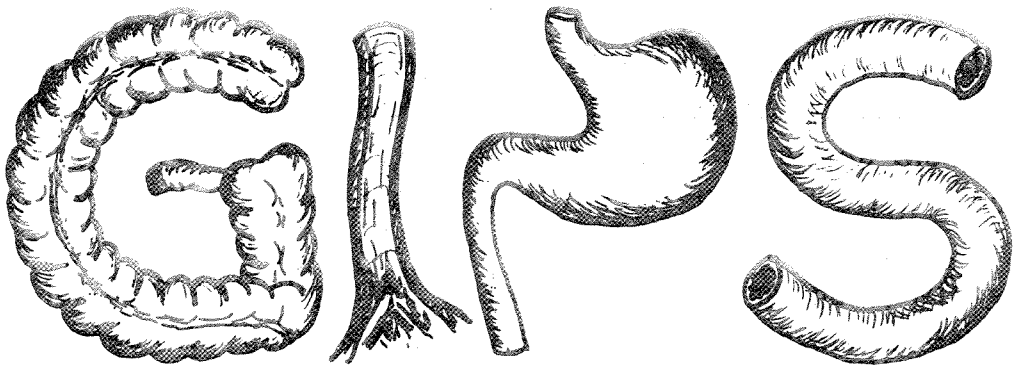

THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

GIPS NEWSLETTER - WINTER 1994

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EDITORIAL COMMENT
WINTER 1994 GIPS NEWSLETTER

GASTROINTESTINAL PATHOLOGY - WHAT IS OUR FUTURE ?

With the recent clamor by the Clintons for more generalists and primary care physicians - How will this affect pathology and more specifically our area of interest - GI pathology?

There may be fewer pathology residency slots in the future. Many departments may have to fund positions out of practice plan funds, a source which I feel will be much smaller as hospitals and universities become less willing to provide departments with the financial entitlements of the past. What about those of us presently practicing GI pathology? Almost all of us devote a major portion of our time to general diagnostic pathology (surgical, cytology, etc). However, in the past we have been able to "steal" time, to devote productive time to our love of the alimentary tract. With institutions being more cost conscious (or scared) we may see down sizing of pathology staffs. In our department, we recently lost 1.5 FTE's and our administration will not let us replace these positions. Because of this, I now have a greater general surgical pathology load and I have been designated as our renal pathologist - this latter role, requiring a major re-educational process and time consumption. Maybe my situation is anomalous - but I do not think so. In the future (or present) we may all have to cover other specialized areas in pathology. Medicine and Pathology have become more and more complex. I believe that a generalist initiative in pathology would be disasterous and would make for a very frustrating practice of pathology. A recent article (McBroom et al, Am J Surg Pathol 17:75-80, 1993) showed that at the Southampton University Hospitals, Southampton, England, 26.5% of GI specimens were "incorrectly" diagnosed (the term they used was altered diagnosis) when secondarily reviewed by a specialist with expertise in GI pathology and 26.5% of these were diagnoses that affected major changes in treatment.

I feel we need pathologists with subspeciality expertise. The patients deserve this. In the future, will we be so inundated with more generalist and/or other speciality chores so that we lose the diagnostic edge of our craft of GI pathology? Will the possible reduction in pathology residency slots along with tight money result in a dearth of a new generation of GI pathologists? However, on the other hand, will services be segregated into "centers of excellence" resulting in the "GI Pathologist" receiving all the GI related specimens from hospitals and/or outpatient facilities. In the above mentioned article - the authors decided that because GI pathology was specialized, they would send all their GI biopsies (yes, every last one) to the specialist with expertise in GI pathology. Que Sera Sera. . . .

This ends my tenure as editor of the GIPS newsletter. I have enjoyed it and I hope the membership has enjoyed the newsletters. I remember seeing a photo with a newspaper headline, *"The Kid Bids the Hub Adieu"* (I believe I am correct but don't hold me to it). To paraphase that headline, *"The Coop bids the GIPS Newsletter Adieu"*. Those of you baseball fans, should understand the above cryptic headline. Hopefully, as I hang up the "spikes" some compasionate hurler will groove one for me so I can exit with a round tipper just like the kid (AKA the splendid splinter).

Harry

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

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

SPECIALTY CONFERENCE

HANDOUT

GASTROINTESTINAL PATHOLOGY

Thursday, March 18, 1993 - 7:30 p.m.
Grand Ballroom D

Moderator:

RODGER C. HAGGITT
University of Washington Medical Center
Seattle, WA

Panelists:

CAROLYN C. COMPTON, Massachusetts General Hospital, Boston, MA

PATRICK DEAN, Baptist Memorial Hospital, Memphis, TN

AUDREY LAZENBY, The Johns Hopkins Hospital, Baltimore, MD

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

DANIEL SHEAHAN, Harper Hospital, Detroit, MI

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

CASE 1

An 11 year old healthy white boy developed abdominal cramps, watery mucoid diarrhea and a fever of 100.1°F. On day three the diarrhea became blood-streaked, and at a local emergency room he was treated by intravenous hydration for presumed self-limited colitis, and discharged. Stool culture was negative. On day seven his stools became frankly bloody and increased from 3 to 10 per day, and his fever rose to 104°F. On admission to hospital he was dehydrated, with a tympanitic, tender, non-rigid abdomen. Bowel sounds were active. The white cell count was 19,000 with 28% band forms, platelets 128,000. Liver and renal function were normal, and there was no hepatosplenomegaly. Radiographs showed dilated loops of bowel without air-fluid levels or free air. Erythematous, friable mucosa without ulceration or exudate was seen on sigmoidoscopy. Next morning he developed acute abdominal pain and distension, hypotension, severe leukocytosis, acidosis and coagulopathy.

At laparotomy three litres of clear ascites were found. The colon from cecum to rectosigmoid was plum colored, intensely congested, and thick-walled. Small bowel and stomach were dusky. The liver was swollen and abnormally firm. The slide is from the subtotal colectomy specimen.

CASE HISTORY CASE # 2

This 73 year old white woman presented to an outside hospital with a recent onset of bloody diarrhea. Four days prior to admission, the patient experienced crampy right upper abdominal pain followed by nausea, vomiting, and watery diarrhea. The diarrhea became bloody just before admission. Physical exam at an outside hospital revealed diffuse abdominal pain with rebound tenderness, guaiac positive stool, and WBC of 28,000. Because of apparent acute surgical abdomen, an emergency exploratory laporatomy was performed. However, at surgery, the small bowel and colon appeared normal externally and there was no evidence of mesenteric atherosclerosis or other mesenteric disorders. Since no gross lesion was found, the patient was simply closed. Postoperatively, the patient was placed on broad spectrum antibiotics and prednisone. Within days, signs of progressive renal failure developed with decreasing urine output (180cc/shift) and rising creatinine (to 3.1). Flexible sigmoidoscopy revealed "patchy areas of raised inflamed mucosa with some bleeding, and normal appearing mucosa in between".

The patient was then transferred to the JHH. At admission, she was found to have diffuse abdominal pain with rebound tenderness. Abnormal laboratories included Hct 31%, WBC 35,000 with a differential of 79% polys, 10% bands, 7% monos, and lymphs of 4%. Blood gases on room air were pH 7.33, pCO_2 47, pO_2 53, and HCO_3 of 25. Endoscopy showed friable edematous mucosa throughout the entire colon. Abdominal CT showed bowel wall thickening involving the right, left, and rectosigmoid colon. Because of continuing clinical deterioration, a colectomy was performed.

CASE 3

HISTORY

This forty-one year old man presented to the Emergency Department with complaints of fatigue, dizziness and the intermittent passage of bright red blood per rectum of three days' duration. He denied nausea and vomiting, hematemesis, constipation or diarrhea, melena and abdominal pain. He was known to have hemorrhoids. On physical examination, the patient was afebrile but orthostatic (BP supine = 140/70 mmHg; BP erect = 90/0 mmHg). Tenderness to deep palpation was elicited in the left lower quadrant of the abdomen. Digital rectal examination showed bright red blood but no palpable mass. The patient's hematocrit was 22.5% with hypochromic & microcytic indices. He had both a mild leukocytosis and slight thrombocytosis. All other laboratory values were within reference ranges.

Following transfusion of four units of packed red blood cells, the patient underwent esophagogastroduodenoscopy; no abnormality was observed. Colonoscopy was then performed to the cecum; multiple diverticular ostia together with several atypical polyps were seen in the sigmoid colon. The remainder of the colon was normal.

A technetium Tc99m pyrophospate labeled red blood cell isotopic scan failed to demonstrate an alternative active gastrointestinal bleeding site at sixteen hours. With the point of blood loss presumptively localized to the sigmoid colon, segmental resection of this area was carried out. Numerous diverticula were confirmed. Four red-brown polyps ranging in size from 0.5 cm to 3.0 cm and contiguous with redundant mucosal folds were present. Submitted for your examination is a section of one of the polyps.

CASE 4

CASE HISTORY

A 59 year old black male was admitted to Pulmonary Service with right sided pneumonia about 3 weeks prior to surgery. The pneumonia responded to antibiotic therapy; however, he was noted to be anemic with guaiac positive stools. An upper GI showed a questionable mass, but endoscopy demonstrated a 5 cm gastric mass situated in the mid-body over the greater curvature of the stomach. The mass was biopsied and one week later, the patient was taken to the operating room for a subtotal gastrectomy.

GROSS DESCRIPTION

The subtotal gastrectomy specimen demonstrated an irregular polypoid mass with a central area of ulceration and measured 4 cm in greatest dimension. On section, the tumor did not invade the wall of the stomach.

CASE 5

CASE HISTORY

A 50 year-old female with a prior history of coronary artery disease was referred for three months of upper abdominal discomfort, anorexia and weight loss. Her abdomen was negative to palpation, and an upper endoscopic examination was normal. An abdominal ultrasound study was inconclusive. Abdominal computed tomograms (CT) showed a mass in the pancreatic body. An ERCP showed a normal papilla, but the pancreatogram showed ductal obstruction and dilatation. The patient was taken to surgery and a distal pancreatectomy was performed.

CASE 6

CASE HISTORY

A 30 year old black man with idiopathic dilated cardiomyopathy developed congestive heart failure 3 years after initial diagnosis. He was given an orthotopic heart transplant and FK-506 as immunosuppressant. Two weeks post transplant, he became febrile with abdominal pain, headache and back pain. WCC was 5,400 without shift, cultures were negative and abdominal CT scan was unrevealing. Moderate acute cellular rejection was treated successfully. Two weeks later, he became febrile again with watery diarrhea, abdominal crampy pain and distention and leukocytosis of 11,000 with 98% neutrophils. There were no neurological symptoms. Two days later he developed respiratory distress and died. Your section is from the small intestine obtained at autopsy.

Case #1: MESENTERIC VENOUS THROMBOSIS

A. Brian West
Department of Pathology, Yale University

Pathologic features

The resected colon was of normal length, but the wall was firm and thickened and the serosa was plum colored with a finely granular surface. Blood was present in the lumen. The mucosa was plum colored and mottled with markedly thickened folds and focal small ulcers. The cut surface revealed that mural thickening was due largely to congestion and hemorrhage in the submucosa.

The microscopic appearances are characterized by numerous recent, organizing and partially recanalized thrombi in the mesenteric venous vasculature, patchy intense venous congestion, intramural hemorrhage and edema, and early ischemic necrosis affecting the mucosa predominantly with ulceration and acute inflammation. There is older ischemic injury also, reflecting the duration of the patient's symptoms and the age of some thrombi (estimated at up to two weeks). The arteries are not involved. Thrombosis is seen in the absence of phlebitis, suggesting a primary thrombotic process. These features are typical of mesenteric venous thrombosis (1), and presentation at this age is suggestive of a hereditary hypercoagulable state. A wedge biopsy of the liver showed acute Budd-Chiari syndrome, accounting for the sudden enlargement of the liver and development of ascites.

Differential diagnosis

Mesenteric venous thrombosis accounts for about 10% of all cases of intestinal ischemia and infarction (for reviews see (2-4)). In over 90% of patients the process involves veins of the superior mesenteric system, with injury to segmental regions of the small bowel and proximal colon (5). The histologic differential diagnosis includes conditions that cause intestinal congestion and mural hemorrhage; venous thrombosis, with or without phlebitis; and intestinal ischemia.

Mehanical obstruction of the venous return, as seen in intestinal strangulation, volvulus, torsion and intussusception, is a common cause of intense congestion and mural hemorrhage. External compression of the vasculature often leads to obstruction of the low pressure venous system before the arterial supply is affected, and the bowel becomes engorged, hemorrhagic and edematous. Ischemic necrosis develops rapidly. In these circumstances, all the features of mesenteric venous thrombosis may be seen, except the thrombi themselves. This differential is rarely difficult: a sharp cut-off between the affected and unaffected segments is usually seen (unlike mesenteric venous thrombosis in which the margins of the affected area are ill-defined), and communication with the surgeon will confirm mechanical obstruction.

Intestinal infection by certain toxigenic bacteria, notably enterohemorrhagic *E.coli* and clostridia, may lead to capillary endothelial injury, severe mural edema, erythrocyte extravasation, and hemorrhage. Ischemic necrosis of the mucosa and deeper tissues develops, in a pattern that may be distinctive as in *Clostridium difficile* infections. In contrast to mesenteric venous thrombosis, however, there is relatively little engorgement of the larger (notably extramural) veins, and venous thrombosis is seen only secondary to ulceration and severe inflammation.

Mesenteric phlebitis, which must be distinguished from vasculitis secondary to ulceration or inflammation of the bowel wall, may lead to venous obstruction and thrombosis. To make this

diagnosis, phlebitis must be seen in vessels surrounded by uninflamed tissues. Pure phlebitis, without involvement of arteries or arterioles, is rare. It has been described in *enterocolic lymphocytic phlebitis* (five cases), a condition of uncertain etiology that has been associated in some cases with use of rutoside, a drug prescribed for treatment of varicose veins in Europe (6, 7). Lymphocytic phlebitis affects both ileum and colon. It is characterized by dense cuffing of veins in all layers of the wall deep to the mucosa and in the mesentery, by a mixed population of B- and T-cells. Rare giant cells may be seen in the infiltrates, raising the possibility that this is related to the otherwise similar entity described in a single case report as *necrotizing and giant cell granulomatous phlebitis* (8). In *idopathic myointimal hyperplasia of the mesenteric veins*, which has been reported in the distal colon of four adult males (9), mesenteric veins show obstructive myointimal hyperplasia without vasculitis or thrombosis, and there is chronic ischemic injury of the involved colon. Pure venous involvement may be seen in *Behçet's syndrome*, in which non-necrotizing lymphocytic vasculitis affects predominantly small veins and venules, without thrombosis or involvement of the larger mural and mesenteric veins (10). Finally, recent studies have suggested that chronic granulomatous vasculitis with ischemic injury may play a key role in the pathogenesis of *Crohn's disease* (11, 12).

Mesenteric phlebitis and arteritis may be seen together in patients with *systemic lupus erythematosus* and *Behçet's syndrome*. In these cases, involvement of the arterial system rules out mesenteric venous thrombosis (10, 13).

Arterial ischemia of any etiology (central hypotension, arteriosclerotic stenosis, thrombosis, embolism, arteritis, etc) can lead to intestinal necrosis with congestion and hemorrhage. Venous congestion and mural hemorrhage may be more pronounced if there is reperfusion injury than if there is simple coagulative necrosis. The absence of venous thrombi and the presence of histologically or radiologically demonstrable arterial lesions or of an appropriate clinical history usually enable the correct diagnosis to be made.

In all cases of hemorrhagic or ischemic bowel in which there is doubt as to the etiology, the resection specimen should be examined in detail and blocks taken from grossly normal and abnormal areas of the bowel wall. Vessels in the supporting mesentery or mesocolon should be scrutinized and sampled meticulously (1, 9). *The histologic 'viability' of the resection margins should be reported.*

Etiology

Spontaneous mesenteric venous thrombosis occurs in most cases in patients with a hypercoagulable state (see Table). A precipitating event is rarely identified, but episodes of dehydration, trauma, peritonitis and infection in susceptable individuals have been implicated. Defects in protein S, protein C, antithrombin III and plasminogen are usually hereditary with autosomal dominant inheritance (14). In the present case, despite exhaustive investigations, an underlying coagulopathy was not detected in the patient or his family.

Management and prognosis

Patients with mesenteric venous thrombosis usually present with an acute abdomen but with a history of abdominal symptoms for several days (5, 15). Many have a history of deep vein thrombosis. Subacute and chronic forms also occur (4). The diagnosis is not generally made preoperatively, though radiologic features can be suggestive or even diagnostic. These include a rigid thick-walled segment of bowel with thumbprinting on plain film or CT (16, 17), spasm of branches of the mesenteric artery with prolongation of the arterial phase on angiography (18), thrombosis of veins on CT or MRI (19), and venous stasis on duplex Doppler ultrasonography (20). Initial thrombolysis with streptokinase or urokinase is usually

contraindicated because of risk of hemorrhage and severe fibrinogenolysis make emergency surgery hazardous. Recombinant tissue plasminogen activator, which has greater selectivity of action, has been used successfully in this setting (21).

In about 50% of cases, despite anticoagulation, thrombosis recurrs or extends postoperatively, necessitating a second resection, as occurred in the patient presented here. For this reason, wide resection margins of grossly normal bowel are recommended if the diagnosis is known at surgery (15). In addition, patients are at risk of developing venous thrombi elsewhere (22), as our patient's Budd-Chiari syndrome exemplifies. Thus, the diagnosis of mesenteric venous thrombosis carries important clinical implications for the early post-operative managament of affected patients, who may also require long-term anticoagulation. All patients with mesenteric venous thrombosis of unknown etiology should be worked up for primary coagulopathy, and if a potentially inherited defect is detected first degree relatives should be screened.

Conditions associated with mesenteric venous thrombosis (4, 23, 24):

Hypercoagulable states:
- Increased fibrin deposition: deficiency of protein S or heparin cofactor II; deficiency or defect in protein C* (25); deficiency or defect in antithrombin III; abnormal fibrinogens
- Decreased fibrinolysis: deficiency or abnormality of plasminogen; deficiency of factor XII or prekallikrein; deficiency of tissue plasminogen activator (26)
- abnormality of plasminogen activator inhibitor (notably PAI1)
- Lupus anticoagulant (antiphospholipid-antibody) syndrome
- Pregnancy and oral contraceptive use (27)
- Malignancy, especially pancreatic and colonic (28)

Hyperviscosity syndromes:
- Polycythemia vera (29)
- Dehydration
- Hyperlipidemia

Other:
- Abdominal trauma and peritonitis (5)
- Cirrhosis and portal hypertension (30)
- Schistosomiasis (31)
- Diabetes mellitus
- Esophageal sclerotherapy (32)

*Patients heterozygous for protein C deficiency have serum levels about 50% of normal and are generally considered to be at increased risk of venous thrombosis, though this is disputed (33). The protein is undetectable in homozygotes, in whom the untreated disease is fatal. As protein C is synthesised in hepatocytes, homozygotes can be treated by liver transplantation (34).

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CASE # 2

HEMORRHAGIC COLITIS DUE TO VEROCYTOTOXIN-PRODUCING E.COLI
JHH S90-10307

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I. HISTORICAL

The term hemorrhagic colitis denotes a clinical syndrome of severe crampy abdominal pain, minimal fever, and diarrhea that progresses from watery to bloody diarrhea - all in the absence of conventional enteric pathogens or established ischemia. The syndrome was first recognized in the 1970's and given such names as "evanescent colitis", "transient ischemic colitis", and "reversible segmental colitis" - but at that time no clear pathogenesis was recognized for this syndrome (1). The investigation of 2 Midwestern outbreaks in 1982 led to the discovery of E.coli O157:H7, a toxin-producing bacterium, as one of the etiologic culprits (2).

II. PATHOGENESIS

Several serotypes of E.coli produce potent toxins called verocytotoxins (named because of the effects on the Vero cell tissue culture line)(3). These toxins are synonymously called Shiga-like toxins because of their similarity to the Shiga toxins of Shigella dysenteriae. E.coli O157:H7 is the most common and widely recognized serotype that produces verocytotoxins, but increasing numbers of E.coli are found to produce these toxins. As a group, these bacteria are termed either verocytotoxin producing E.coli (VTEC) or enterohemorrhagic E.coli (EHEC).

As do most of the VTEC, E.coli O157:H7 produces at least 2 cytotoxins, verocytotoxin 1 (VT 1) and verocytotoxin 2 (VT 2), both of which interact with the same membrane receptor, globotriosyl ceramide (4,5). The toxin-producing E.coli do not invade epithelium, but rather adhere to the lumenal surface and elaborate toxin which may then be absorbed. The absorbed toxins interfere with protein synthesis at the ribosomal level, causing damage or death of epithelial and endothelial cells. Although death of epithelial cells potentially contributes to colonic erosions, much of the pathology comes from toxin-mediated endothelial damage (6). Damaged endothelium may fail to secrete anticoagulant substances (including prostacylcin) and/or may be the target for clotting substances that can occlude vascular lumina (e.g. fibrin thrombi). Thus, endothelial damage contributes to end-organ ischemia and explains the "ischemic" look to the colonic pathology.

III. CLINICAL FEATURES

The "classic" presentation of hemorrhagic colitis is as given above - with marked abdominal pain, diarrhea that begins as watery and then rapdily progresses to bloody, no or low grade fever, nausea & vomiting, and leukocytosis (7). However, as awareness of this disorder and

appropriate laboratory tests both become more widespread, there is a growing awareness that VTEC (including E.coli O157:H7) may have a broader spectrum of clinical presentation including mild diarrhea and asymptomatic infections (3). Reported endoscopic findings include edema, erythema, mucosal friability & erosions - often in a patchy distribution. Common misdiagnoses include intussusception in children, idiopathic IBD in young adults, and ischemic colitis in the elderly.

Extracolonic disease may be present with VTEC infections and includes hemolytic uremic syndrome (microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure), thrombotic thrombocytopenic purpura (TTP)(3,8,9), and neurologic damage. The extracolonic disease is due to toxin-mediated damage to endothelium in other organs. Fortunately, the incidence of extracolonic disease appears to be low. For instance, only 8% of patients with hemorrhagic colitis due to E.coli O157.H7 have the hemolytic uremic syndrome. (But, conversely, 75%-90% of North American patients with HUS have associated VTEC infections of the bowel)(4).

IV. EPIDEMIOLOGY

Small epidemics from these infectious agents have occurred in communities, nursing homes, schools, and day-care centers (1). In many of these outbreaks, contaminated food has been implicated particularly hamburgers, cold-cut sandwiches, and unpasteurized milk (10). Healthy cattle and swine have been implicated as the reservoir for E.coli O157:H7 as well as for other VTEC (11,12). Sporadic cases do occur and person-to-person spread has been reported.

VTEC are relatively common causes of bacterial infectious colitis. For instance, in one study at the Mayo Clinic, E.coli O157:H7 represented 13% of bacterial pathogens isolated from all stools submitted over a 6 month period (13,14). Even higher isolation rates have been isolated from regions of Canada, where E.coli O157:H7 was the most frequently isolated pathogen at one center (15).

V. PATHOLOGY

Two major patterns of histopathology have been reported: ischemic and infectious (7,16,17). Features seen in the ischemic pattern include marked submucosal edema, hemorrhage, and bland mucosal necrosis and ulceration. These cases may also demonstrate fibrin thrombi in mucosal and submucosal capillaries as well as abundant intramural deposits of fibrin. Features seen in the infectious pattern include neutrophils infiltrating crypts and lamina propria as well as adherent pseudomembranes, resembling pseudomembranous colitis due to C.difficile toxin. Numerous studies cite right-sided predominance of colonic disease, although abnormal mucosa may be present anywhere or throughout the colon.

VI. CONFIRMING STUDIES

Diagnostic tests include stool studies (bacteria or toxin isolation) as well as serology (3,18,19). Since E.coli O157:H7 was the first recognized and is the most common VTEC, more information is available on its detection. Unlike most E.coli, O157:H7 does not ferment

sorbitol. Thus, after plating stool on MacConkey-sorbitol agar plates, the pale-staining colonies that do no ferment sorbitol can be recovered and sent to a reference lab and tested with a commercial O157:H7 antiserum or can be assayed for toxin production (7). It must be noted that the bacteria is only recovered from the stool of adults for a short time after infection and thus the most predictable time for a positive culture is with 4-6 days from onset of the illness (7,8).

Free verocytotoxin can be found in the stool for even longer periods of time than the organism can be isolated, and thus stool tests for toxin may be of benefit later in the clinical course. Toxin detection has the additional advantage of identifying non-O157:H7 serotypes. Free toxin can be detected by tissue culture assay, DNA probes for the toxin genes, and ELISA tests. On the horizon is a receptor-specified ELISA (RELISA) for the verocytotoxins. This new test is reported to be as sensitive as the cytotoxicity assay, highly specific, and economical. Finally, acute and convalescent serum can be assayed for antibodies to O group antigens and to verocytotoxin neutralizing antibodies. Serologic tests maybe especially useful late in the course of the illness.

VI. THERAPY

Most cases of VTEC are self-limited, and thus the best therapy is simply supportive. There is no evidence that antibiotic therapy is beneficial, and some evidence suggests that antibiotics in fact have adverse effects with increased incidence of HUS. While most cases are self-limited, the very young and the very old are prone to more complications (including death).

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CASE 3

POLYPOID PROLAPSING MUCOSAL FOLDS IN DIVERTICULAR DISEASE

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CLINICAL SUMMARY: This 41 year old man presented with a 3 day history of dizziness and hematochezia. He was orthostatic and had left lower quadrant tenderness to palpation. His hematocrit was 22.5% with microcytic, hypochromic indices. Upper endoscopy showed no abnormality. At colonoscopy, there were multiple diverticula, prominent folds and several 0.5 cm to 3.0 cm, red-brown polyps in the sigmoid colon. Segmental resection of the sigmoid colon was performed. Diverticula were confirmed. Submitted for your examination is a section of one of the polyps.

Asymptomatic diverticulosis coli is a common condition of developed Western nations, estimated to affect half of individuals who attain the ninth decade of life.[1,2] Symptomatic diverticular disease of the sigmoid colon, albeit less prevalent, is a major cause of morbidity and is often heralded by its complications of hemorrhage, inflammation with abscess and fistulae, intestinal obstruction or colonic perforation.[1,2,3]

Anatomically, diverticular disease has two components: the pulsion diverticulum itself composed of mucosa and investing muscularis mucosae penetrating through the colonic wall, and the muscle.[3,4] Muscularis proprial thickening, often marked, is the most consistent feature seen in diverticular disease. Tonic muscular contracture with consequent foreshortening of the sigmoid colon gives rise to another anatomical hallmark of diverticular disease, viz. prominent, accordian-like, redundant mucosal folds.[3,4,5]

Sigmoid colonic polyps of the type illustrated by this case represent extreme exaggerations of the commonly recognized mucosal redundancy of diverticular disease, presumably produced by peristaltic drag in concert with muscular contraction.[5] Because the forces responsible for the genesis of prolapsed mucosa act indiscriminately on the sigmoid colon, it is not surprising that the polypoid excrescences are often multiple. In common with other mucosal prolapse conditions, the histological features of these polyps include increased mucosal height with crypt elongation and distortion, vascular congestion, hemosiderin deposition, granulation tissue and fibrosis, extension of fibers of the muscularis mucosae high into the lamina propria, and surface erosion. From a conceptual viewpoint, diverticular disease-associated inflammatory polyps are proximal analogues to more distal mucosal

prolapse conditions including overt rectal prolapse[3,6], inflammatory cloacogenic polyp of the anal canal[7,8] and solitary rectal ulcer syndrome.[9-11]

Included in the differential diagnosis of polypoid prolapsing mucosal folds in diverticular disease are inflammatory pseudopolyp of idiopathic inflammatory bowel disease, myoglandular polyp[12], 'cap' polyp[13] and eroded polypoid hyperplasia of the rectosigmoid.[14] Localization of the polyps in the sigmoid colon with normal flanking colorectum effectively excludes ulcerative colitis and Crohn's disease from consideration. Inflammatory myoglandular polyp bears histological similarity to diverticula-associated prolapse polyps[12]; there may in fact be overlap of the two entities. Although they are reported to occur throughout the colorectum, two-thirds of inflammatory myoglandular polyps are found in the vicinity of the sigmoid colon.[12] Both inflammatory 'cap' polyp[13] and eroded polypoid hyperplasia[14] occur in the rectosigmoid colon and are allegedly unassociated with diverticula. While the inflammatory 'cap' polyp shows histological features of mucosal prolapse injury[13], eroded polypoid hyperplasia is said to lack infiltration of muscle fibers into the lamina propria.[14]

Can diverticular disease-associated prolapse polyps be diagnosed by endoscopic biopsy? The answer is a qualified affirmative.[15,16] Assuming the tissue sample is sufficient to demonstrate features of mucosal prolapse and provided the endoscopist confirms origin of the polyp from a "field of diverticula" (an observation which they are adept at making!), it is reasonable to suggest an association between the polyp and a patient's diverticular disease. The potential importance of biopsy recognition lies with patient management. If the gastroenterologist is confident that a patient's symptoms are related to mucosal prolapse polyps, conservative measures directed toward therapy of diverticular disease may forestall surgical intervention.

This case affords the opportunity to remind us of other unusual and potentially perplexing associations of diverticular disease. Crohn's disease in the elderly is an au courant topic in gastroenterologic circles.[17] The coexistence of Crohn's and diverticular diseases has long been known to occur.[18,19] Mucosal and transmural inflammation distant from diverticula, epithelioid granulomas and extensive fistulization raise the suspicion of Crohn's disease coexistent with diverticula. Whether their coexistence is causally related or merely represents a chance collision of two not uncommon conditions is unclear.

Colitis morphologically similar to chronic ulcerative colitis but involving mucosa of the sigmoid colon between diverticula has been recognized.[20,21] Patients with this condition typically present with painless hematochezia. While care must be taken to exclude conventional idiopathic inflammatory bowel disease, this "segmented colitis" seems to be an innocuous condition that pursues an indolent course.

It is well to remember also that occasional patients with diverticulitis present with extraintestinal manifestations of disease including arthritis and pyoderma gangrenosum, disorders that may give rise to considerable confusion in distinguishing diverticular from Crohn's disease.[22]

Finally, a comment about a clinical aspect of this case is in order. A diagnosis of diverticular disease is less frequently entertained but is not unheard of in younger patients.[1] When diverticular disease strikes the young, it is apt to necessitate early surgical intervention.[23,24] The saga of our patient, a forty-one year old who required emergent surgery for florid diverticular disease, reinforces these observations.

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G.I. SUBSPECIALTY CONFERENCE

MICROSCOPIC DESCRIPTION:

Areas of the polypoid mass showed glands lined by regular, stratified, hyperchromatic, mitotically active epithelium. In other areas the tumor was comprised of anaplastic glands which invaded the submucosa.

DIAGNOSIS:

1. Early gastric carcinoma arising in an adenomatous polyp with invasion into submucosa.
2. No tumor identified in 28 lymph nodes.
3. Chronic atrophic gastritis with intestinal metaplasia.

DISCUSSION:

Epithelial polyps of the stomach can be divided into 2 types: adenomatous and hyperplastic or regenerative.(1,2,3,4) Imprecisions in terminology and histologic classification of the reported cases make it difficult to establish the true incidence of each type. Ming & Goldman reported that 75% of polyps are hyperplastic and 21% are adenomatous.(2) The distinction is important because malignant transformation of a hyperplastic polyp is rare.(1,2,3,4) However, the incidence of malignant transformation in adenomatous polyps varies from 40-83%.(2,3) The frequency of cancer associated with adenomatous polyps may be low in patients younger than 50, but high in older patients.(3) It is also important to examine the mucosa away from the adenomatous polyp to look for cancer which has been reported in 25% of the cases.(3) Eighty percent of adenomatous polyps are larger than 2cm.(2) Biopsy specimens are usually satisfactory for diagnosis, however the reactive changes present in inflamed hyperplastic polyps can lead to an erroneous diagnosis of an adenomatous polyp and the improper surgical procedure.(1)

Multiple gastric adenomas can occur in patients with familial adenomatosis coli and Gardner's Syndrome and can undergo malignant transformation.(5) Shemesh et al noted an association between gastric polyps (hyperplastic and adenomatous) and colonic neoplasms.(6) They suggested that gastroduodenoscopic evaluation should be performed in patients with colorectal cancer or with 5 or more colonic adenomas.(6)

Endoscopic polypectomy may provide both a superior diagnostic and therapeutic tool when evaluating the stomach by permitting total removal of small polyps less than 2cm.(1,2) Endoscopic polypectomy may not be appropriate therapy for polyps greater than 2cm which are typically adenomatous and sessile.(4,7,8) In our series of 8 adenomatous polyps, the resected specimens demonstrated one advanced carcinoma, six early gastric carcinoma with invasion of the submucosa and one sessile adenomatous polyp.(8) Endoscopic polypectomy would not have been adequate therapy in the mentioned series in seven of the eight cases.(8)

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MUCINOUS CYSTIC NEOPLASM (MCN) OF THE PANCREAS

Synonyms: Mucinous cystadenoma; Mucinous cystic neoplasm with latent malignancy; Pancreatic cystadenoma/cystadenocarcinoma

Definition: Cystic neoplasm of uncertain malignant potential lined by a mixture of serous and mucinous epithelial cells. Potentially curable by surgical excision.

Presentation: The presentation is largely dependent upon the location of the tumor. Typically, presenting symptoms are vague, and about 1/3 of cases are asymptomatic. Upper abdominal mass may be palpated or discovered incidentally on abdominal imaging studies. Duct obstruction with chronic obstructive pancreatitis or jaundice may occur with tumors in the pancreatic head. Otherwise unexplained recurrent bout or pancreatitis may be seen. About 85% of patients are symptomatic.

Demographics: In a recent review of 67 cystic tumors of the pancreas treated at the Massachusetts General Hospital within a 12-year period, 15 were MCNs. Among MCN patients, 81% were female and the mean patient age was 59 years. These data agree closely with other series: occurence mainly in in women between 40 and 60 years of age (age range 20-82; male:female ratio 1:6).

Clinical Findings and Differential Diagnosis
1) **Ultrasound:** Confirms cystic nature of the tumor.

2) **CT Scan:** Can demonstrate unilocularity vs. multilocularity, calcifications, and areas of solid growth.

3) **Angiography:** Highly vascular lesions with wide displacement of arteries. Blood supply may come directly from the primary branches of the superior mesenteric artery. Truncation of vessels implies malignancy, but differentiation of benign from malignant lesions can be difficult to impossible. Small capillaries filling papillations within cysts can sometimes be visualized. Secondary compression of portal vein or celiac axis may be present.

4) **ERCP:** Demonstrates duct obstruction (if present) and absence of communication of the cystic mass with the duct lumen. Communication with lumen and the presence of mucous in the pancreatic duct lumen suggest mucinous ductal ectasia.

5) **Cyst wall biopsy:** May demonstrate presence and type of epithelial lining. Denuded locules may cause be confused with pseudocyst.

6) **Percutaneous cyst aspiration:** Cytological analysis; Fluid analysis for viscosity, CEA, CA 15.3, CA 72-4 (TAG72), NB/70K, other epithelial or tumor markers. **CEA will differentiate MCNs (levels >25 ng/ml) from pseudocysts (levels <25ng/ml).** Cyst fluid viscosity is also elevated in MCNs. The tumor markers CA 15.3 and TAG 72 are high in MCNs with malignant foci (cystadenocarcinoma) (CA 15.3: >30 U/ml; TAG72: >780 U/ml, mean 10,027) but low in benign MCNs (CA 15.3: <30 U/ml; TAG72: <150 U/ml, mean 44).

Differential Diagnosis of Cystic Lesions of the Pancreas:
MCN
Mucinous cystadenocarcinoma
Microcystic adenoma (serous cystadenoma) or its macrocystic variant
Papillary cystic tumor (solid and cystic tumor)
Cystic pancreatic endocrine tumor (islet cell tumor)
Pancreatic teratoma
Mucinous ductal ectasia
Pseudocyst

Gross and Histopathological Features:
Grossly, tumors range widely in size (2-30 cm; average about 10cm). In the MGH series 56% were located in the pancreatic head, but in other series, the pancreatic tail has been reported as the most common location. Tumors are typically multilocular, and the size of the loculi vary from less than 1 cm to as great as 6-8 cm in diameter. The tuors do not communicate with the pancreatic dctal system. Cyst fluid may vary in consistency from highly viscous to watery or turbid. Cyst fluid analysis can be helpful in establishing a diagnosis (see below). Papillary excrescences may be visible on the inner surface of some of the loculi. Some tumors exhibit extensive denudation of the cyst epithelium, presenting problems in differentiation from a pseudocyst.

Microscopically, cysts are lined by a mixture of serous and micin-producing cells. Mucous cells vary cytologically from cuboidal to tall columnar cells with fine apical mucin granules to goblet cells. Neuroendocrine cells may be interspersed among mucus cells. Tufting of cells may be seen and may be exhuberant. Tumor cells stain for PAS and variably for Alcian blue or mucicarmine. Nuclear pleiomorphism is usually minimal. Mitotic figures should be absent; their presence correlates strongly with malignancy within the tumor (foci of frankly malignant tumor should be sought) and aggressive biological behavior. The surrounding pancreas may show secondary obstructive pancreatitis and/or atrophy. Ducts in surrounding pancreas often mucinous metaplasia and hyperplasia.

Problems in Diagnosis: The epithelial lining of the tumor may be partially denuded (5-98%) in over half the cases leading to misdiagnosis as pseudocyst on frozen or even permanent sections. Communication with the pancreatic ductal system indicates mucinous ductal ectasia rather than MCN by convention, although the two are undoubtedly variants of the same process and have the same uncertain malignant potential. Communication or lack thereof should be documented grossly.

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CASE 6

TOXOPLASMOSIS

DISCUSSION

Together with Sarcocystis, Cryptosporidia, and Isospera, the genus Toxoplasma is now considered to be coccidian and a member of the tissue apicomplexa. Toxoplasma gondii, named after a North African rodent called the gundi, infects many animal species including the human. It usually does little damage to its host. Most human infections are asymptomatic and remain occult unless cellular immunity becomes compromised.

The natural (final) host is the cat. As with other coccidia gametogenesis and oocyst formation occur in the gut epithelium. Cysts are passed in feces and sporozoites are liberated which infect other animal species including man - the intermediate hosts. In these species asexual production of cysts containing dormant bradyzoites occurs. Ingestion of tissues containing cysts activates motile forms which enter the host tissue and set up a new asexual cycle of cyst formation. Sexual cycles occur only when cyst containing tissues are ingested by feline species.

When cellular immunity is compromised, as in AIDS patients, transplant recipients or patients with malignancies treated by radio/chemotherapy, toxoplasma infection assumes a different form. The cysts become activated and liberate actively motile forms called tachyzoites which infiltrate tissue organs, cause cell necrosis, inflammation and produce symptomatic clinical disease.

Human infection can occur horizontally, following cyst ingestion or congenitally. Up to 85% of humans are seropositive for T. gondii the most frequent occurence being in 1) communities which consume uncooked meats 2) meat handlers and 3) rodent infested tropical communities.

HUMAN TOXOPLASMOSIS MAY BE ACQUIRED OR CONGENITAL

A. ACQUIRED

1) Asymptomatic disease. This is by far the most frequent variant of the disease in immunocompetent individuals. IgG and IgM toxoplasma antibody titers rise

and can remain raised for many years.

2) Acute toxoplasma lymphadentis occurs in young immunocompetent individuals. It manifests as fever, enlarged lymph nodes, and a skin rash all of which resolve in a few weeks.

3) Severe symptomatic adult toxoplasmosis occurs in immunodeficient patients. It usually presents as a systemic disease or with predominant CNS involvement.

B. Congenital

Early maternal infection leads to abortion. Late maternal infection leads to TORCH syndrome with life long disabilities.

Reactivated dormant neonatal retinal infections lead to chorioretinitis and blindness.

Immunodeficiency and Toxoplasmosis

Reports from U.K. and U.S.A. indicate that up to 17% of toxoplasma seronegative cardiac transplant recipients have received organs from seropositive donors (Luft, et al 1983) (Nagington and Martin 1983). The disease occurred in 2-5% of recipients and was fatal in 7 of 8 such patients (Nagington and Martin 1983). Renal transplant recipients who received organs from the same donor have been described as developing generalized toxoplasmosis (Renoult, et al 1991). It is estimated that 30% of AIDS patients who are seropositive for toxoplasma will develop toxoplasma encephalitis due to reactivation of latent infection (McCabe and Remington 1988). (Carrazana, et al 1989). Extraneural antemortem diagnosis is extremely rare but there are reports similar to the case under discussion in which pulmonary and gastrointestinal presentations of the disease occur (Garcia, et al 1991).

PATHOLOGY

In asymptomatic disease positive serological findings are noted but tissue examination is not indicated. In adult toxoplasma lymphadenitis there is follicular hyperplasia, focal proliferation of transformed B lymphocytes, small scattered clusters of epithelioid macrophages and rarely focal necrosis. In severe systemic adult toxoplasmosis which is

usually in immunocompromised individuals (T-helper cells) destructive lesions are seen in many organs especially brain, heart, lungs, adrenal kidney, liver, skin, and bone marrow. Recognition of the disease appears to be uncommon in the gastrointestinal tract. The lesions are diffusely scattered and consist of focal areas of necrosis surrounded by inflammation producing a hemorrhagic rim to the lesion with varying numbers of organisms (tachyzoites) present - the latter can be detected by immunohistochemical means. (Conley, et al 1981). In congenital neonatal disease, there are also similar widespread lesions being most pronounced in the CNS. Prenatal diagnosis can be established by detecting the presence of a gene sequence specific for Toxoplasma in samples of amniotic fluid using PCR technique (Grover, et al 1990).

In H & E stained sections, cysts are globoid (30 microns) or elongated, have thin eosinophilic, weakly PAS positive and argyrophilic membranes and are packed with hundreds of organisms showing dark blue nuclei. The organisms are densely PAS positive. Pseudocysts are intracellular collections of weakly PAS positive tachyzoites which push the cell nucleus to one side and have no cyst wall. Intracellular tachyzoites occur in small numbers and may become extracellular in areas of necrosis.

DIAGNOSIS

Recovery of the organisms is rare. Inoculation of laboratory animals and cell cultures with infected tissues can be diagnostic but takes up to 30 days. Serologic tests such as the Sabin-Feldman dye test and the toxoplasmin skin test indicate either previous or active disease. More recent indirect fluorescent or hemagglutination antibody tests and double sandwich ELISA are sensitive tests of acute infection providing results within two hours (Tomasi, et al 1986). AIDS patients with reactivated infection do not react to these serologic tests. The most definitive method of diagnosis is detection of the organism in tissue section with immunohistochemical confirmation.

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CASE 1

Case #1. Kodachromes

Slide 1 Low power view of the bowel wall showing intense transmural venous congestion and extensive red cell extravasation.

Slide 2 There is thrombosis of the submucosal veins in this part of the specimen, which is less severely affected than that illustrated in the low power view. Note focal necrosis of the overlying mucosa, and marked extravasation of red cells in mucosa and submucosa. The thrombi sen here are recent.

Slide 3 An organized and recanalized thrombus in a submucosal vein confirms that the process has been occurring over a period of many days. The accompanying artery is unaffected.

CASE 2

Slide 4 A - VTEC. This low power photomicrograph shows the entire colonic wall. Marked submucosal edema is present, imparting an "ischemic look".

Slide 5 B - VTEC. The mucosa and upper submucosa of the colon are illustrated. An area of bland mucosal necrosis is present adjacent to intact mucosa. Beneath the necrotic mucosa, fibrin thrombi are present in capillaries of the upper submuocsa.

Slide 6 C - VTEC. The lower mucosa (necrotic) and upper submucosa are illustrated, with a band of muscularis mucosae running through the center of the field. This PTAH stain shows several fibrin thrombi, stained dark blue, within capillaries of the muscularis mucosae and the upper submucosa.

CASE 3

POLYPOID PROLAPSING MUCOSAL FOLDS IN DIVERTICULAR DISEASE

LEGENDS

Slide 7 — This whole mount photograph of a full thickness section of sigmoid colon shows muscular thickening and redundant mucosal folds characteristic of diverticular disease. The dominant prolapse polyp retains the slender shape of its fellow redundant folds.

Slide 8 — In the head of the polyp, there is increased mucosal height with distortion of crypt architecture and hemosiderin deposition. Thick-walled blood vessels are prominent in the submucosa.

Slide 9 — Extension of fibers of the muscularis mucosae into the lamina propria, a feature common to mucosal prolapse conditions, is present in this case but is largely obscured by the abundant hemosiderin deposition.

CASE 4

SLide 10 — **The subtotal gastrectomy specimen demonstrated an irregular polypoid mass with a central area of ulceration and measured 4 cm in greatest dimension. On section, the tumor did not invade the wall of the stomach.**

Slide 11 — **Adenomatous glands can be seen at upper left and invading through muscularis mucosae at the center and lower right center.**

Slide 12 — **Residual adenomatous epithelium within the polyp can be seen on the right.**

CASE 5

Slide 13 Whole mount section through the mass shows a multiloculated cystic tumor that is not encapsulated.

Slide 14 High magnification shows both papillary projections of the cyst lining as well as invaginations of the epithelium into the underlying stroma.

Slide 15 The epithelium lining one of the cyst locules is seen on high power magnification as a single layer of cuboidal-to-columnar mucin-containing cells, some of which have true goblet cell morphology and some of which contain multiple small apical mucin vacuoles. Nuclei are basally oriented, and no significant pleomorphism is apparent. No mitotic figures are seen. The tumor stroma is delicate, vascular and contains scattered lymphocytes.

CASE 6

TOXOPLASMOSIS

SLIDE KEY

Slide 16 H & E stain: low power showing vascular congestion with eosinophilic material in submucosa indicating the location of toxoplasma infection.

Slide 17 H & E stain: high power showing small round amphophilic submucosal organisms (tachyzoites) in a fibrinous background.

Slide 18 Toxoplasma immunoperoxidase: Submucosal small round organisms (tachyzoites) stain positively.

GASTROINTESTINAL PATHOLOGY SOCIETY

COMPANION MEETING

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY
1994 SAN FRANCISCO

Sunday, March 13 1:30 p.m

UPDATE ON CANCER OF THE LARGE INTESTINE

HANDOUT