(15). Biopsy of established villus atrophy is easily recognized but more subtle early changes can be difficult to diagnose with confidence. There is a wide variation in villus height and age has no effect on morphometry (16). The normal villus height:crypt depth ratio is 3:5 and the surface enterocyte height is normally 29-34 pm. Crypt hyperplasia is a pointer and counting of intraepithelial lymphocytes is paramount. The normal range is 10-30/1 00 enterocytes (13).

Differential diagnoses of celiac disease include infective enteropathy, tropical sprue, graft *versus* host and transient food sensitivities (eggs, fish, Soya, etc.), immunoproliferative disease and drug damage. Duodenal pathology in partial villus atrophy associated with dermatitis herpetiformis is identical to celiac disease. Celiac disease is a clinicopathological diagnosis with a characteristic lesion of the small intestine, malabsorption and prompt improvement on a gluten-free diet. Symptoms are related to the extent of mucosa involved. Antigliadin antibody screening tests are useful in at risk groups but biopsy is the gold standard for diagnosis (17).

Pathogens

Numerous microorganisms infect duodenal mucosa, particularly in immunosuppressed patients and may be either asymptomatic or symptomatic, leading to endoscopy and biopsy. Principal pathogens are cytomegalovirus, microsporidiosis, cryptosporidiosis in immunosuppression, in which a high index of suspicion is needed for diagnosis, as the changes are subtle. *Giardia lamb/ia* infection also shows nonspecific pathological changes (18). Whipples disease is a rare multisystem bacterial infection with characteristic duodenal pathology. The organism is *Tropheryma whippelli.* The diagnosis is usually established by duodenal biopsy but the gut is not inevitably involved (19).

SugQested reporting orotocol for duodenum

Systematically note:
Site (*+1*– Brunners glands)? DI, D2
Villus architecture – normal/distorted
Surface – erosion, IELs, lENs, gastric metaplasia – *±1*—extent?
Inflammation, active and/or chronic, grade mild, moderate, severe-epithelium/lamina propria
Pathogens
Other pathologies *(e.g.,* granulomas, macrophages)?

This gives the algorithm

Depending on biopsy site:
DI – Active duodenitis, lENs + gastric metaplasia + antral *H. pylon* = DU risk
D2 – Definite villus distortion, no neutrophils, $IELs = partial villus atrophy
D1/2 – Chronic duodenitis – think of other pathology *e.g.,* pathogens, IBD, etc.

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Tumors of the amputla: Pathogenesis and prognostic factors

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Ampullary epithelial neoplasms include benign (5%) and malignant tumors (95%), which represent 5% of all gastrointestinal tumors but which account for up to 36% of the surgically operable pancreaticoduodenal tumors (1). Ampullary carcinoma is a tumor topographically centered in the region of the ampulla of Vater, which is formed by three anatomical components: the ampulla (common channel), the intraduodenal portion of the bile duct and the intraduodenal portion of the pancreatic duct. Thus, it may show infestinal or pancreatobiliary morphology. The unequivocal establishment of ampullary origin is possible in small lesions by applying strict topographical criteria obtained at gross and histological examination. The presence of 'preinvasive" (adenomas or areas of dysplasia) modification in the anatomical structures of the ampulla (2) and the intestinal type of the carcinoma can help in the distinction (3). Periampullary carcinoma, is a widely used term to define a heterogeneous group of neoplasms arising from the head of the pancreas, the terminal common bile duct and the duodenum. The din-

cal importance of differentiating ampullary cancer from those arising from periampullary structures, resides in their significant difference in resectability and prognosis; up to 50% of patients with ampullary carcinoma can be cured by surgery alone (1, 3). Several reasons have been hypothesized for the improved prognosis of ampullary *versus* pancreatic carcinoma, including: i) the earlier diagnosis due to precocious onset of jaundice; ii) the frequent expansive, fungating growth; iii) the presence of a preexisting adenomatous phase; and iv) lesser lymphatic drainage. Unfortunately, the advanced stage at which most cases are diagnosed prevents a precise definition of the structures of origin. This means that some ampullary carcinomas at advanced stages might be erroneously considered pancreatic tumors. This bias may reflect the marked heterogeneity of statistical, epidemiological and molecular data.

Ampullary carcinomas are usually diagnosed when the tumor mass reaches about 2.5 cm in diameter (1, 4-6). They are macroscopically basically divided into polypoid or ulcerating carcinomas. Histologically, the most important distinction to make is between malignant tumors and adenomas. Most carcinomas are well to moderately differentiated. The most frequent type of ampullary carcinoma has intestinal morphology with strict resemblance to the adenocarcinoma of the colorectum and frequently shows an adenomatous component. Pancreatobiliary type carcinoma, the second most frequent subtype, is morphologically indistinguishable from carcinoma of the pancreas and bile duct and usually shows desmoplastic stromal reaction, whereas adenomafous areas are infrequently found.

There is general agreement that local spread of the tumor (T-stage) is the only significant and independent prognostic factor for this cancer, whereas the predictive value of tumor grade, resection margins and lymph node metastasis is controversial (4-10). Nevertheless, any cancer stage includes both long-term survivors and patients dying from the disease.

Based on the observation of adenomatous areas in the majority of malignant tumors, and of foci of carcinoma within adenomas, an adenoma-carcinoma sequence has been postulated (2,11). The fact that a proportion of ampullary cancers do not show any detectable adenomatous area may suggest the existence of alternative pathogenetic mechanisms, such as the development from flat epithelium undergoing dysplastic changes without polyp formation (12).

The study of the molecular anomalies may help to unravel whether the ampullary carcinomas are more similar to those of the pancreas, biliary ducts or gastrointestinal tract.

We will consider the most important molecular anomalies reported in ampullary carcinoma.

Mutations of RAS-family genes

Activating mutations of one of the members of the RAS-gene family have been detected in a variety of human neoplasms with variable frequency (13). The incidence of Ki-ras mutations in ampullary cancers is lower than that in pancreatic carcinoma (35% *vs.* 90%) (2, 14, 15). The overall pattern of mutations more closely resembles that of colorectal than of pancreatic cancer. In the pancreas a similar rate of Ki-ras mutations is observed in intraductal papillary tumor (31%) (16). Mutations in RAS are frequent in adenomas and in advanced cancers with residual foci of adenoma and absent in cancers lacking adenomatous component, which suggests that RAS abnormalities are relatively early phenomena associated with the adenoma-to-carcinoma sequence and these do not significantly correlate with patient survival (2, 14).

D53 Abnormalifies

In ampullary neoplasias p53 mutations are common abnormalities associated with the transformation of adenomas and low-grade cancers into morphologically high-grade and clinically aggressive carcinomas. Mutations were found in 53% of patients who died of the disease *versus* 33% in surviving patients (4). Nuclear accumulation of p53 protein is immunohistochemically detectable in morphologically high-grade areas of cancers harboring a p53 gene missense point-mutation (2).

Chromosome 5a21: APC and MCC genes

The adenomatous polyposis coli (APC) gene is a tumor suppressor gene, which is mutated in the germ-line DNA of individuals affected by familial adenomatous polyposis (17). Allelic losses at chromosome 5q21 are relatively frequent in ampullary tumors (50% of cases); the losses occur independently of the presence or absence of adenomatous areas, as well as of the presence of APC, RAS or p53 mutations (18). Sporadic ampullary cancers differ from those occurring in by familial adenomatous polyposis in the frequency (17% *vs.* 64%) as well as in the site of APG somatic mutations, suggesting a different molecular pathogenesis in the two conditions (19).

Genomic instability

Genomic instability at simple repeat sequences or microsatellites is a recently discovered landmark of some tumors, including the colon and rectum (20). The so-called replication error (RER+) phenotype is manifest by widespread alteration in size of simple repeat sequences secondary to the defect in DNA replication and repair genes (21). Twenty percent of ampullary tumors show microsatellite instability (4). RER+ cases are usually poorly differentiated, show a low representation of p53 mutations and lymph node metastasis. The patients with RER+ cancer usually survive for a long time, including cases with locally advanced or metastatic disease. The important suggestion from these data is that RER-status is useful in discerning prognosis within cancers at the same stage (4).

Ampullary tumors are heterogeneous diseases, according to morphological, biological features and molecular abnormalities. At least two groups might be considered: i) Adenoma/low-aggressive cancers, associated with *Chr 5q21* and/or *RAS* abnormalities or *RER+* phenotype. These neoplasms may progress into high-grade cancer by acquiring additional genetic abnormalities, such as p53 mutations. ii) Highly aggressive cancers, frequently associated with p53 gene mutations, involving early gene alterations different from *Chr 5q21, RAS* anomalies and RER—.

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Duodenal neuroendocrine tumors

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Frequency

Duodenal neuroendocrine tumors are still rarer than gastric neuroendocrine tumors and constitute between 1% and 1.5% of all gastrointestinal and —2% of all neuroendocrine tumors (1). The proportion of neuroendocrine tumors among all duodenal malignancies is 1.6%.

Embroyology

The embryogenesis of the endocrine cells of the digestive system has been the subject of considerable controversy. Initially, it was postulated that they are derived from the neural crest. However, the theory that most endocrine cells of the digestive system are derived from the endoderm is currently favored (2).

Classification

The nomenclature of the endocrine tumors of the digestive system is controversial. Some believe that the term 'carcinoid" should be applied while others prefer the term 'neuroendocrine tumors" for all neoplasms derived from the endocrine cells of the gut. Since they do not appear to be of neural origin, it could be argued that the term "neuroendocrine" is a misnomer. However, the prefix "neuro-" is appropriate if restricted to mean a common program of the synthesis of peptides, amines and certain antigens shared by the diffuse endocrine cells and neurons (3).

Well-differentiated endocrine tumor (carcinoid

Benign behavior	confined to mucosa-submucosa, <1 cm paragangliocytic paranganglioma
Uncertain behavior	confined to mucosa-submucosa, >1 cm and/or angloinvasive

Well-differentiated endocrine carcinoma (malignant carcinoid

Low-grade malignant	extending beyond submucosa or with metastases

Poorly differentiated endocrine carcinoma

High-grade malignant small or intermediate cell type

Hyperolasia

Enterochromaffin cell hyperplasia occurs in the small intestinal mucosa of patients with untreated gluten-sensitive enteropathy. This hyperplasia appears to be directly related to the severity of the disease and represents a nonspecific response to chronic mucosal inflammation and increased repair.

Neoplasms

Neuroendocrine neoplasms of the duodenum belong to the group of foregut tumors, which encompass neoplasms of the esophagus, stomach and duodenum, including those of the ampulla of Vater. They are generally similar to each other and to neuroendocrine tumors from other locations when conventional histological methods are used.

When light microscopy is used, foregut tumors may show several patterns, from clusters and sheets to ribbons and rosettes. These cells, as a rule, have a benign appearance, and mitoses are exceedingly rare. They are usually argyrophilic but on occasions may be argentaffin. Under the electron microscope, their secretory granules vary a good deal in appearance. In some tumor granules identical with those of the G, IG, D or ECL cells are seen, whereas others contain small, ill-defined cytoplasmic granules.

Approximately half of all patients with neuroendocrine tumors of the duodenum present with endocrine symptoms, one-third with mechanical obstruction and a few with bleeding or pain (4).

Sporadic neuroendocrine tumors

Gastrinoma

Most extrapancreatic gastrin-producing tumors are found in the duodenal wall, often accompanied by the typical Zollinger-Ellison