Feeding Response to Change in Absorbable Food Fraction during Growth of Walker 256 Carcinosarcoma

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SUMMARY

Normal animals ingest larger amounts of food diluted with nonnutritive bulk than they do undiluted food, to the extent that nutrient intake remains almost constant. This compensation is complete up to dilutions of 50% and is evident, although incomplete, at 75% dilution. The normal hyperingestive response to 50% diet dilution is depressed within the 1st week of growth of Walker 256 carcinosarcoma, when the tumor weighs about 200 mg. In the 3rd week of tumor growth, when the tumor weighs about 40 g, there is no hyperingestive response to any level of food dilution. At 75% dilution, food intake is depressed to 25% of the intake of the undiluted diet. Dilution of food with unabsorbable bulk is an experimental homolog of uncomplicated malabsorption. These results show that malabsorption associated with tumor growth may contribute to cancer cachexia by virtue of the blocking by the tumor of the normal physiological hyperingestive response to reduction of the absorbed fraction of ingesta.

INTRODUCTION

From time to time, it has been suggested on the basis of both clinical and experimental studies that malabsorption arising from mucosal and villous abnormalities of the gut may be a significant cause of the development of cancer cachexia (4-6, 11, 12, 17, 24, 25, 27, 30). Since cachexia (or at least its central and definitive feature, wasting) must be a result of failure of ingested and utilized nutrient to meet total need, it is superficially plausible that this imbalance could arise from absorptive defects. However, the malabsorption that can be shown to occur in most cachectic cancer is small, and the changes in gut mucosa and villous architecture are slight and even doubtful (11, 17, 29). More importantly, the intake-expenditure imbalance often arises predominantly from a decline in food intake, whether or not there is also a contribution from increased need (14, 17, 19, 23), and there is no a priori reason why malabsorption by itself should depress food intake.

The essential feature of malabsorption is a reduction in the absorbed fraction of the ingesta. An experimental homolog of malabsorption can be produced by dilution of food with nonabsorbable bulk. By this method, reduction of the absorbed fraction is imposed externally, rather than arising internally from reduced absorptive capacity of the gut, and thus is not complicated by the associated and antecedent features of malabsorptive disease. Normal animals respond to such dilution by increasing their bulk ingestion to an extent that maintains nutrient intake constant (1, 7, 9, 10, 15, 16, 28). The expected response to uncomplicated malabsorption would also be a compensatory increase in amount ingested. In thyroid hormone-induced steatorrheic malabsorption, food intake increases to meet the induced increase in metabolic rate and the induced malabsorptive loss (18). In steatorrhea produced by retrograde jejunal diverticula, food intake and rate of gain of body weight are depressed, but there is no progressive hypophagia or wasting (13).

If malabsorption in cancer contributes substantially to the cachexia, it must do so by selective malabsorption of specific nutrients, or because the tumor, as well as inducing malabsorption, also blocks the normal hyperingestive response to reduced absorption. The last possibility is examined in this paper by use of the dilution of food with nonnutritive bulk as an experimental homolog of malabsorption.

MATERIALS AND METHODS

Animals and Tumors. Adult, male Sprague-Dawley rats were used. Body weight, food intake, and water intake were measured 6 times a week for 21 days before transplant of tumor and for 28 days of tumor growth. The method of s.c. inoculation and of assessment of growth of Walker 256 carcinosarcoma was as previously described (22). The rats were killed on the 28th day after tumor transplant (or, in the case of nontumor-bearing controls, the equivalent 28th day) and the tumors were excised and weighed.

Diet. The basic diet, C21, was a casein-based, semisynthetic diet (21% casein, 50% carbohydrate, 25% fat, and adequate minerals and vitamins) of a smooth consistency (20). This diet has a gross energy of 5.4 kcal/g and a metabolizable energy for rats of 4.8 kcal/g (21). The nonnutritive diluent was a 50:50 (w/w) mixture of ground cellulose (Alphacel; Nutritional Biochemicals Corp., Cleveland, Ohio) and mineral oil. This diluent has the same consistency as the basic diet; therefore, acceptance of the diluted diets was not complicated by texture preferences of the rats (8). The 4 dilution levels used in the 1st experiment were (diluent : diet): 0:100 (undiluted basic diet); 25:75; 50:50; and 75:25. In the 2nd experiment, only the basic diet and the 50:50 dilution were used.

Procedure. The rats were housed individually and were allowed food and water ad libitum at all times.

In the 1st experiment, the rats were 62 days old and weighed 350 g at the time of transplant. One group of 5 tumor-bearing rats was subjected to 1 of the 4 dilutions (0, 25,
50, 75%) for 1 week before tumor transplant and for the 3rd week after tumor transplant. A nontumor-bearing group of 3 rats was subjected to the 50% dilution for the same equivalent periods.

In the 2nd experiment, the rats were 70 days old and weighed 350 g at the time of transplant. One group of 5 tumor bearers was given the basic diet throughout; 3 other groups of 5 were given 50% diluted diet for the 1st, 2nd, or 3rd week of tumor growth. One nontumor-bearing group was given the 50% diluted diet for the equivalent of the 3rd week after transplant, and another was given the dilute diet for the equivalent of the 2nd week before and 3rd week after transplant.

RESULTS

The diets at 0, 25, 50, and 75% dilution gave crude, unabsorbed fractions (fecal dry matter/ingested dry matter) of 6, 30, 54, and 67%, respectively.

![Chart 1](Image)

**Chart 1.** Feeding response to diluted food before transplant of tumor and in the 3rd week of tumor growth. •, bulk intake; ○, nutrient intake: ▲, △, average of 7 days on diet; ○, average of last 3 days on diet; ▲, △, 7- and 3-day average intakes of nontumor-bearing control group subjected to diluted diet at the equivalent of the 3rd week of tumor growth. All values expressed as % of undiluted food intake for the same period (average, 14.0 g/day before transplant; 14.6 g/day during 3rd week of tumor growth). Data from Experiment 1.

**Experiment 1.** Before tumor transplant, bulk intake of food increased up to and including 50% dilution, with only a slight fall in nutrient intake (Chart 1). At 75% dilution, bulk intake fell from its maximum but was still substantially above the bulk intake of the undiluted food, and nutrient intake fell markedly (Chart 1).

The hyperingestive response to the dilute diets took 3 or 4 days to develop fully. The bulk intake for the last 3 days of the treatment period showed almost complete adaptation to the dilution with no significant fall in nutrient intake until the dilution exceeded 50% (Chart 1).

During the 3rd week of tumor growth, the animals showed barely any hyperingestive response to any dilution level and showed a fall to about 25% of normal (undiluted) bulk intake at the 75% dilution level (Chart 1). Nutrient intake fell with increasing dilution level, reaching less than 10% of undiluted intake at the 75% dilution level (Chart 1). The depression of response below normal was statistically significant overall (p < 0.001) and for the 25% dilution considered alone.

![Chart 2](Image)

**Chart 2.** Response of bulk food intake to 50% diluted diet at successive stages of tumor growth. •, av. of 7 days on diet; ○, av. of last 3 days on diet; ▲, △, 7- and 3-day av. intakes of nontumor-bearing control group subjected to diluted diet at the equivalent of the 3rd week of tumor growth. All values expressed as % of undiluted food intake for the same period (average, 15.2 g/day before transplant; 14.6 g/day during 3rd week of tumor growth). Data from Experiment 2.
Effect of time difference and repetition of treatment on response of normal rats to 50% dilution of food

Bulk intake of dilute diet is expressed as % bulk intake of undiluted diet.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Group</th>
<th>No. of rats</th>
<th>2 wk before equivalent transplant</th>
<th>3 wk after equivalent transplant</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td>7 days</td>
<td>Last 3 days only</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>5</td>
<td>166</td>
<td>193</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>3</td>
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<td>5</td>
<td>155</td>
<td>182</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>4</td>
<td>128</td>
<td>156</td>
</tr>
</tbody>
</table>

Mean ± S.E.

163.3 ± 4.1 189.4 ± 4.6 136.7 ± 5.0 160.3 ± 5.6

($p < 0.05$). At this time, intake of undiluted food was 92% of pretransplant intake, and average tumor mass was 42.8 g (10% of total body weight). The tumor bearers showed no development of response with length of treatment period, so that the last 3 days of treatment during the 3rd week showed no greater response than the period considered as a whole (Chart 1).

**Experiment 2.** During the 1st week after tumor transplant, the feeding response to the 50% diluted diet was depressed below the pretransplant response (Chart 2). At this time, no depression of intake of undiluted food could be detected, and the tumor was barely palpable (estimated average weight, 200 mg; < 0.1% body weight). With tumor growth, the depression of response progressed until in the 3rd week of tumor growth there was no hyperingestive response, in agreement with 1st experiment (Chart 2). The depression of response from normal was statistically significant overall ($p < 0.001$) and for the 1st week of tumor growth considered alone ($p = 0.05$). Nutrient intake on the dilute diet fell correspondingly with growth of the tumor.

**Effect of Size and Age of Rats on Response to Diet Dilution.** The response to 50% dilution of nontumor-bearing controls was less when the dilute diet was imposed at the equivalent of 3 weeks after tumor transplant than when it was imposed at the equivalent of 2 weeks before tumor transplant. The response was not modified by repetition of the treatment (Table 1) but was reduced linearly and significantly with body weight (or age) (Chart 3). Approximately one-third of the total depression of response apparently produced by the tumor can be attributed to the depression associated with increasing body weight (Chart 2).

**Effect of Diet Dilution on Body Weight Increment.** In nontumor bearers, the diets diluted up to 50% produced a transient reduction in rate of gain of body weight, but this rapidly recovered while the animal was still on the diluted diet (Chart 4). The same diets imposed during the 3rd week of tumor growth produced a sustained depression of body weight gain with failure to recover even when undiluted food was restored (Chart 4). This increased depression of weight gain was progressive with degree of dilution (Chart 5a) and with stage of tumor growth (Chart 5b).

Rats with tumors, subjected to 50 or 75% diet dilution in the 3rd week, showed a higher mortality before the end of the 4th week (5/15) than those subjected to 0 or 25% dilution in the 3rd week or to 50% dilution in the 1st or 2nd weeks (1/25).

**Food Intake on Restoration of Undiluted Diet.** For nontumor-bearing rats, the initial food intake on restoration of undiluted diet, relative to the normal intake of undiluted food, increased with the preceding level of dilution (Chart 6a). For the tumor-bearing animals, this increased intake on restoration...
of undiluted food was barely detectable after any dilution imposed during the 3rd week of tumor growth and was negative after 75% dilution (Chart 6a). Intake showed signs of diminishing even after the 1st week at 50% dilution (Chart 6b).

DISCUSSION

The presence of a Walker 256 carcinosarcoma clearly impairs the ability of a rat to compensate for diet dilution. This impairment appears in the earliest stages of growth of the tumor when there is no evidence of depression of intake of undiluted food. At a stage of tumor growth when intake of undiluted food is only slightly depressed, the ability of the rat to compensate for even minimal dilution is totally abolished. In addition, the tumor impairs the ability of a rat to compensate, when undiluted diet is restored, for losses incurred during the dilution regimen.

The procedure of food dilution is an externally imposed experimental homolog of uncomplicated malabsorption. In otherwise normal animals, this leads to a compensatory increase in ingestion with no reduction in nutrient intake (after the adaptation plateau has been attained) and, from the form of body weight increase (Chart 4), no reduction in total utilized nutrient. Complete compensation holds up to an unabsorbable fraction of at least 50%. In rats with Walker tumor, reduction of absorbable fraction does not induce compensatory hyperingestion and rapidly leads to depression and reversal of body weight gain, i.e., to cachexia. Any idiopathic malabsorption that may be associated with tumor growth would therefore be expected to lead in the same way to depression of available nutrient uncompensated by increased ingestion and, hence, to progressive wasting (4, 5, 30). It would be less able to account for a decline in the amount ingested, as this did not occur experimentally until the unabsorbable fraction exceeded 50%. However, the wasting produced by malabsorption would be predominantly an effect of the failure of the animal to make the normal physiological response to reduced absorbed fraction.

The results also indicate that the cachectic process is already
potential at the earliest stage of tumor growth when the tumor mass is trivial. The cachetic process cannot be detected at that time in normal circumstances, but it seems that some features of it can be elicited by suitably loading one of the deficient mechanisms.

Why the tumor bearer does not respond to food dilution is unknown. The facts that the effect can be detected so early in tumor growth and that the food intake of tumor bearers can be rapidly, although temporarily, stimulated by a variety of methods (20, 26, 29) make it unlikely that the failure can be attributed to reduced gut capacity, attenuation of the gut wall (30), or the gastric lesions that develop latterly (2). It is also unlikely to be a consequence of failure of recognized central controls of food intake, as damage to appropriate hypothalamic areas does not seriously interfere either with development of cachexia (3, 22) or with the normal response to food dilution (7, 8).

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REFERENCES

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