“This isn't wildly beyond what we already know. It's just a modification we haven't seen before. It's as natural, as logical, as any other manifestation of life. It obeys exactly the same laws. The cells are made of protoplasm, their character determined by the nucleus. Only in this creature, the cell-nuclei can control those cells at will.”

John W. Campbell, Jr.
“Who Goes There?” (1938)

Unlike the titular alien in Campbell’s famous story, the transformative abilities of human cells are much more limited, albeit sometimes just as insidious. Metaplasia, the replacement of one adult cell type by another in response to chronic injury, occurs in many anatomic sites under various conditions. One of the clinically significant forms of metaplasia is Barrett’s esophagus, in which columnar mucosa replaces esophageal squamous epithelium damaged by gastroesophageal reflux disease (GERD). This process is asymptomatic, but confers an increased risk for the subsequent development of esophageal adenocarcinoma.

The diagnosis of Barrett’s esophagus requires a combination of endoscopic findings visually consistent with glandular mucosa extending above the level of the gastroesophageal junction, with histologic findings confirming the presence of columnar metaplasia. While the extent of macroscopic involvement determines classification as long-segment (at least 3 cm) or short-segment (< 3 cm) Barrett’s esophagus, authorities disagree on the histologic findings required to confirm the diagnosis. In the U.S., definitive diagnosis of Barrett’s esophagus requires the presence of intestinal metaplasia with goblet cells (specialized columnar metaplasia). This form of metaplasia is a well-established risk factor for adenocarcinoma. However, other professional societies such as the British Society of Gastroenterology, also accept biopsies showing gastric cardiac-type mucosa as diagnostic of Barrett’s esophagus. While cardiac mucosal metaplasia within the esophagus may demonstrate intestinal-type histochemical features and concurrent genetic abnormalities, this finding has not been conclusively linked to an increased risk of malignancy.

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Although the association of Barrett’s esophagus with GERD is well-known, the molecular mechanisms governing the development of its characteristic metaplastic changes remain unclear. Various animal models have suggested that the metaplastic cells may arise from bone marrow stem cells, upwardly-migrating stem cells from the gastric cardia, or expansion of embryonic cells at the gastroesophageal junction. A current hypothesis regards reflux-mediated reactivation of signaling pathways involved in the development of the simple columnar-lined embryonic esophagus as the earliest event in the pathogenesis of Barrett’s esophagus. Reflux-induced upregulation of SHH in the squamous esophageal epithelium appears to lead to the induction of BMP4 in the underlying stromal cells, which in turn signals to the epithelium to express SOX9, leading to columnar differentiation of the squamous epithelium.

The extent of Barrett’s esophagus tends to correlate with the severity of the concurrent GERD, with long-segment Barrett’s usually occurring in the setting of severe reflux esophagitis, and short-segment Barrett’s showing no association with GERD symptoms or endoscopic signs of reflux. Other associated risk factors include obesity and cigarette smoking; a familial form also exists, accounting for 7-11% of cases. Notably, most conditions associated with the development of Barrett’s esophagus are also risk factors for esophageal adenocarcinoma.

Carcinomas arising in association with Barrett’s esophagus evolve through activation of oncogenes and silencing of tumor-suppressor genes; the NF-κB and IL-6/STAT3 pathways have been associated with progression to dysplasia and carcinoma, and may be activated by both intrinsic and extrinsic inflammation, as may occur in reaction to the oxidative stress induced by gastric acid and bile acids. Prior to the development of overt malignancy, the accumulating genetic changes may cause cellular changes histologically identifiable as dysplasia. Despite a certain degree of subjectivity in the grading of dysplasia and its patchy occurrence potentially leading to endoscopic sampling error, the presence of dysplasia remains the basis of clinical decision-making in cases of Barrett’s esophagus.

The diagnosis of low-grade dysplasia typically requires the presence of nuclear enlargement and hyperchromasia involving the crypt and surface epithelium. These changes may be impossible to distinguish from reactive atypia, especially in the presence of active inflammation; indeed, biopsies with this combination of findings may be diagnosed as “indefinite for dysplasia” owing to this difficulty. Investigations of the natural history of low-grade dysplasia have consequently yielded disparate results, with one study showing a cumulative risk of neoplastic progression of 85% at 109 months, but another finding an annual rate of neoplastic progression of only 1.8% in a group of patients followed for a mean of 6.2 years.

The histologic features of high-grade dysplasia include increased nuclear atypia and glandular complexity with cribriform architecture, which are generally beyond the level of abnormality expected in reactive or reparative atypia. In contrast to low-grade dysplasia, the rate at which high-grade dysplasia progresses to carcinoma is considered high enough to warrant intervention; one meta-analysis estimated approximately 6% per year, but markedly higher rates were reported in therapeutic trials. Until recently, the standard form of intervention was esophagectomy, but

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endoscopic resection and ablation techniques are now available, with a much lower risk of complications.

For years, the traditional preventative approach to managing Barrett’s esophagus has been to screen patients with GERD symptoms for Barrett’s esophagus by endoscopy, and to perform regular surveillance endoscopy on Barrett’s patients in order to detect dysplasia or neoplasia. Current recommendations are to screen those patients with chronic GERD symptoms and at least one additional risk factor for esophageal adenocarcinoma, such as obesity or tobacco use, using the Seattle protocol (biopsies from 4 quadrants every 1-2 cm). Those patients whose biopsies show no evidence of Barrett’s metaplasia undergo no further screening, while those with nondysplastic Barrett’s metaplasia are recommended for regular endoscopic surveillance every 3-5 years.

However, a number of recent studies have challenged the efficacy of the current screening practices, and have suggested that improved methods of risk stratification are needed to identify those patients who would benefit most from surveillance or other interventions.

New guidelines by the American College of Gastroenterology (ACG) on the diagnosis and management of Barrett’s Esophagus were recently published. These differ significantly from prior recommendations in several areas (see table below). Key differences include expanded use of endoscopic ablative therapy, encompassing patients with low-grade dysplasia; and further refinement of screening recommendations, including cessation of routine screening of patients with nondysplastic Barrett’s esophagus. These recommendations are based on evidence of lower risk of progression to adenocarcinoma in these patient populations.

A number of advanced endoscopic techniques have been studied for the purpose of improving the sensitivity of biopsies for the diagnosis of Barrett’s metaplasia. Probe-based confocal laser endomicroscopy (pCLE) has been proposed as a method of better visualizing the presence of intestinal metaplasia; this methodology utilizes a scanning laser light coupled with a fluorescent agent to create real-time, cell-level images of the esophageal mucosa. Early studies have suggested that this technique may improve the sensitivity and negative predictive value of biopsy in the detection of intestinal metaplasia. It remains to be seen whether these new techniques will become standard practice or included in formal recommendations/guidelines in the future.

References:
2) Spohler, SJ and Souza, RF. Barrett’s oesophagus. NEJM 2014; 371: 836-845.
3) Shihen NJ et al. ACG Clinical Guideline: Diagnosis and management of Barrett’s Esophagus. Am J Gastroenterol advance online publication, 3 November 2015; doi: 10.1038/ajg.2015.322

Summary of key updated clinical recommendations in the new American College of Gastroenterology (ACG) Guideline for Barrett’s Esophagus (BE)

- Routine screening is limited to men with chronic reflux symptoms and two or more other risk factors.
- Routine screening of women with GERD is no longer recommended, but may be considered if multiple risk factors are present.
- Patients with nondysplastic BE should undergo endoscopic surveillance no more frequently than every 3–5 years.
- Use of biomarkers or advanced endoscopic imaging techniques other than high-definition endoscopy are not currently recommended for surveillance.
- Endoscopic ablative therapy is recommended for patients with BE and high-grade dysplasia, as well as T1a esophageal adenocarcinoma.
- Endoscopic ablative therapy is also recommended for patients with BE and low-grade dysplasia, although endoscopic surveillance is an acceptable alternative.
Current Concepts in Pathology

OVARIAN CARCINOMA, SEROUS TUBAL INTRAEPITHELIAL CARCINOMA, AND THE PATHOLOGIST’S ROLE IN FALLOPIAN TUBE EXAMINATION

INTRODUCTION

Malignant tumors arising in the ovary, fallopian tube, and peritoneum are frightening to contemplate—unlike cervical or endometrial carcinomas, they are free to grow unchecked without producing symptoms until they have achieved a relatively late stage of growth, and there is no effective screening process or minimally invasive biopsy procedure available to assist in early diagnosis. Most of these tumors are carcinomas of surface epithelial origin, and of these carcinomas, approximately three quarters fall into the category of high grade serous carcinoma (HGSC).

SEROUS CARCINOMA: A SERIOUS CARCINOMA

HGSC is one of the most deadly gynecologic malignancies. The vast majority of patients (90% in some studies) present with stage III or IV disease, with spread beyond the pelvis and regional lymph node metastases common. Although surgical debulking to remove all visible tumor (“cytoreduction”) followed by cytotoxic chemotherapy frequently results in a progression-free interval, the rule for advanced stage disease is eventual recurrence and death from disease. As HGSC often presents at a relatively advanced stage with widespread peritoneal involvement, it can be difficult to determine the exact site of origin. Traditionally, the site of origin of HGSC has been assigned to the organ most affected, and it was long thought that the majority of these cases arose within the ovary. Primary fallopian tube tumors were classified as such when the tumor was either restricted to the tube, or when the fallopian tube was most affected, with other sites showing only minimal involvement or a different histology entirely.

There has been a recent shift in thinking about the putative site of origin of HGSC, resulting from increased scrutiny of the changes occurring within the fallopian tube in women undergoing risk-reducing salpingo-oophorectomy (RRSO).

MOLECULAR FEATURES OF HGSC

The signature molecular alteration associated with HGSC is mutation...