

Priorities for Improving the Management of Gastroenteropancreatic Neuroendocrine Tumors

Irvin M. Modlin, Steven F. Moss, Daniel C. Chung, Robert T. Jensen, Elizabeth Snyderwine

A National Cancer Institute summit meeting on gastroenteropancreatic neuroendocrine and carcinoid tumors was held in September 2007 to present the currently accepted standards of care for patients with these tumors and to identify areas requiring investigation and development. These tumors are clinically and pathologically heterogeneous, present commonly with obscure symptoms that lead to delays in diagnosis of years, and have an incidence in the United States of 2.5 to 5 cases per 100 000. The 5-year survival rates range between 15% and 95%, depending on the site and extent of disease. This report delineates the main conclusions of the meeting, including the best practice diagnosis and treatment strategies for gastropancreatic neuroendocrine tumors, and the identification of clinical and scientific areas that are most in need of attention. The most pressing needs were public and physician education, identification of molecular markers for early diagnosis and therapeutic monitoring, improved imaging modalities and molecular prognostication, development of a standardized pathological classification system, and creation of regional centers of expertise with tumor and laboratory data banks. In addition, adequately validated neuroendocrine tumor models and cell lines should be established to investigate the molecular mechanisms involved in the control of their growth and secretion, and to facilitate the development of specific therapies that should be examined in well-designed multicenter studies of defined patient groups.

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The incidence and prevalence of gastroenteropancreatic neuroendocrine tumors, including gastrointestinal carcinoid tumors, have been substantially increasing in the US population over the last 30 years for unknown reasons (1). In particular, there has been a marked increase in diagnoses among African Americans (1). Typically, patients experience long delays before a diagnosis (5–7 years), and most lack access to the multidisciplinary care necessary for optimal management of these complex tumors. Disappointingly, in the last 30 years, there has been no change in mean overall survival for US patients with gastroenteropancreatic neuroendocrine tumors (1,2); the majority are still diagnosed with metastatic disease, and no specific antineoplastic therapy exists.

In view of the slow progress made for this condition, the National Cancer Institute held a neuroendocrine tumor–carcinoid summit in Bethesda, MD, on September 24–25, 2007. More than 40 leading authorities in the field attended, including basic scientists and clinicians from many diverse disciplines. In addition to reviewing the state of the science and clinical management of these neuroendocrine tumors, considerable time was devoted to workshop sessions and open discussions. The aim of the summit meeting was to promote an open exchange of ideas, to critically review the major challenges in the field, and to suggest how these challenges may be overcome to improve the management of patients with gastroenteropancreatic neuroendocrine disease.

Clinical Overview

The meeting started with a review of the epidemiology, biology, and clinical features of gastroenteropancreatic neuroendocrine tumors. These tumors are a heterogeneous group of neoplasms that characteristically have nonspecific symptoms, leading to a

delay in diagnosis of several years (3). Historically, neuroendocrine tumors of the luminal gastrointestinal tract and bronchopulmonary system were referred to as “carcinoid tumors,” a term that was first used a century ago to indicate that these “cancer-like” tumors were less malignant in behavior than intestinal carcinomas (4).

The incidence of gastroenteropancreatic neuroendocrine tumors is approximately 2.5 to 5 cases per 100 000 in the United States, which makes them much rarer than adenocarcinomas of the gastrointestinal tract (1). However, their incidence has increased substantially in the past 30 years, as indicated by an analysis of the National Cancer Institute’s Surveillance, Epidemiology and End Results database (5) (Figure 1). Because patients with gastroenteropancreatic neuroendocrine tumors have better survival than patients with many other malignant neoplasms, the prevalence of the disease is substantial—less than that of colon cancer but greater than that of gastric, esophageal, pancreatic, or hepatobiliary neoplasms. Attendees generally agreed that some of the

Affiliations of authors: Department of Gastroenterological Surgery, Yale University, New Haven, CT (IMM); Department of Medicine, Rhode Island Hospital/Brown University, Providence, RI (SFM); Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital/Harvard University, Boston, MA (DCC); Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases (RTJ) and National Cancer Institute (ES), National Institutes of Health, Bethesda, MD.

Correspondence to: Irvin M. Modlin, MD, PhD, DSc, FRCS, Department of Gastroenterological Surgery, Yale University School of Medicine, PO Box 208062, New Haven, CT 06520-8062 (e-mail: imodlin@optonline.net).

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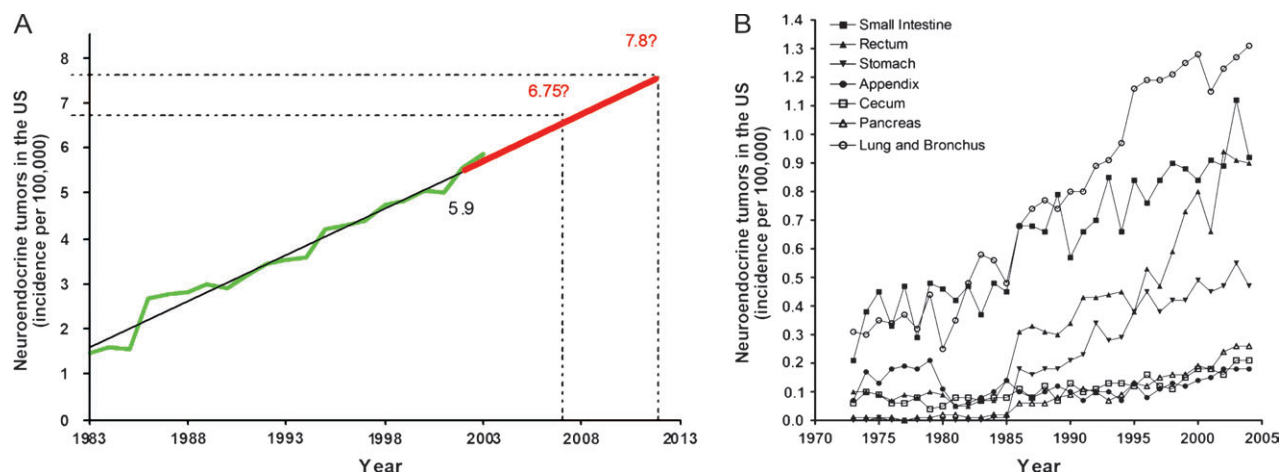


Figure 1. Increasing incidence of gastroenteropancreatic neuroendocrine tumors in the US population, 1973–2005. **A)** Current and estimated future incidence of gastroenteropancreatic neuroendocrine tumors in the United States. The yearly incidence of gastroenteropancreatic neuroendocrine tumors registered in the US National Cancer Institute

Surveillance, Epidemiology and End Results (SEER) database 1983–2003 is shown in **green**. Regression analysis of the calculated increase in incidence 2003–2013 is shown in **red**. **B)** The incidence of neuroendocrine tumors by anatomical location from 1973 through 2004 (SEER database). The range of overall increase is 221%–626%.

increase in incidence noted in the last 30 years likely represents improvements in diagnostic imaging, including the incidental diagnosis of asymptomatic cases with the increasing use of gastrointestinal endoscopy and abdominal computed tomography (CT), for example (3). However, large validated clinical datasets are needed to determine whether the increased rate of diagnosis represents a true increased incidence of disease.

The common feature of gastroenteropancreatic neuroendocrine tumors is that they are composed primarily of neuroendocrine cells, but this group of tumors is otherwise extremely heterogeneous in clinical presentation and behavior. Clinically, these tumors are considered “functioning” when their secreted products produce symptoms such as flushing and diarrhea and “nonfunctioning” when they do not. Nonfunctioning tumors are less likely to be detected unless found incidentally or when the primary or metastatic lesions have grown large enough to cause mass effects (eg, bowel or biliary duct obstruction) (6). In contrast, symptoms due to the bioactive products that are secreted by functioning tumors lead to biochemical and anatomical diagnosis sooner, and may even be recognized when the primary lesion is less than 1 cm in diameter. In the case of small bowel neuroendocrine tumors, which are the most common gastroenteropancreatic neuroendocrine tumors, however, the onset of symptoms is usually indicative of hepatic metastasis. It is notable that although earlier literature considered about a third of neuroendocrine tumors to be nonfunctional (7), recent estimates have increased this proportion to as high as 60%, probably due to the widespread availability of CT scanning and the resultant discovery of incidental lesions, particularly in the pancreas (6).

The heterogeneity in gastroenteropancreatic neuroendocrine tumors is also reflected by large differences in survival rates according to the primary site and cell type of the tumor. For example, the 5-year survival for neuroendocrine tumors in the pancreas may be as high as 97% for benign insulinomas (usually diagnosed very early) and as low as 30% for some neuroendocrine tumors of the pancreas that do not secrete hormones with apparent

biologic activity (7). For many years, gastroenteropancreatic neuroendocrine tumors have been considered relatively benign, but recent population-based data from the United Kingdom (8) indicate a considerably worse prognosis than has often previously been reported from small hospital case series—that is, 5-year survival rates were about 57% for well-differentiated tumors but only 5.2% for small-cell tumors.

It was generally agreed that the understanding of the true natural history of gastroenteropancreatic neuroendocrine tumors is limited, especially regarding survival in this generally slowly growing disease; whereas most tumors grow relatively slowly, others (ie, undifferentiated neuroendocrine carcinomas) exhibit highly aggressive behavior that is clinically indistinguishable from adenocarcinoma. In addition, much of the published literature predates modern imaging methods and includes heterogeneous patient populations that have undergone a wide spectrum of therapies, often serially.

Problems in the Current Management of Gastroenteropancreatic Neuroendocrine Disease

The conference participants highlighted existing deficiencies in the clinical management of patients with suspected or proven gastroenteropancreatic tumors. A delay in diagnosis remains characteristic of gastroenteropancreatic neuroendocrine tumors. Vague or non-specific initial symptoms are typical, with many patients having undergone extensive investigation by a primary care physician, endocrinologist, or gastroenterologist before the diagnosis is reached. This situation reflects the fact that many physicians lack experience with or education about neuroendocrine tumors as a result of inadequate attention to the subject both at medical schools and in training programs. As a consequence, the diagnosis is often not considered until the disease is advanced. Even once it has been considered, identification of neuroendocrine tumors using imaging with radiolabeled octreotide scanning, which recognizes the somatostatin receptors

found on most of these tumors (9), is not available at all institutions. Magnetic resonance imaging and multislice CT are the most sensitive of the widely available imaging modalities and are most effective when performed using protocols that have been optimized for the evaluation of neuroendocrine tumors (2). Once a diagnosis has been made, the therapeutic options include medical therapies (principally with somatostatin analogs) to alleviate the symptoms of excessive peptide and neuroamine or neuropeptide secretion; systemic chemotherapy for advanced disease; surgery, either with curative intent (in practice the only method of achieving a cure) or palliative cytoreductive surgery; and tumor ablation by radio frequency or chemoembolization to reduce metastatic tumor bulk. However, there may be little expertise locally to guide the patient's management, especially for the many patients who are diagnosed with advanced disease. This latter point is particularly important because, unlike the common adenocarcinomas (eg, esophageal, gastric, pancreatic, and colonic), the generally slow growth of gastroenteropancreatic neuroendocrine tumors, combined with their frequent ability to produce specific hormonal symptoms, often results in a protracted clinical course with considerable morbidity and frequent hospitalizations over several years if not properly treated. The conference participants believed that the general lack of multidisciplinary neuroendocrine tumor management teams further amplifies the issue of the current suboptimal clinical management of these tumors.

Why Has Progress in this Disease Been So Slow?

The consensus of the conference participants was that several features of gastroenteropancreatic neuroendocrine tumors provide important challenges to improving patient care. These issues are described in detail below; suggested solutions to these problems are highlighted in Table 1.

Limited Understanding of the Cellular and Molecular Biology of Neuroendocrine Cells and Mechanism of Tumorigenesis

A major impediment to developing more effective therapy was thought by many participants to be the continuing uncertainty about the origins and differentiation of both normal and malignant neuroendocrine cells. Initially it was believed that the gastrointestinal neuroendocrine cells that give rise to these tumors migrated from the neural crest to the gut endoderm (10). It is now apparent that neuroendocrine cells of the gut originate from the multipotent stem cells that give rise to all epithelial cell types in the gastrointestinal tract and pancreas (11). Normal neuroendocrine cell populations in the pancreas include the alpha (glucagon-secreting), beta (insulin-secreting), delta (somatostatin-secreting), and pancreatic polypeptide cells of the islets of Langerhans (12). In the gastrointestinal tract, neuroendocrine cells are diffusely located in the mucosal layer of the gut, and at least 13 different types of specialized gastrointestinal neuroendocrine cells have been described and characterized based on morphology and/or the predominant bioactive peptide or amine that they secrete (13). These specialized cells include enterochromaffin cells (which secrete serotonin), enterochromaffin-like (ECL) cells (histamine), G-cells (gastrin), and

D-cells (somatostatin) (13,14). Other secretory products that are released from neuroendocrine cells from specific regions of the gastrointestinal tract include ghrelin, glucagon-like peptide, motilin, vasoactive intestinal polypeptide (VIP), insulin, peptide YY, and neurotensin (13,14). Secretion of these products is variously regulated by luminal, neural, and hormonal input in a paracrine, neurocrine, or capillocrine manner. Although the symptom complex that is attributable to hyperinsulinemia and VIP hypersecretion is relatively familiar and the physiological effects of some of the other peptides well understood, the symptom complexes that result from certain other tumors, such as those that secrete peptide YY or motilin, are poorly characterized (2).

The differentiation of neuroendocrine cells from the putative gastrointestinal stem cell is regulated by basic helix-loop-helix transcription factors, including math 1, neurogenin 3, and neuro D/beta 2. Loss of function mutations in neurogenin 3, resulting in a loss of enteroendocrine differentiation, were recently identified as the underlying basis of congenital malabsorptive diarrhea (15), emphasizing the potential clinical importance of understanding the molecular pathogenesis of neuroendocrine cell differentiation. In chronic *Helicobacter pylori* infection, gastric somatostatin-secreting neuroendocrine cell populations are decreased, leading to a state of mild hypergastrinemia (16).

The regulation of cell growth and secretion within neuroendocrine tumors remains obscure. Neuroendocrine tumors are characterized by cells displaying the morphology of neuroendocrine cell lineage (secretory granules) and can be further characterized by their dominant secretory products, but the cells of origin remain unknown. Are the cells of origin long lived, committed neuroendocrine progenitors? The early lesions of neuroendocrine tumors are also poorly characterized. In the stomach, diffuse ECL cell hyperplasia appears to be a marker of increased gastric neuroendocrine tumor development, but the ECL cell is not necessarily the direct precursor cell of gastric neuroendocrine tumors (17).

In contrast to most common adenocarcinomas, the molecular pathogenesis of gastroenteropancreatic neuroendocrine tumors, their molecular determinants of malignancy, and the factors that determine aggressive behavior in a subset are largely unknown. The oncogenes (*RAS*, *EGFR*, *MYC*, *JUN*) and tumor suppressor genes (*RB1*, *TP53*, *PTEN*) that are commonly described in adenocarcinomas of the gastrointestinal tract do not seem to be involved in gastroenteropancreatic neuroendocrine tumor pathogenesis (18). Although some insights have been provided by studying inherited disorders that are associated with gastroenteropancreatic neuroendocrine tumors (eg, multiple endocrine neoplasia type 1, von Hippel-Lindau disease, and neurofibromatosis1), the genetic abnormalities in these diseases appear to be important in only a subset of the sporadic forms of gastroenteropancreatic neuroendocrine tumors (18–20). This lack of molecular understanding, combined with the lack of animal models, was considered to have markedly impeded the development of specific therapies.

Paucity of Specific Targets for New Therapies

Neuroendocrine cells have a high density of cell surface receptors for somatostatin, an endogenous peptide that acts through paracrine pathways to inhibit secretion of neuropeptides. Somatostatin recep-

Table 1. Impediments to progress in gastroenteropancreatic neuroendocrine tumors and solutions proposed at the summit workshop*

Issues	Barriers	Solutions
Limited understanding of cellular and molecular biology of neuroendocrine cells and mechanisms of tumorigenesis.	Few investigators focused on neuroendocrine tumor pathogenesis. Little opportunity for basic and clinical training in this field.	Increase and earmark funding from government (NIH) and charitable foundations for gastroenteropancreatic neuroendocrine tumors.
	Paucity of relevant cell and animal models.	Develop novel in vitro and in vivo models.
Paucity of specific targets for new therapies.	Poor definition of specific molecular targets.	Improve understanding of molecular pathogenesis. Develop appropriate cell lines and animal models that can be used to identify possible new targets.
	Paucity of high-quality clinical trials.	Multicenter large clinical trials of homogenous patient groups.
Shortage of in vitro and animal models to study disease pathogenesis and treatment.	Few investigators focused on gastroenteropancreatic neuroendocrine disease.	Designate funding specifically for translational gastroenteropancreatic neuroendocrine model development.
	Existing models have limited correlation with clinical states.	Collaboration between basic and clinical scientists in gastroenteropancreatic neuroendocrine disease.
No uniform pathological classification or staging system.	Community pathologists unfamiliar with neuroendocrine tumors.	Develop a consensus among US pathologists on classification and staging. Educate pathologists.
	Reluctance for US pathologists to adopt WHO system without demonstration of clinical benefit.	Prospectively validate WHO criteria.
	Semantic problems of benign vs malignant states in gastroenteropancreatic neuroendocrine tumors.	Referral for pathological second opinions. Develop minimal standards that are required for diagnosis and classification.
Lack of molecular prognostic factors to identify high-risk patients and lack of an understanding of natural history of these tumors.	Relative rarity of gastroenteropancreatic neuroendocrine tumors. Heterogeneity of tumor types.	Establish regional and national databases.
	Long-term systematic studies of patients difficult. Lack of a surveillance test for gastroenteropancreatic neuroendocrine tumors.	Develop long-term molecular-clinical correlative studies. Fund research into biomarkers of gastroenteropancreatic neuroendocrine disease.
Few centers offer the multidisciplinary expertise required for the diagnosis, staging, and management of gastroenteropancreatic neuroendocrine tumors.	Numerous imaging options available. Lack of widespread availability of sensitive and specific imaging. Local resources and expertise variable.	Development of regional multidiscipline centers of expertise with experienced and focused clinicians and radiologists.
	Paucity of high-quality clinical trials.	Multicenter clinical trials of homogenous patient groups.
Paucity of investigators in neuroendocrine tumor disease.	Gastroenteropancreatic neuroendocrine tumors at the interface between disparate disciplines (oncology, endocrinology, surgery, gastroenterology).	Increase educational programs. Increase medical and public awareness of gastroenteropancreatic neuroendocrine tumors.
	Underemphasized as a source of morbidity and mortality.	Increase funding for clinical and basic scientific research into this disease.
Lack of understanding of the disease complications that lead to morbidity and mortality.	Inexperience of many clinicians in gastroenteropancreatic neuroendocrine tumors.	Develop regional centers of excellence with multidiscipline clinical teams.
	Lack of reliable diagnostic tests.	Establish large prospective databases with well-defined patient groups.

* NIH = National Institutes of Health; WHO = World Health Organization.

tor analogs are highly effective at controlling many of the symptoms caused by excessive neuropeptide release, such as the flushing and diarrhea that are characteristic of the carcinoid syndrome (2). With time, however, many patients develop a variable degree of resistance

to these analogs. Few alternative therapies are available, and in many cases these are only marginally effective. Moreover, although somatostatin therapy may, in some instances, inhibit further tumor growth, it does not cause tumor regression (21,22).

For disseminated disease, particularly for poorly differentiated tumors, combinations of conventional systemic cytotoxic chemotherapeutic agents are the first line of therapy. Etoposide, cisplatin, 5-fluorouracil, streptozotocin, and doxorubicin are among the most commonly used treatments (3). Other drugs that are currently being evaluated for efficacy in systemic disease include inhibitors of vascular endothelial growth factor, of receptor tyrosine kinases (eg, sunitinib, sorafenib, and vatalanib), and of the mammalian target of rapamycin (mTOR; eg, temsirolimus and everolimus) (23–26). However, the clinical and/or radiological response rates in single-agent trials of these newer molecular targeted therapies are less than 20% (3), and their future use will likely depend on combination therapies. Except for somatostatin and its analogs, all of the systemic chemotherapeutic agents that are being evaluated were developed for the treatment of non-neuroendocrine neoplasia and are being applied only secondarily to gastroenteropancreatic neuroendocrine tumors. Exploitation of the relative specificity and overexpression of somatostatin receptors in gastroenteropancreatic neuroendocrine tumors has led to the development of radionuclide therapy tagged to somatostatin analogs. Initial experience in Europe with somatostatin analog radionuclide therapy appears promising (27), but, as for neuroendocrine tumor treatment in general, appropriate randomized clinical trials are lacking. In the United States, availability of this therapy is limited and widely regarded as experimental.

Shortage of In Vitro and Animal Models to Study Disease Pathogenesis and Treatment

Several animal models that develop pancreatic neuroendocrine tumors exist that were considered to be helpful in understanding the molecular pathogenesis of these tumors as well as in the development and testing of novel therapies. Pancreatic neuroendocrine tumors develop in mice with constitutively active *Cdk4* (28) and in *Cdkn2c/Cdkn1b* double knockout mice (29). For example, mutations in the *MEN1* gene are responsible for most cases of the multiple endocrine neoplasia 1 syndrome, which is characterized by endocrine tumors of the upper gastrointestinal tract, pancreas, pituitary, thymus, and bronchial tree (30). Sporadic *MEN1* mutations or deletions are relatively frequent in sporadic foregut neuroendocrine tumors. Heterozygote *Men1*^{+/-} mice also develop pituitary, parathyroid, and pancreatic neuroendocrine tumors (31–33), suggesting that these mice may be a useful model for these tumors. How loss of *menin*, the protein product of the *MEN1* gene, contributes to neuroendocrine tumor formation is not understood, in part because it interacts with many proteins that are involved in DNA damage and repair, growth, transcription, and cytoskeletal organization. Thus, determining the most important pathways for further investigation is difficult.

Two rodent models of gastrointestinal carcinoid tumors have been described (34,35). Few well-characterized gastrointestinal neuroendocrine tumor lines have been derived from human primary lesions (36), and only one pancreatic neuroendocrine cell line exists (37). Appropriate xenograft models to study the biology of metastatic growth and therapy are similarly hampered by the absence of such cell lines.

In general, the lack of animal models of gastroenteropancreatic neuroendocrine tumors was considered by the conference participants to have greatly impeded not only studies of the pathogenesis and the natural history of gastrointestinal neuroendocrine tumors but also, and more important, the development of effective therapies.

That is, all therapies have had to be initially evaluated in patients, which is a particular impediment in this type of disease because of its low frequency, lack of standardized care, dispersal of patients in many centers, and the lack of uniformity of classification systems. Appropriate animal models would greatly expedite the development of new potential therapeutic agents.

No Uniform Pathological Classification or Staging System

Gastrointestinal carcinoid tumors were subdivided for many years according to their anatomical site of origin (ie, foregut, midgut, or hindgut). This classification system provided some prognostic information for clinicians (38) and to some extent reflects differences in the molecular genetics of foregut, midgut, and hindgut tumors (19,20). In recent years, standardizing the pathological reporting of gastroenteropancreatic neuroendocrine tumors has been attempted to further aid clinicians regarding the likely biology of individual tumors. The World Health Organization (WHO) classification (39) has defined these tumors by degree of differentiation and the tumor site of origin. A European group of expert neuroendocrine pathologists have suggested further refining this classification by including the Ki-67 scoring index (an immunohistochemical measure of cell proliferation) and by proposing a new tumor-node-metastasis classification (40,41). However, the WHO classification has not been widely adopted in the United States, even by some pathologists who specialize in neuroendocrine tumor diagnosis. This lack of a defined and widely accepted classification and staging system in the United States has led to a lack of agreement on the minimum pathological investigations required to clearly define these tumors and to difficulties in comparing US data with those from European centers and even in comparing data within the United States. In part, the failure to develop a clear classification system in the United States was believed to reflect unease with designating poorly differentiated neuroendocrine tumors as cancers as well as the continued insistence of the use of the archaic term carcinoid. Indeed, semantic issues continue to obfuscate the field, especially with regard to clinical trials—in which, as a result of the absence of a broadly accepted classification system, heterogeneous patient populations have often been the norm.

Lack of Molecular Prognostic Factors to Identify High-Risk Patients and Lack of a Natural History of These Tumors

Some patients with gastroenteropancreatic neuroendocrine tumors have relatively benign disease and may live for decades, whereas others have a rapidly progressive course. There was consensus among participants that determining the likely biologic behavior of the tumor is important for deciding who, how, and when to treat, but the choice of therapy is currently often empiric because the natural history of the disease is not well understood.

Appropriate long-term treatment of these patients requires a clear understanding of the natural history of these tumors, which at present is unavailable given the recent alterations in therapy (somatostatin analog availability). Because few patients are systematically studied and followed in treatment centers that have an interest in all aspects of the disease, little is known of important natural history factors that might determine survival, including the development of secondary malignancies (15%–20% in some series) (3,42) or the effectiveness of current therapeutic options on altering the natural history of disease.

Few Centers Offer the Multidisciplinary Expertise Required for the Diagnosis, Staging, and Management of Gastroenteropancreatic Neuroendocrine Disease

As noted already, gastroenteropancreatic neuroendocrine tumors can be difficult to diagnose and problematic to stage and manage. Expertise in determining the location and extent of tumor burden is therefore essential in planning treatment. A wide array of endoscopic and radiological techniques are used, including somatostatin receptor scintigraphy, CT, magnetic resonance imaging, and selective angiography, as well as organ-specific techniques, such as endoscopic ultrasound. At the conference, enthusiasm was expressed for scanning positron emission tomography, especially using isotopes that may be relatively specific for neuroendocrine tumors, such as labeled dopamine, tryptophan, or octreotide (43,44). The choice of imaging modality should depend on the clinical question being posed—this may vary from seeking to identify a small primary lesion responsible for a biochemically diagnosed syndrome to evaluating the extent and location of metastatic disease in the liver to plan cytoreductive surgery or embolic ablation. Selecting among diagnostic modalities and determining the optimal protocol for neuroendocrine tumor diagnosis ideally should reflect a close collaboration between clinicians and radiologists.

Participants agreed that, after an accurate diagnosis and evaluation of the site and extent of disease, the choice of therapy should also be highly individualized on the basis of current symptoms, tumor type and burden, and additional prognostic information. The patient's goals and expectations should also be considered in the context of the relative risks and the benefits of available treatments and their impact on quality of life. Choosing no treatment should also be a consideration. Given the paucity of sufficiently powered randomized clinical trials using homogenous patient groups and adequate follow-up in this field, making the right treatment choice is challenging, even for clinicians who have considerable experience in the management of this disease.

The management and treatment of gastroenteropancreatic neuroendocrine tumors differs markedly from the treatment of the common malignancies in the expertise required for diagnosis, pathology, cytoreductive and curative neuroendocrine surgery, oncology, and interventional radiology and nuclear medicine. It is difficult at present not only to acquire but also to maintain this specialized expertise because of the limited number of patients that most individual centers see annually. The limited number of patients also impedes the ability to carry out standardized studies and systematically assess new treatments. The need for specialized expertise combined with the limited numbers seen in most smaller centers led to the proposal that regional centers should be developed for the investigation and management of gastroenteropancreatic neuroendocrine tumors. These centers could also participate in the establishment of a national clinical database and biobank of tumor, serum, and DNA for future collaborative clinical and translational studies of neuroendocrine tumor disease.

Lack of Understanding of the Disease Complications That Lead to Morbidity and Mortality

One of the characteristic features of carcinoid tumors—particularly those of the ileum—is the development of fibrosis, both locally and at sites distant from the primary tumor. Fibrosis occurs as a result of the production of bioactive agents, such as serotonin and connec-

tive tissue growth factor, that have profibrotic effects (45,46). Cardiac fibrosis is particularly evident after metastasis to the liver and is associated with right-sided heart valve fibrosis and impairment of cardiac function. Although the frequency of carcinoid heart disease is as high as 20% at tumor diagnosis, recent advances in its early detection (echocardiography) as well as aggressive surgical and medical management, including balloon valvuloplasty, have led to longer survival (47). The mechanisms of fibrosis are uncertain but have also been noted with 5-HT_{2B} serotonin-receptor agonists, including fenfluramine, dexfenfluramine, pergolide, cabergoline, and ergotamine, which may ultimately activate transforming growth factor- β (48). Fibrosis of the mesentery in proximity to primary intestinal carcinoid tumors can also cause extensive fibrosis that may lead to bowel obstruction, mesenteric ischemia, and intestinal perforation. The presence of extensive fibrosis often renders surgical management very difficult, and, if it is advanced, may even culminate in an abdominal cocoon that is virtually untreatable.

Paucity of Investigators in Neuroendocrine Tumor Disease

There was wide agreement among participants at the conference that, relative to the prevalence of neuroendocrine tumor disease, the amount of basic and translational research in this field is very low, with few federally funded investigators and little appropriation from the National Institutes of Health thus far (Figure 2) (2). The relevant study sections rarely include individuals with expertise in this area, and the review process remains a gray zone between

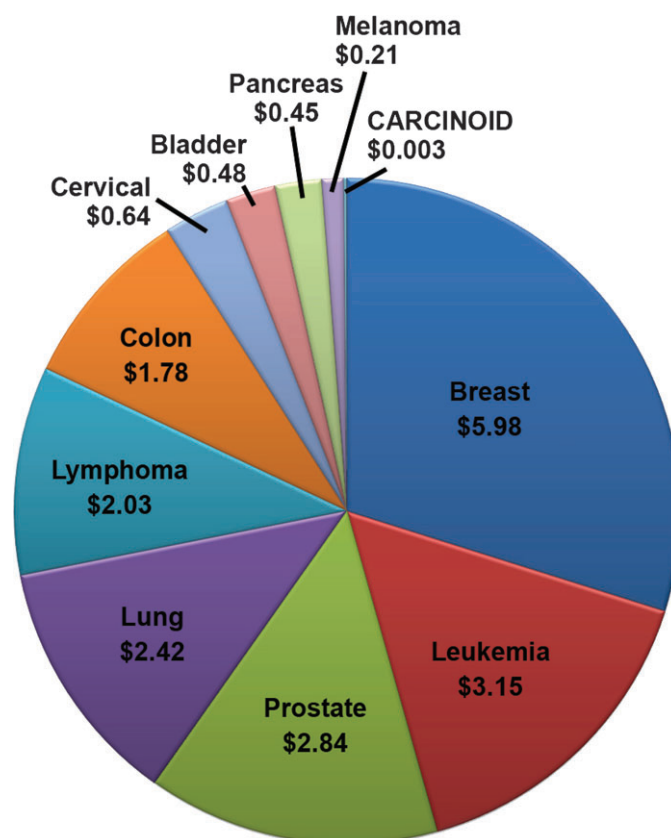


Figure 2. Pie chart of National Institutes of Health disease funding of research in 11 types of cancer, in billions of US\$, 1994–2002.

gastrointestinal, endocrine, and broader aspects of neoplasia. There are no funded fellowships and little subsequent clinical opportunity because these remain “orphan” tumors for clinical investigators as well as scientists. Very few clinicians focus specifically on gastroenteropancreatic neuroendocrine disease. Furthermore, because of the lack of regional specialty centers, few programs allow in-depth training or provide experience for young investigators or clinicians interested in these disorders.

Conclusions and Recommendations

The group of experts at the meeting considered that the increasing incidence and prevalence of neuroendocrine disease in the United States was of considerable concern, particularly in light of the lack of evidence of improvement of outcome and the lack of any tangible evidence of the development of demonstrably effective novel therapies. One particular factor that is limiting progress was thought to be the absence of adequate cell lines and animal models that would facilitate identification of the genetic and mechanistic basis of the disease, thereby enabling the development of new effective diagnostic and therapeutic strategies. A lack of a coherent and accepted pathological classification system was considered to hamper clear identification of the disease and to impede uniform assessment of the efficacy of treatment and prognosis. Overall, these deficiencies were thought to be amplified by widespread lack of funding (clinical and basic science), a lack of understanding of the disease among caregivers, and the absence of regionalized centers of excellence that could deliver expert care and coordinate appropriately powered clinical trials. Based on the evidence reviewed at the conference, there was a broad consensus on the specific measures necessary to move the field forward and thereby improve care for patients with neuroendocrine tumor disease, as summarized below.

General Summit Recommendations

1. Improve the education of physicians and the public in regard to early recognition of the symptoms of disease and the principles of management.
2. Develop tumor and plasma markers that can be used for early diagnosis and to monitor disease treatment.
3. Standardize pathology. Incorporate methods for minimum pathological diagnosis and classification. Use TNM classification for prognosis and coordinate classification systems with WHO and European criteria.
4. Establish regionalized centers of expertise that will expand the number of new investigators in the field and provide tumor banks with appropriate clinical and laboratory data.
5. Develop better imaging modalities (to use pre- and postoperatively) with increased sensitivity that can provide molecular prognostic information.
6. Develop more effective treatments of advanced disease—preferably from increased understanding of molecular pathogenesis and increased use of animal models.
7. Facilitate trials of new agents obtained domestically and abroad, and improve the availability of promising agents.
8. Develop new cell lines and animal models for all gastroenteropancreatic neuroendocrine tumors.

9. Improve the molecular understanding of these tumors through the application of genomic, RNA interference, microRNA, proteomic, and small-molecule screen technologies.
10. Improve understanding of the development of the diffuse neuroendocrine cell system, including EC cells, to better understand the development of abnormalities in these cells.

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Participants: Modlin, Irvin M., MD, PhD, DSc, Yale University School of Medicine, New Haven, CT; Ahlman, Hakan, MD, PhD, Sahlgrenska Universitetssjukhuset, Gothenburg, Sweden; Bogoy, Matt, PhD, Stanford University School of Medicine, Stanford, CA; Chen, Herbert, MD, FACS, University of Wisconsin, Madison, WI; Chung, Daniel C., MD, Massachusetts General Hospital, Boston, MA; Ellis, Lee M., MD, M. D. Anderson Cancer Center, Houston, TX; Fong, Yuman, MD, Memorial Sloan Kettering Cancer Center, New York; Goldenring, James R., MD, PhD, Vanderbilt University School of Medicine, Nashville, TN; Gustafsson, Bjorn I., MD, PhD, Trondheim University, Norway; Jensen, Robert T., M. D. National Institutes of Health, Bethesda, MD; Kidd, Mark S., PhD, Yale University School of Medicine, New Haven, CT; Klimstra, David S., MD, Memorial Sloan Kettering Cancer Center, New York; Krenning, Eric P., MD, PhD, Erasmus Medical Center, Rotterdam, The Netherlands; Kulke, Matthew, MD, Dana-Farber Cancer Institute, Boston, MA; Leiter, Andrew B., MD, University of Massachusetts Medical School, Worcester, MA; Marx, Stephen J., MD, National Institutes of Health, Bethesda, MD; Mooney, Margaret, MD, National Institutes of Health, Bethesda, MD; Moss, Steven F., MD, Brown University, Providence, RI; Nakamura, Eric, MD, University of California, San Francisco, CA; Norton, Jeffrey A., MD, Stanford Cancer Center, Stanford, CA; O'Dorisio, M. Sue, MD, University of Iowa Hospitals and Clinics, Iowa City, IA; Oberg, Kjell E., MD, Uppsala University Hospital, Sweden; Rindi, Guido, MD, PhD, University of Parma, Italy; Roth, Bryan L., MD, University of North Carolina, Chapel Hill, NC; Wang, Timothy C., MD, Columbia University, New York; Washington, Mary Kay, MD, Vanderbilt University Medical Center, Nashville, TN; Welch, Danny R., PhD, University of Alabama, Birmingham, UK; Wright, Nicolas, MD, PhD, Barts and the London School of Medicine and Dentistry, London, UK; Yao, James C., MD, M. D. Anderson Cancer Center, Houston, TX.

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