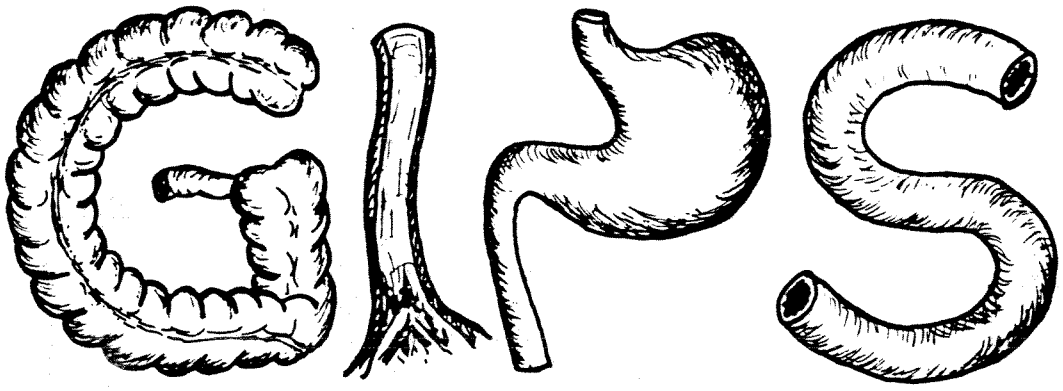

THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

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GASTROINTESTINAL PATHOLOGY OFFICERS AND COMMITTE MEMBERS

February 16, 1993

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IMMUNOCYTOCHEMICAL DIAGNOSIS OF BARRETT'S EPITHELIUM WITH THE MONOCLONAL ANTIBODY $7E_{12}H_{12}$.

P Amenta, I Prasad, S Garia and K Das. Robert Wood Johnson Medical School and University Hospital, New Brunswick, NJ.

The monoclonal antibody (MAb) $7E_{12}H_{12}$ was developed against a colonic epithelial protein. Twenty-four (24) biopsies from benign Barrett's epithelium (BE), 12 from adenocarcinoma arising in BE, 16 from normal esophageal epithelium, 16 from active esophagitis, 13 with esophageal squamous cell carcinoma, 11 from normal gastro-esophageal mucosa and stomach were studied with the MAb. 87.5% of all benign BE specimens and 100% of all adenocarcinomas reacted with the MAb. Two of 16 specimens from active esophagitis without a diagnosis of BE also reacted with the MAb while normal gastro-esophageal junctional epithelium did not. These findings indicate that there is a common reactive epitope shared between BE and colonic epithelium. This monoclonal antibody may be potentially helpful in the diagnosis of BE.

DF-3 ANTIGEN IN NORMAL, INFLAMMATORY AND NEOPLASTIC COLON

C Andrews, Jr., J. Jessup, D. Hayes, G Steele. New England Deaconess Hospital, Department of Pathology and Laboratory of Cancer Biology, Harvard Medical School, Boston, MA.

The DF-3 antigen is a high molecular weight mucin-like glycoprotein found in human mammary tissues. The investigators studied DF-3 expression in formalin-fixed biopsy and resection samples of 19 normal colonic mucosal specimens, 49 inflammatory lesions (39 examples of chronic colitis and 10 other inflammatory conditions), 35 adenomatous polyps, and 38 primary colonic adenocarcinomas. Staining was reported as follows: < 1% = 0, 1-50% = 1+, > 50% = 2+). The location of reactivity (membrane, luminal, or cytoplasmic) was also studied. DF-3 expression was detected in 85% of the adenocarcinomas, 12% of the adenomas and 12% of the inflammatory lesions. All normal colonic mucosa was non-reactive. The degree of staining was 2+ in 66% of the malignant lesions while only 25% of pre-malignant lesions revealed 2+ positivity. Inflammatory lesions demonstrated membrane positivity in a linear fashion restricted to the crypt compartment. In adenoma, staining was also linear and confined to areas of high grade dysplasia. In sharp contrast, carcinomas revealed coarse membrane staining with prominent outlining of luminal spaces and with intense reactivity of secretions and cytoplasm. The investigators conclude that the mammary mucin DF-3 is aberrantly expressed in malignant transformation of the large bowel. No expression is detected in normal mucosa. Inflammatory and pre-malignant lesions stain infrequently in a linear fashion, while most carcinomas react with a distinct distribution of staining.

IMMUNOHISTOCHEMICAL EXPRESSION AND LOCALIZATION OF MAC-2 IN THE NEOPLASTIC PROGRESSION OF COLON CARCINOMA

C Andrews, Jr, M Lotz, A Clarke, G Steele, A Mercurio. Department of Pathology and Laboratory of Cancer Biology, Deaconess Hospital and Harvard Medical School, Boston, MA.

The authors studied the expression of the monoclonal antibody M3/M8 in normal, pre-neoplastic and neoplastic colonic tissues. The M3/M8 antibody detects the MAC-2 S-lectin which plays a role in cell adhesion or recognition. The authors studied the cellular location (nuclear or cytoplasmic) and the percentage of positive cells (< 1% = 0, 1-25% = 1+, 26-75% = 2+, > 75% = 3+). The normal mucosa showed expression of MAC-2 with an increasing gradient such that the upper third of the crypt and surface cells revealed 100% staining. The localization of the MAC-2 was predominantly nuclear with a focal basal and basolateral cytoplasmic positivity. Hyperplastic polyps revealed a similar pattern and extent of positivity. In contrast, adenomas revealed diffuse cytoplasmic activity and only rare isolated nuclear localization. Adenocarcinomas stained heterogenously within tumors with 54% rated as 3+. Like adenomas, the staining was cytoplasmic and rarely nuclear. The authors conclude that MAC-2 nuclear localization is lost in the neoplastic transformation in colonic carcinoma. This data may suggest that MAC-2 may function as a tumor suppressor gene.

EARLY MORPHOLOGICAL CHANGES IN PELVIC ILEAL POUCHES

R Apel, AH Steinhart, R McLeod, Z Cohen, R Odze. Mount Sinai Hospital, Toronto, Canada.

The authors studied the early pathological features in ileal pouches (IP) hoping to provide insight into the pathogenesis of pouchitis. They evaluated in a blinded fashion 46 H & E stained IP mucosal biopsies from 23 patients, all of whom had a proctocolectomy for ulcerative colitis (UC). Two IP biopsies were obtained from each patient, one at the time of ileostomy closure which represent the control biopsy and the other after 6 weeks of IP function which represented the study group. Biopsies were evaluated for the degree of neutrophil (NEUT), eosinophil (EOS) and lymphocytic infiltration. Also evaluated was the degree of villous atrophy (VA) and the number of Paneth cells (PCs). Compared to the control group, the study group showed significantly higher scores of NEUT, EOS and VA but not lymphoid infiltration. The EOS infiltration was striking at the increase of the study group vs controls and was seen in cases with no other evidence of inflammation or VA. Crypt PCs were significantly higher in the study group than in controls. The authors conclude that early inflammatory features in pelvic IPs are characterized by marked EOS infiltration and a lesser degree of NEUT infiltration and VA. These changes, in addition to the proliferation of PCs which are known to possess bacteriostatic activity, may be the result of an adaptive response to an altered luminal environment (fecal stasis) in pelvic PCs.

IMMUNOHISTOCHEMISTRY OF ALTERED p53 SUPPRESSOR GENE PRODUCT IN COLORECTAL NEOPLASMS

IO Baas, JWR Mulder, GJA Offerhaus, B Vogelstein, SR Hamilton. The Johns Hopkins Hospital, Baltimore, MD and Academic Medical Center, Amsterdam, The Netherlands.

In this study, the authors compared p53 alterations at the DNA level with protein expression by immunohistochemistry (IHC) using 6 different antibodies against mutant and wild-type p53. The study was based on archival tissue of colorectal neoplasms. The authors studied 10 adenomas and 9 carcinomas with known status of mutation in exons 5-9 of p53 and known status of allelic loss of 17p (the site of the p53 gene). The immunohistochemistry was assessed with target unmasking fluid (TUF, a novel antigen retrieval system). DO7 mouse monoclonal antibody with TUF fluids stood out as the most sensitive and specific IHC method. All tumors with high expression (labelling index > 40%) had a mutation of p53. Three tumors with low or no expression also had a mutation. Of the 10 tumors without mutation, 9 had low or no expression by IHC. The sensitivity of the IHC method for p53 mutation was 67%, specificity 90%, predictive value of positive IHC 86%, predictive value of negative IHC 75% and efficiency 79%. The authors conclude that IHC for p53 gene product can be a valuable method for assessing p53 mutations but further studies to elucidate the precise link between mutation and over expression are needed.

COMPARISON OF DNA CONTENT WITH CLASSIC PREDICTORS OF PROGNOSIS IN ESOPHAGEAL SQUAMOUS CANCER

F Ballouk, HX Bui, A delRosario, T Jennings, R Ginsburg, JS Ross. Albany Medical College and S Stratton VA Medical Center, Albany, NY.

The authors examined the DNA content of 35 surgically resected esophageal squamous cancers by image analysis (CAS 200 Analyzer) and cytospin preparations of formalin-fixed paraffin embedded tissues along with classic predictors of survival in esophageal squamous carcinoma. Cytospin and tissue analysis revealed that 71% of the tumors were aneuploid and 29% were diploid. The aneuploid status significantly correlated with high tumor grade, lymph node metastasis and depth of mural invasion when compared with diploid status ($P < 0.05$). Eighty-eight percent (88%) of the aneuploid tumors died compared to 60% of the diploid tumors. Ploidy status, depth of mural invasion and lymph node status were independent prognostic indicators of recurrence and death ($P < 0.01$). The authors conclude that most esophageal squamous carcinomas are aneuploid; ploidy status correlates with mural invasion and lymph node status; and that the DNA content analysis independently predicts prognosis and may be helpful in the clinical management of esophageal cancer.

CHARACTERIZATION OF THE INFLAMMATORY RESPONSE TO COLON CARCINOMA

BF Banner, BA Woda, L Savas. University of Massachusetts Medical Center, Worcester, MA.

The authors studied the inflammatory cell population in 11 normal colons and 11 carcinomas in routine H & E sections and frozen tissue. The inflammatory cells were studied immunohistochemically with primary antibodies to CD2, CD7, CD4, CD8, CD20, TCR AB, TCR GD, KP1 and HLA-DR. Each cell type was semi- quantitatively graded in 10 HPFs in the luminal half or the basal half of the normal mucosa and mucosal epithelium and in tumor epithelium or stroma. The authors' findings indicated that: (1) Normal colon contains diffuse luminally oriented population of plasma cells; CD2, CD7 and CD4 positive lymphocytes; monocytes; and HLA-DR positive cells, (2) Intraepithelial lymphocytes are CD2, CD7, and CD8 positive, (3) TCR AB and TCR GD are present in a normal mucosa but not increased in tumors, (4) CD4, KP1 and HLA-DR positive cells predominate in the response to colon carcinomas.

BCL-2 PROTOONCOGENE AND THE GASTROINTESTINAL MUCOSAL EPITHELIAL TUMOR PROGRESSION MODEL AS RELATED TO PROPOSED MORPHOLOGIC AND MOLECULAR ONCOGENETIC SEQUENCES

M Bronner, C Culin, J Reed and E Furth. University of Pennsylavania, Philadelphia, PA.

It has been shown the Bcl-2 protooncogene is known to be expressed in the regenerative crypt compartment of the colon and small intestine of the GI tract. The authors studied immunohistochemically the expression of Bcl-2 protein in various disease stage using a polyclonal rabbit antibody. The authors found increased expression of the Bcl-2 protein in human dysplastic, adenomatous and carcinomatous GI epithelium as compared with internal control adjacent normal epithelium in the stomach, small bowel and colon. The authors also observed increased Bcl-2 expression in the gastric epithelial regenerative compartment - the gastric pit or neck region; and within hyperplastic colonic polyps - benign neoplastic proliferations of the colon. Absence of expression was noted in non-neoplastic inflammatory conditions such as inflammatory bowel disease and juvenile-type polyps. Increased Bcl-2 expression in continuous adjacent morphologically normal epithelium, with gradual diminution away from malignant epithelial proliferations, suggests that Bcl-2 may be involved in an early event in the proposed morphologic and molecular pathooncogenetic sequence.

THE EFFECT OF HOT PEPPER ON GASTRIC MUCOSA: CAPSAICIN DELAYS HEALING OF EXPERIMENTAL GASTRIC ULCERS

HX Bui, AD delRosario, M Abdulla, JS Ross. Albany Medical College, Albany, NY.

Capsaicin, the pungent ingredient of red peppers, is a neurotoxin capable of affecting the sensory neurons of the stomach. The role of capsaicin in gastric motility disorders and peptic ulcer formation is not well understood with many previous studies having conflicting results. The authors exposed 20 male rats with experimentally induced gastric ulcers to twice daily intragastric installations of capsaicin (40 mg/kg/day) on postoperative days 3-10. Twenty (20) control rats received intragastric normal saline. At the end of the study, the capsaicin exposed animals uniformly displayed persistent chronic active ulcers with a mean surface area of 6.22 ± 0.01 mm^2 when compared to the near completely healed ulcers in 90% of control rats averaging $1.27 \pm .07$ mm^2. Capsaicin exposed ulcers showed surface exudates with complete lack of re-epithelialization and extension through the muscularis propria. These results indicate that capsaicin delays experimental ulcer healing and causes persistence of chronic active ulcers. This observation may have significant clinical implication concerning the dietary management of known peptic ulcer patients.

IMMUNOHISTOCHEMICAL STAINING FOR P53 ANTIGEN IN SMALL CELL CARCINOMAS OF THE COLON

AP Burke, W Benson, P Mannan, L Sobin. Armed Forces Institute of Pathology, Washington, D.C.

The authors studied 45 small cell carcinomas of the colon immunohistochemically using a polyclonal antiserum against p53 (Signet Lab, MA). The authors noted nuclear positivity in non-mitotic cells in 18 (40%) of tumors which compared favorably to the 50% incidence of p53 staining of small cell carcinomas of the lung and adenocarcinoma of the colon. The p53 activity range from diffuse to focal cell clusters suggestive of clonal growth. The tumors with immunoreactive p53 were less likely associated with adenomas ($p = 0.05$), more likely associated with squamous differentiation ($p = 0.06$), had higher mitotic rates ($p = 0.01$), and occurred in patients with shorter survival (p not significant). Abnormal p53 is present in small cell carcinomas of the colon with similar frequency as adenocarcinomas of the colon and lung. There is no clear cut association with degree of differentiation or prognosis and expression of immunoreactive p53.

CATHEPSIN B EXPRESSION IN COLORECTAL CARCINOMAS CORRELATES WITH TUMOR PROGRESSION

E Campo, J Munoz, R Miguel, A Palacin, BF Sloan, LA Liotta, A Cardesa, MR Buck. Hospital Clinico, University of Barcelona, Barcelona, Spain; Wayne State University, Detroit, MI; and National Cancer Institute, Bethesda, MD.

Cathepsin B is a cysteine proteinase which has the ability to degrade laminin. The authors studied the cathepsin B expression in colorectal tissues using an affinity purified rabbit antibody which recognizes active and precursor forms of the enzyme. They studied 84 cases consisting of 10 normal mucosa, 11 adenomas and 63 carcinomas. Formalin-fixed paraffin embedded tissues were used for the immunohistochemical studies. Epithelial cells of normal mucosa and adenomas were either negative or showed a weak granular reactivity polarized in the paranuclear region of superficial cells. Histiocytes of the lamina propria were also positive. The authors noticed an increased expression of this enzyme in carcinomas. 85% of localized tumors (Dukes A & B) were negative or low reactive while 49% of metastatic tumors (Dukes C & D) showed a high expression. The increased immunoreactivity of cathepsin B in malignant cells was associated with a deorganized and diffuse cytoplasmic pattern. Increased expression of the enzyme was also observed in tumor stromal cells compared to normal lamina propria. The authors conclude that cathepsin B expression is up regulated in human colorectal carcinomas as compared to normal mucosa and adenomas. Increased expression of this proteinase may facilitate local tumor invasion and metastasis.

GASTRIC ECL CELLS IN ZOLLINGER-ELLISON SYNDROME: A MORPHOMETRIC ANALYSIS

Y Dayal, D Kumar, K Unni, RA Komorowsky and R Bhatnagar. New England Medical Center, Boston MA; UTMB, Galveston, TX; Mayo Clinic, Rochester, MN and Medical College of Wisconsin, Milwauke, WI.

Gastrin is trophic for the histamine-producing ECL cells of the gastric oxyntic mucosa. Both hyperplasias and tumors of ECL cells have been observed in hypergastrinemic states such as chronic atrophic gastritis and pernicious anemia. The authors quantitated these ECL cells in gastrectomy specimens from 22 Zollinger-Ellison (ZE) syndrome patients. Formalin-fixed paraffin-embedded mucosal tissue was examined for light microscopy and stained immunohistochemically for chromogranins (CG) and for argyrophilia by the Sevier Munger (SM) technique. The SM selectively stains ECL cells and a small subset of EC cells. Cells were quantitated and expressed as cells/mm^2. The mean cell count for CG-positive and SM positive was 21 ± 2.8 and 14 ± 2.54 respectively which were higher than normal controls (6 ± 1.9). The ratio SM: CG-positive cells showed that the overall incidence in oxyntic endocrine cell population of ZE patients was due to selective ECL cell hyperplasia. The authors noted no difference in results between familial and sporadic in ZE patients. The authors conclude that ECL cells hyperplasia occurs in both familial and sporadic forms of ZES and its intensity may be comparable.

PANCREATIC (ACINAR) METAPLASIA OF THE GASTRIC MUCOSA

C Doglioni, AP DeiTos, L Laurino, M DeBoni, P Braidotti and G Viale. University of Milan School of Medicine, Milan, Italy.

Using immunohistochemistry and electron microscopy, the authors investigated 8,432 consecutive gastric biopsies and 126 gastrectomy specimens for the presence of pancreatic acinar cells within the mucosa. They were able to identify pancreatic cells in 101 cases. The incidence of pancreatic acinar cells was 12% in gastrectomy specimens and 1% in biopsies. This is probably due to greater sampling. Acinar cells were often arranged in small acini mostly located in the antral glands and less frequently in fundic and cardiac glands. The occurrence of pancreatic acinar cells within gastric glands were restricted to cases showing chronic gastritis and was significantly associated with the simultaneous occurrence of intestinal and pyloric type of gastric metaplasia. The authors' findings are those of a previously unrecognized type of metaplasia of the gastric mucosa.

CYTOKERATIN 20 AS A MARKER OF PRIMARY SITE IN METASTATIC TUMORS TO LIVER

H Driggers, AM Gown. University of Washington, Seattle, WA.

Cytokeratin (CK) 20 has been recently identified as a member of the acidic subgroup of cytokeratins. CK20 expression has been reported to be largely restricted to adenocarcinomas of the gastrointestinal tract, transitional cell carcinoma and Merkel cell tumors of the skin. The authors wished to study the utility of antibodies to CD20 in the identification of the primary site of carcinomas presenting as metastasis to the liver. The authors studied both formalin and methacarn fixed tissues. Standard immunohistochemistry was used with microwave enhancement prior to antibody incubation. Expression of CK20 was found in 7 of 27 cases, 6 of which represented metastatic colorectal carcinomas, and 1 of which represented a probable pancreatic primary. Antibody reactivity in almost all cases was present in the majority of the tumor cell population. Six of seven colorectal and 1 of 2 pancreatic adenocarcinomas were positive for CK20, for an overall sensitivity of 78%. The authors conclude that CK20 is a sensitive and very specific marker of metastatic of GI adenocarcinomas (colorectal and pancreatic). Antibodies to CK20 may be playing an important role in identifying primary site of liver metastasis.

TENASCIN DISTRIBUTION PATTERNS IN BARRETT'S METAPLASIA, DYSPLASIA AND ADENOCARCINOMA

H El Zimaity, L Truong, M Younes, J Lechago. Baylor College of Medicine and The Methodist Hospital, Houston, Texas.

Tenascin is an extracellular matrix component produced by fibroblasts. The object of the study was to determine if a distinctive distribution pattern of tenascin is present which may allow the differentiation between dysplasia and adenocarcinoma in patients with Barrett's esophagus. Sixty formalin-fixed, paraffin-embedded tissue samples from 44 patients with Barrett's esophagus were immunostained with a monoclonal antibody against tenascin (Dako) using immunoperoxidase-streptavidin method. Variable degrees of linear localization of tenascin were found in relation with epithelial and vascular basal laminae in 39 cases of metaplasia and dysplasia. In contrast, 5 cases of adenocarcinoma exhibited diffuse, generally extensive interstitial tenascin deposition, almost always at the surface of the neoplasm. These results strongly suggest that patterns of tenascin localization may be a useful tool in the differentiation between high grade dysplasia and adenocarcinoma in the endoscopic biopsy setting.

THE PROGNOSTIC SIGNIFICANCE OF MINIMALLY INVASIVE CARCINOMA IN ADENOMATOUS POLYPS OF THE COLON

CM Fenoglio-Preiser. University of Cincinnati, Cincinatti, Ohio.

85 patients with minimally invasive carcinomas (cancer into the muscularis mucosae but not into the underlying submucosa) present in adenomas of the colon were evaluated to determine the prognostic significance of this finding. 54 of these patients underwent polypectomy alone and 33 had resections. Clinical follow-up was available in 27 of 54 polypectomy only patients and 14 of 33 patients with resection. Four patients with minimally invasive tumors were poorly differentiated and one involved the lymphatics of the muscularis mucosae. No patient with a minimally invasive tumor had evidence of recurrence or metastatic disease. The single patient with a poorly differentiated carcinoma that involved the lymphatic plexus of the muscularis mucosae survived for 20 years. These findings suggest that patients with only minimally invasive disease can be treated by polypectomy alone.

GENOTYPING OF COLORECTAL CANCER BY SPECIFIC K-RAS-2 MUTATION TYPE PREDICTS TUMOR AGGRESIVENESS

S Finkelstein, R Sayegh, A Bakker, R Przygodzki, P Swalsky. Rhode Island Hospital, Brown University, Providence, Rhode Island.

The authors studied 163 primary, 2 anastomotic recurrent and 90 metastatic colorectal adenocarcinomas which were genotyped according to the specific K-ras-2 point mutation. Mutation type was determined by sequencing the PCR generated DNA directly taken from minute topographical samples removed from formalin-fixed, paraffin-embedded large and needle biopsy specimens. Each primary colorectal tumor was found to be strictly limited to one of eight specific K-ras-2 genotypes; normal, codon 12 substitutions, or codon 13 substitutions. Tumors progessing to hematogenous metastasis were significantly more likely to be mutated (71%) than primary tumors in general (34%, $p < .001$). Codon 12 aspartate substitutions accounted for 50% of all such aggressive cases. Primary tumors with codon 13 substitutions were in no instances associated with metastasis while codon 12 valine substituted tumors spread no further than pericolonic lymph nodes. These results lead to a genotypic classification of colorectal adenocarcinomas by specific K-ras-2 point mutation type which can predict tumor aggresiveness on a case by case basis and in turn provide a means to individualize and optimize oncologic therapy.

CD44 ALTERNATIVE SPLICING IN HUMAN COLON CARCINOMAS

L Finn, M Becich, G Dougherty, G Finley, A Meisler and D Cooper. University of Pittsburgh Medical Center and The Terry Fox Laboratory Vancouver, B.C.

CD44 is a polymorphic integral membrane glycoprotein that displays a diverse range of cellular functions including roles in matrix adhesion, tumor growth and metastasis. Matched sets of RNA from adenocarcinomas of the colon and distant normal mucosa were assayed for CD44 expression by RT-PCR and nuclease protection. The analysis revealed that colon tumor cells had both quantitative and qualitative differences in CD44 expression. These were: 1) an absolute increase in levels of CD44 transcripts, 2) an absolute increase in levels of alternatively spliced transcripts, and 3) the presence of larger alternatively spliced transcripts with inserts > 800 bases. Preliminary data indicates that lower staged tumors with increased expression of the alternatively spliced CD44R1 isoform may have a more unfavorable prognosis.

MESENTERIC INFLAMMATORY VENO-OCCLUSIVE DISEASE: A CAUSE OF INTESTINAL ISCHEMIA

MJ Flaherty, JT Lie and RC Haggitt. University of Washington, Seattle, Washington and University of California-Davis, Sacramento, CA.

The authors describe 7 patients (3 men, 4 women; ages 27-78) who presented with signs of intestinal ischemia requiring surgical intervention. The pathology in each case showed a striking phlebitis and venulitis of the bowel and associated mesentery with ischemic necrosis of the mucosa. Arteritis involving the bowel or the mesentery was not found in any patient. There was no clinical evidence of history of extraintestinal vasculitis. The vasculitis was described as lymphocytic in 4 patients, necrotizing in 2 patients and lymphocytic/granulomatous in one patient. In addition, 2 patients also had myointimal hyperplasia of inflammed mesenteric veins. Of the 4 patients with available clinical follow-up, 3 recovered uneventfully and 1 died of unknown causes. The authors proposed the name mesenteric inflammatory veno-occlusive disease (MIVOD) to describe this unusual and previously unrecognized cause of intestinal ischemia. The etiology of MIVOD is unknown. MIVOD may represent a precursor of the recently described idiopathic myointimal hyperplasia of mesenteric veins (Gastroenterology 101:533, 1991).

PREVALENCE AND NON-SPECIFICITY OF MICROVESICULAR FATTY CHANGE IN THE LIVER

JL Fraser, DA Antonioli, S Chopra and HH Wang. Beth Israel Hospital and Harvard Schook, Boston, MA.

Hepatic microvesicular fat (MVF) has been associated with clinical syndromes of liver failure (acute fatty liver of pregnancy and Reye's syndrome). The authors performed the pilot study to investigate the specificity of MVF. METHODS: Materials obtained prospectively from 17 unselected autopsies. The sections from the liver were snap frozen and stained with Oil Red O (ORO) and H & E. There was a grading system of MVF in the ORO stains and was analyzed semiquantitatively as 3+ = >90% liver parenchyma with MVF; 2+ = 25-90%; 1+ = 1-24%. The H & E sections were also reviewed independently to determine the presence of inflammation, fibrosis and necrosis. Autopsy reports were reviewed for pertinent findings. RESULTS: MVF was identified in 16 patients (94%). It was 1+ and 2+ in the majority of patients but 4 patients (24%) had 3+ MVF. MVF was not associated with the age or sex of the patients, liver weight, postmortem interval to examination, or other histologic features of the liver, such as inflammation, fibrosis or macrovesicular fat. The patients with 3+ MVF did not have history of liver disease and serum ALT and AST were normal. All 4 patients with extensive MVF were using salicylates as opposed to 3/5 with 2+ MVF and 1/8 with 0 to 1+ MVF ($p= 0.015$). CONCLUSIONS: In this autopsy study, the prevalence of MVF was high, with 24% of the patients having extensive MVF. MVF may exist without apparent liver injury and extensive MVF change is associated with salicylate use.

CORRELATION OF DYSPLASIA AND P53 EXPRESSION IN BARRETT'S ESOPHAGUS BY IMMUNOCYTOCHEMISTRY ON PARAFFIN-EMBEDDED SECTIONS

R Fredricks, BM Pedemonte, R Sachdev, J Goris, W Maltzman, R Mesa-Tejada. MetPath Inc, Columbia University and Harlem University, New York, N.Y.

The authors studied the expression of p53 oncogene using the monoclonal antibody BP53-12 on formalin-fixed paraffin-embedded esophageal biopsies from patients with and without Barrett's esophagus. A significant correlation was observed between P53 immunoreactivity and histological grade. Greater than 50% of the cells in all high grade dysplasia (3/3) and adenocarcinomas (3/3) were reactive with BP53-12. Among, histologically low grade lesions, staining of 1-25% of cells was seen in 4 of 6 biopsies while the remaining 2 biopsies were not reactive with the anti-p53 antibody. Twenty biopsies without evidence of dysplasia failed to show any immunoreactivity with BP53-12. The authors conclude that the abnormal expression of p53 is a common feature of Barrett's esophagus and that this can be routinely determined on formalin-fixed paraffin-embedded tissue sections. These alterations in p53 may be predictive of neoplastic progression in Barrett's esophagus.

THE SIGNIFICANCE OF LYMPHOID FOLLICLES IN THE INTERPRETATION OF GASTRIC BIOPSIES

RM Genta and HW Hamner. Depts of Pathology & Medicine and Baylor College of Medicine, Houston, Texas.

BACKGROUND: Lymphoid aggregates with germinal centers are a common feature of Helicobacter pylori-associated gastritis. Previously, demonstrated lymphoid follicles in all patients with H. pylori infection using extensive gastric mapping and semi-serial sectioning of the biopsy specimens. OBJECTIVES: This study was designed to address the following questions: 1) prevalence of lymphoid follicles in routinely obtained gastric biopsies, 2) their correlation with chronic active gastritis, and 3) their positive predictive value with response to H. pylori infection. RESULTS: Active gastritis was present in 153 patients and H. pylori was identified on H & E slides in 123 patients and by the Steiner silver stain in 11 additional patients. Thus, 87% of patients with chronic active gastritis (CAG) had histologically detectable H. pylori. One or more lymphoid aggregates were present in 110 patients (82% of patients with H. pylori and 72% of those with CAG). Of these, 101 (92%) had H. pylori infection. In 6 of the 9 H. pylori-negative patients with lymphoid aggregates biopsies had been obtained from the edges of a gastric ulcers. CONCLUSIONS: Except when biopsies are obtained from the immediate vicinity of a gastric ulcer, lymphoid aggregates in a gastric biopsy are virtually always associated with CAG and provide a useful marker for H. pylori.

SYSTEMATIC ANALYSIS OF THE INFLAMMATORY RESPONSES IN PATIENTS WITH DIFFERENT EXPRESSIONS OF H. PYLORI INFECTION

RM Genta, HW Hamner and DY Graham. Dept of Pathology and Medicine,VAMC and Baylor College of Medicine, Houston, Texas.

BACKGROUND: Several studies have investigated the relationship between density of Helicobacter pylori (Hp) colonization, intensity of mucosal responses and risk for gastric or duodenal ulceration. Such studies, usually relying on the restrospective examination of mostly antral biopsies have not adequately addressed the relative importance of inflammatory changes in all areas of the stomach. OBJECTIVES AND METHODS: Eleven biopsies were obtained from the antrum and body of each of 20 normal subjects, 25 Hp-positive asymptomatic subjects [NI(+)], 23 Hp-infected patients with duodenal ulcer (DU) and Hp-infected 26 patients with gastric ulcer (GU). Each biopsy was scored from 0 to 5 for Hp, neutrophils, eosinophils, lymphocytes, follicles and intestinal metaplasia. Individual scores were summed for a chronic gastritis score. RESULTS: The stomach gastritis score was significantly lower in NI(+) subjects than in either DU or GU patients ($P<0.001$). In all infected subjects, the antral gastritis score was strongly correlated to Hp density ($P<1.001$), especially in GU patients. In all subjects, all inflammatory responses were greater in the antrum than in the body ($P<0.001$). The extent of intestinal metaplasia correlated well with age and with the presence of GU. CONCLUSIONS: The correlation between the density of Hp infection, severity of gastritis, and presence of duodenal and gastric ulcers found in this study lends further support to the hypothesis that H. pylori plays an etiologic role in ulcer disease.

DNA IN SITU HYBRIDIZATION (ISH) DETECTION OF NON-ENTERIC ADENOVIRUS (AV) IN COLON BIOPSIES FROM HIV+ PATIENTS WITH DIARRHEA

AJ Guidi, ER Unger and PA Hanff. Beth Israel Hospital, Harvard Medical School and Emory University.

The authors investigated by both light microscopy (LM) and in situ hybridization (ISH) 8 adenovirus (AV) culture-positive (CP) colon biopsies (bxs) from 6 HIV+ patients with diarrhea. The isolates were "non-enteric" type. LM findings showed evidence of active or chronic colitis in 4 of 8 bxs. Numerous typical AV intranuclear inclusions were seen in 1 bx and rare inclusions were seen in 2 others. AV was detected by ISH in rare superficial enterocytes in 5 of 7 bxs. The authors detected "non-enteric" AV by ISH in superficial enterocytes of AV-CP colon bxs from 5 of 6 HIV+ patients with diarrhea. Colitis was seen in 4 of 8 bxs and the AV inclusions were seen in 3 of 8 bxs. The clinical significance of these findings remains unclear and the presence of AV as the sole organism identified in 3 patients further suggests a pathogenic role for AV in HIV disease.

HIGH INCIDENCE OF NUMERICAL CHROMOSOMAL ABERRATIONS IN COLORECTAL CARCINOMA DETECTED BY FISH

Z Gibas, L Jackson, L Gibas, M Bibbo, M Rupp and G Marks. Thomas Jefferson University Hospital, Philadelphia, PA.

The copy number of chromosomes #1, #7, #17 and #18 was determined in interphase nuclei in 20 colorectal tumors using fluorescence in situ hybridization (FISH) with chromosome specific probes. The series included 17 carcinomas, 2 villous adenomas and 1 tubulovillous adenoma from 18 patients. Tumor ploidy was determined in Feulgen stained nuclei using the Samba 4000 cytometry system. FISH studies were performed on tumor imprints or slides prepared from suspension of tumor cells. The following probes were used: D7Z1/D7Z2 cocktail, D17Z1 and D18Z1 which detect centromeric alpha-satellite sequences of chromosomes #7, #17 and #18 respectively, and D1Z2 which detects a sequence near the telomere of chromosome #1 short arm. The DNA ploidy measurements demonstrated aneuploidy in 62% of carcinomas and none of the adenomas. The results of FISH studies correlated well with the DNA ploidy studies. Chromosome aneusomy was detected by FISH in all 11 carcinomas which showed aneuploid DNA content and in 66% of carcinomas with DNA content in the diploid area. The frequent chromosomal abnormalities detected by FISH were losses of chromosomes #17 and #18 and a gain of chromosome #7. The authors conclude that FISH studies with a small panel of probes can identify chromosomal changes in a significant proportion of cancers which appear diploid based on DNA measurements. The possibility of specific patterns of chromosome aneusomy detected by FISH may have prognostic significance and should be explored.

THE PATHOGENESIS OF ACHALASIA CANNOT BE DETERMINED FROM EXAMINATION OF RESECTED END STAGE DISEASE

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The authors examined 42 esophagi resected for clinical end stage achalasia to determine what could be learned about the evolution of the disease. In 20 cases, myenteric ganglion cells within the esophageal body were completely absent. Twenty cases had ganglion cells proximally where skeletal muscle was associated with the muscularis propria (MP). Fifteen cases had rare, randomly distributed ganglion cells in the totally smooth muscle lined mid and distal esophagus. All cases showed a mixed lymphocytic and eosinophilic infiltrate in the myenteric ganglia or nerves. All esophagi had focal replacement of myenteric nerves by collagen. This was nearly complete in several cases. The authors did not see active destruction of ganglion cells. End stage achalasia has almost total loss of ganglion cells and widespread destruction of myenteric nerves. The only active component, myenteric inflammation, might be primary or secondary. The results of this indicate that the evolution of achalasia remains enigmatic.

DIFFERENTIAL POLYMERASE CHAIN REACTION ASSAY OF PRAD1/CYCLIN-D GENE AMPLIFICATION IN ESOPHAGEAL CARCINOMA

TL Gramlich, C Fritsch and T Gansler.

The PRAD1 gene is located on chromosome 11q13. This is frequently rearranged in parathyroid neoplasms and amplified in some squamous cell carcinomas. Recent evidence indicates that the PRAD1 is amplified in 25 to 50% of squamous cell carcinomas of the esophagus (SCCE) and amplification is associated with reduced survival. In this present study, the authors evaluated a differential polymerase chain reaction (DPCR) assay of PRAD1 amplification. DNA was extracted from formalin-fixed paraffin-embedded specimens of squamous cell carcinoma (22 cases) adjacent non-neoplastic mucosa (NE) and, when present, lymph node metastases (LNM). Using adjacent NE from each case as a control for single copy PRAD1 content, PRAD1 amplification was detected in 36% of SCCE. LNM tended to be more common in patients with PRAD1 amplification (75%) than in those without amplification (36%), but this was not quite significant. Two-year survival with and without amplication was 25% and 50%, respectively, which was not significant.

ADENOCARCINOMA OF TH COLON PRESENTING IN PATIENTS (PTS) UNDER AGE 35 WITHOUT RECOGNIZED PREDISPOSING CONDITIONS.

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The authors reviewed 1,560 consecutive colorectal adenocarcinomas receiving primary therapy at their institution. 6.4% of tumors occurred in pts under age 35. Previous reports have indicated a high incidence of mucinous adenocarcinoma (MA) or signet ring cell carcinoma (SRCA) in these young pts and have been associated with a poor prognosis. The authors presented 40 cases (21 F, 19 M) of adenocarcinoma in pts under the age of 35. No pts had features of any recognized syndrome predisposing to colonic adenocarcinoma. Many pts presented repeatedly prior to definitive diagnosis and had clinically advanced disease at the time of initial staging. At resection 1 pt was Stage A, 3-B1, 5-B2, 4-C1, 11-C2 and 16-D (Astler-Coller system). 28 of 40 patients had lymph node metastases at primary resection. 27 tumors were in the rectum or sigmoid colon, 5 in the cecum and 11 elsewhere. Only 5 tumors were mucinous in nature and only 2 were SRCA. The remaining 33 tumors were non-MA (4 grade I, 18 grade II and 11 grade III). 11 of 36 pts are dead of disease, 25 of 36 are alive, 7 with disease and 18 with no evidence of disease. 6 pts were alive without disease longer than 60 mos and none had MA or SRCA. In this series, only 17.5% of pts presented with MA or SRCA. This may explain improved survival noted in this group when compared to other reports of colorectal adenocarcinoma in the young.

PRIMARY STROMAL TUMORS OF THE MESENTERY AND OMENTUM

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The authors studied clinicopathologic 12 cases of mesentery and omentum stromal tumors. The sex incidence was equal and the mean age diagnosis was 47.8 years. The mean diameter of the tumor was 11.5 cm with moderate to high cellularity and nuclear pleomorphism. Nine tumors showed a spindle cell pattern while 3 tumors had a prominent epithelioid component. Mitotic figures were present in 3 cases with rates ranging from 4 to 20 mitotic figures per 10 hpf. Immunohistochemistry showed positivity for smooth muscle actin in 6 cases, muscle actin in 5 cases, desmin in 1 case and S100 protein in 1 case. One tumor showed both smooth muscle and nerve sheath differentiation. Proliferating cell nuclear antigen (PCNA) was positive in 5.6% to 18% of nuclei counted. Of the 9 cases available for follow-up, 4 patients died of tumor related causes. Two of 3 patients mitotically active tumors died. Tumor recurrences and/or metastases occurred in 5 cases. Three of which were mitotically active in the primary tumor. Survival showed no correlation with the primary tumor and histologic pattern, immunohistochemical profile or degree of PCNA positivity. The authors suggest that this lesion should be considered malignant if mitoses are present or of uncertain malignant potential if no mitoses are present.

SUCRASE-ISOMALTASE EXPRESSION IN GASTRIC DYSPLASIA AND IN DYSPLASIA ASSOCIATED WITH BARRETT'S ESOPHAGUS

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Sucrase-Isomaltase (SI) is an enzyme present in normal small intestine and in both fetal and neoplastic colon, including adenoma, carcinoma and dysplasia associated with ulcerative colitis. The authors used a polyclonal antibody to SI to determine the presence of enzyme in detecting dysplasia in 70 gastric and 29 Barrett's esophagus cases. The investigators looked at the site of staining (e.g. membrane or cytoplasm) and percentage of positivity. Of the 29 Barrett's cases examined, 15 were negative for dysplasia, 1 indefinite, 12 positive and 4 had adenocarcinoma. Surface membrane staining of epithelial cells was noted in all cases However, in contrast, cytoplasmic positivity was present in 2/15 negative cases 0/1 of indefinite cases, 11/12 dysplastic cases, and 0/4 carcinoma areas. Of the 70 gastric cases examined, 23 were negative for dysplasia, 5 indefinite, 39 positive and 4 had carcinoma. Surface membrane staining of epithelial cells were seen in all cases, however, cytoplasmic positivity was present in 1/23 negative, 1/5 indefinite, 37/39 dysplasia and 1/4 carcinomas. Membrane staining of SI was seen in gastric and Barrett's esophageal mucosa. Cytoplasmic staining was absent in cases rated as negative for dysplasia and in adenocarcinomas, however, there was a strong correlation of cytoplasmic staining of SI and dysplastic cells in both the stomach and esophagus.

DIFFUSE PLASMALYMPHOCYTIC ACALCULOUS CHOLECYSTITIS. A DISTINCTIVE FORM OF CHRONIC CHOLECYSTITIS ASSOCIATED WITH PRIMARY SCLEROSING CHOLANGITIS (PSC)

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory disorder of the bile ducts that results in their obliteration and secondary biliary cirrhosis. Many favor an immune-mediated mechanism of injury. However, little is known about the histopathologic features in the gallbladder. In the study, the authors compared the pathology of gallbladders from patients with primary biliary cirrhosis (PBC), common chronic cholecystitis (CC) and PSC. The gallbladders were obtained from 23 patients undergoing liver transplantation (PSC=11, PBC=4, others=8) and cholecystectomies from 13 patients with CC. The sections were evaluated for the location of inflammation, predominant cell type, the distribution of focal or patchy and severity and epithelial abnormalities such as degeneration, hyperplasia, metaplasia and presence of gallstones. The combination of diffuse involvement, predominance of plasma cells and absence of gallstones was seen exclusively in PSC. There appears to be a characteristic form of cholecystitis in PSC. Pathogenesis may be similar to that involved in damage to other areas of the biliary tree.

CLINICAL PATHOLOGICAL ASSOCIATIONS OF P53 SUPPRESSOR GENE PRODUCT OVEREXPRESSION IN COLORECTAL CARCINOMA

H Kim, P Campbell and SR Hamilton. The Johns Hopkins University of School of Medicine and Hospital, Baltimore, MD.

The objective of the study was to evaluate the clinical and pathological associations with p53 overexpression. 149 Stage 2 and Stage 3 colorectal carcinomas were studied. Conventional histological prognostic parameters were examined and representative paraffin-embedded tumor sections were stained for p53 (clone DO7), Factor VIII and Proliferating Cell Nuclear Antigen (clone 19A2). P53 protein was detected immunohisto-chemically in 56% (83/149) of colorectal carcinomas. P53 overexpression was significantly associated with distal tumor location (64/93 left-sided tumors, 19/56 right-sided tumors, $p<0.001$). No association with other clinical variables was found. In univariate analysis p53 showed significant prognostic value along with conventional prognostic parameters such as lymph node metastasis, metastatic tumor nodules and pericolonic fat, Crohn's-like lymphoid reaction, extramural vein involvement and perineural involvement. Tumor angiogenesis detected by Factor VIII immunostaining and tumor cell proliferation detected by PCNA immunostaining yielded no significant prognostic information. The authors conclude that (1) The higher rate of p53 overexpression in the distal colon suggests that the etiologic factors and molecular basis of neoplastic transformation are different in the proximal and distal colon. (2) Overexpression of p53 may be useful in prognostication.

GASTRIC MUCOSAL FIBROSIS [illegible]NS DIFFER BETWEEN CIRRHOTIC (C) AND NON-CIRRHOTIC (NC) PATIENTS

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The gastric mucosa of Cirrhotic (C) patients shows vascular ectasia without significant cellular inflammation (Portal hypertensive gastrophy, PHG). The purpose of this study was to compare the extent of collagen deposition in gastroduodenal mucosal biopsies from 56 morphologically proven C patients with that seen in 38 NC patients with chronic gastritis. Tissue sections were stained by H & E and Trichrome. The distribution and the intensity of Trichrome staining with semiquantitative collagen deposition was infrequent in either superficial or deep duodenal mucosa. Gastric deep mucosal collagen was seen in 87.3% of C patients and in 86.5% of NC patients. Superficial mucosal collagen was seen in 28.6% of C patients in contrast to 76.2% of NC patients. Superficial gastric mucosal collagen deposition in NC patients may reflect mucosal repair following repeated episodes of gastritis. In contrast, if mucosal hypoxia occurs in C patients, it is not apparently associated with appreciable superficial gastric mucosal collagen deposition. These differences may have value in the histological distinction between healed inflammatory gastritides and PHG.

P53 EXPRESSION IN PRE-CANCEROUS GASTRIC LESIONS

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In order to determine the timing of p53 mutation in the gastric carcinogenic sequence, the authors studied p53 over-expression (immunohistochemically) in premalignant lesions including 17 gastric adenomatous polyps (Ad.P)and 18 gastric hyperplastic polyps (Hy.P). Immunohistochemical staining was performed using Pab 1801 monoclonal antibody and was performed on archival material. In addition, the authors assessed proliferation by detecting the proliferating cell nuclear antigen using PCNA 10 Ab. P53 nuclear staining was seen in 10/17 Ad.P but was limited to the foci of adenocarcinoma in 3 cases. 4 of 7 Ad.P with foci of cancer/severe dysplasia showed non-reactivity. Areas of intestinal metasplasia and 14 of 18 Hy.P were negative. Focal p53 reactivity was seen in the 4 Hy.P with adenomatous change. All Ad.P showed evidence of increased proliferation throughout the gland. PCNA staining in Hy.P varied from normal glandular staining only by an elongation of the proliferative zone. In the 4 Hy.P with adenomatous changes, increased proliferation by PCNA was noted in these foci and correlated with p53 over-expression. The authors suggest that p53 over-expression occurs in dysplastic epithelium of precancerous gastric lesions. Its absence in the preneoplastic condition of intestinal metaplasia suggests it occurs late in the gastric carcinogenic sequence.

EXPRESSION OF TUMOR GROWTH FACTOR-α IN THE DYSPLASIA-CARCINOMA SEQUENCE OF BARRETT'S ESOPHAGUS

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The tumor growth factor-alpha (TGF-α) is not expressed, or is expressed only weakly, by the normal gastrointestinal mucosa. Elevated TGF-α levels have been reported in a number of gastrointestinal tumors. Because of this, the authors studied the expression of TGF-α in Barrett's esophagus and Barrett's esophagus with dysplasia and carcinoma. The authors studied 16 cases of Barrett's esophagus including 3 cases with varying degrees of dysplasia and 7 cases with areas of dysplasia and adenocarcinoma. Paraffin-embedded tissue sections were stained with monoclonal antibodies to TGF-α. In one case, there was a strong correlation of staining intensity with the degree of premalignant or malignant changes. TGF-α was weakly positive in areas of uncomplicated Barrett's metaplasia but staining increased to strongly positive in areas of severe dysplasia and adenocarcinoma. The remainder of all the cases failed to show any correlation with staining and uncomplicated cases of Barrett's and cases with dysplasia. These results indicate that the expression of TGF-α does not distinguish between metaplasia and premalignant/malignant cells in Barrett's esophagus.

RETROSPECTIVE ANALYSIS OF FLOW CYTOMETRIC DNA CONTENT AND S-PHASE FRACTION IN DUKES B COLORECTAL ADENOCARCINOMAS: CORRELATION WITH SURVIVAL IN 104 PATIENTS

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The authors retrospectively studied the prognostic value of flow cytometric DNA content and synthesis phase fraction (SPF) and immunohistological expression of proliferating cell nuclear antigen (PCNA) and mutant p53 in a series of 104 Dukes B adenocarcinomas of the colon and rectum. DNA flow cytometry was performed on paraffin embedded tissue by a modified Hedley method. Mutant nuclear p53 expression was semi-quantitated using a lead-thiocyanate, microwave antigen retrieval method (Biogenex) followed by anti-p53 (PAb 1801). Anti-PCNA (clone PC10) was used to determine the tumor proliferation index. Overall, 49% of tumors were aneuploid. There was no statistically significant difference between rectal and colonic sites regarding percentage aneuploidy or SP fraction. There was a significant difference in SPF between aneuploid (16.25 ± 4.90) and diploid tumors (13.62 ± 5.81). There was no difference between mean PCNA index of aneuploid and diploid tumors. P53 expression did not differ between aneuploid and diploid tumors. No association between SPF and PCNA. Using Cox regression analysis, neither ploidy nor SPF were statistically significant predictors of survival in Dukes B carcinomas after accounting for age, site, tumor size, histologic cell type, tumor grade or ulceration.

NSAID GASTROPATHY: A DISTINCT PATTERN OF INJURY WITH HISTOPATHOLOGIC COMPARISON TO OTHER FORMS OF GASTRITIS

JA Lumadue and AJ Lazenby. The Johns Hopkins Medical Institutions, Baltimore, MD.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to cause acute hemorrhagic gastritis and ulcers in humans and experimental animals. Milder patterns of injury have been described but are less recognized. To assess the spectrum of changes in gastric mucosae chronically exposed to NSAIDs, the investigators examined antral biopsies of documented NSAID users (n=27) and compared them to cases of bile-reflux (Bilroth, n=17), H.pylori (n=17), and normals (n=9). Biopsies were blindly graded on 13 separate histo-pathological features such as foveolar (size, shape, and length), neutrophils, eosinophils, etc. The authors conclude that distinct features of NSAID gastropathy include changes in the foveolae, paucity of neutrophils and chronic inflammation, prominence of eosinophils, and muscular hyperplasia. These features are similar to those seen in bile-reflux gastritis and are distinct from those seen in HP gastritis, atrophic metaplastic gastritis, and normal antrum.

RELATIONSHIP BETWEEN HELICOBACTER PYLORI INFECTION AN INTESTINAL METAPLASIA

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Helicobacter pylori (HP) colonizes gastric surface epithelium and appears to cause active chronic gastritis and possibly peptic ulcers. Some reports have shown a negative correlation between HP infestation and intestinal metaplasia (IM). Other reports have linked HP infection with chronic atrophic gastritis and even carcinoma. TO study the relationship between IM and HP infection, the authors examined 220 consecutive adult gastroscopic antral biopsies (85% for dyspepsia and/or gastrointestinal blood loss or for follow-up of patients with peptic ulcers).

IM was found in 18% and HP in 30% of patients. HP was identified in 86% biopsies with active chronic gastritis. The prevalence of both IM and HP was age dependent being more common in patients greater than 50 years (IM 25%, HP 39%) compared with patients with less than 50 years (IM 9%, HP 17%) p.01. Age dependency was seen most in the 49% of patients with IM who also had HP as opposed to 51% of IM patients which were not HP associated. These data indicate that in our study group, half of the cases of IM are HP associated, both increasing with age and half are not. The latter group is not age dependent. This may mean that there are two types of IM and type B antral atrophic gastritis, age-related HP-associated and sporadic HP-unassociated.

CD34 IS A SENSITIVE MARKER OF GASTROINTESTINAL STROMAL CELL TUMORS

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There is much controversy as to the specific differentiation pathway(s) of cell of origin of gastrointestinal stromal tumors (GISTs). Given this controversy, the authors evaluated the expression of CD34, a 115 kd cell surface progenitor cell marker also recently identified in a subset of mesenchymal tumors, including vascular tumors and a fraction of smooth muscle and nerve sheath tumors. Using antibody My10 in deparaffinized formalin-fixed tissue, the authors examined 59 GISTs arising in the esophagus, stomach, small intestine, large intestine, rectum, and omentum. Overall, 78% of GISTs were CD34-positive, this fraction of CD34 positive tumors exceeded the fraction of those GISTs previously identified as showing muscle actin (63%), smooth muscle actin (39%), desmin (6%), or S100 protein (6%) expression. The highest fraction of CD34-positive tumors was found in the malignant spindle cell variant (85%) and the lowest in the malignant epithelioid variant (67%). CD34 is normally expressed by endothelial as well as perivascular cells, perhaps related to, but distinct from vascular smooth muscle cells. While the nature of these latter cells is uncertain, the expression of CD34 in such a large fraction of GISTs may provide evidence of a parallel differentiation pathway in these tumors.

CORRELATION BETWEEN ALPHA 2,6-LINKED SIALIC ACID EXPRESSION AND TUMORIGENICITY IN A HUMAN COLON CARCINOMA CELL LINE

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Increased cell surface sialylation has been shown to be correlated with the invasive and metastatic behaviour of colon cancer cells. The authors have previously shown that the neoplastic transformation of human colonic epithelium is accompanied by the de novo expression of sialic acid in an alpha 2,6 linkage to galactose as visualized with *Sambucus nigra* I lectin. The authors have now studied two clones of human colon carcinoma cell line HCT116 which differ in their tumorigenicity. the weakly aggressive clone HCT116b showed three major reactive bands of ~180, ~150, and ~140 kDa and two minor bands of ~190 and ~170 kDa by lectin blot analysis. In the highly aggressive clone HCT116a, the ~190 and ~170 kDa bands became the major bands and the ~180, ~150, and ~140 kDa were greatly reduced in intensity. Labeling by lectin-gold technique showed that the highly aggressive clone was most intensely labeled. These data demonstrate that the carcinoma-associated occurrence of alpha 2,6-linked sialic acid in human colon carcinoma cells is limited to a few glycoproteins and strongly indicate a correlation between the amount of alpha 2,6-linked sialic acid and tumorigenicity.

PROSPECTIVE 2-COLOR FLOW CYTOMETRIC ANALYSIS (FCA) OF 115 COLORECTAL CARCINOMAS: 3-5 YEAR FOLLOW-UP AND CORRELATION WITH CLINICOPATHOLOGIC PARAMETERS, PCNA AND P53 EXPRESSION

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This is a prospective survival analysis of a 115 patients with 3 three years minimum follow-up using two-color (cytokeratin labeled) FCA. Stage distribution was Dukes A (16%), B (37%), C (30%), and D (17%). The overall frequency of anueploidy was 70% and differed significantly in right colon (63%) compared to left colon (78%), and rectum (78%) (p=.0223). Variables was examined by the Kaplan-Meier survival analysis were: DNA ploidy and index (DI), S-phase fraction (SPF) from ungated, cytokeratin (CK) gated and debris subtracted histograms, tumor site, Dukes and TNM stages, infiltrative pattern, tumor grade, inflammatory response, fibrosis, vascular invasion, PCNA and p53 expression. Univariate analysis showed overall stage (p<.00001), depth of invasion (p=.0001), nodal status (p<.012), metastasis (p<.00001) and vascular invasion (p=.0053) to be statistically significant indicators of survival. DNA aneuploidy and higher SPF were not significant but showed a trend for worse survival beyond 3 years. There was direct correlation between p53 and higher stage. Higher PCNA expression correlated with subserosal involvement of both diploid and aneuploid tumors. We conclude that at 3 years following curative resection: (1) stage, metastases and vascular invasion are the strongest predictors for a negative outcome, (2) DNA ploidy may predict survival but longer follow-up is necessary to validate this trend, and (3) SPF is significantly related to DI and with longer follow-up may predict survival for Dukes stage A & B tumors.

PROLIFERATING CELL NUCLEAR ANTIGEN IS NOT A USEFUL PROGNOSTIC INDICATOR FOR GASTROINTESTINAL STROMAL TUMORS

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The authors studied the proliferating cell nuclear antigen expression in 84 gastrointestinal stromal tumors (GIST) - esophagus 1, stomach 43, small intestine 31, colon 9. This was correlated with histological features and with the clinical pathological outcome. Paraffin sections were stained with the monoclonal antibody PC-10 (DAKO), directed against a cell cycle associated protein present in the nuclei of replicating cells. PCNA staining was seen in 46 cases at rates from 0.2 to 50.6% of nuclei counted. Clinical follow-up was available in 73 cases. PCNA positivity did not correlate with tumor size, histology mitotic rate or clinical outcome. As a group, gastric GIST had a more favorable outcome than small intestinal and colonic. GIST 5 cm or less in diameter were usually benign. However, 5 patients (15%) with such tumors died of disease (3 stomach, 2 small intestine). The results of the study indicate that PCNA activity is not a useful prognosticator in GIST.

THE RELATIONSHIP OF HPV INFECTION TO PLOIDY AND PROLIFERATION IN ANAL CARCINOMAS

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Transformation by HPV 16/18 is thought to occur through the expression of viral genes E6 and E7 as as result of their capability of binding two negative modulators of cell growth, retinoblastoma and p53 gene products. The authors hypothesized that HPV infected neoplasms should show increased proliferative activity. The authors examined 35 anal carcinoma specimens for the presence of HPV DNA with the use of in-situ hybridization and PCR amplification. DNA analysis was performed to determine ploidy and proliferative status. Tissue sections were also stained with antibodies against PCNA and epidermal growth factor receptor (EGFR). Forty percent of anal cancers were positive for HPV 16/18. A consistently higher S-phase fraction was found in the HPV associated neoplasms that in those without evidence of HPV infection. Forty percent of HPV positive carcinomas were aneuploid versus only 12% of those that were HPV negative. Cell sorting experiments demonstrated localization of HPV DNA to aneuploid and not diploid nuclei. The S-phase fraction, PCNA indices were higher in HPV positive neoplasms. The authors conclude that HPV 16/18 infection has an important role in the genesis of anal carcinoma, probably as a result of its effects on cell proliferation and destabilization of the host cell genome.

P53 GENE MUTATIONS IN BARRETT'S ASSOCIATED ADENOCARCINOMA OF THE ESOPHAGUS

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The authors studied 23 cases of resected adenocarcinoma of the esophagus for p53 gene mutations by immunohistochemical staining and DNA sequence analysis. Fifteen of the tumors were associated with Barrett's esophagus. Eleven of these 15 Barrett's associated cases (73%) showed at least focal staining for p53 protein, implying an underlying mutation. Only 2 of 8 cases in which Barrett's metaplasia could not be documented (25%) showed p53 accumulation. In no instance did simple Barrett's metaplasia show p53 staining nor did areas of low grade dysplasia. In 4 cases p53 staining was present in areas of high grade dysplasia or intramembranous carcinoma. Staining character in these dysplastic foci were qualitatively and quantitatively weaker than in that of carcinoma. The results support the hypothesis that most adenocarcinomas of the esophagus associated with Barrett's esophagus harbor a p53 gene mutations and may differ from tumors that do not arise in Barrett's metaplasia.

PHENOTYPIC CHARACTERIZATION OF ABERRANT CRYPT FOCI IN THE HUMAN COLORECTUM

M Nucci, R Robinson and SR Hamilton. The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD.

Abberant crypt foci (ACF) are enlarged crypts demonstrated by macroscopic examination of colorectal mucosa after methylene blue staining. These ACF had been implicated as precursor lesions to neoplasia. The authors studied these ACF by comparing their histopathology and expression of lectins and blood group antigens that control mucosa, hyperplastic polyps and adenomas. Colorectal mucosa from 62 patients were fixed in methanol. ACF were marked with tattoo powder, excised and processed for histopathology. Dolichus biflorus agglutinin (DBA) and antibody CA19-9 to sialosyl-Lewis^a (s-Le^a) were used with avidin-biotin method. ACF expressed DBA and s-Le^a more frequently than control mucosa [48/56 (86%) vs. 7/12 (58%), $p < .05$ for DBA; 38/59 (64%) vs. 3/12 (25%), $p < .03$ for s-Le^a]. Many ACF had the phenotypic characteristics of hyperplastic polyps. The authors' results suggest that ACF are phenotypically heterogeneous but a large subset has the characteristics of hyperplastic polyps. The utility of ACF as preneoplastic markers in human colorectal mucosa remains open to question.

CELL DIFFERENTIATION AND EXPRESSION OF TRANSFORMING GROWTH FACTOR α (TGF·α) IN DUODENAL ADENOMAS IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

R Odze, S Gallinger, K So, and D Antonioli. Mount Sinai Hospital, Toronto, Canada and Beth Israel Hospital, Boston, MA.

The authors evaluated the significance of Paneth cell (PC) and endocrine cell (EC) metaplasia as well as the expression of TGF-α in duodenal adenomas (DA) from patients with FAP. Sections were stained with H & E and immunohistochemically for chromogranin and TGF-α. They were also evaluated as to the type and size of DA, degree of dysplasia, number of PC's and EC's per high power field (HPF) and extent of EC TGF-α. Thirty-four adenomas, 30 (88%) were tubular, 2 each were tubulovillous or villous. Twenty-two DA's (65%) for < 10 mm in size dysplasia was mild at 50%, moderate at 38% and severe at 12%. PC's were identified in 94% of adenomas, averaged 26.7/HPF and their number was inversely related to size and degree of dysplasia ($p=0.0001$). EC's were seen in 97%, an averaged 70.0/HPF. Their number inversely related to degree of dysplasia ($p=0.01$), but had no relation to other polyp features. TGF-α was present in all DAs, the extent of its expression was directly related to DA size ($p=0.003$), degree of dysplasia ($p<0.05$) and villiform shape ($p=0.04$). The authors conclude that prospective evaluation of PC and EC metaplasia and expression TGF-α in DA's in FAP mayt offer insights into their malignant potential, and that TGF-α may be involved in the progression, but not the cellular differentiation of these lesions.

EPITHELIAL DIFFERENTIATION AND MUCIN HISTOCHEMICAL CHANGES IN FLAT DUODENAL MUCOSA IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

R Odze, S Gallinger, K So and D Antonioli. Mount Sinai Hospital, Toronto, Canada and Beth Israel Hospital, Boston, MA.

Colonic mucosa in FAP patient exhibits altered epithelial cell proliferation, differentiation, and mucin histochemical properties. However, little is known regarding these parameters in duodenal mucosa. The investigators evaluated endocrine cell (EC) and Paneth (PC) cells and that goblet (GC) cells have mucin changes in 24 formalin fixed duodenal biopsies from flat mucosa in 24 FAP patients and compared the results with those in 14 normal duodenal biopsies from non-FAP patients. Sections were stained with H & E, chromogranin to evaluate crypt EC, HID-Ab to detect GC sulpho- and sialomucins and 4 with PB/KOH/PAS to determine the extent of o-acylated sialomucins (OAS) in mucosal GC's. Compared to normal controls mucosal biopsies from FAP patients showed a higher average number of PC's/crypt ($p=0.04$) and EC's/crypt ($p=0.01$). GC's from both FAP and control biopsies revealed predominantly sialomucins. Only 1 FAP had focal GC sulphomucins vs. no control cases. However, only 15 of 24 FAP biopsies (63%) contained GC OAS compared to all 14 non-FAP cases ($p=0.01$). No differences regarding PC or EC counts or extent of OAS positivity were noted between FAP patients with or without Ad's. The authors conclude that duodenal mucosa from FAP patients exhibits altered epithelial growth characterized by PC and EC hyperplasia and loss of GC OAS. Since these changes occurred irrespective of the presence of AD's, they may represent a primary abnormality of duodenal stem cell differentiation in FAP.

GEOGRAPHIC VARIATIONS OF EOSINOPHIL CONCENTRATION IN NORMAL COLONIC MUCOSA

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The number of of eosinophils to be expected in normal adult colonic mucosa is not known. The authors wished to test the hypothesis that there may be geographical and seasonal variations in lamina propria eosinophils. The authors examined mucosa of descending colon obtained from surgical pathology departments in several areas of the United States. All specimens had been diagnosed as "normal colonic mucosa" and no specimens with acute or chronic colitis, or in which eosinophils invaded the crypts were included. The specimens were obtained during different seasons of the year. The authors counted the number of eosinophils in the lamina propria of 15 intercryptal spaces. The findings indicated that there was no seasonal correlation between the number of eosinophils and the annual season in which the tissue was obtained. However, the number of eosinophils in the lamina propria of normal colonic mucosa varies among individuals and the average number appears to be

higher in southern regions of the United States. The reason for the geographic variation is unknown but may be related to allergens in the environment and diet. Normal variations in mucosal eosinophil concentrations should be measured before evaluating colonic biopsies for eosinophilia.

IMMUNOHISTOCHEMICAL EXPRESSION OF TRANSFORMING GROWTH FACTOR ALPHA (TGF-α) AND EPIDERMAL GROWTH FACTOR RECEPTOR (EGF-R) IN GASTRIC FUNDIC GLAND POLYPS (FGP).

R Odze, S Gallinger, K So, and D Antonioli. Mount Sinai Hospital, Toronto, Canada and Beth Israel Hospital, Boston, MA.

FGP's are benign lesions of uncertain etiology that occurs as small, sporadic polyps. However, in patients with familial adenomatous polyposis (FAP) they may be numerous and larger. TGF-α is a mitogenic polypeptide that controls cell-proliferation and possibly differentiation in GI mucosa by binding to its corresponding cell surface receptor (EGF-R). The expression of these proteins has been linked with the progression of several malignancies including gastric cancer. Investigators looked at the expression of TGF-α and EGF-R in a series of FAP associated and sporadic FGP's to determine its cellular distribution and possible contribution to the pathogenesis of these lesions. Sixteen routinely processed FGP's (8 FAP, 8 sporadic) were stained with H & E and immunohistochemically with monoclonal Ab's to TGF-α and EGF-R. The staining pattern (cytoplasmic or membranous) and cell-types stained were noted. These results were compared to 10 normal gastric corpus mucosal biopsies (5 FAP, 5 non-FAP). All FGP's and control biopsies showed diffused, intense cytoplasmic staining for TGF-α in surface epithelial (basal portion of cell only) and parietal cells. Chief cells and pit epithelial cells were negative for TGF-α in both types of specimens. EGF-R was expressed focally in 15/16 FGP's (94%), compared to 6/10 control biopsies (60%) ($p=0.02$). In EGF-R positive cases, a membranous pattern of staining was noted in surface and pit epithelial cells and a basal portion only of the gastric gland cells from FGP's and control specimens. Staining was more intense and extensive in FGP's compared to controls. Focally weak cytoplasmic staining for EGF-R was seen in parietal cells of FGP's only. The authors concludes that overexpression of EGF-R in combination with TGF-α, its natural ligand, may be involved in the development of sporadic and FAP associated benign FGP's.

IMMUNOREACTIVITY FOR ADHESION MOLECULES CD29 AND CD44 IN COLORECTAL CANCER

C Patriarca, AKC Lee, S Bosari, G Viale and G Coggi. Dept of Pathology, University of Milano, Italy and Lahey Clinic Medical Center, New England Deaconess Hospital, Harvard Medical School, Boston, MA.

CD29 and CD44 are members of the adhesion molecule family. CD29 is involved in cell-cell and cell-matrix interactions in normal and neoplastic tissues. CD44 splice variants have been reported to confer metastatic properties to transformed cell lines. The authors assessed CD29 and CD44 expression in 74 colorectal carcinomas and correlated with clinico-pathological parameters. CD44 expression was detected in at least 10% neoplastic cells of 46 (63%) cases, and showed a significant correlation with aneuploidy ($p<0.05$), as evaluated by flow cytometry. CD44 immunoreactivity was also related to recurrent disease (46% of disease-free cases vs 61% of the recurred cases were immunoreactive) and to modified Dukes' stages (54% of A and B stages vs. 71% of C and D showed expression of CD44). These latter associations, however, did not reach statistical significance.

CD29 expression was maintained in 93% of the cases. The percentage of tumor cells with membrane immunostaining was correlated to tumor grade, being reduced in poorly differentiated adenocarcinomas. No statistically significant correlations, or definite trends, were observed with disease recurrence, stage or ploidy status supporting the hypothesis that interruption of cell-ceil and cell-matrix interactions of clinical relevance would rather depend on other integrin subunits.

RAPID SEROLOGIC DIAGNOSIS OF HELICOBACTER PYLORI ASSOCIATED GASTRITIS: COMPARISON WITH GASTROSCOPIC FINDINGS

JS Ross, HX Bui, A delRosario, R Venezia, J Shrader, M George, H Malamood. Albany Medical College, Albany, NY.

The authors compared the results of a non-evasive rapid polyvalent latex agglutination serologic test (LAG) with gastroscopic in vitro urease test (UT), direct tissue bacteriologic culture (CUL) and microscopic identification of organisms (BX) in 43 patients. In 12 patients with positive CUL (27%) LAG was positive in all (100%). Two CUL negative patients had equivocal LAG. UT uniformly corresponded to CUL results. BX identification of H. pylori with routine stains was positive in 11 CUL positive patients (92%). Three BX positive CUL negative cases grew non-Helicobacter organisms. BX, UT, and LAG were all significantly associated with CUL status on univariate analysis ($p<.001$). Qualitative assessment of gastric chronic inflammation correlated with H. pylori status. These findings indicate that: there is an excellent correlation between non-invasive LAG and gastroscopic CUL or BX results. There is excellent correlation between biopsy, culture, UT and LAG diagnosis. The simple rapid LAG serological test may obviate the need for gastroscopy in patients with mild symptoms.

PATHOLOGIC CORRELATION OF COLOR FLOW DOPPLER AND ACUTE CHOLECYSTITIS

M Porter, D Harshfield, RF Schaefer, K Griggs and K Roper. University of Arkansas for Medical Sciences and JL McClellan Va Medical Center, Little Rock, AR.

The investigators studied 60 patients presenting with symptoms of gallbladder disease by duplex ultrasound with positive color flow detected in 12 cases and no color flow in 48. The investigators reviewed the histological changes in the resected gall bladders and divided them into four groups: Group I (early acute) showing mucosal hemmorhage, necrosis, PMN infiltrates of the mucosa but no necrosis of the muscularis. Group II (acute) showed marked PMN infiltration and extensive transmural necrosis. Group III (late or resolving acute) showed fewer PMNs, but marked infiltration of eosinophils and granulation tissue. Group IV (chronic) had only chronic inflammatory changes of cholecystitis. Eleven of 12 patients with positive CFD showed acute changes (Group II and Group III). Seven of these 11 true positive patients also had preexisting changes of chronic cholecystitis. Of 48 patients with negative color flow doppler studies, 3 had early acute (Group I) changes and 45 had only chronic changes (Group IV). The investigators conclude that positive CFD studies are useful in identifying patients with acute or late acute cholecystitis, or with other regional disease. Symptomatic gallbladder disease with a positive CFD study has a positive predictive value (91%) for acute cholecystitis. A negative CFD in these group of patients has a negative predictive value (94%) for acute cholecystitis.

CELIAC SPRUE IN PATIENTS WITH LYMPHOCYTIC COLITIS

R Wolber, D Owen, D Carr, H Freeman. University of British Columbia, Vancouver, B.C., Canada.

In 16 patients with histologically confirmed lymphocytic colitis, small bowel biopsies from 14 showed the changes of celiac sprue representing 87% of lymphocytic colitis patients who underwent a small bowel biopsy and 45% of all lymphocytic colitis patients that were seen at the authors' institution. Only 1 patient with collagenous colitis was found to have a biopsy suggestive of celiac sprue. Patients with lymphocytic colitis and celiac sprue showed clinical response to a gluten-free diet. Although a histological response in colonic mucosa was confirmed in only 2 of 6 patients who received a colonic biopsy. These findings indicate that lymphocytic colitis may frequently be encountered in a patient with unrecognized gluten sensitive enteropathy. Their findings suggest that a small bowel biopsy should be considered for all patients diagnosed with lymphocytic colitis, especially those who fail to respond to medications. This study also suggests that at least 2 different clinical presentations of lymphocytic colitis exist, one associated with and one not associated with celiac sprue.

MALIGNANT LYMPHOMATOUS POLYPOSIS (MLP) OF THE GASTROINTESTINAL TRACT (GIT). A RETROSPECTIVE CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL STUDY OF 12 CASES.

Th Radaszkiewicz, M Vesely, A Chott and B Dragosics. Dept of Pathology, Lainz Hospital, Depts of Pathology and Internal Medicine, University Vienna School of Medicine, Austria.

Twelve cases of MLP from the Dept of Pathology were noted from 1979 to 1991. The mean age was 70 years (the male/female ratio = 2/1) and the presenting symptoms of patients were weight loss, bloody diarrhea, abdominal pain and ileus. Main long-segmental polypoid lesions were localized in the colon in 11 cases, in the small bowel in one case. Five patients presented with tumor mass. Tonsil manifestation of lymphoma occurred in 4 patients. Regional lymph nodes were involved in all cases and 4 patients had peripheral lymph node involvement. Bone marrow was positive in 2 of 6 investigated cases, 1 patient was leukemic. Histologically, all cases were small cleaved lymphomas, 4 showing at least a partial nodular pattern. In 3 cases, there was focal transformation to high grade lymphoma. Immunochemistry on paraffin sections revealed CD20+, KiB3+, CD43+, CD45RA+, CDW75+ (n=12). On frozen sections the immunohistochemical findings were CD5+, CD44+, CDW49D+, LEU8+ (N=4). Bcl-2 protein was constantly expressed. Two patients are alive with evidence of disease and 9 patients died of disease (average 28 months). This study indicates that MLP is an aggressive neoplasm derived from mantle zone cells.

DOUBLE IMMUNOSTAINING FOR C-ERB-B2 AND P53 IN HUMAN STOMACH CANCER

H Sasano, F Date, A Imatani, S Asaki, H Nagura. Tohuku University School of Medicine, Sendai, Japan.

The authors examined 32 cases of gastric carcinoma for the immunohistochemical expression of p53 and c-erb-B2 protein. The findings were correlated with clinical outcome and prognostic factors. P53 was observed in the nuclei of 33% of the cases and c-erb-B2 was observed in 27%. In 8 cases, both p53 and c-erb-B2 were positive but double immunostaining revealed that less than a third of the same tumor cells were positive for both p53 and c-erb-B2 in these cases. The immunohistochemical localization patterns of p53 and c-erb-B2 were not related to histopathological differentiation of carcinoma cells. No correlation was observed between the expression of p53 and/or c-erb-B2 and the clinical outcome and established prognostic factors. The authors believe that the abnormalities of p53 and c-erb-B2 may not play major roles in the biological behaviour of human gastric cancer.

MORPHOLOGICAL CHANGES IN COLO-RECTAL CARCINOMA FOLLOWING PREOPERATIVE RADIOTHERAPY: CORRELATION OF DOSAGE WITH MORPHOLOGIC CHANGES

D Saw and D Nori. Booth Memorial Medical Center, Flushing, NY.

Thirteen cases of unresectable stage B3 colorectal cancers were given preoperative radiation therapy at a single dose of 500 rads or 5,040 rads in fractionated doses. Surgery was performed 1 - 2 days following a single dose (7 cases) and 19 to 49 days after completion of high dose radiation therapy (6 cases). The cases given a high dose of radiation showed partial to near complete destruction of the neoplasm. In non-mucinous tumors, (4 cases) there was marked fibrosis and granulomatous reaction. The latter probably represented the tombstones of the previous cells. In colloid carcinomas (2 cases), only pools of mucin were found in the colon wall and in lymph nodes. Multiple blocks eventually revealed sparse isolated malignant cells. There were vascular changes in those cases receiving high dose radiation. The cases given a single dose of radiation did not show any remarkable morphological changes. The authors believe that radiation doses of 5,040 rads could affect direct destruction of the tumor and cause vascular obliteration resulting in ischemic necrosis of residual tumor with apparent better outcome for the patients.

CELLULAR PROLIFERATION IN BARRETT'S ESOPHAGUS

TC Smyrk. Clarkson Hospital, Omaha, NE

The investigator studied cellular proliferation in esophageal biopsies reported to contain contain columnar epithelium by using the monoclonal antibody to proliferating cell nuclear antigen (PCNA). The proliferation index was determined by counting 200 nuclei. In biopsies with gastric cardiac-type epithelium, the proliferation index was 3%, with positive cells confined to the base of the pits. In biopsies with specialized columnar epithelium, the index was 13.2% with positively stained cells at all levels of the glands and pits. In low-grade dysplasia, the mean index was 18.8%. Where there was ulcer and/or acute inflammation, the index was 45.5%. The population of columnar cells with clear cytoplasm located in the interfoveolar surface epithelium were always positive. Barrett's esophagus is characterized by disordered cellular proliferation. PCNA staining is increased in the setting of dysplasia but is more elevated with acute inflammation. The surface epithelium in Barrett's esophagus has groups of "undifferentiated columnar cells" that are uniformly positive for PCNA.

CLEAR CELL CARCINOMAS OF THE GALLBLADDER AND EXTRAHEPATIC BILIARY DUCTS

C Vardaman, E Gould, O Larraza-Hernandez and J Albores-Saavedra. University of Texas Southwestern Medical Center, Dallas, TX, Baptist Hospital, Miami, FL and National University of Mexico, Mexico City, Mexico.

The authors report 9 cases of clear cell carcinomas (CCC) of the gallbladder and extrahepatic biliary ducts (EHBD). Six cases involved the gallbladder and all were females with cholelithiasis. The remaining 3 cases originated in the EHBD. Two were young females and one was a 38-year old male. Gallstones were present in the 2 female patients but not the male patients. The tumors consist of sheets, nests, or trabeculae of clear cells with well-defined cytoplasmic borders. Occasional papillary structures or poorly-formed tubules were seen. The cells contained PAS-positive diastase-labile granules and were positive for cytokeratin and EMA. Foci of conventional adenocarcinoma were seen in 8 cases, often after extensive sampling. The ninth case was a poorly-differentiated squamous carcinoma of the gallbladder composed predominantly of large glycogen-rich cells. These neoplasms must be differentiated from metastatic renal cell carcinoma, based on the presence of areas of conventional squamous or adenocarcinoma since special stains and immunohistochemistry of both neoplasms are similar.

ABNORMAL P53 IMMUNOREACTIVITY IN COLORECTAL CARCINOMAS

J Viale, S Bosari, AKC Lee and G Coggi. Dept of Pathology, University of Milan, Italy, Dept of Pathology, Lahey Clinic Medical Center, New England Deaconess Hospital and Harvard Medical School, Boston.

The authors investigated immunocytochemically a retrospective series of 113 colorectal carcinomas using PAb 1801 monoclonal antibody. The authors intent was to assess the prevalence of p53 immunoreactivity and its relationship with stage and prognosis. The tumor stage distribution was as follows: Dukes A: n=23, Dukes B n=35, Dukes C: n=39, Dukes D: n=16. Overall, 55% of the tumors showed nuclear p53 staining in at least 10% of the tumor cells. P53 positive tumors were more prevalent among carcinomas with regional or distant metastases: Dukes A: 56%, Dukes B: 34%, Dukes C: 59%, Dukes D: 87%, $p<0.004$. P53 positivity was significantly associated with aneuploid tumors ($p<0.04$). The patients with p53 positive tumors showed a higher 5-year mortality rate than p53 negative ones (50% vs. 26%, $p<0.01$). Among Dukes C patients there was a trend towards higher mortality for p53 positive tumors (64% vs 50%) although it did not reach statistical significance. These results confirm the high prevalence of abnormal p53 expression in colorectal carcinomas and demonstrated its association with more aggressive disease.

EXPRESSION OF CELL ADHESION MOLECULE CD44 IN GASTRIC ADENOCARCINOMAS

MK Washington, MR Gottfried, MJ Telen. Duke University Medical Center, Durham, NC.

CD44, an integral membrane glycoprotein serves as the principal transmembrane hyaluronate receptor and may be a determinant of metastatic and invasive behaviour in cancer. The authors examined the expression of CD44 in 23 gastric adenocarcinoma and 12 peptic ulcer disease (PUD) using monoclonal antibody A3D8 on formalin-fixed, paraffin-embedded tissue. In the normal stomach, foveolar epithelium and chief cells were negative. In PUD, foveolar epithelium was focally positive. In carcinomas, intestinal metaplasia stained more strongly than normal pyloric mucosa. The intensity of staining was progressively stronger when comparing metaplasia to low grade dysplasia to high grade dysplasia to intramucosal carcinoma. Invasive carcinoma was invariably more strongly positive than dysplasia or intramucosal carcinoma. Twelve adenocarcinomas were weakly positive, and 11 were strongly positive. For the 12 patients whose carcinomas were weakly positive, the mean survival for the 6 who died was 23.3 months. Mean survival for 5 patients whose carcinomas shows strong expression was 11.0 months. The authors believe that the expression of CD44 may represent a development of the invasive phenotype and stronger expression may indicate a poorer prognosis.

PRIMARY CULTURES OF EPITHELIUM DERIVED FROM BARRETT'S ESOPHAGUS

MK Washington, MR Gottfried, MJ Telen. Duke University Medical Center, Durham, NC.

The epithelial cells of Barrett's esophagus (BE) were isolated from resected esophagus specimens. The methods included trypsinization of small fragments of mucosa, followed by plating in tissue culture dishes and a direct tissue explant technique. A modified MCDB-153 growth medium containing fetal calf serum, ethanolamine, hydrocortisone, insulin, epidermal growth factor, pituitary extract, cholera toxin, amphotericin, and penicillin/streptomycin was used. BE cells were grown in 5% C02. Primary trypsin-technique cultures were plated on uncoated plastic or plastic coated with type I collagen, type IV collagen, or fibronectin. By 20-40 days most cultures formed confluent monolayers made up of cells with epithelioid morphology. The cells were cytokeratin positive, vimentin negative, and contained alcian-blue positive vacuoles, confirming their epithelial origin and suggesting their derivation from BE. Cells proliferated through up to 6 population doublings before growth slowed and cells showed senescent changes. Tissue culture allows preparation of sufficient quantities of BE cells for a variety of studies including cytogenetics and molecular biology investigations.

PRIMARY ANORECTAL MELANOMA: A CLINICOPATHOLOGIC STUDY OF 12 CASES

BW Webb, RE Petras, PM Antoniuk, JJ Tjandra, JW Milsom and VW Fazio. Cleveland Clinic Foundation, Cleveland, OH.

The authors studied the clinicopathological features and surgical management of 12 patients with primary anorectal melanoma. Clinical features studied included patient, age, sex, clinical presentation, tumor size and surgical treatment - either abdominoperineal resection (APR) or local excision (LE). Pathological features examined included cell types(s), pigmentation, mitotic activity, lymphocytic infiltration, tumor thickness, extent of invasion, ulceration and junctional activity. The median age was 69 years and females predominated 3:1. Clinical symptoms were relatively of short duration (mean 6 months) with the most common being rectal bleeding. The clinical diagnosis of melanoma was missed in 75% of cases. The lesion being most often confused with hemorrhoids. Nine patients (75%) died of disease, with 4 dead within 1 year of treatment and 3 more within 2 years. Three patients remain tumor free with limited follow-up. The mean survival was similar in both APR and LE. The authors conclude that: (1) the prognosis of anorectal melanoma is dismal, (2) the poor prognosis could be due in part to treatment delays resulting from the late onset of symptoms or misdiagnosis, (3) no pathological features were clearly associated with outcome, and (4) APR has no apparent survival advantage over LE.

THE DISTRIBUTION OF FACTOR XIIIA+ DENDROCYTES IN THE GASTROINTESTINAL TRACT

WL White, KR Geisinger, TM McCalmont, LR Miller. Bowman Gray School of Medicine, Winston-Salem, NC, University of California Medical Center, San Francisco, CA, Ochsner Clinic, Baton Rouge, LA

Factor (F) XIIIa+ dendrocytes are part of a bone marrow-derived monocyte/macrophage system present in many organs. Their presence has been systematically studied in the gastrointestinal (GI) tract. Investigators evaluated the presence of FXIIIa+ dendrocytes throughout the GI tract by standard immunoperoxidase techniques. Their distribution was semiquantitated and compared to that of S100+ and HAM-56+ mononuclear/dendritic cells and to T-lymphocytes (MT1). FXIIIa+ dendrocytes comprised a major portion of these dendritic cells, are more numerous than S100+ cells and are similar to T-cell density in nonlymphoid nodule areas. Their distribution appears to be identical to that of the HAM-56+ population. FXIIIa+ cells were present throughout the mucosa and muscular wall. They are most prominent in the superficial submucosa and lamina propria. The authors conclude that FXIIIa+ cells are major component of the dendritic cells of the GI tract.

P53 ONCOPROTEIN EXPRESSION IN FAMILIAL AND NON-FAMILIAL COLONIC ADENOMAS

R. Wolber. University of British Columbia, Vancouver, B.C., Canada.

Allelic deletions or mutations of the p53 gene have been detected in more than 75% of colonic carcinomas, but in only 10% of adenomas. The p53 products may be detectable by immunohistochemistry. In order to assess the differential expression of p53 in adenomas from patients with and without familial polyposis coli, immunohistochemistry was performed for mutant and wildtype p53 protein on small adenomas (< 1 cm) from 62 patients: 12 with familial adenomatous polyposis, 27 with flat adenomas, and 23 with sporadic adenomas. Widespread nuclear p53 staining was seen in roughly equal proportions of the 3 groups: 8%, 15%, and 9% respectively. There was intense multifocal single-cell nuclear p53 staining was present in 58%, 48%, and 43% of adenomas, respectively, but not in normal epithelium. Hereditary adenomas do not differ from sporadic adenomas and expression of p53. The presence of focal cells expressing p53 in half of the adenomas tested, suggests that p53 mutations are common events in dysplastic colonic epithelium. P53 mutation may provide cells with a growth advantage leading to clonal expansion in some adenomas, counterbalanced by the continual loss of mutated cells by epithelial sloughing.

NODULAR LYMPHOID HYPERPLASIA MIMICKING LYMPHOMA IN PATIENTS WITH CELIAC SPRUE

R Wolber, R Gascoyne, B Walker and S O'Reilly. University of British Columbia, Vancouver, Canada.

Two patients are reported with celiac sprue and atypical nodular lymphoid hyperplasia. Both patients had abdominal pain and weight loss, one with accompanying drenching night sweats. At laparotomy, enlarged mesenteric lymph nodes up to 4 cm in diameter were noted. Biopsies revealed unique histologic features of effacement of the nodal architecture by a nodular proliferation of small lymphocytes resembling primary follicles, focal aggregates of histiocytes and infiltration of sinusoidal and perisinusoidal spaces by fibrous tissue. Immunoperoxidase showed a proliferation of B-cells. Flow cytometry showed a polyclonal population which confirmed by germline Jh and bcl-2 region DNA by PCR analysis. Bone marrow studies were normal in both patients and upper GI biopsies showed small bowel villous atrophy due to celiac sprue. Both patients had resolution of adenopathy and abdominal symptoms after institution of a gluten free diet. The authors documented a previously unreported pattern of mesenteric lymph node hyperplasia and celiac disease.

P53 PROTEIN ACCUMULATION IN BARRETT'S METAPLASIA, DYSPLASIA AND CARCINOMA

M Younes, R Lebovitz, L Lechago and J Lechago. Baylor College of Medicine and the Methodist Hospital, Houston, TX.

The authors studied p53 expression in sections of formalin-fixed and paraffin-embedded tissue from 108 cases of Barrett's metaplasia, dysplasia and adenocarcinoma using a monoclonal anti-p53 antibody and the immunoperoxidase technique. One of 47 (2%) cases with metaplasia, 2 of 42 (5%) cases indefinite/low grade dysplasia, 1 of 9 (11%) cases with high grade dysplasia and 8 of 10 (80%) with adenocarcinoma were positive. The patient with metaplasia and positive p53 staining had a high grade dysplasia on a follow-up biopsy 3 years later which was also positive for p53 accumulation. The authors suggest that p53 mutation/accumulation plays an important role in the progression of Barrett's metaplasia to dysplasia and carcinoma.

SPECIFIC TYPE OF K-RAS-2 MUTATION TYPE PREDICTS OCCURRENCE AND EXTENT OF VISCERAL METASTASIS IN COLORECTAL ADENOCARCINOMA.

R Przygodski, R Sayegh, A Bakker, P Swalsky, S Finkelstein. Rhode Island Hospital, Brown University, Providence, Rhode Island.

Visceral metastasis in colorectal carcinoma may be aggressive with multiorgan dissemination, or indolent, with solitary or limited tumor deposition. The latter group may be high responsive to surgical/multimodality therapy. To distinguish between these two states, the investigators determined the presence and specific type of K-ras-2 point mutation in 31 hepatic, 12 lung, 5 bone and 5 brain metastasis from colorectal adenocarcinoma. This was correlated with tumor burden and extent of organ involvement. Mutation analysis involved sequencing of PCR amplified DNA in tissue removed under microscopic control from formalin-fixed paraffin-embedded tissues. Virtually, all metastatic deposits with a normal K-ras-2 genotype (5/6 liver, 2/2 lung and 2/2 brain) were solitary or of limited multifocality (less than three discrete deposits) and were confined to a single organ involvement. In contrast, aggressive, disseminated metastasis were characterized by specific point mutations (codon 12 aspartate, alanine, cystine, arginine and serine substitutions). Codon 12 aspartate substitutions, in particular, a relatively infrequent mutation form of primary tumors in general (9%) accounted for 32% of liver and 55% of distant hematogenous metastasis. K-ras-2 genotyping of colorectal metastasis appears to discriminate between indolent and aggressive metastasis enabling individualization of therapy for advanced disease.

LACK OF CORRELATION OF IMMUNOHISTOLOGIC PCNA INDEX WITH SURVIVAL IN DUKES B COLORECTAL CARCINOMAS

MD Linden, DS Nathanson, G Jacobson, RJ Zarbo. Henry Ford Hospital, Detroit, Michigan.

The significance of tumor proliferation activity as a prognostic parameter in colon cancer is controversial with conflicting results from flow cytometric S-phase data and tritiated thymidine studies. The level of proliferating cell nuclear antigen (PCNA), a co-factor for DNA polymerase delta, has been found to directly correlate with cellular proliferation and DNA synthesis. The authors studied the prognostic significance of PCNA expression in a 107 Dukes B colorectal adenocarcinomas with a minimum of 10 years follow-up. The staining was performed on formalin-fixed, embedded tissue. No statistically significant difference in survival for tumors with PCNA considered as an uncategorized numerical value ($p = 0.89$), categorized as above or below median PCNA value ($p = 0.78$) or for tumors divided into the following PCNA staining positive groups: 0-24%, 25-49%, 50-74%, and 75-100% ($p = 0.76$). The authors conclude that tumor proliferative activities determined by PCNA immunostaining does not correlate with disease-free or overall survival in Dukes B colorectal carcinomas.

IS THERE A PREFERRED HISTOLOGIC CLASSIFICATION SCHEME FOR ENDOSCOPIC GASTRIC POLYPS?

PR Lindley and HD Appelman. University of Michigan Hospital, Ann Harbor, Michigan.

Current histologic classification schemes of gastric polyps are based largely on resected specimens. Increased use of endoscopy has lead to the identification of many polyps under different circumstances. The investigators reviewed endoscopic polyps from 1984-92 to determine if older histologic classifications were useful for biopsy specimens. Large polyps were often only biopsied or removed in fragments, obscuring architecture, but classification was still attempted. 11% had no histologic polyps (usually normal mucosa). Of patients with histologic polyps 31% had fundic gland polyps, 24% focal foveolar hyperplasias (FFH), 16% hyperplastic polyps (HP), 12% possible transitional polyps between FFH and HP, 7% adenomas and 6% esophagogastric reflux polyps. 2% had lymphocytic gastritis and 7% xanthelasmas. 9% had unclassifiable polyps. These results suggest that traditional histologic classification schemes for gastric polyps are useful for endoscopic specimens, if it is recognized that small biopsies of large polyps may be difficult to classify and may require new criteria. 10% of polyps do not have standard names and about 10% are not even histologic polyps.

MICROGRANT AWARDS
SPRING 1993

The Microgrants Committee is pleased to announce that at its Spring 1993 meeting, the Executive Committee approved microgrant awards to the following individuals:

Dr. Mary Bronner, Department of Pathology, Hospital of the University of Pennsylvania (University of Washington, Seattle after July 1, 1993) received an award of $1,500. She will study Bcl-2 gene expression in colon cancer cell lines and in normal colon and colonic neoplasms. She also has plans to investigate the GI tract in Bcl-2 transgenic mice and to follow Bcl-2 expression in experimentally induced intestinal tumors using DMH.

Dr. Terry Gramlich, Department of Anatomic Pathology, Emory University Hospital was awarded $1,350 to use differential polymerase chain reaction for assessing the presence of epidermal growth factor receptor (EGFR), protoon-cogene c-erbB-2, and cyclin D1 gene amplification in Barrett's adenocarcinoma. Dr. Gramlich has expressed an interest in hearing from other Society members who might have case material suitable for his studies.

Dr. Christina Surawicz, Division of Gastroenterology, Harborview Medical Center in Seattle (University of Washington) received an $800 award to help in data analysis in a long term follow-up study of histologic findings in acute colitis. Her goal is to determine if there are histologic criteria that help distinguish acute self limited colitis from acute inflammatory bowel disease (UC and Crohn's).

Members can feel justifiably proud that their organization is able to lend support to these research projects. Hopefully, the recent spurt in applications will prove to be a harbinger of continued greater interest. We believe it will, and we will be making efforts to expand the microgrant program by seeking funds from outside sources.

For those who want to apply for their own microgrant, or to just enquire about the program, see the announcement in this issue of the Newsletter. **Remember, the Microgrant Committee invites a broad range of applications - not just for support of research projects.**

MCRGRAWD.NLT

ATTENTION ALL GI PATHOLOGY SOCIETY MEMBERS!

HAVE YOU CONSIDERED A MICROGRANT RECENTLY?

The GIPS Microgrants Committee received four applications in January, 1993 and was able to fund three (see announcement elsewhere in this issue of the Newsletter). This was many more than ever before. Now let's keep up the trend! We are ready and eager to work with you.

The range of possible projects that the Committee is prepared to support is limited only by the GIPS members' needs and imagination. We especially want to promote interaction among the members and between members and others who work in GI disease. Examples of proposals that you could submit are:

- Research projects - single investigator or collaborative
- Fellowships for junior persons (short or long-term)
- Support for a visiting scholar
- Support for a continuing education program in GI disease
- Help in organizing special meetings directed at education or collaborative research that involves Society members

Ground Rules and Procedures: These have been kept to a minimum, but a certain amount of bureaucracy is unavoidable. The formal policies and procedures of the Microgrants Committee are as follows:

1) Projects should fit within the broad goals of the Society to promote education and research in diseases of the gastrointestinal tract. All members are eligible.

2) Write a letter to the address shown below giving a brief (hopefully no more than a couple of pages) description of the project. It should have a defined purpose and set of goals. State briefly how these will be achieved and give an idea of your timetable.

3) While some background information such as references is usually desirable, send supporting documents only when they are essential. All major collaborators should indicate, in writing, their willingness to participate.

4) The period of award will normally be for 1 year, but can be continued. The Committee is authorized to award up to $1500 per year per project. **(Now you know why they're called microgrants.)** Include an itemized budget using standard NIH budget format. Support can be requested for all types of expenses and activities, but the committee is reluctant to support equipment purchases. Also, travel funds are not likely to be approved unless they are directly connected with execution of the project.

5) An annual progress report (again, brief and in the form of a letter) should be provided. You may also be asked to make a verbal report at the annual meeting of the Society.

Timetable: Deadlines for submission of application are May 15, September 15, and January 15. In addition, urgent requests will be given early consideration at the discretion of the Chairman.

Send enquiries and applications to:

John H, Yardley, MD
Department of Pathology
The Johns Hopkins University School of Medicine
632 Ross Bldg - GI Pathology Laboratory
720 Rutland Ave.
Baltimore, MD 21205-2196

Voice: (410) 955-3155
FAX: (410) 614-0614

March 23, 1993
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The Gastrointestinal Pathology Society Pathologist-in-Training Award for 1993 went to Dr. Ronald M. Przygodzki for the abstract reprinted below. This work was doubly blessed, winning not only the GIPS prize but a Stowell Orbison Award as well.

284 SPECIFIC TYPE OF K-RAS-2 MUTATION TYPE PREDICTS OCCURRENCE AND EXTENT OF VISCERAL METASTASIS IN COLORECTAL ADENOCARCINOMA

R. Przygodzki, R. Sayegh, A. Bakker, P. Swalsky, S. Finkelstein. Rhode Island Hospital, Brown University, Providence, Rhode Island

Visceral metastasis in colorectal cancer may be aggressive, with multiorgan disseminated involvement, or indolent, with solitary or limited tumor deposition. Patients having the latter may be highly responsive to surgical/multimodality therapy but require accurate identification of indolent biological behavior. To discriminate these states we have determined the presence and specific type of K-ras-2 point mutation in 31 hepatic, 12 lung, 5 bone and 5 brain metastasis of colorectal adenocarcinoma and correlated it with tumor burden and extent of organ involvement as determined radiologically. Mutational analysis involved sequencing of PCR amplified DNA in tissue removed topographically under microscopic control from formalin-fixed, paraffin-embedded large sized and needle biopsy sized specimens.

Virtually all metastatic deposits with a normal K-ras-2 genotype (5/6 liver, 2/2 lung, and 2/2 brain) were solitary or of limited multifocality (less than three discrete deposits) and were confined to single organ involvement. In contrast, aggressive, disseminated metastasis were characterized by specific point mutations (codon 12 aspartate, alanine, cystine, arginine and serine substitutions). Codon 12 aspartate substitutions, in particular, a relatively infrequent mutation form of primary tumors in general (9%) accounted for 10/31 (32%) of liver and 12/22 (55%) of distant hematogenous metastasis. K-ras-2 genotyping of colorectal metastasis appears to discriminate between indolent and aggressive metastasis enabling individualization of therapy for advanced disease.

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GASTROINTESTINAL PATHOLOGY SOCIETY
PATHOLOGIST-IN-TRAINING AWARD

The Gastrointestinal Pathology Society (GIPS) has established an award for the best poster or platform presentation at the USCAP related to gastrointestinal pathology. The awardee will receive $250 as well as recognition during one of the USCAP platform sessions on gastrointestinal pathology.

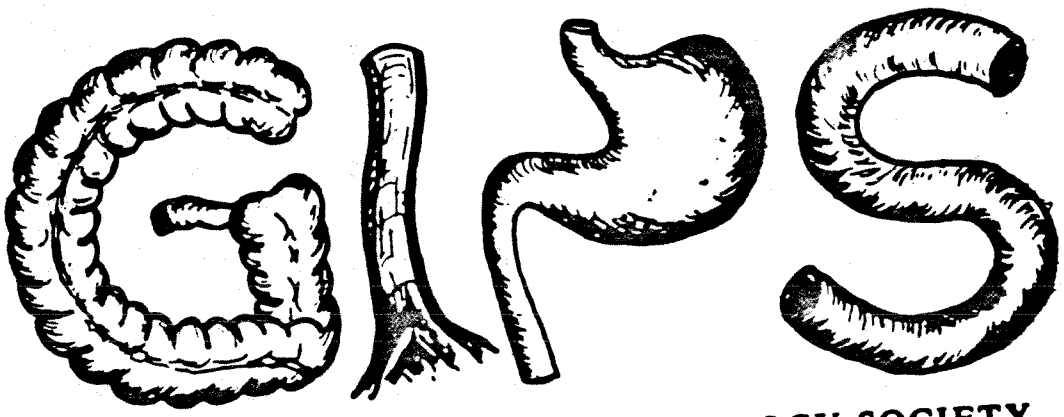
The applicant should be a pathologist-in-training (resident or fellow) and be the first author on the work. The applicant must first submit the abstract to the USCAP and have that abstract accepted. After acceptance by the USCAP, the abstract (and a cover letter Re: GIPS prize) should be sent to:

Audrey Lazenby, M.D.
Ross 632, Dept. of Pathology
The Johns Hopkins Univ. Sch. of Medicine
720 Rutland Ave.
Baltimore, MD 21205

Applying for the GIPS award does not preclude application for the Stowell-Orbison Award, and in fact the winner for 1993 won both. The application procedure is painless and we encourage all members of GIPS to inform your residents and fellows of this prize. You might wish to photocopy this announcement and put a copy in the mailboxes of all your trainees.

* *GIPS LOGO* *

By consensus of the membership at the business meeting this past spring, the membership decided on the following as the official GIPS Logo:



THE GASTROINTESTINAL PATHOLOGY SOCIETY

Re: BIOPSY DIAGNOSIS OF THE DIGESTIVE TRACT - Second Edition
(Biopsy Interpretation Series)
A Two-Volume Set
By Heidrun Rotterdam, Daniel G. Sheehan, and Sheldon C. Sommers
With a chapter on endoscopy by Peter H.R.Green
Retail Price: as of December 1992 - $160.00
Number of pages: 869
Publication date: December 1992

The second edition of this book arrives 12 years after the first. It is enlarged, now in two volumes and has an additional author. The increased length of the book has accommodated much of the information that arrived after the publication of the first edition. This is reflected in the increased length of the already extensive bibliography. The format of the book remains the same. Unlike other recent books where some disease types are covered together rather than geographically, this book is divided into chapters each dealing with an organ. Near the beginning of each chapter is a review of the anatomy and histology. A discussion of almost every conceivable disorder pertinent to that organ follows. This thoroughness is one of the strengths of this book in spite of its modest size.

A brief discussion of relevant clinical, endoscopic and etiological information is given on most topics. The prose follows in paragraphs which works well with small topics. However, a more liberal use of subheadings and tables might improve the organization of information in some of the larger topics. I would have appreciated more emphasis on histological points of differential diagnosis.

There were many sections that I enjoyed reading such as Barrett's esophagus, malabsorption and the approach to small intestinal biopsy evaluation. A reader will always find that some topics are covered less well than others. I felt that the text concerning epithelial metaplasia in the stomach lacked clarity and the flow of information about colonic adenomas seemed awkward with too much emphasis on the differences between tubular and villous adenomas. Some of the photographs were blurred or were too dark or small to be of use.

The range of topics covered was more than one expects in a book from a biopsy interpretation series. As a result it can be considered to be a small textbook of gastrointestinal tract pathology. I believe that it functions well as a small textbook, in fact, more so that as a bench book. I also believe that this book has a place amongst the plethora of recent gastrointestinal pathology books.

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