GASTROINTESTINAL PATHOLOGY SOCIETY
COMPANION MEETING
USCAP 1994 SAN FRANCISCO

Sunday, March 13 **1:30 p.m**

UPDATE ON CANCER OF THE LARGE INTESTINE

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

1:30 p.m. **Neoplasms and neoplastic-like disorders of the vermiform appendix**

Henry D. Appelman, M.D.
University of Michigan Medical School
Ann Arbor, MI

2:00 p.m. **Aneuploidy and p53 allele loss in the progression of intestinal neoplasia in ulcerative colitis**

Rodger C. Haggitt, M.D.
University of Washington
Seattle, WA

2:30 p.m. **Expression of metalloproteinases and their inhibitors in the progression of colorectal neoplasia**

Stefan J. Urbanski, M.D.
University of Calgary and Foothills Hospital
Calgary, Alberta

3:00 p.m. **RECESS**

3:30 p.m. **Dysplasia and early carcinoma in IBD and colorectal adenomas - criteria, terminology, and implications for patient management**

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

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4:00 p.m. **Endoscopically Removed Malignant Polyps of the Colon and Rectum, Clinicopathological Correlations**

Harry S. Cooper, M.D.
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Philadelphia, PA

4:30 p.m. **Discussion and Questions**

NON-ENDOCRINE EPITHELIAL NEOPLASMS AND PROLIFERATIONS OF THE VERMIFORM APPENDIX

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CLASSIFICATION

I. Hyperplastic Mucosa or Polyp

II. Colonic Type Neoplasia

- A. Localized Villous, Tubulovillous or Tubular Adenoma
- B. Adenocarcinoma
- C. Signet Ring Cell Carcinoma

III. Distinctly Appendiceal Neoplasia

- A. Mucinous Cystadenoma
- B. Mucinous Cystadenocarcinoma
- C. Goblet Cell Carcinoid, Crypt Cell Carcinoma, Microglandular Carcinoma, Adenocarcinoid Tumor

In all older series except one, hyperplasias, adenomas and cystadenocarcinomas, have a striking female preponderance, much of which may have been due to the high frequency in the past, of incidental appendectomies in women. The non-cystic carcinomas are about twice as common in men and the goblet cell carcinoid is likely to occur slightly more frequently in men. Most patients with these aberrations are in their fifties and sixties. Those appendiceal lesions which are symptomatic present with right lower quadrant pain, often accompanied by other features of acute appendicitis. Large masses may be palpated in the right lower quadrant.

Appendiceal hyperplastic polyps resemble those in the colon with elongated crypts, patches of piled-up epithelium, serrated lumens, and thick subsurface basement membranes. These hyperplastic foci vary from small to those that cover large areas of mucosa. Some have been described as causing a mucocele, but this association is doubtful, especially since hyperplastic mucosa is generally mucus-cell deficient. In a review of about 200 mucosal proliferations of the appendix accessioned at the University of Michigan in the past 40 years, we have encountered about five typical colonic-style hyperplastic polyps. Many cases described in the literature as the appendiceal hyperplastic polyps are probably peculiar villous adenomas with serrated lumens, irregular villi and stratification of the epithelium, as described below.

The neoplasms can be separated into adenomatous and carcinomatous forms with the same overlap in cytologic characteristics that occurs in the colon. It appears that the carcinomas arise from low grade dysplastic adenomatous epithelium, much as occurs in the colon. Careful study of appendiceal carcinomas frequently discloses the underlying adenoma.

Appendiceal adenomatous epithelium, or low-grade dysplastic epithelium is usually mucinous, resembling ovarian adenomatous epithelium, rather than colonic, with apical mucin vacuoles and basal nuclei. One common adenomatous variant contains goblet cells, often stratified irregularly, so that the architecture resembles the colonic hyperplastic polyp (see above) with serrated lumens to the tubules. These variants are commonly villiform as well. The adenomatous epithelium, no matter what type, tends to cover the appendiceal mucosa circumferentially, so that even small adenomas may completely surround the lumen. Usually the distal appendix is the site for most adenomas, but any segment may be involved.

Architecturally, adenomas of the appendix are mostly either villous or undulating, so that they cover the flat, atrophic-appearing mucosa in a wavy fashion. Localized tubular colonic-style adenomas are rare, unless the patient has familial adenomatous polyposis. As a result of the circumferential growth and mucus production, many appendiceal adenomas, and even carcinomas, turn the appendix into a mucus-filled sac or cyst, traditionally referred to as a **mucocele**. Because the adenomas produce these mucus filled cysts, they are referred to as **cystadenomas** and their malignant counterparts are referred to as **cystadenocarcinomas**. Presumably these cystic tumors result from over-production of mucus in a closed space which may be obstructed, or, at least, drain poorly.

Most appendiceal mucoceles are lined somewhere by adenomatous or dysplastic epithelium, although often the epithelium is flattened by the intraluminal pressure, and focally, the epithelium may be totally obliterated, so that the mucus sac is lined by granulomatous reaction to the mucus or simply by scar. Some mucoceles are thought to arise as a result of overproduction of mucus by normal appendiceal epithelium within an appendix which is obstructed or drains poorly for other reasons. However, such non-neoplastic mucoceles, also referred to as "**retention cysts**", are rare, and, at best, they are likely to be very small. Large mucoceles are invariably produced by neoplastic epithelium.

When any type of mucocele ruptures, its contents may be extravasated into the peritoneal cavity where the mucus incites a scarring or desmoplastic reaction. The peritoneal mucocele extravasation has been called **pseudomyxoma peritonei**. The mucus extravasation can be limited to the periappendiceal region, or it can spread over much of the peritoneal surfaces. It appears that the curability of a pseudomyxoma is dependent upon whether or not neoplastic epithelium is present within the mucus, the dysplastic grade of the extruded epithelium, and the extent of spread (stage) within the abdomen. For instance, it is assumed that carcinomatous epithelium continues to grow and produce more mucin, while adenomatous epithelium seems to have more limited growth. However, the epithelium growing on the peritoneal surfaces can be misleadingly benign- appearing, even when that in the appendix looks obviously malignant. In general, it appears that extruded epithelium from appendiceal mucinous neoplasms tends to cover peritoneal surfaces, not invade them, and metastases are rare. Those cases with extra-appendiceal mucin

limited to the right lower quadrant at diagnosis virtually never become generalized in the peritoneal cavity. Actuarial survival data from reported cases suggests that pseudomyxoma with epithelial implants behaves like a low-grade carcinoma with five year survival rates of about 70% and ten year survival rates of almost 60%

Perhaps 10% of cystic appendiceal neoplasms occur in patients who have a colonic carcinoma or a mucinous cystic ovarian tumor. The colonic and ovarian associations are difficult to define, because many of the appendiceal mucosal transformations have been discovered in normal appearing appendices removed during colectomy for colon cancer or during oophorectomy for ovarian masses. When the ovaries are involved, they may be metastases from an appendiceal primary, or they may be independent primaries. The data are conflicting.

Non-mucinous carcinoma of the appendix is rare. It is an unpredictable neoplasm that can disseminate rapidly or cause death many years after the initial therapy. There are insufficient numbers of reported cases to gather significant survival data, but rough five year survival for all modes of therapy from all of the small series and small groups of reported cases is about 68%, while ten year survival is about 50%. In the older literature, it was felt that right hemicolectomy resulted in better survival than appendectomy alone, but recent reports suggest that there is no difference. It appears that survival for appendiceal carcinoma is dependent upon stage of disease in much the same way as in most other malignancies. Fortunately, most reported cases have been found early and in a limited stage, accounting for the favorable long term survival.

Finally, there are microglandular, very well differentiated neoplasms containing goblet cells, Paneth cells and scattered endocrine cells that grow in the appendix much like carcinoid tumors, and seem to arise from basal mucosa. They have been called "goblet cell carcinoid tumors", "adenocarcinoids" and "crypt cell carcinomas". They are not carcinoid tumors, and they are not all benign. A recent AFIP study indicated that this group of tumors really had 2 subsets. One was a pure tumor of small crypt-like tubules or cell clusters containing goblet cells, Paneth cells and serotonin-positive endocrine cells, which was confined to the appendix and mesoappendix. These did not metastasize A second group contained a mixture of the first type, plus adenocarcinoma which could be of mucinous, signet ring cell or typical tubular patterns. These metastasized often. The sizes of the metastasizing tumors have been remarkably small (about 1.0 cm). Metastases contain pure adenocarcinoma, or the mixed lesion, as in the primary. Peculiarly, this strange neoplasm seems to arise almost exclusively in the appendix, since only rare examples arising elsewhere in the gut have been reported.

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ANEUPLOIDY AND p53 GENE ABNORMALITIES IN NEOPLASTIC PROGRESSION IN ULCERATIVE COLITIS

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Introduction

Dysplasia has been well established as a marker of increased risk for the development of colon cancer in patients with long standing, extensive ulcerative colitis. Surveillance colonoscopy for the detection of dysplasia has been widely used as a method to help control cancer mortality in ulcerative colitis patients. However, a number of problems prevent the detection of dysplasia from being as useful a marker as needed. These problems include sampling error, the distinction of dysplasia from reactive or regenerative changes, observer variation in the diagnosis of dysplasia and lack of knowledge concerning the natural history of dysplasia. For these reasons, more objective markers to detect patients at high risk for developing neoplastic progression in ulcerative colitis are needed. Among the markers that have been studied are PAS staining to detect the presence of neutral mucin in the colonic mucosa outside of goblet cells; high iron diamine-Alcian blue staining to detect alterations in the ratio of sulfated to sialylated mucin; binding of various lectins to detect altered glycoproteins and immunohistochemistry to detect aberrant expression of CEA. The results of these studies indicate that the colonic mucosa responds similarly to inflammation and neoplasia.[1] Studies of colonic epithelial cell kinetics have also been carried out. These have utilized in-vitro labelling of biopsies with tritiated thymidine followed by autoradiography, and labelling with the monoclonal antibody Ki-67.[2,3] The conclusions of these studies have been that the proliferating fraction of cells is increased in active and inactive ulcerative colitis, that the proliferative zone expands to the surface and that there is no apparent relation to cancer risk.

DNA Flow Cytometry for the Detection of DNA Aneuploidy and Cell Cycle Parameters

DNA flow cytometry measures DNA content per cell and can thereby detect aneuploidy with a sensitivity of $\pm$ 5%. The S and G_2/M fractions of the cell cycle can also be determined. Flow cytometry, like the studies utilizing tritiated thymidine in Ki-67 labelling, has shown that there is a high prevalence of abnormal S-phase fractions in patients with ulcerative colitis without dysplasia. Thus, detection of an elevated S-phase fraction of cells does not appear to have prognostic significance for predicting which patients with ulcerative colitis are at risk for developing dysplasia or cancer.

The detection of DNA aneuploidy has been shown by a number of different groups to correlate well with the presence and grade of dysplasia (Table 1).[4,5,6,7] In general, there is a low prevalence of aneuploidy in UC patients whose biopsies are negative for dysplasia. The prevalence rises with indefinite histology and is high with dysplasia or cancer. Thus, the presence of DNA aneuploidy might select patients whose biopsies are negative or indefinite for dysplasia but who are at risk for developing it.

Table 1: **PREVALENCE OF ANEUPLOIDY IN ULCERATIVE COLITIS**

Histology	*Authors/(Type of Tissue)*		
	Rubin (Fresh)	*Löfberg (Fresh)*	*Melville (Paraffin)*
Negative	1/33 (3%)	2/37 (5%)	12/219 (5%)
Indefinite	6/13 (46%)	3/11 (27%)	
Dysplasia	22/25 (88%)	7/8 (88%)	14/36 (39%)
Cancer	9/10 (90%)	---------	25/34 (74%)

Rubin CE, et al. *Gastroenterology* 1992;103:1611
Löfberg R, et al. *Gastroenterology* 1990;99:1021
Melville DM, et al. *Gastroenterology* 1988;95:668

For example, McHugh and colleagues found a 42% prevalence of aneuploidy in UC patients whose biopsies were negative for dysplasia and a 100% prevalence in patients with dysplasia.[8] The DNA index of the aneuploid population of cells in this study clustered

around 1.2 (2.4N). Other investigators, however, have found aneuploidy to be relatively common and non-specific, as it occurred frequently in the absence of dysplasia or carcinoma.[8,9,10,11,12,13,14] Factors that may account for some of these discrepancies include: variations in number of samples studied; use of paraffin embedded tissue retrospectively as opposed to fresh tissue prospectively; observer variation in the diagnosis of dysplasia and aneuploidy; and false aneuploidies induced by the use of partially autolyzed, unfixed tissue.[15] Additional sources of confusion include the failure to report data based on disease duration and extent, the reporting of data by numbers of biopsies rather than by numbers of patients, and different methods of handling the indefinite category, for example, including it in the negative or low-grade category, or reporting it as a separate category.

Some of the discrepancies in the flow cytometric literature undoubtedly relate to the frequency and significance of near diploid aneuploidies. For example, McHugh and coworkers, who found a 42% prevalence of aneuploidy in patients whose biopsies were negative for dysplasia, reported large proportions of their DNA aneuploidies to be in the near diploid range.[8] In contrast, our ploidy distribution in the different histologic categories is similar to results reported in a variety of other organ systems and is almost exactly the same as the spectrum found in adenocarcinoma of the breast.[4]

We prospectively evaluated the predictive value of aneuploidy for the development of dysplasia in patients with ulcerative colitis whose biopsies were either negative or indefinite for dysplasia. The data from this study are shown in Table 2. These data suggest that when a patient with ulcerative colitis enters the high cancer risk category, a comprehensive colonoscopic biopsy study with flow cytometry is potentially valuable for several reasons: it may detect dysplasia that warrants a colectomy, or it may identify aneuploidy in the absence of dysplasia, indicating a need for more frequent follow-up because of a greater risk of future dysplasia. Most importantly, this comprehensive initial

examination will identify the large group of patients whose biopsies are diploid and negative for dysplasia; such patients can probably be safely studied at intervals of 2 or 3 years because they are unlikely to develop cancer during this time period.

Table 2: ANEUPLOIDY PREDICTS DEVELOPMENT OF DYSPLASIA IN ULCERATIVE COLITIS

Initial Histology	*Initial FCM*	*Histologic Progression*	*P value*
Negative	Aneuploid	1/1	< .06
	Diploid	0/15	
Indefinite	Aneuploid	4/4	< .05
	Diploid	1/5	
Combined	Aneuploid	5/5	< .0001
	Diploid	1/20	

Minimum 2 years follow-up

From reference 29

By using data from our prospective surveillance studies and from "mapping" of colectomy specimens, we calculated the number of histologic and flow cytometric samples that would be required to achieve 90 and 95% confidence of detecting an abnormality were it present.[4] This analysis showed that approximately 32 biopsies would be required to achieve 90% confidence that a histologic abnormality would be detected or about 55 biopsies for 95% confidence. Likewise, a total of approximately 20 biopsies analyzed by flow cytometry are required for 90% confidence that aneuploidy will be detected if present, and 30 biopsies for 95% confidence.

We have also found that some patients have multiple aneuploid populations of cells in their colonic mucosa. Mapping studies carried out on colectomy specimens showed that as many as 14 to 15 different and overlapping regions of aneuploidy could be present within the colonic mucosa.[16] The presence of multiple aneuploidies suggests that a high level of genomic instability is present and that the patient probably has a high risk of progressing to develop adenocarcinoma of the colon.[16]

Flow cytometry has the potential to reduce the cost of surveillance by identifying the few patients who require frequent follow-up and those who do not. If this technique can be standardized for use in clinical practice so that the discrepancies in the studies cited previously can be avoided, then it could select that small subset of patients with aneuploidy in the absence of dysplasia who require more frequent surveillance because they may be more prone to the future development of dysplasia. Performing more frequent and extensive colonoscopic surveillance on this subset of high cancer risk patients and less frequent surveillance in the majority of patients without aneuploidy or dysplasia should cost less and prove more effective in finding curable lesions.

Specific Genetic Events in Ulcerative Colitis, Dysplasia and Cancer

Several studies have addressed the prevalence of mutations in various oncogenes, especially K-*ras*. Two studies found a much lower prevalence of *ras* gene mutations in ulcerative colitis, dysplasia and cancer than in sporadic colon cancer, suggesting that neoplastic progression in ulcerative colitis might proceed by different mechanisms than in sporadic cancer.[17,18] However, Chen and co-workers found a higher prevalence of *ras* gene mutations than these other studies.[19] The reasons for this apparent discrepancy are not clear and require further study. Evaluations of other oncogenes in neoplastic progression in UC have shown that many of them may be abnormal but have not provided any information helpful for prognosis or understanding pathogenesis as of yet.

Allelic deletions and mutations in tumor suppressor genes have been identified during neoplastic progression in ulcerative colitis. These include demonstration of loss of heterozygosity for the p53, retinoblastoma and APC/MCC tumor suppressor genes.[20,21] The study by Burmer and colleagues showed a 70% prevalence of allelic deletion in sporadic colon cancer and a similarly high prevalence of deletions in carcinoma and dysplasia in ulcerative colitis. Of interest, allelic deletion in a patient whose biopsies were indefinite for dysplasia was also detected, suggesting that p53 LOH may be a relatively early event in neoplastic progression in UC.[21] Burmer and co-workers also correlated

histologic abnormalities with aneuploidy and p53 LOH by mapping nine colectomy specimens. Their data disclosed that regions of aneuploidy were more extensive than regions of p53 LOH, suggesting that aneuploidy might precede LOH. Also, p53 LOH was detected not only in biopsies that were histologically indefinite for dysplasia, but in some that were negative for dysplasia as well, again, suggesting that p53 abnormalities may be early events in UC neoplastic progression.[22] As a follow-up to these mapping studies, the Seattle group developed a rapid and sensitive screening assay for p53 mutations at codon 248. These studies showed that p53 mutation correlated highly with histologic grade and was more extensively distributed than p53 LOH.[23] p53 mutations were also found in diploid, non-dysplastic colonic mucosa adjacent to dysplastic areas, a new observation which suggests that p53 mutation may be an early genetic event that precedes p53 LOH. The very close correlation between p53 mutation and aneuploidy found in this study raises the possibility that normal p53 may function as a component of the G_1 cell cycle checkpoint that helps prevent entry of genetically damaged cells into the cell cycle.[23] Meltzer's group in Baltimore also found point mutations and loss of heterozygosity in the p53 gene in ulcerative colitis patients with dysplasia or cancer. p53 abnormalities were commonly present and, in contrast to sporadic colorectal carcinoma, were found frequently in dysplasia.[24]

The prognostic value of genetic abnormalities in ulcerative colitis neoplastic progression has not yet been tested by long term, prospective follow-up studies. They hold promise, and the future may see stool assays for tumor suppressor or oncogene abnormalities to detect patients with ulcerative colitis who are at risk for neoplastic progression.

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EXPRESSION OF METALLOPROTEINASES AND THEIR INHIBITORS IN THE PROGRESSION OF COLORECTAL NEOPLASIA

S.J. Urbanski, M.D.

The concept of the adenoma-carcinoma sequence postulates progressive accumulation of phenotypic alterations which eventually lead to the formation of carcinoma. This concept has recently been supported by a hypothesis of Vogelstein et al which states that progressive acquisition of genotypic alterations is responsible for the development of colonic adenocarcinoma (Vogelstein, 1988). Although these hypotheses are generally accepted as correct, such concepts are vulnerable to a criticism that analysis of each separate point does not prove progression to the assumed endpoint (Koretz, 1993). In order to provide additional evidence (albeit still circumstantial) in favor of the adenoma-carcinoma sequence hypothesis, we have approached this problem from the endpoint (carcinoma).

Essential for the malignant phenotype is the ability of the tumor to invade and metastasize. These phenomena are associated with destruction and remodelling of the extracellular matrix (ECM). The EMC has both a structural role as the scaffolding material of tissue architecture and an informational one in controlling cell growth and differentiation via both direct cell-ECM interactions and the presentation of growth factors and morphogens to cells. Many secreted proteinases participate in physiological ECM remodelling, often operating as components in a cascade that resembles the clotting process (Alexander and Werb, 1991). However, the matrix metalloproteinases (MMPs) are quantitatively the most important enzymes involved in the actual attack on ECM components (Matrisian, 1992).

The MMP family is broken into three major subgroups on the basis of structural similarities and substrate specifities (Birkedal-Hansen et al, 1993), namely the collagenases (interstitial and neutrophil) (MMP-1 and MMP-8), gelatinases (72-kDa and

92-kDa) or type IV collagenases (MMP-2 and MMP-9), and stromelysins-1, -2 and -3 (MMP-3, MMP-10 and ST3{MMP-11}) and PUMP-1 or matrylisin (MMP-7). These enzymes are released by specific cell types and their expression is highly regulated, both positively and negatively, by diverse stimuli including growth factors, hormones, morphogens and cytokines (Matrisian, 1992).

The actions of MMPs in tissues are held in check by their tissue specific inhibitors (TIMPs), whose expression is controlled, like the MMPs, by tissue and stimulus-specific mechanisms (Denhardt et al, 1993). At least three mammalian TIMPs exist: TIMP-1, TIMP-2 and TIMP-3. Individual TIMPs have unique properties such as the ability to form specific complexes with pro-gelatinases (TIMP-1/pro-92kDa gelatinase and TIMP-2/pro-72kDa gelatinase) (Stetler-Stevenson et al, 1989, Goldberg et al, 1989; De Clerck et al, 1991a), that suggest that they have distinct physiological roles. Also TIMP-3 and a closely related transformation-associated protein in chickens (ChIMP-3) are ECM-associated proteins, whereas TIMP-1 and TIMP-2 are freely diffusible (Staskus et al, 1991, Pavloff et al, 1992; Yang and Hawkes, 1992). It is important to note that TIMPs are bifunctional proteins since, in addition to their well-characterized actions as MMP inhibitors, they also promote cell growth, recognized first through their actions as erythroid potentiating activities (EPAs) for erythroid precursors in vitro and in vivo (Gasson et al, 1985, Stetler-Stevenson et al, 1993), but more recently as mitogens for many other cell types (Hayakawa et al, 1992).

Work with animal models and malignant and transformed cells has shown that increased production of MMPs is associated with increased invasion into basement membranes in vitro (Mignatti et al, 1986; Nakajima et al, 1987; Liotta et al, 1991). Moreover, in animal models this behavior correlates with metastatic ability (reviewed in Liotta et al, 1991). Conversely, the metastasis suppression role of TIMPs has been demonstrated by the abilities of TIMP-1 and TIMP-2 to inhibit invasion in vivo (Mignatti et al, 1986; Schultz et al, 1988; De Clerck et al, 1991b, 1992c; Khokha et al, 1992) or

induction of malignant behavior in otherwise normal mouse fibroblasts down-regulated for TIMP-1 expression by anti-sense RNA (Khokha et al, 1989).

Though data on human tumors were sparse until recently, they are now accumulating rapidly. The picture emerging from studies of colorectal, breast, skin, esophageal and head and neck carcinomas, as well as more rare entities like giant cell tumor of bone, confirms in vitro findings that malignant tumors express higher levels of MMPs than normal tissues and that different tumors produce different enzymes. For example, ST3 is expressed by human breast carcinomas (Basset et al, 1990; Wolf et al, 1993) and head and neck squamous cell carcinomas (Muller et al, 1993), while esophageal squamous cell carcinomas most commonly express MMP-2 and MMP-3 (Shima et al, 1992). Our data reveal the importance of 92kDa gelatinase (MMP-9) in human non-Hodgkin's lymphomas (Kossakowska 1992, 1993). Different cell types express MMP's and TIMPs, including both tumor and associated stromal cells. Some patterns are very consistent, such as the expression of ST3 by stromal fibroblasts (Basset et al, 1990, Wolfe et al, 1993, Muller et al, 1993) and our own observations of elevated TIMP-1 RNAs in various stromal cell types in non-Hodgkin's lymphomas and lung carcinomas (Kossakowska, 1993, Urbanski, 1992).

Since adenocarcinomas are capable of invasion (or ECM destruction) and adenomas are not, we initiated a study of the expression of MMPs and TIMPs in human sporadic colorectal neoplasia (HSCRN) by analysis of colonic adenocarinoma. Having established the common profiles for MMPs and TIMPs expression by carcinomas, we compared these data with the profiles seen in adenomas. Evidence of gene expression was detection of gene transcript - mRNA using Northern blot technique.

We have analyzed 31 lesions from the spectrum of HSCRN for the expression of several MMPs, TIMP-1 and TIMP-2. The data from this study showed that ST3, 92-kDa gelatinase and interstitial collagenase represent MMPs expressed more frequently by colonic adenocarcinomas and malignant polyps than by adenomas or non-neoplastic

tissue. Based on these findings and previously reported analyses of breast and lung neoplasia (Basset, 1990, Urbanski, 1992) it appears likely that induction of these three enzymes precedes tumor invasion. Morever, it follows that these enzymes serve a function in the malignant phenotype. These observations may be important in subsequent studies of HSCRN. It is very likely that colonic adenomas which express at least two of ST3, interstitial collagenase and 92-kDa gelatinase represent a subgroup of adenomas committed to malignant transformation (= or < 5% of all adenomas). There is little doubt that the activation of the genes coding for MMPs is a secondary event to another genomic alteration which precedes this activation and may be essential for the malignant transformation. It is likely that the knowledge of the changes in the expression of MMPs may be used to select adenomas for future molecular analyses. Subdivision of adenomas based on the MMPs expression pattern would allow distinction between genetic events preceding commitment to malignant transformation from those which occur after genotypic commitment to malignant transformation had taken place.

Studies of gene expression at the mRNA level must be complemented by the assessment of the protein product, as mRNA may not be translated into functional protein. One of the MMPs which is overexpressed in carcinomas and severely dysplastic adenomas 92-kDa gelatinase (MMP-9) has elastolytic activity. Many of the colonic adenomas show demonstrable abnormalities of elastin framework within their stalk. We have chosen therefore to study elastolytic activity in the primary cultures of colonic adenomas and carcinomas.

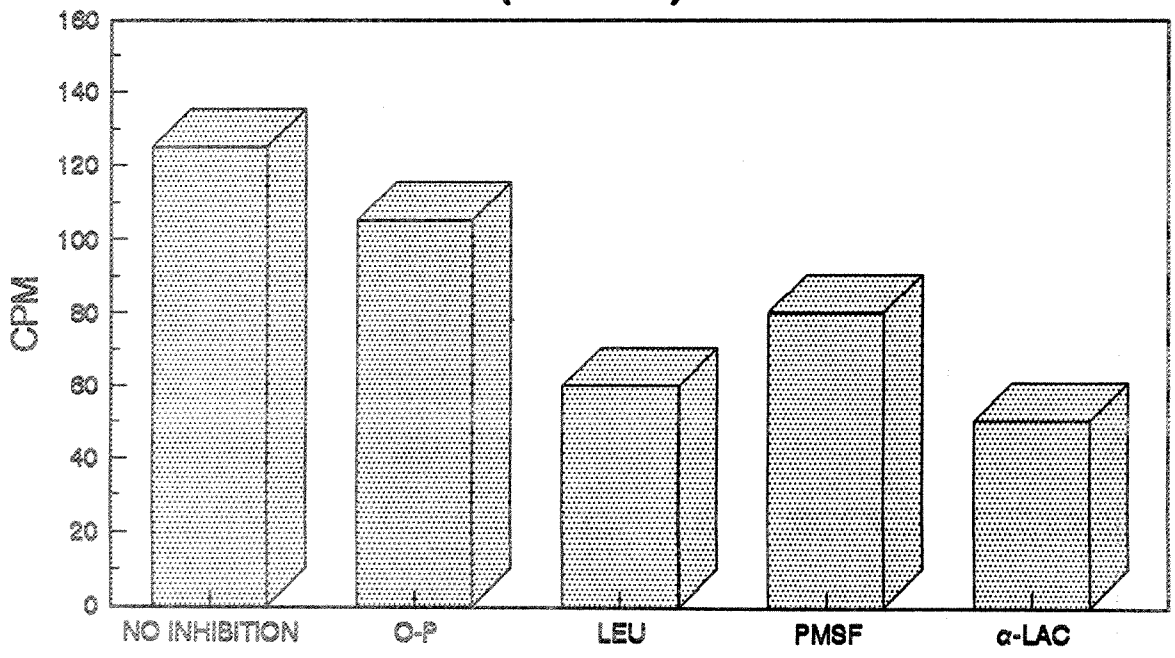
The proteinases capable of elastin degradation belong primarily to three separate families: MMPs, cysteine and serine proteinases (Alexander and Werb, 1991). A serine proteinase which is known to play a role in tumor invasion is urokinase-type plasminogen activator (UPA, 50kDa) while cysteine proteinases are represented by cathepsins. We were studying elastolytic activity of colonic adenomas and carcinomas in primary cultures on elastin discs studying levels of elastin degradation products in supernatant by ELISA or by detection of free counts after addition of [^{3}H] elastin. The

inhibition studies of primary cultures of colonic neoplastic lesions have established a heterogeneity among enzymes responsible for elastolytic activity within these lesions. While invariably elastolytic activity was abolished following administration of leupeptin and PMSF (cysteine and serine proteinases inhibitors) the MMPs inhibitors (O-phenanthroline and EDTA) decreased elastin degradation only in isolated cases (Figure 1).

In view of the existing information on the cysteine and serine proteinases in human neoplasia these observations indicate the necessity of expanding research of MMPs in HSCRN by investigation of the expression patterns and functions of these two additional groups of enzymes.

FIGURE 1

INHIBITION OF ELASTOLYTIC ACTIVITY OF THE PRIMARY CULTURE OF COLORECTAL CARCINOMA (SIGMOID)



CPM - Counts Per Minute
O-P - O-Phenanthroline
LEU - Leupeptin
α-LAC - Alpha-Lactose

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Dysplasia and Early Carcinoma in IBD and Colorectal Adenomas - Criteria, Terminology, and Implications for Patient Management

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Introduction:

Several decades ago, pathologists noted cytologic and architectural variations in colorectal adenomas that were interpreted as stages in the progression to adenocarcinoma. Unfortunately, many of these changes, while still recognized as noninvasive, were often reported as *carcinoma-in-situ*. This, coupled with the imprecise distinction between the two major types of epithelial polyps - adenomatous and hyperplastic - led to many instances of needless colonic resections and an era of controversy regarding the precancerous nature of "polyps". Terms were thus sought to replace *carcinoma-in-situ*. These included *atypia, anaplasia, colorectal intraepithelial neoplasia*, and, most recently, *dysplasia*, the latter being appropriated from the literature on cervical pathology. Paralleling the clarification of the malignant potential of colorectal adenomas was the elucidation of the spectrum of histologic appearances in ulcerative colitis culminating in invasive carcinoma(1, 2). It was here that the term *dysplasia* came to be accepted as conveying a concept of a histologic appearance that was both a precursor and a warning of cancer in the large intestine, but not in itself a malignancy capable of metastasizing. The successful use of *dysplasia* in inflammatory bowel disease (IBD) led to its application to similar histologic changes in adenomas, but with the understanding that the significance of dysplastic epithelium in IBD was far greater than that in most adenomas.

Many of the morphologic features of malignant progression in colorectal mucosa are similar in individuals with and without chronic inflammatory bowel disease (IBD).

Dysplasia is an unequivocal, but non-invasive neoplastic transformation of the intestinal epithelium that can be recognized by its abnormal cellular and architectural alterations. Only two grades - *low-grade dysplasia*, and *high-grade dysplasia* - will be referred to. *High-grade dysplasia* encompasses changes previously called *carcinoma-in-situ*, and replaces that term.

Intramucosal carcinoma is invasive adenocarcinoma that extends no deeper than the muscularis mucosae.

Invasive carcinoma extends into the submucosa or deeper. For simplicity, *adenocarcinoma* or *carcinoma* will be used synonymously.

Polyp refers to any abnormal elevation on the mucosal surface, whether due to a displacement from underlying expansion (e.g. lipoma), inflammatory reaction, non-neoplastic cellular proliferation (e.g. repair, hyperplasia), benign neoplasia, or malignancy. The common epithelial polyps of the colorectum are of two types - *hyperplastic polyps*, and *adenomas*. (3, 4). Adenomas are usually subdivided histologically into *tubular adenomas, villous adenomas*, and *tubulovillous adenomas*.

Pseudopolyp is an outdated term that may be abandoned as a histologic diagnosis. In its place, more precise terms, descriptive of the histologic appearance of the mucosal elevations in inflammatory bowel disease (IBD), such as *inflammatory polyp* , should be employed.

The adenoma-carcinoma sequence is accepted as the usual progression in the development of the vast majority of colorectal adenocarcinomas (5). The events in benign to malignant transformation are believed to take place in both uninflamed and chronically inflamed intestinal mucosa, but at an accelerated pace and with greater frequency in IBD.

Dysplasia in Inflammatory Bowel Disease:

The criteria for the diagnosis of colorectal dysplasia were first codified in mucosal specimens from patients with ulcerative colitis (2). Many earlier reports recognized these changes, and terms such as "atypia", "anaplasia", "precancer", and "carcinoma-in-situ" were used in their description (1, 5, 6). Low-grade dysplasia is characterized by mucosal changes resembling those seen in adenomas; enlarged crypts lined by tall epithelial cells with elongated,

hyperchromic, pseudostratified, basal nuclei, and a failure of those cells to normally mature and differentiate into normal goblet and absorptive cells at the surface. Some mucin may be produced by the neoplastic cells, and "dystrophic" goblet cells have been described in dysplasia (2, 7). The surface of low-grade dysplastic areas in IBD may be villous, but that feature alone does not increase its grade. In high-grade dysplasia, there is true stratification of the neoplastic cells, and that is its most important distinguishing feature. Other features of high-grade dysplasia include a greater degree of cytologic variance, with nuclear pleomorphism, in which they more resemble the cells of invasive carcinoma than the tall, regular cells of an adenoma. In very small areas of high-grade dysplasia, there is a tendency of cells to form expansile nests that appear to push the adenomatous cells to their sides. Mitotic activity at all levels of the crypt is seen in dysplasia of both low and high grades, but the basal polarity of nuclei is maintained in low-grade lesions. The grade of dysplasia in a given specimen is determined by the most severe changes present, but "an increase in rating from low- to high-grade dysplasia based solely on the appearance of high-grade features in one or two crypts is probably not justified" (2). Just how much high-grade dysplasia is necessary to justify its diagnosis in a specimen is not universally agreed upon, but the statement quoted might imply that its recognition in three or more crypts is sufficient.

The recommendations of the Inflammatory Bowel Disease - Dysplasia Morphology Study Group in 1983 (2) included three major diagnostic categories, namely, "Negative for Dysplasia", "Indefinite for Dysplasia", and "Positive for Dysplasia", the latter graded as above. The category of Indefinite is used when the histologic changes meet some, but not all of the criteria for dysplasia, and thus is usually applied to equivocal cases of low-grade dysplasia. This category is also used when changes of low-grade dysplasia are seen in actively inflamed mucosa, since reparative epithelium may show identical features. The Indefinite category was further subdivide into "Probably positive", "Probably negative", and "Unknown". In my opinion, that subdivision is not justified, and should be abandoned. The criteria for such categorization are highly subjective, and the use of the subcategories is of no significant help in patient management. It is far more informative to use an unmodified, honest statement of "Indefinite for dysplasia", and to state the reason, than to attempt to push a diagnosis too far and to risk misleading the clinician with undefined probabilities. The category "Indefinite for Dysplasia" should be used as a diagnostic entity in mucosal biopsy specimens from patients with IBD, and the clinician should be familiar with its meaning and implications for further patient examination.

When activity (acute cryptitis) is present in an IBD specimen, unequivocal changes of high-grade dysplasia may still be recognizable and reportable, but caution should be undertaken in interpreting cytologic changes that are seen in both reparative epithelium and low-grade dysplasia. It has been suggested that dysplastic epithelium is resistant to involvement by acute inflammation (2). Nuclear hyperchromism, enlargement, mitotic activity, and delayed maturation are all features of regenerative epithelium, and cells in the germinative, basal zone of the normal crypt have morphologic similarities to those of adenomatous mucosa.

Although less epidemiologic data exist concerning carcinoma in Crohn's disease, it is reasonable to apply the same approach to the evaluation of dysplasia. The incidence of carcinoma in Crohn's disease, although lower than that in ulcerative colitis, is significantly higher than that in the general population (8, 9), and its association with dysplasia has been reported (10-15).

Dysplasia-Associated Lesion or Mass (DALM):

The significance of isolated polypoid adenomas in patients with ulcerative colitis is controversial (16). It is conceivable that sporadic adenomas arise in colons afflicted with IBD, but the definition of IBD-associated dysplasia would also include these. Should these be considered in the decision to perform a colectomy? Are they signals of synchronous carcinoma? Is their significance no greater than that of the sporadic adenoma in the general population? Few studies have addressed these questions (17, 18). The original description of DALM included 5 cases of isolated pedunculated masses, 2 cases of isolated flat lesions, and 5 cases of multiple polyps among 112 patients with ulcerative colitis (18). Seven of these 12 patients harbored a carcinoma, and all 5 isolated polyps contained cancer. If a polyp is incompletely removed from a

patient with ulcerative colitis, and it contains high-grade dysplasia, the risk of an underlying cancer is probably great, but if it has been totally excised and contains no invasive cancer, it has probably been adequately treated (16). But whether the patient has been adequately treated is not yet known. Despite this uncertainty, I currently regard an adenoma of any configuration, arising in an area involved by ulcerative colitis, as dysplasia associated with IBD, and significant in a decision regarding colectomy. I have regarded at least one pedunculated adenoma without high-grade dysplasia, arising in the ascending colon of a patient with limited left-sided colitis, as a sporadic lesion, not to be considered an indication for colectomy. These are personal judgments, and scientific evidence to support them does not exist. I have not yet been faced with the problem of a high-grade dysplastic lesion remote from diseased bowel in ulcerative colitis or Crohn's disease.

Natural History:

In IBD, both the extent and duration of disease influence the development of carcinoma. Patients with pancolitis or, at least with disease involving the transverse and descending colon, are at higher risk than those with only left-sided colitis (19). Patients who have been symptomatic of ulcerative colitis for at least 7 years are at significant risk for developing carcinoma (19-22), and should be entered in a program of regular surveillance. The duration of disease necessary for the development of dysplasia is not known, but in one study there was a 5% incidence of dysplasia after 10 years of colitis, and a 23% incidence after 20 years (23). The risk of carcinoma increases 0.5% to 2% per year after the first 10 years of disease (19, 20), and these figures provide only an approximation of the time for progression of intraepithelial to invasive carcinoma.

Growth rate and progression to malignancy of colorectal adenomas in the general population can only be estimated by epidemiologic studies. Nine years has been cited as an average lag time between adenoma and invasive carcinoma (24). Among patients with familial polyposis coli, all will develop cancer after 30 years if not treated by colectomy. There is a 10% incidence of carcinoma after 5 years of symptoms, and a 50% incidence after 20 years (25).

Endoscopy and Biopsy Surveillance:

Periodic colonoscopic surveillance of patients with chronic IBD is recommended as a way of identifying those at risk for colorectal cancer (9, 17, 22, 23, 26-29). Annual total colonoscopy with biopsy of 6 to 8 areas from cecum to rectum, in addition to any area suspect for dysplasia, is advised. For the detection of dysplasia, it is important to avoid areas of mucosa that appear actively inflamed. The management of the patient undergoing regular surveillance is highly dependent on the histopathologic findings. Remembering that carcinoma can occur anywhere in the diseased large intestine of a patient with IBD and dysplasia, a decision to employ surgical prophylaxis usually means a total colectomy, with either a permanent ileostomy or an ileo-anal anastomosis. The following general recommendations are in practice:

Histologic Diagnosis	Management Recommendation
Negative for dysplasia	Continue regular surveillance
Indefinite for dysplasia	Shorter interval surveillance
Positive for dysplasia, low-grade	Shorter interval surveillance or colectomy*
Positive for dysplasia, high-grade	Colectomy
DALM	Colectomy

*Consider colectomy when low-grade dysplasia present multifocally or in consecutive biopsy specimens.

There is current disagreement about whether the appropriate interval between colonoscopic examinations is one or two years, for patients negative for dysplasia, but most gastroenterologists will halve the accepted interval when a biopsy is interpreted as indefinite, or low-grade dysplasia. There is also controversy over the benefits of random biopsies for surveillance. One report claims that most dysplasia was found in the rectal mucosa, and that there is a high concordance

between dysplasia and the development of colorectal carcinoma within 6 years (29). Another states that there was a very poor correlation between rectal dysplasia and more proximal carcinoma, and that multiple random biopsies have a low sensitivity and specificity in detecting carcinoma, there being many patients in that study with carcinoma but no dysplasia on previous biopsies (28). Nevertheless, the same investigators recommended colectomy whenever dysplasia of any grade is seen. In a third report, dysplasia was encountered more often in the right than the left side of the colon, but none of the patients developed carcinoma after a five year interval (23). Clearly, additional prospective data are necessary to properly assess the value of surveillance biopsies for the detection of cancer in IBD, but the current trend is away from performing prophylactic colectomies on all patients with ulcerative colitis of ten years duration. Even less data are available concerning surveillance in Crohn's colitis (9).

Dysplasia in Colorectal Adenomas:

Adenomas are the precursors of colorectal carcinoma in the general population (5). Although adenomas and hyperplastic polyps share some common risk factors, they are believed to be unrelated sequentially, and the latter have no malignant potential (3, 4). A spectrum of histologic changes exists between the completely benign adenoma and invasive carcinoma, and the progression includes identifiable high-grade dysplasia. High-grade dysplasia in an adenoma is recognized by the same criteria as those just described for its recognition in IBD. What, then, is low-grade dysplasia in the non-colitis patient? It is the adenoma itself (30). Analogous to the transformation of non-neoplastic mucosa to low-grade dysplasia in IBD, and also analogous to the original concept of the transformation of normal cervical epithelium to mild dysplasia or CIN-I, adenomatous epithelium can be equated with low-grade dysplasia whenever it occurs in the bowel. There is no reason to attempt to change the nomenclature of adenomas, but in examining adenomas for additional cancer risk factors, only one grade of dysplasia - high-grade - is recognized. The "indefinite" category is not used in this setting. Some pathologists have continued to grade dysplasia as "mild", "moderate", and "severe". This deviates from the standardized nomenclature of the IBD-Dysplasia Study Group, and there is no standardized management response to a diagnosis of "moderate dysplasia". In adenomas, it is wiser to be conservative when a small focus of equivocal high-grade dysplasia is encountered.

Occasionally, the question arises as to how much high-grade dysplasia warrants its inclusion in a diagnostic report. The answer is partially dependent on the course of action taken by the treating physicians in response to the diagnosis. Having abandoned the term, "carcinoma-in-situ" in favor of high-grade dysplasia, there is less emotional response leading to needless colectomies. Definitive high-grade dysplasia in an incompletely removed adenoma should prompt an aggressive attempt to excise the remainder of the tumor, either endoscopically or by colotomy, but a complete polypectomy is curative irrespective of the amount of high-grade dysplasia. Arbitrarily, I consider three adenomatous crypts containing high-grade dysplasia the minimum amount to justify the diagnosis. Regardless of the amount of high-grade dysplasia, I will also append a comment that no invasive carcinoma is present, that the high-grade dysplasia is not at a resection edge, that the polyp has been completely removed as judged by the presence of normal mucosa at the base, and that no further therapy is indicated for the particular lesion. Unusual circumstances, such as the finding of high-grade dysplasia in several adenomas removed during one endoscopic procedure, or a totally high-grade dysplastic polyp, should be discussed with the clinician. I have managed to avoid the request to evaluate high-grade dysplasia on frozen section, and have managed to discourage most requests to perform frozen sections on polypectomy specimens.

Intramucosal Carcinoma:

Intramucosal carcinoma will be found more often in a polypectomy specimen than in a mucosal biopsy specimen from a patient with IBD. The larger the adenoma, the greater the chance of encountering carcinoma. There will usually be a zone of high-grade dysplasia above the intramucosal carcinoma. When intramucosal carcinoma occurs, it is frequently surrounded by an early desmoplastic reaction that replaces the normal immunocyte population of the lamina

propria. Invasion into, but not through, the muscularis mucosae is still intramucosal carcinoma. The diagnosis of intramucosal carcinoma may be extremely difficult because of the complex convolutions of adenomatous glands, especially in villous adenomas. When in doubt, even after examining multiple levels of a block, it is better to be conservative and ignore an equivocal focus of intramucosal carcinoma, since it has no more significance in most cases than high-grade dysplasia. The lamina propria of adenomas, as well as that of normal colonic mucosa, is devoid of lymphatics (31), and it is thus believed that intramucosal carcinoma has no ability to metastasize. Even though there are lymphatics in the muscularis mucosae, carcinomas that invade only that layer in a pedunculated adenoma do not metastasize (32, 33). In reporting intramucosal carcinoma in an adenoma, it is important to assess the completeness of the polypectomy and the presence or absence of invasive tumor at the resection line. The histologic grade of the carcinoma, and the observation of lymphatic invasion are probably more significant in tumors that invade the submucosa, but data to support that are currently being analyzed. When including the diagnosis of intramucosal carcinoma in a complete polypectomy specimen report, I will append a comment concerning the extent of invasive tumor, its potential, or lack thereof, to metastasize, and my opinion that the lesion has been adequately treated. When an adenoma containing intramucosal carcinoma has been only biopsied, removed in piecemeal fashion, or is suspected of having been only partially excised, I report that no definitive assessment of completeness of removal can be made, and that there is a possibility that more deeply invasive carcinoma has been left behind. A decision concerning additional treatment is then made by the endoscopist or surgeon after all pertinent findings are discussed.

A special subgroup of adenomas that has received recent study is the flat adenoma (34-39). These are small (usually not exceeding 1 cm), plaques of tubular adenomatous mucosa, unassociated with IBD, that have a high incidence of high-grade dysplasia, and a high association with synchronous and metachronous invasive colorectal carcinoma. I have seen one such lesion that had given rise to a minuscule invasive carcinoma.

Intramucosal carcinoma will rarely be encountered in mucosal biopsy specimens from patients with IBD, but can be expected in colectomy specimens and in excisions of dysplasia-associated lesions or masses (DALM). No large-scale studies have appeared evaluating the significance of intramucosal carcinoma in IBD, but it is reasonable to assume that it carries the same or greater risk of synchronous carcinoma as high-grade dysplasia in this population.

The evidence that annual or biannual colonoscopy or even sigmoidoscopy, of asymptomatic people, with removal of all polyps, results in a dramatic decrease in the incidence of colorectal cancer, is irrefutable (40-46).

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ENDOSCOPICALLY REMOVED MALIGNANT COLORECTAL POLYPS - CLINICOPATHOLOGICAL CORRELATIONS

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The pathologist plays a key and central role in the management of the patient with an endoscopically removed colorectal malignant polyp. In order for the pathologist to carry out this important role, he/she must: 1) handle and process the specimen correctly, 2) communicate closely with the clinicians, and 3) render a diagnosis that will provide information as to whether the polypectomy is curative or a subsequent surgical resection is necessary. Due to space limitation this handout will concentrate on histopathological findings and their clinicopathological correlations. Please see references 2, 3, and 5 for a more complete discussion of above items # 1 and # 2.

A malignant polyp is one in which cancer has invaded into the submucosa. Once a malignant polyp is diagnosed the following parameters should be examined: 1) Status of the transected (resection) margin (usually identified by cautery effect). Is the cancer at or near the resection margin ? ; 2) Grade of the cancer (I, II, or III); 3) Lymphatic or venous invasion (present or absent); and 4) If one is employing the Haggitt system, the grade, status of lymphatics and what Haggitt level the cancer has reached. The presence of cancer at or near the resection margin, and/or grade III cancer, and/or lymphatic or venous invasion, and/or Haggitt level 4, have been associated with adverse outcomes (local or distant recurrence, positive lymph nodes, residual cancer post resection). The magnitude of adverse outcome varies widely with each study. Combining all credable series from the literature, clinicopathological outcome is presented in Tables I, II, and III:

TABLE I.

OUTCOME OF ENDOSCOPICALLY REMOVED MALIGNANT COLORECTAL POLYPS AS RELATED TO STATUS OF RESECTION MARGINS

LITERATURE REVIEW (Data from References [1,3,6,7,8,9,10,13,14,15,17,18])

	Polypectomy Only			*Polypectomy Followed by Resection*			*All Cases*		
	NED (%)	Adverse (%)	Total	NED (%)	Adverse (%)	Total	NED (%)	Adverse (%)	Total
M+ *	28 (84.8)	5 (15.2)	33	75 (62)	46 (38)	121	103 (67)	51 (33)	154
M- *	251 (98.4)	4 (1.6) [A,B]	255	75 (88.2)	10 (11.8) [C,D]	85	326 (96)	14 (4)	340
		2 (0.8) ** [F]			4 (4.7) ** [E]			6 (1.7) ** [E,F]	

Adverse Outcome - Polypectomy only = Recurrence (local or distant). Polypectomy followed by resection = Residual local disease and/or lymph node metastases in resection specimen. NED = No residual disease in resection specimen (polypectomy followed by resection) and no recurrence following polypectomy only. * M+ = Tumor at or near resection margin. M- = Negative resection margin. ** = Excluding cases with negative parameters (e.g. grade III cancer, and/or lymphatic invasion and/or venous invasion). A - 1 patient with venous invasion. B - 1 patient with vascular invasion. C - 4 patients with grade III cancer. D - 2 patients with vascular invasion. E - 4 patients with tumor in stalk, not otherwise specified. "Closeness" to resection margin unknown. F - 2 elderly patients certified as dying of carcinomatosis.

TABLE II.

OUTCOME OF ENDOSCOPICALLY REMOVED MALIGNANT COLORECTAL POLYPS - REGARDING LYMPHATIC INVASION, VENOUS INVASION, AND GRADE III CANCER

LITERATURE REVIEW

	Adverse Outcome *			*NED (%)*	*Incidence (%)*
	+ (%) *	- (%) *	All Cases(%)*		
LI (N = 115)** [1,5,8]	7 (87.5)	1 (12.5)	8 (44)	10 (56)	18 (15.6)
VI (N = 136)** [1,12]	0 (0)	1 (100)	1 (3.1)	31 (96.9)	32 (20.5)
VI/LI (N = 185)** [13,11]	13 (81)	3 (19)	16 (39)	25 (61)	41 (22.1)
III (N = 488)** [1,4,5,6,8,10,11,13]	16 (100)	0 (0)	16 (36)	29 (64)	45 (9.2)

N = Number of total polyps reviewed. * Adverse Outcome = Recurrence following polypectomy only, residual local disease and/or lymph node metastases in resection specimen post polypectomy. ** = References. (+) = Adverse outcome when other associated negative parameters (positive margin, lymphatic invasion, venous invasion, or grade III cancer) are also present. (-) = Adverse outcome when other associated negative parameters are absent. All Cases = Incidence of adverse outcome in all cases (those with and without other negative parameters).

TABLE III.

SUMMARY OF OUTCOME OF MALIGNANT COLORECTAL POLYPS USING HAGGITT CLASSIFICATION

LITERATURE REVIEW [C]

Level	N[A]	P[A]	P+R[AB]	Colect[A,B]	Local[A]	LN[A]	DOD[A,E]	*Recurrence* [A] (Local and/or Distant)
1	57	18	32	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	14	7	4	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	24	5	16	3	0 (0%)	0 (0%)	1 (4.1%) [D]	1 (4.1%)
4	151	11	128	12	3 (1.9%)	18 (11.9%)	5 (3.3%)	5 (3.3%)

A - N = Number of cases. P = Polypectomy. P + R = Polypectomy followed by resection. Colect = Primary treatment colectomy. Local = Residual local cancer in colectomy specimen. LN = Lymph nodes with tumor in colectomy specimen. DOD = Dead of disease. Recurrence = Local or distant recurrence post polypectomy or post polypectomy and resection.. B - Cases of Nivatvongs, et al were P + R or colect, but they were not separated out in their article. All these cases are included in P + R category. C - Data from Kyzer, et al, Nivatvongs, et al, and Haggitt, et al. D - One case with lymphatic invasion. E - Data from Kyzer, et al and Haggitt, et al. DOD status not stated in Nivatvongs, et al publication.

Some years ago members of the GIPS began a clinicopathological study of endoscopically removed malignant colorectal polyps. Polyps were examined for: 1) Whether or not they were truely malignant polyps; 2) Status of resection margin; 3) Grade and type of the cancer; 4) Presence of lymphatic invasion; 5) Presence of venous invasion; and 6) Polypoid carcinoma. Parameters were considered present (or absent) within an individual polyp only with agreement of at least 4 of 5 reviewing pathologists. Any other combination was considered indefinite for the parameter studied. Polypectomy only cases had to have a minimum of a 5-year follow-up to be included in this study. The findings of this study is presented in Table IV.

TABLE IV.

OUTCOME OF ENDOSCOPICALLY REMOVED MALIGNANT COLORECTAL POLYPS

(Malignant Polyp Study Group of the GIPS)

POLYPECTOMY FOLLOWED BY RESECTION (N = 104)
POLYPECTOMY ONLY (N = 36)

	ADVERSE *				*NED**				*TOTAL*
	+ (%) *	Indef (%) *	- (%) *	All (%)	+ (%) *	Indef (%) *	- (%) *	All (%)	
M+*	4 (33.3)	1 (8.3)	7 (58.3)	12 (21.4)	4 (9.0) [A]	11 (25)	29 (66)	44 (78.5)	56
M * >1.0	3 (75)	1 (25) [B]	0 (0)	4 (4.9)	13 (16.6) [C,D]	19 (24) [E]	46 (59)	78 (95)	82
LI*	1 (25)	0 (0)	3 (75)	4 (22.2)	5 (35.7) [D]	1 (7.1)	8 (57.1) [C]	14 (77.7)	18
LI_I *	2 (66.6)	0 (0)	1 (33.3)	3 (14.2)	5 (27.7)	3 (16.6) [E]	10 (55.5)	18 (85.7)	21
VI *	2 (100)	0 (0)	0 (0)	2 (40)	2 (66.6) [D]	0 (0)	1 (33.3)	3 (60)	5
VI_I *	0 (0)	0 (0)	0 (0)	0 (0)	4 (44.4)	0 (0)	5 (55.5)	9 (100)	9
III *	2 (66.6)	0 (0)	1 (33.3)	3 (37.5)	5 (100) [A]	0 (0)	0 (0)	5 (62.5)	8
III_I *	0 (0)	0 (0)	0 (0)	0 (0)	5 (50) [E]	2 (20)	3 (30)	10 (100)	10
PC *	4 (80)	1 (20)	0 (0)	5 (20)	10 (50)	5 (25)	5 (25)	20 (80)	25
PC_I *	3 (75)	1 (25)	0 (0)	4 (17.4)	10 (52.6)	2 (10.5)	7 (36.8)	19 (82.6)	23

Adverse outcome in polypectomy followed by resection specimen = Residual local disease and/or lymph node metastasis. Adverse outcome in polypectomy only = Later recurrence, local, and/or distant). NED = Negative findings in resection specimen and no recurrence in polypectomy only cases. +, Indef, - = Outcome when parameters studied are present (+), indefinite (indef), or absent (-) with other negative parameters. M+ = Cancer at or near (<1.0 mm) resection margin. M > 1.0 = cancer > 1.0 mm from resection margin. LI, VI, III, PC = Lymphatic invasion, venous invasion, grade III cancer, and polypoid cancer, respectively. LI_I, VI_I, III_I, PC_I - Indefinite for lymphatic invasion, venous invasion, grade III cancer, and polypoid cancer, respectively. A - One patient with negative resection, distant metastasis 5 years later. B - One patient with LI_I and colloid cancer. C - One patient with negative resection, liver metastasis 2 years later. D - One patient with negative resection, liver metastasis 7 years later. E - One patient with negative resection, liver metastasis 2 years later.

CONCLUSIONS:

Data from the literature and the GIPS study indicate that cancer at or near the resection margin, grade III cancer, lymphatic and/or venous invasion, and Haggitt level 4 are parameters that are associated with an adverse outcome and should necessitate a resection, post polypectomy. Endoscopically removed malignant

colorectal polyps with a negative margin (or cancer > 1.0 mm from the margin), grade I or II cancer, and the absence of lymphatic or venous invasion can probably be successfully treated with polypectomy alone. The incidence of adverse outcome in the absence of negative parameters is low (1.7% from the literature and 1.3% from the GIPS study). The only adverse outcome without "negative parameters" in the GIPS study was a case which was indefinite for lymphatic invasion (which means by some observers, this case would have had a negative parameter). Of the 6 cases from the literature with negative margins (and no other negative parameters) but adverse outcome; 4 were described as cancer into the stalk, however, the distance from the resection margin is not stated and 2 were elderly patients certified as dying of carcinomatosis.

In the GIPS study, there was good interobserver interpretation of margin status, grade of the cancer, and venous invasion, however, there was wide observer variation in diagnosing lymphatic invasion.

Even with the presence of negative parameters a subsequent definitive resection will reveal no residual cancer in 78.5% (GIPS) and 67% (literature review) of cases.

Polypoid cancers in of themselves are not an indication for resection, as all polypoid cancers with adverse outcome had negative parameters present.

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In last winter's newsletter (Vol II, No. 1) I wrote an editorial about useage of the term *high grade dysplasia* vs. *in situ carcinoma* in colorectal adenomas. What follows are letters I received in response to that editorial . . . .

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19 Feb. 1993

Dear Harry,

In response to your editorial in the current newsletter of the GIPS about the terminology used for non-invasive epithelial growth in the GI mucosa: early in my career, a colleague made a diagnosis of "carcinoma-in-situ" in a polyp removed with a (then rigid) endoscope. The surgeon, reading the word "carcinoma," wanted a cure and did a segmental resection - but the patient died on the operating table of an arrhythmia. So, problem #1 - the codeword "carcinoma" is scary for patients, physicians, and insurance carriers. Should we properly scare them with the C-word; is the biology of the lesion that of cancer? So, problem #2 - are the cells that make up the (usually) cribriform (ie, growth into a gland lumen, not into the tissue) biologically cancer cells (capable of invading and metastasizing)? I think the evidence is that the cells have to go through another step in the polyp-dysplasia-carcinoma sequence before they acquire the ability to invade and survive outside their normal surface habitat. Your study is struggling to answer the question whether early invasive lesions do not metastasize until a certain size, depth of invasion, or cell differentiation (clone?) is reached.

I stopped using the term "CIS" long ago and use the less scary, still biologically vague term of dysplasia of differing degrees. I was glad to read Bob Riddell's essay in

Gastroenterology in 1985 bringing the issue before a wide U.S. forum. (I know he is "British," but there were natives of the former British Colonies worrying about the issue and reaching the conclusion that "CIS" is not a good diagnostic term for the GI mucosal lesions).

Sincerely,

Bill

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Genève, le 22 February 1993

Harry S. Cooper, M.D.
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USA

Dear Doctor Cooper,

I read with interest your editor's message of your GIPS news letter Nr 1, winter 1993. I fully agree with your proposal to introduce the term "severe dysplasia" instead of in situ cancer. As a pupil of Basil Morson, I have always used this designation, which Basil coined in order to protect the patient from the surgeon, as you make an allusion to in your message. Moreover I think that the term "in situ cancer", applied to the digestive tract (apart from the esophagus) is one of the most silly existing in the pathologist's language : if one would be really strict from the point of view of semantics, the in situ should be the crypt itself, thus a pathologist should be very experienced or highly sharp eyed to discover a cancer in a single crypt. For these reasons I do heartily encourage your attempt to introduce severe dysplasia on your side of the pond ! I do hope that this item might be discussed at the next meeting of your Society in New Orleans, at which I look forward to participate.

Yours sincerely,

Sven Widgren, M.D.

CEDARS-SINAI MEDICAL CENTER

DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE

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Gynecologic Pathology; Endocrine Pathology

Delver R. Cain, M.D.
Genitourinary Pathology; Cytopathology

Arthur H. Cohen, M.D.
Renal Pathology

Irene Davos, M.D.
Gynecologic Pathology; Neuropathology

Stuart B. Dubin, M.D., Ph.D.
Clinical Chemistry; Laboratory Computerization

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Clinical Chemistry; Reference Laboratory

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Cardiovascular Pathology

Dennis Goldfinger, M.D.
Transfusion Medicine; Immunohematology

Neal S. Goldstein, M.D.
Gastrointestinal and Dermatopathology

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February 18, 1993

Harry S. Cooper, M.D.
Hahnemann University Hospital
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Dear Harry:

Your editor's message, in the current GIPS Newsletter, was thoughtful and appreciated. I am happy to share my opinion with you.

I never use the term "in situ carcinoma", and have always used the term "severe (high grade) dysplasia", whether it be colonic polyp, cervix, bronchial epithelium, or any place else. In many of these settings the patient may be relatively young, the lesion may be eminently curable, and the implications for both employment and insurance may be significant. I have always also supposed, but never tested, that patients have far less anxiety when they obtain a pathology report and see the word "dysplasia" as opposed to the word "carcinoma". I also support your view that the GIPS should serve an educational role for our subspecialty. I am not sure how that should be done, of course, and look forward to seeing further ideas from you and other members of the Society. It might be both amusing and instructive to ask our colleagues to submit a list of other terms that they are uncomfortable with.

Finally if you are taking votes for the logo at this time, I would select number 4.

I look forward to seeing you in New Orleans. Best regards.

Sincerely,

Stephen A. Geller, M.D.

SAG/ee

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Form No. 4509 Rev. 12-92

WAKE FOREST

The Bowman Gray

School of Medicine

Department of Pathology
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February 17, 1993

Harry S. Cooper, M.D.
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Dear Harry:

I have just read your recent Editor's Message (GIPS, Newsletter, Vol II, No. 1). This brief note is in response to some of your questions.

I have used for several years now the terms low-grade and high-grade glandular dysplasia in reference to colonic adenomas. Actually, I do not use the term low-grade dysplasia to any extent as I believe it is implied in the definition of most adenomas. On infrequent occasions I have used the term in-situ carcinoma. I am currently a review pathologist for the national Polyp Prevention Trial. Terminology for the PPT does not permit the use of in-situ carcinoma. In this clinical trial, the term in-situ carcinoma is incorporated into severe glandular dysplasia. Furthermore, the PPT does not permit the use of intramucosal carcinoma.

I believe that it is time for greater standardization in terminology of colonic adenomas. Perhaps the GIPS is the proper organization promulgating alterations for analogous to the recent nomenclature changes for cervical vaginal cytology smears. Perhaps we should devise the "Philadelphia System." Perhaps the terms low-and high-grade glandular intraepithelial lesion would be preferable, but I certainly hope not. I would support any effort to eliminate archaic terms such as adenomatous polyp and glandular atypia which I still find rampant in use in this region.

Thank you for the opportunity to write a letter longer than your editorial. Onward to New Orleans.

Sincerely,

Kim R. Geisinger, M.D.
Professor and Director
Surgical Pathology and Cytology

KRG/plm

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ADDRESS REPLY TO THE DIRECTOR
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23 February 1993

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Dear Harry,

I was pleased to read your message in the GIPS Newsletter regarding standards in GI pathology.

There are a number of groups that are concerned with developing standards in this field: WHO has been working on standard definitions and terms for the International Histological Classification of Tumors (now in the second edition); the International Union Against Cancer (UICC), together with the American Joint Committee on Cancer (AJCC), have recently revised the staging classification for all GI carcinomas and is developing classifications for GI sarcomas and carcinoids; the College of American Pathologists is soon to publish guidelines for pathology evaluation of colorectal carcinoma; the AJCC is preparing staging checklists for gastric and colorectal carcinomas; the Council for International Organizations of Medical Sciences has devoted Volume IV of its International Nomenclature of Diseases to Diseases of the Digestive System.

I think the Society could play an important role in promoting standardized reporting of GI cases. First, it could draw attention to the above national and international standards and foster their use. Second, it could make its expertise available to these bodies for evaluation and testing of published classifications and elaboration of new proposals. The International Society of Gynecological Pathologists served in this manner in the development of the WHO histological classifications of tumors of the female genital tract and ovary.

I would be glad to provide you with more information and examples of some of these works if you wish.

Best wishes.

Yours sincerely,

Leslie H. Sobin, MD
Chief, Gastrointestinal Pathology

TALES OF THE AMPULLA OF VATER

xix

By the shores of Duodenum
where the villi bathe in bile
It was once upon a time
a hapless gland was placed on trial.

T'was a case of cell atypia
to which she had to answer
Claims of treason and subversion
accusation was Precancer.

Prosecution gave the evidence
a high mitotic rate
She had nuclear enlargement
and a basophilic state.

Said her S-phase was unusual
cell contact she'd avoid
Also then of course the hearsay was
that she was aneuploid.

All alone she stood in her defense
against this accusation
You're deceived by basophilia
it's just regeneration.

I had undergone erosion
from a lapse of surface mucus
Just a victim of the acid tide
a justified excuse is.

Then the polyps came and macrophages
cleared up the detritus
You can find it in the records
here "a mild duodenitis".

Well so there I was with surface bare
at risk of ulceration
There was only one recourse
reactive cell regeneration.

After listening most patiently
Great Judge Ampulla spoke
He would summarize for he was wise
and justice was his cloak.

Yes the gland is right and innocent
and not a risk for cancer
Her regenerative changes
do not provide us with the answer.

Though atypical she may well be
this is a fair reaction
It may simulate dysplasia
but it's not a true infraction.

You must be on guard and be alert
give benefit to the doubt
So you do not harm the innocent
and cast the injured out.

Then Ampulla bade the polyps
to release the gland accused
With apologies and recompense
her case was now excused.

Leslie H. Sobin, M.D.

As editor of the GIPS newsletter, I have decided to add a new section to the GIPS newsletter. In order to disseminate new information of GI Pathology to our members, I am asking the membership to submit to the GIPS newsletter any new and recent publications. We will print the abstract and the reference. The first such article is:

Saul S.H.
The Watery Diarrhea - Colitis Syndrome
A Review of Collagenous and Microscopic/
Lymphocytic Colitis
Int J Surg Pathol 1: 65-82, 1993

For abstracts contact Dr. Saul at:

Department of Pathology
Charter County Hospital
701 East Marshall Street
West Chester, PA 19380

The abstract follows . . .

ABSTRACT

Collagenous and lymphocytic/microscopic colitis represent a distinct histopathologic spectrum of findings, with occasional transition, observed in patients with normal or near-normal colonoscopic findings and chronic watery diarrhea. Biopsies are characterized by surface epithelial damage, an increased number of chronic inflamatory cells in the lamina propria, intraepithelial lymphocytosis, intact crypt architecture and in the cases of collagenous colitis, a thickened SCL. While their precise interrelationship is unclear, as their clinicopathologic similarities far outweigh their differences it appears reasonable for pathologists and clinicians to consider them conceptually together as part of a syndrome of chronic watery diarrhea and colitis distinct from other forms of chronic inflammatory bowel disease.

The etiology and pathogenesis of this syndrome is unclear. Colorectal surface epithelial damage appears to be for the most part responsible for the secretory diarrhea while, the thickened SCL appears to be a variable response to the surface epithelial damage. Why the thickened SCL occurs only in some cases, does not occur in other forms of colitis and whether it functions as a diffusion barrier are unknown. The propensity of the watery diarrhea-colitis syndrome to preferentially affect middle-aged and elderly females, an association with autoimmune disorders and clinicopathologic similarities to celiac disease suggests that host immune factors are important. Other dietary factors, medications or other agents may also play a role and this is currently under investigation. Small bowel villous atrophy appears to account for the presence of steatorrhea noted in some reports.

Definitive diagnosis is facilitated by the procurement of multiple well oriented biopsies, preferably extending at least into the proximal left colon. A thickened SCL occasionally can only be demonstrated in biopsies from the right colon. An appreciation of the normal variation found in colorectal biopsies and recognition of artefactual thickening of the subepithelial basement membrane in maloriented sections and in

relation to bowel preparation will eliminate overdiagnosis of normal biopsies, while the absence of features typical for other forms of inflammatory bowel disease facilitates differential diagnosis. Patients may respond dramatically to therapeutic intervention with drugs often used for ulcerative colitis and Crohn's disease, however spontaneous remissions are well documented. A colitis- dysplasia-carcinoma sequence has not as yet been documented to occur in this patient population.

In just over one decade we have come to recognize the morphologic features of the watery diarrhea-colitis syndrome. Hopefully the next decade of observation and investigation will help to clarify the precise relationship between cases with and without a thickened SCL as well as the etiology and pathogenesis of the secretory diarrhea.

GIPS AT DIGESTIVE DISEASE WEEK 1994

INFECTIONS OF THE ALIMENTARY TRACT

New Orleans, Louisiana
Tuesday, May 17, 1994 , 3:30 to 5:30 PM

Moderator: Robert R. Pascal, M.D.

1. Protozoal and Helminthic Infestations
   David Schwartz, M.D.

2. Infections in the Immunocompromised Patient
   Jan Orenstein, M.D.

3. Gastritis due to Helicobacter and Other Spiral Organisms
   Robert Genta, M.D.

4. Infectious Colitides
   Robert Petras, M.D.