Origins of Nutritional Imbalance in Cancer

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Summary

Some parallels and differences are considered between the nutritional circumstances that favor carcinogenesis and those that favor tumor growth and host cachexia. From evidence on deactivation of physiological feeding controls and changes in feeding behavior during tumor growth and from evidence on differences in sets of available feeding controls and in feeding behavior among normal individuals, it is suggested that acquisition of possibly carcinogenic dietary habits may originate, in part, from innate deficits in physiological feeding controls.

There are 2 broad aspects of the interrelationship between cancer and nutrition (Chart 1). In one, the inner loop of Chart 1, it is proposed that the organismic nutritional environment dictates a cellular nutritional environment that is favorable to neoplasia and relatively unfavorable to euplasia. It is this aspect that is being discussed at this conference. The other aspect proposes that, after induction of a tumor, the organismic environment dictates a cellular environment that is favorable to tumor growth and relatively unfavorable to host growth and maintenance. The question can be asked whether these 2 sets of environments are the same, that is, whether tumor growth is favored by the same set of circumstances that favored carcinogenesis initially. Chart 1 is constructed as if these sets of environments were indeed the same.

There are some broad but ill-defined lines of evidence in support of this unitary speculation. Caloric restriction reduces tumor incidence and also inhibits growth of established tumors (26, 31). The same is generally true of protein restriction, but with greater variability in response among tumor types (27, 31). High-fat diet has been proposed to be conducive to the induction of some cancers and to reduce survival with existing cancers (3, 31, 33), and forced feeding of a high-fat diet can accelerate the deterioration of the host (2). Some specific nutrients, such as some vitamins (4, 15, 31) or zinc (5, 24), sometimes appear to have corresponding effects on induction and growth of some tumors, but the evidence of these is often equivocal. On another aspect of the organismic environment, high exercise reduces tumor incidence, inhibits growth of established tumors, and maintains host condition (9).

However, there are some aspects that are superficially not consistent with this notion. Particularly, the tissue depletion of the host, which is the central feature of its deterioration, is directly and quantitatively attributable to progressive hypophagia (13, 17, 19); that is, food intake falls progressively short of metabolic need, and there is no apparent parallel to this in the precancerous state. While this is an organismic deficit, it would be easy to refer it to the cellular level by proposing inability of host cells to utilize available nutrient with depression of food intake following via normal mechanisms of control of food intake.

However, there is now ample evidence that i.v. alimentation of the cancer patient will reverse the cachetic drive, restore the depletion and, to a substantial degree, restore voluntary food intake (29, 30). To a lesser but still considerable extent, this is also true of forced enteral alimentation, although there may be a greater sensitivity to nutrient composition in this case (2, 23). It must be noted here that the composition of the parenteral and enteral aliments used is dictated predominantly by what can feasibly be got into solution and only slightly by the preferred nutrient mixture for the cells, which is largely unknown. The host cells, then, are capable of utilizing effectively and profitably a quite haphazard nutrient environment. Also, this does not further depress voluntary food intake, as straightforward incapacity of host cells would have predicted, but actually restores it. This places the immediate origin of cachectic hypophagia not at the interaction of function and environment of host cells, but between the gut lumen and the dinner table. Cachexia is predominantly the consequence of a breakdown in control of food intake. However, if this problem is followed further, a rather different interpretation can emerge.

Normal control of food intake is directed toward matching metabolizable intake to metabolic need, if food is freely available. There is quite a wide array of normal control mechanisms, and the overall control system is highly redundant. Tumors affect different control mechanisms in different ways, and not all individuals or species possess all the control mechanisms that have been identified (21). The particular array of controls that an individual possesses or lacks and the susceptibility of these to tumor influence should probably be considered as a part of the organismic deficit.
Cachectic Process by Spontaneous Modification of Feeding Behavior, subordinated to breakdown is generated prior to the neoplastic transformation and on tumor growth, incorporating the speculation that both processes are favored by the same sets of nutritional conditions.

environment, both in the carcinogenic loop and in the cancer growth loop (Chart 1). This can be illustrated with 2 control mechanisms.

The normal response to reduction in nutrient density of food is increase in bulk intake to the extent that nutrient intake is maintained. This is what happens in the normal Sprague-Dawley rat (Chart 2; Ref. 18). With growth of the W256 tumor, this response deteriorates progressively, eventually falling to zero (Chart 2; Ref. 18). In contrast, this feeding response to dilution is normally almost totally absent in the Buffalo rat (Chart 2; Ref. 21). Growth of the Morris 5123 hepatoma (original tumor line) in this strain converts a normal zero response to a progressively negative response (Chart 2).

The effect of tumor growth on response to dilution, as shown in Chart 2, and a similar effect on response to lowered environmental temperature (unpublished data), demonstrate a move from the normal constant nutrient intake toward constant bulk intake. The same thing is indicated by changes in feeding pattern induced by tumors, in which at first the duration and then, later, the frequency of meals is reduced but the average meal mass is unchanged. This suggests that initiation of feeding in response to hunger and its termination by preabsorptive signals, such as gastric distension, are normal, but the metabolic modulation of this immediate control, to maintain ongoing intake until metabolic need is met, breaks down.

An important aspect of all these changes is that they start long before intake falls short of requirement. For the tumor-bearing organisms considered here, there is no shortfall in food intake until the last one-half or one-third of tumor life (17, 19). Up to that point the changes in feeding mode and in feeding control are fully compensated. Only when the compensatory capacity is exhausted does the organismic food intake collapse, producing the classic overt cachectic deterioration. However, the Walker 256 and Morris 5123 are transplanted tumors. It is conceivable that, in induced or spontaneous tumors, this compensated phase of breakdown is generated prior to the neoplastic transformation and contributes to it, just as, in the Buffalo rats, one control is already innately absent. The mechanism responsible for the compensation is so far totally unknown and, obviously, this is something that it is quite important to find.

The normal feeding response to exogenous insulin, and to other agents that produce hypoglycemia or glucoprivia, is an increase in food intake (6, 12). This normal response occurs in both rat strains (Chart 3; Refs. 20, 21). In both rat strains, also, the response does not diminish even in late tumor growth, and is enhanced in early and middle tumor growth (Chart 3). Again there is a change in response, although not necessarily a deleterious one, well before there is a tumor-induced change in intake. In spite of this control mechanism being intact or enhanced, it probably has little effect on the development of cachexia. The lateral hypothalamus is essential to its operation (6), but destruction of the lateral hypothalamus does not modify the cachectic development in any way (16).

Although the failure to control food intake is an organismic deficit, it must arise eventually from failure of the cellular level to signal appropriately to the central nervous areas that organize the behavioral output of feeding. Several suggestions have been made to the effect that the tumor, directly or indirectly, generates spurious signals that are interpreted centrally as indicating satiety, before the true satiety signals are generated (10, 32). If this indeed were the case, then the feeding failure would be entirely a function of the established tumor and not at all a continuation or exacerbation of a pretumorous tendency. However, if this indeed were the case, then it should be possible to block the effect by destroying the central loci that respond to the spurious signals. It is possible to block some normal satiety signals by destruction of the ventromedial hypothalamus (14), but this procedure does not block the cachectic hypophagia (1, 11), and no other central nervous locus has been suggested or demonstrated to do so either.

Chart 1. Representation of conditional effect of nutrition on neoplastic transformation and on tumor growth, incorporating the speculation that both processes are favored by the same sets of nutritional conditions.

**A UNITARY SPECULATION**

![Diagram](attachment:diagram.png)

**ORGANISMIC ENVIRONMENT**

**CELLULAR ENVIRONMENT**

**NEOPLASIA**

**EUPLASIA**

**TUMOR**

**HOST**


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![Chart 2](attachment:chart2.png)

**Chart 2.** Mean feeding response to 50% food dilution in 2 strains of rat before and during growth of 2 tumors. ■, S-D/W256, Walker 256 carcinosarcoma growing in adult male Sprague-Dawley rats; □, B/H5123, Morris 5123 hepatoma (original line) growing in adult male Buffalo rats. Full tumor life-span for W256 is 30 days; for H5123, it is 50 days. For S-D/W256, the 2nd and subsequent blocks are each significantly less than their predecessor (p < 0.05). For B/H5123, the 3rd and subsequent blocks are each significantly less than their predecessor (p < 0.05). Each B/H5123 block is significantly less than the corresponding S-D/5123 block (p < 0.01). Data for S-D/256 were adapted from Ref. 18.
There is a possible total alternative that could be consistent with continuation of a pretumorous tendency. Instead of peripheral production of spurious satiety signals, there could be peripheral blocking of some hunger signals, particularly those concerned with sustaining an ongoing meal. There is accumulating evidence that the hepatic-portal area is the receptor site for this control (22, 25, 28).

As stated at the beginning, hypophagia and cachexia are the most obvious manifestations of nutritional deficit in the tumor-bearing host. They have no parallel in the precancerous or early cancerous organism and, therefore, do not appear to fit the hypothesis that neoplastic transformation and tumor growth are favored by the same sets of nutritional imbalance. However, the processes that generate the hypophagia and cachexia do exist but are occult in the early cancerous organism and can exist innately in precancerous organisms and may contribute to their susceptibility to neoplasia. On the assumption that people are at least as variable as laboratory rats, they would be at least as likely to lack particular feeding control mechanisms. It is worth considering the possibility that the selection of putatively carcinogenic diets, such as the high fat-low fiber diet, may be partly the result of deficit of physiological control mechanisms with a resultant shift toward learned control of feeding.

References


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