THE GASTROINTESTINAL PATHOLOGY CLUB NEWSLETTER

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THE GASTROINTESTINAL PATHOLOGY CLUB

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Membership: David Owen (Chairman), Tom Norris, Ali Qizilbash, Si-Chun Ming, Bill Dobbins, Jim Phillips

Newsletter: Don Antonioli and Henry Appelman, Editors

EDITORIAL

Well, fellow tube-lovers, we finally made it! Gastrointestinal pathology has at long last achieved its deserved place as a recognized subspecialty. It probably received its initial boost with the long course on gut diseases at the annual meeting of the International Academy of Pathology in 1976. This was followed the next year by the first subspecialty evening panel on gastrointestinal pathology at the I.A.P., organized by Jack Yardley, who kept it going for several years. Harvey Goldman, in turn, has been its guiding light for the past two years. It was conceived of as a forum for lively discussion of cases with educational merit to be presented by a group of G-I pathologists who rotated on the panel for three or four years with new people becoming members each year.

After the first such panel, plans were laid for testing the waters to determine if there was interest among known gut pathologists in establishing a subspecialty society. Such a society was perceived as a mechanism for propagating interest in G-I pathology, for emphasizing its importance as a highly sophisticated, complex area of pathology, for sharing information among members, for eventually developing joint investigative efforts, for potentially establishing referral centers for specific types of case problems and possibly for devising some type of a registry for unusual cases. Needless to say, the interest was there. The first organizational meeting was held during the I.A.P. meeting of 1979 with about 25 people attending. At that meeting, the establishment of a formal society was approved and four subcommittees were formed to 1) create a set of by-laws, 2) evaluate procedures for recruiting and selecting the members, 3) determine the financial requirements and prepare dues schedules and 4) examine the educational capabilities and direction of such an organization. At the 1980 meeting, the by-laws were approved, the first officers elected and the first educational program offered, this one being given only to the members in attendance. At the 1981 meeting, our first as a recognized companion society meeting with the I.A.P., the initial scientific session was offered to the general membership of the I.A.P. The response was overwhelming. Close to 300 pathologists attended that session. This was followed in 1982 with a second, also highly successful, scientific session with about 350 people in attendance. From an initial membership of just over 40 the Gastrointestinal Pathology Club has steadily grown to its current membership of about 70, which includes not only American and Canadian gut pathologists, but several from the United Kingdom, and a number of gastroenterologists who have recognized expertise in G-I pathology.

Now we have a newsletter, the purpose of which is to keep the members of the club informed as to what is happening in the subspecialty. This includes the whole gamut of educational activities being conducted by the members, publications that are in press and reviews of books and papers in the field. The newsletter can also serve as a forum for debate among the members, a discussion of the thorny issues confronting us all, and a mechanism for sharing technical information and methods of problem solving. The success of this newsletter depends upon two factors: First, the willingness of the membership to participate actively in its intended goal by submitting editorials, letters

to the editor, reviews of books and papers, and technical tid-bits, and second, the nagging of its two editors, who are likely to request, if not demand, your cooperation at any given time.

It is amazing that, in five years, the Gastrointestinal Pathology Club has become firmly established, has developed an expanding membership, has produced two superb, well-attended scientific sessions, and now is getting about the business of working toward its initial goals of responding to the needs of its members, the first step being this newsletter.

We are in the middle of an explosion in interest in gastrointestinal pathology. The number of seminars and courses sponsored by various pathology societies and educational institutions are increasing yearly. For the past ten years there has only been one reference text book in G-I pathology. Within the next two years or so, there will be probably four or five more.

Yes, fellow tube-lovers, we finally made it! Now we must get busy and make our organization exciting and vigorous, and functional in the ways that are most beneficial for us all.

SCHEDULE FOR GASTROINTESTINAL PATHOLOGY CLUB MEETING
Sunday, February 27, 1983, Atlanta, Georgia

Scientific Session
2:00 - 5:15 p.m.

I. GASTROINTESTINAL MANIFESTATIONS OF IMMUNODEFICIENCY DISORDERS
Moderator: Klaus J. Lewin

Normal Structure and Function of the Gut Immune System - David F. Keren, M.D.

The Pathologist's Role in the Work-Up of the Immunodeficiency Patient - Klaus J. Lewin, M.D.

Congenital and Acquired Immunodeficiency Syndromes - Marvin Ament

Epidemic Immunodeficiency in the USA - Wilfred Weinstein

Mechanisms of Injury in Chemotherapy and Bone Marrow Transplantation - William E. Beschorner

II. CLASSIFICATION AND PROGNOSIS OF COLORECTAL CARCINOMA
Basil C. Morson

Business Meeting
5:15 - 6:00 p.m.

PRESIDENT'S NOTE
Harvey Goldman

In our fourth year we are attempting to expand considerably the activities of the GPC. The most notable new accomplishment is the launching of this Newsletter, thanks to the major efforts of Donald Antonioli and Henry Appelman. It is expected that this regular feature will serve to promote our unity of common purpose and interest, and its content and success will be directed by your active participation.

The Club will continue to provide a full scientific program at our annual meeting just before the IAP session in Atlanta. For 1983, the Education Committee, chaired by Klaus Lewin, has arranged another exemplary program which will concentrate mainly on immunodeficiency disorders. It will conclude with a special talk by Basil Morson on his experience and recommendations regarding colonic carcinoma; full details of the program are listed in this letter. Beginning this year, with the support and sponsorship of the IAP, we will be able to grant CME category I credit for the scientific session. Considering our previous educational efforts, this credit is highly deserved and surely no gimmick. From past experience I would suggest that you arrive a bit early, if only to get into the room, let alone acquire a seat!

Pursuant to the interest expressed by members for an additional interim meeting where we might explore some research topics in greater depth, the GPC has made a formal request for inclusion on the program of the annual AGA meeting at its Digestive Disease Week in late May, beginning probably in 1984. The decision to join this group was predicated on the observation that many members of our Club, including both pathologists and clinicians, also regularly attend the clinical meetings. Our acceptance by the AGA is not assured, however, given their large and expanding program, but I believe that our proposal is attractive and competitive. I would urge all Club members to lobby their local AGA politicians on our behalf.

We have also attended to the refinement of the qualifications for membership in the Club and preparation of a revised nomination form, a copy of which is enclosed. The Membership Committee, chaired by David Owen, and the Executive Committee believe that we have responded to the majority opinion of the Club members by accenting a proven interest and involvement in the gastrointestinal tract proper. It is not our intent to exclude persons with an associated or dominant concern for the pathology of the liver, pancreas or biliary tract, and we would hope that all applications will be considered on their individual merit. I would ask you to review the new nomination form, which can be discussed further at our next business meeting.

Additional activities of the Club this year have included an attempt to identify a scientific project that might involve our membership; exploration of the potential need, features and funding of a clinical fellowship in GI Pathology; and further notice of our existence by announcements in appropriate journals. I believe that the GPC has expanded, more than complying with any sunshine clause, and that we are here to stay. The Executive Committee and I would welcome any comments regarding our present activities and future development.

GASTROINTESTINAL PATHOLOGY CLUB
BUSINESS MEETING
28 February 1982
Sheraton Hotel, Boston, Massachusetts

Members Present: Drs. Abrams, Antonioli, Appelman, Cooper, Dayal, Dobbins, Enterline, Frei, Goldman, Gourley, Haggitt, Hamilton, Kay, Keren, Lechago, Lev, Lewin, Madara, Manley, Ming, Mitros, Norris, Owen, Qizilbash, Rickert, Riddell, Schenk, Smith, Sommers, Sprinz, Tomasulo

1. The meeting was called to order by Dr. Haggitt at 5:15 p.m. following the Scientific Session, a quorum having been determined to be present.

2. The minutes of the March 1, 1981 meeting were approved as circulated.

3. The financial report for 1981 was presented by Dr. Abrams as follows:

Balance as of March, 1981.....		$ 746.85
Receipts, March 1, 1981 - February 28, 1982 (Dues).....		$1175.00
		$1921.85
Expenses, March, 1981 - Feb. 28, 1982....		-491.70
IAP printing charge	$192.61	
Duplicating costs (programs)	212.45	
Postage	36.64	
	$491.70	
Balance as of February 28, 1982.....		$1430.15

4. Dr. Hamilton, reporting for the Education Committee, indicated that future programs would be shaped, as this year's program had, along lines suggested by questionnaires submitted by members and attendees.

5. Dr. Yardley, reporting for the Membership Committee, reviewed the concept, developed by the Committee, of an "Associate Membership" to replace the current Junior Membership. The proposed amendment to the By-Laws formally effecting this change (as stated in a memorandum dated March 5, 1981) was circulated to the membership and subsequently approved without dissent. The effect of this vote is:

   a) to replace the original language of Article III, Section A, paragraph 2 with the following: "Associate Member: Any person holding a doctorate (or doctorate-equivalent) degree with an interest in gastrointestinal pathology. This membership is limited to five years and cannot be renewed. Associate members may apply for Regular membership in the usual way at any time if post-doctoral training has been completed.

b) to replace the word "Junior" with "Associate" in Article III, Section C, paragraph 2, lines 1,2, and 6.

Dr. Yardley reported that the Membership Committee and the Executive Committee had approved 16 new members and 2 associate members. He described the evolution and refinement of criteria for membership in the Club. He expressed the Committee's opinion that the Club should remain a "lumen" association, (with an interest in hepatopathology being neither a qualifying nor a disqualifying characteristic). Ordinarily, in order to qualify for membership, applicants must have a record of publications in gastrointestinal pathology as well as teaching and sign-out responsibilities. Applications will be accompanied by a nominator's cover letter in which any exceptional circumstances will be explained. The membership application form will be revised by the Membership Committee and Executive Committee, and then circulated. Prospective new members will be informed that applications will be acted upon only once a year, just prior to the IAP meeting.

6. The following changes in standing committees were announced by Dr. Haggitt:

a) Education Committee

Expiring terms - Drs. Hamilton and Lechago
Continuing - Drs. Lewin, Antonioli, Mitros, and Schenk
Newly appointed - Drs. Keren and Rickert
Chair - Dr. Lewin

b) Membership Committee

Expiring terms - Drs. Yardley and Gourley
Continuing - Drs. Norris, Qizilbash, Owen, and Ming
Newly appointed - Drs. Dobbins and Phillips
Chair - Dr. Owen

7. The results of a questionnaire distributed to the membership earlier in the year were presented and discussed. The consensus was that the annual scientific meeting should be directed primarily to gastrointestinal pathology specialists, but open to, and with some content for, the 'general' pathologist.

Another message that emerged from the questionnaire was that the Club membership perceives a need for formal fellowship training in GI pathology, and that the Club is deemed to be an appropriate agency to explore the matter. Accordingly, Dr. Haggitt announced the formation of an ad hoc committee to investigate the issues. This committee, consisting of Drs. Yardley, Goldman, Lewin and Haggitt, will be charged to explore the desirability and feasibility of establishing formal fellowships. They will attempt to formulate guidelines and criteria for fellowship training, and consider related issues such as possible subspecialty certification.

8. There was a general discussion of future Club activities. Dr. Haggitt emphasized the importance of recruiting young pathologists into associate membership as a means of interesting them in the field. Some members expressed concern about the scheduling of activities during the IAP meeting; and there was agreement with the idea of trying to move the Sunday meeting of the Club into the evening, and to move the Thursday evening meeting to a point earlier in the week. The idea of holding an intensive, working type meeting once a year in addition to the IAP companion meeting was discussed. Such an interim meeting could be used for dealing with "esoteric" subjects, cooperative studies, and the like. The Education Committee was directed to consider the possibility of such a meeting; and was also asked to explore the desirability of publishing proceedings of our meetings, although some sentiment against the latter idea was expressed.

9. Dr. Riddell was nominated by the Membership Committee for the office of Vice President/President-Elect. There were no other nominations from the floor, and Dr. Riddell was elected by acclaim.

10. Dr. Goldman was formally installed as President, and he addressed the membership about future directions and activities of the Club. He stated his intent to enhance the value of our membership list by annotating it with respect to members' special interests. He announced that he had asked Drs. Appelman and Antonioli to produce a club newsletter. Dr. Goldman also spoke to the importance of the Club as an agency for the conduct of cooperative studies. He asked that the members contact him directly with their ideas and opinions about potential club activities.

11. The meeting was adjourned at 6:00 p.m.

Respectfully submitted,

Gerald D. Abrams

Gerald D. Abrams, M.D.
Secretary-Treasurer

Items of Interest

To be successful, this Newsletter must encourage discussions and exchanges of information among the GI Club membership. To achieve this goal, we solicit your help by asking you to send us material concerning these areas of interest:

1. Announcements of postgraduate courses, symposia, etc., involving GI pathology. Please include the name of the course, location, inclusive dates, fees, and how to obtain further information.

2. Letters to the Editor. Let us know what you think about the content of the Newsletter and what you would like to have changed, deleted, or added.

3. Questions of any type; for example, concerning use of fixatives; technical procedures; diagnostic problems, etc. We will refer your questions to appropriate Club members and publish your questions and their replies in the next issue of the newsletter.

4. A listing of your papers in press. Each citation should be accompanied by a brief summary abstract of the content of the article.

5. Information on fellowships and electives in GI and liver pathology at your institutions.

6. Announcement of the establishment and availability of tissue or cell culture lines.

Also, two of our Club members, Cecilia Fenoglio and Harvey Goldman, are members of the Education Committee of the IAP. They would be pleased to receive your comments on the educational content and direction of the IAP annual meetings (scientific sessions, posters, short courses, etc).

Please send all correspondence on these items to:

Donald Antonioli, M.D.
Department of Pathology
Beth Israel Hospital
330 Brookline Avenue
Boston, MA 02215

For inclusion in the second issue of the Newsletter, all correspondence must be received by January 10, 1983.

THE ULCERATIVE COLITIS DYSPLASIA ATLAS

For the past three years, there has been a concerted attempt to histologically and cytologically characterize all of the epithelial changes occuring in ulcerative colitis and to define them in terms of the problems of dysplasia and eventually carcinoma. This study has been conducted by a group which has been identified as the "Inflammatory Bowel Disease Dysplasia Morphology Study Group". The members include Drs. Ahrens, Appelman, Correa, Fenoglio, Goldman, Haggitt, Hamilton, Morson, Ransohoff, Riddell, Sommers, and Yardley. As a result of the efforts of this group, an Atlas of these epithelial alterations is being produced. The early drafts of the manuscript have been completed and circulated among some of the members of the study group who comprise a small steering committee. It is hoped that the final manuscript will be ready to submit to the editors of Human Pathology, sometime early in the fall of 1982. If the manuscript is accepted by the editors, then, hopefuly, it will be published in a reasonably short time thereafter.

COURSES INVOLVING GI CLUB MEMBERS

Surgical Pathology of the GI Tract (ASCP) Directors: R. Haggitt and R. Riddell. Washington, D.C., June 20-24, 1983. Members participating include Haggitt, Riddell, Yardley, Tomasulo, Appelman, Lechago, Schffler.

PAPERS IN PRESS BY THE MEMBERSHIP
(List as of 7/13/82)

1. Antonioli DA, Goldman H: Changes in the location and type of gastric adenocarcinoma. Cancer.

2. Crocket KV, Reising J, Gav M, Wirman JA, Joffe SN: Effect of aprotinin and dextran 40 on acute experimental pancreatitis. Journal of Surgical Research.

3. Dobbins WO III: Alterations in intestinal structure associated with micro-organisms. In: Attachment of Micro-organisms to the Gastro-intestinal Mucosal Surface. E. Boedeker (editor). CRC Press, Inc.

4. Dobbins WO III: Small bowel biopsy in malabsorptive states. In: Contemporary Issues in Surgical Pathology, Volume 4; Pathology of the Small Intestine, Colon and Anus. HT Norris (editor). Churchill Livingstone, Inc., New York.

5. Dobbins WO III: Whipple's disease. In: Bockus Gastroenterology, Fourth Edition, Volume III, The Intestine. WS Haubrich, MH Kaiser, JLA Roth, F Schaffner (editors). WB Saunders, Philadelphia.

6. Fenoglio, CM, Pascal RR: Colorectal adenomas and cancer: pathologic relationships: Cancer in press.

7. Goldman H, Antonioli DA: Mucosal biopsy of the rectum, colon and distal ileum. Human Pathology.

8. Hamilton SR, Bussey HJR, Morson BC: En face histopathologic technique for examining colonic mucosa of resection specimens. American Journal of Clinical Pathology.

9. Hamilton SR, Keren DF, Yardley JH, Brown G: Effects of parenteral keyhole limpet cyanin or cholera toxin on intestinal immune response to keyhole limpet hemocyanin. International Archives of Allergy and Applied Immunology.

10. Henschke C, Goldman H, Teele RL: The fatty liver in childhood. Its causes and ultrasonic appearance. American Journal of Roentgenology.

11. Kahn E: Hepatobiliary morphology in arteriohepatic dysplasia. Hepatology.

12. Kahn E: Histology of the gastrointestinal tract. In: Disorders in Pediatric Gastroenterology and Nutrition. G. Silverberg (Editor).

13. Kahn E: Proliferative defect in ulcerative colitis. Cancer Investigation.

14. Kahn LB, Mir R: Lymphoid proliferation of the gastrointestinal tract. In: Frontiers in Gastrointestinal Cancer.

15. Kumar NB, Nostrant TT, Appelman HD: Acute self-limited colitis. American Journal of Surgical Pathology.

16. Lev R, Griffiths WC: Colonic and small intestinal alkaline phosphatase. Gastroenterology.

17. Lipper S, Kahn LB, Ackerman LV: The significance of microscopic invasive cancer in endoscopically removed polyps of the large bowel: A clinical-pathologic study of 51 cases. Cancer.

18. Madara JL: Cup cells: Structure and distribution of a unique class of epithelial cells in guinea pig, rabbit and monkey small intestine. Gastroenterology.

19. Madara JL, Trier JS: Structure and permeability of goblet cell tight junctions in rat small intestine. Journal of Membrane Biology.

20. Madara JL, Wolf JL, Trier JS: Structural features of the rat small intestinal microvillous membrane in acute experimental diabetes. Digestive Diseases and Sciences.

21. Mitros FA, Schuffler MD, Teja K, Anuras S: Pathology of familial visceral myopathy. Human Pathology 13:825, 1982.

22. Perzin KH, Fenoglio, CM and Pascal RR: Tumors of the small and large intestine. In Principles and Practice of Surgical Pathology. Steven Silverberg (Ed.), John Wiley & Sons, Inc., New York, 1982 in press.

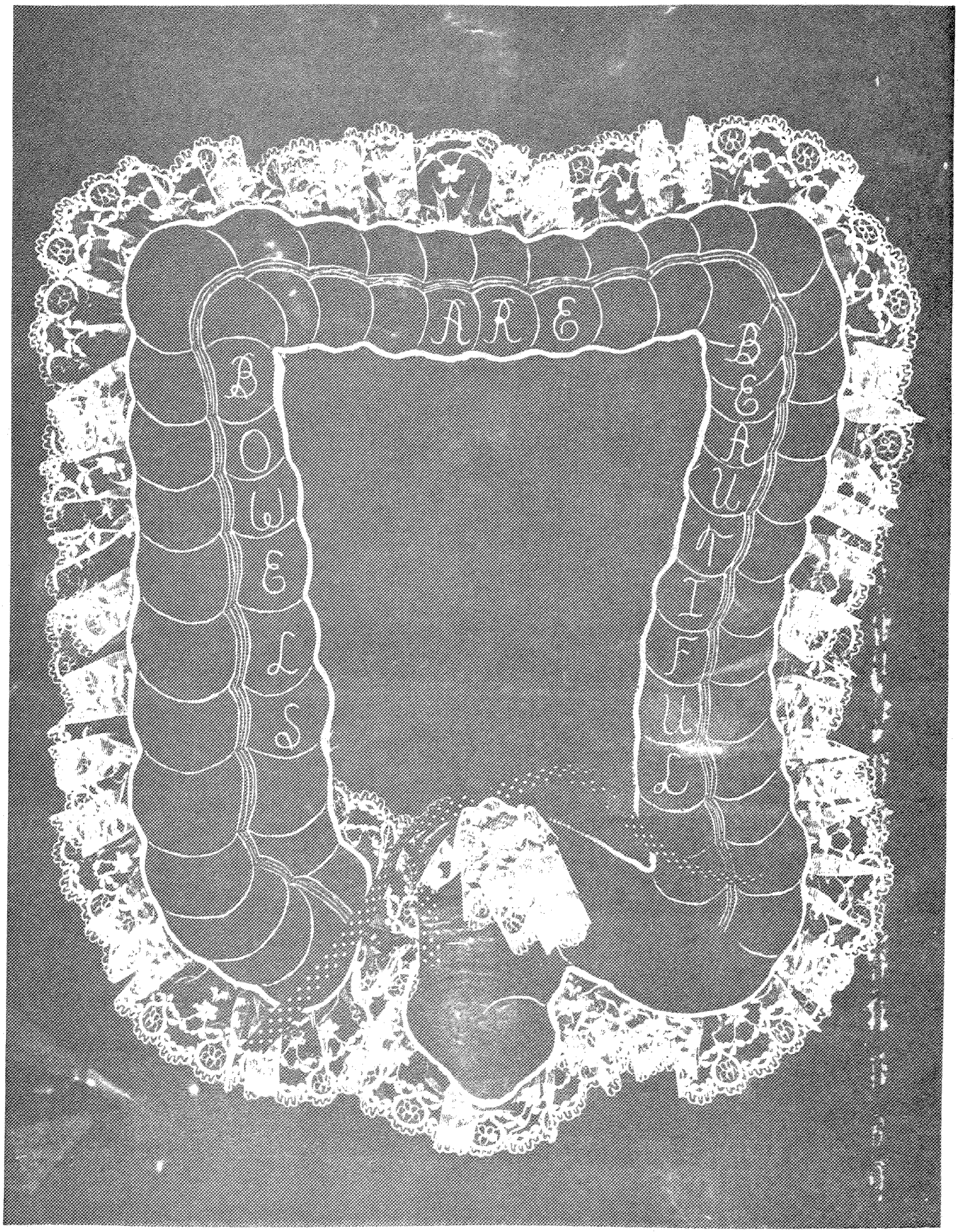
23. Riddell R (editor): Pathology of Drug-Induced and Toxic Diseases. Churchill Livingstone, Inc., New York.

24. Schnitt SJ, Antonioli DA, Goldman H: Massive mural edema in severe pseudomembranous colitis. Archives of Pathology and Laboratory Medicine.

25. Trnka Y, Glotzer DJ, Kasdon E, Goldman H, Steer M, Goldman L: The long-term outcome of restorative operation in Crohn's disease: Influence of location; prognostic factors; surgical guidelines. Annals of Surgery.

26. Winter HS, Madara JL, Stafford RS, Grand RJ, Quinlan J, Goldman H: Intraepithelial eosinophils: A new diagnostic criterion for reflux esophagitis. Gastroenterology.

PLAYMATE OF THE MONTH



GASTROINTESTINAL SPECIALTY CONFERENCE
IAP, March 4, 1982

GIS2-1 (UCLA Medical Center, Dr. Klaus Lewin):
A 60-year-old female with a history of abrupt onset of diarrhea of six months duration had approximately 10 watery dark stools per day but no anorexia, weight loss, abdominal pain or other symptoms. Extensive x-ray and laboratory studies were negative except for a 9% eosinophilia, and presence of polymorphonuclear leukocytes and eosinophils in the stools. Stools were negative for ova, parasites and culture. Colonoscopy was grossly normal. Multiple biopsies were taken of which this biopsy is representative.

Case #1 Diagnosis: Collagenous colitis

Pathology of Rectal Biopsy

a) Light Microscopy: Surface epithelium is intact although in places there appears to be artifactual disruption. The subepithelial tissues show acellular collagenous fibrosis and in places the collagen appears to be distinct from the basement membrane. In some areas the subepithelial tissues show a rather loosely arranged stroma with a prominent vascularity. The lamina propria shows an increased round cell infiltrate below the collagen deposition. Rectal glands are focally distorted but no crypt abscesses are seen.

b) Electromicroscopy: The basement membrane is focally disrupted and no immune complex deposition is seen.

c) Immunohistochemistry: Sections were stained for immune complexes by immunoperoxidase and immunufluorescence. No deposits were found.

DISCUSSION

Collagenous colitis is a newly described distinctive clinicopathologic entity manifesting as chronic watery diarrhea in middle aged patients. Histologically, the colon is characterized by collagenous thickening of the subepithelial basement membrane (10 μ, normal - 5μ). Other changes such as shortening and distortion of glands and an increased round cell infiltrate of the lamina propria have been described. In addition our case showed a focal decrease in density of the lamina propria with vascular ectasia. It is thought that the above changes block the normal resorption of water and electrolytes by the mucosa, resulting in diarrhea.

The etiology and pathogenesis of this entity are unclear. It is uncertain whether the histologic features represent non-specific tissue response to injury or are the consequence of a specific mucosal injury such as an immune complex disease. Morphologically, the changes are pretty distinctive and unlike any of the changes seen in ulcerative colitis, Crohn's disease, ischemic colitis, pseudomembranous colitis, TB, amebiasis or collagen disorders. Although amyloidosis might resemble this lesion in hematoxylin and eosin sections, the absence of vascular lesions and the negative Congo red stains should differentiate the two. Freeman et al. found immune complex deposition below the basement membrane with lysis of the latter, in one case. They have postulated that collagenous colitis represents an immune complex disorder. We have been unable to confirm these findings by electron microscopic or immunohistochemical studies in our case. This suggests to us that collagenous colitis may in fact result from different causes and thus represent a non-specific response to injury. Finally, the term collagenous colitis may not be the most appropriate for this lesion, since other changes such as subepithelial alterations of the lamina propria may overshadow the changes in the basement membrane.

REFERENCES

Neilson, V.T., Vetner, M., Harslof, E.: Collagenous colitis. Histopathology 4: 83-86, 1980.

Linstrom, C.G.: Collagenous colitis with watery diarrhea: A new entity? Path. Europ. II: 87-89, 1976.

Bogomoletz, W.V., et al.: Collagenous colitis: An unrecognized entity. Gut 21: 164-168, 1980.

Freeman, H.J., Weinstein, W.M. et al.: Watery diarrhea syndrome associated with a lesion of the colonic basement membrane-lamina propria interface. Annals of the Royal College of Physicians and Surgeons of Canada p 45, Jan. 1976. (abstract)

GI82-2 (St. Barnabas Medical Center, Livingston, NJ, Dr. Robert R. Rickert): This 5-year-old boy was admitted with a four day history of abdominal pain, nausea and vomiting. Initially, the pain was ill-defined but at the time of admission was well localized to the right lower quadrant. Physical exam revealed a temperature of 103, pulse 130, respiration rate of 38 and B.P. of 88/40. Findings were otherwise limited to the abdomen which showed right lower quadrant tenderness, spasm and guarding with rebound. Laboratory studies were normal except for a WBC of 16,000. The patient was thought to have acute appendicitis and was explored. At surgery the appendix was grossly normal. A mass was noted in the terminal ileum with diffuse thickening of the wall and enlargement of regional lymph nodes to a diameter of 2.5 cm. A clinical diagnosis of probable malignant lymphoma was made and a right hemicolectomy was performed. Sections are from terminal ileum.

Case #2 Diagnosis: Yersinia entercolitis

The Yersinia group of organisms has been demonstrated to cause several types of illness both in animals and in humans. The most common agent responsible for Yersinia infection in Europe is Yersinia pseudotuberculosis which for many years was known to cause infection in guinea pigs and turkeys as well as a variety of other animals and birds. In man it was recognized as an occasional cause of a rare although often fatal septicemic illness. Since 1954 it has been known to be responsible for a self-limited enteritis as well as mesenteric adenitis. Infections caused by Yersinia pseudotuberculosis have only rarely been reported in North America. The more frequent variety of Yersinia infection in the United States and Canada is due to Yersinia enterocolitica.

The morphologic and clinical features of the intestinal infection caused by these two organisms are essentially identical. Most patients develop an acute gastrointestinal illness characterized by fever, abdominal pain, nausea, vomiting, diarrhea and leukocytosis. Many patients have a history of recent respiratory infection often consisting of a prominent pharyngitis. The abdominal symptoms closely resemble acute appendicitis frequently justifying exploratory laparotomy. At the time of operation the surgeon usually finds disease localized to the ileocecal region consisting of combinations of acute appendicitis, mesenteric lymphadenitis, an inflammatory mass in the ileocecal region or peritonitis. The least common variety of infection is the frequently fatal septicemic form. The infection has also been associated with erythema nodosum, septic arthritis, inflammatory skin lesions, hepatosplenic abscess and glomerulonephritis.

The characteristic lesions occuring in the ileocecal region consist of marked mesenteric lymphadenopathy in virtually every case. Multiple, frequently matted, enlarged lymph nodes up to 4 or more cm. in diameter are commonly seen. Gross changes in the region of the terminal ileum are seen in about 20% of patients who undergo exploratory surgery. The ileal wall is commonly edematous with a congested serosa. The morphologic changes of the mucosa consist of marked lymphoid hyperplasia with mucosal ulceration. Although the terminal ileum is the most common site, the process may also extend into the cecum and ascending colon. Frequently, the lymphoid hyperplasia and focal ulceration are also seen in the appendix.

Microscopically, there is a striking hyperplasia of mucosal and submucosal lymphoid tissue often associated with microabscess formation and ulceration of the overlying mucosa. The changes in the enlarged regional lymph nodes are microscopically similar. There may be microgranulomas with necrotic centers but giant cells are rare. In the bowel the inflammation is commoly transmural with edema and necrosis.

The early lesions are of particular interest since they suggest that the intestinal lymphoid tissue is the probable portal of entry. Early lesions reveal only marked hyperplasia with central necrosis and microabscess formation. The overlying mucosa becomes focally ulcerated giving rise to a lesion which is not dissimilar from the minute aphthoid ulcer of Crohn's disease. The lesion in Yersinia, however, is characterized by a greater degree of necrosis and abscess formation.

The gram negative coccobacilli causing this infection may be demonstrated in tissue. They may be identified by culture of the lesions in the bowel or regional lymph nodes. Serologic testing is important both in establishing a diagnosis and in distinguishing between infection by Yersinia pseudotuberculosis and enterocolitica. Although antibiotic therapy is usually not necessary in the typical self-limited infection, several broad spectrum agents have been effective including streptomycin, tetracycline, chloramphenicol, ampicillin and the aminoglycosides.

The oral route is generally accepted as the mode of infection in man. Organisms have been isolated from the feces of patients both with enteritis and with infection apparently limited to mesenteric lymphadenitis. Occasional familial outbreaks have been reported. Of great interest was the recent report of an outbreak of Yersinia enterocolitica infection in a group of school children in which the infection was traced to contaminated chocolate milk. This outbreak resulted in the hospitalization of 36 children, 16 of whom underwent appendectomy.

The pathologic differential diagnosis includes Crohn's disease, tuberculous enteritis and other infectious diseases such as tularemia, actinomycosis, amebiasis and schistosomiasis. Accurate diagnosis depends upon demonstration of antibodies in patients' serum or culture of either feces or tissue removed should surgical intervention have occured.

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3. Braunstein, H., Tucker, E.B. and Gibson, B.C. Mesenteric lymphadenitis due to Yersinia entercolitica. Am. J. Clin. Path. 55: 506-510, 1971.

4. El-Maraghi, N.R.H., and Mair, N.S. The histopathology of enteric infection with Yersinia pseudotuberculosis. Am. J. Clin. Path. 71: 631-639, 1979.

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3. Tanikawa K. Ultrastructural aspects of the liver and its disorders. Tokyo: Igaku-Shoin Ltd. 1979; 88-97.

4. Phillips MJ, Oda M, Funatsu K. Cholestasis, its ultrastructural aspects. In: Farber E, Fisher MM ed. Toxic Injury of Liver. New York, Basel: Marcel Dekker Inc., part A, 1979; 333-383.

GIS2-4 (University of Michigan, Ann Arbor, Dr. David F. Keren):
A 40-year-old woman with a history of intermittent diarrhea and steatorrhea for the past several years. A small bowel series had shown an "abnormal mucosal pattern" without evidence of tumor or obstruction. Repeated stool examination showed cysts of Giardia lamblia. Serum immunoglobulin determinations showed IgG 230 mg/100 ml; IgA 25 mg/100 ml; IgM 10 mg/100 ml. There was no anemia and the serum vitamin B-12 and folic acid were within normal limits. A jejunal biopsy was performed.

Case #4 Diagnosis: Nodular lymphoid hyperplasia

Isolated lymphoid follicles are a normal morphologic feature of the gut mucosa. When lymphoid follicles are particularly large and numerous they constitute nodular lymphoid hyperplasia. Nodular lymphoid hyperplasia can be seen in hypogammaglobulinemia (1,2,3), selective IgA deficiency (occasionally associated with Giardia lamblia) (4), or as part of a local hyperimmune response to gut antigens.

Some workers have found that the nodular aggregates in common variable immunodeficiency contain T-cell antigens by immunohistology (3). The latter group also found that T cells from their patients were able to suppress the immunoglobulin production of both normal B cells and B cells from their patient. Nagura et al. (5) found that the nodules contained mainly pre-B cells. They hypothesized that the pre-B cells (immature lymphocytes with weak-staining cytoplasmic IgM) are not able to mature properly to B cells and then to plasma cells. This could be consistent with Tytgat's findings (3) of excessive suppressor T cell response which would be expected to halt B-cell maturation. Further, in the present case, the lymphoid nodules gave weak cytoplasmic staining for IgM (consistent with pre-B cells). Such a defect in pre-B cell maturation is known to occur in patients with infantile x-linked agammaglobulinemia (6). In hyperreactive states, the nodules may reflect excessive stimulation of pre-B cells, although this is not clear at present.

The distinction between immunodeficiency and hyperreactive state is made by examining the plasma cell content in the lamina propria. Serum immunoglobulin levels are usually helpful, but it is possible to have low serum IgA with normal local content of IgA plasma cells (7). By examining the plasma cell content with immunohistology, a diagnosis of selective local immunoglobulin deficiency often can be made.

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GI82-5 (University of Chicago, Dr. Robert H. Riddell):
Female 32-years-old presenting with a 2 year history of multiple episodes of right-sided abdominal pain. On examination she was found to have an exquisitely tender liver. All laboratory tests were normal, as was an oral cholecystogram, but a Tc 99m sulfur colloid liver scan showed multiple large defects. Laparotomy was carried out and the tumor biopsied.

Case #5 Diagnosis: Primary well-differentiated angiosarcoma of liver with histiocytoid (epithelioid) features, possibly related to oral contraceptives and with long-term survival.

Pathology: The tumor was characterized by cells that have both a spindle-cell and an apparent gland-forming appearance that initially might raise the question of cholangiocarcinoma or metastatic adenocarcinoma. However, closer examination reveals that some of these glands contains red cells and that atypical sinusoidal cells are present in the residual liver. The endothelial nature of this tumor was confirmed by electron-microscopy and stain for factor VIII-related antigen.

The differential diagnosis of endothelial lesions in the liver is a cavernous hemangioma (which this obviously is not), a benign hemangio-endothelioma, an hemangio-endothelial sarcoma, or possibly an histiocytoid (epithelial) histiocytoma affecting the liver. Although the latter has not been officially described, there is one report in the literature that may be an example of this, [1] and a possible second [2].

There are certainly similarities between histiocytoid hemangioma and this tumor[3]. We hedge towards this lesion being malignant because of the manner in which it is destroying the hepatic parenchyma (local aggressiveness - this is not seen in benign hemangioendothelioma), the fact that atypical sinusoidal cells can be seen as in typical hepatic angiosarcoma, and the presence of occasional mitoses including atypical forms.

Further history: The patient is para 2, gravida 2, and following the birth of her second child had been on continuous oral contraceptives. There is not evidence of any other primary tumor. There is no history of exposure to any of the other known substances associated with angiosarcoma (v.i.).

Relationship to oral contraceptives: The association between O.C. and liver tumors is well documented. The majority of these are hepatocellular adenomas or focal nodular hyperplasia, but other tumors such as hepatocellular carcinoma are also described.[4,5] There has also been a suggestion that angiosarcomas may be associated with estrogens[6-8] and also androgens/anabolic steroids,[9]. Angiosarcomas may be associated with thoratrast, vinyl chloride, arsenicals, radium and hemochromatosis,[10] and possibly phenelzine[11].

In this patient the possibility that the tumor may be related to O.C. ingestion is raised because of the temporal eligibility, the fact that other changes that may be O.C.-related are seen in the adjacent hepatic parenchyma, (sinusoidal dilatation, mild peliotic changes) and also because the patient's tumor has not advanced in the three years since she was taken off of O.C., unlike most angiosarcomas in which the patient usually expires rapidly.

Possible counterarguments are that there is no baseline Tc - scan, so that we do not really know that the tumor was still growing when the patient presented. Also, the tumor seems to be low-grade and morphologically unlike usual hepatic angiosarcomas, so that it might be expected to behave in a relatively benign manner. The possibility that it might be totally unrelated to O.C. ingestion remains.

For consideration: If this patient develops pulmonary metastases, will they resemble the so-called intravascular (sclerosing) bronchiolo-alveolar tumor (IV/BAT)?

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GI82-6 (Harbor General Hospital, UCLA, Dr. Juan Lechago):
This 67-year-old caucasian male presented with epigastric pain for several months. Radiologic and endoscopic examination revealed a large duodenal ulcer. Significant hypergastrinemia was documented by repeated radioimmunoassays. A subtotal gastrectomy and exploration of the abdominal organs was carried out for a presumptive Zollinger-Ellison syndrome. No pancreatic tumor was found during the operation, but careful examination of the gastrectomy specimen revealed a discrete nodule in the wall of the duodenal bulb, next to the pylorus measuring 1 cm. in diameter. The patient recovered uneventfully and has now low blood gastrin levels, two years after surgery.

Case #6 Diagnosis: Duodenal carcinoid tumor associated with the Zollinger-Ellison Syndrome.

MICROSCOPIC DESCRIPTION:

Sections stained with hematoxylin and eosin show a portion of duodenal wall at the pylorus containing a small neoplasm with a well-defined trabecular pattern in the submucosa. Cords, clusters, and rossettes of tumor cells are separated by well vascularized fibroconnective strands of variable thickness. At high magnification, the individual tumor cells appear quite uniform, have abundant somewhat granular cytoplasm, and display no nuclear atypia or significant mitotic activity.

SPECIAL STUDIES:

Fontana-Masson silver impregnation for argentaffinity was totally negative. Grimelius' silver stain for argyrophilia, on the other hand, showed a number of positive cells, some isolated, some arranged in small clusters. Electron microscopic examination showed intracytoplasmic secretory granules in most tumor cells. Some were small, rounded, and electron dense, and resembled those of the normal IG (intestinal gastrin) cells. Other granules were 300 - 400 nm in diameter and had a core of medium electron density closely surrounded by the limiting membrane. These were reminiscent of the normal somatostatin-producing D-cells of the digestive tract and pancreas. Yet other tumor cells contained granules with a somewhat ambiguous morphology which did not lend itself to classification. Deparaffinized sections were incubated with antibodies to gastrin, somatostatin, VIP, GIP, secretin, ACTH, and calcitonin, and then subjected to the PAP immunoperoxidase technique. Many tumor cells, some isolated and some scattered, were positive for gastrin, while others, less numerous, were positive for somatostatin and for VIP. All other peptides tested were negative.

DISCUSSION:

The Zollinger-Ellison syndrome was originally characterized by the presence of a pancreatic islet cell tumor, gastric acid hypersecretion, and intractable peptic ulcers of stomach, duodenum, and even jejunum. It was later determined that these pancreatic tumors produced and released gastrin, and that the resulting hypergastrinemia was responsible for the gastric hyperacidity leading to peptic ulceration. It has been reported that 85% of gastrinomas are pancreatic, 13% are duodenal, and less than 2% have been localized in the stomach or the biliary tree.

Duodenal gastrinomas generally appear as small solid nodules in the submucosa and muscularis. Under light microscopic examination they have the appearance of carcinoid tumors, composed of rossettes and ribbons of generally benign-appearing cells. Lymph node metastases, however, have been reported in approximately 25% of duodenal gastrinomas. Immunocytochemistry shows the presence of gastrin in the cytoplasmic granules of the tumor cells. Electron microscopic analysis often reveals, either granules like those of the normal antral and duodenal G (gastrin producing) cells, or like those of the so-called D_1 cells. A subpopulation of D_1 cells has been recently reclassified as the IG (intestinal gastrin producing) cell of the duodenum and ileum. While surgically exploring a patient with the Zollinger-Ellison syndrome, it is important to keep in mind that a significant proportion of gastrinomas lie outside the pancreas. Moreover, extrapancreatic gastrinomas, no matter how severe the hypergastrinemia they cause, can be very small (1 cm in diameter, or less) and very difficult to find, even after careful exploration by an experienced surgeon.

Another interesting aspect of this tumor is that immunocytochemical analysis revealed the presence of somatostatin and VIP, in addition to that of gastrin. Production of multiple hormones by digestive endocrine tumors was considered to be a rarity in the past. However, as more extensive and careful immunolocalizations are being carried out in these neoplasms, it is becoming increasingly evident that they often produce a variety of peptides. Although the evidence is not conclusive in all instances, it would appear that these multiple peptides are produced by different cell types within individual tumors. It seems, therefore, that the concept of "multihormonal tumors", as enunciated a few years ago, is becoming the rule, rather than the exception, in the digestive system.

It is useful to find out, either by immunocytochemistry or by extraction and radioimmunoassay, what peptides these tumors produce. When detected in circulation, these peptides can be used as early humoral markers in the detection of metastatic activity. Since these neoplasms are of low malignancy, even after spread has occurred, knowing the substance they are capable of producing and releasing is of great potential help in understanding and even treating the sometimes life-threatening functional manifestations of the hypersecretion of some of those peptides.

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A 73-year-old white man presented with vague upper abdominal distress of 10 days duration. Past medical history included diabetes mellitus, atherosclerotic heart disease with old myocardial infarcts in 1958, removal of rectal polyp in 1971, ureteral calculus and colectomy for carcinoma in 1974, and viral labyrinthitis in 1979. An upper GI radiograph revealed irregular, large folds along the greater curvature of the stomach. This abnormality was confirmed at endoscopy, and multiple mucosal biopsies were obtained from the gastric corpus and antrum.

Case #7 Diagnosis: Granulomatous gastritis, isolated

1. Granulomatous disorders of the stomach usually affect the antral region, resulting in thickening of the wall and partial outlet obstruction, and such cases may mimic infiltrating carcinoma. Endoscopy typically shows irregular folds, and mucosal biopsies reveal multiple well formed granulomas without necrosis.

2. Differential diagnosis of gastric granulomas:
   a. Sarcoidosis: Involvement of the stomach and other portions of the gut is rare, and it is probable that sarcoidosis limited to the GI tract does not occur. The diagnosis depends on the exclusion of other granulomatous disorders and the demonstration of lesions in other more typical locations such as the lungs and mediastinum.

   b. Crohn's disease: Gross ulcerations and deep mural fissures are often present in the symptomatic cases. In patients with intestinal Crohn's disease, about one-quarter reveal microscopic abnormalities in the antral and duodenal mucosa in the form of focal inflammation and/or scattered granulomas.

   c. Infections: The major cause is tuberculosis which is almost always secondary to pulmonary disease. The granulomas often lack necrosis, and special stains in such cases are negative. There are usually lesions in other organs, and the diagnosis requires specific culture. Rare infectious causes include syphilis, histoplasmosis and other fungi.

   d. Foreign body granulomas: These include reactions to sutures, barium, food and other foreign material; and the specific diagnosis is based on identification of the particular element in the granulomas. Food granulomas are more often noted as a complication of ulceration, but they may be present in otherwise intact mucosa.

3. Isolated granulomatous gastritis:
   Upon elimination of all other known causes, there are cases of isolated idiopathic gastric granulomas. These tend to occur in older persons, and mucosal ulceration is infrequent and typically superficial. Follow-up studies have shown no progression or involvement of other tissues, and it appears that the lesion may regress.

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QUESTION OF THE ISSUE: This was submitted by Heidrun Rotterdam, Department of Pathology, Lenox Hill Hospital, New York, New York.

"Has anyone come across a congenital short small bowel? I recently saw a 240 cm. short bowel in a 38 year old black homosexual who died of disseminated CMV infection (GRID syndrome). There was no surgery and no gross or microscopic abnormality in the small intestine other than its shortness."

Editor's Note: This is an appeal for information by a fellow member. Do not let her down. The Editors will offer the first response: "No".

SECOND PLACE QUESTION OF THE ISSUE: This was submitted by H. D. Appelman, Department of Pathology, The University of Michigan, Ann Arbor, Michigan.

"I just saw an 8 cm. Peutz-Jegher's type hamartoma of the colon. Can any of you primma donnas beat that?"

Editor's Note: This is not an appeal for information. It is blatently an example of one-upmanship and should not be taken seriously.