

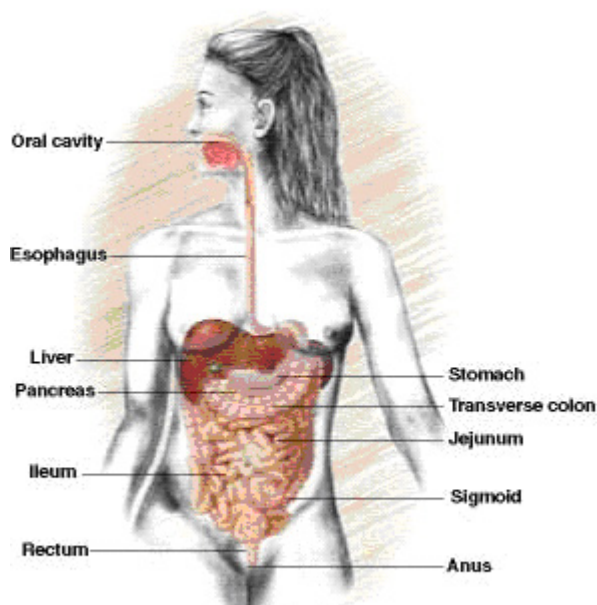
Gastroenteropancreatic Neuroendocrine (GEP NE) Tumors

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What Are GEP NE Tumors?

Gastroenteropancreatic neuroendocrine (GEP NE) tumors are rare, generally slow-growing tumors that occur in the pancreas and the gastrointestinal tract, which includes the stomach, small intestine, and large intestine. GEP NE tumors include carcinoid tumors and pancreatic endocrine tumors (also called pancreatic islet cell tumors).



The Digestive System (Courtesy of Jones and Bartlett Publishers)

Normally, neuroendocrine cells in the pancreas and the gastrointestinal system produce hormones and other potent chemicals that help regulate various functions that keep the body in working order. GEP NE tumors are thought to arise from neuroendocrine cells. When they occur, the tumors sometimes have the ability to overproduce proteins and other substances, causing a variety of symptoms throughout the body.

Statistics

Carcinoid tumors are more common than pancreatic endocrine tumors. They are found in about 1 or 2 out of 100,000 people in the United States. They occur most frequently in the appendix, small intestine, and rectum. These tumors tend to grow slowly; in fact, many people are believed to have tiny carcinoids that never cause any health problems. Nevertheless, because it is not possible to distinguish such noncancerous (benign) carcinoids from potentially cancerous (malignant) ones, all discovered carcinoid tumors should be treated as having malignant potential.

Pancreatic endocrine tumors are found in about 4 out of every 1 million people. A number of different pancreatic endocrine tumors have been described. The most commonly occurring types include:

- **Insulinomas:** These tumors are found most often in people between 30 and 60 years of age. They occur slightly more frequently in women. Patients with an insulinoma commonly come to medical attention because of symptoms of hypoglycemia.
- **Gastrinomas:** These tumors are found most frequently in people between the ages of 45 and 50. They are somewhat more common in men than in women. Gastrinomas may be found either within the pancreas itself or in an area immediately adjacent to the pancreas. Patients with gastrinoma typically have symptoms of acid hypersecretion.
- **VIPomas:** These tumors secrete a substance called vasoactive intestinal peptide that can cause profound diarrhea.
- **PPomas:** These tumors are also called nonfunctioning pancreatic endocrine tumors. They do not secrete specific hormones but can be detected through their production of a protein called pancreatic polypeptide.
- **Glucagonomas:** These tumors are less common than other pancreatic endocrine tumors. Patients with glucagonomas often have higher than normal blood sugars and are often diagnosed with diabetes. A rash is another common symptom of glucagonomas.

Risk Factors

Certain conditions that run in families can increase a person's risk of developing a GEP NE tumor. One genetic condition associated with pancreatic endocrine tumors is multiple endocrine neoplasia type I (MEN1), a rare genetic inherited disorder linked to tumors in the pancreas and the parathyroid and pituitary glands. About 20% of gastrinomas and 7% to 8% of insulinomas are associated with MEN1. Genetic tests are available to detect mutations in the gene, *MEN1*, which are implicated in this disease.

Conditions that affect the production of stomach acid, such as Zollinger-Ellison syndrome, gastritis, and pernicious anemia, can also increase the risk of developing gastric carcinoid tumors.

Screening

Unfortunately there is no general screening test to check for GEP NE tumors. However, the earlier a tumor is discovered, the better is a person's chance of survival. For this reason, people who notice symptoms of GEP NE tumors should discuss them with their doctor right away.

Symptoms

GEP NE tumors often do not produce symptoms in the early stages of disease. When symptoms do appear, they usually are caused by the higher than normal amounts of a particular hormone, or hormones, produced by the tumor cell. The effects of the tumor vary depending on the type of hormone being overproduced.

Carcinoid tumors can secrete too much of the hormone serotonin. High amounts of serotonin, as well as other less well characterized substances in the blood, can cause carcinoid syndrome, which includes:

- A red flushing of the face and neck
- Diarrhea
- Less commonly, asthma-like wheezing

Heart valve disease and other cardiac disturbances can also occur in patients who have had carcinoid syndrome for many years. Carcinoid syndrome usually occurs when carcinoid tumors have spread to other parts of the body. When tumors have spread, they are said to have metastasized. The syndrome generally occurs in patients with metastatic small bowel or

appendiceal carcinoids, and rarely, if ever, occurs in patients with metastatic bronchial or rectal carcinoid tumors.

Insulinomas secrete large amounts of the hormone insulin. High levels of insulin can cause low blood sugar, which in turn causes:

- Visual disturbances
- Weakness
- Sweating
- Confusion
- Less commonly, seizures

Symptoms often occur early in the morning or at night, when blood sugar levels are lowest.

Gastrinomas release high amounts of gastrin, which causes hypersecretion of acid in the stomach. This can cause:

- Abdominal pain
- Diarrhea
- The development of peptic ulcers, a syndrome also known as Zollinger-Ellison syndrome

VIPomas secrete a hormone called vasoactive intestinal peptide (VIP). Patients with VIPomas may have Verner-Morrison syndrome, which is characterized by profound secretory diarrhea.

Glucagonomas secrete high amounts of the hormone glucagon. Glucagon causes high blood sugar levels and diabetes. Patients with glucagonomas may develop a rash, called necrolytic migratory erythema. This occurs on the lower trunk, buttocks, perineum, and thighs. A dermatologist can diagnose it. Patients may also lose weight.

Why GEP NE Tumors Develop (Causes)

GEP NE tumors are thought to arise from neuroendocrine cells that grow in an uncontrolled fashion and develop into tumors. What causes these cells to escape the normal brakes that stop them from growing uncontrollably is not entirely understood.

Defective genes often play a role in the development of tumors, and several genes that contribute to the development of GEP NE tumors have been identified. Some of these genes are associated with the inherited disorder, multiple endocrine neoplasia type 1 (MEN1), which increases the risk of developing pancreatic endocrine tumors. Mutations in a gene called *MEN1* are involved in causing these tumors to arise.

How GEP NE Tumors Are Diagnosed (Diagnosis)

If a person has symptoms that can be caused by a GEP NE tumor, the doctor will carry out blood and urine tests to determine whether such a tumor may be present. These tests measure the amounts of certain hormones and other substances associated with GEP NE tumors. Abnormal levels of a particular hormone can help point to the presence of a specific type of GEP NE tumor.

Carcinoid tumors, for example, release large amounts of serotonin. This hormone breaks down into smaller chemicals. One of these chemical byproducts is 5-hydroxyindoleacetic acid (5-HIAA), which can be detected in urine. The laboratory test used most frequently to detect carcinoid tumors measures the amount of 5-HIAA in the urine over a 24-hour period. The 5-HIAA test, however, does not always pick up carcinoid tumors, particularly if they are in the lungs, stomach, or rectum.

Another substance that can indicate the presence of a carcinoid tumor—as well as other types of neuroendocrine tumors—is chromogranin A (CgA). CgA levels in the blood can be measured to detect the presence of a GEP NE tumor. Because CgA can also be elevated in a variety of other conditions, it is not specific to neuroendocrine tumors and is not generally used as either a screening or a diagnostic test.

To determine where the tumor is, how large it is, and whether it has spread, the doctor relies on a variety of tools.

- **Endoscopy.** This procedure involves using an endoscope—a thin tube with a light on the end. This instrument can be used to locate where a tumor is in the gastrointestinal tract. Endoscopy is most commonly used to detect gastric or rectal carcinoid tumors. Because the small intestine is difficult to visualize, endoscopy may not be able to detect small bowel carcinoids.
- **Computed tomography (CT) scans and magnetic resonance imaging (MRI).** These imaging tests are used to take pictures of the gastrointestinal tract and pancreas. They can be used to find the primary tumor and to determine whether the tumor has spread.
- **Somatostatin receptor scintigraphy (Octreoscan®).** Somatostatin receptor scintigraphy (SRS) is another technique used to identify GEP NE tumors. Many GEP NE tumors contain proteins called somatostatin receptors. These receptors bind the hormone somatostatin, which occurs naturally in the body. Somatostatin receptors can also bind to drugs similar to somatostatin, such as octreotide, which are called somatostatin analogues. To carry out SRS, octreotide is labeled with a radioactive substance called indium-111 and injected into a vein. The radiolabeled octreotide travels through the bloodstream until it meets up with a tumor containing somatostatin receptors and binds to them. A device that measures radiation is then used to detect the radiolabeled octreotide, revealing where the tumor is in the body. The radioactive isotope breaks down and is eliminated from the body in a few days and so is considered safe. This scan can also be used to determine whether somatostatin analogues can be used in treatment for GEP NE tumors, as tumors that carry somatostatin receptors are more likely to respond than those that do not.

How GEP NE Tumors Are Treated (Treatment)

GEP NE tumors are treated with a variety of approaches, including surgery and medical therapies such as somatostatin analogues, interferon therapy, chemotherapy, and radiation therapy.

These treatments are listed in order from most common to less common.

Surgery. Surgery is performed whenever possible to remove the tumor. If the tumor can be removed completely, it can potentially cure the disease. Even if the entire tumor cannot be removed, "debulking" surgery may be considered to eliminate as much of the tumor as possible. This can help relieve some symptoms, sometimes for a long period, since many tumors are slow growing.

Embolization. Embolization is performed in some patients with liver metastases. This procedure mechanically blocks the blood supply to liver metastases, causing them to shrink and become less active. It is usually performed by an interventional radiologist and can be performed either with or without chemotherapy.

Somatostatin analogues. In addition to its use as a diagnostic tool, the somatostatin analogue octreotide can be used to alleviate symptoms brought about by the high amounts of various hormones produced by neuroendocrine tumor cells.

The hormone somatostatin inhibits the effects of many other hormones in the body. It does this by binding to somatostatin receptors on tumor cells, which prevents the release of hormones. Somatostatin analogues, such as octreotide, act in the same way as somatostatin.

Somatostatin analogues are most useful in reducing the symptoms, such as severe diarrhea and flushing, of functional GEP tumors (e.g. metastatic carcinoid tumors and VIPomas).

Alpha-interferon. Interferon is a natural substance produced by the white blood cells in the body that fight infection. It may also stimulate the immune system to fight cancer. One type of interferon—alpha-interferon—seems to inhibit the release of hormones from tumor cells and also may be able to control the growth of GEP NE tumors.¹ However, interferon may cause side effects, such as flu-like symptoms and extreme fatigue.

Some, but not all, studies suggest that the combination of alpha-interferon and somatostatin analogues may be more effective than using either therapy alone.²⁻⁴

Chemotherapy. A number of chemotherapy drugs have been used to treat GEP NE tumors. Many standard chemotherapy regimens utilize drug combinations that include the drugs streptozocin (Streptozotocin, Zanosar), doxorubicin (Adriamycin), 5-fluorouracil (5-FU), or dacarbazine (DTIC-Dome, DIC, Imidazole carboxamide). While useful in selected patients, the

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overall success of such regimens has been mixed, and potentially more effective and less toxic treatments are actively being investigated.⁵⁻¹⁰

Radiation therapy. X-rays or other types of radiation can be used to treat GEP NE tumors.

External beam radiation therapy, in which a machine is used to send a beam of radiation to kill tumor cells, is sometimes used to alleviate symptoms of the disease, and is particularly useful in patients with bone metastases.

Resources

If you have more questions about GEP NE tumors, you should first speak with your healthcare professional because he or she understands your specific medical needs. The Internet is another good source of information about GEP NE tumors and offers ways to connect with other patients and families to share experiences, resources, and support.

Certain links on this site lead to resources located on servers maintained by third parties over whom Novartis AG has no control. As such, Novartis Pharmaceuticals Corporation makes no representation as to the accuracy or any other aspect of the information contained on such servers.

The Carcinoid Cancer Foundation

Offers research and education on carcinoid tumors. <http://www.carcinoid.org>

National Organization for Rare Disorders (NORD)

NORD includes various types of GEP NE tumors in its rare-disease database and will e-mail or fax you a full report for a nominal fee. <http://www.raredisease.org>

Society for Endocrinology

A professional association whose membership is open to anyone working in an endocrine-related field anywhere in the world and at any stage in his/her career. Membership benefits include a newsletter, professional meetings, training, and networking. <http://www.endocrinology.org>

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