The Impact of Endoscopic Technology on Gastrointestinal Pathology*

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ABSTRACT

Since its introduction in the 1950s, fiberoptic endoscopy has dramatically altered the scope and practice of gastrointestinal (GI) pathology. Whereas examination by rigid instruments was generally restricted to the proximal digestive foregut and distal 25 cm of the large bowel, fiberoptic endoscopy extended these limits considerably, which resulted in a greater volume of biopsies submitted to the pathology laboratory. Furthermore, this technique is associated with a lesser degree of patient discomfort and a lower risk of complications compared to rigid or semiflexible endoscopy. In established endoscopy units, flexible endoscopy is performed increasingly with the videoscope rather than the fiberscope. With the added advantage of direct visualization, flexible endoscopy has eclipsed barium radiology as the premier investigative modality for GI diseases.

Although upper GI endoscopy and colonoscopy account for the majority of biopsy material, there are other flexible endoscopic techniques, including endoscopic retrograde cholangiopancreatography and enterostomy. Flexible endoscopy has not only impacted the diagnosis of important disease entities (eg, reflux esophagitis, H. pylori gastritis, celiac disease and GI polyps and neoplasia), but it has also become a key component of surveillance protocols for dysplasia in Barrett’s esophagus and idiopathic inflammatory bowel disease. Predicting major trends that may emerge from GI flexible endoscopy in the future is somewhat difficult, but promising new avenues of investigation include increased use of endoluminal ultrasound and trans-bowel fine needle aspiration. Biopsy material will be submitted with more frequency for genetic molecular studies such as tumor development and progression and identification of infectious agents; the priorities for handling biopsy material may have to be re-examined.

Gastrointestinal (GI) biopsies constitute a substantial proportion of the surgical pathology load in most tertiary care medical centers. Based on topographic site of origin, the GI tract is the single largest component of the biopsy service in this institution. This relates in part to the high frequency of patients' complaints referable to the digestive tract and is also a result of the advances in GI endoscopy that have

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led to more widespread application of this technique.\textsuperscript{1–3} To gain a better appreciation of the impact of the changes in endoscopic techniques on gastrointestinal pathology, it is pertinent to examine the historical perspective from which the technology arose.

**Historical Perspective**

The origins of endoscopy can be traced back to 400 BC, when Hippocrates described the use of rudimentary anal specula under natural light.\textsuperscript{3,4} The next significant step came only in the last few centuries, with the development of better light sources, mirrors and lenses, which in turn permitted the introduction of longer endoscopy instruments. In the late 19th century, the light bulb was a major impetus to the advancement of endoscopy; in conjunction with further refinement in lenses, it greatly improved the quality and intensity of light.\textsuperscript{2–4} Dr. Basil Hirschowitz and others have described the development of fiberoptics technology.\textsuperscript{2–7} Introduced in the 1950s, it was initially used in rigid endoscopes.\textsuperscript{2–5} This paved the way for the development of flexible fiberoptic bundles which, by the 1960s, rapidly found application in flexible endoscopy.\textsuperscript{5–7} By the end of the decade, lens-optic had replaced fiberoptic instruments.\textsuperscript{2,3,5–7} Key features of the fiberscope were an open channel for insufflation, aspiration and passage of accessories such as biopsy forceps. Furthermore, instead of the instrument carrying a miniaturized electric light bulb, a second fiber bundle could transmit cold light from an external source.\textsuperscript{5} This technology effected a radical change in the scope and practice of gastroenterology. It vastly improved access to and visualization of the GI tract and greatly increased the range of diagnostic and therapeutic procedures.\textsuperscript{2,3,8–7}

In the last two decades, GI endoscopy has witnessed the introduction of charged-couple device (CCD) chips and video imaging.\textsuperscript{2,3} Whereas the real image is transmitted to the eye with a fiberscope, the videoscope does not require an eyepiece since the chip converts the image into electronic impulses, which are then transmitted to a video processing unit. This computer and video technology offers distinct advantages over the fiberscope. Although the fiberscope is portable and can be used in the physician office or taken to the operating room or patient's bedside, video-endoscopy has become more popular in established GI endoscopy units for several reasons: the videoscope does not have to be held close to the eye, mechanical manipulation of the instrument is easier and several persons can view the screen simultaneously. Moreover, the recording and storage of images is more efficient, and CCD technology has great potential for enhancing the images further.\textsuperscript{2,3}

**Impact on GI Pathology**

The impact of endoscopy technology on GI pathology can be assessed from a number of viewpoints. Consideration may be given to: i) the changing roles of endoscopy and medical imaging in the diagnostic work-up of the patient,\textsuperscript{2,6,8,9} ii) the anatomic site of origin of the biopsies, iii) the nature of the specimen and iv) the questions that have to be addressed from evaluation of the material or the clinicopathologic correlation.

**Changing Roles of Endoscopy and Medical Imaging**

Before the introduction of fiberoptic endoscopy, barium radiology was probably the principal investigative tool for delineating GI morphologic abnormalities.\textsuperscript{2,3,6–10} At that time, endoscopes were less maneuverable, and consequently areas such as the pylorus were generally not well visualized. Radiologic examination, with contrast medium, usually delineated the morphologic abnormalities more completely.

Flexible endoscopy permits direct visualization of the gut, in contrast to medical imaging,
which largely offers black and white images primarily in an indirect fashion. Additionally, diagnostic and therapeutic procedures can be performed simultaneously. Nonetheless, medical imaging continues to assume an important role in the diagnostic work-up of GI disorders, motility disorders such as achalasia of the esophagus, hiatal hernias of the stomach, diverticular disease of the colon and Hirschsprung's disease. Thus, the intention here is not to minimize the role of barium radiology or other medical imaging techniques, such as abdominal ultrasonography and computerized tomography, but, rather, to emphasize the advances made possible through the use of various endoscopic techniques and the manner in which this interfaces with GI pathology.

Anatomic Site of Origin

From an anatomic viewpoint, GI endoscopy procedures can be classified under four broad headings, namely: 1) upper GI endoscopy, 2) endoscopic retrograde cholangiopancreatography (ERCP), 3) enteroscopy and 4) colonoscopy. However, in order to convey a sense of what actually happens in practice, it is worth pointing out that well over 90 percent of the biopsy and cytology material submitted to most anatomic pathology laboratories is derived from upper GI endoscopy and colonoscopy, with only a relatively small proportion from ERCP and enteroscopy.

1) Upper GI Endoscopy

Compared to rigid and semi-flexible instruments, fiberoptic and video endoscopy allows much greater reach into the GI tract. With relative ease, it permits examination of the esophagus, stomach and proximal duodenum up to the Ampulla of Vater with rigid or semiflexible endoscopy, observation of some areas of the stomach, particularly the more distal regions, is limited, resulting in so-called blind areas. Furthermore, the procedure is more uncomfortable for patients and carries a higher risk for development of complications. Nonetheless, it may be advantageous to use rigid endoscopy in some situations.

Since rigid upper GI endoscopy is restricted primarily to examination of the esophagus and only part of the stomach, fiberoptic and video endoscopy created new avenues for the study of gastric pathology. A number of examples follow.

(i) Current opinion is that H. pylori has been a gastric pathogen in humans for a long time, but it was only in the 1980s that this organism was definitely associated with gastritis and peptic ulcer disease. Detailed characterization of the spectrum of H. pylori-associated disease mandated systematic studies involving the integration of such factors as clinical symptomatology, gastric acid status, endoscopy findings, biopsy histology, treatment protocols and patient follow-up. From a pathologic point of view, key features of this process were: (a) multiple biopsies could be obtained easily during the procedure, vis-à-vis difficulties encountered with rigid instruments. (b) the topographic origin of biopsies could be defined (eg, cardia, fundus, body, antrum, pylorus, lesser or greater curvature and (c) if necessary, the procedure could be repeated for follow-up purposes with little risk to the patient. Hence, flexible instruments were critical in setting the stage for delineating the role of H. pylori in chronic gastritis and peptic ulcer disease. It is now known that the antrum is a predilective site for this microorganism, and various hypotheses have been proposed to account for chronic antral gastritis, multifocal gastritis, gastric and duodenal ulcers, intestinal metaplasia, gastric dysplasia and carcinoma and malformations.

(ii) Gastric endocrine cell hyperplasia and neoplasia is another area of study which has benefited immensely from flexible endoscopy. A number of biopsy-based studies have documented endocrine cell hyperplasia and its progression or regression in relation to the acid status of the stomach. In this regard, chronic autoimmune gastritis in pernicious anemia is of interest. Abnormal proliferation of gastric intra-epithelial neuroendo-
crine cells and fundic gland polyps as well as hyperplastic polyps have also been described in patients on long-term H-2 receptor antagonists, such as cimetidine, or proton pump blockers, such as omeprazole. Both classes of drugs are potent inhibitors of gastric acid secretion and are highly efficacious in gastroesophageal reflux and peptic ulcer disease. Because of their inhibitory action on gastric acid secretion, they have been associated with gastric endocrine cell hyperplasia and the evolution of carcinoids. The unravelling of the time course for the development of neuroendocrine morphologic changes in relation to prolonged hypergastrinemia was facilitated by studies based on sequential biopsy material.

iii) More recently, reactive gastropathy has been described. This is thought to be an adaptive response to persistent mucosal injury resulting from such factors as non-steroidal anti-inflammatory drugs, alcohol or bile reflux. The histologic abnormalities of this condition include foveolar cell hyperplasia, which may give the gastric pits a corkscrew appearance, and an increase in the fibrous connective tissue of the lamina propria not necessarily with an inflammatory cell infiltrate. Because these abnormalities can be of a subtle nature, a better delineation of this entity was aided by clinicopathologic correlation with attention to the patient’s history, endoscopic findings and histologic features. Apart from the difficulties of obtaining directed biopsies using rigid endoscopy, surgically removed gastrectomy specimens or autopsy material are prone to iatrogenic damage and agonal or autolytic change, respectively.

2) ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAHY

The greater access to the GI tract provided by flexible endoscopy paved the way for development of ERCP. By cannulating the duodenal papilla and injecting contrast medium (pancreatography and/or cholangiography), this technique combines endoscopic and radiographic techniques to visualize and manipulate the pancreaticobiliary tract. A variety of diagnostic and/or therapeutic procedures can be carried out. As such, ERCP is a more complex process than simple endoscopy, but it is now routinely practiced in medium- and large-sized hospitals.

(3) ENTEROSCOPY

Whereas endoscopic examination of the upper GI tract can be conducted with relative ease up to the level of the duodenum, inspection of the portion of the small intestine that is more distally situated is a greater challenge. This, however, can be achieved by a variety of techniques, such as specialized enteroscopes, or intraoperatively. Fortunately, by using colonoscopic procedures, the terminal ileum can be examined more easily from the opposite end.

(4) COLONOSCOPY

Introduced probably in the 1950s, flexible colonoscopy has surpassed barium enema as the method of choice for examining the large bowel. In many instances, however, endoscopy and medical imaging are used in conjunction to give a better delineation of pathologic abnormalities. In conditions such as colorectal cancer and diverticular disease, the characteristic radiologic appearances can be very useful in defining the disease process. Depending on clinical indications, flexible colonoscopy can be employed in a more limited form, eg, to visualize only the left side of the colon, as in proctoscopy or sigmoidoscopy. On the other hand, the procedure can be carried out as total colonoscopy to view the entire colon and even the terminal ileum.

Nature of Specimen

Tissue biopsies and brush cytology samples are the two main types of specimens which the anatomic pathology laboratory receives for
evaluation. In practice, most of the material submitted is in the form of biopsies with or without cytology samples. In some instances, however, only brush cytology material is obtained. The decision as to the type of specimen presented to the laboratory is influenced by a number of factors, such as clinical indications of the endoscopy, findings at the time of the procedure, local expertise available in pathology and diagnostic accuracy of the laboratory.

Flexible endoscopy has affected the nature of biopsy specimens. Firstly, the relative ease of obtaining multiple biopsies with flexible instruments has simplified the process of identifying conditions such as cancer since diagnostic accuracy is significantly enhanced with the number of tumors sampled. Secondly, forceps biopsies realized with flexible endoscopy tend to be smaller than suction biopsies commonly obtained with rigid or semi-flexible instruments. For example, suction biopsies from the body of the stomach were sizable and usually extended to the muscularis mucosae and sometimes even included part of the submucosa. Thirdly, forceps biopsies accomplished with flexible endoscopy tend to be somewhat distorted at the edges as a result of crush artefact, whereas suction biopsies tend to have sharp edges and a regular outline.

As such, it is more difficult to orient forceps biopsies for the purposes of embedding for histologic processing. However, since the use of flexible endoscopy has outpaced that of rigid instruments and appears to be here to stay, pathologists have gradually had to adjust to the notion of dealing with such specimens. In the diagnostic work-up of small intestinal malabsorption, for example, pathologists are now more likely to be presented with a duodenal biopsy obtained by videoscope forceps. These tend to be smaller than those realized from, say, a Crosby capsule, but this disadvantage is far outweighed by the direct visualization and survey of the upper GI tract that flexible endoscopy offers. Thus, in a patient with suspected small intestinal villous disease, it is not uncommon for the laboratory to receive esophageal and gastric biopsies concurrently with small intestinal biopsies to eliminate the possibility of other foregut digestive pathology. Suction biopsies can also be procured simultaneously with flexible endoscopy, but the experience of the writers is that, despite emphasizing the advantages of suction biopsies from a pathologic viewpoint, performing a forceps biopsy is technically less labor-intensive and, consequently, this is the specimen generally submitted to the laboratory.

The flexible endoscopy technique can produce larger biopsies, but this is usually more uncomfortable for the patient and is associated with a higher rate of complications. Thus, a re-evaluation of the criteria relating to the adequacy of duodenal mucosal biopsies was mandated. It is now accepted that, even with a biopsy having as few as four normal villi in a row, a statement as to whether small intestinal villous disease could be ruled out could be made with a high degree of confidence.

Although flexible colonoscopy procedures tend to produce biopsies of relatively small size, more areas of the large bowel can be surveyed and biopsied and more diagnostically useful information provided. This can be very beneficial in conditions, such as Crohn's disease, that are characterized by skip lesions. In instances in which larger or deeper biopsies are deemed helpful, as in suspected congenital aganglionosis or in studies correlating morphology and molecular biology, larger biopsy forceps (eg, jumbo-jaw forceps) can also be used.

Brush cytology specimens are commonly taken in upper GI endoscopy for assessing such conditions as Barrett's esophagus, dysplasia and carcinoma. A distinct advantage of brush cytology over tissue biopsies is that larger areas of the esophageal mucosa can be sampled. This is particularly useful in surveillance studies because normal, dysplastic and cancerous areas of the esophageal mucosa can be haphazardly admixed, as has been shown by mapping studies. It is especially useful as a screening procedure for both squamous cell carcinoma and adenocarcinoma in high incidence areas for these lesions.
Clinicopathologic Correlations

This is probably the area in which flexible endoscopy has had the broadest impact. The issues that can be addressed from specimens procured at endoscopy can be discussed within the context of specific topographic regions of the GI tract. This is a far-reaching topic in its own right, but examples of the effect of flexible endoscopy on the process can be given.

In the esophagus, flexible endoscopy relates in large measure to the diagnosis of reflux esophagitis and its attendant complications, such as columnar cell metaplasia, dysplasia and carcinoma. Because of the frequency of complaints of chest pain by the middle-aged and elderly population and the importance of establishing the cause of this pain, upper GI endoscopy has become a key component in diagnostic algorithms for atypical or anginalike retrosternal discomfort in this patient group. As an indication of the magnitude of the problem, it is estimated that 10 percent of patients with symptomatic reflux go on to develop Barrett’s esophagus, a condition associated with a high risk for the development of carcinoma. The long-term endoscopy surveillance protocols recommended for the timely detection of dysplasia in this environment would probably be less acceptable if they had been carried out with rigid endoscopy.

H. pylori gastritis is a relatively new frontier in gastroenterology. The gold standard for establishing this diagnosis remains endoscopy and biopsy. Following treatment of this infection, patients often undergo follow-up biopsies to verify eradication of the microorganism.

Because it paved the way for better characterization of focal conditions such as chronic antral gastritis or multifocal gastritis, flexible endoscopy has played a very important role in our understanding of the chronic gastritides. Heretofore, it was possible to detect diffuse disease, but almost impossible to rule out focal disease, on the basis of blind biopsies. Peptic ulcer disease is another area of gastric disorders which engenders a significant number of endoscopy procedures.

Endoscopy and biopsy/cytology brushings are crucial in establishing the diagnosis and excluding the likelihood of ulcer cancer.

In the small intestine, flexible endoscopy has a primary function in the diagnosis of infectious diseases. This has become pivotal in view of the AIDS epidemic, the increasing use of potent chemotherapeutic regimens in oncology centers and the burgeoning numbers of organ transplant recipients. As a result, opportunistic infections have become a major problem in today’s medicine, and many hitherto unknown pathogens, including cytomegalovirus duodenitis, atypical mycobacteriosis, microsporidiosis and cryptosporidiosis, have been described. Other small intestinal infectious diseases that are not necessarily related to AIDS-enteropathy or immunosuppression are giardiasis, H. pylori, tuberculosis and yersiniosis. Biopsy and/or brush cytology specimens are most useful in helping to form the diagnosis in most of these instances.

In the colon and rectum, a substantive part of endoscopy is devoted to the diagnosis and follow-up of idiopathic inflammatory bowel disease. Biopsies may be taken from multiple sites to determine the pattern and extent of the disease and, in this way, aid in arriving at the correct diagnosis. In conjunction with the patient’s clinical history, idiopathic inflammatory bowel disease may be differentiated from its mimics (e.g., acute self-limited colitis, ischemic colitis). Biopsies may also be directed at mass lesions occurring in the...
context of idiopathic inflammatory bowel disease. Elegant classifications for dysplasia have been developed, and the information so generated occupies a conspicuous place in patient management.

Relatively recently, other types of colitis, including lymphocytic colitis, collagenous colitis and diversion colitis, have been described. Because the clinicopathologic profile of these conditions includes patient symptomatology, endoscopic appearances, histologic features and biologic outcomes or endpoints, flexible colonoscopy played a significant part in their characterization. Similarly, in the area of adenomatous polyps and cancer, endoscopy is assuming an increasingly prominent place. Not only does it help in making the diagnosis, but it also allows for the performance of various curative procedures, such as endoscopic polypectomy.

Conclusion

It is apparent that since its introduction about 40 years ago, flexible endoscopy has dramatically changed the scope and practice of GI pathology. The number of GI biopsies accessioned in pathology laboratories has increased exponentially. The anatomic origin of these biopsies has been greatly broadened to include areas beyond the proximal digestive foregut and distal 25 cm of the large bowel. The institution of surveillance protocols for monitoring dysplasia and the recognition of hitherto unknown diseases such as H. pylori gastritis, AIDS enteropathy and collagenous colitis have firmly established flexible endoscopy in the diagnostic armamentarium of GI diseases.

Future Directions

The manner in which endoscopy has revolutionized GI pathology makes predicting its future course difficult, but several frontiers are emerging. Biopsy material is increasingly submitted for genetic studies and molecular pathology, particularly as this relates to microbiologic agents, immunology and tumor pathogenesis and progression. A number of changes have served to strengthen the role of these studies in laboratory medicine. For example, initially, some of the newer genetic and molecular markers generally required the use of fresh tissue, which is more demanding in processing costs and storage. However, developments in antibody technology and antigen retrieval methods now allow even formalin fixed tissues for this work. This was a significant step forward, and most pathology laboratories now routinely process tissue biopsies in this manner.

Although small intestinal transplantation is not yet an everyday procedure in most hospitals, the advances now being made in transplantation technology could well lead to an increase in cases of small bowel transplantation, particularly for conditions such as short bowel syndrome, chronic pseudo-obstruction syndrome and Crohn’s disease. Monitoring and follow-up protocols for these patients are likely to involve considerable endoscopic and pathologic correlations.

Endoscopic fine needle aspiration of submucosal gut lesions or masses extrinsic to the GI tract is being carried out. A reasonable expectation may be a marked increase in the use of fine needle aspirations of abdominal lesions being performed endoscopically in much the same way that transrectal biopsy of the prostate or transduodenal needle aspiration of pancreatic lesions is being accomplished. Concurrently, advances in medical imaging have facilitated procedures such as endosonography-guided endoscopic resection. The combined use of endoscopy, medical imaging techniques and laparoscopy will no doubt result in change in the management of patients with GI disease.

References


