Energy Metabolism and Requirements in the Cancer Patient

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Summary

As a basis for assessing energy metabolism and requirements in cancer patients, selected aspects of whole-body energy metabolism are considered, with particular reference to basal energy metabolism and factors that affect it. The importance of protein metabolism in relation to whole-body energy metabolism is emphasized. The need to consider the intimate relationships between protein and energy nutrition and metabolism in the comprehensive evaluation of the energy needs of cancer patients also is stressed. Published data on the basal metabolic rate of patients with malignant disease are difficult to evaluate for their metabolic and nutritional significance. Quantitative estimates of the utilization of major fuel sources in cancer patients are still quite limited, but the available data suggest that there may be a change in the pattern of fuel utilization, with lipid sources predominating, an altered regulation of glucose metabolism, and a reduced efficiency of energy utilization in some, but not all, cancer patients. The best balance of the major exogenous energy sources and level of total energy intake sufficient to meet the energy demands of organs and the whole body cannot be easily predicted and, therefore, only crude guidelines can be suggested.

Introduction

Investigations of the characteristics of energy metabolism and of the assessment of energy requirements in cancer patients are limited. However, the maintenance of cell and organ function involves decreased entropy, and this implies an increased requirement for energy. Thus, an adequate understanding of the metabolism and utilization of fuel sources and of the regulation of whole-body energy expenditure is important in considerations of nutritional therapy for cancer patients.

An important question to explore is whether the presence of cancer per se presents a unique set of problems in relation to energy metabolism and requirements, or whether the problems are similar to those of patients with nonmalignant disease. Because cachexia, accompanied by reduced food intake, is often a prominent feature of advanced cancer (17, 77, 80), it could be argued that there is a failure to maintain normal regulation and efficient patterns of fuel utilization and, therefore, body protein composition and cell mass. Hence, some selected aspects of energy metabolism and factors that alter basal metabolism and the utilization and need for energy will be reviewed here as a basis for assessing the status of energy metabolism and requirements in the cancer patient. It is hoped that this brief review will help to identify those aspects of energy metabolism and nutrition that deserve more critical and extensive investigation, in order to develop more effective and rational approaches to the nutritional support of patients with malignant disease. Major emphasis will be given here to data from human studies.

Basal and Resting Metabolic Rate

Physical activity and basal metabolism are among the major factors that determine total daily energy expenditure. The former will not receive detailed mention here; for the present, it will be assumed that, in energy expenditure due to physical activity, differences between cancer patients and those suffering from other disease states and normal subjects are due to the intensity of physical exercise and time devoted to such activities. The metabolic aspects of energy expenditure and utilization will receive the major focus in this paper.

For individuals who spend a large portion of the day "at rest," the BMR, defined as the energy output of an individual under standard resting conditions (bodily and mentally at rest, 12 to 18 hr after a meal, in a neutral, thermal environment), accounts for a significant proportion of total daily energy expenditure (16). It is appropriate, therefore, to consider first the biochemical basis of the BMR and some of the factors that affect it.

At the outset, it must be noted that a precise determination of BMR is not easy to achieve in practice (20), and a more useful measure of metabolic rate may be obtained by measurement of the resting metabolic rate (14). This may be determined in a person at rest, 2 to 4 hr after a light breakfast. However, a distinction between basal and resting metabolism does not require particular emphasis in the discussion that follows and, for the present purpose, these parameters of energy metabolism will be used synonymously.

Resting energy metabolism represents the combustion of fuel sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs and for the mechanical processes involved in keeping the body alive. Synthetic processes, such as protein, nucleic acid and lipid synthesis and gluconeogenesis, transport processes, including the pumping of ions to maintain ion gradients within cells and organelles and, finally, mechanical processes involving muscular ac-

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1 Based on a paper presented at the Conference on Nutrition and Cancer Therapy, November 29 to December 1, 1976, Key Biscayne, Fla.

2 The abbreviation used is: BMR, basal metabolic rate.
tivity, require energy inputs. These are obtained from high-energy phosphate compounds, usually ATP, generated during the oxidation of the major energy-yielding substrates. Hence, these various processes and their associated energy needs constitute a biochemical basis of the basal rate of energy expenditure. Various factors alter the activities of these processes and the types of substrate used for supplying energy.

The contribution made by the various body organs to BMR in the healthy adult is summarized in Table 1. It has been estimated that the liver accounts for approximately 27% of resting metabolism, with the brain, skeletal muscle, and remainder also being important sites of total body energy expenditure (65). Thus, the proportion of these body organs in relation to total body weight will affect values for BMR when expressed per unit body weight or surface area. Because the relative contributions of the body organs to total body weight change with growth and development (53), aging (72), malnutrition (21), and pathological states, interpretation of the metabolic significance of differences in BMR among differing groups of patients must be cautious. It is possible that alterations in the body organ compartments would bring about differences in BMR without any real change in the status of energy metabolism within the organs themselves.

Fuel Sources in Relation to Resting Metabolism

The major substances used as sources of energy in mammalian tissues are glucose, fatty acids, ketone bodies, amino acids, and lactate (9, 45). Although these are interchangeable sources of energy in the whole organism, individual organs show some specificity with respect to their use of fuel sources (Table 2).

For a well-nourished adult subject in the basal state, glucose is utilized at a rate of 140 g/day, equivalent to 560 kcal. The oxidation of amino acids, liberated during the course of tissue protein breakdown, can be estimated to amount to 75 g/day, or 375 kcal. The rest of the daily energy flux is accounted for largely by the oxidation of 130 g triglyceride, equivalent to 1170 kcal. This cyclic metabolic pathway, involving conversion of glucose to lactate and the return of lactate to glucose, is termed the Cori cycle. Utilization of lactate for glucose synthesis is an energy-requiring process, and an increased rate of conversion of lactate to glucose has been proposed as a mechanism for the increased energy expenditure of the tumor-bearing patient (17, 25). It is well known that tumors show high rates of anaerobic glycolysis with production of lactic acid (24, 79), and studies in cancer patients show increased lactate production.

Holroyde et al. (36) recently reported a series of studies on Cori cycle activity in a heterogeneous group of patients with metastatic carcinoma (Table 3). Patients without progressive weight loss appeared to have normal glucose metabolism, but Cori cycle activity was increased in patients with progressive weight loss, showing that lactate production rates were higher in these patients.

Gold (25) proposed that the increased rate of resynthesis of glucose in the liver from the lactate produced by the tumor acts as a significant energy drain on host tissues. However, from the data shown in Table 3 and from additional estimates of the rate of lactate production and recycling in cancer patients (68, 81), increased Cori cycle activity does not appear to account for a significant fraction of daily energy expenditure. Thus, if 6 moles of high-energy

### Table 1

**Distribution of oxygen utilization among the major body organs in a resting, healthy man**

For a 65-kg man [from Passmore and Draper (65)].

<table>
<thead>
<tr>
<th>Organ</th>
<th>Oxygen consumption (ml/min)</th>
<th>Resting metabolism (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (including splanchnic area)</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td>Brain</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>Kidneys</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Heart</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Skeletal muscles</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Remainder</td>
<td>48</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2

**Fuels of individual tissues**

[Modified from Krebs (45).]

<table>
<thead>
<tr>
<th>Major source of energy</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Erythrocytes, leukocytes, renal medulla, brain, skeletal muscle (exercise), some malignant tumors, fetal tissue, intestinal mucosa</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>Liver, kidney cortex, cardiac muscle, skeletal muscle (except in severe exercise)</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>Cardiac muscle, renal cortex, skeletal muscle, brain</td>
</tr>
</tbody>
</table>

*These sources can be used in quantitatively significant amounts by tissues shown.*

### Table 3

**Glucose turnover and Cori cycle activity in patients with metastatic carcinoma**

Calculated from data of Holroyde et al. (36).

<table>
<thead>
<tr>
<th>Status of body wt loss</th>
<th>Glucose turnover rate</th>
<th>Cori cycle activity</th>
<th>% glucose turnover</th>
<th>Glucose oxidation (mg/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive</td>
<td>196 ± 26</td>
<td>90 ± 21</td>
<td>43 ± 7</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>None</td>
<td>110 ± 26</td>
<td>19 ± 2</td>
<td>18 ± 2</td>
<td>48 ± 6</td>
</tr>
</tbody>
</table>

*Mean ± S.D. for 8 patients.

*Mean ± S.D. for 6 patients.*
phosphate are consumed for each mole of glucose produced from lactate (51), this would involve a substrate energy requirement of about 110 kcal. From the data provided by Holroyde et al. (36), it can be estimated that less than 10% of daily energy expenditure can be accounted for by the conventional cost of lactate recycling. Analyzing this problem from a somewhat different perspective, it can be estimated that, if 15% of total lactate production is oxidized to CO₂ and H₂O, and 85% of lactate is converted to glucose, there will be a maintenance of high-energy phosphate balance. This assumes, of course, that lactate is the only metabolite being utilized (51). It is difficult to accept, therefore, that changes in Cori cycle activity are a significant cause of the marked body wasting in patients with progressive neoplasia. Nevertheless, it is of interest that Holroyde et al. (36) observed highest Cori cycle activity in patients with greatest total energy expenditure.

The pattern of fuel sources changes markedly if fasting continues significantly beyond the usual overnight period. For a fast lasting 3 days or longer, glucose oxidation is decreased, in parallel with reduced rates of gluconeogenesis (9, 64) and the oxidation of fatty acids and ketone bodies is increased, with the brain making major use of the latter as its principal fuel source (63). A picture of fuel utilization during short and long-term fasts is shown in Chart 1. This change in the pattern of fuel sources and utilization is accomplished by alterations in substrate availability, in hormonal balance, and by the regulatory effects of ketone bodies on amino acid oxidation in peripheral tissues (71).

In terms of energy requirements, glucose and lipid sources are utilized with about the same efficiency, at least when assessed in terms of the potential yield of ATP (44) from isocaloric intakes of glucose and fat. Protein is somewhat less efficient as a source of energy, depending upon the amino acid composition of the protein and because energy is used for the elimination of nitrogen via urea synthesis (44).

It should be recognized, however, that an estimation of the availability of utilizable energy from carbohydrate (glucose) and lipid fuel sources, based on calculation of maximum ATP yield, may have limited significance in relation to an assessment of the status of energy metabolism and substrate utilization in the whole organism. Various factors serve to modify the yield of utilizable energy which may be derived from the combustion of these fuel sources. The importance of these factors may vary among individuals and within subjects due to changes in physiological and pathological states (34).

The efficiency of generation of ATP might vary due to changes in the coupling of oxidative phosphorylation, and the efficiency of utilization of ATP does not necessarily remain constant, due to factors such as tissue phosphatase activity and ion concentration. Furthermore, a variable activity of "futile" cycles would result in changes in the amount of energy available for use in energy-requiring processes. These cycles occur when there are two opposing metabolic pathways in the cell in which the reactions in the forward and reverse directions are catalyzed by separate enzymes (40, 60). For example, 3 futile cycles in carbohydrate metabolism are shown in Chart 2. In one direction, the
reaction requires the participation of a high-energy compound, such as ATP, while the reaction in the opposite direction is energetically spontaneous. Although there is no net flux of reactants in these cycles, the cycling causes ATP hydrolysis, and thus an energy "wastage." However, the recycling may not be as wasteful as it appears, as pointed out by Katz and Rognstad (40), if these cycles serve a role in metabolic regulation.

Although there are no adequate experimental data to estimate the fraction of total ATP formed and used in recycling, a variation in the activity of futile cycles has been proposed as a basis for adaptation to high-energy intakes (74) and for differences in the propensity of individuals with generous energy intakes to become obese (39). Similarly, it can be speculated that the changes in the availability of ATP and in the efficiency of energy utilization might arise as a consequence of changes in recycling in disease states and under the varying conditions of therapy. This problem deserves investigation.

Another factor that must be mentioned is that, if glucose or other carbohydrate sources are converted first to fat for the temporary storage of energy, before being used to meet energy requirements, there is a reduction in the amount of utilizable energy obtained from the intake of a given amount of carbohydrate. Krebs (45) estimated that this loss of utilizable energy is equivalent to 2 molecules of ATP per C₂ segment of long-chain fatty acid or about 7% of the utilizable energy to be stored. Flatt (18) estimates the loss of utilizable energy to be equivalent to about 20% of the caloric value of the glucose channeled into lipogenic pathways, and this appears to be a significant energy cost. Whatever the precise value, there is an energy cost associated with storage and the later utilization of fuels. Hence the efficiency of substrate utilization for meeting the basal energy requirement will be determined, in part, by the metabolic pathways followed before the fuel sources reach the terminal stage of oxidation.

Significance of Ion Pumping and Protein Turnover in Energy Expenditure

Two processes thought to account for a significant fraction of the basal energy expenditure are ion pumping and protein turnover (synthesis and breakdown). The maintenance of electrochemical gradients through the active transport of ions requires energy; it has been suggested that 40 and 52% of the in vitro aerobic energy expenditure of kidney cortex and brain slices, respectively, is linked to sodium-potassium pumping (91). Similarly, the transport of sodium and potassium in liver (15) and tumor cells (48) has been estimated to account for 35 and 85% of energy metabolism in these tissues, respectively. Support for the concept that ion pumping is an important component of basal energy metabolism is suggested from the increased metabolic rate in response to thyroid hormone and catecholamines which appears to be due to increased ATP utilization as a consequence of altered activity of sodium-potassium-ATPase (35). However, Himms-Hagen (35) has concluded that, for most normal tissues, the proportion of total cell and organ energy metabolism controlled by, or directly related to, the sodium pump is relatively small.

Cell protein synthesis appears to be of quantitative significance in relation to the utilization of energy substrates under basal conditions, and various observations may be used to support this concept. Thus, the relationship between the intensity of whole-body protein metabolism in mammalian species and adult body size is described by the same power of body weight as is basal energy metabolism among these species. Brody (7) showed that the variation in obligatory nitrogen losses, assumed to be an index of the dynamic state of body protein metabolism, among 9 mammalian species, ranging in size from the mouse to the cow, correlated with the 0.72 power of body weight, expressed in kg (Chart 3). This is essentially the same function of body weight that best correlates basal energy metabolism among these various species (43). More recently, Munro (58) reviewed this aspect of body protein metabolism and computed the power function of body weight that best correlated various parameters of tissue and whole-body protein metabolism, including albumin and ceruloplasmin turnover and liver RNA content, among mammals of different body size. The estimates of Munro (58), together with those of Brody (7), demonstrate a close relationship between the intensity of body protein metabolism and rate of energy expenditure in mammals, including man.

Estimates of the rate of whole-body protein synthesis in adult human subjects provide additional support for the view that protein turnover (synthesis and breakdown) accounts for a significant proportion of basal energy expenditure. Table 4 summarizes some published estimates of rates of whole-body protein synthesis in well-nourished adult subjects. Although the estimates vary, depending upon the method used for the determination (86), whole-body protein synthesis approximates 3 to 4 g per kg body per day or 200 to 300 g for a 70-kg subject. Assuming each mole of peptide bond requires the equivalent of about 5 moles of ATP and that ATP is formed from glucose at a cost of 18 kcal/mole (44), it can be calculated that about 180 kcal of substrate would be required to support this amount of peptide bond synthesis. This would be equivalent to about 10% of basal energy expenditure.
energy expenditure. This estimate does not account for the energy costs of amino acid transport, RNA synthesis, turnover of the -CCA terminus of tRNA, synthesis of nonessential amino acids, and energy cost of protein breakdown. Furthermore, it is assumed that the oxidation of glucose results in the generation and availability of 36 moles ATP per mole glucose oxidized, but as discussed earlier, this maximum yield of ATP is subject to variation and in all likelihood it will be less. Millward et al. (54) have estimated the energy cost of protein synthesis to be about 1.4 kcal/g protein. On this basis, protein turnover in the adult subject would account for about 25% of the basal metabolic rate. These figures underestimate the quantitative contribution of protein synthesis and breakdown to basal energy metabolism. Thus, it is reasonable to assume that about one-half of resting energy metabolism may be associated with protein turnover. For this reason, it would be anticipated that the replenishment of tissue and organ protein content in the initially depleted patient would require an increased energy intake above that required for normal maintenance. Furthermore, evidence indicating a high energy cost of growth in infants and children (47, 66) supports this view.

Finally, resting energy metabolism per unit of body weight declines with progressive growth and development within a mammalian species (43). This fall parallels the reduced intensity of whole-body protein synthesis during this period (e.g., Ref. 88). We (95) have explored the relationship between whole-body protein synthesis rates and energy metabolism in human subjects at various ages, and the results of these studies are shown in Table 5. It can be seen that there are marked differences in the intensity of whole-body protein synthesis, expressed per unit of body weight, among the various age groups. However, these differences are not as evident for whole-body protein synthesis expressed per unit of resting energy metabolism. These observations emphasize further the close and, presumably, causal relationship between whole-body protein turnover and resting energy metabolism.

Changes in host tissue and total-body protein metabolism due to the presence of a growing tumor (26), physical trauma (19), and surgery (62) and alterations that may occur as a result of chemotherapy and radiation treatment would influence also the utilization and requirements for energy. Thus, a critical assessment of energy utilization and requirements in the cancer patient should take into account these intimate interrelationships among body protein and energy metabolism.

**Factors Affecting BMR**

Age, nutritional status, temperature, hormones, and pathological states, including trauma and infection, affect the resting metabolic rate. The effects of age have been discussed by others (43, 66, 72). Also, changes in deep body temperature are well established (20). If body temperature is raised by 1°, either by fever or by warming the body, the metabolic rate increases by about 12%.

The effect of nutritional state is important in the context of energy metabolism, particularly because body nutrient depletion is common in cancer patients. The effects of starvation and undernutrition on basal metabolism have received considerable investigation, and this has been the topic of several reviews (20, 30, 42, 87). Brief fasting does not change total-body oxygen consumption and, thus, heat production, but a longer period of restricted food intake does influence whole-body energy expenditure (31).

Chart 4 summarizes results, discussed previously by Garrow (20), of a study by Benedict et al. (2). The major findings of this study are shown here to emphasize a number of points that should be considered in evaluating results of studies of energy metabolism in cancer patients. First, it can be seen that undernutrition reduces BMR to a greater extent than the effect on body weight. Thus, the fall in BMR, under these conditions is due to changes in the metabolic activity of tissue as well as a loss of active tissue mass. On the basis of studies during acute starvation, Grande et al.

*Table 5*

<table>
<thead>
<tr>
<th>Group</th>
<th>Total body protein synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>newborn</td>
<td>18, 0.15 ± 0.09</td>
</tr>
<tr>
<td>infant</td>
<td>7, 0.11 ± 0.01</td>
</tr>
<tr>
<td>young adult</td>
<td>3, 0.11 ± 0.01</td>
</tr>
<tr>
<td>elderly</td>
<td>2, 0.11 ± 0.03</td>
</tr>
</tbody>
</table>

*Table 4*

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Whole-body protein synthesis (g/kg/day)</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. and sex</td>
<td>Age (yr)</td>
<td>Label</td>
</tr>
<tr>
<td>3 M</td>
<td>19-50</td>
<td>L-[U-14C]Lysine</td>
</tr>
<tr>
<td>3 M, 1 F*</td>
<td>52-75</td>
<td>L-[1-14C]Leucine</td>
</tr>
<tr>
<td>6 M</td>
<td>31-64</td>
<td>L-[U-14C]Tyrosine</td>
</tr>
<tr>
<td>5 M</td>
<td>31-46</td>
<td>L-[α-14N]Lysine</td>
</tr>
<tr>
<td>4 M, 2 F</td>
<td>20-25</td>
<td>[14N]Glycine</td>
</tr>
</tbody>
</table>

*Preoperative patients. Other studies involved healthy subjects.*
Changes in rates of whole-body protein synthesis and breakdown in 5 moderately obese women after a 1-week total fast. From unpublished results of J. C. Winterer, B. R. Bistrian, and V. R. Young. Estimates of protein synthesis and breakdown were made with the use of the [15N]glycine model of Picou and Taylor-Roberts (67).

<table>
<thead>
<tr>
<th>Diet period</th>
<th>Protein synthesis (g/kg/day)</th>
<th>Protein breakdown (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Fast</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 6

<table>
<thead>
<tr>
<th>Burn size (% surface area)</th>
<th>No. of observations</th>
<th>Whole-body protein (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Synthesis</td>
</tr>
<tr>
<td>0</td>
<td>11</td>
<td>3.5</td>
</tr>
<tr>
<td>0.5–25</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>25–60</td>
<td>10</td>
<td>5.2</td>
</tr>
<tr>
<td>≥60</td>
<td>10</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Table 7

(31) suggested that the loss of tissue accounts for about 30% of the decrease in metabolism. On the other hand, in long-term undernutrition, the loss of tissue is a major factor determining the reduction in energy expenditure (20).

The results shown in Chart 4 also indicate that basal metabolism is rapidly restored to normal levels upon refeeding. In this case, BMR, expressed per unit of body weight, increases to greater than normal during early refeeding. An increased rate of energy expenditure also occurs after meals in children during early recovery from severe protein-calorie malnutrition (1, 8, 46). Brooke and Ashworth (8) propose that this increased energy expenditure with refeeding is due to the increased rate of protein synthesis which would involve an increased rate of ATP generation and utilization. Of additional interest is that the fall in BMR with continued fasting in obese subjects (5) also appears to be related to a fall in whole-body protein synthesis. Using a constant [15N]glycine infusion model, we (J. C. Winterer, B. R. Bistrian and V. R. Young, unpublished results) have observed that there is a significant decrease in the overall body protein synthesis rate during a week-long fast in obese women (Table 6).

Finally, the results of Benedict et al. (2) suggest that BMR falls more rapidly with fasting after a period of temporary refeeding than during initial adaptation to a fast in a healthy subject.

In addition to undernutrition, the effects of excessive energy intakes on energy expenditure and BMR have been reviewed recently by others (20, 52, 74). Overfeeding of normal subjects does not always result in the expected weight gain despite unaltered physical activity. Various studies indicate that, over a period of excess energy intake, there is an increase in oxygen consumption in the resting state and that this thermogenic effect of high energy intakes is greater during exercise (52, 74).

From these various observations it is difficult to generalize about the effect of nutritional state on basal metabolism. It will depend upon when it is measured, how it is calculated, and current as well as previous nutritional history. These points should be kept in mind in the critical evaluation of energy metabolism in cancer patients.

Physical trauma, e.g., due to burns or leg fracture, alters the basal metabolic rate, the degree of change depending upon the severity of trauma (92). The hypermetabolism may cause a marked weight loss if it is not met by substantial increases in energy intake, and Wilmore et al. (93) have proposed that the calorogenic action of catecholamines is the cause of the increased metabolic rate. However, the mechanism of increased heat production in burned patients requires further exploration, and accelerated rates of gluconeogenesis and ureagenesis would account, in part, for this increase in metabolic rate (92). Furthermore, it seems likely that an increased rate of whole-body protein turnover is an important factor. Recent studies (C. L. Kien, J. F. Burke, and V. R. Young, unpublished results) summarized in Table 7, on the effects of thermal injury, have shown that the rates of whole-body protein synthesis and breakdown are higher in children with larger burns. This higher rate correlates with
the increased basal metabolic rate and energy expenditure which occur in extensive body burns (92).

It must be concluded, therefore, that the basal metabolic rate changes in response to various physiological and pathological conditions. This makes it difficult to evaluate fully the limited published data obtained in studies of energy metabolism in patients with malignant disease, and to determine whether cancer has a direct influence on energy metabolism and, particularly, on energy requirements.

**Resting Metabolism in Cancer Patients**

In Table 8, a summary is made of some results of studies on the basal metabolic rate in patients with cancer. In view of the various factors that affect metabolic rate, and, in part, because of the limited information supplied in many of the papers, it cannot be concluded that resting metabolism is consistently increased in the cancer patient, compared with healthy controls. Resting energy metabolism appears to be increased in many patients with Hodgkin's disease or leukemia. There is considerable variation in reported BMR's among and within the various studies. This presumably reflects differences in methodological and biological variables, as well as possible effects of different cancers and severity and stage of disease. In a study of the partition of energy expenditure between host and tumor in tumor-bearing rats, Morrison (56) did not find evidence of a consistent change in resting metabolism.

**Response of Energy Metabolism to Dietary Intake in the Cancer Patient**

Potentially of greater nutritional significance is the possibility that the response of the cancer patient to semistarvation or nutritional rehabilitation may differ from that of healthy subjects or from patients suffering from nonmalignant diseases. Waterhouse and Kemperman (83) have examined this possibility by determining rates of glucose and free fatty acid oxidation, as well as carbon dioxide production, in 5 patients with metastatic malignant disease; studies were conducted in patients under basal conditions and during glucose loading. The results of their studies are shown in Charts 5 and 6. Under basal conditions, rates of glucose and free fatty acid ([1-14C]palmitate) oxidation, and total CO2 production did not differ substantially between cancer patients and controls. However, when a glucose load was given, these investigators observed that the oxidation of free fatty acid was suppressed less in cancer patients and that there was a lower rate of "slow" oxidation of glucose, compared with controls (Chart 5).

Calculation of the contribution to CO2 production by nonprotein sources, unlabeled by the administered [14C]glucose and [14C]palmitate, indicated that glucose loading reduced their oxidation in normal subjects but not in cancer patients (Chart 6). Waterhouse and Kemperman (83) interpret this finding to mean that continued intracellular oxidation of free fatty acids occurs with glucose loading.

**Chart 5. Estimates of glucose pool and rates of glucose ("rapid" and "slow" pools) and free fatty acid (FFA) oxidation in normal and cancer patients studied under basal conditions and during a glucose load (+G).**

<table>
<thead>
<tr>
<th>Description of population</th>
<th>Description of metabolic rate</th>
<th>Comment</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia, 16 cases</td>
<td>Usually &gt;120% normal</td>
<td>Few details</td>
<td>Boothby and Sandiford (3)</td>
</tr>
<tr>
<td>Chronic myelocytic leukemia, 4 cases</td>
<td>Low, normal, increased</td>
<td>Few details</td>
<td>Watkin (89)</td>
</tr>
<tr>
<td>Malignant disease, 5 cases</td>
<td>~10% above normal</td>
<td></td>
<td>Waterhouse (82)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>~14-60% above normal</td>
<td>Few details</td>
<td>Silver et al. (73)</td>
</tr>
<tr>
<td>Carcinoma, localized</td>
<td>~6-57% above normal</td>
<td>Few details</td>
<td>Silver et al. (73)</td>
</tr>
<tr>
<td>Leukemia, myeloid and lymphatic plasmas, 4 cases</td>
<td>~12-91% above normal</td>
<td></td>
<td>Waterhouse et al. (84)</td>
</tr>
<tr>
<td>Malignant neoplasms, 4 cases</td>
<td>0-30% above normal</td>
<td>Few details</td>
<td>Minot and Means (55)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Increased</td>
<td>Few details</td>
<td>Watkin and Steinfield (90)</td>
</tr>
<tr>
<td>Neoplastic disease, 4 cases</td>
<td>Low and above normal</td>
<td></td>
<td>Terpeka and Waterhouse (76)</td>
</tr>
<tr>
<td>Various cancers, 9 cases</td>
<td>Usually above normal</td>
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Table 8

*A listing of some published results on the basal metabolic rate of cancer patients*
This suggests that there is a disturbance in normal homeostatic mechanisms involving the utilization of glucose and other important fuel sources in patients with malignant disease. In this context, changes in hormonal balance may be of significance, and Goodlad et al. (28) found reduced insulin production in tumor-bearing male rats. Thus, an alteration in insulin function might account for the abnormal glucose regulation.

The nutritional implications of these findings are more difficult to assess. If glucose is not oxidized directly but is first converted to fat before supplying utilizable energy, this would involve an energy cost and, thus, a relatively higher energy intake to meet the needs of body tissues. Whether gluconeogenesis is inhibited by exogenous glucose as effectively in the cancerous as in the normal patient does not appear to have received critical investigation. However, sepsis increases gluconeogenesis, and this pathway is not responsive to the administration of glucose during the stress of infection (32). Thus, of possible interest in relation to metabolic regulation by exogenous substrate is the observation that treatment of rats with hepatocarcinogens results in a loss of dietary feedback control of cholesterol biosynthesis (70). Additional studies would be desirable to explore the regulation of carbohydrate and lipid metabolism and the dynamic interrelationships between glucose, lipid, and amino acid metabolism in cancer patients.

Several investigators (12, 84, 89, 90) have stated that the level of energy intakes needed to maintain body energy balance are higher for cancer patients than for other subjects. Thus Waterhouse et al. (84) determined energy balance, using the indirect method of Newburgh et al. (59) in a group of 4 patients with leukemia, Hodgkin’s disease, and carcinoma of the pancreas. The results obtained with 2 of these patients are summarized in Chart 7, and it may be seen for 1 patient that, even at a liberal energy intake, body energy balance was markedly negative throughout. This implies that, in some but not all cancer patients, dietary energy sources are utilized with relatively low efficiency. However, it must be recognized that the precision of the estimates of energy balance made by Waterhouse et al. (84) is not known and that accurate determinations of energy balance are difficult to undertake. The magnitude of the error in energy balance which could lead to marked body weight loss is quite small compared with the range of energy intakes and requirements within a group of subjects (20). Furthermore, Garrow (20) concluded from his review of the literature that rarely is energy balance established over a period of a week or even longer periods in normal subjects, and that an energy imbalance of up to 60,000 kcal is tolerated by the control system in many people. It is not surprising that little is known about the quantitative effects of cancer on energy utilization and body energy balance in human subjects.

As reviewed above, continued weight loss and clinical deterioration have been observed in some patients, even when given generous energy and protein intakes. However, the effects of the cancer or treatment conditions may not be
exerted directly on the yield or availability of utilizable energy from energy sources. Changes in energy balance or in the capacity to achieve body energy equilibrium may be secondary to alterations in the status of protein metabolism in body tissues.

Goodlad et al. (27-29) and Clark and Goodlad (11) have shown that myofibrillar protein synthesis in skeletal muscle of tumor-bearing rats is reduced and they (11) have concluded that this impairment is due to a defect in the capacity of the 40 S ribosome subunit to promote a postinitiation step in polypeptide synthesis. Lundholm et al. (50) have examined in vitro protein synthesis in muscle biopsies obtained from a heterogeneous group of cancer patients, and the results of these studies are shown in Chart 8. Protein synthetic activity was impaired and the rate of protein breakdown was increased in muscle samples from cancer patients, compared with metabolically healthy controls. However, Lundholm et al. (50) also observed that protein synthesis in muscle from cancer patients, as well as normal subjects, could be stimulated by the addition of high levels of amino acids to the incubation medium (Chart 8). This suggests that in the cancer patient there is a reduced efficiency of amino acid utilization for muscle protein synthesis at normal levels of amino acid supply, but that this may be overcome by raising the supply of amino acids to muscle. The favorable gains in body weight and nitrogen retention, as well as reduced morbidity and mortality, achieved by i.v. feeding of cancer patients (e.g., Ref. 13), support this conclusion.

Energy Requirements of the Cancer Patient

Partly because the effects of cancer on host tissue and whole-body energy metabolism are only partially understood, it is not possible to be precise about the minimum intake of energy which would be sufficient to meet energy needs and maintain body energy balance in cancer patients. Furthermore, the balance between major exogenous energy sources, glucose or other carbohydrates, and lipid, which would promote maximum efficiency of energy utilization, cannot be stated yet. There are no more than a few studies that help to provide only crude guidelines for this purpose. Rutten et al. (69) have shown in a group of postsurgical patients, including some with cancer, that hyperalimentation with a fluid providing 160 kcal/g nitrogen could support body nitrogen balance when total energy intake approximated 1.7 to 2.0 times the calculated basal metabolic rate (Chart 9). Similarly, at nitrogen intakes of 240 mg nitrogen per kg per day, or more than twice the nitrogen allowance for healthy adults (16), Long et al. (49) concluded that energy balance was achieved in a group of septic patients, including 2 with cancer of the bladder, with energy intake being about 1.5 times basal energy expenditure.

The studies of Rutten et al. (69) and Long et al. (49) provide only a partial basis for assessing the adequacy of levels of energy intake, and studies of this kind should be extended, particularly in view of the close interrelationships between energy and protein in nutrition and metabolism. We (22, 23) and others (10, 37) have explored the sensitivity of body nitrogen balance to changes in energy intake in healthy subjects. In these studies it was shown that generous intakes of energy result in a sustained increase in nitrogen retention and dietary nitrogen utilization. However, the effects of changes in the level of energy intake on protein and energy utilization may be modified by the level of protein intake (57). Hence, the definition of an adequate energy intake for the nutritional therapy of the cancer patient is dependent upon a variety of dietary and host factors. These factors, together, will determine the appropriate energy intake for the individual patient. Finally, the attending physician and hospital dietitian have little useful information to follow in deciding on the level and sources of energy to provide a particular patient and they must rely upon the clinical progress of the patient, supplemented with some objective biochemical and physiological assessment of the patient's nutritional state.

Better knowledge of the interrelationships among energy
and protein metabolism clearly would help to develop better diagnostic aids for the evaluation of nutritional status and lead to the design of improved nutritional therapies for treatment of cancer patients. In addition, this information is necessary for an understanding of the anorexia that is regarded as a major contributory factor to body energy loss and the eventual cachexia in cancer patients (77). Obviously, energy balance will not be achieved if intake and absorption fail to meet the energy demands of the body. Alterations in intestinal function due to alimentary tract neoplasms or the effects of surgery, chemotherapeutic agents, and radiation may affect energy metabolism by changing the digestive-absorptive phase of nutrient utilization. This topic is discussed elsewhere in this symposium.

The regulation of energy intake in normal and cancer patients is beyond the scope of this paper, and the reader is referred to reviews which have discussed this aspect of energy metabolism in normal subjects (e.g., Ref. 61) and in relation to cancer (78). Of particular interest, however, is a review by Bray and Campfield (6) which considers the various metabolic factors involved in the regulation of food intake. These investigators proposed that body energy stores are the regulated variable and that energy intake or expenditure is altered to maintain a particular level of total caloric storage. The major features of the control system discussed by Bray and Campfield are given in Chart 10. As seen from this chart, the plasma concentrations of amino acids, glucose, glycerol, and free fatty acids, as well as the state of peripheral metabolism, including the quantity of adipose tissue, glycogen, and protein, serve as feedback signals on the ventromedial nucleus, which is assumed to be the long-term monitor of energy balance in the body. This model was proposed to provide a possible framework which might help identify possible changes of system error in relation to obesity, or body energy excess. Similarly, it might offer an approach to testing hypotheses proposed to explain the actual or relative reduction in food intake and development of negative energy balance which occurs during the onset and development of neoplasia. Of significance in the present context is that the model involves considerations of important energy-yielding substrates, glucose, and fatty acids, and of the amino acid levels in blood plasma. Changes in glucose, fatty acid metabolism, and in amino acid and protein metabolism in cancer patients have been discussed above. Furthermore, differences in blood amino acid levels of cancer patients, compared with controls, have been described (e.g., Refs. 4, 41).

An adequate exploration of energy metabolism and nutrition should, for these reasons alone, include as many observations as possible within a single patient, on the utilization and metabolism of the principal fuel sources (carbohydrate, lipids, and protein). There is also a great need to apply and improve upon modern methods for measurement of whole-body energy expenditure in human subjects in general and in patients with malignant disease in particular.

**Conclusion**

Based on the above, it is clear that various factors affect basal and total daily energy expenditure. This makes it difficult to assess the significance of published data on basal metabolism in cancer patients. Also, there are significant quantitative relationships between whole-body energy and protein metabolism, and these must be considered in assessing energy status and requirements in cancer patients who may often be depleted of body protein and require vigorous nutritional support to reverse this state and to maintain adequate nutritional status. Although the limited data available suggest that the pattern of fuel utilization

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**Chart 10. Simplified elements of the system responsible for regulation of body energy stores in human subjects, as proposed by Bray and Campfield (6). The model consists of a controller, acting upon the controlled system, with effectors including plasma glucose, amino acids, fatty acids, and status of metabolism in peripheral tissues.**
in neoplastic disease states may differ from that of healthy subjects, with lipid sources predominating, an altered regulation of glucose metabolism, and less efficient utilization of food energy, further studies are needed to verify and establish the nutritional and metabolic significance of this observation. Whether particular cancers, other than those directly involving the neuroendocrine system, affect energy metabolism and requirements in different ways cannot be determined from the available literature, nor is the role of severity of the disease state, in this regard, adequately understood. Only crude guidelines can be suggested for the levels of energy intake and optimum relationship between protein and energy requirements for the feeding of cancer patients. A better understanding of the characteristics of the utilization and metabolism of the major fuel sources in cancer patients should lead to improved diagnostic tests for assessing body energy balance and needs during the various phases of the disease and under the differing conditions of therapy. In part, this will require much better information on the regulation of energy metabolism and utilization of energy sources at the whole-body level in healthy subjects. 

References

Energy Metabolism and Requirements in the Cancer Patient

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