Gastrointestinal Pathology Society Newsletter
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Contents

Editor's Address - Winter 1992

In the January 1992 issue of Gastroenterology (102:360-361, 1992) there is an excellent editorial written by Cyrus E. Rubin, M.D. After reading this editorial, I thought I would take the liberty of using this article as a jumping off point for this GIPS's Newsletter editorial. The first 1/2 to 3/4 of the article talks about chronic gastritis (which all should read). I also highly recommend in the same issue the article on Grading and Classification of Chronic Gastritis by Correa and Yardley (102:355-359, 1992).

Dr. Rubin comments regarding gastritis - "a plague on all complex histological classifications!" He feels that a clinicopathological approach to the diagnosis of gastritis, integrating clinical, endoscopic, and histological findings is most helpful. I guess what Dr. Rubin is saying (and he does so later) is that the gastroenterologist can't practice his/her speciality without knowledge of pathology, nor can the pathologist practice his/her craft without knowledge of the clinical and endoscopic findings. To me this speaks to the concept of practicing GI pathology.

I was happy to read Dr. Rubin's editorial - because to me it talked about (or I interpreted it as such) what makes GI pathology fun, how we should practice it, and how patients benefit from these interactions. To me, sitting down across the multiheaded microscope with the clinician (gastroenterologist or GI surgeon) adds spice and life to the case in question. It provides an opportunity for me to learn and hopefully for me to teach GI pathology to my colleagues. Looking at x-rays is also helpful. For many years I was fortunate that our surgical pathology suite was adjacent to the GI endoscopy suite and I could pop in on a second's notice and appreciate the endoscopic findings as they related to the subsequent pathology slides. All the above talks about the practice of GI pathology as a dynamic entity (rather than a mysterious black box where tissues go into and reports are generated) - something which I think is great and makes GI pathology fun to practice.

In his editorial, Dr. Rubin asks the clinicians to provide more clinical history on request slips, "invite a pathologist to an endoscopy," and sit down across the double-head scope with the pathologist. I hope that the clinicians who read this editorial will take these recommendations to heart.

If so, they may also experience the fun, excitement, and gratification of close clinician-pathologist interaction.

Dr. Rubin ends with . . . . . "a holistic approach, integrating all clinical and histological data has the greatest probability of diagnosing a disease process and suggesting appropriate management of the patient "- Bravo!! and besides - it makes the practice of GI pathology fun and enjoyable.

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December 5, 1991

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Dear Harry:

I enjoyed your Editor's Address in the fall, 1991 issue of the Gastrointestinal Pathology Society Newsletter. I was particularly interested in the percentage of GI pathology articles in the various American anatomic pathology journals. I think, however, that you may have missed a major source of GI pathology journals - namely, gastroenterology and British and European anatomic pathology journals. Specifically, *Gastroenterology* tends to publish excellent GI pathology papers. I have no idea what the percentage of their total output represents pathology, but certainly some of the key pathology papers appear in this source. I also have the impression that there are many excellent GI pathology papers in the *Journal of Clinical Pathology* and in *Histopathology*, both British journals. If you can talk anyone into doing the same analysis on these journals, I would be curious as to the results.

Best wishes for a happy holiday season.

Sincerely yours,

Rodger

Rodger C. Haggitt, M.D.
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January 27, 1992

Dear Rodger:

Thank you for your letter of December 5, 1991 regarding my editorial in the fall 1991 GIPS newsletter. You are 100% correct in that there are excellent GI pathology papers in Gastroenterology and in the British publications, Journal of Clinical Pathology and Histopathology. I have found many important and seminal GI pathology articles in these publications. I would also like to add to the the list - Gut. This journal also has excellent GI pathology articles. For future editorials, I just might look at the major "gastrointestinal journals" (Gastroenterology, Gut, etc.) and see what percentage of their articles relate to gastrointestinal pathology. However, if any of the GIPS members wish to undertake such a project, please submit your findings to me and we will publish it in our newsletter.

With best regards.

Sincerely,

Harry S. Cooper, M.D.

UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

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

SPECIALTY CONFERENCE

HANDOUT

GASTROINTESTINAL PATHOLOGY

Tuesday, March 19, 1991 - 7:30 p.m.
Grand Ballroom A

Moderator:

DAVID A. OWEN
Vancouver General Hospital
Vancouver, BC

Panelists:

KATHERINE DeSCHRYVER, Case Western Reserve University, Cleveland, OH

BRYAN WEST, Yale University School of Medicine, New Haven, CT

HARVEY GOLDMAN, New England Deaconess Hospital, Boston, MA

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

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

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

USCAP, Chicago
Gastrointestinal Subspecialty Conference
Tuesday, March 19, 1991

Katherine DeSchryver, M.D.
Case Western Reserve University
Cleveland, Ohio

Case 1.

The patient is a 54 year old back male who presented with severe low back pain at an outside hospital and who was discovered to have multiple lytic lesions of pelvis, both femurs, as well as lumbar vertebrae. A biopsy of the femur showed metastatic adenocarcinoma. The lesion was negative for mucin or prostate specific antigen and prostatic acid phosphatase. The patient had multiple severe gastrointestinal bleeding episodes, and remained in unstable hemodynamic condition despite 25 units of blood transfused. Your section is from a 0.5 X 0.5 cm polypoid hemorrhagic nodule in the transverse colon.

Microscopic

The nodule consists of a highly vascular lesion mostly in the superficial submucosa also involving the deeper portion of the mucosa. Large pleomorphic tumor cells, form irregular intraluminal tufting collections, and are also seen in interstitial locations individually, in clusters and in cords. Tumor cells are extensively vacuolated. Mitotic figures are numerous.

The differential diagnosis includes metastatic carcinoma, metastatic melanoma, and some very rare entities such as gastrointestinal sinus histiocytosis (Osborne, et al., Am J. Surg. Pathol. 5:603-611, 1981) and a metastatic vessel-forming tumor such as hemangioendothelial sarcoma. Immunohistochemical stains were negative for monoclonal melanoma antigen and S-100 protein. Cytokeratin, Factor VIII-related antigen and Ulex europaeus I lectin positivity were seen.

This patient had multicentric malignant hemangioendothelial sarcoma of bone, metastatic to the transverse colon.

This case represents an extremely rare occurrence. The value of its presentation, however, lies in the timely topics involved in the diagnosis and differential diagnosis. These borderline malignant tumors are rare at all sites, but particularly rare in the gastrointestinal tract. A previous case report of epithelial hemangioendothelioma in the small intestine occurred following radiation therapy (1). Another case presented as a gastric polyp (2), and one as a malignant epithelioid hemangioendothelioma primary in the colon (3). At sites where these tumors are relatively more common such as bone and lung, they are regularly mistaken for epithelial neoplasms (4,5): in the lung this lesion was called intravascular broncho-alveolar tumor (IVBAT); in bone, in middle aged or elderly patients, metastatic carcinoma is statistically much more likely than vascular tumors, and the organoid pattern and vacuolated cytoplasm of tumor cells is not inconsistent with such a diagnosis. The major tool in the differential diagnosis of such cases is the immunohistochemical reactivity. In the present case, a cytokeratin positivity might have substantiated the diagnosis of metastatic carcinoma to the colon.

Recently, substantial interest focused on the histiocytoid endothelial phenotype expressed in reactive, borderline malignant, and frankly malignant lesions at the various organ sites(1,5,6,7,8). The conditions under which this phenotype is expressed as well as its biological significance remain to be elucidated (9,10). From a diagnostic point of view however, keratin positive non-epithelial benign and malignant neoplasms are increasingly recognized. The diagnostic immunocytochemical "battery" may now need to be expanded to routinely include endothelial markers as well...

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CASE 2 - Dr. A. B. West

DIAGNOSIS: Glomus tumor of the stomach

CASE HISTORY

A 75 year old man on hemodialysis for end-stage renal disease presented with hematemesis. On gastroscopy, an actively bleeding polypoid mass, 3 cm in diameter, was found on the lesser curvature of the proximal antrum. A hemigastrectomy was performed. The resection specimen contained this protuberant lesion, which was a well-circumscribed 3.5 cm tan rubbery to fleshy intramural tumor. The overlying mucosa was stretched and ulcerated. In addition, a separate mass of similar size and appearance was situated in the distal antrum, and several smaller tumor nodules were present in the perigastric fat. The slide is from the lesion in the proximal antrum.

The patient had an uneventful post-operative course, and at last follow-up (seven months after surgery) had no evidence of residual disease.

DISCUSSION

The differential diagnosis of hemorrhagic polypoid lesions of the stomach includes a number of benign non-neoplastic polyps, benign neoplasms of epithelial and stromal origin, and both primary and metastatic malignant neoplasms. The lesion seen here had gross features suggestive of an intramural proliferation, with a protuberant contour and bleeding from an area of ulceration near the apex.

The microscopic features of this lesion are typical of a glomus tumor [4]. It is composed of a predominantly solid mass of small uniform polygonal or round cells with scant, faintly eosinophilic cytoplasm and central nuclei. The nuclei are round or slightly ovoid, and contain stippled chromatin without prominent nucleoli. Mitoses are extremely rare. The cell borders are pronounced. The cells are arranged in solid masses, especially in the center of the lesion, and towards the periphery they are in characteristic intimate relationship with thin-walled, endothelial-lined dilated vascular channels. Areas of hyalinization are present, often around vessels. There is no tumor necrosis. The tumor is mainly located in the muscularis propria, and extends into the submucosa and adventitia. Though grossly circumscribed, microscopically it has a lobulated pattern at the margins and lacks a capsule. Tumor lobules surround and separate fascicles of the muscularis propria, and entrap nerves. The tumor cells express immunoreactive vimentin and alpha smooth muscle actin, but not desmin, keratins, factor VIII related antigen, chromogranin or neuron-specific enolase. The prominent cell borders are due to the presence of a basement membrane which surrounds each cell, as is evident in reticulin preparations and when immunostained for laminin or type IV collagen.

Gastric glomus tumors. Glomus tumors arise from the modified smooth muscle cells of the normally occurring glomus bodies [13], or differentiate towards their phenotype [12]. Ultrastructural and immunohistochemical studies confirm the smooth muscle differentiation of these tumor cells, though characteristically desmin is absent [11,15,17,18]. Glomus tumors are commonest in the skin and subcutaneous tissues, but have been reported in many other sites [7]. In the gastrointestinal tract they are rare: fewer than 100 cases have been reported in english-language journals, over 90% of which are from the stomach [4,11], where glomus bodies have also been observed [6]. Glomus tumors have rarely been reported from jejunum

[10], colon [5] and rectum [7]. Gastric glomus tumors are typically solitary and usually arise in the antrum. Presentation with gastrointestinal hemorrhage is common. They occur in adults of all ages, with equal sex distribution [11]. All reported cases are benign.

Microscopic differential diagnosis. The frozen section diagnosis of gastric glomus tumors can be difficult, and many are misidentified as lymphoma or carcinoid tumor. This distinction is important, however, since glomus tumors require only local excision [2]. In paraffin sections the uniform cells with prominent cytoplasm, sharply demarcated cell boundaries, and basement membrane permit differentiation from lymphoma, and the intimate association with vascular spaces and lack of an organoid growth pattern separates them from carcinoids. Immunostains for lymphocyte and carcinoid markers are negative. Although the relationship of the tumor cells to vessels may be similar to that seen in hemangiopericytoma, the cells are not usually spindled, are morphologically distinctive, lack mitoses and atypia, and express alpha smooth muscle actin [17]. Paraganglioma can usually be excluded by the absence of a nesting pattern, though when this is present sustentacular cells and evidence of neuroendocrine differentiation should be sought. In the skin, glomus tumors can occasionally be confused with carcinomas (usually adnexal), but this is rarely a problem in the stomach.

Differentiating glomus tumors from leiomyoblastomas (epithelioid leiomyomas, bizarre smooth muscle tumors) may be more difficult, and indeed it has been suggested that leiomyoblastomas represent an incompletely differentiated form of glomus tumor [3,4,16]. The presence of areas of transition to more typical spindle cell leiomyoma, the absence of an intimate relationship of the tumor cells to vascular structures, and desmin positivity are helpful in diagnosing leiomyoblastomas. Moreover, features suggestive of malignancy such as a high mitotic count, anaplasia and loss of basement membrane, are not usual in glomus tumors.

Aggressive glomus tumors. Glomus tumors are not known to metastasize, though sarcomatous transformation within them has been described rarely [1,7], and some lesions have been identified as glomangiosarcomas in the absence of non-sarcomatous glomus tumor elements [9]. In addition, some glomus tumors of the skin which exhibit no cytologic atypia have an infiltrative growth pattern and are termed "locally infiltrative glomus tumors" (LIGT), invading into skeletal muscle and around nerves [19]. These lesions, none of which has been reported from the stomach, have an increased liklihood of recurence.

Unusual features of this case.
Multiple glomus tumor nodules. There were two separate intramural tumors and four isolated tumors in the perigastric adipose tissue (none in lymph nodes), all of which were similar microscopically, raising the possibilities of multifocality and of metastatic spread. We are unaware of reports of multiple glomus tumors in the stomach, though in the skin this is a well-known phenomenon [8,14], and there seems to be no de facto reason why it should not occur in other tissues. However, in the skin this is usually seen in young patients (often children), it may be familial, and the lesions most commonly resemble cavernous hemangiomas.
Foci of cytologic atypia. Rare microscopic foci were observed where cells with epithelioid and signet ring features, reminiscent of those seen in leiomyoblastoma, merged imperceptably with typical glomus cells. Mitoses were present in increased numbers in these areas. These features, however, were not sufficient to warrant a diagnosis of sarcoma.
Local infiltration. Focally, typical glomus tumor cells surrounded and infiltrated nerves, and in one area such cells were present within the lumen of a vein.

These features are suggestive of overlapping differentiation of typical glomus tumor, LIGT and leiomyoblastoma, and give credence to the view that these entities may not always be separable. However, the predominant features of each lesion were those of a benign glomus tumor and we interpret this as a case of multiple glomus tumors of the stomach with infiltrative features and focal atypia.

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USCAP Subspecialty Conference 1991
Gastrointestinal Pathology

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Case 3

Specimen: Colonic polyp

Diagnosis: Mixed hyperplastic adenomatous polyp

Comment:

Hyperplastic (or metaplastic) polyps are the most commonly observed mucosal polyps in the human colon[1-6]. They occur in all parts of the colon and rectum, are typically small and barely elevated, are invariably sessile, and have a smooth surface. Most lesions are less than 5 mm in diameter and probably all are less than 1 cm. The histological features are characteristic, revealing a prominent papillary infolding of the epithelium (so-called serrated appearance), variable mucin production, an attenuated striated border similar to that seen in surface epithelial cells, and basal nuclei without atypism. Some polyps have a thickened collagen layer beneath the epithelium like that observed in collagenous colitis. It is thought that the polyps develop by a hyperplasia or persistent maturation of the upper crypt and surface epithelial cells; these cells fail to shed, and the papillary infoldings represent an accommodation to the excess growth. The polyps are frequently multiple, and rare cases of polyposis have been described[7]. The vast majority of hyperplastic polyps either persist as such or spontaneously resolve, the latter supported by the lack of an observed increase in prevalence with age. Their detection in older patients, however, may be a marker that the patient has other more significant polyps such as adenomas in the colon.

Foci of adenomatous change and rarely of adenocarcinoma have been observed in hyperplastic polyps, particularly in larger lesions[2,6,8-10]. It is probable that these cases originated as hyperplastic polyps and developed the neoplastic change, there being no reason to suppose that the polyps are immune from the transformation. In such instances, the possibility of a collison of two separate lesions should also be considered. Mixed hyperplastic adenomatous polyps (or serrated adenomas) essentially represent adenomas with an architectural pattern of prominent papillary infoldings of the epithelial cells into the glandular lumina[10-12]. The basic adenomatous nature is revealed by the evident dysplasia of the epithelial cells, consisting of elongated and pallisading nuclei with variable hyperchromatism and loss of polarity. These cytological features are identical to those seen in ordinary adenomas, including both the villous and tubular forms, without the hyperplastic growth pattern. Compared to the simple hyperplastic polyps, the mixed lesions reveal a more convoluted surface and are generally larger with most greater than 1 cm in diameter[2,11]. Like other adenomas, they can develop carcinoma.

The mixed polyps are relatively rare, with only 110 lesions (0.6%) noted in one series of 18,000 colonic polyps examined[11]. It is not known whether the mixed polyps develop from preexisting hyperplastic lesions or if the hyperplastic and neoplastic features are a consequence of separate and independent processes. Of interest, some examples of dysplastic epithelium in cases of ulcerative colitis also disclose a serrated growth pattern[13]. At

a practical level, if biopsies of a polypoid lesion larger than 1 cm reveal hyperplastic glands, it is important to look for signs of nuclear atypism, and if they are absent, additional samples should be sought to exclude an adenoma or even a carcinoma[14].

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CASE 4

TUBULAR CARCINOIDS OF THE APPENDIX

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The tubular carcinoid is a distinctive lesion, essentially limited to the appendix. Despite being considered a form of adenocarcinoid, its indolent behavior sets it apart from the other adenocarcinoid, the goblet cell type.

The tubular carcinoid typically occurs as a nodule at the tip of the appendix. The cells are arranged as short tubules and trabeculae, the former with narrow lumens containing mucin, set haphazardly in a fibrous stroma. They appear to arise in the crypt base region of the mucosa and submucosa extending into the muscularis propria.

They react strongly for glucagon, neuron specific enolase, CEA and cytokeratin (AE1/3); weakly and variably for chromogranin and argyrophilia; and are typically serotonin and argentaffin negative. This is in contrast to the usual insular carcinoid which is argentaffin, strongly positive for serotonin and negative for CEA and glucagon.

Goblet cell carcinoids share the strong reactivity for CEA and cytokeratin but contain scattered argentaffin and serotonin positive cells. Small numbers of glucagon positive tubular elements may occur in otherwise typical goblet cell carcinoids and a rare goblet cell component may be found in some tubular carcinoids. This suggests a relationship between the two. However, their growth patterns and behavior are distinct: the tubular carcinoid occurs as a nodule; the goblet cell form grows in a diffuse, linear, often concentric, manner without forming a distinct tumor; goblet cell carcinoids may transform into carcinomas; tubular carcinoids do not appear to share this tendency. Unlike goblet cell carcinoids, which have a behavior somewhere between the usual carcinoid and adenocarcinoma, the tubular carcinoid has, in our experience, invariably been cured by simple appendectomy.

Appendiceal tubular carcinoids present at a younger age than do other appendiceal carcinoids: their average is 32 years compared with 45 for the typical insular variety, 53 for the goblet cell type and 68 for mixed carcinoid-adenocarcinomas (AFIP data). (The average age of patients with gastrointestinal carcinoids is 54 years).

Tubular carcinoids have been grouped with the goblet cell variety as adenocarcinoids. Although a histogenetic relation between the two is possible, they are clinically distinct entities. The tubular carcinoid contains mucin and CEA and is nonargentaffin, features which suggest a more aggressive lesion; however, they are as indolent as the usual, appendiceal insular variety.

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MULTIPLE LYMPHOMATOUS POLYPOSIS OF THE GI TRACT

Case 5 - Dr. D. G. Sheahan, University of Pittsburgh

This lesion was first described by Cornes in 1961 and is distinctly rare as described in recent reviews (Shepherd et al 1988) (O'Briain et al 1989) and in one series it constituted less than 3% of gastrointestinal lymphomas (Lewin et al 1978).

There were five reports purporting to describe the entity between 1961 and 1970 but the descriptions were of heterogeneous types of lymphoma. Beginning in 1971 (Sheahan et al) and including the latest (O'Briain et al 1989) there were 20 reports, 17 of which described 35 cases as an apparent distinct clinicopathological entity. It occurs world wide, usually in older men (88% men; mean 61 years). Symptoms include fatigue, weight loss, diarrhea melena with or without blood in stools was present in 79% of patients. Protein losing enteropathy was documented in four patients and malabsorption was noted only in two patients both of whom were from Israel.

Histologically all cases were non Hodgkin's lymphoma composed of small lymphoid cells. Various descriptive terms including lymphocytic lymphoma, centrocytic lymphoma, mantle zone lymphoma, and small cleaved cell lymphoma have been applied, but in general their descriptive appearance would indicate a histological low grade lymphoma. The pattern also varied being described as diffuse, nodular or of mantle zone type. The nodules were composed of lymphoid elements infiltrating the mucosa and submucosa and occasionally became confluent. Lymphoepithelial lesions were uncommon. Multiple lymphomatous polyposis shares many features of mantle zone (intermediate lymphocytic or centrocytic) lymphoma except for its predilection for the gastrointestinal tract and poorer survival rate.

Prognosis is generally poor. Some patients have demonstrated a short term response to chemotherapy. Survival of 19 patients for whom wuch information is available indicates that 11 died between six months and five years after diagnosis (only one survived more than 3 years), with mean survival of 20 months and eight were alive between six and 34 months after diagnosis.

Immunohistochemical studies have shown all 16 cases studied to date to be of B cell lineage with immunoglobulin MD or M and light chain restriction. Pan-B-cell (CD20) and HLA-DR monoclonal antibody staining is positive but CD5 and CD10 are apparently variably expressed.

The present case extends this information by being the first case of multiple lymphomatous polyposis in which gene rearrangement studies have been performed. The B cell lineage demonstrated immunophenotypically is confirmed by the same clonal rearrangement of the heavy chain gene in all biopsies from each of nine separate polypoid lesions. The T-cell rearrangement was germline.

The bcl-2 gene rearrangement which represents a t (14:18) chromosomal translocation is the most frequent karyotypic abnormality in follicular center cell lymphoma. This form of gene rearrangement is not found in mucosa associated lymphoid term (MALT) B cell lymphomas (Pan et al 1989) suggesting that these two forms of B cell lymphoma are genetically different.

Origin of these and perhaps also other MALT lymphomas from the mantle zone of lymphoid aggregates has been suggested.

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USCAP GI Speciality Conference
March 19, 1991
Case # 6

ALLERGIC PROCTOCOLITIS

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Allergic proctocolitis is a distinctive form of colitis that occurs in infants. It represents an example of gastrointestinal food sensitivity, presumably produced by an immunologic reaction to dietary proteins. Although the exact nature of the reaction is unknown, abnormal development of tolerance to ingested antigens is likely at fault. The inciting antigens are those commonly encountered by infants: cow's milk or soy formula proteins. Some solely breast-fed infants have also been affected, possibly because breast milk may contain foreign food proteins ingested by the mother. Sensitivity to these proteins is usually transient, and most infants are able to ingest the offending foods after the age of two or three years.

Symptoms begin shortly after the foreign protein is introduced, so that allergic proctocolitis usually presents within the first few months of life. Rectal bleeding, with or without diarrhea, is the dominant manifestation; other symptoms -- vomiting, abdominal pain, weight loss, or fever -- are less common. In some patients, a family history of allergy or mild peripheral eosinophilia is noted.

Endoscopic examination usually shows mild nonspecific abnormalities (erythema, friability, and loss of normal vascular pattern), but superficial ulcerations may be found with more severe disease. These changes are well-described in the rectum and sigmoid colon, and have been commonly identified in the more proximal colon at colonoscopy. The small bowel is infrequently involved, and such symptoms as malabsorption are accordingly uncommon.

Mucosal biopsies vary in appearance from normal to active colitis with ulceration, but are usually characterized by prominent eosinophil infiltrates. Eosinophils are diffusely scattered within the lamina propria and focally invade the surface or crypt epithelium, at times forming eosinophilic crypt abscesses. When mucosal erosion is present, neutrophils and marked epithelial damage may be superimposed on the eosinophilia. The architecture is usually maintained, although some long-standing cases have shown changes of chronic colitis -- crypt branching and fibrosis of the lamina propria.

The histologic differential diagnosis centers on mucosal eosinophilia. Eosinophils are, of course, present in varying numbers in normal colonic mucosa, and may rarely be found among the epithelial cells. Conversely, eosinophils may be increased in conditions other than allergic proctocolitis. Specific criteria that distinguish allergic disease are needed, and several have been suggested. The number of eosinophils exceeds 60 per 10 high power fields in most cases of allergic proctocolitis; lesser numbers are not diagnostic. In addition, the finding of eosinophils in the muscularis mucosae or invading the epithelium in more than rare numbers

also supports an allergic diagnosis. These changes are often focal and may require multiple levels for demonstration.

Mucosal eosinophilia also raises the question of eosinophilic gastroenteritis, another putatively allergic GI condition. This disorder primarily affects the upper GI tract -- although the colon can be involved -- and affected patients are often older and have other evidence of allergy including marked peripheral eosinophilia and elevated serum IgE levels. Multiple food allergies are the rule, but dietary changes are usually not effective therapy.

The diagnosis of allergic proctocolitis rests upon an appropriate clinical setting, exclusion of other causes of colitis such as infections, and consistent biopsy findings. The symptoms promptly remit once the responsible agent is identified and removed from the diet. The diagnosis is best confirmed by documenting a recurrence with dietary rechallenge, but this is often not done. Treatment consists of an elimination diet, which may require a hydrolyzed protein formula; the offending food can usually be successfully reintroduced later, presumably once normal colonic tolerance of antigens has developed.

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~ Gastrointestinal Pathology Society
USCAP Companion Meeting
Sunday, March 15, 1992
Preliminary Program

Colitis

"Many shall run to and fro, and knowledge shall be increased."

Daniel 12:4

Robert R. Pascal, M.D. - Moderator:

1:30	Distinguishing Between Inflammatory Bowel Disease and Other Types of Colitis.	Harvey Goldman
2:00	Acute Versus Chronic Colitis.	Henry Appelman
2:30	Granulomatous Inflammation of the Colon.	Rodger Haggitt
3:00	The Association of Mycobacteria with Inflammatory Bowel Disease.	David Graham
3:30	The Mucosa-associated Immune System and Inflammatory Bowel Disease.	David Keren
4:00	Complications of Inflammatory Bowel Disease (Excluding Carcinoma and Dysplasia)	Robert Petras

GI Pathology Society
USCAP Meeting
March 15, 1992

DISTINGUISHING BETWEEN INFLAMMATORY BOWEL DISEASE and OTHER TYPES of COLITIS

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New England Deaconess Hospital and Harvard Medical School

I. DEFINITIONS

Idiopathic inflammatory bowel disease (IBD) consists of two principle conditions, ulcerative colitis (UC) and Crohn's disease (CD). These disorders are characterized by a lack of known etiology and pathogenesis, by chronicity, and by inflammatory and destructive lesions of the gut. Their diagnosis depends on the exclusion of other diseases with a specific etiology (such as infections, ischemia and mechanical conditions) and of other disorders with distinctive clinical and morphological features (such as collagenous and lymphocytic colitis).

II. GENERAL PATHOLOGICAL FEATURES

Lacking knowledge of a specific cause, both UC and CD are best defined by a combination of clinical and structural alterations, including the distribution of the disease and both gross and microscopic features[1-5].

A. Ulcerative Colitis

There is a diffuse involvement of the rectum and of a variable amount of the colon ranging from disease limited to the left side to that affecting the entire colon. The lesions are confined to the large intestine and appendix. The distal ileum may reveal dilatation and increased inflammatory cells (so-called "backwash ileitis") but lacks ulcerations, and other parts of the gut are not affected. The disorder is characterized by ulcerations and inflammatory pseudopolyps that are usually limited to the mucosa and submucosa. Deeper ulcers and serosal inflammation are seen in about one-third of the more severe cases that require surgery. The histological features are entirely non-specific. The diagnosis depends on the finding of ALL of the following features: diffuse disease that is limited to the large intestine; the absence of a normal rectum or other skip areas, except for the right side of the colon; no mural fissures or sinus tracts; and the lack of granulomas, excluding those related to foreign material or to ruptured crypts.

B. Crohn's Disease

This disorder can affect any part of the alimentary tract with lesions most commonly noted in the small intestine and colon. Characteristic features include the frequent occurrence of skip lesions, the presence of mural sinus tracts and fistulae, a prominent serosal inflammation even in areas with relatively superficial ulceration, and the early development of strictures. Granulomas are noted in about one-half of the cases and can be seen in any part of the bowel wall and both in areas of ulceration and in normal tissue. Other prominent findings, but less specific, include pronounced lymphoid nodules, lymphatic dilation and proliferation of neural elements within the bowel wall.

It should be emphasized, however, that none of these features is present in every case of Crohn's disease. For example, relatively superficial disease is seen in about 20% of the patients. When the disease is confined to the colon, it is distinguished from ulcerative colitis by the demonstration of ANY one or more of the following: a normal rectum (50%) or other sign of focal disease, either as a gross skip area or microscopically (90%); the presence of gross sinus tracts (one-third) or microscopic mural fissures (two-thirds); or the appearance of granulomas that do not have a ready cause such as a reaction to a ruptured crypt or foreign material (50%).

C. Indeterminant Colitis

This term has been used for cases of idiopathic IBD involving the colon in which the criteria for UC or CD are not entirely clear or conclusive[2,6,7]. It is most often employed before there is complete information about the distribution of the disease and there is no operative specimen to evaluate. Although it has been claimed that 10% of colonic IBD may be indeterminant, this is probably overstated and due to an unwillingness to accept some of the criteria used. Examples include cases with superficial disease that reveal a normal rectum or other skip areas but lack other features of CD, cases with diffuse disease resembling UC that have granulomas, and cases with gross suggestions of skip areas but which show microscopic inflammation. By the proper application of the criteria, it is probable that the great majority of the cases can be designated as either UC or CD.

III. SELECTED COMPLICATIONS[5]

A. Post-Surgical Ileal Abnormalities

Non-specific lesions including focal ulcers develop in about 5% of ileostomy segments in patients with either UC or CD[2,5,8,9]. These are mainly due to infections, vascular or mechanical problems and are corrected, if persistent, by surgical revision. A greater frequency is noted in the Kock's continent ileostomy. These effects are ordinarily distinguished from recurrent CD by the presence of dilation rather than stenosis of the segment, the absence of sinus tracts away from the stoma, and the relatively superficial nature of the lesions. Similar lesions are being noted in cases with ileoanal pouches, and the cause and significance of this pouchitis needs further clarification[10,11].

B. Diversion Colitis

Following enterostomy or colostomy, the distal diverted segment of gut frequently develops inflammatory changes that can simulate IBD. The pathologic features are non-specific and are eliminated by reanastomosis of the gut.

C. Dysplasia and Carcinoma

Patients with long standing and extensive IBD, particularly UC, have an increased incidence of intestinal carcinomas, and the tumors develop, on the average, about 10 years earlier than in persons without chronic colitis[12]. In an effort to detect early lesions or to prevent them, while preserving the intestine as long as possible, surveillance endoscopy and biopsy have been employed to look for epithelial dysplasia. Specific criteria have been developed, and the finding of high grade dysplasia which is confirmed can serve as a marker to decide which patients should be considered for a prophylactic colectomy[13,14].

IV. USES OF ENDOSCOPY and MUCOSAL BIOPSY

There are multiple reasons for endoscopic examination and mucosal biopsy in patients with UC and CD[15-21]. These should be provided in the requisition forms so that the particular questions can be addressed in the pathological reports. The pertinent clinical data and results of the gross endoscopic examination should be included to ensure the optimum interpretation.

1. Identification of colitis or enteritis
2. Exclusion of other specific disorders
3. Distinction between acute self-limited and chronic colitis
4. Separation of ulcerative colitis and Crohn's disease
5. Determination of severity and extent of disease
6. Monitoring the course following therapy
7. Detection of dysplasia and carcinoma

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ACUTE VERSUS CHRONIC COLITIS: THE DIFFERENTIAL DIAGNOSIS OF THE ACUTELY PRESENTING COLITIDES

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Definitions

Acute colitides have a sudden onset of symptoms, usually explosive diarrhea , bright red rectal bleeding or both, and which resolve rapidly, generally with complete or almost complete healing. In general, these colitides are self-limited; they resolve spontaneously. These colitides include

1. Acute Self-Limited or Infectious Colitis [ASLC]
2. Clostridium difficile induced Pseudomembranous Colitis [PMC]
3. Acute Hemorrhagic Colitis due to Verotoxin-producing E. coli
4. Acute Hemorrhagic Colitis secondary to Ischemia
5. Other and Miscellaneous, possibly including allergic colitis of infants

Chronic colitides may first present or exacerbate in the same explosive fashion as the acute forms. Those flares of clinical activity may resolve either spontaneously or with medical help. The chronic colitides last for months to years, and when their exacerbations resolve, they leave profound architectural residuals, either in the colonic mucosa, deeper in the colonic wall or in both places. Chronic colitides which have acute colitis-like exacerbations include

1. Ulcerative Colitis [UC]: by far the most common.
2. Crohn's Colitis [CC]: much less likely to present or exacerbate acutely

The role of the pathologist in the diagnosis of these conditions:

Most cases of colitis will be easily diagnosed by clinical and endoscopic findings. In such cases, biopsies are only needed for documentation, mainly to determine if the process is one of the chronic colitides. There are 4 situations when some of the acute and chronic colitides may cause grief to clinician and pathologist:

1. Acute onset of bloody diarrhea, no past history of colitis, endoscopically severe extensive disease: colitides,particularly ASLC and UC, the endoscopic appearances may overlap so much that they can be indistinguishable.
2. Acute onset of bloody diarrhea about a week ago, now subsided, with endoscopic focal disease: the differentiation between healing ASLC and CC. In the later stages of ASLC, the endoscopic changes may be focal, thus mimicking Crohn's disease.
3. Acute onset of bleeding without diarrhea and an endoscopic right-sided segment of hemorrhagic mucosa: the differentiation between acute ischemic damage and verotoxin E. coli colitis.
4. Acute onset of diarrhea, often in debilitated elderly patients on antibiotics with endoscopic pseudomembranes detected during a limited exam: the differentiation between C. difficile PMC and acute ischemia with pseudomembranes.

If the presentations and endoscopic findings can be the same for for all these situations, then the pathologist serves no helpful role by offering a differential diagnosis which is already obvious. The pathologist is responsible either for making the final diagnosis or for admitting that the final diagnosis cannot be made histologically. However, diagnosis is always easier and better when the pathologist knows the clinical and endoscopic findings. Not a lot of information is needed. We want to know the type of sypmtoms and their duration, whether there was documented colitis in the past and what kind, and the clinical impression. Any clinician who does not share this data with the pathologist at the time the biopsy is submitted should be assaulted with a deadly weapon.

There are two sets of morphologic expressions of acutely presenting colitides, the changes of chronicity and the changes of activity.

CHANGES OF CHRONICITY
1. Architectural Abnormalities [Distortion]
   a. loss of crypts [atrophy]
   b. variation in crypt size and shape
   c. villiform surface
2. Inflammatory Abnormalities
   a. plasmacytosis / eosinphilia in the lamina propria
   b. lymphoid hyperplasia
   c. granulomas
3. Chronic ulcers: granulation tissue and scar at the base

CHANGES OF ACTIVITY
1. acute mucosal necrosis, involving surface epithelium through full thickness +/- hemmorhage
2. neutrophilic cryptitis [neutrophils in crypt epithelium] +/- destruction [ulcers and abscesses]
3. neutrophilia in the lamina propria
4. exudate on the surface: fibrin, neutrophils, mucus, and necrotic debris in unpredictable proportions.

Optimally, the acute colitides will have changes of activity and no changes of chronicity. The chronic colitides wil have some of the changes of chronicity PLUS some of the changes of activity. Unfortunately, as these diseases heal, they can change from diffuse to focal, both endoscopically and microscopically. They are best diagnosed during their peak phases which last only a few days after the onset of symptoms.

Why is it important to diagnose these diseases during the active phases, if the acute colitides resolve quickly and spontaneously?

1. It is important to know if the disease is an active phase of a chronic colitis, especially ulcerative colitis, so that emergent treatment with high dose steroids may be used if the disease becomes very severe clinically.

2. Theoretically, it should be important to know if the process is one of the infectious diseases, in order to institute antibiotic therapy, but that is only important in C. difficile induced PMC. The other acute colitices usually resolve with no treatment.

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GRAULOMATOUS INFLAMMATION OF THE COLON

GASTROINTESTINAL PATHOLOGY SOCIETY
March 15, 1992

Rodger C. Haggitt, M.D.

Definition: A granuloma is defined as a compact, organized collection of mature mononuclear phagocytes.[1] Granulomas develop in three stages: infiltration of young mononuclear phagocytes, maturation and aggregation of these cells into a mature granuloma and the potential further maturation into an epithelioid granuloma.[1] The lesion is not a true granuloma until it reaches the second stage in this evolutionary sequence, i.e., when the mononuclear phagocytes aggregate into a compact mass. Typically, this second stage produces a rather ill-defined aggregate of phagocytes that might appropriately be called a focus of "granulomatous inflammation" to distinguish it from an epithelioid granuloma in which the phagocytes take on an epithelioid appearance (abundant cytoplasm, elongated ovoid nuclei) and produce a more discrete lesion.

Etiology: Granulomas may be initiated by immunologic mechanisms, by activation of chemical mediators of inflammation or directly by toxic substances.[9] The precise mechanism involved in the pathogenesis of many granulomatous disorders is not completely understood. I have classified them based on their etiology, as shown in Table 1. Careful histologic examination of the granulomas, including the use of polarized light and special stains, sometimes permits identification of the etiologic agent and allows a specific diagnosis. Most often, the appearance of the granuloma is non-specific and provides no clue to the etiology of the process. In such cases, secondary features such as necrosis or the pattern of inflammation may suggest that a certain diagnosis is more likely than another. Since the diagnosis of many granulomatous diseases depends on a combination of clinical

and pathologic data, all the available information in a given case should be considered prior to establishing the final diagnosis.

Table 1: ETIOLOGIC CLASSIFICATION OF GI GRANULOMATOUS DISEASES

- Infectious granulomas
  - Chlamydiae
  - Bacteria
    - Campylobacter/Salmonella
    - Mycobacteria
    - Syphilis
    - Yersinosis
  - Fungi
    - Paracoccidioidomycosis
    - Histoplasmosis
    - Cryptococcosis
    - Phycomycosis
  - Parasites
    - Schistosomiasis
    - Anisakiasis
- Foreign body granulomas
  - Exogenous foreign bodies
    - Food and fecal granuloma
    - Barium granuloma
    - Oil granuloma (sclerosing lipogranuloma) of the rectum
    - Suture granuloma
    - Talc granuloma
    - Starch granuloma
    - Mercury granuloma
  - Endogenous foreign bodies
    - Mucin granuloma
    - Pneumatosis cystoides intestinalis
- Granulomatous diseases of unknown etiology
  - Crohn's disease
  - Sarcoidosis
  - Granulomatous vasculitides
- Miscellaneous
  - Chronic granulomatous disease of childhood
  - Granulomatous reaction to carcinoma
  - Others

From reference 4.

Structures that may be confused with granulomas: Various tissues structures may be mistaken for granulomas.[4] These include ganglia and nerve trunks in the submucosa and muscularis propria of the gut wall, especially when an inflammatory infiltrate surrounds them. Tangential or oblique sections through the edges of crypts may pass through the pericryptal fibroblast sheath yielding an appearance that resembles granulomatous inflammation; examination of adjacent sections usually resolves the problem. Aggregates of muciphages may be mistaken for a small granuloma. Muciphages are so frequently identified in otherwise normal mucosa that their appearance has to be considered normal. However, large numbers of muciphages suggests that there may have been a previous episode of inflammation with release of mucin into the lamina propria from injured crypts. Focal, nodular hyperplasia of the smooth muscle cells of the muscularis mucosae, as commonly seen in idiopathic inflammatory bowel disease, may resemble a small granuloma. A trichrome stain reveals the smooth muscle nature of the nodule. "Epithelioid" germinal centers are easily mistaken for granulomas, especially if they occur in inflammatory bowel disease. The cells within the germinal center resembling epithelioid histiocytes are dendritic reticulum cells and appear to result from anomalous natural killer cell activation with destruction of the B-cells within the follicular center.[7] Epithelioid germinal centers characteristically occur in children dying from overwhelming infections, but may also be seen in adults and not always in the context of a fatal illness.

Infectious Granulomas

Since you are quite familiar with infectious granulomas, I will not dwell on them here except to point out a few diagnostic problems. Chlamydiae, specifically *Chlamydia trachomatis*, must be considered in the differential diagnosis of granulomatous inflammatory lesions in the rectum. This organism does not characteristically produce discrete, epithelioid granulomas, but may occasionally do so. Several of the reports of this

organism eliciting granulomas have illustrated structures that appear to be mucin granulomas (see below). Infections with the enteric pathogens *Campylobacter jejuni* and various Salmonellae produce the histologic appearance of an acute self-limited colitis. Not infrequently, these organisms stimulate macrophages to aggregate and form foci of granulomatous inflammation. Discrete, epithelioid granulomas are not, however, seen with these infections. Infections with *Mycobacterium tuberculosis* typically result in the production of numerous, large, epithelioid granulomas with central necrosis and multiple giant cells that contain large numbers of nuclei. *Mycobacterium avium* usually elicits a diffuse proliferation of macrophages, but may on occasion form foci of granulomatous inflammation or discrete granulomas. Inflammation produced by *Yersinia enterocolitica* is typically a necrotizing process with microabscesses involving lymph nodes or lymphoid tissues of the bowel wall; mononuclear phagocytes are prominent components of the infiltrate, particularly around the edges of the microabscesses, but discrete granulomas are not found in the usual case.[3] In contrast, *Yersinia pseudotuberculosis* infections may produce discrete epithelioid granulomas with central necrosis. Table 2 provides data concerning the various fungal infections that involve the GI tract.

Table 2: FUNGAL INFECTIONS AFFECTING THE GASTROINTESTINAL TRACT

Disease	Granulomatous inflammation	Gastrointestinal involvement	
		Primary	Secondary
Paracoccidioidomycosis	Yes	Yes, ?frequency	Common
Histoplasmosis	Yes	Very rare	Common
Cryptococcosis	Yes	Very rare	Rare
Phycomycosis	Rarely	Yes	Yes
Candidiasis	No	Yes	Yes
Aspergillosis	No	Yes	Yes
Actinomycosis	No	Yes	No

From reference 4.

Foreign Body Granulomas

Foreign body granulomas in the gastrointestinal tract can be divided into two types, those arising endogenously from native sources, and those secondary to the ingestion or mechanical introduction of foreign material. Granulomas of both types are characterized by aggregates of mature macrophages which in some, but not all instances, developed into compact nodules. Epithelioid granulomas rarely develop as a result of foreign material. In the exogenous foreign body granulomas, recognition of the foreign body, such as barium,[6] is the key feature in establishing the diagnosis. Polarized light often discloses foreign substances that are otherwise inconspicuous, and its use as a routine procedure in investigating granulomas increases the yield of those recognizable as being of this type. See reference 4 for a description of foreign body granulomas.

Endogenous foreign body granulomas: The most important endogenous foreign body granuloma is the mucin granuloma induced by the release of mucin and luminal contents into the lamina propria secondary to rupture of crypts. These granulomas contain mucus that gives a positive reaction with PAS and Alcian blue early in their course, but the mucus later becomes organized and may not be recognizable. Mucin granulomas are identified by noting their relationship to injured crypts, their predominance of foreign body giant cells and by their content of stainable mucin, if present. They are usually small, less than the size of a crypt, but occasionally may reach relatively large proportions. Tangential sections through the edges of larger mucin granulomas may be indistinguishable from the granulomas of Crohn's disease; inspection of serial sections of such a lesion usually permits the correct diagnosis. Mucin granulomas may be seen in adenomas, diverticulitis, ulcerative colitis, Crohn's disease and in the mucosa overlying submucosal lesions. Since extracellular mucus in the colonic mucosa does not always elicit a granulomatous inflammatory response, as for example, with the extracellular mucin produced by

carcinomas, one wonders why mucin granulomas occur. Perhaps communication with the colonic lumin is an essential element in their pathogenesis.

Pneumatosis intestinalis is a condition in which gas is present within the bowel wall. This may be the result of infection with gas-producing bacteria, secondary to endoscopy (where gas in the lumin under pressure enters the mucosa secondary to the trauma of the procedure) and in a group of patients with various diseases, particularly chronic pulmonary disease and peptic ulcer, in which it forms cysts with a granulomatous lining. Such granulomatous cysts are typically in the submucosa and biopsies of them may include only the upper portion of the cyst lining along the base of the biopsies.

Granulomatous Diseases of Unknown Etiology

Crohn's disease: My comments concerning Crohn's disease will be limited to the prevalence and variety of appearances that the granulomas in this condition may assume. Granulomas appear in from 15 to 30% of biopsies from patients with Crohn's disease (Table 3) and in 50 to 65% of resected specimens. They appear to be more numerous in the more distal portions of the gut. The ileum, for example, contained an average of 1 granuloma per section, the colon 6, the rectum 18 and the anus 36 in the study done by Chambers and Morrison.[2] Although there have been a number of attempts to relate the presence of granulomas to clinical outcome, their prognostic significance remains controversial.

Table 3: PREVALENCE OF GRANULOMAS IN RECTAL BIOPSY OF PATIENTS WITH CROHN'S DISEASE

Author	Site of Disease	% Rectal Biopsies with Granulomas
Hill (NCCDS)	Small bowel	0.9
	Small bowel and colon	7.5
	Colon	5.9
	Colon and rectum	30
Korelitz	Small bowel	13
	Small bowel and colon	13
	Colon only	37
Surawicz	All	28
Ward	Colon	39
Meuwissen	Colon	60
Hyams	Small bowel	60
Lockhart-Mummery	Colon	84

From Reference 4.

The etiology of the granulomas in Crohn's disease is not known. Repeated attempts over many years have failed to produce definitive evidence of an infectious agent. The most likely explanation for the disease is that there is an on-going immunoregulatory defect in response to a common antigen or set of antigens present in the mucosal environment.[5]

The granulomas of Crohn's disease not infrequently encroach on or appear to lie within lymphatic channels. They may also encroach on arteries and veins, they may extend into the wall of the artery or vein or there may be an actual granulomatous vasculitis in a minority of cases.[8] The granulomas may be quite small and difficult to identify without a careful search. In general, we do not do special stains for microorganisms unless the granulomas are unusually numerous, unusually large or have focal necrosis within them.

Miscellaneous Granulomatous Diseases

The most frequently encountered of these conditions is granulomatous inflammation as a reaction to adenocarcinoma of the colon. Because transmural lymphoid aggregates may

also be present as a reaction to colonic cancer, one must be cautious not to over interpret these granulomas as evidence of Crohn's disease. If there is no prior history of Crohn's disease in the patient and no evidence of Crohn's disease remote from the carcinoma, the granulomatous inflammation should be considered a reaction to the cancer.

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Microbial aetiology of Crohn's disease: Mycobacteria - cause or or commensal?

Inflammatory Bowel Disease ed. Anagnostides AA, Hodgson HJF, and Kirsner JB. Chapman and Hall, 1991. p. 179-200, London.

Due to the size of this handout, it will not be included in the newsletter. The referenced article is included above for your interest.

Immunopathology of Inflammatory Bowel Disease

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The pathogenesis of inflammatory bowel disease (IBD) is not known. No candidate microorganisms have consistently been found in tissues from these patients, and although some genetic linkage has been found in association with HLA, there is no dominant pattern of inheritance. This coupled with the fact that tissues from IBD patients are characterized by increased numbers of lymphocytes, plasma cells and acute inflammatory cells has led many investigators to study the possible immunologic mechanisms which may be involved in the creation of these lesions. In this session, we will summarize data about immunologic mechanisms of injury in the bowel and try to provide a rational basis for looking at the data in the context of IBD.

Many experimental models of IBD have as their basis an immune-mediated mechanism. Indeed, the histopathologic features of IBD could be explained by invoking well established immunopathologic mechanisms. For instance, the acute inflammation and cryptitis seen in active IBD is consistent with features known to result from deposition of immune complexes in blood vessel walls with activation of complement locally. Local complement activation sets up a chemotactic gradient which encourages granulocytes to enter this region, release superoxide radicals and digestive enzymes which damage the epithelial surface and lamina propria. Another proposed mechanism for acute injury in IBD involves cytotoxic antibodies directed against surface epithelial cells which would result in complement activation at that site with damage to the integrity of the epithelial barrier. However, in patients with ulcerative colitis and Crohn's disease of the colon, it has been difficult to demonstrate immune complexes beneath the epithelium, although some terminal complement components (C5b-9) can be found.

Other evidence of increased acute inflammatory mediator activity in IBD includes the presence of significantly raised fecal concentrations of the serum protease prohibitor (serpin) alpha-1-antitrypsin in patients with IBD. Fecal alpha-1-antitrypsin levels have been recommended to assess disease activity. The clinical disease activity in IBD also correlates with sedimentation rate and acute phase reactants. Fibronectin is a large glycoprotein which binds to fibroblasts and interacts with connective tissue during inflammation and repair. Individuals with extensive Crohn's disease had significantly lower levels of plasma fibornectin than those with disease confined to one segment of the bowel. High plasma fibronectin levels are also positively related to the presence of strictures. Leukotriene B_4 (LTB_4) is released into the rectal fluids in considerably greater amounts in patients with IBD than in controls. Suppression of LTB_4 synthesis significantly improves healing following administration of an intracolonic irritant in their rat model of IBD. These findings indicate that leukotrienes play a key role in the pathogenesis of injury in IBD and that use of agents which inhibit LTB_4 provides a logical approach for future therapy.

Patients with IBD have been shown to have increased neutrophil receptors for the proinflammatory bacterial peptide formyl-methionyl-leucyl-phenylalanine (FMLP), as well as an enhanced response when this chemotactic peptide is presented *in vitro*. FMLP promotes chemotaxis, adhesion and release of damaging enzymes and superoxide radicals from leukocytes. In one model system for acute colitis, colonic inflammation

was produced in rodents by instillation of FMLP into the colon. This resulted in edema and an acute inflammatory infiltrate within 2 hours suggesting that the classic acute inflammatory reactions in IBD may relate to a change in mucosa which allows bacterial products such as FMLP to initiate chemotaxis of granulocytes.

The chronic changes in IBD show crypt distortion, increased numbers of plasma cells, and increased numbers of lymphocytes in the lamina propria. The distorted crypts clearly relate to a repair process that follows acute cryptitis. The increased numbers of plasma cells in the lamina propria of patients with IBD could have at least two possible meanings. They may increase secondarily to enhanced local antigenic stimulation following damage to the surface epithelium which allows numerous intraluminal products to gain access to the gut mucosa. Alternatively, some of these plasma cells may produce antibodies that mediate local tissue damage.

The role of circulating immune complexes in the pathogenesis of IBD is controversial. Although an ultrastructural study by Otto demonstrated both IgG and complement beneath the epithelium in the colon of patients with IBD and experimental models have demonstrated that immune complexes can play a role in producing a histopathologic lesion that resembles IBD, more recent studies question the role of immune complexes in human IBD.

High serum levels of prostaglandin have been reported in patients with ulcerative colitis. This increase in prostaglandins in patients with ulcerative colitis may be due to a rate of synthesis of prostaglandin E_2 that is twice normal. The levels were increased 3-fold in patients with ulcerative colitis in remission, but 13-fold in those patients with active disease. Mean synthesis of prostaglandin E_2 by inflamed IBD tissues is significantly greater than that of noninflamed tissues. Although the increased synthesis of prostaglandins could be inhibited *in vitro* by sulfasalazine, when 14 patients with active ulcerative colitis were treated with flurbiprofen or prednisolone enemas and/or sulfasalazine, no evidence was found for efficacy of the prostaglandin inhibitor in decreasing symptoms.

Despite the evidence of systemic activation of complement components in patients with IBD, studies of leukocyte function in these patients indicate that their directed migration into experimentally induced areas of injury is retarded compared to controls. By using the skin window technique, Morain and colleagues and, independently, Wandall and Binder found that neutrophils *in vivo* from patients with Crohn's disease have a decreased ability to migrate into these chambers. This decreased migration may merely reflect the fact that so much complement is being activated due to the acute injury in the bowel, that there is insufficient circulating C5 to deal with other stimuli in some of these patients. In addition to poor chemotaxis *in vivo*, there is good evidence that neutrophils from patients with IBD are not effective in phagocytosing and destroying ingested microorganisms. The poor chemotaxis of leukocytes to areas where foreign material accumulates has been offered as an explanation for the presence of the chronic granulomatous inflammation in Crohn's disease.

Specific cytotoxic IgG antibodies against the colon cancer cell line RPMI 4788 have been detected in the serum of 29% of patients with ulcerative colitis, 3% of patients with Crohn's disease and in none of the healthy controls when a four hour cytotoxicity assay was used. This antigen is particularly prevalent in colonic tissue from patients with ulcerative colitis, although it is also present in normal bowel, liver and kidney. There is a high incidence of humoral immunity against an epithelial-cell-associated (ECAC) macromolecule from human intestinal epithelium in patients with IBD.

The numbers of immunoglobulin-containing cells in the lamina propria is a useful parameter in distinguishing acute self-limited colitis (ASLC) from active IBD. ASLC has some features which are reminiscent of active IBD including cryptitis, crypt abscesses, and regenerative surface epithelium. However, it lacks crypt distortion, has

relatively normal numbers of plasma cells in the lamina propria, and does not have granulomas, crypt atrophy or basal lymphoid aggregates often seen in IBD. There are significantly fewer IgG-containing plasma cells in the bowel of patients with ASLC compared to active IBD. Quantification of the numbers of IgG, IgA, and IgM plasma cells in the lamina propria is useful in providing quantitative information to help in the differential diagnosis of difficult cases.

The increased numbers of immunoglobulin-containing cells in the lamina propria of patients with IBD mainly reflect the result of IBD injury rather than the cause of it. That is, after injury has occurred to the surface epithelium, large numbers of antigens become readily available to the gut lamina propria. A tremendous immune response of both a local and systemic nature results in the large numbers of plasma cells that are seen. It is possible that a few of the plasma cells in the gut lamina propria are making either anti-colon antibodies, as described earlier, or other antibodies reacting with the gut epithelium. Indeed, the disparity in the IgG subclasses which are found in controls, ulcerative colitis and Crohn's suggests a differential effect that may be due to specific subisotype expansion to particular stimuli (which are as yet unknown).

Cell-mediated immunity may also play a role in the pathogenesis of IBD. Mononuclear cells from the peripheral blood of patients with IBD, in the absence of complement, are able to kill *in vitro* cultured colonic epithelial cells. The effector cells for this phenomenon are null lymphocytes and are especially prevalent in mesenteric lymph nodes from patients with Crohn's disease. In IBD there is evidence for defective suppression in the ability of T lymphocytes to inhibit self-reactivity. The autologous mixed lymphocyte reaction (an *In vitro* test for the the ability of T cells to respond to self antigens) has demonstrated a marked defect in suppressor T cell function to inhibit IgG, IgA and IgM production in patients with IBD. Irradiated T lymphocytes from patients with Crohn's disease produce a significantly greater increase in IgA production *In vitro* than control T lymphoctyes. This may relate to the eventual production of antibodies directed against epithelial antigens. Not all individuals with IBD have increased levels of immunoglobulins. Some patients with excessive suppressor T cell functions resulting in hypogammaglobulinemia have been described suggesting that a nonsystematic alteration in T cell activity exists in these individuals. Nonsystematic processes are always more difficult to make sense of than systematic ones and may help us to understand the diverse, occasionally conflicting information that has been produced on samples from patients with IBD.

The delayed-type hypersensitivity response is poor in patients with IBD. Impaired skin test responses to PPD have been recorded, and cutaneous anergy to dinitrochlorobenzene (DNCB) have been found in patients with IBD. *In vitro* studies have demonstrated poor reactivity in lymphocytes from the peripheral blood of patients with IBD when these lymphocytes were mixed with normal lymphocytes. Studies on peripheral blood T and B lymphocytes in an attempt to explain the altered cell-mediated immunity in these patients provided only marginally useful information.

There is also controversy and conflicting data from studies of natural killer cell activity in the peripheral blood. Natural killer lymphocytes are thought to be part of host defense against virally infected cells and against neoplastic transformation. Although the numbers of circulating natural killer cells have been found to be normal when using surface marker techniques, their functional activity has been found to be impaired in one study, while another with similar methodology found a wide variation in activity with no significant difference from controls. A decrease in natural killer lymphocyte activity would be consistent with the proclivity of these patients to develop colon cancer.

Another functional capability of lymphocytes is to suppress production of antibody by B cells or to suppress the cytotoxic activities of antigen-specific killer T lymphocytes. Some early studies found that suppressor T cell activity was decreased in 7 of 11 patients with IBD. Since suppressor T cells are important in preventing

autoimmune disease in some experimental animal models of systemic lupus erythematosus, the decreased numbers of suppressor T cells may be related to the development of autoreactive phenomena such as the anticolon epithelial cell antibodies and lymphocytotoxic antibodies described above. In addition, other workers found that the activation of suppressor T cells from the peripheral blood of patients with IBD was diminished in the vast majority of patients with IBD that they examined. Their finding was independent of disease type, activity, or steroid therapy. Decrease in suppressor cell activity, however, may only be relative to the techniques used to assess it. When still other groups used a technique that involved separating the suppressor cell population *in vitro*, they found that the suppressor T cell activity was not impaired in patients with IBD. Yet, patients with IBD have increased numbers of indomethecin-sensitive prostaglandin-producing suppressor T cells in the peripheral blood. These findings may explain the increased levels of prostaglandin in the dialysates of the colon. It is very difficult to sort out the significance of the suppressor cell studies. These studies use different techniques to isolate the cells for study, and have different assay systems for suppression. Perhaps one can only safely conclude that a dysregulation of mucosal immune function exists.

Recent studies have begun to examine the cells in the mucosa itself which may be more likely to provide us with useful information about mechanisms of damage at the gut surface epithelium. The functions of the lymphoid cells are controlled by the intercellular communication mechanism using lymphokines. Interleukin 1 (IL-1) is secreted by macrophages and serves as endogenous pyrogen, elicits production of acute phase proteins such as alpha-1 antitrypsin and haptoglobin from the liver, and activates T lymphocytes. The IL-1 level was found to be much greater in the cultures from IBD patients than from controls. This difference was not accounted for by increased numbers of macrophages in the population, since they found similar numbers of macrophages from normal and inflamed colonic mucosa. Interleukin 2 (IL-2) is another lymphokine which is altered in the gut mucosa of patients with IBD. IL-2 is a soluble product of activated T lymphocytes which stimulates proliferation, and clonal expansion of T cell populations. Lamina propria mononuclear cells from patients with IBD have significantly decreased release of IL-2 *in vitro* compared to mononuclear cells from control lamina propria. This inability to respond appropriately to an antigen could result in the chronicity of inflammation which we see in IBD. When exogenous IL-2 was added to cultures the mononuclear populations from patients with IBD had equivalent activity to controls. However, IBD cells produced considerably less IL-2 in culture than did control cells.

Of interest is a case report of a patient with an 18 year history of Crohn's disease of the colon who had a complete remission of symptoms following development of AIDS. The most impressive feature of this case was that the patient had well documented regular attacks of severe Crohn's disease, until after diagnosis of HIV infection. This single case is the strongest evidence to date that cellular immunity, specifically CD4 positive T helper lymphocytes, plays a key role in the pathogenesis of Crohn's disease.

A highly significant association of HLA-B12 has been described in patients with Crohn's disease compared with control individuals or with patients with ulcerative colitis in a population of 27 Vietnamese with Crohn's disease. Other studies have demonstrated a significant association of HLA-BW35 and HLA-AW24 with ulcerative colitis in European born Jews. Further, HLA-AW24 was associated with an early onset of the disease. Genetic linkage has also been found with immunoglobulin genes. Patients with Crohn's disease have been associated with immunoglobulin heavy chain (Gm) allotypes . The implications of these Gm and HLA associations with IBD is that there is some linkage between the occurrence of IBD with genes regulating the immune response. The HLA antigens themselves may be the cell surface receptors for antigens or microorganisms involved in initiating IBD. It is possible that the causative antigens or microorganisms may contain HLA-like surface antigens and may result in a poor

immune response, allowing the antigen to dwell longer in affected tissues, and thereby to initiate the chronic inflammation so characteristic of IBD.

For the diagnostic pathologist there are few take home lessons from the past 20 years of work on the immunopathogenesis of IBD. The presence of large numbers of plasma cells in the lamina propria can provide the pathologist with supportive evidence for IBD versus acute self-limited colitis. However, the newer technologies of flow cytometry, monoclonal antibodies and cellular immunology are yet far from any useful application in aiding with diagnosis of IBD. Yet, we must keep ourselves attuned to new developments in this field. The striking observation that a patient with Crohn's disease had a prolonged remission during development of AIDS shows that the T helper lymphocyte plays some role in the overt manifestations of this disease.

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UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

GASTROINTESTINAL PATHOLOGY SOCIETY SEMINAR 1992

Robert R. Pascal, M.D. - Moderator

COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE (EXCLUDING DYSPLASIA AND CARCINOMA)

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INTRODUCTION

Patients with primary inflammatory bowel disease (IBD) frequently develop extra-intestinal manifestations and gut complications (1). Similar extra-intestinal manifestations occur in patients with Crohn's disease and ulcerative colitis. These include joint inflammation (arthritis, spondylitis), ocular lesions (iritis, episcleritis), dermatologic disorders (erythema nodosum, pyodermic gangrenosa), liver dysfunction (pericholangitis, sclerosing cholangitis), renal disorders (nephrolithiasis) and thromboembolism. Although hemorrhage, toxic megacolon, and carcinoma can complicate both Crohn's disease and ulcerative colitis, patients with Crohn's disease can develop an array of relatively unique problems including small bowel obstruction, recurrence of inflammatory bowel lesions following excision, perianal disease, and fistula. This discussion will focus on those gut complications of IBD highlighting the pathologist's changing role in patient management and emphasizing diagnostic challenges presented by the new IBD surgical techniques.

SURGERY AND RECURRENCE IN CROHN'S DISEASE

The most common indication for major surgery in Crohn's disease is intestinal obstruction (2). Obstruction usually results from thickening of the muscularis mucosae causing stenosis. Resection of the stenosed segment remains the standard therapy but even in patients with localized totally excised lesions, two-thirds will suffer anastomotic recurrence within 10 years (3-5). This high recurrence rate has prompted some surgeons to perform more "radical" excision, some advocating frozen section analysis of the margins to determine the anastomotic site (3,4,6). However, numerous studies

have established that the histologic status of the resection margin in Crohn's disease is not associated with anastomotic recurrence (5,7,8). Anastomoses created through transmural granulomatous inflammation have done as well as those performed with "negative" margins. Therefore, frozen section of margins is not justified in Crohn's disease and the routine histologic examination of resection margins is of doubtful importance and probably should not continue.

The advent of strictureplasty has reduced the number of Crohn's patients requiring excisional therapy for bowel obstruction. Strictureplasty usually employs a longitudinal enterotomy through the stenotic bowel. The enterotomy incision is closed in the transverse axis similar to a pyloroplasty. The technique effectively eliminates obstruction and despite suturing through actively inflamed bowel, the rate of fistula or enteric leak is surprisingly low.

POUCHES, POUCHITIS, AND PROBLEMS WITH FULMINANT COLITIS

Evolving surgical technique have changed the pathologist's role in the analysis of IBD. Patients with ulcerative colitis have several operations available that either create continence in an ileostomy (Kock's ileostomy) or preserve anal sphincter function and restore the continuity to the bowel (ileal reservoir with ileoanal anastomosis) (9,10). These operations share the creation of a reservoir (pouch) formed by connecting loops of terminal ileum. In general, these pouch procedures are contraindicated in patients with Crohn's disease because of increased morbidity (e.g., fistula, abscess) (11). Furthermore, complications requiring pouch removal can result in the loss of considerable lengths of small bowel, sometimes enough to cause the "short bowel syndrome." In my experience, there is nothing quite like a pouch to bring out the Crohn's in someone.

Accurate pathologic diagnosis of colonic IBD contributes greatly to patient management. Originally, pouch procedures involved two separate operations: an initial colectomy, followed by pouch construction and ileoanal anastomosis. This strategy permitted relaxed pathologic examination of the colectomy specimen, however, it exposed the patient to the increased risks of a second operation. Currently, the colectomy, pouch construction, and ileoanal anastomosis are preferably done at one operation. This approach requires accurate preoperative/perioperative diagnosis emphasizing the importance of mucosal biopsy specimen interpretation. Many patients with fulminant colitis requiring urgent or emergent colectomy will still have the pouch procedure performed as a two stage procedure.

Pouch complications include fistula, obstruction, incontinence and anastomotic leaks (9). Although some complications result from surgical and mechanical difficulties, and others relate to the development of "primary" inflammation in the pouch ("pouchitis"), many of these complicated cases likely represent pouch recurrence of initially undiagnosed Crohn's disease. These cases highlight the pathologist's inability to reliably differentiate ulcerative colitis from Crohn's disease in severe colitis, even after examination of the colectomy specimen (12).

A late pouch complication is the development of "primary" inflammation in the pouch with its associated clinical syndrome termed "pouchitis" (13,14). Patients develop nausea, vomiting, malaise and fever, commonly accompanied by abdominal cramping. There is increased effluent/stool from the ileum that may be watery, foul smelling, or grossly bloody and patients often become incontinent. Pouchitis usually responds to antibiotics suggesting a bacterial etiology but some patients require the addition of sulfasalazine and/or corticosteroids (9,14-16). Pouch biopsy may be performed to confirm the presence of inflammation or to evaluate the possibility of Crohn's disease. Pouch biopsy specimens in pouchitis usually show villous shortening, increased chronic inflammation with decreased epithelial cell mucin. Decreased or absent lymphoid follicles is characteristic. The most common finding has been patchy accumulations of neutrophils within epithelial cells and in the lamina propria (14,17,18). Recently, we have found an inconsistent relationship between histologic changes and patients symptoms, and reliable criteria to differentiate "pouchitis" from the "new onset" or recurrence of Crohn's disease in the pouch do not yet exist.

DIVERSION COLITIS/DEFUNCTIONALIZED BOWEL

A rectum placed surgically out-of-circuit acquires histologic changes associated with defunctioning alone irrespective of the original reason for diversion (19-22). The changes probably reflect either a physiologic response to stasis or loss of trophic factors present in the feces, most notably short chain fatty acids (23). The patient, however, is usually asymptomatic. The mucosa of the diverted segment appears erythematous, granular, and friable. Histologic changes include marked lymphoid hyperplasia with germinal center formation, usually accompanied by mild colitis with crypt drop out, cryptitis, and crypt abscess formation. The changes can be indistinguishable from follicular proctitis (ulcerative proctitis, localized ulcerative colitis) (24). With time, the muscularis mucosae hypertrophies, the submucosa shows fatty and fibrous tissue infiltration, the muscularis propria thickens, and the lumen becomes progressively smaller. The mucosal lymphoid hyperplasia can be accompanied by lymphoid aggregates scattered in the deep submucosa, the muscular wall, and perirectal adipose tissue. Since these changes may occur in out of circuit segments in patients without IBD, care must be taken not to make a diagnosis of primary IBD especially Crohn's disease in such specimens. In many patients, the rectum is placed surgically out-of-circuit during an operation for IBD. In these instances the rectum can show changes of both primary IBD and diversion colitis.

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REMINDER

THE GASTROINTESTINAL PATHOLOGY SOCIETY RECEPTION WILL BE HELD IN THE BONN ROOM AT THE ATLANTA MARRIOTT MARQUIS FROM 5:45 - 8:00 P.M. ON SUNDAY, MARCH 15. MEMBERS AND GUESTS ARE WELCOME. FREE HORS D'OEUVRES, CASH BAR.

ANNOUNCEMENT

The GIPS has had an on-going study of endoscopically removed malignant colorectal polyps for some time now. The study is progressing nicely, however, may again we ask the GIPS membership to contribute cases to our study. We realize that all society members are very busy and we do not wish them to go out of their way, however, if without much effort they can retrieve appropriate cases, the study group would be greatly appreciative. Cases for our study are:

1. Any endoscopically removed malignant colorectal polyp with a subsequent surgical resection.
2. Malignant colorectal polyps treated solely by endoscopic removal, but with a minimum of a five-year follow-up.

Again, if any of the members can get their hands on such cases without too much hassle, would you please send the appropriate materials (slides, pathology report, and follow-up) to:

Harry S. Cooper, M.D.
Department of Pathology
Hahnemann University Hospital
Broad & Vine Streets - Mail Stop 435
Philadelpia, PA 19102

ATTENTION

One of the functions of this newsletter is to promote and foster communication between the membership. Should any of the membership have any announcements or notices that he or she wishes to communicate to the GIPS, please feel free to send them to my attention and I'll "publish" them in our newsletter. Please send these communications to:

Harry S. Cooper, M.D.
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Book Review

AUTOIMMUNE LIVER DISEASE
Edited by Edward L. Krawitt and Russell H Wiesner
Retail price : $89.00
Published May 1991

This is a multi-authored text with 16 chapters and 28 authors. The concept and design of this book is well thought out. The focus of this text is on three autoimmune diseases, namely autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis. The final three chapters are devoted to unrelated but equally appropriate topics of drug induced chronic active hepatitis, immunologically mediated extrahepatic manifestations of viral hepatitis and autoimmune manifestations of alcoholic liver disease. As it is stated in the preface, this book is intended for gastroenterologists, hepatologists and pathologist. I would expand that this book is not suited for the general pathologist, but is for pathologist interested in liver disease. Those interested in autoimmune diseases may also find this book useful. It provides good and somewhat detailed information on what is currently known about experimental and clinical aspects of autoimmune liver disease. While the book does not presume that the reader have a background in immunology by presenting general concepts of autoimmunity in the first chapter, it would be cumbersome to attempt to read this book without some knowledge of immunology. In general the book is well written with slight variation from chapter to chapter. In some chapters, the reader may have a sense of fragmentation as various bits of experimental evidence are presented, but in most instances a reasonable summary is provided with a valid attempt to pull the current state of knowledge into a comprehensive understanding of the disease at hand. In conclusion, I would strongly recommend this book for pathologists and clinicians with an interest in liver disease or autoimmunity

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