
The Relationship Between Resting Energy Expenditure and Weight Loss in Benign and Malignant Disease

DOUGLAS T. HANSELL, F.R.C.S.

JOHN W. L. DAVIES, D.Sc.

HENRY J. G. BURNS, F.R.C.S.

The relationship between cancer, weight loss, and resting energy expenditure (REE) has been investigated in 136 patients using indirect calorimetry. Ninety-one patients had gastric, colorectal, or non-small cell bronchial neoplasm, seven patients had other malignancies, and 38 patients had nonmalignant illness. Four groups were studied: weight stable cancer patients (CWS: N = 56), weight losing cancer patients (CWL: N = 42), weight stable patients with nonmalignant illness (NCWS: N = 22), and weight losing patients with nonmalignant illness (NCWL: N = 16). In each group REE correlated significantly with body weight, metabolic body size, and lean body mass (LBM: estimated from total body water measurements). The closest correlation was between REE and lean body mass, with the slope of the CWL regression line differing significantly from that of the CWS ($p < 0.05$) and NCWS ($p < 0.02$) groups. However, there was no difference in REE expressed as kcal/kg LBM/d between the groups. The slopes of the regressions between REE and LBM were almost identical when all cancer patients were compared with all patients with nonmalignant illness. However, when all weight stable patients were compared with all weight losing patients, there was a highly significant difference between the slopes of the regressions ($p < 0.005$). This indicates that the weight losing state rather than the presence or absence of cancer is responsible for an alteration in the relationship between REE and LBM. There were no differences in REE between the different tumor types. It is concluded that REE is not elevated in patients with gastric, colorectal, or non-small cell bronchial cancer. Elevation of REE contributes very little to the etiology of cancer cachexia.

CACHEXIA IS a common feature of advanced malignancy.¹⁻⁶ In many patients, anorexia or alteration in the function of the gastrointestinal tract could account for the observed weight loss.⁷⁻⁹ In some patients, however, weight loss seems to occur in the absence of any obvious cause.¹⁰ Over the past 70 years, many authors^{2,11-22} have suggested that an increased resting energy expenditure (REE) may be a contributing factor in the development of cancer cachexia. Most of these studies, however, have been poorly controlled. For example,

From the University Department of Surgery, Royal Infirmary, Glasgow, Scotland

Macfie and colleagues²⁰ compared cancer patients with younger weight stable controls, while others¹⁸⁻¹⁹ have studied patients with cancer but have offered no control data.

The aim of this study was to determine whether REE was increased in cancer patients who were losing weight. These patients were compared with three other groups: cancer patients without weight loss and groups of weight losing and weight stable patients with nonmalignant illness. The relationship between REE and various expressions of body size has been investigated, and the effects of cancer and weight loss on these relationships have been determined.

Patients and Methods

One hundred thirty-six patients were included in the study. Cancer was proven histologically in 98 patients, and a control group of 38 had nonmalignant disease. Of the 98 cancer patients, 56 had lost little or no weight (weight stable) and 42 had lost more than 10% of their pre-illness weight (weight losing). The controls were similarly divided into 22 weight stable and 16 weight losing patients. Pathological diagnoses are shown in Table 1. The mean weight loss expressed as a percentage of the mean pre-illness weight and the mean weight loss per month during the period of illness are shown in Table 2. Patients who had clinical or bacteriological evidence of infection and those who had undergone surgery in the preceding year were not included in the study. In the cancer patients, the presence or absence of liver metastases was assessed by hepatic ultrasound and computerized tomography and confirmed histologically at subsequent laparotomy. Eleven of the weight stable patients and eight of the weight losing patients had liver metastases.

Reprint requests: D. T. Hansell, University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, Scotland.

Submitted for publication: September 13, 1985.

Measurements of energy and carbon dioxide production were made using an indirect calorimeter with a rigid canopy,²³ a very sensitive paramagnetic oxygen analyser (Servomex Ltd, Crowborough, Sussex, U.K.), and an infrared carbon dioxide analyser (Sieger Ltd, Poole, Dorset, U.K.). The whole system provides measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ that have an error of less than $\pm 5\%$. The equipment was calibrated frequently using oxygen-free nitrogen, 0.80% carbon dioxide, and air of a known barometric pressure. The sensitivity and accuracy of the calorimeter was checked periodically by burning butane gas in the canopy. The 80 estimates of $\dot{V}O_2$ and $\dot{V}CO_2$ collected during each calorimeter run of 40 minutes were processed on line by a microprocessor and converted to mean energy production (watts) and respiratory quotient (RQ) using the formula of Weir²⁴:

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

where

$$\text{kcal/d} = \text{watts} \times 20.65$$

$$\dot{V}O_2 = \text{oxygen consumption (1/min)}$$

$$\dot{V}CO_2 = \text{carbon dioxide production (1/min)}$$

$$RQ = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

As the patients received nothing orally, they were given 80 ml of 5% dextrose solution per hour intravenously for the 12 hours prior to calorimetry to maintain body hydration. This input provided only 192 kcal of energy, which is a small proportion of the total resting energy expenditure. Each study began at 9:00 AM, patients having remained in bed since waking. The 40 minute calorimeter run was preceded by a 30 minute acclimatization run.

TABLE 1. Pathology

	Cancer	
	Weight Stable (N = 56)	Weight Losing (N = 42)
Colorectal	36	19
Gastric	12	12
Bronchial	5	7
Other	3	4
	Control	
	Weight Stable (N = 22)	Weight Losing (N = 16)
Peptic ulceration	3	8
Cholelithiasis	14	3
Other	5	5

Lean body mass (LBM) was derived from the measurement of total body water. Tritiated saline (4 MBq) was injected intravenously, and serum samples were obtained 3 and 4 hours after injection. During the period of equilibration, all urine passed was collected to measure the loss of tritium in urine. LBM was derived from the volume of body water, assuming that lean tissue contains 73% water.²⁵

An estimate of daily protein and energy intake prior to the overnight fast, together with measurements of mid-arm muscle circumference (MAMC) and triceps skinfold thickness (TST), were obtained by a dietitian who was unaware of each patient's diagnosis. In addition, serum albumin and transferrin concentrations were measured.

The Mann-Whitney U-test was used for the statistical analysis of nonparametric data. Correlations between REE and body weight, metabolic body size, and LBM have been tested by deriving linear regression values (r) by the

TABLE 2. Clinical and Nutritional Data

	Cancer		Control	
	Weight Stable	Weight Losing	Weight Stable	Weight Losing
Number of patients	56	42	22	16
Age (years)	66 \pm 1.4	65 \pm 1.7	62 \pm 3.0	63 \pm 3.9
Male/female	40/16	23/19	6/16	8/8
Body weight (kg)	64.7 \pm 1.6†	52.6 \pm 1.9*	65.2 \pm 3.2†	56.3 \pm 3.3
Lean body mass (kg)	51.2 \pm 1.59	44.8 \pm 1.60§	48.2 \pm 2.57	46.7 \pm 2.28
% weight loss	3 \pm 0.4	18 \pm 1.0*	1 \pm 0.6‡	16 \pm 1.3*
Weight loss/month (kg)	0.8 \pm 0.2	2.7 \pm 0.3*	0.3 \pm 0.2	2.7 \pm 0.4*
Energy intake (kcal/d)	1779 \pm 79.6	1676 \pm 133.8	2013 \pm 171.7	1564 \pm 286.3
Protein intake (g/d)	68.8 \pm 3.3	68.2 \pm 5.6	76.8 \pm 6.0†	60.5 \pm 6.5
MAMC (% expected)	96.7 \pm 1.4	86.6 \pm 1.9*	98.0 \pm 2.1†	89.1 \pm 2.9
TST (% expected)	102.0 \pm 6.2	67.1 \pm 5.2*	112.7 \pm 8.4	74.5 \pm 7.6
Serum albumin (g/l)	37.9 \pm 0.7	33.1 \pm 0.9*	39.8 \pm 0.8	35.7 \pm 1.3
Serum transferrin (g/l)	2.41 \pm 0.1	2.07 \pm 0.1†	2.90 \pm 0.14§	2.33 \pm 0.20

Mean \pm S.E.M.

* $p < 0.0005$ vs. weight stable cancer patients and weight stable controls.

† $p < 0.05$ vs. weight losing controls.

‡ $p < 0.05$ vs. weight stable cancer patients.

§ $p < 0.005$ vs. weight stable cancer patients.

|| $p < 0.005$ vs. weight losing controls.

¶ $p < 0.05$ vs. weight stable cancer patients and weight stable controls.

TABLE 3. Resting Energy Expenditure and Respiratory Quotient (RQ)

	Cancer		Control	
	Weight Stable	Weight Losing	Weight Stable	Weight Losing
kcal/kg/d	22.5 ± 0.4	24.4 ± 0.4*	20.6 ± 0.7	23.5 ± 0.8
kcal/kg ^{0.75} /d	63.6 ± 1.0	65.5 ± 1.0	57.8 ± 1.4†	63.8 ± 1.9
kcal/kg				
LBM/d	29.3 ± 0.8	28.9 ± 0.6	28.1 ± 0.8	28.7 ± 0.8
RQ	0.814 ± 0.117	0.801 ± 0.117	0.816 ± 0.171	0.830 ± 0.183

Mean ± S.E.M.

* $p < 0.005$ vs. weight stable cancer patients and weight stable controls.

† $p < 0.01$ vs. other three groups.

method of least squares. The slopes of the linear regression lines were compared using Student's *t*-test.

Results

Clinical and nutritional details are shown in Table 2. There was no significant difference in mean age between the groups. There were more males in the weight stable cancer group and more females in the weight stable control group. The weight losing cancer patients had a significantly lower weight and LBM than their weight stable counterparts. The weight losing controls had a significantly lower body weight but no difference in LBM compared with the weight stable controls. In both the weight losing groups, the mean weight loss was in excess of 15% of pre-illness weight. The rate of weight loss in these groups was 2.7 kg per month. Mean measurements of MAMC and TST were significantly lower in both weight losing groups when they were compared with their weight stable counterparts. No significant differences could be detected in

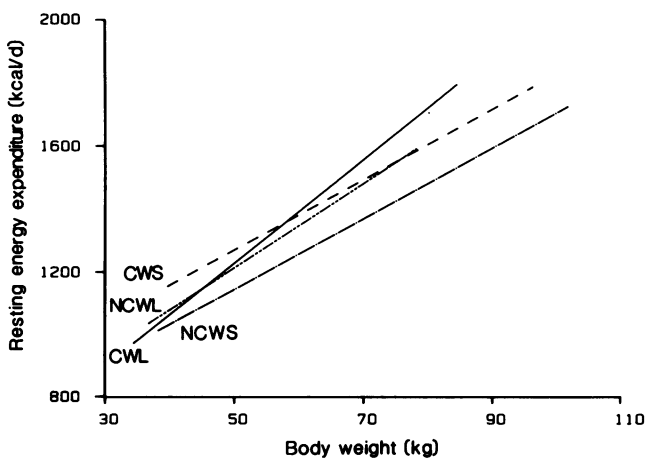


FIG. 1. The relationship between resting energy expenditure (REE) and body weight. CWL (cancer weight losing): $N = 42$; $r = 0.79$; $p < 0.001$. CWS (cancer weight stable): $N = 56$; $r = 0.65$; $p < 0.001$. NCWL (control weight losing): $N = 16$; $r = 0.75$; $p < 0.001$. NCWS (control weight stable): $N = 22$; $r = 0.77$; $p < 0.001$. The CWL slope is significantly different from CWS ($p < 0.05$) and NCWS ($p < 0.05$).

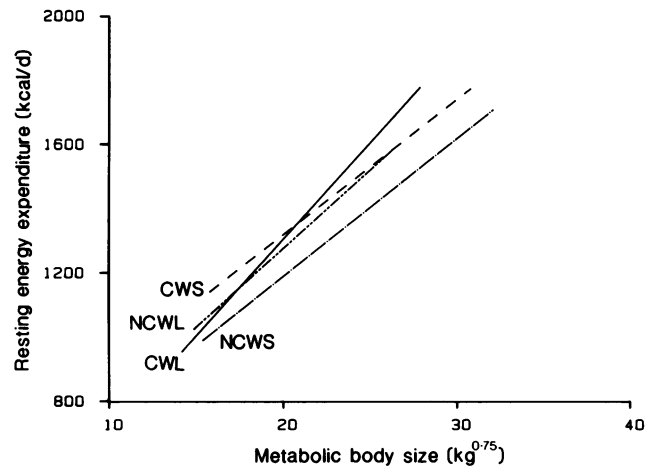


FIG. 2. The relationship between resting energy expenditure (REE) and metabolic body size. CWL (cancer weight losing): $N = 42$; $r = 0.79$; $p < 0.001$. CWS (cancer weight stable): $N = 56$; $r = 0.64$; $p < 0.001$. NCWL (control weight losing): $N = 16$; $r = 0.75$; $p < 0.001$. NCWS (control weight stable): $N = 22$; $r = 0.77$; $p < 0.001$. The CWL slope is significantly different from CWS ($p < 0.05$).

mean total energy intake between the groups, although the weight losing controls had a significantly lower mean protein intake compared with the weight stable controls. When compared to their weight stable counterparts, both the weight losing groups had significantly reduced serum albumin and transferrin levels. In addition, weight stable cancer patients had lower transferrin levels than weight stable controls.

Measurements of REE are shown in Table 3. REE has been expressed in three ways: as kcal/kg body weight/day, kcal/kg LBM/day, and kcal/kg^{0.75}/day. This last term was derived by Kleiber,²⁶ who felt that the value obtained approximated to metabolic body size. When REE is expressed in kcal/kg body weight/day, the weight losing cancer patients have a significantly increased REE compared with both the weight stable groups. There is no significant difference between the groups when REE is expressed in terms of LBM. When the Kleiber formula is used, weight stable control patients have a significantly reduced REE compared with the other three groups. Significant correlations are shown between REE and body weight, the Kleiber formula, and lean body mass (Figs. 1-3). For reasons of clarity, the scatter of points around each line has been omitted. The strongest correlation was found between REE and LBM. The gradient of the cancer weight losing (CWL) regression line is significantly steeper than both the weight stable groups when REE is plotted against body weight and lean body mass. When plotted against metabolic body size, the CWL regression line differs significantly only from the weight stable cancer group (CWS). There were no significant differences in RQ between the groups (Table 3). No significant differences in REE were found when patients with liver metastases were

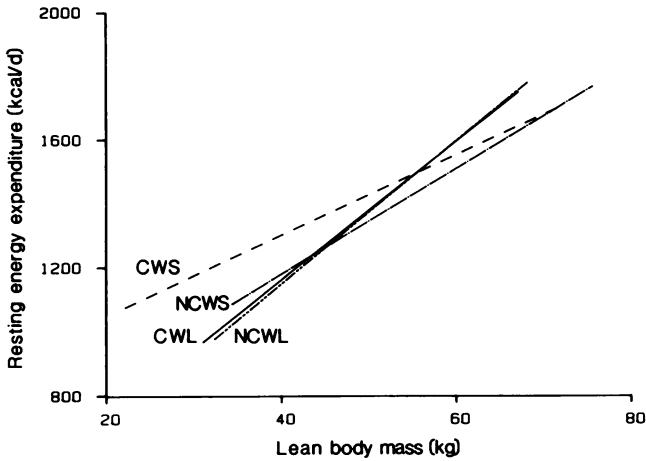


FIG. 3. The relationship between resting energy expenditure (REE) and lean body mass. CWL (cancer weight losing): N = 42; r = 0.83; p < 0.001. CWS (cancer weight stable): N = 56; r = 0.66; p < 0.001. NCWL (control weight losing): N = 16; r = 0.87; p < 0.001. NCWS (control weight stable): N = 22; r = 0.90; p < 0.001. The CWL slope is significantly different from CWS (p < 0.05) and NCWS (p < 0.02).

compared to those without, irrespective of weight loss (Table 4). There were no significant differences in REE when differing tumor types were compared (Table 5).

When REE is related to LBM and all cancer patients are compared with all control patients, there is no significant difference between either the slope or the position of the regression lines (Fig. 4). However, when weight losing patients are compared with weight stable patients irrespective of the primary diagnosis, the slopes of the regression lines are significantly different (Fig. 5).

Discussion

There have been many studies of energy expenditure in cancer patients, and most have reported an increase in REE associated with the tumor bearing state.^{2,11-22} It has been suggested that this increased energy expenditure could contribute to the weight loss commonly seen in these patients.^{14,15,17,18,20,21} Other studies, however, have failed to show any alteration in REE when comparing cancer patients to controls.²⁷ Indeed, Mullen and his colleagues have suggested that some cancer patients may in

TABLE 4. Resting Energy Expenditure in Patients with and without Liver Metastases

	Weight Stable		Weight Losing	
	No Metastases (N = 45)	Metastases (N = 11)	No Metastases (N = 34)	Metastases (N = 8)
kcal/kgLBM/d	29.5 ± 1.0	27.7 ± 0.8	28.5 ± 0.6	28.5 ± 1.2

Mean ± S.E.M.
No significant differences.

TABLE 5. Resting Energy Expenditure in Different Tumor Types

	kcal/kg LBM/d
Colorectal (N = 55)	29.1 ± 0.74
Gastric (N = 24)	27.7 ± 0.83
Bronchial (N = 12)	29.9 ± 0.93

Mean ± S.E.M.
No significant differences.

fact have a reduced energy expenditure.²⁸ However, measurement of REE must take into account patient size, and it is apparent from this present study that an error can be made when energy expenditure is expressed solely as kcal/day or in terms of kcal/kg body weight/day. The weight losing patients in this study have lost predominantly fat. Therefore, the proportion of total body weight that is represented by lean body mass increases. Since lean body mass contributes more to REE than does fat mass, any attempt to predict REE related to body weight will tend to underestimate energy expenditure in weight losing patients. This source of error has been ignored in earlier publications in this field. In this present study, when energy expenditure is expressed as kcal/kg body weight/day, weight losing cancer patients have a significantly higher energy expenditure than weight stable cancer patients or controls. When REE is related to lean body mass this difference disappears. It follows, in addition, that when formulas are used to predict expected energy expenditure in patients with altered body composition, they will underestimate REE if total body weight is part of the formula. Such formulas are the Kleiber formula²⁶ and the Harris Benedict formula,²⁹ both of which have been used in the past to predict expected energy expenditure in weight losing cancer patients. Since these formulas do not take into account changing body composition, it is not surprising

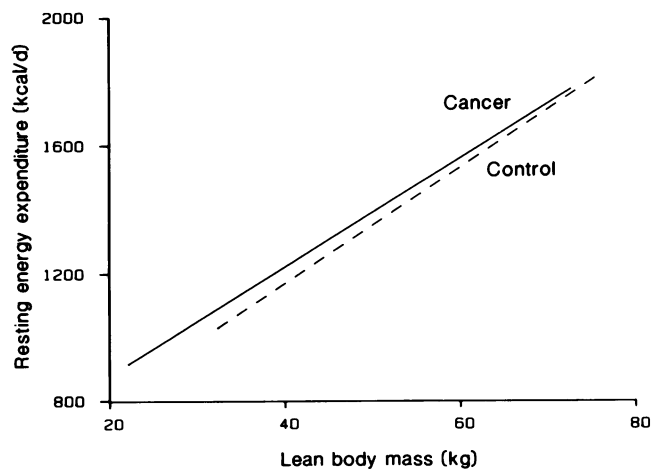


FIG. 4. The relationship between resting energy expenditure (REE) and lean body mass for all cancer patients and all controls. Cancer: N = 98; r = 0.759; p < 0.001. Control: N = 38; r = 0.876; p < 0.001.

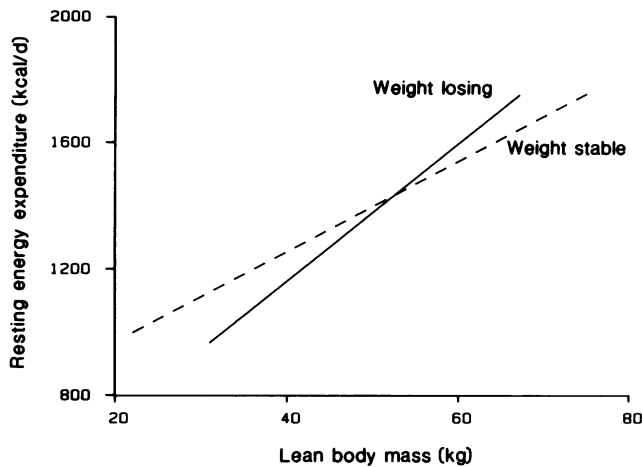


FIG. 5. The relationship between resting energy expenditure (REE) and lean body mass for all weight stable patients and all weight losing patients. Weight stable: $N = 78$; $r = 0.739$; $p < 0.001$. Weight losing: $N = 58$; $r = 0.837$; $p < 0.001$. The weight stable slope is significantly different from the weight losing slope ($p < 0.005$).

that they have erroneously suggested elevated energy expenditure when weight losing cancer patients are compared to control groups.

We have attempted to minimize this error by measuring lean body mass using the isotope dilution method. We accept that this method will tend to overestimate lean body mass. Shizgal³⁰ has pointed out that malnourished patients have an expanded extracellular fluid volume, and this expansion will result in an error when body composition is derived from isotope dilution measurements. Correction of this overestimation would result in a small increase in the measured caloric expenditure per kilogram of lean body mass, but it is unlikely that such a correction would greatly alter the conclusions of the present study. It has recently been pointed out that a commonly used alternative method of deriving body composition, namely total body potassium measurement, may also be subject to error. Burkinshaw and Morgan³¹ have estimated that, as a patient loses weight, his intracellular potassium content decreases. The use of intracellular potassium to derive body cell mass therefore may conceivably underestimate the metabolically active body compartments.

Our conclusion that the weight losing cancer patients studied in this paper have no detectable alteration in REE when compared to weight stable cancer patients or non-cancer bearing controls is similar to that reached by Lindmark and his colleagues, who compared 28 cancer patients with 43 noncancer bearing controls.²¹ These workers found that weight losing cancer patients have an increase in REE of 148 kcal per day compared to weight losing controls. If it is accepted that complete oxidation of 1 g of fat gives 9.1 kcal, 1 g of carbohydrate gives 4.1 kcal, 1 g of protein gives 4.1 kcal, and that body tissues contain 20% protein, Lindmark and his colleagues, using the RQ

values obtained from calorimetry, estimated that this increase in energy expenditure could account for the loss of between 1 and 2 kg of body weight per month.²¹ Macfie and coworkers²⁰ found an increase in REE of 289 kcal per day when patients with metastatic cancer were compared to healthy controls. They suggested that this increase could account for a weight loss of 1 kg of fat per month. In the present study, neither of the weight losing groups had any detectable increase in REE when compared to their weight stable counterparts. Both groups however had a reported weight loss of almost 3 kg per month before coming into hospital. We conclude, therefore, that an elevation in REE seems to contribute little to the weight loss seen in these cancer patients. Furthermore, unlike Macfie and colleagues,²² we have been unable to find evidence that the presence of liver metastases significantly alters REE. Previous studies have suggested that advanced disease was associated with an increased REE. This observation has not been confirmed in the present study.

When regression lines relating REE to body size are drawn for the four groups (Figs. 1–3), the fact that the lines seem to converge supports the argument that cancer patients can ultimately adapt their energy expenditure to the weight losing state.²¹ The patients with the lowest lean body masses appear best able to adapt to the weight losing state. However, when all cancer patients are compared to all control patients (Fig. 4), there is no significant difference in the slope of these lines. The most interesting comparison is seen when weight losing patients are compared to weight stable patients, irrespective of the presence of tumor (Fig. 5). The fact that the slopes of the regression lines are significantly different suggests that the weight losing state is more closely associated with metabolic abnormalities in patients than with the presence or absence of cancer. It seems to us that some cancer patients and some patients who develop nonmalignant illness respond to their illness by producing an associated metabolic abnormality that leads to the weight losing state. To claim that the presence of a solid tumor will necessarily result in elevated energy expenditure is, we believe, an oversimplification. Some cancer patients respond to their illness by losing weight, as do some patients who develop a non-malignant illness. It is not the primary pathology, but the patient's endogenous responses to it determine whether weight loss will result. However, in speaking of cancer as a uniform entity, we ourselves are guilty of an oversimplification. It has been suggested that the primary site of a tumor may be important in determining the magnitude of the REE.²⁸ In the present study, we have measured REE in patients with colorectal, gastric, and nonsmall cell bronchial carcinomas and found no difference among the groups. Bronchial neoplasms, however, did show a trend toward a slightly higher energy expenditure. Although this has not been shown to be statistically signif-

icant, it may be that a small subset of bronchial neoplasm patients do, in fact, have a higher than anticipated energy expenditure.

A possible explanation for the extent of the observed weight loss in our patients could be anorexia. Standard dietary histories have been used to assess energy and protein intakes of the patients studied. Both weight losing groups had a lower energy intake than the weight stable groups, but this difference was not statistically significant. Protein intakes were similar between the groups apart from the weight losing controls, who had a significantly decreased intake compared with their weight stable counterparts. Standard dietary assessment techniques are inaccurate and have wide variability, and a small difference in intake may be obscured. An alternative explanation for the observed weight loss may be that weight losing patients have altered utilization of ingested nutrients. For example, the thermogenic response to food may be altered in cancer patients, leading to a reduction in the efficiency with which ingested substrate is stored.

We have found no evidence for the hypothesis that patients who lose weight, whether they have cancer or not, have an increase in energy expenditure. Nor is there any evidence that their weight loss is due to anorexia. The present study has shown no evidence that tumor type or tumor stage is important in determining REE in cancer patients. It is possible that substrate handling in weight losing cancer patients may be altered. We believe, however, that the evidence points to altered response to illness as major determinant of increases in REE, rather than any factor associated with the tumor itself.

Acknowledgments

We thank Mrs. W. Hughes for typing the manuscript. JWLD is supported financially by the United Kingdom Medical Research Council.

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