Comment. The precise mechanism of HDV replication has remained elusive. Replication of defective HDV requires coinfection with a helper virus, namely human hepatitis B virus or another of the mammalian or avian hepadnaviruses. The HDV virion does not have a nucleocapsid structure (Infect Immunol 1984;43: 10000–5); it has an outer envelope of hepadnavirus surface antigen and a small internal RNA genome and HDV antigen. The HDV antigen appears to be a phosphoprotein that interacts directly with virion RNA, possibly playing a role in replication of HDV (J Virol 1988;62:2403–10, Virology 1988;167:274–8). Alternatively, it is possibly a structural antigen uninvolved in replication. The gene for HDV antigen appears to be present on the antigenomic RNA (J Virol 1988;62:1855–61). Neither viral polymerase activity nor a polymerase gene have been identified in HDV particles (Nature 1986;323:508–14). In HDV-infected hepatocytes, genomic RNA, and predominantly double-stranded antigenomic RNA have been localized to the nuclei of infected cells (Virology 1988;167:274–8). Hence, HDV replication is believed to occur in the hepatocyte nucleus.

The structural similarities between HDV and certain plant RNA agents, i.e., viroids, virusoids, and satellite RNA viruses, and the identification of a viroidlike domain in HDV RNA (Science 1989;243:649–52), has led to the concept that HDV may be a satellite RNA virus of hepatitis B virus and that HDV replication may involve the rolling-circle model initially postulated for plant RNA agents (Science 1984;223:450–5). In this model, cleavage and ligation of precursor linear multimeric RNAs, larger than genome length, precede the production of genomic RNA. Consistent with this model are earlier observations that both genomic and antigenomic HDV RNA could undergo self-cleavage and that this occurred near the 3′ end of the HDV antigen gene (J Virol 1988;62:2674–9).

The present study, demonstrating that self-cleavage and self-ligation of a relatively small subfragment of the RNA of HDV are dependent on magnesium ions, and that these reactions are reversible, provides new information concerning possible replicative strategies of HDV. Although this new information is compatible with the rolling-circle model of RNA replication, it is not yet known whether larger HDV RNA precursor intermediates are also processed by the same magnesium-dependent cleavage and ligation mechanisms. Other questions concern whether or not cleavage and ligation are dependent on specific nucleotide sequences, whether interfering sequences are present at other sites, and what role conformational changes in RNA might play in favoring or inhibiting these reactions. The putative role of HDV antigen in cleavage and ligation reactions also requires further study.

Continuing investigation of HDV with the tools of molecular biology will undoubtedly advance our knowledge of this curious virus. Perhaps more interestingly, it seems likely to provide important new information on mechanisms of viral replication and, through this, the development of effective methods of replication inhibition by chemotherapy.

R. S. KOFF, M.D.

ANTIMICROBIAL THERAPY OF DUODENAL ULCER? HOLD OFF FOR NOW!

Marshall BJ, Goodwin CS, Warren JR, et al. (Departments of Gastroenterology, Microbiology, Histopathology, and Pharmacy, Royal Perth Hospital, Perth, Western Australia; and Center for Advanced Studies in Health Sciences, Curtin University, Perth, Australia) Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet 1988;ii:1437–42 (December 24/31).

Table 1. Summary of Results With Four Treatment Regimens

Treatment group	n	Clearance of CP at 10 wk	Ulcer healed at 10 wk	Ulcer recurrence during 12 mo
Cim	22	0 (0%)	13 (59%)	12/13 (92%)
Cim + T	29	1 (3%)	22 (76%)	18/22 (82%)
Bi	22	7 (32%)	15 (68%)	8/15[a] (53%)
Bi + T	27	20 (74%)	20 (74%)	5/20[b] (25%)

Bi, colloidal bismuth subcitrate (q.i.d.); Cim, cimetidine (400 mg b.i.d. for 8 wk); CP, *Campylobacter pylori*; T, tinidazole (500 mg b.i.d. for 10 days). [a] $p = 0.027$ compared with combined cimetidine group. [b] $p < 0.0001$ compared with combined cimetidine group.

One hundred patients with an active duodenal ulcer at least 3 mm in size, and with concomitant *Campylobacter pylori* (CP) in their antrum, were randomly assigned to treatment for 8 wk with either cimetidine (400 mg twice a day) or colloidal bismuth subcitrate (DeNol) (1 tablet four times a day). Each of these two groups were divided into subgroups of patients who took, in addition to cimetidine or bismuth, either the antibiotic tinidazole (500 mg) or an identical placebo twice a day for the first 10 days of therapy. The four treatment groups were balanced for sex, age, history of smoking, and duration of ulcer disease. Two weeks after completion of therapy, patients again underwent endoscopy to assess ulcer healing. Antral biopsy specimens were taken for culture and stain to assess for the continued presence or absence of CP. Those patients whose ulcers had healed were then followed for up to 1 yr, with endoscopy performed routinely at 12, 24, and 52 wk or, presumably, upon any symptom of relapse during this period, although the paper does not clearly state this. The purpose of the study was to determine the relationship between eradication of CP and both acute ulcer healing and long-term ulcer relapse.

As shown in Table 1, clearance of CP was noted in only 1 of 51 patients treated with cimetidine with or without tinidazole, whereas treatment with bismuth or bismuth plus tinidazole eradicated the organism in 32% and 74% of patients, respectively. Ulcers healed in 59%–76% of patients, with no significant differences among the four treatment regimens. Although there was obviously no correlation between the eradication of CP and ulcer healing in the cimetidine groups (as only 1 patient was cleared of CP), there was a significant correlation in the combined group of 49 patients treated with the bismuth regimens. Acute ulcer healing occurred in 25 of 27 (93%) patients in whom CP was eradicated compared with 10 of 22 (45%) patients in whom CP was still present after 8 wk of therapy. Ulcer recurrence during the next 12 mo for patients whose ulcer had healed on each of the four treatment regimens is displayed in the last column of Table 1. Recurrence was significantly lower in patients

Table 2. Duodenal Ulcer Recurrence as a Function of Presence (+) or Absence (−) of Campylobacter pylori *After Initial Therapy With Four Treatment Regimens*

Original treatment group	Recurrence IF: CP+	Recurrence IF: CP−
Cim	12/13 (92%)	0/0
Cim + T	18/21 (86%)	0/1
Bi	7/8 (88%)	1/7[a] (14%)
Bi + T	0/2	5/18[b] (28%)

Bi, bismuth; CP, *Campylobacter pylori*; Cim, cimetidine; T, tinidazole. [a] Two of these 7 later noted to be CP+; neither relapsed. [b] One of these 18 noted to be CP+ at week 12 and relapsed at week 24.

whose ulcer had healed with bismuth or bismuth plus tinidazole than in the combined group of patients whose ulcer had healed with cimetidine. As shown in Table 2, recurrence in the bismuth-treated patients was correlated with the presence or absence of CP after the initial course of therapy. Ulcers recurred in 7 of 10 (70%) patients in whom CP was still present, compared with 6 of 25 (24%) ($p < 0.05$) of those in whom CP had been eradicated. The authors also suggest that patients in whom CP was eradicated after initial therapy had fewer symptoms during the 1-yr follow-up than those in whom CP was still present. However, the differences appear to be rather slight and were obtained using a scoring system for depression (Zung scale) that is not familiar to most gastroenterologists. Side effects (primarily diarrhea and dyspepsia) occurred more frequently in patients taking tinidazole compared with those who did not, but the difference was not significant.

Comment. Dr. Barry Marshall is well known as the individual who, with Dr. Warren and Dr. Goodwin, brought CP to the attention of the medical community in 1983, when they described a number of patients with CP-associated chronic active gastritis (Lancet 1983;i:1273–5). They hypothesized that the organism was causally responsible for the gastritis, and, as many of their patients had peptic ulcer disease, that CP gastritis was a contributing factor to ulceration. Although direct evidence (e.g., a reliable animal model) remains scarce, most investigators have come to accept their first hypothesis as valid. On the other hand, that CP gastritis (presumably in areas of gastric metaplasia in the duodenal bulb) contributes to duodenal ulceration has not been accepted. As the authors believe that the results in their latest paper "imply that *C. pylori* is the most important etiologic factor so far described in duodenal ulcer," their work deserves careful scrutiny.

There are several points to be made from the paper. First, treatment for 8 wk with colloidal bismuth subcitrate alone resulted in eradication of CP in barely one-third of patients. Second, tinidazole, when given in conjunction with cimetidine for the first 10 days of therapy was ineffective in eradicating CP. This is because resistance of CP to tinidazole developed in 19 of 27 organisms originally sensitive to tinidazole (J Clin Pathol 1988; 41:207–10). By comparison, resistance developed in only 2 of 22 organisms from patients treated with bismuth plus tinidazole. Third, acute healing of duodenal ulcer in those treated with bismuth or bismuth plus tinidazole was correlated with eradication of CP. As the treatment groups were well-balanced for other variables (e.g., smoking and duration of ulcer disease), the authors suggest that the well-described effect of bismuth on duodenal ulcer healing is related to its antibacterial activity. Fourth, ulcer recurrence during the 12 mo following initial healing with bismuth alone (53%) was significantly lower than that experienced by patients whose ulcer had been treated with one of the cimetidine regimens. This finding is similar to results described by other investigators (Lancet 1981;i:7–10, 1985;1:1299–302, Gut 1986; 27:106–10), but is at variance with a recent study by Coghlan (Lancet 1987;ii:1109–11), who found that overall ulcer recurrence was not significantly different in patients whose ulcer had healed with cimetidine or with colloidal bismuth subcitrate (67% vs. 52%, respectively). Fifth, treatment with bismuth plus tinidazole resulted not only in more frequent eradication of CP, but a rate of recurrence lower than that seen with either bismuth alone or with the cimetidine regimens, although the difference from bismuth alone was not statistically significant. Finally, these results from Australia support the observation of Coghlan, who reported that ulcer recurrence after bismuth was directly related to the presence or absence of CP after acute ulcer therapy. The results of the current paper, 7 of 10 (70%) recurrence if CP were still present compared with 6 of 25 (24%) if CP were eradicated, are very similar to those of Coghlan, who reported 8 of 10 (80%) instances of ulcer recurrence in patients in whom CP was still present compared with 3 of 11 (27%) in those in whom CP had been eradicated.

Based on their observations, Marshall and his colleagues would argue that "detection of *C. pylori* should be part of the routine management of patients with acid peptic disease and eradication of the bacterium a major therapeutic goal." Should this advice be accepted? My answer to this question is—Not yet! There are a number of problems with this paper that compel me to urge that its recommendations not be accepted.

First, sample sizes of patients healed with a bismuth regimen and followed for relapse in this paper (and Coghlan's) are relatively small, 35 and 21 respectively. Confirmation of their results from larger studies are needed before we abandon the currently used safe and effective modalities for duodenal ulcer. Second, the definition of recurrent ulcer in this paper is not clear. There is the suggestion that symptomatic recurrences alone are counted. Indeed, we are told that patients at week 0 (i.e., 2 wk after cessation of therapy) were considered as relapses if they still had symptoms even though the ulcer had healed. Further, an objective definition of "symptom relapse" is not provided. Third, acute ulcer healing in only 59% of cimetidine-treated patients is lower than in most studies and 1-yr ulcer recurrence of 92% is a bit higher than in most studies. The relatively low rate of ulcer healing after 8 wk of therapy may be explained by the authors by the 2-wk hiatus before endoscopy, during which "early" recurrence might occur. However, this is only speculation. Fourth, the study was not adequately blinded. It would have been better to use a double-dummy technique whereby patients receiving cimetidine also received a bismuth placebo and patients receiving the bismuth regimens received a cimetidine placebo. As it was, patients knew they were taking either bismuth or cimetidine. Granted, the blinding of studies with bismuth is difficult because of the darkening effect of bismuth on the tongue and on stool color. That does not mean, however, that blinding is impossible. For example, charcoal could perhaps be administered to all patients, assuming that interference with the test medications did not occur. Rigorous blinding of the investigators was not carried out. Anything less than scrupulous attempts at blinding the study leaves open the possibility that patients could "spill the beans" to the otherwise "blinded" endoscopist. Finally, even if this study were perfect, colloidal bismuth subcitrate is not available for use in the United States and the available bismuth subsalicylate (Pepto Bismol) has been inadequately studied.

Three other issues deserve comment. First, the authors suggest that bismuth with or without tinidazole exerted its ulcer-healing effect via eradication of CP. However, overall ulcer healing with bismuth plus tinidazole was only slightly better than with bismuth alone, even though the combination therapy eradicated CP significantly more often. Second, are there variables besides CP status to account for the lower incidence of relapse in patients treated with bismuth? Other factors regarding the patients seem unlikely, as the authors show that neither sex, age, smoking, nor previous ulcer history confound the relationship between CP status and recurrence. On the other hand, most of the relapses in CP-positive subjects occurred during the first 3 mo after therapy. As patients who remained symptomatic after the original 8 wk of therapy were considered relapsed at that time even though their ulcer had healed, one wonders how many of these relapses were symptomatic but not endoscopic. Third, are there mechanisms by which bismuth, with or without tinidazole, could produce a salutary long-term effect other than an effect on CP? The authors think not, and point to the 70% relapse rate in bismuth-treated patients *not* cleared of CP, comparable to the recurrence rate of patients treated with cimetidine. However, there were only 10 "healed" patients treated with the bismuth regimens who were still CP-positive. Thus, it remains highly possible that the effects of bismuth on CP and ulcer recurrence are independent.

In summary, the data are not yet convincing that bismuth therapy, either per se or by eradication of CP, leads to a relapse-reduced life for patients with duodenal ulcer. Further studies involving large numbers of patients, rigorous blinding, endoscopic confirmation of ulcer recurrence, and, ideally, regimens that effectively eradicate CP but do not contain bismuth, are needed. Widespread use of antibiotics to treat duodenal ulcer is to be condemned until we know more about CP and its role in ulcer disease.

W.L. PETERSON, M.D.

Reply. The investigators recognized the problem with blindedness in this study and for that reason there was a 2-wk delay between the end of therapy and the assessment of healing by endoscopy at week 10, so that mouth-staining would not be evident in patients who had taken bismuth. Dr. Peterson fails to record that this precaution was not taken in previously published so-called "double-blind studies" involving bismuth and H_2-blockers. Second, to prevent investigator bias if patients did inadvertently "spill the beans" regarding their De-Nol therapy, a clinical endpoint was given as much weight as an endoscopic ulcer recurrence. If a patient developed any symptoms requiring further ulcer medication (such as antacids or H_2-blockers), or developed symptoms that the patient regarded as being due to ulcer recurrence (for example, vomiting episodes), then that patient was terminated from the study as a relapse and underwent endoscopy at that time. Thus, the endoscopist only determined the presence or absence of an ulcer crater, not whether the patient had relapsed.

These measures were successful as evidenced by relapse of CP-negative patients. There were 5 such patients, all of whom were removed from the study by the investigator at one of the follow-up endoscopies. Two patients had symptoms of heartburn and endoscopic esophagitis with trivial duodenal lesions who were removed by the investigator because they could not reasonably have been expected to remain off ulcer therapy. Two patients had duodenal erosions and small areas of ulceration accompanied by mild symptoms and were removed from the study as actual duodenal ulcer relapses. The fifth patient was a woman with mild, intermittent, atypical symptoms and a completely normal endoscopy who was removed because before endoscopy she felt that her symptoms were due to recurrence of her ulcer. In the data analysis these patients were regarded as CP-negative relapses, although in fact only 2 had lesions that could reasonably be called duodenal ulcers. If the usual ulcer-relapse criteria were used, our results would have shown a relapse of 10%, not the 20% stated in the paper for our CP group.

The low healing rate of patients treated with cimetidine (59%) and the high relapse rate (92%) should be regarded as evidence that the patients who took part in this study had severe duodenal ulcer disease. Although the numbers in each group were relatively small, highly significant differences were found between patients in whom CP persisted and patients from whom CP was eradicated. As pointed out by Dr. Peterson, this difference was evident even within the group of patients who took bismuth. There is thus no evidence to suggest that bismuth has an effect on ulcer relapse independent of CP eradication.

I agree with Dr. Peterson that our study should be the stimulus for much larger, rigorously blinded multicenter studies of therapy for duodenal ulcer incorporating the assessment of clinical symptoms, ulcer craters, and gastroduodenal microbiology and histology. As eradication of CP involves treatment with generic antibiotics and bismuth, there is little incentive for pharmaceutical companies in the United States to fund therapeutic trials. Even if funding was available today, double-blind follow-up data would not be published for at least 3 yr.

BARRY J. MARSHALL, M.D.

MANAGEMENT OF NECROTIZING PANCREATITIS

Beger HG, Buchler M, Bittner R, et al. (Department of General Surgery, University of Ulm, Ulm, Federal Republic of Germany) Necrosectomy and postoperative local lavage in necrotizing pancreatitis. Br J Surg 1988;75:207–12 (March).

This report reviews the outcome of 95 patients judged to have necrotizing acute pancreatitis and managed by operative debridement of necrotic tissue or "necrosectomy" followed by postoperative lavage of the pancreatic bed. These patients were selected from an overall group of 744 patients treated for acute pancreatitis over a 5-yr period. Five hundred sixty-seven patients (76%) were judged to have "edematous-interstitial" pancreatitis. Forty-seven patients (6%) had pancreatic "abscesses" or "pseudocysts." One hundred thirty patients (17%) were judged to have pancreatic necrosis. This diagnosis was confirmed in "most cases" by findings on contrast-enhanced computed tomography. In this group, 95 were treated by necrosectomy and postoperative lavage. Twenty patients were managed nonoperatively with a 10% mortality, and 15 underwent formal pancreatic resection or local pancreatic drainage with a 13% mortality. Patients managed nonoperatively or by alternative operations were believed to be less seriously ill.

In the 95 patients treated by necrosectomy and lavage, signs of an acute surgical abdomen were present in 57%. Systemic complications were present in 82% and included evidence of sepsis in 27%. Other systemic complications were arterial hypoxemia in 55%, renal insufficiency in 30%, and arterial hypotension in 17%. Persistent or increasing local complications were described in 15% of