Uncomplicated Starvation versus Cancer Cachexia

Murray F. Brennan

Section of Surgical Metabolism, Surgery Branch, National Cancer Institute, NIH, Bethesda, Maryland 20014

Summary

Host starvation is a common accompaniment to the presence of cancer. Diminished intake is a major contributor to this starvation and does not require that the oropharynx or gastrointestinal tract be the primary site. There is suggestive evidence that the normal adaptive mechanisms of the nontumor-bearing host to starvation that result in body protein conservation are not functioning in the tumor-bearing host. Cancer cachexia has some similarity to the metabolic disturbances of host metabolism that are seen in major injury or sepsis. The growing tumor shows little respect for normal constraints of host tissue growth. With the widespread availability of methods of total parenteral nutrition, the interrelationship of nutrition and host-tumor growth assumes greater importance.

The starvation that accompanies cancer is so well-recognized as to be entitled "cancer cachexia." Cachexia alone—that syndrome of emaciation, debilitation, and malnutrition—is seen in many other diseases, but, apart from thyroid disease, none ennobled as a distinctive cachexia entity. The significance of such cachexia has long been neglected, but with the advent of an effective means of reversal by aggressive use of i.v. total parenteral nutrition, cancer cachexia is no longer obligatory (7).

To determine whether or not the starvation that accompanies cancer is an entity of itself, or simply a manifestation of the malnutrition that accompanies any severe illness, is difficult. Patients with gastrointestinal neoplasms have a clear reason for malnutrition, i.e., inadequate intake based on organic pathology that prevents either the ingestion or digestion of food. In the gastrointestinal tract, however, weight loss is often seen as a reflector of a "hidden" cancer such as cancer of the pancreas. In other small primary lesions not involving the gastrointestinal tract, such as carcinoma of the lung, weight loss is a similar, almost invariable accompaniment of the presence of cancer. The degree of debility and malnutrition often seems to far exceed that which might be reasonably expected on the grounds of the extent of the neoplastic process.

To examine the problem of cancer cachexia, basic body composition, energy and protein reserves, and the effect of simple starvation on these entities must be reviewed before examining the effect of superimposition of cancer.

As a result of the work of Moore et al. (18, 20) and Cahill et al. (5, 6), which has recently been reviewed (19), we can make some statements about body composition and body tissue reserves. Table 1 gives the distribution of the body cell mass as it is divided into muscle, viscera, supporting tissue, and the red cell mass. Body cell mass makes up approximately 55% of total body weight and is equivalent to about 10 to 13 kg of actual protein. Caloric stores, on the other hand, are predominantly maintained in the 13 or 14 kg of fat that the well-developed, often mythical 70-kg man carries around (Chart 1).

In acute starvation, there is early rapid proteolysis with amino acid mobilization from muscle, gluconeogenesis, and the production of urinary urea nitrogen. This urinary urea nitrogen, about 12 g a day, is equivalent to the loss of approximately 75 g of muscle protein, or 320 g of wet muscle mass. The continuation of this simple starvation catabolism of muscle mass would mean that, in 10 days of unabated loss, 15% of the total muscle mass would be lost; unabated for 20 days, 30% of the muscle mass would be totally consumed.

Obviously, this process does not continue in as rapid a catabolic fashion as man undergoes adaptation to starvation. His initial urinary losses of nitrogen fall back and are reflected, not just as urea, but predominantly as ammonia nitrogen. Renal ammoniagenesis from glutamine increases to aid excretion of the excess acid resulting from utilization of the ketones, β-hydroxybutyrate and acetoacetate, as fuel (2, 22). This starvation adaptation is accompanied by the ability of the brain to adapt to the use of ketone bodies (23). Some small quantities of glucose are still produced by gluconeogenesis, but the drain on muscle is markedly diminished, with total urinary nitrogen falling to approximately 3 g/day. Man has, by this adaptation, begun to live off his major source of stored energy, fat. With adaptation, chronically starving man will lose approximately 400 g of muscle mass in 20 days, or about 2% of total body muscle mass, allowing survival for long periods of time in the chronic fasting state.

The situation changes considerably with the superimposition of any major insult. With major injury, the ability to continue to conserve lean tissue masses is lost, and the patient moves into a hypercatabolic state in excess of that seen with acute fasting. It should be emphasized that, when speaking of major injury or insult, we are not talking of the mild elective operation taking place in a fit, healthy person, where nitrogen losses and subsequent lean tissue mass loss are often little different from the effects of acute fasting (1). This injury may be a major surgical procedure or a major episode of sepsis. The most classical examples are seen in major burns, but are not uncommonly seen in patients with and without cancer who have major septic episodes. The acute tissue mass loss from severe trauma, which may

1 Presented at the Conference on Nutrition and Cancer Therapy, November 29 to December 1, 1976, Key Biscayne, Fla.
theoretical calculations and predictions are made to de
of the body store of protein.

reach as great as 15 to 20 g of nitrogen per day is, in fact, equivalent to 400 to 500 g of wet muscle mass (9). Such an insult, if perpetuated for 10 days, can result in a loss of 23% of the total lean tissue mass and a comparable percentage of the body store of protein.

These metabolic events are summarized in Table 2, where theoretical calculations and predictions are made to describe the length of time required under varying conditions of starvation that would result in loss of 50% of either the total muscle mass or the total body cell mass. It can be seen that the addition of sepsis or major injury results in rapid catabolism and must be accompanied by the rapid demise of the patient unless arrested and/or corrected. Looked at in a different way, we can more simply gauge these losses as they are reflected by body weight change. A single, prolonged episode of major sepsis extending over 30 days can result in the loss of 30% of total body weight (Table 3). Many studies have attempted to quantitate weight loss with loss of lean tissue. It would appear that, regardless of the amount of weight loss, protein makes up approximately 10% of the total, and fat, 20% (14). From these and other studies, attempts have been made to correlate weight loss with survival (26). It has been suggested that 30% body weight loss is almost invariably fatal; however, the rare patient may survive weight loss as extensive as 50% of total body weight. The converse is also true, in that other catabolic patients are seen who have lost a lesser percentage of their body weight in a rapid, fulminating course that has preceded death. It is the rapidity and severity of the weight loss that is the most reliable predictor of outcome. It should be emphasized that many patients that are thought to be chronically starving have been admitted to a hospital and rehydrated, thereby often showing much less weight loss than one might expect for the length of relative starvation. This is not to be falsely interpreted, as many of these patients merely reflect the electrolyte and fluid retention that accompanies rehydration following long-term, or even short-term, starvation. This is commonly seen with the acute weight gain that accompanies the first few days of parenteral hyperalimentation (Chart 2).

The addition of cancer to the situation makes interpretation much more difficult. All of the events previously described may occur in the cancer patient, but the important questions are (a) is the patient starving primarily because of lack of intake, or inability to digest and absorb? and (b) does the cancer patient adjust to starvation as does normal man? There is little question that, in many cancer patients, much of the weight loss and apparent starvation can be directly attributed to the lack of intake that is now readily reversible by the use of TPN\(^2\) (7). The typical intake of a group of inpatient patients over the 2 weeks preceding commencement of TPN is illustrated in Table 4. This highly select group emphasizes what little intake many inpatient cancer patients receive either as a consequence of their primary disease, or related to the side effects of their aggressive therapy. Most of these patients had already received a 2-week course of aggressive nutritional repletion p.o. where possible, using liquid and elemental oral dietary formulas. Support for the fact that this group of patients were nutritionally depleted, even after these attempts, is reflected in their weight loss (Table 5). Unfortunately, the ability to characterize degrees of malnutrition in these complex patients on multimodality therapy is difficult. Standard parameters of protein and albumin concentrations are poor reflectors of protein synthesis and can be widely distorted by intravascular volume depletion and the use of albumin infusion as a means of volume expansion (Table 6). These difficulties are indicated by the wide range of values for conventional determinants in a group of cancer patients prior to instigation of TPN, rendering such profiles of little value in generic terms. In individual patients, however, these determinations (corrected for renal function and volume dependence) and those of the acute phase reactants, trace metals and vitamins, can provide biochemical support for clinical malnutrition.

There is considerable evidence that a specific tumor-induced anorexia and inadequate intake are present in a large percentage of patients with cancer (4, 10, 11). This particular syndrome has been examined on many occasions experimentally (3, 17) and has led to various experiments designed to modify and examine the hypothalamic mechanisms that control food intake. There seems to be little good evidence that invasive mechanisms can arrest the hypophagia. Clinically, the vicious cycle of decreased intake, decreased motor activity, lethargy, apathy, and further decreased food intake is a common event. Other workers (21) have attempted to correlate food intake during tumor growth with the progressive incapacity to undertake the

---

Footnote: 2 The abbreviation used is: TPN, total parenteral nutrition.
Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nitrogen loss/day (g)</th>
<th>Equivalent protein loss (g)</th>
<th>Equivalent lean tissue (g)</th>
<th>Days to lose 50% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute starvation</td>
<td>10</td>
<td>63</td>
<td>280</td>
<td>41</td>
</tr>
<tr>
<td>Chronic starvation</td>
<td>3</td>
<td>19</td>
<td>84</td>
<td>137</td>
</tr>
<tr>
<td>Sepsis/major injury</td>
<td>20</td>
<td>125</td>
<td>560</td>
<td>21</td>
</tr>
<tr>
<td>Month prior starvation + sepsis</td>
<td>15</td>
<td>94</td>
<td>420</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>30-day wt loss* (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen loss/day (g)</td>
<td></td>
</tr>
<tr>
<td>Acute starvation</td>
<td>10</td>
</tr>
<tr>
<td>Chronic starvation</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis/major injury</td>
<td>20</td>
</tr>
<tr>
<td>Pre-illness</td>
<td></td>
</tr>
<tr>
<td>Pre-TPN</td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td></td>
</tr>
</tbody>
</table>

* Often minimized by water and electrolyte gain.

A, assumed appropriate energy expenditure: 1, 1500 cal/day; 2, 1200 cal/day; 3, 3500 cal/day. B, stable energy expenditure of 1800 cal/day.

motor activity of feeding. While this entity clearly appears to exist, it cannot always account for the major portion of the decrease in food intake in the animal model. It should be emphasized that reduction in food intake in the normal animal has no effect on the total motor activity, so that it can be inferred that decline in activity of the tumor-bearing animal is not a consequence of the decline in food acquisition per se.

The second question is whether or not the tumor-bearing host can adapt to chronic starvation in the manner seen in normal man. In chronic starvation, with conversion to a "fat fuel economy," one sees a decrease in oxygen consumption and a greater decrease in carbon dioxide production, so that the respiratory quotient falls toward 0.7. In the tumor-bearing host, there is some evidence that the fall in CO2 production (30) does not occur. While these changes are small, when taken in the light of a chronic, malnourished tumor-bearing host, they become of much greater
significance. In a similar manner to the studies performed in trauma (16) where the quantity of $^{14}$C-labeled gluconeogenic precursor appearing as glucose was examined, studies in the tumor-bearing host have suggested that the ability of simple substrates to decrease gluconeogenesis in the cancer-bearing host are to some degree impaired. In addition, there is an increase in the apparent recycling of pyruvate and lactate to glucose (28), an increased oxidation of labeled acetoacetate by neoplastic tissues (30), and a slower disappearance rate of glucose in the cancer-bearing host, which is consistent with other data on impaired glucose tolerance. In vitro, there is an increase in $[^{14}$C]$\text{glucose}$ appearance from amino acid precursors in tumor tissue (25). This is surprisingly analogous to the situation seen in severe sepsis (16). A voluminous literature exists as to the presence or absence of multiple abnormalities of substrate metabolism in the tumor-bearing host (8, 12, 13).

More supportive evidence for the inability to arrest normal amino acid-derived gluconeogenesis and inferential evidence as to the existence of increased metabolic need in the cancer patient can be seen by examining some patients who are fed TPN i.v. during their cancer course (Chart 2). Despite the ingestion of 3000 to 4000 cal in a patient with diffuse histiocytic lymphoma, and adequate quantities of nitrogen (Chart 3), no weight gain was obtained, although weight loss was not manifest. The patient was not hypermetabolic from conventional causes, such as increased stress or exercise, and was afebrile and biochemically stable, factors not exclusive of but suggesting the absence of sepsis. The measured basal metabolic rate in this patient was only minimally elevated at 115% of predicted normal. The analogy to the postoperative patient is seen in Charts 4 and 5, where a patient 2 weeks poststernal resection for osteogenic sarcoma is unable to be maintained by peripheral nitrogen and nonprotein calories, and, even with the addition of 3500 cal and 15 g of nitrogen, barely maintains weight and nitrogen balance. Such observations raise the question as to whether the apparent continued increase in caloric need of such patients is a reflector of the continued presence of neoplasia. Forced-feeding experiments p.o. in patients with cancers (28) emphasize the often increased calories and nitrogen that are required for positive energy and nitrogen balance, in malnourished, inactive, near-terminal patients. This variability of need is also seen in patients fed i.v. (Charts 2 to 5). Calculations of oxygen consumption in other studies have further suggested that the decreased oxidative metabolism that appears in normal patients with starvation is not seen in the cancer patient (11).
Uncomplicated Starvation versus Cancer Cachexia

In the animal model, starvation has been found to decrease total-body and liver weight in the animals bearing a Flexner-Jobling carcinoma. Tumor weight during the period of starvation increased over prefasting control but increased to a lesser (although not significant) extent than the comparable fed control (15). Liver weight in these studies fell in the fasting tumor-bearing animal, whereas liver and tumor protein were the same in both fed and fasted tumor-bearing animals. In our own laboratory, we have attempted to obtain more accurate information (about cell cycle activity) than that reflected by tumor volume and tumor weight determinations. The latter determinations are imprecise and cannot correct for areas of necrosis and hemorrhage. With the use of a transplantable methylcholanthrene implanted s.c. in the thigh, the effects of brief-to-moderate (24 to 96 hr) total starvation has been examined (25). Standard growth curves for tumor- and nontumor-bearing animals have been constructed (Chart 6) and the effect of starvation has been described, combining determinations of tumor volume and tumor weight at the time of sacrifice. A regression line has been developed (Chart 7) that allows some prediction of tumor weight according to tumor volume prior to sacrifice. With the use of these calculations, very little difference in total body weight between tumor-bearing and nontumor-bearing animals can be determined up to a time where the tumor was less than 7% of total body weight. During this time, there was no change in water content of the tumors. When one came to examine the effect on tritiated methyl thymidine incorporation into DNA corrected for quantity of DNA present, i.e., “specific activity” of DNA, some considerable changes were evident (Chart 8). The tumor increased its specific DNA activity throughout starvation, whereas the specific activity decreased in the liver DNA of both the tumor- and nontumor-bearing animals.

These data suggested to us that this was a further example of the failure of the tumor to recognize normal host controlling mechanisms and, in the presence of host starvation, the tumor was able to maintain its activity at the expense of the host. It should be emphasized that this was at a

---

* J. T. Goodgame, Jr., S. F. Lowry, J. J. Reilly, Jr., D. C. Jones, and M. F. Brennan. The Effect of Starvation on Tumor Activity and Host Growth, submitted for publication to CANCER RESEARCH.
time when the tumor effects alone on the host were not clinically manifest. As starvation proceeds, the tumor-bearing host is further required to support tumor activity at the expense of the host.

In summary, then, the tumor-bearing host seems less well-adapted to respond to an added insult of starvation than the nontumor-bearing host. The nontumor-bearing host has clearly defined mechanisms to conserve lean tissue mass and to preserve total body protein. The tumor-bearing host seems less well able to utilize these lean tissue-conserving mechanisms and to decrease gluconeogenesis from protein stores in the presence of host starvation. This results in ongoing lean tissue mass destruction. These aspects in a tumor-bearing host are invariably compounded by a decrease in intake and a variable decrease in efficient utilization of ingested nutrient.

The tumor, on the other hand, shows considerable disarray for any attempts at limitation of growth by substrate restriction of the host.

I would suggest that at the present time there is considerable information that would support and encourage the nutritional support of the host while other adjuvant methods of attacking the tumor are used.

Whether or not nutritional support of the host will allow more efficacious use of such adjuncts and consequent prolongation of meaningful survival remains to be critically examined.

Acknowledgments

Much of the work referred to here would not have been possible without the active support of Dr. Francis D. Moore, Dr. George F. Cahill, Dr. J. T. Goodgame, Jr., Dr. S. F. Lowry, Dr. J. J. Reilly, Jr., C. Gorschboth, M. Maher, D. White, and G. C. Jones.

References


Uncomplicated Starvation versus Cancer Cachexia

Murray F. Brennan


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/37/7_Part_2/2359

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.