THE GASTROINTESTINAL PATHOLOGY CLUB NEWSLETTER

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GASTROINTESTINAL PATHOLOGY CLUB OFFICERS AND COMMITTEES

Executive Committee : 1984-85

John H. Yardley, President
Klaus Lewin, Vice-President, President-Elect
Robert H. Riddell, Past-President
Robert R. Rickert, Secretary-Treasurer
Cecelia Fenoglio, Chairman, Education Committee
M. James Phillips, Chairman, Membership and Nomination Committee

Education Committee	Term Expires
David Keren	1985
Robert Rickert	1985
James Madara	1986
Cecelia Fenoglio (Chairperson)	1986
Fred Weinstein	1987
Horatio T. Enterline	1987

Membership Committee, 1983-84	
M. James Phillips (Chairperson)	1985
William Dobbins	1985
Gerald Abrams	1986
Sheldon Sommers	1986
Leonard Kahn	1987
Paul Manley	1987

Fellowship Committee (ad hoc)

John H. Yardley
Harvey Goldman
Klaus Lewin
Rodger Haggitt

Editors of the Newsletter

Donald Antonioli
Henry Appelman
David Owen
Juan Lechago

PRESIDENTS

1980	Henry D. Appelman
1981	Rodger C. Haggitt
1982	Harvey Goldman
1983	Robert H. Riddell
1984	John H. Yardley

SECRETARY-TREASURERS

1980-83	Gerald Abrams
1983-86	Robert R. Rickert

EDUCATION COMMITTEE CHAIRMAN

1980	Donald A. Antonioli
1981	Stanley Hamilton
1982	Klaus Lewin
1983	David F. Keren
1984	Cecelia Fenoglio

MEMBERSHIP/NOMINATION COMMITTEE CHAIRMAN

1980-82	John H. Yardley
1982-84	David A. Owen
1984-85	M. James Phillips

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PRESIDENT'S NOTE

John H. Yardley, M.D.

Greetings!

There is evidence from all sides that the Club continues to grow and mature. The well-received companion program given at the annual meeting of the International Academy of Pathology (US-C) in San Francisco was joined in May by a lively evening program during Digestive Disease Week in New Orleans. This, too, will be an annual event henceforth. For next year, the Education Committee under Cecilia Fenoglio is planning a program during Digestive Disease Week in New York City. Also, the regular companion meeting at the IAP (Toronto) being organized for 1985 is innovative: it is to be sponsored jointly with the Pediatric Pathology Club. In September of this year the Club will be represented at the International Congress of Pathology with a program organized earlier by Harvey Goldman, and the Club will host a party for visitors to the Congress.

To me, participation by the Club in Digestive Disease Week and collaboration with the Pediatric Pathology Club has a very special significance: It is visible evidence of the ecumenical outlook which has been intended for the Club from its inception. Surely, too, cooperation with other organizations will encourage additional non-pathologists to join the Club, an outcome we can all welcome. Currently, 10% of our members are clinicians/pathologists.

Still another sign of growth: In his President's Note to the members last year, Bob Riddell discussed development of a Club journal. This matter will be resolved by the decision to negotiate a special relationship with the American Journal of Surgical Pathology as the "official" journal of the Club. These negotiations should be completed shortly. Association with the Journal will give us a forum for various announcements and for publishing presentations made at Club meetings. It could also provide members with an opportunity to subscribe to the Journal at a reduced rate.

A number of us* participated in an unusual educational experience during Digestive Disease Week that I believe will be of interest to you. As part of the Postgraduate Course in Idiopathic Inflammatory Bowel Disease during Digestive Disease Week, we conducted special sessions on colo-rectal biopsy in inflammatory bowel disease and on dysplasia in IBD. The unusual feature was that a large number of registrants (about 500, almost all of whom were gastroenterologists) were shown actual biopsy specimens using video microscopy and multi-headed (10-headed) microscopes (both generously supplied by Nikon). In each of four sessions a 30 minute didactic session was followed by 60 minutes of microscopy and discussions of case material with preceptors. The response from the registrants strongly suggests that the approach has great potential for expanded use in gastrointestinal pathology. It also suggested a large unmet desire among gastroenterologists for more direct contact with pathologists who have special skills in gastrointestinal disease.

I expect to provide a full report of this experience at a later time, but it was already apparent that the participants were greatly impressed with the direct interaction. The numerous comments from registrants were essentially all favorable and included such statements as: "I learned more about rectal histo-

*Donald Antonioli, Henry Appelman, Rodger Haggitt, Stanley Hamilton, Robert Riddell, Christina Surawicz, and John Yardley. They were joined by Warren Nugent. Cecilia Fenoglio was also scheduled to be present, but she was unable to attend at the last minute.

pathology in one hour than in two years of Fellowship!" "Need this in private practice." "You should have a session at every AGA (and AASLD). Thanks!" "Wonderful. Do it again!" "Fantastically good!! Should become a regular feature with unrestricted attendance. Very, very valuable for all practicing gastroenterologists and trainees! Educational events like this could make real difference in quality of patient care."

Both the video microscopy and multi-headed microscope approaches were well-received, with many proponents of each method (most registrants were exposed to only one). It looks very much like we could and should explore ways to take advantage of the technological advances afforded by the newer equipment to conduct similar sessions at other meetings of clinicians and pathologists.

There was also another message: We should all be working to increase the everyday accessibility that practicing physicians have to pathologists with special experience in gastrointestinal disease. The ways to do this are obvious: Increased training opportunities for pathologists at all levels of experience and adoption of new techniques such as the video and multi-headed microscopy on our home-courts. In this connection, questions were addressed to the registrants about their level of satisfaction with the pathologist service in their own hospitals. The responses were split down the middle: Half of the attendees who responded were either highly or generally satisfied, but the other half indicated at least some dissatisfaction with their own pathologists in the GI area. There could well be some connection between the favorable response to the microscopy sessions at the Postgraduate Course, and the mixed level of satisfaction with their home hospitals, a connection having to do with communication between pathologists and clinicians.

This issue of the Newsletter is the last one to be edited by Henry Appelman and Don Antonioli. We are all indebted to Henry and Don for their enormous contribution to the Club. The Newsletter, which has been their baby from its inception two years ago, provides an important measure of identity and coherence as well as information to the members. Don and Henry have also seen to it that we had some good laughs. Who can forget the cartoons, spoofs and witticisms they have come up with?

At the same time, I am happy to announce that Drs. Juan Lachago (UCLA) and David Owen (Vancouver) have agreed to assume the co-editor roles. I'm sure that Juan and David will continue the solid record begun by Henry and Don.

I want to close by inviting all members to contact me or the editors with their comments and ideas. Someone noted previously that we need correspondence from members in the Newsletter -- here's your chance! I also hope that every member who wishes to participate more actively in the affairs of the Club will make me aware of this so that this opportunity can be extended to as many as possible.

EDITORIAL: HOW FANCY DO WE WANT TO BE?

All of us are subspecialists in gastrointestinal pathology. We belong to an organization which won't let us in unless we admit to such subspecialization. All of us also have egos. Our subspecialty is, in reality, superspecial to each of us. We chose it because it is exciting, intellectually stimulating and sophisticated. It affords us recognition by our colleagues in pathology and in gastroenterology. It sets us apart from other pathologists, both those with no special interests and those with different specialties. Our particular interest area makes us professionally exclusive, and this exclusivity is critical to our intellectual well-being and to our egos, be they vastly inflated or just minimally enlarged. Some of us are not even pathologists; we are gastroenterologists whose interest in pathology has evolved over the years, possibly as a result of lack of interest or intellectual curiosity by the pathologists with whom we have dealt.

The establishment of the Gastrointestinal Pathology Club formalized our subspecialty. Now we have an organization with officers, dues, scientific activities, and, most critical, a committee which helps us decide whom we want to include or exclude from sharing our exalted status. However, the committee members are human: in the future, will criteria for membership in the Club be bent or modified to admit applicants with marginal credentials for a subspecialty society?

One obvious way for us to maintain the glorious days of exclusivity is the board examination. Imagine, if you will, an American Board of Pathology subspecialty exam in Gastrointestinal Pathology and its resultant gilded certificate signed by a cadre of internationally

recognized gut necrophiles, hopefully drawn from among the membership of the GIPC.

As is true with all subspecialty board examinations, the first exam has to be written by someone. Presumably, these would be the same people who signed the gilded certificate. In devising the first examination, it would be difficult for them to be asked to take it. As a result, it is likely that there would be a small group of gut pathologists who would receive Board Certification as the charter grandfathers. This immediately sets such a group apart from the rest of the drones and raises the question as to why they are so special. Presumably their special status results simply from their being asked to write the exam by the American Board of Pathology.

What kind of things should be tested on such an examination? Obviously, as those of us who are active in the field recognize, there are some issues which are cut and dried and not at all controversial. Cancer occurs in the stomach and in the colon, peptic ulcers occur in the stomach and duodenum, but not in the colon, and esophagitis is a disease which requires the presence of an esophagus for its manifestations. At the same time, however, there are a number of issues in our business which probably are controversial and in which pertinent information changes from month to month. Do all colonic carcinomas arise from an adenoma precursor? Is Hodgkin's disease ever a primary gastrointestinal lymphoma? How high above the lower esophageal sphincter must the biopsy be taken before Barrett's mucosa can be diagnosed? Any examination testing the knowledge of gut pathologists should raise these as controversial issues and should avoid testing on them as non-debatable factual matters. However, such an approach would demand

that the examiners understand the controversies as much and as well as the examinees. This also emphasizes the problem of who will be the grandfathers.

Another issue to consider is who would be eligible to take this examination. If specific training in gastrointestinal pathology is one of the requirements, then virtually none of us would be allowed to take the examination, since fellowships in gut pathology have not been available and most of us are self-taught to a great extent. On the other hand, if certain requirements for subspecialty training are required, then we have to develop programs which will allow such training to occur. This would then require a whole series of certification procedures, inspections, and the resultant bureaucracy. On the other hand, if no subspecialty training is required, then anyone could take the examination who felt ready and who could pay the necessary fee. This would result in a further loss of exclusivity, since now anyone who wanted to read a few books could presumably take and pass the examination. Believe it or not, there are members of our profession who take pride in collecting Board Certifications.

In this editorial, the issue of a subspecialty board examination in gastrointestinal pathology has been brought to your attention as members of the GIPC. Your editors have their own points of view, and they request letters to the editor from the membership concerning this most important issue.

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DAA/SR
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GASTROINTESTINAL PATHOLOGY CLUB

SUNDAY, MARCH 10, 1985

PEDIATRIC AND ADULT MANIFESTATIONS OF GI TRACT DISEASE

CO-SPONSORED BY THE SOCIETY FOR PEDIATRIC PATHOLOGY

Moderators: Cecilia M. Fenoglio, M.D.
V.A. Medical Center
Albuquerque, New Mexico

Arthur C. Weinberg, M.D.
Children's Medical Center
Dallas, Texas

Gastroesophageal Reflux in Children and its Sequelae - Beverly Barrett Dahms, M.D., Rainbow Babies' and Children's Hospital and Case Western Reserve College of Medicine, Cleveland, Ohio

The Biopsy Diagnosis of Infectious Diarrhea in Children - John Fisher, M.D. Children's Hospital, Buffalo, New York

Allergic Diarrhea - Harvey Goldman, M.D., Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts

Polyposis Syndromes - Rodger Haggitt, M.D., Baptist Memorial Hospital, and University of Tennessee Center for the Health Sciences, Memphis, Tenessee

Hirschsprung's Disease: Current Issues - Arthur C. Weinberg, M.D., Children's Medical Center of Dallas, Dallas, Texas

Muscular Disorder of the Hollow Viscera - Michael D. Schuffler, M.D., University of Washington, Seattle, Washington

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LAWRENCE D. TRUE, M.D. 962-9318

March 22, 1984

Gastrointestinal Pathology Club
Executive Committee Meeting
March 11, 1984

The meeting was held in the Hilton Hotel, San Francisco at 9:00 a.m. Present were Goldman, Keren, Owen, Rickert, Riddell, and Antonioli, Appelman and Haggitt by invitation.

1. The minutes of the last meeting were approved.

2. Financial Statement: A copy is enclosed with the minutes of the Business Meeting. A further increase in the balance was reported together with interest as a result of prudent investing. It was pointed out that there will be further expenses this year including those for Dr. Isaacson, and the Newsletter, secretarial help for which a rate of $8 an hour was approved. A fee will also be required for room charges at the AGA, for room charges and a brunch at the IAP congress. At the latter, a reception will be held in the Voltaire Room of the Fontainbleu Hotel on September 5th 1984 at 6:00 p.m. to discuss future collaborative plans with analagous Societies/Clubs in other countries. It was decided that the Club should not pay for drinks, but that a cash bar should be requested.

   The question of delinquent dues was raised, 4 members and I associate (of 71 and 4) being involved. Each will be approached personally and reminded.

   In view of increased expenditure but also an increased balance, it was decided to keep membership fees the same for 1984.

3. Appointments: The members of the newly-constituted Education and Membership/Nomination Committees are as follows:

   a) Education Committee: New members are Weinstein and Enterline. Fenoglio will be the new chairperson. Rotating off are Schenk and Mitros; remaining are Keren, Rickert and Madara.

   b) Membership/Nominating Committee: New members are L. Kahn and Manley; Phillips will be the new chairperson. Rotating off are Owen and Ming; remaining are Dobbins, Abrams and Summers.

4. Committee Activities:

   a) Education: The afternoon session and those at the AGA and the IAP congress are arranged (see last Newsletter). Concern was raised about whether the AGA program

would be appealing. Goldman responded that it was meant to be a more research-oriented session. The response to this session will be carefully evaluated. Keren reported that the Pediatric Pathology Club had agreed to a joint meeting on Sunday afternoon in Toronto next year and mentioned several speakers and possible topics. Several other possiblities were also suggested, but the final decisions will be left to the Education Committees of both Organizations.

Subjects of future Educational Sessions of the Club were raised as most of those received from the initial questionaire had been covered. Rickert said that he could send a new questionaire to the membership for their ideas; this was approved.

b) Membership/Nominations: There were 19 applications for full membership of which 17 were approved. The remaining two will be offered associate member status. Two further applications for associate membership were approved. Lewin was the Committee nominee for the position of President Elect, a position that he was willing to accept. This was approved unanimously.

c) Fellowship: Yardley outlined this committees works since being formed as an Ad Hoc Committee by Haggitt. Numerous responses from members regarding their training programs had been obtained and a first draft of the Committees report had been prepared. Yardley will address the membership briefly at the business meeting and the final report will be published in the Newsletter.

d) Newsletter: Antonioli and Appelman had been asked to look into the best means of appointing successors to themselves as Editors. The question of whether overlapping terms would be better than changing both editors together was discussed. They argued strongly that two editors should be appointed together for a 3 year period and that an editorial board would be formed by the 2 editors and the 2 past-editors. These suggestions were approved. A short list of possible candidates for the next editors was submitted to the President Elect (Yardley) who would attempt to appoint new editors from this list.

5. Affiliation of GPC and American Journal of Surgical Pathology: The rationale for this had been raised by the Editors and responded to in the Newsletter presidential note. Masson's interest, the publicity that would be obtained, publications of proceedings and the possible subscription advantages were mentioned. The question was raised as to whether such an affiliation is necessary and what the Club would gain. It was suggested that an Ad Hoc Committee be formed to investigate the advantages and disadvantages of such an affiliation. Riddell agreed to set up such a committee.

6. Co-operative Projects: The two projects suggested for the Club (Menetrier's disease and G.I. lymphomas) had met with total apathy and there had been no response to either project. To try and do better two Ad Hoc Committees will be formed for the 2 projects in which these was considerable Club interest. Cooper had agreed to chair the committee investigating invasive adenomas, and Frei that on Barrett's esophagus. Club members interested in participating in these projects will become members of these committees.

7. Other Business:

Executive Committee: It was suggested that there should be a second meeting of the Executive Committee possibly during Digestive Diseases Week in view of the amount of business arising. It was generally agreed that this would be valuable. Although, all members might not be able to attend, it would still offer the time when the greatest number were likely to be present together.

It was also apparent that it would have been of tremendous help to have incoming Chairpersons of the Club Committees, particularly that for Education, present at the Executive Committee Meeting as a variety of problems in which they will become involved are discussed and are handed over to them; the Editors of the Newsletter should also attend. It was agreed that all 4 became ex officio members of the Executive Committee and be invited to their meetings.

The meeting was adjourned at about 11:45 a.m.

Respectfully submitted,

Robert H. Riddell, M.D.
Past-President, Gastrointestinal Pathology Club

GASTROINTESTINAL PATHOLOGY CLUB
Hilton Hotel - San Francisco, California
Annual Business Meeting - March 11, 1984

Members Present: Drs. Abrams, Antonioli, Appelman, Chejfec, Cooper, Dayal, Dunn, Fenoglio, Goldman, Gourley, Haggitt, Hamilton, Isaacson, E. Kahn, Kelly, Keren, Lechago, Lee, Lewin, Madara, Manley, Mitros, Nassar, Norris, D. Owen, R. Owen, Pascal, Rickert, Riddell, Schenk, Snover, Sobin, Sommers, Sprinz, Sternberg, Tomasulo, Wirman, Yardley

The meeting was called to order by Dr. Riddell at 5:10 P.M.

1. The minutes of the meeting of February 27, 1983 were approved as distributed.

2. Financial Report: Dr. Rickert presented the 1983 Financial Report as noted below:

Balance As of February 27, 1983.	$2,426.96
Receipts, March 1, 1983 - February 29, 1984 (Dues)	$1,770.00
Interest Earned, - March 1, 1983 - February 29, 1984 . . .	$ 78.99
	$4,275.95
Expenses, March 1, 1983 - February 29, 1984	(578.52)

1983 Meeting Expenses	$118.76
Duplication and Mailing Costs of Spring '83 Newsletter	326.32
Transfer of Records & Files	3.65
Bank Charge	4.79
Secretarial and Mailing Costs of Fall '83 Newsletter	125.00
	$578.52

Balance As Of February 29, 1984 . . . . . $3,697.43

3. Committee Reports
   A. Education: 1) It was reported that the plans for the G.I. Pathology Club presentation during Digestive Disease Week have been finalized. The meeting will take place at the New Orleans Hilton and Towers on Tuesday, May 22, 1984 from 8:00 -10:00 P.M. 2) The program for the IAP Congress in Miami (September 3 - 5, 1984) has also been arranged. A reception also will be held during the meeting in the Voltaire Room of the Fontainbleu Hotel on September 5, 1984 at 6:00 P.M. At this reception future collaborative plans with companion societies in other countries will be discussed. A cash bar will be available. 3) Dr. Keren reported that the 1985 scientific session of the G.I. pathology Club in Toronto will be held jointly with the Pediatric Pathology Club. Details are being discussed by the Education Committee.

B. Membership/Nomination - Dr. David Owen reported that there were 19 applications for Regular Membership of which 17 were approved. The other two were recommended for Associate Membership along with two additional applications for Associates. The Committee also recommended the nomination of Dr. Klaus Lewin for the position of President Elect. This nomination was unanimously approved by the membership.

C. Fellowship - Training Program: Dr. Yardley reported on the responses received thus far from members who have G.I. Pathology training programs. A final report will appear in the next Newsletter.

D. Newsletter - Dr. Riddell announced that Drs. Antonioli and Appleman will be stepping down as editors. It has been recommended that two editors serve together for a three-year term and that the two current and two past editors serve together as an Editorial Board. The new President (Dr. Yardley) will appoint two new editors after he assumes office.

4. Changes in Standing Committees - Dr. Riddell announced the following changes in committee membership:
   A. Education: New members will be Drs. Weinstein and Enterline. Dr. Fenoglio will be the new Chairperson. Leaving the committee will be Drs. Schenk and Mitros and remaining will be Drs. Keren, Rickert and Madara.

   B. Membership/Nominating: New members will be Drs. L. Kahn and Manley. Dr. Phillips will be the new Chairperson. Leaving the committee will be Drs. D. Owen and Ming and remaining will be Drs. Dobbins, Abrams and Sommers.

5. Participation in Other Meetings
   A. Digestive Disease Week - New Orleans - see Education Committee Report above
   B. IAP Congress - Miami - see Education Committee Report above.
   C. IAP 1985 - Toronto - see Education Committee Report above.
   D. Digestive Disease Week 1985 - program to be developed by Education Committee. G.I. Pathology Club Executive Committee will also meet.
   E. World Association of Pathologists, 9/29 - 10/4/85 - Brighton, U.K. Dr. Goldman announced this meeting. Any members interested in presenting should contact Dr. Goldman.

6. Old Business
   A. Timing of G.I. Pathology Club Meeting and G.I. specialty conference; - Efforts are underway to schedule these two sessions on more proximate days than the traditional Sunday and Thursday. In the future these will be on a rotational basis for the various clubs and specialty groups.

7. New Business
   A. Association with the American Journal of Surgical Pathology - Dr. Riddell reported on preliminary discussions with the Journal. Dr. Riddell will appoint an Ad Hoc Committee to further discuss what, if any, relationship should be developed between the Club and the Journal. The membership will be kept informed concerning these discussions.

B. Cooperative Projects - Dr. Riddell reported that the results of the questionaire about cooperative projects indicated considerable interest in a study of invasive cancer in adenomas and of Barrett's esophagus but no interest in studies of Menetrier's disease or G.I. lymphomas. Two Ad Hoc Committees will be formed to organize the two projects which generated interest. Dr. Harry Cooper will chair the malignant polyps project and Dr. John Frei the Barrett's project. As far as the other projects are concerned it was suggested the examples of Menetrier's disease be sent to Dr. David Owen and fresh tissue from gastrointestinal lymphomas be referred to Dr. Leonard Kahn.

8. Election of Officers - Dr. Klaus Lewin was elected Vice President/ President Elect.

9. Announcement of New Members - Dr. Owen reported that the following physicians have been elected to regular membership: Drs. Beverly Dahms, Ludwig Deppisch, Stephen Geller, Hugo Jauregui, James Kelly, Neelam Kumar, M. Peter Lance, Robert Owen, Eugene Perrin, Robert Petras, Mukunda Ray, Helen Shields, Monamed Shousha, Hattan Sumner and Jerry Trier. He further reported that the following physicians have been elected to associate membership: Drs. Paramjit Bhatia, Linda Ferrell, Steven Freestone and Jan Silverman.

10. Induction of New President - at this point Dr. Riddell introduced Dr. John Yardley as the new President of the Gastrointestinal Pathology Club. Dr. Yardley made a few remarks and commended Dr. Riddell for his excellent job as President.

11. There being no further business, the meeting was adjourned at 5:30 P.M.

Respectfully submitted,

Robert R. Rickert, Secretary

RRR/th

GIPC MALIGNANT COLORECTAL POLYP STUDY

At the last IAP meeting, an Ad Hoc Committee was formed to study malignant polyps of the colon and rectum. The Committee is asking members of the GIPC to contribute cases. This study will be a retrospective study of histopathological determinants of endoscopically removed malignant polyps of the colon and rectum. Our goal is to see which histological findings determine adequacy (or inadequacy) of therapeutic polypectomy. This will be a clinico-pathological study. It is hoped that by obtaining enough cases, we can have a statistically significant study which we believe will be of great help in the management of the patient with a malignant polyp. The following materials are requested:

1- Slides of endoscopically removed malignant (invasive cancer) polyps of the colon and rectum.

   a- Those cases treated by polypectomy only- with a minimum of a 5 year follow-up.

   b- All cases treated by polypectomy with subsequent surgical resection.

2- Copies of: Pathology reports and endoscopic reports (if available), status of patient (NED, DOD, etc), data as to previous or subsequent colo-rectal lesions.

Please send material to: Harry S. Cooper, M.D., Department of Pathology, Thomas Jefferson University Hospital, 111 S. 11th Street, Philadelphia, PA 19107.

Note: All materials will be returned upon completion of this study.

NOTICE

The World Association of Societies of Pathology (WASP) Meeting, scheduled for Brighton (UK) from 29 September - 4 October, 1985, has been CANCELLED.

Review of A Recently Published GI Manuscript

"A Freeze Fracture Study of Crohn's Disease of the Terminal Ileum: Changes in Epithelial Tight Junction Organization" Morin M, Greenstein AJ, Geller SA, Gordon RE, Aufes AH, Amer. J. Gastro. 78:537, 1983.

Background

When tissues are frozen at low temperature and fractured, one preferential plane of fracture is along the internal hydrophobic plane of phospholipid bilayers. Thus cell membranes are separated into two lipid monolayer leaflets-that adjacent to the "protoplasm" (P leaflet) and that adjacent to the extracellular space (E leaflet). The fractured faces of these leaflets are referred to as the P-face and the E-face. Additionally, it appears that integral membrane proteins may preferentially segregate with one of the two membrane leaflets. Indeed, some integral membrane proteins which partition with the P-face actually have extracellular glycosylated residues that are pulled through the E leaflet during the fracture process (Science 203:1343, 1979)! Thus both the E and P faces which result from the above process consist of smooth planes littered by "bumps" believed to correspond to integral membrane proteins or protein complexes. If, at high vacuum, one coats such a surface, at an angle, with an electron dense metal (platinum), one then obtains a metallic replica of the fracture face which can be visualized with exquisite resolution and examined in an electron microscope. This technique has been extremely useful in probing the ultrastructural characteristics of membranes both in native and in modulated states.

In the specific case of the intercellular tight junction, the constitutive structural subunits appear, under routine conditions of fixation, as linear arrays of fused particles thus resembling strands. Each strand represents a linear fusion site or kiss between the lateral membranes of adjacent cells. When these strands are intact they restrict the flow of macromolecules across them. However, a substantial degree of interest also has flourished over the number of horizontal strands comprising the tight junction in various epithelia for evidence indicates that as strand count rises arithmetically, paracellular conductance (i.e. passive paracellular ion flow) decreases logarithmically (J. Membrane Biol. 39:219, 1978). Thus by analyzing tight junction structure with freeze fracture techniques one can obtain some idea of the ability of the junction to resist both passive macromolecular and passive ion flow across it. This junctional barrier represents one of the most biologically important barriers in epithelia for it allows epithelia to maintain transepithelial gradients of charge and solute.

Newer freeze fracture techniques permit investigators specifically to label lipids by methods which result in distinct perturbations of the membrane faces thus allowing one to define specific lipid domains within membranes. Thus the utility of this technique in analyzing cell membranes is constantly growing.

Freeze fracture has recently been utilized to great advantage in the gastrointestinal tract in projects ranging from studies of the structural control of passive intestinal permeability to the localization of proton pumps within parietal cell cytoplasmic vesicles. In my view, however, this technique is predominantly a research tool which currently has no role in diagnostic surgical pathology. This may change in the

future, however. For example, some intestinal epithelial cells exhibit highly specific arrangements of their intramembrane-particles (Gastroenterology 83:981, 1982) and perhaps such phenomena could be used to identify intestinal-type differentiation in problematic tumors. Indeed, such potential uses of freeze fracture would probably already have been probed were it not for one major limitation of this technique: it is highly cumbersome and expensive.

Summary of Paper

The study by Marin et al, referenced above, utilizes freeze-fracture techniques to examine the structure of intercellular tight junctions in the ileal mucosa of patients with active ileal Crohn's disease. They report (non-quantitatively) a variety of abnormalities in tight junction structure between epithelial cells including tight junction strand fragmentation, loss of horizontal polarity, and focal absence of the tight junction. They opine that the tight junction abnormalities in these patients may contribute to a disturbance in epithelial barrier function.

Comment

In general the technical aspects of replication have been well managed in this paper and the replicas are of suitable quality. However, one might have reservations concerning the basic approach of this study. The authors ask the question: Could abnormalities in tight junction structure substantially contribute to a defective epithelial barrier in active Crohns Disease of the ileum? They certainly utilize the correct structural technique to probe sensitively for potential structural defects in the paracellular pathway which may be functionally important. However, they apply these techniques to tissues which largely have existing mucosal erosions and ulcerations (i.e. paracellular defects so great as to be appreciated grossly or at least by light microscopy).

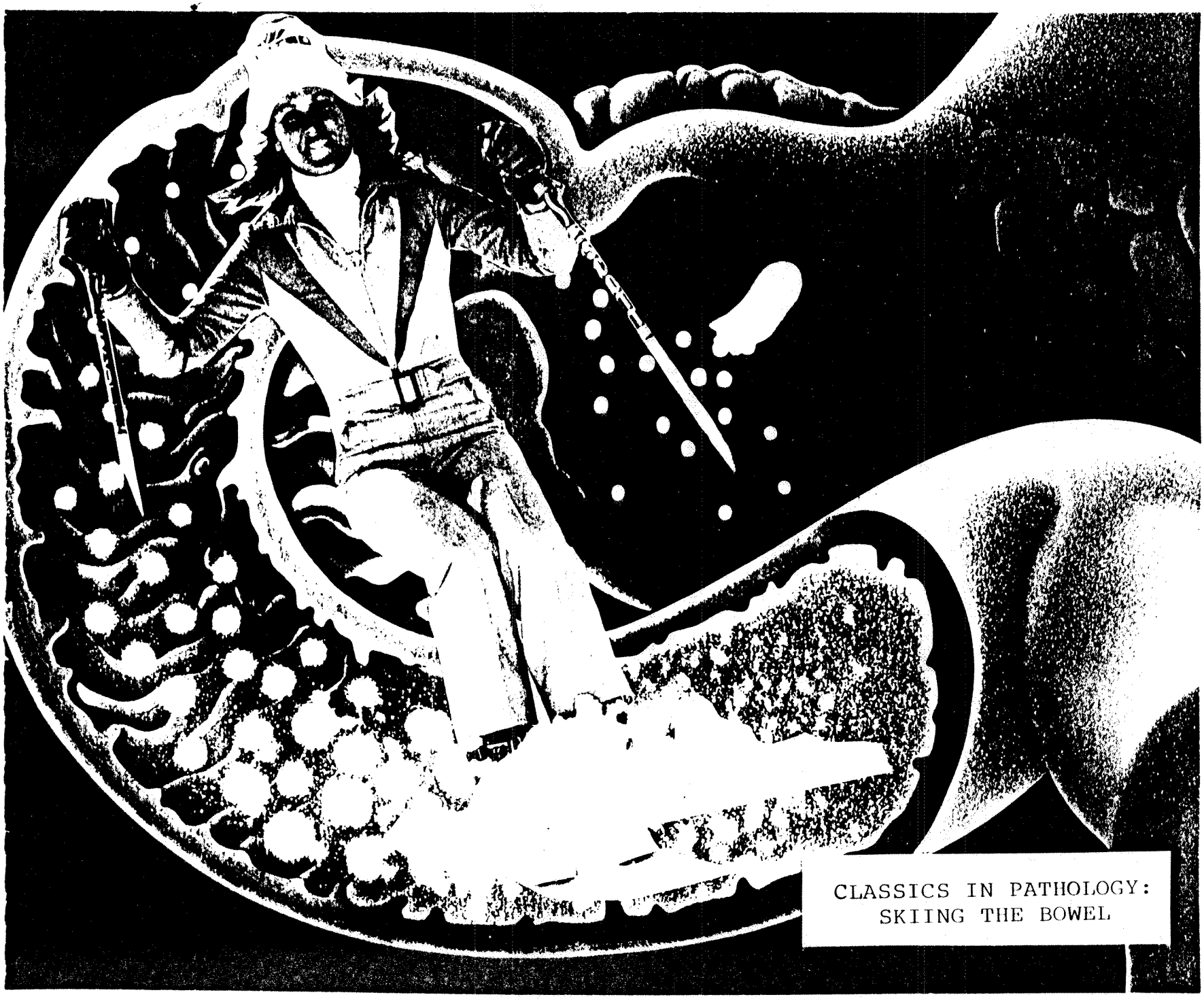
This paper does highlight how treacherous interpretation of freeze-fracture images can sometimes be. For example, the tight junction image shown to illustrate a frank transjunctional break (Figure 5) might be interpreted differently. The apical strand appears intact at this point. Moreover the P face strand discontinuities which are present below the apical strand could represent foci in which the strand focally partitions with the complementary unexamined E face. Such P face discontinuities have been shown to commonly occur in undisrupted native tight junctions and have been clearly documented by retrieving and simultaneously studying both faces of the membrane (J. Cell Biol. 96:745, 1983). Similarly the example of an absent tight junction given in Figure 11, in my view, really is a fracture plane through an apical membrane of a goblet cell which is invaginated into the apex of the cell due to mucous release. This membrane should not be expected to display a tight junction since it is not a lateral membrane. This interpretive problem and its recognition in association with intestinal goblet cells has previously been documented (J. Membrane Biol. 66:145, 1982). Moreover the structural characteristics of the microvilli of the particular cell in question clearly identify it as a goblet cell (Gastroenterology 78:963, 1980) and

the crossfractured space identified as the paracellular space is actually the portion of the goblet cell cytoplasm between the lateral membrane and the indented apical membrane (J. Membrane Biol. 66:145, 1982). Although for these reasons, this is not an adequate example of complete tight junction disruption, it is still clear that junctional disruption must be present in the tissues studied since they contain disruptions in epithelial continuity (erosions and ulcers).

In summary the freeze-fracture technique is currently a powerful tool with which to analyze various aspects of membrane structure. However interpretation of the images produced requires great care as does identification of appropriate questions which may be reasonable approached with this tool.

— James Madara, M.D.

(Editors' Note: We thank Dr. Madara for his succinct review of freeze fracture theory and technology as well as for his critique of the paper. Determination of the usefulness and limitations of this technique will be of great interest to GI pathologists.)


CLASSICS IN PATHOLOGY:
SKIING THE BOWEL

THE GPCN GOES TO THE IAP, MARCH 1984

Once again, fellow readers, your wondering co-editors were assigned the onerous task of reviewing the tube-related odds and ends at the IAP Annual Meeting. Fortunately the meeting was held in San Francisco, and the weather was generally good, so there was no excuse for boredom. In fact, your co-editors found the city more to their liking than the papers and posters which is why this discussion is shorter than usual.

The annual Yogesh vs. the Yalies battle for supremacy in the case: author ratio race was a total bust this year. First of all, the Yalies pulled out of the GI sections completely. This was a huge disappointment. After all, last year they described carcinoid tumors of the appendix with pale cells. This year, the least we all expected was dark cells, but those sons of guns forfeited. Yogesh, in the meantime, as if to thumb his nose at us after his record setting performance last year, turned in a mediocre seven cases by four author paper with no fewer than 46 brown stained pictures. Dear Readers, it was a disaster, a non-battle, a wash out. Your editors fell asleep. Meanwhile, Rodger Haggitt, sporting a new butch haircut and spats, decided to talk about adenomas and cancer. He had a real problem. He and his buddies and buddietts generated so much data that they had to feed it into a computer that had been programed to understand the adenoma-carcinoma sequence better than people could. However, as we discovered during the presentation, Rodger's data was being held for ransom by the computer; in other words, he was a prisoner of his own data base. That is why he decided to designate all carcinomas by the all inclusive term: "invasive adenomas".

The lovely and talented Neelam B. Kumar, a newly elected member of this august society had the gall to get up in front of the audience and present some data on a common problem. Not only did she break all precedents by doing that, she had the audacity to present such data accumulated in an un-named institution in, of all places, the mid-west! Yes, that's mid-west, middle America! Well, you cannot believe the fury this caused in Baltimore and Boston. Neelam and her co-worker, an unnamed balding newsletter co-editor, were bodily thrown from the room and carried off by a flying wedge of eastern gut pathologists to the bathrooms where they were forced to have acute bloody diarrhea.

Meanwhile, Antonioli, Goldman, and the rest of the Boston Brahmins reported on the eosinophil in the reflux esophagus. Beth Isreal hospital is also known as "heartburn heaven", an allusion to their kosher kitchen. The cooks use a highly allergenic schmaltz (chicken fat for you non-believers) which tends to coat the esophagus calling forth an eosinophilic infiltrate. At the same time, the kosher cooking induces chronic reflux. These factors explain why only in Boston, and only at Beth Israel, does reflux come with eosinophils. Of course, they tried to make all this sound very scientific and hide all these realities, but we all know the truth.

Probably the most disgusting thing we encountered during the entire meeting was a discussion about warts in the esophagus. It was bad enough having papilloma virus in the crotch, but putting them in the esophagus was the last straw. This study came from Columbia after Cel Fenoglio left. She never ever would have allowed something as kinky as this to happen had she still been there.

Then, to top it all off, as if DRG's were not enough, Robert Riddell proceeded to heal Barrett's esophagus which cuts the hell out of our business, but he doesn't care - he went off to Canada. In an attempt at rebuttal, Stanley Hamilton made colon cancer in cute little animals. At least we still have veterinary pathology to fall back on.

At this point, Dear Readers, your valiant co-editors had had enough. We tucked our notebooks in our pockets and headed for the North Beach section in search of an esophageal wart.

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The Editors Review GI Papers at the IAP, 1984

Two platform sessions were devoted to gastrointestinal pathology this year. Winkler and coworkers (Columbia) began the first session by demonstrating that human papillomavirus (HPV) infection can be documented (albeit rarely) in the esophagus. The histology is like that of HPV infection of the cervix, with koilocytosis, anisonucleosis, and multinucleation predominating. Immunoperoxidase staining for HPV antigens was positive in about 30% of their 13 cases and was confined to the nuclei of koilocytotic cells. Nine patients had symptoms of esophagitis. Of interest, eleven of the 13 cases were identified in biopsies from flat mucosa; only two were papillomas. Thus, analogous to the situation in the lower genital tract, most esophageal HPV infections will probably be nonexophytic and fairly subtle in their endoscopic appearance. (Editors' note: We suspect the pathologist will most often be the first to make the diagnosis.)

Bacterial esophagitis was the next topic, presented by Dr. Walsh et al (Johns Hopkins). This is an unusual cause of esophagitis; they presented 21 cases, 20 of which were diagnosed at autopsy (but we were not told what percentage of autopsies these cases represented for the period surveyed). As might have been expected, the patients had severe underlying diseases. In 16 of the 21, the mucosa was grossly abnormal but in 5 was intact, the diagnosis being evident only at microscopy. Microscopic evidence of injury and bacterial proliferation varied from superficial to transmural, the latter being associated with septicemia. (We were intrigued with the fact that some of the patients were neutropenic, and wondered whether some of the cases could be the esophageal analog of neutropenic enterocolitis. Dr. Walsh informed us that none of the 20 autopsy patients had evidence of the latter condition.)

Continuing with esophageal pathology, Dr. Brown and colleagues (Beth Israel and Brigham and Women's Hospitals, Boston) documented intraepithelial eosinophils as a common (and often the only) finding in endoscopically-derived grasp-type mucosal biopsies from adults with reflux esophagitis. Grasp biopsies usually cannot be properly oriented so that evaluation of basal layer thickness and papillary length as evidence for esophagitis is not possible; intraepithelial eosinophils can be identified regardless of tissue orientation. (The documentation of intraepithelial eosinophils in adults with reflux now extends the age range for this finding, which has previously been noted in infants and children.)

Riddell et al (U. Chicago) presented evidence that Barrett's esophagus may regress after successful antireflux surgery. Of 11 patients having surgery, several had "descent of the squamocolumnar junction" postoperatively; in 3 the esophageal surface developed squamous epithelium but underlying glands of Barrett's type persisted. (The topic of regression of Barrett's esophagus after anti-reflux surgery is controversial. Dr. Riddell's data suggest that regression can occur, but raise another issue: what is the natural history of the residual glandular epithelium under the squamous surface? How should such cases be followed? At the minimum, patients with apparent regression require biopsies, whether grasp or suction type, deep enough to sample the subepithelial stroma).

Moving to the stomach, Lewin and coworkers (UCLA) presented five patients with primary antral gastrin (G) cell hyperfunction, a clinical syndrome defined as basal hypergastrinemia, excessive gastrin response to feeding, peptic ulcer disease (PUD) and no ectopic source of gastrin secretion. All 5 patients were male, had early onset of PUD, and 4 of 5 had a family history of PUD, all in male relatives, suggesting the possibility of a male sex-linked hereditary disorder. The number of antral G cells in the 5 men was twice than in 12 controls (tissue from patients having normal antral tissue and a variety of inflammatory conditions) ($p < 0.05$). Of the 12 controls, only one reached the lower end of the range of G cell numbers noted in the 5 patients. (This elegant study confirms that primary G cell hyperplasia exists as a clinical entity. Another practical point made by the authors was that in biopsy specimens, if G cells form clusters within glands, G-cell hyperplasia, either primary or secondary, should be considered.)

Fundic gland polyposis (FGP) is characterized by the development of multiple small sessile proximal gastric polyps consisting of simple corpus-type glandular hyperplasia with glandular microcysts. When first described, the lesion was felt to be specific for patients with familial adenomatosis coli. However, Choi et al (Jefferson) reported that among their 8 cases of FGP, only 2 had colonic polyposis. The clinical significance of FGP remains unclear. (This study confirms other recent reports that 50 to 75% of cases of FGP occur without colonic adenomatosis (AJ Gastro 1984; 79:98. Gastroenterology 1984; 86:1437). We have noted FGP in several biopsies of gastric remnants after gastroenterostomies.)

Hepatic arterial infusion of chemotherapeutic agents to treat carcinoma metastatic to the liver has been associated with the development of benign but atypical gastric ulcerations which clinically and microscopically may mimic primary or metastatic carcinoma. Petras and Hart (Cleveland Clinic) analyzed tissue from 5 such cases to determine criteria to separate these lesions from ulcerated early gastric cancer. Useful features for diagnosing chemotherapy-induced ulcers included: bizarre glandular cell atypia greater than that seen in most cancers; low epithelial cell nuclear:cytoplasmic ratio; resemblance to radiation effect; preservation of architecture despite atypia; and detection of similar atypia in mesenchymal cells of the associated granulation tissue. (This study extends the observation of Weidner et al (Am J Surg Pathol 1983; 7:261) about atypical gastric ulcers after hepatic arterial chemoperfusion. As the present authors stress, knowledge of the clinical history is essential for correct tissue interpretation in this situation.)

In a series of elegant immunocytochemical studies, Dayal and his colleagues (Tufts), using newly-characterized antibodies, documented the presence of growth hormone-releasing factor (GRF) in 23% of a series of pancreatic endocrine tumors and 4% of GI carcinoids. GRF immunoreactivity was not present in normal GI mucosal cells or pancreatic parenchyma. (GRF joins the list of regulatory peptides formerly thought to be present in brain only which also occur in endocrine tumors of the gut and pancreas.)

Sheehan et al (Dublin) characterized subtypes of O-acyl sialomucins in foregut metaplasias and adenocarcinomas. One subtype occurred more frequently in metaplasia and dysplasias, another occurred predominantly in cancers; the reader is referred to the abstract in Lab. Invest. for details. The authors postulate that the polyhydroxy side chain of the sialic acid molecule may be

modified in a stepwise fashion in association with malignant transformation. (Use of histochemical methods may help to elucidate the chain of events in metaplastic and neoplastic transformation. The overlap of findings among metaplasias, dysplasias and carcinomas, however, make the techniques of limited practical value at this time in the diagnosis of difficult cases.)

The second GI session began with an evaluation of upper GI biopsies in the detection of graft versus host disease (GVHD). Snover and associates (Minnesota) studied gastric and small intestinal biopsy specimens from 16 bone marrow transplantation patients with UGI symptoms. Eight of the 16 were shown to have UGI GVHD (4 gastric, 4 intestinal). The biopsies showed a variety of cytodestructive and inflammatory charges, but the hallmark of GVHD injury was the presence of single necrotic epithelial cells in the regenerative zone, i.e., in the neck region of gastric glands and at the base of small intestinal crypts. Other features were less specific and in some cases might have been secondary to CMV infection and/or cytoreductive therapy. (Snover stressed the importance of single cell necrosis and also the fact that it may be very focal, so that examination of multiple levels (at least 3 per biopsy) is indicated.)

Lee and coworkers (Henry Ford Hospital, Detroit) demonstrated that the granules of Paneth cells, when viewed through a fluorescence microscope, have a yellow-green fluorescence in H&E-stained paraffin-embedded sections fixed with either 10% buffered formalin or Helly solution. Unstained sections did not fluoresce; the authors feel the use of eosin-Y is related to the development of fluorescence. In addition, no fluorescence was observed in H&E-stained sections fixed in solutions containing acetic acid, such as Bouin's or Carnoy's fluid. (This technique seems to be most useful as a research tool, in survey searches for Paneth cells.)

The problem of separating acute self-limited colitis (ASLC) from first attacks of chronic ulcerative colitis (CUC) was investigated by Kumar and associates (U. Michigan) in a large retrospective study of colonic and rectal biopsies. They concluded that a distinction between ASLC and CUC can be made in most cases if a biopsy is done very early (0 to 4 days) after the onset of symptoms. Both ASLC and first attacks of CUC specimens may show edema and increased inflammation in the lamina propria, crypt injury and abscesses, and erosions and mucin depletion. However, CUC cases, in addition, will have crypt distortion and plasma cells around the bases of crypts, features not seen in ASLC. (ASLC needs to be separated from CUC because of the obvious differences in surveillance requirements and prognosis. This study offers some potentially useful guidelines. It seems that the later biopsies are taken during the acute attack, the less discriminatory the features become. One problem is the question of how many patients get biopsied at the very onset of their illness. Also, do CUC patients <u>always</u> show chronic changes in every endoscopically-derived biopsy? What is needed is a prospective study to evaluate the utility of the above criteria.)

This year's adenoma-carcinoma paper came from Glotzbach <u>et al</u> (Baptist Memorial Hospital, Memphis), who retrospectively analyzed 129 colorectal carcinomas that arose in adenomas but had invasion no deeper than the submucosa. Mean patient follow-up was 6.7 years. They confirmed results from earlier studies that 1) gross appearance, 2) histologic type of adenoma, and 3) cancer within the mucosa, confined to the head of the polyp, or in the upper part of the stalk were features not associated with an adverse outcome (i.e., positive

nodes on colectomy; recurrent disease; or death). However, 25% of 28 patients with submucosal invasion had an adverse outcome, as did 6 of 42 (14%) of those with rectal lesions, in which location lesions with submucosal invasion were over-represented. There were insufficient cases with poor differentiation or lymphatic invasion to make valid prognostic comments concerning these parameters. (It now seems clear that stalked adenomas with typical well-to-moderately differentiated carcinomas confined to the mucosa, head of the polyp, or upper stalk can be treated conservatively, whereas those extending into the true submucosa require a resection. The data to be generated from the GIPC cooperative study headed by Harry Cooper will, we hope, give us some hard data on the relative importance of lymphatic invasion and poor differentiation in determining outcome.)

In the final paper, Hamilton and others (Johns Hopkins) evaluated by electron microscopy cellular changes in grossly normal colonic mucosa from rats given azoxy-methane (AOM), a colonic carcinogenic agent. Their aim was to define short-term changes related to drug toxicity versus persistent changes more likely to be precursors of cancer. Persistent, dose-dependent EM changes noted at 15 weeks after cessation of AOM included: numerous mid-crypt mitoses; numerous crypt cells with enlarged nucleoli; decreased number of goblet cells; and fewer apical cytoplasmic vacuoles in upper crypt cells. (Although persistent, the changes noted could still be regenerative; persistence should not be equated with dysplasia in this context).

GI84-1 (Beth Israel Hospital, Boston, Dr. Donald A. Antonioli):

A 49-year-old white female was well until 1978, when she developed epigastric pain and nausea. UGI series demonstrated enlarged folds in the gastric corpus and antrum. She received antacid therapy for a diagnosis of gastritis and was asymptomatic within two months. She was well until early 1983 when the prior symptoms recurred, accompanied by vomiting, occasionally blood-streaked. No other GI symptoms, weight loss, or alcohol or aspirin ingestion. PE: Unremarkable except for epigastric tenderness and bilateral lower leg edema. Lab: Unremarkable except for an hematocrit of 31 and serum albumin of 3.0. Gastric secretory study: BAO 5.7 and MAO 30 mEq/hr. Serum gastrin: 60 pg/ml. UGI series and endoscopy revealed diffuse gastric mucosal nodularity, enlarged folds, and three large polyps up to 9.0 cm diameter. Esophagus and duodenum unremarkable. Despite vigorous medical therapy with antacids, cimetidine, and probanthine, her symptoms persisted. A subtotal gastrectomy was performed.

Menetrier's Disease
(Hyperplastic gastropathy, mucous cell type)

A. An unusual condition characterized by protein-loosing enteropathy, hypoalbuminemia, edema, and hypo- or achlorhydria. First described in 1888; now, over 200 reported cases.

B. Clinical features in adults
1. Peak ages of occurrence: 30-60 yrs.; 3-4M:1F
2. Chief symptom: Epigastric pain. Other complaints: nausea, vomiting, anorexia, weight loss, ± diarrhea
3. P.E.: Epigastric pain; peripheral edema (25%)
4. Laboratory findings
   a. Decreased serum albumin
   b. Decreased or absent HCl output in 75%; normal in remainder
   c. Evidence of nonselective loss of serum proteins into gastric lumen
   d. Normal serum gastrin
   e. Iron deficiency anemia
5. X-ray and endoscopy findings: enlarged folds, ± polyps. Characteristically, changes most prominent in corpus, but often involve stomach diffusely or, less often, the antrum selectively. Motility variably impaired; wall not rigid.

C. Microscopic features
1. Diagnosis difficult or impossible in superficial grasp-type mucosal biopsies; need full-thickness mucosal sample via aspiration technique or surgery.
2. Major findings
   a. Hyperplasia of surface-foveolar zone, with proliferation of normal mucous cells. Glands often lengthened
   b. Focal extension of surface-foveolar mucous cells deep into glands, with cystic dilatation at base
   c. Normal or decreased number of oxyntic and pepsin cells.
   d. Edema and variable inflammation (usually mild) in lamina propria; strands of smooth muscle from muscularis mucosae may extend into lamina propria.

3. Differential diagnosis
   a. Tissue infiltration by carcinoma or lymphoma
   b. Zollinger-Ellison syndrome: Increased oxyntic cells; elevated serum gastrin.
   c. Hypertrophic, hypersecretory gastropathy: Increased acid output; normal or increased numbers of oxyntic and pepsin cells
   d. Infections (Tuberculosis; fungus; syphilis); sarcoidosis
   e. Eosinophilic gastroenteritis: Antral predominance; focally numerous eosinophils
   f. Cronkite-Canada Syndrome: Clinical features; lesions elsewhere in intestine.
   g. Gastric varices.

D. Etiology and pathogenesis: Cause unknown; numerous postulates (irritants, allergens, infectious agents, etc.). Mechanisms of protein loss: excessive glycoprotein production by proliferating mucous cells; and loss through intercellular spaces (opening and widening of tight junctions noted in study by Kelly et al). Possible mechanisms of a- or hypochlorhydria: decreased oxyntic cell mass; acid neutralization by exudated proteins in gastric juice; back diffusion of HCl.

E. Therapy and prognosis
   1. Medical therapy: symptomatic, using antacids, Cimetidine, and anticholingerics. Results variable.
   2. About 70% of patients have had surgery (usually subtotal gastrectomy) for severe or persistent symptoms.
   3. Course in adults: Most cases persist over time. Some progress to more prominent folds and polyps, and a small number have been reported to regress to normal or to atrophic gastritis. In a retrospective study, Scharschnidt raised the possibility of gastric carcinoma as a complication of chronic Menetrier's disease; cancer developed in 3 of 26 patients (10%) followed over one year. Verification needed by prospective analysis of cases not having surgery.
   4. Course in children: Disease is uncommon in children (mean age of onset: 5.75 yrs.), but symptoms and laboratory findings generally same as in adults. However, there are differences in childhood cases compared with those developing in adults:
      a. Onset usually more abrupt
      b. Edema in 80% (versus 25% in adults)
      c. Eosinophilia in two-thirds
      d. Excellent prognosis: complete recovery is the rule
      e. Above features suggest allergy and/or infection as causes in children. CMV inclusions noted in two cases.

References

1. Chouraqui JP, Roy CC, Brochu P, Gregoire H, Morin CL, Weber AM. Menetrier's disease in children. Gastroenterology 1981; 80:1042-1047.
2. Fieber SS, Rickert RR. Hyperplastic gastropathy: analysis of 50 selected cases from 1955-1980. Am J Gastro. 1981; 76:321-329.
3. Kelly DG, Miller LJ, Malagelada JR, Huizenga KA, Markowitz H. Giant hypertrophic gastropathy (Menetrier's disease): pharmacologic effects on protein leakage and mucosal ultrastructure. Gastroenterology 1982; 83:581-589.
4. Scharschmidt BF. The natural history of hypertrophic gastropathy (Menetrier's disease). Am J Med. 1977; 644-652.
5. Whitehead R. Mucosal Biopsy of the Gastrointestinal Tract, Second Edition. W.B. Saunders Co., Philadelphia, 1979:51-56.

GI84-2 (Kingston General Hospital, Kingston, Dr. Paul M. Manley):
A bright active 80 year old man presented with jaundice, dark urine, pale stools, and pruritis one month prior to admission. He had an associated 15 lb. weight loss. On examination a large nodular mass was felt in the right upper quadrant. Chest x-ray showed a 1.5 cm. mass in the right upper lobe. CT scan showed a lobulated 10 cm. soft tissue mass within the head of the pancreas, with central calcification. Percutaneous aspiration cytology biopsies were unsuccessful in obtaining tissue on two occasions. A percutaneous transhepatic catheter demonstrated markedly dilated bile ducts and complete obstruction at the head of the pancreas. At operation a 10 x 10 cm. rock hard mass was present in the head of the pancreas. A choledochojejunostomy and gastrojejunostomy were performed to bypass the mass and these needle biopsies were taken. Slides are stained with Hematoxylin-Phloxine-Saffron.

MICROCYSTIC ADENOMA OF THE PANCREAS

Paul N. Manley, M.D.

There are two main types of cystic neoplasms of the pancreas[1,2] - the mucinous cystadenoma and the serous cystadenoma, now referred to as a microcystic adenoma or glycogen-rich cystadenoma. Both are usually large, well circumscribed and likely arise from the epithelium of large pancreatic ducts[3]; however, mucinous cystadenomas are potentially malignant and microcystic adenomas are invariably benign.

These two uncommon neoplasms can and should be distinguished by their characteristic pathologic and clinical findings.

	Microcystic Adenoma[1]	Mucinous Cystadenoma[2]
Patient profile	Elderly male or female	Middle aged female
Site in Pancreas	Even distribution	Body and tail
Pathology	Tiny cysts (< 2 cm) lined by uniform small cuboidal cells containing glycogen	Large multilocular or unilocular cysts lined by tall, mucin-producing cells often forming papillae
Predisposition to malignancy	No atypical epithelium or progression to malignancy	Frequently contain adenocarcinoma or markedly atypical epithelium
Imaging pattern	Small cysts within central stellate calcified connective tissue	Large cysts with septae better seen on ultrasound than C.T.

One case of a cystadenocarcinoma arising from acinar cells and containing zymogen granules has been recently described[4].

Microcystic adenomas usually present as a large abdominal mass associated with pain and occasionally with weight loss or jaundice. Until recently, they were often diagnosed preoperatively as carcinomas of the pancreas, colon and kidney, or pancreatitis with pseudocyst formation and frequently had extensive surgical resections. With the widespread use of C.T. and ultrasound, the diagnosis may be confirmed preoperatively with a guided percutaneous thin needle biopsy[5] or, as in our case, with a needle biopsy taken during a bypass procedure. The small cysts lined by diastase-sensitive PAS-positive cuboidal cells separated from the atrophic pancreatic acini and remaining islets by fibrous tissue is diagnostic. In distinction to the mucinous cystadenoma which should and, as it is often in the tail, can be resected, the invariably benign microcystic adenoma should be treated conservatively.

References

1. Compagno J, Oertel JE. Microcystic adenomas of the pancreas (glycogen-rich cystadenomas). A clinicopathologic study of 34 cases. Am. J. Clin. Pathol. 1978; 69: 289-298.

2. Compagno J, Oertel JE. Mucinous cystic neoplasms of the pancreas with overt and latent malignancy (Cystadenocarcinoma and Cystadenoma). A clinicopathologic study of 41 cases. Am. J. Clin. Pathol. 1978; 69: 573-580.

3. Glenner GG, Mallory K. The cystadenoma and nonfunctional tumours of the pancreas. Pathogenesis, classification and significance. Cancer 1956; 9: 980-996.

4. Cubilla AL, Fitzgerald PJ. Cancer (Non-endocrine) of the pancreas. A suggested classification. In The Pancreas, pp. 82-110. IAP Monograph, 1980

5. Wolman NT, Ramquist NA, et al. Cystic neoplasms of the pancreas: C.T. and sonography. A.J.R. 1982; 138: 37-41

6. Beazley RM. Needle biopsy diagnosis of pancreatic cancer. Cancer 1981; 47: 1685-1687

GI84-3A,B (University of Michigan, Ann Arbor, Dr. David F. Keren):

The patient is an 11 month old white male who enters the hospital with a history of having episodes of anaphylaxis in response to ingesting baby food beef and baby food chicken (commercially prepared). He had been well until seven months of age when he and his older sister (three years old) developed a "viral enteritis". They recovered in about one week. Shortly thereafter, severe vomiting was noted after feeding. Initial evaluation at a large regional children's hospital for a metabolic disorder was unrevealing. The child was originally thought to have had Reye's Syndrome. However, the blood ammonia was normal. On the present admission, he was brought to Mott Children's Hospital for a formal oral challenge with beef. Twenty-four hours prior to the challenge, a small bowel biopsy was performed. Subsequently, he was fed commercially prepared baby food beef and had a severe anaphylactic- type reaction. The symptoms began with projectile vomiting three hours following the challenge. This was accompanied by tachycardia and tachypnea. The prechallenge IgG, IgA, and IgM were all in the normal range for a one year old infant. The CBC, differential were normal with normal numbers of eosinophils. Postchallenge, there was decreased serum complement. A repeat challenge shortly thereafter using cow's milk elicited no response. The pre and post beef baby food challenge biopsies are labelled 13872 CI and 13923 CI respectively (GI84-3A and B).

DISCUSSION

Gut Food Hypersensitivity
David F. Keren, M.D.
The University of Michigan

Both acute and chronic gastrointestinal reactions of infants to ingested cow's milk, soya protein, and meat protein are well established. Clinical signs of acute reactions include palor, diarrhea, vomiting, and shock. Chronic reactions include anemia (iron loss) hypoproteinemia (protein loss), and steatorrhea. Usually, during the first month, or so, of life the infants are asymptomatic as was the case with the present child. Thereafter, they developed frequent stools which were often loose and can be watery. In the present case, it should be noted that an incident of "viral gastrointeritis" was said to have preceded the severe symptoms observed. A frequent finding is failure to thrive.

On physical examination, the infants are usually irritable and listless, often with a low-grade temperature. In addition, they are pale and mildly dehydrated. Bowel sounds are hyperactive. Laboratory evaluation shows an elevated white blood count with a shift to the left. Due to this leukocytosis, enteropathogenic infections are often suspected in these children.

Soya protein allergy was first described by Amant and Rubin in 1972. In the infant they described, within one hour of drinking soya protein he became pale and listless. After two hours, the child began vomiting, and within four hours the temperature rose to 40°C. The white blood cell count elevated from 10,500 to 18,500 with a shift to the left also within four hours. By twelve hours stools became loose and blood tinged. Yet, by 24 hours the child had recovered clinically. By twelve hours, villi were absent and microulcerations with granulocytes, hemorrhage and edema were prominent. By 24 hours, the microulcerations had recovered, although villi were still absent. There was no change in the CH 50 titer at 90 minutes, 4 hours, or 12 hours. The violent acute enteritis they described was not related to cow's milk, gluten, lactose, or sucrose intolerance. In our own studies on the child in the present case with meat intolerance, we have demonstrated IgG deposition between the surface epithelial cells and increased numbers of IgE-containing plasma cells. However, an enzyme-linked immunosorbent assay failed to demonstrate specific antibodies against the protein.

The development of food hypersensitivity in infants is often attributed to altered gut mucosal permeability to potentially antigenic macromolecules. There are at least six proteins which commonly cause enteritis: gluten, cow's milk protein, soya protein, chicken protein, fish protein, and rice protein.

Although in normal individuals only trace amounts of such potentially antigenic food pass unchanged across the mucosal barrier into the blood, Gallagher et al. recently have demonstrated that a very transient rise in circulating immune complexes can be detected in almost all normal individuals following ingestion of such food. Killshaw and Slade have demonstrated that the uptake of the antigen Beta-lactoglobulin by calves was significantly increased for 24 hours after the mucosa was injured by ingestion of heated soya bean flour (to which the animals had been orally sensitized). They were not able to inhibit these permeability changes with prostaglandin inhibitors such as indomethicin.

It is probable that secretory IgA plays a protective role against the development of cow's milk allergy and other food allergies. Cruz et al. have shown that breast milk from normal women contains IgA antibodies to food antigens present in the maternal diet. These antibodies in breast milk would combine with the infants food in the gut lumen and help prevent passage of the intact molecules across the mucosa. While maintaining the molecules in the gut lumen, the secretory IgA could help to subserve a digestive role. The reason why many children "outgrow" these allergies is not known at the present time. It could relate to a delayed maturation of the normal secretory IgA or suppressor T cell immune mechanisms in these infants.

References

1. Amant, M.E. and C. E. Rubin: Soya protein - another cause of the flat intestinal lesion. Gastroenterology 62, 2, 227-234, 1972.

2. Cruz, J.R., B. Garcia, J.J. Urritia, B. Carrlson, and L.A. Hanson: Food antibodies in milk from Guatamalan women. J. of Pediatrics 99:600-602, 1981.

3. Killshaw, P.J. and H.Slade: Passage of ingested protein into the blood during gastrointestinal hypersensitivity reactions: experiments in the preruminant calf. Clin. Exp. Immunol. 41:575-582, 1980.

4. McCalla, R., E. Savilahti, M. Perkkio, P. Kuitunen, and A. Backman: Morphology of the jejunum in children with eczema due to food allergy. Allergy 35:563-571, 1980.

5. Pang, K.Y., W.A. Walker, and K.J. Bloch: Intestinal uptake of macromolecules: differences in distribution and degradation of protein antigen in control and immunized rats. Gut 22:1018-1024, 1981.

6. Gallagher, P.J., M.J. Joulding, M.J. Gibney, D.B. Jones, and J. Morgan: Acute and chronic immunological response to dietary antigen. Gut 24:831-835, 1983.

7. Watt, J., J.R. Pincott, and J.T. Harris: Combined cow's milk protein and gluten-induced enteropathy: common or rare? Gut 24:165-170, 1983.

GI84-4 (Hospital for Sick Children, Toronto, Dr. M. James Phillips):

This 7 month old boy was born after a normal pregnancy and normal delivery to parents who are consanguinous and second cousins. He presented at one month of age with failure to thrive. On admission, he was found to have a urine culture that grew E. coli and was treated with ampicillin. Ultrasound showed irregularity of the left kidney and an IVP/voiding cystogram showed normal kidneys but reflux on the right. The child responded to antibiotic therapy and was discharged. At 4 months of age, he was re-admitted because of continued failure to thrive. It was noted that he had been floppy and tired easily. Physical examination revealed an ill-looking, lethargic infant with normal colour, no jaundice, no pallor and no cyanosis or clubbing. The abdomen was soft and slightly distended with a firm liver 9-10 cm below the right costal margin, and a firm spleen 4 cm below the left costal margin. A liver biopsy was performed and the child was discharged. At 6 months of age, was re-admitted. He was very hypotonic and developmentally delayed. His abdomen was distended with a firm liver that was 10-12 cm below the right costal margin and the spleen was enlarged and firm. He was afebrile, very wasted in appearance and had pitting oedema of the legs. He was given albumin and lasix and his oedema gradually decreased. Laboratory investigation showed that his blood sugar, electrolytes, calcium and phosphorus were normal; his SGOT was elevated. His cultures were negative except for the blood that grew Hemophilus influenza that was sensitive to ampicillin and gentamicin. Chest x-ray was negative. He was also bleeding excessively and his PT and PTT were prolonged, and his platelets were low. He was started on a course of antibiotics and plasma. During this hospital stay, he had a right-sided convulsion which was treated with I.V. valium. He had hypoglycemic episodes for which he was given intravenous glucose. He improved and was discharged home on frequent feeds. Several days later, he was re-admitted to hospital because he was not eating well; also, his urine output had decreased. He was found to be jaundiced, lethargic and ill-looking. He continued on a downhill course and despite supportive attempts died. Specimen submitted is a wedge biopsy of the autopsy liver.

Glycogen Storage

Type IV glycogen storage disease is the rarest form of the glycogen storage diseases. It was first described by Andersen in 1952, and sometimes is called Andersen's disease. It is also called amylopectinosis as well as brancher enzyme deficiency disease. This metabolic disorder, which has a genetic transmission as an autosomal recessive trait affects siblings of both sexes. It is characterized by the accumulation primarily in the liver of glycogen which has reduced but not absent branch points, and increased chain length. The deficiency or absence of the branching enzyme α-1, 4-glucan: α-1, 4-glucan

6-glycosyl transferase is responsible for this disease. Infants with this disease are normal at birth, and after the first six months of life present with poor weight gain and non-specific gastrointestinal symptoms.

On investigation, hepatosplenomegaly and absence of glucosuria, ketonuria, or abnormal carbohydrate tolerance test is found. As the disease progresses, hypotonia, non-specific gastroenteritis, anemia, osteoporosis, torticollis, sepsis and continued failure to thrive are observed. Also, the initial normal blood glucose response to glucagon that is observed diminishes, and infants become hypoglycemic. The most distinctive pathological change is seen in the liver and is characterized by abnormal glycogan accumulation in liver parenchymal cells. This abnormal glycogen stains intensely with PAS, colloidal iron, and iodine, and is only partially digested with diastase, amyloid or B-amylase, but completely digested with pectinase. This is accompanied by extensive hepatic fibrosis with progression to micronodular or mixed cirrhosis. Ultrastructurally, glycogen rosettes, distinctive finely granular material and fibrils have been recognized in the liver cells. Similar deposits have been found in myocardial cells, splenic and lung macrophages, skeletal and smooth muscle, lymph nodes, the lamina propria of gut and the loop of Henle of the kidney. The prognosis for infants with this disease is very poor. Most infants usually die during the first year of life from chronic liver failure or cardiac failure due to polysaccharide deposits within myocardial cells. Patients who live beyond infancy develop cirrhosis of the liver with accompanying portal hypertension, ascites and oesophageal varices.

ANDERSEN, D.H. Studies on glycogen disease with report of a case in which the glycogen was abnormal. In: Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease", edited by Najjar, V.A. pp. 28-42. Baltimore, Johns Hopkins Press, 1952.

ANDERSEN, D.H. Familial cirrhosis of the liver with storage of abnormal glycogen. Lab. Invest. 5: 11, 1956.

REED, G.B., DIXON, J.F.P., NEUSTEIN, H.B., DONNELL, G.N. and LANDING, B.H. Type IV. Glycogenosis. Lab. Invest. 19: 546, 1965.

McADAMS, A.J., HUG, G. and BOVE, K.E. Glycogen storage disease. Types I to X. Human Path. 5: 463, 1974.

BANNAYAN, G.A., DEAN, W.J. and HOWELL, R.R. Type IV glycogen storage disease. Light microscopic, electron-microscopic and enzymatic study. Amer. J. Clin.Path. 66: 702, 1976.

CANTIN,M., BROCHU,P., TURGEON-KNAACH,C., BERDINKOFF,G., SIMARD, and MORIN,C. Rectal niopsy in type 4 glycogenosis. An ultrastructural cytochemical study. Arch. Pathol.Lab. Med. 100: 422, 1976.

IWAMASA, T., NINOMIYA, N., FUKUDA, A., HAMADA, T., HIRASHIMA,M. and OSAME, M. Glycogen storage disease. Studies related to the mechanism of glycogenosome formation. Path. Res. Prac. 176: 236, 1982.

GI84-5 (University of Iowa, Iowa City, Dr. Frank A. Mitros):

The patient is a 35 year old moderately obese woman who had been in good health until 4 months prior to admission. At that time she began to experience the symptoms of fatiguability, generalized weakness, and light headedness. When she presented to her local physician, she was noted to have a hemoglobin of 2.2 g/dl and a hematocrit of 8.7%. Her red blood cells were hypochromic and microcytic; stool was positive for occult blood loss. Further questioning revealed a weight loss of 40 pounds during the past year while she had originally been dieting; the last 10 pounds lost were unintentional. It was also discovered that her mother died at age 38 of a cancer, apparently of the gastroduodenal area. Physical examination was unremarkable. Radiographic studies included an upper gastrointestinal series (UGI) and barium enema (BE). The UGI was reported to show an "irregular distortion consistent with tumor infiltrative changes throughout". No small bowel lesions were noted. The BE with air contrast was reportedly normal. The patient was referred to the University of Iowa. An endoscopy was performed, revealing myriads of polypoid lesions carpeting the stomach, but sparing the antrum. They ranged from 1 to 2 mm to several cms; some were noted to be oozing blood. The stools were noted to be melanotic on several occasions. Despite multiple transfusions, a stable hemoglobin was not obtained. Because of this uncontrollable bleeding, a total gastrectomy was performed. Your slides are from this specimen. Two years later the patient felt reasonably well, but was noted to have mild iron deficiency anemia on her follow-up exam. A BE revealed a 5 cm mass in the region of the hepatic flexure.

GENERALIZED JUVENILE GASTROINTESTINAL POLYPOSIS

The patient presented is a new member of a kindred previously reported from our institution.[1] She suffers from a syndrome which is a variant of gastrointestinal polyposis in which polyps that have features primarily of juvenile polyps are found throughout the gastrointestinal tract, but in greatest numbers in stomach and colon. Some polyps, particularly those in the colon, have features of adenomas. There is a high incidence of carcinoma involving stomach, small bowel, colon, or pancreas, not necessarily involving the same areas as the polyps in a given patient.

Juvenile polyps of the colon are single in over 70% of cases; in the remaining 25-30%, up to 5 polyps can be found. Juvenile polyposis is quite uncommon. the exact number of polyps needed to distinguish polyposis from the patient with multiple juvenile polyps is uncertain, but reported cases have usually had dozens to hundred of polyps.

Juvenile polyposis has been separated into 3 entities.[2] While there are usually some differences amongst these three forms (see below), it is not entirely certain that they are clearly separable from one another.

1) Juvenile polyposis of infancy - rare; stomach to colon involved; life threatening diarrhea and bleeding in infancy; not familial.

2) Juvenile polyposis coli - most common form; usually limited to the colon; onset of rectal bleeding at 3-6 years of age usual; often familial.

3) Generalized juvenile gastrointestinal polyposis (GJGP) - uncommon; stomach to colon involved; some polyps may resemble adenomas; increased cancer risk; often familial.

Anomalies such as malrotation of the gut, amyotonia congenita, macrocephaly, and intracranial cysts have been described in the latter 2 forms, but are present in the minority of cases.[3]

In patients with GJGP several types of polypoid lesions have been noted in the various portions of the GI tract. These include: 1) hyperplastic polyps; 2) typical juvenile polyps; 3) juvenile polyps with focal adenomatous epithelium; 4) adenomas; 5) carcinomas.[4]

The gastric lesions present an interesting differential diagnosis. Entities that need to be considered and some features allowing differentiation from GJGP include:

1) Cronkhite - Canada syndrome - extraintestinal features including hyperpigmentation, hair loss, and nail atrophy; later age of onset; not familial.[5]

2) Menetriere's Disease - not familial; lesions limited to the stomach.

3) Fundic polyposis - usually associated with adenomatous polyposis coli; cysts and polyps much smaller than GJGP.[6]

4) Gastrititis - while hyperplastic polyps and focal small areas of cystic dilatation may occur, the disease is presumably non-familial and limited to the stomach.

While there has been one report of familial juvenile polyposis limited to the stomach[7], it is well to remember that one patient in the Iowa series[1] had gastric polyps documented 17 years before colonic polyps were observed.

REFERENCES

1. Stemper, TJ, Kent, TH, and Summers, RW.: Juvenile Polyposis and Gastrointestinal Carcinoma. ANN INT MED 83: 639-646, 1975.

2. Sachatello, CR and Griffin, WO.: Hereditary Polypoid Diseases of the Gastrointestinal Tract. AM J SURG 129: 198-203, 1974.

3. Donari, G, Rosenbach, Y, Wolloch, Y, et al.: Generalized Gastrointestinal Juvenile Polyposis and its Treatment. AM J PROCT GASTRO COL RECTAL SURGERY 34: 5-8, 1983.

4. Goodman, SC, Yardley, JH, Milligan, FD: Pathogenesis of Colonic Polyps in Multiple Juvenile Polyposis. CANCER 43: 1906-1913, 1979

5. Daniel, ES, Ludwig, SL, Lewin KJ, et al.: The Cronkhite-Canada Syndrome. MEDICINE 61: 293-309, 1982.

6. Watanabe, H, Enjoji, M, Yao, T, and Ohsato, K.: Gastric Lesions in Familial Adenomatous Coli. HUM PATH 9: 269-283, 1978.

7. Watanabe, A, Nagashima, H, Motoi, M, and Ogawa, K.: Familial Juvenile Polyposis of the Stomach. GASTROENTEROLOGY 77: 148-151, 1979.

GI84-6A,B (Lenox Hill Hospital, New York, Dr. Heidrun Z. Rotterdam):
32 year old homosexual male with a history of repeated episodes of amebiasis was admitted to the hospital with fever, night sweats, weight loss and right upper quadrant pain. A cholecystectomy was performed. Two slides (GI84-6A, 6B).

Diagnosis: Cytomegalo- and Cryptosporidial Cholecystitis and Colitis.

Cytomegalovirus infection and cryptosporidiosis are opportunistic infections frequently encountered in AIDS patients. Cytomegalovirus most commonly affects lungs, adrenal glands and all segments of the gastrointestinal tract. In the G-I tract the colon is the most commonly and most severely affected segment. The initial diagnosis of CMV infection is most often made on the basis of a colonoscopic biopsy case. CMV cholecystitis is a highly unusual condition and to my knowledge has not been reported in AIDS nor in other immunocompromised patients. In the present case the diagnosis was only made retrospectively after CMV was discovered in a colonoscopic biopsy.

Cryptosporidiosis is a protozoal infection initially described in animals, later in immunocompromised children and now with increasing frequency also in patients with AIDS. Cryptosporidia infect primarily the small and large intestine. A single case of cryptosporidial cholecystitis was reported recently. This patient had cryptosporidial infection of the colon and gallbladder. He died 9 months later of Pneumocystis carinii pneumonia and CMV pancreatitis.

REFERENCES

1. Reichert CM, O'Leary TJ, et al: Autopsy pathology in the acquired immune deficiency syndrome. Am J Pathol 1983; 112: 357-382.

2. Mobley K, Rotterdam H: Autopsy findings in the acquired immune deficiency syndrome. Pathol Annu (in press).

3. Rotterdam H, Lerner CW, Tapper ML: Biopsies of the digestive tract in patients with acquired immunodeficiency syndrome. Lab Invest 1983; 48: 72A (abst.)

4. Macher AM, Reichert CM, et al: Death in the AIDS patient: role of cytomegalovirus. N Engl J Med 1983; 23: 1454.

5. Current WL, Reese NC, Ernst JV, Bailey WS et al: Human cryptosporidiosis in immunocompetent and immunodeficient persons. N Engl J Med 1983; 308: 1252-1257.

6. CDC: Cryptosporidiosis: assessment of chemotherapy of males with acquired immunodeficiency syndrome (AIDS). MMWR 1982; 31: 589-592.

7. Pitlik SD, Fainstein V, Rios A, Guarda L, Mansen PWA, Hersh EM: Cryptosporidial cholecystitis. N Engl J Med 1983; 308: 967.

8. Weinstein L, Edelstein SM, Madara JL et al: Intestinal cryptosporidiosis complicated by disseminated cytomegalovirus infection. Gastroenterol 1981; 81:584-591.

GI84-7 (Johns Hopkins Hospital, Baltimore, Dr. Stanley R. Hamilton):

A 17-year-old white female presented with a 6-month history of intermittent purulent, bloody diarrhea. She noted that her symptoms were worse with high intake of fruit. The remainder of the history, including social and family history, as well as the review of systems were non-contributory. The patient's occupation was described as "professional beauty pageant contestant". Physical examination was normal except for rectal examination which revealed a polypoid area on the left lateral wall of the rectum. Proctoscopy showed granularity of the mucosa to 25 cm with multiple small nodular inflamed areas on the rectal valves. Laboratory examination was non-contributory except for guiac positive stool. Air contrast barium enema showed a granular appearance to the rectal and distal sigmoid mucosa with normal proximal colon, interpreted as consistent with ulcerative colitis. The patient was begun on azulfidine and corticosteroid enemas without relief, and six weeks after presentation, oral prednisone 40 mg per day was added. Colonoscopy showed nodular valves of Houston with exudate and friability, and biopsies showed exudate and detached fragments of colonic epithelium. The clinical diagnosis was Crohn's disease.

The patient was referred to a major university medical center where the diagnosis of ulcerative proctitis was favored by the consultant gastroenterologist. He noted that the patient was having an extreme emotional reaction to her illness with "great reluctance to accept the diagnosis of ulcerative proctitis". In addition, he noted that the patient "gets bent out of shape if she gains two pounds" while on steroids, as the weight gain interfered with her beauty pageant activities.

Because of continued symptomatology, the patient was seen by a second gastroenterologist 11 months after initial presentation. Examination again revealed a nodular lesion 4 to 5 cm in diameter extending along the entire posterior half of the anal canal from eight o'clock to four o'clock in the knee-chest position. The lesion was most prominent on the left lateral wall and extended superiorly to the upper rectal valve. The lesion was described as being a discrete, white, nodular verrucoid excresence which was slightly tender to palpation. The margin between the lesion and surrounding normal mucosa was distinct. A surgical biopsy was obtained and the specimen is provided for your assessment.

DIAGNOSIS: Solitary rectal ulcer syndrome.

DISCUSSION: Patients with this condition usually present with passage of blood and mucus, change in bowel habits including constipation as well as diarrhea, and sometimes rectal pain. The patients are more commonly females and are generally of young age, in the third to fourth decade of life. When an ulcer is present, it is typically found on the anterior wall of the rectum within about 15 cm of the anus. The condition is associated with rectal mucosal prolapse when appropriate examination is carried out. The ulcers may be multiple, overshadowed by nodularity, or inapparent, hence the designation as "syndrome". The lesions may show variability in appearance as the patient is followed, and the relationship between the appearance and symptomatology is poor. The pathogenesis is most likely related to rectal prolapse and hypertension of the puborectalis sling, although controversy remains.

Diagnosis is based on histopathologic findings. Solitary rectal ulcer syndrome shows a characteristic proliferation of smooth muscle from the muscularis mucosae into the lamina propria, often accompanied by evidence of erosion or ulcer in the form of inflamed granulation tissue and/or scarring. Proliferated, villiform mucosa with elongated, redundant, serrated crypts resembling hyperplastic polyp and mucin cell hyperplasia are seen in some cases. In occasional specimens, entrapment of glands in the submucosa and deeper layers of the bowel wall is identified, representing "colitis cystica profunda". Biopsy is most likely to be useful if taken at the edge of the ulcer or from nodular areas, as biopsies from the center often show only inflamed granulation tissue. The difficulty in obtaining good specimens is often commented upon by clinicians, as tissue is often hard to obtain from the lesions.

Some of the problems in diagnosis are illustrated by this case. The clinical impression is often incorrect. Biopsies are often interpreted as showing nonspecific ulcer when the smooth muscle proliferation is not included in the specimen or is overlooked. Repeated biopsies may then be required. In addition, because of the prominence of inflammation, the biopsy specimens may be misinterpreted as showing idiopathic inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease). Finally, in occasional cases with proliferative mucosa, the lesions are misdiagnosed as hyperplastic polyp, adenoma, or even carcinoma.

REFERENCES

1. Ford MJ, Anderson JR, Gilmour HM, et al: Clinical spectrum of "solitary ulcer" of the rectum. Gastroenterology 1983; 84:1533-1540.

2. Feczko PJ, O'Connell DJ, Riddell RH, Frank PH: Solitary rectal ulcer syndrome: Radiologic manifestations. AJR 1980; 135:499-506.

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REPORT OF THE TRAINING COMMITTEE OF THE GI PATHOLOGY CLUB

Introduction:

There is increasing interest in training programs in gastrointestinal pathology among department directors, trainees in pathology, and among some clinicians, especially gastroenterologists. The desire for more information about training programs and sources of support was evident from the response to the questionaire sent out in 1982 by Dr. Rodger Haggitt when he was President.

This Committee was appointed originally by Dr. Haggitt primarily to consider fellowship opportunities. Inquiries showed, however, that few, if any, funds are available outside of regular residency programs to support training in gastrointestinal pathology, but it was also noted that it would be useful to compile a list of available training opportunities of all types. Hence the charge to the Committee was broadened to include an overview of training opportunities.

The main focus of this report is a survey of training programs conducted among members of the GIPC.

Methods:

Letters were sent to all members during the spring and summer of 1983, and a follow-up notice appeared in the Newsletter in late 1983. An initial attempt to develop a questionnaire which could simply be filled in was thwarted by the numerous variations in training programs. Thus, answers were provided in the form of letters which usually followed a suggested outline.

The original memorandum went to seventy-six club members, representing an estimated 50-60 institutions. Thirty responses were received from as many institutions. Some kind of GI pathology training program was described by twenty three responders, and these were used to tabulate the data given in the Results.

Results

In tabulating the results, it was necessary to categorize them, and this inevitably led to both simplification and possibly some inappropriate categorizing. We apologize if any programs are inadequately or inaccurately described in the tabulation.

The greatest difficulty was encountered in developing some way to separate training in GI pathology during residency programs into the various forms it can take.

The divisions finally used were:

REGULAR (R)- Training experience that is obtained when serving on standard surgical pathology and autopsy rotations.

REGULAR PLUS SPECIALTY (RS)- In these programs some type of separate specialty experience in GI pathology is provided in the context of regular training in anatomic pathology. There is much variation from institution, but common features are some kind of organized and sustained exposure of residents to case interpretation by GI pathology specialists along with other activities such as lectures and participation in conferences. These are often attended by clinicians and clinical trainees, as well as pathologists.

SEPARATE EXPERIENCE (SE)- Residents are provided with a block of time (rotation) that is devoted solely or mainly to GI pathology. They work directly with a GI pathologist and have some responsibility for case review, conference presentations, etc.

For purposes of the survey, Fellowships were defined as training opportunities standing outside of regular residency training. These require separate funding, which is available from the institution in only a few instances. Fellowships are sometimes open to clinicians as well as pathologists. They typically run for a year or more, and research as well as diagnostic work is often emphasized.

Several institutions indicated willingness, indeed even eagerness, to have persons participate in their program on an ad hoc basis. There are usually no important restrictions as to eligibility, and time spent at the guest institution is flexible. Funding must come from the visitor in all instances that we know of.

Results of the survey are summarized in Table I and given on an institution-by-institution basis in Table II (attached).

TABLE I
GI PATHOLOGY TRAINING SURVEY - 1983

No. of institutions responding	30
TRAINING OFFERED/ NOT OFFERED	23/7
Residency Based Programs:	
REGULAR	6
REGULAR PLUS SPECIALTY	12
SEPARATE SPECIALTY	6
Fellowships	8
UNFUNDED/ FUNDED	3/5
Research Opportunities	11
Ad hoc	10

The data provided here unquestionably represent only a sample of what is actually available. However, it is possible that there are not too many more

programs of the REGULAR PLUS SPECIALTY or SEPARATE EXPERIENCE types because of a bias favoring response among institutions having those programs. Fellowships in GI pathology are undoubtedly rare. It is clear, therefore, that expansion of training opportunities is needed if the general level of expertise in GI pathology and the number of persons who are dedicated to GI pathology as a sub-specialty are to be increased.

The individual program descriptions, which will be provided to members on request, contain much detail about actual training program operation. These descriptions must be read to fully comprehend the range of possibilities. Many institutions have regular, well-attended, case-oriented conferences, involving both clinicians and pathologists. Biopsy review sessions over a multi-headed microscope are becoming increasingly popular. This also leads to valuable interaction between pathologists and clinicians. Other institutions have didactic exercises for house staff and Fellows from both the pathology and clinical areas. A few respondents mentioned teaching aids such as slide collections which residents and others can study on their own time.

Future Actions:

This survey brought forth enough information and expressions of opinion to indicate that there is a genuine interest in and need for training programs. It also suggests that the GI Pathology Club can fill a useful function in coordinating and stimulating training activities. There are a number of possible future courses of action. These will not be elaborated on here, but might include:

- Have a standing committee on training programs in GI pathology.
- Conduct a survey of this type annually.
- Publish a booklet announcing and describing individual program (a la Pathology Residency Book).
- Develop teaching packages.
- Develop funding sources.
- Develop guidelines for GI pathology training program.
- Develop programs of accreditation of training programs.
- Develop linkage with other organizations (e.g., AGA Committee on Training and Education).

The committee hopes that this report will be helpful to members of the Gastrointestional Pathology Club, and we look forward to learning their reactions and suggestions.

John H. Yardley, M.D. (Chairman)
Harvey Goldman, M.D.
Klaus Lewin, M.D.
Rodger Haggitt, M.D.

TABLE II

SUMMARY OF GI PATHOLOGY TRAINING OPPORTUNITIES - 1983-84*

State or Province	Institution/ City	Residency Training		Fellowships		Backgrd. Needed	Confs.	Re-search Oppor.	Preceptors /Contact Persons	REMARKS
		Type(s)	Length	Description	Funded					
USA California	UCLA Med. Center Los Angeles	RS	--	AP and GE combined. Research.	No	--	P&C	Yes	K. Lewin W. Weinstein	Ad hoc available
District of Columbia	Armed Forces Inst. of Pathology Washington	--	--	Diagnostic - 2 wks. to several mos.	No	AP 2 yrs. or GE 6 mos.	--	--	E.B. Helwig L.H. Sobin B.M. Hjermsted	Up to 2 positions
Georgia	VA Medical Center Atlanta	RS	--	--	--	--	P&C	--	V. Nassar	--
Illinois	Univ. of Chicago Chicago	RS SE	-- 3 mos.	--	--	--	P&C	--	R. Riddell	--
Kansas	Univ. of Kansas Kansas City	RS	--	AP	No	--	P&C	--	H. Sprinz F. Lim N. Greenberger	Ad hoc available
Maryland	Johns Hopkins Baltimore	R SE	-- 3 mos.	1-2 yr. AP & research	Yes	SE-2 yrs AP F-3 yrs AP	P&C	Yes	J. Yardley S. Hamilton J. Boitnott	Ad hoc available
Massachusetts	Beth Israel Hosp. Children's Hosp. Boston	RS	--	--	--	--	P&C	Yes	H. Goldman D. Antonioli	Ad hoc available
	Brigham & Women's Boston	RS	--	2 yrs. AP & research	Yes	F-3 yrs AP	P&C	Yes	J. Madara	Ad hoc available
Michigan	Univ. of Michigan Ann Arbor	RS SE	-- 1 mo.	--	--	--	P&C	--	H. Appelman G. Abrams D. Keren	Ad hoc available
Minnesota	Univ. of Minnesota Minneapolis	R	--	--	--	--	P	--	J. Rosai Dehner D. Snover	--
Missouri	Washington Univ. St. Louis	Not mentioned		1 year - diagnostic & experimental	Yes	F-AP	--	Yes	K. DeSchyver	--

*Based on survey information received April-Dec. 1983. See page 2 for explanation of abbreviations and terms.

(CONTINUED)

TABLE II (CONT.)

State or Province	Institution/ City	Residency Training		Fellowships		Backgrd. Needed	Confs.	Re-search Oppor.	Preceptors /Contact Persons	REMARKS
		Type(s)	Length	Description	Funded					
New York	Lenox Hill New York City	R	--	--	--	--	P&C	Yes	H. Rotterdam	--
	Long Island Jewish New Hyde Park	R SE	-- 2 mos.	--	--	--	P&C	--	L. Kahn	Ad hoc available
	North Shore Univ. Manhasset	RS	--	--	--	--	P&C	--	E. Kahn	--
Ohio	U. of Cinncinnati Cinncinnati	RS	--	--	--	--	P&C	--	J. Wirman	--
Pennsylvania	Hahneman Philadelphia	R	--	--	--	--	P&C	--	R. Pascal G. Lumb	Ad hoc available
	Temple Philadelphia	R	--	--	--	--	P&C	Yes	S. Ming	Ad hoc available
Rhode Island	Roger Williams Gen. Providence	R	--	--	--	--	P&C	Yes	R. Lev	--
Tennessee	Baptist Memorial Memphis	RS	--	1 yr. diagnostic	No	AP-3 yrs (or GE)	P&C	--	R. Haggitt	Ad hoc available
Virginia	Med. Col. Virginia Richmond	R	--	--	--	--	P&C	--	S. Kay S. Mills	--
Washington	Seattle Public Health Hosp. Seattle	--	--	1 yr. Neuromusc Dis.	Yes	GE	--	Yes	M. Schuffler	--
CANADA Ontario	University Hosp. London	RS SE	-- 3-6 Mos.	--	--	-- 2yrs - AP, Med or Surg.	P&C	Yes	J. Frei	Slots for Path, Med, & Surg. Residents
	Ottawa Civic Hosp. Ottawa	RS SE	-- 1 mo.	--	--	--	P&C	Yes	J. Barr	--

Types of GI Pathology

Training in Residency: R (Regular) - GI path training provided in general context of Regular AP rotations.
RS (Regular + Specialty) - Separate GI path specialty experience during Regular AP rotations.
SE (Separate Experience) - Provides separate rotation devoted mainly to GI pathology

Fellowships: "Funded" refers to salary available via institution. When "No", salary must come from outside source.

Background needed: Minimum completed training for participation in residency component (R, RS, or SE) or Fellowship (F). Anatomic Pathology (AP) may be specified. Some programs are open to gastroenterologists (GE), internists (Med.) or surgeons (Surg.)

Conferences (Conf.): Given in relation to pathology (P) and/or clinical (C) aspects.

Research Opportunities: When "yes", opportunities were specifically mentioned.

REMARKS: "Ad hoc available" means outside persons are welcome for training of varied length. Make arrangements with person(s) named.

6/5/84

GIPC Session at the AGA

May, 1984

J. Madara: Freeze Fracture Analysis of Jejunal Mucosa in Celiac Sprue.

W. O. Dobbins III: Intraepithelial Lymphocytes.

Freeze Fracture Analysis of Jejunal Mucosa in Celiac Sprue

James L. Madara

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Harvard Medical School

Freeze fracture techniques have proven to be useful tools for probing many aspects of epithelial structure-function relationships. This has been particularly true of studies dealing with the intercellular tight junction (TJ) which serves as a barrier separating the lumen from the paracellular space. By electron microscopy of thin sections, TJs consist of a series of apparent fusion sites between the lateral membranes of adjacent cells. When these areas of the plasma membrane are viewed en face after being freeze-fractured, linear interconnecting strands or grooves appear within the plane of the lateral membrane (1) (for a general review of the freeze fracture process see the manuscript review by J. Madara in ~~the last~~ this Club Newsletter). The utility of this finding is that the number of strands or grooves in the TJ correlates positively with the TJs ability to resist passive ion flow across it (2, 3, 4). Thus one can generally assess the functional state of this important epithelial barrier by detailed examination of its structure. We have applied this technique to intestinal jejunal epithelium in patients with active celiac sprue to analyze the state of the TJ barrier in this disease. However, to better understand the potential functional significance of altered TJ

structure, recent data concerning intestinal TJ structure-function relationships will first be reviewed.

Freeze fracture analysis shows that TJ structure is heterogeneous in small intestinal epithelium (1, 5). For example while absorptive cell-absorptive cell TJs are multistranded and highly uniform, TJs of villus goblet cells are very heterogeneous with many having only few irregular strands (5). Such findings suggest that goblet cell TJs might be more "leaky" than absorptive cell-absorptive cell TJs and indeed goblet cell tight junctions have been shown to be preferentially permeable to small molecules as assessed with ionic tracer techniques (5). Further evidence providing insight into intestinal TJ structure-function relationships comes from <u>in vitro</u> studies of modulated sheets of small intestinal epithelium. For example, jejunal mucosa exposed to osmotic loads for short periods of time equivalent to the time intervals this epithelium would experience osmotic loads physiologically, respond with an increased resistance to passive ion flow across absorptive cell-absorptive cell TJs (6) (i.e. the epithelium increases its barrier function). Furthermore, this alteration in TJ function is accompanied by alterations in both absorptive cell TJ structure and absorptive cell cytoskeletal structure. Lastly the above alterations can be inhibited with agents which disrupt microfilaments. Thus one can have dynamic alterations which "up-regulate" both TJ structure and barrier function and which presumably are mediated by the cytoskeleton. However, one can also "down-regulate" TJ structure and function in this epithelium. Indeed, using the same osmotic stimulus as described above but for time intervals which would only be seen in

pathological states, one can adversely effect both TJ structure and function in this epithelium (7).

In jejunal epithelium obtained from patients with celiac sprue, absorptive cells have structurally impaired TJs with focal wide transjunctional gaps (8). With the background outlined above, such findings indicate that, in this disease, an important "mucosal" barrier is impaired - specifically, the TJ at the site of damaged surface absorptive cells. Functional evidence of such a defective barrier in celiac sprue jejunal mucosa has been available for some time. The above structural studies point to the specific location of this barrier defect and help to demonstrate the importance of morphological analysis of diseased tissue: if function-structure relationships are clear, then with morphological studies one can tentatively pinpoint at the cellular level of origin of functional abnormalities.

Note: For an up-to-date comprehensive discussion of TJ structure and function with emphasis on the intestine see reference 9.

1) Madara JL, Trier JS, Neutra M. Gastroenterology 78:963-975, 1980.
2) Claude P, Goodenough DA. J. Cell Biol. 58:390-400, 1973.
3) Claude P. J. Membrane Biol. 39:219-232, 1978.
4) Marcial M, Carlson S, Madará JL. J. Membrane Biol., in press.
5) Madara JL, Trier JS. J. Membrane Biol. 66:1-13, 1982.
6) Madara JL. J. Cell Biol. 97:125-136, 1983.
7) Marcial M, Madara JL. Gastroenterology 86:1172 (a), 1984.
8) Madara JL, Trier JS. Lab. Invest. 43:254-261, 1980.
9) Madara JL, Marcial M. In: Regulation of Intestinal Ion Transport; M. Donowitz, G. Sharpe, eds; A. Liss, Inc., in press.

INTRAEPITHELIAL LYMPHOCYTES

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Lymphocytes found within the epithelium of the human gastrointestinal tract are termed intraepithelial lymphocytes (IEL), i.e. lymphocytes found above the basal lamina and between epithelial cells. In the normal human intestine, there are 20 IEL per 100 epithelial cells in the jejunum, 13 per 100 epithelial cells in the ileum, and only 5 per 100 epithelial cells in the colon. Virtually all epithelial leukocytes are T cells, and 90% of these T cells are suppressor ($T8^+$) T cells while the remainder are helper ($T4^+$) T cells. Plasma cells and B cells are not found within the epithelium while macrophages and mast cells are occasionally present within the epithelium. PMN leukocytes and eosinophils are seen in the epithelium very rarely, except in inflammatory states. In contrast, lamina propria lymphocytes in the normal intestine consist predominantly of helper T cells and with a smaller component of suppressor T cells. B cells are not found within the lamina propria, while plasma cells are profusely present. Macrophages, fibroblasts, and occasional mast cells are also present throughout the lamina propria. Thus, it is quite clear that the epithelial population of mononuclear cells is distinctly different from the lamina propria population of mononuclear cells. Further, epithelial lymhocytes are rarely activated and are not natural killer cells while some activated T cells and natural killer cells may be found in the normal lamina propria.

Functionally, intraepithelial lymphocytes have very limited immune activity when assayed in vitro. IEL do not respond to non-specific mitogens and are not capable of mediating spontaneous cell mediated cytotoxicity (SCMC), nor do they mediate antibody-dependent cellular cytotoxicity (ADCC). IEL can mediate mitogen-induced cellular cytotoxicity (MICC) for Chang cells. Lamina propria lymphocytes in contrast are capable of some natural killer activity and do mediate ADCC and MICC. IEL have been demonstrated to possess immunoregulatory activities in that they have a helper activity for immunoglobulin synthesis by autologous peripheral blood mononuclear cells when added in small numbers, but in larger numbers, IEL suppress immunoglobulin synthesis by PBM.

Human IEL, in contrast to rodent IEL, do not contain large granules and do not resemble large granular lymphocytes. Occasional small granules are seen within human IEL, granules generally described as lysosomes. Few if any human IEL have a morphological appearance similar to human large granular lymphocytes (natural killer cells). Similar to human IEL, rodent IEL are largely suppressor T cells and do not respond to mitogens.

IEL are clearly increased in numbers in several disease states, when expressed as a ratio of IEL to number of epithelial cells. There is clearly an increase in IEL in both celiac sprue and in tropical sprue and in the celiac sprue lesion found in patients with dermatitis herpetiformis. IEL are often increased, but not consistently so, in other inflammatory disease states of the intestine such as intestinal stasis syndromes. IEL are not increased in inflammatory bowel disease. In celiac sprue, the T8:T4 ratio of IEL is unchanged when compared to normal, but the proportion of $T8^+$, IEL expressing

the surface antigen Leu1 is significantly increased when compared to normal (56% vs 32%). In inflammatory bowel disease, the T4:T8 ratio remains similar to that seen in normal intestine. There is, an interesting heterogeneity of changes when Crohn's colitis is compared to ulcerative colitis and to Crohn's ileitis. There is a significant decrease in IEL in ileal Crohn's disease, this decrease consisting predominantly of a decrease in number of suppressor T cells so that there is a significant increase in T4:T8 ratio. The T4:T8 ratio in ileal Crohn's disease is 0.37 ± 0.5, in the "normal" margins of ileal Crohn's disease 0.22 ± 1.0 and in control ileum 0.13 ± 0.1. When tissues of patients treated with steroids are compared to tissues of patients not treated with steroids, the steroid treated tissues have IEL counts similar to control values. This implies, but does not prove, a morphologically beneficial effect of steroid treatment in these patients.

In summary, IEL are a unique set of T cells that are predominantly suppressor ($T8^+$) and which have a varied expression of other T cell antigens, at least in celiac sprue. IEL are not activated as determined by expression of HLA-DR antigen, do not respond to non-specific mitogens, and do not have natural killer phenotype or function. IEL in rodents have some similarity to mast cells, but there is little evidence in man that the IEL is related to mast cells. IEL may play an immunoregulatory role in man, possibly by suppressing the systemic immune response to antigens that simultaneously promote a mucosal immune response.

References

Human studies

1. Austin LL, Dobbins WO III: Intraepithelial leucocytes of the intestinal mucosa in normal man and in Whipple's disease. A light and electron microscopic study. Digest Dis Sci 27:311-320, 1982.

2. Selby WS, Janossy G, Goldstein G, Jewell DP: T lymphocyte subsets in human intestinal mucosa: the distribution and relationship to MHC-derived antigens. Clin Exp Immunol 44:453-458, 1981. Suggest that MHC determinants direct migration of IEL.

3. Selby WS, Janossy G, Jewell DP: Immunological characterization of intraepithelial lymphocytes of the human gastrointestinal tract. Gut 22:169-176, 1981.

4. Selby WS, Janossy G, Bofill M, Jewell DP: Lymphocyte subpopulations in the human small intestine. The findings in normal mucosa and in the mucosa of patients with adult celiac disease. Clin Exp Immunol 52:219-228, 1983.

5. Selby WS, Janossy G, Bofill M, Jewell DP: Intestinal lymphocyte subpopulations in inflammatory bowel disease: An analysis by immunohistological and cell isolation techniques. Gut 25:32-40, 1984.

6. Cerf-Bensussan N, Schneeberger EE, Bahn AK: Immunohistologic and immunoelectron microscopic characterization of the mucosal lymphocytes of human small intestine by the use of monoclonal antibodies. Immunology 130:2615-2622, 1983.

7. Ferguson A: Progress report. Intraepithelial lymphocytes of the small intestine. Gut 18:921-937, 1977.

8. Greenwood JH, Austin LL, Dobbins WO III: In vitro characterization of human intestinal intraepithelial lymphocytes. Gastroenterology 85:1023-1035, 1983. The "gold standard".

Animal studies

1. Rudzik O, Bienenstock J: Isolation and characteristics of gut mucosal lymphocytes. Lab Invest 30:260-266, 1974. First report of collection of IEL separate from LPL.

2. Guy-Grand D, Griscelli C, Vassalli P: The mouse gut T lymphocyte, a novel type of T cell. Nature, origin, and traffic in mice in normal and graft-versus-host conditions. J Exp Med 148:1661-1677, 1978. The "gold standard" for mouse IEL.

3. Arnaud-Battandier F, Nelson DL: Immunologic characteristics of intestinal lymphoid cells of the guinea pig. Gastroenterology 82:248-253, 1982.

4. Lyscom N, Brueton MJ: Intraepithelial, lamina propria and Peyer's patch lymphocytes of the rat small intestine: isolation and characterization in terms of immunoglobulin markers and receptors for monoclonal antibodies. Immunology 45:775-783, 1982.

5. Nauss KM, Pavlina TM, Kumar V, Newberne PM: Functional characteristics of lymphocytes isolated from the rat intestine. Response to T-cell mitogens and natural killer cell activity. Gastroenterology 86:468-475, 1984.

6. Tagliabue A, Befus AB, Clark DA, Bienenstock J: Characteristics of natural killer cells in the murine intestinal epithelium and lamina propria. J. Exp Med 155:1785-1796, 1982. Convincing data that mouse IEL are NK cells with T cell lineage.

7. Mowat AM, Tait RC, Mackenzie S, Davies MDJ, Parrott DMV: Analysis of natural killer effector and suppressor activity by intraepithelial lymphocytes from mouse small intestine. Clin Exp Immunol 52:191-198, 1983.