A collaboration between Penn Gastroenterology and the Penn Renal, Electrolyte and Hypertension results in an interdisciplinary program to diagnose, stage and treat neuroendocrine tumors.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare (~2 percent of all GI tumors), heterogeneous group of malignancies occurring in the digestive tract. Pheochromocytomas are tumors of neuroendocrine chromaffin cells, and are found in both the adrenal glands and in extra-adrenal locations. They are rarer (~2/100,000 persons) than GEP-NETs. With early diagnosis and treatment, tumors in both neuroendocrine classes are potentially curable and manageable for the long term.

Originating in cells having both nervous and endocrine properties, GEP-NETs are classified by histology as either alimentary tract carcinoid lesions (NETs) or pancreatic endocrine tumors (PETs) and subcategorized by whether or not they secrete neuroamines, hormones or peptides at levels sufficient to cause a syndromic response. A recent standard WHO classification has proposed that GEP-NETs be assigned to one of three categories (well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma) based on histology, size and proliferative indices.

The Penn Neuroendocrine Tumor Treatment Program was developed under the direction of Debbie Cohen, MD (Nephrology) and David Metz, MD (Gastroenterology), shown above with NET Program patient coordinator Bonnie Bennett, BSN.

The Penn Neuroendocrine Tumor Treatment Program provides a comprehensive, interdisciplinary approach to the diagnosis, staging, and medical and surgical treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and pheochromocytomas. GEP-NETs are a rare (~2 percent of all GI tumors), heterogeneous group of malignancies occurring in the digestive tract. Pheochromocytomas are tumors of neuroendocrine chromaffin cells, and are found in both the adrenal glands and in extra-adrenal locations. They are rarer (~2/100,000 persons) than GEP-NETs. With early diagnosis and treatment, tumors in both neuroendocrine classes are potentially curable and manageable for the long term.

Originating in cells having both nervous and endocrine properties, GEP-NETs are classified by histology as either alimentary tract carcinoid lesions (NETs) or pancreatic endocrine tumors (PETs) and subcategorized by whether or not they secrete neuroamines, hormones or peptides at levels sufficient to cause a syndromic response. A recent standard WHO classification has proposed that GEP-NETs be assigned to one of three categories (well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma) based on histology, size and proliferative indices.

A Foundation in Experience: The Penn NET Treatment Program

As a result of the rarity and indolent character of GEP-NETs and pheochromocytomas, their early diagnosis depends largely on the experience and expertise of treating clinicians and access to advanced imaging and laboratory facilities—a combination of advantages unique to Penn in the Philadelphia region.

Both Dr. Metz and Dr. Cohen have researched and published on NETs and both have wide experience in the long-term management of NET patients within their respective specialties. In addition, the Penn
Continued from page 1

Each patient in the **Penn NET Treatment Program** is linked to a central physician who is the primary contact for both the patient and the treatment team.

NET Treatment Program incorporates the full armamentarium of services, procedures and technologies at Penn into the management of NETs, engaging the diagnostic services of the Divisions of Gastroenterology, Hematology-Oncology (Weisberg, MD; Director of GI medical oncology), Renal Electrolyte and Hypertension, Interventional Radiology and Medical Genetics, as well as the capabilities of the Abramson Cancer Center. Thus, Dr. Cohen explains, at Penn patients with NETs have the advantage of a clinical environment capable not only of familiarity with these rare and idiopathic tumors, but also of heightened diagnostic scrutiny.

The Penn NET Treatment Program include accurate diagnosis and staging, effective symptom control, curative surgery (when possible), prevention of tumor progression (including surgical, radiological and surgical approaches), genetic counseling (when indicated), and individualized long-term patient management depending on disease progression. Patients enter the program by being referred to a gastroenterologist, nephrologist, oncologist, surgeon or endocrinologist at Penn. This specialist then refers the patient for further diagnostics, which may involve biochemical measurements and imaging studies, or treatment via surgery, medical or radiation oncology and nuclear medicine.

“Each patient has a central physician,” Dr. Metz says.

“This specialist, who might be a gastroenterologist, an oncologist or a nephrologist, is the primary contact for both the patient and the treatment team.”

**Clinical Diagnosis and Management of GEP-NETs at Penn**

Secreting (functional) alimentary tract NET lesions represent only a small portion of carcinoids and are associated with a variable and nonspecific array of symptoms collectively termed the carcinoid syndrome. These symptoms include intense flushing, diarrhea, abdominal pain, heart rate variability and blood pressure changes. The symptoms are typically caused by the vasoactive neurotransmitter serotonin among others. Functional pancreatic NETs (PETs) produce a variety of clinical syndromes in association with the substances they secrete (e.g., Zollinger-Ellison syndrome [gastrin], insulinoma syndrome [insulin], glucagonoma syndrome [glucagon], VIPoma syndrome [vasoactive intestinal polypeptide], etc). Several inherited conditions are associated with PETs. These include multiple endocrine neoplasia-type 1 (MEN1) and von Hippel Lindau syndrome. Nonfunctional GEP-NETs are clinically silent and indolent. Most are identified late in their course when tumor bulk or metastases to the liver cause abdominal pain and other symptoms.

Surgery can be curative, and is typically the first-line treatment for resectable patients with GEP-NETs. At Penn, surgery is offered through the divisions of Gastrointestinal Surgery and Endocrine and Oncologic Surgery. In patients with unresectable lesions, hormonal therapy with octreotide, a somatostatin analogue, is used to inhibit tumor growth. (MBG therapy is particularly suited to patients with malignant, unresectable pheochromocytoma). Patients with resectable PETs are candidates for surgery. Patients with unresectable lesions may benefit from debulking surgery. Surgery in patients with MEN-1 is used in some, but not all, situations. Biotherapy is usually the first modality employed for patients with metastatic PETs because it is generally well tolerated. Typically, systemic or regional therapies are reserved until symptoms occur or tumor growth accelerates. Patients with advanced disease may have access to newer agents and receptor-directed radiotherapy, as well as interventional radiologic procedures. As in GEP-NETs, CgA appears to be the most useful serum marker for diagnosis, staging and monitoring.

**Case Study 1:** A 49-year-old female with metastatic carcinoid tumors of the liver

Mrs. G, a 49-year-old female, was referred to the Penn Neuroendocrine Tumor Treatment Program for carcinoid tumor surgery. Several months before presenting at Penn, she had developed lower leg edema, flushing and diarrhea. This specialist led her to visit her obgyn, who ordered an abdominal CT scan that found widely dispersed tumors in her liver. At Penn, a 24-hour urine test for 5-hydroxyindoleacetic acid (the main urinary metabolite of serotonin), measured >150 mg/dl (normal=6-5 mg/dl), an assessment of chromium A (CgA) a NET marker, found levels >100 u/l (normal range = 2-18 u/l). An octreoscan identified a primary tumor in the terminal ilium and an extensive tumor burden in the right lobes of her liver but no metastases beyond the liver. Mrs. G was diagnosed with widely metastatic carcinoid tumors in her liver and carcinoid syndrome and began octreotide LAR, 20 mg/month, which improved, but did not resolve her symptoms. Her dose was increased to 30mg/month and following an interdisciplinary review of her tests and scans, it was recommended that Mrs. G have chemoembolization of the tumors in her right liver followed by debulking surgery. Following two visits to interdisciplinary radiology for chemoembolization, she had liver resection surgery in the division of gastroenterological surgery. She recovered from these procedures without incident. At this time, her CgA and CgA levels were within normal levels. Six months post-surgery, another octreoscan revealed no new hepatic lesions and no new metastases. At one year, Mrs. G’s status remains stable on octreotide maintenance therapy.

**Case Study 2:** Bilateral adrenal pheochromocytoma

Mr. R presented at age 12 with headaches and diarrhea; he was diagnosed with a right adrenal pheochromocytoma and underwent right adrenalectomy. At age 37, Mr. R was seen at the Penn Center for Complex Hypertension with recurrence of diarrhea and headaches. His BP was 132/80 mm Hg and he was not on any antihypertensive medications. He was found to have a left adrenal mass consistent with pheochromocytoma and was scheduled for a second adrenalectomy. He was treated with dibenzyline for proprerceptive alpha blockade and alpha methyl tyrosine. A left-sided adrenalectomy was performed, now unable to produce endogenous steroids. Mr. R began a regimen of hydrocortisone and fludrocortisone. Because certain genetic mutations are associated with bilateral adrenal pheochromocytoma, Mr. R was referred for genetic testing. Genotyping studies were positive for Von Hippel Lindau VHL mutation, an autosomal dominant trait with a 50 percent risk of inheritance. Mr. R’s 18-year-old son, JW, was also found to be carrying the VHL mutation, JW had no symptoms; supine and sitting BP were 120/78 mm Hg and 110/82 mm Hg. Standing blood pressure was 96/74 mm Hg with a heart rate of 120 beats/minute. Urine studies showed elevated normetanephrine levels. MRI of the abdomen showed a left adrenal mass and liposarcoma adrenocortical sparring surgery was performed. While his BP remained normal with home BP monitoring, JW’s plasma and urine metanephrines never “normalized.” A repeat MRI performed a year later revealed a new tumor in the right adrenal gland and a second adrenal cortex sparing surgery for his second pheochromocytoma was performed. Both Mr. R and JW remain disease-free several years later with yearly surveillance with blood tests and imaging for recurrent pheochromocytoma.

To refer a patient to the Penn NET Treatment Program, call 215.615.4646 or 800.789.7366 or visit PennMedicine.org/referral.

**CT scan with contrast of the abdomen of a patient with neuroendocrine tumors (NETs) demonstrating metastases to the liver.**

**MRI scan of a left adrenal pheochromocytoma (arrow).** Penn is a major regional source of referrals for patients with neuroendocrine tumors, who are diagnosed and treated by an interdisciplinary team of clinicians with the renal electrolyte and hypertension division and the divisions of medical genetics and endocrine and oncologic surgery.