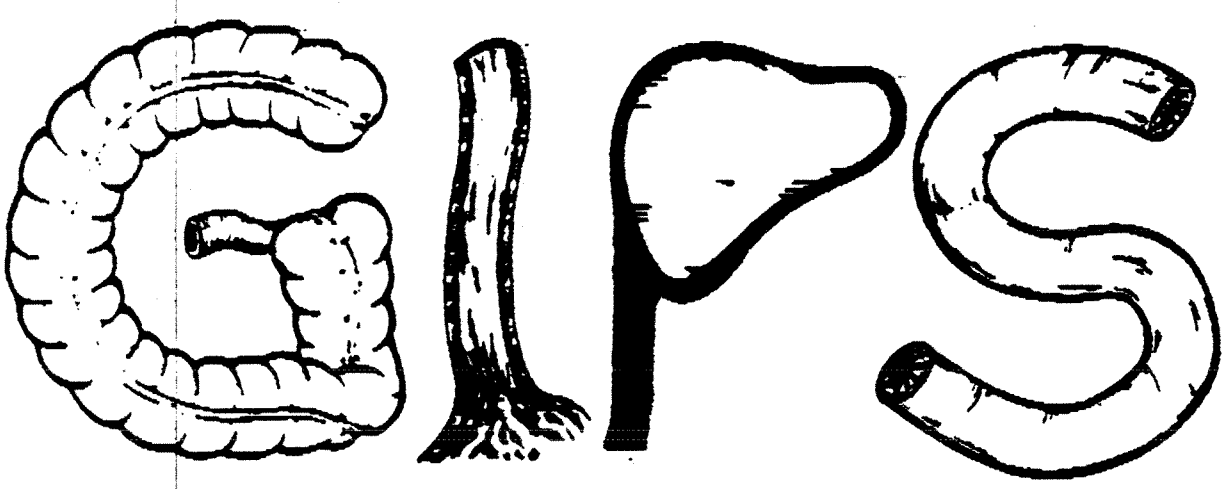

THE GASTROINTESTINAL PATHOLOGY SOCIETY
NEWSLETTER

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GASTROINTESTINAL PATHOLOGY SOCIETY
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To the Editor:

Should the Society create and endorse a timetable for interviewing and selecting applicants into gastrointestinal pathology fellowship programs? Some pros and cons immediately come to mind. On the plus side it would protect applicants (and training programs as well) from the jeopardy of having to make a decision prematurely, before hearing from all the programs in which one might have an interest. It would provide more order and a sense of fair play in a process which involves several institutions and dozens of candidates. On the other hand does the Society have an interest in or the right to impose even suggested guidelines and timetables for processing of fellowship applicants? How would such suggestions be regulated, or should they be? The Training Programs Committee is interested in opinions regarding these questions from program directors, faculty and interested members of the Society. I would welcome any and all comments sent or called to me or expressed to members of the committee at the March meetings in Boston.

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904-393-2006

GI Pathology Fellowships

The Training Programs Committee is currently compiling the new list of available gastrointestinal pathology fellowships for publication later this year in the *American Journal of Surgical Pathology* and *Gastroenterology*. All program directors who listed programs last year have already been contacted to update and revise any information which has changed. This appeal for new listings is directed at any member of the Society who wishes to list a new program. The table below requests the information which is required for listing. For anyone desiring to see the general format of listing which has been previously used, the 1989 list was published the July issue of the *American Journal of Surgical Pathology* and the August issue of *Gastroenterology*. The completed forms should be returned to Kenneth W. Barwick, M.D., Department of Pathology, Baptist Medical Center, 800 Prudential Drive, Jacksonville, FL, 32207.

Institutions and Locations _____

Duration _____

Prerequisites _____

Salary source _____

Program director(s) & address _____

Comments _____

Editor's Comment

In this issue of GIPS, we have invited two experienced workers in GI pathology who have used DNA analysis to study neoplasms and premalignant lesions to comment on the current and future use of ploidy analysis as it applies to our specialty. How many of you are currently using ploidy analysis by either flow cytometry or image analysis on these or other gastrointestinal lesions? This is an important and rapidly moving area in pathology. I would be surprised if there were less than 50 papers at the USCAP meeting that at least touch on ploidy analysis in various neoplasms. Yet, how many centers currently use these techniques on their patients. Is this still a research tool, or is it something that we should be doing routinely. Can we justify the cost on the basis of information currently available? Please send us your comments on this issue for the Summer newsletter!

Address your letters to:

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DNA CONTENT AND CELL CYCLE ANALYSIS BY FLOW CYTOMETRY IN COLORECTAL CARCINOMA AND DYSPLASIA

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DNA CONTENT AND COLORECTAL CARCINOMA

Investigators have reported conflicting results regarding the significance of DNA abnormalities as detected by flow cytometry in colorectal adenocarcinoma. Some conclude that DNA aneuploidy is independently associated with poor prognosis (1-3) while others think that it is either not significant or not independently associated with outcome (4-7). Several factors might explain these conflicting results including technical differences between studies, variation in criteria used to classify DNA histograms, and tumor heterogeneity.

No standardized technique for flow cytometry currently exists. Very few investigators have used fresh tissue in a prospective fashion (8,9). The vast majority of studies have retrospectively studied nuclei obtained from paraffin blocks using various different modifications of the technique of Hedley et al (10). Results of DNA analysis using fresh versus paraffin-embedded tissue can differ and results among various paraffin-embedded techniques can also vary (11,12). DNA fragmentation and partial nuclei, inherent to paraffin-embedded techniques, can increase background debris and can cause higher coefficients of variance (i.e., larger peak widths). High background in a DNA histogram can prevent recognition of small aneuploid peaks and larger peak widths can obscure peridiploid DNA aneuploidy (12). Therefore, many investigators prefer fresh tissue for DNA analysis by flow cytometry (11-13). In addition, a variety of techniques are available for processing fresh specimens for flow cytometry. We have used a whole cell technique (9) and are now actively investigating a modification of the naked nuclear technique of Vindelov et al (14). This latter method reportedly increases the sensitivity of the system (14).

Additionally, there are also no universally accepted guidelines for interpreting DNA histograms and criteria utilized to classify DNA content as aneuploid or abnormal vary. Some investigators require a minimum proportion of events to occur in a peak and require that that peak's DNA content vary by at least 10% from diploid to consider it abnormal. Proportion of events in S phase and in the G2 + M peak that are considered abnormal also vary from study to study.

Finally, tumor heterogeneity could contribute to the differences in the results and conclusions of various studies. It is known that DNA content in colorectal carcinoma can vary between primary and metastatic tumors in the same patient and from area to area within the same primary tumor (3,12,15,16). How much sampling is required for accurate DNA analysis is unknown at this time.

DNA indices can also be measured by image analysis of touch preparations. A prospective comparison study of flow cytometry versus image analysis showed that discordant results occur in up to 10% of specimens. Most of the discrepancies were populations of near tetraploid aneuploid cells identified by image analysis that were missed by flow cytometry (17). Therefore, reliable DNA content measurements may require more than one technique to ideally identify all abnormal cell populations.

In 1987, Muleris et al (18) reported that in the 18 "diploid" colorectal carcinomas that could be successfully karyotyped, all showed objective karyotypic abnormalities (aneuploidy). Thus, all colorectal carcinoma might be aneuploid if sensitive enough techniques were employed. With this information in mind, one would not expect DNA aneuploidy per se to have any predictive value in patient outcome. Since a tumor's DNA content must deviate from normal or "diploid" by at least 5-10% to be detected as DNA aneuploid by current techniques (19) it could just be this marked deviation from normal rather than DNA aneuploidy that relates to prognosis.

Bauer et al (4) found that DNA aneuploidy was not independently associated with adverse outcome, but that high proliferative activity as measured by the proportion of cells in S phase correlated independently with poor prognosis. Calculation of S phase fraction using flow cytometry is at best an indirect measure of a tumor's proliferative activity. Methods for determination of S phase fraction also lack standardization and results can vary remarkably depending upon which mathematical model (curve-fitting program) is used and whether pulse processing has been employed to correct for harmonics (doublets, triplets, etc.) and partial nuclei. Most mathematical models cannot universally determine an accurate S phase fraction for "DNA aneuploid" tumors. All current modeling programs are unable to subtract events contributed to the distribution by "normal" cells (inflammatory and stromal cells). Therefore, the "normal" G2 + M and S phase contaminate the aneuploid tumor S phase. Finally, if steps are not taken to correct for or eliminate the effects of "diploid" inflammatory cells in a tumor sample (e.g. by multiparameter gating) the inclusion of their nuclei in the DNA histogram can artificially and unpredictably lower the S phase fraction in any tumor.

DNA CONTENT AND COLONIC DYSPLASIA

Melville et al recently demonstrated a strong positive statistical correlation between DNA aneuploidy, as assessed retrospectively by flow cytometry of paraffin-embedded material, and the presence of dysplasia and carcinoma in patients with ulcerative colitis (20). They emphasized that interpretation of DNA histograms was less subjective than histologic assessment of dysplasia (not something we totally agree with) and that DNA analysis may become useful as a complement to histologic examination. DNA aneuploidy was detected in 48% of epithelial dysplasias and in 78% of invasive carcinomas in this study (20). These data suggest that DNA analysis could never be used alone in a cancer surveillance program (21). DNA aneuploidy was also identified in 6% of specimens in which all observers agreed that the histologic sections were negative or showed changes indefinite for dysplasia (20). Although it is tempting to speculate that this "histology negative - aneuploid group" represent the patients who would later develop carcinoma, there is currently no follow-up data to support this

(21). Whether the cancer risk is high enough in this "histology negative-aneuploid group" to warrant colectomy (21) or whether these patients would go through recognizable histologic dysplasia before the onset of invasive carcinoma are unknown. Therefore the utility of DNA analysis by flow cytometry in dysplasia or carcinoma in ulcerative colitis requires further study.

SUMMARY AND CONCLUSIONS

In summary, the current evidence associating DNA aneuploidy as determined by flow cytometry with poor prognosis in colorectal adenocarcinoma is inconclusive. Similarly, the role of DNA content analysis in inflammatory bowel disease associated dysplasia or carcinoma is undefined. Therefore, we would not advise investment in a flow cytometer for these purposes unless one is specifically interested in clinical research. DNA content analysis by flow cytometry is currently of no proved clinical value in colorectal carcinoma or dysplasia. The technology and methods are in their infancy. There is no standardization of technique or interpretation and in general the results between groups are not comparable. We must await standardization of techniques and results of large prospective studies using fresh tissue (or the best available or standard technique) in order to adequately assess the value of DNA content analysis.

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FLOW CYTOMETRY IN BARRETT'S ESOPHAGUS AND ULCERATIVE COLITIS

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Flow cytometric analysis of DNA content of epithelial nuclei provides objective information about the ploidy status and cell cycle events in populations of cells. Suitable cells/nuclei for analysis can readily be derived from "jumbo" endoscopic forceps biopsies. Such biopsies measure approximately 4-5 mm. in diameter and can be divided in half, with one half being used for flow cytometric analysis and one half for a histologic control.

Three prospective studies have investigated the correlation between flow cytometric and histologic abnormalities in Barrett's esophagus. In one study, the prevalence of aneuploidy and an increased 4N (G_2/tetraploid) fraction was found to correlate with the presence of dysplasia and carcinoma.[9] All three studies have shown an increasing prevalence of aneuploidy with increasing degrees of histologic abnormality. Direct comparison of the studies is not possible because different histologic classifications were used, some reported the results of Barrett's adenocarcinoma, while others grouped gastric, Barrett's and esophageal squamous cell carcinoma together, and because some studies had very small numbers of patients in the various diagnostic categories.[1,6,9] All three studies detected patients whose biopsies were histologically negative or indefinite for dysplasia, but who had flow cytometric abnormalities similar to those otherwise seen only in dysplasia or carcinoma. Thus, the detection of aneuploidy in a patient without histologic dysplasia may prove to be a valuable tool in identifying patients who merit intensive endoscopic biopsy surveillance because they are at increased risk for carcinoma. As the group of patients reported by Reid and coworkers has been enlarged and longer follow-up has become available, the correlation between aneuploidy and/or an increased G_2/tetraploid fraction with abnormal histology has become stronger.[10] Thus, patients with these flow cytometric abnormalities may merit more frequent endoscopic biopsy surveillance because of an increased risk of progression to high-grade dysplasia or carcinoma. The presence of multiple different aneuploid populations of cells has been shown to be strongly associated with adenocarcinoma in Barrett's esophagus, and the combination of high-grade dysplasia and multiple aneuploid cell populations in endoscopic biopsies may identify patients at very high risk for developing adenocarcinoma.[8]

The quantitative data on cellular DNA content obtained by flow cytometry can also be used to calculate the percentage of cells that are in the S phase fraction of the cell cycle. The proportion of cells in this fraction, as for the G_2/tetraploid fraction, appears to increase with increasing degrees of histologic abnormality in Barrett's esophagus, and proliferative abnormalities may prove to be predictors of dysplasia or cancer.[9] The accurate assessment of S phase and G_2/tetraploid fractions is technically challenging and requires optimal flow cytometric techniques.

Several studies employing flow cytometry for the analysis of nuclear DNA content in ulcerative colitis have been reported, but their significance is difficult to interpret. In two reports from different institutions, aneuploidy was found to correlate well with cancer or dysplasia[3,5,7]; however, reports from other investigators have found aneuploidy to be relatively nonspecific, as it occurred frequently in the absence of dysplasia or carcinoma.[2,11] These disparities may be explained in several ways. The results in one study were reported by biopsy diagnosis rather than by patient or case diagnosis, making interpretation difficult.[2] In another study, the biopsies were not taken by a protocol that provided correlation of specific biopsy histology with the presence or absence of aneuploidy.[3] Finally, adequate prospective data to determine the histologic evolution of aneuploid mucosa was not obtained in any of the studies.[2,5,7,11] We have found aneuploid cells in eight of ten patients with dysplasia in ulcerative colitis, while all patients whose biopsies have been negative for dysplasia contained diploid populations of cells. Interestingly, five of eight patients whose biopsies were indefinite contained aneuploid cell populations. As in Barrett's esophagus, the presence of multiple aneuploid populations of cells appears to be highly associated with carcinoma and may indicate patients at high risk for progressing to carcinoma.[4]

In summary, the technique of flow cytometry shows great promise as a tool in identifying and following patients with Barrett's esophagus and ulcerative colitis who may be at increased risk for developing carcinoma. However, the lack of standardization between laboratories for the performance of flow cytometry must be overcome before the technique is recommended for widespread application. The cost effectiveness of flow cytometry as a tool in managing cancer risk in patients with Barrett's esophagus and ulcerative colitis needs to be addressed in future studies.

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VEROCYTOTOXIN-PRODUCING AND OTHER ESCHERICHIA COLI

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Vero cell cytotoxin (Shiga-like toxin) producing Escherichia coli (VTEC) rank with C. pylori as the most important new gut bacteria of the eighties. In 1983 the prototypic member of this group, E. coli O157:H7, was linked to a food-borne outbreak of bloody diarrhea and abdominal pain. VTEC are now implicated strongly in the sporadic hemolytic uremic syndrome and in some cases of thrombotic thrombocytopenic purpura. Where do they fit into the overall picture of pathogenic E. coli?

Diarrhea-causing E. coli has been classified as enteropathogenic, enterotoxigenic, enteroinvasive or enterohemorrhagic.[1] Most pathogenic E coli possess two or more potential virulence mechanisms, often including a colonization mechanism and a toxic mechanism.

Enteropathogenic E. coli as described by Neter were: single serotypes found as the predominating aerobic organism in the majority of affected infants in outbreaks of diarrhea; the serotype was isolated in much lower frequency from healthy individuals; antibiotics effective in vitro were usually effective in therapy; specific serum antibody response could often be shown; virus isolation was negative and disease was experimentally reproduced in volunteers.[2] EPEC include O serogroups 18, 26, 44, 55, 86, 111, 114, 119, 125, 126, 127, 128ab, 142 and 158. Though not invasive by the Sereny test, some strains are capable of epithelial cell invasion. They do not produce heat-labile or heat-stable enterotoxins. They are now recognised to form intimate attachment complexes to enterocytes with effacement of microvilli.[3] Initial adherence is mediated by a plasmid-borne factor but attachment and microvillous effacement requires distinct chromosomally-inherited factor(s).[4-6] Toxin production has not been consistently identified in most serotypes. Pediatric pathologists may see these bacteria in biopsies of the jejunum or rectum. The affected mucosa displays moderate to severe enteropathy, irregular atrophy of the surface epithelium, subnuclear vacuolation of the crypt epithelium and bacteria glued onto the surface of the enterocytes. Ultrastructurally the enterocyte surface membrane forms attachment complexes with individual bacteria in which the bacterium sits in a cup or pedestal formed by the enterocyte plasma membrane. The microvilli are lost and actin filaments of the terminal web condense beneath the adhesion complex. The enterocytes are injured and show large lysosomes, dilated endoplasmic reticulum, deformed mitochondria and swollen watery cytoplasm.[7-9]

Enterotoxigenic E. coli (ETEC) are a common cause of travellers diarrhea. They produce either a heat-labile toxin, which is similar to cholera toxin, or a heat-stable toxin. Either toxin elicits secretion from the small intestinal crypts. Labile toxin stimulates adenyl cyclase; stable toxin stimulates guanyl cyclase. They are neither enteroinvasive nor do they form attachment-effacement complexes with microvillous destruction. Some serotypes have plasmid-encoded adhesions or "colonization factor antigens" which attach to enterocyte surfaces and permit colonization.

Enteroinvasive E. coli (EIEC) produce dysentery like shigellosis, and in vitro invade HeLa or HEp-2 cell monolayers. They share biochemical and antigenic properties with shigella and give a positive Sereny test (i.e. elicit keratoconjunctivitis in the guinea pig eye). EIEC include O serogroups 124, 143 and 164. EIEC possess a 140Md plasmid, as do shigella, which encodes polypeptide antigens essential for invasion, but, as with Shigella, chromosomal factors may additionally be requisite for pathogenicity.[11,12] DNA probes to the virulence plasmid of Sh. flexneri also detect EIEC with high sensitivity and specificity.[13-15]

EHEC (VTEC) were first recognised in 1983. The most frequently isolated serotype is O157:H7 but other isolates include O serogroups 26, 103, 111, 113, 121 and 145. Sorbitol-MacConkey agar facilitates isolation of E. coli O157:H7, since this strain does not ferment sorbitol in 2 days as do most E. coli. These organisms are neither enterotoxigenic not enteroinvasive but possess a plasmid encoded adherence factor[16] and also form attachment-effacement complexes with enterocytes in experimental animals (as do EPEC)[17,18]. Attachment-effacement is a chromosomally-mediated function. In addition they form large amounts of Vero cell cytotoxins (Shiga-like toxins, SLT).[19] The toxins are phage-encoded and the DNA has been cloned.[20-22] At least three distinct verocell cytotoxins (or shiga-like toxins) are now reported of which one is identical to shiga toxin.23

In parts of Canada, VTEC is isolated as frequently as Campylobacter or Salmonella and accounts for up to 40% of acute bloody diarrheas but the incidence elsewhere is considerably lower.[17,18]. Highest infection rates occur during summer. Undercooked beefburger and unpasteurised milk are implicated in transmission and naturally-occuring VTEC-induced diarrheas in calves are reported. There have been several outbreaks in nursing homes with appreciable mortality rates. Though the majority of infections are self-limited, an unpredictable serious complication is the idiopathic hemolytic uremic syndrome (the triad of microangiopathic hemolytic anemia, thrombocytopenia and renal failure) and VTEC is implicated in up to 75% of cases.[19] Rare cases of thrombotic thrombocytopenic purpura (the triad of HUS with fever and neurologic signs) are also reported. The toxin genotype of the infecting strain may influence the risk of developing these complications.[24] Young children, the elderly and the immunosuppressed are more susceptible to HUS and TTP. Antimicrobial treatment does not influence the duration of symptoms and do not appear to alter the risk of HUS or TTP.

Flexible sigmoidoscopy shows normal mucosa with blood coming from above in the majority of patients. A minority show erythema, congestion, friable mucosa, exudate or pseudomembranes. Biopsies taken at sigmoidoscopy may show normal mucosa, features of mild infective colitis, or rarely, pseudomembranous colitis. Few resected or autopsy colons are yet described. The gross pathology includes patchy ulceration of the right side of the colon with variable surface exudation sometimes of pseudomembranous proportions, and extreme submucosal swelling and hemorrhage which may narrow or obliterate the lumen. The latter feature accounts for the thumbprinting seen radiologically. The entire colon may be involved, especially in children. Microscopically extreme submucosal edema, hemorrhage, and fibrin exudation correspond to the submucosal swelling. Partial or full-thickness mucosal ulceration, mucosal regeneration, capillary thrombosis and pseudomembranes similar to those due to Cl. difficile may be seen. Pseudomembranes are rare in distal colonic biopsies in adults but may be seen in colonoscopic

biopsies, resection or autopsy specimens, and possibly more often in children.[22,25,26] Mucosal-adherent bacteria have not yet been identified in humans infected with VTEC. Some cases diagnosed formerly as transient ischemic colitis on the basis of acute bloody diarrhea and radiological thumbprinting in the right side of the colon may in fact have been VTEC infection.

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Guide to Clinical Aspiration Biopsy: Liver and Pancreas by Denise Frias - Hidvegi, M.D., F.I.A.C. Igaku-Shoin Medical Publishers, Inc., New York, 1988, pg 332, ISBN 0-89640-146-4.

Over the past decade, the impact of needle aspiration biopsy in our day to day practice has been considerable. This particular monograph, which is part of a guide to clinical aspiration biopsy series should be of particular interest to members of our society.

The book is divided into fourteen chapters and with the exception of two chapters, the text is written by one author who is a practicing cytopathologist. Dr. Harvey L. Neiman discusses the indications, technique and complications from the radiologic point of view. This chapter is somewhat brief, though the subject matter is adequately summarized with up to date references. Drs. Hunter S. Neal and Howard Schacter discuss the clinical usefulness and intraoperative applications of needle aspiration biopsy. This chapter unfortunately is very brief and will make the book less attractive to our clinical colleagues.

The purpose of the book according to the preface, was to present a practical guide to the cytologic diagnosis of lesions of the liver and pancreas for the practicing cytotechnologists and pathologists and to that end, I think the author has succeeded admirably. The remaining twelve chapters relate to the technique and cytodiagnosis in various conditions involving the liver and pancreas. There is good histocytologic correlation with many comprehensive tables and line drawings. The one feature that deserves special mention is the quality of both the gross and microscopic photographs. These are excellent with good cytoplasmic and nuclear detail. This is important in a text such as this and needs emphasis. Igaku-Shoin Medical Publishers is well recognized for its color reproduction and the quality of the color plates is in keeping with their high standard.

The book will be of interest to residents, cytotechnologists and pathologists and act as a practical guide to the interpretation of needle aspiration from lesions of the liver and pancreas.

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BOOK REVIEW

GASTROINTESTINAL DISEASE: PATHOPHYSIOLOGY, DIAGNOSIS, MANAGEMENT

By Sleisenger MH and Fordtran JS
Philadelphia, WB Saunders Company
4th edition, 1989.

The fourth edition of this widely read and respected textbook contains 106 chapters by 106 authors, and is substantially similar in format to previous editions. In theory at least it covers the entire spectrum of GI disease including the biliary tract and pancreas. There are sections on anatomy and physiology as well as gastroenterology and GI surgery. No pathologists are included in the authorship and there are no contributions devoted exclusively to morphology or histologic diagnosis. This is probably to be expected in a book of this type, although several radiologists are among the contributors In my opinion future editions would be improved if some chapters were co-written with the aid of pathologists.

This paucity of formal pathologic input is not a problem in some areas, for example, the chapter on gastritis provides an excellent clinico-pathologic account of this confusing and rapidly changing field. The pathology of colonic polyps and of gastric cancer are also well covered. Omissions do arise, however in discussion of gastric polyps where little distinction is made between different morphologic subtypes as regards treatment and prognosis. Also, some of the rarer lesions well recognised by GI pathologists are hardly covered at all. Examples here include, multiple gastric carcinoids, and mucoceles of the appendix.

These rather minor criticisms of the book do not detract from its value as a reference text. Of particular use to me and I suspect to many pathologists are the sections dealing with diseases whose morphology is non-specific or largely irrelevant to clinical diagnosis. In this respect "Gastrointestinal Disease" fills the gaps left by traditional pathology texts. I also found that this book is an excellent resource when preparing for clinico-pathologic teaching sessions. The concise discussions provide an up to date summary of clinical knowledge and practice that is so necessary for modern GI pathology practice.

David A. Owen,
University of British Columbia,
Vancouver, Canada.

GASTROINTESTINAL PATHOLOGY SOCIETY
SUNDAY, MARCH 4, 1990, 1:30 P.M.
MOLECULAR BIOLOGY AND THE DIGESTIVE SYSTEM

MODERATOR: Daniel G. Sheahan, M.B., M.Sc.
University of Pittsburgh School of Medicine
Pittsburgh, Pa.

1:30 P.M. Gene Alterations and Neoplasia

Joseph Locker, M.D.
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

2:15 P.M. Regulation of Intestinal Epithelial Barrier Function

James Madara, M.D.
Harvard Medical School
Boston, Mass.

3:00 P.M. Coffee Break

3:30 P.M. Diagnostic Molecular Biology of Lymphoid Neoplasms

Jeffrey Sklar, M.D.
Harvard Medical School
Boston, Mass.

4:15 P.M. Molecular Clues to the Etiology and Prognosis of Colorectal Cancer

Stanley Hamilton, M.D.
Johns Hopkins University Medical School
Baltimore, Md.

GENE ALTERATIONS AND NEOPLASIA

JOSEPH LOCKER, University of Pittsburgh School of Medicine

Pathologists study tumors to learn about derivation, behavior, extent, and prognosis. This has had little relationship to research in experimental carcinogenesis which established that tumors are the product of initiation, promotion, and progression. Recently, molecular biology has provided insight into carcinogenesis and also defined many new parameters which the pathologist can incorporate into his assessment of tumors.

In a unifying view, cancer arises from sequential accumulation of lesions in the genes that regulate cell proliferation and behavior. Cells with mutations are selected by the environment in tissues. Dominant gene lesions will be expressed when the other allele is normal, while recessive lesions will require a second lesion in the other allele. If a defective gene is inherited, then a mutation in the other allele, ordinarily recessive, would act as if it were dominant. Classical mutations result from chemicals that damage DNA and alter bases. For example, *ras* protooncogenes (normal genes) are mutated to become *ras* oncogenes. This is a dominant mutation, and *ras* oncogenes act by continuously activating cellular regulatory pathways that are normally active only briefly. Unlike *ras*, however, most mutations will inactivate a gene and are recessive.

DNA rearrangements are nonmutational lesions that result from DNA strand breaks that are abnormally rejoined. Breakage may result not only from direct DNA damage, but also as a byproduct of DNA repair, or by disruption of the normal timing of DNA replication. DNA rearrangements include: Gene amplification (dominant), where extra gene copies increase gene activity (genes include *c-myc*, *N-myc*, *epidermal growth factor receptor*, etc.); translocation (dominant), where a gene is moved and placed under the influence of control elements that normally

do not regulate it (*c-myc* and numerous other genes); and deletion (recessive), where loss of a DNA segment can inactivate tumor suppressor genes (*retinoblastoma susceptibility gene* and *p53*).

Aneuploidy may be a dominant or recessive mechanism. Extra chromosome copies may lead to overexpression of a gene while loss of a chromosome may unmask a mutated or deleted antioncogene.

Viral genes (dominant) may provide abnormal stimulation of cell proliferation. Viral integration may activate genes near the integration site (dominant, viral transduction), or disrupt a gene at the integration site (recessive, insertional mutagenesis).

Overview. Following an initial gene alteration, a cell must proliferate to provide a target population for further alterations. Each successive gene alteration will lead to a new clone of cells with enhanced proliferative or competitive behavior. Each disruption of cell cycle control will make the next gene alteration more probable. The early steps are the most poorly understood and will be highly tissue specific. In liver, the normal hepatocyte proliferates when stimulated by liver damage. In liver carcinogenesis, the initial gene lesion might activate cell proliferation. Alternatively, a promoting agent will cause altered hepatocytes to proliferate even if the initial gene lesion does not stimulate proliferation. In colon, the mucosal cell proliferates constantly, but rapidly matures and sloughs. The initial gene lesion might act to prevent maturation, so that the altered population is not lost. Thus, though the gene lesions may be similar, the specific genes that are altered or inactivated will explain differing pathways to neoplasia among tissues, and to biological differences among tumors arising in the same tissue. The future surgical pathologist will define the gene abnormalities of individual tumors leading to their customized therapy.

REGULATION OF INTESTINAL EPITHELIAL BARRIER FUNCTION

James L. Madara, M.D.
Brigham and Women's Hospital
Harvard Medical School

Intestinal (and other) epithelia restrict passive transepithelial solute flow via the establishment of intercellular tight junctions (TJ). Recent evidence shows that these TJ barriers are not the static structures they were assumed to be. Rather, rapid changes in TJ structure and permeability can be elicited by a variety of pharmacologic manipulations. Recently we have shown that TJ permeability in the intestine is regulated by dietary constituents. Specifically, dietary glucose, at concentrations as low as 10 mM, can result in substantial alterations of TJ structure and increased TJ permeability (although charge selectivity is maintained). We have now shown that such physiological regulation of the TJ is triggered by activation of the Na^+-glucose co-transporter present in the apical membranes of villus absorptive cells. The intracellular cascade linking co-transporter activation to TJ alterations is as yet undefined, although a specific component of the cytoskeleton - the perijunctional actomyosin ring appears to be involved. Furthermore, the enhanced TJ permeation elicited by glucose allows paracellular absorption of nutrients via solvent drag and recent studies indicate this novel pathway of nutrient uptake is of major importance to absorption of many dietary components.

The Diagnostic Molecular Biology of Lymphoid Neoplasms

Jeffrey Sklar
Division of Diagnostic Molecular Biology
Department of Pathology
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts
02115

Certain rearrangements which occur somatically in the DNA of lymphocytes and their precursors provide useful diagnostic markers for the evaluation of tissue biopsy specimens containing lymphoid infiltrates.[1,2] These DNA rearrangements can be considered as belonging to two different types: (1) intragenic rearrangements of DNA within antigen receptor genes (ARGs), and (2) intergenic rearrangements resulting from chromosomal translocations, deletions, and inversions.

Of the two types of rearrangements, intragenic rearrangements of ARGs have so far been more widely used in diagnostic pathology. These rearrangements take place in early normal B and T lymphocyte precursors as attempts are made to assemble intact, functional immunoglobulin and T cell receptor genes from multiple, discontinuous gene segments encoded in the DNA of each ARG. The ultimate configuration of DNA in a rearranged ARG (i.e., which individual gene segments have been joined to which other gene segments) marks the cell in which that rearrangement has occurred and any clonal descendents of that cell.

It is the latter fact that makes analysis of ARG rearrangements diagnostically useful. Malignant lymphocytic processes, like other cancers, are virtually always clonal, whereas benign lymphocytic processes are polyclonal. The clonal cells composing the malignancy generally carry uniform rearrangements, while the vast majority of cells in benign tissues carry diverse rearrangements.

The method most often used for analyzing ARG rearrangements in tissue is the Southern blot hybridization procedure. This procedure essentially permits assessment of the frequency of a particular ARG rearrangement in the cells of a biopsy specimen. Uniform rearrangements are detected if they are present in 1% or more of the cells in the specimen; that is, if 1% or more of the cells are clonal. Diverse rearrangements or uniform rearrangements present in numbers of cells below the 1% threshold are not detected.

In addition to providing information about the clonality (and, thereby, indirectly about the malignancy) of tissues, ARG rearrangements have been used to determine the B- or T-lineage of lymphoid tumors and to identify multiple B- and/or T-lineage clones or subclones within single cases of lymphoproliferative disease. In the context of gastrointestinal pathology, these

applications have been used to examine such issues as the existence of pseudolymphoma of the gut . the lineage of various lymphoid tumors of the gastrointestinal tract , and the multiclonality of gastrointestinal lymphomas in immunosuppressed patients .

Recent experience with diagnostic applications of ARG rearrangements has revealed several problems with this type of analysis. For example, certain clinically benign disorders are sometimes clonal: occasional T cell lymphomas may lack detectable ARG rearrangments; the ARG rearrangements detected may be discordant with the tumor phenotype; and under various circumstances, rearrangements may not be stable in subpopulations of tumor cells. However, these problems are relatively rare and do not ordinarily preclude the usefulness of this approach to diagnosis in most situations.

Other problems with analysis of ARG rearrangements are technical and relate to features of the Southern blot procedure (e.g., the limited sensitivity, the week to 10 day interval necessary to obtain results, and the reliance on radioactively tagged probes to detect rearrangements). It now seems that use of the recently devised technique of the polymerase chain reaction (PCR) may overcome these problems. PCR is a technique which permits rapid *in vitro* amplification of defined regions of DNA from whole genomes. This technique can be used to analyze ARG rearrangements in a variety of ways--in some applications, with a sensivity for detecting clonal lymphocytic population at levels down to one in a million total cells.

Intergenic DNA rearrangements are similar to intragenic rearrangements in that separate sequences of DNA which lie apart in the germline are brought together as a result of rearrangement. except that in intergenic rearrangements the DNA sequences involved are not part of the same locus but are part of different loci, usually located on different chromosomes. The two most important intergenic rearrangements associated with lymphoid neoplasms are the t(8;14) and t(14;18) chromosomal translocations found in most cases of Burkitt's and follicular lymphomas, respectively. Additionally, these translocations may coexist in certain cases of high grade lymphoma. In these two translocations, DNA in or around the immunoglobulin heavy chain gene on chromosome 14 is joined to DNA somewhere near either the *c-myc* oncogene on chromosome 8 or the *bcl-2* oncogene on chromosome 18.

At the DNA level, translocations can be analyzed by the same techniques as are ARG rearrangements. Unlike detection of clonal ARG rearrangements, which is specific only for clonal proliferation of lymphocytes, detection of the two above translocations appears to be specific for malignancy, as well. However, the case-to-case variability of the precise translocation breakpoints in the DNA of the two participating loci sometimes poses problems in detection of these translocations for routine diagnostic purposes.

(1). Sklar, J. and L.M. Weiss. Applications of antigen receptor gene rearrangements to the diagnosis and characterization of lymphoid neoplasms. Ann Rev Med 1988, 39:315-334.

(2). Sklar, J. What can gene rearrangements tell us about solid hematolymphoid neoplasms? Am J Surg Path 1990, in press.

MOLECULAR CLUES TO THE ETIOLOGY AND PROGNOSIS OF COLORECTAL CANCER

Stanley R. Hamilton, M.D. and Scott E. Kern, M.D.
Department of Pathology and Oncology Center
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Baltimore, Maryland 21205 U.S.A.

Our collaborative group has studied molecular genetic alterations in colorectal neoplasms. Ras gene mutations were studied due to their importance in carcinogenesis. Based on nonrandom cytogenetic abnormalities, we investigated allelic deletions on chromosome 17 and 18. We studied genetic probes on the long arm of chromosome 5 which have been linked to adenomatous polyposis syndrome. To examine the extent and variation of allelic loss, we studied polymorphic DNA markers from every nonacrocentric autosomal arm, resulting in an "allelotype" analogous to karyotype. We compared these molecular genetic alterations to the clinical and pathologic features of the 56 colorectal carcinomas studied.

Ras gene mutations were found in approximately half of the colorectal carcinomas. Sequences on the long arm of chromosome 5 were lost in about 1/3 of carcinomas whereas those on the short arm of chromosome 17 (p53 gene) and on the long arm of chromosome 18 (gene for a cell adhesion molecule) were lost in about 3/4 of the cancers. Allelic losses were remarkably common, as one of the alleles of each polymorphic marker tested was lost in at least some carcinomas. Some tumors lost more than half of their parental alleles.

As regards the etiology of colon cancer, patients with a family history of cancer in a first-degree relative had a mean fractional allelic loss (FAL, defined as the number of chromosomal arms lost divided by the number of evaluable chromosomal arms) which was twice that of patients without a positive

family history (0.296 vs. 0.150, p=.002). When the specific deletions were assessed, a positive family history of cancer was associated with deletion of 17p, the site of p53. 17p deletion was more common in left-sided carcinomas than in right-sided carcinomas (93% vs. 60%, p=.004). Allelic deletions of 17p and of 18q were less common in mucin-producing carcinomas than in non-mucin producing tumors (17p deletion in 44% vs. 88%; 18q deletion in 47% vs. 85%). Molecular genetic alterations also appeared to relate to prognosis. We found that the presence of distant metastases was significantly associated with high fractional allelic loss and with deletions of 17p and 18q, whereas mutation of ras proto-oncogenes and deletion of 5q had no prognostic importance.

Our findings suggest that: 1) Familial colorectal carcinoma may differ in pathogenesis from "sporadic" tumors, or familial factors may increase the tendancy of an established tumor to tolerate or promote the accumulation of clonal genetic abnormalities. 2) The differences in molecular genetics of right- vs. left-sided carcinomas may be related to different pathogenetic factors and are of interest due to the recent historical trend toward a higher proportion of right-sided tumors in the USA. 3) Identification of molecular clues to aid in prognostication among patients without initial evidence of disseminated colorectal cancer may be at hand.

GIPS

GASTROINTESTINAL PATHOLOGY SOCIETY SEMINAR
TUESDAY, MAY 15, 1990

UNUSUAL AND UNCOMMON COLITIDES

MODERATOR: Daniel G. Sheahan, M.B., M.Sc.
Presbyterian-University Hospital
University of Pittsburgh School of Medicine
Pittsburgh, Pa.

Allergic Colitis in Children and Adults

5:30 p.m. Donald Antonioli, M.D.
Beth Israel Hospital
Harvard Medical School
Boston, Mass.

5:50 p.m. **Infectious Colitis**

James Kelly, M.D.
Foothills Hospital
Calgary, Alberta

6:10 p.m. **Collagenous and Lymphocytic Colitis**

Audrey Lazenby, M.D.
Johns Hopkins Hospital and Medical School
Baltimore, Md.

6:30 p.m. **Sexually Transmitted Colitis**

Christine Surawicz, M.D.
University of Washington
Seattle, Wash.

6:50 p.m. **Parasitic Colitis**

David Schwartz, M.D.
Emory University School of Medicine
Atlanta, Ga.

7:10 p.m. **Pathology of Colorectal Disorders Associated With Surgery and Instrumentation**

Michael O'Brien, M.D.
Boston University
Boston, Mass.

7:30 p.m. Conclusion

XVIII INTERNATIONAL CONGRESS OF THE INTERNATIONAL ACADEMY OF PATHOLOGY

Sheraton Hotel, Buenos Aires, Argentina

September 9-14, 1990

GASTROINTESTINAL PATHOLOGY SYMPOSIUM

Tuesday, September 11, 1990

THEME: "PREMALIGNANT CONDITIONS OF THE GASTROINTESTINAL TRACT"

CHAIRMAN: JUAN LECHAGO, M.D., PH.D.

PROGRAM

8:30		**Introductory Remarks** Juan Lechago, Dallas, U.S.A.
8:35 -	9:05	**Barrett's Metaplasia and Adenocarcinoma of the Esophagus** Francois Potet, Clichy, FRANCE
9:10 -	9:40	**Chronic Gastritis, Intestinal Metaplasia, and Gastric Adenocarcinoma** Teruyuki Hirota, Tokyo, JAPAN
9:45 -	10:15	**Pernicious Anemia, Gastric Atrophy, and Gastric Carcinoids** Juan Lechago, Dallas, U.S.A.
10:20 -	10:50	**Lymphoproliferative Disorders and Lymphoma of the Digestive Tract** To be announced
10:55 -	11:25	**Inflammatory Bowel Disease, Dysplasia, and Colonic Malignancy** To be announced
11:30		**Adjournment**