Effects of Cancers of the Endocrine and Central Nervous Systems on Nutritional Status

Mortimer B. Lipsett

Clinical Center, National Institutes of Health, Bethesda, Maryland 20014

Summary

Tumors of the endocrine system and cancers exhibiting paraendocrine behavior can secrete peptides that stimulate secretions of the gastrointestinal tract. This may lead to malabsorption diarrhea and consequent weight loss. Tumors may also utilize excessive amounts of specific nutrients thereby creating deficiencies. Within the central nervous system, strategically placed tumors can cause major deviations from normal in appetite. Some of these perturbations, in lesser degree, may contribute to the weight changes frequently observed in patients with cancer.

Introduction

Cancer or benign tumors of the endocrine glands or of the central nervous system can alter nutritional status by any of several mechanisms. Although the specific nutritional disturbances are rare, they may serve as paradigms for the many, apparently routine, clinical states of weight loss accompanying cancer. As primary events, the mechanisms vary among marked deviations of food intake, loss of specific nutrients, and effects of substances produced by the cancers on the gastrointestinal tract. These possibilities are detailed in Table 1. Since almost each topic listed in this table has been the subject of a monograph, the "References" will cite only recent or seminal papers.

Food Intake

It is clear that the centers concerned with regulation of food intake lie in the hypothalamus. Experimentally, destruction of the ventromedial hypothalamus by either an electric current or gold thioglucose produces hyperphagia and obesity (2), and destruction of the ventrolateral hypothalamus causes aphagia (2). Thus, tumors impinging on these areas might well be expected to produce similar results.

There are several reports of bulimia and rapid weight gain in children with acute leukemia due to infiltration of leukemic cells in the hypothalamus (8). In adults, similar documentation has been more difficult to obtain, and even in the 5 patients reported by Bray and Gallagher (8) the rate of weight gain was modest.

The converse of hypothalamic obesity, a specific central nervous system lesion producing aphagia, has been reported rarely (17, 27). The presumption is that the tumor has destroyed or denervated the ventrolateral hypothalamus. Of course, many intracranial cancers, primary or metastatic, will produce inanition, but this may be considered a relatively nonspecific event and can be associated with any widespread central nervous system disease.

Of some relevance to central nervous system tumors and nutrition is the development of diabetes insipidus due to tumors. In 1 large series (7), almost half of the cases of diabetes insipidus were due to tumors in and around the pituitary gland and median eminence. Somewhat less than 5% of the cases of diabetes insipidus were due to metastatic involvement of the pituitary stalk. Breast cancer and bronchus cancer can have as their 1st manifestation diabetes insipidus, when the metastasis interrupts the fibers between the supraoptic nuclei and the posterior pituitary gland.

Although such lesions affect only water exchange, there may be secondary results on nutrition. Severe diabetes insipidus will lead to decreased food intake because of the large volumes of fluid necessary to maintain water balance; this is particularly relevant for children. Another reason for nutritional effects is the use of calories to bring the large volumes of cold water to body temperature. In small children, this may be a significant fraction of the calories derived from the diet.

Deviations in Metabolic Pathways

Tumors can affect nutrition by causing deviation of specific essential food substances. This is different from the tumor "nitrogen trap" discussed in the past (25). Niacin, the vitamin necessary to prevent pellagra, is nonessential since it is normally synthesized in vivo from dietary tryptophan, an essential amino acid. The use of tryptophan for serotonin synthesis preempts the amino acid so that the rate of niacin synthesis is greatly reduced. The clinical signs of pellagra that have appeared in patients with the carcinoid syndrome have responded well to supplementary niacin. Hypoalbuminemia may also occur in the carcinoid syndrome caused, in part, by the lack of tryptophan for protein synthesis.

Hypoalbuminemia may result from involvement of the gastrointestinal tract lymphatics with cancer (35) and the
triiodothyronine is derived almost exclusively from plasma thyroxine. It is, therefore, not assured by plasma thyroid-stimulating hormone or speed of clearance how changes in plasma triiodothyronine during periods of starvation and refeeding will alter metabolic parameters, but thyroid function will certainly need to be considered in sophisticated studies of intermediary metabolism in cancer cachexia.

**Table 1**

**Mechanisms of tumor-induced weight change**

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resultant protein-losing enteropathy. This has often been described in association with the carcinoid syndrome. The reasons are multiple. First, the tricuspid insufficiency and the right heart failure that complicate the carcinoid syndrome can cause the protein-losing enteropathy. However, some patients with metastatic carcinoid but without tricuspid disease have also demonstrated albumin loss into the gut, so that additional mechanisms must be postulated. The diarrhea produced by metastatic carcinoid should also be noted since it may contribute to the malnutrition. In contrast to some of the other manifestations of the carcinoid syndrome, it is likely that the serotonin increases small bowel mobility, thereby producing the diarrhea.

A rare manifestation of a tumor causing loss of a specific nutritional substance is the hypocholesterolemia produced by an adrenal tumor. Leichter and Daughaday (18) reported studies of a patient with a large adrenal adenoma whose serum cholesterol concentration was 70 mg/100 ml. It has been shown that plasma cholesterol is the preferred precursor for adrenal cortical steroid synthesis (4) so that the active synthesis of steroid by the tumor may be assumed to have used plasma cholesterol at a rate faster than it could be synthesized. This may be related to the finding observed by me more than 10 years ago that some patients with adrenal cancer who responded to Ortho Para prime DDD ethane mitotane had a rise in serum cholesterol (19).

An interesting alteration of metabolism that should be recognized in analyzing the metabolic events accompanying cancer cachexia is the effect of malnutrition on thyroid hormone metabolism. It seems probable that triiodothyronine is the active intracellular thyroid hormone, and plasma triiodothyronine is derived almost exclusively from plasma thyroxine. In protein-calorie malnutrition, plasma triiodothyronine falls in spite of a normal or slightly increased plasma thyroxine (10). On refeeding, triiodothyronine increases. Evidence for physiological hypothyroidism as measured by plasma thyroid-stimulating hormone or speed of the Achilles tendon reflex is lacking. It is, therefore, not clear how changes in plasma triiodothyronine during periods of starvation and refeeding will alter metabolic parameters, but thyroid function will certainly need to be considered in sophisticated studies of intermediary metabolism in cancer cachexia.

**Substances Produced by Endocrine Glands and Paracrine Tumors**

**Hypercalcemia.** Whether hypercalcemia results from parathormone excess or is a product of tumor-induced osteolysis, it exerts a marked anorexigenic effect. In 1 series of patients with hypercalcemia due to hyperparathyroidism, 30% of the patients had weight loss ranging between 10 and 65 pounds (20). When the hypercalcemia is caused by a nonendocrine gland cancer, it is difficult to dissociate the factors causing weight loss, but hypercalcemia needs always to be considered.

**Vasoactive Intestinal Peptide.** There are many peptides produced by endocrine and nonendocrine tumors that act at the gastrointestinal tract. Only as immunoassays have been developed has it been possible to relate these peptides to specific illnesses.

The syndrome of watery diarrhea or pancreatic cholera has been described in association with non-beta-cell tumors of the pancreas. The name, pancreatic cholera, is descriptive of the usual origin of the peptide as well as the clinical manifestations of the syndrome (34). The diarrhea is due to stimulation of small bowel secretions by the peptide hormone, vasoactive intestinal peptide. Vasoactive intestinal peptide has been shown to activate small bowel adenyl cyclase as does choleragen with resultant secretion of fluids (32).

This peptide can be bioassayed by its smooth muscle-relaxing property, but, more recently, an immunoassay has been developed sensitive enough for plasma measurements (6, 31). Using this assay, the vasoactive intestinal peptide level was often too low to measure in normal individuals and rarely exceeded 1 ng/ml. In a series of 30 patients with watery diarrhea, the average plasma concentration of vasoactive intestinal peptide was 5 ng/ml (31). Since vasoactive...
intestinal peptide occurs throughout the gastrointestinal tract, it is not surprising that some tumors of the gastrointestinal tract continue to secrete it.

Of particular interest was the finding of high plasma vasoactive intestinal peptide levels in association with squamous carcinoma of the bronchus in patients with watery diarrhea (31). This is another example of the paraendocrine behavior of lung cancer and explains the poorly understood diarrhea and weight loss occasionally noted in these patients. How often vasoactive intestinal peptide is secreted is in lesser amounts by patients with lung cancer is unknown.

There is another and rarer type of diarrhea with weight loss that is seen in children (38) and rarely in adults with ganglioneuroblastoma (9). It seemed unlikely that the catecholamines could be the cause of the diarrhea because patients with pheochromocytomas more often suffer from constipation than diarrhea. The identification of vasoactive intestinal peptide in plasma of patients with ganglioneuroblastoma (26, 31) suggests the explanation for the diarrhea. In general, the ganglioneuroblastomas associated with diarrhea have been functional as defined by the excretion of large amounts of catecholamine metabolites.

**Enteroglucagon.** Although only a single patient with a tumor secreting enteroglucagon has been reported (14), the occurrence of malabsorption and weight loss makes the case worthy of notice. Measurement of enteroglucagon has not been performed routinely so that the extent of occurrence of the syndrome is unknown.

The patient was a 47-year-old man with diarrhea and intestinal malabsorption. He was subsequently shown to have a renal tumor that appeared histologically to resemble pancreatic alpha cells. Resection of the tumor caused remission of the symptoms. Subsequent analysis of the tumor showed it to contain enteroglucagon, as distinguished from pancreatic glucagon, in high concentration (5). The mechanism of production of the sprue-like syndrome remains unexplained but does suggest that this cause should be sought in unexplained cases of malabsorption. It should be noted in passing that 1 glucagonoma has been associated with diarrhea and weight loss (21), although others are not manifested in this way (22). The identification of enteroglucagon or glucagon does not prove that they are the etiologic agents; tumors produce many peptides, and as yet unidentified peptides may be causative.

**Gastrin.** The Zollinger-Ellison syndrome is characterized by secretion of large volumes of gastric acid, refractory peptic ulcer, diarrhea, malabsorption, and weight loss (24). Definition of the role of gastrin as the etiologic agent required the isolation of gastrin and the development of a radioimmunoassay (24). The malabsorption and weight loss may be attributed to damage to the duodenal mucosa by the large volumes of acid as well as precipitation of bile salts and denaturation of pancreatic lipase.

Eighty % of patients with the Zollinger-Ellison syndrome have a pancreatic tumor of which 60% are cancerous. Gastrin is most abundant in the pyloric and proximal duodenal mucosa, but it is present in small amounts in pancreatic delta cells. It should, therefore, not be unexpected that tumors of these pancreatic islet cells retain the capacity to synthesize gastrin. As with other peptide-secreting cancers, there is heterogeneity of the secreted products with at least 2 higher-molecular-weight immunoreactive gastrins having been described (16, 39).

It should be recognized that a high percentage of patients with Zollinger-Ellison syndrome have 1 or more manifestations of multiple endocrine adenomatosis Type I (12). This hereditary syndrome is characterized by functional adenomas of the pituitary gland, parathyroids, and islet cells. Hormones that may be produced in excess are growth hormone, parathormone, and insulin. Of the patients with multiple endocrine and adenomatosis Type I, about 50% have ulcers that can probably be related to gastrin secretion (3). The aggregation of these adenomas and the interactions of the secreted hormones may make it difficult to identify with surety the reasons for weight loss.

The question of gastrin secretion by gastric cancers has been considered. In general, patients with gastric cancer involving the pylorus have lowered gastrin secretion, whereas carcinoma of the body of the stomach has been associated with high plasma gastrin levels, due presumably to destruction of the acid-producing cells (23). In 1 case of gastric cancer, however, convincing evidence of gastrin secretion has been obtained (30).

The similarity of structure among many of the gut peptide hormones has only recently become apparent (36, 37). Thus tumors may be expected to synthesize 1 or more of these peptides at times, and a systematic study should be made of all islet-cell pancreatic tumors, whether or not they are symptomatic. The existence of other gut peptides (28, 29) that have seldom been analyzed in humans may provide explanations for some of the alterations of appetite and the weight loss seen in patients with cancer.

**Histamine.** There are several reports of malabsorption and diarrhea occurring in patients with systemic mastocytosis (1, 11), a disease associated with increased secretion of histamine from the mast cells. The etiology of the malabsorption is not clear since it is not always a result of gastric acid hypersecretion. When malabsorption and diarrhea occur together in patients with systemic mastocytosis, there may be profound weight loss. Blood histamine has been normal and tissue histamine high in some patients (1). The marked improvement in 1 patient treated with Metiamide, a histamine blocker (13), suggested that the histamine was exerting its effects on other than gastric histamine receptors since the effects of Metiamide were much more pronounced than in patients with peptic ulcer and high acid secretion.

**Calcitonin.** Medullary cancer of the thyroid is generally recognized as part of multiple endocrine adenomatosis Type II. Diarrhea and weight loss may be associated with this cancer and have been variously attributed to secretion of prostaglandins and serotonin. Calcitonin, the important secretory product of this tumor, has been shown to cause secretion of water and electrolytes by the jejunal mucosa, thereby explaining the diarrhea (15). This adds to the list of peptides involved in stimulation of the gut with resulting diarrheogenic syndromes.

**References**

2. Assimacopoulos-Jeannet, F., and Jeannen, B. The Hormonal and
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