more threatening than benign tumors, any tumor, even a benign one, may cause morbidity and mortality.

Local and Hormonal Effects

Location is a critical determinant of the clinical effects of both benign and malignant tumors. Tumors may impinge upon vital tissues and impair their functions, cause death of involved tissues, and provide a nidus for infection. A small (1 cm) pituitary adenoma, although benign and possibly nonfunctional, can compress and destroy the surrounding normal gland and thus lead to serious hypopituitarism. Cancers arising within or metastatic to an endocrine gland may cause an endocrine insufficiency by destroying the gland. Neoplasms in the gut, both benign and malignant, may cause obstruction as they enlarge. Infrequently, peristaltic movement telescopes the neoplasm and its affected segment into the downstream segment, producing an obstructing intussusception (Chapter 17). Symptoms produced by a cancer due to its position can (ironically) be lifesaving; for example, the few survivors of pancreatic cancer are those whose tumors "fortuitously" obstruct bile ducts early in their course, leading to the appearance of jaundice and other symptoms at a stage of the disease when surgical cure is still possible.

Benign and malignant neoplasms arising in endocrine glands can cause clinical problems by producing hormones. Such functional activity is more typical of benign than of malignant tumors, which may be so undifferentiated to have lost such capability. A benign beta-cell adenoma of the pancreatic islets less than 1 cm in diameter may produce sufficient insulin to cause fatal hypoglycemia. In addition, nonendocrine tumors may elaborate hormones or hormone-like products and give rise to paraneoplastic syndromes (discussed later). The erosive and destructive growth of cancers or the expansile pressure of a benign tumor on any natural surface, such as the skin or mucosa of the gut, may cause ulcerations, secondary infections, and bleeding. Melena (blood in the stool) and hematuria, for example, are characteristic of neoplasms of the gut and urinary tract. Neoplasms, benign as well as malignant, may cause problems in varied ways, but all are far less common than our next topic, the cachexia of malignancy.

Cancer Cachexia

Individuals with cancer commonly suffer progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia, and anemia, referred to as *cachexia.* Cancer cachexia is associated with:

- Equal loss of both fat and lean muscle
- Elevated basal metabolic rate
- Evidence of systemic inflammation (e.g., an increase in acute phase reactants, Chapter 6)

The mechanisms that underlie cancer cachexia are not understood. Inflammation related to the interplay between cancer and the immune system is likely to have a role. TNFα (originally known as cachectin) is a leading suspect among several mediators released from immune cells that may contribute to cachexia. Humoral factors released from tumor cells such as proteolysis inducing factor have been implicated in the loss of muscle mass, which is discussed further in Chapter 9.

Paraneoplastic Syndromes

Some cancer-bearing individuals develop signs and symptoms that cannot readily be explained by the anatomic distribution of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose; these are known as paraneoplastic syndromes. These occur in about 10% of persons with cancer. Despite their relative infrequency, paraneoplastic syndromes are important to recognize, for several reasons:

- They may be the earliest manifestation of an occult neoplasm.
- In affected patients they can cause significant clinical problems and may even be lethal.
- They may mimic metastatic disease and therefore confound treatment.

A classification of paraneoplastic syndromes and their presumed origins is presented in Table 7-11. A few comments on some of the more common and interesting syndromes follow.

Endocrinopathies are frequently encountered paraneoplastic syndromes. The responsible cancers are not of endocrine origin and the secretory activity of such tumors is referred to as ectopic hormone production. *Cushing syndrome* is the most common endocrinopathy. Approximately 50% of individuals with this endocrinopathy have carcinoma of the lung, chiefly the small-cell type. It is caused by excessive production of corticotropin or corticotropin-like peptides. The precursor of corticotropin is a large molecule known as pro-opiomelanocortin. Lung cancer patients with Cushing syndrome have elevated serum levels of both pro-opiomelanocortin and corticotropin. The former is not found in serum of patients with excess corticotropin produced by the pituitary.

Hypercalcemia is probably the most common paraneoplastic syndrome; in fact, symptomatic hypercalcemia is more often related to some form of cancer than to hyperparathyroidism. Two general processes are involved in cancer-associated hypercalcemia: (1) *osteolysis* induced by cancer, whether primary in bone, such as multiple myeloma, or metastatic to bone from any primary lesion, and (2) the production of *calcemic humoral substances* by extraosseous neoplasms. Only the second mechanism is considered to be paraneoplastic; hypercalcemia due to primary or secondary involvement of the skeleton by tumor is not a paraneoplastic syndrome.

Several humoral factors have been associated with paraneoplastic hypercalcemia of malignancy. The most important, *parathyroid hormone-related protein* (PTHRP), is a molecule related to, but distinct from, parathyroid hormone (PTH). PTHRP resembles the native hormone only in its N terminus. It has some biologic actions similar to those of PTH, and both hormones share a G protein–coupled receptor, known as PTH/PTHRP receptor (often referred to as PTH-R or PTHRP-R). In contrast to PTH, PTHRP is produced in small amounts by many normal tissues, including keratinocytes, muscles, bone, and ovary. It regulates calcium transport in the lactating breast and across the placenta, and seems to modulate pulmonary development and remodeling. Tumors most often associated with paraneoplastic hypercalcemia are carcinomas of the breast, lung, kidney, and ovary. In breast cancers, hypercalcemia