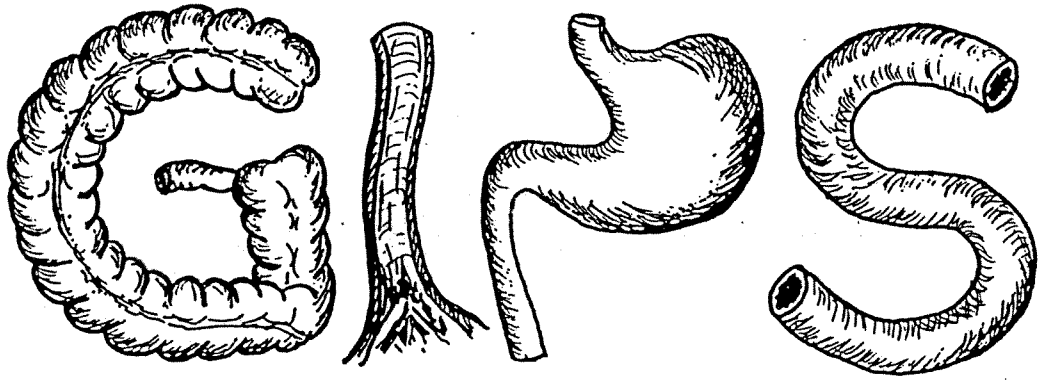

THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

GIPS NEWSLETTER - FALL/WINTER 1994
Volume 12, No. 2

1994-95
OFFICERS AND EXECUTIVE COMMITTEE OF THE GASTROINTESTINAL PATHOLOGY SOCIETY

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Newsletter	Patrick Dean
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MESSAGE FROM THE PRESIDENT

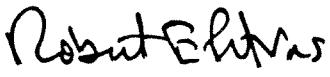
This year, the Gastrointestinal Pathology Society celebrates its fifteenth anniversary. Fortunately, the society shows the signs of stability, maturity and vitality. Interest and membership continue to increase and we have many new faces serving on committees and as committee chairs. The scientific programs at USCAP, DDW, and ASCP continue to be successful and this fall the Gastrointestinal Pathology Society will be sponsoring and presenting a scientific program at the World Congresses of Gastroenterology in Los Angeles.

Several new developments are on the horizon. The Society's relationship with the American Journal of Surgical Pathology appears to be undergoing a transition that should benefit our members. This new relationship creates new interactions including a gastrointestinal pathologist associate editor responsible for soliciting and reviewing papers, additional society membership on the editorial board, and the ability to disseminate GIPS specific information through the Journal.

Probably the most exciting part of the society's maturation process is the work going on with the microgrant committee. Under the leadership of John Yardley (the father of us all) this committee is exploring new areas of fund development and is looking at ways to expand the program into other areas of research and education.

The society's continued success requires an involved membership. If you should have suggestions or wish to serve on a committee or program, remember to fill out the form that comes with the dues statement or contact the Secretary-Treasurer or myself directly. Remember, it is your society.

Yours sincerely,



Robert E. Petras, M.D.
President,
Gastrointestinal Pathology Society

FROM THE EDITOR

Dear Fellow GIPS Members:

Thank you for your patience in awaiting this current issue of the GIPS Newsletter. The new captain of the editorial ship has been getting his sea legs.

The format of the newsletter remains unchanged, with one notable exception. Since abstracts of work presented at the March USCAP Meeting are readily available in the January issues of both Modern Pathology and Laboratory Investigation, their republication in our newsletter has been waived in favor of reviews of material pertinent to GI pathology from literature not immediately accessible to all GI pathologists. Hence, in this addition, manuscripts published in Gut, Histopathology, Journal of Clinical Pathology and Gastroenterology are reviewed. My thanks to GIPS members, Brian West, Bob Genta, Terry Gramlich and Jim Crawford for amassing this material. This new venture is not chiselled in stone. We welcome feedback from the membership.

A few additional notes. Eamon Sweeney has agreed to grace our newsletter with his brilliant artistry; savor the Laocoon. To encourage recruitment of new members, a copy of the GIPS membership application is included in the newsletter. For your pathology residents in training, a listing of GI pathology fellowships is also included.

I wish to thank my predecessor, Harry Cooper, for so ably guiding the editoral ship of state. A second thanks goes to Harry in his current position as Chairman of the Education Committee for providing us advance copy of the syllabus of the 1995 USCAP Gastrointestinal Pathology Society Companion Meeting on Update on Pathology of the Stomach.

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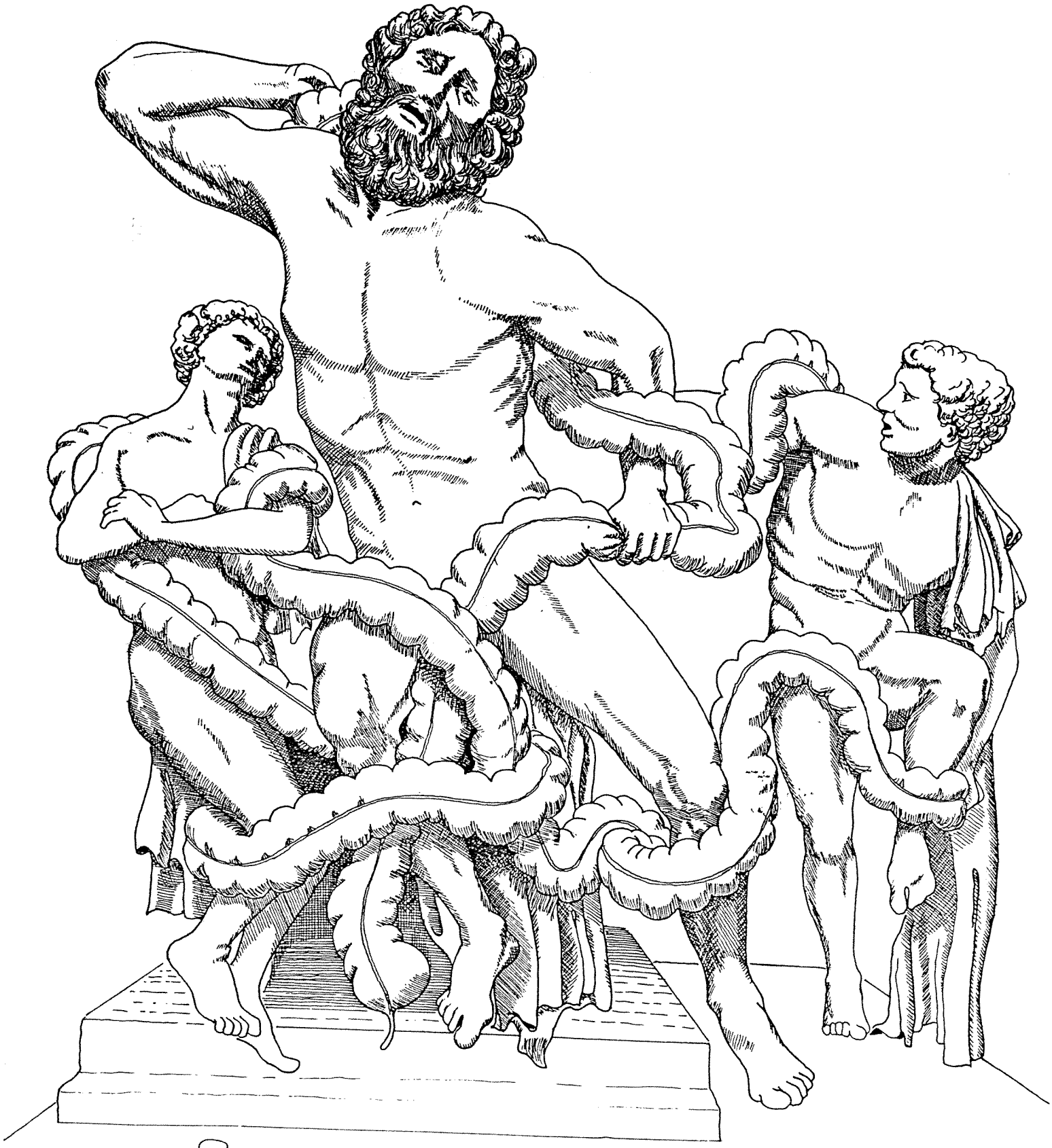

Sweeney WITH APOLOGIES TO AGESANDER, POLYDORUS AND ATHENODORUS.

The Laocoon is a sculpture depicting a traitorous high-priest and his two sons being devoured by sea-snakes at the command of the gods. The cartoon derived from this is entitled "**The Laocolon**"* and represents a gastrointestinal pathologist and two chief residents wrestling with a case of indeterminate colitis!

Courtesy of: Eamon C. Sweeney, M.D., FRCPI., FRCPath.
Professor of Pathology
St. James's Hospital
Dublin, Ireland

*Exhibited at the European Society of Pathology Congress, Athens, Greece - 1985

SECTION FOR GASTROINTESTINAL PATHOLOGY IN THE AMERICAN JOURNAL OF SURGICAL PATHOLOGY

As a result of negotiations conducted on behalf of the GI Pathology Society by Drs. Henry Appelman and Robert Petras, and by Dr. Stephen Sternberg of the American Journal of Surgical Pathology, a Section for Gastrointestinal Pathology will be added to the Journal. This development represents a step forward for GI pathology, as it provides a specific forum for the publication of our subspecialty papers. This vehicle for the dissemination of new developments in GI pathology within an established and internationally recognized journal should attract GI pathology manuscripts that are currently being published elsewhere.

Dr. Rodger C. Haggitt has been named Editor for the Section for Gastrointestinal Pathology. The editorial board for the section will be listed separately in the masthead of the Journal and includes the following individuals:

Dr. Henry D. Appelman
Dr. Donald A. Antonioli
Dr. Wladimir V. Bogomoletz
Dr. Leonard S. Gottlieb
Dr. Klaus J. Lewin
Dr. Robert H. Riddell
Dr. Daniel G. Sheahan
Dr. Dale C. Snover

Authors will be instructed to send GI and liver manuscripts directly to Dr. Haggitt's office, where the review process will be initiated.

Rodger C. Haggitt, M.D.

The American Journal of Surgical Pathology *18(11): 1077, 1994*

Special Announcement

Newly Created Gastrointestinal Pathology Section

We are pleased to announce that the Gastrointestinal Pathology Society and the *journal* are creating a special section within *The American Journal of Surgical Pathology* devoted to gastrointestinal pathology papers. The section is being established to acknowledge the expanding interest in GI pathology, and to provide a forum for presentation of the latest pathological studies in this area.

We are equally pleased to announce that Dr. Rodger C. Haggitt has agreed to serve as the Section Editor for this new section. All gastrointestinal pathology manuscripts, including liver, should be directed to the office of Dr. Haggitt for the administration of this section at the following address: University of Washington Medical Center, RC-72, 1959 NE Pacific Street, Seattle, WA 98195 U.S.A.; (206)548-6404; FAX (206)548-4928.

Dr. Haggitt has developed the following Gastrointestinal Pathology Editorial Board to serve as primary reviewers:

Donald A. Antonioli
Henry Appelman
Wladimir V. Bogomoletz *(France)*
Leonard S. Gottlieb
Klaus J. Lewin
Robert H. Riddell *(Canada)*
Daniel G. Sheahan
Dale C. Snover

Our special thanks to Dr. Henry Appelman and Dr. Robert Petras for assisting in the creation of this new journal feature in association with the Society. We believe this will be a successful and fruitful relationship.

As with any journal matter, we welcome the input and comments of our readers.

Stephen S. Sternberg, M.D.
Editor-in-Chief

ANNOUNCEMENTS

INTERNET USERS: If any GIPS members would like to receive announcements concerning the Society's activities by E-mail, please send the following message.
TO: rpascal@emoryyl.cc.emory.edu
SUB: GIPS via Internet
MESSAGE: subscribe GIPS e-mail
Name
Office address
Tel #
Fax #
If there is enough interest in this form of communication, suggestions will be solicited for the establishment of a discussion group.

Robert R. Pascal, M.D.
Vice-President

****

The Gastrointestinal Pathology Society offers its congratulations to **Dr. Shari L. Taylor**, Chief Resident in Pathology at the University of Tennessee-Baptist Memorial Hospital, Memphis, Tennessee. Dr. Taylor has been awarded an Arthur Purdy Stout Society Study Stipend to work with GIPS member Dr. Linda Ferrell at the University of California, San Francisco.

****

Congratulations go to GIPS member Mary Bronner and spouse Peter Cooley on the birth of their daughter, LAUREN AMANDA COOLEY. Lauren arrived September 26, 1994. She weighed in at 5 lbs., 15 oz.

****

A hearty congratulations also to GIPS member Audrey Lazenby and spouse David Clements on the birth of their daughter, CAROLYN ANITA CLEMENTS. Carolyn arrived September 29, 1994 and tipped the scales at 8 lbs., 15 oz.

****

Congratulations to the following GI pathologists accepted for membership in GIPS at the March, 1994 meeting:

Applicant	Location
John Reid Goldblum	Cleveland Clinic
Yves Gregory Lauwers	University of Florida
Elizabeth Ann Montgomery	Georgetown University
Amy Elisabeth Noffsinger	University of Cincinnati Medical Center

Welcome aboard!

$$250$250$250$250$250$250$250$250$250$250$250$250$250$250$250$$

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.
University of Alabama School of Medicine
Pathology Department - Kracke 524
619 S. 19th Street
Birmingham, AL 35233

Phone (205)975-8880
Fax (205)975-7284

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.

Protocol for the Examination of Specimens Removed From Patients With Colorectal Carcinoma

A Basis for Checklists

Donald Earl Henson, MD; Robert V. P. Hutter, MD; Leslie H. Sobin, MD; Harold E. Bowman, MD; for the Members of the Cancer Committee, College of American Pathologists, and the Task Force for Protocols on the Examination of Specimens From Patients With Colorectal Cancer

The Cancer Committee of the College of American Pathologists has developed a protocol for data to be included in routine consultation reports for patients with carcinoma of the colon or rectum. The Committee, as part of its program in quality assurance for anatomic pathology, continues to develop protocols for the examination of surgical specimens from patients with cancer. Previously, the Committee published protocols for cancers of the breast and urinary bladder and for Hodgkin's disease.[1,2] This protocol is not a mandate, but a guide for pathologists who would like assistance. It is not intended for pathologists who have already satisfied their quality assurance commitments with their own protocols.

PURPOSE

The purpose of this protocol is to serve as a basis for the development of checklists, as an outline for full narrative reporting, as a basis for research protocols, or as a guide for other types of synoptic or reporting formats. The protocol specifies information that documents appropriate examination of the specimen, as well as the anatomic extent of tissue removed, the anatomic extent of carcinoma in the specimen, histologic type, and other information that may be used by the referring physician to select primary or adjuvant treatment, evaluate new types of therapy, estimate prognosis, and analyze outcome. Pathologists may report additional information not specified by the protocol or modify this protocol to suit individual institutional needs.

See also p 120.

This protocol applies only to carcinomas arising in the colon or rectum. The protocol is stratified to accommodate the surgical procedures usually employed for carcinomas of the colon or rectum—bowel resection, (eg, hemicolectomy, anterior resection, total colectomy), excisional biopsy (local excision, polypectomy), and incisional biopsy.

PROTOCOL DEVELOPMENT

A provisional protocol was developed by a multidisciplinary task force established by the Cancer Committee. Pathologists, surgeons, medical oncologists, and radiation oncologists constituted the Task Force, which initially met in 1989. The Task Force's charge was to document the basic pathology data appropriate for the treatment of patients with colorectal carcinoma. Documentation was obtained from the medical literature, personal experience, and consultation with colleagues. The provisional protocol was further reviewed by pathologists, surgeons, and other specialists involved in the care of patients with colorectal carcinoma. The protocol was approved by the Board of Governors of the College of American Pathologists.

SURVEY

After the Cancer Committee and the Task Force approved the provisional protocol, a process survey was conducted to determine whether pathologists agreed with the contents of the proposed protocol and whether they would follow it in practice. Three hundred pathologists were randomly selected from a laboratory master list and surveyed by mail. The survey was stratified by different types of laboratory practice, including governmental, community hospital, independent, and university medical centers; by the number of surgical specimens processed; and by hospitals with or without residency programs and with or without residents in pathology. For the Cancer Committee, these surveys provided the opportunity for broad consultation with pathologists on the types and extent of data that should be transmitted in consultation reports on patients with colorectal carcinoma. The survey results were compiled, analyzed, and taken into consideration in developing the final protocol.

SYNOPTIC REPORTING

Recently, significant interest in the synoptic form of reporting has emerged as a replacement for the usual narrative descriptive format.[3,4] Checklists or other descriptive reporting formats based on this protocol would ensure a uniform system of reporting consonant with quality care. All appropriate information that is needed clinically would be provided. The Cancer Committee is developing checklists based on this protocol that will be available from the College of American Pathologists.

Accepted for publication July 20, 1993.

From the Early Detection Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Md (Dr Henson), the Department of Pathology, St Barnabas Hospital, Livingston, NJ (Dr Hutter), the Division of Gastrointestinal Pathology, Armed Forces Institute of Pathology, Washington, DC (Dr Sobin), and the Department of Pathology, Michigan State University College of Human Medicine, East Lansing (Dr Bowman).

Members of the Task Force and of the Cancer Committee are listed at the end of the article.

Reprint requests to Early Detection Branch, Division of Cancer Prevention and Control, National Cancer Institute, EPN Building, Room 305, 9000 Rockville Pike, Bethesda, MD 20892 (Dr Henson).

PROTOCOL FOR THE EXAMINATION OF SPECIMENS REMOVED FROM PATIENTS WITH COLORECTAL CARCINOMA

I. BOWEL RESECTION

CLINICAL INFORMATION

Appropriate clinical information should be provided to the pathologist for optimal pathologic evaluation:

- *Patient identification*
- *Relevant history* (previous diagnosis and treatment)
- *Endoscopic findings* (when available)
- *Manner of bowel excision*
- *Anatomic site(s) of specimen(s)*
- *Describe orientation of specimen* by the surgeon with identification of margins as appropriate with sutures or other markers

MACROSCOPIC (GROSS) EXAMINATION

- *Bowel specimen*
  - Fixation
  - Number of pieces
  - Dimensions
  - Color
  - Consistency
- *Other tissues/organs* (specify)
- *Tumor*
  - Location
  - Dimensions
  - Configuration (see note A)
  - Gross ulceration
  - Bowel obstruction and/or perforation
  - Margins (see note B)
  - Invasion through visceral peritoneum (T4)
  - Direct extension to other organ(s) or structure(s) (T4)
  - Metastasis to other organ(s) or structure(s) (M1)
- *Lesions in noncancerous bowel*
- *Regional lymph nodes* (N)
- *Tissues selected for microscopic evaluation*
  - Carcinoma: interface with uninvolved adjacent bowel (include point of deepest penetration) overlying visceral peritoneum/pericolic/perirectal tissue(s)
  - Margins (as appropriate) (see note B)
  - Lymph nodes: label those along a major named vascular trunk (see note C)
  - Label apical node(s) when marked by surgeon
  - Other lesions (eg, polyps, ulcers)
  - Section(s) of bowel uninvolved by tumor
  - Other tissue(s)/organ(s)

MICROSCOPIC EVALUATION AND DIAGNOSES

- *Tumor*
  - Histologic type (see notes D and E)
  - Histologic grade (see note F)
  - Depth of invasion (pT) (see note G)
  - Interface of carcinoma with adjacent bowel
  - Vascular invasion (specify intramural or extramural)
  - Margins (as appropriate)
- *Regional lymph nodes* (pN)
  - Number
  - Number with metastases (see note G)
  - Metastasis to node(s) along a major named vascular trunk (pN3) (see note C)
  - Metastasis to apical node(s) (when marked by surgeon) (pN3) (see note C)
- *Other tissues submitted* (specify)
  - If distant metastasis (pM1): specify site
- *Other lesions* (eg, adenoma, other types of polyps, inflammatory bowel disease, dysplasia)

SPECIAL STUDIES

Designate special studies, if done, and include results in report (eg, special histochemical stains, immunohistochemistry, flow cytometry, morphometry)

II. EXCISIONAL BIOPSY (Local Excision, Polypectomy)

CLINICAL INFORMATION

Appropriate clinical information should be provided to the pathologist for optimal pathologic evaluation:

- *Patient identification*
- *Relevant history* (previous diagnosis and treatment)
- *Endoscopic findings* (when available)
- *Manner of excision*
- *Anatomic site(s) of specimen(s)*
- *Describe orientation of specimen* by the surgeon with identification of margins as appropriate with sutures or other markers

MACROSCOPIC (GROSS) EXAMINATION

- *Specimen*
  - Fixation
  - Number of pieces
  - Dimensions
  - Color
  - Consistency
  - Layers of bowel present (if grossly discernible)
- *Tumor* (if discernible)
  - Dimensions
  - If pedunculated: length of stalk
  - Configuration
  - Margins of excision (as appropriate)
  - Invasion of tissues
- *Uninvolved tissue* (eg, inflammatory bowel disease)
- *Tissue selected for microscopic evaluation*
  - Significant lesion
    - If a polyp: include apex and stalk in same section (if possible)
  - Margin of excision (if identifiable)

MICROSCOPIC EVALUATION AND DIAGNOSES

(If sufficient tissue)

- *Tumor*
  - Histologic type (see notes D and E)
  - Histologic grade (see note F)
  - Depth of invasion (pT) as appropriate (see note G)
  - Interface of carcinoma with adjacent bowel
  - Vascular invasion (specify intramural or extramural)
- *Carcinoma in a polyp*
  - Specify histologic type of polyp
  - Specify presence/absence of invasion of:
    - Stalk
    - Submucosa at base of stalk or base of sessile polyp
    - Vascular invasion
  - Specify status of margins of resection: indicate whether involved by carcinoma or adenoma (when possible)

SPECIAL STUDIES

Designate special studies, if done, and include results in report (eg, special histochemical stains, immunohistochemistry, flow cytometry, morphometry)

III. INCISIONAL BIOPSY (Endoscopic or Other)

CLINICAL INFORMATION

Appropriate clinical information should be provided to the pathologist for optimal pathologic evaluation:

- *Patient identification*
- *Relevant history* (previous diagnosis and treatment)
- *Endoscopic findings* (when available)
- *Manner of excision*
- *Anatomic site(s) of specimen(s)*
- *Describe orientation of specimen* by the surgeon with identification of margins as appropriate with sutures or other markers

MACROSCOPIC (GROSS) EXAMINATION

- *Specimen*
  - Fixation
  - Number of pieces
  - Dimensions
  - Color
  - Consistency
  - Layers of bowel present (if grossly discernible)
- *Selection of tissues for microscopic evaluation*

MICROSCOPIC EVALUATION AND DIAGNOSES

- *Tumor*
  - Histologic type (see notes D and E)
  - Histologic grade (see note F)
  - Depth of invasion (pT) as appropriate (see note G)
  - Interface of carcinoma with adjacent bowel
  - Vascular invasion (specify intramural or extramural)
- *Carcinoma in a polyp*
  - Specify histologic type of polyp (if possible)
  - Specify presence/absence of invasion of:
    - Stalk
    - Submucosa at base of stalk or base of sessile polyp
    - Vascular invasion

SPECIAL STUDIES

Designate special studies, if done, and include results in report (eg, special histochemical stains, immunohistochemistry, flow cytometry, morphometry)

EXPLANATORY NOTES

A: Configuration includes exophytic, endophytic, diffusely infiltrative (linitis plastica), or annular. Exophytic is divided into pedunculated and sessile.

B: Includes the proximal, distal, and radial margins. The "radial" margin is the distance from the outermost part of the tumor to the lateral margin of resection along a radius drawn from the center of the lumen through the deepest penetration of the carcinoma and continued through the bowel wall. The radial margin has a demonstrated meaning for carcinomas arising in the rectum.[5,6] For the colon, the radial margin represents the distance between the mesenteric resection margin and deepest penetration of tumor when the tumor is on the mesenteric aspect of the colon. If the tumor is on the antimesenteric aspect, the radial margin is not relevant.

C: N3 corresponds to the involvement of the highest mesentery node when marked by a surgeon or to those along the course of the respective named vascular trunks. Named vascular trunks include:

Ileocolic artery
Right colic artery
Middle colic artery
Left colic artery
Inferior mesentery artery
Superior rectal (superior hemorrhoidal) artery
Internal iliac artery

Lymph nodes along the sigmoid arteries are considered pericolic nodes. They are classified N1 or N2 according to the number involved. Details about lymph node examination can be found in the *TNM Supplement*.[7]

D: For consistency in reporting, the histologic classification proposed by the World Health Organization, Geneva, Switzerland, is recommended.[8] However, this protocol does not preclude the use of other systems of classification or histologic types. The World Health Organization classification is as follows:

Adenocarcinoma in situ/severe dysplasia
Adenocarcinoma
Mucinous (colloid) adenocarcinoma (>50% mucinous)
Signet-ring cell carcinoma (>50% signet-ring cells)
Squamous cell (epidermoid) carcinoma
Adenosquamous carcinoma
Small-cell (oat cell) carcinoma
Undifferentiated carcinoma
Other (specify)

The term *carcinoma, NOS* (not otherwise specified) is not part of the World Health Organization classification.

E: Some pathologists classify in situ carcinoma under the diagnostic term *severe, or high-grade, dysplasia*, especially in cases of inflammatory bowel disease.[9]

F: The World Health Organization system of grading is recommended as follows[8]:

Grade X	Grade cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
Grade 4	Undifferentiated

To standardize grading, grade 4, ie, "undifferentiated," is reserved for carcinomas that show no specific differentiation. According to the definition of grading, an adenocarcinoma arising in the colon or rectum can be classified only as G1, G2, or G3, because by definition, an adenocarcinoma contains glandular differentiation. Tumors containing areas of glandular differentiation adjacent to areas of undifferentiation are classified as "poorly differentiated," that is, G3. If there are variations in the differentiation within the tumor, the highest (least favorable) grade is recorded, using G1 through G3. For carcinomas of the colon and rectum, the growing edge of the tumor is usually not assessed in grading.[8] For all stage groupings, grading correlates with outcome.[10]

G: A tumor nodule greater than 3 mm in the perirectal or pericolic tissue without histologic evidence of residual lymph node in the nodule is classified as regional perirectal/pericolic lymph node metastasis. However, a tumor nodule less than 3 mm is classified in the T category as a discontinuous extension, that is, T3.[7]

TNM STAGING SYSTEM

The following classification is according to the TNM Staging System of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.[11,12]

Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ—intraepithelial or invasion of the lamina propria

T1 Tumor invades submucosa
T2 Tumor invades the muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures and/or perforates the visceral peritoneum†

Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in one to three pericolic or perirectal lymph nodes
N2 Metastasis in four or more pericolic or perirectal lymph nodes
N3 Metastasis in any lymph node along the course of a named vascular trunk and/or metastasis to apical node(s) (when marked by the surgeon)

Distant Metastasis

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Groupings

Stage 0	Tis,	N0, M0
Stage I	T1,	N0, M0
	T2,	N0, M0
Stage II	T3,	N0, M0
	T4,	N0, M0
Stage III	Any T,	N1, M0
	Any T,	N2, M0
	Any T,	N3, M0
Stage IV	Any T, Any N,	M1

*Note: Tis, carcinoma in situ, includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal); extension may be into but not through the muscularis mucosae into the submucosa. (Extension through the muscularis mucosae is T1.)

†*Note:* Direct invasion of other organs or structures includes invasion of other segments of colorectum by way of serosa: for example, invasion of the sigmoid colon by carcinoma of the cecum.

The symbol "pT" refers to the pathologic classification of the TNM, as opposed to the clinical classification. Pathologic classification is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category; pN entails removal of nodes adequate to validate lymph node metastasis; and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.[11]

Members of the Task Force: Harold Bowman, MD (*Chairman*); L. Peter Fielding, MD; Rodger C. Haggitt, MD; Gerald E. Hanks, MD; Donald Earl Henson, MD; Robert V. P. Hutter, MD; Kenneth D. McClatchey, MD, DDS; Mary L. Nielsen, MD; Ali Qizilbash, MD; Robert R. Rickert, MD; Charles R. Smart, MD; Leslie H. Sobin, MD; Steven Sternberg, MD; Sidney Winawer, MD; and David Winchester, MD.

Members of the Cancer Committee: Robert V. P. Hutter, MD; George M. Farrow, MD; Harold E. Bowman, MD; Fred Gorstein, MD; Mary L. Nielsen, MD; Robert E. Scully, MD; Dean G. Taylor, MD; and Donald Earl Henson, MD.

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FELLOWSHIP PROGRAMS IN GASTROINTESTINAL PATHOLOGY

Institutions and location	Duration[a]	Prerequisites[b]	Salary source[c]	Program director(s) and address	Comments
Yale University New Haven Connecticut	2 yr	3 yrs AP or AP/CP	Institution	A. Brian West, M.D. Department of Pathology Yale University School of Medicine 310 Cedar Street New Haven, CT 06510	Basic research in GI cell biology. Specialist training in diagnostic GI and liver pathology.
Emory University School of Medicine Affiliated Hospitals Atlanta, Georgia	2 yr	AP or AP/CP	Institution	Robert R. Pascal, M.D. Department of Pathology Emory University Hospital 1364 Clifton Road, N.E. Atlanta, GA 30322	2 yr program in surgical pathology with emphasis on GI pathology and research
Louisiana State University New Orleans Louisiana	1 yr	Pathology training complete	Contact Dr. Correa	Pelayo Correa, M.D. Department of Pathology LSU Medical Center 1901 Perdido St. New Orleans, LA 70112	Research in GI pathology and epidemiology
The Johns Hopkins University Baltimore, Maryland	2 yrs	2 yrs AP	Institution or outside	Stanley R. Hamilton, M.D. John H. Yardley, M.D. Department of Pathology The Johns Hopkins University 720 Rutland Ave., Ross 632 Baltimore, MD 21205	Experience in diagnostic GI/liver pathology both at a fellow and attending level, combined with applied and/or basic research
[d]Beth Israel Hospital Children's Hospital Harvard Medical School Boston, Massachusetts	1 yr	AP or AP/CP	Institution	Donald Antonioli, M.D. Department of Pathology Beth Israel Hospital 330 Brookline Avenue Boston, MA 02215	Includes general service responsibility in AP and specific training in adult and pediatric GI pathology.

Institutions and location	Duration[a]	Prerequisites[b]	Salary source[c]	Program director(s) and address	Comments
Tufts University School of Medicine New England Medical Center Boston, Massachusetts	2 yrs.	3 yrs AP	Institution	Yogeshwar Dayal, M.D. Department of Pathology New England Medical Center (Box 802) 750 Washington Street Boston, MA 02111	Combines research in GI endocrinology and surgical pathology
[d]New England Deaconess Hospital Boston, Massachusetts	1 yr	3 yrs AP or AP/CP	Institution	Harvey Goldman, M.D. Department of Pathology New England Deaconess Hospital 185 Pilgrim Road Boston, MA 02215	Includes general service responsibility in AP and specific training in adult and pediatric GI pathology.
Brigham & Women's Hospital Boston, Massachusetts	1. 1 yr. or 2. 2-3 yrs.	AP training or AP/CP	Institution (NIH T.G.) or outside	James L. Madara, M.D. Department of Pathology Brigham & Women's Hospital Boston, MA 02215	Two fellowship positions available: 1. Diagnostic GI and liver path with research (1 yr). 2. Basic research oriented to GI tract (2-3 yrs)
Massachusetts General Hospital Boston, Massachusetts	1-2 yrs.	AP or AP/CP	Institution	Carolyn Compton,M.D.,Ph.D. Department of Pathology MGH Boston, MA 02115	Combines research (min. 50% effort) and clinical experience
Mayo Clinic Rochester, Minnesota	1-2 yrs	3 yrs AP or 4 yrs AP/CP	Institution	Herschel Carpenter, M.D. Department of Pathology Mayo Clinic 200 First St., SW Rochester, MN 55905	Combines diagnostic GI and liver pathology with general AP and research. Over 11,000 GI and liver biopsies

Institutions and location	Duration[a]	Prerequisites[b]	Salary source[c]	Program director(s) and address	Comments
University of Minnesota Hospital & Clinics, Minneapolis, Minnesota	1 yr.	2 yrs AP	Outside	Dale Snover, M.D. Jose Jessurun, M.D. Surgical Pathology Box 76, UMHC 420 Delaware St. Minneapolis, MN 55455	Includes service responsibility in gastrointestinal and liver pathology combined with research
Long Island Jewish Medical Center New Hyde Park, NY	1 yr	3 yrs AP or 4 yrs AP/CP	Institution	Leonard B. Kahn, M.D. Department of Pathology Long Island Jewish Medical Center 270-05 76th Avenue New Hyde Park, NY 11042	
The Mount Sinai Medical Center New York, NY 10029	1-2 yr	2 yr AP or 3 yrs AP/CP	Institution	Noam Harpaz, M.D.,Ph.D. Department of Pathology The Mount Sinai Medical Center One Gustave L. Levy Place New York, New York 10029	Combines diagnostic pathology and research
Roger Williams Medical Center and Brown University Providence, Rhode Island	1-2 yrs	2 yrs AP	Institution	Robert Lev, M.D. Roger Williams General Hosp. Department of Pathology 825 Chalkstone Avenue Providence, RI 02908	Combines diagnostic pathology and research
Baptist Memorial Hospital Memphis, Tennessee	1 yr.	Completed pathology training	Institution	Patrick J. Dean, M.D. Department of Pathology Baptist Memorial Hospital 899 Madison Ave. Memphis, TN 83146	Diagnostic pathology and clinically oriented research

Institutions and location	Duration[a]	Prerequisites[b]	Salary source[c]	Program director(s) and address	Comments
Baylor University College of Medicine Houston, Texas	1-2	2 yrs AP	Institution	Juan Lechago, M.D.,Ph.D. Department of Pathology Baylor University College of Medicine One Baylor Plaza Houston, TX 77030	Flexible, combines diagnostic pathology and research
University of Texas Southwestern Medical School & VA Hospital Dallas, Texas	1 yr.	3 yrs AP	Institution	Edward L. Lee, M.D. Department of Pathology VA Hospital 4500 S. Lancaster Rd. Dallas, TX 75216	Combines diagnostic pathology and clinical research
University of Washington Seattle, Washington	1-2 yrs	2 yrs AP or 2 yrs GI fellowship	Institution/ Outside	Rodger C. Haggitt, M.D. Director, Division of Hospital Pathology, RC-72 University of Washington Seattle, WA 98195	
		- - - C A N A D A - - -			
Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia	1 yr	4 yrs pathology	Institution	David A. Owen, M.D. Department of Pathology Vancouver General Hosp. 855 West 12th Avenue Vancouver, British Columbia V5Z 1M9 Canada	Includes research. Pediatric GI pathology experience
McMaster University Hamilton, Ontario	1 yr	2 yrs AP	Institution	Robert H. Riddell, M.D. McMaster University Medical Center 1200 Main Street West L8N 325, Canada	

[a] Fellowship is defined as an organized training program lasting for one or more years.

[b] Minimum completed training necessary for participation in Fellowship. Anatomic Pathology (AP) may be specified. Some programs are open to gastroenterologists, internists, and surgeons.

[c] "Institution" means salary is available via institution. "Outside" means salary must come from outside source (application or otherwise by the candidate).

[d] Programs are combined.

GASTROINTESTINAL PATHOLOGY SOCIETY NOMINATING INFORMATION

The Gastrointestinal Pathology Society was founded in 1979 as the Gastrointestinal Pathology Club with the objectives of disseminating and increasing knowledge about pathology of the gastrointestinal tract and of encouraging the development of gastrointestinal pathology as a subspecialty. At present the Society meets once a year immediately preceding the annual March meeting of the United States and Canadian Academy of Pathology. Further activities include the distribution of a newsletter, a scientific session in May at the American Gastroenterological Association annual meeting, and participation in the cooperative projects.

The Society exists to unite persons with an interest in the pathology of the gastrointestinal tract and liver. An exclusive involvement in hepatopathology will not ordinarily be considered adequate for membership.

Two categories of membership are available: regular membership and associate membership.

Regular Membership: This is open to individuals holding an M.D., Ph.D., or equivalent, and is not restricted to persons who are board certified in Anatomical or Clinical Pathology. The principal criterion for admission is evidence of active involvement and commitment to the pathology of the gastrointestinal tract. This may include diagnosis, education, and research but is not intended to encompass persons with only a vague general interest. Scholarly achievement in the form of publications relevant to G.I. pathology is required for admission, but special note will also be taken of other activities, especially regular educational efforts such as undergraduate or postgraduate lecturing. Annual dues for regular members are $40 U.S., payable after formal acceptance.

Associate Membership: This category is open to persons holding an M.D. or its equivalent, who have an interest in G.I. pathology. This membership is limited to five years and cannot be renewed. it is intended that persons in this category will have a developing interest in G.I. pathology, but less documented experience and involvement. This type of membership is most suited to residents and fellows, but is not restricted to them. Associate membership may be converted to regular membership after five years, or sooner if the individual meets the criteria outlined above. Annual dues for associate members is S10 U.S., payable after formal acceptance.

Nomination Form: Applications for membership should be made on the attached form. It is particularly important that a full bibliography be included in applications for regular membership. This information is used for more than establishing grounds for membership. The Society needs a comprehensive picture of the background and capabilities of its members in order to develop its programs.

Applicants for Associate membership need only fill out items 1 through 9 and

obtain a nominator's signature.

Applicants who do not personally know a member of the Society who will act as sponsor, should contact the Secretary-Treasurer who will provide name(s) of potential sponsors.

Normally it is sufficient for the nomination to be signed by any regular Society member. Nominators are used, however, to provide a letter of recommendation or amplification if there are any special or unusual aspects of the application which need to drawn to the attention of the Membership Committee.

Identifying information about all members including address and phone numbers will be listed in the Society Directory and submission of this nomination will be construed as permission to list such information. The directory will be distributed to the members annually.

The original application together with seven completed copies should be mailed to:

**********Cecilia M. Fenoglio-Preiser, M.D.
MacKenzie Professor and Director
Department of Pathology and Laboratory Medicine
University of Cincinnati Medical Center
231 Bethesda Avenue
Cincinnati, Ohio 45267-0529
Phone (513) 558-4500
Fax (513) 558-2289

Applications should be received by the Secretary-Treasurer by January 15th. Applicants should expect to receive information concerning their membership after the GIPS annual meeting which is held during the March meeting of the United States and Canadian Academy of Pathology.

GASTROINTESTINAL PATHOLOGY SOCIETY

Nomination for Membership
(Use Typewriter Only)

1. Type of Membership: ___ Regular ___ Associate Date _____

2. Nominee's Name in Full _____
Last First Middle

3. Office Address _____

_____
City State Zip Code

4. Telephone numbers: Office ( ) _____ Home ( )_____

FAX: ( ) _____

5. Date of birth _____ Place _____

6. EDUCATION Name of Institution Degree Year Graduated

Academic or College _____

Medical School _____

Other _____

_____

7. POST DOCTORAL TRAINING (Housestaff and other. List chronologically)

Name of Institution Field Inclusive Dates

_____

_____

_____

_____

_____

8. TRAINING IN G.I. PATHOLOGY (Brief summary. Include any special coruses, post-doctoral training, etc., give names of teachers. If none, write "none."

_____

_____

_____

9. ACADEMIC APPOINTMENTS (past and present). Mark the present ones with asterisk.

Name of Institution	Title	Inclusive Dates

10. HOSPITAL APPOINTMENTS: (Non-housestaff, past and present). Mark present with asterisk.

Name of Institution	Title	Inclusive Dates

11. MEMBERSHIPS (past and present)

Medical and Scientific Societies: _____

_____

_____

_____

Other: (Editorial Boards, Advisory Groups, Study Sections, etc.): _____

_____

_____

_____

12. BOARD CERTIFICATION:

American Board of Pathology: Anatomic (Date) _____

Clinical (Date) _____

Other [Type, date(s)] _____

13. PROFESSIONAL ACTIVITY:

a. What proportion of <u>total</u> time is spent in:

Practice ____% Teaching ____% Research ____% Other ____%

(Nature?) _____

b. Percentage of total time in GI pathology: _____%

C. Nature of activities relating to GI disease. (Give basic details about activities, including types of diseases, disease mechanisms, and organ systems dealth with, methodology used, etc.):

Diagnostic: _____

_____

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_____

Teaching: _____

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Research: _____

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_____

14. PUBLICATIONS: Attach your <u>complete</u> bibliography. Mark each GI-related publication with an asterisk in the left margin.

15. NOMINEE (Signature): _____

Name (typed): _____

Signature: _____

NOTE: When this form has been signed by both nominee and nominator, the original and 7 copies should be returned to:

****
Cecelia M. Fenoglio-Preiser, M.D.
MacKenzie Professor and Director
Department of Pathology and Laboratory Medicine
University of Cincinnati Medical Center
231 Bethesda Avenue
Cincinnati, Ohio 45267-0529
Phone (513) 558-4500
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GASTROENTEROLOGY 1994, Vol. 106 (Jan-Jun)
James M. Crawford, M.D., Ph.D.
Dept. of Pathology, Brigham and Women's Hosp., Boston
Emphasis is given to studies based on human surgical pathology material.

Esophagus

Neshat K, Sanchez CA, Galipeau PC, Blount PL, Levine DS, Joslyn G, Reid BJ. *p53* Mutations in Barrett's adenocarcinoma and high-grade dysplasia. *Gastroenterology* 106:1589-1595.

The concept of clonal evolution of dysplastic foci containing allelic losses involving chromosomes 17p and 5q was explored. Since the *p53* gene is located on 17p, *the authors examined whether a two-hit mechanism of p53 inactivation might be occurring: allelic loss from one chromosome 17p, and mutation of the other chromosome 17p.* Tissue was obtained from 14 patients with Barrett's esophagus who had high-grade dysplasia, adenocarcinoma, or both. All 14 patients had chromosome 17p allelic losses and aneuploidy. Diploid cell populations in 4 patients had *p53* mutations, and the same *p53* mutations were found in multiple different aneuploid populations in the adenocarcinomas of 2 of these 4 patients. Of 6 patients with high-grade dysplasia, all had *p53* mutations in the high-grade dysplasia. In 3 of these patients, the same *p53* mutations were present in coexistent adenocarcinoma. Thus, mutations could be detected in diploid cell populations marking for Ki-67 (and hence in a proliferative phase), in aneuploid cell populations in high-grade dysplasia, and in multiple aneuploid cell populations in adenocarcinomas. The authors conclude that *p53 mutations occur frequently in Barrett's adenocarcinomas and dysplasia, developing in diploid cell populations and persisting in the aneuploid cell populations.* Given that *p53* is part of a signal transduction pathway that causes cells to arrest in G_1 in response to DNA-damaging agents, the authors speculate that loss of the *p53* "checkpoint" (via mutation of one *p53* allele and loss of the other) predisposes to the development of aneuploidy. *ED*: One patient exhibited a 17p allelic loss before the *p53* mutation, retaining a wild-type *p53* allele. Progression to aneuploidy was associated with development of a *p53* mutation. In all other patients, mutations and allelic losses at 17p were detected at the same stage of neoplastic progression. Thus, it is unclear whether multistep evolution follows a particular sequence, or is instead a matter of accumulation of lesions.

Stomach

Rhyu M-G, Park W-S, Jung Y-J, Choi S-W, Meltzer SJ. Allelic delections of *MCC/APC* and *p53* are frequent late events in human gastric carcinogenesis. *Gastroenterology* 106:1584-1588.

In addition to *p53* on chromosome 17p, the tumor suppressor genes for *APC* (adenomatous polyposis coli) and the nearby *MCC* (mutated in colon cancer) are found on chromosome 5q. *The authors examined 52 matched sets of normal gastric tissue, gastric carcinoma, and adjacent gastric dysplasia for allelic losses (loss of heterozygosity) in 17p and 5q.* Allelic deletion was found at *p53* in 64% of cancers. Losses at *MCC* or *APC* always occured together, in 34% of cancers, and never without a *p53* loss. There was no allelic loss in gastric dysplasia. The authors conclude that *allelic deletions involving p53 and MCC/APC are common late events in gastric cancer, and*

that MCC/APC losses never occur independent of losses at p53. ED: It will be interesting to determine whether *p53* mutations also are present and whether they follow or precede allelic loss, akin to the work above with Barrett's mucosa.

Colon

Hamelin R, Laurent-Puig P, Olschwang S, Jego N, Asselain B, Remvikos Y, Girodet J, Salmon RJ, Thomas G. Association of *p53* mutations with short survival in colorectal cancer. *Gastroenterology* 106:42-48.

Increased intracellular concentrations of *p53* are frequently but not always related to mutation in the *p53* gene. *Since p53 mutations have been proposed to be associated with poor prognosis in some tumors, the authors screened 85 colorectal carcinomas for mutations in exons 5-8 of this gene.* Forty-four tumors (52%) were found to be mutated. There was a strong correlation between the presence of a mutation and short survival (35% 5-year survival vs. 65% in mutation-free patients). When tumors were classified according to histological stage, the *p53* mutation (rather than 17p allelic loss) was retained as an independent prognostic factor. The authors conclude that, combined with staging, *direct monitoring of p53 mutation improves prognostic accuracy for colorectal cancer.* ED: Two points must be emphasized. First, direct molecular analysis of *p53* mutation was performed, rather than assessing cytoplasmic immunoreactive *p53* glycoprotein. Second, allelic loss at 17p also was occurring, but correlated with histological stage and therefore was not an independent prognostic factor in the Cox proportional hazards model. When histological staging is not taken into account, the 17p allelic status of the tumor confers more prognostic information than does *p53* mutation.

Nakamori S, Ota DM, Cleary KR, Shirotani K, Irimura T. MUC1 mucin expression as a marker of progression and metastasis of human colorectal carcinoma. *Gastroenterology* 106:353-361.

Cell surface glycoproteins change in structure and distribution during malignant progression and tumor progression. The MUC1 gene encodes core polypeptides corresponding to highly glycosylated, high molecular weight glycoproteins synthesized in normal and malignant epithelial tissues, but not in normal intestinal epithelia. The authors examined the levels of MUC1 mucin expression in 113 colorectal carcinoma specimens with a direct gel immunostaining method and a monoclonal antibody for highly glycosylated MUC1, HMFG1. In tissue from the primary tumors, mature MUC1 mucin expression progressively increased with histological stage, reaching the highest levels in patients with metastatic disease. The results strongly suggest that *mature MUC1 mucins become ectopically expressed in colorectal carcinoma, and that MUC1 mucin expression may be a useful marker for advanced colorectal carcinoma.* ED: Two aspects of MUC1 expression are of particular interest. First, the precursor core polypeptide of MUC1 mucins are detectable in normal tissue as well; thus, the regulatory basis for ectopic expression may lie in altered processing or stability of the polypeptide. Second, it will be of interest to explore whether cell surface expression of MUC1 mucin may play a role in the ability of cells to disseminate, adhere, invade and survive at distant sites.

Nakamura S-I, Goto J, Kitayama M, Kino I. Application of the crypt-isolation technique to flow-cytometric analysis of DNA content in colorectal neoplasms. *Gastroenterology* 106:100-107.

Traditional flow cytometric analysis of DNA content of nuclei from formalin-fixed, paraffin-embedded material or from nuclei isolated from fresh tissues results in inclusion of stromal cell nuclei. The authors have isolated normal and neoplastic crypts from freshly resected colorectal carcinomas prior to DNA analysis, by incubating fresh mucosa/neoplasm with calcium- and magnesium-free Hanks' balanced salt solution containing EDTA over 1 h for 37°C. Aneuploid peaks were not observed nuclei isolated from normal epithelia, but they were occasionally observed in those from adenomas. DNA aneuploidy was frequently observed ($\geq$70%) in nuclei from adenocarcinomas. Generally, there was no relationship between the histological grade of cancer and DNA ploidy. However, cases with hypodiploid stemlines had significantly higher lymph node metastases than other cases. *The authors propose crypt-isolation as an improvement on conventional methods for assessment of DNA ploidy in colorectal neoplasms.*

Minamoto T, Sawaguchi K, Ohta T, Itoh T, Mai M. Superficial-type adenomas and adenocarcinomas of the colon and rectum: A comparative morphological study. *Gastroenterology* 106:1436-1443.

It has been uncertain whether colorectal carcinomas preferentially arise on preexisting adenomas or de novo. The "adenoma-carcinoma" sequence posits that malignant polyps (of any type) precede the development of invasive carcinomas. However, from a morphological standpoint, it can be argued that pedunculated or exophytic malignant polyps are an unlikely source of the deeply ulcerated advanced carcinomas found clinically. *The authors examined the hypothesis that not all colorectal carcinomas develop out of the adenoma-carcinoma sequence.* They examined 26 non-polypoid, superficial-type colorectal tumors (17 adenomas and 9 adenocarcinomas), in an attempt to clarify the developmental route of colorectal carcinoma. Intact adenomas and adenocarcinomas could be distinguished on the basis of their surface appearance under the dissection microscope (loss of crypt architecture in the latter). Histologically, no adenomatous tissue was found in any case of superficial-type adenocarcinoma. Five of the nine adenocarcinomas, even those of small size, invaded the submucosal layer, and two showed lymph node metastasis. Thus, superficial-type adenocarcinomas may show rapid growth and aggressive behavior. The authors suggest that *superficial carcinomas may not arise from adenomas, but instead arise as a de novo lesion.* *ED*: Care must be taken in applying terminology, since criteria differ among pathologists for diagnosing carcinoma, especially "in-situ" and "intramucosal." Thus, a Western classification might posit that superficial-type adenocarcinomas simply arise from smaller superficial-type adenomas. The extent to which this semantic issue has relevance to the molecular events in colorectal carcinogenesis remains unclear.

Recent Articles of GI Interest in HISTOPATHOLOGY

Articles on the gastrointestinal tract, extra-hepatic biliary tree and pancreas were reviewed. Those I considered most interesting are listed with their abstracts, a star indicating that I found a paper to be of particular interest. The titles and authors of the remaining GI papers (both full articles and brief reports) are also given.

Brian West

HISTOPATHOLOGY 23 (July - Dec 1993)

ECTORS N.L., DIXON M.F., GEBOES K.J., RUTGEERTS P.J., DESMET V.J. & VANTRAPPEN G.R.

(1993) *Histopathology* 23, 55-61

Granulomatous gastritis: a morphological and diagnostic approach ★

The final diagnosis of granulomatous gastritis is based on morphological findings and clinical and laboratory data. Detailed analysis of the morphological features of the granulomas together with associated mucosal changes could generate more information on aetiology and pathogenesis. Biopsies from 71 patients diagnosed as having granulomatous gastritis were reviewed. Thirty-seven of these patients (52%) had Crohn's disease. In 18 patients (25%) an isolated granulomatous gastritis was diagnosed. In seven patients (10%) the final diagnosis was a foreign body reaction. Of the remaining cases, four (7%) corresponded to tumour-associated granulomas and one case each of sarcoidosis (1%), Whipple's disease (1%) and vasculitis-associated disease (1%). Two cases (3%) were unclassifiable. The granulomas were mainly found in the antrum (64% antrum only, 11% antrum and corpus, 6% transitional mucosa corpus-antrum). Granulomas were usually small. This was particularly true for those found in patients with Crohn's disease. Multiple granulomas were observed in the sarcoidosis, the Whipple's disease and vasculitis-associated cases. A pattern of chronic gastritis with atrophy was present in 95% of the biopsies (68/71 patients). *Helicobacter pylori* was detected in 92% of the biopsies (64/71 patients).

CHETTY R., BHATHAL P.S. & SLAVIN J.L.

(1993) *Histopathology* 23, 63-67

Prolapse-induced inflammatory polyps of the colorectum and anal transitional zone

A clinicopathological study of polypoid lesions of the lower gastrointestinal tract from 12 patients was undertaken. Clinically, the majority had signs and symptoms of rectal prolapse despite having a variety of other primary diagnoses (e.g. carcinoma of the bowel or diverticular disease). Three patients were asymptomatic. The polyps were more common in females and were usually solitary. Histologically, fibrin 'caps', fibromuscular hypertrophy and obliteration of the lamina propria, goblet cell hypertrophy and serrated tubules were consistently noted. The fibromuscular tissue often extended into the lamina propria in a radial fashion. This study shows that mucosal prolapse underpins a variety of lesions that are part of a histological spectrum of changes. Inflammatory cloacogenic polyps, inflammatory 'cap' polyps, polypoid prolapsing mucosal folds of diverticular disease and inflammatory myoglandular polyps are all due to mucosal prolapse.

GHADIALLY F.N., BOONE, S.A. & WALLEY V.M.

(1993) *Histopathology* 23, 167-172

A comparison of the ultrastructure of pigment granules in melanosis ilei and pulmonary lymph nodes

Two cases of melanosis ilei were studied, in which grossly visible blackish pigmentation of the ileal mucosa was incidentally discovered at autopsy. Light microscopy showed that the pigment granules lay within macrophages in atrophic Peyer's patches. Ultrastructural studies showed that the pigment granules were heterolysosomes containing crystalline material, particles, granules and, occasionally, lipid droplets. The morphological similarity between these pigment granules and granules in pulmonary macrophages was established through ultrastructural studies of pulmonary lymph nodes obtained during routine autopsies. These data, plus results of past electron-probe X-ray analytic studies by us and others, leads us to conclude that the pigment granules in melanosis ilei contain exogenous material derived from inspired and ingested materials.

HISTOPATHOLOGY 23 (July - Dec 1993)

QUINN C.M., BJARNASON I. & PRICE A.B.

(1993) *Histopathology* 23, 341–348

Gastritis in patients on non-steroidal anti-inflammatory drugs

This study investigated the spectrum of gastric mucosal pathology, including the prevalence of reactive gastritis in patients on non-steroidal anti-inflammatory drugs (NSAIDs). The histological findings were correlated with upper gastrointestinal symptom status and endoscopic findings and were also compared with the histological appearances of the gastric mucosa in a corresponding age-matched control group of 75 patients not receiving NSAIDs or any other drug therapy. Reactive gastritis of the gastric antrum was more common in the NSAID group and was observed in 34 patients (45.3%), as an isolated phenomenon in 24 patients (32%) and with evidence of coexistent chronic gastritis in 10 patients (13.3%). In the control group reactive gastritis of the antrum was seen in 10 patients (13.3%), as an isolated finding in eight cases (10.7%) and with accompanying chronic gastritis in two cases. Chronic antral gastritis of usual type was observed in 36 patients on NSAIDs (48%) and *Helicobacter*-like organisms were identified histologically in 18 of these (50% carriage rate). These organisms were not seen in any of the patients in whom the picture of reactive gastritis was present. In the control group chronic antral gastritis was seen in 51 patients (68%) with organisms in 34 (66.6% carriage rate). No correlation was found between the presence or absence of upper gastrointestinal symptoms, endoscopic findings and the histological appearances of the gastric mucosa. We conclude that NSAIDs are an independent cause of reactive gastritis in the antrum and do not appear to alter gastric mucosal colonization by *Helicobacter*-like organisms. However, the changes of reactive gastritis, of whatever cause, appear to produce a local micro-environment, hostile to these organisms.

JOYPAUL B.V., VOJTESEK B., NEWMAN E.L., HOPWOOD D., GRANT A., LANE D.P. & CUSCHIERI A.

(1993) *Histopathology* 23, 465–470

Enzyme-linked immunosorbent assay for *p53* in gastrointestinal malignancy: comparison with immunohistochemistry

Mutations in the *p53* nuclear oncogene occur frequently in a wide spectrum of human malignancies and the mutant protein may prove to be a useful diagnostic or prognostic marker. It can be detected in fixed tissues by immunohistochemistry, but the type of fixative and conditions of fixation used can introduce variability. For routine clinical use, a method of analysis which is more easily standardized would, therefore, be of benefit. A two-site enzyme-linked immunosorbent assay (ELISA) was used to measure the level of *p53* protein in soluble extracts from 20 gastrointestinal cancers (11 colonic, nine gastric). Immunohistochemistry was also performed on the paraffin-embedded sections of these tumours and the results of the two assays were compared. ELISA detected *p53* at various levels in 10 cases, all of which were also positive by immunohistochemistry. Of the other 10, eight were immunohistochemically negative but two were positive. When the immunohistochemically positive specimens were ranked by scoring the degree of staining, there was a highly significant correlation with the quantitative ELISA results. Our study shows that the ELISA is sensitive and highly specific. It offers an alternative and simple method of assessing the *p53* status in human tissues.

Proliferating cell nuclear antigen in gallbladder carcinoma. I.Roa, J.Araya, T.Shiraishi, R.Yatani, M.Villaseca, I.Wistuba, X.de Aretxabala. 179-183.

DNA content in gallbladder carcinoma: a flow cytometric study of 96 cases. I.Roa, J.C.Araya, T.Shiraishi, R.Yatani, I.Wistuba, M.Villaseca, X.de Aretxabala. 459-464.

HISTOPATHOLOGY 23 (July - Dec 1993)

BRIEF REPORTS:
Inflammatory pseudotumor of the pancreas. J.P.Palazzo, C.D.Chang. 475-477.
Giant gastric polyp. J.M.Radhi, F.W.Coop, P.M.Dubois. 570-572.
Gallbladder vasculitis: a report of two cases. D.E.Fish, D.J.Evans, C.D.Pusey. 584-585.
Kaposi's sarcoma presenting as acute appendicitis in an HIV-1 positive patient. R.Chetty, J.L.Slavin, R.A.Miller. 590-591.
Inflammatory myoglandular polyp causing ileo-ileal intussusception. A.P.Griffiths, J.M.Hopkinson, M.F.Dixon. 596-598.

HISTOPATHOLOGY 24 (Jan - June 1994)

ISLAM M.M., AZAD A.K., BARDHAN P.K., RAQIB R. & ISLAM D.

(1994) *Histopathology* 24, 65–71

Pathology of shigellosis and its complications

One hundred and thirty-three colonic biopsies of proven cases of *Shigella* colitis were examined and post-mortem examinations were carried out on 29 fatal cases at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) hospital between 1988 and 1992. The distribution of pathological lesions and the spectrum of histopathological changes in the intestinal tract of these patients, and the features of intestinal and extra-intestinal complications of shigellosis are presented. Septicaemia, hyponatraemia, hypokalaemia and hypoglycaemia were present in a high percentage of these cases. All but two patients were malnourished at the time of autopsy. Shigellosis patients rapidly became hypoproteinaemic and were susceptible to other infections including opportunistic infections. Mortality amongst shigellosis patients admitted to our hospital continues to be high in spite of adequate antibiotic and supportive therapy.

PYKE C., RALFKIÆR E., RØNNE E., HØYER-HANSEN G., KIRKEBY L. & DANØ K.

(1994) *Histopathology* 24, 131–138

Immunohistochemical detection of the receptor for urokinase plasminogen activator in human colon cancer

Paraffin-wax embedded specimens from 30 cases of colonic adenocarcinoma were investigated for immunoreactivity for the receptor of urokinase-type plasminogen activator (uPAR). In all cases there was a strong signal, predominantly at the invasive foci. The positive cells were mainly tumour-infiltrating macrophages but neutrophils and eosinophils were also strongly stained. The neoplastic cells were positive in 19 of the samples with staining of occasional or a moderate number of cells. In uninvolved, normal-appearing mucosa adjacent to the malignant infiltrates, immunostaining of both macrophages and neutrophils was seen, but the labelling was less intense than that seen in the malignant lesions. Weak to moderate staining of normal intestinal epithelium was also seen at the luminal surface. Comparison between immunoreactivity and in situ hybridization showed a similar distribution of protein and mRNA with two exceptions: first, neutrophils (strongly immunoreactive for uPAR) were negative or only weakly positive for uPAR mRNA; and second, many cancer cells at invasive foci showed prominent hybridization signals but no detectable uPAR immunoreactivity. Together with previous findings of urokinase plasminogen activator (uPA) protein and mRNA being expressed in tumour-infiltrating fibroblast-like cells at the invasive foci, these results support the view that the uPA pathway of plasminogen activation is involved in tissue degradation in colon cancer. The results also extend and consolidate an emerging picture of non-neoplastic tumour stromal cells producing molecules involved in the generation and regulation of extracellular proteolysis in cancer.

HISTOPATHOLOGY 24 (Jan - June 1994)

KWEE W.S., WILS J.A., SCHLANGEN J., NUYENS C.M. & ARENDS J.W.

(1994) *Histopathology* 24, 151–154

Gastric epithelial atypia complicating hepatic arterial infusion chemotherapy

Severe gastric lesions developed in five patients during hepatic arterial infusion chemotherapy employing 5-fluorouracil plus either leucovorin or mitomycin C. Ulceration with marked epithelial atypia was observed with striking structural distortion and cellular pleomorphism of the affected gastric mucosa. These features should be considered to be a complication of such treatment and should not be misinterpreted as malignancy.

SCHMID C., VAZQUEZ J.J., DISS T.C. & ISAACSON P.G.

(1994) *Histopathology* 24, 357–362

Primary B-cell mucosa-associated lymphoid tissue lymphoma presenting as a solitary colorectal polyp

We describe two patients with low-grade and one patient with mixed low- and high-grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT) type arising in the large intestine. In each patient the lesion occurred as a single polyp. Two patients presented with rectal bleeding and in one the lesion was discovered incidentally. The bone marrow was uninvolved in all three cases but in the patient with mixed low- and high-grade lymphoma involvement of mesenteric lymph nodes and liver was found. CT scan revealed no lymphadenopathy or splenomegaly in any of the patients. Two patients remain well 9 and 24 months respectively after polypectomy whereas the patient with mixed low- and high-grade lymphoma died 7 days after hemicolectomy due to cardiac failure. These previously undescribed solitary polypoid MALT lymphomas can closely resemble both benign lymphoid polyposis of the colon and lymphomatous polyposis (mantle cell lymphoma). Because of their different behaviour accurate diagnosis of polypoid MALT lymphoma is important.

CUVELIER C.A., QUATACKER J., MIELANTS H., DE VOS M., VEYS E. & ROELS H.J.

(1994) *Histopathology* 24, 417–426

M-cells are damaged and increased in number in inflamed human ileal mucosa

Ileocolonoscopy and biopsies of patients with spondylarthropathy reveal gut inflammation in 62% of cases. In order to better understand the pathogenetic mechanisms of spondylarthropathy-related gut inflammation, the follicle-associated epithelium was examined. Biopsies from nine controls and 18 patients with spondylarthropathy were studied by electronmicroscopy. Membranous (M) cells were investigated in normal and inflamed ileum. In normal mucosa, M-cells were scarce whereas in inflamed mucosa their number was increased (up to 24% of follicle-associated epithelial cells). They showed a thin rim of cytoplasm covering groups of lymphocytes. In chronic ileitis, necrotic M-cells, rupture of M-cells and lymphocytes entering the gut lumen were observed. The bursting of M-cells at the top of the lymphoid follicles leads to interruption of the gut epithelial lining and gives the luminal content access to the lymphoid tissue. This pathogenetic mechanism may cause aphthoid ulcers.

J Clin Pathol 1993;46:997–999

Gastric cancer and *Helicobacter pylori* infection

K S Clarkson, K P West

Abstract

***Aims*—To identify differences in the prevalence of *Helicobacter pylori* infection in different groups of patients with gastric cancer.**

***Methods*—In total 224 cases of gastric cancer were studied: 120 (53·6%) intestinal; 69 (30·8%) diffuse; and 35 (15·6%) unclassified. Site of tumour, presence and severity of gastritis, presence and extent of intestinal metaplasia, and age and sex were also recorded. Infection by *H pylori* was assessed using modified Giemsa staining.**

***Results*—*H pylori* infection was found in 96 (43%) cases. There was no significant association between infection and histological type of tumour, nor was there any significant association between infection and site of tumour, the presence of intestinal metaplasia, age, or sex. The only significant association identified was between infection and gastritis.**

***Conclusions*—These results are in broad agreement with those of other similar studies, although the overall prevalence of infection, at 43%, was lower than has been reported in some series. The findings do not support a role for *H pylori* in any particular subgroup of patients with gastric cancer but do not exclude a role for the organism in the pathogenesis of gastric cancer as a whole.**

(*J Clin Pathol* 1993;46:997–999)

There are wide geographical variations in the incidence of gastric cancer. This has led to speculation about environmental factors that may be important in its pathogenesis.[1 2] population and to identify any subgroups amongst which there were significant differences in prevalence.

Methods

All cases of gastric carcinoma diagnosed at Leicester Royal Infirmary between 1982 and 1986 were identified and the histopathological blocks retrieved. The tissues had all been fixed in 10% formol-saline. Wher possible, resection specimens were used but biopsy material was included if it contained sufficient non-tumour tissue. Sections were stained with haematoxylin and eosin, alcian blue-periodic-acid Schiff, and modified Giemsa for assessment of tumour type, the presence and degree of gastritis, intestinal metaplasia and *H pylori* infection. No attempt was made to differentiate the various subtypes of intestinal metaplasia. Tumours were typed using the Lauren classification.[5] Gastritis was graded mild, moderate, or severe according to the intensity of the neutrophil polymorph and mononuclear infiltrate in accordance with previous studies.[6 7] Cases were not separated by topographical sites as we were concerned with the overall prevalence of gastritis rather than its distribution within the stomach. Intestinal metaplasia was scored as follows: 0 = none; 1 = focal; 2 = affecting less than half of the epithelium present, 3 = affecting more than half of the epithelium present. *H pylori* colonisation was recorded simply as present or absent. All sections were examined independently by the authors and disagreements resolved by discussion. The semiquantitative scoring system used for metaplasia has been described by Loffeld *et al*.[8]

Statistical analysis of the results was per-

J Clin Pathol 1993;46:832

Prevalence of lymphoid follicles and aggregates in *Helicobacter pylori* gastritis in antral and body mucosa

S Eidt, M Stolte

Abstract

***Aims*—To evaluate the prevalence of lymphoid follicles and aggregates in the antral and body mucosa in *Helicobacter pylori* gastritis and to assess if there were correlations with ulcers in the duodenum, pylorus, or stomach, and with chronic antral erosions.**

***Methods*—Patients (n = 2692) with histologically confirmed *H pylori* antral gastritis were investigated. These comprised five groups: those with duodenal ulcers; those with pyloric ulcers; those with gastric ulcers; those with chronic erosions; and those with no associated lesions. In 1446 cases at least two additional biopsy specimens from the oxyntic mucosa were available.**

***Results*—Lymphoid follicles and aggregates were found in 53·8% of cases in the antral mucosa compared with 14·8% in the oxyntic mucosa ($p < 0·001$). The various diseases showed significant differences in terms of the prevalence of follicles and aggregates: The highest numbers in the antral mucosa as well as the lowest in the oxyntic mucosa were found in patients with duode- ulcers (60·5% and 9·2%, respectively). The highest numbers of follicles and aggregates in the oxyntic mucosa occurred in patients with gastric ulcers.**

***Conclusions*—The detection of lymphoid follicles and aggregates in oxyntic mucosa and the higher prevalence in antral mucosa fits well with the distribution of primary gastric lymphomas. This adds further weight to the notion that the development of follicles and aggregates, triggered by *H pylori*, might be an early precursor to gastric lymphoma. The differences between the groups investigated might be due to different strains of *H pylori* or differences in the respective sizes of antral and oxyntic mucosa.**

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The normal gastric mucosa contains very few T cells and almost no B cells in the lamina propria.[1] In the most common type of gastritis—that induced by *Helicobacter pylori*—colonisation of the gastric mucosa by *H pylori* is followed by both a local and systemic immune response.[2–5] Lymphoid follicles and lymphoid aggregates are repeatedly detected at the base of the antral mucosa in cases of *H* [illegible] have not been found, however, in chemically induced gastritis or normal antral mucosa.[2 3 6 7] No data are available regarding the prevalence of lymphoid follicles or lymphoid aggregates in the oxyntic mucosa.

Methods

A total of 2692 patients were investigated from whom two or three biopsy specimens from the antrum were available. Additional biopsy specimens from the oxyntic mucosa were available in 1446 of these patients. Further prerequisites for inclusion in the study were histologically confirmed *H pylori* gastritis of the antral mucosa, no treatment with antibiotics and no medication with non-steroidal anti-inflammatory drugs (NSAID).

Tissue sections were stained with haematoxylin and eosin and Warthin-Starry stain. Lymphoid follicles were diagnosed when an aggregation of lymphoid cells at the base of the mucosa showed a germinal centre, while lymphoid aggregates were defined as accumulations of lymphocytes and plasma cells located at the base of the mucosa without evidence of germinal centres.

The degree and activity of the gastritis as well as the density of *H pylori* colonisation were evaluated semiquantitatively in accordance with the Sydney system,[8] as described elsewhere.[9–11] The infiltration of the gastric mucosa by lymphocytes and plasma cells (degree of gastritis) and polymorphonuclear neutrophils (activity of gastritis) and the density of the *H pylori* colonisation were graded as follows: 0 = none, 1 = minimal, 2 = mild grade, 3 = medium grade, 4 = high grade. A mean gastritis score was obtained by adding together the figures for degree and activity in each case and dividing the result by the number of cases in each group of patients. "Chronic antral erosions" were diagnosed when regenerative changes occurred in the mucosa at the border of an erosive lesion.

The diagnosis of duodenal ulcer was based on endoscopic appearances whereas pyloric or gastric ulcers were histologically confirmed. In patients with associated lesions the evaluation of gastri

Table 1 Age and sex distribution of groups of patients investigated

	Number	Mean age
Gastritis without lesions	(n = 1196)	51·9
Chronic erosions	(n = 227)	54·6
Gastric ulcers	(n = 154)	56·9
Pyloric ulcers	(n = 210)	55·0
Duodenal ulcers	(n = 905)	48·6

Helicobacter pylori gastritis and primary gastric non-Hodgkin's lymphomas

S Eidt, M Stolte, R Fischer

Abstract

***Aims*—To evaluate further the relation between gastric malignant lymphoma of the mucosa associated lymphoid tissue (MALT) and *Helicobacter pylori*.**

***Methods*—One hundred and sixty two surgical specimens of MALT lymphoma were retrospectively investigated to determine tumour type and inflammatory patterns. In 121 cases biopsy specimens obtained before surgery were available and stained with haematoxylin and eosin, periodic acid Schiff, Giemsa and Warthin-Starry stains.**

***Results*—Residual lymphoid follicles were found less often in high grade malignant than in low grade malignant MALT lymphomas. Chronic active gastritis was shown within the mucosa at some distance from the tumours in 143 of 146 specimens. In all the cases for which biopsy specimens could be evaluated, colonisation of the mucosa by *H pylori* had occurred. Lymphoid follicles and lymphoid aggregates were detected in 82·7% of the antral, and in 85% of the body mucosa specimens.**

***Conclusions*—These data support the hypothesis that *H pylori* has an important role in the development of MALT lymphomas. Furthermore, the chronic inflammation preceding malignant transformation might enhance the probability of malignant transformation via chronic stimulation of the lymphoid tissue. This might in part indicate why MALT lymphomas occur most often in the stomach.**

(*J Clin Pathol* 1994;47:436–439)

One of the most exciting current developments in gastroenterology is the discovery that *Helicobacter pylori* has a decisive role in gastroduodenal disease.[1-3] Recently, several groups have published data showing a correlation between *H pylori* and gastric carcinomas.[4-6] Wotherspoon *et al* were the first to investigate the presence of *H pylori* in larger numbers of gastric lymphomas of the mucosa associated lymphoid tissue (MALT lymphomas): in 92% of cases *H pylori* was indeed detected.[7] On the basis of earlier observations that the prevalence of lymphoid follicles correlated significantly with the detection of *H pylori*,[8,9] they suggested that *H pylori* might trigger the acquisition of MALT in the gastric mucosa which usually contains only a few T lymphocytes.[7] In the light of these findings *H pylori* and the subsequent inflammatory response might be prerequisites for the development of a MALT lymphoma in the stomach. Further support for this hypothesis was provided by data published by Doglioni and coworkers which showed that the high prevalence of gastric MALT lymphoma correlated closely with a high prevalence of *H pylori* infection in a town in northern Italy.[11] If the suggested route to MALT through *H pylori* infection to the malignant transformation holds true, then not only *H pylori* but an inflammatory response to *H pylori* infection should be evident in almost all cases of MALT lymphoma as well. To elucidate further this association we retrospectively investigated 162 cases of gastric resection specimens for gastric lymphoma.

Methods

One hundred and sixty six surgical specimens of gastric lymphoma (56 gastrectomies, 95 arboral resections, nine local excisions, six resections of the gastric remnant were examined at the Institute of Pathology, Bayreuth, over a period of 11 years. They were fixed in 10% formalin, embedded in paraffin wax and routinely stained with haematoxylin and eosin periodic acid Schiff and Giemsa. The lymphomas were classified according to the proposal of the European Lymphoma Study Group.[12] Only B cell lymphomas of MALT type were included in this study. Two plasmocytomas and two T cell lymphomas were excluded, reducing the number of cases investigated to 162.

The phenotypic evaluation of lymphomas was done using monoclonal antibodies recognising formalin fixation resistant antigens (L26, UCHL1, MT1, all from Dako) and a subsequent peroxidase-antiperoxidase method. The high grade malignant MALT lymphomas were divided into those with and without a low grade component. Furthermore, the depth of infiltration into the gastric wall was evaluated using the International Union against Cancer classification of gastric cancer (table 1).[13] Clinical staging of lymphoma was also carried out in all patients using abdominal computed tomograms or ultrasonography, liver and bone marrow biopsies

Table 1 UICC classification of gastric carcinoma

pT1	Tumour restricted to mucosa and submucosa
pT2	Tumour infiltrating beyond the submucosa into the muscularis propria and the subserosal layer
pT3	Tumour penetrating the serosa
pT4	Tumour continuously infiltrating other organs (liver, spleen)

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tissue but there is no foamy macrophage infiltration and the process does not extend above the pelvic brim. Although there may be inflammatory changes in the serosa in Whipple's disease, the mesenteric nodules represent enlarged lymph nodes which contain numerous periodic acid Schiff positive macrophages and bacilli and there is no sign of fat necrosis.

The three cases that we have presented demonstrate the clinical spectrum of mesenteric lipodystrophy. Case 1 presented with an acute abdomen and in cases 2 and 3, despite extensive investigations, the diagnosis was made at necropsy. Only histological examination of the mesenteric masses indicated the diagnosis.

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Multinucleated stromal giant cells of the colonic lamina propria in ulcerative colitis

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Abstract

Multinucleated stromal giant cells were seen in the colonic mucosa in biopsy specimens from two patients with long-standing quiescent ulcerative colitis. Similar cells have been described at other sites associated with chronic inflammation, including the lower female genital tract, bladder and anus. The immunophenotype of the cells in the colonic mucosa suggested that they had originated from fibroblasts rather than histiocytes, in common with cells seen at other sites of inflammation.

These examples lend support to the concept of there being a reactive morphological change possibly related to interaction with mast cells. These multinucleated giant cells are distinct from histiocytic giant cells and should not be confused with them.

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So-called (atypical) multinucleated str giant cells have been described in a varie sites including the lower female genital t bladder, anus, skin, breast and nose.[1–4] V numerous they have been confused w diagnosis of sarcoma or pseudosarcom carcinoma. Their association with pc chronic inflammation and changes after ation has suggested that these are rea cells and studies suggest an origin fron indigenous stromal cells.[1–4] An intera between stromal cells and mast cells has suggested as being crucial to the inducti this morphological change.[1]

Case reports

CASE 1

A 62 year old woman with an 18 year h of ulcerative proctitis that had been trolled by salazopyrine had a r colonoscopy at which the mucosa looked mal. Biopsy specimens were taken to disease activity and exclude dysplasia.

Gut 1993; 34: 1-3

Gut

Leading article – Molecular biology series

Recent advances in the molecular biology of hepatitis B virus: mutant virus and the host response

Recent advances in molecular biology have revolutionised the study of the hepatitis B virus. The polymerase chain reaction technique has allowed viral DNA from patients to be amplified and sequenced.[1] Such studies have shown that the genome of hepatitis B virus is highly variable and it is likely that no two viral isolates are genetically identical. Because hepatitis B virus gives rise to a number of distinct diseases it is tempting to suppose that different viral genotypes cause different diseases. Recipients of contaminated blood from patients with hepatitis B virus, however, do not necessarily develop the same disease,[2] indicating that different hepatitis B virus infections are caused by the interaction between a particular viral genotype and their host. In this review we shall discuss the association between various hepatitis B virus genomes and particular diseases and discuss the way in which variant viruses develop and give rise to disparate diseases.

Spectrum of hepatitis B virus hepatitis

Adult infection with hepatitis B virus causes a number of different diseases. The majority of infected adults develop an acute infection characterised by a hepatitis and a cellular immune response directed against the hepatitis B virus nucleocapsid protein, core.[3] In a minority of patients hepatitis B virus infection causes a severe, fulminant, hepatitis. A small number of infected adults do not develop an overt hepatitis and the normal immunological response to hepatitis B virus is impaired.[4] These patients do not eliminate the virus but develop a chronic infection which persists for many years and leads, ultimately, to either cirrhosis or hepatocellular carcinoma. Interferon is the treatment of choice for patients with chronic hepatitis B virus infection and a significant proportion respond and appear to eliminate the virus.[5] Many patients, however, do not respond to interferon. Adult infection with hepatitis B virus thus gives rise to a spectrum of diseases ranging from the relatively minor acute hepatitis through chronic interferon sensitive and interferon resistant hepatitis to the very severe fulminant hepatitis. There are two possible explanations for this disease spectrum: different viruses may differ in their virulence or the host response may vary.

Specific viral mutations associated with specific diseases

In 1989 Carman *et al*[1] identified a variant strain of hepatitis B virus that was associated with a specific disease. Although the majority of patients chronically infected with hepatitis B virus secrete hepatitis B virus e antigen (HBeAg) a minority do not. Carman *et al* studied patients with HBeAg-negative chronic hepatitis B virus infections. HBeAg is a protein encoded by the hepatitis B virus core gene. This gene contains two start codons (genetic sequences that initiate translation and protein production). When the first start codon is used for protein translation a large protein (precore) is formed. Precore contains a 'signal sequence' peptide that causes it to enter the endoplasmic reticulum, where it is degraded to form HBeAg. Translation from the second start codon of the core gene produces a smaller protein, core, that does not contain the signal sequence necessary for entry into the endoplasmic reticulum. Core protein cannot be degraded to HBeAg and its sole function is to form the viral nucleocapsid. When DNA from patients with HBeAg negative infections was sequenced a point mutation was identified between the two start codons. This mutation causes a stop codon to form which prevents the formation of the precore protein (the precursor for HBeAg) but does allow the nucleocapsid protein to be produced, by translation initiation at the second start codon. Hence viral particles are produced but HBeAg is not formed. The discovery of a mutant virus that was associated with a particular form of hepatitis B virus infection led to speculation that other mutations might be associated with specific diseases and a number of studies have addressed this issue.

One mutation – two diseases

In the early 1990s a number of groups studied the genotype of viruses that were associated with fulminant hepatitis. A common viral variant was identified in the majority of cases.[2 6] This mutation, however, was the same as that recognised in 1989 as the cause of HBeAg negative chronic hepatitis. Hence the same viral genotype can cause two distinct diseases, and clearly factors other than viral mutations must be involved in the pathogenesis of HBV infections.

Host response to hepatitis B virus

The observation that viral mutations alone cannot explain the variability of hepatitis B virus infections has led to a reevaluation of the patient's response to the virus. Two factors contribute to the host response to hepatitis B virus –

interferon production and the immunological response to hepatitis B virus antigens.

(a) INTERFERON PRODUCTION AND ITS EFFECTS

In an acute hepatitis B virus infection interferon is produced in large amounts.[7] Interferon increases the expression of hepatocyte HLA antigens[4] and induces the production of a group of enzymes (known as the RING genes)[8,9] that process viral proteins and allow them to associate with HLA antigens. In patients who are able to respond to hepatitis B virus proteins the HLA antigen processed viral antigen complex stimulates an immune response which results in the generation of cytotoxic T cells that lyse infected cells. Interferon thus interacts with the immune system and assists in the resolution of acute hepatitis B virus infections by presenting viral proteins to responsive immunocytes.

In patients who develop chronic hepatitis B virus infections interferon production is impaired[10] and an appropriate immune response does not develop. It is not yet clear why some patients do not produce interferon. Hepatitis B virus contains two proteins which affect the production of interferon – the X protein can stimulate the production of β-IFN[11] while the core protein can inhibit its production.[12] Presumably the amount of interferon produced in any HBV infection depends upon the relative activities of these two proteins. It should be noted that studies of interferon induction to date have examined the effects of hepatitis B virus on the induction of β-IFN. Hepatocytes produce α-IFN and not β-IFN however (Foster, Thomas, MacNair, and Thurz – unpublished data) and hence the interactions between hepatitis B virus and interferon production have not yet been adequately studied.

Interferon deficiency cannot be the sole determinant of chronic hepatitis B virus infection – if it was, then all patients with chronic hepatitis B virus infections should respond to interferon therapy. Recent work has shown that hepatitis B virus contains a protein (terminal protein) that can inhibit the cellular response to interferon.[13] In patients with chronic hepatitis B virus infections the amount of terminal protein in biopsy specimens varies and patients who express large amounts of this interferon inhibitor usually fail to respond to interferon therapy (Foster, Goldin, Stark, and Thomas – submitted for publication). The outcome of any hepatitis B virus infection may therefore depend upon the induction of and the cellular response to interferon.

(b) IMMUNOLOGICAL RESPONSE TO HEPATITIS B VIRUS

In an acute infection, or a chronic infection that resolves with interferon therapy, viral eradication is the result of elimination of infected hepatocytes by cytotoxic T cells.[4] Cytotoxic T cells only recognise viral antigens which have been processed by the RING proteins (see above) and then presented on the cell surface by HLA class I antigens. Only a small number of viral proteins are processed in this way and within each target protein there are antigenic epitopes that combine specifically with certain HLA antigens.[3] The epitope that combines with an HLA antigen depends on the nature of the HLA protein. Hence the viral target for cytotoxic T cell mediated lysis varies in different patients and depends upon the patient's HLA type. For hepatitis B virus it is now clear that the core protein is the main target for cytotoxic T cells and the antigenic epitopes within the core protein that associate with the HLA antigen A2 have now been identified.[3] The epitopes that associate with other HLA antigens have not yet been found.

CHANGING VIRUSES AND THE HOST RESPONSE

Sequential studies from patients with chronic hepatitis B virus infections have shown that viral mutations develop during the course of an infection and that the dominant viral strain changes.[14,15] We believe that 'new' viruses arise spontaneously during a chronic infection and that immunological pressure then selects mutant viruses that have a survival advantage. Some viruses – for example, human immunodeficiency virus – HIV – are known to escape from the immune system by generating novel cytotoxic T cell epitopes[16] that cannot be recognised by the host and it seems likely that variant hepatitis B viruses develop in the same way. The HBeAg negative mutation (described above) often develops during a chronic hepatitis B virus infection and its development is associated with an exacerbation of the hepatitis.[15] Presumably the host immune system develops a response to HBeAg (either humoral or cell mediated) and is able to eliminate hepatocytes that express HBeAg. The virus responds to this host selection pressure by eliminating the immunological target – HBeAg negative mutant viruses will have a significant survival advantage and hence HBeAg negative infection develops.

The production and effects of interferon may profoundly influence the course of an hepatitis B virus infection and both core and terminal protein are known to alter the interferon system (see above). These proteins are encoded by a closely related region of hepatitis B virus DNA (the two genes overlap, and the proteins are produced from different open reading frames). We now know that in chronic infections the DNA that encodes these two proteins often mutates,[14,15] presumably because of immunological selection pressure and the 'new', mutated viruses may differ in their interferon response characteristics. In a host in which HBV has mutated such that the immune system cannot recognise viral antigens the effects of IFN may be of little consequence. If the same virus infects another host whose immune system can respond to the presented viral antigens, then the production and actions of interferon may play a vital role in either the elimination of the virus or its persistence. Hence a virus that has adapted to one host may cause a quite separate disease in a new one.

Conclusion

Recent advances in molecular biology and immunology have greatly increased our understanding of the pathology of hepatitis B virus. The different diseases caused by this variable virus are caused by a complex interaction between the host's immune system, the interferon response and the viral genotype. It seems likely that in chronically infected patients viral variants develop that are able to avoid the host's antiviral mechanisms and hence the virus is able to persist for many years. A virus that has adapted to one host may, however, be poorly adapted to another and when transferred to a new patient the same virus may be rapidly eliminated or give rise to an overwhelming hepatitis. A complete understanding of how this virus evolves to escape the immune system is now within sight and such an understanding may lead to improved therapy for the millions of patients infected with this ubiquitous pathogen.

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Gut

Leading article – Molecular biology series

Molecular biology and gastric carcinoma

The molecular study of gastric carcinoma has much to offer the medical scientist, pathologist, clinician, and patient. Morphological classifications are not completely satisfactory in predicting biological and clinical behaviour. Molecular diagnostic markers are needed to discriminate between inflammation and neoplasia[1] in biopsy and cytology specimens, to show invasion in those biopsies currently difficult to interpret,[2] to define disease subgroups with differing natural history or response to various treatments, and to identify high risk groups for surveillance. It is also hoped that molecular analysis of the disease will identify new therapeutic targets for more precise and effective treatments with fewer side effects.

The genes underlying inherited susceptibility to gastric carcinoma have not yet been identified, and the molecular mechanisms of cancer promotion by environmental influences, such as diet and *Helicobacter pylori* infection, await elucidation. Some progress has been made, however, in identifying abnormalities of oncogenes, tumour suppressor genes, and growth factors including their receptors and related gene products. This will provide a structural framework for analysing molecular mechanisms of disease development. Comparisons can now be made between gastric carcinoma and other cancers (particularly colorectal cancer), between diffuse and intestinal morphological types of gastric carcinoma, and between early and advanced cases. Many of the problems which have limited previous progress are now being resolved.

Which chromosomes are involved?

Early cytogenetic studies were done on malignant effusions from very advanced cases,[3] so it was unsurprising that a large variety of chromosomal abberations were found, differing from case to case. More recent studies of solid tumour material have also found marked heterogeneity both between cases and within each case, but two studies[4,5] have reported frequent breakpoints at 3p21, which is the site of deletions in lung cancer and may involve a phosphatase tumour suppressor. Rodriguez *et al* found translocations and deletions of 11p13–15 (often abnormal in other solid tumours) in four of five cases, two involving reciprocal translocations of 3p21. They observed the same rearrangement in adenocarcinomas of the lower oesophagus, supporting the view that these cancers are similar in pathogenesis to gastric carcinomas, as they usually arise in the metaplastic glandular mucosa of Barrett's oesophagus. A cytogenetic analysis of nine cases of Barrett's metaplasia, however, did not find chromosomal abnormalities at either the 11p13–15 or 3p21 sites.[6]

Chromosomal losses important in the pathogenesis of cancers can be studied by using DNA polymorphism marker techniques to identify separately maternal and paternal alleles (comparable with HLA typing). Patients are informative if their constitutional DNA (from peripheral blood, or hair roots) shows two patterns – one for each allele. Allele loss is indicated if one of these disappears in tumour tissue, and may signify loss of a tumour suppressor gene. Studies on gastric carcinomas were relatively few and only analysed small numbers of tumours, most finding a low level of deletion. The high proportion of stromal cells in many gastric cancers, particularly the diffuse type, may have caused a dilution of tumour DNA and consequent failure to detect allele loss. A recent study by Sano *et al* selected cases comprising over 50% of tumour cells microscopically assessed on immediately adjacent tissue, and found a much higher rate of allele loss.[7] Deletion of 5q was found only in well differentiated cases and not in undifferentiated tumours. The 5q sites correspond with the sites of the familial adenomatous polyposis (APC) gene, also deleted in some spontaneous colon carcinomas, and the adjacent mutated in colon carcinoma (MCC) gene. In contrast, both types of gastric tumour showed a 60% rate of allele loss on 17p at the site of the p53 gene. Extrapolating from this, we would then expect to find mutations of the p53 gene in both cancer types, but 5q gene mutations only in differentiated carcinomas. Paradoxically, Horii *et al* have found APC gene mutations in only diffuse or poorly differentiated types, but not in differentiated intestinal types of gastric carcinoma, in a study of 44 tumours.[8] It will be interesting to see if this curious paradox is clarified by other studies in progress.

Allele loss has also been reported on the 18q chromosomal site of the deleted in colon cancer (DCC) gene in a series of intestinal type gastric carcinomas (diffuse cancers were not examined).[9] 18q deletions were found in over 60% of informative cases including many early intramucosal cases, compared to 17p losses (p53 gene) found at a lower rate and in more advanced cases. Thus the overall pattern of allele loss in gastric cancers shows many similarities with colon cancer, with losses at 5q, 18q, and 17p, with 17p loss associated with progression.

Ras oncogenes and proteins

The *ras* protein p21 is encoded by three *ras* genes, *Ha-ras*,

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Leading article

Ischaemic colitis: two distinct patterns of severity

Ischaemic colitis accounts for only a small percentage (1 to 2%) of patients with colonic pathology seen in gastrointestinal and surgical wards. Because its presentation is non-specific and as numerous conditions may favour its development, ischaemic colitis is probably frequently misdiagnosed and its incidence underestimated.

At presentation, the severity of early stage disease may vary considerably with the prevalent benign 'transient' forms being amenable to conservative regimens and the severe 'gangrenous' forms, requiring surgery.[1 5] The percentage of surgical cases in a given series ranges widely (from 2[6] to 42%).[7] These differences have been referred to repeatedly[2 4 8] since the key report by Marston *et al* in 1966 (these authors also specify a third category, ischaemic stricture; however, this will not be dealt with here because, even if it does exist,[9] it will only be diagnosed at a later date).[1]

This review covers diagnosis, predisposing factors, lesion distribution, treatment, and results. It is based on reports (in the literature) and our own six year series of 34 patients of which 13 were treated surgically and 21 conservatively.[3 5]

Diagnosis

Ischaemic colitis should be suspected in patients presenting with abdominal pain and rectal bleeding.[1 2 10 11] In practice, a correct diagnosis is usually made 'after the ischaemic episode is over';[2] but this is only possible in mild 'transient' cases[1 9] in which a conservative approach can be adopted until a complete investigation is carried out.

No test specific for ischaemic colitis has yet been developed.[9 12] Enzyme determinations are routinely used in the assessment of cardiac or hepatic necrosis, but we still have no specific and early marker of intestinal viability.[13] Ischaemic colitis is usually diagnosed on the basis of a heterogeneous collection of clinical, radiological, endoscopic and pathological evidence.[14] Radiological evidence includes 'thumb printing,' 'saw toothing,' tubular narrowing, and thickened mucosal folds but is not always sufficient to make a firm diagnosis of ischaemic colitis.[1] Contrast studies should be obtained early as certain indicative images may be transient.[2] Endoscopy may include (in addition to pathognomonic but inconstant submucous haematoma) mucosal loss or other changes (fragility, oedema, hypervascularisation) and even ulceration and pseudomembranes. Skip lesions[15] are rare,[11] and progression to other colonic segments unusual.[9] Pathological findings[16 17] are seldom unequivocal,[18 19] except for images of patchy tubular atrophy[20] or superficial coagulation necrosis.[21] Biopsy usually involves only superficial mucosal fragments and therefore yields no information on the depth of ischaemic involvement.

Whether radiology or endoscopy[4] is superior for the diagnosis of these benign forms of ischaemic colitis is uncertain. Angiography seems an attractive option but the information it provides is seldom decisive,[2 8 9 14 19 20 22–24] probably because the lesions are very peripheral and therefore difficult to detect.

Computerised tomography[25 26] is unlikely to provide useful diagnostic information, but it may help in assessing intra or retroperitoneal involvement and consequently disease severity in much the same way as it is now used in acute colonic diverticulitis.[27] The same problems apply to indium-111 labelled leucocytes which are useful for preoperative determination of the site and extent of the disease.[28]

Severe forms of ischaemic colitis require surgery, usually without delay.[9] Preoperative diagnosis is often incorrect, however, because of insufficient time for evaluation; this occurred in eight of 13 cases in our series. Gastrografin enema offers the promise of higher diagnostic yield and, in view of its peritoneal tolerance can be used even when perforation is suspected.

Aetiological aspects

The key role is a sudden fall of colonic blood supply.[1 9 29] The mechanism is illustrated clearly by those cases of ischaemic colitis (no more than 2%)[19 30 31] that follow abdominal aorta reconstruction[2 10] – which is more common when aortic repair is undertaken as an emergency.[10 32 33] Ligation of a patent inferior mesenteric artery does not seem decisive *per se* in the development of ischaemic colitis.[34]

Regional low flow is the crucial factor in ischaemic colitis and is more likely where there has been previous impaired regional vascularisation. This impairment, however, is not an essential prerequisite as ischaemic colitis has been reported in healthy young joggers,[35 36] occasionally severe enough to require subtotal colectomy.[37] Intermediate pathogenic phases include hyperthermia, dehydration, and splanchnic vasoconstriction. It is not clear why the colon is preferentially affected in healthy individuals since other abdominal organs such as the pancreas are more sensitive to hypovolaemia.[38–40]

Blood deprivation may occasionally be of embolic origin including cholesterol emboli[41 42] and sickle cell crises.[43] Other conditions (drugs or diseases) may favour or cause ischaemic colitis.[2 11 17 44]

Whatever the exact pathophysiological mechanism, ischaemic colitis is favoured by atherosclerosis or vasculitis. Most patients with ischaemic colitis are elderly probably as a result of the presence of atherosclerosis in this age group. The severity of ischaemic colitis might be directly related to the extent of atherosclerosis; in our series, cardiovascular conditions were far more frequent in the group requiring surgical exploration: eight of 13 operated patients suffered from atherosclerosis (three with a history of coronary heart disease, two with intermittent claudication, one 'stroke,' one Buerger's disease, and one cardiac insufficiency; two others developed ischaemic colitis after aortic reconstruction for ruptured aneurysms).[3] The corresponding figure in the conservative group was only four of 21 patients.[5]

Site of ischaemic lesions

Involvement of the splenic flexure in ischaemic colitis is explained by the weakness of the arc of Riolan (marginal artery of Drummond), located at the peripheral junction of the superior and inferior mesenteric arteries.[45 46] This site was found 22 times in our series; it was never isolated and was usually associated with involvement of the descending colon (20 cases). The rectum is seldom involved[1] even though it shares a similar precarious vascularisation at the tip of the hypogastric and inferior mesenteric territories.[47]

The rare reports of ascending colon involvement[10 11 29] are

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Familial primary gastric lymphoma

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Abstract

Familial lymphoma is uncommon and is usually associated with various forms of hereditary immunodeficiencies. Primary gastric lymphomas that occurred in three adults from the same family, who had no overt immunodeficiency or cancer of non-lymphomatous origin, are reported. Two sisters presented with a low grade lymphoma of the mucosa associated lymphoid tissue type. Their father presented with a high grade form of later onset. All lymphomas have been phenotypically characterised as being of B cell origin. Epstein-Bar virus DNA was detected by polymerase chain reaction in the biopsy specimen of the high grade lymphoma but *bcl*-2/JH protooncogene rearrangement, t (14:18), was not identified in either the low or high grade lymphoma specimens tested.

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Primary lymphoma of the gastrointestinal tract is the most frequent non-Hodgkin's lymphoma arising from extranodal sites,[1] and accounts for 30% or more of all primary extranodal lymphomas.[2 3] Lymphomas arising from mucosa-associated lymphoid tissue (MALT) may constitute, as recently suggested, a distinct clinicopathological entity.[4] These are low grade lymphomas that run a rather indolent course, depending on their location.[5] Pain, weight loss, and bleeding are the chief presenting symptoms and signs in patients with gastric lymphomas.[6] Transformation of a low grade into a high grade form has been suggested by immunohistochemical studies comparing MALT lymphomas of small cell type (centrocyte like) with the more prevalent large B cell gastric lymphomas.[7]

Nodal and extranodal lymphomas may occur in a familial form associated with clinical or laboratory immunodeficiency[8 9] but they have seldom been reported in families devoid of obvious immunodeficiencies.[10] We describe the case histories and laboratory and immunopathological findings in a father and two of his four daughters who presented with primary gastric lymphomas.

Methods

PATIENTS

Members of the second generation of this family (II in Fig 1) agreed to participate in this study. They all live in a rural area of Switzerland and no one is or has been exposed to noxious substances suspected of inducing malignancy. Blood samples were collected the same week at a single medical centre and were sent for laboratory investigation. At the same time the pedigree of the family was ascertained and medical histories were recorded.

METHODS

Histological studies were performed on 4 μm sections stained with haematoxylin and eosin,

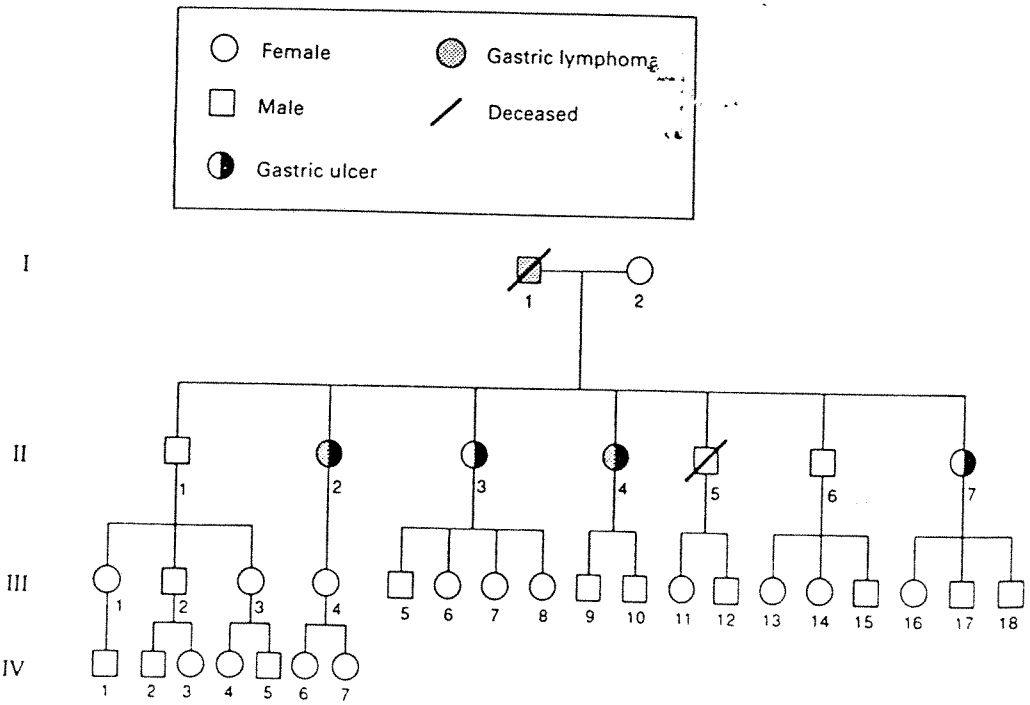

Figure 1: Pedigree of family with gastric lymphoma through two generations.

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Cystic dystrophy of the gastric and duodenal wall developing in heterotopic pancreas: an unrecognised entity

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Abstract

Ten patients in whom cystic dystrophy developed in a heterotopic pancreas of the duodenal (nine patients) or gastric (one patient) wall are reported. All were young or middle aged white men, only two of whom were alcoholic. The symptoms were caused by intestinal or biliary stenosis, or both, secondary to the inflammation and fibrosis. Only endosonography provided strong evidence for the diagnosis in three patients. All patients underwent surgery: a pancreaticoduodenectomy was performed in eight patients. The surgical specimen showed cystic lesions of the gut wall, occurring in inflammatory and fibrous heterotopic pancreatic tissue. The pancreas proper was normal in all patients. It is suggested that cystic dystrophy is an uncommon and serious complication of heterotopic pancreas. Similar cases associated with chronic pancreatitis of the pancreas have been observed and it is suggested that this process could be responsible for some of the chronic pancreatitis encountered in young, non-alcoholic patients.

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Pancreatic heterotopia is defined as the presence, outside its usual location, of pancreatic tissue that lacks anatomical and vascular continuity with the pancreas proper.[1] It has an incidence ranging from 1 to 14% on necropsy examination,[2] and the most common locations are the stomach, duodenum, and jejunum. Although heterotopic pancreas is usually asymptomatic, symptomatic cases have been described. Symptoms are non-specific, and they have been attributed mainly to the presence of overlying mucosal ulceration in the stomach or duodenum.[3]

We have observed the development of cystic dystrophy, an uncommon and serious complication of heterotopic pancreas, in 10 patients, in all of whom we have met major difficulties in diagnosis and treatment.

Patients and methods

Cases were selected from the records of the Department of Pathology, Beaujon hospital, between 1959 and 1991. During this period we observed 17 surgical specimens that showed

TABLE 1 *Clinical data, diagnostic procedures, treatment, and outcome in 10 patients who developed cystic dystrophy in heterotopic pancreas*

Case no	Year of surgery	Age (y)	Sex	Chronic alcoholism	Clinical manifestations	Weight loss (kg)	Symptom duration (y)	Diagnostic procedures	Preoperative diagnosis	Type of surgery	Outcome
1	1959	31	M	No	Abdominal pain	0	7	0	Tumour of the duodenum	PD	Recurrence of pain at 5 y, then lost to follow up
2	1960	55	M	No	Abdominal discomfort, vomiting	26	0·5	Barium meal	Duodenal stenosis	PD	Well (5 y)
3	1963	36	M	No	Abdominal pain, nausea, jaundice	10	1·5	Barium meal	Tumour of the pancreas	PD	No postoperative complication, then lost to follow up
4	1968	37	M	No	Jaundice	17	1	Barium meal, oral cholecystography	Tumour of the papilla of Vater	PD	No postoperative complication, then lost to follow up
5	1970	42	M	No	Abdominal pain, vomiting, jaundice	6	7	Intravenous cholangiography	Tumour of the pancreas	PD	Well (1 y)
6	1970	56	M	No	Jaundice	4	0·3	Barium meal, intravenous cholangiography, endoscopy	Biliary stenosis due to tumour	CJ	Death due to acute pancreatitis 10 days after surgery
7	1982	38	M	No	Abdominal pain, vomiting	15	4	Barium meal, endoscopy, US	Tumour of the pancreas	PD	No postoperative complication, then lost to follow up
8	1989	41	M	Yes	Abdominal pain, vomiting	7	0·7	Barium meal, endoscopy, US, ERCP, CT, endosonography	CDHP of the duodenum	PD	Well for 1·5 y, still alcoholic, regressive acute pancreatitis
9	1990	37	M	No	Haemorrhage, abdominal pain, vomiting	14	0·3	Barium meal, endoscopy, US, ERCP, CT, endosonography	CDHP of the antrum	Antrectomy	Well (1 y)
10	1990	34	M	Yes	Abdominal pain, vomiting	10	1	Barium meal, endoscopy, US, ERCP, CT, endosonography	CDHP of the duodenum	PD	Well (1·5 y), dumping syndrome, still alcoholic

PD: pancreaticoduodenectomy; CJ: choledocojejunostomy; US: ultrasonography; ERCP: endoscopic retrograde cholangiopancreatography; CT: computed tomography; CDHP: cystic dystrophy in heterotopic pancreas

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Gut

Leading article – Molecular biology series

Molecular biology of colorectal neoplasia

Large bowel cancer is a major cause of morbidity and mortality in the western world. In England and Wales approximately 8500 men and 9000 women die of the disease every year.[1] Yet despite this, relatively little is known of its pathogenesis in the vast majority of sporadic cases. In 1954, Armitage and Doll proposed that common cancers arise as a result of the accumulation of as many as seven events.[2] Most scientists now believe that the molecular substrate for these critical events in tumorigenesis are genes that regulate cell proliferation and differentiation – that is, oncogenes and tumour suppressor genes. Alterations to the expression or structure of these genes may result in the perturbation of cell growth, which is the hallmark of neoplasia.

The past 10 years has seen an explosion in our knowledge of the molecular biology of cancer, and nowhere has this been as exciting as in the field of large bowel cancer. Research into colorectal tumours has directly or indirectly contributed to the discovery of three new tumour suppressor genes; APC, DCC, and p53, the latter probably representing the commonest genetic abnormality so far described in human cancer.[3] Therefore, despite being unclear about the environmental agents that promote genetic changes in the large bowel, in few other tumour systems are we as close to identifying the critical events which underlie malignant, neoplastic behaviour as we are in colorectal cancer.

Oncogenes

Originally described as retroviral genes responsible for in vitro cell transformation and the development of certain animal tumours (v-onc), homologs have subsequently been identified in normal human cells (proto-oncogenes) and, in activated form, in human tumours (v-onc). Many have a physiological role in the regulation of cell division and differentiation. It is not surprising therefore that they are a common target for mutagenesis in neoplasia.

Most frequently altered in large bowel tumours are c-Ki-ras and c-myc. c-Ki-ras, one of the family of ras oncogenes, encodes a 21kD G-protein involved in the transduction of mitogenic signals across the cell membrane.[4] Point mutations in codons 12, 13, or 61 have been identified in 39 to 71% of large bowel cancers, as well as 42% of adenomas.[5–7] This results in the inability of the protein to hydrolyse bound GTP to GDP, and since GTP-ras is believed to be the active form of the protein this may deliver a continual signal to the cell to divide. Apart from point mutation, another way in which oncogenes can be activated is by over expression. This seems to be the mechanism for c-myc activation in colorectal tumours. C-myc encodes a nuclear phosphoprotein that is induced during cell proliferation, and is probably necessary for DNA synthesis.[8,9] Several groups have reported raised c-myc RNA values in 60-70% of carcinomas.[10,11] Similar levels have also been described in adenomas. While in some cases this may merely reflect the larger growth fraction found in tumours compared with normal mucosa, genuine over expression does seem to occur in a proportion of cases.[12] Amplification of c-myc has been described in a minority (7%) of tumours but correlates poorly with RNA content.[11–13] The reason for deregulated expression of the gene is therefore presently unknown.

Other oncogenes less frequently altered in large bowel tumours include c-src, raised in 62% of cancers; c-myb deleted in 9%, and c-erbB-2, amplified in 4%.[13–15]

Tumour suppressor genes

Numerically a much smaller group, tumour suppressor genes inhibit cell proliferation and tumorigenicity. Whereas oncogenes classically act in a transdominant fashion – that is, alteration to *one* allele is sufficient to cause transformation, suppressor genes are recessive. Loss of tumour suppressor function requires inactivation of *both* alleles, usually by chromosomal deletion or point mutation, or both.

Tumour suppressor genes seem to be very important in colorectal carcinogenesis. The hereditary condition, familial adenomatous polyposis (FAP), which confers susceptibility to colonic cancer, is determined by point mutations in a tumour suppressor gene, APC, inherited through the germ line. Localised to chromosome 5q.21 by Bodmer *et al* in the United Kingdom, and Leppert *et al* in the United States, the candidate gene encodes a large 2843 amino acid protein, whose function is, as yet, poorly understood.[16–18] While the inherited allele is mutated, the normal allele is subsequently deleted in a somatic, mitotic event involving variable sized fragments of the long arm of chromosome 5. This acquired loss of heterozygosity for chromosome 5q can be detected using restriction fragment length polymorphism (RFLP) markers in 36% of sporadic cancers, as well as FAP carcinomas.[6,19] In a survey of 79 unrelated FAP patients, mutations were found in the APC gene in 67%.[20] More than two thirds of mutations were located in the 5′ half of the last exon, and over 90% resulted in truncation of the APC gene product. Miyoshi has described similar mutations in sporadic adenomas and carcinomas.[21] Inactivation of the APC gene therefore seems to play an important role in sporadic colorectal tumorigenesis as well as in FAP.

Natural history of AIDS related sclerosing cholangitis: a study of 20 cases

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Abstract

A case control study of AIDS related sclerosing cholangitis indicates that it has no overall influence on prognosis, but is responsible for a striking reversal of the usual inverse correlation of age and survival in HIV infection. Pain, the principal symptom, was controlled in surviving patients with analgesics alone. Twenty consecutive patients with AIDS related sclerosing cholangitis, defined from at least two characteristic lesions at endoscopic retrograde cholangiopancreatography, were followed for a minimum of 10 months or until death. Median age was 33·5 years (range 27–50). All had abdominal pain; 11 had diarrhoea. Alkaline phosphatase was >2× normal in 13, but the bilirubin was raised in only three. The median CD4 was 0·024×10⁹/l (0·005–0·341). Thirteen had cryptosporidiosis, six had active cytomegalovirus, five had no gastrointestinal pathogen. Three patients are alive without AIDS related sclerosing cholangitis symptoms at 10, 11, and 21 months. Seventeen have died at median 7 (1–23) months. Cytomegalovirus therapy had no apparent influence. The initial CD4 was <0·11 in all those dying within six months, but correlation of CD4 with prognosis was otherwise poor. Controls, matched for age, CD4, and opportunistic infections had virtually identical overall outcome (median survival 7·5 months) and the expected worse prognosis with increasing age. Increasing age, however, appeared protective in AIDS related sclerosing cholangitis (r=+0·6; p<0·05): this is not explained by disproportionate degrees of immunosuppression, nor by opportunistic infections.

(*Gut* 1993; 34: 116–121)

Investigation of HIV infected patients with abdominal pain has led to the recognition of a condition now widely termed AIDS related sclerosing cholangitis.[1,2] Typically patients have right upper quadrant or epigastric pain and obstructive liver function tests. Ultrasound scanning may show thickening of the bile ducts and less often provides evidence of bile duct stricturing and/or dilatation.[1,3] Diagnosis is made from features on direct cholangiography indistinguishable from those of primary sclerosing cholangitis, but there is no link with inflammatory bowel disease. In some cases AIDS related sclerosing cholangitis and cryptosporidial or cytomeglaovirus enteritis coexist,[1,4] but whether this is a causal relationship remains unresolved. The natural history of AIDS related sclerosing cholangitis has not been clearly documented, and it is not known whether its presence has an independent influence on the prognosis of the affected patient. Twenty consecutive patients with AIDS related sclerosing cholangitis have therefore been studied to address these questions.

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Methods

PATIENTS

All patients presenting to the Westminster AIDS Unit with abdominal pain severe enough to require admission and with a life expectancy considered to be of three months or more are investigated in accordance with a previously described protocol.[5] This usually implies upper gastrointestinal endoscopy, ultrasound examination, and investigation for enteric pathogens. Unexplained pain, abnormal liver function tests or biliary abnormality at ultrasound lead to endoscopic retrograde cholangiopancreatography, and thereby a potential diagnosis of AIDS related sclerosing cholangitis. The present report concerns consecutive patients with a firm diagnosis of AIDS related sclerosing cholangitis made between March 1987 and May 1991: all were investigated prospectively to the agreed standard protocol.

Diagnosis of AIDS related sclerosing cholangitis for the purpose of this study required HIV seropositivity by two separate methods, and changes on direct cholangiography that were compatible with diagnostic criteria for primary sclerosing cholangitis.[6] Thus all patients had at least two biliary lesions (strictures/irregularities) shown at endoscopic retrograde cholangiopancreatography. Patients with gall stones or established inflammatory bowel disease were excluded.

All patients were investigated for bowel pathogens at the time of diagnosis of AIDS related sclerosing cholangitis. At least three stools were cultured for faecal pathogens and mycobacteria; concentrated specimens were examined by direct microscopy for ova, cysts, and parasites, and smears were stained by a modified Ziehl Neelsen method with concentration for cryptosporidium. Each patient had a sigmoidoscopy with rectal biopsy; specimens were fixed in buffered formol saline, and standard paraffin sections were examined after staining with haematoxylin and

Early mucosal changes in Crohn's disease

E A Sankey, A P Dhillon, A Anthony, A J Wakefield, R Sim, L More, M Hudson, A M Sawyerr, R E Pounder

Abstract

Aphthoid ulceration has been regarded as an early macroscopic feature of Crohn's disease, yet the cause of this mucosal lesion is unknown. Examination of areas of apparently normal and non-inflamed bowel in Crohn's disease has allowed the identification of mucosal changes which occur before macroscopic and microscopic ulceration. Thirty five resection specimens from patients with Crohn's disease were compared with 12 specimens from patients with ulcerative colitis and 13 controls. Specimens were fixed either by immersion in formalin in the routine way or by perfusion fixation with formalin at mean arterial pressure. Immunostaining for macrophages, vessel wall, and blood constituents allowed identification of small mucosal capillaries which were not apparent otherwise. In Crohn's disease damage and rupture of these small capillaries occurred before infiltration of the lamina propria by inflammatory cells. Loss of the overlying epithelium seemed to follow this vascular damage.

(*Gut* 1993; 34: 375–381)

Mucosal ulceration is a common feature of many diseases of the small and large intestine. The pattern of ulceration varies in different conditions and may show characteristic appearances in certain diseases, so forming the basis of histological diagnosis. The 'aphthoid' ulcer, first described by Brooke in 1953,[1] has been recognised for many years to be an early macroscopic feature of Crohn's disease. More recently, the use of fibreoptic endoscopic equipment has allowed the identification of subtle mucosal changes which are present before the development of aphthoid ulcers. These include patchy hyperaemia and friable mucosa,[2] a 'worm eaten' mucosal pattern,[3] and pinpoint haemorrhages the size of a single villus.[4] Histological examination of these areas shows that inflammation and granulomas are present in these 'early' lesions[2-4] suggesting that the disease process is already well established by this stage. Cellular inflammation also occurs before the 'epithelial surface erosions', described as a reliable feature of early inflammatory bowel disease by Allison *et al.*[5] Indeed, inflammation and granulomas have been recognised in areas of macroscopically normal bowel.[2 3 6-8]

Early lesions, with features that have yet to be characterised, must occur before established ulceration, inflammation, and granulomas in Crohn's disease. A search for these subtle changes in 'normal' areas of bowel from patients with Crohn's disease may allow a chronological sequence of events to be postulated, which would help the understanding of the pathogenesis of Crohn's disease. We have compared areas of bowel resected from patients with Crohn's disease, ulcerative colitis, and controls which appeared normal macroscopically and showed no cellular inflammation histologically. Using both immersion and perfusion fixation of specimens, together with immunohistochemical staining, we have been able to visualise damage to small mucosal capillaries which is not apparent after routine processing and staining. We have found early, mucosal vascular changes in areas of apparently normal non-inflamed bowel. The areas selected for study were not ulcerated, and showed no morphologically discernible, or only minimal inflammation or fibrosis.

Methods

Small and large bowel resection specimens from 35 patients with Crohn's disease, 12 patients with ulcerative colitis, and 13 controls were either immersion fixed in 10% formalin (13 Crohn's disease, four ulcerative colitis, five controls) or perfusion fixed with 10% normal formalin or 4% paraformaldehyde in phosphate buffered saline at 100 mm Hg (mean arterial pressure).[9] As many of the cases of ulcerative colitis were total colectomies resected for extensive disease, fewer areas of macroscopically normal bowel were available for study. Patients forming the control group included seven undergoing resection for large bowel carcinoma, one with diverticular disease of the colon, one with polyposis coli, and one who had normal bowel removed during excision of an ovarian carcinoma. Blocks of tissue were selected from macroscopically normal areas (>5 cm from tumour) and paraffin processed in the routine way. Sections (4 μm) were cut and stained with haematoxylin and eosin. Sections showing areas of microscopically non-inflamed, non-ulcerated bowel were selected and examined in detail by two independent pathologists, one of whom was kept in ignorance of the diagnosis. Occasionally, in sections included in the study there was a minimal focal surplus of lymphocytes or plasma cells, or both, which on routine histological assessment would usually be regarded as very mild changes within normal limits. Sections were discarded from this study if there was any ulceration, significant inflammation, or fibrosis. Our observations were therefore only concerned with 'preinflammatory' changes in non-ulcerated areas.

Independent opinions were noted, and differences were resolved by consensus and by arbitration by a third histopathologist. 112 sections from patients with Crohn's disease (68 large bowel, 44 small bowel), 56 sections from patients with ulcerative colitis (52 large bowel, four small bowel), and 90 sections from controls

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Diversion colitis and involution of the defunctioned anorectum

A M Roe, B F Warren, A J M Brodribb, C Brown

Abstract

To measure the effects of defunction in the anorectum, 12 patients (seven men and five women aged 59 (44–81) years) were studied after the Hartmann operation. The operation was for septic complications of diverticular disease in nine and sigmoid carcinoma in three patients. Physiology studies were undertaken 1 and 3 months after surgery, and diversion colitis was assessed endoscopically and by mucosal biopsy at 3 months. There was no change in anal sphincter function by three months. Proctometrogram studies, however, showed an appreciable decrease in rectal volume in all cases, by a mean of 35% of the 1 month volume. The maximum tolerable volume at 1 month was 157 (111–210) ml and at 3 months 87 (71–145) ml; $p<0.01$. There was no change in rectal sensation or compliance. Erythema and granularity without gross erosions or ulceration were found at endoscopy. Histology showed abnormalities in all cases by 3 months. The characteristic features were of a chronic inflammatory cell infiltrate with surface exudate, microscopic erosions, and lymphoid follicular hyperplasia. Crypt abscesses were not a feature at this stage and there was no distortion of crypt architecture. After defunction the previously normal rectum is affected by diversion colitis which, at 3 months, is mild but has characteristics that distinguish the changes from those of inflammatory bowel disease. It is associated with progressive rectal stump involution.

(*Gut* 1993; 34: 382–385)

Diversion colitis is the term given to the inflammatory condition occurring in the defunctioned colon and rectum. It is often not apparent clinically until it becomes symptomatic, with pain and discharge of mucus and blood.[1,2] At surgical reanastamosis after the Hartmann operation, the defunctioned rectal stump often seems to have shrunk into the pelvis.

Inspection of the rectal stump in diversion colitis shows mucus plugs, erythema, friability, nodularity, oedema, aphthous ulceration, and erosions with bleeding.[3,4] The mucosal nodularity and ulceration can be seen on double contrast barium enema[4] and inflammation can be shown on In-111 labelled white blood cell scan.[5]

Mucosal biopsy specimens show a spectrum of disease comprising acute and chronic inflammation,[1] crypt abscesses,[1,3] mucin granulomas, and lymphoid follicular hyperplasia with minimal distortion of crypt architecture.[3,6] In severe cases the changes may be difficult to distinguish from those of acute ulcerative colitis.[7,8] In resected specimens the inflammatory process tends to be confined to the mucosa.[3] Hypoplasia, with crypt cell production rates decreased by half those of normal, has been described in the defunctioned rectum.[11] Also, impaired bacterial flora in the defunctioned segment has been found, with a reduction in strict anaerobes and an increase in enterobacteria.[12]

The changes of diversion colitis rapidly regress after surgical reanastamosis.[13] The dependence of colonic epithelial cells on luminal short chain fatty acids is implicated in the aetiology of the condition and successful treatment with topical short chain fatty acids has been reported with regression of the inflammatory changes.[5,10,13]

It is not known how rapidly the changes of diversion colitis occur or whether apparent rectal involution after defunction is related to diversion colitis and sequential physiological changes in the defunctioned anorectum have not been previously reported. This study, therefore, aimed to (i) measure changes in physiological parameters of the anorectum with time after defunction and (ii) to describe accurately the histopathological changes that occur in the early defunctioned anorectum.

Patients and methods

Twelve patients were studied, seven men and five women aged 59 (44–81) years. All had the Hartmann operation, nine for septic complications of diverticular disease and three for sigmoid carcinoma. None of the patients had a diagnosis of inflammatory bowel disease and none had any pre-existing disease of the anorectum.

Physiology studies were undertaken 1 month after operation. This was considered a reasonable time to allow the oversewn rectal stump to heal before pressure volume studies. The studies were repeated at 3 months, before reversal of the operation. Endoscopic and histological assessment of diversion colitis were made at the time of the second physiology studies 3 months after the Hartmann operation.

All patients gave informed consent for the studies, which were approved by the ethical committee of the Plymouth Health Authority.

PHYSIOLOGY

Standard, 4 mm water filled microballoon manometry systems were used. These were attached via an external transducer to a Urodynamics System GR860 (Aspen Medical Ltd, Dingwall, Scotland) for screen display and print out recording of the data.

Anal sphincter manometry was used to measure sphincter length, maximum resting pressure, and maximum squeeze pressure.

Proctometrography was used to measure the first sensation of rectal filling, maximum toler-

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Pathology of the defunctioned rectum in ulcerative colitis

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Abstract

Faecal stream diversion may induce inflammatory changes in the defunctioned segment of the large intestine. These changes are predominantly mucosal, although confusing histological features including granulomas may be present. The pathology of 15 defunctioned rectal stumps has been studied. All patients had previously undergone urgent total colectomy for ulcerative colitis and rectal stumps had been left in situ while they awaited pelvic ileal reservoir construction. All rectal stumps showed predominantly mucosal disease but there were additional features such as florid lymphoid follicular hyperplasia (12 cases), transmural inflammation (nine cases), granulomas (four cases), fissures (eight cases), and changes akin to ischaemia or to pseudomembraneous colitis (four cases). These changes may result from a combination of defunctioning and of active ulcerative proctitis. Some induce a histological appearance that may mimic Crohn's disease. Nevertheless review of all 15 colectomy specimens showed unequivocal ulcerative colitis and none of the patients has subsequently shown any clinical, radiological, or pathological evidence to support a diagnosis of Crohn's disease. Histology of the rectal stump in ulcerative colitis may lead to an erroneous diagnosis of Crohn's disease and the patient may subsequently be denied the advantage of a pelvic ileal reservoir.

(*Gut* 1993; 34: 514–516)

Faecal stream diversion may cause a variety of pathological changes in the colon and rectum. These changes are predominantly mucosal but the pathological features may mimic inflammatory bowel disease, both macroscopically and histologically.[1–6] Chronic inflammation with activity in the form of intraepithelial polymorphs together with crypt abscesses are a common feature while crypt architectural changes are more unusual but when present may mimic ulcerative colitis.[2 3] These pathological changes are seen in the large intestine when faecal stream diversion has been performed for colonic cancer, diverticular disease, or functional bowel disease.[6 7] Occasionally, granulomatous inflammation and even well formed granulomas are seen in diversion colitis[1 3] and lymphoid follicular hyperplasia is also a characteristic feature.[1 2 6]

Patients with acute severe ulcerative colitis frequently undergo total colectomy with ileostomy and preservation of a defunctioned rectal stump. This operation is performed in the hope that the profound inflammatory changes in the rectum will improve with time allowing a definitive operative procedure to be performed at a later date. Excision of the rectal stump and construction of a pelvic ileal reservoir is probably the operation of choice among coloproctological surgeons and patients alike in this situation.[8 9] At this time a defunctioning ileostomy is maintained in order to allow reservoir suture lines to heal. The ileostomy is subsequently taken down and the pelvic ileal reservoir is connected to the faecal stream. We describe a pathological study of the changes in the defunctioned rectum in 15 patients with ulcerative colitis who had undergone such pelvic ileal reservoir surgery.

Methods

Fifteen patients who had undergone total colectomy with preservation of a rectal stump were included in this study. In each case the macroscopic and microscopic features of the original colectomy specimens were reviewed. All resected rectal stumps were received fresh and pinned to a cork board. Specimens were then fixed in formalin for 24 hours, unpinned, and float fixed for a further 24 hours. Two longitudinal strips were cut from the rectal stumps, blocked sequentially, and processed routinely through paraffin wax to 2 μ sections. Subsequent to rectal stump excision, each patient underwent quadruple loop (W) pelvic ileal reservoir construction[10] with a covering temporary ileostomy. After 6 weeks, the ileostomy was taken down and the reservoir was connected to the faecal stream. Each patient has been followed up for between 13 and 28 months (mean 22·5) subsequent to pelvic ileal reservoir construction.

Results

CLINICAL

The patients's age range was 19–61 (mean 30) years and there were nine men and six women. The duration of ulcerative colitis to the time of total colectomy ranged from 12 months to 18 years, with a mean disease duration of 7·5 years. The rectal stumps had been defunctioned for between 2 and 28 months before fashioning of the pelvic ileal reservoir. Follow up of patients subsequent to fashioning of the pelvic ileal reservoir and reversal of ileostomy has shown two with clinical, endoscopic, and histological features of pouchitis.[11] Both patients responded well to metronidazole.[12] One developed anterior strip pouchitis[13] which required surgical treatment. No other surgery has been necessary. In no case was there any clinical, radiological, or pathological evidence of Crohn's disease.

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Cap polyposis – an unusual cause of diarrhoea

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Abstract

'Cap polyposis' is a poorly recognised condition with distinct clinical, sigmoidoscopic, and pathological features that may be confused with other inflammatory conditions of the large intestine including pseudomembranous colitis and idiopathic chronic inflammatory bowel disease. The pathogenesis is unknown but on the basis of the characteristic histological appearances, which are similar to those seen in situations where mucosal prolapse is the underlying mechanism, it has been suggested that the latter may be an important aetiological factor. Two cases are described. Histological features in the first (presence of intramucosal elastin) and clinical features in the second (rectal prolapse) support the above hypothesis.
(*Gut* 1993; 34: 562–564)

'Cap polyposis' was first described by Williams, Bussey, and Morson in 1985.[1] This poorly recognised condition has distinctive clinical, sigmoidoscopic, and pathological features. The pathogenesis is unknown but the histological appearances resemble those seen in solitary rectal ulcer syndrome or in areas of prolapse – for example, adjacent to diverticula or in relation to prolapsing colostomies. It has therefore been postulated that prolapse may be an important aetiological factor. Two cases are described in which the clinical and histological features may point to a possible pathogenic mechanism.

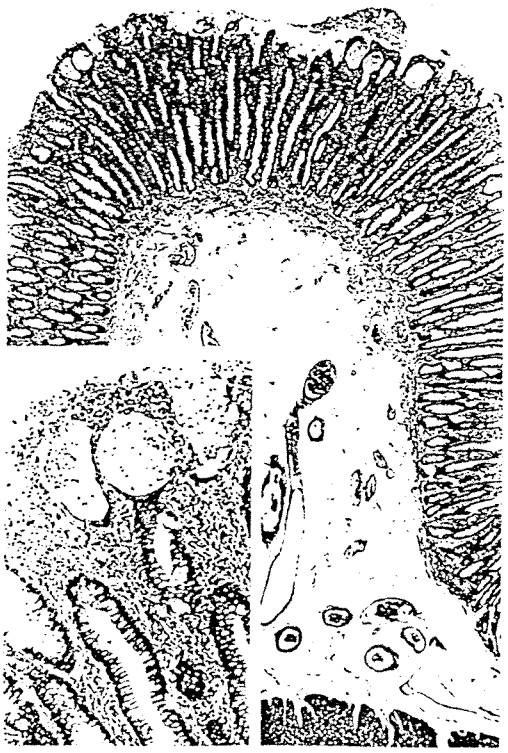

Figure 1: Low power view of a typical polyp with granulation tissue cap (high power inset) (original magnification ×17; high power inset ×87).

Case 1

A 68 year old white man presented in September 1988 with weight loss (approximately 1 st (6 kg) over the previous year), lower abdominal pain, and persistent watery diarrhoea. He had not noticed any blood or mucus. Barium enema showed marked spasm in the mid sigmoid colon associated with a localised area of diverticulosis. This was not, however confirmed subsequently. Initial biopsy specimens were thought to be suggestive of pseudomembranous colitis but examination of stool for *Clostridum difficile* toxin was negative and treatment with metronidazole was unhelpful. Later sigmoidoscopy and biopsy showed changes thought to be more suggestive of inflammatory bowel disease with 'pseudopolyps'. Treatment with sulphasalazine and prednisolone was unsuccessful and the patient underwent a left hemicolectomy in February 1990. The histological findings were multiple metaplastic polyps separated by normal mucosa with no evidence of inflammatory bowel disease.

Unfortunately the patient's symptoms recurred and 5 months later he presented again with a 2 month history of persistent diarrhoea which now contained copious amounts of mucus. Sigmoidoscopy showed multiple haemorrhagic polyps in the rectum. These occurred on the apices of the transverse mucosal folds and were separated by normal mucosa. Microscopic examination of biopsy specimens showed ulcerated inflamed mucosa with elongated tortuous crypts attenuated towards the mucosal surface. Review of the sections taken from the previous colectomy specimen showed polyps at the apices of exaggerated mucosal folds with similar histological features to those described above. They were covered by a 'cap' of inflammatory granulation tissue (Fig 1). The intervening mucosa was normal. The appearances were those of cap polyposis.

The patient was treated with hydrocortisone and mesalazine enemas. These were unsuccessful and a total colectomy with ileostomy was performed, from which he made an uneventful recovery. Macroscopic examination showed sessile haemorrhagic polyps on the apices of mucosal folds over the distal 12 cm of the specimen. The mucosa between the polyps and proximal to them was normal (Fig 2). Microscopic features were as described above. Sections from the two resection specimens were examined with an orcein stain for elastin fibres.[2] Intramucosal elastin was present in small quantities at the edges of some of the cap polyps (Fig 3).

Case 2

A 65 year old Belgian woman presented with a 6 month history of recurrent mucoid diarrhoea. Previous investigations had been inconclusive and a differential diagnosis of infection, solitary

GASTROINTESTINAL PATHOLOGY SOCIETY

Sunday, March 12 1:30 p.m. GRAND BALLROOM CENTER

Update on Pathology of the Stomach

Moderator: Harry S. Cooper, Fox Chase Cancer Center, Philadelphia, PA

1:30 From Babel to Houston - via Sydney. The Continuing Saga of the Classification of Gastritis
Robert M. Genta, Baylor College of Medicine, Houston, TX

2:00 Polyps of the Stomach
Dale C. Snover, University of Minnesota, Minneapolis, MN

2:30 Markers of Precancerous Gastric Lesions
Pelayo Correa, Louisiana State University Medical Center, New Orleans, LA

3:00 Recess

3:30 Miscellaneous Forms of Gastritis
David Owen, University of British Columbia, Vancouver, BC

4:00 Gastric Involvement by Low Grade Lymphomas: Differential Diagnosis and Clinical Implications
Nancy Lee Harris, Harvard Medical School, Boston, MA

4:30 Discussion and Questions