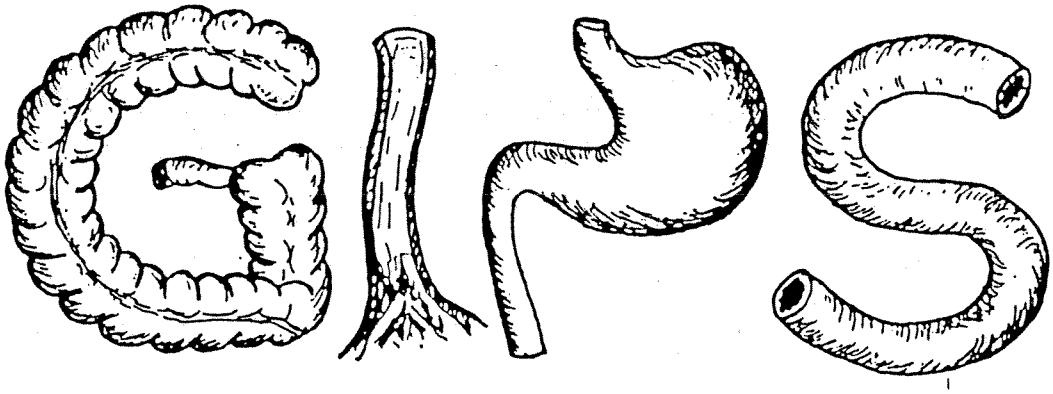

THE GASTROINTESTINAL PATHOLOGY SOCIETY NEWSLETTER

GIPS Newsletter - Fall/Winter 1995
Volume 13, No. 1

1995-96

OFFICERS AND EXECUTIVE COMMITTEE OF THE GASTROINTESTINAL PATHOLOGY SOCIETY

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EMORY UNIVERSITY HOSPITAL
DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE
1364 Clifton Road, N.E. Atlanta, Georgia 30322

OFFICE OF DIRECTOR
DIVISION OF ANATOMIC PATHOLOGY

(404) 727-7009

December 7, 1995

Dear GIPS Member:

Enclosed is a copy of the GIPS Bylaws as revised by the ad hoc committee consisting of Patrick Dean, Daniel Sheehan, Robert Petras, and me.

We will vote on the acceptance of these bylaws, and the nullification of the previous version, at our annual Business Meeting in March, at the U.S.C.A.P. meeting in Washington, D.C. If you know that you will NOT attend that meeting, I ask that you assign me your proxy by returning the bottom portion of this letter.

I hope to see you in March.

Sincerely,

Bob Pascal

Robert R. Pascal, M.D.
President

.....

I will not attend the 1996 GIPS annual Business Meeting, and I hereby assign my proxy for the vote on the revision of the bylaws to Dr. Robert R. Pascal.

_____
Signature

_____
Printed Name

BY-LAWS OF THE GASTROINTESTINAL PATHOLOGY SOCIETY

Revised December 7, 1995

Article I

Name: The name of the organization shall be the Gastrointestinal Pathology Society, herein abbreviated as GIPS.

Article II

Objectives: The objectives of the GIPS are to disseminate and to increase knowledge about pathology of the gastrointestinal tract and to encourage the development of gastrointestinal pathology as a subspecialty.

Article III

Membership:

A. Categories of Membership -

1. Regular Member - Any individual who has completed postdoctoral medical training with demonstrated interest and involvement in the field of gastrointestinal pathology as determined by the Membership Committee.

2. Associate Member - Any person holding a doctorate (or doctorate-equivalent degree) with an interest in gastrointestinal pathology. This membership is limited to five years and cannot be renewed. Associate members may apply for Regular membership in the usual way at any time if postdoctoral medical training has been completed.

3. Emeritus Member - Any regular member who, upon reaching the age of 65 years, has requested this status by letter to the Secretary-Treasurer, and whose request has been approved by the Executive Committee.

4. Inactive Member - A member can become "inactive" by requesting this status in writing to the Secretary-Treasurer. This status would be considered appropriate for a member who has become ill or incapacitated and is not presently actively practicing pathology. An inactive member would be excused from paying annual dues, but would maintain the full benefit of society membership.

This status can change by request to the secretary treasurer.

B. Conferring of Membership -

Nomination of an individual to Regular membership can be made by any Regular member. An application form (designed by the Membership Committee) must be countersigned by the sponsoring Regular member and then sent to the Secretary-Treasurer. The Membership Committee will review the applications and recommend approval or disapproval by the Executive Committee of the GIPS.

Nomination for Associate membership can be made by any Regular member. Applicants for Associate membership will not need to provide evidence of their involvement with GI pathology in their application. Such decision of involvement will rest with the sponsoring regular members. The procedure for application, review, and conferring of Associate Membership is otherwise identical to that for Regular Membership.

Membership can be terminated by written resignation addressed to the President or Secretary-Treasurer.

D. Right of Members -

Only Regular members will have the right to hold office and to vote. Each Regular member has one vote.

All members have the right to participate in the scientific sessions and in deliberations and discussions at the business meeting.

No member shall use the name, property, or the organization of the GIPS for personal benefit.

Only currently elected officers shall represent the GIPS in official business.

Article IV

Governing Body:

A. Elected Offices -

1. President: term of office one year.

2. Vice-President/President-Elect: serves on year as Vice-President and the next year as President.

3. Secretary-Treasurer: term of office three years.

B. Election of Officers -

Any Regular member of GIPS is eligible to hold office. Nominations will be recommended by the Membership Committee and may be offered from the floor by a Regular member at the Annual Business Meeting, or by mail ballot if the election is so held. Election ordinarily will be held at the Annual Meeting, or by mail ballot if deemed necessary by the Executive Committee. When the election is held at the Annual Business Meeting, a simple majority vote of the Regular Members in attendance is required to elect the officer. A simple majority vote of the Regular members in case of a mail ballot, is required to elect the officer.

C. Duties of Each Officer -

1. The President shall be the principal executive officer of the GIPS. The President shall preside at all meetings, serve as chairman of the Executive Committee, and take responsibility as a representative of the GIPS. The President officially receives donations, bequests, or gifts to the GIPS on behalf of the GIPS. The President shall make all appointments to the Standing Committees, as described in Article V. The President will also appoint a members of the GIPS to complete the term of any member of a Standing Committee whose position on that Committee is vacated. Ad hoc committees are appointed by the President as needed. The President will appoint the Editor of the Newsletter.

2. The Vice-President, in absence or incapacity of the

President, shall perform the duties of the President. The Vice-President shall serve on the Executive Committee.

3. The Secretary-Treasurer shall keep minutes of the Annual and Executive Committee meetings, distribute notices to members of GIPS, keep custody of documents of GIPS, including mortgages, deeds, and contracts that the Executive Committee has approved, serve on the Executive Committee, receive membership applications and dues, keep records of financial documents for governmental agencies, banks or other financial institutions with approval of the President for expenses used solely for the GIPS. All such disbursements will be reported at the Annual Meeting, as part of the financial report of the Secretary-Treasurer.

D. An Officer may not succeed him/herself in office.

Article V

Standing Committees:

A. Executive Committee.

1. The Executive Committee shall consist of the current officers, the past president, and chairman of the standing committees.

2. The Executive Committee shall:
   a. Represent the GIPS in official business.
   b. Carry out the directives and policies approved by the membership.
   c. Approve or disapprove all requests for change in membership status.
   d. Organize and coordinate all meetings of the GIPS.
   e. Exert leadership in the development and implementation of scientific programs according to the above stated objectives of the GIPS.
   f. Deal specifically with matters related to the incorporation of the GIPS.

B. Membership and Nominating Committee

1. The Membership and Nominating Committee shall consist

of six members appointed by the President. The term of office will be three years, with terms staggered so that two members are appointed each year. One member of the Committee will be appointed or reappointed each year by the President to serve as Chairperson.

2. The Membership and Nominating Committee shall annually prepare a slate of nominations for officers of the GIPS to be presented to the membership at the Annual Business Meeting, or by mail ballot, if deemed necessary by the Executive Committee.

C. Education Committee. The Education Committee shall consist of six members appointed by the President. The term of office will be three (3) years, with terms staggered so that two members are appointed each year. The President will appoint one member of this Committee to serve as Chairperson for three (3) years. This Committee shall plan all scientific meetings of the GIPS, and will prepare the programs for such meetings to be distributed by the Secretary-Treasurer and by the appropriate officials of any other organization sponsoring such programs. The Executive Committee will provide the Education Committee with an annual budget to defray costs of invited speakers as deemed appropriate by the Education Committee and as approved by the Executive Committee.

D. Publications Committee. The Publications Committee shall consist of the Editor of the Newsletter, and the GI Section Editor of the American Journal of Surgical Pathology, whose terms shall coincide with their editorial appointments, a Senior Advisor, appointed by the President for a term of three (3) years, and one member-at-large, appointed by the President for a term of three (3) years. The Editor of the Newsletter shall serve as Chairperson of the Publications Committee. The Publications Committee shall review all material to be submitted for publication in the name of the GIPS, and will make its recommendation to the Executive Committee regarding the submission of such material for publication. Final approval for submission of material for publication will rest with the Executive Committee. Once approval is granted by the Executive Committee, the Publications Committee will coordinate the arrangements for submission, and publication with the appropriate publisher(s) and editor(s).

E. Training Programs and Awards Committee. The Training Programs and Awards Committee shall consist of six members appointed by the President. The term of office will be three years, with terms staggered so that two members are appointed each year. One member of the Committee will be appointed or reappointed each year by the President to serve as Chairperson. This Committee will:

1. Encourage organized graduate training programs in Gastrointestinal Pathology, and will collect and disseminate information about such programs, and will identify and assist in the development of sources of support for trainees.
2. Review all applications for Micrograms, and recommend to the Executive Committee, recipients of the GIPS Micrograms for research in Gastrointestinal Pathology.
3. Select the recipient of the annual GIPS prize for the most meritorious platform or poster presentation by a pathologist-in-training, on a subject of Gastrointestinal Pathology, at the Annual Meeting of the United States and Canadian Academy of Pathology.

Article VI

Scientific and Business Meeting.

This meeting shall be held annually. The time and place will be determined by the Executive Committee. A quorum must be present to conduct business, but the scientific meeting can proceed in absence of a quorum.

Article VII

Amendments:

Amendments to the by-laws may be suggested in writing to the Secretary-Treasurer by any Regular member at least two months prior to the Annual Meeting. If approved by the Executive Committee, these amendments need to be accepted by a two-thirds majority vote of the Regular members at the Annual Meeting.

Article VIII

Dues and Assessments:

The amount of annual dues shall be determined each year by the Executive Committee. Special assessments may be made by the Executive Committee. New applicants shall be subject to assessments and dues if they participate in GIPS activities while being considered for membership.

After acceptance, new applicants shall be required to pay an initial fee not to exceed that of the annual dues.

Any member in arrears of dues for more than one year, failing satisfactory explanation, shall be dropped from membership. Such member may be reinstated on approval of the Executive Committee.

Article IX

Sunset Provision and Liquidation:

A. Sunset Provision.

Every five (5) years the President shall appoint an ad hoc committee to review the GIPS and its bylaws, and will, within the following year, prepare, and present to the membership its findings and recommendation concerning the continuation of the Society. If this does not occur the GIPS will be dissolved automatically. The ad hoc committee shall consist of the current President, the immediate Past-President, the President-Elect, and two members-at-large.

B. Liquidation.

Motion for liquidation must be made in writing to the Executive Committee at least two months prior to the Annual Meeting. A 2/3 vote of Regular members present at the annual meeting is required. In the event of liquidation, after payment of obligations, all remaining assets pass to the United States and Canadian Academy of Pathology (changed from the International Academy of Pathology, March 15, 1992).

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Tales of the Ampulla of Vater: XXIX

By the shores of Duodenum
where there flows the River Bile
Stern Ampulla faced his Villi
he was weary ne'er a smile.

After signing out the surgicals
all day with deep frustration
Their misspelling of the lesions
gave him cause for consternation.

So upon the slopes of Oddi
the assembled Villi knelt
To hear Ampulla's discourse
his gravity they felt.

Let us start with *Peutz* and *Jeghers*
then go on to *Dukes* and *Crohn*
Jejunum and the *ileum*
not spelled like it's a bone.

The Villi mumbled as they wrote
Peutz-Jeghers ends in "s"
But Chron Cronh Crone's impossible
we'll never pass this test.

Oh *Cronkhite-Canada* he cried
Menetrier and *sprue*
Yes *Dieulafoy* and *Hirschsprung*
Laennec and *aphthous* too.

Strongyloides phrygian
of course *hydatidosis*
Bezoars and *typhlitis*
and *mucoviscidosis*.

Spell *mucous* as an adjective
and *mucus* when a noun
The rule's the same for *villous*
no difference in the sound.

The Villi mumbled *mucous mucus*
one of them's a noun
Then *villous villus* Vater will us
learn or he will frown.

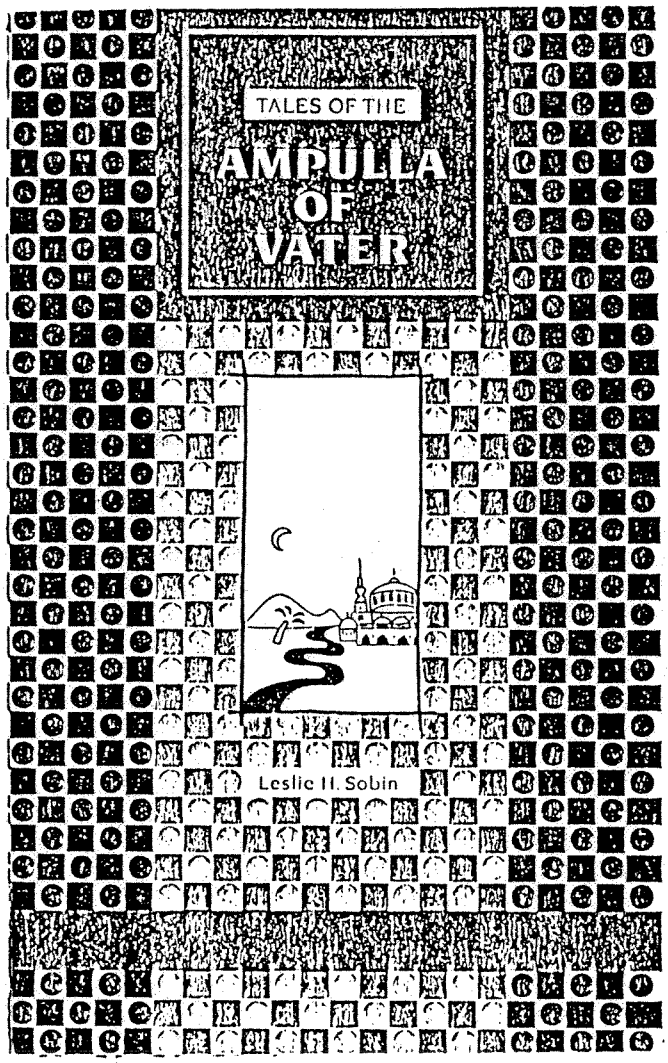
Langhans is not *Langerhans*
both cells and one an islet
And *frequency's* not *incidence*
makes editors turn violet.

Intussusception all do dread
and *Meckel's* divertic
Barrett has a double "t"
and *syphilis* makes you sick.

Thus great Ampulla vented spleen
while Villi quaked with fear
Forgive us dearest Vater
who has no living peer.

Apply ourselves we surely will
we'll start again today
To spell correctly trust in us
we will not disobey. Praise Vater.

Leslie H. Sobin, M.D.



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GASTROINTESTINAL PATHOLOGY SOCIETY

ASCP COMPANION MEETING

SEPTEMBER 16, 1995, NEW ORLEANDS, LA

UPDATE ON COLORECTAL CARCINOMA

TOPICS AND SPEAKERS

- Nongenetic Indicators of Prognosis in Colorectal Carcinoma - Old Wineskins - New Wine
  Patrick Dean, MD, Baptist Memorial Hospital, Memphis Tennessee

- Molecular Genetics of Colorectal Carcinoma
  Ruth Padmore, MD, Ph.D, Fox Chase Cancer Center, Philadelphia, Pennsylvania

- Dysplasia and Early Invasive Carcinoma in Colorectal Polyps and in Inflammatory Bowel Disease
  Robert R. Pascal, MD, Emory University Hospital, Atlanta, Georgia

- Endoscopically Removed Malignant Colorectal Polyps, Clinicopathological Correlations, and the Role of the Pathologist
  Harry S. Cooper, MD, Fox Chase Cancer Center, Philadelphia, Pennsylvania

- Update on Staging of Colorectal Tumors and Its Relation to Other Prognostic Factors
  Leslie H. Sobin, MD, Armed Forces Institute of Pathology, Washington, DC

NONGENETIC INDICATORS OF PROGNOSIS IN COLORECTAL CANCER
OLD WINESKINS - NEW WINE

Patrick J. Dean, M.D.
Baptist Memorial Hospital and the University of Tennessee
Memphis, Tennessee

With simple genius, Cuthbert Esquire Dukes cut to the heart of staging of adenocarcinoma of the colon and rectum(1). Dukes observed that patient survival was related to two activities of the neoplasm -- its vertical penetration into and through the bowel wall and its spread to regional lymph nodes. All subsequent permutations of the Dukes system have been tied to these two characteristics(2). Today's investigators have the advantage over Dukes by the availability of sophisticated technology. Advanced statistical methodology driven by modern computers ("computer-assisted multivariate statistical analysis") allows putative prognostic factors to compete independently with each other thus permitting their relative importance to emerge.

Today we will discuss six morphological features -- some recently described -- that impact staging of colorectal carcinoma. It is important to note that we are referring to histopathological features present in hematoxylin and eosin-stained tissue sections that are thus readily available for consideration by all pathologists [molecular biologists need not apply!].

DEPTH OF TUMOR INVASION. The tradition inherited from Dr. Dukes casts the main prognostic breakpoint at the interface of the muscularis propria externa and pericolic fibroadipose tissue. Put baldly, intramural tumor is good and extramural extension is bad. However, practicing pathologists recognize that extramural spread covers a wide spectrum. Some carcinomas barely transgress the muscularis propria externa while others permeate widely throughout the pericolic fat. Common sense dictates that patient prognoses for these differing scenarios may be dissimilar.

Harrison et al have given form to this rational assumption(3,4). In their work, the group of patients with modest degrees of invasion through the muscularis propria carry prognosis similar to those patients with intramural tumor, whereas patients with locally widespread tumor fare less favorably. In fact, no survival difference could be appreciated

for any level of invasion short of extensive local tumor dissemination.

EXTRAMURAL VEIN INVASION. From the time of Dukes, extramural venous invasion by tumor has been recognized as an adverse prognostic indicator. [Intramural venous invasion carries no weight]. In all large studies of resected colorectal carcinoma, vein invasion relates to outcome in univariate analysis(5). In some studies, it retains independent prognostic significance in multivariate analysis(3). Suffice it to say that irrespective of its final resting place in the staging scheme, extramural vein invasion should not go unnoticed.

TUMOR GROWTH PATTERN. Ming first called attention to the pattern of tumor invasion in resected gastric carcinoma(6). An expanding, bulbous, pushing tumor border is preferable to knife-like, infiltrative tumor penetration.

The same applies to resected colorectal carcinoma. In the recently described Jass staging system, tumor growth pattern achieved independent prognostic significance in multivariate analysis, with the expanding pattern importing improved survival(7-9). Unfortunately, the expanding growth pattern occurs in a relative minority of colorectal cancers, although in the individual case it can be used to prognostic advantage.

PERITUMORAL LYMPHOCYTIC INFILTRATION. Measures of host immune response to neoplasia have long fascinated the medical community. Peritumoral lymphocytic infiltration -- the cuff of mononuclear cells that borders the leading edge of invasive colorectal carcinoma -- has been shown by Jeremy Jass to have independent significance as a prognostic indicator in colorectal cancer in multivariate statistical analysis(7-9). Jass' data go so far as to indicate that patients with intramural tumor exhibiting an expanding growth pattern and conspicuous peritumoral lymphocytic infiltration have 100% 5-year survival(8)!

CROHN'S-LIKE LYMPHOID REACTION. Graham and Appelman first observed the collection of lymphoid aggregates at the interface of the muscularis propria externa and

pericolic fibroadipose tissue in advance of invasive colorectal carcinoma(10). Christened the Crohn's-like lymphoid reaction, it was noted to be prognostically significant in a univariate analytical model. In a study of 350 resected right-sided colonic carcinomas, Harrison et al found the Crohn's-like lymphoid reaction to be an independent indicator of prognosis by multivariate statistical analysis(4). Although peritumoral lymphocytic infiltration was a significant indicator of prognosis in univariate analysis in the Harrison study, it was supplanted by the Crohn'-like reaction in the multivariate analysis. A happy coincidence with the Crohn's-like lymphoid reaction is the ease with which it is visualized. Harrison et al noted 96% interobserver agreement on the presence or absence of a Crohn's-like response; the high degree of correlation was ascribed to ready recognition of lymphoid aggregate formation.

METASTATIC TUMOR NODULES IN PERICOLIC FAT. When examining resected colorectal carcinoma, pathologists not uncommonly encounter ovoid nodules of tumor unassociated with recognizable lymph node structure in the pericolic fibroadipose tissue(11). It is common practice to lump these nodules together with lymph node metastases on the assumption that they represent obliterated nodal tissue. Yet Harrison et al showed metastatic tumor nodules in pericolic fat to have prognostic significance independent of lymph node metastasis(4). Why?

Stiles et al performed serial sectioning of 57 nodules to determine their association with underlying tissue structures(12). Not surprisingly, the majority of metastatic tumor nodules in pericolic fat represent vein invasion, although some are also related to nodal obliteration and neural/perineural involvement. Either way, all bear adverse prognostic significance.

Depth of invasion, vein invasion, growth pattern, lymphocytic infiltration, Crohn's-like reaction and tumor nodes in pericolic fat may serve to modify and give nuance to the traditional staging of patients with colorectal carcinoma. They should not be construed as subversive attempts to undermine the TNM staging classification! At the same time, TNM must come to grips with newly recognized prognostic indicators that by computer-

assisted multivariate statistical analytical technology offer additional prognostic information for patient care.

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The Molecular Genetics of Colorectal Cancer

Ruth Padmore MD PhD
Fox Chase Cancer Center
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Recent advances in the molecular genetics of colorectal adenocarcinoma have allowed insight into the origin of a variety of inherited colonic polyposis syndromes. The hamartomatous syndromes (Peutz-Jeghers syndrome, Cowden's syndrome, juvenile polyposis) have not yet been characterized at the molecular level.

Lynch syndrome (hereditary non-polyposis colonic cancer, HNPCC) is an inherited condition characterized by three or more relatives with colorectal cancer in a family, occurring before 50 years of age and affecting at least one first degree relative and at least two generations. The observation of microsatellite instability in Lynch syndrome has lead to the identification of germline mutations in mismatch repair genes including one MutS (hMSH2) and three MutL (hMLH1, PMS1, PMS2) homologues. A specific subset of Turcot's syndrome (colonic polyps and glioblastoma) have an underlying heterozygosity for mutations in hMLH1, whereas the majority of Turcot's syndrome families have mutations in the APC gene and medulloblastomas as the brain tumor manifestation. The Muir-Torre syndrome (colonic polyps and multiple sebaceous tumors) has been associated with germline mutations in hMSH2 close to the highly conserved "P loop" domain responsible for ATP binding.

Familial adenomatous polyposis (FAP) syndrome is an autosomal dominant trait associated with mutations of the adenomatous polyposis coli (APC) gene. The majority of mutations in the most severe form of the disease occur in the large terminal exon (exon 15). This portion of the gene codes for catenin binding domains; catenins are important in contact inhibition, causing cells to stop dividing once the epithelial sheet is complete. A dominant negative phenotype

is thought to be conferred by the formation of mutant/wild type homodimers mediated through the coiled coils at the amino-terminus of the protein. Attenuated adenomatous polyposis coli (AAPC or flat adenoma syndrome) is associated with frameshift or nonsense mutations in the 5' end of the gene; exon skipping modified by splicing factor levels may account for the variable phenotype in members of the same family.

Mutations in these and other tumor suppressor genes and oncogenes have also been identified in sporadic colorectal cancer. Studies by Vogelstein and co-workers (Vogelstein and Kinzler, 1994) have correlated specific mutations with the step-wise progression from adenoma to carcinoma as follows: FAP with hyperproliferative epithelium, hypomethylation with early adenoma, k-RAS with intermediate adenoma, DCC with late adenoma and p53 with carcinoma.

General Reading:

The Molecular Genetics of Cancer. Volume LIX, Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor Laboratory Press, 1994.

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DYSPLASIA AND EARLY ADENOCARCINOMA OF THE COLON AND RECTUM

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General Comments.

Since many of the morphologic features of malignant progression in colorectal mucosa are similar in individuals with and without chronic inflammatory bowel disease (IBD), they are presented together, with appropriate subheadings to highlight differences between these two groups. The following definitions will be used throughout this section:

Dysplasia is an unequivocal, but non-invasive neoplastic transformation of the intestinal epithelium that can be recognized by its abnormal cellular and architectural alterations. Only two grades - *low-grade dysplasia*, and *high-grade dysplasia* - will be referred to (1). High-grade dysplasia encompasses changes previously called *carcinoma-in-situ*, and replaces that term.

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

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

Polyp refers to any abnormal elevation on the mucosal surface, whether due to a displacement from underlying expansion (e.g. lipoma), inflammatory reaction, non-neoplastic cellular proliferation (e.g. repair, hyperplasia), benign neoplasia, or malignancy. The common epithelial polyps of the colorectum are of two types - *hyperplastic polyps*, and *adenomas*. (2). Adenomas are usually subdivided histologically into *tubular adenomas*, *villous adenomas*, and *tubulovillous adenomas*.

Pseudopolyp is an outdated term that will not be used. In its place, more precise terms, descriptive of the histologic appearance of the mucosal elevations in inflammatory bowel disease (IBD) will be employed.

The adenoma-carcinoma sequence is accepted as the usual progression in the development of the vast majority of colorectal adenocarcinomas (3). The events in benign to malignant transformation are believed to take place in both uninflamed and chronically inflamed intestinal mucosa, but at an accelerated pace and with greater frequency in IBD.

Histologic Features.

The histologic characteristics of colorectal adenomas are well established (2). Whether the polyp is tubular or villous, the surface epithelial cells are tall, with crowded, elongated, and pseudostratified nuclei that lack significant pleomorphism. Cell division is present at all levels of the neoplastic, but benign, gland. The adenomatous mucosa itself is regarded as low-grade dysplasia. When, at the base of the tubular or villous adenoma, there is histologically normal colonic mucosa, the polyp has

probably been completely removed. If the endoscopist is confident that he has excised the entire polyp, no further therapy is advised for this lesion. .

High grade dysplasia is characterised by cytologic features of malignancy, and true stratification of nuclei. In contrast to the simple adenoma, nuclei are pleomorphic, rounded, and exhibit variable abnormalities of chromatin distribution. The combination of these cytologic and architectural abnormalities is necessary for a confident diagnosis of high grade dysplasia. The basement membrane zone is intact, and the lamina propria is normal. High grade dysplasia may be present as a focus, or several foci, within a tubular or villous adenoma. If the polyp has been completely removed, as evidenced by normal mucosa at its base, no further treatment is necessary for that lesion. High grade dysplasia may occur with or without adjacent low grade dysplasia in either flat or elevated mucosa in inflammatory bowel disease. In that setting, the implications for further treatment are far different from those that apply to the isolated adenoma in the non-colitis patient (see below).

Intramucosal carcinoma in an adenoma of the colon or rectum usually, if not always, arises in an area of high-grade dysplasia. Abnormal glands with easily recognized cytologic and architectural features of malignancy invade only the lamina propria, and are surrounded by an early desmoplastic reaction. The remainder of the polyp is composed of typical pseudostratified, adenomatous epithelium with either a tubular, a villous, or a tubulovillous pattern. A complete endoscopic polypectomy is considered to have been curative. Intramucosal carcinoma in the setting of ulcerative colitis or Crohn's disease is an indication for total colectomy.

Dysplasia in Inflammatory Bowel Disease

The criteria for the diagnosis of colorectal dysplasia were first codified in mucosal specimens from patients with ulcerative colitis (4). Many earlier reports recognized these changes, and terms such as "atypia", "anaplasia", "precancer", and "carcinoma-in-situ" were used in their description (3, 5, 6). Low-grade dysplasia is characterized by mucosal changes resembling those seen in adenomas (1); enlarged crypts lined by tall epithelial cells with elongated, hyperchromic, pseudostratified, basal nuclei, and a failure of those cells to normally mature and differentiate into normal goblet and absorptive cells at the surface. Some mucin may be produced by the neoplastic cells, and "dystrophic" goblet cells have been described in dysplasia (4, 7). The surface of low-grade dysplastic areas in IBD may be villous, but that feature alone does not increase its grade. In high-grade dysplasia, there is true stratification of the neoplastic cells, and that is its most important distinguishing feature (1). Other features of high-grade dysplasia include a greater degree of cytologic variance, with nuclear pleomorphism, in which they more resemble the cells of invasive carcinoma than the tall, regular cells of an adenoma. In very small areas of high-grade dysplasia, there is a tendency of cells to form expansile nests that appear to push the adenomatous cells to their sides. Mitotic activity at all levels of the crypt is seen in dysplasia of both low and high grades, but the basal polarity of nuclei is maintained in low-grade lesions. The grade of dysplasia in a given specimen is determined by the most severe changes present, but "an increase in rating from low- to high-grade dysplasia based solely on the appearance of high-grade features in one or two crypts is probably not justified" (4). Just how much high-grade dysplasia is necessary to justify its diagnosis in a specimen is

not universally agreed upon, but the statement quoted might imply that its recognition in three or more crypts is sufficient.

The recommendations of the Inflammatory Bowel Disease - Dysplasia Morphology Study Group in 1983 (4) included three major diagnostic categories, namely, "Negative for Dysplasia", "Indefinite for Dysplasia", and "Positive for Dysplasia", the latter graded as above. The category of Indefinite is used when the histologic changes meet some, but not all of the criteria for dysplasia, and thus is usually applied to equivocal cases of low-grade dysplasia. This category is also used when changes of low-grade dysplasia are seen in actively inflamed mucosa, since reparative epithelium may show identical features. The Indefinite category was further subdivide into "Probably positive", "Probably negative", and "Unknown". In this author's opinion (1), that subdivision is not justified, and should be abandoned. The criteria for such categorization are highly subjective, and the use of the subcategories is of no significant help in patient management. It is far more informative to use an unmodified, honest statement of "indefinite" and to state the reason, than to attempt to push a diagnosis too far and to risk misleading the clinician with undefined probabilities. The category "Indefinite for Dysplasia" should be used as a diagnostic entity in mucosal biopsy specimens from patients with IBD, and the clinician should be familiar with its meaning and implications for further patient examination (see below).

When activity (acute cryptitis) is present in an IBD specimen, unequivocal changes of high-grade dysplasia may still be recognizable and reportable, but caution should be undertaken in interpreting cytologic changes that are seen in both reparative epithelium and low-grade dysplasia. It has been suggested that dysplastic epithelium is resistant to involvement by acute inflammation (4). Nuclear hyperchromism, enlargement, mitotic activity, and delayed maturation are all features of regenerative epithelium, and cells in the germinative, basal zone of the normal crypt have morphologic similarities to those of adenomatous mucosa.

Although less epidemiologic data exist concerning carcinoma in Crohn's disease, it is reasonable to apply the same approach to the evaluation of dysplasia. The incidence of carcinoma in Crohn's disease, although lower than that in ulcerative colitis, is significantly higher than that in the general population (8, 9), and its association with dysplasia has been reported (10-15). In a large, retrospective study (16), clinicopathologic features, such as duration of disease, multiplicity of tumors, incidence of dysplasia, and survival rates, were strikingly similar among patients with Crohn's disease and ulcerative colitis complicated by colorectal carcinoma.

Dysplasia in Colorectal Adenomas

Adenomas are the precursors of colorectal carcinoma in the general population (3). Although adenomas and hyperplastic polyps share some common risk factors, they are believed to be unrelated sequentially, and the latter have no malignant potential (2, 17). A spectrum of histologic changes exists between the completely benign adenoma and invasive carcinoma, and the progression includes identifiable high-grade dysplasia. High-grade dysplasia in an adenoma is recognized by the same criteria as those just described for its recognition in IBD. What, then, is low-grade dysplasia in the non-colitis patient? It is the adenoma itself (1, 18). Analogous to the transformation of non-neoplastic mucosa to low-grade dysplasia in IBD, and also analogous to the original

concept of the transformation of normal cervical epithelium to mild dysplasia or CIN-I, adenomatous epithelium can be equated with low-grade dysplasia whenever it occurs in the bowel. There is no reason to attempt to change the nomenclature of adenomas, but in examining adenomas for additional cancer risk factors, only one grade of dysplasia - high-grade - is recognized. The "indefinite" category is not used in this setting. Some pathologists have continued to grade dysplasia as "mild", "moderate", and "severe". This deviates from the standardized nomenclature of the IBD-Dysplasia Study Group, and there is no reason, other than indecision, to employ the middle gradation (personal opinion). In adenomas, it is wiser to be conservative when a small focus of equivocal high-grade dysplasia is encountered.

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

Intramucosal Carcinoma

Intramucosal carcinoma will be found more often in a polypectomy specimen than in a mucosal biopsy specimen from a patient with IBD. The larger the adenoma, the greater the chance of encountering carcinoma. There will usually be a zone of high-grade dysplasia above the intramucosal carcinoma. When intramucosal carcinoma occurs, it is frequently surrounded by an early desmoplastic reaction that replaces the normal immunocyte population of the lamina propria. Sometimes, the invasive epithelium is less differentiated than the intraepithelial malignancy. Invasion into, but not through, the muscularis mucosae is still intramucosal carcinoma. The diagnosis of intramucosal carcinoma may be extremely difficult because of the complex convolutions of adenomatous glands, especially in villous adenomas. When in doubt, even after examining multiple levels of a block, it is better to be conservative and ignore an equivocal focus of intramucosal carcinoma, since it has no more significance in most cases than high-grade dysplasia. The lamina propria of adenomas, as well as that of normal colonic mucosa, is devoid of lymphatics (19), and it is thus believed that intramucosal carcinoma has no ability to metastasize. Even though there are lymphatics

in the muscularis mucosae, carcinomas that invade only that layer in a pedunculated adenoma do not metastasize (20, 21). In reporting intramucosal carcinoma in an adenoma, it is important to assess the completeness of the polypectomy and the presence or absence of invasive tumor at the resection line. The histologic grade of the carcinoma, and the observation of lymphatic invasion are probably more significant in tumors that invade the submucosa, but data to support that are currently being analyzed. When including the diagnosis of intramucosal carcinoma in a complete polypectomy specimen report, I will append a comment concerning the extent of invasive tumor, its potential, or lack thereof, to metastasize, and my opinion that the lesion has been adequately treated. When an adenoma containing intramucosal carcinoma has been only biopsied, removed in piecemeal fashion, or is suspected of having been only partially excised, I report that no definitive assessment of completeness of removal can be made, and that there is a possibility that more deeply invasive carcinoma has been left behind. A decision concerning additional treatment is then made by the endoscopist or surgeon after all pertinent findings are discussed.

A special subgroup of adenomas that has received recent study is the flat adenoma (22-27). These are small (usually not exceeding 1 cm), plaques of tubular adenomatous mucosa, unassociated with IBD, that have a high incidence of high-grade dysplasia, and a high association with synchronous and metachronous invasive colorectal carcinoma. I have seen one such lesion that had given rise to a minuscule invasive carcinoma. Complete endoscopic removal of a microinvasive carcinoma arising in a flat adenoma has been reported (28). The growth pattern of flat adenomas has been correlated with underdevelopment of the colonic pericryptal fibroblast sheath (17, 29).

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

Dysplasia-Associated Lesion or Mass (DALM)

The significance of isolated polypoid adenomas in patients with ulcerative colitis is controversial (30). It is conceivable that sporadic adenomas arise in colons afflicted with IBD, but the definition of IBD-associated dysplasia would also include these. Should these be considered in the decision to perform a colectomy? Are they signals of synchronous carcinoma? Is their significance no greater than that of the sporadic adenoma in the general population? Few studies have addressed these questions (31, 32). The original description of DALM included 5 cases of isolated pedunculated masses, 2 cases of isolated flat lesions, and 5 cases of multiple polyps among 112 patients with ulcerative colitis(31). Seven of these 12 patients harbored a carcinoma, and all 5 isolated polyps contained cancer. If a polyp is incompletely removed from a patient with ulcerative colitis, and it contains high-grade dysplasia, the risk of an underlying cancer is probably great, but if it has been totally excised and contains no invasive cancer, it has probably been adequately treated (30). But whether the patient has been adequately treated is not yet known. Despite this uncertainty, I currently regard an adenoma of any configuration, arising in an area involved by ulcerative

colitis, as dysplasia associated with IBD, and significant in a decision regarding colectomy. I have regarded at least one pedunculated adenoma without high-grade dysplasia, arising in the ascending colon of a patient with limited left-sided colitis, as a sporadic lesion, not to be considered an indication for colectomy. These are personal judgments; and scientific evidence to support them does not exist. I have not yet been faced with the problem of a high-grade dysplastic lesion remote from diseased bowel in ulcerative colitis or Crohn's disease.

Invasive (Advanced) Carcinoma

Once a carcinoma penetrates the muscularis mucosae and enters the submucosa, it has the potential to metastasize, and should be regarded as clinically significant cancer. When it occurs in sessile adenomas, or without detectable precursor lesions, or in IBD, it should be considered to be advanced carcinoma, requiring more than local excision for cure. The special circumstance, for this discussion, is the invasive carcinoma arising in a pedunculated adenoma, and the question to be considered is, "When is polypectomy enough?"

Despite our knowledge that the muscularis mucosae and submucosa have a rich lymphatic network, only a very small proportion of carcinomas that gain access to the submucosa of pedunculated adenomas will metastasize (20, 21). Thus, recommendations for therapy continue to be based on empiricism. The most important factor has always been the proximity of the invasive cancer to the resection line, and that is dependent on the length of the polyp's stalk and the extent of cancer. Carcinomas invading only the head of polyps on a long stalk (3 mm or greater) neither recur nor metastasize after polypectomy alone; carcinomas invading only the head of polyps on a short stalk (0.4 to 2.6 mm) have a 9.5% chance of metastasizing, but usually do not recur locally; carcinomas invading the submucosa of sessile polyps have a 14% chance of recurring and metastasizing after polypectomy (20). Carcinomas invading the stalk of a polyp and reaching the base of a polypectomy specimen should be further treated, usually by segmental resection. When stalk invasion is present, how close does the carcinoma have to approach the resection line to require additional surgery? A study designed to answer that question has recently been undertaken, and the results are to be published shortly (Cooper, et al, Conclusions of the Malignant Polyp Study Group, Gastroenterology, in press, 1995).

Two other factors - tumor grade (20, 33, 34), and lymphatic invasion (19, 20, 35) - influence the decision regarding additional treatment of apparently adequately resected malignant polyps. Poorly differentiated carcinomas behave aggressively. Grade III (33)carcinomas in adenomas have had a 66% overall incidence of regional lymph node metastasis (20). Such poorly differentiated carcinomas will be found in only a minority of adenomas with cancer, since there is a correlation between histologic appearance, tumor size, and depth of invasion (36). The presence of a significant (50%) mucinous component in the carcinoma has some negative effect on the prognosis(36). Invasion of lymphatic vessels may be difficult to distinguish from tissue shrinkage around tumor nests, and the recognition of an endothelial lining will confirm true lymphatic invasion. Some reports have suggested a higher incidence of metastatic disease when that is seen, but lymphatic permeation may be partially dependent on tumor grade (20, 36).

Endoscopic Features.

In ulcerative colitis, the appearance of dysplastic mucosa may not differ from surrounding areas. Sometimes it appears "velvety" or "brush-like", and is usually poorly circumscribed (31, 32). Polypoid lesions may be inflammatory, hyperplastic, or dysplastic. Among patients without colitis, it is difficult or impossible to distinguish between hyperplastic and adenomatous polyps when their size is 5 mm or less (2). The endoscopic appearance of adenomas with high-grade dysplasia does not differ from ordinary adenomas.

Periodic colonoscopic surveillance of patients with chronic IBD is recommended as a way of identifying those at risk for colorectal cancer (9, 16, 32, 37-41). Annual total colonoscopy with biopsy of 6 to 8 areas from cecum to rectum, in addition to any area suspect for dysplasia, is advised. For the detection of dysplasia, it is important to avoid areas of mucosa that appear actively inflamed. The management of the patient undergoing regular surveillance is highly dependent on the histopathologic findings. Remembering that carcinoma can occur anywhere in the diseased large intestine of a patient with IBD and dysplasia, a decision to employ surgical prophylaxis usually means a total colectomy, with either a permanent ileostomy or an ileo-anal anastomosis. The following general recommendations are in practice:

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

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

There is current disagreement about whether the appropriate interval between colonoscopic examinations is one or two years, for patients negative for dysplasia, but most gastroenterologists will halve the accepted interval when a biopsy is interpreted as indefinite, or low-grade dysplasia. There is also controversy over the benefits of random biopsies for surveillance. One report claims that most dysplasia was found in the rectal mucosa, and that there is a high concordance between dysplasia and the development of colorectal carcinoma within 6 years (41). Another states that there was a very poor correlation between rectal dysplasia and more proximal carcinoma, and that multiple random biopsies have a low sensitivity and specificity in detecting carcinoma, there being many patients in that study with carcinoma but no dysplasia on previous biopsies (40). Nevertheless, the same investigators recommended colectomy whenever dysplasia of any grade is seen. In a third report, dysplasia was encountered more often in the right than the left side of the colon, but none of the patients developed carcinoma after a five year interval (38). In a report from Great Brtain, 332 patients with ulcerative colitis were followed in a surveillance program for 21 years, with the detection of 11 symptomless cancers, and 25 cases of dysplasia (42). A mean of nine biopsy samples was taken at each endoscopic examination. Eight of the cancers were Dukes A lesions.

Clearly, additional prospective data are necessary to properly assess the value of surveillance biopsies for the detection of cancer in IBD, but the current trend is away from performing prophylactic colectomies on all patients with ulcerative colitis of ten years duration. Even less data are available concerning surveillance in Crohn's colitis (9).

The evidence that annual or biannual colonoscopy or even sigmoidoscopy, of asymptomatic people, with removal of all polyps, results in a dramatic decrease in the incidence of colorectal cancer, is irrefutable (43-49).

Differential Diagnosis.

Most of the features that distinguish dysplasia from repair in IBD have been mentioned above, and in other sections. The misinterpretation of inflammatory and reparative changes as neoplastic ones is the main concern.

Pseudocarcinomatous entrapment of benign glands in adenomas is encountered in up to 10% of adenomas(50, 51)The phenomenon is probably the result of ulceration and subsequent healing. The lack of cytologic characteristics of malignancy, the maintenance of lamina propria around the deeply situated glands, and the presence of hemosiderin-filled macrophages, identify the change as benign. Sometimes prior inflammation results in fibrosis, simulating desmoplasia, and cytologic features of the epithelium must be relied on. On one occasion, a pseudoinvasive focus of glands lined by high-grade dysplastic epithelium was seen in an adenoma, and serial sections were necessary to demonstrate the continuity of the herniated glands with the surface of the benign tumor (52)

Predisposing Factors.

The risk factors for dysplasia and early carcinoma of the colon and rectum are, of course the same as for advanced cancer, and will not be discussed here in detail. The reader is referred to a general review of colorectal neoplasia with extensive references to polyposis syndromes, carcinoma in IBD, dietary considerations, and epidemiologic factors (53).

Natural History.

In IBD, both the extent and duration of disease influence the development of carcinoma. Patients with pancolitis or, at least with disease involving the transverse and descending colon, are at higher risk than those with only left-sided colitis (54). Patients who have been symptomatic of ulcerative colitis for at least 7 years are at significant risk for developing carcinoma (37, 54-56), and should be entered in a program of regular surveillance. The duration of disease necessary for the development of dysplasia is not known, but in one study there was a 5% incidence of dysplasia after 10 years of colitis, and a 23% incidence after 20 years (38) The risk of carcinoma increases 0.5% to 2% per year after the first 10 years of disease (54, 56) and these figures provide only an approximation of the time for progression of intraepithelial to invasive carcinoma.

Growth rate and progression to malignancy of colorectal adenomas in the general population can only be estimated by epidemiologic studies. Nine years has been cited as an average lag time between adenoma and invasive carcinoma (53)Among patients

with familial polyposis coli, all will develop cancer after 30 years if not treated by colectomy. There is a 10% incidence of carcinoma after 5 years of symptoms, and a 50% incidence after 20 years (57).

Special Procedures and Molecular Biology.

Many immunohistochemical procedures have been applied to tissue sections in an attempt to refine the early detection of neoplastic change. Unfortunately, the results have lacked the specificity, sensitivity, or both, to allow these procedures to be of practical diagnostic value. Mucin histochemistry and lectin-binding studies have shown some differences among the mucins expressed by the colorectal epithelium in normal, inflamed, and neoplastic mucosa (58-61), but there is considerable overlap in the mucin profiles among these groups, especially the latter two. Patterns of glycoconjugation, sulfomucins, and sialomucins, while abnormal in dysplastic and carcinomatous epithelium, are similar in regenerating mucosa (60, 62). P-glycoprotein is overexpressed by colonic cancer epithelium, and by dysplastic cells (63)but the difference in expression between those and normal epithelium is a quantitative one, and of uncertain value in a diagnostic setting. Furthermore, the levels of P-glycoprotein expression in inflamed mucosa, compared to normal and dysplastic, in the same patient, were variable (63) The histochemical demonstration of glucose-6-phosphate dehydrogenase distinguished dysplastic and malignant from normal colonic epithelial cells, but the method required the reaction of cryostat sections to take place in a pure oxygen atmosphere (64) The utility of this method applied to endoscopic biopsy specimens is debatable. Dystrophic goblet cells have been cited as a possible marker for nearby dysplasia (4). Although dystrophic goblet cells were found only rarely in normal mucosa, they were identified in approximately equal numbers in malignancy, chronically inflamed mucosa of IBD patients, and non-neoplastic polyps (7). No difference was detected between the mucin histochemistry of dystrophic goblet cells and that of normal goblet cells (7).

The elaboration of a number of tumor-associated glycoproteins, including carcinoembryonic antigen (CEA), has been investigated as a diagnostic aid (65-69). Once again, the presence of these antigens on regenerating, as well as neoplastic cells diminished the value of their detection. Increasing tissue levels of CEA were present in samples of inflamed, adenomatous, and carcinomatous colonic mucosa (67), but the absence of qualitative differences between benign and early malignant tissues and the method of analysis are more useful in an investigational than a diagnostic setting. In one study, the application of a monoclonal antibody, prepared against the MCF-7 human breast cancer cell line, seemed to distinguish between inflamed and dysplastic mucosa in IBD (70), but those results have yet to be confirmed.

Patterns of epithelial cell proliferation in colonic crypts have also been investigated as a tool in identifying early malignant change (71, 72). Although one consistently finds an increased rate of cell division and an "upward shift" of the proliferative zone in dysplastic and adenomatous crypts, this is also seen in regeneration, and can also be inferred from histologic appearances.

Morphometric analysis of such features as cellular stratification, N/C ratio, and shape factors, has been useful in distinguishing between low-grade and high-grade

dysplasia, confirming the value of a two-tier over a three-tier grading system (73), but has not been of great use in discriminating neoplastic and non-neoplastic changes.

Studies of DNA ploidy among patients with familial polyposis coli have shown a greater aggressiveness of non-diploid carcinomas, a higher frequency of non-diploid polyps in patients with synchronous cancers, and a positive correlation between age and non-diploid tumors (74). Among patients with ulcerative colitis and Crohn's disease, a correlation between aneuploid tumors and CEA tissue concentrations was observed (67). An analysis of DNA content by flow cytometry in multiple colonic mucosal biopsy specimens from patients with ulcerative colitis showed a significant correlation between aneuploidy and risk of developing neoplastic lesions (75). The presence of aneuploidy in non-dysplastic mucosa was associated with progression to dysplasia within 2.5 years, whereas the absence of aneuploidy was unassociated with subsequent development of dysplasia. The authors of that study also point out that to achieve a useful confidence level for the predictive value of such flow cytometric studies, 30 to 56 endoscopic biopsy specimens may be required, and that a 4 to 6 year interval elapses between the detection of aneuploidy and the diagnosis of high-grade dysplasia.

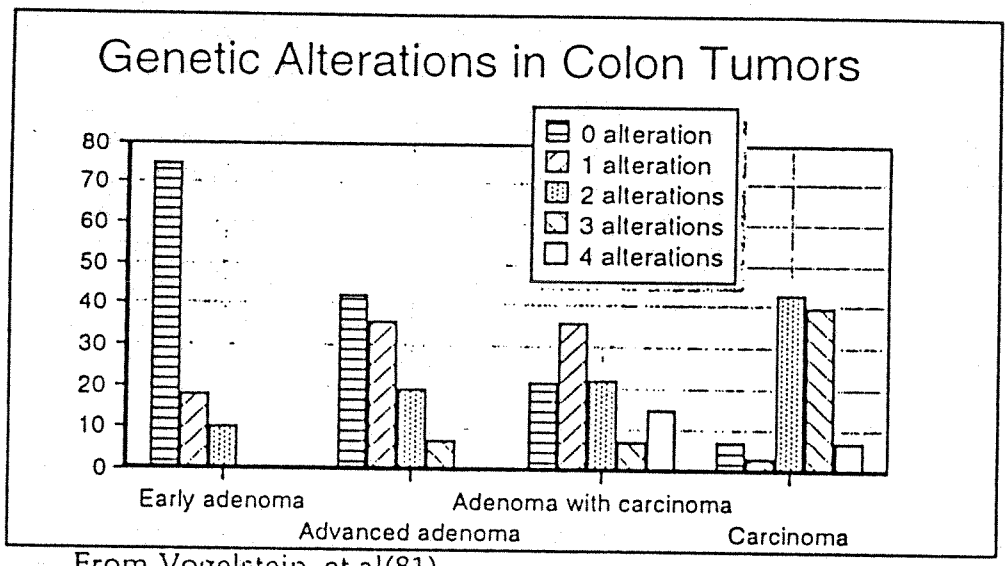
Since the discovery of the genetic abnormality linked to familial polyposis coli, a number of gene alterations have been described in sporadic colorectal cancer and in cancer arising in the setting of IBD. The polyposis gene ("FAP" or "APC" gene) was localized to the long arm of chromosome 5 (76-78). Somatic mutations of the APC gene were also found in cases of sporadic colon cancer (79). A number of other genetic alterations, including amplification of oncogenes and deletions of tumor suppressor genes, have subsequently been described in colorectal cancer, and these are summarized in the table below.

GENES ALTERED IN COLON CANCERS*

Gene	Chromosome	Frequency**	Class	Action
"FCC"	2	15%	?	Maintains DNA replication accuracy
K-ras	12	50%	Oncogene	Intracellular signaling molecule
Cyclins	Various	4%	Oncogene	Help regulate cell cycle
neu/HER2	17	2%	Oncogene	Growth factor receptor
myc	8	2%	Oncogene	Regulates gene activity
APC	5	70%	Tumor suppressor	Unknown
DCC	18	70%	Tumor suppressor	Cell adhesion molecule
p53	17	70%	Tumor suppressor	Regulates gene activity

*From Marx (80)
**Proportion of tumors with mutations.

It is not established whether any specific genetic abnormality is directly associated with susceptibility to colorectal neoplasia in the general population. Some or all of the alterations are associated with neoplastic progression. Allelic deletions of tumor suppressor genes on chromosomes 5, 17, and 18, and *ras* -gene mutations, are found with increasing frequency in adenomas, adenomas with carcinoma, and invasive carcinomas, respectively (81). The accumulation of genetic alterations with increasing severity of neoplasia, as illustrated below, parallels the adenoma-carcinoma sequence of morphologic changes and its clinical reflection.



From Vogelstein, et al(81)

The deregulation of *ras* and *myc* -genes may be dependent on prior alterations of other regulatory genes, such as the "familial colon cancer" ("FCC") gene, the APC gene, or loss of heterozygosity at chromosome 17 for p53. The sequence of the multiple genetic abnormalities found in colon cancers has not yet been established.

There is much work in progress regarding the clinical implications of the genetic abnormalities found in colon cancers, and no generalizations are yet possible. Patients with tumors expressing *ras* protein by immunohistologic examination have had a somewhat lower (44%) 5-year survival than those negative for *ras* protein, but no such correlation was seen when c-*myc* protein was studied (82). Mutations of the K-*ras* oncogene was found more frequently among carcinomas arising in ulcerative colitis than in sporadic colon cancers (83-85). That *ras* mutations may precede the development of invasive carcinoma is suggested by their detection in dysplastic mucosa of ulcerative colitis (86). In one study, no ras mutations were found in non-neoplastic mucosa of patients with IBD (87). However, in a more recent study, mutations of the K-ras gene were found in carcinoma, dysplasia, and regenerative and inflamed mucosa of colons affected by ulcerative colitis (88). Concommitant p53 alterations were discovered in carcinomatous tissue and in a single focus of dysplasia in that study. The authors suggest that K-ras mutation may be a marker for neoplastic potential in colitic mucosa, even in the absence of histologically identifiable neoplastic change.

Alterations on chromosome 17 are a frequency finding in colorectal carcinomas, especially among those arising in ulcerative colitis , and loss of a p53 allele occurs in dysplastic as well as in carcinomatous epithelium (89-92). Deletion of p53 has also been correlated with DNA analysis (91). Only aneuploid cells showed loss of heterozygosity for p53, and it has been inferred that the combination of aneuploidy and p53 loss is a specific marker for dysplasia in ulcerative colitis (91).

In a study of ten patients with neoplasia occurring in a setting of both Crohn's colitis and ulcerative colitis, mutiple genetic alterations were found, which paralleled those previously described in sporadic colorectal cancer (93). The alterations included multiple sites of allelic deletion, and mutations of the K-ras, p53, and APC genes. The progression of dysplasia to carcinoma was accompanied by accumulation of mutations, but there was no consistent pattern of genetic abnormalities among the patients. In another, more limited study, p53 mutation was found in carcinomatous, dysplastic, and adjacent non-neoplastic mucosa associated with ulcerative colitis, while loss of p53 heterozygosity was found only in neoplastic tissue, suggesting that the mutation is the earlier event in carcinogenesis (94). A high degree of correlation was found between p53 mutation and the immunohistologic detection of p53 protein overexpression in dysplastic and carcinomatous mucosa of patients with ulcerative colitis (95). The immunohistologic examination was performed on paraffin embedded tissue, and is thus applicable to retrospective as well as prospective analyses.

Kim and coworkers (96) studied DNA replication errors in a group of colorectal carcinomas, and discovered a subset of 13 percent in which such replication errors was associated with right-sided location, exophytic growth, poor differentiation, extracellular mucin production, and a prominent host inflammatory reaction. These tumors also showed less p53 overexpression than did the other colonic cancers. The genetic alterations in this subset resembled those seen in hereditary nonpolyposis colorectal cancer syndrome.

These and numerous other genetic alterations in colorectal neoplasia are being described with increasing frequency, and one looks forward to a synthesis of these data, and further applications to diagnostic procedures.

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UPDATE ON COLORECTAL CARCINOMA

ENDOSCOPICALLY REMOVED MALIGNANT POLYPS

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A malignant polyp of the colon or rectum is defined as a "polyp" containing invasive adenocarcinoma (cancer that has invaded throughout the muscularis mucosa into the submucosa). Polyps with intramucosal or in-situ carcinoma should not be considered malignant polyps because their biological potential for metastasis is zero. A malignant polyp may be either a polypoid carcinoma (a polyp in which the head is totally replaced by cancer and no residual adenoma is present) or may represent focal malignant degeneration in an adenoma.

In order to properly evaluate a malignant polyp, the gross polyp must be cut (sectioned) so that all important landmarks are easily evaluable. This requires that the polyp be adequately fixed prior to sectioning (2-3 hours in a large volume of fixative for polyps 1.5 cm. or smaller and longer periods of fixation for larger polyps).

When examining a polyp with invasive cancer, the following parameters should be reported: (1) Histologic grade of the cancer. (2) Status of the resection margin and the distance of cancer from the resection margin, and (3) The presence or absence of lymphatic and/or venous invasion. Most investigators believe that if the margin of resection is free of tumor (or tumor > 1 mm from the resection margin) and the cancer is grade I or II, and there is no evidence of lymphatic and/or venous invasion, then these polyps can be effectively treated by polypectomy alone. However, if cancer is at or near the margin ($\leq$ 1 mm) and/or

grade III, and/or lymphatic or venous invasion is present then the patient should undergo a definitive surgical resection post polypectomy if medically feasible. In a large multi-institutional study (ref. 12), the incidence of adverse outcome (lymph node metastases and/or recurrence post polypectomy only) in the presence of unfavorable histological parameters (cancer at/or near the resection margin, and/or grade III cancer, and/or lymphatic and/or venous invasion) was 19.7% while the incidence of adverse outcome was 0% in the absence of unfavorable histological parameters. The incidence of adverse outcome with tumor at or near the resection margin, lymphatic invasion, venous invasion, and grade III cancer was 21.4%, 17.6%, 40%, and 37.5% respectively. Review of the literature reveals: the incidence of adverse outcome with tumor at or near the resection margin, lymphatic invasion, venous invasion, and grade III cancer is 33%, 38.8%, 39%, and 36%, respectively. In the literature, all those cases with lymphatic and/or venous invasion and an adverse outcome were associated with other unfavorable histological parameters (grade III cancer, positive margin, or Haggitt level 4). In our interinstitutional study lymphatic invasion by itself was independently associated with an adverse outcome. In the interinstitutional study the strength of agreement between pathologists was substantial to almost perfect for margins of resection, grade, and venous invasion, but was fair to moderate to substantial for lymphatic invasion. This variability in detecting lymphatic invasion may be responsible for false negative cases (2.9% in our study and 1.5% in the literature). Polypoid carcinomas are no more aggressive than cancers arising in adenomas and should be treated using the same criteria as adenomas with invasive cancer.

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UPDATE ON STAGING OF GASTROINTESTINAL CARCINOMAS

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1 Why stage cancer?
*to plan treatment, select type and extent of treatment;
a T1 polypoid colon carcinoma vs a T3; an M0 vs an M1
*to estimate prognosis
in the GI tract, extent of disease (stage) is the strongest determinant of both prognosis and choice of therapy.
*to compare results: nationally and internationally
*to communicate data: provide a shorthand system
*to measure health care management

1.1 What's new in staging GI neoplasms is related to:
* how we determine anatomic extent, i.e. new methods
* how we express anatomic extent, i.e. new classifications
* how non-anatomic factors interact with stage of disease

2. How we determine anatomic extent
clinically: grossly and by imaging; an estimate; cTNM
pathologically: microscopically; the gold standard; pTNM

2.1 **Clinically**: precedes resection, determines choice of primary treatment and/or ends at the point when the choice of treatment is made; tries to approach the pathological classification in accuracy.
New methods, e.g. in imaging, can visualize anatomic layers of bowel, lymph node and distant metastasis

2.2 **Pathologically**: classification follows resection; estimates prognosis and choice of adjuvant therapy

3. TNM vs Dukes classification
* TNM allows separation of the 3 components; Dukes lumps them
* Dukes has too many variants

4. TNM Supplement 1993: facilitates uniform application of TNM
* explanatory notes, eg regional nodes for gastric stump carcinoma
* optional expansions, eg T3 colon
* pT & pN rules, eg # of negative nodes for N0
* proposed classifications, eg GI sarcomas

5. Prognostic Factors

Although anatomic extent is the strongest determinant for GI carcinomas, nonanatomic factors play a role in prognosis and may be important clinically for certain subsets, e.g. selected stages.
What markers are independently significant?
How can they be integrated into a prognostic system that will be meaningful and manageable?

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College of American Pathologists Conference XXVI on Clinical Relevance of Prognostic Markers in Solid Tumors

Report of the Colorectal Cancer Working Group

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• The College of American Pathologists Conference XXVI in June 1994 was devoted to a discussion of the clinical relevance of prognostic factors in three solid tumors (breast, prostate, and colorectal). The group considering prognostic factors for adenocarcinoma of the large gut consisted of 15 pathologists, investigators, and surgeons. The group concluded that only a few items are well supported in the existing literature and can be recommended for routine clinical use at this time (pathologic TNM information and stage, tumor type, tumor grade, extramural venous invasion, and preoperative serum carcinoembryonic antigen level). According to the classification system used at the conference, these markers warrant categorization as important prognostic factors (category I). A few factors should be considered as potentially useful after further study (category II). Furthermore, the group agreed that all other current measurements of so-called prognostic factors do not warrant the same recognition of importance, either because they have been studied insufficiently or studies have demonstrated that they do not contribute to prognostication. These additional items were placed in category III. It was also concluded that the statistical methods used to identify and validate prognostic markers, as well as their integration into single statements of prognosis, need further national evaluation and standardization.

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In 1993, the Board of Governors of the College of American Pathologists (CAP) asked the Cancer Committee of the College to sponsor a conference on prognostic markers for solid tumors. This review was thought necessary because the apparent confusion about the role of prognostic markers in clinical practice was leading clinicians and laboratories to perform unnecessary and expensive tests that had little or no demonstrated relevance for patient management. Therefore, the Cancer Committee of the CAP convened a group of pathologists, clinicians, and investigators who have an interest in prognostic markers to study these factors in breast, prostate, and colorectal cancer.[1]

The conference considered the prognostic markers derived from tissue and blood that are of primary interest to pathologists. Clinical factors, diagnostic information, and markers of tumor recurrence were not discussed. The general purpose of clarifying prognostic markers is to identify more homogeneous populations for treatment and study. Markers should help minimize the variance in outcome in the subpopulations, which is currently present in stage groupings because the TNM stages produce overly broad groups. Reduced subpopulation heterogeneity should allow for small but important treatment effects to be detected more easily in clinical studies and, consequently, the number of patients needed for clinical trials should decrease. Thus our purpose was to identify pathology markers for routine clinical use that can improve the accuracy of patient prognosis. The assumption was that such improved patient prediction will lead to changes in management of individual patients to enhance their outcome.

The conferees discussed a possible definition of the term *prognostic factor.* It was agreed that it is necessary to distinguish between a biological measurement, which assays cellular function (and its deviance, which occurs within a tumor), and the application of such measurements to the process of outcome estimation (prognostication). Thus, a prognostic factor can be defined as an item of information concerning the tumor or the host that can increase the accuracy of prognostic estimation.

A pictorial representation of our ability to improve accuracy of prognostic prediction can be helpful (Figure); the level of accuracy progresses from a prognostic statement derived from a simple diagnosis (ie, an actuarial estimate of outcome based only on diagnosis), to the increased accuracy provided by TNM stage (a five-bin model), to the additional accuracy of using TNM information without its amalgamation into stages (a 40-bin model). Our goal is to reach a further increment of accuracy from an analysis and amalgamation of information from multiple prognostic factors in addition to that derived from the anatomic extent of tumor spread.

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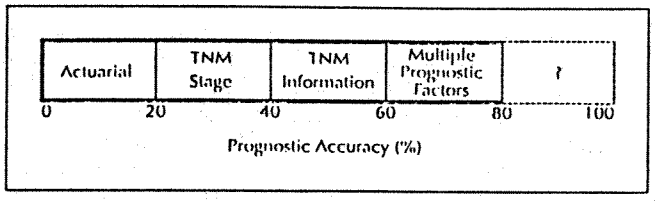

Representation of the added value of prognostic information to prediction. The actuarial category indicates prognosis based on diagnosis only; TNM stage, a five-bin model with TNM information being collapsed into the five TNM stages; TNM information, a 40-bin model in which the raw data, T, N, and M information, are used as the input variables for the predictive model; and multiple prognostic factors, the next step in the evolution of prognosis prediction.

Table 1.—College of American Pathologists Working Classification for Prognostic Markers

Category I:	Well supported by the literature; generally used in patient management
Category II:	Extensively studied biologically and/or clinically
	A: Tested in clinical trials
	B: Biological and correlative studies done, few clinical outcome studies
Category III:	Currently do not meet criteria for category I or II

Statistical and other multivariate methods for combining the data from multiple markers to improve the accuracy of outcome predictions were briefly considered.[2-5] However, the group concluded that the relative efficacy of existing statistical and other analytic methods should be evaluated in more detail, and the sources of error in such analyses need further consideration. An additional priority for a future meeting will be to consider the best method to describe statements of outcome (either the likelihood of being alive at 5 years or an estimated time to death). Despite these concerns, the conferees concluded that the information derived from multiple factors needs to be integrated into a single statement of outcome for these factors to be of greater value in the decision-making process. Meanwhile, it was agreed that it would be worthwhile to categorize prognostic factors according to a schema that was developed at the conference (Table 1). Markers were assigned to three categories (I, II, or III), depending on the current level of confidence that can be ascribed to each of the many putative prognostic factors found in the literature.

CURRENT USE OF PROGNOSTIC FACTORS IN COLORECTAL CANCER

The group noted that the prognostic factors (as single or multiple markers) assigned to categories I and II are currently being used for the following clinical decisions after the initial treatment of surgical excision of the primary tumor: (1) for adjuvant chemotherapy with 5-fluorouracil and levamisole in pathologic TNM (pTNM) stage III colon cancer[6]; (2) for irradiation and adjuvant chemotherapy in pTNM stages II and III in rectal cancer[6]; (3) in poorly differentiated rectal tumors to decide local versus radical excision; (4) in poorly differentiated rectal tumors to decide between abdomino-perineal excision and anterior resection of the rectum for radical surgery; (5) in poorly differentiated tumors of the rectum treated by local tumor excision to consider adjuvant irradiation and/or chemotherapy; (6) in a polyp, the presence of an area of vascular invasion or a poorly differentiated tumor leading to a decision to carry out surgical excision of the bowel with its lymph node and vascular supply; and (7) for possible adjuvant treatment selection in colon cancer TNM stage II (T3-4, N0, M0), aneuploid, and/or high proliferation-rate tumors. Some of these decisions are being made as a consequence of research, while others are used on the basis of "reasonableness."

PROGNOSTIC FACTOR REVIEW

Consideration of individual prognostic markers was divided into a series of presentations and discussions. After discussing the data and the opinions of the conferees, the following consensus views of the group emerged.

Flow Cytometry

DNA Ploidy.—*Conclusion: Category IIB Factor.*—This marker relates to the neoplastic process, but DNA ploidy has been shown to be only a weak independent prognostic marker.[7] Further studies should, perhaps, be stratified by anatomic stage, as current evidence is strongest for tumors classified as pTNM stages II and III.[8]

Technical quality assurance of samples, processing, and analysis is essential, but it is yet to be achieved on an interinstitutional basis.[7,9] A technical problem for DNA ploidy measurement that should be addressed to eliminate sampling error is the ratio of neoplastic to stromal cells in the suspension.

Because of its potential as a predictive marker for colorectal cancer and other tumors, it was suggested that the CAP should become increasingly responsible for standardization of this methodology. Flow cytometrists and statisticians should be well represented in any evaluative group.

Cell Proliferation Studies

S-Phase Fraction.—*Conclusion: Category IIB Factor.*—S-phase fraction measured by flow cytometry has the potential to be a powerful predictor of outcome.[8,10] However, as in ploidy studies, the methodology and statistical analysis are not yet sufficiently standardized for this technique to be generally applicable.[7,11] The possibility of using paraffin-embedded archival material adds to the potential value of this technique but is in need of standardization.

Mitotic Index.—*Conclusion: Category III Factor.*—Because of its simplicity, the concept of routine counting of mitotic figures to calculate a mitotic index should be revisited in colorectal cancer. The methods to achieve standardization should be developed and should include a recommended accepted number of malignant cells that need to be counted to establish a reliable index. This was only an observation by the conferees, however, and perhaps a simpler assay of proliferation rate (such as Mib I may be a more useful approach.[12]

Silver-Stained Nucleolar Organizer Regions (AgNORs).—*Conclusion: Category III Factor.*—Estimation of AgNORs is a technique that appears to correlate with cell proliferation (and thus with prognosis) in some studies.[14-15] Because the methodology for estimation of silver-stained nuclear organizer regions requires additional work for standardization and a considerable investment of time in the assessment of the specimen, and because clinical studies have been inconsistent, it is not recommended as a prognostic marker in colorectal cancer at this time.

Tritiated Thymidine and Bromodeoxyuride.—*Conclusion: Category III Factor.*—Tritiated thymidine and bromodeoxyuridine (BrdU) studies currently require in vitro incubation of fresh tissue, and although they are reliable predictors of cell proliferation, they are too difficult and cumbersome to use on a routine basis.

Immunologic Proliferation Markers.—*Conclusion: Category III Factors.*—The newer proliferation-related antigens, for example, Proliferating cell nuclear antigen and Ki-67, are useful in the assessment of tumor proliferation rate, are applicable to fixed paraffin-embedded tissue sections, and therefore may be useful as prognostic markers.[16] The methods by which they are measured and the interpretation of results require standardization. Their relationship to patient survival needs further substantiation.

Tumor Vascularity

Extramural Venous Invasion.—*Conclusion: Category I Factor.*—A number of multivariate statistical and analytical studies have shown tumor involvement of extramural veins to be an independent prognostic factor for 5-year patient survival in colorectal carcinoma.[17-20]

Adenomas Harboring Carcinoma.—*Conclusion: Category I Factor.*—Submucosal vascular invasion by carcinoma present in adenomas removed by polypectomy is associated with an increased metastatic potential,[21-25] as indicated by a greater risk of regional lymph node positivity under these circumstances.

Tumor Neovascularization.—*Conclusion: Category III Factor.*—In contrast to the current interest in tumor neovascularization (angiogenesis) in breast cancer,[26] at the time of the conference there were no published data describing the relationship between neovascular proliferation and prognosis in patients with colorectal cancer. However, a recent report suggests a correlation of angiogenesis activity with tumor metastasis and patient survival.[27]

Differentiation Markers

Histologic Tumor Type.—*Conclusion: Category I Factor.*—The World Health Organization tumor type classification is recognized.[28] The presence of signet-ring cells in a tumor is associated with poorer prognosis.[29] The significance of mucin production when more than 50% of the tumor is composed of mucus should be recorded as a probable factor of poor prognosis.[30] However, the data are conflicting; older studies indicate mucin levels above 60% are associated with a poor prognosis,[31,32] whereas more recent studies suggest that stage for stage, mucin production has no association with a diminished prognosis.[30,33,34] Neuroendocrine differentiation, especially small-cell type, has a very poor prognosis.[35]

Histologic Tumor Grade.—*Conclusion: Category I Factor.*—Although many studies of observer variation have demonstrated relative inconsistency within the pathology community between well-differentiated and moderately differentiated adenocarcinoma of the colon and rectum, there is a strong central tendency for the results in the identification of poorly differentiated tumors. In addition, multivariate analyses in which histologic tumor differentiation is dichotomized into poorly differentiated versus others have demonstrated independent prognostic value.[36]

Serum Carcinoembryonic Antigen (CEA) Level.—*Conclusion: Category I Factor.*—Elevation of preoperative serum CEA level is recognized as a valid predictor of tumor burden, a possible predictor of tumor recurrence, and also as a response to therapy.[37] Further refinement with regard to classification of various antibodies to CEA may further improve the sensitivity and specificity of this test.[38] The yield of cures attributable to CEA monitoring, however, remains low compared with the cost and the associated patient stress.[39] However, a meta-analysis of this subject suggests that vigorous CEA-led follow-up regimens may provide a 9% better 5-year survival rate for those patients who develop tumor recurrence, because of an increased lead time in diagnosis.[40]

Other Serologic Markers.—*Conclusion: Category III Factors.*—Additional serologic markers (CA 195, CA 19-9) do not appear to improve the assessment derived from serum CEA levels.[41,42]

Mucin-Related Tissue Markers.—*Conclusion: Category III Factors.*—Mucin- and carbohydrate-related factors (eg, Sialosyl-Tn and sialyl-Lex) appear to be promising markers associated with prognosis and metastasis. However, at the present time they are at the investigational level.[43,44]

Gene Products.—*Conclusion: Category III Factors.*—Gene products, such as CD44, may also prove useful in the relationship to tumor progression, but at the present time are research tools only.[45]

Stromal Changes.—*Conclusion: Category III Factors.*—Currently, there are a number of interesting reports regarding stromal changes related to the cellular basement membrane. Type 4 collagen and laminin may be of value in assessing the future behavior of colorectal tumors.[46]

Cytokeratin Subtypes.—*Conclusion: Category III Factors.*—Studies regarding cytokeratin subtypes show changes during the adenoma-cancer progression, but these measurements do not appear to be related to prognosis.[47] (The use of cytokeratin staining to find small clusters and single metastatic cells in lymph nodes and bone marrow may have an impact on the accuracy of anatomic staging. Thus, these reagents might be helpful to improve staging as a morphologic assessment adjunct rather than as prognostic factors per se. However, it must be emphasized that the finding of such tumor spread [single cells or small tumor clusters in lymph nodes] does not necessarily mean a worse patient prognosis, and careful prospective evaluation of such staining methods is needed.)

Antibodies to Cell Surface Antigens.—*Conclusion: Category III Factors.*—Studies using antibodies to immunohistochemically detect HLA surface antigens on colonic tumor cells suggest that reduced HLA class 1 expression is related to early neoplastic transformation.[48] However, its relationship to prognosis has been questioned and further research is indicated.[49]

Histologic Evidence of Immune Response

Peritumoral Lymphoid Response.—*Conclusion: Category IIB Factor.*—Several studies have demonstrated the prognostic significance of peritumoral lymphocytic infiltration,[36,50-53] particularly when a "Crohn's-like" pattern is observed.[20,54,55] Previous studies on the histologic appearance of lymph nodes draining a tumor do not appear to relate to prognosis.

Infiltrative Tumor Border.—*Conclusion: Category IIB Factor.*—A few tumors have a pushing rather than an infiltrating border with normal tissue. In a few reports, the pushing variety was associated with a better prognosis.[36,50] However, this observation requires confirmatory study and therefore would not be recommended for routine use.

Table 2.—Recommended Data Elements for Colorectal Cancer Documentation
Patient identification, demographics, and clinical features
Clinical features (some of which are prognostic)
Major management events
Surgery
Chemotherapy
Irradiation
Pathology
Routine description[58]
Prognostic information
TNM information and stage
Differentiation markers
Tumor type
Tumor grade
Serum carcinoembryonic antigen
Extramural venous invasion
Peritumoral lymphoid host response
Ploidy status
Patient follow-up information

Genetic Factors

Cytogenetics.—*Conclusion: Category III Factor.*—Cytogenetic studies, although potentially examining the fundamental biology of neoplasia, are technically demanding and are not yet feasible for routine practical application. There is a need for increased standardization of methodology.[56]

Oncogenes, Tumor Suppressor Genes, and Growth Factors.—*Conclusion: Category III Factors.*—This rapidly developing area appears to have great potential for application of immunohistochemistry,[57] in situ hybridization, and molecular techniques to elucidate a patient's prognosis. However, at present, these methods are still at the research level. K-*ras* is the most likely factor in this group to move to category IIB.

BROADER ISSUES

In addition to differentiating categories I, II, and III for prognostic factors, the CAP Conference identified other needs that require ongoing attention.

Standardization of Laboratory Methods

DNA content and S-phase measurements require CAP guidance to track interinstitutional result comparisons and to diminish currently observed variance caused by inconsistent laboratory methods. The group producing such recommendations should include experts in the field of laboratory measurement and statistical evaluation of method reproducibility and interpretation.

Advisory Notes

The circulation of advisory notes to all pathologists would be helpful to indicate that a few additional factors are worth studying properly. These advisory notes could also provide guidance for measurement and interpretation and should include the following: (1) tumor vascular involvement, (2) peritumoral cluster and tumor nodule interpretation, (3) peritumoral lymphoid (Crohn-like) host reaction, and (4) mitotic figure counting with index calculation.

Analytic Methods

The Colorectal Cancer Working Group recommended that a meeting of those specifically interested in the analytic issues of multiple prognostic factors should be convened. Although there has been interesting work concerning artificial neural networks in the identification and use of multiple prognostic factors in this field, these newer techniques are not yet accepted as methods of choice to carry out such analyses. It would be helpful if this subject were addressed at two levels: technical aspects and adequate explanation for clinicians' understanding.

Expression of Results

There is an urgent need to identify the similarities and differences by which prognostic results are expressed, either as group data defined as survival to a particular point in time (eg, 5 years with appropriate confidence limits) or as individual outcomes in terms of time to death (expressed as an estimate with appropriate confidence limits). It is clear that the former is a conglomeration of the data supplied by individual patient results. However, our objective should be to optimize an estimate of outcome for each individual patient such that it can influence treatment decisions. Thus, optimizing individual prognosis estimation is our goal, and this may demand a somewhat different set of assumptions and model instructions than is used for the traditional group 5-year survival estimates.

As our ability to analyze multiple prognostic factors against time increases, it becomes possible to calculate the likelihood of survival from year to year after initial treatment. This year-to-year survival statement is called *conditional survival* (the condition being that the patient has survived to the beginning of the period of analysis). Such conditional survival may be useful in understanding the changing risk of mortality as the patient moves away in time from initial diagnosis and treatment. After the first few years, the patients who survive are increasingly likely to survive, and this gradually improving cancer-specific survival may influence the treatment of other conditions.

As part of the clinical implementation of these projects, we should consider how results from the use of multiple prognostic factors should be expressed. We concluded that TNM information and staging should be separate and distinct from the results derived from a multiple prognostic system. This will help the clinician move from a known parameter (TNM stage) toward a more accurate, but more complex, single statement of prognosis for the individual patient, which uses all the information contained in the recommended multiple prognostic factors.

Database Generation

One of the most disturbing rate-limiting factors for the development of databases is the relative paucity of established, well-organized prospective databases, which can form the backdrop for further analyses. The Cooperative Oncology Groups are attractive organizations for this type of development because archival material can be used to expand the information, inferences, and conclusions that can be drawn from their well-maintained databases. In addition, even before we can identify all prognostic parameters that should be recorded in a database, we should encourage the establishment of new databases (preferably in association with tumor banks) because these resources will be invaluable for rapid research progress.

It follows, therefore, that site-specific, uniform, and standardized databases are needed so that new, more accurate prognostic systems can be supplied to clinicians who treat patients with cancer. This, then, would allow for

the future process of database generation to be enhanced further, so that additional prognostic factors can be identified.

Prognostic Factor Labeling

It was pointed out that invalidated and unsubstantiated claims are being made for various individual or groups of putative prognostic factors. It was also noted that where technology, or information derived from technology, is used in the clinical arena, it is appropriate for some level of regulatory activity to establish "efficacy" and "safety" for its use. It would follow that these tests should be appropriately labeled in regard to their ability to support clinical decision-making and therapeutic intervention.

It was recognized that this is a potentially sensitive issue, which, if appropriately applied, could diminish the currently perceived abuses that are taking place. However, it must also be recognized that if inappropriately applied, regulation could stifle the development of prognostic markers and consequently hold up improvement in patient care based on improved prediction of outcome derived from the integration of information contained in reliable and reproducible prognostic factors.

COMMENT

It was agreed that the conclusions of the conference would be submitted to the Board of Governors of the CAP so that the College might consider drafting recommendations on the use of prognostic factors in the light of current information. It was also recognized that this subject area is evolving rapidly and future conclusions and recommendations will need further development.

We gratefully thank the organizing group of the College of American Pathologists, the presenters, and participants of the meeting. *Presenters:* Dennis J. Ahnen, MD (Nuclear Proliferation Markers); Kenneth D. Bauer, PhD (DNA Analysis, Ploidy, and S-Phase), Patrick J. Dean, MD (Tumor Vascularity Markers); Stanley R. Hamilton, MD (Genetics: Oncogene Amplification and Suppression); Steven Itzkowitz, MD (Genetics: Molecular Cytogenetics); Norman Pettigrew, MD (Differentiation Markers); and Leslie H. Sobin, MD (Host Responses). *Additional Participants:* Carolyn C. Compton, MD, PhD; Diane L. Coppock, MD; J. Milburn Jessup, MD; Jeffrey W. Milsom, MD; Stephen Gerard Ruby, MD; and James H. Webb, DO.

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GASTROINTESTINAL PATHOLOGY SOCIETY
PATHOLOGIST-IN-TRAINING AWARD

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

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

A. Brian West, M.B., M.R.C.Path.
Professor of Pathology
Director of Surgical Pathology
John Sealy Hospital, Room 2.180
University of Texas Medical Branch
301 University Boulevard, Route 0588
Galveston, Texas 77555-0588

Phone: (409) 772-2853; Fax: (409) 772-4676

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.

I'm writing to let you know that a GI pathology Internet mailing list has been established. A mail list is an e-mail discussion group. If you have access to the Internet the mail-list should provide an enjoyable way to stay in touch with other GI pathologists and take advantage of your colleagues' experience and expertise.

To subscribe, all you need to do is send the message:

subscribe gipath
to
majordomo@list.mc.duke.edu.

The message should be in lower case and should be in the body of the message, not the subject line.

Copies of all messages sent to the mail-list will come to your mailbox. You can read what you're interested in and delete the rest. If you feel the urge to respond, you can send your answer to the entire list or to an individual subscriber. You can also post notices, questions or topics of discussion to the group.

I hope that this mail-list will help us keep in touch and make the exchanges we enjoy when we get together at meetings a year round process. Please subscribe and encourage your colleagues to as well.

If you have any questions, let me know. You can reach me at

gottf001@.mc.duke.edu
or
919-684-5084.

I look forward to hearing from you electronically, but I still keep in touch with my 'snail-mail' colleagues too.

Sincerely,

Marcia

Marcia R. Gottfried, M.D.

• Durham, North Carolina 27710 •

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 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
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	

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 gastro-intestinal 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

[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 sununary. 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 total 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 complete 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
Fax (513) 558-2289