

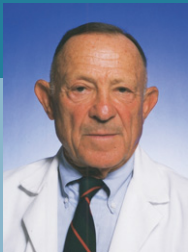
GASTROENTEROLOGY Turns 65



Anil K. Rustgi, MD, Editor

GASTROENTEROLOGY, the leading journal of the specialty, was born 65 years ago. We want to mark this anniversary with a look back through the eyes of the journal's distinguished editors. Starting with the 1965 term, I asked each editor to select and highlight critical and enduring articles that have since shaped the landscape of biomedical research and clinical medicine. I am appreciative of their

magnanimous spirit toward these contributions. There are important caveats in this endeavor for such selections cannot be exhaustive, much to our dismay, and do not diminish the value of many, many other articles through the decades in the journal. Nevertheless, it is our sincere hope that the reader's imagination is captured through this journey.



Marvin H. Sleisenger, MD

1965–1970

The reports published in GASTROENTEROLOGY from 1965 to 1970 heralded a transition for research in a number of important areas of gastroenterology. During this time, we acquired fundamental knowledge of the basic physiology and biochemistry of gastric secretion, of local immunologic responses (such as for celiac disease), of the genetic predisposition to colorectal cancer, and of the biological processes by which aspirin and congeners damage the gut. The pace at which we learned more about gastroenterology only accelerated in succeeding decades, and the magic of molecular biology yielded solutions to major gastrointestinal problems. GASTROENTEROLOGY caught the wind that was blowing research ever deeper into scientific inquiry, away from a past of predominantly empirical observations.

Detecting the Causes of Extreme Hyperacidity

Gregory RA. Memorial Lecture: The Isolation and Chemistry of Gastrin. *Gastroenterology* 1966;51:953–959.

Summary

The isolation of the hormone gastrin was performed by Rod Gregory and Hilda Tracy in an effort to chemically define the active principle in gastric extracts that stimulated gastric secretion. This work followed that of Edkins and Komarov, who suggested that such an agent might also weakly stimulate pancreatic secretion. The various purified gastrins, isolated from dog, pig, and human extracts, were found to be heptadecapeptide amides, and studies with synthetic amides showed that the terminal peptide displayed all the effects of the total peptide. These studies resulted in the availability of a small peptide for stimulating secretion and a method for measuring serum gastrin, leading to our present knowledge of states of normal and abnormal acid secretion.

Editor's comment

Investigators sought for decades to define the integrated mechanism that regulates secretion of gastric acid, not only for its own sake, but also to elucidate its alterations in both peptic disease and atrophy of the gastric mucosa. Histamine, contained in gastric fundus and antrum, was long known to be a potent stimulator of gastric acid secretion but of questionable physiologic importance. Nonetheless,

the stimulation of acid output in animals by antral extracts continued to be attributed to it until 1938, when Komarov showed that a protein fraction from a dilute acid extract of antral mucosa, free of histamine, greatly increased acid secretion. The work, confirmed by Uvnas, was continued by Gregory and Tracy, who in 1962 isolated the first pure peptide, gastrin I. Later that year, gastrin II was isolated; both peptides were synthesized in 1964 by G. W. Kenner at London University.

Gastrin proved to be 500 times more potent, on a molar basis, in stimulating acid secretion in humans than histamine. Its isolation and synthesis have led to its accurate measurement in plasma and serum by radioactively labeled antibodies raised against gastrin I (Yalow RS, Berson SA. *Gastroenterology* 1970;58:1–14; McGuigan JE, Trudeau WL. *Gastroenterology* 1970;58:139–150). These investigators then clearly showed marked increases in gastrin levels in patients with Zollinger–Ellison syndrome and in patients with pernicious anemia. The observations that gastrin levels are reduced after meal-induced acid secretion (“gastrin shut-off”) and increased after stimulation of the vagus nerve or, for example, during drug-induced suppression of acid have resulted from the brilliant work of Gregory and Tracy, who allowed researchers to measure serum gastrin levels.

Gluten as the Culprit in Celiac Disease

Kowlessar OD. Effect of Wheat Proteins in Celiac Disease. Gastroenterology 1967;52:893–897.

Summary

Almost 2 decades had passed since W. K. Dicke described, in his doctoral thesis, the harmful effects of certain cereals on patients with celiac disease. This article described the toxic substance gliadin, which is a component of gluten. The intestinal mucosa reacts to the gliadin peptides, leading to eventual villous atrophy. These peptides, the residues of ultrafiltrates and dialysates of peptic-tryptic and peptic-tryptic-crude pancreatic extract digests of gliadin, are neutral and acidic, with molecular weights less than 1500 daltons, and cause steatorrhea in patients with celiac disease. This article asked an important question: does celiac disease result from a hypersensitivity reaction of intestines to a peptide(s) containing glutamine and proline that is (are) not broken down by the mucosa?

Editor's comment

Although the whole story of gliadin toxicity has not yet been told, we are heading to the final chapter. Demography and strong family histories of celiac disease have pointed to a hereditary factor, and individuals with specific HLA class II haplotypes are susceptible to the disease. One particular heterodimer, HLA-DQ2, is found in many of these patients, and another, HLA-DQ8, is found in others. They have gliadin-specific HLA-DQ2-restricted T cells that recognize

gliadin peptides and then stimulate B lymphocytes to secrete immunoglobulins (Igs) and other T cells to secrete cytokines.

Further, an imbalance between intra-epithelial lymphocyte populations in these patients might contribute to pathogenesis via a decrease in production of interleukin-10. Celiac sprue develops in only a small percentage of the population, although HLA-DQ2 and -DQ8 are expressed in up to 60% of some European populations. Another gene(s) at an unlinked locus must be involved. The immune responses to fractions of gliadin are both humeral and cellular; the latter predominates. Studies have shown that the reaction to a target antigen, tissue transglutaminase (tTG), released from damaged cells, preferentially deamidates the neutral glutamine residues in gliadin, converting them to glutamic acid residues that are taken up into antigen-binding grooves of the heterodimer HLA-DQ2. These "activated" T cells then initiate a local immune inflammatory response via cytokines, including interferon- γ , and tumor necrosis factor α . The stimulatory gliadin peptides are small, single-peptide chains. Therefore, although an enzyme is involved in the pathogenesis of gliadin toxicity, it is not its absence but its increased activity that mediates disease pathogenesis. Assays with the antibodies IgA-tTG and IgG-tTG are used to diagnose celiac disease. A strict gluten-free diet remains the mainstay of therapy.

Colorectal Cancer—It's in the Genes

Lynch HT, Krush AJ. Heredity and Adenocarcinoma of the Colon. Gastroenterology 1967;53:517–527.

Summary

This report emphasized 2 important factors in our understanding of the pathogenesis of colorectal cancer. First, based on the high incidence of colorectal cancer in individuals with familial polyposis syndromes (100% of patients with familial adenomatous polyp syndrome), a similar progression is likely to also occur in sporadic colorectal cancer. Second, genetics could underlie the development of colorectal cancer in families with a high incidence of multiple organ cancers, particularly of colon and endometrium.

Lynch and Kruh meticulously amassed all relevant clinical data for a pedigree analysis of 6 families with so-called "family cancer syndrome," dating back to Warthin's first description in 1913. They concluded that the colon cancers in these patients probably did not arise from polyps, that the hereditary (genetic) defect was transmitted in a dominant fashion, and that this defect is quite different from the classic polyposis syndromes.

Editor's comment

The observations of Lynch et al of the autosomal dominance of the polyposis syndromes and the question of the relevance of the adenoma to the pathogenesis of sporadic

colorectal cancer, as well as to Lynch's "family cancer syndrome," stimulated much work on 2 fronts: in the clinic and in the laboratory. The landmark National Polyp Study (initially funded by the American Gastroenterological Association) found that patients with adenomas who had undergone clearing colonoscopy had a 76%–90% reduction in the incidence of colorectal cancer compared with the expected incidence in reference populations. Thus began the widespread colonoscopic screening and surveillance programs, with timing for each dependent on age, family history, prior presence of polyps or cancer, and so on.

Studies into the genetics of colorectal cancer proceeded apace. We now know that colorectal cancer develops as the result of genetic and epigenetic alterations that lead to malignant transformation of normal mucosa.

It is possible that the "2-hit" hypothesis, postulated by Alfred Knudson as a mechanism by which malignant transformation occurs in the colon, encompasses aberrant promoter hypermethylation to silence transcription of one copy of a gene and chromosomal deletions that inactivate the second copy. This is an unfolding story that perhaps will lead to more definitive markers of risk to prevent cancer and clues to successful therapies.

Old and New Reliable Arthritis Medicines Can Do Harm

Menguy R. *Gastric Mucosal Injury by Aspirin. Gastroenterology 1966;51:430–432.*

Summary

In this brief communication, Menguy brought attention to the potentially serious toxic effects of aspirin, which at the time was perhaps the most commonly ingested medicine in the world. In 1955, this prescription drug was believed to be responsible for one in 7 cases of gastrointestinal bleeding, particularly in patients with a history of peptic ulcer. It also appeared to be responsible for iron deficiency anemia due to occult blood loss in many other patients.

Satisfied that aspirin somehow injures the stomach and exacerbates duodenal ulcers, the author examined the existing theories of its adverse effects: local tissue injury by undissolved aspirin particles, increased peptic activity, or damage by salicylate to the protective mucous layer, which permitted the back-diffusion of acid that injured the mucosa and caused bleeding. The author chose the last of these possibilities, but with some prescience did not exclude erosion/ulceration via a substance acting systemically.

Editor's comment

Since Menguy's report, the advent of the widely used (there are now 50 or more) nonsteroidal anti-inflammatory drugs (NSAIDs), acting pharmacologically and toxically on the gut in a similar manner to aspirin, stimulated much research into the biological bases of both anti-inflammation and injury exerted by these drugs.

A high incidence of gastrointestinal bleeding due to NSAID-induced peptic ulcers and erosions quickly became evident. A meta-analysis of 16 studies of the relationship concluded that the overall odds ratio for risk of bleeding while taking these drugs was 3-fold, with increasingly greater risks for people older than 60 years, for those with

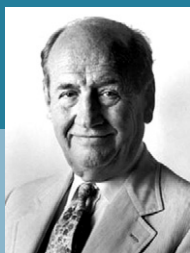
histories of peptic ulcer disease, and for those who are concomitantly treated with aspirin or corticosteroids. Risk is also increased in those taking anticoagulants and possibly in those taking selective serotonin reuptake inhibitors. An additional hazard, of course, is the presence of *Helicobacter pylori*, which should be treated before NSAID therapy.

An evident explanation has also been found for this complication in the inhibition by NSAIDs of prostaglandin H synthetases 1 and 2 (PGHS-1 and PGHS-2) (or cyclooxygenases 1 and 2 [COX-1 and COX-2]). These enzymes break down arachidonic acid into prostaglandins and thromboxanes. Prostaglandins, particularly PGG-2 and PGH-2, protect mucosal integrity; reducing these prostaglandins by inhibiting COX-1 would significantly compromise this protection.

Because NSAIDs are prescribed for millions worldwide (approximately 17 million in the United States), important efforts to diminish the possibility of hemorrhage have been, to some extent, beneficial. One has been the design of NSAIDs, so-called coxibs, which inhibit only COX-2. These appear to reduce the incidence of bleeding but must be used with caution because they can cause myocardial infarction and should not be administered with aspirin or corticosteroids. The other approach is the concomitant administration of a proton pump inhibitor that reduces the risk for bleeding.

Although an increased understanding of the pharmacology of aspirin and its companion anti-inflammatory agents, and the evolution of the means to minimize the side effects, are important advances, an aging world population with an ever-increasing use of NSAIDs will stimulate further study to minimize the toxicity of these drugs.

Dr Sleisenger discloses no conflicts.



Anil K. Rustgi, MD, Editor, for Robert Donaldson, MD

1970–1977

Dr Robert Donaldson of Yale University led an outstanding team of associate editors in his capacity as editor from 1970 to 1977. Sadly, Dr Donaldson is not with us, but he left an indelible mark on the journal, apart from the field itself through his distinguished work. In that vein, I surveyed each issue of GASTROENTEROLOGY from his editorship and was fascinated by the staggering number of outstanding articles in research, with a heavy emphasis on physiology and clinical gastroenterology. Certainly, it was a golden era of physiology in gastroenterology, and a number of pivotal discoveries in clinical technology were being made. Thus, with deference to Dr Donaldson and his team, I offer one viewpoint of key articles from that term.

Clues From Family History

Sleight DR, Galpin JE, Condon RE. *Ulcerative Colitis in Female Monozygotic Twins and a Female Sibling. Gastroenterology 1971;61:507–512.*

Summary

This is a report of a family in which well-documented ulcerative colitis occurred in monozygotic twins and

an additional sibling (nontwin), all female. Neither parent was affected. The authors cited few reports of ulcerative colitis in monozygotic twins to date, and

this represented the first of a sibling involvement of monozygotic twins. The authors speculated upon environmental exposures (eg, an infectious pathogen) or, more likely, the following: “One or more autosomal predisposing factors, in addition to genetic factors, must be implicated to account for the random initiation of disease.”

MacDermott RP, Kramer P. Adenocarcinoma of the Pancreas in Four Siblings. Gastroenterology 1971;65:137–139.

Summary

The authors describe a family in which 4 siblings were affected with well-documented pancreatic adenocarcinoma at ages 59, 60, 61, and 72 years. None of the affected individuals had evidence of pancreatitis, either acute or chronic, and at that point in time, the clinical entity of hereditary pancreatitis (and an association with pancreatic adenocarcinoma) had been appreciated in the literature. However, the authors emphasized an absence of hereditary pancreatitis and pancreatic adenocarcinoma in this family, representing the first such observation to date.

Editor’s comment

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic malignancy, with about 37,000 new

Editor’s comment

Through elegant work over the past 10 years, it is known that ulcerative colitis and Crohn’s disease represent polygenic diseases with important considerations of genotypic-phenotypic correlations. Unbiased genome-wide association studies reveal many susceptibility loci, and among the genes identified, *NOD2/CARD15* and *IL23R* are critical but by no means are the final answer.

cases each year in the United States and a similar number of deaths annually. It is estimated that about 5%–10% of PDAC cases have a hereditary or familial basis with approximately 80% penetrance. Certain predisposing syndromes with an underlying genetic basis have been identified, such as hereditary pancreatitis (*PRSS1* or cationic trypsinogen gene), familial atypical mole and multiple melanoma (*p16* gene), hereditary breast cancer in which there is increased risk of PDAC (*BRCA1* or *BRCA2* genes), and Peutz-Jeghers syndrome (*LKB1* gene). Yet, the vast majority of familial PDAC cases do not have identification of the relevant gene(s) to date.

Hyperplastic Versus Adenomatous Polyps

Lane N, Kaplan H, Pascal R. Minute Adenomatous and Hyperplastic Polyps of the Colon: Divergent Patterns of Epithelial Growth With Specific Associated Mesenchymal Changes. Gastroenterology 1971;60:537–551.

Summary

Distinctions between hyperplastic and adenomatous polyps had been recently made, and this comprehensive study of more than 2100 polyps (from surgery and sigmoidoscopy) identified polyps ≤ 3 mm in 30% of the cases. Pseudopolyps and inflammatory polyps were not considered. The authors provided a detailed distinction between hyperplastic and adenomatous polyps and found the vast majority of diminutive polyps to be hyperplastic (“epithelial and mesenchymal characteristics with high degree of differentiation”) and not adenomatous (“low level of differentiation in the epithelium”), with the exception being in familial adenomatous polyposis. No transition from hyperplastic to adenomatous polyps was observed in sporadic polyps. The authors recommended the following: “Therefore, in the periodic examination of any large number of people, it might be more effective to maintain close surveillance over

the small minority of individuals who had adenomatous lesions, with less frequent examinations for the remaining majority.”

Editor’s comment

This type of study provided a foundation for rigorous histologic distinction between hyperplastic polyps and adenomatous polyps and set the stage for the focus of many seminal studies on screening and surveillance of adenomatous polyps. One entity that has emerged is that of uncommon hyperplastic polyposis, in which there is an increased risk of colon cancer. In addition, it is now appreciated that sessile serrated adenoma, part of a new nomenclature for hyperplastic or serrated polyps (classic hyperplastic polyps-microvesicular, goblet-rich, mucin-poor; tubular serrated adenoma (TSA); sessile serrated adenoma; mixed polyps-TSA and tubular adenoma), requires close scrutiny as well.

The Gut Microbiota: A Glance Into the Future

Bounous G, Devroede J. Effects of an Elemental Diet on Human Fecal Flora. Gastroenterology 1974;66:210–214.

Summary

Fourteen healthy volunteers were given an elemental diet for 12 days. The diet led to decreased stool frequency. It

was noted that there was a significant decrease in the number of enterococci in diet-challenged stool collections versus control stool collections.

Editor's comment

This article posed a clear hypothesis and turned to be prescient. It has been increasingly appreciated that the gut microbe is complex and alterations induced by antibiotics and probiotics might either induce or ameliorate disorders

and diseases, respectively. Nowhere is this more evident than in inflammatory bowel disease and perhaps irritable bowel syndrome as well. Perhaps the most compelling emerging concept is that alterations in the gut microbiota may mediate, at least in part, diet-induced obesity.

Leimbach GE, Rubin CE. Eosinophilic Gastroenteritis: A Simple Reaction to Food Allergens. Gastroenterology 1970;59:874–889.

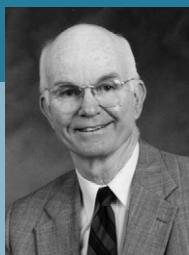
Summary

A 23-year-old man with eosinophilic gastroenteritis was followed up for 2.5 years for eosinophilic gastroenteritis through a number of serial peroral small bowel biopsy specimens. Dietary modification (elimination diets) failed to improve the patient's clinical condition or histologic abnormalities. He improved, however, on prolonged corticosteroids, representing an important advance and underscoring previous observations.

Editor's comment

The authors stated the following: "The etiology and pathogenesis of eosinophilic gastroenteritis are currently an enigma. Thus, in our present state of ignorance regarding the cause of this disease, we can only recommend symptomatic treatment with corticosteroids, if necessary on a prolonged basis." Prophetic words.

Dr Rustgi, on behalf of Dr Donaldson, discloses no conflicts.

**John S. Fordtran, MD****1977–1981**

We believed GASTROENTEROLOGY should emphasize both clinical and research aspects of gastroenterology. We published 14 historical profiles that we thought added important perspective. We increased the number of editorials associated with research articles. This time period included the fiber endoscopy revolution, and we published an ongoing debate on the effects of endoscopy workload on the training of gastroenterology fellows. Much was published on the physiology and pathophysiology of acid secretion and mucosal defense, which were considered to be the main if not the only causes of peptic ulcers and their associated mucosal inflammation. We ended our tenure just as acquired immunodeficiency syndrome was recognized; in searching articles we published, I found no hint of the upcoming epidemic.

Understanding Colitis

Bartlett JG, Onderdonk AB, Cisneros R. Clindamycin-Associated Colitis in Hamsters: Protection With Vancomycin. Gastroenterology 1977;73:772–776.

Summary

Bartlett et al used a hamster model of clindamycin-associated colitis, previously described by Small in 1968 (*Lab Animal Care* 1968;18:411–420). Clindamycin produced lethal enterocolitis in these animals, an effect that was prevented by vancomycin. This strongly suggested that the disease was caused by bacteria. This might have been the first report to suggest that vancomycin would be effective in the treatment of patients with antibiotic-associated colitis.

Editor's comment

The oral form of clindamycin became available in 1970, and within 2 years an association between ingestion of this drug and severe and often lethal colitis was recognized. The cause

of the colitis was unknown, and there was no effective treatment. Physicians primarily treated patients as if they had fulminate ulcerative colitis, using high doses of glucocorticoids. Other publications in GASTROENTEROLOGY soon followed, with Bartlett et al describing a clostridial toxin in feces of hamsters with clindamycin-associated colitis (*Gastroenterology* 1978;74:52–57; *Gastroenterology* 1978;74:246–252). The first mention of *Clostridium difficile* in GASTROENTEROLOGY was in an editorial on the paradox of treating antibiotic-associated colitis with an antibiotic (*Gastroenterology* 1978;74:952–953). *C difficile* first appeared in the title of an article and in the index of GASTROENTEROLOGY in November 1978 (*Gastroenterology* 1978;75:778–782). Many other excellent articles on this topic were published in ensuing issues.

Reevaluating the Link Between Cancer and Colitis

Lennard-Jones JE, Morson BC, Ritchie JK, Shove DC, Williams CB. *Cancer in Colitis: Assessment of the Individual Risk by Clinical and Histological Criteria. Gastroenterology 1977;73:1280–1289.*

Summary

In the 1960s and 1970s, it was generally believed that the incidence of colon cancer was very high in patients who had extensive ulcerative colitis for 10 years and that such patients should be encouraged to have a total colectomy with construction of a permanent abdominal stoma. This report reevaluated this policy, largely on the basis of 2 developments. First, in 1967, it had been shown that carcinoma anywhere in the colon of a patient with ulcerative colitis was associated with epithelial dysplasia in biopsy specimens of the rectum and sigmoid colon. Second, the recent development of colonoscopy enabled biopsy specimens to be obtained from all parts of the colon. Lennard-Jones et al observed more than 200 patients with extensive colitis for 10 years. Their results suggested that histologic examination of sequential biopsy specimens, taken throughout the colon, would identify a small group of patients with dysplasia who required surgical treatment for established precancerous change or car-

cinoma with a high likelihood of cure. Those who did not have or develop dysplasia (a large majority) could safely continue under medical supervision. This reasoning presumed that the true incidence of cancer in ulcerative colitis was not nearly as high as had been suggested by earlier reports from tertiary referral centers.

Editor's comment

At the same time that the study by Lennard-Jones et al was published, William Dobbins wrote an independent clinical trends report encouraging prospective studies using yearly colonoscopy with multiple biopsies in search of "precancer" or "severe dysplasia." He pointed out that negative findings on biopsy do not exclude colonic carcinoma. About 2 years later, a retrospective and a preliminary prospective study (*Gastroenterology 1979;76:1–5*) supported the concept proposed by Lennard-Jones et al. Surveillance colonoscopy was quickly adopted into clinical practice, without the more extensive prospective studies that had been advocated.

Effects of an H₂ Receptor Antagonist

Binder HJ, Cocco A, Crossley RJ, Finkelstein W, Font R, Friedman G, Groarke J, Hughes W, Johnson AF, McGuigan JE, Summers R, Vlahcevic R, Wilson EC, Winship DH. *Cimetidine in the Treatment of Duodenal Ulcer: A Multicenter Double Blind Study. Gastroenterology 1978;74:380–388.*

Summary

This article, which was part of a symposium published in the journal, showed that the healing rate of patients given the H₂ receptor antagonist cimetidine was statistically significantly higher than of those given placebo after 2 weeks, but not 4 or 6 weeks of therapy. (I believe Howard Spiro said that this was the most expensive *P* value in the history of American medicine.)

Editor's comment

The publication of reports describing the effects of cimetidine on the symptoms and healing of peptic ulcers was an exciting event that occurred during our editorial tenure. We learned much about peptic ulcer disease from these reports. In clinical trials in some countries (including the United States) a very high rate of healing was frequently observed in the placebo group, whereas in other countries the placebo groups had much lower healing rates. Furthermore, relief of symptoms was poorly correlated with ulcer healing. Increased healing of peptic ulcers required only a modest reduction of gastric acidity, not near-achlorhydria as previously believed. Cimetidine was no better than

intensive treatment with antacids in healing ulcers but was a lot easier for patients to take. After an ulcer was healed, cimetidine (given once a day at bedtime) prevented ulcer recurrences, perhaps the most important clinical advance. Only a short while later we learned that Zollinger–Ellison syndrome should be treated medically rather than by total gastrectomy.

There were some exciting scientific as well as clinical implications of these studies. Not long before H₂ receptor antagonists were introduced, an article was published entitled "No Room for Histamine" (*Gastroenterology 1971;61:106–118*). The relatively marked inhibition of gastric acid secretion by H₂ receptor antagonists (compared with anticholinergic drugs) established an important role for histamine in acid secretion that contradicted the views of some of our best physiologists.

Finally, the discussion of the symposium papers on gastric ulcer illustrated historically divergent views of US versus European gastroenterologists on the value of antacids in ulcer healing and revealed strikingly different views of US gastroenterologists on the necessity and ethics of a placebo arm in controlled clinical trials of gastric ulcer disease.

Details of Crohn's Disease

Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: Adverse Reactions to Study Drugs. *Gastroenterology* 1979;77:870–882.

Summary

This multicenter study was published in 12 separate reports containing a total of 117 pages of text. Article subjects included study design, rederived values for 8 coefficients of the Crohn's Disease Activity Index, results of drug treatment, adverse reaction to study drugs, natural history, and factors determining recurrence. The design of the study closely modeled the contemporary management of Crohn's disease and used all of the scientific features that are needed to improve the likelihood of obtaining valid results in a randomized, double-blind, placebo-controlled clinical trial.

Editor's comment

My admiration for those who conceived, organized, and conducted this project is immense. It must have required enormous patience, perseverance, selflessness, and sacrifice, as well as faith in the statistical analyses and methods; given the diversity of Crohn's disease, I would have questioned whether such a study would yield valid results. However, the careful design and execution of these studies did not prevent serious and spirited challenges. See, for example, the critiques by Goldstein et al (*Gastroenterology* 1980;78:1647–1648) and by Korelitz and Present (*Gastroenterology* 1981;80:193–194), each of

which was published with a detailed response from John Singleton, who was the editor of the special issue of *GASTROENTEROLOGY* that described the studies.

To learn more about how this project was conducted, I spoke with John Singleton, who now lives in Santa Fe, New Mexico. He said that the inspiration for the study came mainly from discussions with Fred Kern. The financing came mainly from the National Institutes of Health. From planning to publication, the study required 9 years at a cost of \$1.5 million. Probably the most enduring result of the study was the development of the Crohn's Disease Activity Index, the brainchild of Dr William Best of the VA Clinical Support Center in Hines, Illinois. This index allowed a patient's degree of illness to be expressed by a single number. It was highly controversial, but it provided the basis for most subsequent clinical trials of Crohn's disease. Some criticisms of the study and its design were valid, but the investigators remain proud of the study. Consistent with the ethics of the time, none of the authors gained financial reward from their participation in this project.

Much time has passed, but I agree with Goldstein et al, who said that the National Cooperative Crohn's Disease Study would long remain the standard against which other studies in Crohn's disease will be compared.

Safety of Percutaneous Needle Biopsy of the Liver

Knauer CM. Percutaneous Biopsy of the Liver as a Procedure for Outpatients. *Gastroenterology* 1978;74:101–102.

Perrault J, McGill DB, Ott BJ, Taylor WJ. Liver Biopsy: Complication in 1000 Inpatients and Outpatients. *Gastroenterology* 1978;74:103–106.

Summary

These back-to-back studies provided evidence that percutaneous needle biopsy of the liver could be performed safely in an outpatient setting. The authors showed that with the absence of the most severe complications (ie, bleeding, severe pain), which usually occur within the first 3 hours after the procedure, most patients could be discharged within 6 hours.

Editor's comment

These articles were selected for inclusion in the anniversary tribute by De Burton Combes, MD, associate editor for liver diseases of *GASTROENTEROLOGY* during my editorship. These studies set the standard of practice for patients who undergo this procedure and reduced health care costs.

Dr Fordtran discloses no conflicts.



Robert K. Ockner, MD

1981–1986

I look upon my 1981–1986 term as editor of *GASTROENTEROLOGY* as a great honor and privilege. It was a highly eventful period for the American Gastroenterological Association for digestive diseases research and clinical practice and for the journal itself. Rapid progress was under way in many areas of basic and clinical research. Orthotopic liver transplantation became no longer experimental, revolutionizing the care of patients with end-stage liver disease. Operations of the journal depended critically on the editorial staff and my editor friends: the late Rudi Schmid, Marvin Sleisenger, Young Kim, Bruce Scharschmidt, Raj Goyal, and the late John Walsh. The articles that I have chosen to discuss reflect the efforts of distinguished investigators and symbolize first-rate research and review. Viewed in the perspective of today's realities, each provides insight into the long-term impact of high-quality research.

Fecal Occult Blood Testing and the Prevention of Colon Cancer

Winawer S, Fleisher M. *Sensitivity and Specificity of the Fecal Occult Blood Test for Colorectal Neoplasia. Gastroenterology* 1982;82:986–991.

Winawer S, Fleisher M, Sherlock P. *Sensitivity of Fecal Occult Blood Testing for Adenomas. Gastroenterology* 1982;83:1136–1138.

Simon J. *Occult Blood Screening for Colorectal Carcinoma: A Critical Review. Gastroenterology* 1985;88:820–837.

Summary

Although guaiac-based testing for fecal occult blood had been used clinically for decades, attention had become more sharply focused on its potential value in detection of colorectal neoplasia and prevention of death from colon cancer. Ongoing efforts addressed resolution of several issues, including technology, methodology, sensitivity/specificity, compliance, and cost, and newer methods were under active investigation. Despite its shortcomings, however, early studies of the guaiac-based method had already provided evidence that if properly used, this technology could decrease colon cancer deaths

by identifying early-stage colorectal adenomas and carcinomas.

Editor's comment

This concept has been amply confirmed and development of methods based on this technology continues, including immunochemical and molecular approaches. In addition, newer technologies including colonoscopy have contributed to the overall success in diminishing colon cancer deaths. The early progress in testing for fecal occult blood proved that it could save lives and contributed to the understanding of colorectal cancer.

The Non-A, Non-B Hepatitis Virus

Yoshizawa H, Itoh Y, Iwakiri S, Kitajima K, Tanaka A, Tachibana T, Nakamura T, Miyakawa Y, Mayumi M. *Non-A, Non-B (Type 1) Hepatitis Agent Capable of Inducing Tubular Ultrastructures in the Hepatocyte Cytoplasm of Chimpanzees: Inactivation by Formalin and Heat. Gastroenterology* 1982;82:502–506.

Bradley D. *Post Transfusion Non-A, Non-B Hepatitis in Chimpanzees. Physicochemical Evidence That the Tubule-Forming Agent Is a Small Enveloped Virus. Gastroenterology* 1985;88:773–779.

Perrillo R, Chau KH, Overby LR, Decker RH. *Anti-Hepatitis B Core Immunoglobulin M in the Serologic Evaluation of Hepatitis G Virus Infection and Simultaneous Infection With Type B, Delta Agent, and Non-A, Non-B Viruses. Gastroenterology* 1983;85:163–167.

Dienstag J. *Non-A, Non-B Hepatitis, I and II. Gastroenterology* 1983;85:439–462 and 743–768.

Miyamura T, Saito J, Katayama T, Kikuchi S, Tateda A, Houghton M, Choo QL, Kuo G. *Detection of Antibody Against Antigen Expressed by Molecularly Cloned Hepatitis C Virus cDNA: Application to Diagnosis and Blood Screening for Posttransfusion Hepatitis. Proc Natl Acad Sci U S A* 1990;87:983–987.

Summary

The hepatitis A virus had been identified and characterized in the mid-1970s. This important advance followed

the recognition of hepatitis B virus by several years, established the predominant cause of acute fecal-oral transmitted viral hepatitis, and made it clear that not all cases of acute viral hepatitis could be attributed to vi-

ruses B or A. Thus, at least one additional agent of clinical importance must exist, and it soon became clear that such “non-A, non-B” agent(s) accounted for the vast majority of cases of posttransfusion and “serum” hepatitis. Because of its clinical importance, identification leading to prevention of the causative agent(s) became major foci of effort by the hepatology and infectious disease communities. Although the results of many of these efforts were published in journals dedicated to virology, epidemiology, and liver disease (including the newly established journal *Hepatology*), GASTROENTEROLOGY contributed significantly as well, carrying studies of the

nature of the putative agent(s) (Yoshizawa et al and Bradley), its clinical diagnosis (Perrillo et al), and important reports of progress in the field (Dienstag).

Editor’s comment

These reports, together with numerous publications in other journals, provided a growing foundation of knowledge that paved the way to later advances, leading to the identification and cloning of the hepatitis C virus (Miyamura et al) and its recognition as the major causative agent of non-A, non-B hepatitis.

Gallstone Dissolution

Park YH, Igimi H, Carey MC. Dissolution of Human Cholesterol Gallstones in Simulated Chenodeoxycholate-Rich and Ursodeoxycholate-Rich Biles. An In Vitro Study of Dissolution Rates and Mechanisms. *Gastroenterology* 1984;87:150–158.

Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Cholelitholysis Using Methyl Tertiary Butyl Ether. *Gastroenterology* 1985;88:122–125.

Allen M, Borody T, Thistle J. In Vitro Dissolution of Cholesterol Gallstones. A Study of Factors Influencing Rate and a Comparison of Solvents. *Gastroenterology* 1985;89:1097–1103.

Summary

Early studies had provided insight into the physicochemical characteristics of bile and its solubilization of cholesterol and an understanding of the pathogenesis of cholesterol gallstone formation, stimulating efforts toward development of nonsurgical, physicochemical approaches in its management. Scientifically sound and imaginative methods for in situ dissolution of cholesterol gallstones were developed in model systems and animals and adapted for clinical trials. Agents used in these studies included chenodeoxycholic and ursodeoxycholic acids as well as organic solvents, especially methyl tertiary butyl ether. Biliary concentrations of these agents could be manipulated by systemic bile acid administration or intragallbladder, intracystic, or intraductal solvent perfusion.

Editor’s comment

Toward the end of the decade, the surprising and promising first reports of laparoscopic cholecystectomy appeared. This technique used minimally invasive surgical techniques, required only brief in-hospital convalescence, and circumvented most disadvantages of conventional cholecystectomy. Together with advances in biliary endoscopy, laparoscopic cholecystectomy for practical purposes revolutionized the treatment of gallstone disease. Gallstone dissolution, despite its promise, was relegated to a relatively minor but significant role as an ancillary method for use in patients in whom open, laparoscopic, and endoscopic approaches were not feasible and/or in whom the presence of a T-tube facilitated direct application of solvent for nonoperative treatment (eg, of common bile duct stones).

Hepatic Adenomas in Type Ia Glycogen Storage Disease

Parker P, Burr I, Slonim A, Ghishan FK, Greene H. Regression of Hepatic Adenomas in Type Ia Glycogen Storage Disease With Dietary Therapy. *Gastroenterology* 1981;81:534–536.

Ockner R. *Integration of Metabolism, Energetics, and Signal Transduction: Unifying Foundations in Cell Growth and Death, Cancer, Atherosclerosis, and Alzheimer Disease*. New York, NY: Springer, 2004.

Summary

A report by a respected interdepartmental team at Vanderbilt appeared in the September 1981 issue of GASTROENTEROLOGY (Parker et al). It described several patients whose inborn deficiency of glucose-6-phosphatase prevented hepatocyte release of glucose, resulting in hypoglycemia and other metabolic abnormalities, growth retardation, and, if untreated, risk of brain injury and early death. Curiously, the condition is also associated with unexplained multiple hepatic adenomas and even hepatocellular carcinoma. This report showed that continuous administration of glucose

or starch not only corrected the metabolic defect, but also prevented formation of new tumors while arresting the growth and causing regression of existing adenomas. Because understanding of cell growth regulation was still quite limited, these observations remained unexplained.

Editor’s comment

More than a decade later, I “rediscovered” this report. Its demonstration of the glucose effect on tumor growth, together with other phenomena that linked intermediary metabolism to cell growth and tumorigenesis, were key elements in my recently initiated pursuit of the mecha-

nism and significance of this linkage. This pursuit led unexpectedly to new and far broader questions and insights, as well as the formulation of hypotheses in several surprisingly related areas. They were incorporated in a

book that I published in 2004, in which the report by Parker et al is the first cited.

Dr Ockner discloses no conflicts.



Raj K. Goyal, MD

1986–1991

The period of our editorial tenure was an era of advances in physiology and pathophysiology relevant to human diseases. Some of these advances required major financial funding, but many of them resulted from simple creativeness by determined individual investigators. The most dramatic example of the latter was demonstration of the pathogenetic role of *Helicobacter pylori* infection, which transformed our understanding and management of peptic ulcer disease and gastric cancer. The newer radiologic imaging techniques revolutionized the diagnosis and management of gastrointestinal disorders, including those of the pancreas. Another area of research involved study of the psychosomatic factors and visceral hypersensitivity in functional disorders of the gut. Examples of advances in metabolic liver disease and emergence of prospective studies for screening of premalignant lesions are illustrated in the following text.

The editors and the editorial board strived hard to engage our busy readers in the basic science and clinical articles published in GASTROENTEROLOGY. One of these efforts resulted in the development of a brief section entitled “This Month in Gastroenterology.”

Diagnosing Pancreatic Infection by Computed Tomography–Guided Aspiration

Gerzof SG, Banks PA, Robbins AH, Johnson WC, Spechler SJ, Wetzner SM, Snider JM, Langevin RE, Jay ME. *Early Diagnosis of Pancreatic Infection by Computed Tomography-Guided Aspiration. Gastroenterology* 1987;93:1315–1320.

Summary

Computed tomography (CT)-guided percutaneous needle aspiration of pancreatic inflammatory masses was performed in 60 patients suspected of harboring pancreatic infection. Thirty-six patients (60%) were found by Gram stain and culture to have a total of 41 separate episodes of pancreatic infection. Among 42 aspirates that were judged to be infected, based on CT-guided aspiration, all but one were confirmed by surgery or indwelling catheter drainage. Among 50 aspirates judged to be sterile, no subsequent evidence of infection was found. All patients tolerated the procedure well, and no complications were noted. As a result of this technique, the authors observed that pancreatic infection occurred earlier than previously believed (within 14 days of the onset of pancreatitis in 20 of the 36 patients) and that infection could recur during prolonged bouts of pancreatitis. The authors concluded that guided

aspiration is a safe, accurate method for identifying early-stage infection of the pancreas.

Editor’s comment

Advances in abdominal imaging techniques such as CT scans provided a major step in the evaluation of deep-seated structures such as the pancreas. CT scanning with contrast can distinguish between various grades of severity of pancreatitis. This often-cited report has established that CT-guided percutaneous aspiration is a safe, reliable method of diagnosing pancreatic infection. The procedure has become the standard of care in the management of severe pancreatitis and the gold standard in the diagnosis of pancreatic infection. These studies also helped define the natural history of pancreatic infection and showed that pancreatic infection occurs early and may recur during prolonged bouts of pancreatitis.

Alcohol-like Liver Disease Without Alcohol

Diehl AM, Goodman Z, Ishak KG. *Alcohol-like Liver Disease in Non-alcoholics. A Clinical and Histologic Comparison With Alcohol-Induced Liver Injury. Gastroenterology* 1988;95:1056–1062.

Summary

To determine whether any clinical or histologic features distinguish alcoholic and nonalcoholic subjects with “alco-

hol-like” liver injury, the clinical records and liver biopsy specimens of 68 alcoholic and 39 nonalcoholic patients with alcohol-like injury, based on liver biopsy, were compared. The clinical and biochemical features of the 2 groups

differed significantly. Alcoholism was associated with more severe clinical and biochemical manifestations of liver disease. However, there was considerable overlap among histologic features of the 2 clinically defined groups. Based on histology alone, alcoholic and nonalcoholic patients were often indistinguishable. The observations suggest that the clinical differences between the alcoholic and nonalcoholic patients cannot be attributed to qualitative or quantitative differences in liver histology. On the other hand, histologic similarities between the 2 groups raised the possibility that a shared condition, perhaps nutritional or hormonal, is responsible for the histologic features of alcohol-like injury in both groups.

Editor's comment

This careful study showed that there were no qualitative and quantitative differences in liver histology among individuals with liver disease who ingested or did not ingest alcohol. These studies indicated that nutritional and hormonal factors could produce hepatic changes that are indistinguishable from alcohol toxicity and reflected on the pathogenesis of alcoholic liver disease. This has led to the identification of nonalcoholic steatohepatitis, a very important clinicopathologic entity.

Patients With Irritable Bowel Syndrome Seek Excessive Health Care

Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, Burger AL. Psychosocial Factors in the Irritable Bowel Syndrome. A Multivariate Study of Patients and Nonpatients With Irritable Bowel Syndrome. Gastroenterology 1988;95:701-708.

Summary

In this multivariate analysis of patients with irritable bowel syndrome (IBS), the authors described the symptomatic and psychological features of patients with the condition and the possible factors that led them to seek health care. They studied 72 patients with IBS, 82 people with IBS who had not sought medical treatment, and 84 healthy subjects. All subjects received a complete medical evaluation, diary card assessment of abdominal pain and stool habit, and standard psychological tests of pain, personality, mood, stressful life events, illness behavior, and social support. Pain and diarrhea were the most important symptoms associated with patient status. In controlling for these symptoms, they found that patients with IBS had a higher proportion of abnormal personality patterns, greater illness behaviors, and lower positive stressful life event scores than the other groups studied. People with IBS who did not seek treatment were psychologically intermediate between patients and

healthy individuals and had higher coping capabilities, experienced illness as less disruptive to life, and tended to exhibit less psychological denial than patients. The authors proposed that these factors contributed to "wellness behaviors" among people with chronic bowel symptoms.

Editor's comment

Certain psychological profiles are believed to be associated with IBS. This study showed that patients who fulfill a diagnosis of IBS could be divided into 2 groups, based on whether they sought medical help or did not, and that these groups were different. These studies led to the important conclusion that psychological factors that were previously attributed to the pathophysiology of IBS were related to the patient status rather than to the disease. This article opened avenues for careful, well-designed studies to critically define psychosomatic abnormalities in patients with IBS and other functional disorders of the gastrointestinal tract.

Type of Polyp Determines Risk for Colorectal Carcinoma

O'Brien MJ, Winawer SJ, Zauber AG, Gottlieb LS, Sternberg SS, Diaz B, Dickersin GR, Ewing S, Geller S, Kasimian D, et al. The National Polyp Study. Patient and Polyp Characteristics Associated With High-Grade Dysplasia in Colorectal Adenomas. Gastroenterology 1990;98:371-379.

Summary

Data from 3371 colonic adenomas from 1867 patients who participated in the National Polyp Study were carefully analyzed for endoscopic features of the adenoma and histologic evidence of high-grade dysplasia. Adenoma size and the extent of the villous component were found to be the major independent polyp risk factors associated with high-grade dysplasia. The adjusted odds ratios were 3.3 for medium-sized adenomas and 7.7 for large adenomas relative to small adenomas and 2.7 for villous A adenomas, 3.4 for villous B adenomas, and 8.1 for villous C and D adenomas relative to tubular adenomas. Increased frequency of high-grade dysplasia in ade-

nomas located distal to the splenic flexure was attributable mainly to increased size and villous component rather than to location per se. The adjusted odds ratio was 1.4 for left-sided location. Multiplicity of adenomas affected the risk of high-grade dysplasia in patients but depended on adenoma size and villous component and was not an independent factor. The adjusted odds ratio was 1.3 for multiplicity. Increasing age was associated with risk of high-grade dysplasia in patients, and this effect was independent of the effect of adenoma size and histologic type. The adjusted odds ratio was 1.8 for people 60 years of age or older.

Editor's comment

This large, extremely well-designed prospective study on high-grade dysplasia in colonic adenomas, in relation to their histology, established that the size of the adenoma and the extent of the villous component were major risk factors associated with high-grade dysplasia. These ob-

servations have formed the basis of our current frequency of repeat colonoscopy, although some specific recommendations are being further defined. In addition, this study set the gold standard for future studies on colorectal cancer screening and surveillance.

Dr Goyal discloses no conflicts.

**Nicholas F. LaRusso, MD****1991–1996**

The celebration of the 65th anniversary of GASTROENTEROLOGY by the current board of editors inspired me to look back on the 50th anniversary, which occurred when I was editor. During the early 1990s, GASTROENTEROLOGY underwent substantial change in operations, form, scope, and content. A centralized office model, located in the AGA's national office in Bethesda, Maryland, allowed staff to process manuscripts in one location, streamlining efficiency. Use of fax machines allowed quicker communication with authors and reviewers worldwide. A new cover containing a figure chosen both for artistic value and scientific importance was established; sections of the journal were modified in response to reviewer and author surveys. Manuscripts were selected based on the philosophy that only the best basic and clinical research articles were appropriate and balanced to accommodate the heterogeneity of the readership. The success of these approaches was supported by the substantial increase in the impact factor and the journal's rank among the top 1% of more than 6000 scientific journals.

Gene Mutations in Cancer: What's the Connection?

Tada M, Obashi M, Shiratori Y, Okudaira T, Komatsu Y, Kawabe T, Yoshida H, Machinami R, Kishi K, Omata M. Analysis of K-ras Gene Mutation in Hyperplastic Duct Cells of the Pancreas Without Pancreatic Disease. Gastroenterology 1996;110:227–231.

Summary

Mutations of *K-ras* were previously found in pancreatic secretions associated with malignant transformation; this study assessed the incidence and types of mutations in hyperplastic foci in patients with pancreatic carcinoma or chronic pancreatitis. DNA extracted from microdissected hyperplastic epithelia of pancreatic ducts in autopsies of patients with pancreatic adenocarcinoma or chronic pancreatitis was analyzed by assessing the nucleotide sequence of the *K-ras* gene in codon 12. Whereas none of the normal portions of the ducts had the mutation, one third of the patients with chronic pancreatitis had mutations in hyperplastic foci; mutations were not found in cases of adenocarcinoma. The results suggested that *RAS* mutations occur frequently in multifocal hyperplastic foci of pancreatic ducts but might not have direct relevance to the carcinogenesis of pancreatic cancer.

Editor's comment

The study described new mutations associated with hyperplastic pancreatic duct cells with no sign of malignant transformation. The group detected either a TGT or an AGT mutation in codon 12 of *K-ras* in foci of duct hyperplasia but not in 30 cases of adenocarcinoma that had the classic "oncogenic" pattern of mutation. No changes were found in normal duct epithelium from the same patients. The study raised the possibility that these changes did not have a transformation-promoting effect. The study was relevant to efforts to identify populations at risk for developing pancreatic cancer and to the development of technologies to detect early pancreatic cancer, such as imaging (endoscopic ultrasonography or spiral computed tomography) and detection of circulating peptides (IAPP). At this time, analysis of genetic markers appeared to be the most promising approach to early detection of this devastating disease. (See commentary in *Gastroenterology* 1996;110:306–310.)

The More Iron the Worse the Outcome

Niederau C, Fischer R, Pürschel A, Stremmel W, Häussinger D, Strohmeyer G. Long-term Survival in Patients With Hereditary Hemochromatosis. Gastroenterology 1996;110:1107–1119.

Summary

A cohort of more than 250 patients with hereditary hemochromatosis was followed up on a long-term basis to eval-

uate the impact of early diagnosis and iron removal on survival and complications. In the group as a whole, survival was reduced compared with a matched normal population.

In subgroups, survival was reduced in patients with severe iron overload versus those with less severe iron overload. Over time, the percentage of patients in which an early diagnosis was made increased. Liver cancer, cardiomyopathy, liver cirrhosis, and diabetes mellitus not only increased compared with expected rates but also were the causes of death in the population. Importantly, liver cancer was associated with cirrhosis and the amount of mobilizable iron.

Editor's comment

The study represents one of the most complete studies on the natural history of hereditary hemochromatosis. The study confirmed the relationship between the amount and duration of iron excess to survival and complications and strongly suggested that early diag-

nosis and therapy can prevent the adverse consequences of iron overload. The study confirmed that the amount of total mobilizable iron is closely related to liver iron concentration. Although the prognosis for patients with untreated hemochromatosis is poor, protocols for screening the relatives of patients with this condition, including the use of genetic testing, allowed earlier identification of this condition. Research now focuses on the role of generalized screening of subjects in the population for early detection. The data strongly support the need for early diagnosis and removal of excess iron to improve the patient's prognosis to normal life expectancy and to prevent most of the complications of iron overload. (See commentary in *Gastroenterology* 1996;110:1304-1307.)

Treating Cancer With Light

Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long-term Survival After Photodynamic Therapy for Esophageal Cancer. Gastroenterology 1995;108:337-344.

Summary

This study evaluated the effects of photodynamic therapy (PDT), adapted for endoscopy, in 123 patients with squamous cell cancer and adenocarcinoma of the esophagus. The 5-year disease-specific survival rate was 74% and did not differ between patients given PDT alone and patients given PDT with multimodal treatment or between patients with different histologic types and stages of esophageal cancer. PDT-related complications were minimal and limited to esophageal stenosis and cutaneous photosensitization. The study demonstrated that in patients with small esophageal tumors who pose high surgical risk, PDT is an effective therapy.

Editor's comment

This study showed the efficacy of PDT for early carcinomas of the esophagus, as an alternative to esopha-

gectomy, in selected patients. Endoscopic PDT involves laser activation of an intravenously injected photosensitizing drug, creating a highly reactive singlet state when the light-activated drug interacts with oxygen; the singlet oxygen produces oxidative death in the cells exposed to light. Additional studies defining the efficacy of PDT for small esophageal neoplasms in randomized trials with long periods of observation, assessment of quality of life issues, and cost analysis were needed. Nevertheless, it appeared that endoscopic management of superficial malignancies was a good alternative, in selected subpopulations, to surgical resection for esophageal malignancies. (See commentary in *Gastroenterology* 1995;109:1406-1407.)

IBS Is Big Bucks!

Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical Costs in Community Subjects With Irritable Bowel Syndrome. Gastroenterology 1995;109:1736-1741.

Summary

To assess the economic impact of irritable bowel syndrome (IBS), an age- and sex-stratified random sample of residents in a community in Minnesota, between the ages of 20 and 95 years, was evaluated by a validated questionnaire. All charges for health services rendered in the year before completing the study were obtained. Overall, median charges incurred by subjects with IBS, with or without symptoms, were approximately 50% higher for patients compared with controls. This amounted to approximately \$300 on average more direct medical charges per patient with IBS compared with control subjects of the same age and sex. Extrapolating the data from this community to the United States as a

whole would result in a cost of \$8 billion for IBS yearly. Thus, the economic impact of IBS is significant.

Editor's comment

This was the first study to directly estimate the medical care costs in a cohort of individuals with IBS; the findings were staggering and emphasized the costly nature of the condition. Nevertheless, as impressive as the costs determined by the study were, they may actually underestimate the total financial impact of this condition, because outpatient drug costs and indirect costs such as the economic effect of work absenteeism were not measured. The reasons why the costs of this nonthreatening life disorder are so much are still unclear; possible expla-

nations include the fluctuating natural history of IBS and the possibility that patients with IBS receive unnecessary tests and therapies, including hospitalization and surgery. In the current climate of rapidly growing costs for a host of medical conditions, more research is neces-

sary to learn why so much money is spent on patients with IBS and how costs can be reduced. (See commentary in *Gastroenterology* 1995;109:2029–2031.)

Dr LaRusso discloses no conflicts.



Daniel K. Podolsky, MD

1996–2001

During the late 1990s and early 2000s, there was an expanding research enterprise fueled by a growing National Institutes of Health budget, an increasing rigor of clinical investigation, and a focus on the molecular mechanisms of pathophysiologically relevant function in the gastrointestinal area. New therapeutics were galvanizing the vitality of clinical trials. The most highly cited articles reflected this spectrum of events. The increase in the impact factor of *GASTROENTEROLOGY* significantly raised its appeal to potential authors and increased selectivity for publication.

Sobering Insight Into Nonalcoholic Fatty Liver Disease

Matteoni C, Younossi ZM, Gramlich R, Boparai N, Liu YC, McCullough AJ. *Nonalcoholic Fatty Liver Disease: A Spectrum of Clinical and Pathological Severity*. *Gastroenterology* 1999;116:1413–1419.

Summary

The spectrum of nonalcoholic fatty liver disease ranges from fatty liver alone to nonalcoholic steatohepatitis. However, follow-up in previous studies was too limited to enable delineation of the range of clinical outcomes associated with the histologic forms of nonalcoholic fatty liver disease. In this study, liver biopsy specimens from 1979 to 1987 with fat accumulation were assessed for other associated histologic findings and correlated with outcomes of cirrhosis mortality and liver-related mortality. Fatty liver (type I) did not differ from the other 3 types, in which fat was associated with additional histopathologic abnormalities with respect to gender, race, age, or obesity. Cirrhosis was more common in the other types combined than in fatty liver alone. Most of the liver-related deaths occurred in patients with type IV disease. Thus, the outcome of cirrhosis and liver-related death is not uniform across the spectrum of nonalcoholic

fatty liver. Poor outcomes are more frequent in patients in whom biopsy specimens show ballooning degeneration and Mallory hyaline or fibrosis.

Editor's comment

Although this was not the first publication to show that nonalcoholic fatty liver disease did not necessarily have a benign course, which had been thought in the past, this report made a seminal contribution in correlating the degree of liver injury (on an index biopsy) with later clinical outcome. Previous studies had limited biopsy data and lacked the length of follow-up described in this report. The authors demonstrated that histology and outcome correlated with, but were often independent of, more routine clinical and laboratory data. This study is also a testimony to the value of rigorous correlation between histology and subsequent outcome to provide clinically useful insights.

Anti-TNF: Not Just a Solo Shot for Crohn's Disease

Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. *Efficacy and Safety of Retreatment With Anti-Tumor Necrosis Factor Antibody (Infliximab) to Maintain Remission in Crohn's Disease*. *Gastroenterology* 1999;117:761–769.

Summary

A single administration of infliximab, an anti-tumor necrosis factor (TNF) chimeric monoclonal antibody, was found to reduce the signs and symptoms of active Crohn's disease. This study aimed to determine whether repeated infusions

of infliximab could effectively and safely maintain this effect. The efficacy, safety, pharmacokinetics, and immunogenicity of 4 repeated doses of infliximab (10 mg/kg) given every 8 weeks were compared with the effects of placebo in a randomized, double-blind, parallel-group trial encompassing 73 patients with active Crohn's disease who had not

adequately responded to conventional therapies but had demonstrated a clinical response to an initial infusion of infliximab. Repeated treatment with infliximab maintained the clinical benefit throughout the re-treatment period and 8 weeks after the last infusion in nearly all the patients in the treatment group. Median values for the Crohn's Disease Activity Index and C-reactive protein, among other end points, were maintained at remission levels in patients given repeated infliximab re-treatment but not in those given placebo. Repeated treatment was well tolerated, although one case of lymphoma and one case of suspected lupus were reported. Thus, this study pointed to the efficacy and tolerability of long-term treatment with infliximab for the management of symptoms in patients with active Crohn's disease who do not respond to conventional treatment.

Editor's comment

Whereas previous studies demonstrating the effectiveness of initial administration of infliximab for inducing response (and, for many, remission) in patients with Crohn's disease were a watershed—a fundamentally new

therapeutic strategy after a decade of only incremental innovations—the overall value of the anti-TNF agent in the management of this chronic disorder remained uncertain. Although subsequent large-scale phase 3 trials validated the usefulness of infliximab in controlling disease in patients who responded to anti-TNF agents over the long-term, this study provided the first evidence for its sustained impact. At the same time, the observation that one patient developed lymphoma and another developed suspected lupus raised a specter, which remains in the background as infliximab is routinely used in clinical practice. Although additional anti-TNF agents are available and still newer therapeutics aimed at different targets are emerging (eg, natalizumab), there is little doubt that anti-TNF agents have been a boon to many patients with inflammatory bowel disease. Further, this study established an important place for biologic therapies in clinical management strategies, based on increased insight into the immunopathophysiology of inflammatory bowel disease.

Perhaps There Really Are “Good Bacteria”

Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral Bacteriotherapy as Maintenance Treatment in Patients With Chronic Pouchitis: A Double-Blind, Placebo-Controlled Trial. Gastroenterology 2000;119:305–309.

Summary

Pouchitis is a major long-term complication that occurs after ileal pouch-anal anastomosis for ulcerative colitis and arguably represents a human model of inflammatory bowel disease. Most patients have relapsing disease, and no maintenance treatment has proven effective. In this study, a mixture of so-called probiotic bacteria (containing 4 strains of lactobacilli, 3 strains of bifidobacteria, and 1 strain of *Streptococcus*) or placebo was given to 40 patients after ileal pouch-anal anastomosis and they were followed up for a 9-month period for evidence of recurrence of pouchitis. Only 15% of patients receiving the probiotic experienced a relapse, in contrast to 100% of those receiving placebo during the same interval. These findings suggest that probiotic bacteria therapy is a safe and effective approach to this often-challenging clinical problem.

Editor's comment

Beyond the potential therapeutic usefulness of the probiotic mixture in this specific context, the findings of this

clinical trial presaged a key concept in understanding the pathogenesis of the major forms of inflammatory bowel disease. Observations in murine models, especially genetically engineered strains that “spontaneously” develop colitis, as well as in humans indicate that the inflammatory process is driven by luminal bacteria or their products in genetically susceptible hosts. Further evidence suggests that the microbial population(s) responsible for driving these immune and inflammatory responses may not be pathogenic in the conventional sense but produce products recognized by receptors in the innate immune system. In this conceptual construct, modulation of the microbial populations by administration of those less prone to stimulate these responses would be predicted to have therapeutic benefit. Although this study does not define the mechanistic basis for the preventative effect observed, the observed efficacy lends credence to the overall relevance of these concepts and the possibility that they can be experimentally leveraged when there is better understanding of the daunting complexity of the luminal flora.

Not Perfect—Adenomas Missed by Colonoscopy

Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic Miss Rates of Adenomas Determined by Back-to-Back Colonoscopies. Gastroenterology 1997;112:24–28.

Summary

In this study, Rex and colleagues assessed the reliability of colonoscopy for the detection of colonic neoplasias. Patients (n = 183) underwent 2 consecutive colonosco-

pies on a single day, either by the same or different endoscopists. The overall miss rates for adenomas were 24%; 27% for adenomas ≤ 5 mm, 13% for adenomas 6–9 mm, and 6% for adenomas ≥ 1 cm. There was evidence of

variation in sensitivity between endoscopists, but significant miss rates for smaller adenomas were found among essentially all endoscopists.

Editor's comment

This study provided a sobering reality test for gastroenterologists and underscored the concept that even conventional colonoscopy falls short of uniform effectiveness in detecting adenomas. This issue has taken greater salience in the intervening years. As computed tomographic (CT) colonography has been evaluated as an alternative technology for colorectal cancer screening, this study has often been cited by those advocating the

value of CT colonography to underscore the limitations of colonoscopy as the criterion standard. Ironically, this study actually highlights the same concern that has emerged from a critical assessment of CT colonography: the failure to consistently detect all small adenomas. Indeed, the number of adenomas <10 mm missed in this study was 6%, in contrast to the 27% of those missed that were <5 mm. The latter is comparable to reported miss rates for these smaller lesions by CT colonography, begging the following questions: what is the clinical importance of these small lesions, and what are the implications for screening strategies?

Dr Podolsky discloses no conflicts.



David A. Brenner, MD

2001–2006

“It was the best of times; it was the worst of times. . .” During our editorship we saw the beginning of flat funding from the National Institutes of Health, which became decreased funding in real dollars. This decreased funding resulted in an incredible mismatch between the prospect of applying the fruits of the Human Genome Project to digestive diseases and the severe limitation of research funds, especially for young physician-scientists. Despite the crisis in funding, there was still an unprecedented burst of research activity in gastroenterology. Clinical and epidemiologic studies in gastroenterology became the basis of evidence-based medicine. Identifying and then characterizing the *NOD2/CARD5* variants in patients with Crohn's disease represented the first great advance in the genetics of a complex disease. These and other advances in areas such as pharmacogenetics and the genetics of liver fibrosis launched the concept of personalized medicine for the patient with digestive diseases.

To reflect the importance of clinical and translational research in our field, a more balanced editorial board evolved at *GASTROENTEROLOGY*. Additionally, to encompass new advances and approaches, we developed separate sections for evidence-based medicine and for the publication of useful microarrays and other large data sets.

Hungry? Blame Ghrelin

Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, Makino S, Fujimiya M, Nijima A, Fujino MA, Kasuga M. Ghrelin Is an Appetite-Stimulatory Signal From Stomach With Structural Resemblance to Motilin. *Gastroenterology* 2001;120:337–345.

Summary

Ghrelin is a 28-amino acid peptide identified in the rat stomach as a ligand for the growth hormone secretagogue receptor. This study showed that ghrelin strongly stimulates feeding behavior in mice; its mechanisms of action involve deactivation of hypothalamic receptors and an increase in gastric emptying. Ghrelin induces a positive energy balance and increases body weight by promoting food intake, decreasing energy expenditure, and stimulating growth hormone secretion. Ghrelin is the first orexigenic peptide identified in the periphery and acts through vagal afferent pathways.

Editor's comment

This report was the most highly cited article in *GASTROENTEROLOGY* between 2001 and 2006, surpassing all

the usual suspects of hepatitis C clinical trials and colon cancer screening. The study showed that the stomach has a critical role in the regulation of appetite by secreting the orexigenic and prokinetic peptide ghrelin. Numerous articles have followed this report, studying ghrelin in mice and humans. Some of the most clinically relevant results have been reported in bariatric surgery for morbid obesity in patients. It has been found that one of the primary effects of this surgical intervention is the down-regulation of ghrelin in the gastric remnant and the increased reduction of the anorectic hormones peptide YY and glucagon-like peptide 1. In patients who have a poor response to bypass surgery, it has been reported that they have a suboptimal gut peptide response.

A Nod to the Genetics of Inflammatory Bowel Disease

Abreu MT, Taylor KD, Lin YC, Hang T, Gaiennie J, Landers CJ, Vasiliauskas EA, Kam LY, Rojany M, Papadakis KA, Rotter JI, Targan SR, Yang H. Mutations in NOD2 Are Associated With Fibrostenosing Disease in Patients With Crohn's Disease. *Gastroenterology* 2002;123:679–688.

Summary

Variants in the *NOD2/CARD5* gene are associated with Crohn's disease. This study correlated the *NOD2* variant genotype with fibrostenotic Crohn's disease of the small intestine.

Editor's comment

NOD2/CARD5 was the first genetic variant associated with inflammatory bowel disease. Subsequent genetic studies examined how various aspects of Crohn's disease

correlated with genotype, including a relationship to ileal disease and to fibrostenotic disease, but not to response to therapy. Of even greater interest has been the continuation of the whole-genome analysis to identify 11 novel loci that are associated with Crohn's disease, including well-replicated variants of the *IL23R* and the *ATG16L1* genes. These studies support the importance of the immune system and its interactions with the intestinal microflora in the pathogenesis of inflammatory bowel disease.

Changed Priorities for Liver Transplant Recipients

Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for End-Stage Liver Disease (MELD) and Allocation of Donor Livers. *Gastroenterology* 2003;124:91–96.

Summary

The original liver transplant allocation system used the classic Child–Turcotte–Pugh score and overall waiting time on the transplant list. As a result of problems with this approach, the Model for End-Stage Liver Disease (MELD) was evaluated as an alternative. The MELD score is based on reproducible and objective variables consisting of serum bilirubin level, serum creatinine level, and prothrombin time. This model was originally developed to predict the outcomes of transjugular intrahepatic shunt procedures in patients with chronic liver disease. The report by Wiesner et al described a prospective study in which the MELD score accurately predicted 3-month mortality among patients with chronic liver disease on the liver transplant waiting list.

Editor's comment

Since 2002 and the publication of this report, priority for liver transplantation has been determined by the

MELD score, which provides donor organs to listed patients with the highest estimated short-term mortality. Due to this change in patient priority and the elimination of waiting times as a means of accumulating priority, patients who present for liver transplantation currently have higher MELD scores and more advanced liver disease than before the use of the MELD score. The MELD score for liver transplantation was subsequently modified to take into account the benefits of liver transplantation for patients with hepatocellular cancer. Despite the advantages of the MELD score, survival is not accurately predicted for approximately 15% of patients. Further refinements and validation of the MELD score will continue with the aim of improving its predictive accuracy.

Can We Replace the “Gold Standard”?

Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective Comparison of Transient Elastography, Fibrotest, APRI, and Liver Biopsy for the Assessment of Fibrosis in Chronic Hepatitis C. *Gastroenterology* 2005;128:343–350.

Summary

Liver biopsy has been the gold standard to assess liver fibrosis in patients with chronic liver diseases. Recently multiple, less invasive tests have been proposed as alternatives to assess liver fibrosis. This study assessed 4 tests for liver fibrosis: FibroScan (transient elastography), FibroTest, APRI (aspartate transaminase to platelets ratio

index), and liver biopsy. This study concluded that FibroScan was an effective method for assessing liver fibrosis. Furthermore, combined use of FibroScan and FibroTest to evaluate liver fibrosis could allow most patients with chronic hepatitis C to avoid undergoing a biopsy procedure.

Editor's comment

A noninvasive test to assess liver fibrosis is critical for determining the prognosis of patients with chronic liver disease and for measuring the efficacy of therapeutic interventions in patients. The APRI and FibroTest consist of a collection of serum markers that were empirically associated with fibrosis in patients with chronic hepatitis C. On the other hand, the FibroScan represents a pathophysiologic measurement of liver stiffness resulting from increased fibrosis. Under careful review of these available

tests, most experts conclude that they are effective in distinguishing severe fibrosis from no or mild fibrosis, but not for distinguishing gradients of fibrosis such as provided by the histologic fibrosis score of a liver biopsy specimen. Further studies are needed to assess the performance of these tests in patients with liver diseases other than chronic hepatitis C and to determine how these tests change in individual patients during therapeutic interventions.

Dr Brenner discloses no conflicts.