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EDITOR'S MESSAGE

Two or three times a year I am asked by my clinical colleagues, "What is the difference between severe (high grade) dysplasia in a colonic adenoma vs. in situ carcinoma". My answer is always the same, "They essentially are the same. Our British pathology colleagues use the term severe (high grade) dysplasia while here in the States we use the term in situ carcinoma". Recently, after being again presented with this situation, I gave this matter a little more thought. Which is correct or preferable? Am I correct about the nomenclature used by my fellow pathologists here in the U.S.A or am I in the dark as how our fellow pathologists are calling these lesions? And finally if so, is it time for a change?

In this last presidential campaign, we heard about the need for change. We are also seeing change in medicine and no doubt will see more changes in the future. I called some of my fellow pathologists (both GIPS members and non-GIPS members) and asked them whether they use severe and/or high grade dysplasia or in situ carcinoma for what we all were taught to diagnose as in situ cancer. I found that both terms were still used. However, in this small and non-scientific sample, it seemed that many of the GIPS members polled were using high grade dysplasia or at least thinking of going in that direction. Some said that they were using the term intramucosal cancer (yet another term) when tumor showed invasive features, but was limited to the mucosa. I felt that maybe my usual pat answer might be outdated and of a disservice. "In situ carcinoma" biologically has been shown not to metastasize and is biologically a non-lethal neoplasm. Why then to persist with the term cancer. Surgeons may needlessly react with the knife and the term cancer on a patient's record might affect future life insurance or disability insurance applications.

I realize that many terms in pathology are firm and used by by many and that change is "difficult", but nothing is etched in stone (only fossils are etched in stone - need I say more?). Should we abandon for colonic adenomas, the term in situ carcinoma for a more biologically "proper" term such as high grade (or severe) dysplasia? As times are changing, I now feel that maybe I should change and jump off the in situ cancer bandwagon onto the high grade dysplasia one. I would like to hear from our GIPS members as to their practice and thoughts on this matter. I may sorely regret this editorial and find that I am in the dark ages and my colleagues are enlightened as to the politically correct use of these terms. But, I'll take my licks.

This in situ cancer vs. severe dysplasia question also brings into play the need for continuing education (learning) and

uniformity in nomenclature. If we abandon "in situ" for high grade dysplasia, then should GIPS be spearheading use of this new terminology through education? Certain pathology groups have proposed standards for pathology reports, quality assurance, etc. Should our society be also proposing guidelines and standards for gastrointestinal pathology? How should various lesions or disorders be reported? How should certain biopsies or resection specimens be handled so that the proper thing is done? What do the GIPS members think of this? Should our society be involved in implementing these procedures?

President Clinton was successful on running on a "for change platform". Taking a page from his campaign, I will slowly change and evolve into using severe dysplasia vs. in situ cancer. Is this the right decision and should we all use severe or high grade dysplasia like our British colleagues have for many years? I guess biologically it is correct. However, it will only become correct if its usage becomes standard and acceptable. Maybe our society can be proactive in this area and reeducate ourselves and others. What do you think?

Harry

HARRY S. COOPER, M.D.

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

The United States-Canadian Division of The International Academy of Pathology

SPECIALTY CONFERENCE

HANDOUT

GASTROINTESTINAL PATHOLOGY

GASTROINTESTINAL PATHOLOGY
Monday, March 16, 1992 - 7:30 p.m.
Marquis, Salons I & II

Moderator:

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University of British Columbia
Vancouver, B.C.

Panelists:

AUDREY LAZENBY, Johns Hopkins Hospital, Baltimore, MD

BRIAN WEST, Yale School of Medicine, New Haven, CT

DANIEL G. SHEAHAN, Presbyterian-University Hospital, Pittsburgh, PA

EDWARD L. LEE, V.A. Medical Center, Dallas, TX

LESLIE H. SOBIN, Armed Forces Institute of Pathology, Washington, DC

HARVEY GOLDMAN, New England Deaconess Hospital, Boston, MA

CASE HISTORY
GI Speciality Conference, Case # 1
Dr. Lazenby

The patient was a 33 year old, homosexual man with AIDS, who came to the hospital for elective take-down of an ileostomy. During pre-operative work-up, it was discovered that he was putting out over 6 liters of watery fluid a day through the ileostomy. Surgery was delayed to investigate the cause of this severe diarrhea. The patient was afebrile and had no abdominal pain. Stool cultures and exam for ova and parasites were negative. The patient had endoscopy of the ileum (through the ileostomy site), and the ileal mucosa appeared grossly normal to the endoscopist. Additionally, the patient had an upper endoscopy which was also essentially normal. You are provided with either ileal or duodenal biopsies for examination.

PAST MEDICAL HISTORY. Two years prior to admission, the patient had been diagnosed with AIDS, based on Pneumocystis infection. Subsequently, he was admitted to the hostpital with severe abdominal pain, fever to 39^{o}, and obstruction of the distal small bowel. At surgery a perforated distal ileum was resected and an ileostomy placed. Pathologic examination of the resected bowel showed ischemic changes and numerous CMV inclusions, consistent with CMV ileitis. The patient was begun on DHPG and discharged home, much improved.

The patient was relatively well for several months but was readmitted with profound dehydration, hyponatremia, pre-renal azotemia and a 20 lb. weight loss. He was found to have a high output (3 to 6 liters) of watery fluid from his ileostomy site. The patient had no complaints of abdominal pain and was afebrile. The cause of the diarrhea was unclear despite extensive workup. After rehydration, the patient was discharged home with instructions to measure his ileal output and drink enough Gatorade to replace his losses.

DR. B. WEST

Case # 2 . A 20-year old white female college student with poorly controlled diabetes mellitus walked into the Emergency Room complaining of weakness, abdominal pain, nausea and vomiting which had developed over the previous two hours. She had a record of frequent episodes of ketoacidosis, and was ketoacidotic on this occasion. Fifteen minutes after presentation she passed about 0.5 litre of maroon stool. Plain abdominal film showed multiple gas-fluid levels in non-dilated loops of small bowel, without evidence of obstruction, suggestive of ileus. At emergency laparotomy, 38 cm of necrotic jejunum and ileum were resected. Significant labs drawn pre-operatively confirmed ketoacidosis, and included WCC 28,500 (70% neutrophils), AST 3,730 (normal <35 U/L), ALT 1,390 (normal <35U/L), and CPK 27,500 (normal <170 U/L) with <2%MB.

CASE HISTORY

CASE3 DR. SHEHAN

A 67 year old white male was admitted to hospital with "stomach problems", fever, weight loss, night sweats, nausea, light headedness and dark colored stools. He had hypertensive cardiovascular disease with bundle branch block and abdominal aortic aneurysm. Six months prior to this admission, his usual state of health was changed by the sudden onset of episodic crampy midepigastric pain, nausea and vomiting associated with epigastric tenderness without guarding, rebound or palpable mass. Urinalysis and rectal examination were negative. Lab values showed Hb 15.5 g, WCC 11,000 (71% segs, 2 bands, 1 eosinophil, 21 lymphs, 4 atypical lymphs, 1 normoblast). A clinical diagnosis of cholecystitis was suggested.

On this admission, there was a palpable non tender RUQ mass, normal liver function tests and serum electrolytes but the Hb was now 10.2g with a WCC of 8,500 and an abnormal smear. Bone marrow biopsy was abnormal and CT scan showed an abdominal mass with perforation from colon into an abscess cavity and an enterocolic fistula. At surgery, contiguous segments of small and large bowel and associated mesentery were infiltrated by tumor. Your section is from the small bowel mass.

CASE HISTORY CASE 4 DR. E.L. LEE

The patient is a 76 year old black male who presented in 1976 complaining of chest pain. EKG and cardiac enzymes did not demonstrate any evidence of myocardial infarction. An esophagram revealed a mass which was thought to be a leiomyoma. The patient was readmitted to the hospital in 1978 complaining of chest pain. Cardiac catheterization demonstrated normal coronary arteries. The patient was readmitted in 1983 complaining of dysphagia. Endoscopic examination revealed an esophageal mass measuring about 3cm, which was locally resected. He did well until October 1990, when he presented with dysphagia. Endoscopic examination revealed an esophageal mass and biopsies were taken. The histopathology of the mentioned biopsies was similar to the histopathology of the mass removed in 1983. In December 1990, he was admitted with paraparesis and lower extremity hyperreflexia. A myelogram, CT scan, and MRI demonstrated an epidural mass. The mass did not appear to be continuous with the esophageal mass. The patient was taken to the operating room in February 1991 for a T4-6 laminectomy and tumor removal. At surgery, the paraspinous muscle was extensively involved with tumor. The patient received 4500 Rads to the region of the tumor but developed pneumonia and sepsis and died 56 days postoperatively. The enclosed slides and blocks are from the biopsy material (S91-497) taken from the paraspinous muscle and the tumor involving the esophagus at autopsy (A-37-91).

Case 5 DR. L. SOBIN

A 19-year-old man presented with acute abdomen. An intussusception of the small bowel was found at the head of which was a 2-cm polyp.

Harvey Goldman, M.D.

CASE 6

An eight year old girl presented with diarrhea, edema, and abdominal pain. She had a respiratory infection three months previously which subsided, but this was followed by the current symptoms. She was otherwise well, without prior allergies or other medical problems. Laboratory tests disclosed a marked reduction in serum albumin and a slight decrease in the globulins. There was no urinary protein or anemia, and the peripheral white blood cell count including percent of eosinophils was normal. Both radiographic and endoscopic studies revealed enlarged gastric folds with scattered polyp formation that were concentrated in the proximal half of the stomach. The antrum appeared normal. Biospies were taken from the gastric corpus mucosa and are represented in the three transparencies: low power (A), high power (B), and PAS stain (C).

"MICROSPORIDIOSIS"

Audrey J. Lazenby, M.D.
The Johns Hopkins Medical Institutions

I. Background

Microspora is a huge phylum with hundreds of genera (1), all of which are very primitive since they lack mitochondria and have prokaryotic type ribosomes (70S rather than the 80S of eukaryotes)(2,3). The name of the phylum refers to the production of unique and characteristic spores. These spores contain a hollow, coiled tubule (polar tube) that can be extruded with sufficient force to penetrate cell membranes. Infectious material (sporoplasm) can then be ejected through the lumen of the polar tube and thus inoculate host cells to start a new cycle of infection (4,5,6).

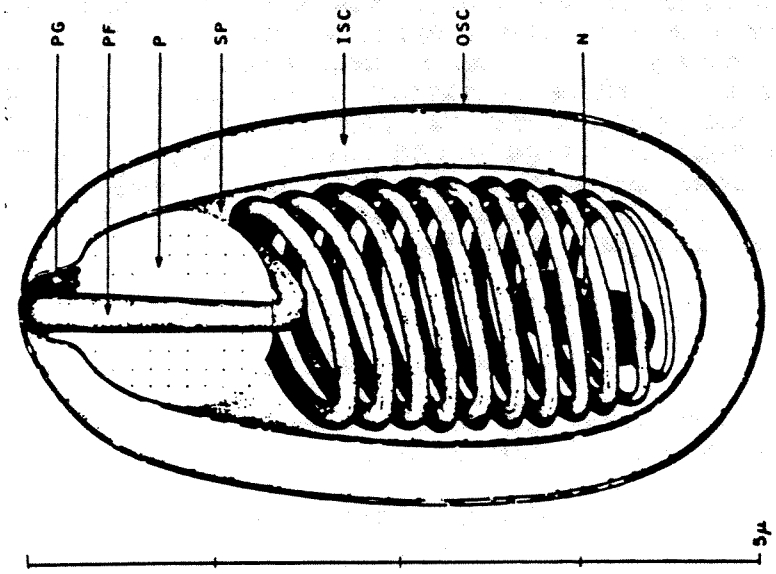


Fig. 7-14-1. Diagram of internal structure of a microsporidan spore. Polar granule (PG), polar filament (PF), polaroplast (P), sporoplasm (SP), inner spore coat (ISC), outer spore coat (OSC), nucleus (N). AFIP 75-5984. (Photograph contributed by Dr. A. Huger. Published in J Insect Pathol, 2:101, Fig. 16. 1960.)

Although various of the Microspora have been recognized for decades, they have received scant medical attention because the most frequent hosts are insects, fish, and rodents (7). Microsporal infections in lower animals, while not of help in passing the Boards, are of economic and historical interest. For example, the French silk industry suffered enormous losses in the 1800s from a disease in silkworms caused by a microsporidan, Nosema cunicull. No less than Louis Pasteur devised a way to separate out infected from noninfected silkworm eggs and thus "saved" the silk industry (7).

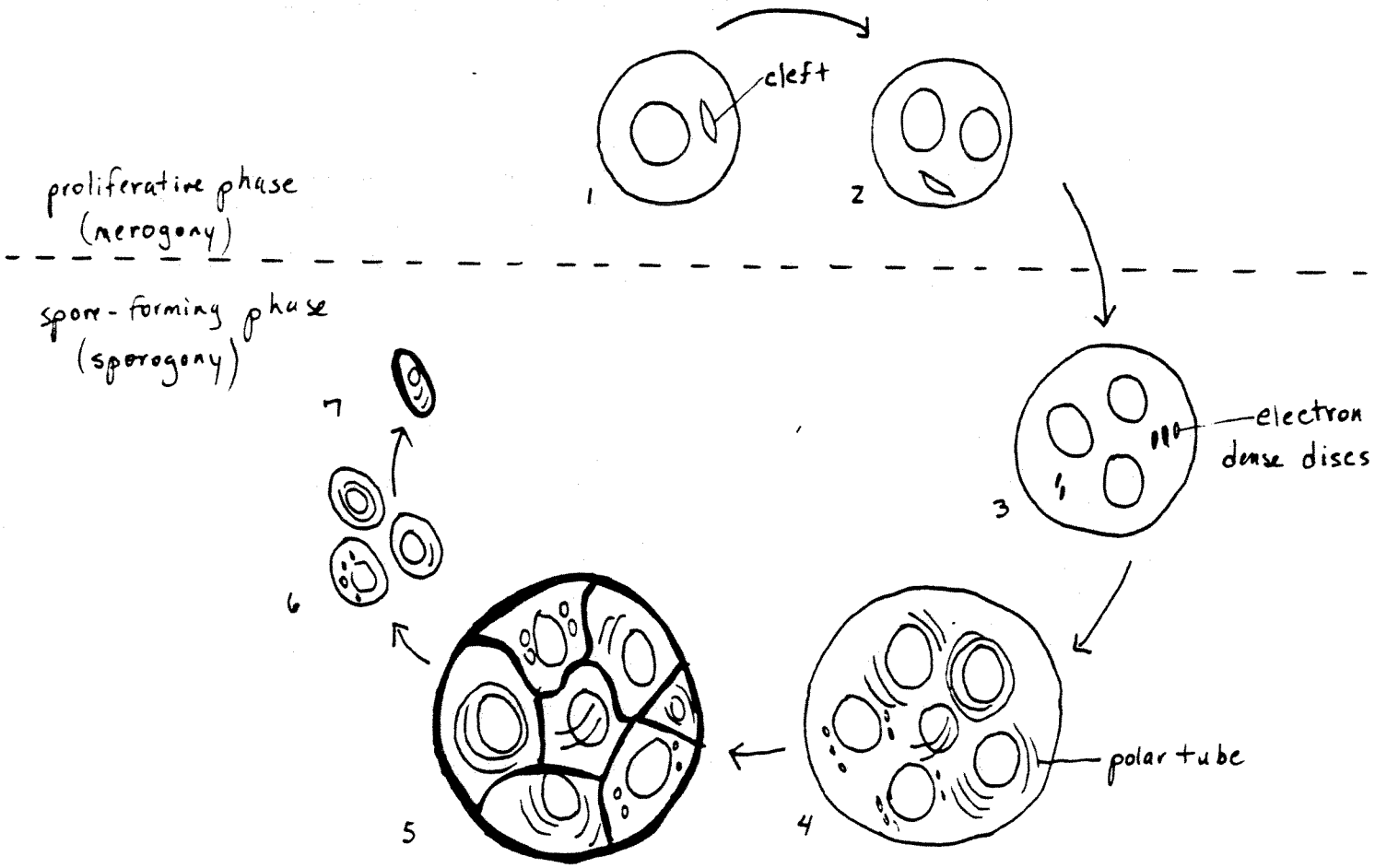
In humans, Microspora have only been recognized thus far in immunodeficient individuals or in "immuno–privileged" sites (like the brain or cornea). However, given the ubiquitous distribution of these microorganisms in nature, it is likely that normal hosts are exposed to and develop self–limited infections, but that they are unrecognized due to the crudity of our current detection methods (2,4). All organisms in the phylum Microspora that have been demonstrated in humans belong to the order Microsporida and include (1,8):

Genus	Normal Host	Human Disease
Pleistophora	Fish & insects	Myositis
Encephalitozoon	Rodents	Hepatitis
Nosema	Insects	Corneal ulcers, diarrhea & malabsorption
Enterocytozoon	?	Diarrhea & malabsorption
Microsporidium*	?	*Genus created for organisms identified but with insufficient data to place in genus

II. Enterocytozoon bieneusi

The most prevelant and clinically significant microsporidan infection is that due to Enterocytozoon bieneusi. This organism, first recognized in 1985 (9,10), has thus far been detected only in the small bowel of humans with immunodeficiency. The prevelance of E.bieneusi ranges from 23 to 30% of AIDS patients who have diarrhea and no other known pathogen (11,12). The clinical symptoms are mainly severe watery diarrhea and malabsorption leading to weight loss and imbalance of fluids and electrolytes (12,13,14). This symptomatology is thus similar to that due to Cryptosporidia or Isospora infections in the AIDS population. There is no effective antibiotic therapy for E.bieneusi, but control of the diarrhea with octreotide (somatostatin analog) has been reported (14). The 3 methods to detect infection with Enterocytozoon bieneusi are electron microscopy, light microscopy, and stool exam for spores.

ELECTRON MICROSCOPY. EM of small bowel biopsies is currently the gold standard for diagnosis (1,2,12), but new advances have been made in stool examination (see below). Two phases of the lifecycle of E.bieneusi can be identified by EM, a proliferative phase (merogony) and a spore-forming phase (sporogony). In the proliferative phase, the organisms are small rounded objects with 1 to 6 nuclei, and are more electron-lucent than the surrounding cytoplasm of the host cell. Very few structures are present in the cytoplasm of the organisms except for empty clefts (called electron-lucent inclusions by the wordy). The herald of the spore-forming phase is the presence of stacks of electron dense discs. At later stages, the discs aggregrate end-to-end to form the longer, curved profiles of polar tubes. During sporogony, the nuclei continue to divide, resulting in large organisms with up to twelve nuclei with each nucleus surrounded by several coils of polar tube. Finally, these large multinucleated forms break up into immature spores (sporoblasts) which then develop into mature spores. Mature spores are extremely electron dense, have a single nucleus, and an extrusion appartus consisting of several coils of polar tube, an anchoring disc, and a polarplast. Both phases of the life cycle are localized to the apical portion of enterocytes (supranuclear), and multiple or all stages of the life cycle can be identified in a single cell. All phases of the life cycle lie free within the host cytoplasm, with no limiting vacuole or membrane. Frequently, E.bieneusi (which lack their own mitochondria) are closely apposed to host mitochondria, presumably siphoning off energy.



LIGHT MICROSCOPY. With a little experience and some luck, E.bieneusi can be recognized by conventional light microscopy (12). The mature spores (1-1.5 microns) are gram-positive, and appear as clusters of tiny dots in the apical cytoplasm (12,15). Unfortunately, mature spores are not present in all cases. The nucleated stages (3-5 microns) are rounded, lightly basophilic structures in the apical cytoplasm that may be surrounded by a clear halo or may ident the nucleus. At present, no special stain has been found to highlight the nucleated forms.

Since E.bieneusi are quite small, the number of positive diagnoses can be increased by concentrating a 40X search in high-yield areas. The organisms are present only in the villi, particularly the tips, and are absent in the crypts. Because organisms are found more frequently in degenerating cells, it is useful to search bits of detached and degenerating surface epithelium as well as the more intact tissue fragments. Also, there is a greater diagnostic yield in jejunal than in dudodenal biopsies and the organisms are easier to recognize in thin plastic sections stained with azure II methylene blue, basic fuchsin than in conventional sections (12).

Small bowel biopsies from patients infected with E.bieneusi have more villus blunting and increased chronic inflammation in the lamina propria compared to normal individuals. However, the above inflammatory findings can be seen in any HIV positive individual, regardless of whether or not they are infected or have diarrhea. In small bowel biopsies of HIV positive individuals, the best clue to an enteric infection may be provided by intraepithelial lymphocytes. Intraepithelial lymphocytes are increased in patients with enteric pathogens compared to uninfected individuals (11).

STOOL EXAM. Significant advances have been made in detection of E.bieneusi by stool examination. Previously, spores have been recognized in the stool by EM as well as by Giemsa stains of fecal smears (16,17). However, Geimsa stained smears do not provide reliable contrast between the microsporidal spores and other fecal matter. Happily, a new staining procedure has been developed that stains the spores a pink color against a green background of other fecal material. This new method uses smears of unconcentrated, formalin-fixed stool stained with a modified trichrome stain that has concentrated chromotrope. While results are still preliminary, fecal smears using this chromotrope stain may be more sensitive than electron microscopic evaluation of biopsies. Thus fecal smears may become the new diagnostic gold standard.

III. Differential Diagnosis

Other diagnostic entities that can be confused with E.bieneusi are infections with Cryptosporidia or Isopora belli, or apical lysosomes. Cryptosporidia have a different localization, appearing as small blue dots stuck onto the luminal surface, while E.bieneusi are positioned clearly within the apical cytoplasm. Isospora belli are located within the cytoplasm of enterocytes, but are larger, more discreet, and banana-shaped with a prominent nucleus. Both Isospora and Cryptosporidia can be readily identified in stool preparations. Finally, apical lysosomes in enterocytes can be a source of confusion, but these tend to be smaller and can be stained with some silver preparations.

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Case # 2

Brian West
Department of Pathology, Yale University

CLOSTRIDIAL NECROTIZING ENTEROPATHY WITH SYSTEMIC *CLOSTRIDIUM* INFECTION AND METASTATIC MYONECROSIS.

History: A 20-year old white female college student with poorly controlled diabetes mellitus walked into the Emergency Room complaining of weakness, abdominal pain, nausea and vomiting which had developed over the previous two hours. She had a record of frequent episodes of ketoacidosis, and was ketoacidotic on this occasion. Fifteen minutes after presentation she passed about 0.5 litre of maroon stool. Plain abdominal film showed multiple gas-fluid levels in non-dilated loops of small bowel, without evidence of obstruction, suggestive of ileus. At emergency laparotomy, 38 cm of necrotic jejunum and ileum were resected. Significant labs drawn pre-operatively confirmed ketoacidosis, and included WCC 28,500 (70% neutrophils), AST 3,730 (normal <35 U/L), ALT 1,390 (normal <35U/L), and CPK 27,500 (normal <170 U/L) with <2%MB.

Pathology: The specimen was opened and fixed within 10 minutes of resection. It comprised 38 cm of dusky brown-purple jejunum with a mottled serosal surface, edematous thickened wall, and extensively necrotic mucosa. Pneumatosis was evident focally. The mesentery was congested and edematous and contained small nodes. Mesenteric vessels were unremarkable.

Microsopic examination confirms the presence of extensive mucosal necrosis, most severe on the crests of the valvulae conniventes, often with preservation in the intervening troughs. Numerous large Gram-positive bacilli are present on the luminal surface of the necrotic mucosa. The submucosa is edematous, and there is capillary dilatation and some red cell extravasation. Neutrophil infiltration is relatively sparse, and is concentrated around the areas of mucosal necrosis. Vasculitis with fibrin thrombi is seen is some superficial submucosal vessels underlying these areas. In the muscularis propria, myocytolysis is present focally. Deep and mesenteric vessels are unremarkable. Foci of pneumatosis are present. The subserosa is edematous, and there is fibrinous serositis.

Course: Immediately post-operatively the patient did poorly, requiring resection of much of the remaining small bowel. She also developed deep muscle pain, with serum enzyme levels of AST 20,300, ALT 1,390, and CPK 93,000; myoglobinuria; and renal failure. Subsequently she made a slow recovery.

DIFFERENTIAL DIAGNOSIS OF NECROTIZING ENTEROPATHY

The most important considerations in the differential diagnosis of the necrotizing enteropathies are toxic and ischemic. However, on one hand primary ischemic injury to the bowel may be secondarily complicated by colonizing or invasive bacteria, even with systemic spread; and on the other, primary bacterio-toxic enteropathy may be mediated in part by vasoconstriction or other vascular injury: thus, it may be impossible to determine the primary agent in a particular case. It is essential, therefore, to search carefully for

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clinical and pathologic evidence supportive of ischemic disease in all cases of necrotizing enteropathy. A detailed cardio-vascular history should be obtained. Arteries and veins should be liberally sampled and scrutinized for thrombi, emboli and vasculitis. The presence of inflamed vessels in uninflamed surroundings strongly favors a primary vasculitis, but inflamed vessels adjacent to areas of necrosis are more difficult to interpret.

The term *necrotizing enteropathy* has been used to encompass several conditions in which the dominant pathologic finding is intestinal necrosis [Price, 1985]. Such conditions include necrotizing enterocolitis, neonatal necrotizing enterocolitis, neutropenic enterocolitis, enteritis necroticans, hemorrhagic enterocolitis, and phlegmonous enterocolitis. Enterotoxigenic bacteria have been implicated in the etiology of all of these conditions. In some, they have been demonstrated to be the causative agents, for example enterohemorrhagic *E.coli* in hemorrhagic enterocolitis [Griffin, 1990], *Clostridium perfringens* type C in enteritis necroticans [Murrell, 1966], and *C.septicum* in neutropenic enterocolitis [King, 1984].

A firm bacteriologic diagnosis of an appropriate pathogen is helpful in making a diagnosis of these conditions, but the presence of the pathogen alone is not sufficient: the clinical and morphologic features must be compatible. More troublesome is the fact that in many cases the clinical diagnosis is ischemic enterocolitis, and an infectious etiology has not been considered, no cultures have been taken, and antibiotics have been administered. Even if stool or bowel have been submitted for culture, the liklihood of detecting the pathogens concerned is not high. Unless specifically requested, many labs will not select for enterohemorrhagic *E.coli* from among its abundant commensal relatives. Clostridia also are normal inhabitants of the intestinal tract, and are usually disregarded in fecal cultures. An added problem with *C.perfringens* type C in enteritis necroticans is that it is usually much less abundant than type A, and therefore is difficult to isolate in culture [Lawrence, 1984]. Alternative methods for making a bacteriologic diagnosis are available for some of the organisms involved, for example detection of serum antibodies to the beta-toxin of *C.perfringens* type C [Murrell, 1966] and immunostaining of these organisms in tissue sections [Arbuckle, 1972], are available, but generally only as research tools.

For these reasons, consideration of the diagnosis of necrotizing enteropathy is often dependent upon morphologic evaluation.

The affected bowel may show patchy or continuous involvement. It is congested, often brown or plum colored, and may show fibrinous peritonitis. The wall is thickened, and the valvulae conniventes are strikingly prominent, sometimes giving a "washboard"-like appearance to the mucosal surface. Areas of mucosal ulceration varying from pin-points to confluent regions are covered by a purulent membrane. In more severe lesions there may be transmural necrosis with thinning of the wall, yellow patches visible on the serosa, or perforation.

On microscopic examination the thickening of the wall is seen to be due to marked submucosal edema. This is one of the most characteristic features of necrotizing enteropathy, and is probably due to the effects of toxins on capillary permeability. There is mucosal necrosis which is often full-thickness with an infarct-like quality, with associated hemorrhage and with neutrophil infiltration at the margin. Submucosal vessels close to these areas of mucosal necrosis frequently contain fibrin thrombi and are acutely inflamed. Fewer neutrophils are present deeper in the submucosa. Mucosa in the valleys between the thickened edematous valvulae may escape necrosis and inflammation. Focal myocytolysis is commonly seen, and is usually associated with a mild neutrophil infiltrate. The subserosa is edematous, and fibrinous peritonitis is common. Vessels away from the areas of necrosis are uninvolved by vasculitis and thrombosis.

Specific features may be imposed on this general pattern. Clostridia may form a dense encrustation on the surface of the necrotic villi, may be demonstrable invading the bowel wall, and may be associated with pneumatosis cystoides intestinalis. The large Gram-positive spore-forming bacilli associated with gas production are essentially diagnostic of this genus. Interestingly, clostridial necrotizing enteropathies in man bear striking similarity to the lesions seen in clostridial infections of several animal species, including guinea pig [Lawrence, 1980], pig [Arbuckle, 1972], sheep [Walker, 1985] and domestic fowl [Helmboldt, 1971].

Helpful morphologic clues to the diagnosis include the following:

- patchy distribution of the lesions;
- severe submucosal edema;
- areas of mucosal necrosis with a neutrophil border;
- preservation of mucosa between the valvulae conniventes;
- focal myocytolysis;
- appropriate bacteria on or in the tissues;
- pneumatosis;
- and absence of vasculitic, thrombotic or embolic lesions.

In some cases with systemic involvement, isolation of the pathogen from blood culture may lead to consideration of it as the cause of enteritis or colitis, and is supportive of the diagnosis in the right clinico-pathologic setting. Similarly, biochemical evidence of rhabdomyolysis may alert one to the possibility of a clostridial infection, or support a diagnosis of "necrotizing enteropathy, probably clostridial".

CLOSTRIDIAL INVOLVEMENT OF THE GI TRACT

Enteritis necroticans

This is the clostridial disease which most closely resembles the findings in the case presented, though they were probably not due to the usual strain. It has been extensively studied, and because it is little known in North America, some details are summarized here.

Etiology: Enteritis necroticans is caused by infection with *Clostridium perfringens* (formerly *C.welchii),* usually of type C but occasionally of type A [Walker, 1985; Van Kessel, 1985]. These organisms most commonly grow on meat products and poultry, and a heavy challenge is required to establish infection [Lund, 1990].

Epidemiology: The classic form of enteritis necroticans is Pig-bel, an often fatal affliction of the natives of Papua New Guinea which occurs typically after a ceremonial feast of sweet potatoes and pig meat [Murrell, 1966; Walker, 1985]. The pigs are cooked slowly at low temperatures in unhygenic conditions, allowing a rich growth of clostridia. *C.perfringens* beta-toxin, which can initiate the disease if injected as a pure filtrate, is normally inactivated by trypsin. The sweet potatoes, however, contain a trypsin inhibitor, thus allowing the toxin to reach its destination intact. The disease has also been encountered in outbreaks in Germany in the period after world war II, where it was called darmbrand [Siegmund, 1948]; and among Khmer children in evacuation camps in Thailand [Johnson, 1987]. It has been reported to occur sporadically in Uganda [Wright, 1967],

and there are occasional reports of its occurrence in Europe and North America [Devitt, 1983; Severin, 1984; Van Kessel, 1985].

In Papua New Guinea, where pigbel is second only to respiratory infections as a cause of death in childhood, a program of active immunization against the beta-toxin of *C.perfringens* has been introduced. This has led to a reduction in hospital admissions for pigbel to 20% of the previous level [Lawrence, 1990].

Clinical Features: Patients present with anorexia, upper abdominal pain, bloody diarrhea, and vomiting. Clinically there is an ileus, and septicemia is common. Complications include fulminant toxemia and shock; small bowel obstruction; small bowel perforation and peritonitis; strictures, fistulas and adhesions. The mortality is high -- up to 80% in fulminant toxemia [Murrell, 1966].

Pathology: On gross examination, typically there is segmental involvement of the small bowel with intervening unaffected areas. The gross and microscopic features are as described above [Cooke, 1979; Wright, 1967].

Clinical Diagnosis: The diagnosis is suspected clinically and can be made on pathologic examination in the right setting. The difficulties of making a bacteriologic diagnosis are described above: detection of elevated serum antibodies to *C.perfringens* beta-toxin can be particularly helpful [Murrell, 1966].

C.perfringens food poisoning

C.perfringens type A, well known as the causative agent of gas gangrene, is a fairly common cause of food poisoning. Spread mainly through inadequately refrigerated cooked meat and poultry, it causes diarrhea and severe abdominal pain, but rarely fever and vomiting. The enterotoxin is thought to be produced after ingestion, and a heavy challenge is required to establish infection [Lund, 1990]. It may also cause some *C.difficile*-negative cases of antibiotic-associated diarrhea [Borriello, 1984]. Because the symptoms are generally mild and short-lived, there is no indication for biopsy or resection.

Neutropenic enterocolitis (typhlitis)

Necrotizing enteropathy involving primarily the cecum in patients with neutropenia is commonly due to *C.septicum* or *C.perfringens* [Caya, 1986; Ahsan, 1987]. The neutropenia can be from any cause, and sepsis and metastatic myonecrosis may result [King, 1984; Anon, 1987]. It has been suggested that *C.septicum*, which is commensal in the cecum, becomes pathologic in neutropenia when white cell protease levels are too low to neturalize its toxin [Hopkins, 1983].

Malignancy-associated clostridial sepsis

Systemic clostridial sepsis, with generalized gas gangrene or metastatic myonecrosis, may occur in association with many malignancies, unassociated with neutropenia. [Burrell, 1980; Furste, 1986].

Pseudomembranous colitis

Well known as a form of antibiotic-associated colitis, this is commonly caused by toxin-producing *C.difficile*. Non-toxigenic strains are common in the intestinal tract, and therefore detection of toxin is important in making the diagnosis. The histology is described in detail by Price and Davies [Price, 1977]. *C.difficile* is generally held to be non-invasive, causing toxin-mediated tissue injury. In fatal pediatric cases of pseudomembranous colitis, however, invasion of the gut wall and the presence of toxin has been demonstrated in serum and ascites [Qualman, 1990].

Neonatal necrotizing enterocolitis

Although morphologically NNEC falls into the necrotizing enteropathy group, the circumstances of its occurrence distinguish it from all the other members. The etiology of NNEC is still uncertain, despite years of intensive work on this problem, and although clostridia have been implicated, their role in the pathogenesis of NNEC is questionable [Kliegman, 1990; Kosloske, 1990].

Botulism

Upon ingestion, *C.botulinum* toxin is absorbed and causes neuroparalytic disease, without specific effects on the GI tract.

Pneumatosis cystoides intestinalis

Primary pneumatosis (i.e. not associated with respiratory disease or peptic ulcer), is strongly associated with infection by *C.septicum* or *C.perfringens*, and should alert the pathologist to search for these organisms. In this form cysts occur in the submucosa, and may be present in the subserosa; in the secondary form, subserosal cysts predominate [Price, 1985].

"Metastatic" myonecrosis

Myonecrosis is a common feature of infections by *C.perfringens* and *C.septicum*. In addition to necrosis of intestinal smooth muscle, rhabdomyolysis may occur, due either to circulating toxin or to systemic spread of the pathogen to skeletal muscle ("metastatic" myonecrosis) [Furste, 1986]. Biochemically, this results in elevation of CPK and AST, and myoglobinuria which may result in renal failure -- as occurred in this case.

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CASE 3

GRANULOCYTIC SARCOMA

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The small bowel is involved by leukemic infiltrates in up to 25% of cases (1) and is amenable to diagnosis following examination of small bowel mucosal biopsy. It is recognized that B-cell lymphoma may arise in leukemic patients who have had intensive chemotherapy (2). Granulocytic sarcoma, a tumor which is composed of immature myeloid cells, occurs de novo (3) (4) or in association with acute myelogenous leukemia or myeloproliferative disorders (5). It involves the gastrointestinal tract in up to 13% of cases (3) and has been described in the small intestine (3) (4) (6) where intestinal obstruction may ensue. Grossly the tumors are ulcerated, often show a greenish hue, tend to be circumferential and may perforate.

Histologically the tumors are uniformly cellular and composed of sheets or aggregates of pleomorphic mononuclear cells showing prominent nucleoli which infiltrate between muscle fibers and into adipose tissue. Multinucleate cells resembling cells of megakaryocytic lineage and both mature and immature eosinophil leucocytes are also recognizable the latter being considered diagnostic of the condition. The more prominent the numbers of eosinophil myelocytes the better differentiated the tumor is considered to be (5).

Distinction from lymphoma, with which it is often confused, (5) is provided by positive lysozyme and Leder (naphthol AS-D chloracetate esterase) staining which identifies elements of the granulocytic series in more than 95% of cases (5). Recently, immunohistochemical staining using polycolonal antibodies against myeloperoxidase has been utilized on paraffin sections with remarkable specificity to identify both mature and immature myeloid elements (7).

The differential diagnosis may include, dependent on patient age, other poorly differentiated round cell neoplasms which may involve the intestines. These include malignant lymphoma, malignant melanoma, neuroblastoma, angiosarcoma rhabdomyosarcoma and even oat cell carcinoma.

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DIAGNOSIS: Glomangiosarcoma of the Esophagus

CASE HISTORY

The patient is a 76 year old black male who presented in 1976 complaining of chest pain. EKG and cardiac enzymes did not demonstrate any evidence of myocardial infarction. An esophagram revealed a mass which was thought to be a leiomyoma. The patient was readmitted to the hospital in 1978 complaining of chest pain. Cardiac catheterization demonstrated normal coronary arteries. The patient was readmitted in 1983 complaining of dysphagia. Endoscopic examination revealed an esophageal mass measuring about 3cm, which was locally resected. He did well until October 1990, when he presented with dysphagia. Endoscopic examination revealed an esophageal mass and biopsies were taken. The histopathology of the mentioned biopsies was similar to the histopathology of the mass removed in 1983. In December 1990, he was admitted with paraparesis and lower extremity hyperreflexia. A myelogram, CT scan, and MRI demonstrated an epidural mass. The mass did not appear to be continuous with the esophageal mass. The patient was taken to the operating room in February 1991 for a T4-6 laminectomy and tumor removal. At surgery, the paraspinous muscle was extensively involved with tumor. The patient received 4500 Rads to the region of the tumor but developed pneumonia and sepsis and died 56 days postoperatively. The enclosed slides and blocks are from the biopsy material (S91-497) taken from the paraspinous muscle and the tumor involving the esophagus at autopsy (A-37-91).

PATHOLOGIC EXAMINATION

The esophageal mass removed in 1983 measured 3.5 x 2.3cm and the cut surface demonstrated yellow firm areas admixed with areas of cystic degeneration, hemorrhage and calcification. The mass was comprised of large cavernous vessels surrounded by uniform cuboidal cells characteristic of a glomus tumor. There were prominent areas of calcification and hyalinized stroma. Mitotic figures were not present. The tumor extended to the margins of resection. The recurrent esophageal mass and epidural mass which were removed were microscopically similar and resembled the original esophageal mass. Mitotic figures were not conspicuous.

DIFFERENTIAL DIAGNOSIS

Glomus tumors may be confused with smooth muscle tumors especially the variant leiomyoblastoma, lymphoma, carcinoid, and hemangiopericytoma.(2,6,9) Glomangiosarcomas must be differentiated from other small round blue cell tumors e.g. extra-osseous Ewing's sarcoma, rhabdomyosarcoma, peripheral neuroblastoma and small cell carcinoma.(5) The histopathological features, immunohistochemical studies, and electron microscopic examination may be helpful in differentiating the mentioned tumors.(1,2,4,7,9)

DISCUSSION

Glomus tumors of the esophagus are rare tumors and there is only one case report in the literature. (8) In a personal communication with Dr. Raffaele Lattes, who reviewed the material in 1983, mentioned that there was one case of glomangioma of the esophagus in the files of the Dept. of Surgical Pathology, College of Physicians and Surgeons of Columbia Univ. Drs. HD Appelman and EB Helwig also reviewed the material in 1983 and concured with the diagnosis. Glomus tumors may be found wherever there are arteriovenous anastomoses. In the gastrointestinal tract, most are found in the stomach. (3) Since the tumor was incompletely resected recurrence was anticipated.

Glomangiosarcomas are rare tumors and none has been reported in the gastrointestinal tract. Gould et al proposed the following classification. a, locally infiltrative glomus tumor which has the usual glomus histologic features; b, cytologically malignant tumor arising and merging with a typical glomus tumor; c, de novo glomangiosarcoma (5). Since the original tumor, the recurrence, and the metastasis to the paraspinous muscle and lung were all cytologically similar, this would be an example of de novo glomangiosarcoma. This tumor is unusual for the following reasons:

1. Anatomic site of the tumor.
2. Long interval between initial presentation and death (8 yrs).
3. Metastasis to the paraspinous muscle and lung.
4. Cytologic similarity between original tumor, recurrence, epidural mass and lung metastasis.

The immunostains and electron microscopic examination of the original tumor, recurrence and metastasis were consistent with a glomus tumor.

In conclusion, this is the first reported example of a glomangiosarcoma arising in the esophagus or G.I. tract and first report of a metastasis from a glomangiosarcoma.

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Case 5

Pseudoinvasion in Peutz-Jeghers Polyps

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Peutz-Jeghers (PJ) polyps are characterized by an abnormal mixture of smooth muscle and mucosa. The smooth muscle usually consists of branching bands of muscularis mucosae arranged in an arborizing manner. The muscle makes the polyp firm and well anchored, preventing autoamputation and facilitating intussusception. The mucosal component represents that normally found at the site of the polyp, i.e. colonic, small intestinal or gastric. The glands may be hyperplastic or cystic.

At the base of a PJ polyp, islands of mucosa, often associated with mucinous cysts, may be found within bundles of muscle simulating invasion. The muscle may be part of the muscularis mucosae or muscularis propria. Cases occur in which mucosal components completely penetrate the muscularis propria, but without cytological signs of malignancy. This may be the result of forces exerted during intussusception and/or an expression of the hamartomatous mixture of glands and muscle. Evidence for the role of intussusception in producing pseudoinvasion is the fact that extensive pseudoinvasion in PJ polyps is essentially limited to the small bowel, where intussusception is most frequent.

In a report from the Polyposis Registry of the St. Mark's Hospital, London, 409 PJ polyps were studied. Over 10% of 176 jejunal and ileal polyps had pseudoinvasion, while only 1 of 21 duodenal polyps showed the change; none of the 85 gastric or 127 large bowel polyps were pseudoinvasive. Fifteen cases of pseudoinvasion in PJ polyps were accessioned at the AFIP during the past nine years. All were from the jejunum or ileum. The average age of the patients was 29 years.

Pseudoinvasion can be a pitfall in diagnosis and may account for some cases reported as carcinoma in PJ polyps. The following help to distinguish between pseudoinvasion and true invasion in PJ polyps: presence of small bowel mucosa with brush borders, goblet cells and lamina propria; absence of dysplasia; and lack of desmoplasia. Problems in diagnosis are: distortion, partial disruption and necrosis of the mural glandular elements due to compression, especially from intussusception; reactive atypia in the epithelium simulating dysplasia; and stromal fibrosis around extravasated mucus resembling desmoplasia.

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USCAP Subspecialty Conference 1992
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CASE 6

Specimen: Gastric corpus mucosal biopsy

Diagnosis: Menetrier's disease

Comment:

Menetrier's disease was originally described in 1888[1], and is a rare disorder characterized by a diffuse hyperplasia of the surface/foveolar mucous cells of the stomach, usually limited to the corpus/fundic region[2-6]. Other typical features include a diffuse or polypoid enlargement of the gastric folds in the proximal stomach, a marked hypersecretion of mucus leading to severe hypoalbuminemia and a tendency for edema formation[7,8]. Other proteins may be reduced, but there is ordinarily no anemia or alteration of the white blood cell count. Most cases are seen in adults of ages 30 to 60, and three quarters are in men. Medical treatment is largely limited to albumin replacement and other nutritional care; although some cases regress spontaneously, surgical resection is often required for the persistent cases in the adults.

The essential pathologic feature in Menetrier's disease is a marked hyperplasia of the foveolar (pit) mucous cells[4-6,9]. The foveolae are greatly elongated, often tortuous and cystic in appearance, and composed mainly of mature mucous cells with little evidence of active regeneration or of mitoses. There are no ulcerations, the amount of inflammatory cells in the epithelial layer and lamina propria is typically slight, and intestinal metaplasia is uncommon. The foveolar mucous cells can be accented with mucin stains such as the PAS reaction, revealing an intense staining throughout the cytoplasm in contrast to the typical concentration of the mucous granules in the apical region of normal folveolar cells. Mucosal biopsies can identify the foveolar hyperplasia and help to exclude other causes of enlarged rugae[10]. The sample may consist entirely of the hyperplastic pits as opposed to a biopsy of a normal or inflamed mucosa which would ordinarily contain a large component of the specialized corpus glands.

The diagnosis of Menetrier's disease is dependent on the identification of a pure foveolar mucous cell hyperplasia that is exclusively present in or largely confined to the fundus and body of the stomach, unassociated with any significant inflammation, and to the exclusion of other causes of enlarged gastric folds[5,6]. In the Zollinger-Ellison syndrome, the enlarged folds are due to a hyperplasia of the parietal and chief cells, and the surface-foveolar mucous cells are ordinarily normal or even slightly reduced in number. Lymphocytic gastritis (also termed varioliform gastritis and chronic erosive gastritis) shows greater inflammation with a special tendency for a large infiltrate of lymphocytes in the epithelial layer[11-13]. Other inflammatory conditions can be associated with prominent gastric mucosal folds; examples include granulomatous diseases[14] and allergic gastritis[15], and these lesions are typically limited to the antral region. Some tumors such as the linitis plastica type of carcinoma and lymphomas may create the image of large folds, but these are readily distinguished by the greater macroscopic abnormality and ultimately by biopsy examination. In the evaluation of small endoscopic biopsies, it is essential to realize that foveolar mucous cell hyperplasia is by itself a nonspecific finding which can be seen in association with many inflammatory disorders and next to other tumors. Accordingly, the finding of the mucous cell hyperplasia, unrelated to other inflammation, should be combined with the appropriate clinical and functional findings before a diagnosis of Menetrier's disease is considered.

A relation of Menetrier's disease to the development of gastric carcinoma has been frequently cited, but there still remains very little evidence to support an important association[5,6,16]. It is more likely that the foveolar hyperplasia seen in cases that evolve to cancer are more a reflection of associated chronic gastritis. When one limits the diagnosis of Menetrier's disease to those instances with a pure hyperplasia and no inflammation, there appears to be little relationship to tumor development.

Menetrier's disease can also be seen in children[17-21], where there is typically an antecedent history of a respiratory infection and a peripheral blood eosinophilia, but there is no relation to other allergic disorders. Compared to the cases in adults, those seen in children are self-limited and regress spontaneously after several weeks, and there is no need for surgical excision. The childhood cases are not associated with recurrences and do not reveal any propensity to tumor development. The major differential in children is with allergic gastroenteritis which may have enlarged gastric folds and protein loss. In the allergic condition, however, the lesion is typically in the gastric antrum, there is often evidence of blood loss and anemia, and an increase of eosinophils is observed within the mucosal tissue.

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TALES OF THE AMPULLA OF VATER: XVIII

To the Editor:

By the shores of Duodenum
where there flows the River Bile
Once again came tribulation
to the Ampulla's tribe came trial.

How insidious it started
with the seeping blood and pain
As the far off Magenstrasse
poured forth floods of acid rain.

Villi young and old eroded
both the large and small consumed
From the pancreatic border
to the distant Jejunum.

Twas a massive ulceration
not the solitary kind
Like a moonscape pocked with craters
deep necrotic bases lined.

Vater suffered for his villi
and was steeped in solemn thought
Ever searching for an answer
from the legends he was taught.

Then to him a revelation
Gastrinoma! did explode
Acid rain from Magenstrasse
must be blocked before it flowed.

Oh Great Zollinger and Ellison
he cried throughout the nights
Til it echoed from Pylorus
to the Ligament of Treitz.

With a further incantation
as his brow with sweat was drenched
Send us Zantac or Cimetidine
the fire they will quench.

Oh Lord Pious Great Ampulla
how soon answered were your prayers
When the acid rain abated
and the ulcers then repaired.

Gastrinemia still persisted
but Cimetidine held fast
Yes the blockage was successful
and the crises now had past.

Craters deep began to granulate
the blood it ceased to flow
Villi raised their heads erect again
like buds through April snow.

So although the Gastrinoma lived
in Sweetbread by the Spleen
Blessed land of Great Ampulla
now was verdant and serene.

Leslie H. Sobin, M.D.

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With the Editor's Permission

Gastrointestinal Pathology Society
USCAP Companion Meeting
New Orleans

Sunday, March 14, 1993 **1:30-5:00 PM**

Disorders of the Esophagus

Moderator: Robert R. Pascal, M.D.
Emory University School of Medicine, Atlanta, GA

1:30 Infections of the Esophagus
Jan Orenstein, M.D. *George Washington University School of Medicine, Washington, D.C.*

2:00 Reflux Esophagitis
Beverly Dahms, M.D. *University Hospitals, Cleveland, OH*

2:30 Barrett's Esophagus - Morphologic and Pathophysiologic Considerations
Wilfred Weinstein, M.D. *UCLA Center for Health Sciences, Los Angeles, CA*

3:00 Recess

3:30 Barrett's Esophagus - Neoplastic Considerations
Klaus J. Lewin, M.D. *UCLA Center for Health Sciences, Los Angeles, CA*

4:00 Molecular Biology of Squamous Cancer
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4:30 Discussion and Questions

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Molecular Biology of Esophageal Squamous Cell Carcinoma
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There has been extensive interest in the biologic events contributing to the development of specific human cancers. We are currently involved in a comparative study of the molecular biologic events occurring in anal and esophageal squamous cell carcinomas to gain a further understanding of the role of specific viral infections, oncogene abnormalities and tumor suppressor gene alterations. The reason for the comparison of the two sites is that both develop squamous cell carcinomas. However, the known risk factors for developing tumors in these two areas differ. HPV infections are thought to play an important role in the genesis of anal squamous cell neoplasias (Noffsinger), whereas dietary factors seem to be important in the pathogenesis of esophageal lesions (Fenoglio-Preiser). For this reason tumors from both anal and esophageal regions allow one to compare the molecular biologic similarities and differences in the two sites to determine whether these differences can be accounted for by differences in the likelihood of infection by tumor-inducing viruses versus changes such as mutations in the genome potentially induced by the diet This presentation will concentrate on our findings in esophageal squamous cell tumors.

Our initial approach was to determine how frequently we could detect **HPV viral genomes** in the tumor cells in neoplasms arising at each of the two sites. Esophageal tumors appeared to have a higher percentage of cases associated with HPV 31 than anal cancers. The latter appeared to be primarily associated with HPV genotypes 16, 18. These results were based on analysis by In situ hybridization and await confirmation by PCR amplification techniques. In surveying the literature, HPV genotypes have been found associated with esophageal carcinomas with HPV 6, 11, 16, 18 & 30 having been found (Chang). These have been detected using PCR amplification. In our material, examined by in situ hybridization without PCR amplification, we have not seen these genotypes.

We have also examined the role of oncogenes known to be important in the genesis of gastrointestinal tumors. **ras gene** mutations were searched for using the PCR approach. We found that ras gene mutations do not appear to play an important role in the genesis of esophageal squamous cell carcinomas. This is in keeping with findings described in the literature (Jiang).

Frequent gene amplification is see at the chromosome region 11q13 that contains the **hst and int-2 genes**.(Tsuda). Amplification of this region is associated with metastasis (Tsuda) and with deep invasion (Mori). The latter group did not see a correlation with metastasis (Mori). The INT-2 gene encodes a peptide that resembles fibroblast growth factor (Dixon). The amplification unit also often includes the protooncogene **BCL-1** (Tsuda, Berenson).

MYC gene amplification is also common. The MYC protein appears to play a critical in regulating the cell cycle by triggering the G_0-G_1 transition. MYC overexxpression leads to autonomous cell proliferation by bypassing the need for extrinsic growth stimulation.

p53 is a 53 kda nuclear phosphoprotein that is expressed by many normal cells. The protein appears to be involved in the normal control of cell proliferation. This gene is commonly mutated in a number of human malignancies including carcinomas of the esophagus. Mutant p53 proteins form stable complexes with heat shock protein 70, a constituitively expressed member of the heat shock family. As a result of this complex with hsp 70 the mutant p53 proteins have an increased half life. In the esophagus immunoreactive p53 is present in the nuclei of the majority of tumors. This is not associated with increased p53 mRNA (Sasano). Dysplastic areas are also positive for p53. The mutations are found in exons 6,7 and 8 (Tamura).

Epidermal growth factor receptor (EGFr) is an integral transmembrane plasma membrane glycoprotein that possesses intrinsic tyrosine specific protein kinase activity (Pfeiffer, Velu, Sporn). The receptor has an extracellular ligand binding domain connected to a cytoplasmic kinase domain by a short transmembrane region (Carpenter). The intracellular domain shows close sequence homology with c-erbB-2. The receptor binds epidermal growth factor, a potent mitogenic polypeptide that plays an important role in wound healing (Hopenreijs), maintenance of tissue integrity, intercellular communication and normal cell growth and differentiation. The receptor also binds transforming growth factor-alpha (TGF-alpha) (Burgess).

The receptor is involved in cellular proliferation and differentiation as well as participating in tumor formation when it becomes abnormal (Fleming, Yoshida, Tahara, Ozawa). The tyrosine kinase activity is required for its mitogenic activity (Ullrich). Abnormalities in the receptor that predispose to the development of malignancy include point mutations, truncations, internal deletions in the cytoplasmic domain of the receptor, overexpression and amplification (Raines, Sainsbury, Pelley, Gammett) Increased expression of the EGFr gene in tumors, often indicates a worse prognosis compared to those with low or normal expression (Neal, Yasui), although his is not invariably the case (Dazzi). The receptor is expressed in the gastrointestinal tract, including gastrointestinal tumors (Yoshida, Yasui, Tahara, Ozawa). It is also known to be expressed in squamous cell carcinomas of the head and neck region (Partridge, Ishitoya, Weichselbaum), lung (Gorgoulis) cervix and vulva (Gullick). The gene is strongly overexpressed in esophageal tumors. Those tumors containing the largest amounts of the receptor have high proliferative rates and are commonly aneuploid.

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Barrett's esophagus: The metaplasia-dysplasia-carcinoma connection.

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Dysplasia in Barrett's esophagus[1-8]

In assessing biopsies from patients with Barrett's esophagus, the main role of the pathologist is to be on the alert for histologic features of dysplasia and adenocarcinoma. Dysplasia is defined as a benign neoplastic change of the epithelium and is considered to be a precursor lesion for adenocarcinoma. The presumption that dysplasia, especially high grade, is a precursor lesion for adenocarcinoma comes largely from retrospective histologic studies of adenocarcinoma in which dysplasia is commonly found in the adjacent mucosa [6]. Thus, in a given patient the dysplastic epithelium may not only be a marker for heightened cancer risk but may itself already be associated with invasive carcinoma. The time sequence for the development of adenocarcinoma is variable.

Since dysplasia in Barrett's is endoscopically invisible, multiple biopsies are necessary if surveillance is to be successful in detecting dysplastic lesions and early carcinoma. Originally it was thought that dysplasia was a multifocal process. However, recent studies indicate that it is more commonly a focal process. Furthermore, we have found that carcinoma in Barrett's can occur in any part of the esophagus and that the risk is unrelated to the length of Barrett's [9].

Histology of Dysplasia

The grading of dysplasia is now fairly well accepted and is similar to that employed in dysplasia of ulcerative colitis, namely: high grade; low grade; and indefinite for dysplasia[10-11]. Intramucosal carcinoma refers to neoplastic change that has invaded into the lamina propria.

The diagnosis of dysplasia is based on both architectural and cytologic changes that suggest neoplastic transformation. Both architectural and cytologic changes may be present but one category alone may predominate. A virtual constant in dysplasia is mucus depletion and prominent cytoplasmic basophilia, easily recognized at low power. In general dysplastic changes are more prominent in or are confined primarily to the lower half of the crypt columns. Occasionally there are exceptions to this "bottom-half" phenomenon with the top half (surface and upper crypt column) containing the predominant change. The architectural changes of pits and glands include: budding, branching, crowding and irregular shapes with papillary extensions into the lumina. An exaggerated villous configuration may be present. The nuclear changes consist of loss of nuclear polarity, stratification, hyperchromatism, variation in size and shape, enlargement of nuclei and/or

nucleoli, increased nuclear to cytoplasmic ratios and increased numbers of abnormally-shaped mitoses. Metaphases may exhibit a horizontal rather than the usual vertical orientation relative to the cytoplasm-lumen interface. Dystrophic goblet cells occur in Barrett's esophagus both with and without dysplasia, and thus are not very helpful in making a diagnosis of dysplasia.

The finding of mucosal cysts in association with dysplasia should be of concern because Barrett's associated adenocarcinomas frequently contain mucosal cysts. The distinction between dysplasia and carcinoma depends on the demonstration of invasion of the cysts into the lamina propria. Also, the degree of cytologic atypia is usually much greater in carcinoma.

Reactive or regenerative changes. In areas adjacent to erosions or ulcerations, inflammatory reactive changes may be difficult to differentiate from low grade dysplasia and this can lead one to use the term indefinite for dysplasia. Biopsies adjacent to esophageal ulcers or erosions in Barrett's esophagus often exhibit a megavillous appearance. In general the nucleoli in regenerative change are not as large as those seen in dysplasia nor are they as irregular. Some architectural disturbances with crypt branching may be present; therefore one should not lean towards a diagnosis of low grade dysplasia unless cytologic changes are also present. Inflammation is not nearly as frequent, nor as prominent in Barrett's esophagus as in ulcerative colitis; thus it is not as confounding a problem in relation to the diagnosis of dysplasia as it may be in ulcerative colitis.

Clinical Implications of Dysplasia

Criteria for grading dysplasia have been tested in a prospective study of observer variation among eight morphologists[10]. For high grade dysplasia and intramucosal carcinoma versus other categories agreement was in the range of 85%. For negative for dysplasia versus other grades agreement rate was in the range of 70%. This 70% figure is similar to that recorded for low grade dysplasia in the multi-observer study of ulcerative colitis. With lesser degrees of dysplasia where interobserver variation is greater, it would be desirable to have other markers of heightened cancer risk.

Ancillary techniques in the diagnosis of dysplasia.

Flow cytometry, and DNA image cytometry have two potentially important roles in regard to dysplasia and cancer in Barrett's esophagus[11]. One is when biopsies show low grade dysplasia or are called indefinite for dysplasia. Here a normal pattern would provide a measure of reassurance, whereas an abnormal pattern might prompt rebiopsy or more frequent endoscopic biopsy surveillance. An even more untested role is to predict heightened cancer risk in a subset of patients with Barrett's esophagus having DNA aneuploidy who do not have any evidence of dysplasia. Because dysplasia and carcinoma are not common in unselected patients with Barrett's esophagus, longitudinal studies of larger numbers of patients will be required in order to determine just how beneficial these techniques might be.

Management of Barrett's esophagus and dysplasia

The global value of screening for dysplasia and curable adenocarcinoma has not been defined [12-21], and consequently recommendations for management are, of necessity, quite arbitrary. We believe that endoscopic biopsy surveillance every two years is sufficient if dysplasia is absent on an adequate initial biopsy evaluation. For high grade dysplasia there should be immediate rebiopsy to see if a coexistent carcinoma was missed. Intramucosal carcinoma or carcinoma superficially invasive into submucosa can occur in Barrett's esophagus without any associated grossly visible target lesions. If intramucosal carcinoma is found on rebiopsy, then surgery is recommended. If only high grade dysplasia is detected on rebiopsy, then the decision concerning whether to perform esophagectomy has to be individualized. Whenever high grade dysplasia without associated carcinoma is detected, it is recommended that a second opinion be obtained from a pathologist who has considerable experience with dysplasia in Barrett's esophagus.

Esophagectomy in the setting of high grade dysplasia usually entails a near total resection with proximal mobilization of the stomach and anastomosis to the remaining esophagus in the neck. In younger patients without other conditions that would markedly enhance operative risk, the recommendation at UCLA is for esophagectomy for high grade dysplasia. The alternative is not just the risk of developing carcinoma but the attendant chronic worry and need to have rebiopsy every three to six months for the rest of the person's life. In patients who are frail careful follow-up is recommended.

Not surprisingly, we and others have now encountered patients with only a small zone of high grade dysplasia. The practice of the future in some of these instances may be to use local endoscopic treatment such as snare biopsy (mucosectomy), ablation by laser therapy or by electrocoagulation.

If low grade dysplasia is detected and agreed upon by several observers, then we recommend rebiopsy at six-monthly intervals. We do not know how long to continue this more intensive surveillance. For now we recommend that it be performed six-monthly for at least two years before considering reducing the frequency.

For cases that exhibit changes that are indefinite for dysplasia, we recommend rebiopsy at yearly intervals, rather than the customary two-yearly intervals.

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REFLUX ESOPHAGITIS

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GASTROESOPHAGEAL REFLUX (GER) is regurgitation of acid-peptic stomach contents into the esophagus, a phenomenon that occurs transiently and asymptomatically in normal individuals. GER is to be distinguished from GASTROESOPHAGEAL REFLUX DISEASE (GERD), which denotes symptomatology or tissue damage and therefore an abnormal degree of GER. The more specific term REFLUX ESOPHAGITIS means inflammation and other objective evidence of injury to the esophageal mucosa from GERD. In the decade that has elapsed since reflux esophagitis was last discussed in a GIPS seminar, progress in the field has led to a better understanding of the pathophysiology, recognition of unusual clinical presentations, refinement of diagnostic modalities, ready availability of new drugs for treatment and recognition of the premalignant potential of Barrett's esophagus. The histopathology has not changed but, despite a decade of discussion (?argument), there is still not complete agreement among pathologists as to what constitutes minimal criteria for a diagnosis of reflux esophagitis.

Diagnostic evaluation is not initiated if classic symptoms of GER (heartburn, gastric regurgitation) occur in an adult patient without more serious symptoms; these patients are treated with H2 blockers.[18] In adults, endoscopy and biopsy are usually reserved for dysphagia, weight or blood loss, failure of therapy or extraesophageal manifestations such as respiratory symptoms, ENT complaints or atypical chest pain.[20] Endoscopy is performed to examine the mucosa for gross evidence of esophagitis, obtain tissue for histologic verification and to rule out additional pathology such as infection, Barrett's esophagus, stricture and malignancy. In preverbal pediatric patients, particularly infants, the classic adult history of heartburn cannot be elicited. Less specific symptoms such as regurgitation, prolonged crying and irritability, failure to thrive, apnea, choking, stridor, respiratory disease and neurobehavioral manifestations prompt referral to a pediatric gastroenterologist, who very frequently depends on endoscopy and biopsy to determine whether the symptoms are due to reflux.[17]

It is true of both pediatric and adult patients that histologic esophagitis is found in approximately 30% of those with symptoms of GERD, but with grossly normal endoscopy (i.e., no erythema, friability, erosions or ulcerations).[2,15,19] Thus, any individual whose symptoms suggest GER and whose clinical picture warrants endoscopy should have esophageal biopsy during the procedure. Twenty-four hour monitoring of intraluminal esophageal pH is a sensitive way of detecting GERD, but is not often done in practice. There is, however, excellent correlation between histologic esophagitis and pathologic GER on prolonged pH monitoring.[3,13,22]

Endoscopic biopsies for evaluation of reflux esophagitis should be multiple, since diagnostic changes can be focal. Optimally, biopsies are obtained from the lower one-third of the esophagus, at two levels, usually 3 cm. and 5 cm. proximal to the lower esophageal sphincter region. More distally, some of the histologic findings used to

diagnose esophagitis may be found in normal subjects. Suction biopsies are larger and easier to orient on filter paper or other mounting material and are the quality standard often required for prospective studies and textbook photographs. However, in daily work with most adults and nearly always with children, the pathologist is given much smaller grasp biopsies which are more difficult, if not impossible to orient prior to embedding. Serial sectioning of grasp specimens with a ribbon of tissue on three or more slides often overcomes the deficits of small, randomly oriented biopsies.[5,7,8,9]

HISTOLOGIC CHANGES OF REFLUX ESOPHAGITIS

1. INTRAEPITHELIAL INFLAMMATION WITH EOSINOPHILS, NEUTROPHILS, AND "SQUIGGLE CELLS". In most adult cases, but not all, inflammation occurs together with recognizable signs of epithelial hyperplasia (#2 below). However, in randomly oriented grasp biopsies, inflammation is more dependably recognized than are subtle epithelial changes. In pediatric cases, intraepithelial inflammation may be the only demonstrable biopsy change,[6,14,19] since pediatric biopsies are often small and randomly oriented.

A. EOSINOPHILS: Intraepithelial eosinophils are the single most specific diagnostic feature of reflux esophagitis, though not particularly sensitive, since they are present in only 40-50% of children and adults biopsied for symptomatic GER.[4,19,22] There is excellent correlation between intraepithelial eosinophils and acid reflux on prolonged esophageal pH monitoring.[3] As few as one to two eosinophils in several high magnification microscopic fields (at least 5 eosinophils total) or the presence of eosinophil clusters is significant. Intraepithelial eosinophils may be focal, necessitating a search for them in serial sections. Some infants with reflux esophagitis have massive eosinophilic infiltration to the exclusion of other inflammatory cells in the epithelium. In addition, infants and children with GER frequently demonstrate intraepithelial eosinophils prior to developing other biopsy evidence of reflux esophagitis.[14,22] Adults with intra-epithelial eosinophils usually show other histologic findings of esophagitis, though in 23% of adult refluxers in one study, intraepithelial eosinophils were the sole histologic abnormality.[4] Neither the presence nor the number of eosinophils in a biopsy correlates with severity of symptoms.
INTRAEPITHELIAL EOSINOPHILS ARE NOT PATHOGNOMONIC FOR REFLUX ESOPHAGITIS, though certainly they are associated more often with GER than with any other esophageal condition. Eosinophils may also be seen in infectious esophagitis (Candida, herpes), drug associated esophagitis, eosinophilic gastroenteritis, and potentially in other inflammatory conditions of the esophagus.[10,14] Rare isolated eosinophils may be found in normal adult subjects.[21]

B. NEUTROPHILS. Neutrophils are found in the epithelium of approximately

20% or fewer of patients with reflux esophagitis, making them a relatively insensitive marker. They tend not to appear until inflammation is severe; they are most reliably present with ulceration.

C. LYMPHOCYTES. Small numbers of lymphocytes with identifiable round nuclei are normally present in esophageal epithelium and submucosa, particularly near the lower esophageal sphincter. These are not of diagnostic significance in reflux esophagitis.

D. SQUIGGLE CELLS. Squiggle cells or, as they are called in more erudite circles, "intraepithelial cells with irregular nuclear contours" and little recognizable cytoplasm have recently been identified as T-lymphocytes, after years of uncertainty and speculation on their origin.[16] Until this study, these cells were regarded as having no diagnostic significance, since they are often seen in small numbers in normal individuals. Mangano et al[16] demonstrated that intraepithelial cells with irregular nuclear contours (CINC) were increased in active esophagitis as defined by established histologic criteria. Biopsies with esophagitis averaged >6 CINC per hpf. These cells were not specific for any one condition; they were increased in esophagitis of diverse etiologies. In this same study, squiggle cells were increased in a number of patients with endoscopic and/or clinical evidence of esophagitis but without other histologic features of esophagitis, suggesting that, when present in large numbers, they may be a useful marker of esophagitis. Certainly subjectively squiggle cells are often present in large numbers in patients with reflux esophagitis.

2. EPITHELIAL HYPERPLASIA. Prolonged or persistent acid-peptic bathing of the esophageal mucosa causes accelerated surface shedding of squamous cells and initiates compensatory epithelial regeneration. Epithelial hyperplasia correlates well with prolonged pH monitor evidence of GER.[3,13] Convincing demonstration of epithelial hyperplasia is sufficient to suggest the diagnosis of reflux esophagitis.[1,5,11,13] Unfortunately, optimal evaluation of these changes is often impossible because of random orientation of small grasp biopsies and is particularly limiting in work with pediatric biopsies. Large suction biopsies are better, but seldom routinely encountered. Serial sectioning of small randomly oriented grasp biopsies may allow for evaluation of epithelial hyperplasia if an area with three perpendicular papillae is found. Normal individuals show some degree of epithelial hyperplasia within 2 or 3 cm. of the lower esophageal sphincter; therefore these criteria should not be used on sections showing squamocolumnar junction.

A. BASAL CELL HYPERPLASIA. Normally the basal layer is only 1 to 4 cells thick and occupies less than 15% of squamous epithelial thickness. BASAL CELL HYPERPLASIA IS PRESENT WHEN THIS ZONE EXCEEDS 25%, a

somewhat arbitrary figure but one readily appreciated without micrometry. In severe cases the entire thickness of the squamous epithelium consists of basal cells. The distinction between basal layer and more superficial layers is also somewhat arbitrary. Most observers determine the upper basal layer to be reached when nuclei are separated by a distance of one nuclear diameter or more.[15] Another aid in distinction is PAS staining: Basal cells are negative and more superficial cells have positive cytoplasm due to glycogen content.

B. ELONGATION OF LAMINA PROPRIA PAPILLAE TO EXTEND GREATER THAN TWO-THIRDS OF SQUAMOUS EPITHELIAL THICKNESS is a regular occurrence in most adult patients with reflux esophagitis, but requires optimal specimen orientation. Perhaps just as useful as a criterion, and more useful on randomly sectioned tissue, is A DISTINCT INCREASE IN THE NUMBER OF PAPILLAE. The latter can be estimated even in a section parallel to the mucosal surface (en face).

C. BASAL LAYER SPONGIOSIS (EDEMA), NUCLEAR ENLARGEMENT, NUCLEAR SIZE AND SHAPE VARIATION, PROMINENT NUCLEOLI AND, INCREASED NUMBERS OF MITOTIC FIGURES in epithelium are features encountered in reflux esophagitis, but usually only in the most severe cases.

3. VASCULAR DILATATION in papillae, (also known as vascular lakes or telangiectasia) is often one of the earliest signs of esophageal inflammation. It is found in many cases of reflux esophagitis but is not a very specific finding.

4. BALLOON CELLS are pale, distended squamous cells with pyknotic nuclei occurring in focal clusters within the epithelium. Increased permeability of the cell membrane from injury allows plasma proteins and fluid to enter and distend the cytoplasm. Balloon cells are a marker for epithelial injury, but are found in a number of other conditions in addition to reflux esophagitis.[12]

5. EROSION AND ULCERATION. These are seen in severe reflux disease. In adults the possibility of an ulcerated carcinoma presenting with symptoms of reflux esophagitis must be considered. At any age, infectious esophagitis, either primary or secondary, must be ruled out. Candida, in particular, may secondarily infect an inflamed mucosa.

DIFFERENTIAL DIAGNOSIS:
NONE OF THE HISTOLOGIC FINDINGS LISTED ABOVE ARE SPECIFIC FOR REFLUX ESOPHAGITIS, but rather indicate a pattern of response by stratified squamous epithelium to injury of diverse etiologies. The clinical setting and associated conditions

in the patient are often clues to another etiology. The following should be considered in the differential diagnosis. (Modified from S. Hamilton in Ref. 10)

1. Infection, especially fungi and viruses. This may occur in immunocompetent individuals as well as in the immunosuppressed. Infection may be superimposed on reflux esophagitis or infection may be the primary process.
2. Systemic and dermatologic disease, particularly eosinophilic gastroenteritis, collagen vascular diseases, Crohn's disease, Behcet's and Graft vs. Host disease.
3. Exogenous chemicals, particularly caustic ingestion in pediatric patients, pill esophagitis, chemotherapy (mucositis), and other drugs.
4. Physical agents, particularly radiation.

CAVEATS IN EVALUATING A BIOPSY FOR REFLUX ESOPHAGITIS

1. Changes can be patchy. Encourage clinicians to biopsy 2 levels. Examine serial sections.
2. Evaluation for features of epithelial hyperplasia requires a perpendicular section. Orient specimen before embedding. Examine serial sections.
3. Avoid overdiagnosing changes in a section of squamocolumnar junction. Near the lower esophageal sphincter, columnar epithelium and glands and some squamous epithelial hyperplasia and inflammatory cells are normal findings.
4. Consider Barrett's esophagus when columnar epithelium is present.
5. Do not equate the presence of eosinophils with reflux esophagitis. Conversely, the absence of eosinophils does not rule out reflux esophagitis.
6. Always consider infection, primary or secondary.
7. Rule out dysplasia and malignancy in adults with erosion, ulceration or stricture.

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INFECTIONS OF THE ESOPHAGUS IN HIV/AIDS

by

Jan Marc Orenstein, M.D., Ph.D.

Gastrointestinal disease is a common complication of HIV-infection, with dysphagia and odynophagia as common symptoms. Up to 50% of HIV-patients experience one or both symptoms during the course of their disease. The etiologies differ from those routinely seen in the non-HIV population, and they are all AIDS-defining diagnoses. There are opportunistic infections, especially candida, which is associated with one or both symptoms, and viruses such as herpes simplex virus and cytomegalovirus which cause painful ulcers. Kaposi's sarcoma is infrequently seen involving the esophagus, but can be present in the absence of cutaneous lesions. Over 50% of symptomatic patients have candidiasis, and over 40% these patients have a concurrent viral infection. Viral infections, particularly CMV, are diagnosed in roughly one-third of all patients, with over 70% of CMV infections accompanied by candidiasis. Approximately 25% of all symptomatic patients have at least 2 processes. Serological studies are available, but are of little diagnostic value because of the high prevalence in HIV-infected patients.

Large, painful, aphthous or idiopathic ulcers, identical in appearance to those seen in the mouth, are encountered in the esophagus. These lesions have responded to both thalidomide and corticosteroids (oral, intravenous, or intra-lesional). Epstein-Barr virus and zidovudine (AZT) have been implicated as causes of esophageal ulcers. Mycobacterium tuberculosis usually involves the esophagus by forming fistulas from infected mediastinal lymph nodes. Mycobacterium avium complex infrequently involves the esophagus. It has been proposed that the self-limiting esophageal ulcers (accompanied by odynophagia or dysphagia) seen in acute HIV-infection are due to HIV itself. Cryptosporidium infection of the small bowel can extend to involve the stomach and the esophagus. Possibly as a consequence of hypochlorhydria, reflux disease is an infrequent cause of symptomatic disease, especially as compared to the general population. A significant percentage of patients with esophageal symptoms, regardless of whether the endoscopy appeared normal or revealed large ulcerations, lack a diagnosis even after biopsy,

cytology, and culture.

Odynophagia accompanies swallowing of liquid and solids. Sometimes, the pain is experienced in the chest and does not necessarily relate to swallowing. As a consequence of the symptoms, intake decreases and weight loss results. Esophageal disease is a poor prognostic sign: half of patients will die within 5 months of diagnosis.

There are several diagnostic approaches for esophageal symptoms: barium esophagography, "blind" esophageal brushing, and endoscopy with brushing and biopsy. Initial examination of the oral pharynx is helpful since, for example, over 70% of patients with esophageal candidiasis also have oro-pharyngeal disease. However, since dual causes are common, a complete work-up is still important. The initial study is often a double-contrast barium swallow radiologic examination. Although the various patterns are becoming more familiar, the barium studies are negative in at least half of all patients, even those with candidiasis (high specificity and low sensitivity) and viral ulcerations (low specificity), and especially in patients with Kaposi's lesions. In the final analysis, endoscopy is still required.

Although the gross appearance during endoscopy may be suggestive, a specific tissue diagnosis is still necessary. H&E-stained sections are generally adequate for diagnosis; Gomori-methenamine silver and periodic acid-Schiff stains can be used to enhance the appearance of candida and immunoperoxidase or *in situ* methods can be used to detect viral infections. Mucosal smears, made before endoscopic biopsy, are stained by the Papanicolaou method or with Giemsa, potassium hydroxide, and PAS-staining, and are reported by some to be significantly more sensitive for candida and viral diagnosis than histologic examination. Brushings and/or biopsies are taken for viral culture, e.g., human fetal foreskin and fetal lung fibroblasts, a method that is about twice as sensitive as histologic examination. It is important to note that blood contamination can be the cause of a positive CMV culture. Blind brushings can be used particularly for candida diagnosis, but care must be taken to avoid contamination from oro-pharyngeal lesions. Because effective therapy is available for the most common conditions, pursuit of a specific diagnosis is important.

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REMINDER

GASTROINTESTINAL PATHOLOGY SOCIETY RECEPTION

Sunday, March 14, 1993
New Orleans Hilton Hotel
Melrose Room
5:30 - 8:00 p.m.

BOOK REVIEW

Textbook of Gastroenterology edited by T. Yamada, D. H. Alpers, C. Owyang, D. W. Powell, F. E. Silverstein. J. B. Lippincott Company, 1991. Two vols, 2683 pages.

This large comprehensive textbook of gastroenterology has 139 chapters and 166 contributors. It is divided into 4 major sections: I. Basic mechanisms of normal and abnormal function, II. Approaches to common GI problems, III. Specific disease entities, IV. Diagnostic and therapeutic modalities.

When compared with other major gastroenterology texts this book has a heavy emphasis towards basic science, including biochemistry, immunology, cell biology and animal physiology. Unfortunately, its coverage of histopathology is poor, and the fact that there are only two pathologists among the contributors is clearly relevant to the problem.

The design of this book with its four subsections means that information on a particular subject may be inappropriately divided up. For example, Helicobacter pylori is discussed at length in sections on intestinal microflora, peptic ulcer disease and biopsy diagnosis. This design also means that there is some redundancy with the same information and references appearing in different chapters which have different authors. Particularly as this is a two volume book, the sections may be separated by several pounds of paper.

These criticisms apart, I have found the book extremely useful as a reference work. I particularly liked the emphasis on basic sciences and the critical approach adopted by the majority of contributors. Much of the material is not available to use in any other easily accessible form, so I find that I am consulting it regularly. For my purposes it is superior to its current competitors. I can therefore, thoroughly recommend this book as a useful addition to the library of anybody who is seriously interested in the broad er aspects of gastroenterology.

DAO:ff

David A. Owen, M.B.
University of British Columbia

BOOK REVIEW

GASTROINTESTINAL PATHOLOGY AND ITS CLINICAL IMPLICATIONS

VOLUMES 1 AND 2, Eds. Klaus Lewin, Robert Riddell and Wilfred Weinstein (1992), Igaku-Shoin Medical Publishers, New York, NY

This book represents a major undertaking to fill a nitch in the surgical pathology library that has long been neglected. Dr. Lewin and Weinstein exploit the close working relationship they have developed over the years in this text. Their stated aim to provide a reference text that guides the practicing general pathologist and academic subspecialist in gastrointestinal surgical pathology with diagnostic information and its clinical correlations. This goal is a worthy one and the authors accomplish it for the most part in their first edition of this text. Delightful additions in the text include chapters on processing of endoscopic biopsies, an overview of neuroendocrine gastrointestinal pathology and the ever expanding (and every confusing) nomenclature for the mucosal associated lymphoid lesions. The text is up-to-date and covers most bases thoroughly and their accomplishment is hampered only by the fact that they repeat similar information in several of the chapters. An example of this is their coverage of polyps and another is their coverage of opportunistic infections. Another shortcoming of the text is the color reproduction of the hematoxylin and eosin micrographs. In comparison to the x-rays, endoscopic pictures, gross photos and black and white micrographs; the color reproduction used for light microscopic images seems of lower quality. Since the primary focus of the pathologist will be

toward these figures, the publisher would have done well to pay more attention to their reproduction. Although this is not a severe limitation of the text it certainly detracted from the otherwise excellent use of figures the authors have demonstrated throughout the text. Since it is a first edition and a major work in gastrointestinal surgical pathology the authors deserve laudits and will find their text being used along side other major texts of surgical pathology. When a second edition occurs the text should be compressed to avoid redundancy and chapter on special techniques (in-situ hybridation, polymerase chain reaction, quantitative histomorphometry, electron microscopy and immunohistochemistry) as applied to gastrointestinal surgical pathology specimens should be added. The ever expanding special diagnostic aids utilized in gastrointestinal pathology today does not receive adequate coverage in any of the major texts to date. My use of this textbook continues to grow and I will require it of my fellows as the primary text and plan to add it to our anatomic pathology resident's library. Dr. Lewin and Weinstein's long relationship has now borne the sweetest fruit of all; a text to commemorate their working relationship which illustrates that a cooperative, synergistic relationship between a gastroenterologist and surgical pathologist is necessary for the high standards of patient care demanded today.

Michael J. Becich MD PhD
University of Pittsburgh

bookrev.doc
Updated 6/26/92
M. J. Becich

Sometimes it is difficult to determine whether a polyp is a benign adenoma or an adenoma that has undergone malignant change. Recently, during a signout, my life was made easier when the lesion in question "showed me a sign". The following lesion was giving me a happy face - so I knew that this lesion had to be benign. Or rather, should we consider this a new and rare type of polyp - called "*A Happy Polyp*".

Harry S. Cooper

In the Volume 9, Number 1 issue (winter 1991), Dr. Ermes Garnica A. presented some drawings for possible new logo's for the GIPS. At the last executive committee meeting I was given the charge of investigating the subject of the GIPS logo. I have taken the liberty of using Dr. Ermes Garnica A. suggestions and with modifications by our departmental photographer to come up with some possible logo's. On the following pages you'll find some examples. At the spring business meeting in New Orleans, you will have the opportunity of voting for your favorite.

P.S. These are photocopies and do not represent the true quality of the logos.

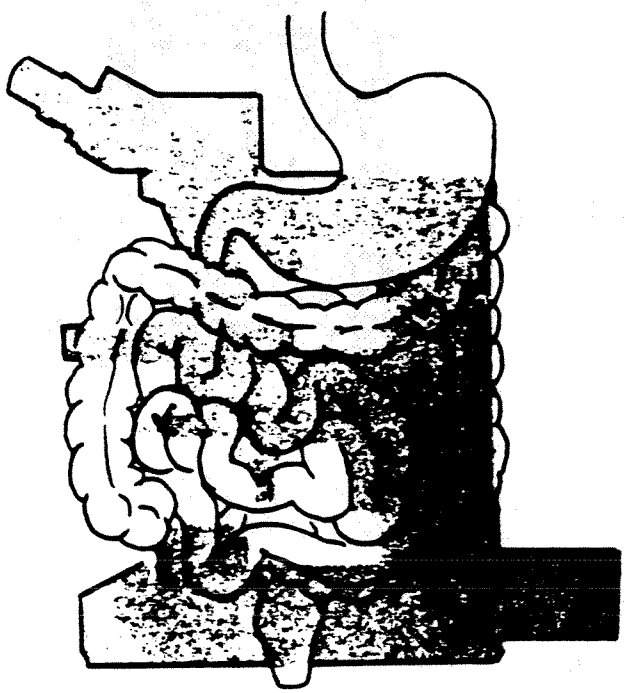
Harry

Harry S. Cooper

THE GASTROINTESTINAL PATHOLOGY SOCIETY

1

THE GASTROINTESTINAL



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THE GASTROINTESTINAL PATHOLOGY SOCIETY

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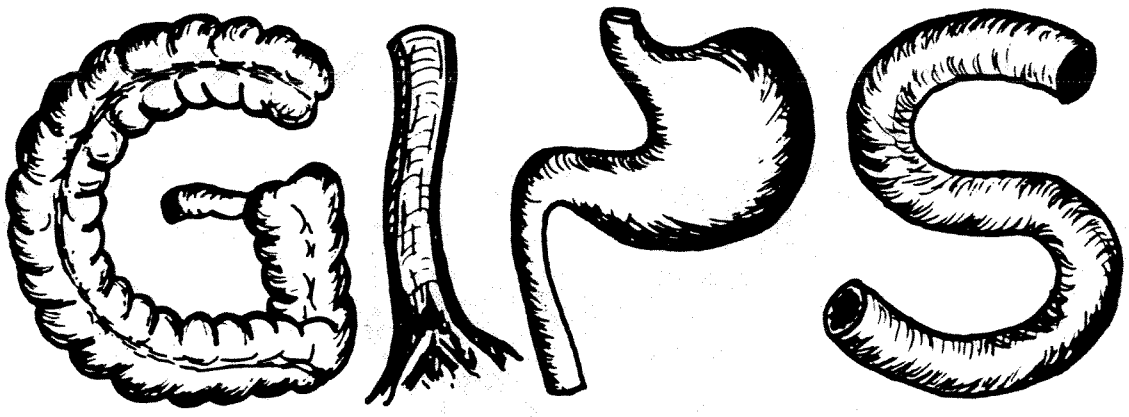
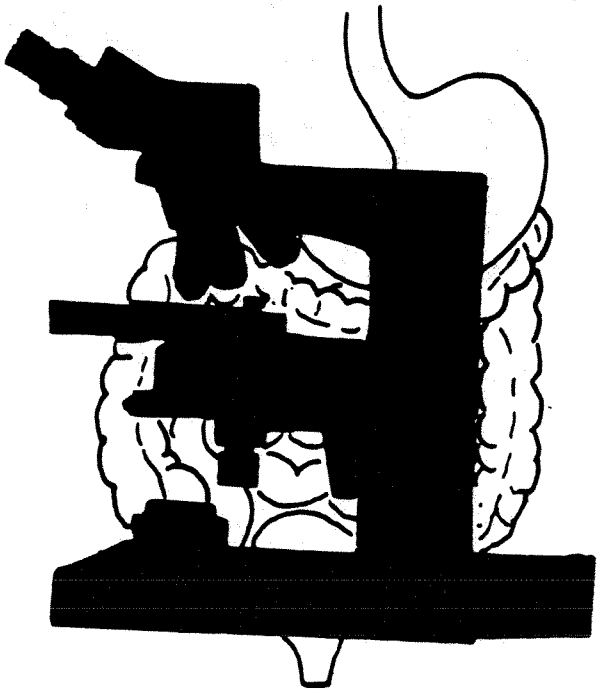


THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

#4

THE GASTROINTESTINAL



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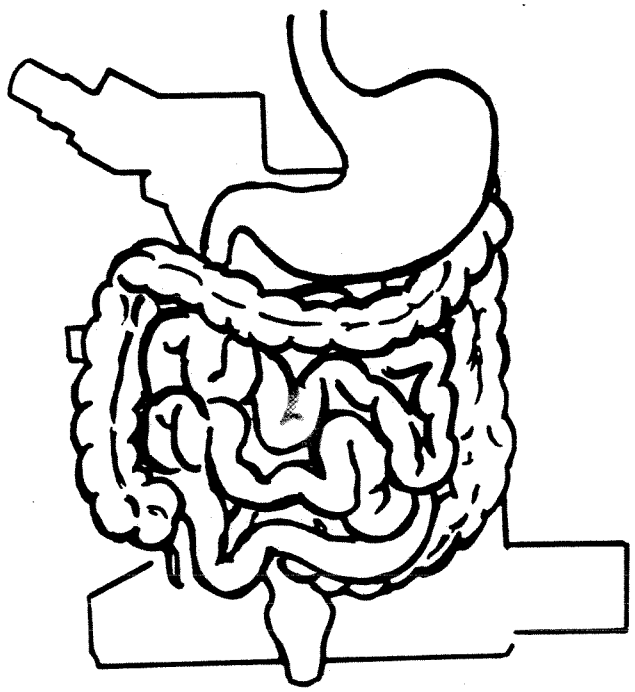
THE GASTROINTESTINAL



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