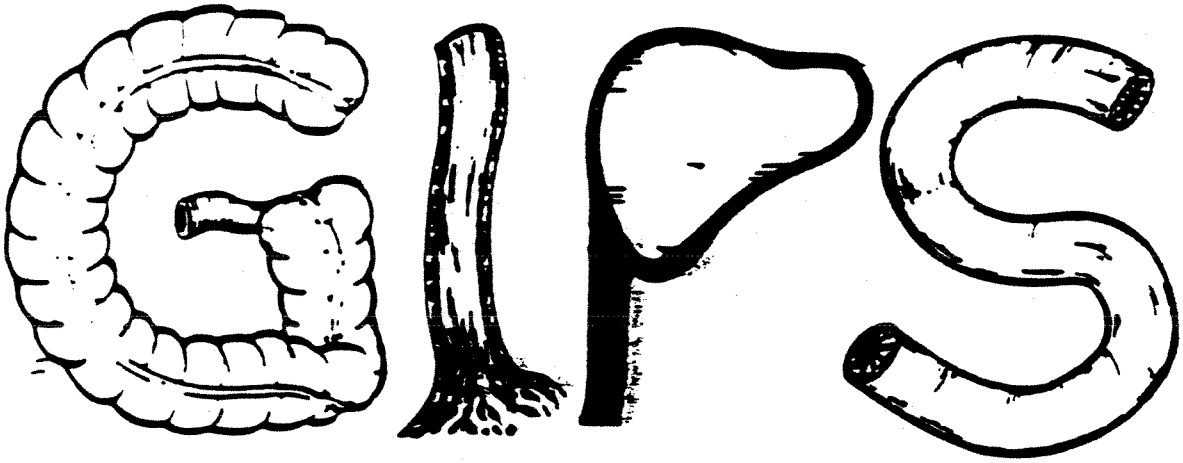

THE GASTROINTESTINAL PATHOLOGY SOCIETY
NEWSLETTER

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GASTROINTESTINAL PATHOLOGY SOCIETY
1990-91 OFFICERS AND COMMITTEE MEMBERS

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Vice-President/President-Elect (1-year term):	
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Secretary-Treasurer (3-year term):	
Robert Petras	1993
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Klaus Lewin	1993
Ludwig Deppisch	1992
Wilfred Weinstein	1992
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Leslie Sobin	1992
Joseph Tomasulo	1992
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William Dobbins (Associate Editor)	
International Liaison:	
Harvey Goldman	

Tales of the Ampulla of Vater: X

By the shores of Duodenum
near the banks of Choledochus
Peered the Ampulla of Vater
through his microscope he focused.

On a tiny curved bacillus
that was caught in villi's net
As they fished the chylomicron
on a day they'll ne'er forget.

Please your name and what's your provenance
Ampulla asked the germ
Do you understand my language
can you recognize my term?

I was born in gastric antrum
with my tribe I plied the shore
We are called *Campylobacter*
merely scavengers, no more.

Then one day the gastric juices
turned from tan to shades of red
'twas the sign of Pepto-Bismol
that's what *Campylobacter* dread.

Oh I panicked and let go the shore
was swept through the Pylorus
To find myself in chylous nets
and hear your villi's chorus.

Now they say we cause dyspepsia
perhaps a mild gastritis
Some postulate we ulcerate
but that is just detritus.

We're not a threat to villi
your land is not our site
(Unless there's metaplasia
to a gastric antral type).

Oh have mercy Great Ampulla
please release me to the stream
I promise you I'll not return
my record will be clean.

I am sorry curved bacillus
for I trust you as you stand
But some day may come your progeny
and plunder villous land.

I'm obliged first to the Duode'en
compassion is no factor
As he signaled to the polys, said
Farewell Godspeed young bacter.

Leslie H. Sobin, M.D.
Armed Forces Institute of Pathology
Washington, DC

MESSAGE FROM THE PRESIDENT

Usually, the duties of the President of GIPS are mainly ceremonial (to chair the annual business meeting) with the real work of the Society being done by the Secretary-Treasurer, the Editor(s) of the Newsletter, and the chairmen of committees (particularlay the Education Committee). However, as you will read elsewhere in the Newsletter, this year has been different with your President heavily involved in coordinating discussions and negotiations aimed at promoting a closer relationship between GIPS and the American Gastroenterological Association. The items under consideration have included the status of GIPS contribution to Digestive Disease Week and appointing a GIPS representative somewhere in the AGA's labyrinthine committee structure.

Some people have expressed an opinion that the difference in size and complexity between our two organizations is a cause for worry. They view this situation as negotations between a sardine and a great white shark, noting the latter's capacity for engulfment. I would like to think that a better analagy is negotiations between a fox and a dinosaur, one small and cunning, the other large and mainly herbivore. Probably, neither of these views is correct and the truth lies in the middle ground. The objective for GIPS is to maintain a presence at DDW that presents to gastroenterologists our society and our subspecialty expertise in the best possible light, with the least cost to GIPS and the least expenditure of effort to ourselves.

I suspect that most, but not all, members of GIPS regard themselves as pathologists first and gastroentrophiles second. Certainly, we do not wish to "swallowed up" by a larger group. Nevertheless, there are some extremely valid political as well as scientific reasons for maintaining a close relationship with the AGA.:

1. Sharp distinctions cannot and should not be drawn between morphologic and clinical aspects of GI disease. We can learn from gastroenterologists and they can learn from pathologists.

2. Morphologic diagnosis is highly appealing to some gastroenterologists. Indeed, we have a small number of highly distinguished gastroenterologists who are members of our Society. If we choose to shun the AGA it is quite conceivable that gastroenterologists will start up their own pathology section that will rival GIPS.

3. Gastroenterologists can be powerful allies for us when we are faced with Pathology Chairmen who are heavily oriented to basic science and think that morphological diagnoses can safely be delegated to board certified chimpanzees. GIPS participation at DDW raises our profile and promotes an understanding of the difficulties and subtleties of biopsy diagnosis.

David A. Owen, M.B.
President, GIPS

DAO:ff

GIPS Journal Affiliation

Henry Appleman and David Owen have been busy reviewing the journal affiliation interests of the GIPS members. As a result of their work, GIPS will not pursue an affiliation with Human Pathology, Surgical Pathology, or Modern Pathology.

We will continue our present affiliation with the American Journal of Surgical Pathology (AJSP). This will be a short-term commitment. AJSP will continue to publish our notices and fellowship announcements. It is understood that material presented at our annual symposium may or may not go into a supplement. The decision would be based on the interest of the author in submitting the material and the presence of sufficient material for the supplement.

We would be interested in comments from any GIPS members who have opinions as to the journal affiliation for the future.

GIPS Agreement with AGA

Our President, David A. Owen, has been in correspondence with David Alpers, the current President of the AGA in order to seek a more formal relationship between the two societies, particularly in regard to pathology presentations at Digestive Diseases Week. Drs. Owen, Goldman, Madara, and Yardley formed an ad hoc subcommittee to coordinate these discussions.

As a result of their efforts, it has been proposed that the GI Pathology session would move to the Wednesday afternoon of Digestive Diseases Week. As before, this would be organized by GIPS who would control its content. The session would be fully advertised and would appear in the program. It will be scheduled in an appropriately sized meeting room. The AGA would provide substantial financial support for speakers who are non-AGA members. We will need to provide the AGA with an outline of the proposed session by the end of August.

GIPS may also submit suggestions for "state of the art" lectures to the AGA scientific committee.

In addition, the AGA is prepared to consider having our President (or his or her delegate) as an ex-officio member of the AGA research council. This would enable us to have input into the Digestive Diseases Week activities, as well as to provide a possible focus for pathology becoming an official AGA subsection.

Indeed, the AGA encourages GIPS members to also become AGA members. To this end, they would like to send membership applications to GIPS members.

The proposal to allow GIPS input into Digestive Disease Week represents a considerable logistical and financial advance over the present situation and we should accept them. The closer liaison between GIPS and AGA will benefit both organizations. The possibility of pathology being made an AGA subsection has some liabilities as well as benefits. Dr. Owen suggests that we must guard our independence to avoid a split in GI pathology such would occur if half of the pathologists are in GIPS and half in the AGA.

However, it is acceptable to both Dr. Owen and Dr. Alpers for a letter to be sent encouraging GIPS members to <u>also</u> subscribe to the AGA. He encourages us to remember that the "raison d'etre" for GIPS is to promote GI pathology. If we fail to take advantage of this opportunity, we will cut ourselves off from an important area of clinical and scientific interest.

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APPLICATION OF MOLECULAR BIOLOGY TO PROGNOSIS AND RISK OF COLORECTAL CARCINOMA

Stanley R. Hamilton, M.D.

Approximately 110,000 new cases of colonic cancer and 45,000 new cases of rectal cancer occur each year in the United States. About 60,000 patients die each year of colorectal caricnoma (CRCa), accounting for about 12% of all cancer deaths and nearly 3% of deaths from all causes. Thus, CRCa is a major public health problem.

The molecular genetics and molecular biology of CRCa are among the best understood of any common human cancer (1,2). The advances in molecular biology, however, have not yet been translated into improved patient care. Two potential areas for application of molecular genetics to reduce CRCa mortality are in prognostication and in prediction of risk of developing the disease.

Prognosis in CRCa is determined by the presence or absence of metastasis. The vast majority of patients with CRCa undergo resection of the primary tumor, but death occurs in about half of these patients because metastatic disease, which is often occult at the time of initial surgery, remains after operation. Estimation of prognosis is now based on clinical and pathological staging, but the majority of patients have moderate risk of recurrence, and outcome for a given individual cannot be predicted accurately (3). Better markers to predict which patients have occult metastasis would lead to improved surgical and medical management.

In surgical management of rectal carcinoma, patients have a strong desire to avoid permanent colostomy, and therefore local excision or sphincter-saving operations are performed. Some patients, however, have occult local metastasis better managed by abdominal-perineal resection. Better indicators of metastatic risk would help patient selection for local excision or radical resection (4). Secondly, the decision for surgical resection after colonoscopic polypectomy in the 3% to 5% of patients whose specimens contain invasive carcinoma is difficult (5). Potential morbidity and mortality of operation must be balanced against the risk of residual carcinoma and local metastasis amenable to resection. Pathological criteria are very sensitive in identifying patients with metastases in regional lymph nodes, i.e. the vast majority of patients with metastases have one of these criteria (poor differentiation of the carcinoma, angiolymphatic involvment, sessile configuration producing invasion into the bowel wall, incomplete excision of the carcinoma, and extensive carcinoma in the polypectomy specimen). On the other hand, the predictive value of a positive criterion is low, in that only about 5% to 10% of patients with these criteria are found to have lymph node metastases, and therefore the surgical resection could have been avoided. Better markers would lead to improved decision-making for patient management and utilization of medical care resources.

Medical management of CRCa includes postoperative adjuvant chemotherapy and/or radiotherapy for treatment of occult metastatic disease. Although a large number of clinical trials have been conducted, only recently have successful regimens been reported (6). Because of the availability of effective adjuvant therapy, patient selection based on prognosis is an important issue. On April 16-18, 1990, the National Cancer Institute and Office of Medical Applications of Research convened a National Institutes of Health Consensus Development Conference entitled "Adjuvant Therapy for Patients with Colon and Rectum Cancer" (7). After extensive review, the Consensus group concluded that the results of a large trial of 5-fluorouracil and levamisole by Moertel et al. (6) indicated that postoperative adjuvant chemotherapy should be offered to patients with TNM Stage III colonic cancer (metastasis to regional lymph nodes; Dukes' C; Astler-Coller C1 or C2). They also concluded that combination postoperative adjuvant chemotherapy and radiotherapy should be offered for TNM Stage II and III rectal carcinoma (local extension beyond the muscularis propria with negative lymph nodes or metastasis to regional lymph nodes; Dukes' B or C; Astler-Coller B2, C1, and C2). Whether or not these recommendations will become standard therapy remains to be seen. However, the Consensus group stressed the inadequacy of the

current staging methods for determining prognosis and emphasized the need for development of better markers.

A third impact of improved markers for prognosis lies in patient life-planning after resection of CRCa. Most patients are anxious about their likelihood of survival from cancer and consider major changes in their approach to life. Improved markers would be helpful in advising patients.

Metastasis is a complicated, multi-step process (8). Malignant cells must detach, invade through basement membrane and extracellular matrix, gain access to and survive in the vascular system, adhere and immigrate into the target organ, and then proliferate autonomously in the new site. The complexity of this process is reflected in the many factors reported as having prognostic value in CRCa. These include characteristics of the primary tumor, vascular invasion, host response, consequences of surgical technique, and nonpathological features (9). For example, prognostic features reported for the primary tumor include site, size, configuration, extent of circumferential involvement, mobility, obstruction, perforation,depth of invasion, pattern of infiltration, grade of differentiation, mucus production, total DNA content ("aneuploidy"), proliferative activity, surface and intracellular glycoproteins, nucleolar organizing regions, gastrin receptor, and abnormalities of various oncogenes and tumor suppressor genes.

The molecular genetic changes described in CRCa involve many genes including ras, myc, src, APC (adenomatous polyposis coli), p53, and DCC (deleted in colorectal carcinoma) (10). It is unrealistic to believe that the complicated process of metastasis could be under the control of a single gene. More likely, multiple genes are involved at the various steps. Relatively little data are available on molecular markers for prognosis of CRCa. Our previous study showed that an allelic deletion on the long arm of chromosome 18 (18q, the site of the DCC gene), a deletion on the short arm of chromosome 17 (17p, the site of the p53 gene), and high proportion of evaluable chromosomal arms deleted (termed "fractional allelic loss") were associated with distant metastasis and reduced survival (11). Additional studies are needed to validate these markers and determine their mechanistic effects on the biology of human colorectal carcinoma cells. Nonetheless, these markers offer an opportunity for improved assessment of prognosis.

A second area where molecular genetics has potential to contribute to reduced mortality from CRCa is in prediction of risk. In the past, CRCa was considered a prototypic example of an environmentally determined human cancer. Dietary factors, particularly high dietary fat and low dietary fiber, were implicated in the etiology (12). Except for rare syndromes such as adenomatous polyposis syndrome and hereditary nonpolyposis colorectal cancer syndrome, inheritance was thought to play a relatively minor role. However, recent attention has been directed at familial aggregation of colorectal cancer. In particular, analysis of large pedigrees has suggested that susceptibility to CRCa may be inherited in an autosomal dominant fashion (13).

Knudson proposed that the genes for hereditary cancers are also involved in the pathogenesis of the "sporadic" forms of the disease (14). Adenomatous polyposis syndrome has hundreds of colorectal adenomas, and CRCa invariably develops unless prophylactic colectomy is performed. This syndrome is linked to the long arm of chromosome 5 (5q21-22), and deletion of this site is frequent in "sporadic" colorectal carcinoma (15-18). Gene probes linked to adenomatous polyposis are now in use for diagnosis of affected family members. A second inherited syndrome is hereditary nonpolyposis colorectal cancer syndrome (HNPCC, Lynch syndrome). This disease has autosomal dominant inheritance of CRCa with young age of onset and proximal predominance and multiplicity of tumors (19). HNPCC has been linked to the Kidd blood group (20) which is assigned to chromosome 18q11-12. Thus, it is possible that the DCC gene on the same region of chromosome 18q is the gene for HNPCC (21). Definition of the gene for HNPCC on chromosome 18q or elsewhere in the genome could have a major impact on prediction of risk and contribute to lowered CRCa mortality by permitting aggressive surveillance and early intervention in persons who have inherited the abnormal

gene.

In summary, studies of molecular genetic markers for metastatic phenotype and risk of colorectal carcinoma have the potential for rapid impact on the surgical and medical management of patients. In addition, identification of markers for risk assessment offers the possibility of improved surveillance and early intervention. The use of molecular genetic markers in this fashion would represent a prime example of technology transfer to address an important clinical problem and improve medical care.

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GIPSPROG

GIPS Abstract Reviews

From M.D. Anderson Cancer Center in Houston, Dr. Adair and coworkers describe study of 41 cases of malignant melanoma involving the gastrointestinal tract. The small intestine was the most commonly involved site (28 cases) followed by the stomach (14 cases). Less commonly involved locations included the rectum, gall bladder, colon, and esophagus with less than 6 cases each.

Drs. Alonso and colleagues from Chicago and Minneapolis describe the histologic findings in progressive familial intrahepatic cholestasis. This is an autosomal recessive chronic cholestatic syndrome which results in progressive fibrosis and sclerosis in childhood. In examining 83 biopsies from 23 patients, key features on initial biopsy included giant cell hepatitis, cholestasis, canalicular bile plugs, and pseudoacinar formation. Later in the disease, ductular proliferation was seen at the periphery of portal tracts, bridging fibrosis developed in 15 patients and pericentral sclerosis was seen in 58%.

Drs. Kandel and coworkers from Toronto report their findings using *in situ* hybridization to localize Herpes simplex virus in esophageal biopsies from 33 patients who were immunosuppressed due to malignancy or chemotherapy. Nine of 11 culture positive cases were also positive by *in situ* hybridization. One culture negative case was also positive by *in situ* hybridization. The herpes DNA was seen both in cells containing intranuclear inclusions and in normal appearing cells. *In situ* hybridization facilitates rapid diagnosis of Herpes simplex virus esophagitis to allow early treatment with acyclovir.

From Calgary, Alberta, Drs. Kelly and colleagues report on the efficiency of avidin to stain mucosal mast cells in the human stomach, small and large bowel. The samples were fixed in formaldehyde, Bouin or Carnoy. Avidin binds to the mucosal mast

cells. By using avidin-biotin complex, they were able to quickly and reliably stain mucosal mast cells in these routinely processed tissues.

Drs. Kennedy and Jaffe from the University of Pittsburgh reported their findings on 13 children with progressive intrahepatic cholestasis. Mean age at presentation was 6.5 months with an initial diagnosis of intrahepatic biliary atresia in 7 of the 13. Twelve patients underwent orthotopic liver transplantation. Key features in the initial biopsies included canalicular and hepatocellular cholestasis, periportal fibrosis, and giant cells.

From Boston, Drs. Khettry and coworkers describe the histology of 50 donor gall bladders and correlate their appearance with subsequent graft function. They found that the degree of mucosal hemorrhage and/or necrosis was a specific lesion which correlated highly with poor liver graft function. When more than 10% of the mucosa had such lesions, the graft function was rated poor.

Drs. Kim and coworkers from Yonsei University in Korea and the M.D. Anderson Cancer Center in Houston found that the elevation of gastric juice ammonia levels in patients with gastritis is an indicator of the presence of gastric Campylobacter pylori infection. The infection had no effect on blood urea nitrogen or blood ammonia levels. Only the gastric juice ammonia levels were increased.

From the Cleveland Clinic, Drs. Kramer and colleagues performed a clinicopathologic study of 185 cases of Crohn's disease. In general, cases with granulomas were younger at onset of Crohn's disease and at resection (23.6 and 24.2 years) versus individuals lacking granulomas (28 and 31.8 years). No relationship between the presence of granulomas and recurrence of Crohn's disease was found, however.

From the National Navel Medical Center in Bethesda, Drs. Lapa and Kragel studied the expression of a CEA epitope, D-14, in Barrett's esophagus and esophageal adenocarcinoma. Using an

immunoperoxidase staining technique, they found moderate staining of the lumen and cytoplasm of the adenocarcinomas and cases with dysplastic Barrett's esophagus. Two-thirds of the cases of non-dysplastic Barrett's esophagus also stained. The use of monoclonal antibodies did not help to differentiate dysplastic from non-dysplastic Barrett's esophagus.

From the University of Minnesota, Drs. Manivel and Fasola performed a left lobe hepatectomy and portacaval shunt and clamped the hepatic artery in 15 pigs. Five underwent auto-transplantation by having hepatocytes injected into a branch of the splenic vein. The others served as controls. Both bile ductules and well-preserved hepatocytes arranged in cords and nests were found within the spleen. Thus, hepatocyte transplantation may provide temporary support for ischemic acute liver failure. These same workers also reported that hepatocytes could be implanted into urethane sponges which were placed into the right flank of Wistar rats. Syngeneic grafts showed nests and cords of well-preserved hepatocytes. Allogeneic hepatocytes did not fare as well.

From the University of Nebraska, Drs. Markin and coworkers examined 130 potential hepatic allografts using frozen section examination prior to transplantation of the liver. Findings which indicated potential post transplantation dysfunction included: Chronic portal inflammation, parenchymal necrosis, prominent peri-ductular fibrosis, steatosis, bridging fibrosis, and granulomas.

Drs. McLachlin and colleagues from Victoria Hospital and the University of Western Ontario examined 74 biopsies from 58 patients with celiac disease. By using Congo red they found amyloid present in 29 (39.2%) of the biopsies. There was no correlation of the amyloid with clinical or histologic severity of the disease. There was a positive correlation with increasing age of the patient and duration of disease.

From the University of Oklahoma, Dr. Min reported on lymphoepithelioma-like carcinoma of the stomach in 3 patients. In all 3, poorly differentiated tumor cells were diffusely spread through a rich lymphocytic background. The features are similar to those of lymphoepithelioma lesions seen in other organs and he suggests that they are a unique subtype of gastric carcinoma.

Drs. Nakhleh and colleagues from the University of Minnesota compared the duodenal and pancreatic tissues in human pancreaticoduodenal transplants. Ten of 22 resected allogeneic transplants showed acute vascular rejection and 12 showed chronic vascular rejection. Intraepithelial inflammation was found in 7 of the 10 duodenal transplants with acute rejection and individual epithelial cell necrosis was found in 5. Four pancreas transplants were extensively necrotic of 22. Some of the duodenal transplants survived up to 10 months. Dr. Nakhleh found that 5 of 10 rejected pancreas transplants showed endothelialitis and 3 showed arteritis. Two others showed intimal thickening with foam cells similar to chronic rejection of other organs. No inflammation was seen in the islets. They believe that acute and chronic rejection may be diagnosed if vascular lesions are present. Duct inflammation, however, is not absolutely diagnostic.

From Akron Ohio, Dr. Novak reviewed the morphometry findings in infantile allergic colitis. He found lamina propria eosinophils in normals range between 0.7-0.26/100 cells while they ranged from 0.22-0.51/100 cells in allergic colitis patients. Intraepithelial eosinophils range from 0.3-2.7/1000 epithelial cells in normals and from 2.7-5.7/1000 cells in patients with allergic colitis. Thus, both intraepithelial and lamina propria eosinophilia characterize this lesion.

Dr. Masada and coworkers from the University of Nebraska evaluated the histopathology of primary allograft failures. They studied 7 patients with hepatic dysfunction during the first 10 days

post transplant. Seventy-one percent had hepatocellular necrosis, 57% had steatosis and cholestasis was seen in 28%.

From the University of Pittsburgh, Drs. Ohori and colleagues studied 123 liver specimens following transplantation. Shell vial assay, viral culture, H + E morphology and immunocytochemistry were compared. Sensitivity was 100% for H + E inclusions, 70.6% for antigen, 29.4% for culture and 17.7% for shell vial assay. Since antigen is readily applicable in paraffin-embedded tissues, CMV cultures are not needed.

From the Cleveland Clinic, Drs. Petras and coworkers reported 4 cases of fibrovascular polyp of the esophagus. The polyps had sparsely cellular and focally myxoid fibrous tissue, prominent blood vessels, scattered lymphoid aggregates and varying amounts of adipose tissue.

CEA immunoassay was found to be a useful adjunct to cytology in fine needle asperse of liver in a study by Drs. Pinto and coworkers from Bridgeport Hospital. Serum CEA levels measured by the enzyme immunoassay method (Abbott) was used. One-hundred µl per specimen was sufficient for CEA analysis. The highest value (greater than 800 ng/ml) was obtained in metastatic adenocarcinoma. The high levels of CEA provided useful information in suggesting the source of metastatic carcinoma as the gastro-intestinal tract in patients with unknown primary source.

From the University of Pittsburgh, Drs. Randhawa and coworkers examined 10 cases of Epstein-Barr virus infections in liver transplant recipients. Four cases resembled infectious mononucleosis, whereas, 6 patients had a typical symptoms including jaw pain, arthralgias, diarrhea, encephalitis, pneumonitis, mediastinal lymphadenopathy and ascites. Liver biopsy showed mixed mononuclear portal infiltrates with a typical large cells and occasionally lobular activity indicative of a hepatic process. They could not demonstrate EBV with *in situ* hybridization.

From the M.D. Anderson Center, Drs. Robey-Cafferty and colleagues reviewed 69 squamous carcinomas of the mid and lower esophagus. They found that grade and stage of the tumor were independently significant prognostic factors: 5 years survival was 54% in well-differentiated and moderately-differentiated versus 5.8% in poorly-differentiated tumors; 4% in those with lymphoid metastases versus 31.5% in those without. DNA ploidy was not significantly associated with histologic grade, stage or 5 year survival. The same group examined P-glycoprotein expression in gastroesophageal adenocarcinomas. In 16 resection specimens, there were 8 adenocarcinomas of the stomach, 7 of the esophagus/stomach junction and 1 with dysplasia in Barrett's esophagus. When tumors were positive, P-glycoprotein was diffusely present in all types of benign gastric and Barrett's mucosa, both adjacent to and distant from the tumor. P-glycoprotein is commonly present in these neoplasms. In another report, this same group correlated the histologic observations with P-glycoprotein expression in these neoplasms treated with preoperative chemotherapy. They conclude that chemotherapy causes histologic changes in sensitive esophageal adenocarcinoma and gastric adenocarcinoma. Infrequently, P-glycoprotein is induced by chemotherapy.

Drs. Rouse and colleagues from Creighton University compared clinical and histopathologic findings in 73 patients with symptoms of alkaline reflux gastritis. There were 31 patients with alkaline reflux defined if pH study was positive or TcHIDA scan was positive. Only 14 had foveolar hyperplasia, but 9 of the negatives showed active gastritis without Campylobacter. Among 42 patients without alkaline reflux, 11 biopsies showed foveolar hyperplasia. Clearly, other insults may result in foveolar hyperplasia or the TcHIDA scan and pH monitoring missed some cases of alkaline reflux.

From the AFIP, Drs. Selby and coworkers described 90 cases of infantile hemangioendothelioma of the liver. Forty-one presented with abdominal mass which was symptomatic while 33 had an

asymptomatic mass. Seventy-three percent of the tumors marked with Ulex europaeus. There was a 71% survival for 7.7 years.

Drs. Selby and Ray from the University of Cincinnati used a monoclonal antibody to demonstrate the presence of fetal types of cytokeratins in primary liver carcinomas. They looked at the expression patterns of monoclonal antibodies AEI and 903 on 6 cases of hepatocellular carcinoma, 1 case of cholangiocarcinoma and 1 combined case. They found that 903 marks a true bile duct type cytokeratin antigen and is useful in differentiating hepatocellular carcinoma from cholangiocarcinoma.

From the University of Pittsburgh, Drs. Sever and Locker studied the retinoic acid receptors in hepatocellular carcinoma. They found that most hepatocellular carcinomas have abnormal expression of retinoic acid receptor alpha, not beta and the retinoic acid itself may inhibit growth of well differentiated hepatocellular carcinomas.

Drs. Shah and Gerber from New York and New Orleans used an immunohistochemical technique to study expression of epithelial membrane antigen and carcinoembryonic antigen by the intrahepatic biliary system during development. They conclude that during differentiation of primitive hepatocytes, bile canaliculi tend to loose expression of epithelial membrane antigen while carcinoembryonic antigen persists. In contrast, the bile ducts acquire epithelial membrane antigen during early development and later express CEA.

Drs. Shimosato and colleagues from the National Cancer Center in Tokyo used the polymerase chain reaction and oligonucleotide hybridization techniques to detect point mutations in codon 12 or 13 of the c-Ki-ras gene in cases of gastric adenocarcinoma, gastric adenoma and lung adenocarcinoma. Fifteen percent of the lung adenocarcinomas had this mutation, 43% of tubular adenomas of the stomach had this mutation and 21% of well to moderately differentiated tubular adenocarcinomas had it. None of 18 poorly differentiated adenocarcinomas of the stomach showed point mutation.

From the Mallory Institute in Boston, Drs. Stahl and coworkers examined the lymphocyte associated antigen expression in epithelium of colorectal adenomas. They used monoclonal antibodies against HLA-DR, invariant chain class II MHC, T-cell markers, B-cell

markers, and NK cell markers. They found that the HLA-DR was expressed more frequently in villous than tubular adenomas (7 villous versus 3 tubular). Invariant chain of class II MHC was expressed in almost 50% of the adenomas studied but did not correlate with growth pattern. T-cell markers were only found in high grade dysplasia and B-cell markers were found in 39 of 40 cases. Neither B nor T expression correlated with growth pattern or dysplasia. Natural killer cell markers appeared to be confined to neuroendocrine cells.

The relationship of multiple juvenile polyposis to carcinoma was studied by Drs. Subramony and Colleagues from the University of Mississippi. They report on a family of 42 containing 9 members found to have multiple juvenile polyposis. Two of these individuals developed adenocarcinoma associated with juvenile polyps. The others died of a gastrointestinal malignancy. They found a gradient of malignant change from early dysplasia to adenocarcinoma.

Drs. Teot and coworkers from Wake Forest University compared cytology and histology with regard to the evolution of dysplasia in Barrett's esophagus. They reviewed 66 cases in which both cytology and concurrent biopsies were available. In 12 cases cytologic brushing revealed a higher grade lesion than biopsy, while in 5 cases biopsy showed a higher grade lesion. Agreement between the two occurred in 74%. They conclude that the techniques are complimentary detecting a greater number of serious lesions than either techniques alone.

From Yale University, Drs. True and coworkers examined the expression of CEA in colonic and gynecologic carcinomas using newly generated CEA specific monoclonal antibodies. Monoclonal antibody 46.1 stained 13 colonic lesions intensely with no staining of ovarian or endometrial carcinomas. Two other monoclonal antibodies gave variable staining of colonic neoplasms while the pan-reactive polyclonal antibody stained all colonic neoplasms intensely with some staining of gynecologic neoplasms. Therefore, by using the newer monoclonal antibodies, one can distinguish between these types of neoplasms.

From Calgary, Drs. Urbanski and Hemmerich compare the detection of early gastric cancer in teaching hospitals versus nonteaching hospitals. The frequency of early gastric cancer detection was 3.6% over a 10 year period of all gastrectomy treated carcinomas. There

was no significant change in the frequency of diagnosis when the two 5 year periods were compared (1975-1979 versus 1980-1984). This contrasts with a teaching hospital report of early gastric cancer detection of 10.7%.

Drs. Wilson and colleagues from Emory University examined 27 cases of esophageal carcinoma for the presence of human papillomavirus. All 27 cases were negative for human papillomavirus by immunohistochemistry, in situ hybridization and by polymerase chain reaction.

Drs. Wolber and coworkers from the University of British Columbia used a polyclonal immunoperoxidase method on fine needle aspiration specimens to study hepatic lesions from 54 patients. The cytologic diagnosis was hepatocellular carcinoma in 21 cases, metastatic or cholangiocarcinoma in 22 cases and benign hepatocytes in 11 cases. Follow-up data reversed cytologic diagnosis in only 2 cases. Bile duct staining by polyclonal CEA was found in 17 of 21 cases of hepatocellular carcinoma and in all benign hepatocellular aspirates. All 22 cases of metastatic or cholangiocarcinoma were negative for bile duct polyclonal CEA staining. Note, however, that 8 cases had diffuse cytoplasmic staining.

Drs. Wolber and Owen from the University of British Columbia examined 34 colonic biopsies from patients with histologic features of celiac sprue. Twenty-nine percent showed striking lymphocytic infiltration of the surface epithelium. These patients had 31.3 lymphocytes per 100 superficial epithelial cells, the same number seen in 9 cases of typical lymphocytic colitis. Thus, sprue-associated colonic lymphocytosis and lymphocytic colitis are histologically indistinguishable. They further suggest that lymphocytic colitis may be due to a number of antigens, including gluten. This may represent a common sensitized response to absorbed lumenal antigens.

Dr. Yano from the Kurume School of Medicine in Japan reported the establishment of a new human cholangiocellular carcinoma cell line. These cells (KMC-1) have been stable over an 18 month period with 49 passages. Doubling time was 54 hours and the chromosomes number ranged from 73 to 83. They found an increase of tumor markers including CA125, TPA and DUPAN-2 in the supernatant.

Drs. Zarbo and coworkers from Henry Ford Hospital reported on a flow cytometric DNA analysis of 72 colorectal carcinomas using a multiparametric 2-color cytokeratin labeling method. They found that the diploid range correlated with larger tumor size as a continuous variable and was significant regardless of lymphoid involvement however, ploidy was otherwise unassociated with age, site, depth of invasion, lymphoid states or vascular invasion. They conclude that ploidy and S-phase fraction values in colorectal carcinomas bear no significant correlation to clinicopathologis parameters used in conventional prognostic assessment of these tumors.

From Massachusetts General Hospital, Dr. Zukerberg and coworkers examined the presence of lymphoepithelial lesions in 24 low grade gastric lymphomas and 55 benign inflammatory infiltrates. Dutcher bodies and moderate cytologic atypia were associated with lymphomas. Lastly, prominent lymphoepithelial lesions were also useful in distinguishing lymphoma.

Drs. Abramowski and Patterson from Case Western Reserve University report on 4 spontaneously aborted female fetuses (17-23 weeks) that showed spirochetal microorganisms mainly in the intestinal lumen and mucosa and to a lesser extent in other organs. The placenta showed severe chronic villitis. The silver stained spirochetes were morphologically different from Treponema pallidum.

From the Children's Hospital of Los Angeles, Drs. Aoyan and colleagues studied 7 patients with hepatic sarcoma. Serum AFP values were not elevated in these patients. Three tumors were composed of spindle cells, these were positive immunohistochemically for alpha-antichymotrypsin.

Drs. Conran and coworkers from the AFIP reviewed 67 cases of hepatoblastoma. Twenty-one of 24 cases with recorded AFP levels had elevated values. Six of 20 stage 1, one of 8 stage 2 and all 22 stage 3 and 4 patients were dead within 2 years with metastatic disease. Their data support the view that tumor resectability is a key factor for long term survival.

Drs. Kahn and colleagues from the North Shore University Hospital in Manhasset evaluated 56 resected specimens from 30 children with Crohn's disease for the presence of sinus and fistula formation. They

found that sinus and fistula formation occurred randomly about strictures and it was associated with inflammation, although the severity of the inflammation did not correlate with the presence or absence of sinus and fistula formation. When sinuses and fistulas are associated with strictures they are as likely to be found distal as poximal to the stricture.

From the Indiana University School of Medicine, Drs. Warfel and Hull performed an ultrastructural and immunohistochemical study of hepatoblastomas. They found that 5 cases were purely epithelial and 2 were mixed epithelial and mesenchymal. Epithelial cases had both embryonal and fetal elements. Two cases had numerous chromogranin positive cells. They were also positive for neuron-specific enolase and S100.

From the University of Pennsylvania Medical School, Drs. Witzleben and Steigman performed an immunohistochemical investigation of the defined duct element patterns in pediatric liver disease. They found that duct element staining for EMA and cytokeratin were significantly increased in extrahepatic biliary atresia and in cogenital hepatic fibrosis.

Drs. Shah and Gerber from Mount Sinai School of Medicine in New York and Tulane University in New Orleans studied the livers of 9 patients with a paucity of intrahepatic bile ducts. By using a monoclonal antibody to cytokeratin and to epithelial membrane antigen, they found that 7 cases showed paucity while 2 cases showed complete absence of interlobular bile ducts. EMA was found along the luminal surfaces of bile ducts whereas cytokeratin stained the cytoplasm. They believe that cytokeratin staining is useful in the diagnosis of paucity of bile ducts.

Drs. Amin and colleagues from Henry Ford Hospital. Found a correlation of duodenal morphology with pancreas rejection in canine pancreas allografts. Intracrypt lymphoid infiltrates and varying degrees of mucosal infiltrates were present in 29 of the 30 dogs. Erosion of the surface epithelium was associated with increasing severity of mucosal infiltrates and rejection. Thus, morphologic features of duodenal graft rejection may be used to monitor rejection of the pancreas.

Villin, a gastrointestinal-associated protein, was found by Bacchi and colleagues from the University of Washington to be preferentially

associated with GI neoplasms. Using a monoclonal antibody ($BDID_2C_3$), they found that virtually all neoplasms of the GI tract were positive, hepatocellular carcinomas contained positive bile canalicular regions, whereas carcinomas of the lung, breast, endometrium, thyroid and kidney were negative. Occasional non GI tumors, including ovarian and prostate carcinoma, were positive.

Drs. Benning and Tucker from East Carolina University School of Medicine and Duke found that there is heterogeneity in the dense core granules of rectal neuroendocrine cells. Classically, foregut-derived tumors of the neuroendocrine system are associated with small, round dense core granules, midgut tumors contain pleomorphic dense core granule and hindgut tumors contain round dense core granules slightly larger than those of the foregut. Their findings confirm that midgut dense core granules are not limited to the midgut tumors and pleomorphic dense core granules in a metastatic carcinoid do <u>not</u> rule out the hindgut as a possible primary site.

From the University of Parma, Italy, Bordi and coworkers performed a histologic and immunohistochemical study of 23 cases of gastric carcinoids. Immunohistochemically diffuse staining was seen for chromogranin A and synaptophysin but not for chromogranin B or HISL-19.

From the Armed Forces Institute of Pathology, Drs. Burke and coworkers followed 77 patients with biopsy proven glandular dysplasia of the esophagus or stomach for a mean of 44 months. Twenty-nine of the 34 patients with mild dysplasia had no progression of the disease, 3 died of unrelated causes and 2 had progression to severe dysplasia. Twenty-eight of the 43 patients with severe dysplasia had no progression, 6 died of unrelated causes, however 15 developed invasive cancer. Thirteen of the 15 diagnoses of invasive cancer were made within 12 months of the original endoscopy.

Drs. Carpenter and colleagues from the Mayo Clinic reported on the histologic features of rejection in needle biopsies from pancreatoduodenal allografts. The first finding was diffuse infiltration of acinar tissues by neutrophils followed by mixed acinar inflammatory infiltrates. Vasculitis was seen only rarely. Fibrosis and duct epithelial damage were more common.

Immunocytochemistry was found to be a highly sensitive method to identify Campylobacter (Helicobacter) pylori in gastric biopsies in a study by Cartun and coworkers from Hartford Hospital and St. Luke's/Roosevelt Hospital Center. They compared culture, special stains and immunocytochemistry. Of 51 gastric biopsies examined, 57% were positive with immunocytochemistry, 49% by gram stain cytology and 47% by culture.

The search goes on for the causative agent of Crohn's disease. In their immnocytochemical study, Drs. Cartun and coworkers from the University of Connecticut examined formolin-fixed, paraffin-embedded sections from 16 cases. Reactivity was observed with E. coli and streptococcal antibodies in 9 of 16 and 8 of 16 cases, respectively. Most likely these findings represent invasion through a compromised mucosal by common enteric organisms.

Drs. Chan and coworkers from Queen Elizabeth Hospital in Hong Kong and University College Hospital in the United Kingdom examined 48 consecutive gastric lymphomas. In 10 cases the found coexistence of the common low grade B cell "MALToma" and large B-cell gastric lymphoma. The intimate association between the two suggests that high grade components may arise from blastic transformation of the low grade component.

From the M.D. Anderson Center, Drs. Connelly and coworkers studied 20 signet ring cell carcinomas of the colorectum. DNA ploidy did not correlate with stage of disease or survival. The survival of patients with signet ring carcinoma was not significantly different from those with typical colorectal adenocarcinoma. Dr. Connelly and colleagues reported an analysis of mucinous carcinomas of the colon and rectum in a separate abstract. They examined 62 mucinous carcinomas were the mucinous component was at least 60% of the tumor. The overall survival of these patients did not differ from those with nonmucinous carcinomas.

From Rush University, Drs. Coon and colleagues examined the multi-drug resistance transporter (P-glycoprotein) in normal and neoplastic colon epithelium. Forty of 53 carcinomas stained for multi-drug resistant protein showed considerable intratumor heterogeneity. The heterogeneity must be taken into consideration when tumor assays from multi-drug resistance are performed.

Brunner's gland hamartoma was studied histologically and immunohistochemically by Drs. Coppola and coworkers from Temple University. These glands are PAS positive with and without diastase, occasional cells contain Alcian blue and others contain mucicarmine. Scattered chromogranin positive cells were found in 2 of 3 hamartomas studied. These endocrine cells support the hamartomatous nature of the Brunner's gland lesions.

Diffuse gastrointestinal ganglioneuromatosis was examined in 6 patients by Drs. d'Amore and colleagues from the University of Minnesota and the University of Napoli, Italy. Two patterns of the involvement of mucosal were found: without concomitant hyperplasia of the myenteric plexus (mucosal type) and with marked hyperplasia of the myenteric plexus and less hyperplasia of the submucosal and mucosal plexus (transmural type). Increased VIP reactivity was limited to the lamina propria in the mucosal type and was predominant in the myenteric plexus in the transmural type.

From the M.D. Anderson Center Drs. El-Naggar and coworkers studied DNA content of colon cancer in 25 patients. Eighteen primary neoplasms in which multiple different tissue blocks were studied showed 78% concordant histograms and 22% discordant. Of 14 metastatic liver samples with multiple different blocks analyzed, 79% were identical and 21% were different. Thus, intratumoral and intertumoral variabilities in colon adenocarcinoma were approximately 22% and 16% in this study. Sampling is an important factor to consider in DNA studies of colon cancer.

Drs. Fernandes and coworkers from the University of Toronto used L-PHA lectin histochemistry to examine normal and neoplastic colonic mucosa. L-PHA requires the beta 1-6 linked lactosamine antenna in Asn-linked oligosaccharides for high affinity binding. They found that malignant epithelium showed a marked increase in staining intensity compared to normal colonic epithelium. Benign polyps had intermediate staining intensity.

From the University of Virginia Health Sciences Center, Drs. Frierson, Jr. and colleagues studied duodenal bulb biopsy specimens from 85 patients with nonulcer dyspepsia for the presence of gastric surface epithelial metaplasia, acute inflammation and Helicobacter. They found Alcian blue-PSA stain superior to H+E for detecting gastric metaplasia. Twenty-seven percent of patients with Helicobacter

gastritis also had duodenitis. The microorganisms are typically patchy and several biopsy fragments need to be examined.

A feline model of acid-induced esophagitis is described by Drs. Geisinger and coworkers from Wake Forrest University. By infusing 0.1 N HCl at a rate of 1 ml/minute into the distal esophagus of cats, they were able to create a model of human reflux esophagitis. The histologic effects were correlated with the duration of acid exposure. This model will be useful to follow the morphogenesis of esophagitis and evaluation of possible therapeutic measures.

From Cedars-Sinai Medical Center, Drs. Geller and coworkers describe development of dysplasia and hepatocellular carcinoma in transgenic mice who have received the human alpha-1 antitrypsin difficiency gene. Varying degrees of dysplasia were seen in 19 of 33 Z mice, especially those older than 9 months. One had a nodule resembling adenoma. Two, both older than 15 months, had multifocular hepatocellular carcinoma.

Drs. Genta and Haggitt from the University of Washington reported 4 patients with segmental ischemic colitis caused by idiopathic intimal thickening in the mesenteric veins. By using immunohistochemistry with antibodies to muscle-specific actins (HHF35) they found that the intimal thickening was due to subintimal proliferation of smooth muscle cells in a proteoglycan matrix.

From the Johns Hopkins Medical Institutions, Drs. Greenson and coworkers examined biopsies from 22 patients with ulcerative herpetic esophagitis and compared them to those from 44 patients with nonherpetic esophageal ulcers. They found that aggregates of large mononuclear cells with convoluted nuclei (possibly activated T-cells) were characteristic of ulcerative herpetic esophagitis, only 1 of 22 cases did not show this feature.

The recurrence of autoimmune hepatitis following transplantation and was reported by Drs. Hart and Lewin from the UCLA Medical Center. Of 7 patients transplanted for autoimmune hepatitis who survived for 1 year, histologic study after liver transplantation showed no evidence of recurrence of autoimmune hepatitis in 6 patients. The 7th patient developed leukopenia after the first 9 months necessitating discontinuance of azathioprine therapy. The latter patient developed rising liver enzymes and diffuse arthralgies. The ANA titer was 1:80 and anti-double stranded DNA was 3500

IU/ml. Liver biopsy revealed chronic active hepatitis with no evidence of acute rejection, consistent with recurrent autoimmune hepatitis.

From the M.D. Anderson Center, Drs. Kalomiris and coworkers reviewed features of 16 primary colorectal small cell carcinomas and 2 malignant carcinoid tumors. Twelve of the 14 small cell carcinoma lesions had lymphoid metastases. Mean survival was 6.3 months. Immunoperoxidase studies revealed 13 of 14 positive for keratin and all positive for neuron-specific enolase. Only 5 were positive for chromogranin. The finding of at least 1 specific neuroendocrine cell product in 7 of 12 small cell carcinomas supports the neuroendocrine nature of this neoplasm. However, no single marker appears particularly useful as a diagnostic tool (neuron-specific enolase is known to be relatively non-specific).

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

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

SPECIALTY CONFERENCE

HANDOUT

GASTROINTESTINAL PATHOLOGY

Wednesday, March 7, 1990 - 7:30 p.m.
Grand and Independence

Moderator:

DAVID OWEN
Vancouver General Hospital
Vancouver, BC

Panelists:

RANDALL G. LEE, Oregon Health Sciences University, Portland, OR

WILLIAM K. GOURLEY, University of Texas Medical Branch, Galveston, TX

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

HARRY S. COOPER, Hahnemann University, Philadelphia, PA

KATHERINE DeSCHRYVER, Case Western Reserve University, Cleveland, OH

ROBERT E. PETRAS, The Cleveland Clinic Foundation, Cleveland, OH

USCAP GI Subspecialty Conference
Case # 1
Randall G. Lee, M.D.

Syphilitic Proctitis

The gastrointestinal tract shares in the diverse and widespread manifestations of *Treponema pallidum* infection. Although the anus represents a prominent extragenital site of disease, the columnar-lined GI tract is uncommonly affected. Gastric syphilis is well documented (1,2), and small intestinal involvement has been reported (3). The rectum, however, is the most frequently infected locale. Rectal syphilis often develops in conjunction with anal disease, but can also be found alone.

Anorectal syphilis, one of several venereal diseases afflicting the GI tract, occurs primarily in homosexual males. Although often asymptomatic and undiagnosed, the disease may manifest with anorectal pain, mucopurulent discharge, constipation, or rectal bleeding, and may be mistaken clinically for fissures, traumatic injury, hemorrhoids, or even malignancies (4).

Syphilitic proctitis can assume a wide range of macroscopic (and endoscopic) appearances. This variability leads to uncertainty whether some lesions represent manifestations of secondary syphilis or simply persistence of atypical primary lesions. Nevertheless, the most common presentation is the anorectal chancre, recognized in 15 to 34% of homosexual males with primary syphilis (5). Rectal chancres may be single or multiple and are frequently associated with chancres in the anal canal and perianal region. Although they may conform to the classic description of a well-defined, indurated ulcer, some adopt a more nondescript ulcerative or papular appearance (6-8). Rectal syphilis, particularly in the secondary stage, can also confusingly present as mass lesions (nodules, polyps, or ulcerated inflammatory masses) or as zones of mucosal erythema, friability, or thickening (as in this case), confined to the rectum and extending no further than 15 to 20 cm from the anal verge (9-12). These lesions represent an inflammatory expansion of rectal mucosa and submucosa that is the pathogenetic and histologic analogue of condyloma latum, the classic lesion of secondary syphilis involving the squamous epithelium of the perineum.

The most prominent histologic feature of all these lesions is an intense mononuclear inflammatory infiltrate of the lamina propria and submucosa (13,14). This infiltrate comprises the expected plasma cells, along with lymphocytes, macrophages, and a variable number of neutrophils. Epithelioid granulomas (noted in this case), typically small and poorly-developed, are an inconstant feature. At times the density and polymorphism of the infiltrate, coupled with the endoscopic appearance of an indurated mass, can lead to a misdiagnosis of malignant lymphoma (15). Crypt damage with its accompanying neutrophilic infiltrate is common and ranges from focal cryptitis to crypt abscess; mucosal erosion or ulceration can be the final result. Crypt architecture may be left intact, but in some cases crypt distortion or atrophy may supervene. The traditional obliterative endarteritis of syphilis has been best recognized in the submucosa and not prominently in the mucosa.

These histologic features are not specific, but only indicate an active proctitis with a broad differential diagnosis. The diagnosis is further complicated by the frequent presence of abnormalities such as crypt distortion and atrophy, a diffuse plasmacytic infiltrate, and granulomas; these changes are not those of the usual infectious colitis, but rather suggest ulcerative colitis or Crohn's disease. A correct diagnosis relies on attention to clinical details. The clinical setting -- a homosexual male with proctitis -- should lead to consideration of

infection, since one (or more) pathogens are found in about 80% of such patients (16). Both syphilitic and Chlamydial proctitis can histologically mimic idiopathic inflammatory bowel disease (14). A presumptive diagnosis of syphilitic proctitis is made by compatible clinical history, positive syphilis serology and appropriate response to therapy. Definitive diagnosis, however, requires the identification of *T. pallidum* organisms. Darkfield examination suffices for anal and perianal lesions, but is not reliable for rectal disease because nontreponemal spirochetes normally reside in the colon and rectum. Standard silver stains such as Warthin-Starry can be used, but these stains are technically capricious and are difficult to interpret accurately. *T. pallidum* can be most specifically identified by immunohistochemistry, either immunofluorescence or immunoperoxidase (17).

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CASE # 2

U.S. and CANADIAN ACADEMY of PATHOLOGY
GASTROINTESTINAL PATHOLOGY SPECIALTY CONFERENCE, 1990

Solid and Cystic Papillary Tumor of the Pancreas "Frantz's Tumor"

William K. Gourley, M.D.

Clinical Summary: After the birth of her first child, a 26 year-old woman had abdominal pain thought to be due to idiopathic pancreatitis. Two operations were done to drain a presumed pseudocyst. The lesion was resected 3.5 years after the putative pancreatitis. There was no clinical evidence of enzyme or hormone hypersecretion.

Discussion: In the section on Benign Neoplasms of Exocrine Glands in her 1959 AFIP Fascicle on Tumors of the Pancreas, Dr. Virginia Frantz classified large tumors from two young women as papillary cystadenomas because the patients had lived tumor-free for decades after surgery, but she captioned the micrographs: "Papillary Tumors of the Pancreas - Benign or Malignant (?)." Subsequent reports of similar tumors (38 papers with 127 patients reviewed) draw a highly characteristic clinical picture: a female (98%), usually of child-bearing age; discovery of a large pancreatic mass (5-20 cm.), days to 15 years before removal; no evidence of endocrine secretion; and clinical or radiologic diagnoses of pseudocyst, cystadenoma, or nonfunctioning islet-cell tumor.

The lesion can be anywhere in the pancreas and it sometimes extends to the duodenum, porta hepatis, or mesentery (3% of reports). It is rimmed by a fibrous pseudo-capsule and the interior is solid to "cystic" (often described as hemorrhagic or necrotic). Microscopically, three histologic patterns are seen: 1) cuboidal cells in solid sheets or cords that are punctuated by stubby fibrovascular septa, around which the tumor cells radiate (pseudo-rosettes); 2) cystic spaces walled by the solid areas; and 3) pseudo-papillae composed of a fibrovascular septum coated by remnants of the inter-septal tumor cells. The pseudo-capsule is often focally breached or absent (47% of reports).

The tumor cells are of medium size. They have oval to grooved nuclei with fine chromatin and small chromocenters. There are few or no mitoses. The cytoplasm is faintly eosinophilic and finely granular. Clusters of foamy histiocytes, cholesterol granulomas, and cells with PAS-diastase-resistant globules were described in 24%, 29%, and 39% of reports, respectively.

Substances identified in immunohistochemical studies (26 papers) were: alpha-1-antitrypsin (A-1-AT), 65%; "neuron specific" enolase, 35%; islet-cell peptides (insulin, VIP, glucagon, or somatostatin), 15%; amylase, 12%; alpha-1-chymotrypsin, trypsin, or vimentin, 8% each; and CEA, desmoplakin, cytokeratin, serotonin, and estrogen-receptor protein, 4% each. Chromogranin has not been found. Estrogen and progesterone receptor assays were positive for both in one study, and for progesterone alone in another. One group identified a P21 oncogene protein. In 26 papers with results of electron microscopic studies, the authors described many mitochondria (62% of papers), large zymogen-like bodies (31%), "neurosecretory" granules and annulate lamellae (19% each), and "mucin" or A-1-AT material (4% each).

Twenty authors concluded that their evidence allowed them to postulate a neoplastic "cell of origin." Most (50%) elected a primordial or pluripotential cell, 30% voted for an acinar cell, 15% nominated a ductal cell, and only 5% chose an islet cell. Some students of the tumor maintain that evidence of differentiation "toward" is not the same as evidence of differentiation "from"

and if every pancreatic cell has the same genome, any could daughter a confused neoplastic cell that dressed in a variety of garbs.

The three histologic patterns have spawned variations of the name given to the neoplasm, with permutations of solid, cystic, and papillary. Perhaps the mother pattern is solid and the pseudo-papillae and cystic spaces are not a reflection of an intrinsic growth pattern, but they are secondary to necrosis (autodigestion by enzymes released from tumor cells that have differentiated "toward" an exocrine phenotype?). But why the non-committal term "tumor" - why not adenoma? Impressed with the large size, the micro (and sometimes macro) invasion, the 1.5% incidence of recurrence, and the 5 (3 poorly documented) reports of metastases to liver, lymph nodes or colon, some worry with Dr. Frantz that the tumor is malignant. Current evidence supports the position that surgery is usually the only treatment necessary and the probability of death from metastases is quite small.

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CASE 3

Cronkhite-Canada Polyposis

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Cronkhite and Canada described the acquired, non-familial syndrome of multiple gastrointestinal polyps, onycholysis, alopecia and skin hyperpigmentation in 1955 (4).

The patients are adults whose gastrointestinal manifestations include diarrhea, abdominal pain, nausea, vomiting, weight loss, protein-losing enteropathy and malabsorption.

The polypoid lesions of the gastrointestinal tract of patients with CC syndrome have not been precisely characterized. They have been referred to as inflammatory pseudopolyps (7), adenomas (4), hyperplastic polyps (22), juvenile polyps (32) and hamartomatous polyps (6). The stomach and colon are almost invariably involved, the small bowel somewhat less frequently and the esophagus rarely. The polyps may regress especially during remissions.

We have recently studied polyps from nine patients with the CC syndrome and compared them with nine cases of juvenile polyposis and gastric hyperplastic polyps (Burke, AP & Sobin, LH. The pathology of Cronkhite-Canada polyps. Am J Surg Path 13:940, 1989). We found that the most constant features of CC polyps are a sessile base, an expanded edematous lamina propria and dilated glands. Variable features were inflammation, small numbers of smooth muscle fibers, and a complex contour.

CC polyps are easily distinguished from the typical sporadic form of juvenile polyp which is pedunculated, has a smooth round eroded surface and lacks smooth muscle. This contrasts to the broad-based noneroded CC polyp. However, CC polyps more closely resemble lesions from patients with juvenile polyposis which have an expanded lamina propria, cystic glands and an irregular contour. Although colonic polyps in the patients with juvenile polyposis were not as pedunculated as are sporadic juvenile polyps, they still had narrower bases than the CC polyps. Therefore pedunculation was the only feature that separated colonic CC and juvenile polyposis lesions. In the stomach we did not find any reliable features distinguishing CC from juvenile polyposis or hyperplastic polyps.

Not only are juvenile polyposis and CC polyposis similar histologically, they may resemble each other clinically, as both may share protein-losing enteropathy (12,37). In fact, the term "juvenile Cronkhite-Canada syndrome" was used when juvenile polyposis was associated with hypoproteinemia (37). This underlines the importance of the clinical findings, namely the presence of ectodermal changes, for their distinction. However, the dermatologic lesions may not yet be manifest when abdominal symptoms occur. Patient age is most helpful to distinguish CC from juvenile polyposis (especially in cases where the CC polyps precede the ectodermal changes). In our series of nine juvenile polyposis patients, the age range was 7 to 28 years (average 18); the 9 CC patients were 34 to 83 years (average 60). Our 14 patients with gastric hyperplastic polyps were 38 to 73 years old.

The lack of a prominent smooth muscle infrastructure in CC polyps readily distinguishes them from Peutz-Jeghers polyps, and the absence of dysplasia separates them from adenomas.

Hyperplastic polyps of the stomach had similar features as CC polyps, despite the fact that the former show a greater tendency towards surface erosion and pedunculation. We have not found any reliable histologic criteria to distinguish the two. Biopsies of enlarged gastric folds in Menetrier disease may resemble CC lesions.

Irregularly regenerated mucosa following radiotherapy or ingestion of corrosives can have histologic features similar to the CC lesion.

Thus, there is considerable overlap of histologic features between CC polyps, juvenile polyposis, gastric hyperplastic polyps and some postinflammatory states. The clinical history and patient age are vital for a correct diagnosis.

A number of unresolved features characterize the CC syndrome:

1- its relation to other diseases: carcinoma of the colon and stomach, myeloma and collagen vascular diseases have occurred in CC patients;

2- the relation between the gut and the skin lesions: eg does the malabsorption cause the skin lesions or are the GI and skin lesions manifestations of a single disorder?

3- treatment: corticosteroids, anabolic steroids, antibiotics (for bacterial overgrowth), surgery and nutritional support have all been tried; sometimes they are effective, sometimes not. Spontaneous clinical remission with regression of polyps has been reported (21,30,34).

4- prognosis: some cases resolve spontaneously, some after a variety of treatments. Death is generally associated with nutritional and electrolyte problems. Maintaining adequate nutrition appears most important. Mortality is over 50%.

5- mechanism of the gut lesions: Ultrastructural study of CC polyps suggests that damage to crypt epithelium results in leakage of fluid into the interstitium (18). Protein loss has been attributed to excessive mucus secretion (40). It has been proposed that the GI and skin lesions are basically atrophic with epithelial damage secondary to failure of synthesis or release of growth factors (8).

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CASE 4

INFLAMMATORY CLOACOGENIC POLYP

This case is an example of what is known as Inflammatory Cloacogenic Polyp (ICP). Lobert and Appleman in 1981 introduced the term ICP to encompass these characteristic polypoid villiform lesions which are localized to the anorectal transitional (cloacogenic) zone mucosa. Previous investigators had described similar lesions, however, they erroneously thought them to represent neoplasms, using the term "well differentiated adenomas."

Characteristically patients present with rectal bleeding, although local tenderness and local symptoms upon defecation may also be present. The age range is the teens to the 9th decade of life, with the mean age being the 5th and 6th decades. There is a slight female predominance. By definition, the ICP is localized to the anorectum and it may be polypoid or prolapse and protrude out of the anus. These lesions vary in size from 0.5-5.0 cm and most often are located on the anterior or anteriorlateral wall of the anorectum. Histologically at low power one sees a complex tubulovillous pattern. The tips of the villi are often eroded and may show superficial "pseudomembranous" changes. The cells lining the villi have bland basally placed nuclei and their cytoplasm varies from simple (non-mucinous) columnar to plump mucous filled. The epithelium may at times have a saw tooth or serrated-like appearance. In some cases, one may see "obliteration" of the lamina propria by bundles of proliferating fibromuscular cells.

The glands may be irregular and "trapped" within the fibromuscular proliferation imparting a pseudoinvasive pattern. Mucinous pseudo-cysts in the lamina propria and submucosa may also be present. Special stains indicate that the epithelial cells produce sialomucins rather than the normally present sulphated mucins, however, this is a non-specific finding.

At low power, ICP can easily mimic a hyperplastic polyp. Personal experience indicates that many lesions diagnosed as hyperplastic polyps of the anorectum are indeed ICP. Another pitfall in diagnosis is to diagnose ICP as an invasive adenocarcinoma. At low power, the entrapment of glands by proliferating fibromuscular cells may superficially mimic invasive adenocarcinoma. However, the glands lack atypia, are benign, as is the superficial portion of the lesion.

Total excision is "curative", however, "recurrences" have occurred in patients with concomitant rectal prolapse.

The exact etiology of this lesion is unknown. However, it is believed that the etiology may be rectal prolapse. This is based on the presence of rectal prolapse in approximately a 1/3rd of reported cases and the almost identical histology to the entities of the rectal prolapse (Solitary Rectal Ulcer Syndrome and Localized Colitis Cystica Profunda) syndromes.

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GASTROINTESTINAL SUBSPECIALTY CONFERENCE

Case 5

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MICROSCOPIC DESCRIPTION:

The polyp consists of an edematous fibro-inflammatory proliferation with a cellular infiltrate of plasma cells, eosinophils, scattered mast cells, and occasional small lymphoid aggregates. The overlying mucosa is focally ulcerated with an acute inflammatory reaction.

DIAGNOSIS: Small intestine, ileum, partial resection - Fibro-inflammatory polyp (inflammatory pseudotumor).

COMMENT:

Inflammatory pseudotumors occur at various sites in the body, including lung, liver, lymph nodes, spleen, and urinary bladder. In the GI tract, this lesion is now called inflammatory fibroid polyp and is still a poorly understood entity. It occurs at all levels of the GI tract (10, 16), but most commonly in the stomach (7, 11, 14). The small bowel, and particularly the ileum, are the next in frequency, often presenting with intussusception (1, 2, 10, 11, 12, 14) as was our case. Clinically, the presentation, radiology, and gross appearance mimic a malignancy. The lesion is also unusual in that it is clearly reactive and non-neoplastic both in its morphology and clinical behavior, and yet there is transmural involvement with replacement/"destruction" of the muscularis and subserosal extension even in the "early" lesions (1, 14). Typically inflammatory pseudotumors are sharply circumscribed but not encapsulated. Sizable vessels may be entrapped. Polyclonal plasma cells and myofibroblasts are a major component (11). Systemic symptoms such as fever, weight loss, and growth failure in children may be present and disappear following resection of the lesion (4). Inflammatory fibroid polyps in the stomach have recently been reported to co-exist with gastric malignancies (9). No such association has been reported in the small intestine.

In the differential diagnosis, proliferative fibroblastic lesions such as fibromatosis are easily ruled out by the paucicellular aspect of the lesion A possible relationship of inflammatory pseudotumors in the urinary bladder to nodular fasciitis was recently entertained (13); similar considerations have been made for the lesions of the GI tract (11). Rare reports relate the lesion to documented iatrogenic trauma, mostly, the reported cases are "idiopathic". A single report documents a familial occurrence (1).

Eosinophilic gastroenteritis is presumed to be a related entity (3, 8), although both the clinical features and the morphology are quite different except for the presence of eosinophils and mast cells. Eosinophils and mast cells are increasingly recognized in the GI tract in physiologic (15) and various pathologic states (5, 6). Clearly, numerous etiologic mechanisms have the common pathway of eosinophil/mast cell infiltrates with various

degrees of vascular/stromal reactions possibly resulting in heterogenous groups of clinical diseases. Whether inflammatory fibroid polyps represent part of a spectrum of these eosinophil/mast cell diseases is not clear at this time. Whether an unusual pathogen or an allergen might play a role in the development of the lesion is a tantalizing question. The history of a bout of acute gastroenteritis-like syndrome five weeks prior to admission in the present case may be relevant in this respect. A report of these inflammatory pseudotumors clustering in Malawi and Sierra Leone further raises the possibility of infectious agents/repair having an etiologic role (12).

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GASTROINTESTINAL SPECIALTY CONFERENCE

DISCUSSION FOR CASE 6
DEVELOPMENTAL CYSTS OF THE RETRORECTAL SPACE

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Many conditions enter into the differential diagnosis of lesions in the retrorectal(presacral) space. These include developmental cysts, inflammatory conditions, metastatic neoplasms, and primary neoplasms of osseous, neurogenic, nonosseous-mesenchymal, and germ cell origin. Table 1 summarizes the Cleveland Clinic experience with tumors (excluding inflammatory conditions and metastatic neoplasms) in the retrorectal space.

TABLE 1

TUMORS OF THE RETRORECTAL SPACE
CLEVELAND CLINIC EXPERIENCE
1929 - 1989

TUMOR	NUMBER
Chordoma	25
Teratoma	15
Developmental cysts	14
Giant cell tumor	3
Endodermal sinus tumor	2
Sarcoma, NOS	2
Ependymoma	2
Hemangiopericytoma	1
Liposarcoma	1
Ewing's sarcoma	1
Chondrosarcoma	1
Aneurysmal bone cyst	1
Myelolipoma	1
TOTAL	69

This discussion will focus upon cystic lesions (developmental cysts and teratoma) in the retrorectal space.

The major retrorectal developmental cysts include epidermoid and dermoid cysts, rectal duplication cyst, and cystic hamartoma (tailgut cyst) (1-4). Distinguishing features are summarized in Table 2.

TABLE 2

DEVELOPMENTAL CYSTS OF THE RETRORECTAL SPACE: DISTINGUISHING FEATURES*

Feature	Epidermoid (Dermoid) Cyst	Rectal Duplication Cyst	Retrorectal Cystic Hamartoma (Tailgut Cyst)
Gross appearance:	Unilocular	Unilocular	Multicystic, ± solid areas
Cyst lining:	Squamous epithelium ± skin adnexal structures	Colonic, gastric, or respiratory epithelium	Squamous, anal transition zone or glandular epithelium
Smooth muscle wall:	None	Yes, organized and recapitulates muscularis propria	Yes, disorganized bundles
Other findings:	———	———	Foreign body giant cell reaction often seen

*From: Reference 5

Epidermoid and dermoid cysts are usually unilocular, lack a muscular wall and are lined by keratinizing squamous epithelium. The dermoid cyst, also contains dermal adnexal structures. These cysts presumably arise from faulty closure or invaginations of the ectoderm during embryologic development (1). Rectal duplication cysts (enterogenous cysts) are also unilocular and can be lined by a variety of columnar epithelia (colonic, respiratory, or gastric). Anomalous lumen formation probably causes duplication cysts. Some of these cysts communicate with the gut lumen. The rectal duplication cyst is recognized by the presence of a well-developed outer muscular layer recapitulating the muscularis propria of the bowel (2,3). Retrorectal cystic hamartoma (tailgut cyst) is thought to represent persistence of the embryologic tailgut because of its anatomic location and because the tissue types encountered resemble those of cloacal derivation (1,2-4). Tailgut cysts are usually multicystic and solid. The cysts are

characteristically smooth-walled and may contain seromucoid or purulent material. Histologically, variable mixtures of squamous, anal transition zone, colonic, and mucinous epithelia line the cysts. Varying amounts of smooth muscle surround the cysts but in contrast to rectal duplication cysts, this muscle appears disorganized. On occasion, granulomatous inflammation of the foreign body type can be seen, apparently in response to ruptured cysts.

Sacrococcygeal teratoma involving the retrorectal space must be distinguished from other developmental cysts. Sacrococcygeal teratomas typically occur in children, are multicystic, and contain elements of all three germ layers, features that help to separate teratoma from epidermoid/dermoid cysts and rectal duplication cyst. Tailgut cyst could be arguably considered a form of mature teratoma since tailgut cysts contain ectodermal, endodermal, and mesodermal elements. It is probably best, however, to separate tailgut cysts from teratomas since teratomas represent true germ cell neoplasms that can coexist with malignant germ cell elements and can also have immature areas. Teratomas frequently contain dermal appendage structures, neural elements, and mesenchymal derivatives (bone and cartilage), elements not encountered in tailgut cysts.

Developmental cysts in the retrorectal space are prone to infection and fistula and associated malignancy has been rarely reported (2,4). Therefore, total excision is recommended.

Clinical Summary for Case 6: This 50-year-old woman presented with worsening constipation. Digital rectal examination identified a retrorectal mass. Computed tomography confirmed the presence of a complex solid and cystic mass in the retrorectal space. This was surgically excised.

Microscope Slide #6: Sections show multiple epithelial-lined cysts separated by fibrous tissue and surrounded by incomplete layers of disorganized smooth muscle. The cysts are lined by a variety of epithelia including transitional, intestinal, squamous, simple columnar and anal transition zone-type. In some sections, hemosiderin-laden macrophages and a foreign body giant cell reaction are prominent in adjacent soft tissues. One of the grossly solid areas contains a neoplasm composed of islands of epithelial cells surrounded by a fibrous and focally hyalinized stroma. The neoplastic cells cluster around delicate capillaries. The nuclei of these cells are regular, round to oval, and contain coarsely granular chromatin. These neoplastic cells were positive for chromogrannin, neuronspecific enolase, and cytokeratin by immunohistochemistry. Ultrastructural examination documented the presence of intermediate filaments and neuroendocrine granules within the cytoplasm of these neoplastic cells.

Diagnosis for Case 6: Carcinoid tumor arising in association with a retrorectal cystic hamartoma (tailgut cyst).

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BOOK REVIEW

Hepatology: A textbook of liver disease. Second edition, Edited by David Zakim and Thomas D. Boyer 1990 . W.B. Saunders Company.

This magnificent two-volume textbook boasts 83 contributors to a total of 61 chapters. 37 contributors to this second edition were not represented in the first. The chapters are grouped in four sections entitled: I. Physiology and Biochemistry of normal hepatic function, II. Manifestations of abnormal liver function, III. Evaluation of hepatic function and IV. Toxic injury to the liver.

The stated goal of the editors is "to provide a framework of pathophysiology as a basis for understanding liver function and liver disease in addition to authoritative, up to date descriptions of the clinical laboratory manifestations of liver disease and of the diagnostic and therapeutic strategies for managing them". They have succeeded.

This is a highly readable book. Over a period of two months I dipped into it for information on current cases and read several chapters as background to this review. I like the general layout. The discussions are sufficiently detailed to give perspective. The referencing is extensive and one chapter has almost 1,000 references. Unfortunately, only the first page number is given for each reference.

The editors have done a remarkable job of ensuring consistency of style throughout. The chapters on Physiology and Biochemistry of normal hepatic function are very satisfactory and give excellent expositions on topics such as synthesis and secretion of plasma proteins, receptor mediated endocytosis, metabolism and function of vitamins A,D, and K, hepatic drug metabolism, bile formation and cholestasis, among many others. Figures and diagrams are used well and include molecular structure diagrams where appropriate. For easy reference several chapters, including chapter 31 on drug-induced liver disease, would be easier to use if they began with an index or list of the subsections. I noticed that malignant lymphoma is not mentioned as a cause of fulminant liver failure in chapter 17.

Six pathologists contributed to this book - Valeer Desmet, Jay Lefkowitch, Carolyn Montgomery, Robert Peters, Boris Ruebner, and Camillus Witzleben. The Lefkowitch chapter entitled Pathologic Diagnosis of Liver Disease includes a magnificent set of 69 colour photomicrographs of liver histopathology, a glossary of terms and a review of the approach to the liver biopsy. This would make excellent reading for GI and pathology residents and fellows.

This book should be available to pathology residents and staff in departmental libraries because it puts so much up do date information at ones fingertips. Pathologists with a primary interest in liver disease should have a personal copy but the price ($295) is a deterrent. The advent of Medline on CD has not vitiated the need for this type of textbook.

James Kelly, M.B. University of Calgary

Gastrointestinal Pathology: An Atlas and Text.
By Drs. C.M. Fenoglio-Preiser, P.E. Lantz, M. Davis, M.B. Listrom, and F.O. Rilke.
New York, Raven Press, 1989. $195.00

This book features 2,157 illustrations of which 1,919 are in color! It has 906 pages, including information on the anatomy, infectious diseases, clinical manifestations, radiology and pathologic analysis of lesions of the gastrointestinal tract. Each anatomical region (esophagus, stomach, small bowel, large bowel, and anus) is divided into chapters on normal anatomy, non-neoplastic conditions, and neoplasms involving that site. In addition several chapters on general topics are included, such as inflammatory bowel disease, alimentary tract lymphomas, mesenchymal tumors and polyposis syndromes. There is a separate chapter on the appendix as well as one on cytology. The illustrations are high quality and very informative. Deserving particular mention are the gross photographs with corresponding x-ray images and microscopic appearance of the same lesions. The stated purpose of this book was to gather in a single source much of the information now available in a fragmented scattered manner with a need to consult multiple sources. This was quite an undertaking and the book has succeeded in doing this in a substantial way. The information is gathered in a well organized practical and very accessible manner for easy reference. The slide set containing 250 illustrations from the book is handy either as an addition to the book or by itself, obviating to the need of collecting and photographing this material oneself for instant comparisons as well as for teaching. The book will be an excellent reference book for gastrointestinal radiologists, pathology and gastroenterology house staff, and both beginner and experienced students of gastrointestinal pathology. Moreover, anyone needing a quick reference will turn to this book, and will not be disappointed.

Book Review: Enteric Infection - Mechanisms, Manifestations & Management
Farthing, M.J.G. & Keusch, G.T., Editors
Raven Press, New York, 1989
ISBN 0-88167-537-7, 550 pages, $85.00

The editors of this 36-chapter, 54-author, monograph set the perspective in the introduction: "Infectious diseases are only one of the many conditions that afflict the human gastrointestinal tract, but in terms of morbidity and mortality their importance greatly exceeds that of other common intestinal diseases including gastrointestinal malignancy, non-specific inflammatory bowel disease and other relatively uncommon malabsorptive conditions such as coeliac disease." You, or your patients, may be "Among the approximately 16 million of [the] travelers ... who will leave industrial parts of the world and travel to less developed communities, about one-third will develop a diarrheal illness." Bacterial disease of the stomach (Helicobacter - nee Campylobacter - pylori) and the dark flowers that bloom in the garden of AIDS are no longer exotic curiosities in our practices.

This book is a gold mine of summarized data, lucid critiques of concepts, and discussions of the major directions of research through 1988. The evidence is presented for the basis of the current "big ideas" about viral, established and emerging bacterial, and protozoal pathogenic interactions with the human gut. Colonization factors, species and site specific receptor-ligands, the mucus gel, toxin production and effects, enterocyte and "M-cell" absorption and secretion mechanisms that are usurped by some invasive pathogens, bacterial chromosome areas that code for the ability to exist inside host cells, plasmids that code for antibiotic resistance, diagnostic tips that range from collection to serology to molecular biology techniques, treatment, control and prevention programs - the dominant stars and novae of the intestinal microecologic firmament are (almost) all to be found in this terse encyclopedic text.

There are many valuable tables and clever diagrams that condense and illustrate the text. Morphology, which has contributed much to our view of the agent-host interaction and has stimulated a search for answers to more than one basic question, is represented by 7 gross, 26 histologic, and 49 electron microscopic photographs (rather too contrasty, but the information is there). The chapters written by The GI Path Society members Jim Kelly (Shiga-like toxin-producing Escherichia coli) and Bob Owen (Cryptosporidiosis and Microsporidiosis) are superb - of course.

What are the deficiencies? Information about immunology is sparse and scattered in too many places. A summary chapter on basic immunologic concepts, similar to those that were included for the reader's understanding of the mechanisms of intestinal secretion and the molecular basis of microbial attachment, would be useful. Diseases caused by the metazoa and the roles of normal flora in health are not discussed. There is nothing about blind-loop or bacterial overgrowth syndromes, or about Whipple's disease. References at the end of each chapter usually include both historical classics and yesterday's soon-to-be-refuted-by-tomorrow's papers (a reference to one of my papers had a serious misspelling - check yours).

I liked using this book. It is not a sign-out-bench or microbiology lab reference, but it is a good place to start when you want to understand the past, present, and perhaps the future of an important area of GI disease.

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