cancer patients that have not been tested by this study design. In general,

they fall into four groups: 1) changes in the size of the body cell mass; 2) changes in activity level of a unit of the body cell mass; 3) changes due to the tumor cellular metabolically active mass; and 4) changes in host body cell mass activity induced directly or indirectly by the tumor. Future studies can be designed to test these hypotheses.

Conclusion

Based upon assessment of REE in 200 malnourished cancer patients it is concluded that most cancer patients have major aberrations in energy metabolism. Fifty-nine per cent of the patients exhibited abnormal energy metabolism, with 33% being hypometabolic and 26% hypermetabolic. These findings do not support the hypothesis that energy expenditure is uniformly elevated in cancer and cannot be explained at present by the usual major determinants of energy expenditure (height, weight, age, sex, nutritional status, and nutrient intake). Duration of disease may be an important factor in energy metabolism since patients with the shortest duration of disease were normometabolic. As data of more homogenous populations become available, site specific tumor effects may be clarified. If effective nutritional therapies are to be designed, there must be a full understanding of the energy metabolism of the cancer patient. This will help to decrease metabolic consequences of overfeeding the hypometabolic patient and increase the efficacy of adjuvant nutritional support by meeting the requirements of the hypermetabolic patient.

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