Regulation of Plasma-free Fatty Acid Mobilization by Dietary Glucose in Ehrlich Ascites Tumor-bearing Mice

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ABSTRACT

We studied the ability of dietary glucose to cause an abrupt inhibition of free fatty acid (FFA) mobilization in mice bearing advanced Ehrlich ascites carcinoma. FFA irreversible disposal rates were estimated after i.v. injection of tracer [1-14C]palmitate complexed to mouse serum albumin. Four groups of mice were studied: 16-hr-fastened mice versus 16-hr-fastened mice refed a 58% glucose, fat-free test meal for 10 min; control versus tumorous mice. Plasma FFA fell significantly [from 0.97 ± 0.06 (S.E.) to 0.37 ± 0.02 μEq/ml (n = 30 and 134, respectively)] following the ingestion of the small test meal. The lowered plasma FFA pool size remained approximately constant between t = 15 and 45 min after the mice began to eat. Tracer studies in the fasted-refed mice, carried out during that interval, showed that the plasma FFA irreversible disposal rate was reduced by 50% in both control and tumor-bearing mice. Although cancerous mice tended to have elevated plasma FFA levels in the early morning, these animals appear to have normal control mechanisms for inhibiting FFA mobilization following ingestion of carbohydrate.

INTRODUCTION

Although much attention has been given the phenomenon of fat depletion in cancer-bearing experimental animals and in humans, there remains much uncertainty and confusion as to whether a growing cancer elicits fat-mobilizing factors (19), whether lipolysis in adipose tissue is actually increased, and whether the regulatory mechanisms that control lipolytic rates in the host are altered in cancerous subjects and cancer-bearing animals (11). Very few dynamic, quantitative studies of FFA3 turnover in cancerous animals (5) or humans (30) have been reported. Further work is required in this area, especially studies of the effect of cancer upon the host's ability to regulate adipose tissue lipolysis by dietary carbohydrate and insulin.

In an earlier attempt to clarify the effects of cancer upon FFA production and turnover in experimental animals, Baker et al. (5) studied the IDR of essential and nonessential plasma FFA in mice bearing Ehrlich ascites carcinoma. These experiments, carried out in animals that were either fasted or fed ad libitum, failed to show any remarkable differences between control and tumorous mice. However, 2 major problems were encountered in the course of that study. First, the plasma FFA levels of the "fed" mice were not significantly lower than those of the fasted animals. Second, the kinetics of plasma FFA turnover after i.v. injection of labeled FFA were poorly defined because of the slow terminal slope, inadequate number of data points, and irregularities in some of the plasma 14C- and 3H-labeled curves at later times.

As one means of overcoming these difficulties, we have carefully controlled the nutritional states of the mice in the present study. Our approach was similar to that used by Waterhouse et al. (29) and Waterhouse and Kemperman (30) in cancerous humans and by Baker and Rostami (4) to study the effects of glucose feeding on FFA turnover in previously fasted normal rats. In both cases the replacement of plasma FFA was studied in animals in which plasma FFA levels were either elevated by fasting or reduced by previous glucose feeding. First, we established conditions that would ensure steady-state plasma FFA pool sizes in both fasted and fasted-refed control mice. Then we defined the effect on plasma FFA levels (both the time course and the magnitude of the fall) of refeeding (without force) a fat-free, 58% glucose test meal to previously fasted control and cancerous mice. Finally, on the basis of these observations we carried out tracer studies of plasma FFA turnover at elevated and experimentally lowered levels of plasma FFA in both control and cancerous mice. The techniques that we used were tested to ensure that postmortem lipolysis of newly formed labeled plasma very-low-density lipoprotein:TGFA would not perturb artificially the slow exponential fall of plasma [14C]FFA following i.v. injection of a [1-14C]palmitate:mouse serum albumin complex. The results of these experiments show that cancerous mice, even at advanced stages of cancer growth, have the full regulatory capacity to respond to dietary carbohydrate by a prompt and normal reduction in the rate of FFA production in vivo.

MATERIALS AND METHODS

Cancer Cells

Ehrlich-Lettré hyperdiploid ascites tumor cells (chromosome number, 44) were originally obtained from the subline maintained in Swiss-Webster mice by Dr. Ralph McKee, Biological Chemistry Department, UCLA School of Medicine. Each mouse was inoculated with 0.2 ml Krebs-Ringer phosphate buffer (controls) or 0.2 ml (15 x 10⁶) tumor cells.
Mice, Dietary Conditions, and Nutritional States

For all studies we used male Swiss-Webster mice (Hilltop Lab Animals, Inc.; Chatsworth, Calif.), 8 to 10 weeks old (30 to 35 g), housed in community cages (6 mice/cage). Three kinds of studies were carried out. The first was an initial survey of plasma FFA levels in which we neither fed the animals test meals nor gave them injections of tracer FFA. The second type was a controlled-feeding experiment in which we used fasted and fasted-refed mice and measured the plasma FFA levels, although we did not inject labeled FFA. The third was based on the results of the second study and was carried out under the same nutritional conditions, but this time we injected labeled FFA to follow the disappearance and replacement of the tracer and tracee in fasted and in fasted-refed mice.

Initial Survey of Plasma FFA Levels. In the initial study we used mice fed either Purina laboratory chow or a special 58% glucose, fat-free diet (2) obtained commercially (ICN Pharmaceuticals Inc., Cleveland, Ohio). The mice ate ad libitum until the experiment was begun or until food was removed at 8 a.m. for 6-hr fasting conditions or at 4 p.m. for 16-hr fasting conditions.

Controlled Feeding Studies. The mice used in controlled feeding studies were fed a 58% glucose, fat-free diet in pellet form ad libitum, except during brief training periods. A special training program was required since our experimental protocol demanded that some mice be transferred from group cages to individual metabolism cages in which they were expected to consume (in a short, fixed period of time) most or all of the same 58% glucose diet, although the diet was fed as a small test meal in powder form to facilitate the monitoring of food consumption. We first tried to transfer mice that had been fasted overnight to metabolism cages containing the test meal in the hope that they would consume the meal. However, we found that the ingestion of food was prolonged, erratic, and highly variable under these conditions. Therefore we used the following training procedure, designed to maximize the utilization of a limited number of expensive metabolism cages and to allow the animals to live together in group cages in which they tend to grow and to tolerate tumor growth better than they do in individual metabolism cages (Ref. 22; unpublished observations). For the first 4 days, the mice were adapted to the pellet, 58% glucose, fat-free diet fed ad libitum. The food was removed at 4 p.m. on Day 4. On the morning of Day 5, the mice were placed in individual metabolism cages for 45 to 60 min and offered a meal of powdered, 58% glucose, fat-free diet. Each mouse was removed from the metabolism cage and returned to his original community cage after he had located and eaten a portion of his meal. On each of the next 2 mornings, the mice were placed in the individual cages with a test meal available but without prior fasting (to minimize effects of repeated, intermittent fasting). On Day 7 the mice were again fasted at 4 p.m. and, on the morning of Day 8 (experimental day), were given 250 mg of the 58% glucose, fat-free test meal, which they usually ate within 10 min. The exact amount of food eaten by each mouse was measured, and the time of each mouse's first nibble was noted and taken as zero time when determining the plasma FFA response to feeding. In these experiments fasted mice were subjected to the same training procedure but, in contrast to the fasted-refed group, were not fed a test meal on the experimental day.

Experimental Protocol

Effect of Glucose Refeeding on Plasma FFA Levels. Four groups of 16-hr-fasted mice were used: fasted versus fasted-refed mice; control versus cancerous mice. All of the mice had been trained to consume a small, 58% glucose test meal, as described previously. Care was taken to ensure that all 4 groups were studied between 8 a.m. and 12 noon on the morning following the 16-hr fasting period. Each experiment was repeated several times until the number of animals (including some with and without tail vein injections and/or with and without serial orbital blood sampling) totaled 80, 35 fasted and 55 fasted-refed mice. Blood was either drawn with 50-μl heparinized capillary tubes from the orbital venous sinus (3, 23) or collected following decapitation. No anesthesia was used. The capillary tubes were placed in ice baths immediately after collection of blood, and plasma was collected shortly thereafter for analysis of plasma FFA concentrations, unless otherwise indicated in the text.

Tracer Studies of FFA Production (Irreversible Disposal) Rates. The same 4 groups of mice were studied as in the nontracer experiments above. Prior to preparing the tracer:serum complex, [1-14C]palmitic acid (Dhom Products Ltd., North Hollywood, Calif.) was shown by thin-layer chromatography to be at least 98% pure. As a precaution, immediately before an experiment, it was repurified by the FFA extraction method of Hagenfeldt (14). The [1-14C]-palmitate:mouse serum albumin complex was prepared by a slight modification of the method of Friedberg et al. (13); approximately 1 μEq of [1-14C]palmitate was added per ml of mouse serum (diluted about 10% with 0.9% NaCl solution in which the soap was dissolved). The mixing of heated (70°) sodium palmitate (with trace potassium used to prepare the original soap in a more soluble form) and serum was carried out at 40°. The [1-14C]palmitate:serum complex (40 μl containing 2 to 4 × 10⁶ cpm 14C and approximately 0.06 μEq palmitate, including both that in the serum and the added tracer) was injected into the tail veins of unanesthetized fasted (16 hr) or fasted-refed mice. The palmitate in the injected dose was equivalent (at maximum) to 10% of the total pool size of fasted-refed mice and to <10% in fasted mice. Two serial venous capillary blood samples were drawn from the ophthalmic sinus, as described previously. At the termination of the experiment, the mice were decapitated and their blood was collected in heparinized tubes kept at 4°. Plasma FFA levels were determined from the terminal samples.

Chemical and Radioactive Analysis

Blood samples were kept at 4° until processing on the
same experimental day. Radioactivity in plasma FFA was measured as follows: plasma (20 to 100 µl) was added to 1.0 ml of Dole’s extraction medium (isopropyl alcohol:heptane:3 m H₂SO₄, 40:10:1), mixed well, and stored (1 to 2 weeks) at -25°C for later extraction of FFA by the method of Hagenfeldt (14). The ¹⁴C in the extracted FFA samples was measured in a Beckman liquid scintillation spectrometer with toluene:Insta-Gel (1:1; Packard Instrument Co., Downers Grove, Ill.). No change in FFA values was observed during storage under these conditions, as discussed below. Recovery of [¹-¹⁴C]palmitate added to plasma in vitro was 96% by this method. For FFA quantitation, 50 to 100 µl of the plasma were mixed with 4 ml of chloroform:hexane:methanol (4:3:2) on the day of the experiment and stored at -25°C for later FFA analysis by the method of Smith (25).

**Kinetic Analysis**

The data from FFA turnover experiments were analyzed with simple, 2-pool models to estimate the IDR’s. The fitting of the models to data and the estimation of fractional and transport rates were accomplished by using the SAAM (Version SAAM 25) program (6) and an IBM 360/91 computer. The basis and assumptions involved in this type of analysis have been reviewed elsewhere (1).

**Effect of Storage on Plasma FFA Values**

In confirmation of previous reports of increases in plasma FFA during storage (12, 28), we observed increases of 2 to 5%/min in mouse plasma FFA concentrations at ambient temperatures immediately after sampling. Plasma FFA concentrations increased to 171 and 134% of the original levels after 4 and 14 days, respectively, of frozen storage (-25°C). Attempts to inhibit the in vitro production of FFA with either Triton WR 1339 (4 to 20 mg/ml serum (24) or NaCl (1.0 M) resulted in no more than 20% inhibition with either the Triton or the highest concentration of Triton. The rate of FFA accumulation in vitro was also independent of the presence of RBC or of anticoagulant (heparin or EDTA). No detectable increase in FFA concentration was observed when plasma was stored at -25°C after mixing with the extraction mixtures used in the FFA isolation methods of either Smith (25) or Hagenfeldt (14).

When plasma was left standing at ambient temperature for 90 min, the plasma FFA specific activity was reduced by 25%. However, storage of plasma for 2 weeks at -25°C increased the specific activity by 50%. Thus special precautions must be taken not only to prevent erroneous plasma FFA quantitation but also to eliminate error in determination of radioactive FFA remaining in the plasma after i.v. injection of tracer. This error is most serious at later times in our study when TGFA is maximally labeled and very little radioactivity remains in plasma FFA. Under these conditions, if the TGFA were to be hydrolyzed in vitro, erroneously high levels of labeled FFA would result. This could lead one to conclude, incorrectly, that the degree of FFA recycling in vivo is greater than it actually is; it could also lead to distortions of the FFA disappearance curve such as may have occurred in some of our earlier studies (5).

**RESULTS**

**Plasma FFA Levels in Control and Tumorous Mice under Varying Nutritional and Dietary Conditions.** Plasma FFA concentrations and pool sizes of mice under varying dietary conditions are shown in Table 1. Pool sizes (total µEq plasma FFA per mouse) were calculated by multiplying µEq FFA per ml plasma by plasma volume (ml/mouse). Plasma volumes have been previously determined to be 5% of body weight for both control and tumorous mice (5). Low FFA levels were demonstrated in plasma taken at 8 a.m. from control mice fed ad libitum overnight; however, tumorous mice under the same conditions had elevated plasma FFA. By 10 a.m., plasma FFA levels of both control and tumorous mice were elevated. Mice on the 58% glucose, fat-free diet showed essentially the same plasma FFA concentration and pool sizes as those on Purina chow. The inability to demonstrate low plasma FFA levels in ad libitum-fed tumorous mice led us to do controlled feeding experiments to determine whether or not the tumorous animals would show a postmeal drop in plasma FFA pool sizes similar to that in controls. The results of several such experiments were pooled and are shown in Chart 1. As described in "Materials and Methods," the mice were trained to eat a 58% glucose, fat-free meal; 15 min after the first nibble, orbital blood samples were taken at 10- or 15-min intervals. Although tumorous mice ate an average of 20% less of the test meal

<table>
<thead>
<tr>
<th>Mice</th>
<th>Dietary state</th>
<th>Concentrations (µEq/ml)</th>
<th>Pool size (µEq/mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (11)</td>
<td>Ad libitum-fed (8 a.m.)</td>
<td>0.16 ± 0.09c</td>
<td>0.27 ± 0.15</td>
</tr>
<tr>
<td>Tumorous (10)</td>
<td>Ad libitum-fed (8 a.m.)</td>
<td>0.57 ± 0.18d</td>
<td>1.18 ± 0.48d</td>
</tr>
<tr>
<td>Control (11)</td>
<td>Ad libitum-fed (10 a.m.)</td>
<td>0.47 ± 0.13</td>
<td>0.82 ± 0.19</td>
</tr>
<tr>
<td>Tumorous (5)</td>
<td>Ad libitum-fed (10 a.m.)</td>
<td>0.42 ± 0.19</td>
<td>0.93 ± 0.39</td>
</tr>
<tr>
<td>Control (18)</td>
<td>6-hr-fasted</td>
<td>0.60 ± 0.22</td>
<td>1.00 ± 0.42</td>
</tr>
<tr>
<td>Tumorous (18)</td>
<td>6-hr-fasted</td>
<td>0.71 ± 0.19</td>
<td>1.65 ± 0.51d</td>
</tr>
<tr>
<td>Control (18)</td>
<td>16-24-hr-fasted</td>
<td>1.18 ± 0.43</td>
<td>1.90 ± 0.61</td>
</tr>
<tr>
<td>Tumorous (18)</td>
<td>16-24-hr-fasted</td>
<td>0.91 ± 0.21</td>
<td>1.86 ± 0.38</td>
</tr>
</tbody>
</table>

* Purina laboratory chow diet.
* Numbers in parentheses, number of mice.
* Mean ± S.D.
* Significantly different from control mice, p ≤ 0.01.
than did controls (200 versus 250 mg), the plasma FFA pool sizes declined in both groups from a fasting level of approximately 1.8 μEq/mouse [0.97 ± 0.06 (S.E.) μEq/ml plasma] to <0.8 μEq/mouse (0.37 ± 0.02 μEq/ml plasma) in 15 min. Thus the cancerous mice showed a prompt response (lowering of plasma FFA) when fed a high-carbohydrate test meal. The response was the same as that of the control mice.

**Turnover of Plasma FFA in Fed and Fasted, Control and Tumorous Mice.** The conditions established for inducing low and nearly constant plasma FFA levels in control and tumorous mice allowed us to study FFA turnover in mice under clearly defined nutritional states. The rates of disappearance of i.v. injected [1-14C]palmitate complexed to mouse serum albumin were determined during a 30-min period in both control and tumorous mice under the following nutritional conditions: (a) fasted 16 hr and (b) fasted 16 hr and then fed a 250-mg test meal. In the latter case the tracer was injected 15 min after the animals started to eat their test meals. The tracer study was carried out in the subsequent 30-min period, during which time the plasma FFA pool sizes remained constant, as shown in Chart 1. The disappearance curves of plasma 14C-labeled FFA following the i.v. injection of [1-14C]palmitate in controls and tumorous-bearing mice are shown in Chart 2. The fractional rate constants (min⁻¹) shown in the models are also common to both controls and tumorous mice and are derived from a least-squares fit of the corresponding models to the data (see text). Points are from 2 experiments and represent the mean ± S.E. (bars) of 7 mice per point, except for 30-min points which are the means of 18 to 22 mice per point.
of the composite data shown in Chart 2 indicated that
approximately 200% of the plasma FFA was removed each
min; 120%/min was removed "irreversibly," and 76%/min
was transferred to a compartment from which 6%/min
of the composite data shown in Chart 2 indicated that
approximately 200% of the plasma FFA was removed each
min; 120%/min was removed "irreversibly," and 76%/min
were observed between cancerous and control mice in
there were no significant differences between control and
tumorous mice in either nutritional state and that the FIDR's
This difference was reflected in the rate constants derived
recycled back to the plasma FFA compartment.

A similar presentation of data derived from the fasted-
refed mice is shown in Chart 2B. Again, no evidence of a
faster fractional removal of labeled FFA from the circulation
was found in the cancerous mice; if anything, radioactive
FFA tended to disappear faster from the plasma of the
control mice. However, as in the fasted mice, no significant
difference in the rates of disappearance between control
and cancerous fed animals was observed.

The initial fractional disappearance of labeled FFA was
faster in the fed than in the fasted mice. Thus, at 30 sec
after tracer injection, about 80% of the dose had been
removed in the fed mice (cf. 65% in the fasted animals).
This difference was reflected in the rate constants derived
from our compartmental analysis of the data. Three
hundred %/min of the plasma FFA was removed in the fed
mice (cf. 200%/min in the fasted mice); 150%/min of the
plasma FFA was removed irreversibly in the fed mice (cf.
120%/min in the fasted mice); and, in the fed mice, 160%/min
of the plasma FFA was transferred to an "extraplasma
FFA" pool that recycled FFA to the plasma (cf. 76%/min
in the fasted mice), as shown in the models depicted in Chart
2, B and A, respectively.

The FIDR of plasma FFA corresponds to the arrow leaving
Compartment 1 (Chart 2) irreversibly (i.e., not going to
Compartment 2). The separate mean values for the FIDR for
controls and cancerous mice, based upon the data in Chart
2, are summarized in Table 2. We have already noted that
there were no significant differences between control and
tumorous mice in either nutritional state and that the FIDR's
were somewhat faster in the fasted-refed mice than in the
fasted animals. When the FIDR's were multiplied by the
by the corresponding total plasma FFA pool sizes (Table 2),
the resultant irreversible transport rates (μEq FFA per min per
mouse) showed the reverse relationship; i.e., the fasted
mice produced and removed plasma FFA twice as rapidly
as did the fed mice. These differences were highly signifi-
cant (p = 0.005). However, no differences in these rates
were observed between cancerous and control mice in
either nutritional state.

DISCUSSION
The view that a growing cancer causes an enhanced
mobilization of depot triglycerides, that the cancer feeds off
of the resultant circulating FFA, and that the cancer literally
drains the host of its lipid stores is common (10, 16, 26).
However, the transport rate of circulating plasma FFA to at
least one type of tumor is known to be extremely slow,
although in this case the cancer (Ehrlich ascites carcinoma)
is one of the fastest growing experimental tumors (17). This
observation coupled with recent evidence that FFA turnover
in plasma is unaffected by cancer growth, both in fasted
mice (5) and in humans (11, 21, 30), casts doubt on one of
the commonly expressed views of fat metabolism in cancer-
bearing animals. However, some subtle, cancer-induced
defects in the regulation of the host's lipid metabolism can
be envisaged. In this regard, several authors have presented
strong evidence indicating that cancer patients may have
depressed glucose tolerance (7, 8), increased insulin resist-
ance (8), and defects in the metabolic response to a glucose
load (11). We have hypothesized that a similar defect occurs
in mice bearing the Ehrlich ascites carcinoma and that this
defect would manifest itself by an abnormality in the regu-
lation by dietary carbohydrate of FFA mobilization. Thus
the high levels of plasma FFA, observed previously in
cancerous mice fed ad libitum (5, 9), could have reflected
an inability of dietary carbohydrate (and subsequent endog-
ogenous insulin release) to suppress FFA mobilization from
fat depots.

We have obtained 2 new lines of evidence that bear on
our hypothesis. First, although our cancerous mice differed
from normals in that they had elevated plasma FFA levels at
8 a.m., the high levels of FFA that occurred after a 16-hr
fast were promptly reduced by ingestion of a small, glucose-
rich test meal. The rate of fall of plasma FFA levels was almost identical in both groups of
fasted and refed mice (5) and in humans (11, 21, 30). Second, the response to glucose feeding in both cancer-
ous and control mice undoubtedly reflects a decrease in
lipolysis and/or an increase in the esterification rate of FFA
within the adipocyte (27). [Measurements of total rates of
lipolysis, which would require analysis of glycerol turnover
(15), were not done in the present study.] Since the fall of
plasma FFA levels was almost identical in both groups of

Table 2
Effect of dietary glucose on plasma FFA IDR's in control and tumor-bearing mice

<table>
<thead>
<tr>
<th>Mice</th>
<th>Dietary state</th>
<th>Plasma FFA pool size (μeq/mouse)</th>
<th>FIDR (min⁻¹)</th>
<th>Irreversible transport rate (μeq/min/mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (19)</td>
<td>16-hr-fasted</td>
<td>1.69 ± 0.53</td>
<td>1.2 ± 0.06</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>Tumor-bearing (19)</td>
<td>16-hr-fasted</td>
<td>1.82 ± 0.42</td>
<td>1.2 ± 0.02</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Control (19)</td>
<td>Fasted-refed glucose</td>
<td>0.69 ± 0.37</td>
<td>1.5 ± 0.23</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>Tumor-bearing (22)</td>
<td>Fasted-refed glucose</td>
<td>0.69 ± 0.52</td>
<td>1.4 ± 0.06</td>
<td>1.2 ± 0.7</td>
</tr>
</tbody>
</table>

a Numbers in parentheses, number of mice.
b Mean ± S.D.
c Fasted 16 hr and refed a 58% glucose, fat-free test meal for 10 min. The experiment was carried out between 15 and 45 min after the re-fed mice began eating their 10-min test meals.
d Significantly different from the corresponding 16-hr-fasted group, p ≤ 0.005.
mice, we assume that the release of FFA by adipose and other tissues had been reduced equally in both groups. This was confirmed by tracer studies with [1-14C]palmitate. The IDR's in the fasted state were equal in control and cancerous mice. In contrast to some of our earlier experiments (5), no irregularities in the tracer kinetics at later times were observed, and data analysis was straightforward. Thus both tracer kinetics and the dynamics of pool size change provide independent and consistent evidence to support the view that cancerous mice respond normally to a glucose load by reducing FFA turnover. This implies that the normal, complex control mechanisms are not grossly altered by tumor growth. Our data do not establish that the rate of FFA formation is comparable in cancerous and control mice when they eat ad libitum. Clearly, the FFA production rate in both groups could vary depending upon the amount of food eaten.

Finally, we may relate the present plasma FFA IDR's to our earlier estimates of FFA transport to the Ehrlich ascites tumor. Values for plasma FFA transport (IDR's) are clearly greatest in the fasted mice. The rates observed for fasted mice in the present study are almost exactly equal to those we published earlier (5). Therefore we have now completed 2 independent studies of FFA turnover in plasma and 2 independent studies of FFA transport from plasma to the tumor (5, 20). Comparison of these data shows that no more than 1% of the plasma FFA that is irreversibly removed from the circulation is transferred to the tumor for its growth and energy needs. This observation is consistent with our view that body fat is lost due to prolonged inanition rather than to any "draining effect" that results directly from cancer growth.

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