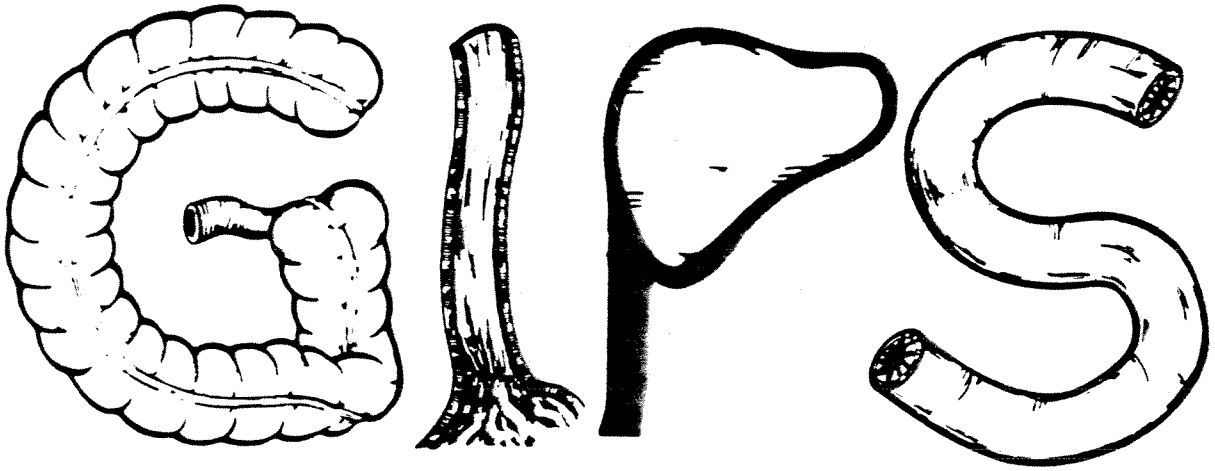

THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

VOLUME 7, NUMBER 2
Summer, 1989

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GASTROINTESTINAL PATHOLOGY SOCIETY
1989-90 OFFICERS AND COMMITTEE MEMBERS

POSITION	TERM ENDS
President: (1-year term)	
G. Abrams	1990
Vice-President/President-Elect: (1-year term)	
D. Owen	1990
Secretary-Treasurer: (3-year term)	
S. Hamilton	1990
Education Committee: (3-year term)	
L. Deppisch	1992
W. Weinstein	1992
D. Sheahan (Chairman)	1991
R. Pascal	1991
S. Sternberg	1990
J. Wirman	1990
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J. Tomasulo	1992
A. Qizilbash (Chairman)	1991
P. Correa	1991
R. Petras	1990
S. Saul	1990
Training Programs Committee: (3-year term)	
Y. Dayal	1992
P. Manley	1992
K. Barwick (Chairman)	1991
E. Lee	1991
E. Cohen	1990
H. Shields	1990
Publications Committee: (Standing)	
H. Appelman (Chairman)	
R. Riddell	
S. Sternberg (Ex-officio: Editor of Amer J Surg Path)	
G. Abrams (Ex-officio: President of GIPS)	
D. Sheahan (Ex-officio: Chairman of Education Committee)	
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G. Abrams (Ex-officio: President of GIPS)	
S. Hamilton (Ex-officio: Secretary-Treasurer of GIPS)	
K. Barwick (Ex-officio: Chairman of Training Programs)	
D. Sheahan (Ex-officio: Chairman of Education Committee)	
D. Owen (Ex-officio: President-Elect of GIPS)	
Newsletter Editors: (3-year term)	
D. Keren	1991
W. Dobbins (Associate Editor)	1991
International Liaison: (Standing)	
H. Goldman	

PRESIDENT'S MESSAGE

Although the mid-summer weeks afford a relatively quiet hiatus, it appears that 1989 will prove to be an extraordinarily busy and productive year for the Society, especially on the educational front. As most of you know, the March 5 Scientific Session in San Francisco, dealing with transplantation and the digestive system, continued the established tradition of excellence of our IAP companion meetings. Then, on May 16th, the Society was responsible for a highly successful and enthusiastically well attended session on small bowel at the AGA meeting. This fall, the Society will convene a companion meeting during the ASCP festivities in Washington, the program being similar to the one presented at the AGA. Amidst all of this activity, which is under the sure hand of Gerry Sheahan, Education Committee Chairman, planning is also under way for the 1990 IAP companion meeting. The afternoon's presentations at that meeting will deal with Molecular Biology and the digestive system.

On a related front, our relationships with the American Journal of Surgical Pathology have entered a new phase. You will recall that the Publications Committee under Henry Appelman had been galvanized into action some time ago with the discovery that the papers for our IAP companion meeting were being published as a supplement which was not being made available to all subscribers as part of their basic subscription. Pursuant to the recommendations of Henry's Committee and the Executive Committee of the Society, the membership voted at our business meeting to stipulate to the AJSP that if we are to continue submitting papers from our scientific session, they must be published in a form which would give automatic access to all of the Journal's subscribers. In May we learned that Raven Press was unwilling to meet these stipulations. In keeping with your collective views, as communicated at the business meeting, we shall be exploring alternative options in time for the 1990 session.

Obviously, a lot of energy has been expended and is being expended by a lot of folks interacting with a lot of other folks to accomplish the things outlined above. The same is true with regard to keeping up with the myriad of maintenance/membership/secretarial tasks of the Society, to publishing this newsletter, and tending to other Society activities such as the Microgrants Program, the tracking of Training Programs, and the development of international liaison. I would like to disclaim any credit for all of this, having inherited a smoothly functioning organization from Bob Rickert (who is responsible for a lot of the interacting alluded to above), with vigorous committees and chairpersons in place. Thanks!

Should any of you know of matters which should be addressed by this Society or should you wish to join in some activitity in which you are not now engaged, please let us know.

Happy summer.

Gerald D. Abrams, M.D.
President, Gastrointestinal Pathology Society

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Editorial

This issue of GIPS has set a new record for the number of pages in a newsletter (we have submitted an application to Guiness). This reflects the large number of abstracts and the many contributions from our members, including yet another "Tale from the Ampulla" and a list of possible contacts from our colleagues in the Scandinavian Group of GI Pathologists. Believe me, setting such records is not the goal of this editor!

At the present time, much pertinent information about gastrointestinal pathology is sprinkled fairly broadly through the literature. It is found in a wide variety of journals including: Gastroenterology, Gut, Human Pathology, American Journal of Clinical Pathology, Laboratory Investigation, Modern Pathology, American Journal of Pathology, American Journal of Surgical Pathology (just to name a few). It would be nice if there was a journal which would bring these articles to focus. There comes a time when a newsletter makes a transition to a Journal (perhaps this follows a club making a transition to a society!). We would be interested in your comments about the "Journal of Gastrointestinal Pathology".

Send your contributions to the GIPS Newsletter to the address below.

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LETTERS TO THE EDITOR

To the editor:

I don't remember if the GIPS newsletter has given up on humor or not. In the latter case, you might consider the enclosed contribution. You might start a contest for "the best title" for the photograph. My candidate title will be: Hirschprung may be bigger than Jim

Jim Brown is the pathologist holding the specimen. The photograph was taken by my son Dr. Hernan Correa.

Pelayo Correa, M.D.
Professor of Pathology
Louisiana State University Medical Center

To the editor:

Many thanks for the GIPS Newsletter which have been mailed to me, and which I have further distributed to the GI pathologists in the Scandinavian (Nordic) countries. I hope that this mailing would continue also in future.

We have succeeded to establish (at Dr. Goldman's and Dr. Morson's suggestions) a "Scandinavian Group of GI pathologists" which is intended to be an informal network of pathologist interest in same topics. For the present, I have promised to be a contact person of this group. Enclosed, please, find the most recent list of members of the group. The names of persons who further are local "contact" persons in their own country are underlined.

With best wishes for your activities in GIPS and in gi pathology.

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POETRY
Tales of the Ampulla of Vater, II

To the Editor:

By the shores of Duodenum
where there flow the River Bile
There had come a time for sorrow
non could laugh or even smile.

A blight had struck the villi
but the cause was yet unknown
And even great Ampulla sat
perplexed upon his throne

The onset wasn't sudden
still the change was all diffuse
The ville seemed so shrunken
filled with lymphoid cells profuse.

And as their stature shortened
the crypts grew deeply down
The fine brush bordered lining
had become a ragged crown.

Because no chylomicron
could be fished within the bowel
The contents of the lumen
became bulky, fat, and foul.

The malabsorbing villi
to their wise Ampulla prayed
Great Vater help us quickly
or we soon will waste away.

Ampulla learned from messengers
that traveled days and nights
This malady went well beyond
the Ligament of Treitz.

He pondered deeply on the cause
no worms were in his land
The River Bile flowed swift and full
so free of stones and sand.

Lymphoma was not in the realm
nor other neoplasia
The pancreas was not inflamed
nor showed signs of dyscrasia.

So Grat Ampulla then deduced
what's clear to me and you
The Duode'en was stricken by
a classic case of Sprue.

He ordered that all gluten
be forbidden on his shores
All wheat would be excluded by
strict importation laws

And so as if by miracle
the villi rose anew
First little buds, then tall and proud,
they all came into view.

They stretched and reached into the sea
around the River Bile
And fished the chylomicron
with zest and with a smile.

Then turning to Ampulla great
they bowed their slender form
Oh thank you dear old Vater
for now we are reborn.

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

GIPS MICROGRANT PROGRAM REPORT

Heidrun Rotterdam, M.D.

Dr. Yi-jin She, the recipient of a microgrant from the Gastrointestinal Pathology Society, graduated from Beijing Union University, College of Chinese Traditional Medicine, in 1985, and worked as a research assistant in the Department of Pathology of the Institute of Medical Laboratory Animals, Chinese Academy of Medical Sciences, until she came to New York University in May 1988. Dr. She's parents have both been in contact with a variety of institutions and persons in the medical field in the United States and Europe. Her mother had spent six months of research on ovarian carcinoma at Lenox Hill Hospital in New York, where I first met her. Her father is the president of the Chinese disvision of the IAP. Dr. She learned to do in-situ hybridization and immunoperoxidase staining in our histology laboratory at NYT and applied these techniques to colon biopsies with CMV colitis from AIDS patients. Her work is summarized in the enclosed abstract submitted to the upcoming AIDS meeting in Montreal, where is will be presented as a poster.

The microgrant was obviously not sufficient to support Dr. She, for the 6 months she stayed at NYU, but served as a challenge to Dr. Douglas Dieterich from the division of gastroenterology who contributed $4500 from a Syntax grant for the study of Gancyclovir in CMV colitis.

Dr. She is presently working as a research assistant at Memorial Sloan-Kettering Hospital in Dr. Safac's laboratory doing Southern blotting. She is applying for various PhD programs and intends to stay in the United States. The seed money of the microgrant seems to have grown into a big plant. I hope that future microgrants are as successful as this one was.

SILVER STAIN FOR INTESTINAL PSEUDO-OBSTRUCTION SYNDROME NOW AVAILABLE

Patrick J. Dean, M.D.

Smith's silver staining has been advocated as an adjunctive technique for the study of myenteric plexus abnormalities of patients with intestinal pseudo-obstruction syndromes.[1,2,3] Pat Dean and histotechnologist co-worker Dolores Carter have worked directly with and been able to reproduce the silver staining method of Mike Schuffler and colleagues. They are willing to perform the silver staining technique in pseudo-obstruction cases for fellow members of the GIPS. Pat can be contacted at Baptist Memorial Hospital, Department of Pathology, 899 Madison Avenue, Memphis, TN 38146, telephone number (901)522-5297.

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SPECIALTY CONFERENCE

HANDOUT

GASTROINTESTINAL PATHOLOGY

Thursday, March 10, 1989 - 7:30 p.m.
Continental Ballroom 6

Moderator:

DAVID A. OWEN
Vancouver General Hospital
Vancouver, BC

Panelists:

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

KATHERINE DeSCHRYVER, Case Western Reserve University, Cleveland, OH

HARRY S. COOPER, Thomas Jefferson University Hospital, Philadelphia, PA

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

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

JAMES K. KELLY, Foothills Hospital, Calgary, AB

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY
GASTROINTESTINAL SPECIALTY CONFERENCE

DISCUSSION FOR CASE #1: Vascular Anomalies of the Stomach

Robert E. Petras, M.D.
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The Cleveland Clinic Foundation
Cleveland, OH

Many conditions enter the differential diagnosis of upper gastrointestinal blood loss (Table 1) including a group of newly recognized gastric vascular anomalies that are not yet well characterized. Reasons for continued confusion concerning classification and pathogenesis of gastric vascular anomalies are many. For example, fiberoptic endoscopic equipment and techniques have been refined only in the last 10 to 15 years. Furthermore, mucosal vascular lesions are often prominent when blood-filled at endoscopy, but become less dramatic or even unrecognizable in pathological specimens. Risks associated with endoscopic biopsy, have limited the material available for histological analysis and gastric resection specimens have been difficult to study with injection techniques. Although often referred to as arteriovenous malformations (AVM's) by endoscopists, most of these vascular lesions are simple capillary ectasias and are difficult to recognize as abnormal when not distended with blood or when they have been compressed by the biopsy technique itself. Finally, many of these vascular lesions have a predominant submucosal location and are simply not sampled in mucosal biopsy specimens.

Currently, a lack of information precludes accurate definition and classification of the spectrum of gastric vascular anomalies. This discussion will focus on gastric antral vascular ectasia (GAVE) - "the watermelon stomach," a lesion that is evolving into a distinct clinical pathologic entity.

The "watermelon stomach" was first described and popularized by Jabbari et al in 1984 (1). They described three patients with severe iron deficiency anemia and gastrointestinal blood loss. These patients had a distinctive antral lesion composed of longitudinal red folds radiating from the pylorus that resembled "the stripes of a watermelon." Subsequently, several additional cases have been reported (2). GAVE predominantly affects elderly females causing a profound iron deficiency anemia due to occult gastrointestinal blood loss. Arteriography has consistently failed to demonstrate a vascular lesion. Achlorhydria has been found when sought. Many patients have also had autoimmune diseases and there may be an association with cirrhosis.

Jabbari et al (1) described mucosal capillary ectasia, thrombosis and fibromuscular hyperplasia of the lamina propria in GAVE. We compared GAVE specimens to gastric mucosal biopsy

specimens from patients with gastric ulcers, gastritis, and atrophic gastritis. Our studies verified Jabbari's observations and we concluded that the histologic changes were sufficiently distinctive to allow its recognition in biopsy specimens (2).

The etiology of GAVE is uncertain but the clinical presentation and the endoscopic and microscopic appearance suggest that the lesion is acquired and that it may result from mucosal trauma. Most affected patients are elderly. The location of the red stripes corresponds to the area of the gastric mucosal surface that would be subjected to the greatest trauma during vigorous contraction. Finally, vascular ectasia and fibromuscular hyperplasia of the lamina propria, both characteristic of GAVE, are common to other gastrointestinal lesions known to be associated with trauma and mucosal prolapse such as the solitary rectal ulcer syndrome, stomal sites, intussusception and prolapsed hemorrhoids (3).

Therapy for GAVE has included antrectomy, corticosteroids, sclerotherapy, and Heatprobe thermal coagulation (2). At least two-thirds of reported patients have had antrectomy with correction of the anemia. This supports the contention that the antral lesion caused the blood loss. We have avoided antrectomy in these typically elderly patients because of the operative risks. Steroids have been unpredictable and treatment failures have been reported. Although a case successfully treated with sclerotherapy has been reported, we think this form of therapy is extremely dangerous in the stomach because of the high risk of visceral perforation. We currently use Heatprobe thermocoagulation (4) to treat GAVE. The Heatprobe is applied directly to the erythematous mucosa through the endoscope. The device thermocauterizes the area, the mucosa ulcerates and subsequently heals. Usually multiple treatments are required. This therapy has been uniformly successful and free of serious complications.

The lack of a standardized nomenclature has led to confusion and difficulties in evaluating the literature. In Table 2 I have constructed a provisional classification system that considers the endoscopic and histologic findings and their possible clinical pathologic correlates as an aid to differential diagnosis. Currently, the most difficult and confusing area concerns the relationship between GAVE and the gastric vascular lesions described in cirrhosis. The diffuse antral erythema (diffuse antral vascular ectasia) has been described most often in patients with cirrhosis and portal hypertension. Histologically, there is mucosal capillary ectasia sometimes with changes similar to GAVE. This "gastropathy" seen associated with portal hypertension is the subject of several articles (2,5). We have noticed red linear stripes on a background of diffuse antral erythema in some patients with portal hypertension. GAVE (the watermelon stomach) may be a closely associated lesion or may even progress to the more diffuse form of antral vascular ectasia (6,7). Nevertheless, GAVE is clearly recognizable either as a distinct lesion or at

least as a point in a spectrum of gastric antral vascular ectasias.

Kodachrome #1: Typical endoscopic view of the gastric antrum in GAVE - "the watermelon stomach." Linear red stripes traverse the gastric antrum.

Microscope Slide #1: Capillary ectasia with microthrombosis dominate the sections. As a guideline, capillaries with diameters similar to the widths of adjacent gastric glands or pits should be considered ectatic. The fibromuscular hyperplasia in this case takes the form of numerous smooth muscle cells expanding and obliterating the lamina propria adjacent to the gastric pits. The mucosal architecture is focally distorted while chronic inflammation is minimal.

Diagnosis for Case #1: Gastric antral vascular ectasia - "the watermelon stomach."

TABLE 1

CAUSES OF UPPER GASTROINTESTINAL BLEEDING

Duodenal ulcer
Gastric ulcer/erosion
Gastritis
Esophagitis
Mallory-Weiss tear
Esophageal/gastric varices
Barrett's ulcer
Esophageal and gastric neoplasia
Gastric vascular anomalies

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TABLE 2

ENDOSCOPIC AND PATHOLOGIC CLASSIFICATION OF GASTRIC VASCULAR ANOMALIES (REFERENCES 6 - 12)

Endoscopic Appearance	Histology	Clinical Pathologic Correlate
Erythematous nodule or plaque	Proliferation of arteries and veins with evidence of AV shunting	Arteriovenous hemangioma (true AVM)
	Increased numbers of dilated thin-walled blood vessels	Capillary or cavernous hemangioma
	Irregular anastomosing vascular channels with atypical hyperchromatic endothelial cells and papillations	Angiosarcoma
	Spindle cell proliferation with vascular slits	Kaposi's sarcoma
Localized erythematous macules	Proliferation of arteries and veins with evidence of AV shunting.	Arteriovenous hemangioma (true AVM)
	Dilated capillaries	1. Hereditary hemorrhagic telangiectasia
		2. Mucosal lesions associated with progressive systemic sclerosis
		3. Some patients with cirrhosis and portal hypertension
		4. Localized vascular ectasias not associated with other conditions
Diffuse antral erythema	Dilated capillaries	Cirrhosis with portal hypertension
	Dilated capillaries with thrombi, fibromuscular hyperplasia of lamina propria	? end-stage GAVE - the watermelon stomach
Erythematous antral stripes	Dilated capillaries with thrombi, fibromuscular hyperplasia of lamina propria	GAVE - the watermelon stomach
Small mucosal ulcer most often encountered in cardia or fundus	Large caliber (1-3 mm) artery adjacent to to muscularis mucosae	Dieulafoy's ulcer

CASE 2

K. DESCHRYVER, M.D.
Department of Pathology
Case Western Reserve University
Cleveland, Ohio

Diagnosis: Small intestine, ileum, partial resection -
- ulcers
- consistent with NSAID related injury

It has long been known that aspirin and non-steroidal anti-inflammatory drugs (NSAID) induce gastric mucosal disease including erosions, ulceration and hemorrhage in up to 30% of patients taking these agents. The effects of these drugs on the small intestine, however, are less widely appreciated. The role of drugs in small-intestinal disease (enteric coated potassium chloride, enteric-release salicylate) causing ileal ulcers has previously been explored but the pathogenesis was thought to be strictly mechanical/topical. More recently, in the so-called primary, non-specific ulceration of the small bowel, NSAID have come under suspicion(1,2).

Proximal (duodenal) injury has been documented by endoscopy in healthy volunteers as well as patients with musculoskeletal disorders receiving indomethacin. This has been shown to be a systemic effect. More distally in the jejunum, and even more consistently in the ileum, ulceration, presenting as iron deficiency anemia, obstruction or frank hemorrhage is increasingly reported. The obstruction is due to local stricture formation. Sometimes multiple resected specimens show nonspecific changes. No features of vasculitis or Crohn's disease are usually present(3-6).

Interestingly, recrudescence of quiescent inflammatory bowel disease has also been recently reported with NSAID(7). Colonic disease (ulcers) has also been noted. The NSAID associated ulcerations of the GI tract are not uncommonly asymptomatic, possibly in part because of coexistent analgesic effects of the drugs, presenting with life threatening hemorrhage and perforation, especially in the elderly. Elderly patients take NSAID very commonly for the spectrum of progressive arthritides, osteoarthritis and other aches and pains.

The pathogenesis of NSAID-induced intestinal injury is not elucidated. Their antagonism of prostaglandin synthesis, implicated in "cytoprotection" has been thought to be the cause of mucosal injury in the stomach and proximal intestine. NSAID are also known to increase mucosal permeability in the small intestine with disruption of inter-cellular junctions. This is evidenced clinically and by investigative techniques by protein loss, and leukocytes and red cells leaking into the bowel lumen.

This effect, possibly combined with suppression of some neutrophil function, may promote bacterial invasion. It has also been speculated that salicylates injure mucosa by producing intravenous platelet thrombi and subsequently hemorrhagic lesions - as a result of the inhibition of synthesis of prostaglandins. NSAID-associated injury is most likely multifactional.

Theoretically NSAID might be thought as useful therapeutic agents in inflammatory bowel disease (IBD), as excess prostaglandins are known to be present in these conditions. The reports of NSAID exacerbating or causing recurrence in quiescent IBD is of note. In experimental animals, NSAID induced lesions are reproducible including those of the ileum.

In summary, this patient with rheumatoid arthritis had recurrent ileal ulcers. On the resected specimens, the features were nonspecific. Patients with connective tissue diseases can have a variety of gastro-intestinal lesions(8-11)A drug related etiology, such as long-term NSAID is a very likely candidate in causing the present injury. Awareness of this association will be very important in the differential diagnosis of the so-called primary nonspecific ulcerations of the small bowel (and of other sites of the GI tract probably as well) - as discontinuation of the offending agent usually resolves the patient's symptoms.

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CASE 3 Harry S. Cooper, M.D.

Small Cell Undifferentiated Carcinoma of the Colon and Rectum

Small cell undifferentiated carcinoma (neuroendocrine carcinoma) of the colon and rectum is an uncommon but well characterized neoplasm of the large intestine. While there have been only 28 cases reported in the literature, these neoplasms are probably more common than the literature would indicate and most pathologists will come in contact with a case or two sometime during their career.

The age, sex, and site distribution of small cell undifferentiated carcinoma is similar to that of colorectal adenocarcinoma, however, small cell undifferentiated carcinoma is uniformly lethal. Of 24 reported cases with adequate follow up, all patients were dead of disease with the longest survivor being 16 months. The vast majority of cases present with advanced stage (79% with liver metastases and 71% with lymph node metastases). Grossly, small cell undifferentiated carcinoma is indistinguishable from routine adenocarcinoma. These neoplasms are histologically identical to small cell undifferentiated carcinoma of the lung. Fourteen percent of the cases have shown areas of squamous differentiation, 21% have been intimately associated with an adenoma and 11% have been associated with adenocarcinoma. Interestingly, in some cases, there has been a small focus of small cell undifferentiated carcinoma within an adenoma, however, these cases also eventuated in widespread metastatic carcinoma. Electron microscopic

studies show the presence of classic neurosecretory granules. In some cases, there have been tonofilaments and neurosecretory granules within the same cells, findings which indicate both squamous and neuroendocrine differentiation.

In general, the diagnosis of small cell undifferentiated carcinoma is not difficult, however, small biopsies of lesions of the lower rectum may at times be confused with cloacogenic carcinomas. It is important to differentiate between these two lesions as the latter may be effectively treated with combined radiation therapy and chemotherapy. In this situation, electron microscopy can be helpful in making the proper diagnosis. Recently Wick et al have provided an immunohistochemical profile to differentiate between small cell undifferentiated carcinoma and cloacogenic carcinoma. Small cell undifferentiated carcinoma will express Neuron Specific Enolase, Chromogranin, Neurofilaments, and Leu 7 and will be negative for CEA and Blood Group Antigens while cloacogenic carcinoma will express CEA, and Blood Group Antigens, but not Neuron Specific Enolase, Chromogranin, Neurofilaments and Leu 7. These small cell undifferentiated carcinomas have uniformly been immunohistochemically negative for expression of hormone production.

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Case # 4
Randall G. Lee, M.D.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (NE) is a clinicopathologic syndrome characterized by fulminant necrosis and edema of the bowel wall that involves principally the ileocecal region and occurs in the setting of severe neutropenia. Cases have been reported under a variety of names including agranulocytic colitis, the ileocecal syndrome, necrotizing enteropathy, and typhlitis (from the Greek word "typhlon", meaning cecum); these terms variously emphasize the key features of the condition. NE typically follows myelo-suppressive chemotherapy for malignant disease, most often acute leukemia, and is recorded at autopsy in 10-46% of leukemic patients. However, NE can also complicate neutropenia attributable to other causes such as aplastic anemia, drug-induced agranulocytosis, and cyclic neutropenia.

The clinical diagnosis can be difficult and requires a high index of suspicion. Patients usually manifest with fever and abdominal pain (which may localize to the right lower quadrant), but can also suffer bloody or watery diarrhea, nausea, vomiting, or septicemia. Radiographic studies, including plain films, barium enema, sonography, and CT may reveal an ileocecal distribution of various nonspecific abnormalities (thumbprinting, diffuse mural thickening, mass density). Colonoscopy has been used in a few instances to similarly document right-sided ulceration and edema. Although NE has previously been considered almost uniformly fatal, increased recognition and earlier diagnosis have yielded better survival. Treatment includes broad-spectrum antibiotics, blood product administration, and fluid replacement, with prompt surgical intervention for the 20-25% of patients whose symptoms persist or condition deteriorates.

Pathologic findings are generally confined to the cecum, ascending colon, and terminal ileum. Grossly the involved bowel is dilated with a thickened boggy wall, occasionally appearing hemorrhagic or gangrenous. The mucosa is congested and interrupted by well-demarcated ulcers, single, multiple or coalescent. The histologic features comprise mural necrosis ranging in extent from mucosal to transmural, prominent edema of submucosa and mucosa, and a relatively sparse inflammatory infiltrate containing few or no neutrophils. Intramural hemorrhage, bacterial organisms, submucosal gas cysts, and leukemic infiltrates are occasionally noted.

These pathologic changes are not specific, but instead represent the morphologic correlate of acute intestinal failure--severe mucosal insult resulting in loss of normal bowel integrity, secondary bacterial invasion, necrosis, and ultimately sepsis--exacerbated in NE by neutropenia. The changes therefore also

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CASE # 5 : STRONGYLOIDIASIS - William K. Gourley, M.D.

CASE SUMMARY - An 18-year-old male with Down's syndrome was given corticosteroids and cimetidine for idiopathic thrombocytopenia and suspected peptic ulcer. There was slight pre-treatment eosinophilia (7%). Increasing abdominal pain, a groin rash, diarrhea, cough, and loss of eosinophilia developed in 1 month. Biopsy of the duodenum led to a diagnosis of strongyloidiasis when an enteritis, eggs, larvae, and adult worms were found. Larvae were present in sputum, but not in his stool. Larvae were also found in feces of the patient's asymptomatic father. The family lived on a farm and obtained water from a pump. Steroids were discontinued and the patient was well after 1 month of cyclic thiabendazole therapy. The case illustrates the increased autoinfection ("hyperinfection") that occurs when a patient with unrecognized strongyloidiasis is treated with corticosteroids, which in this instance were given for idiopathic thrombocytopenia.

Strongyloides stercoralis (Greek strongylos = round, Latin stercus = feces) is a nematoid (Gr. nema = thread) helminth (Gr. helmins = worm) parasite. It has a unique life cycle that promotes chronic and, in certain host states, disseminated infection.

LIFE CYCLE (Beaver, et al, 1984)

SOIL -
ADULTS (1-3 mm long) live in wet soil. EGGS hatch NONINFECTIVE RHABDITIFORM LARVAE (Gr. rhabdos = rod) that mature to INFECTIVE FILARIFORM LARVAE (L. filum = thread).

SKIN -
FILARIFORM LARVAE penetrate the skin of the human host.

BLOOD -
FILARIFORM LARVAE enter the blood stream.

LUNG -
FILARIFORM LARVAE exit pulmonary capillaries and travel the bronchial-tracheal lumens to the esophagus.

SMALL INTESTINE -
FILARIFORM LARVAE traverse the digestive lumens to the lower duodenum and upper jejunum where they mature only into ADULT FEMALES. These burrow tunnels in the epithelium of mucosal crypts and lay EGGS. A single RHABDITIFORM LARVA quickly develops in each egg, which hatches locally.

FECES -
RHABDITIFORM LARVAE are present in feces and they mature into adults in wet soil, but they CAN TRANSFORM INTO INFECTIVE FILARIFORM LARVAE IN THE INTESTINES OR ON THE SKIN.

AUTOINFECTION -
Autoinfection can occur if FILARIFORM LARVAE develop when there is a prolonged intestinal transit time or peri-anal skin soiling. For example, such autoinfection is thought to explain a 9% incidence of strongyloidiasis found in a cohort of ex-prisoners of war more than 30 years after leaving an endemic area (Pelletier, et al, 1988).

characterize several intense and clinically fulminant necrotizing conditions of the bowel, including ischemic colitis and neonatal necrotizing enterocolitis. NE is distinguished primarily by its ileocecal predilection and clinical setting. (Although a greater neutrophil response is to be expected in the other conditions, this is not always the case.)

The pathogenesis of NE is unclear and probably multifactorial; its association with neutropenia and preference for the ileocecal region remain a mystery. The mucosal injury that appears to trigger the process could potentially result from numerous factors: cytotoxic chemotherapy, necrosis of leukemic infiltrates, local ischemia, mucosal hemorrhage, or apparently even neutropenia itself. The further pathogenetic role of enteric gram-negative bacteria has been emphasized, but recent data implicate Clostridium septicum as an etiologic agent. C. septicum bacteremia, which is often associated with neutropenia and leukemia, is recognized in an increasing number of NE cases, and the organism has been specifically identified invading the affected bowel wall. Although not conclusive, the evidence incriminates C. septicum in at least some instances of NE.

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SYMPTOMS and SIGNS -

Some infected people are asymptomatic. Many have only epigastric pain and diarrhea. A rash can be present at the site of larval migration from the initial skin penetration. In cases of external autoinfection, the rash can spread from the perineum as far as the axilla at a rate of 10 cm/hr ("larval currens," L. currens = running). Blood eosinophil counts >5% are common. Major pulmonary symptoms are unusual (Milder, et al, 1981).

DIAGNOSIS -

The diagnosis is based on the presence of:

epigastric pain;
diarrhea;
eosinophilia;
RHABDITIFORM LARVAE IN THE FECES (rhabditiform larvae, about 300 x 20 µm, have a short buccal cavity and esophagus with a distal bulb), but fecal concentration techniques or duodenal aspiration may be necessary because of variable and periodic larval passage (Case Records, M.G.H., 1987);
serology and skin tests (Neva, 1986).

In duodenal biopsy material (Case Records, M.G.H., 1986):

embryonated eggs (50-60 x 30-34 µm, thin wall, frequently contain a curled larva);
thin larvae (15-20 µm diameter);
adult worms (30-40 µm diameter) with:
- a striated cuticle;
- paired dark ovaries adjacent to a single tubular intestine.

The identification of a worm with all stages of development (ie, eggs, larvae, and adults) in a small intestinal biopsy specimen allows differentiation of Strongyloides from other intestinal nematodes such as:

hookworm; Ascaris; Enterobius; Tricuris; Trichinella; Anisakis simplex or Pseudoterranova decipiens (Sakanari, et al, 1988); and Capillaria philippinensis, the only mimic with all stages present in the intestine, has eggs with bipolar plugs and a pitted shell (Sun, 1988).

HYPERINFECTION -

Is it important to correctly identify Strongyloides? It is, because of the nature of the parasite's biology and the host's response - the determining factors in all infectious diseases. At one end of a spectrum is a nearly asymptomatic or relatively mild disease with diarrhea. A balance may be reached that results in chronic autoinfection due to the premature development of infective filariform larvae. Tissue injury is usually confined to the upper intestinal mucosa, but rarely the colon can be affected (Berry, et al, 1983). At the other end of the spectrum is "hyperinfection," with a high parasite concentration in the lung and intestine that can progress to systemic disease due to dissemination of filariform larvae, which can be found in the sputum, liver, brain, heart, lymph nodes, and even the urine (Cook, 1987). Blood eosinophilia is frequently absent and ileus with constipation rather than diarrhea can be

found, so the diagnosis is obscured. Bacterial sepsis is common, with a fatality rate of up to 77%, and special thiabendazole treatment schedules have been recommended (Morgan, et al, 1986: Cook, 1987).

The fulcrum of the balance between the parasite and the host is the host's immunologic capability. Strongyloides hyperinfection usually occurs in patients with immune defects due to AIDS, lymphoma, immune suppression for renal transplantation, or corticosteroid therapy. Some experts recommend that all candidates for renal transplantation or steroid treatment should be examined for Strongyloides (Morgan, et al, 1986: Cook, 1987).

THE IMMUNE RESPONSE -

The host response to Strongyloides, and to most metazoa with their multiple cell (multiple antigen) types, is poorly understood. In contrast to the immune response to other gastrointestinal infectious agents, IgA does not seem to be the main component of a protective response to the intestinal phase of the worm. ELISA tests that detect IgG and IgE antibodies to larval antigens have been reported to be positive in 90-97% of infected individuals and to become negative after treatment with thiabendazole (Neva, 1986; Genta, 1988). The protective action of these antibodies is unproven (Badaro, et al, 1987).

An immediate hypersensitivity type of cellular immune response in the intestine is suggested by the presence of eosinophilia, mast cells, and a variably elevated serum IgE (Neva, 1986). Eosinophil abscesses and granulomas around filariform larvae in the colon wall are evidence of a cellular hypersensitivity when there is internal autoinfection (Berry, et al, 1983). Experimental immunization of rats with antigens derived from adult S. ratti produces increased intestinal mast cells and a marked reduction in adult worm production after challenge with larvae, but larval migration is not affected (Mimori, et al, 1987).

Cyclosporin has been found to eliminate experimental infection in dogs. This apparent paradox was attributed to a parasitocidal effect of the immunosuppressive drug (Schad, 1986), but a blunted lymphocyte blastogenic response to larval antigen with incubation in serum from infected patients raises the possibility that the worm may produce substances which inhibit cell-mediated immunity (Genta, et al, 1983). Stimulation of suppressor T-cells by a parasite product is thought to be the explanation for an immune depression found after infection by Trichinella, another nematode with intestinal and tissue phases; cyclophosphamide has been shown to reverse this suppressor-cell activation (Faubert, 1982). Thus, the factors that affect the immune balance is quite complex in metazoal infections.

There are questions about the biology of the parasite and the host response that, if answered, could provide clues for the prevention and treatment of the infection. What is the mechanism of penetration of the skin, alveoli, and intestinal mucosa by filariform larva (Rege and Dresden, 1987: Grove, et al, 1987)? Could penetration be inhibited? What limits the itinerary of migrating filariform larvae to the skin, lungs, and intestinal lumen in immune-competent individuals? Does cimetidine therapy increase the worm burden by allowing more larvae to survive

passage through the stomach (Ainley, et al, 1986)? Which arms of the immune response are most important? Can they be supplemented? Does the parasite itself produce substances that suppress cellular immunity? Could they be counteracted?

It is clear that when public health measures fail, humans are subject to infection by this parasite with its complicated life cycle, which allows persistent autoinfection. The host defenses can limit the infection, but potentially disastrous hyperinfection shadows immune-deficient patients (Purtilo, et al, 1974).

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CASE 6

Segmental Ileal Ischemic Stricture Mimicking Crohn's Disease

Dr. James Kelly, University of Calgary

History: Two months before surgery this 59 year-old man developed nausea and sudden severe epigastric pain, which radiated to the back. Plain films of the abdomen showed an ileus. Symptoms resolved after 3 days of fasting and intravenous fluids but over the following weeks he became intolerant of solid food because it induced colicky abdominal pain leading to vomiting and he voluntarily adopted a liquid diet. At laparotomy a segment of mid ileum 8cm in length was strictured and inflamed and there was proximal dilatation. The remainder of the bowel was normal.

Pathology: Grossly the specimen was an 18cm length of ileum containing a stricture 8.5 cm in length, together with mesentery up to 5 cm in width. The stricture was sharply delimited and showed a thickened wall, totally ulcerated mucosa and congested serosa. The dilated proximal ileum and the distal ileum showed normal mucosal folds with no aphthoid ulcers or mucosal scars. Microscopy showed ulceration, transmural chronic inflammation, submucosal lymphoid aggregrates and "fissures" penetrating into the muscularis propria, but granulomas and hemosiderin were absent. The bowel outside the stricture was normal. Initial blocks of mesenteric vessels were normal but recuts showed organising occlusive arterial thrombus establishing the diagnosis of ischemic stricture.

Subsequent echocardiography revealed no cardiac morphological abnormality and there was no family history or laboratory evidence of thrombotic tendency. The patient is alive and well two years later.

Discussion: The demonstration of occlusion of a mesenteric artery firmly establishes a diagnosis of ischemia but the differential diagnosis of this histology lies between Crohn's disease and ischemia. Features favouring ischemia are (i) the mid-ileal location, (ii) the completeness of ulceration in the diseased area, (iii) the sharp delineation of the stricture from the normal bowel, (iv) the absence of aphthoid ulcers or mucosal regeneration outside the stricture and (v) the absence of granulomas. In ischemic strictures (of the small bowel) the ulcers involve the entire circumference whereas in Crohn's disease ulceration is typically patchy and leaves islands of mucosa. The resemblance of ischemic strictures of the ileum to Crohn's disease has been recognised for many years both pathologically (1,2) and clinically (2-4). This case illustrates that transmural inflammation, inflammation with lymphoid follicles and fissuring may be seen in ischemic ulceration, a point not stressed in the literature.

A variety of vasculopathies may be seen in the gut in Crohn's disease (5) but are usually readily distinguishable from primary necrotising arteritis which may produce either multiple

independent segmental lesions or confluent lesions with foci of mucosal sparing. In primary arteritis there are often ischemic lesions of different ages including areas which show tissue necrosis, either of the mucosa alone or of the full thickness of the wall. Necrosis is not seen in Crohn's disease.

Ischemic strictures result from single episodes of acute ischemia which cause mucosal necrosis but leave the wall viable. Segmental ischemic strictures may be due to **strangulation by hernia or bands, atheromatous emboli, non-occlusive ischemia, and blunt mesenteric trauma** including **seatbelt injury** (1, 6-13). **Potassium-related ulcers** and non-specific ulcers form napkin-ring strictures, 1 to 3 cm long and may also be ischemic (14). **Chronic radiation enteritis** includes an element of chronic ischemia but does not affect sharply delineated segments of gut and is marked by hyaline serosal fibrosis and radiation fibroblasts. **Behcet's disease** of the gut may mimic Crohn's disease but is distinguished by the clinical picture. **NSAID-related strictures** are circumferential, concentric mucosal diaphragms (15).

"Segmental ischemic lesions show the whole range of possible pathology ranging from superficial mucosal lesions which heal completely, through a more severe stage involving deeper strictures and culminating in a fibrous stricture, to full-thickness involvement with gangrene, perforation, and peritonitis (16).

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GI NEWSLETTER
ABSTRACT REVIEWS

Dr. Azumi, and coworkers. from City of Hope National Medical Center and Georgetown University School of Medicine presented an immunohistochemical study of prostatic acid phosphatase in rectal carcinoid tumors. While no cases were positive for prostate-specific antigen, all five rectal carcinoid tumors studied were positive for prostatic acid phosphatase with some monoclonal reagents. Forgut and midgut carcinoid tumors were negative. They are not sure whether this indicates that prostatic acid phosphatase is present in these neoplasms or whether the reactivity represents cross-reaction from an unknown substance.

From Case Western Reserve University Medical School, Drs. Barrow and colleagues report their results following administration of the carcinogen 1,2-dimethylhydrazine (DMH) to rats. They found that all of these animals had decreased in N-acetyl-beta-D-glucosaminidase, alpha-naphthyl butyrate esterase and mucus in colonic epithelial cells. These changes prior to development of neoplasms suggested that they are putative preneoplastic lesions.

Drs. Berena and Coon from Rush-Presbyterian-St. Luke's Medical Center studied the DNA content on paraffin-embedded samples of biopsies with hepatocellular dysplasia and other with hepatocellular carcinoma. They found that while healthy liver is usually euploid, hepatocellular dysplasia is usually diploid. Hepatocellular carcinoma is predominantly anuploid as is the uninvolved parenchyma adjacent to hepatocellular carcinoma.

From the University of Chicago, Drs. Bibbo and coworkers described an image analysis study of the nuclei in normal tissue adjacent to resected colon adenocarcinoma. They suggest that nuclear features may be useful indicators for possibly premalignant changes in histologically normal-appearing colon resection margins.

Drs. Bigio and colleagues from the University of Texas Medical Branch at Galveston tried to identify *Campylobacter pylori* on brush cytology from endoscopic examinations. They found that biopsy specimens stained by H&E had a greater yield of detection of this microorganism than when samples were processed for cytology and stained by Papanicolaou.

Drs. Bramwell and colleagues from McMaster University performed immunohistochemical studies using two antibodies against specific epitopes on neuron-specific enolase, anti-PGP9.5 and anti-NSE (neuron-specific enolase) to examine the nerve supply in the bowel. They found a dense nerve network in the lamina propria. Processes from neuroendocrine cells were frequently in contact with axons. These studies provide baseline information on the distribution of nerve-related cells in the gut.

Drs. Burke and colleagues from the AFIP correlated the histology of appendiceal carcinoids with different immunohistochemical stains. A few trends emerged including: endocrine cells were scarce in goblet cell carcinoids, S-100 stained scattered sustentacular cells, human pancreatic polypeptide stained goblet cell carcinoids strongly, and tubular carcinoids stained strongly with glucagon. Overall, chromogranin and neuron-specific enolase were the best overall markers for appendiceal carcinoids.

Drs. Byard and coworkers from Repatriation General Hospital in Australia report that they investigated the persistence of *Strongyloides stercoralis* in stool specimens from former World War II prisoners-of-war. In a group of Tasmanian ex-servicemen exposed to infestation 40 years ago, 16.7% still had this parasite isolated from fresh stool specimens. They devised a screening index which allowed them to predict the likelihood of strongyloidiasis in a suspected carrier who may have negative stool samples but had various clinical symptoms including abdominal discomfort, frequency of bowel motions, skin rashes and eosinophilia.

Drs. Carroll and colleagues from Washington University School of Medicine in St. Louis describe a new immunoreactive marker which may be useful for colorectal adenocarcinomas. They use an immunohistochemical technique to demonstrate liver fatty acid binding protein (LFABP). They found LFABP cells in 7/10 colorectal adenocarcinomas, 0/2 mucinous adenocarcinomas and 3/5 adenomas, but no staining was seen in carcinomas of the stomach, breast, kidney and endometrium.

From the Baptist Memorial Hospital and University of Tennessee in Memphis, Drs. Causey and Dean compared the immunoreactivity of Pepsinogen II in proximal and distal gastric carcinoma and in Barrett's adenocarcinoma. They found that antigenic expression of Pepsinogen II is similar in all sites tested. This provides support for a common histogenesis of these tumors.

Dr. Cho and colleagues from the VA Medical Center and State University of New York investigated possible differences in the adaptive response of small intestinal mucosa from old and young rats. They found that young rats were able to respond quickly to a 70% enterectomy. The animals would develop a significant increase in total mucosal area (especially in the crypt). In contrast, older rats did not show significant increases in mucosal areas. The reason for this difference is not clear at the present time.

Dr. Choi from the Bronx-Lebonon Hospital compared the diagnostic efficiency of *in situ* hybridization using a biotinylated DNA probe versus immunohistochemistry on formalin-fixed liver biopsies from patients with hepatitis B infections. Dr. Choi found that *in situ* hybridization was superior to immunohistochemistry in detecting the hepatitis B virus.

Drs. Cote and Urmacher from Memorial Sloan-Kettering Cancer Center reported a study on 13 primary sarcomas of the liver. They found that an important prognostic feature was liver function: of 9 patients with severe abnormalities, 3 died immediately post-operative while of the four patients with minimal abnormalities, 2 were alive at 5 and 37 months. Bony and lung metastases were the most common in the series with bony metastases frequently being multiple.

From Washington University Medical School of St. Louis, Drs. DeSchryver-Kecskemeti and colleagues reported their studies on an intestinal surfactant-like material secreted by enterocytes. In ultrastructural studies, they found lamellar bodies reminiscent of lung surfactant in rat enterocytes. The lamellar bodies are secreted into the basolateral space and are present in the lumenal microvillus surface. The function of this material is not known at the present time.

In a study by Donnelly and coworkers from the Massachusetts General Hospital, it was found that examination of the bowel for fibrosis and/or lymphoid infiltration was a good predictor of the success for local excision of rectal carcinoma. Cases showing fibrosis or lymphoid infiltration were much more likely to suffer from treatment failure.

Dr. Donner from Scott & White Clinic in Temple, Texas reviewed 315 malignant exocrine tumors of the pancreas and found 7 giant cell pleomorphic carcinomas. The lesions all presented with liver metastases and proved fatal within 3 months of diagnosis. A tumor stained positively with cytokeratin and some had ultrastructural mucinogen granules. These tumors were likely poorly differentiated variants of duct carcinoma.

From The Johns Hopkins Medical Institutions, Drs. Dowell and colleagues noted that pancreatitis was a common cause of morbidity in AIDS patients. In a review oft he 82 autopsies performed on AIDS patients at The Johns Hopkins Hospital, pancreatic lesions were detected in 56%. The most common lesion was acinar dilatation by inspissated secretions followed by acute pancreatitis and opportunistic infections or cancers of the pancreas.

Drs. Eisen and West from Yale University describe the immunostaining characteristics in Hirschsprung's disease. They examined ganglionic and aganglionic sections of bowel from 21 patients with this disease by monoclonal antibodies to two specific epitopes of neuron-specific enolase and polyclonal antibodies to S100 and PGP 9.5. Ganglion cells in the formalin-fixed paraffin-embedded tissue were stained to advantage with the monoclonal antibody against the AD epitope of neuro-specific enolase. Antibodies to the CF epitope stained the hypertrophic submucosal nerves.

A clinicopathologic and DNA flow cytometric analysis of 54 cases of gastrointestinal stromal neoplasms was performed by Drs. El-Naggar and colleagues from The University of Texas, M.D. Anderson Cancer Center. The tumors were from the stomach (40%), small intestine (30%) and large intestine (22%). Seven of the 12 patients with diploid neoplasms were alive and were without evidence of disease while 41 of the 42 patients with anuploid neoplasms had died of disease by the time of the study. In this study, DNA content was a significant predictor of the biologic aggressiveness of gastrointestinal stromal tumors.

Drs. Estaban and coworkers from the City of Hope National Medical Center reported on studies of immunophenotypic alteration of human colon carcinoma xenografts after immunotherapy with radiolabeled monoclonal antibody directed to CEA. They label the monoclonal antibody ZCE025 which is directed against CEA with ^{90}Y. This radiolabeled monoclonal antibody can have a significant tumoricidal effect when human colon carcinomas are grown in the peritoneal cavity of mice. They found that there were residual colon carcinoma cells 95% of which did not bare immunohistochemical and flow cytometric evidence of CEA expression. If this proves to be a general phenomenon, the use of monoclonal antibodies as single radiopharmaceutical agents for immunotherapy may be limited.

From the V.A. Medical Center, Bronx, New York and The Mount Sinai School of Medicine of the City University of New York, New York, Drs. Federman and colleagues examined colon cancer cytoscreening using an oral colonic lavage. In a series of 35 patients tested with this cytoscreening, 16 had biopsy proven adenocarcinoma and 19 had no evidence of malignancy. 15 of these 16 patients had cells with features above the studies threshold for dysplasia. Only 10, however, were definitively diagnostic of adenocarcinoma. The study demonstrates that colon washings from orally administered colonic lavage solution may be useful in cytoscreening for malignancy.

A spiral bacterium that resembles "*spirillum rappini*" distinct from *Campylobacter pylori* has been found in association with gastritis in humans by Drs. Frierson and colleagues from the University of Virginia Health Sciences Center. *Spirillum rappini* is a microorangism commonly found in the stomach of various animals. In the present study, two adults with these sprial bacteria were found from a group of 400 patients investigated for possible *Campylobacter pylori* infection. The bacteria could be seen in H&E- and by Giemsa-stained sections. There were 0.5 um in diameter, 3-7 um long, and had 4-8 evenly spaced spirals. Typically they were seen in the mucus over the surface of foveolar cells, within the lumens of glands, and occasionally within the intracellular canaliculi of parietal cells.

Drs. Galera-Davidson and coworkers from the University of Saville, University of Cordoba and University of Chicago report on the cytometric and histologic predictors of prognosis in ampullary carcinoma treated with pancreaticoduodenectomy. DNA studies were performed using high-resolution morphometric evaluation of Feulgen-stained nuclei. Neither tumor staged nor the presence of positive lymph nodes were significant prognostic indicators. However, an aneuploid DNA profile, higher mean ploidy and larger nuclei were associated with a lower survival rate. Long term survivors (> than 5 years) had a mean ploidy of 2.8N, and a mean nuclear area of 41 square microns, while short term survivors (< 5 years) had mean ploidy of 1.9N and a mean nuclear area of 26 square microns. High-resolution karyometry provide

significant prognostic information for the management of ampullary carcinoma patients treated by Whipple's resection.

Drs. Geisinger and colleagues from Wake Forest University and The Bowman Gray School of Medicine report a study on mucosal alterations produced by radiation in rats. 36 female Wistar rats received 22.5 Gy of radiation to the rectum and were followed for 1 year. In 20 rats, a total of 29 rectal adenocarcinomas developed. They also identified colitis cystica profunda and its related precursor lesions in 17 rats.

From the Cedars-Sinai Medical Center, Drs. Geller and coworkers studied the histopathology of alpha-1-antitrypsin liver disease in a transgenic mouse model. They constructed transgenic mice using human alpha-1-antitrypsin M and Z genomic clones. They found that nine- and 12-month old mice which had high copy (12 copies per haploid mouse genome) did have early fibrosis.

Drs. Graham and Appelman from the University of Michigan examined Crohn's type lymphoid reaction in colon carcinoma, they found 67 with distinctive "Crohn's-like reaction consisting of discrete lymphoid aggregates, some with germinal centers, and surrounding sclerosis." They found that the individuals would better survival had a considerable amount of this lymphoid reaction.

From The Johns Hopkins Medical Institutions, Drs. Greenson and coworkers reported on the recurrence of anti-reticulin antibodies in collagenous colitis and lymphocytic (microscopic) colitis vs. celiac disease. They found that anti-reticulin antibodies occur in collagenous colitis and lymphocytic colitis in approximately the same number reported in normal individuals. However, 27.8% of patients with celiac disease had these antibodies in their serum. Despite some morphologic similarity of collagenous colitis and lymphocytic colitis with celiac disease, they do not share the occurrence of this antibody.

Stromal neoplasms of the rectum and anus were studied by Drs. Haque and Dean of the Baptist Memorial Hospital and University of Tennessee. They found two distinct groups. In tumors restricted to the submucosa, there were mitoses and the lesions lacked cellular atypia. None of these patients experienced tumor recurrence after local excision with a mean follow-up of 7.4 years. In the second group, there were 7 neoplasms in the muscularis propria and 2 in the submucosa. These neoplasms were characterized by necrosis, higher mitotic rates, and cellular atypia which graded from mild to marked. At time of follow-up, 5 patients had died of the disease.

From Northwestern University Medical School, Drs. Harlow and colleagues reported on the flow cytometric quantitation of a panel of intracellular antigens and DNA content in colonic cancer specimens. They use monoclonal antibodies recognizing c-myc and pan-ras and 89E5 (a carcinoma-associated cytoplasmic protein). They also examined cellular DNA content, histologic grade and Dukes stage. The data indicate the utility of this approach for "phenotyping" colon cancers based on protein expression.

Drs. Harrison and colleagues from Baptist Memorial Hospital and University of Tennessee report on a study of gastric cancer with invasion limited to the muscularis propria. They reviewed 266 cases of gastric cancer resected between 1964 and 1983. 42 cases were limited to the invasion of the muscularis propria. They found that this group had a significantly better five year survival advantage over gastric cancer which had penetrated to the serosal surface. However, the 26% five year survival for the American population was considerably less than the 70% five year survival reported in Japanese patients.

From Emory University, Drs. Hertzler and colleagues report on a study of 249 liver biopsies from 32 orthotopic liver transplant patients. Acute cellular rejection was characterized

by interlobular bile duct injury with large activated lymphocytes. Ongoing or recurrent rejection was accompanied by proportionately less lymphocytic infiltration but bile ducts were distinctly injured. The bile duct injury best reflected the rejection severity. Chronic rejection was manifest as bile duct loss. 63% of their patients developed cytomegalovirus hepatitis. The CMV hepatitis was associated with OKT3 therapy for acute rejection.

Drs. Kelly and colleagues from Foothills Hospital, Rockyview Hospital and Holycross Hospital report on the colonic pathology of E. coli 0157:H7 infection. They find extreme edema, fibrin exudation and hemorrhage in the submucosa as the most distinctive feature. Typically the right colon was most severely infected with a patchy mucosal ulceration, mucosal hemorrhage, neutrophil infiltration and microvascular thrombi. Later in the course, regenerative mucosal changes and lymphoplasmacytic infiltrates are noted. These features are more consistent with verotoxin than bacterial invasion.

Drs. Lanston and coworkers form Texas Children's Hospital, Baylor College of Medicine and The Children's Hospital of Alabama report on the intrinsic innervation of the bowel in teratomas. They examine well-differentiated bowel within four teratomas from four sites for the presence of ganglion cells. The bowel had completely differentiated layers and apparent intrinsic neural innervation with myenteric and submucosal plexuses containing variably mature neuronal elements. Since this innervation did not occur through conventional mechanisms of migration from the vagal region of the neural crest it suggested that migration of neural elements into the bowel might be influenced by intrinsic factors and that abnormalities of such influences could represent an alternative to neuronal migration failure in the pathogenesis of aganglionosis.

From Washington University School of Medicine, St. Louis, Drs. Lee and colleagues describe the immunohistochemistry in neuroendocrine carcinomas of the right colon. They found substance P immunoreactivity in all right colon carcinoids while pancreatic polypeptide immunoreactivity was absent. These findings are similar to those in ileal carcinoids and dissimilar to rectal carcinoids. This study supports the concept that neuroendocrine carcinoma peptide production depends largely on anatomic site of the tumor origin and on the degree of differentiation.

Drs. Lee and coworkers from Washington University School of Medicine, St. Louis, report that thickened muscularis mucosa may play a role in stricture formation in Crohn's disease. In some cases, the muscularis mucosa assumed the thickness of nearly 10% of the total bowel wall. It was felt that this contributes to stricture formation in Crohn's disease. In addition, local inflammatory cell infiltrates play a role.

From the University of Minnesota, Drs. Lillemoe and Snover performed a clinicopathological study of mixed hyperplastic-neoplastic polyps of the large intestine. They found that mixed hyperplastic-neoplastic colonic polyps, adenomas with papillary and eosinophilic change, and neoplastic polyps were significantly larger than hyperplastic polyps. Further, metaplastic polyps and adenomas with papillary and eosinophilic change were more often associated with synchronous or metachronous neoplastic polyps than with hyperplastic polyps. They recommend treating metaplastic polyps and adenomas with papillary and eosinophilic change as variants of neoplastic polyps.

Drs. Little and coworkers from the Veterans Administration and University of New Mexico Hospitals use the monoclonal antibody B72.3 to examine the tumor-associated glycoprotein in normal, hyperplastic and neoplastic samples of colon. Using formalin-fixed, paraffin-embedded samples, they found that reactivity for this monoclonal antibody was seen in 79% of normal colon samples, all invasive carcinomas, all hyperplastic polyps and 91% of adenomas. The staining pattern was consistently supranuclear (presumably Golgi). From the same institution, Drs. Longacre and Fenoglio-Preiser reported on the mixed hyperplastic-adenomatous polyps. They find that mixed hyperplastic-adenomatous polyps display a variety

of changes ranging from hyperplastic polyps with some nuclear stratification and loss of collagen table thickness to a tubular adenoma with a markedly serrated epithelial pattern. These lesions are frequently associated with tubular adenomas (30%) and have a propensity for the right colon, including the appendix. In their study, 10% of mixede hyperplastic-adenomatous polyps contain foci of intraepithelial carcinoma. Also from this institution, Drs. McKinley and colleagues reported on the expression of cytokeratin in normal and hyperplastic colonic mucosa using a battery of monoclonal antibodies. All hyperplastic polyps were CK-19 positive while 73% of mixed hyperplastic-adenomatous polyps stained with CK-19. In contrast, 44% of adenomas and 55% of colon cancers reacted with this antibody.

Drs. Marco and colleagues from Barcelona described immunohistochemical staining on 42 cases of gastrointestinal stromal tumors. Vimentin reactivity was present in 85%, desmin in only 7.1%, synaptophysin was found in 84% and cytokeratin in 80.7%. They felt this provided indirect evidence of the smooth muscle origin of most gastrointestinal stromal tumors. The reader may wish to refer to Dr. Appelman's article in the previous issue of this newsletter for further information on gastrointestinal stromal tumors.

Four patients with massive hepatic necrosis due to hepatitis A infection were reported by Drs. Masada and coworkers from the University of Nebraska Medical Center. All of the patients had some degree of encephalopathy and one had hepatorenal syndrome. Histologically, a spectrum of findings were noted including focal collapse with prominent bile duct proliferation to massive hepatic necrosis with complete loss of hepatic architecture. The hepatitis A viral infection was documented by the presence of serum hepatitis A virus IgM.

Drs. Mills and colleagues from the University of Virginia reported nine patients with small cell undifferentiated carcinoma of the colon. This aggressive neoplasm resulted in the death of all patients after 1-6 months. Five of the lesions arose in association with colonic adenomas. Histologically, the lesions resembled their pulmonary counterparts consisting of small-intermediate-sized cells with scant cytoplasm. Necrosis and vascular invasion were common. All of the lesions stained with antibodies to neuron-specific enolase and to epithelial membrane antigen. Seven of 8 lesions examined stained with antibodies to synaptophysin and 5 of 8 stained with antibody to chromogranin. The use of monoclonal antibodies to neuron-specific enolase, synaptophysin and chromogranin help distinguish this lesion from less aggressive poorly-differentiated non-neuroendocrine colon carcinomas.

Drs. Nakhleh and colleagues from the University of Minnesota describe the pathology of liver allografts in patients surviving beyond 1 year. From 33 patients, 12 had minimal non-specific changes including cholestasis, spotty necrosis and minimal lymphocytic infiltration. Four had manifestations of late acute rejection while two had vascular thromboses leading to ischemic changes. Three showed focal fibrosis, polymorphonuclear infiltration and bile ductular proliferation and another four had a picture of acute hepatitis. Eight patients had chronic persistent hepatitis pattern and three had the chronic active hepatitis picture.

From the Mallory Institute of Pathology, Drs. O'Keane and coworkers compared phenotypic markers in 15 pairs of villous and tubular adenomas which were matched for size and degree of dysplasia.. The monoclonal antibody LN3 correlated with villous morphology and antibody against secretory component stained mainly tubular morphology. CEA epitopes did not relate to growth pattern.

Drs. Omar and coworkers form New York Medical College and VA Hospital reported on Mallory bodies in alcoholic liver disease. The hepatocytes of alcoholics contain Mallory bodies which represent mainly degenerated cytokeratin filaments. Within these hepatocytes, heat-shock proteins tend to accumulate. They found that cells with Mallory bodies showed positive reactions for three heat-shock proteins: ubiquitin, HSP70 and HSP85.

Drs. Orenstein and coworkers from George Washington University Medical Center, St. Lukes-Roosevelt Hospital and New York University performed transmission electron microscopy to identify gastrointestinal microsporidiosis in individuals suffering from HIV infection. The Microsporidia infections were associated with focal degeneration and necrosis of enterocytes. They recommend Microsporidia be considered as possible etiologic agents of the diarrhea in patients with AIDS.

Drs. Olmstead and coworkers from he Cleveland Clinic Foundation describe the histologic findings in 10 cases of patients suffering from E. coli 0157:H7-associated colitis. All specimens from these patients contained hemorrhage and edema in the lamina propria. In addition, 67% had necrosis, hemorrhage and acute inflammation in the superficial mucosa with preservation of the deep crypts. This pattern was similar to injury seen with acute ischemic colitis. Small fibrin-platelet thrombi were occasionally seen within mucosal capillaries. In about half of the cases neutrophils infiltrated the lamina propria and crypts. These features resembled toxin-mediated epithelial injury.

From the University of Alberta, Drs. Pauw and colleagues studied the effects of two dideoxypurines in ducks infected with duck hepatitis B virus (a hepadnavirus related to human hepatitis B virus). They found that dideoxyadenosine was significantly toxic to the liver in infected ducks. In contrast, ducks receiving dideoxy-2,6-diaminopurine riboside showed a 50% reduction in the mean hepatic injury index after 24 days of treatment compared to ducks receiving placebo. These studies encourage interest in dideoxypurines as potential therapeutic agents for hepadnavirus infections.

From the University of Pennsylvania School of Medicine, Drs. Perez and colleagues reported on expression of neurofilaments in normal and neoplastic neuroendocrine cells of the gastrointestinal tract. Neurofilament immunoreactivity was only rarely detected in normal gastrointestinal tract and pancreatic neuroendocrine cells whereas chromogranin was always present. Expression of neurofilament subtypes appears to be related to tumor site and chromogranin is a more sensitive marker than neurofilaments for these cells.

Drs. Qizilbash and coworkers from Henderson General Hospital reported on a group of patients who underwent Roux-en-Y procedures for a diagnosis of reflux gastritis. Five of seven with previous biopsies had a reflux score greater than ten prior to surgery. In all five patients the relux score returned to normal following surgery.

Drs. Quinonez and coworkers from McMaster University reported that eosinophils in normal and nematode-infected rat intestine are in direct contact with p-type post-ganglionic axons. This close association between eosinophils and nerves were seen in both normal animals and rats infected with Nippostrongylus brasiliensis. One third of the eosinophils were found adjacent to nerves but separated by some collagen. Similar results were recorded for mast cells. These results suggest a microanatomical basis for "neuroimmunological" interactions in the gut mucosa.

Drs. Radaszkiewicz and coworkers from Vienna, Austria report a clinicopathologic study of 311 cases of primary malignant lymphoma of the gut-associated lymphoid tissue in adults. The major influences on survival were stage I and radical resectability. So-called "early lymphomas" confined to the mucosa and or submucosa showed an excellent prognosis and were mostly of the centrocytic-like variety. Clinically, these cells behave as localized tumors in most cases.

From The Ohio State University College of Medicine, Drs. Roberts and colleagues cultured human umbilical vein endothelial cells with three different human serum specimens which were positive for hepatitis e antigen. Using immunohistochemical stains for hepatitis surface and core antigen and techniques for hepatitis B DNA in situ hybridization, one of the

three cultures showed positive staining for both antigens and DNA, one showed rare positive cells for surface antigen and the third was negative.

Drs. Rogers and colleagues from Baylor College of Medicine and Texas Children's Hospital examined the PiZ alpha-1-antitrypsin gene in transgenic mice. Transgenic mice carrying multiple copies of the PiZ or the normal PiM gene were generated. They found that the PiZ transgenic mice had a significant increase in necrosis and inflammation compared to the normal mice. These findings support the concept that the presence of the Z gene is related to liver damage.

From the University of Texas M.D. Anderson Cancer Center, Drs. Robey-Cafferty and colleagues examined 61 stage B colonic adenocarcinomas for features which would correlate with prognosis. Rectal carcinomas were excluded from this study. Prognosis was correlated with the histologic grade of the tumor (80.8% 5 year survival in well and moderately differentiated versus 33.3% in poorly differentiated tumors). Mitoses, presence of vascular invasion and extracellular mucin did not correlate with survival. DNA ploidy did not correlate with survival. Further, no significant correlations were observed between ploidy and substage or histologic grade. Also from the University of Texas, Drs. Robey-Cafferty and co-workers describe the expression of the multidrug resistance gene in adenocarcinomas of the esophagus and stomach. This gene codes for a membrane protein which is normally expressed in some gastrointestinal epithelia and acts as an efflux pump for toxins and various oncolytic agents. They used a monoclonal antibody (C219) to detect the gene product. 42% of untreated stomach adenocarcinomas expressed this gene in both the tumor and adjacent gastric mucosa. Staining was observed on the luminal surface in a small supranuclear region (golgi?). 80% of Barrett esophagus stained and the tumor staining correlated with dysplastic and metaplastic regions. They conclude that expression of this gene may be indicative of nonresponsiveness of the tumor to chemotherapy.

Drs. Schofield and Yunis from the Children's Hospital of Pittsburgh reported on 447 consecutive acetylcholinesterase-stained rectal biopsy specimens in the diagnosis of Hirschsprung's disease. The stain was both sensitive and specific with no false positive or negative results. They conclude that this stain is a reliable diagnostic technique even in young children and in biopsies from the anorectal junction.

Drs. Schwartz and colleagues from the University of Pittsburgh described 12 cases of Herpes simplex hepatitis. 11 cases occurred in individuals having immunosuppression for organ transplantation, the other was a patient on hemodialysis. Histology showed either focal or diffuse coagulative necrosis with typical intranuclear inclusions. Four patients survived after a course of acyclovir therapy. Since the disease may be focal, it is recommended the biopsy be submitted for virologic cultures to rule out the diagnosis. Early diagnosis may be crucial for instituting acyclovir therapy.

From the University of Cincinnati, Drs. Selby and coworkers used an immunohistochemical technique to study the expression of low and high molecular weight cytokeratin antigens in normal and alcoholic livers. In normal liver, antibodies to high molecular weight keratins stained the bile duct epithelium. The plasma membrant of hepatocytes stained faintly with the same antibodies. In contrast, liver biopsies from alcoholic patients demonstrated moderate staining of hepatocytes and bile duct epithelium with a few Mallory bodies. In addition, antibodies to high molecular weight keratin diffusely stain hepatocyte cytoplasm, the bile duct epithelium and most Mallory bodies. This indicates that there is a parallel increase and aggregation of both high and low molecular weight keratins in alcoholic liver disease.

Drs. Sepulveda and colleagues from Baylor College of Medicine created transgenic mice using the human alpha-1-antitrypsin gene. They constructed a fusion gene with the 5^{1} end flanking region of alpha-1-antitrypsin driving the SV40 large T-antigen (a potent oncogene able

to transform any cell types). Of the 9 transgenic mice, three developed carcinoma of the stomach one with carcinoma of the pancreas and 8 developed hepatic neoplasms. This approach provides a new model system for the study of human cancer.

From the University of Maryland, Drs. Shamsuddin and coworkers looked at the relationship between dietary inositol hexaphosphate and inhibition of large intestinal cancer in F344 rats. Dietary use of this compound inhibited azocymethane-induced neoplasia in these animals. Even administration 5 months following the carcinoma significantly inhibited large intestinal cancer in rats. Since inositol hexaphosphate is non-toxic and is consumed through cereal diet, the authors recommend early clinical trials in humans.

Drs. Sheahan and coworkers from the Mallory Institute of Pathology examined enzymes in colorectal carcinomas and correlated them with the tumor development. They found the ratios of tumor to normal mucosa cathepsin B-like and L-like activities demonstrated a significant increase in protease levels in the tumor tissue for cathepsin B and cathepsin L while levels of cysteine protease inhibitor remained unchanged. No significant correlation was noted between cathepsin enzyme activity levels and mucinous or non-mucinous histologic subtypes. Patients with Dukes' A tumors had higher cathepsin B- and L-like activities than those with more advanced tumors.

From the City of Hope National Medical Center, Drs. Sheibani and colleagues found that tumor DNA content was the single most important prognostic parameter in resectable primary colorectal adenocarcinoma. They analyzed DNA ploidy of 147 patients with primary resectable colorectal carcinomas. Significantly increased rate of recurrent disease was demonstrated in patients with aneuploid tumors as opposed to diploid tumors (46.7% versus 4.8%).

Drs. Shulman and colleagues from Fred Hutchinson Cancer Research Center and Swedish Hospital Medical Center evaluated 13 transjugular liver biopsies on bone marrow transplant recipients in whom percutaneous biopsy was contraindicated. Quality of the samples ranged from multiple small distorted fragments to 0.5 cm fragments. All contain greater than 2 triads and 10 contained at least 2 central venules. One patient developed intraabdominal hemorrhage after the procedure. Six of the 13 biopsies yielded diagnoses not clinically available: graft versus host disease (2), cholestasis, herpes simplex infection, adenovirus infection and cytomegalovirus.

From the University for Sick Children and University of Toronto and University of Western Ontario, Drs. Silver and coworkers examined the iron and copper content in perinatal hemochromatosis. Normal liver iron was found to be 2.94 mg and 6.11 mg in infants with congenital hepatic fibrosis and galactosemia. In patients with perinatal hemochromatosis, the iron was found to be 5.24 mg. Clearly, no significant difference existed between the latter two groups for total iron. The same was true for copper. Since liver iron content was similar in perinatal hemochromatosis to controls with known portal hypertension or siderosis, they concluded that hepatic siderosis may prove to be an epiphenomenon in this disease.

Drs. Smyrk and colleagues from Creighton University reviewed the sensitivity and specificity of histological parameters in reflux esophagitis. For papillary height (% epithelial thickness) 65% was found to be the best combination of sensitivity and specificity. Isolated intraepithelial eosinophils were not specific, but specificity increased to 84% when greater than 5 ntraepithelial eosinophils per tissue section were seen. Balloon cells were a sensitive indicator being present in 82% of patients. A combination of four criteria: squamous hyperplasia, intraepithelial neutrophils, intraepithelial eosinophils, and balloon cell degeneration identified 97% of acid refluxers. Other injuries such as alkaline reflux and drug-induced injuries can produce similar pictures accounting for low specificity. Also from Creighton University, Drs. Smyrk and colleagues reported that balloon cells were an early finding in pill-induced injury to the esophagus. Six medications were studied: doxycycline, acetylsalicytlic acid , potassium

chloride, ascorbic acid, ibuprofen, and ferrous sulfate. There was thinning of squamous epithelium in rabbits after 60 minutes of exposure. Swollen, pale squamous cells developed in the stratum spinosum. The degree of balloon change was most significant for doxycycline, ascorbic acid and potassium chloride.

From McMaster University, Drs. Stead and colleagues studied human intestine to demonstrate the relationship between mast cells and nerves. 47-77% of mast cells were directly opposed to nerves in the intestine. The majority of mast cells were close to nerve fibers but separated by a 100-300 nm basal lamina. Numerous dilated axon-like profiles were found in membrane/membrane contact with the mast cells.

From the University of Nebraska Medical Center, Drs. Strobach and colleagues performed a study of 10 cases of regional enteritis, ulcerative colitis and normal colonic samples. They found that neuron specific enolase and S-100 were not useful to distinguish between normal tissues and those with inflammatory bowel disease. In contrast, synaptophysin had a unique staining pattern in 8 of 10 cases of both regional enteritis and ulcerative colitis. It showed delicate arborising nerve fibers in the lamina propria in areas of inflammation and areas that lacked typical features of IBD.

Drs. Talbert and co-workers from Massachusetts General Hospital evaluated 32 stromal tumors that had low mitotic rates (2-9 mitoses per 50 high power fields). They found that significant variables which would discriminate these tumors in terms of prognosis were size (> 6 cm), necrosis and cystification. The presence of 2 or 3 of the aggressive features greatly increased the chance of recurrence as opposed to 1 or 0 variables.

From Michael Reese Hospital, Drs. Swerdlow and co-workers reported on the hepatic extraction of IgA in experimental hepatic injury in rabbits. Animals were variously given ethanol, carbon tetrachloride, Shigella flexneri, or none of the above. After 2 years, all the rabbits that received alcohol or Shigella flexneri had increased levels serum IgA. When radiolabeled IgA was injected intraveinously, the groups receiving alcohol and carbon tetrachloride showed reduced biliary secretion. The authors feel that this indicates that the GI tract may serve as the origin for increased IgA in the portal vein. Alcohol and carbon tetrachloride reduces biliary secretion of IgA (hepatic extraction of IgA was noted only in the alcohol treated rabbits).

Drs. Thomas and Rotterdam from the NYU Medical Center used the Elastic Van Gieson stain to detect blood vessel invasions from 100 consecutive cases of adenocarcinoma of the colon. In 48 cases, blood vessel invasion was evident by Elastic stain whereas no or equivocal invasion was detected by examination of the H&E slides in 32 of those cases. They conclude that blood vessel invasion is frequently missed or impossible to recognize on routine sections and that Elastic stains would add significant information in almost one-third of cases.

From the Mount Sinai School of Medicine in New York and Tulane University School of Medicine in New Orleans, Drs. Thung and coworkers reported on cytokeratin expression in proliferating duct structures in liver disease. Immunohistochemical staining for cytokeratin of different molecular weights distinguished ductular structures from hepatocytes. Cytokeratin should serve as a useful marker for understanding mechanism of ductular proliferation and may help in the diagnosis of liver diseases.

Drs. Toner and colleagues from St. James's Hospital and Trinity College Medical School in Dublin, Ireland described ulceroinflammatory lesions occurring proximal to colonic obstructions. Perforation of acutely distended bowel mucosal pressure necrosis from impacted feces have been reported previously. Less well recognized lesion is termed obstructive colitis. They found that a segmant of normal mucosa always intervened proximally between the obstruction and the colitis. The colitis showed ulceration, granulation tissue, pseudopolyps,

cobblestone surface, frequent transmural inflammation and deep fissure ulcers. This lesion may have an ischemic pathogenesis.

Drs. Tuthill and colleagues from the Cleveland Clinic Foundation reported 3 patients with an intrahepatic destructive cholangiopathy which appears to be unique. None of the patients had antimitochondrial antibodies and cholangiography was unremarkable in all 3 patients. While they had portal inflammation and fibrosis, no granulomata or destructive duct lesions typical of primary biliary cirrhosis were seen. One patient improved on steroids although the gamma glutamyl transpeptidase remains elevated. The second patient died of heart failure and the third has Hodgkin's disease.

Drs. Washington and coworkers from Duke University determine the prevalence and histology of Campylobacter pylori gastritis in young ferrets. The microorganisms were identified with H&E and Warthin Starry stains. The bacteria were found in the stomach of 35 of 36 normal ferrets examined. Nor ulcers were seen. Chronic active gastritis was present in all animals with Campylobacter pylori. This infection is common in ferrets and is acquired at a young age (2-4 months).

From Yale University, Drs. West and colleagues examined the effects of the solvent dimethylformamide on the liver. In a group of 58 workers in plant using this chemical, 27 had elevated transaminases. 7 of these patients were biopsied. One was excluded because of possible non-A non-B hepatitis. The remainder showed slight lobular disarray, increased numbers of binucleate and multinucleate hepatocytes, anisocytosis, prominent mitoses, occasional acidophil bodies, and mild steatosis. This suggests that DMF acts as an intrinsic hepatotoxin. Histologically the appearances are, however subtle.

Drs. Wisecarver and coworkers from the University of Nebraska examined 5 patients who had undergone liver transplantation and had elevated plasma or whole blood level of cyclosporine A. Key features included Ito cell hyperplasia, intracellular and canalicular cholestasis, individual hepatocyte necrosis, chronic inflammatory cells in the portal regions and interlobular and septal bile ducts with swollen epithlial cells. These were found in cases where the whole blood levels of cyclosporine A were greater than 1,000 ng/ml.

From the University of British Columbia and University of Michigan, Drs. Wolber and colleagues described simultaneous small bowel and gastric biopsies from 10 patients with diarrhea or malabsorption who showed small bowel changes characteristic of sprue. Half of the patients had striking lymphocytic antral gastritis. A mean of 59.9 lymphocytes per 100 epithelial cells was seen compared to 4 in normal gastric controls and 5.7 in abnormal controls from individuals with Campylobacter gastritis. These features suggest that lymphocytic gastritis is a manifestation of sprue.

Drs. Younes and Morrow from Yale University examined the distribution of fodrin (a 474,000 heterodimeric protein found at cytoplasmic base of plasma membranes) in human colonic neoplasms. In adenocarcinomas of the colon, there was a 2-3 fold increase in the amount of this protein and a dramatic redistribution to the cytoplasm and the apical domain. These suggests that fodrin may be a marker of neoplastic activity.

Drs. Hoogstraten and coworkers from the Children's Hospital of Winnipeg, McMaster University Medical Center and Children's Hospital of Philadelphia examined a stillborn and two live siblings all of whom had evidence of liver disease. Diffuse hepatic fibrosis with cholestasis, cholangiolar proliferation, pseudoacinar and giant-cell change were seen as well as marked hepatic and extrahepatic siderosis which spared reticuloendothelial elements. These three met accepted criteria for neonatal hemochromatosis. Interestingly, the stillborn had giant-cell change but no siderosis. If these three siblings have the same disease, the sibship provides evidence that liver disease may precede siderosis in neonatal hemochromatosis. Interestingly, the mother had

chronic active hepatitis. Since neonatal hemochromatosis is phenotypically defined, it is likely to be a disorder of multiple etiologies.

From the Children's Hospital in Pittsburgh, Dr. Jaffe reported on the pathology of a multivisceral intestinal transplant. The child was a 3 1/2 year old girl with intestinal atresia who underwent en-bloc transplantation of stomach, small bowl, colon, pancreas and liver. She died at 6 months from Epstein-Barr virus related lymphoproliferative disease. Neither rejection nor graft-versus-host disease was documented. At autopsy, there were areas of mucosal atrophy and hyperplasia with diffuse submucosal fibrosis. The pancreas functioned well and had only focal microcystic ductular proliferation. The liver had bacterial cholangitis at day 11 and cholestasis with progressive hyperalimentation effect thereafter.

From the North Shore University Hospital, Drs. Kahn and coworkers described gastrointestinal tract pathology in biopsies from 34 children with AIDS. Necrotizing esophagitis was either nonspecific, or associated with Candida or CMV. Gastric ulcers and gastritis were occasionally seen. Lymphoid depletion was common in the small intestine and colon. Other microorganisms seen included M. avium-intracellulare, cryptosporidia, and Blastomyces hominis. The same authors also described hepatic pathology in 45 children with AIDS. In addition to the above microorganisms, they found P. carinii and other viruses including Herpes simplex. They found that the hepatopathology differs in biopsy and autopsy material. In biopsies, chronic active hepatitis predominates while at autopsy non-specific changes are seen.

Drs. Metzman and coworkers from Pennsylvania Hospital and Children's Hospital of Philadelphia described hepatic insufficiency with bile duct proliferation and marked periportal fibrosis due to intrauterine parvovirus B19 infection in a newborn premature infant. This virus is a known human pathogen which attacks principally pronormoblastic erythroid cells. The mother had a rash on her extremities which resolved within the 21st week of gestation. At the 26th week the child was born. The hydropic infant lived for 4 days. The liver was siderotic with marked extramedullary hematopoiesis. Intranuclear inclusions characteristic of this virus cytopathic effect were rare in necropsy material but were seen on review of the placenta.

Drs. Ruebner and coworkers from the University of California Davis Medical Center described the development and transformation of the human hepatocyte-ductal plate. They examined livers from 14 fetuses measuring from 0.5 cm to 21 cm in CR length. The smallest fetus did not have ductal plates or portal bile ducts. Ductal plate formation in the hilum was first seen in a 1.8 cm fetus. Multiple plates in the hilum were seen in the 2.5 cm fetus and an 8.0 cm fetus had plates throughout the liver. Portal bile ducts throughout much of the parenchyma was first seen at 15.0 cm. The ductal plates were now no longer continuous. There are two stages in transformation of hepatocytes to bile ducts. During the first, hepatocytes of the ductal plate are flattened and developed increased cytokeratin, while in the second, the flattened cells become focally cuboid or columnar, lose their biliary glycoprotein I, and become strongly positive for epithelial membrane antigen.

Drs. Schofield and Yunis from Children's Hospital of Pittsburgh explored the entity of neuronal intestinal dysplasia. To further define this entity, all acetylcholinesterase-stained rectal biopsies performed between 1981 and 1988. 34 of 410 children had biopsies which were characterized by increased staining with this enzyme and either increased numbers of ganglion cell clusters or abnormally large submucosal ganglia. Seven infants had a diagnosis of hypoplastic left colon, four of meconium plug, two with gastroschisis, one with small bowel stenosis, one with volvulus obstruction, one with transient ileus, two with necrotizing enterocolitis, one with hypothyroidism, and three with cow's milk allergy. The histologic finding of neuronal intestinal dysplasia as diagnosed by parasympathetic and routine histologic staining, is seen in a clinically and pathogenetically heterogeneous group.

Microvillus Inclusion Disease Register

Microvillus inclusion disease presents as intractable congenital diarrhea. Babies with this condition die unless they have total parenteral nutrition with special attention being paid to fluid balance. The disease may occur as an autosomal recessive, and a family history of infant death from diarrheal disease is a helpful pointer towards the diagnosis. Small intestinal biopsies show crypt hypoplastic villous atrophy with loss of brush border, and small PAS-positive inclusions may be seen on close examination of surface epithelial cells. Electron microscopy is diagnostic, showing loss or disorganization of apical microvilli, with vesicular inclusions lined by a well developed brush border, within the epithelial cell cytoplasm (see review by Cutz et al, NEJM 1989; 320:646-51).

We have established a register of cases of Microvillar Inclusion Disease in order to study its etiology and pattern of inheritance, and seek the assistance of fellow gastrointestinal pathologists in enrolling patients with this rare disorder. The most likely defect in microvillus inclusion disease is in synthesis, assembly or stabilization of the brush border. These processes are a major focus of interest of our brush border research group which comprises Drs. Jim Anderson, Mark Mooseker, Jon Morrow and myself, and we have begun to investigate this disease at both tissue and genomic levels.

Since many patients with MID die early, information about live patients is particularly valuable. If you know of such a case, I would greatly appreciate an urgent phone call: we need to obtain specially taken blood samples when possible, and if the opportunity arises, fresh intestinal tissue (biopsy or early post mortem) is extremely helpful. Patients who have died, and have been diagnosed either premortem or post-mortem, are of interest because of the familial nature of the disease and the possibility of obtaining autopsy tissue as well as blood samples from first degree relatives.

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