Resting energy expenditure (REE) was determined in 30 patients with newly detected non-small cell lung cancer. Measured values were compared with the values predicted by the Harris-Benedict (HB) formula. Mean REE was 20% higher than predicted. Sixty percent of the patients (18 patients) had an elevated REE (greater than or equal to 115%) compared with this formula. The prevalence of hypermetabolism in a group of patients with gastric and colorectal cancer was only 13% (13 of 104 patients). When corrected for fat-free mass (FFM), REE was still significantly higher (P < 0.001) in the lung cancer group compared with the gastric and colorectal cancer group. Whereas weight loss in healthy men leads to an adaptational decrease in energy expenditure (EE), weight loss in the patients with lung cancer was accompanied by an increase in REE. Tumor stage, tumor localization, pulmonary function, or smoking behavior could not explain the observed increase in REE in patients with lung cancer. Therefore, these metabolic alterations appear to be tumor mediated. Cancer 68:1616–1621, 1991.

Weight loss is a well-known phenomenon in patients with cancer. Weight loss is caused by a negative energy balance resulting from decreased energy intake or increased energy expenditure (EE) or both. Several authors have suggested that patients with cancer have an increased energy metabolism that significantly contributes to the development of cancer cachexia.1-3

It is a common clinical finding that weight loss and cachexia occur frequently in patients with lung cancer. Hansell and coworkers4 compared the resting energy expenditure (REE) of 11 patients with non-small cell lung cancer with the values of patients with gastric and colorectal cancer and found a significantly higher REE in the patients with lung cancer. When corrected for fat-free mass (FFM), this difference lost significance. Russell and coworkers studied energy metabolism in a larger group of 31 patients with small cell lung cancer and demonstrated measured REE to be 31% higher than predicted REE.7

The current study was designed to additionally elucidate the contribution of hypermetabolism to the development of cachexia in patients with non-small cell lung cancer.

Methods

Thirty patients with newly detected non-small cell lung cancer were included in the study. All patients had histologically documented tumor, and none had been treated previously with chemotherapy or radiation therapy.

REE was measured by indirect calorimetry using a ventilated hood system. Gas analyses were performed using a paramagnetic oxygen analyzer (Mijnhardt module, Bunnik, The Netherlands) and an infrared carbon dioxide analyzer (modified UG51, Mijnhardt, Bunnik, The Netherlands). Dry gases were measured, and the results were converted to standard temperature and pressure. Flow through the canopy was kept constant during measurements and was adjusted to the body weight of the patient (30 to 40 L/min). System control and calculations were performed on a microcomputer. The equipment was calibrated at the start and at the end of every experiment. The hood consisted of clear Plexiglas and had a volume of 30 liters. REE was calculated using the abbreviated Weir formula,8 After an overnight fast and while at com-
plete rest, a measurement was made over a 30-minute period.

Measured REE was compared with predicted REE calculated by the Harris–Benedict (HB) formula. Patients with a measured REE more than 115% of that predicted by the HB formula were considered hypermetabolic. REE in these patients with lung cancer was compared with REE in a group of 104 patients with newly detected gastric and colorectal cancer measured according to the same procedure.

FFM was estimated with the bioelectrical impedance method (RJL Systems, Detroit) and was calculated using the formula of Segal. The percentage weight change from reported pre-illness stable weight was used to divide patients into weight-stable (less than 5% weight loss) or weight-losing (more than 5% weight loss) groups. Actual body weight was also presented as a percentage of ideal body weight (PIBW). Tumor stage was assessed according to the Union Internationale Contre Cancer (UICC) classification. Spirometric tests included measurement of forced expiratory volume in 1 second (FEV₁), which was expressed as a percentage of the reference value.

REE was expressed in absolute terms per kg body weight (REE/BW), per kg fat-free mass (REE/FFM), and as a percentage of the HB value (REE/HB). The Mann–Whitney U-test and the Kruskal–Wallis test were used for non-parametric statistical analysis. Additional statistical procedures included the Student’s paired t-test and chi-square analysis. Results are presented as mean ± standard deviation (SD). P values less than 0.05 were regarded as statistically significant.

Results

Twenty-seven men and three women with lung cancer were included in the study (Table 1). Their mean PIBW was 92% and their mean FEV₁ was 85% of the reference value. One hundred and four patients with gastric and colorectal cancer were included in the study. Percentage weight loss was the same for both groups. Compared with the gastric and colorectal cancer group, men were relatively overrepresented in the lung cancer group. Patients with lung cancer were younger and had a lower PIBW.

REE/HB showed a significant elevation of 20% in patients with lung cancer (Table 2). Sixty percent of the patients with lung cancer (18 of 30 patients) were hypermetabolic, and 40% (12 of 30 patients) had a REE within the range 85% to 115% of predicted.

REE in patients with lung cancer, even when corrected for FFM, was significantly increased when compared with patients with gastric and colorectal cancer. Significantly more patients with lung cancer than patients with gastric and colorectal cancer were hypermetabolic (P less than 0.001) (Table 2).

A significant correlation existed between REE/FFM and percent weight loss (r equals 0.69; P less than 0.001) (Fig. 1). REE/BW and REE/FFM were significantly higher in the weight-losing patients compared with the weight-stable patients (P less than 0.01 and P less than 0.001, respectively). Both weight-stable and weight-losing groups had an elevated REE/HB (Fig. 2).

A comparison between the hypermetabolic and the normometabolic patients showed no significant differences with respect to body temperature, pulmonary function, smoking behavior, tumor localization, and tumor stage (Table 3). There were also no significant differences between the hypermetabolic and normometabolic patients with respect to body weight, FFM (kg), or weight loss (in kg or %).

Significant correlations, however, existed between REE/FFM and body temperature (r equals 0.56; P less than 0.01), FEV₁ (r equals −0.41; P less than 0.05), and smoking frequency (r equals 0.34; P equals 0.07). The correlation coefficients for REE/FFM and tumor localization and tumor stage were not significant. An elevated REE was found for patients with a FEV₁ less than 75% of the reference value, for patients with a body temperature of 37.5°C or higher, and for smokers (Table 4).

Discussion

Weight loss is a well-known phenomenon in patients with cancer, particularly in patients with lung cancer. Weight loss is the result of a disbalance between energy intake and EE. Especially in patients with lung cancer, the relative importance of elevated EE is interesting because apart from the possible tumor-mediated thermogenesis, the deterioration of pulmonary function may influence energy metabolism. Also, most patients with lung cancer are heavy smokers, which is associated with an increased EE. Therefore, these and several other aspects
TABLE 2. Resting Energy Expenditure in Patients With Lung Cancer and Patients With Gastric and Colorectal Cancer

<table>
<thead>
<tr>
<th></th>
<th>Patients with lung cancer (n = 30)</th>
<th>Patients with gastric and colorectal cancer (n = 104)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kcal/d)</td>
<td>1615 ± 246*</td>
<td>1352 ± 231</td>
<td></td>
</tr>
<tr>
<td>REE (%HB)</td>
<td>120 ± 13</td>
<td>104 ± 10</td>
<td></td>
</tr>
<tr>
<td>REE (kcal/BW)</td>
<td>25.4 ± 3.7</td>
<td>20.9 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>REE (kcal/kg FFM)</td>
<td>33.1 ± 4.1</td>
<td>29.2 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>Hypermetabolism (%)</td>
<td>60</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>RQ</td>
<td>0.79 ± 0.03</td>
<td>0.78 ± 0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

REE: resting energy expenditure; HB: Harris-Benedict formula; RQ: respiratory quotient; FFM: fat-free mass; NS: not significant.
* Mean ± SD.
† P < 0.001.

were taken into account to estimate their relative contribution leading to an increased EE.

In the current study, REE measurements in patients with newly detected non-small cell lung cancer indicated that 60% had an elevated REE compared with the HB formula as a reference. The validity of the HB formula to predict REE accurately in patients is under debate, particularly in patients with weight loss.16 However, in the current study, REE of patients with lung cancer was also compared with REE of patients with gastric and colorectal cancer. The prevalence of hypermetabolism in the patients with gastric and colorectal cancer was 13%. Both groups of patients had the same percentage of weight loss. Data on energy intake of a small group of patients with gastric, colorectal, and lung cancer showed a reduced energy intake in approximately one third of the patients with gastric and colorectal cancer in contrast to only one patient (out of 17 patients) with lung cancer.17 Therefore, these results suggest that weight loss in patients with gastric and colorectal cancer is most likely the result of a decreased food intake, and weight loss in patients with lung cancer represents a combination of an elevated REE and a relative anorexia. Patients with lung cancer reported no decrease in energy intake, but REE was elevated and therefore resulted in a relatively low energy intake.

A number of studies have estimated the changes in energy metabolism associated with lung cancer (Table 5). Some of these studies have found no change in REE18 and others have demonstrated an increase of 10% to 30%.19,20 The observation in the current study that REE was significantly increased, no matter how it was expressed, is in contrast to the observation in the study by Hansell et al.,6 that REE/FFM was not significantly different between the lung cancer and gastric and colorectal cancer groups. This different result in REE/FFM between both studies probably depends on methodologic problems. In the study by Hansell et al., FFM was derived from the measurement of total body water, which tends to overestimate FFM. In our study, FFM was measured by means of the bioelectrical impedance method. Although the latter is considered a reliable and valid approach for the estimation of FFM, it needs additional validation in patients with abnormal body composition (e.g., in patients with weight loss).22 Deurenberg et al.23,24 reported that after weight loss in healthy and obese persons, the bioelectrical impedance method overestimates the FFM.

REE was higher in weight-losing patients with lung cancer compared with weight-stable patients with lung cancer. This is in contrast to the decrease in EE that normally occurs during starvation and weight loss in healthy
TABLE 3. Characteristics of Hypermetabolic and Normometabolic Patients With Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>Hypermetabolic patients</th>
<th>Normometabolic patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (%SHB)</td>
<td>128 ± 11.0†</td>
<td>109 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.3 ± 11.6</td>
<td>67.9 ± 11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>48.0 ± 8.7</td>
<td>52.3 ± 8.5</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>83 ± 22</td>
<td>90 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.1 ± 0.7</td>
<td>36.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>16/2</td>
<td>8/4</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor localisation</td>
<td>10/8</td>
<td>9/3</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor stage (1-2/3-4)</td>
<td>11/7</td>
<td>7/5</td>
<td>NS</td>
</tr>
</tbody>
</table>

REE: resting energy expenditure; HB: Harris-Benedict formula; FEV1: forced expiratory volume in 1 second; NS: not significant.
* REE/HB = 115%.
† Mean ± SD.

energy expenditure in patients with lung cancer, these patients had an obstructive infiltrate as the result of a central tumor.

Six patients stopped smoking at least 6 months before study entry, and four of them were not hypermetabolic. It is suggested in the literature that cigarette smoking influences REE by stimulation of the sympathetic nervous system. Therefore, it is likely that smoking is important in explaining the observed increase in REE. The magnitude of the effect has to be studied in more detail.

REE was not significantly different between tumor stages. Only two patients with distant metastases were measured. Therefore, it could not be established if patients with metastatic disease have a higher REE compared with patients who have a localized malignancy.

In a group of patients with chronic obstructive pulmonary disease (FEV1 equals 35%), Schols and coworkers found that 51% of patients exhibited an increased REE. In the hypermetabolic patients, mean FEV1 was significantly lower than in the normometabolic patients with chronic obstructive pulmonary disease (29% versus 42%; P < 0.001). In the current study, mean FEV1 was normal for the patients with lung cancer. Therefore, an increased work of breathing secondary to an airway obstruction does not seem to have had an important influence on energy metabolism in this study group.

To test whether REE was also elevated for nonsmoking patients with a normal body temperature (36.7°C), a multiple regression model was used with REE/HB as a dependent variable and body temperature and smoking behavior as independent variables. The estimated REE/HB for these patients was 113.7% ± 4.8% (standard error of the mean [SEM]), thus significantly higher than 100% (P equals 0.01).

In this study, the observed increase in REE in patients with lung cancer cannot be explained by tumor stage, tumor localization, pulmonary function, smoking behavior, or body temperature. Also, with the other information
TABLE 5. Resting Energy Expenditure in Groups of Patients With Lung Cancer

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>Sex (M/F)</th>
<th>Type</th>
<th>Compared with</th>
<th>Change in RIE (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>9/3</td>
<td>1</td>
<td>Healthy</td>
<td>NS</td>
<td>Controls</td>
</tr>
<tr>
<td>19</td>
<td>total 20</td>
<td>1</td>
<td>(Non-) GI cancer patients</td>
<td>NS</td>
<td>F patients + 31% vs an.</td>
</tr>
<tr>
<td>20</td>
<td>27/11</td>
<td>1</td>
<td>(Non-) GI cancer patients and healthy controls</td>
<td>NS</td>
<td>nervosa (REE/FFM)</td>
</tr>
<tr>
<td>6</td>
<td>9/2</td>
<td>1</td>
<td>Patients with GI cancer</td>
<td>NS</td>
<td>Per kg FFM</td>
</tr>
<tr>
<td>21</td>
<td>5/—</td>
<td>1</td>
<td>Healthy controls</td>
<td>+13</td>
<td>Per kg BW</td>
</tr>
<tr>
<td>7</td>
<td>21/10</td>
<td>2</td>
<td>Predicted RIE (HB)</td>
<td>+31</td>
<td>First day of fast</td>
</tr>
<tr>
<td>This study</td>
<td>28/3</td>
<td>1</td>
<td>GI cancer</td>
<td>+22</td>
<td>Fourth day of fast</td>
</tr>
</tbody>
</table>


available it is difficult to explain why a considerable number of patients with lung cancer is hypermetabolic. It appears that the elevated RIE is induced by the tumor itself. To test this hypothesis, it is necessary to measure RIE in patients before and after tumor resection. It is unlikely that the metabolic demands of the tumor contribute significantly to energy metabolism of the host. Even a tumor of 0.1% of the weight of the host can induce metabolic alterations contributing to weight loss. Whole-body protein turnover has been estimated to account for between 10% and 20% of RIE in humans. Thus, the EE of the cancer-bearing host might be abnormally high as a result of an elevated whole-body protein turnover. Feaon et al. measured whole-body protein turnover in patients with lung or colorectal cancer and in controls without cancer. Both groups of patients with cancer had significantly elevated rates of whole-body protein turnover compared with controls. Whole-body protein turnover was more elevated in patients with lung cancer when compared with patients with colon cancer. An alternative theory is that tumors induce production of substances that are capable of altering the activity of various host enzymes. In recent years, macrophage products capable of inducing metabolic alterations in infectious and neoplastic diseases (tumor necrosis factor and interleukins) have been identified. Starnes et al. reported an enhanced EE in patients with cancer who had a single dose of tumor necrosis factor administered to them intravenously. However, the hypothesis that some of the metabolic abnormalities in cancer cachexia are due to tumor-specific products or to mediators of the immune system remains to be examined in detail. Finally, there is still the question of why a tumor in the lung would act differently compared with a tumor in the gastrointestinal tract and why it induces an increase in energy metabolism.

We conclude that a considerable number of patients (60%) with newly detected primary lung cancer are hypermetabolic. Although the pathogenesis most likely is multifactorial, the tumor appears to mediate these metabolic alterations to a significant degree.

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