# Reaching Beyond the Borders

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The JOURNAL OF GASTROINTESTINAL SURGERY began two years ago with a primary goal of disseminating knowledge in the diagnosis and management of alimentary tract diseases. We aimed to reach not only members of our own Society, The Society for Surgery of the Alimentary Tract, but also surgeons, gastroenterologists, basic scientists, residents, and other students of surgical gastroenterology beyond the borders of our Society. We wanted to create not just another "American" journal, but a journal that would be read world wide. Indeed, we established an Editorial Board to reflect this international perspective.

We have recently learned that our new JOURNAL has gained a benchmark that will greatly help in achieving our goal. The JOURNAL OF GASTROINTESTINAL SURGERY will now be listed in *Index Medicus*®/MEDLINE®. *Index Medicus*®/MEDLINE® is an index of biomedical work compiled by the National Library of Medicine. Inclusion in the Index is dependent on a number of factors that include a rigorous process of peer review of the material submitted to the JOURNAL, the originality and scientific quality of papers published in the JOURNAL, and the excellence of the printed publication. The first seven issues of our JOURNAL were carefully reviewed by *Index Medicus*®/MEDLINE®. We recently learned that the JOURNAL received a favorable review and was accepted for inclusion in the Index.

Inclusion in *Index Medicus*®/MEDLINE® means that persons searching the biomedical literature from all over the world will have ready access to the material printed in our JOURNAL. Clearly, we will reach beyond our borders. The authors who wrote the superb papers, the Editorial Board along with others who reviewed the papers and offered suggestions for improvement, and the publisher who brought forth each outstanding issue deserve credit for the recognition achieved. Your editors thank all involved.

What additional borders do we have yet to cross? In regard to size, the JOURNAL is adding more pages to each issue beginning with the present issue. Sometime in the future we will begin to publish monthly instead of bimonthly. In regard to format, we find most readers still prefer the printed page to the computer disc. Our subscribers like the ease of reading the printed page and prefer to have those pages stored in a repository on their own bookshelves. Nonetheless, the addition of sight, sound, and movement to the words on an electronic disc offers an exciting option for the future. Video is especially attractive in surgery where the live operation has such a key role in the field. What better way to communicate advances in operative technique to others than via the voice and video of the presenting surgeon! Although these techniques are currently beyond our present approach, your editors and publisher are aware of them and will be ready to implement them when the time is right.

The important message today is that papers from our JOURNAL will now be cited in *Index Medicus*®/MEDLINE®. Our thanks to all involved in making this possible. We look forward to the future.

# Use of Controlled Randomized Trials to Evaluate New Technologies and New Operative Procedures in Surgery

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Modern surgery has been driven by numerous technologic advances. New operations are devised and old operations performed with new instruments. But are we as surgeons embracing these innovations with too much haste? Most of all, have our patients benefited? In this era of evidence-based medicine, we are forced to examine our beliefs and results critically, and new operations and innovations should only be popularized when their value has been proved.

In the evaluation of new procedures and treatments, the most reliable evidence no doubt should come from properly conducted randomized controlled trials. This method is superior to the nonrandomized concurrent or historical cohort comparisons or the simple case series. It is less subject to bias in case selection and changes in techniques and management over time. These latter investigations can be regarded as hypothesis generating, to be proved or disproved in the more vigorous context of the randomized controlled trial. The surgical community, however, has been accused of poor quality research output in recent years.[1] Few randomized trials are carried out and even when performed, they are often flawed. The finding that much of the surgical literature is based on second-rate evidence has prompted us to rethink our scientific research methodology.

The article by Horton[1] entitled "Surgical research or comic opera: Questions, but few answers" demonstrated to us our ability to raise important questions but showed that we lack the appropriate means to answer them. Even in major surgical journals, only 7% of papers are randomized controlled trials, 46% are case series, and 18% are laboratory animal experiments.[1] It has been estimated that 40% of surgical procedures could be evaluated by randomized controlled trials, yet such trials are performed by surgeons in only one third of cases, and different surgical therapies are compared in only one fourth of studies.[2,3]

Why are clinical trials not performed more often? Surgeons are not unaware of the importance of randomized controlled trials, but there are inherent difficulties, especially in surgical trials that deter their employment, such as blinding, preference by patients and surgeons of certain treatment options, uncommon conditions, and lack of funding, as well as legal, ethical, and political issues.[3,4] In addition, the unique difficulty in a surgical trial as compared to a medical trial is the variability of the surgical procedure itself. A learning curve invariably exists for any new procedure, and for procedures that demand great expertise and experience, few centers may reach the level of competency needed for quality control. Thus "inferior" laparoscopic fundoplication may be compared to standard "optimal" therapy for gastroesophageal reflux disease. Multicenter trials are often needed to generate enough statistical power for analysis. But it is precisely problems such as the difficulty in controlling surgical technique inherent in surgical trials that make multicenter trials difficult to conduct. The organization needed to coordinate such activity also adds to the cost. New technology changes rapidly. It takes considerable time to recruit sufficient patients in a randomized trial, and such a trial may become obsolete by the time its fruits are reaped.

Even if randomized controlled trials are performed, quality in the design and reporting is often lacking.[5,6] Clinicians, epidemiologists, biostatisticians, and journal editors have made a valiant effort to implement the CONSORT (Consolidated Standards of Reporting Trials) statement, which sets forth guidelines (perhaps ideal) for the reporting of randomized controlled trials.[7-10] The title of the manuscript should identify the study as a randomized controlled

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trial. The summary must be structured. A checklist of 21 points states what should be included in the report, for instance, study population, end points, method of masking, statistical analysis, and sample size calculation. A flow diagram depicting the progress through the various stages of a trial, including flow of participants, withdrawals, and timing of primary and secondary outcome measures is also a necessity. All manuscripts reporting on randomized controlled trials submitted to *Lancet* and the *Journal of the American Medical Association (JAMA)* are now required to adhere to the CONSORT guidelines.

How well have randomized controlled trials been utilized to evaluate modern surgical technologic advances? New instruments are usually greeted with zeal. The advent of surgical staplers was claimed to markedly reduce anastomotic leaks for esophageal anastomosis. It was only through a randomized controlled trial that its value could be ascertained as compared to the traditional hand-sewn method. Although similar leakage rates were found, staplers resulted in a much higher rate of stricture, which was technique rather than size dependent. The hand-sewn technique was also found to be the most cost-effective.[11]

Minimal access surgery has been embraced with enthusiasm by the surgical community. Less morbidity and mortality, a shorter hospital stay, earlier return to work, and improved cosmesis are aims and results claimed by advocates of this type of surgery. Few randomized controlled trials, however, have been performed to substantiate these conclusions. Beliefs may not stand up to appropriate investigations. One recent trial showed that laparoscopic cholecystectomy required a longer operating time than small incision cholecystectomy, but resulted in no benefits.[12] It is trials such as these that help disprove myths believed by patients and surgeons alike.

Another report analyzed published randomized controlled trials in laparoscopic surgery.[13] Forty trials were identified in leading surgical journals published between 1990 and 1996. More than half of these trials were poorly constructed or at least poorly reported. Two of the major outcomes of minimal access surgery (quality of life and cost-effectiveness) were addressed in only five and eight of the 40 trials, respectively. Prospective calculation of sample size and unbiased assessment of outcome were also lacking. The advent of minimal access surgery has not improved the quality of randomized controlled trials. It is hoped that endeavors such as the CONSORT statement will help to redress this balance.

Randomized controlled trials are certainly not a panacea for all deficiencies in surgical research. Observational studies have their unquestionable values.[4] The two types of studies should complement each other. What surgeons need is more encouragement, education, and resources to take part in randomized controlled trials. Assistance from epidemiologists and biostatisticians is invaluable. Although laboratory experiments and case studies can easily generate results leading to rapid publication of findings, clinical practice is ultimately influenced by the results of the longer term randomized controlled trials. Patients' perceptions, the surgical community, and society as a whole are becoming increasingly technology and mass media driven. Therapies based on good evidence are also demanded. Good-quality randomized controlled trials are ever more essential to help support or refute claims. The characteristics of a good clinical trial have been established by CONSORT. We can and should be critical in examining our own technologic innovations by putting them to the test.

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# Role of Antibiotics in Acute Pancreatitis: A Meta-Analysis

*Robert Golub, M.D., Faizi Siddiqi, M.D., Dieter Pohl, M.D.*

In an attempt to decrease the infectious complications of acute pancreatitis and its high mortality, many investigators have conducted randomized prospective trials on the efficacy of prophylactic antibiotics. The results of these studies are conflicting, and many have called for a large multicenter study. Because multicenter trials are costly and difficult to organize, we believe that meta-analysis is a reasonable alternative. A meta-analysis of all eight previously published trials of prophylactic antibiotics in acute pancreatitis was performed. The end point was death. The Mantel-Haenszel statistic was used to summarize odds ratios across studies in a fixed effects model, after homogeneity was assessed. Sensitivity analysis was performed as appropriate. The meta-analysis of all eight trials showed a positive benefit for antibiotics in reducing mortality. Sensitivity analysis showed that the advantage was limited to patients with severe pancreatitis who received broad-spectrum antibiotics that achieve therapeutic pancreatic tissue levels. It is recommended that all patients with severe pancreatitis be treated with broad-spectrum antibiotics that achieve therapeutic levels in pancreatic tissue. (J GASTROINTEST SURG 1998;2:496-503.)

KEY WORDS: Pancreatitis, treatment, antibodies, meta-analysis

The use of antibiotics in acute pancreatitis is controversial. Eight prospective randomized trials have examined this issue, but the results are conflicting.[1-8] Only one trial was able to show a statistically significant decrease in mortality with the use of antibiotics.[6] The small sample size of most of these reports, combined with a negligible incidence of mortality in the control population, may have contributed to a type II error in reporting significant reductions in mortality. We therefore conducted a meta-analysis of all the prospective randomized trials to determine the role of antibiotics in acute pancreatitis.

## MATERIAL AND METHODS

Criteria for inclusion in the meta-analysis were prospective randomized trials of systemic or oral antibiotics in acute pancreatitis. A MEDLINE search was conducted from 1966 through June 1997, with various search terms including pancreatitis, antibiotics, and randomized studies. A total of eight trials were identified. Additionally, the bibliographies of these trials, as well as other recent publications on the treatment of pancreatitis, were reviewed for evidence of other randomized controlled studies. The eight studies were critically reviewed by two independent investigators using a 10-point scale proposed by Solomon and McLeod.[9] Interobserver agreement was assessed by the intraclass correlation.[10] Pertinent results including demographic data, methods, and end points including death were extracted and coded by two of the authors, and any differences were arbitrated by a third investigator.

Differences between control and treatment groups in individual studies were determined by calculating log odds ratios with 95% confidence intervals as described by Fleiss.[11] Because log odds ratios were used, 0.5 was added to individual cells in the $2 \times 2$ tables to allow meaningful results. Treatment effects across multiple studies were summarized by calculating the Mantel-Haenszel statistic,[12] as well as the standard error[13] and corresponding 95% confidence intervals. Alternatively, the log odds ratio was calculated when totaling the results of $2 \times 2$ tables resulted in division by zero.[11] This meta-analysis used a fixed effects model, which assumes that there is a single true effect, which is estimated by each of the published studies. Homogeneity, a measure of the common true

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**Table I.** Summary of randomized prospective trials

| Reference | Study period | Average age (yr) | Sex (%M/%F) | Eligibility | Type of pancreatitis | Severity | Dosage of antibiotics | Duration of antibiotics |
|---|---|---|---|---|---|---|---|---|
| Finch et al.[3] | 1971-1973 | 35.7 | 59/41 | Clinical pancreatitis and amylase >160 Somogyi units/ 100 ml | ETOH 66% Idiopathic 28% Gallstones 5% Other 1% | | Ampicillin, 500 mg-1 gm q 6 hr | 7 days |
| Howes et al.[1] | 1972-1974 | 39.5 | 77/23 | Clinical pancreatitis and amylase >160 caraway units/ 100 ml | ETOH 91% Gallstones 5% Idiopathic 2% Other 2% | | Ampicillin, 1 gm q 6 hr | 5 days |
| Craig et al.[2] | Pre-1975 | 40.5 | 100% male | Clinical pancreatitis | ETOH 93% Gallstones 4% Other 3% | | Ampicillin, 1 gm q 6 hr | 7 days |
| Delcenserie et al.[7] | 1988-1993 | 42.7 | 91/9 | Acute pancreatitis and ≥2 fluid collections on CT | ETOH 100% | Average Ranson[36] score 2.3 | Ceftazidime, 2 gm q 8 hr; Amikacin, 7.5 mg/kg q 12 hr; Flagyl, 500 mg q 8 hr | 10 days |
| Pederzoli et al.[4] | 1989-1991 | 52.0 | 59/41 | Clinical pancreatitis and necrosis on CT or ultrasound | Gallstones 50% ETOH 32% Other 18% | Average Ranson score 3.7 | Imipenem, 500 mg q 8 hr i.v. | 14 days |
| Sainio et al.[6] | 1989-1993 | 40.5 | 88/12 | C-reactive protein >120 mg/L and low contrast enhancement on CT | ETOH 100% | Average Ranson score 5.5 | Cefuroxime, 1.5 gm/day i.v. | 14 days or until C-reactive protein normal |
| Schwarz et al.[8] | 1991-1994 | 44.5 | Not stated | Clinical pancreatitis with necrosis on CT | ETOH 54% Gallstones 42% Trauma 4% | Average Ranson score 4.5 | Ofloxacin, 200 mg b.i.d.; Metronidazole, 500 mg b.i.d. | 10 days |
| Luiten et al.[5] | 1990-1993 | 55.5 | 59/41 | Imrie score[38] ≥3 and/or Balthazar CT grade[37] D or E | Not stated | Average Imrie score 3.2 Balthazar 52% grade E 41% grade D | Colistin sulfate, 200 mg; Amphotericin, 500 mg Norfloxacin, 50 mg; All p.o. q 6 hr and daily enema Cefotaxime, 500 mg q 8 hr i.v. | Oral until patient was extubated and on regular diet Cefotaxime until gram-negative bacteria eliminated from oral cavity and rectum |

treatment effect across individual studies, was assessed by calculating the Q statistic. A Q statistic that is not significant is evidence of a small degree of between-study variability and suggests that a fixed effects model is appropriate. Odds ratios are expressed followed by the 95% confidence intervals in parentheses. Sensitivity analysis was performed when appropriate.

## RESULTS

Demographic data and pertinent methodologic and outcome data from the eight trials are summarized in Table I. The average study quality score was 7.5 with an intraclass correlation of 0.41 ($P < 0.0001$). There was 100% agreement on data extraction among the investigators. Three distinct classes of trials are evident. Studies by Finch et al.,[3] Howes et al.,[1] and Craig et al.[2] were performed in the 1970s on patients with mild pancreatitis, and all treated patients received ampicillin. The trials by Delcenserie et al.,[7] Pederzoli et al.,[4] Sainio et al.,[6] and Schwarz et al.[8] were conducted between 1993 and 1997 on patients with more severe pancreatitis, and broader spectrum antibiotics were used. The trial by Luiten at al.[5] was conducted on patients with severe pancreatitis, but the antibiotics were administered as a combination of parenteral, oral, and rectal routes. All control patients in the above-mentioned trials received standard care including pain medication, nasogastric suction, intravenous hydration, and nutritional support, and some studies used atropine[1,3] or antiprotease drugs.[4] Antibiotics were well tolerated in all trials, but one patient in the study by Howes et al.[1] had an anaphylactic reaction to ampicillin but made a full recovery.

The odds ratios and 95% confidence intervals for all eight trials are summarized in Table II. Only the study by Sainio et al.[6] showed a significant decrease in mortality with antibiotics. The Mantel-Haenszel log odds ratio, which summarizes the mortality data across all eight trials, was −0.77 (−0.14 to −1.40, $P = 0.016$). This shows a significant decrease in mortality when prophylactic antibiotics are used (Fig. 1). The probability of dying was 6.6% in the antibiotic-treated patients as compared with 13.3% in the control subjects. The homogeneity of variance was Q = 3.60 ($P = 0.82$), which indicates that effect sizes do not differ excessively between individual study results, and it is appropriate to combine the trials in a fixed effects model. If the study by Luiten et al.[5] using systemic and oral antibiotics is removed from the analysis, the Mantel-Haenszel log odds ratio was still significant (log odds ratio = −1.16 [−0.19 to −2.15], $P = 0.016$, and the homogeneity Q = 3.19, $P = 0.78$). If the trial by Sainio et al.[6] is not considered with the remaining seven trials, the log odds ratio was −0.56 (0.12 to −1.24), $P = 0.10$.

The three early trials using ampicillin[1-3] were analyzed as a separate group. None of these studies showed a significant decrease in mortality when examined individually, and this was also the case when they were analyzed as a group (Fig. 2). The combined log odds ratio was 0.40 (−1.71 to 2.52), $P = 0.71$, and the homogeneity Q = 0.20 ($P = 0.91$).

The analysis of the four studies[4,6-8] that used broader spectrum antibiotics in sicker patients is illustrated in Fig. 3. There is a significant beneficial treatment effect in the patients given prophylactic antibiotics (Mantel-Haenszel log odds ratio = −1.38 [−0.32 to −2.44], $P = 0.008$, and homogeneity Q = 1.41, $P = 0.70$). Patients who received antibiotics had a 5.3% probability of dying compared to a 18.2% incidence in the control group.

If the study of Luiten et al.,[5] using systemic and oral antibiotics is analyzed with the trials of Sainio et al.,[6] Pederzoli et al.,[4] Schwarz et al.,[8] and Delcenserie et al.,[7] there is a smaller but significant treatment effect in favor of antibiotics (Mantel-Haenszel odds

**Table II.** Raw data and odds ratios from randomized prospective trials

| | Control | | Antibiotics | | | | | |
|---|---|---|---|---|---|---|---|---|
| Reference | Survived | Mortality (%) | Survived | Mortality (%) | Log odds ratio | 95% Confidence | Interval | P value |
| Finch et al.[3] | 27 | 0 (0) | 31 | 1 (3) | .96 | 4.20 | −2.28 | .56 |
| Howes et al.[1] | 47 | 0 (0) | 48 | 0 (0) | −.02 | 3.92 | −3.96 | .99 |
| Craig et al.[2] | 23 | 0 (0) | 23 | 0 (0) | 0 | 3.96 | −3.96 | 1 |
| Delcenserie et al.[7] | 9 | 3 (25) | 10 | 1 (9) | −.95 | 1.16 | −3.05 | .38 |
| Pederzoli et al.[4] | 29 | 4 (12) | 38 | 3 (7) | −.52 | .96 | −1.99 | .49 |
| Sainio et al.[6] | 23 | 7 (23) | 29 | 1 (3) | −1.84 | 0 | −3.67 | .05 |
| Luiten et al.[5] | 52 | 18 (26) | 50 | 11 (18) | −.44 | .39 | −1.27 | .30 |
| Schwarz et al.[8] | 11 | 2 (15) | 13 | 0 (0) | −1.77 | 1.37 | −4.91 | .27 |
| All studies | 221 | 34 (13) | 242 | 17 (7) | −0.77 | −.14 | −1.40 | 0.016 |

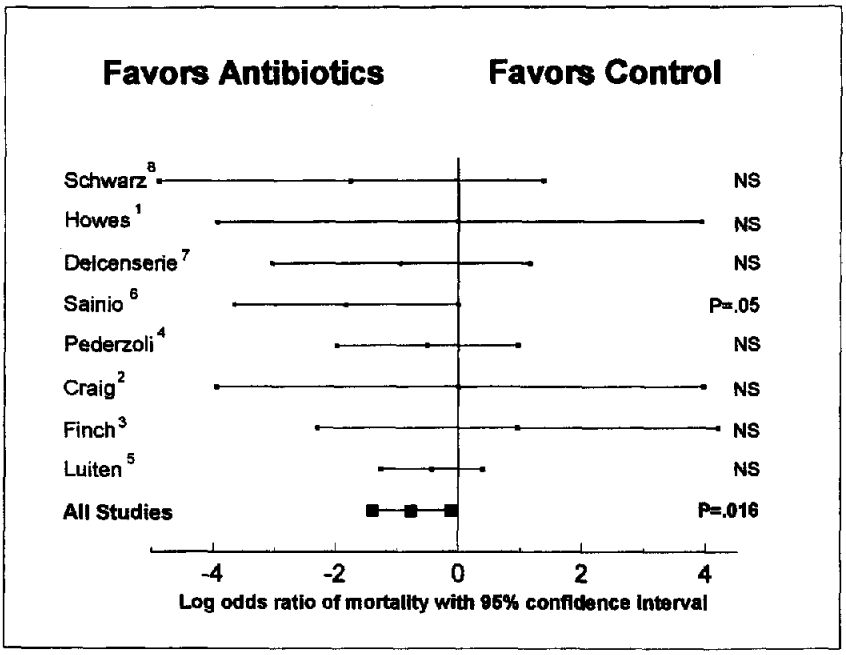


**Fig. 1.** Meta-analysis of all randomized prospective trials showing a positive benefit for prophylactic antibiotics in reducing mortality.

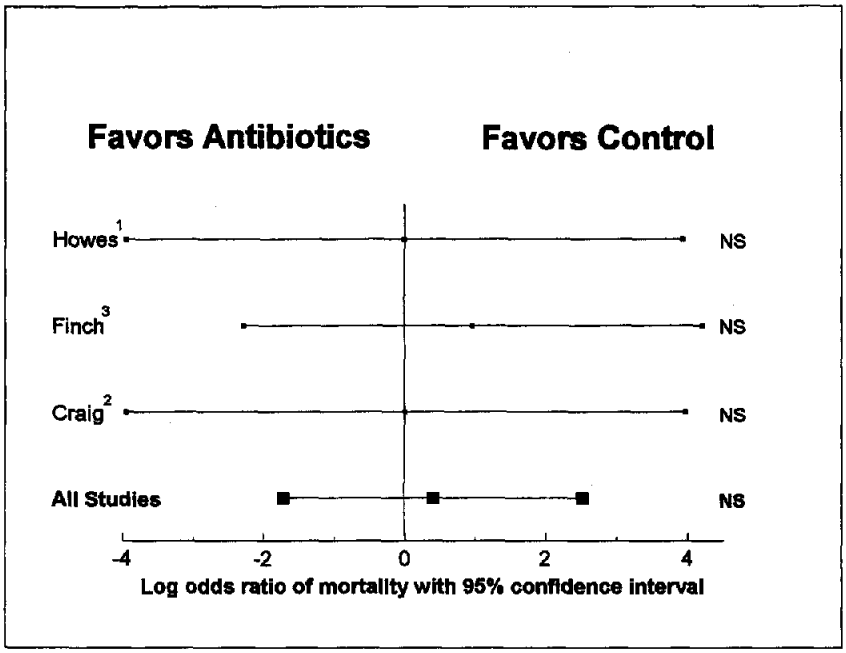


**Fig. 2.** Meta-analysis of three early trials that used ampicillin for prophylaxis. No overall benefit is shown.

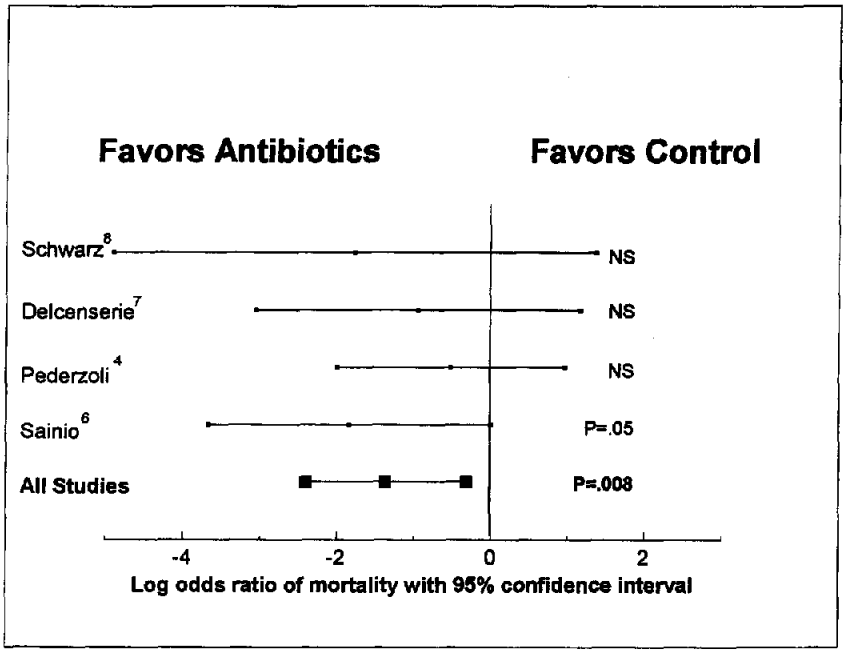


**Fig. 3.** Meta-analysis of four trials that used broad-spectrum antibiotics in patients with severe pancreatitis. There is an overall reduction in mortality with antibiotics.

ratio = −0.84 [−0.19 to −1.49], $P = 0.01$, and homogeneity $Q = 2.42$, $P = 0.66$).

## DISCUSSION

Most patients with acute pancreatitis have a relatively benign course, and they recover with standard conservative therapy.[14] However, approximately 5% to 13% of patients have severe disease with areas of pancreatic necrosis,[15,16] and up to 80% of these patients will die of the disease.[15] Because of advances in supportive care, most patients survive the initial metabolic complications of pancreatitis, but many go on to die of infectious complications in the ensuing weeks.[17-19] The mortality rate for patients with infected necrosis or pancreatic abscess is much higher than that for noninfected patients.[16,17,19] Although infection is more prevalent after the first week, Beger et al.[16] found a 23.8% infection rate in the first 7 days, and others have reported similar figures.[19,20] It is currently thought that enteric bacteria translocate from the bowel and infect necrotic pancreatic tissue.[5,21-25] In an attempt to prevent infection and reduce mortality, many clinicians use prophylactic antibiotics,[18,19] which have been shown to be beneficial in several animal[21,26,27] and retrospective studies.[19,28]

There have been eight randomized prospective trials that have examined the role of prophylactic antibiotics in acute pancreatitis.[1-8] Three trials using ampicillin were conducted in the 1970s, and all failed to show a beneficial therapeutic effect.[1-3] These studies have been justifiably criticized because the patients had mild pancreatitis, as evidenced by a zero mortality rate in the control group, and therefore they would be expected to do well with or without antibiotics. Furthermore ampicillin is a poor choice for use in prophylaxis because it has been demonstrated to have poor penetrance into pancreatic tissue, and its spectrum of activity is limited against the organisms most commonly found in infected necrosis.[18,29]

The studies by Delcenserie et al.,[7] Pederzoli et al.,[4] Schwarz et al.,[8] and Sainio et al.[6] were conducted in patients with severe pancreatitis who were treated with broad-spectrum antibiotics. Ceftazidime, ofloxacin, and imipenem have been shown to achieve therapeutic concentrations in pancreatic tissue, but there is less information about cefuroxime.[18,30,31] Pederzoli et al.,[4] found a significant decrease in nonpancreatic and pancreatic sepsis in patients treated with imipenem, and no pancreatic sepsis occurred in patients when the necrosis was less than 50% of the pancreatic volume. This is especially significant because 14 patients in the antibiotic group had severe necrosis as compared with only two patients in the control population. There was no difference in the incidence of multiorgan failure or in the need for surgery. There

was no difference in mortality, but because of the small sample size the study had insufficient power to detect a significant difference. Additionally, the dose of imipenem was modest by most standards, and better results might be expected with higher doses.[32] Delcenserie et al.[7] also showed a significant decrease in infectious complications in patients treated with multiple antibiotics, but the difference in mortality failed to achieve statistical significance, and there was no difference in the incidence of multiorgan failure.

In the study of Sainio et al.,[6] there was no difference in pancreatic infections in the group treated with cefuroxime as compared with the control group, but there was a significant decrease in the mean number of infections per patient and in mortality in the treatment group. Cefuroxime was chosen based on the hospital's sensitivity data, but little is known about its penetrance into pancreatic tissue. In fact, the antibiotics had to be changed in two thirds of the treatment group at a mean of 9.2 days after admission.

Schwarz et al.[8] found that antibiotics could not prevent sterile necrosis from becoming infected, but there were higher rates of sepsis in the control group, and the clinical condition, as measured by APACHE II scores, deteriorated significantly more in the control group. There was a trend toward lower mortality in the antibiotic group, but because of the small sample size this did not reach significance.

A case can be made for early antibiotic intervention because 77% of the control patients in Sainio's study[6] and 54% in Schwarz's trial[8] were ultimately treated with antibiotics. The early timing of antibiotic administration seems to have been the critical factor in outcome.[33] Recent experiments by Wang et al.[25] have demonstrated that acute pancreatitis results not only in bacterial translocation, but also in suppression of host bacterial defense systems. This might account for the high incidence of secondary infections seen in necrotizing pancreatitis and could explain the diminution of nonpancreatic infections[34] in the trials by Sainio et al.,[6] Pederzoli et al.,[4] and Delcenserie et al.,[7] and the improved clinical outcome in Schwarz's study.[8]

One can question the inclusion of the trial by Luiten et al.[5] in this meta-analysis, as the treatment modality was selective decontamination of the gastrointestinal tract. However, the patients also received systemic cefotaxime until gram-negative bacteria were eliminated from the oral cavity and rectum, and it is not stated for how long the patients received intravenous antibiotics. As discussed earlier, it appears that early administration of systemic antibiotics may be an important component in reducing morbidity and mortality. We therefore included this study in the analysis, but we also examined the data without this trial. There was a significant reduction in mortality whether the study was included or omitted.

Meta-analysis is a useful technique to summarize and clarify controversial topics. It is especially appropriate when the end point in question has a low incidence, and individual studies do not have the necessary number of patients or power to show a statistically significant benefit from a given treatment. Multicenter prospective randomized trials would be preferable, but their logistic complexities and cost make them difficult to carry out. One well-recognized problem with meta-analysis is publication bias, which is concerned with the effect of unpublished studies on the results. There is evidence that most unpublished papers report negative results, and their exclusion could bias the conclusions of a meta-analysis.[35] We believe that publication bias is not evident in this subject matter, because the majority of published reports on antibiotics in pancreatitis showed no treatment effect. It is reasonable to conclude that any prospective randomized trial on this controversial topic would be accepted for publication.

The results of the present meta-analysis suggest that the use of prophylactic antibiotics in acute pancreatitis significantly reduces mortality. The odds ratio was $-0.77$ ($-0.14$ to $-1.40$), $P = 0.016$. Sensitivity analysis revealed that the effect was only seen in patients with severe pancreatitis who were given broad-spectrum antibiotics. Patients in this subset had a Ranson score of 2.3 or greater,[36] or CT evidence of advanced pancreatitis as measured by a Balthazar grade of D or greater.[37] In this cohort 6.6% of the patients who received prophylactic antibiotics died, compared to 13.3% of the patients in the control group. If the study by Sainio et al.[6] is removed from consideration, the treatment effect is no longer significant. It is not apparent from this review if the diminution in mortality is secondary to an overall decrease in nonpancreatic infections, as was noted by Pederzoli et al.,[4] Sainio et al.,[6] and Schwarz et al.,[8] or by a decrease in pancreatic sepsis, as reported by Pederzoli et al.[4] and Luiten et al.[5]

It should be noted that although these studies were all prospective and randomized, none of them were blinded, and therefore the possibility of investigator bias must be considered. The results are further obfuscated by the fact that considerable numbers of patients in the control group ultimately received antibiotics in the studies by Sainio et al.,[6] Pederzoli et al.,[4] and Schwarz et al.[8] Nevertheless, we believe that the observed diminution in mortality cannot be discounted. At our hospital a 2-week course of imipenem and ofloxacin costs $798 and $364, respectively.

There was only one serious complication (anaphylaxis) from the routine use of antibiotics, and therefore the risk-benefit ratio would seem to favor the use of prophylactic antibiotics.

## CONCLUSION

Strong consideration should be given to treating patients with severe pancreatitis with broad-spectrum antibiotics such as imipenem or one of the fluoroquinolones, which have been shown to achieve therapeutic concentrations in pancreatic tissue.[29,31] We believe that this conclusion is supported by the current understanding of the pathophysiology of pancreatic infections in acute pancreatitis. What constitutes severe pancreatitis is not specifically defined, but based on the randomized trials, patients with an Imrie or Ranson score greater than or equal to three, or a Balthazar grade of D or greater, should be considered for prophylaxis.[38] There is no consensus regarding duration of treatment, but a 10- to 14-day course as was used in the most recent trials seems reasonable, although others have proposed longer regimens.[19,39,40]

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# Presentation and Management of Cystic Neoplasms of the Pancreas

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Pancreatic cystic neoplasms are uncommon, but it is important to differentiate them from pseudocysts and ductal adenocarcinoma. A retrospective review was performed to determine distinguishing characteristics and optimal treatment. In 51 patients operated on between 1981 and 1994 at a referral center, the following cystic neoplasms were found: 20 serous cystadenomas, 10 mucinous cystadenomas, 11 mucinous cystadenocarcinomas, five cases of mucinous ductal ectasia, and five papillary cystic neoplasms. Both mucinous ductal ectasia and papillary cystic neoplasms had distinguishing features when compared to other cystic neoplasms. Mucinous ductal ectasia was seen only in men, presented with typical symptoms, and had distinctive features on endoscopic retrograde cholangiopancreatography. Papillary cystic neoplasms occurred in young women (mean age 31 years) and were larger (mean 10.3 cm). Mucinous tumors were always symptomatic, whereas 55% of serous tumors were asymptomatic ($P < 0.001$). The overall rate of resectability was 80%, and there was one operative death (2%). Intraoperative biopsy was diagnostic in 18 (78%) of 23 cases. An actuarial 5-year survival of 52% was found for resected mucinous cystadenocarcinomas.

In conclusion, papillary cystic neoplasms and mucinous ductal ectasia have distinct characteristics that differentiate them from other types of pancreatic cystic tumors. Serous cystadenoma should be considered in asymptomatic patients and these patients should be closely observed. Symptomatic neoplasms should be resected with long-term survival expected for malignant forms. (J GASTROINTEST SURG 1998;2:504-508.)

KEY WORDS: Cystic neoplasms, pancreatic cysts, pancreatic resection

Cystic neoplasms of the pancreas are uncommon, comprising 10% to 13% of all the pancreatic cysts and 1% of pancreatic cancers.[1] Histologically they are epithelial-lined tumors with benign or malignant cytopathology. The nomenclature has recently been clarified and now includes serous and mucinous varieties.[2,3] Serous cystadenomas are truly benign, whereas mucinous cystadenomas, mucinous ductal ectasia, and papillary cystic neoplasms are considered premalignant. It is important that these pancreatic neoplasms be diagnosed, since their management and outcome differ from other cystic pancreatic diseases and the more common ductal adenocarcinomas. The clinical challenges involve distinguishing these neoplasms from pancreatic pseudocysts, and benign from malignant or premalignant varieties. We retrospectively reviewed our surgical experience with cystic neoplasms in an attempt to determine any differences in clinical characteristics between these pathologic groups.

## PATIENTS AND METHODS

Fifty-one patients with cystic neoplasms of the pancreas were operated on at The Cleveland Clinic Foundation between January 1981 and December 1994. The demographics, clinical presentation, diagnostic studies, surgical treatment, and outcome were analyzed retrospectively. Since the aim of the study was to define clinical differences between pathologic groups, the clinical presentation of each type of cystic neoplasm was compared to that of other cystic tumors. A comparison between the serous and mucinous varieties seemed the most clinically valuable. Mucinous tumors included the combination of mucinous cystadenomas

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and mucinous cystadenocarcinomas because mucinous cystadenomas are considered premalignant.[2]

When not available from the medical records, follow-up information was obtained by telephone contact with patients or relatives. The size and location of the tumors were determined from pathology specimens or radiologic reports when a resection was not performed. The pathologic findings were reviewed to reconcile the original diagnosis with the current nomenclature—specifically, to identify all patients with mucinous ductal ectasia. The following variables were analyzed: age, sex, tumor size, symptoms, preoperative diagnosis, appearance on CT scan, intraoperative biopsy results, and resectability. Fisher's exact test was used to analyze differences in the categorical variables, and the two-tailed *t*-test was used for the continuous variables. A $P$ value $<0.05$ adjusted to 0.017 (0.05/3) was considered significant. Survival rates were calculated using life-table analysis.[4]

## RESULTS

The following cystic neoplasms were found: 20 serous cystadenomas, 10 mucinous cystadenomas, 11 mucinous cystadenocarcinomas (a total of 21 mucinous cystic tumors), five cases of mucinous ductal ectasia, and five papillary cystic neoplasms. Considering the total group, the mean age was 53 years, 38 patients (75%) were female, 39 (79%) were symptomatic, and 18 lesions (35%) were primarily located in the pancreatic head.

Table I summarizes the characteristics of the serous and mucinous cystic neoplasms. Two significant differences were found between serous cystadenomas and the mucinous tumors: on average, patients with mucinous tumors were younger (mean age 51 years, range 26 to 77 years) than patients with serous cystadenomas (mean age 65 years, range 25 to 86 years) ($P$ <0.008), and the incidence of symptoms was 100% in mucinous tumors and 45% in serous tumors ($P$ <0.001). The most frequent complaint among patients with mucinous neoplasms was abdominal pain in 20 (95%). Five of 11 patients with mucinous cystadenocarcinoma presented with obstructive jaundice, significant weight loss (more than 10% over 6 months), and/or steatorrhea—symptoms that were not seen in those with serous cystadenomas, except for weight loss in one patient. Among the nine symptomatic patients with serous cystadenomas, eight complained of abdominal pain. The remaining 11 were incidentally discovered during laparotomy (n = 4) or on CT scans (n = 7).

All patients underwent surgical exploration. Intraoperative biopsies were performed in 23 patients and were diagnostic of cystic neoplasm in 18 (78%).

**Table I.** Characteristics of serous and mucinous (benign and malignant) cystic pancreatic neoplasms

| Variable | Serous (n = 20) | Mucinous (n = 21) |
|---|---|---|
| Age (mean ± SD, yr) | 64.9 ± 17 | 51.3 ± 14* |
| Size (mean ± SD, cm) | 6.3 ± 3.3 | 5.3 ± 2.5 |
| Female | 15 (75%) | 18 (86%) |
| Symptomatic | 9 (45%) | 21 (100%)† |
| Tumor location | | |
| Head | 11 (55%) | 6 (29%) |
| Body/tail | 8 (40%) | 15 (71%) |
| Diffuse | 1 (5%) | 0 (0%) |
| CT appearance | | |
| Uniloculated | 5 (28%) | 7 (41%) |
| Multiloculated | 11 (61%) | 6 (35%) |
| Solid | 2 (11%) | 4 (24%) |
| Preoperative diagnosis as cystic neoplasm | 14 (70%) | 10 (48%) |
| Biopsy | | |
| Diagnostic | 8 (89%) | 10 (71%) |
| Nondiagnostic | 1 (11%) | 4 (29%) |
| Resectability | 14 (70%) | 18 (86%) |

*$P$ <0.008.
†$P$ <0.001.

Fourteen (70%) of the 20 patients with serous cystadenomas underwent resection: four pylorus-preserving pancreatoduodenectomies (Whipple resection), eight distal pancreatectomies, and two enucleations. Five underwent a biopsy only, and one had a biopsy combined with gastrojejunostomy. Five of the six patients who were not resected were elderly and would have required a Whipple procedure; the other patient was a 25-year-old who had von Hippel-Lindau disease with diffuse pancreatic involvement. There was one operative death, and the remaining 19 patients (95%) are alive and well 7 months to 12 years after surgery. Nine (90%) of 10 patients with mucinous cystadenomas underwent resection: distal pancreatectomy in eight and enucleation in one. Four of these nine patients had undergone a cystojejunostomy at another institution 4 months to 3 years before their definitive surgery. All nine of these patients recovered without complications and are well 8 months to 7 years postoperatively. The remaining patient had a cystojejunostomy based on the fact that a frozen-section biopsy was interpreted as a pseudocyst. This patient was not reoperated because she refused to undergo a Whipple resection; she is asymptomatic 5 years after the operation. Nine (82%) of 11 patients with mucinous cystadenocarcinomas were resected. Two patients were deemed unresectable because of invasion of vascular structures and the presence of liver metastases; they died 5 and 13 months, respectively, after diagnosis. The patient with liver metastases had

undergone a cystojejunostomy 7 months earlier when there was no evidence of metastatic disease. Among the remaining nine patients who were resected, five had Whipple procedures and six had distal pancreatectomies performed (one patient underwent three separate pancreatic resections for recurrences and died 9 years after the first operation). One patient who is alive 7 years after an en bloc distal pancreatectomy, gastrectomy, and colectomy underwent a cystojejunostomy 3 years before the definitive operation. The overall actuarial survival rates at 1, 2, and 5 years were 79%, 40%, and 40%. The actuarial survival rates for resected patients at 1, 2, and 5 years were 87%, 52%, and 52%, respectively. The median survival for unresected patients was 9 months. A total of five patients with mucinous tumors underwent resection following a prior cyst-enteric anastomosis at another institution.

The clinical characteristics of patients with mucinous ductal ectasia are summarized in Table II. All patients with mucinous ductal ectasia were male, a feature that was unique to this particular cystic neoplasm, and they presented with a history of recurrent pancreatitis and/or steatorrhea. CT scans were obtained in three patients; in one patient only pancreatic duct dilatation was found, and cystic neoplasms were detected in the remaining two. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all of these patients and revealed a patulous papilla exuding mucin, a diffusely or localized dilated pancreatic duct communicating with cysts, and filling defects secondary to mucin plugs. This was the only group in which a correct preoperative diagnosis was made in all patients. One patient underwent only a sphincteroplasty because he refused a total pancreatectomy. The other four underwent successful resections: two total pancreatectomies, one distal pancreatectomy, and one Whipple procedure. One patient died 2 years after surgery of unrelated causes; the other four are alive and well at 1 to 3 years, including the patient who was not resected.

The clinical characteristics of the five patients with papillary cystic neoplasms are summarized in Table II. Papillary cystic neoplasms were large (mean size 10.3 cm), they were seen only in women, and the mean age of these women was 31 years. All the patients were treated with distal pancreatectomy and are alive with no recurrence of disease at 1 to 11 years, including one patient who underwent hepatic wedge resection for an isolated metastasis (alive for 10 years). One patient underwent definitive resection for persistent symptoms 9 months after a partial excision at another institution.

ERCP was performed in the five patients with mucinous ductal ectasia and in another eight patients (three with serous cystadenomas, three with mucinous cystadenomas, and two with mucinous cystadenocarcinomas). Of these latter patients, obstruction of the pancreatic duct was seen in three patients; two had normal but extrinsically displaced ducts, one with cyst-duct communication and cytologic findings suggestive of mucinous neoplasm, and the three with serous cystadenomas were normal.

**Table II.** Characteristics of mucinous ductal ectasia (MDE) and papillary cystic neoplasm (PCN)

| Variable | MDE (n = 5) | PCN (n = 5) |
|---|---|---|
| Age (mean ± SD, yr) | 64 ± 6 | 31 ± 5 |
| Female | 0 | 5 (100%) |
| Symptomatic | 5 (100%) | 4 (80%) |
| Tumor location | | |
| Head | 1 (20%) | 0 |
| Body/tail | 1 (20%) | 5 (100%) |
| Diffuse | 3 (60%) | 0 |
| Correct preoperative diagnosis | 5 (100%) | 3 (60%) |
| Resectability | 4 (80%) | 5 (100%) |

## DISCUSSION

Cystic pancreatic neoplasms are an infrequent but important entity; they need to be recognized and treated differently from the more common neoplasms and cystic diseases of the pancreas. Despite the increased awareness of these neoplasms, they can be misdiagnosed and inappropriately treated as pseudocysts. Fourteen percent of our patients, and up to 37% in other series,[1] were referred when the cystic lesion persisted or the patient had continuing symptoms. The diagnosis of a pancreatic pseudocyst is made primarily on the basis of a patient's history of an antecedent episode of pancreatitis with a recognized etiology. Findings on CT scans,[5,6] ERCP,[7,8] and intraoperative biopsy[1] are not always diagnostic and do not supplant an accurate clinical history. Pancreatic cysts should be treated as cystic neoplasms in the absence of an etiology for pancreatitis. Patients with a previous cyst-enteric anastomosis should undergo reexploration for resection if the final pathology specimen reveals an epithelial-lined cyst or the patient has persistent pain or a mass. Definitive resection should be performed promptly, as one of our patients had developed liver metastases at reexploration 7 months following enteric drainage of a mucinous neoplasm.

Once a presumptive diagnosis of a cystic neoplasm is made, it would be valuable to determine the pathologic type without resection. The natural history of each type is distinct and ranges from a predictably be-

nign course for serous cystadenoma to poor survival with aggressive types of mucinous cystadenocarcinoma, and a favorable long-term outcome with the intermediate forms of mucinous cystadenoma and papillary cystic neoplasm.[2,3,9] The inability to distinguish among the various types of cystic neoplasm could lead to a recommendation to resect all suspicious lesions.[10] This may be imprudent when more incidental lesions are now being diagnosed.[11] Eighty percent of the patients in our series had serous or mucinous tumors. Their differing clinical outcomes make it important to try and distinguish them. In this series only two variables were found to be significant in differentiating between serous and mucinous neoplasms. Mucinous neoplasms, which should be considered for resection, were found in younger patients (mean age 51 years vs. mean age 65 years), and all were symptomatic. Serous lesions were asymptomatic in 55% of patients. Symptoms included weight loss, jaundice, diarrhea, and/or abdominal pain. Despite being statistically different, the range within the clinical variables is wide, making the precise diagnosis in an individual patient difficult. It does appear reasonable to observe some patients with asymptomatic or incidental cystic lesions, presuming these represent a benign serous neoplasm. Other investigators have suggested additional endoscopic and radiologic findings that may aid in distinguishing these two entities. These include CT findings of calcifications, a "honeycomb" appearance, and multiple septations in patients with serous cystadenomas.[5,6] ERCP findings in patients with malignant and premalignant lesions include changes in the main pancreatic duct such as displacement and stenoses or obstruction with or without communication between the cyst and the duct.[7,8] Although cyst aspiration was used infrequently in our experience, others have shown that biochemical features, tumor markers, and cytologic analysis may aid in differentiating between serous and mucinous lesions.[12-15]

Mucinous neoplasms were considered as a group since resection is advised for all these lesions to eliminate the malignant potential of mucinous cystadenoma and achieve long-term survival in patients with mucinous cystadenocarcinoma. The survival advantage conferred by resection of invasive mucinous cystadenocarcinoma as compared to ductal adenocarcinoma represents one of the advantages of making a correct preoperative diagnosis of a cystic neoplasm. Our actuarial survival of 52% for resected mucinous adenocarcinoma compares favorably with the recent survival rate of 8% to 21% reported for ductal adenocarcinoma.[16-19] Similar favorable 5-year survival rates ranging from 68% to 76% have been reported by other centers for cystic carcinomas.[1,20] These results support an aggressive approach toward resection even for large lesions with local lymph node involvement. The outcome for patients with unresectable lesions is expectedly dismal; the median survival for our two unresected patients was 9 months.

Papillary cystic neoplasms and mucinous ductal ectasia are uncommon entities that presented with characteristic findings which can aid in correctly identifying these neoplasms preoperatively. In our experience papillary cystic neoplasms were seen in younger women and were larger. These results concur with those from a recently collected series of 292 patients.[9] Despite the relatively large size of these lesions, all of our patients were resected with long-term survival of up to 11 years. These neoplasms demonstrate a variable malignant potential based on histologic criteria[9,21,22] and the presence of local invasion of surrounding structures, nodal and distant metastases.[9] The presence of advanced disease again does not preclude resection, including concomitant liver resection, since long-term survival can be achieved. One of our patients underwent resection of a liver metastasis and is without recurrent disease 10 years later, and a similar experience has been reported by others.[9] The roles of chemotherapy, radiation therapy, hormonal manipulation, and chemoembolization are uncertain despite anecdotal reports.[21-25]

Mucinous ductal ectasia is a similarly uncommon neoplasm that has recently been recognized.[26] The presentation of our small cadre of patients is typical of other series in that this neoplasm occurs predominantly in males with recurrent pancreatitis and/or steatorrhea. The ERCP findings of a patulous papilla draining mucin with diffuse cystic dilatation of the main pancreatic duct without strictures are characteristic.[27,28] The natural history of patients with mucinous ductal ectasia is variable and it may follow a benign or malignant course. Cytologic evaluation of pancreatic duct secretions and endoscopic biopsy of the ductal mucosa may be beneficial in distinguishing benign from malignant lesions.[29,30] The appropriate treatment for all patients with mucinous ductal ectasia is unknown, but resection of the involved pancreatic segments, including total pancreatectomy, is advised. The extent of resection, including total pancreatectomy when indicated by tumor extent, is tailored based on ERCP findings and frozen-section analysis of the resected ductal margin, which may show malignant or premalignant ductal changes.

## CONCLUSION

Cystic pancreatic neoplasms are uncommon; only 51 patients were operated over a 14-year period at a referral center. These tumors are usually distin-

guished from pancreatic pseudocysts by clinical history, and in 12% of our patients these neoplasms were initially erroneously treated as pseudocysts. Benign serous neoplasms are difficult to distinguish from other cystic neoplasms, but in general they tend to be asymptomatic and occur in older patients. Papillary cystic neoplasms are larger and are seen in younger women. Mucinous ductal ectasia typically is found in men with characteristic ERCP findings. Resection of premalignant and malignant lesions can be performed safely and is associated with long-term survival.

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# Is There a Place for Central Pancreatectomy in Pancreatic Surgery?

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Tumors located in the neck of the pancreas that are not small and superficial enough to be enucleated are usually resected with a pancreaticoduodenectomy or left splenopancreatectomy. Such operations may cause digestive disorders, glucose intolerance, and late postsplenectomy infection. Central pancreatectomy is a segmental resection whereby the cephalic stump is sutured and the distal stump anastomosed with a Roux-en-Y jejunal loop. The purpose of this study was to evaluate whether central pancreatectomy has a place in pancreatic surgery. Thirteen patients with the following tumors underwent central pancreatectomy: five endocrine tumors, one mucinous and six serous cystadenomas, and one solid cystic-papillary tumor. Mean operative time was 250 minutes. Operative mortality was zero. Complications occurred in three patients (23%). At mean follow-up of 68 months, no recurrences were found. Postoperative oral glucose tolerance, pancreolauryl, and fecal fat excretion tests were normal in all patients. We believe that central pancreatectomy does have a place in pancreatic surgery; it is a reliable technique for benign or low-grade malignant tumors and has a surgical risk similar to that of standard operations. Its principal advantage is that it preserves pancreatic parenchyma and the anatomy of the upper gastrointestinal and biliary tract and the spleen better than pancreaticoduodenectomy or distal pancreatic and splenic resection. (J GASTROINTEST SURG 1998;2:509-517.)

KEY WORDS: Pancreatic resection, segmental resection, pancreatectomy, benign pancreatic tumors

Resection of benign tumors located in the neck or in the proximal portion of the body and the head of the pancreas creates technical problems when the tumor measures up to 2 cm or more in diameter or when it is encased within the pancreatic parenchyma. As a result, enucleation, which might be the most obvious solution, may ultimately cause damage to Wirsung's duct through transection of the parenchyma. On the other hand, standard pancreatectomies (pancreaticoduodenectomy and distal pancreatectomy) may result in impaired endocrine and exocrine function.

A segmental resection (central pancreatectomy) may therefore lower the risk of functional impairment of the pancreatic parenchyma, biliary tract, upper gastrointestinal tract, and spleen in cases of benign and low-grade malignant tumors.

The technique was first described by one of us (G.S.) in 1984 after it had been used in 1982 to treat an insulinoma of the neck of the pancreas.[1] After a central segmental resection of the pancreas is performed (Fig. 1, *A*), a Roux-en-Y jejunal loop is constructed and anastomosed to the distal part of the gland (Fig. 1, *B*), as described by Letton and Wilson[2] in 1959 for two cases of traumatic transection of the pancreatic isthmus. Subsequently Beger et al.[3] in 1985, Fagniez et al.[4] in 1988, Ikeda et al.[5] in 1990, Rotman et al.[6] in 1993, Asanuma et al.[7] in 1993, and Takada et al.[8] in 1993 reported cases of partial resection of the pancreas for chronic pancreatitis[3,8] or tumors[4-8] with jejunal anastomosis of both the proximal and distal stumps[3] or of only the distal stump,[4-7] or with pancreaticoduodenal anastomosis.[8]

The purpose of our study was to assess whether central pancreatectomy has a place in pancreatic surgery.

## PATIENTS AND METHODS

During the period from January 1982 and December 1996, 13 patients (11 males and 2 females; mean

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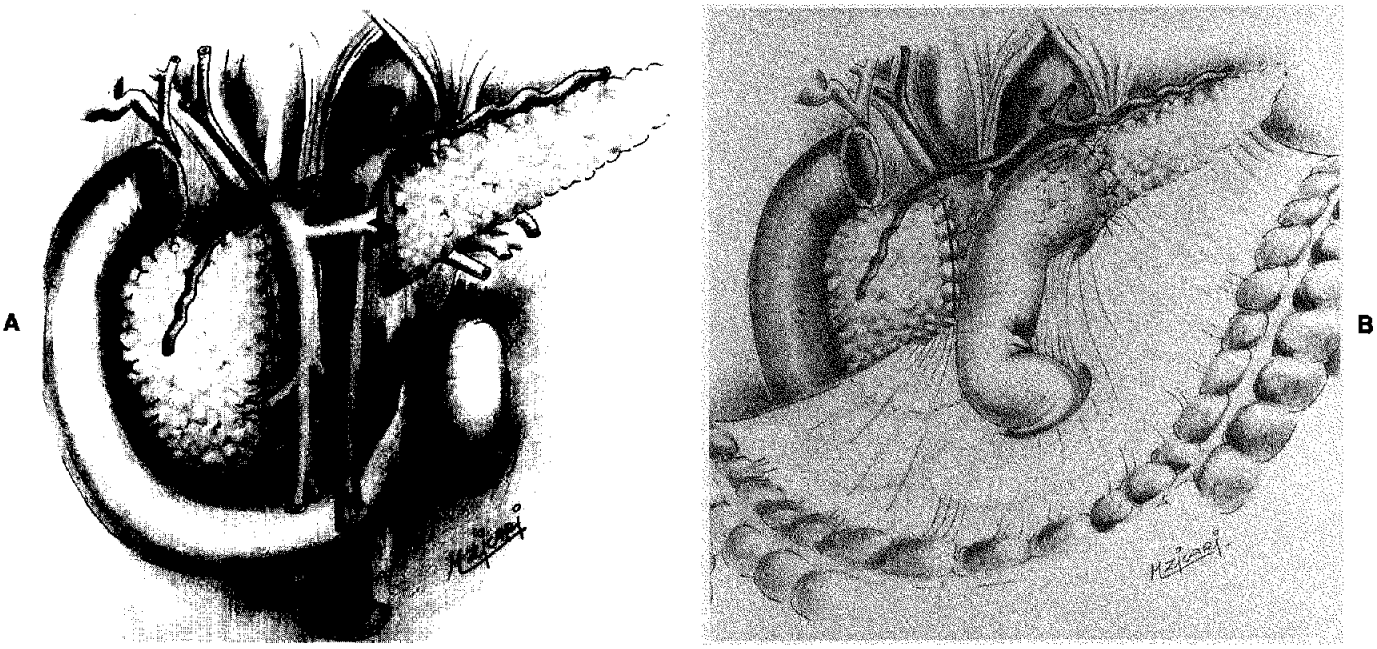

**Fig. 1. A,** Drawing of central pancreatectomy technique. **B,** Management of the pancreatic head and body stumps.

age 51 years [range 27 to 70 years]) underwent central pancreatectomy (Table I). All were symptomatic. Three patients with insulinomas complained of Whipple's triad.* The tumors were detected by means of abdominal ultrasound and CT scans in two cases and angiography in one. Ten patients complained of abdominal pain, dyspepsia, and weight loss. All of them underwent abdominal CT and ultrasound imaging; abdominal MRI and endoscopic retrograde cholangiopancreatography (ERCP) were performed in four patients and one patient, respectively. Imaging techniques identified the lesion in all patients, but a correct preoperative diagnosis was achieved in only seven cases (5 serous cystadenomas, 1 mucinous cystadenoma, and 1 nonfunctioning cystic tumor). The preoperative imaging studies were misleading in three cases. In two of these, fine-needle aspiration biopsy under ultrasound control, performed preoperatively in one case and intraoperatively in the other, revealed a nonfunctioning cystic tumor[9] and a solid cystic-papillary tumor, respectively. The latter was diagnosed preoperatively as a nonfunctioning endocrine tumor, and the definitive diagnosis of serous cystadenoma was made only after histologic assessment of the surgical specimen of the central pancreatectomy.

* Neurologic/psychiatric disturbances during fasting or during exercise, disappearing after ingestion or injection of sugar with fasting blood glucose levels below 50 mg/dl (275 mmol/L) on several occasions.

Three patients underwent intraoperative ultrasound imaging. Frozen-section analysis of the tumor and surgical margins was performed in all cases.

Specimens were fixed and sections stained with hematoxylin and eosin. Testing for immunohistochemical detection of generic and specific markers was performed for the endocrine tumors. Proliferating cell nuclear antigen (PCNA), Ki-67 antigen, and progesterone receptors were also evaluated as prognostic predictors; in fact, we showed that endocrine tumors of the pancreas with low levels of proliferative indexes (PCNA and Ki-67 antigen) and high level of progesterone receptors are correlated with a good prognosis.[10,11]

Follow-up examinations were based on evaluation of laboratory data and abdominal ultrasound and Doppler ultrasound scans. Endocrine function was tested in 12 patients by means of the oral glucose tolerance test (OGTT) from 6 months to 7 years after the operation and values were compared with those from 40 normal control subjects. Seven patients also underwent preoperative glucose tolerance evaluation.

The areas under the glucose curves were calculated by a standard trapezoidal method. The results are presented as mean and 95% confidence interval (CI). Differences between groups were analyzed by means of two-tailed Student's $t$ test. $P$ value $<0.05$ was considered significant.

Exocrine function was evaluated by means of pancreolauryl (normal value T/K >20%) and fecal fat ex-

**Table I.** Clinicopathologic data and follow-up of 13 patients undergoing central pancreatectomy

| Patient | Age/Sex | Tumor | Size (mm) | Complication | Treatment of complications | Length of follow-up (mo)* |
|---|---|---|---|---|---|---|
| 1 | 41/M | Insulinoma | 20 | | | 162 |
| 2 | 70/F | Insulinoma | 25 | | | 111 |
| 3 | 67/F | Serous cystadenoma | 30 | Low-output pancreatic fistula | TPN + maintenance of intraoperatively placed drains | 100 |
| 4 | 64/F | Serous cystadenoma | 30 | | | 90 |
| 5 | 42/M | Insulinoma | 12 | | | 79 |
| 6 | 45/F | Mucinous cystadenoma | 35 | Purulent drainage | Maintenance of intraoperatively placed drain and transdrain lavage | 82 |
| 7 | 62/F | Serous cystadenoma | 25 | | | 68 |
| 8 | 62/F | Serous cystadenoma | 20 | Low-output pancreatic fistula and pulmonary complications | TPN + somatostatin or analogues + maintenance of intraoperatively placed drain | 67 |
| 9 | 31/F | Nonfunctioning endocrine tumor | 30 | | | 59 |
| 10 | 27/F | Solid cystic-papillary tumor | 30 | | | 24 |
| 11 | 33/F | Nonfunctioning endocrine tumor | 40 | | | 23 |
| 12 | 56/F | Serous cystadenoma | 50 | | | 12 |
| 13 | 66/F | Serous cystadenoma | 25 | | | 5 |

TPN = total parenteral nutrition.
*All patients alive without evidence of disease.

cretion (normal value <7 gm/24 hr) tests in 12 patients from 6 months to 7 years after the operation. None of the patients received pancreatic enzyme replacement.

## Surgical Technique

A midline incision is used. The lesser sac is entered and the anterior aspect of the pancreas is exposed. The posterior peritoneum along the inferior and superior margin of the pancreatic segment to be resected is incised. The splenic artery is dissected free, and the dorsal pancreatic artery and some other minor collaterals may be ligated. The posterior surface of the pancreas affected by the lesion is isolated from the portomesenteric axis and from the splenic vein with division of the collaterals. The segment of parenchyma harboring the tumor is transected along the margins of the head and the body. The cephalic stump is sutured with interrupted stitches after elective ligation of Wirsung's duct (10 cases) or by means of a stapler (3 cases), whereas the body-tail stump is anastomosed end to end (12 cases) or end to side (1 case) with a Roux-en-Y jejunal loop without a stent. Two closed-system suction drains are used to drain the cephalic stump of the pancreas and the pancreaticojejunostomy.

## RESULTS

Mean operating time was 250 minutes (range 210 to 300 minutes). Five patients (38.4%) required intraoperative blood transfusion (2 to 3 units). Postoperative mortality was zero. The postoperative course was complicated in three patients (23%): two had low-output pancreatic fistulas and one had purulent drainage due to an infection of the peritoneal drain site. One patient also had pneumonia and pleural effusion (Table I). Mean length of postoperative hospital stay was 19 days (range 10 to 38 days).

The mean diameter of the resected lesions was 28.9 mm (range 12 to 50 mm) (see Table I). Five patients

had endocrine tumors (three insulinomas and two nonfunctioning endocrine tumors), whereas six had serous cystadenomas, one had a mucinous cystadenoma, and one had a solid cystic-papillary tumor (see Table I).

Histologic examination showed the resection margins to be free of disease. None of the sections demonstrated cytohistologic features of malignancy. All of the endocrine tumors had PCNA and Ki-67 antigen values below 5% and a positive progesterone receptor assay indicating a benign evolution of the tumor.[10,11]

All of the patients were doing well at a mean follow-up of 68 months (range 5 to 162 months) with no evidence of disease (none of the three patients with insulinoma complained of endocrine syndromes (see Table I). Abdominal ultrasound revealed no alterations of the remaining pancreatic parenchyma and spleen. The portomesenteric axis, splenic artery, and vein appeared normal on Doppler ultrasound scans.

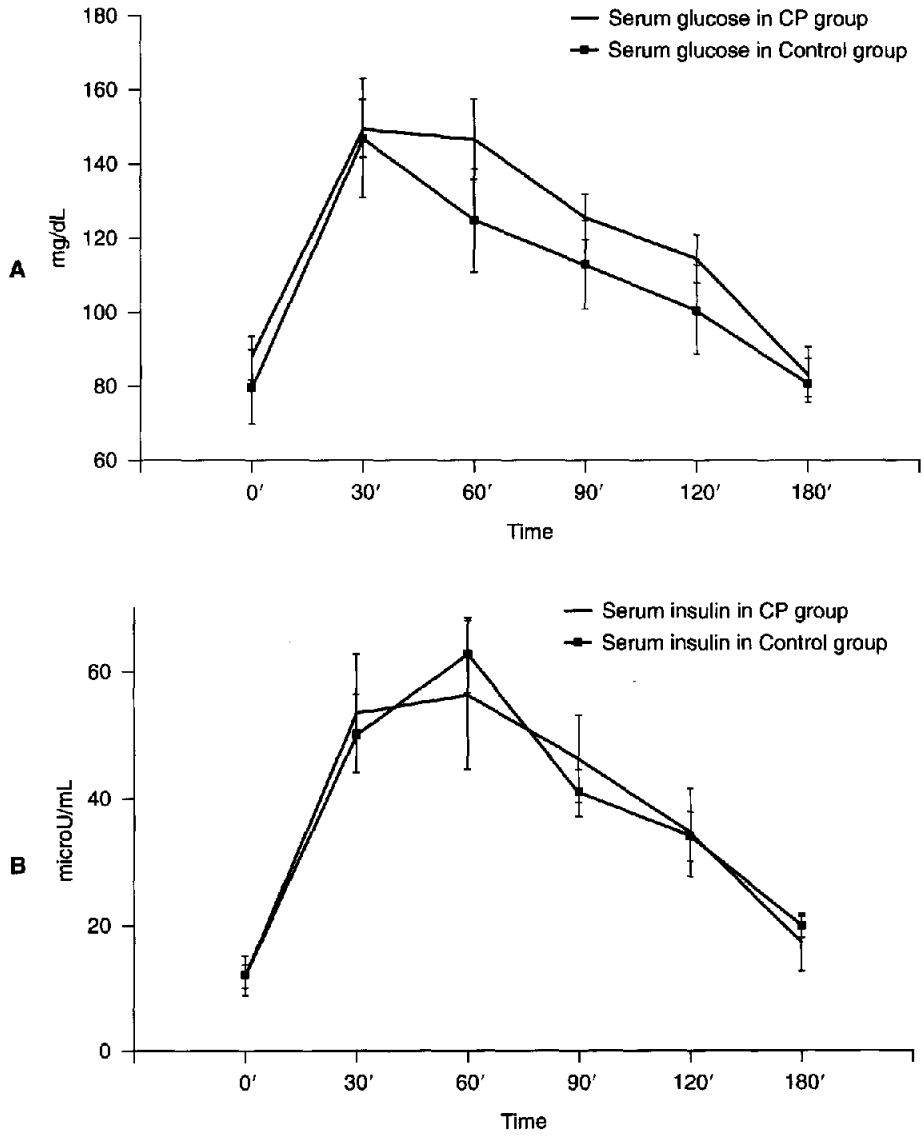


**Fig. 2.** Mean and 95% confidence interval for serum glucose **(A)** and serum insulin **(B)** levels during oral glucose tolerance tests in patients undergoing central pancreatectomy (CP) and in 40 normal control subjects.

OGTT findings were within the normal range in all but one of the patients examined; this patient who presented with preoperative glucose intolerance did not show OGTT deterioration after the operation. A comparison between patients undergoing central pancreatectomy and a control group, in terms of glucose tolerance and insulinemia, showed no significant difference. The means for the area under the glucose curve during OGTT in the central pancreatectomy group vs. the control group were 120.5 mg/dl/min (95% CI: 127.9 to 86.4) and 109.7 mg/dl/min (95% CI: 121.5 to 97.9), respectively, and the difference was not significant (Fig. 2).

In the six patients who underwent OGTT pre- and postoperatively, there was no significant difference before and after central pancreatectomy (Fig. 3). The postoperative pancreolauryl test and fecal fat assay showed normal exocrine function in those patients tested who were not on pancreatic enzyme replacement (Fig. 4).

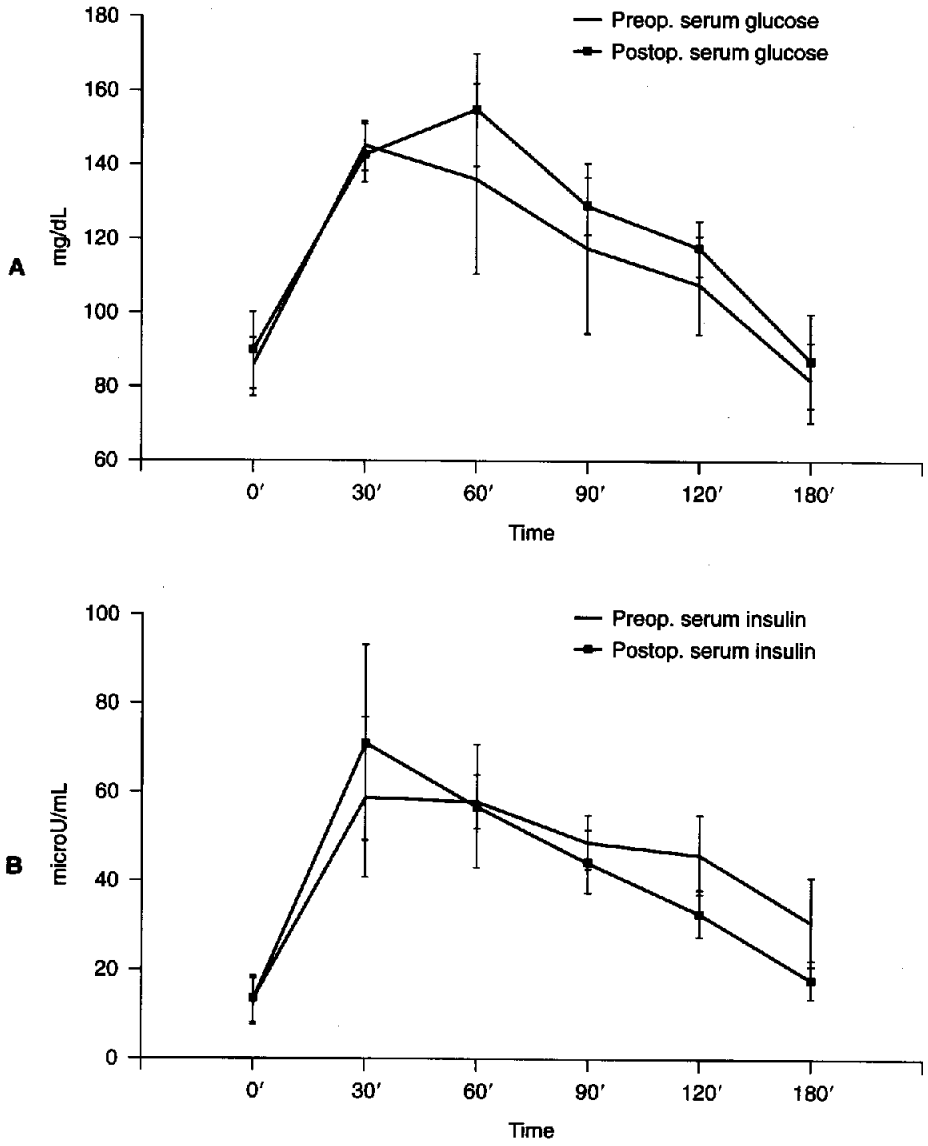


**Fig. 3.** Mean and 95% confidence interval for serum glucose **(A)** and serum insulin **(B)** levels during oral glucose tolerance tests in six patients before and after central pancreatectomy.

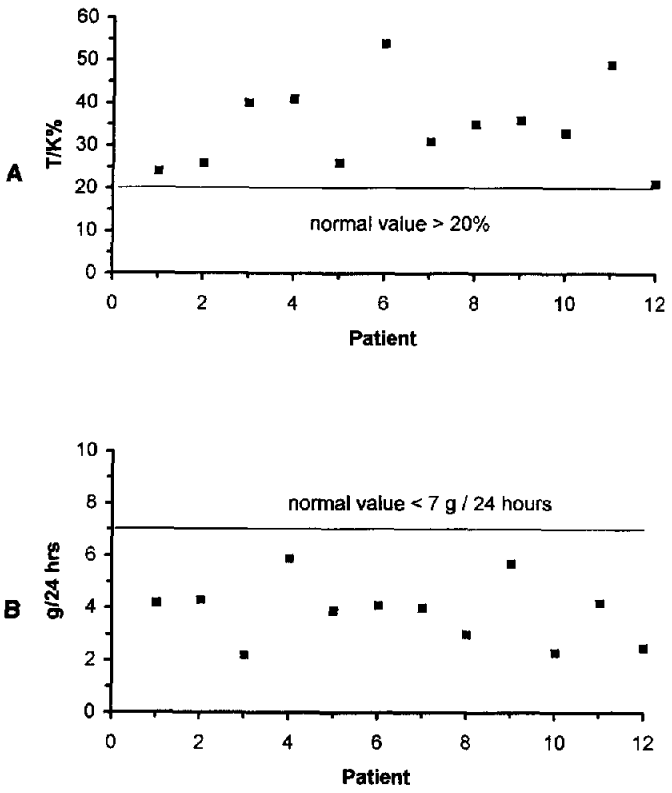


**Fig. 4.** Pancreolauryl **(A)** and fecal fat excretion **(B)** test values after central pancreatectomy in 12 patients.

## DISCUSSION

Tumors located in the neck or in the contiguous portion of the head or body of the pancreas that are not small and superficial enough to be enucleated are usually resected with a pancreaticoduodenectomy or left splenopancreatectomy, even when they are benign. Such wide resections have a low operative mortality rate when performed by experienced surgeons,[12,20] yet this type of surgery may cause digestive disorders (e.g., delayed gastric emptying, dumping syndrome, exocrine deficiency), glucose intolerance, and late postsplenectomy infection.[21-27] Central pancreatectomy, by contrast, permits sparing of pancreatic parenchyma and the anatomy of the upper gastrointestinal tract, biliary tract, and spleen.[1]

The literature reports 42 cases of central pancreatectomy[4-7,28,29]; 14 have been described by Rotman et al.,[6] two of which had previously been reported by Fagniez et al.,[4] two by Asanuma et al.,[7] two by Takada et al.,[28] and 24 by Ikeda et al.[29]

Specific indications for the use of this technique include the following: (1) small lesions (<5 cm in diameter); (2) benign (serous and mucinous cystadenoma, insulinoma) or low-grade malignant tumors (insulinoma, mucinous tumor, nonfunctioning islet cell tumor, solid cystic-papillary tumor); (3) lesions in the neck of the pancreas or in its contiguous portion; and (4) a distal pancreatic stump that is at least 5 cm in length.

An accurate preoperative diagnosis is indispensable for the application of these criteria. An intraoperative ultrasound scan is helpful to determine the location and extent of the tumor and to rule out metastases or multiple lesions. Frozen-section examination is essential to confirm that the lesion is benign and to verify the existence of a free resection margin. In cases of malignancy, distal splenopancreatectomy or a pancreaticoduodenectomy is carried out, as in the case reported by Rotman et al.[6] for cystadenocarcinoma.

The main step is the mobilization of the pancreatic segment harboring the tumor. Freeing the posterior surface of the pancreas from the splenic vessels is much more difficult than freeing it from the portal-mesenteric axis. The splenic artery is cleared and a number of collaterals and the dorsal pancreatic artery are ligated. This may prove difficult if the tumor involves the splenic artery or if this artery is within the pancreatic parenchyma.[30,31]

The splenic vein is cleared and very gently separated from the posterior surface, tying all the numerous fragile collaterals[32] and taking care to avoid damaging the vessels that could cause splenic infarction, as reported by Rotman et al.,[6] or require splenopancreatectomy.

The extent of the resection depends on the size of the tumor. The cephalic pancreatic stump is stapled or sutured with a row of interrupted nonabsorbable sutures after Wirsung's duct is ligated.

A Roux-en-Y jejunal loop is anastomosed end to end, which is our preference, or end to side, to the body of the pancreas in a retrocolic fashion. Unlike other authors, we do not place a stent in the pancreatic duct.[7,29]

A central pancreatectomy is not performed when the body-tail of the pancreas receives its arterial blood supply exclusively from the transverse pancreatic artery (left branch of the dorsal pancreatic artery); this variation, which can be clearly seen on angiography, is defined by Mellière and Moullé[33] as type III and was present in 25% of their cases. Division of these vessels can cause necrosis of the body-tail of the pancreas[34]; to avoid this complication a left pancreatectomy (with splenic preservation if possible) instead of a central pancreatectomy is indicated. Angiography, however, is not essential, since this anatomic variation is suspected whenever the absence of collaterals from the splenic artery or a large dorsal pancreatic artery is detected during the operation.

The operative mortality was zero both in our study and in the cases reported in the literature.[4-7,28,29] One major complication is pancreatic fistula, as is true of other surgical pancreatic procedures [12,35,36]: 2 of 14 cases in the study by Rotman et al.,[6] both of which required reoperation because of peritoneal fluid collection, 1 of 24 cases in the study by Ikeda et al.,[29] and 2 of 12 cases in our own experience, both treated conservatively (see Table I). Additional complications reported in the literature are one case of biliary tract stenosis and one cephalic pseudocyst.[29]

We believe that central pancreatectomy is a meticulous procedure with very precise applications, but one that yields good results in terms of lower mortality and morbidity compared to major resection techniques.

Endocrine function was evaluated by means of the OGTT. The operation induced no change in glucose tolerance in any of our patients, as it did in the cases reported by Rotman et al.[6] and Ikeda et al.[29] Asanuma et al.[7] reported one case of borderline glucose tolerance after surgery, but values returned to within normal range 36 months later.

In contrast, pancreaticoduodenectomy and left splenopancreatectomy affect endocrine function in a substantial percentage of cases.[37-45] These data, however, may have been affected by the pathology for which the operation was performed (tumor, chronic pancreatitis). A recent study by Kendall et al.[46] has shown that in healthy donors of pancreatic grafts, hemipancreatectomy resulted in a deterioration of insulin secretion and glucose tolerance 1 year after the operation.

Alteration of exocrine function depends on the type of resection performed (pancreaticoduodenectomy or distal splenopancreatectomy) and the amount of pancreatic tissue removed.[37,39,44] Central pancreatectomy, however, did not cause impairment of exocrine function in our series or in those of other authors,[7,8] except in one case reported by Rotman et al.[6] and two cases of chronic pancreatitis reported by Ikeda et al.[29]

## CONCLUSION

We believe that central pancreatectomy does have a place in pancreatic surgery; it is a reliable technique for treating benign or low-grade malignant tumors of the neck of the pancreas and its contiguous portions. It constitutes a valid alternative to major pancreatic resections. Central pancreatectomy can be used as a curative technique when properly applied with a surgical risk similar to that of standard procedures. The main advantage is it allows the surgeon to preserve more of the pancreatic parenchyma along with the anatomy of the upper gastrointestinal tract, biliary tract, and spleen.

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## *Discussion*

***Dr. T. Gadacz*** (Augusta, Ga.). In managing these patients, did you use octreotide to control any of the complications from the two ends of the pancreas?

***Dr. C. Iacono.*** At our institution we do not use somatostatin prophylaxis. We use it with total parenteral nutrition only if a pancreatic fistula develops.

***Dr. A. Warshaw*** (Boston, Mass.). We have had experience with 10 of these operations with almost identical indications for the endocrine tumors and the cystic tumors. We tend to stent our anastomoses. We have had one fistula, which was from the head of the gland that healed spontaneously. Be advised that it might not be possible in all cases to determine whether the tumor is malignant at the time of the operation. One of our neuroendocrine tumors was an insulinoma that we thought was benign. There was evidence of vascular invasion on the final pathology report.

Subsequently that patient has not had a local recurrence but has developed liver metastases. So the operation, per se, appears to have been adequate.

***Dr. B. Langer*** (Toronto, Ontario, Canada). It may be a good operation but I have concern about the real indications. From one of your CT scan slides, it appeared to me that there was a very small amount of tail that was going to be preserved. I am not convinced that the benefit of using this procedure rather than a distal pancreatectomy is worth the potential risk. In a couple of small series that we just heard about today, there were no deaths reported, but we know that the major problem in patients undergoing a pancreatic head resection is pancreatic fistula, pancreatitis, and death. There are some data suggesting that glucose tolerance becomes abnormal; however, we have not yet quantitated what that means to the patient in terms of the long-term risk of having a total left-sided pancreatectomy rather than a partial left-sided pancreatectomy.

**Dr. Iacono.** The CT scan slide that I presented shows only the lesion and not all the volume of the pancreatic body-tail, which has to be evaluated on the series of subsequent scans. On the other hand, the amount of pancreatic parenchyma that is left is assessed intraoperatively, and the portion of body-tail must be at least 5 cm.

I think that this operation has two goals: (1) to save the pancreatic parenchyma and (2) preserve the spleen. The results in the literature regarding pancreatic insufficiency after major pancreatic resections are controversial. Nevertheless, three different studies have shown specifically endocrine pancreatic insufficiency after distal pancreatectomy. The other aim is to preserve the spleen as its role has been shown by the effort to spare it after traumatic rupture. You are correct about the risk of pancreatic fistula; however, the mortality rate related to the fistula is presently very low and the treatment is mainly conservative.

# Intestinal Microcirculation and Gut Permeability in Acute Pancreatitis: Early Changes and Therapeutic Implications

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Translocation of bacteria from the intestine causes local and systemic infection in severe acute pancreatitis. Increased intestinal permeability is considered a promoter of bacterial translocation. The mechanism leading to increased gut permeability may involve impaired intestinal capillary blood flow. The aim of this study was to evaluate and correlate early changes in capillary blood flow and permeability of the colon in acute rodent pancreatitis of graded severity. Edematous pancreatitis was induced by intravenous cerulein; necrotizing pancreatitis by intravenous cerulein and intraductal glycodeoxycholic acid. Six hours after induction of pancreatitis, the permeability of the ascending colon was assessed by the Ussing chamber technique; capillary perfusion of the pancreas and colon (mucosal and subserosal) was determined by intravital microscopy. In mild pancreatitis, pancreatic capillary perfusion remained unchanged (2.13 ± 0.06 vs. 1.98 ± 0.04 nl·min$^{-1}$·cap$^{-1}$ [control]; $P$ = NS), whereas mucosal (1.59 ± 0.03 vs. 2.28 ± 0.03 nl·min$^{-1}$·cap$^{-1}$ [control]; $P$ <0.01) and subserosal (2.47 ± 0.04 vs. 3.74 ± 0.05 nl·min$^{-1}$·cap$^{-1}$ [control]; $P$ <0.01) colonic capillary blood flow was significantly reduced. Severe pancreatitis was associated with a marked reduction in both pancreatic (1.06 ± 0.03 vs. 1.98 ± 0.04 nl·min$^{-1}$·cap$^{-1}$ [control]; $P$ <0.01) and colonic (mucosal: 0.59 ± 0.01 vs. 2.28 ± 0.03 nl·min$^{-1}$·cap$^{-1}$ [control], $P$ <0.01; subserosal: 1.96 ± 0.05 vs. 3.74 ± 0.05 nl·min$^{-1}$·cap$^{-1}$ [control], $P$ <0.01) capillary perfusion. Colon permeability tended to increase with the severity of the disease (control: 147 ± 19 nmol·hr$^{-1}$·cm$^{-2}$; mild pancreatitis: 158 ± 23 nmol·hr$^{-1}$·cm$^{-2}$; severe pancreatitis: 181 ± 33 nmol·hr$^{-1}$·cm$^{-2}$; $P$ = NS). Impairment of colonic capillary perfusion correlates with the severity of pancreatitis. A decrease in capillary blood flow in the colon, even in mild pancreatitis not associated with significant protease activation and acinar cell necrosis or impairment of pancreatic capillary perfusion, suggests that colonic microcirculation is especially susceptible to inflammatory injury. There was no significant change in intestinal permeability in the early stage of pancreatitis, suggesting a window of opportunity for therapeutic interventions to prevent the later-observed increase in gut permeability, which could result in improved intestinal microcirculation. (J GASTROINTEST SURG 1998;2:518-525.)

KEY WORDS: Acute pancreatitis, colon, microcirculation, permeability, bacterial translocation

Death from acute pancreatitis occurs biphasically from two different causes.[1] Within the first week it is usually a consequence of the systemic inflammatory response syndrome, which develops as an overwhelming reaction to proteases, cytokines, and other yet unknown vasoactive mediators released at the onset of acute pancreatitis, whereas later death occurs largely as a result of septic complications.[2,3] At present, septic complications have emerged as the major cause of morbidity and mortality, and it has been recognized that patients with infected pancreatic and peripancreatic tissue have an increased risk of developing septic complications.[2,4-6]

The bacteria identified in infected pancreatic tissue resemble common gastrointestinal flora and have been demonstrated to reach the pancreas by translocation from the gut.[4,7-9] The mechanism leading to increased bacterial translocation is not completely understood but it is believed to involve (1) disturbances in the ecologic balance of the gut microflora, (2) dis-

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ruption of the local and the systemic immune system, and (3) alterations in the morphologic and/or functional integrity of the bowel wall.[10] In acute pancreatitis all these factors are present, and it has been shown that intravenous antibiotic prophylaxis,[11,12] selective decontamination of pathologic bacteria from the gut,[13,14] therapy with immunomodulators,[15] and stabilization of increased gut permeability[16] reduce pancreatic infections in experimental and human settings. The finding that intestinal permeability facilitates bacterial translocation, which has also been observed in other diseases,[17] has prompted further research on the mechanism leading to increased gut permeability. The underlying hypothesis of the present study is that microcirculatory disorders play an important role in the functional impairment of the colon in severe acute pancreatitis. Although the reduction of pancreatic capillary blood flow has been shown to be a hallmark of severe acute pancreatitis[18,19] and to occur despite stable cardiorespiratory function, colonic capillary blood flow has not yet been investigated. We speculated that the colon is also susceptible to microcirculatory disorders in early acute pancreatitis and that there may be a correlation between colonic capillary blood flow impairment and increased colon permeability. To further substantiate this hypothesis, we measured capillary blood flow in the mucosal and subserosal (muscular) layer of the ascending colon by intravital microscopy and permeability in adjacent colon segments by means of the Ussing chamber technique in two well-established models of acute pancreatitis in the rat.

## MATERIAL AND METHODS

All experiments were conducted in accordance with the national guidelines for the care and use of laboratory animals, and the experimental protocol was approved by the Subcommittee on Research and Animal Care of the Berlin Senate.

Experiments were performed in 44 male Sprague-Dawley rats (350 to 400 g) housed individually in rooms maintained at 21° ± 1° C using a 12-hour dark cycle. The animals were given standard rat chow and fasted overnight with water allowed ad libitum prior to the experiment. Surgical anesthesia was induced with vaporized ether followed by intraperitoneal pentobarbital (20 mg/kg; Nembutal, Pharmazeutische Handelsgesellschaft, Garbsen, Germany) and intramuscular ketamine (40 mg/kg; Ketanest, Parke, Davis & Company, Berlin, Germany). The right internal jugular vein and the left carotid artery were cannulated with catheters for blood sampling and blood pressure measurements as described elsewhere.[20] Both catheters were subcutaneously tunneled to the suprascapular area and brought out through a steel tether to monitor the unrestrained animal. Animals received continuous ketamine (2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$) for analgesia.

### Induction of Pancreatitis and Experimental Protocol

Edematous acute pancreatitis was induced in 12 rats by an intravenous infusion of 5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ cerulein (Farmitalia, Freiburg, Germany) over 6 hours. Necrotizing acute pancreatitis was induced in 12 animals using the same procedure superimposed on a standardized infusion of 10 mmol/L glycodeoxycholic acid (GDOC; Sigma, St. Louis, Mo.) into the biliopancreatic duct after clamping the hepatic duct as described elsewhere.[21] As an innovation of this technique, a special infusion pump (model 770, Ivac Corp., San Diego, Calif.) was used for volume (1.25 ml/kg)–, pressure (30 mm Hg)–, and time (10 minutes)–controlled intraductal GDOC infusion. Twelve sham-operated animals (intraductal and intravenous saline infusion) served as a control group. A continuous intravenous infusion of 2 $ml \cdot kg^{-1} \cdot hr^{-1}$ Ringer's solution was given to all animals during the first 6 hours.

After acute pancreatitis induction (or sham operation), six animals per group were randomly assigned to one of two experimental procedures. The first set of animals were killed, and a segment of the ascending colon was excised and mounted in a Ussing chamber to determine colon permeability. The pancreas was fixed for histologic examination. In the second set of experiments, animals underwent laparotomy to quantify pancreatic and colonic capillary blood flow by intravital microscopy.

### Quantification of Colon Permeability

Electrophysiologic experiments for determining colon permeability were performed in Ussing chambers as described previously.[22-24] A segment of the ascending colon was harvested, opened along the mesenteric border, and washed in cool medium to remove the luminal contents. The serosal side of the tissue was glued (Histoacryl, B. Braun AG, Melsungen, Germany) on a plastic ring (inside diameter 9 mm, outside diameter 11 mm) and inserted between the two halves of a Ussing-type chamber. Sealing was provided at a diameter of 6 mm by soft silicone rubber seals.[22] Effective chamber area was of 0.28 $cm^2$.

The bathing fluid consisted of the following (in mmol/L): $Na^+$ 140.5, $K^+$ 5.4, $Ca^{2+}$ 1.2, $Mg^{2+}$ 1.2, $Cl^-$ 123.8, $HCO_3^-$ 21, $HPO_4^{2-}$ 2.4, $H_2PO_4^-$ 0.6, D(+)-glucose 10, β-hydroxy-butyrate 0.5, glutamine 2.5, and D(+)-mannose 10. A combination of 50

mg/L azlocillin (Securopen, Bayer AG, Leverkusen, Germany) and 10 mg/L imipenem (Zienam, MSD Sharp & Dohme, Munich, Germany) was added to the bathing solutions, which was found to be most effective against bacterial growth in the course of this study. Solutions were gassed with a mixture of 95% oxygen and 5% carbon dioxide and had a pH of 7.4. All Ussing chamber experiments were performed at 37° C. Unidirectional $^{3}$H-mannitol flux studies from mucosa to serosa were performed under short circuit conditions. Mannitol flux as a parameter of colonic permeability was calculated using a standard formula.

## Quantification of Pancreatic and Colonic Capillary Blood Flow

Animals were reanesthetized with intravenous ketamine and pentobarbital and placed on a warming tray to maintain body temperature at 37° ± 1° C. The abdominal incision was reopened, and the ascending colon was gently exteriorized, fixed with four sutures on a Plexiglas slide, and continuously moistened with Ringer's solution at 37° ± 1° C. After determination of subserosal (muscular) colonic capillary perfusion, the colon was opened at the antimesenteric border with a microscissors. Special care was taken to avoid any bleeding or mechanical damage to the mucosa. Subsequently capillary perfusion of the colonic mucosa was assessed opposite the incision line.

To determine pancreatic capillary blood flow, the duodenum with the head of the pancreas was exteriorized and placed in an immersion chamber containing Ringer's solution maintained at 37° ± 1° C by a feedback-controlled heating system.

Pancreatic and colonic capillary blood flow was quantified by intravital microscopy according to the methods described by Mithöfer et al.[25] Homologous erythrocytes were labeled with fluorescein isothiocyanate (FITC isomer I; No. F-7250, Sigma Chemical, Deisenhofen, Germany). All animals received an intravenous injection of 0.5 ml/kg FITC-labeled erythrocytes (hematocrit 50%) and were allowed to stabilize for at least 30 minutes. The animals were placed under a fluorescence microscope (Leitz, Wetzlar, Germany). Epi-illumination was achieved with a short-arc xenon lamp (XBO 100W/2, Osram, Berlin, Germany) in the presence of a heat-protecting and an excitation (450 to 490 nm) filter. Ten different regions (each 400 × 325 μm) of the colonic mucosa, colonic subserosa, and the pancreas were analyzed, each with an average number of 25 ± 5 capillaries. The microscopic image was transferred to a monitor by video camera (model CCD-4810; Cohu Inc., San Diego, Calif.) and recorded on standard VHS video tape (Panasonic AG 7350; Panasonic Broadcast Deutschland, Wiesbaden-Biebrich, Germany) for subsequent analysis.

Off-line analysis of video recordings was performed in a blinded fashion by an independent observer. Blood flow in each capillary was calculated by correlating the number of passing labeled erythrocytes with the labeled fraction of capillary hematocrit.[25] The concentration of fluorescent erythrocytes per unit of arterial blood was measured in all animals at the time of each video recording by counting them in 50 different fields of a Neubauer chamber. Since previous capillary studies described a capillary/systemic hematocrit ratio of 0.76 for pancreas-sized capillaries,[26] capillary hematocrit could be calculated by multiplying systemic hematocrit by 0.76.

## Histopathologic Analysis

Histopathologic analysis of the pancreas was performed according to a scoring system as described previously.[27] Briefly, the entire pancreas was removed and fixed in 10% buffered formalin in anatomic orientation. The organ was divided into a duodenal (pancreatic head) and a splenic (pancreatic tail) segment; each portion was embedded in paraffin, and a longitudinal section through each of the two parts was stained with hematoxylin and eosin. Morphometric documentation of acinar necrosis was obtained by mapping the entire surface of the pancreas into 20 geographic fields and evaluating each field separately. The histopathologic evaluation was performed by a pathologist who had no knowledge of the experimental protocol.

## Systemic Hemodynamic and Laboratory Parameters

Mean arterial pressure was continuously monitored during intravital microscopy with an electronic sphygmomanometer (Hellige GmbH, Freiburg, Germany). Six hours after induction of pancreatitis (or sham operation), hematocrit was measured and blood samples were taken for determination of arterial blood gases (IL 1610; Instrumentation Laboratory, Kirchheim, Germany).

Trypsinogen activation peptides (TAP) are generated when inactive trypsinogen is cleaved and converted to active trypsin. TAP levels have been shown to correlate with acinar necrosis and death in our model.[28] Therefore TAP in plasma was measured according to the method of Hurley et al.[29,30] to confirm the homogeneity of disease severity within the exper-

imental groups in all animals 6 hours after pancreatitis induction or sham operation.

### Exclusion Criteria

Animals were excluded from the study when one of the following criteria was present: surgical trauma to the preparation as described previously[31] and/or cardiorespiratory derangement as indicated by mean arterial pressure <80 mm Hg, $pCO_2$ >50 mm Hg, $pO_2$ <80 mm Hg, or pH <7.3 or >7.5 at any point during the experiment. Eight animals were excluded according to these criteria. The remaining 36 animals were entered into the statistical analysis.

### Statistical Analysis

Data are presented as means ± standard error of the mean. Continuous variables were tested for group differences by a one-way analysis of variance. A 5% probability of type I experimental error ($P \leq 0.05$) was accepted for statistical significance.

## RESULTS

### Hemodynamic and Laboratory Parameters

Mean arterial pressure and arterial blood gases measured 6 hours after pancreatitis induction or sham operation, respectively, confirmed a stable cardiorespiratory condition in all animals included in the study (Table I).

### Histopathology, Protease Activation, and Hematocrit

Animals with mild edematous pancreatitis had significantly higher hematocrit values in comparison to healthy control rats. Increases in plasma TAP and acinar cell necrosis were not statistically significant. Animals with severe necrotizing pancreatitis showed a significant increase in all target parameters (Table II).

### Pancreatic Capillary Blood Flow (Fig. 1)

Rats with mild edematous pancreatitis, demonstrated pancreatic capillary blood flow that was slightly but not statistically significantly increased as compared to healthy control animals (2.13 ± 0.06 vs. 1.98 ± 0.04 $nl \cdot min^{-1} \cdot cap^{-1}$; $P$ = NS). Severe necrotizing pancreatitis was associated with a significant reduction in pancreatic capillary blood flow (1.06 ± 0.03 $nl \cdot min^{-1} \cdot cap^{-1}$).

### Colonic Capillary Blood Flow (Fig. 1)

Subserosal capillary blood flow was significantly reduced in animals with edematous (2.47 ± 0.04 vs. 3.74 ± 0.05 $nl \cdot min^{-1} \cdot cap^{-1}$ [control]; $P$ <0.01) and

**Table I.** Mean arterial pressure and arterial blood gases 6 hours after pancreatitis induction or sham operation (control)

| | Control | Edematous AP | Necrotizing AP |
|---|---|---|---|
| MAP (mm Hg) | 130 ± 4 | 120 ± 8 | 128 ± 4 |
| pH | 7.40 ± 0.03 | 7.41 ± 0.02 | 7.44 ± 0.02 |
| $pO_2$ (mm Hg) | 100 ± 5 | 108 ± 10 | 110 ± 8 |
| $pCO_2$ (mm Hg) | 39 ± 4 | 42 ± 2 | 40 ± 3 |

MAP = mean arterial pressure; AP = acute pancreatitis.

**Table II.** Acinar cell necrosis, trypsinogen activation peptides, and hematocrit 6 hours after pancreatitis induction or sham operation (control)

| | Control | Edematous AP | Necrotizing AP |
|---|---|---|---|
| Necrosis | 0.3 ± 0.1 | 0.6 ± 0.1 | 1.7 ± 0.2* |
| Trypsinogen activation peptides (nmol/L) | 0.2 ± 0.05 | 0.4 ± 0.1 | 2.8 ± 0.2* |
| Hematocrit (%) | 47.8 ± 0.9 | 54.3 ± 0.9† | 57.3 ± 1.6† |

*$P$ <0.01 necrotizing vs. edematous acute pancreatitis (AP).
†$P$ <0.01 vs. control.

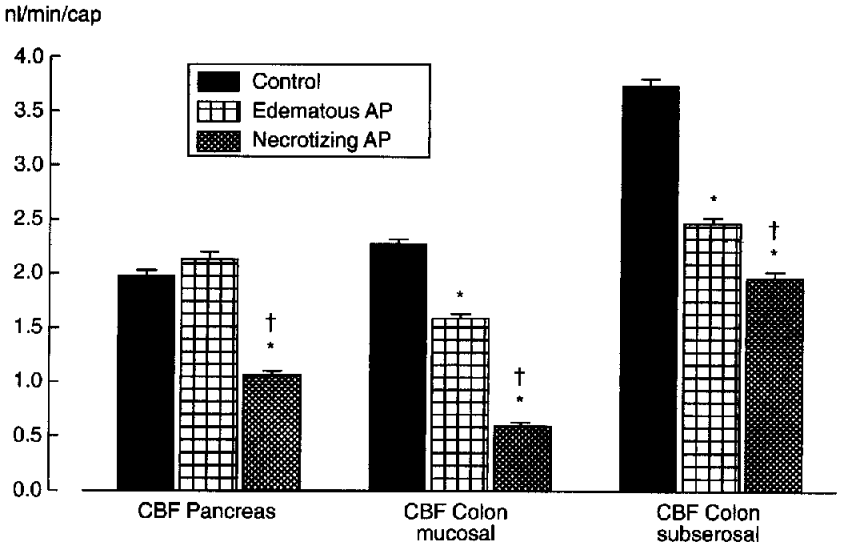


**Fig. 1.** Capillary blood flow *(CBF)* of the pancreas and the colonic mucosa and subserosa 6 hours after induction of acute pancreatitis *(AP)* or sham operation *(control)*. Pancreatic CBF remained unchanged in mild edematous AP, whereas mucosal and subserosal colonic CBF were significantly reduced. Severe necrotizing AP was associated with a reduction in both pancreatic and colonic CBF and a more pronounced reduction in colonic mucosal CBF than in subserosal CBF. * = $P < 0.01$ vs. control; † = $P < 0.01$ necrotizing vs. edematous AP.

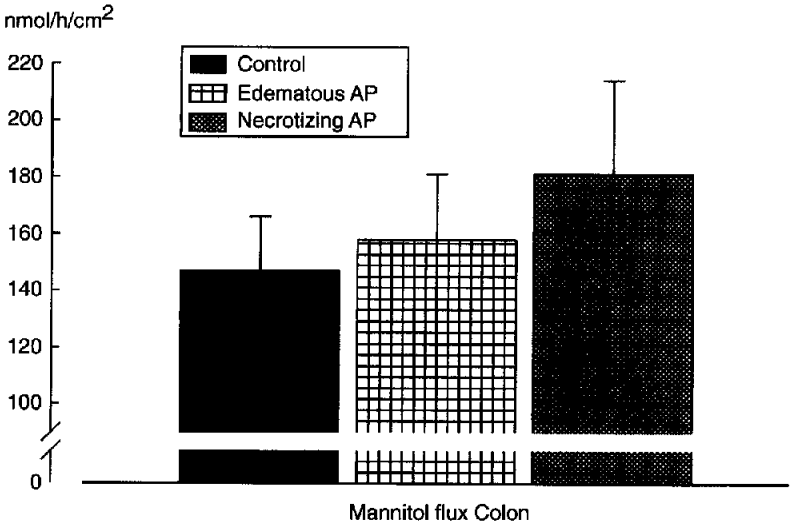


**Fig. 2.** Colon permeability (mannitol flux $J_{MAN}$) 6 hours after acute pancreatitis *(AP)* or sham operation *(control)*. $J_{MAN}$ tended toward increased permeability in animals with pancreatitis. Differences were not statistically significant.

necrotizing (1.96 ± 0.05 vs. 3.74 ± 0.05 nl·min$^{-1}$·cap$^{-1}$ [contro]; $P < 0.01$) pancreatitis. The decrease in subserosal capillary blood flow was significantly more pronounced in necrotizing as compared to edematous acute pancreatitis ($P < 0.05$). The same observations were made for the colonic mucosa (control: 2.28 ± 0.03 nl·min$^{-1}$·cap$^{-1}$; edematous acute pancreatitis: 1.59 ± 0.03 nl·min$^{-1}$·cap$^{-1}$; necrotizing acute pancreatitis: 0.59 ± 0.01 nl·min$^{-1}$·cap$^{-1}$; $P < 0.01$ between all groups). In necrotizing acute pancreatitis, the reduction in mucosal capillary blood flow was more pronounced than that in the subserosa (74.1% vs. 47.6%; $P < 0.01$).

## Colon Permeability (Fig. 2)

Paracellular permeability of the colon from the mucosal to the serosal side of the tissues, as indicated

by mannitol flux $J_{MAN}$, tended toward increased permeability in animals with pancreatitis (control: 147 ± 19 nmol·hr$^{-1}$·cm$^{-2}$; edematous pancreatitis: 158 ± 23 nmol·hr$^{-1}$·cm$^{-2}$; severe pancreatitis: 181 ± 33 nmol·hr$^{-1}$·cm$^{-2}$). Differences did not reach statistical significance.

## DISCUSSION

Secondary pancreatic infection and subsequent septic complications have emerged as the major causes of morbidity and mortality in severe acute pancreatitis.[2] Bacteria isolated from infected pancreatic tissue resemble common gastrointestinal flora, suggesting that they reach the pancreas by translocation from the gut.[3-5] The mechanisms leading to bacterial translocation are not completely understood and may involve (1) disturbed enteric bacterial ecology with subsequent overgrowth of facultative pathogenic bacteria, (2) impaired local and systemic host immune defense, and (3) injured integrity of the gut mucosa, resulting in compromised intestinal barrier function.[5,10,32] All these factors are involved in severe acute pancreatitis. Consequently there have been numerous experimental and clinical efforts aimed at improving these disorders. Early intravenous antibiotic prophylaxis could reduce infectious complications in patients with necrotizing pancreatitis.[11,12] Selective decontamination of the gut with orally administered nonabsorbable antibiotics has been shown to prevent bacterial overgrowth, reduce the incidence of pancreatic infection,[13,14] and improve survival in patients with severe acute pancreatitis.[14] Interleukin-10 averted the lethal course of nerotizing pancreatitis in mice,[33] tumor necrosis factor antibody improved survival and ameliorated the pathophysiologic sequelae in rodents with severe acute pancreatitis,[34] and levamisol reduced pancreatic infections in a cat model of acute pancreatitis.[15]

Efforts to stabilize impaired integrity of the gut mucosa have been hampered by the fact that the functional components of gut integrity are not known. Ryan et al.[35] were the first to demonstrate increased gut permeability as one possible factor for intestinal barrier failure in acute pancreatitis. Using the same models of edematous and necrotizing pancreatitis as applied herein, they found increased gut permeability for the macromolecule polyethylene glycol, which correlated with disease severity, and they speculated that these changes were due to direct injury of the mucosa by inflammatory mediators such as tumor necrosis factor or interleukin-1 leaking from mucosal capillaries. However, they did not find any inflammatory changes in the bowel wall on light or electron microscopy. This led us to the hypothesis that it is probably a systemic vascular effect or microcirculatory disturbance secondary to vasoactive mediators that causes functional impairment of mucosal integrity.

To our knowledge this is the first study to evaluate colonic capillary blood flow in acute necrotizing pancreatitis by intravital microscopy, differentiating between mucosal and subserosal capillary blood flow. The term subserosal capillary blood flow describes the capillary perfusion in the longitudinal and transverse capillaries of the two muscle layers of the colon.[36] To correlate microcirculation with permeability, we simultaneously assessed the permeability of the colonic wall by measuring mannitol flux in a modified Ussing chamber, which is a well-established method for studying transport across flat epithelia.[17,22]

Our results demonstrate that impairment of colonic capillary blood flow occurred early in our model of acute pancreatitis and correlated with disease severity. Microcirculatory changes were not due to an alteration of systemic arterial pressure, since all animals included in the study maintained a stable cardiorespiratory condition. A reduction in colonic capillary blood flow was even observed in mild edematous pancreatitis not associated with significant protease activation, acinar necrosis, or impaired pancreatic capillary blood flow. In necrotizing pancreatitis, the reduction in capillary blood flow was more pronounced in the mucosa (74% reduction) than in the subserosal colonic layers (48% reduction) or the pancreas (46% reduction). These data imply that colonic microcirculation, especially of the mucosa, is particularly vulnerable in early acute pancreatitis. This agrees with the observations of Andersson et al.,[37] who proposed that the colon may be the most susceptible part of the gastrointestinal tract in acute pancreatitis, resulting in a spectrum of morphologic changes ranging from pericolitis to ischemic necrosis of the colon.[38-40]

The colons of animals with severe acute pancreatitis tended toward increased permeability (see Fig. 2). Differences between the three groups *6 hours* after induction of acute pancreatitis did not, however, reach statistical significance. In contrast to our findings, Ryan et al.[35] described significantly increased permeability for macromolecules in the same model of acute pancreatitis after *24 hours*, suggesting that the increase in colon permeability develops over a period exceeding the 6-hour observation period of the present experiment. This is in accordance with the observations of Andersson et al.,[37] who studied intestinal permeability for radiolabeled albumin in another rat model of (less severe) acute pancreatitis and found that an increase in mucosal permeability in the colon begins 6 hours after induction of pancreatitis. In additional experiments assessing colon permeability and capillary blood flow after 24 hours, we found a further increase in colon permeability (thereby confirming the results

and conclusions discussed earlier), whereas there was a significant improvement in mucosal capillary blood flow compared to the values assessed at 6 hours (but blood flow was still significantly decreased as compared to healthy control animals). Our finding that a reduction in colonic capillary blood flow precedes increased permeability (and subsequent bacterial translocation) also agrees with the bacteriologic data obtained from the same model, that is, vital bacteria in the pancreas were never found earlier than 12 hours after induction of pancreatitis.[41]

The hypothesis that the reduction of colonic capillary blood flow is an important contributor to increased gut permeability (thereby promoting bacterial translocation) and our observation that it precedes increased gut permeability are intriguing because they open up a new opportunity for therapeutic interventions aimed at stabilizing gut integrity by improving impaired mucosal capillary blood flow. Klar et al.[42] have previously demonstrated that isovolemic hemodilution and infusion therapy with dextran significantly increased pancreatic capillary blood flow, limited the spread of pancreatic necrosis, and improved survival in experimental acute pancreatitis. We concluded that this beneficial effect, also seen in patients with severe acute pancreatitis,[43] was due to the improved capillary perfusion in the pancreas and the subsequent limitation of pancreatic necrosis. In light of the present results and a recent report by Banks et al.,[44] who could not confirm the correlation between pancreatic necrosis and outcome in a series of 47 patients, it is also conceivable that the beneficial action of dextran is due to its effect not only on pancreatic but also on colonic capillary blood flow. Further experimental work is warranted to determine whether an improvement in colonic capillary blood flow, that is, by infusion therapy with dextran or other colloids, reduces increased intestinal wall permeability and subsequent bacterial translocation. Second, the mechanisms leading to microcirculatory disorders in acute pancreatitis need to be investigated further, including analysis of the role of vasoactive mediators such as bradykinin,[45] platelet-activating factor, and endothelin.[46]

In summary, we have shown that a significant reduction in colonic capillary blood flow, most pronounced in the mucosa, occurs early in acute pancreatitis, correlates with the severity of the disease, and precedes the development of increased intestinal wall permeability. A reduction in colonic capillary blood flow, even in mild pancreatitis not associated with significant protease activation, acinar cell necrosis, or impaired pancreatic capillary perfusion, suggests that colonic microcirculation is particularly vulnerable in acute pancreatitis. Our hypothesis that improving impaired colonic capillary blood flow may stabilize the impaired gut barrier in severe acute pancreatitis, thereby reducing bacterial translocation and secondary pancreatic infection, is intriguing and warrants further evaluation.

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# Pancreatic Polypeptide Islet Cell Tumor: Case Report and Review of the Literature

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Pure pancreatic polypeptide–containing tumors (PPomas) are quite rare. Only 20 cases have been described. In this article we report a 75-year-old woman with such an endocrine islet cell tumor. The patient had no specific symptoms that could be ascribed to the tumor. An abdominal CT scan revealed a 3 cm soft tissue mass arising inferiorly from the tail of the pancreas. Local resection by way of a distal pancreatectomy was performed. A well-circumscribed hemorrhagic multiloculated mass, 3.7 cm in greatest dimension, was present in the tail of the pancreas. The patient has remained well and tumor free for the past 22 months. The endocrine characterization of the tumor was achieved by means of immunohistochemical analysis. Staining specific for insulin, glucagon, somatostatin, and gastrin was negative. In contrast, staining of the tumor for pancreatic polypeptide was strongly positive. A number of nonfunctioning islet cell tumors of the pancreas have been described. The lack of function has previously been suggested to indicate the lack of secretion of an endocrine product. This report documents that islet cell tumors may function by secreting pancreatic polypeptide but not cause symptoms. (J GASTROINTEST SURG 1998;2:526-532.)

KEY WORDS: Pancreatic polypeptide, islet cell tumor, pancreatic endocrine tumor

Pancreatic polypeptide (PP) was discovered serendipitously nearly three decades ago.[1] However, very little is known about its physiologic function or the clinical implications of elevated circulating levels of PP. Human pancreatic polypeptide (hPP) is composed of 36 amino acids. It has been localized within distinct cells in the islet of Langerhans of the pancreas, the F cells that store and secrete PP into the bloodstream.[2] Histologically, F cells are abundant in the head and uncinate process of the pancreas.[2,3]

The release of hPP from the normal pancreas is mediated by the cholinergic nerve fibers that innervate the pancreas. Plasma levels of this linear polypeptide have been shown to increase after a meal, with increasing age, in chronic renal failure, and in patients with islet cell tumors.[4-7]

Neoplasms originating in islet cells commonly contain more than one type of endocrine cell. PP is most commonly associated with vasoactive intestinal polypeptide–containing tumors (VIPomas) and glucagonomas[7]; however, endocrine tumors composed entirely of hPP immunoreactive cells (i.e., pure PPomas) are very rare. Pure PPomas are still enigmatic, since no distinct clinical symptoms have been solely ascribed to the presence of this neoplasm. This report describes a patient with an asymptomatic pure PPoma and reviews the world experience with this tumor.

## CASE REPORT

A 75-year-old African-American woman was first seen with complaints of left flank and abdominal pain of 2 days' duration. She stated that the pain was nonradiating and colicky in nature. The patient also admitted to nausea, vomiting, and inability to eat. However, she denied having diarrhea, fever, chills, clay-colored stools, dark urine, or steatorrhea. Her medical history was significant for microhematuria, abnormal urine cytology, and filling defects involving the upper poles of both kidneys. One week prior to admission, she had undergone CT imaging of the abdomen as part of a urologic workup. This imaging study revealed bilateral renal calculi with a large nonobstructive calculus within the left renal pelvis as well as bilateral parapelvic and parenchymal renal cysts. Interestingly, however, a 3 cm soft tissue mass arising inferiorly from the tail of the pancreas was also serendipidously identified (Fig. 1).

On admission, the physical examination revealed a thin female in no acute distress. She was significantly dehydrated with marked left costovertebral angle tenderness. No significant lymphadenopathy was noted.

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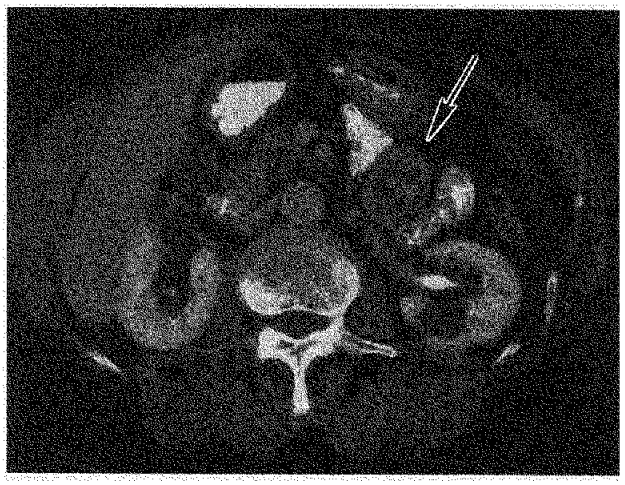

**Fig. 1.** Contrast-enhanced images demonstrate a 3 cm soft tissue mass arising from the tail of the pancreas inferiorly *(arrow)*. No significant para-aortic lymphadenopathy is identified.

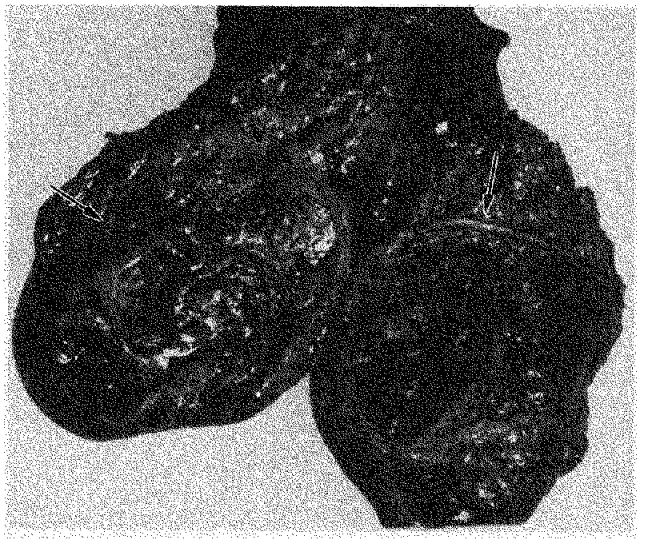

**Fig. 2.** Partial pancreatectomy specimen consisting of the body and tail of the pancreas. A single well-demarcated hemorrhagic mass, 3.7 cm in greatest dimension, is present in the tail of the pancreas. Note that the tumor is multiloculated with a well-defined capsule *(arrow)*.

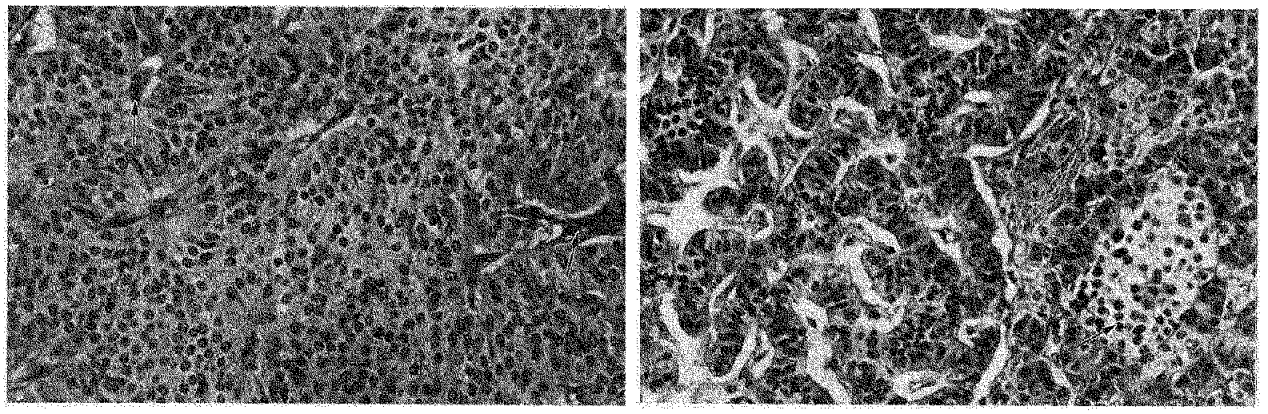

**Fig. 3.** Histologic appearance of the pancreatic endocrine tumor showing the neoplasm to be composed of small cells with centrally placed round to slightly elongated hyperchromatic nuclei. **A,** Tumor has a solid growth pattern with a vascular stroma *(arrow)*. **B,** Other areas of the tumor have a gyriform growth pattern with ribbons of tumor cells separated by vascular stroma. Note the normal pancreas and pancreatic islet *(arrow)* on the right side. (Hematoxylin and eosin stain; magnification ×350.)

Significant laboratory data included a creatinine level of 1.6 mg/dl (normal 0.6 to 1.0 mg/dl) and an alkaline phosphate level of 142 U/L (normal 40 to 120 U/L). Aspartate aminotransferase and alanine aminotransferase levels were all normal as were total bilirubin, serum albumin, hematocrit, leukocyte and platelet counts, serum electrolytes, and coagulation studies. Urinalysis revealed only moderate occult blood with nine red blood cells and two white blood cells per high-power field. Nitrates, leukoesterase, and bacteria were absent. Endoscopic ultrasound examination confirmed the presence of a hyperechoic complex mass in the region of the body and tail of the pancreas.

An exploratory celiotomy was performed and a 3 cm solid mass was identified in the tail of the pancreas. Distal pancreatectomy and splenectomy were performed with a 3 cm margin of normal pancreas. Further exploration of the abdomen revealed no evidence of metastatic disease. No lymph nodes were involved with the tumor. The postoperative course was uneventful, and the patient has remained well and tumor free for the past 7 months.

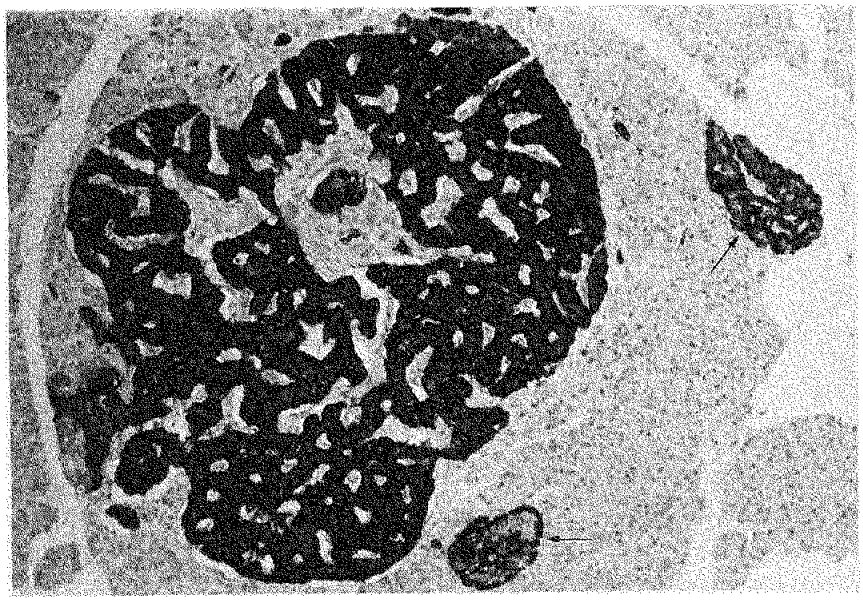

**Fig. 4.** Chromogranin, an immunohistochemical marker for neuroendocrine differentiation, strongly staining the endocrine tumorlet found away from the main tumor mass. Note that the normal pancreas islets are also positive for the stain *(arrow)*. (Immunoperoxidase staining; magnification ×175.)

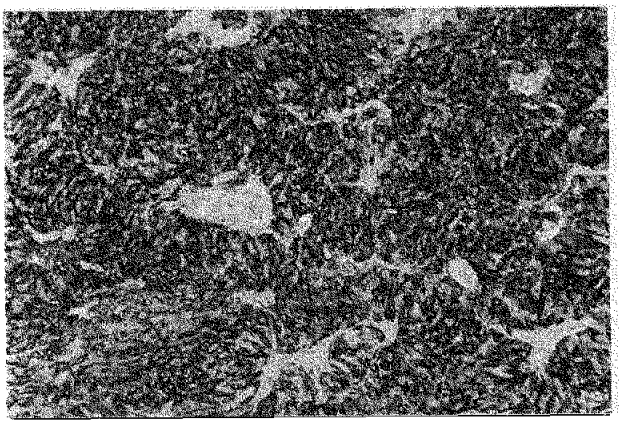

**Fig. 5.** Immunohistochemical staining for PP strongly and diffusely staining the tumor cells. (Immunoperoxidase staining; magnification ×175.)

Her most recent serum PP level, after removal of the tumor, was 162 pg/ml. The age-matched normal range of serum PP is less than 332 pg/ml. Serum PP levels are to be checked on a regular basis.

## Histopathologic Examination

The partial pancreatectomy specimen consisted of the body and tail of the pancreas measuring 13 × 5.2 × 2.7 cm. A well-circumscribed hemorrhagic multiloculated mass, 3.7 cm in greatest dimension, was present in the tail of the pancreas (Fig. 2). Microscopically the neoplasm was an endocrine tumor with a very vascular stroma. It had a well-defined capsule and was made up of small cuboidal to slightly elongated cells with round nuclei and clear to eosinophilic cytoplasm. The tumor cells were arranged in various patterns, a characteristic feature of islet cell tumors. These included solid, ribbon-like or gyriform, and glandular growth patterns (Fig. 3). A single separate microscopic focus of endocrine tumor, which may represent a second primary tumor, was present in the tail of the pancreas several centimeters away from the primary tumor mass (Fig. 4). Multiple islet cell tumors are relatively common, so this is not an unexpected finding. Results of immunohistochemical staining specific for insulin, glucagon, somatostatin, and gastrin were negative. However, staining for pancreatic polypeptide was strongly positive in the main tumor mass (Fig. 5) as well as the tumorlet (see Fig. 4).

## DISCUSSION

Isolation and characterization of a contaminant found during the purification of avian insulin resulted in a new 36 amino acid straight-chain polypeptide with a molecular weight of 4240 daltons,[1,8] avian pancreatic polypeptide. Six years later, Chance and Jones[9] isolated and sequenced a homologous linear polypeptide from the human pancreas.

hPP is produced in F cells of the islets of Langerhan,[2] which are located on the periphery of the islets.

The full spectrum of physiologic actions of PP remains incompletely defined. To date, circulating PP has been shown to induce a general splanchnic vasoconstriction[10] and exert an inhibitory effect on pancreatic and biliary secretions in humans.[11] Other effects include stimulation of gastric motility in rats.[12]

Recent studies in animals have shown that blood-borne PP crosses the blood-brain barrier and acts on PP receptors, resulting in both a feedback inhibition of pancreatic secretion and activation of gastric motility via vagal-dependent pathway.[12-15] Additional PP receptors have been discovered on rat hepatic membranes; however, the functional significance of these receptors is unknown.[16]

Secretion of hPP from normal pancreatic islet cells is governed by nutrient, neural, and hormonal factors. Ingestion of a meal, primarily one rich in protein, is a potent stimulus for hPP release.[4] Cholinergic fibers directly mediate this response and muscarinic receptor blockade inhibits it. Hormonal stimulation also plays a role in hPP release. Infusion of cholecystokinin and secretin results in a substantial increase in plasma levels of hPP during fasting.[4]

There are a number of conditions that cause elevation in circulating levels of hPP including increased age,[5] alcohol abuse,[17] consumption of laxatives,[18] duodenal ulcers,[19] medications (e.g., erythromycin, cisapride),[20,21] chronic renal failure,[6] diabetes mellitus, and insulin-induced hypoglycemia.[22]

Unlike other islet cell tumors, in which elevated levels of insulin, glucagon, somatostatin, and VIP are heralded by definite clinical symptoms, no striking physiologic characteristics have been ascribed to elevated levels of plasma PP. In fact, the majority of tumors that secrete hPP are considered clinically nonfunctional. Because of its silent nature, the diagnosis of PPoma is elusive and rarely made preoperatively. The definite diagnosis of an authentic pure PPoma can only be made by immunohistochemical analysis of the tumor.

Immunohistochemical analysis of our patient's tumor revealed positive staining for pancreatic polypeptide, whereas staining for glucagon, insulin, somatostatin, and gastrin was negative. Several studies have shown a good association between pancreatic tumors that contain a high concentration of VIP and the presence of watery diarrhea (Verner-Morrison syndrome or WDHA syndrome).[23,24] Thus, in the absence of severe watery diarrhea and hypokalemia, the possibility of VIPoma was excluded.

Review of the literature has revealed only 10 other documented cases of pancreatic islet cell tumors that display solely PP immunoreactivity (Table I). In addition, Heitz et al.[32] reported 10 endocrine tumors composed entirely of immunoreactive PP cells but provided no clinical data concerning these patients. On the other hand, Welbourn et al.[33] mentioned the "pure PPomas" among 79 tumors. However, since no specific immunocytochemical information was reported, they were not included in our table.

The vast majority of PPomas are found within the pancreas. However, a few cases of neoplasms harboring hPP cells have been described in other organs including the liver,[34] papilla of Vater with duodenal wall involvement,[35] and stomach.[36]

PP islet cells (or F cells) are relatively abundant in both the murine ventral and dorsal pancreatic buds by day 15.5 of gestation.[37] Subsequently, at day 18.5 of gestation, the total number of PP cells in the ventral bud has doubled, whereas the number in the dorsal bud has essentially remained unchanged.[37] This nonhomogeneous distribution of PP cells can also be seen in the human neonate. Indeed, PP cells are considerably more numerous in the posterior-inferior (uncinate) part of the head region (ventral bud) than in the body and tail and superior head of the pancreas (dorsal bud).[38] This anatomic distribution of PP cells is also present in the adult human pancreas.[2,3]

Based on these findings, it is not surprising that Howard et al.[39] confirmed that PP-secreting islet cell tumors tended to have a predilection for the regions of the pancreas rich in F cells. Nevertheless, the islet cell tumor described in this study originated in the pancreatic tail, a site where the F cells are scarce. At least six other cases of pure PPomas (see Table I) have also been reported to arise from this region of the pancreas.

Patients affected with pure PPomas have presented with such atypical tumor symptoms as abdominal pain,[28,31] skin rash,[29] weight loss,[25,27] and the WDHA syndrome.[26] The patients have ranged in age from 20 to 67 years (mean 54 years). A few have occurred as part of the multiple endocrine neoplasia, MEN-1, syndrome,[27] but the majority of tumors are sporadic. Benign tumors are more frequent; however, malignancy, as defined by the presence of metastatic disease, has been reported.[28-31]

It has been estimated from the reported cases that excessive hPP secretion into the peripheral blood does not cause any life-threatening metabolic or clinical consequences. However, the malignant tendency for these tumors has not yet been defined. Thus the appropriate treatment for patients with islet cell tumors is surgical resection. Pancreatectomy with en bloc lymphadenectomy can be curative in many cases, even in the face of lymph node metastases from islet cell tumors.[27] Although the presence of metastatic foci is associated with a worse prognosis, long-term survival is possible when the patients are suitably man-

**Table I.** Summary of previously reported pure PPomas originating in the pancreas

| Reference | Age(yr)/ Sex | Clinical symptom(s) | Tumor site/Size (cm) | Metastases | Immunohistochemical analysis | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Bordi et al.[25] (1978) | 45/M | Weight loss, PUD | Two masses—pancreas body and tail/(0.7-0.8) | None | (+)PP (−)VIP,G,In,Glu,SS,Se | Surgical removal of tumors, Billroth II gastrectomy | Alive, 5 yr |
| Hayes[26] (1980) | 55/M | WHDA, weight loss | Pancreas body/(5) | None | (+)PP (−)VIP,In,Glu,SS | Rehydration, replacement of electrolytes, antibiotics | Died of disease |
| Strodel et al.[27] (1984) | 53/M | Epigastric pain, gastritis | Pancreas head/(5) | None | (+)PP (−)VIP,G,In,Glu,SS | Whipple procedure | Unknown |
| | 20/F | Weight loss, jaundice | Pancreas head/(15) | None | (+)PP (−)VIP,G,In,Glu,SS | Whipple procedure | Alive, 3 yr |
| | 62/F | Weight loss, MEN-1 | 3 masses; pancreas head, neck, and tail/(5) | None | (+)PP (−)VIP,G,In,Glu,SS | 80% pancreatectomy, enucleation | Unknown |
| Nobin et al.[28] (1984) | 57/F | Abdominal pain | Pancreas head | Liver and lymph node | (+)PP (−)VIP,G,In,Glu,SS | Laparotomy, biopsy | Alive, 2 yr |
| Choksi et al.[29] (1988) | 59/F | GI bleeding, skin rash | Pancreas NOS/(10) | Liver | (+)PP (−)G,In,Glu,SS | Debulking + 5-FU and decarbazine | Alive, 1 yr |
| Mårtensson et al.[30] (1990) | 55/F | Unknown | Pancreas NOS/(3) | Liver or lymph node | (+)PP (−)VIP,G,In,Glu,SS | Unknown | Unknown |
| Guiro et al.[31] (1994) | 67/F | Renal colic | Pancreas tail/(10) | None | (+)PP (−)VIP,G,In,Glu,SS | Distal pancreatectomy | Hypovolemic shock, upper GI bleeding, death |
| | 66/F | Abdominal pressure | Pancreas tail/(10) | Lymph node | (+)PP (−)VIP,G,In,Glu,SS | Total pancreatectomy | Alive, 6 yr |

PUD = peptic ulcer disease; WHDA = watery diarrhea syndrome; MEN-1 = multiple endocrine neoplasia; GI = gastrointestinal; PP = pancreatic polypeptide; G = gastrin; In = insulin; Glu = glucagon; SS = somatostatin; VIP = vasoactive intestinal peptide; Se = secretin; 5-FU = 5-fluorouracil; NOS = not otherwise specified; (+) = presence of immunoreactivity; (−) = no immunoreactivity.

aged. In patients who are poor operative candidates, or patients with advanced or nonresectible disease, nonoperative management with specific pharmacotherapy or tumor embolization may be useful.[36,40,41] Moertel et al.[42] reported that streptozocin alone or combined with fluorouracil is beneficial.

Nonfunctional pancreatic tumors should be removed regardless of the plasma PP levels. The finding of elevated PP levels, as compared to levels in age-matched subjects, only serves to confirm the diagnosis. However, plasma levels within the normal range do not exclude the presence of this endocrine tumor. Therefore the preoperative determination of plasma hPP levels has limited clinical utility. Moreover, no correlation has ever been conclusively demonstrated between plasma hPP concentrations and resectability or clinical outcome. On the other hand, once the diagnosis of PPoma is made and treatment is achieved, plasma hPP levels should be monitored. Resurgence of plasma levels of hPP after tumor excision should be regarded as evidence of the recrudescence of the disease.[40] Increased basal hPP concentration after surgical excision of the tumor may also reflect either incomplete resection of all endocrine islet cell tumor or the presence of hyperplastic, not neoplastic, hPP cells.[43] In our patient, postoperative levels of pancreatic polypeptide were within normal limits, implying a good prognosis.

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# Cystic Glucagonoma: A Rare Variant of an Uncommon Neuroendocrine Pancreas Tumor

*Kimberly Brown, M.D., Theresa Kristopaitis, M.D., Sherri Yong, M.D., Gregorio Chejfec, M.D., Jack Pickleman, M.D.*

Glucagon-producing neuroendocrine tumors typically present with a characteristic constellation of symptoms including necrolytic migratory erythema, non–insulin-dependent diabetes, weight loss, anemia, glossitis, and an increased thrombotic tendency. Most glucagonomas are solid and arise in the body or tail of the pancreas. We report two cases of cystic glucagonoma, one found incidentally in an asymptomatic patient and one in a patient with weight loss and diabetes but no rash. In the first patient, distal pancreatectomy and splenectomy were curative, whereas the second patient continued to exhibit elevated serum glucagon levels and symptoms of glucose intolerance in the absence of demonstrable metastases. Cystic glucagonoma is a unique variant of classic glucagonoma and should be considered in the differential diagnosis of cystic pancreatic neoplasms. (J GASTROINTEST SURG 1998;2:533-536.)

KEY WORDS: Glucagonoma, cystic pancreatic neoplasm

McGavran et al.[1] first described a patient with a glucagon-producing islet cell tumor in association with glucose intolerance, normochromic anemia, and a characteristic skin rash, later termed necrolytic migratory erythema.[2] Subsequent reports further characterized the glucagonoma syndrome to include weight loss, glossitis, hypoaminoacidemia, and a tendency for thrombosis.[3-5] The majority of reported glucagonomas are solid tumors with only individual case reports of six patients with cystic glucagonomas described in the English literature.[6-11] Like other pancreatic neuroendocrine tumors, glucagonomas are highly vascular, a characteristic believed to be responsible for the infrequency of cystic degenerative changes.[9] We describe two patients with cystic glucagonomas and consider the unique pathologic findings and pathogenesis in this rare variant of an uncommon pancreatic tumor.

## CASE REPORTS

### Case 1

A 37-year-old man was referred for evaluation of a cystic lesion of the pancreas found incidentally on an abdominal ultrasound examination. The patient had sustained a right rib fracture at work several weeks prior to referral and complained of persistent abdominal pain for which abdominal ultrasonography was performed. This examination was followed by an abdominal CT scan, which demonstrated a cystic lesion of the pancreas (Fig. 1). His medical history was significant only for a motor vehicle accident 4 years previously, in which the patient sustained lower chest and abdominal injuries requiring hospitalization for 2 days. No CT imaging was performed at that time. Results of physical examination were normal. Laboratory values were as follows: hemoglobin 13.1 g/dl, glucose 96 mg/dl, and amylase 298 U/L. No preoperative serum glucagon levels were obtained. It was assumed that the patient harbored a cystic pancreatic neoplasm, and he underwent a distal pancreatectomy and splenectomy with closed-suction drainage of the pancreatic bed. The patient recovered uneventfully with hospital discharge on postoperative day 5. Following pathologic diagnosis, a serum glucagon level obtained 1 month postoperatively was 59 pg/ml (normal <200 pg/ml).

Within the resected segment of pancreas was a 10 × 10 × 8 cm cyst (Fig. 2). Grossly the cyst cavity was filled with thick red-brown necrotic debris, whereas the cavity lining was smooth and focally ulcerated. The cyst wall was extensively sampled and microscopically consisted of dense collagen devoid of an epithelial lining. There was one single microscopic focus of tumor protruding into the cavity lumen (Fig. 3). This neoplasm was composed of monotonous cuboidal to oval cells with round nuclei, occasional prominent nucleoli, and eosinophilic cytoplasm arranged in trabeculae separated by thin bands of connective tissue and capillaries.

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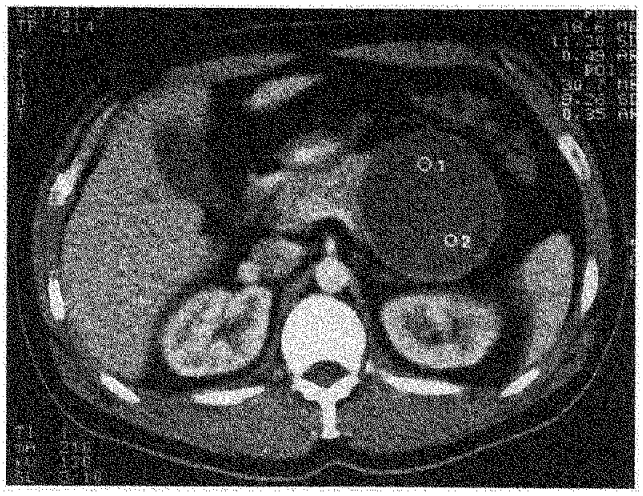

**Fig. 1.** Case 1. CT scan showing cystic tumor in body of pancreas.

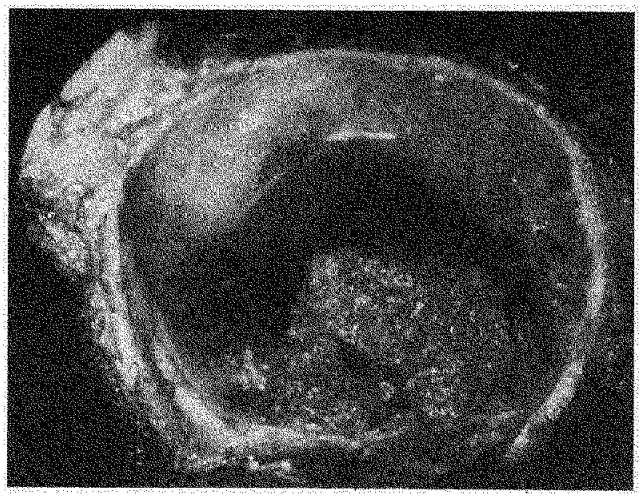

**Fig. 2.** Case 1. Cross section of 10 cm pancreatic tumor showing a thick-walled cavity filled with adherent intracystic necrotic-appearing debris.

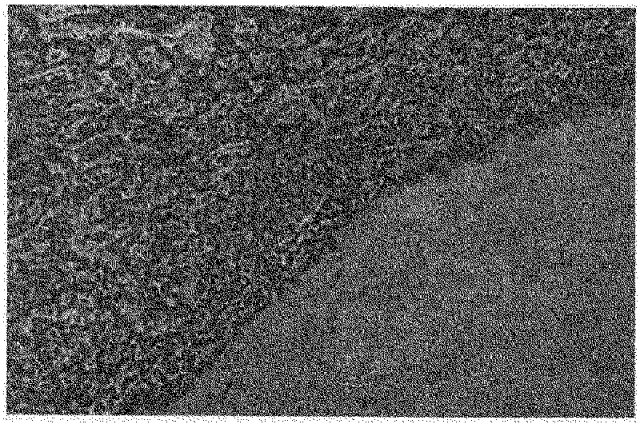

**Fig. 3.** Case 1. Neoplastic epithelial cells arranged in a gyriform pattern surrounded by a dense collagenous capsule. (Hematoxylin and eosin stain; ×100.)

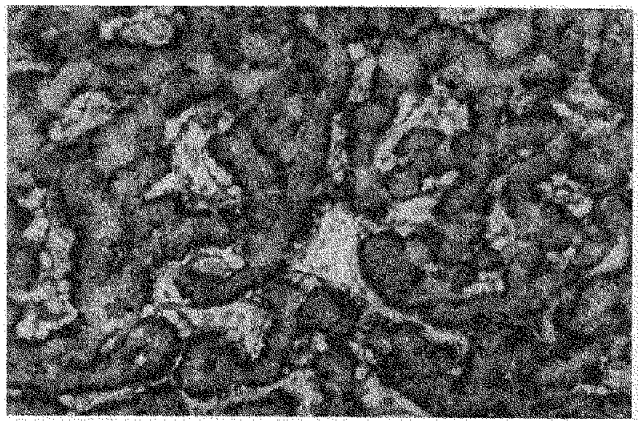

**Fig. 4.** Case 1. Neoplastic cells with strong immunopositivity for glucagon. (Formalin-fixed, paraffin-embedded tissue; ×400.)

Immunohistochemical staining was performed using a modified streptavidin-biotin system. The tumor cells showed diffuse reactivity for glucagon, neuron-specific enolase, synaptophysin, chromogranin, and alpha-1-antitrypsin (Fig. 4). The tumor cells stained focally positive for pancreatic polypeptide and keratin. There was no staining with insulin, vasoactive intestinal polypeptide, gastrin, somatostatin, or serotonin. The diagnosis of cystic glucagonoma was made. The uninvolved resected pancreas showed aberrant distribution of glucagon immunoreactive cells.

## Case 2

A 48-year-old man with no history of diabetes presented to his primary care physician 6 months prior to admission with a 3-month history of fatigue, polyuria, polydipsia, and weight loss. Despite treatment with insulin and oral hypoglycemic agents, his weight loss continued, and an abdominal ultrasound examination was performed, which demonstrated a cystic mass in the body of the pancreas. An abdominal CT scan confirmed the finding and the patient was referred for surgical consultation (Fig. 5). Physical examination findings were unremarkable with no evidence of a rash and no palpable abdominal mass. Hemoglobin was 11 g/dl, serum glucose 215 mg/dl, and serum glucagon 4200 pg/ml (normal <200 pg/ml).

At laparotomy, no evidence of metastatic disease was found, and the patient underwent a 70% distal pancreatectomy and splenectomy. He did well and was discharged on postoperative day 5.

The patient's serum glucagon level remained elevated, with a value of 5700 pg/ml 1 month after the operation.

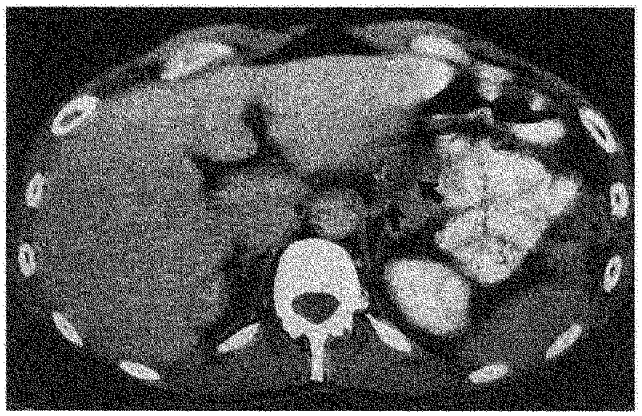

**Fig. 5.** Case 2. CT scan demonstrating cystic tumor *(arrows)* in body of pancreas.

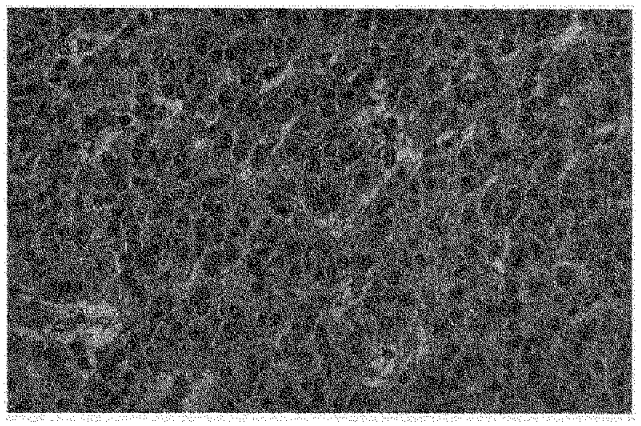

**Fig. 6.** Case 2. Trabecular arrangement of uniform tumor cells with granular cytoplasm. (Hematoxylin and eosin stain; ×400.)

The patient is asymptomatic 26 months postoperatively, with a serum glucagon level of 3000 pg/ml, well-controlled diabetes, and a normal octreotide nuclear scan. He has, however, developed classic Grave's disease and is currently undergoing radioiodine therapy.

Within the distal pancreatectomy specimen was a 4.5 × 3 × 2 cm thick-walled cystic mass filled with hemorrhagic, necrotic debris. Grossly the cyst lining was irregular and focally ulcerated. Sections of the cyst wall revealed a neoplasm encapsulated by a dense fibrous wall. The tumor cells were uniform with acidophilic granular cytoplasm and had round to oval nuclei with clumped chromatin and occasional prominent nucleoli arranged in a trabecular pattern (Fig. 6). The tumor cells stained profusely with glucagon, synaptophysin, chromogranin, neuron-specific enolase, alpha-1-antitrypsin, and keratin. The tumor cells did not display reactivity with insulin, somatostatin, or serotonin. The diagnosis of cystic glucagonoma was made. Within the remainder of the resected pancreas, the islet cells were diffusely hyperplastic with an aberrant distribution pattern that has been described as nesidiodysplasia. The majority of islet cells stained positively for glucagon, synaptophysin, neuron-specific enolase, and to a lesser extent chromogranin. Insulin staining was present in scattered cells and was decreased overall.

## DISCUSSION

Glucagonomas are rare pancreatic neoplasms generally found in the body and tail of the pancreas, the areas of maximum alpha cell concentration. Difficulties in diagnosis related to nonspecific symptoms may contribute to an underestimation of the actual incidence of these tumors.[12,13] Presenting symptoms may include adult-onset diabetes, a migratory necrolytic skin rash with typical histologic changes, weight loss, glossitis, and abdominal pain or a mass.[3,4,14] Other tumors are asymptomatic and found incidentally on imaging studies. Laboratory findings include hyperglycemia, anemia, hypoaminoacidemia, and an elevated serum glucagon level.[3,10] Imaging studies most helpful in the diagnosis include ultrasonography, CT scans, and more recently endoscopic ultrasonography and radiolabeled octreotide scans.[6,15,16] Despite this, delayed diagnosis of these lesions is the rule, with most reports noting the presence of symptoms for years before the diagnosis is finally made.[4,14,17]

Sixty to 80% of glucagonomas are either malignant or metastatic at the time of diagnosis, with regional lymph nodes and liver being the preferred sites of spread.[3,18] As with other neuroendocrine tumors, glucagonomas are slow growing, and excision or surgical debulking of primary or metastatic tumors may result in significant palliation of symptoms.[19-21] For patients with symptomatic recurrent disease not amenable to excision, chemotherapy may provide palliation. Initially, streptozotocin was the drug of choice, but more recently dimethyltriazenylimidazole (DTIC) or somatostatin analogues are being used to manage refractory symptoms.[22,23]

Only six patients with cystic glucagonomas could be found in the English literature.[6-11] Cyst formation in glucagonomas may result from vascular compromise of the normally abundant vascular supply found in neuroendocrine tumors, resulting in central necrosis and cyst formation.[24] It has also been hypothesized that the slow growth of glucagonomas allows a desmoplastic response to form surrounding the tumor, and that this may compromise tumor blood supply.[9,25] The presentation of our second patient was typical for glucagonoma with adult-onset diabetes and weight loss. However, his serum glucagon levels re-

mained elevated postoperatively, because of either occult metastatic disease, diffuse islet cell hyperplasia, or aberrant distribution of glucagon immunoreactive cells, known as nesidiodysplasia.[26]

As with other cystic neoplasms of the pancreas, cystic neuroendocrine tumors may initially be diagnosed as pseudocysts, leading to either inappropriate observation or internal drainage. In some series, as many as one third of patients with cystic tumors have been so treated.[9,27-29] Both patients presented here were originally believed to harbor inflammatory pseudocysts, but the absence of a history of pancreatitis in either rendered this only a remote possibility. In our first patient the vast majority of the cyst wall was composed of fibrous tissue devoid of epithelial lining, but careful pathologic examination revealed a small focus of viable tumor. This case underscores the difficulty in differentiating pseudocysts from cystic pancreatic tumors in which up to three fourths of patients may have significant denuding of the neoplastic epithelial lining.[29] Clearly in such an instance, percutaneous or operative biopsy of the cyst wall could give rise to false information leading to inappropriate therapy.

Cystic glucagonomas are very rare tumors and must be considered in the differential diagnosis of any patient presenting with a cystic lesion of the pancreas and no history of pancreatitis. Complete excision will be curative in many patients.

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# Mucosal Production of Complement C3 and Serum Amyloid A Is Differentially Regulated in Different Parts of the Gastrointestinal Tract During Endotoxemia in Mice

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The effect of endotoxemia and sepsis on mucosal production of the acute-phase proteins complement component C3 and serum amyloid A (SAA) was studied in mice. In addition, the role of the proinflammatory cytokines tumor necrosis factor-alpha, interleukin (IL)-1β, and IL-6 on mucosal C3 and SAA production was examined. Endotoxemia was induced by the subcutaneous injection of 250 μg/mouse of lipopolysaccharide. Control mice were injected with corresponding volumes of sterile saline solution. Sepsis was induced by cecal ligation and puncture, and sham-operated mice served as controls. Endotoxemia resulted in increased mucosal C3 levels in all parts of the gastrointestinal tract examined, from the stomach to the colon, with the most pronounced effects noticed in the proximal gastrointestinal tract. The influence of endotoxemia on mucosal SAA production was more differentiated with increased levels noted in the jejunum and ileum, and no changes seen in gastric and colonic mucosa. Sepsis resulted in similar changes in mucosal C3 and SAA levels as seen in endotoxemic mice, except that SAA levels were increased in colonic mucosa of septic mice. Among the cytokines, IL-1β resulted in the most pronounced changes in mucosal acute-phase proteins. The increase in C3 and SAA levels in the mucosa of the small intestine during endotoxemia was partially blocked by IL-1 receptor antagonist. The results suggest that endotoxemia is associated with increased mucosal C3 production in different parts of the gastrointestinal tract and increased SAA production in the mucosa of the small intestine. Mucosal acute-phase protein synthesis may, at least in part, be regulated by IL-1β. (J GASTROINTEST SURG 1998;2:537-546.)

KEY WORDS: Acute phase, proteins, intestine, sepsis

The acute-phase response is an important component of the host defense during infection and following tissue injury.[1,2] Although the majority of acute-phase proteins are synthesized in the liver, recent evidence suggests that extrahepatic tissues may contribute to the production of acute-phase proteins. Acute-phase proteins synthesized outside the liver may be more important for the local than for the systemic effects, although that is somewhat unclear at present.

Among extrahepatic tissues that produce acute-phase proteins, the intestinal mucosa is particularly important considering its essential immune and barrier functions during sepsis and other critical illness. In recent studies, cultured enterocytes expressed a number of acute-phase proteins, including alpha-1-antitrypsin and complement components C3, C4, and factor B.[3-7] In other studies, mucosal protein synthesis in vivo was increased during both local[8] and systemic inflammation.[9-11]

In recent studies in our laboratory, the production of complement component C3 and serum amyloid A (SAA) was increased in the mucosa of the jejunum during endotoxemia in mice, and increased mucosal messenger RNA (mRNA) levels suggested that the C3 and SAA production was regulated at the transcriptional level.[12] C3 is an important acute-phase protein involved in the local defense against invading bacteria.[13] SAA is one of the most abundant acute-phase proteins in mice[14] and although its functions are

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not completely understood, there is evidence that SAA participates in the clearance of high-density lipoproteins.[15]

It is not known from our previous results[12] whether increased mucosal C3 and SAA production is unique for the jejunum or if other parts of the gastrointestinal tract participate in the acute-phase response as well. In addition, mediators of mucosal acute-phase protein synthesis during sepsis and endotoxemia have not been defined. In the present study, we examined the influence of endotoxemia and sepsis in mice on mucosal levels of C3 and SAA in different parts of the gastrointestinal tract, from the stomach to the colon. In addition, we tested the role of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 in the regulation of mucosal C3 and SAA production. Proinflammatory cytokines regulate acute-phase protein synthesis in the liver[16] and in cultured enterocytes,[3-7] but the role of the cytokines in mucosal acute-phase protein synthesis in vivo is not known.

## MATERIAL AND METHODS

### Experimental Animals

Male A/J mice (20 to 27 g) were purchased from Jackson Laboratory (Bar Harbor, Maine) and housed at a temperature of 22° C in a room with a 12-hour light/dark cycle for 1 week before experiments. Four series of experiments were performed. In the first series of experiments, endotoxemia was induced by the subcutaneous injection of 250 μg/mouse of lipopolysaccharide (*Escherichia coli* 0111:B4, Calbiochem, LaJolla, Calif.). Control mice were injected with a corresponding volume of sterile saline solution. The dose of endotoxin used in these experiments was based on a recent report in which the same dose resulted in increased C3 and SAA levels in the mucosa of the jejunum.[12] Water was provided ad libitum but food was withheld after the injection of endotoxin or saline solution, to avoid the influence of any differences in food intake between the groups on metabolic changes in the intestinal mucosa.

Sixteen hours after injection of endotoxin or saline, mice were anesthetized with pentobarbital (40 mg/kg intraperitoneally) and blood was collected by heart puncture for determination of plasma C3 and SAA levels. The left lobe of the liver, 10 cm segments of the jejunum and ileum, and the entire stomach and colon were excised. Mucosa was harvested by scraping the luminal side with a microscopic slide. The mucosa and the liver specimen were immediately frozen in liquid nitrogen and stored at −70° C until analysis. The time point of 16 hours was chosen based on previous studies in which metabolic changes were observed in intestinal mucosa for 16 hours after the induction of sepsis or injection of endotoxin or proinflammatory cytokines in rats or mice.[9-12,17]

In the second series of experiments, the influence of sepsis on mucosal C3 and SAA production was examined. Sepsis was induced in mice by cecal ligation and puncture (CLP), as described previously.[9-11,17] Control mice were sham operated, that is, they underwent laparotomy and manipulation, but no ligation or puncture, of the cecum. All mice were resuscitated with 100 ml/kg body weight of normal saline administered subcutaneously on the back at the time of surgery. Food was withheld but drinking water was provided ad libitum after the surgical procedures. Sixteen hours after sham operation or CLP, blood and tissues were harvested and stored as previously described for subsequent determination of C3 and SAA.

In the third series of experiments, mice were injected intraperitoneally with 100 μg/kg of human recombinant TNF-α (Endogen Inc., Woburn, Mass.) and an identical dose was repeated after 8 hours. Control mice received corresponding volumes of solvent (phosphate-buffered saline, pH 7.4). Sixteen hours after the first injection, blood and tissue samples were harvested as described earlier. Using an identical protocol, mice were also injected with human recombinant IL-1β (Endogen Inc.) or IL-6 (Endogen Inc.). The doses of cytokines used here were similar to those used in previous reports from our laboratory and in which cytokines induced increased mucosal total protein synthesis.[9]

Because results in the third series of experiments suggested that IL-1β, but not TNF-α or IL-6, stimulated mucosal C3 and SAA production, a fourth experiment was performed to test the role of IL-1 in endotoxin-induced protein synthesis. This was done by treating mice with 15 mg/kg intraperitoneally of recombinant IL-1 receptor antagonist (IL-1ra) (Amgen, Boulder, Colo.) 15 minutes before endotoxin or saline injection. An identical dose was administered after 8 hours. Control mice received corresponding volumes of phosphate-buffered saline (pH 7.4). Sixteen hours after endotoxin or saline injection, blood and tissue samples were harvested as previously described. The protocol for treatment with IL-1ra used here was based on a previous study from our laboratory in which IL-1ra prevented endotoxin-induced muscle proteolysis.[18]

All experiments were performed and the animals were cared for according to the "Guide for the Care and Use of Laboratory Animals" published by the National Research Council. The experimental proto-

cols were approved by the University of Cincinnati Institutional Animal Care and Use Committee.

### Measurement of Complement Component C3 and SAA

Plasma and tissue levels of C3 and SAA were measured by enzyme-linked immunosorbent assay (ELISA). For determination of complement C3 and SAA in mucosa and liver, tissue was ultrasonicated for 20 seconds in 1 ml of phosphate-buffered saline containing 2 μg/ml each of the protease inhibitors leupeptin, aprotinin, pepstatin A, and Antipain (Sigma, St. Louis, Mo.) and 2 mmol/L phenylmethylsulfonyl fluoride (Sigma) and then centrifuged at 12,000 g at 4° C for 30 minutes. The supernates were used for determination of complement C3 and SAA. Complement C3 was determined as previously described[19] using a goat antimouse C3 antibody (IgG fraction 55463, Chappel, Durham, N.C.). SAA was measured with a commercially available ELISA kit (Biosource International, Camarillo, Calif.). The lower limits of detection were 10 ng/ml for complement C3 and 0.23 μg/ml for SAA.

### C3 and SAA mRNA Levels

Northern blot analysis was employed to determine the expression of mucosal and hepatic C3 and SAA mRNA. Mucosal samples were harvested as previously described and samples from three mice were pooled for each time point. RNA was extracted by the guanidinium thiocyanate–phenolchloroform method[20] using an RNA Stat-60 kit (Tel-Test "B" Inc., Friendswood, Tex.).

For Northern blot analysis, RNA was denatured and separated by electrophoresis on 1% agarose gel containing formaldehyde. The RNA was transferred from the gel to nylon membranes (Micron Separations Inc., Westboro, Mass.) by capillary action in 2× SSC (1× SSC = 0.15 mol/L NaCl, 15 mmol/L sodium citrate) overnight. RNA was immobilized either by baking at 80° C for 2 hours or by ultraviolet cross-linking. The blots were hybridized at 42° C for 4 hours in 50% formaldehyde and 6× SSPE (1× SSPE = 0.15 mol/L NaCl, 10 mmol/L $NaH_2PO_4$, and 1 mol/L EDTA), 5× Denhardt's solution, 0.5% SDS, and 100 μg/ml salmon sperm DNA. cDNA probes for C3 and SAA were labeled by random priming with [$^{32}$P] dATP or [$^{32}$P] dCTP (Stratagene, LaJolla, Calif.). The blots were hybridized with the $^{32}$P-labeled cDNA probes at 42° C overnight. The blots were then washed twice in 1× SSC and 0.1% SDS, once in 0.1× SSC and 0.1% SDS at room temperature, and autoradiographed at −70° C. The blots were stripped and rehybridized with an 18S oligonucleotide probe to control for equal loading of RNA.

### Statistics

Results are presented as means ± standard error of the mean. Analysis of variance followed by Tukey's test was used for statistical comparisons.

## RESULTS

There were no deaths among the endotoxemic or saline-injected mice, similar to a previous report in which an identical dose of endotoxin was injected into mice.[17] However, endotoxemic mice exhibited signs of illness in the form of piloerection and moderate lethargy 16 hours after injection of endotoxin. Several of the mice had diarrhea as well.

The C3 concentration was increased approximately 1.5-fold in jejunal mucosa 16 hours after induction of endotoxemia (Fig. 1), similar to a recent report from this laboratory.[12] The present study expanded our previous observations by determining the influence of endotoxemia on mucosal C3 levels in other parts of the gastrointestinal tract in addition to the jejunum. Endotoxemia resulted in increased C3 levels in all parts of the gastrointestinal tract examined, with the most pronounced effect noticed proximally (more than a twofold increase in gastric mucosa) and a smaller increase in the ileum and colon (50% and 80% increase, respectively) (see Fig. 1). The increased liver and plasma levels of C3 noted in Fig. 1 are consistent with an acute-phase response in the endotoxemic mice.

In contrast to C3, mucosal levels of SAA were not consistently elevated throughout the gastrointestinal tract (Fig. 2). The increased SAA levels in the mucosa of the jejunum are similar to the results in a recent report from this laboratory.[12] The elevated SAA levels in the ileum suggest that different segments of the small intestine respond similarly to endotoxin. In contrast, no significant changes in SAA levels were noted in the mucosa of the stomach or the large bowel (see Fig. 2). The almost fourfold and approximately fivefold increases in liver and plasma SAA levels, respectively, illustrate the fact that SAA is a strong acute-phase reactant in mice.[14]

To test whether the changes in mucosal C3 and SAA levels were specific to endotoxemia, we next induced sepsis in mice by CLP. Septic mice exhibited lethargy, piloerection, and diarrhea 16 hours after CLP and had a mortality rate of approximately 25%,

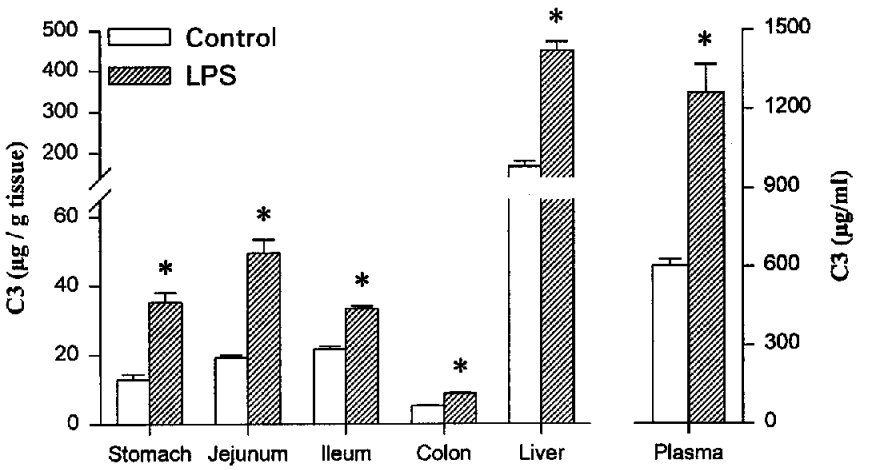


**Fig. 1.** Effect of endotoxemia on mucosal C3 levels in different parts of the gastrointestinal tract and in the liver and plasma. Endotoxemia was induced in mice by subcutaneous injection of 250 μg/mouse of lipopolysaccharide *(LPS)*. Control mice were injected with a corresponding volume of sterile saline solution. C3 was determined by ELISA 16 hours after induction of endotoxemia or saline injection. n = 6 per group. * = $P < 0.05$ vs. control.

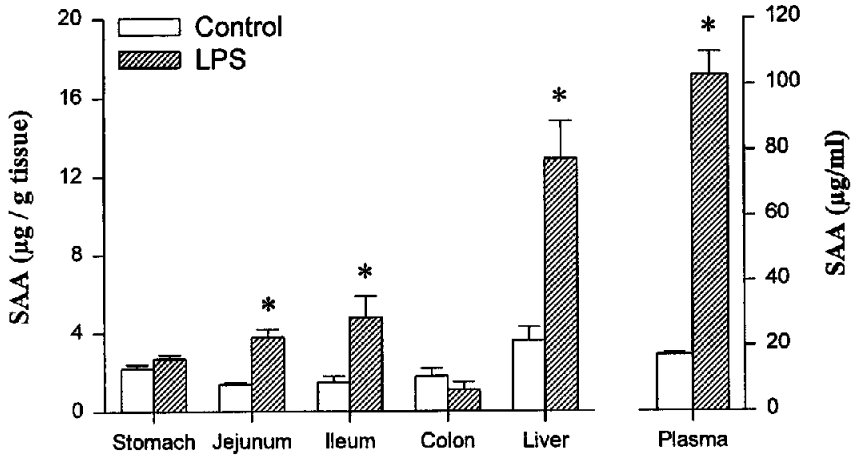


**Fig. 2.** Effect of endotoxemia in mice on mucosal SAA levels in different parts of the gastrointestinal tract and in the liver and plasma. Experimental conditions and symbols were identical to those in Fig. 1.

similar to a previous report.[17] Mucosal C3 levels were increased in all segments of the gastrointestinal tract examined 16 hours after CLP (Fig. 3), similar to the response to endotoxemia (see above). Mucosal SAA levels were unchanged in the stomach and were increased in the jejunum and ileum (Fig. 4), similar to the response to endotoxemia. In contrast, the response to sepsis in the colon of SAA was different than the response to endotoxemia, with an approximately 50% increase in large bowel SAA levels noted in septic mice (Fig. 4) and no changes noted in endotoxemic mice (compare with Fig. 2). The somewhat higher basal C3 and SAA mucosal levels noted in the second compared to in the first series of experiments may reflect the fact that control mice underwent sham operation (laparotomy) in the second series of experiments, whereas in the first experiment control mice only received a subcutaneous injection of saline solution.

In a previous report, the increased mucosal levels of C3 and SAA in the jejunum of endotoxemic mice were associated with increased expression of mRNA for the proteins.[12] Because C3 mRNA concentrations were too low to be detected by Northern blot analy-

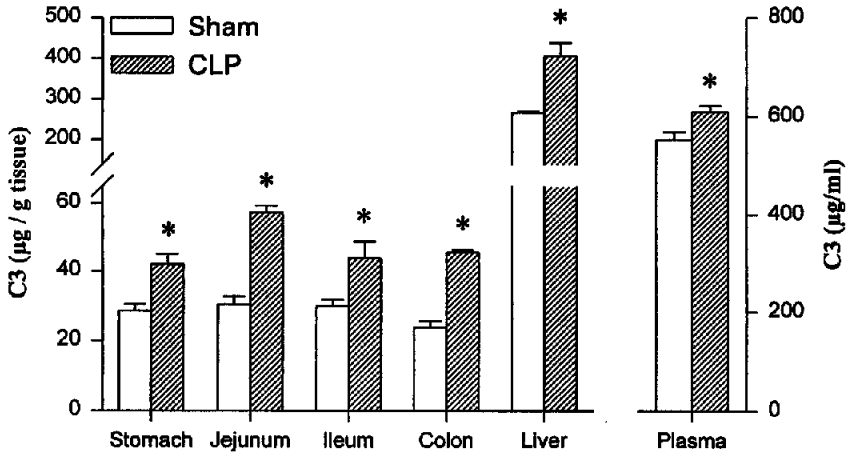


**Fig. 3.** Effect of sepsis on mucosal C3 levels in different parts of the gastrointestinal tract and in the liver and plasma. Sepsis was induced in mice by CLP. Sham-operated mice served as controls. C3 was determined by ELISA 16 hours after CLP or sham operation. n = 6 per group. * = $P < 0.05$ vs. control.

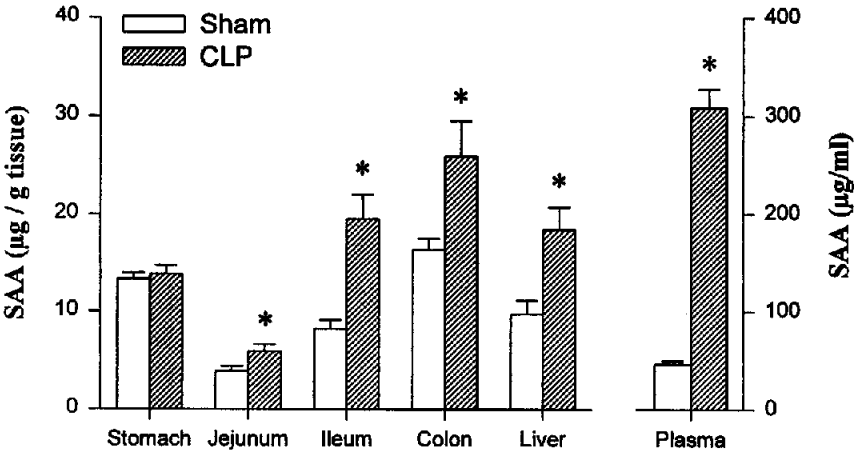


**Fig. 4.** Effect of sepsis in mice on mucosal SAA levels in different parts of the gastrointestinal tract and in the liver and plasma. Experimental conditions and symbols were identical to those in Fig. 3.

sis, polymerase chain reaction (PCR) was performed in that study. In the present experiments, no signal for C3 mRNA was detected by Northern blot analysis in any part of the gastrointestinal tract in control or endotoxemic mice, similar to our previous report,[12] whereas C3 mRNA levels were detected in the liver of control mice and were increased during endotoxemia (Fig. 5).

SAA mRNA was not expressed in the mucosa of the stomach, jejunum, and ileum of saline-injected control mice but was induced in the mucosa of the jejunum and ileum of endotoxemic mice (Fig. 6). The SAA transcript was strongly expressed in colonic mucosa of control mice and was increased during endotoxemia. Liver tissue expressed SAA mRNA constitutively and a massive increase in SAA mRNA concentrations was noted in the liver of endotoxemic mice (Fig. 6). Thus some of the changes in SAA mRNA levels paralleled changes in protein levels (increased SAA protein and mRNA levels in the jejunum, ileum, and liver), whereas the unchanged SAA protein levels in colonic mucosa were associated with increased mRNA levels. In gastric mucosa, no changes in protein or mRNA levels were noted in endotoxemic mice.

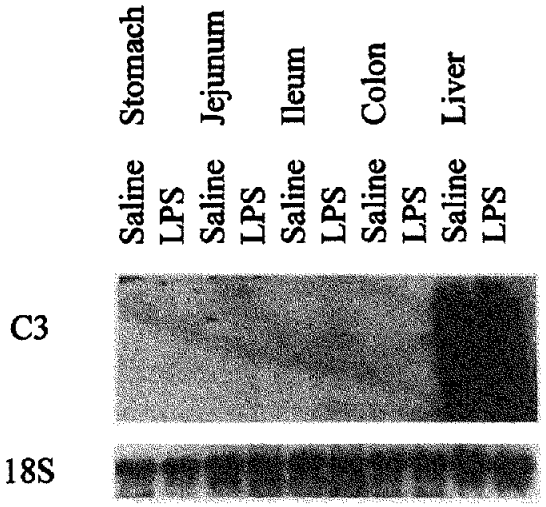


Fig. 5. Northern blot analysis of RNA extracted from mucosa of different parts of the gastrointestinal tract and from the liver of saline-injected control mice and endotoxemic mice *(LPS)*. No evidence of expression of C3 mRNA was found in intestinal mucosa 16 hours after injection of saline or endotoxin.

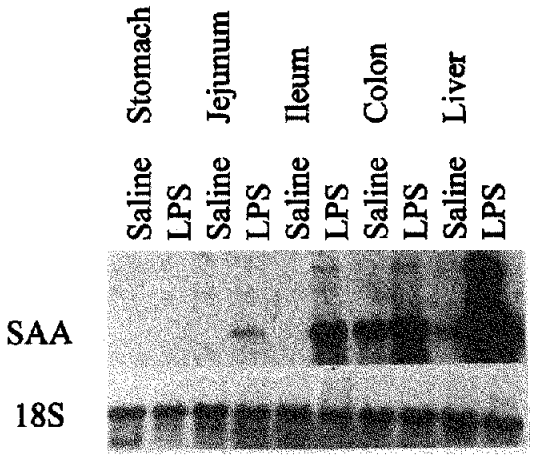


Fig. 6. SAA mRNA in mucosa of different parts of the gastrointestinal tract and the liver determined by Northern blot analysis in saline-injected control mice and endotoxemic mice *(LPS)*.

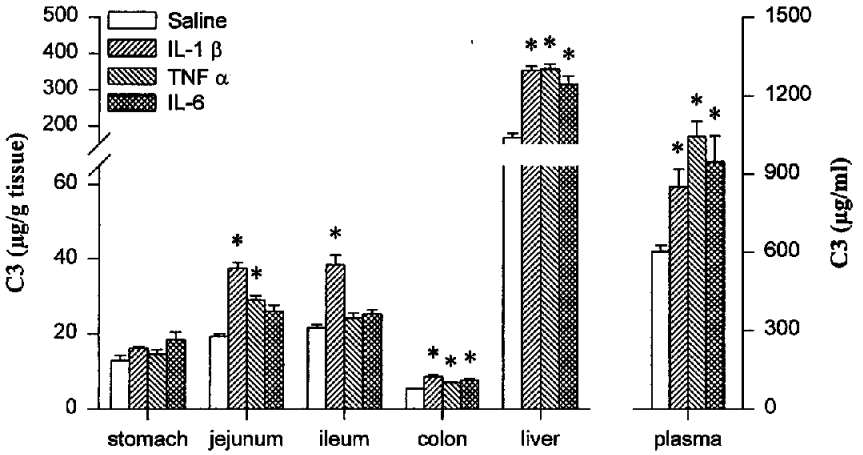


Fig. 7. C3 levels in mucosa of different parts of the gastrointestinal tract and in the liver and plasma of mice injected with saline or one of the proinflammatory cytokines: IL-1β, TNF-α, or IL-6. For details of experimental conditions, see text. n = 6 per group. * = $P < 0.05$ vs. saline-injected control group by analysis of variance.

To test the role of proinflammatory cytokines in the regulation of mucosal C3 and SAA production, mice were injected with TNF-α, IL-1β, or IL-6. Treatment of mice with IL-1β resulted in increased mucosal C3 levels in the jejunum, ileum, and colon (Fig. 7) TNF-α increased C3 production in the jejunum. A small (but statistically significant) increase in C3 levels in the mucosa of the colon was noted following injection of TNF-α or IL-6. All three cytokines stimulated C3 production in the liver, which probably also explains why plasma C3 levels were increased by all cytokines.

Mucosal SAA levels increased in the ileum following treatment with IL-1β (Fig. 8). No other changes in mucosal SAA levels were seen in any part of the gastrointestinal tract after injection of either cytokine.

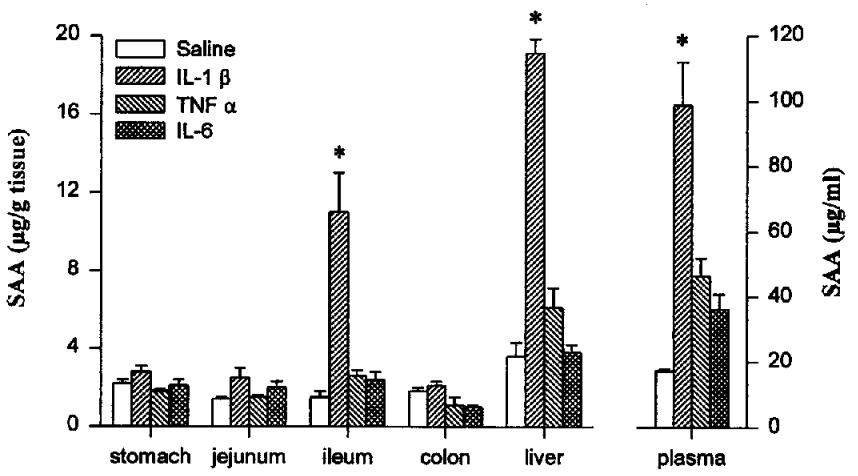


**Fig. 8.** SAA levels in mucosa of different parts of the gastrointestinal tract and in the liver and plasma following injection of mice with saline or one of the proinflammatory cytokines: IL-1β, TNF-α, or IL-6. Experimental conditions and symbols were identical to those in Fig. 7.

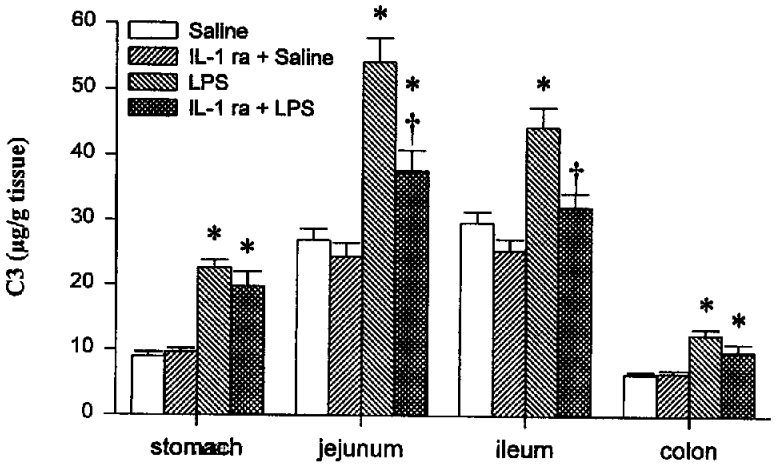


**Fig. 9.** Effect of IL-1ra on endotoxin-induced changes in mucosal C3 levels. Groups of saline-injected or endotoxemic mice were treated with repeated injections of IL-1ra or corresponding volumes of solvent (phosphate-buffered saline, pH 7.4). n = 6 per group. * = $P < 0.05$ vs. corresponding saline-injected group; † = $P < 0.05$ vs. lipopolysaccharide *(LPS)*.

Liver and plasma levels of SAA were increased by IL-1β but not by TNF-α or IL-6 (Fig. 8).

Because the results in the third series of experiments suggested that IL-1β may be particularly important among the proinflammatory cytokines in regulating mucosal C3 and SAA production, the role of IL-1 in endotoxin-induced mucosal C3 and SAA production was tested by treating endotoxemic mice with IL-1ra. Treatment of mice with IL-1ra did not influence basal C3 levels but blocked the endotoxin-induced increase in C3 levels in the mucosa of the jejunum and ileum (Fig. 9), suggesting that IL-1 participates in the regulation of mucosal C3 production during endotoxemia in these parts of the gastrointestinal tract. Similar results were noted for SAA following treatment with IL-1ra (Fig. 10).

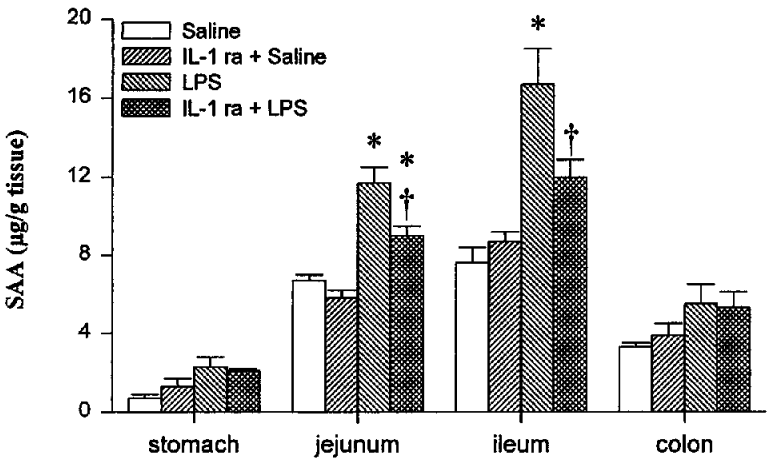


**Fig. 10.** Effect of IL-1ra on endotoxin-induced changes in mucosal SAA levels. Experimental conditions and symbols were identical to those in Fig. 9.

## DISCUSSION

Results of the present study suggest that endotoxemia in mice is associated with increased mucosal C3 production in all parts of the gastrointestinal tract and with a selective increase in small intestinal SAA production. The effect of endotoxemia on C3 production was most pronounced in the mucosa of the stomach and jejunum and least pronounced in the colon, which is consistent with a proximal-distal gradient of C3 production during endotoxemia. The response to endotoxin of SAA production was even more differentiated with no changes seen in gastric or colonic mucosa, but increased production was noted in the mucosa of the jejunum and ileum. Although the response of colonic SAA to endotoxemia and sepsis was different, other changes in mucosal SAA and C3 were similar in endotoxemic and septic mice, indicating that changes observed after injection of endotoxin reflected changes in a clinically relevant model of sepsis. The results from the experiments in which normal mice were treated with cytokines and endotoxemic mice were treated with IL-1ra suggest that C3 and SAA production may, at least in part, be regulated by IL-1β in the mucosa of the small intestine. It should be noted that although biologic effects of repeated injections of IL-1ra were seen here and in a previous report from our laboratory,[18] it is possible that the role of IL-1 is underestimated with this protocol. Because of the short half-life of IL-1ra,[18] a constant infusion of IL-1ra may be necessary to fully assess the role of IL-1 in a metabolic response.

The influence of endotoxemia on mucosal C3 production was examined in the present study because C3 is particularly important for the inflammatory response in the intestine. Complement C3 causes the classical and alternative pathways to converge into a final common pathway in the complement cascade, which participates in the local defense against invading microorganisms and may cause lysis of bacteria.[13] SAA was studied because it is the major acute-phase protein in mice.[14,21] Although the exact biologic role of SAA in the acute-phase response is unidentified, SAA is an apoprotein of high-density lipoprotein and may influence the formation and clearance of high-density lipoproteins.[15]

Although we interpreted our results of changes in mucosal C3 and SAA levels as indicative of changes in mucosal production of the proteins, this interpretation should be viewed with caution for several reasons. First, increased mucosal levels of the acute-phase proteins may represent local deposition of circulating proteins. This was less likely in the present study, however, because the increase in mucosal concentrations of C3 was different in different parts of the gastrointestinal tract and SAA levels were unchanged in gastric and colonic mucosa, despite a substantial increase in circulating SAA levels. In addition, we recently found that the increased C3 and SAA levels in jejunal mucosa of endotoxemic mice were not influenced by perfusion of the intestinal vasculature prior to harvesting of the mucosa.[12]

Second, increased mucosal C3 and SAA levels do not necessarily reflect increased production but may also be caused by reduced degradation and/or secretion of the proteins from the mucosa. The increased mRNA levels for SAA noted here in the mucosa of the jejunum and ileum and for C3 determined by PCR in jejunal mucosa in our previous report[12] support (but do not prove) the concept of upregulated local production of C3 and SAA.

Third, the cellular origin of the acute-phase proteins is not known from the current study. Mucosa harvested by means of the present technique contains multiple cell types from both the lamina propria and submucosa, including enterocytes, macrophages, lymphocytes, endothelial cells, and smooth muscle cells. Previous studies using cultured enterocytes in vitro[3-7] or immunohistochemistry in vivo[12] suggest that the enterocyte may be a source of acute-phase proteins during endotoxemia, although other cell types in the mucosa may also contribute to the acute-phase response.

In a previous report, we examined the influence of sepsis on total protein synthesis in different parts of the gastrointestinal tract.[10] Mucosal protein synthesis, measured in vivo following a flooding dose of $^{14}$C-leucine, was increased during sepsis in the small and large intestine and was decreased in the stomach. Thus total protein synthesis as well was differentially regulated in different parts of the gastrointestinal tract, although the changes in total protein synthesis and C3 and SAA levels were not identical. Changes in total protein synthesis reflect changes in the mucosal production of a number of different proteins in addition to C3 and SAA, and changes in the production rate of individual proteins may not be reflected in total protein synthesis.

The present finding of a regulatory role for IL-1β in mucosal C3 and SAA production is similar to results of recent in vitro studies in which cultured Caco-2 cells were treated with different cytokines.[3-7] Although TNF and IL-6 stimulated C3 production in the cultured enterocytes, IL-1β was the most potent mediator resulting in more than a threefold increase in C3 production.[7] The stimulatory effect of IL-1β on acute-phase protein synthesis in cultured Caco-2 cells suggests that the effect noted here following administration of IL-1β in vivo may reflect a direct effect of the cytokine. The regulatory effect of IL-1 on enterocyte acute-phase protein synthesis is particularly interesting in light of previous reports of increased mucosal levels of IL-1 in endotoxemic mice.[22] It remains to be determined whether enterocyte acute-phase protein synthesis is regulated in vivo in an autocrine or a paracrine fashion by cytokines locally produced in the mucosa or by cytokines produced elsewhere in the body and reaching the enterocyte through the circulation.

The upregulated C3 production in the mucosa of the jejunum and ileum after treatment of mice with IL-1β and the inhibited C3 production in endotoxemic mice by IL-1ra strongly support a role for IL-1 in C3 production in these parts of the gastrointestinal tract. Similar conditions were found for SAA in the mucosa of the ileum. The reason for the apparently contradictory results regarding SAA levels in the mucosa of the jejunum (unchanged SAA levels following injection of IL-1β and reduced SAA levels following treatment of endotoxemic mice with IL-1ra) is not known at present. It may be speculated that SAA production is less sensitive to IL-1β in the jejunum than in the ileum, and a higher dose of IL-1β may be needed to induce SAA production in the mucosa of the jejunum. Further experiments will be needed to test that possibility.

The lack of effect of IL-6 on mucosal C3 and SAA production noted here and in previous in vitro experiments[7] is noteworthy because IL-6 is the most prominent regulator of acute-phase protein synthesis in the liver.[16] This finding suggests that the production of certain acute-phase proteins may be regulated by different mediators and mechanisms in different cell types.

The mechanism of the differential regulation of C3 and SAA production along the gastrointestinal tract during endotoxemia and sepsis is not known from the present study. It may be speculated that the responsiveness to cytokines or other endotoxin-induced mediators may be different in enterocytes from different regions of the intestine. Alternatively, the mucosal production of regulatory cytokine(s) may vary along the gastrointestinal tract. It is also possible that the time course of the mucosal acute-phase protein synthesis during sepsis and endotoxemia may be different in different parts of the gastrointestinal tract, something that would not be appreciated if only one time point is studied, as in the present report. It will be important in future studies to determine the biologic significance of mucosal acute-phase proteins and their differential expression at different levels of the gastrointestinal tract.

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# Gastroesophageal Reflux Disease and Mucosal Injury With Emphasis on Short-Segment Barrett's Esophagus and Duodenogastroesophageal Reflux

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Gastroesophageal reflux disease has been associated with long segments of Barrett's esophagus (≥3 cm), but little is known about its association with shorter segments. The aim of this study was to evaluate anatomic and physiologic alterations of the cardia and esophageal exposure to gastric and duodenal juice in patients with short and long segments of Barrett's esophagus. Furthermore, these patients were compared to each other and to patients with erosive esophagitis and those with no mucosal injury. Two hundred sixty-two consecutive patients with foregut symptoms were divided into the following four groups based on endoscopic and histologic findings: group 1, no mucosal injury; group 2, erosive esophagitis; group 3, short-segment Barrett's esophagus; and group 4, long-segment Barrett's esophagus. Esophageal exposure time to acid and bilirubin, lower esophageal sphincter characteristics, and endoscopic anatomy of the cardia were compared between the groups. Patients with short-segment Barrett's esophagus had elevated esophageal acid and bilirubin exposure, decreased lower esophageal sphincter pressure and length, and a high incidence of hiatal hernia. These abnormalities were similar to those in patients with esophagitis and in general less profound than those found in patients with long-segment Barrett's esophagus. The length of intestinal metaplasia was higher in patients with a defective lower esophageal sphincter. Short-segment Barrett's esophagus is a complication of severe gastroesophageal reflux disease and is associated with the reflux of both gastric and duodenal juice similar to that seen in patients with long-segment Barrett's esophagus. (J GASTROINTEST SURG 1998;2:547-554.)

KEY WORDS: Barrett's esophagus, short-segment Barrett's

Traditionally Barrett's esophagus has been defined by the presence of columnar lining of 3 cm or more in the distal esophagus. This defining measurement was arbitrary. Later it was recognized that the presence of intestinal metaplasia in the columnar-lined segment was associated with the risk of adenocarcinoma.[1-3] Consequently the current definition of Barrett's esophagus is the presence of a columnar-lined esophagus of any length, in which intestinal metaplasia is confirmed histologically. It has been subsequently shown that adenocarcinoma may arise in both short and long segments of intestinal metaplasia.[4,5] This provides an explanation for the parallel increase in the incidence of adenocarcinoma of the esophagus and the gastroesophageal junction.[6-8]

The association of duodenogastroesophageal reflux with long segments of Barrett's esophagus is now well established,[9-13] and has been suggested to play a role in the development of Barrett's esophagus and its progression to malignancy.[9-15] Little is known of the composition of reflux in patients with segments of intestinal metaplasia less than 3 cm in length. The aim of this study was to evaluate esophageal exposure to gastric and duodenal juice in patients with short and long segments of Barrett's esophagus, and to compare them to each other and to patients with esophagitis and those with no mucosal injury. The status of the lower esophageal sphincter was also compared.

## PATIENTS AND METHODS

### Patient Population

Between April 1993 and April 1997, 281 consecutive patients (177 males and 104 females; median age

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53.4 years [range 18 to 89 years]) with symptoms of foregut disease and no previous history of gastric or esophageal surgery were examined. Patients with a named motility disorder were excluded. The foregut symptoms consisted of heartburn, regurgitation, dysphagia, chest pain, epigastric pain, or symptoms suggestive of aspiration such as recurrent pneumonia, wheezing, and persistent cough. All patients underwent upper gastrointestinal endoscopy with biopsy, standard esophageal manometry to evaluate the lower esophageal sphincter, and 24-hour esophageal pH and spectrophotometric bilirubin monitoring to measure esophageal exposure time to gastric and duodenal juice. Nineteen patients were excluded because of technical problems with bilirubin monitoring. In the remaining 262 patients, esophageal acid and bilirubin exposure time, lower esophageal sphincter characteristics, and the anatomy of the cardia as seen on endoscopy were analyzed. Medications known to affect gastrointestinal motility or acid secretion were discontinued 3 days before testing, except for omeprazole, which was discontinued at least 2 weeks earlier.

## Diagnostic Methods

***Stationary Manometry.*** Standard stationary motility was performed after an overnight fast. Lower esophageal sphincter resting pressure was measured at the respiratory inversion point as previously described.[16] The resting pressure, overall length, and abdominal length were calculated from the mean of five recordings. A structurally defective sphincter was defined by the presence of one or more of the following: a resting pressure of less than 6 mm Hg, overall sphincter length of less than 2 cm, or abdominal length of less than 1 cm.

***Ambulatory 24-Hour Esophageal pH Monitoring.*** Esophageal pH monitoring was performed using a glass electrode (Ingold Inc., Urdorf, Switzerland) placed 5 cm above the upper border of the manometrically defined lower esophageal sphincter. Esophageal pH was recorded on a portable digital data recorder and analyzed as previously described.[17] The subjects were instructed to carry out their normal daily activities but to avoid strenuous exertion. A diary was kept of food and fluid intake, symptoms, and time spent in the supine and upright positions. Patients with esophageal pH <4 for more than 4.4% of the recording time were classified as having increased esophageal acid exposure.

***Ambulatory 24-Hour Spectrophotometric Bilirubin Monitoring.*** A fiberoptic probe designed to detect bilirubin[18-20] (Bilitec 2000, Medtronic-Synectics, Shoreview, Minn.) was passed transnasally and positioned at the same level as the pH electrode. Esophageal bilirubin exposure was measured by spectrophotometry based on the specific light absorption of bilirubin at a wavelength of 453 nm and recorded on a portable optoelectric data logger.[18-20] An absorbance threshold of 0.2 was selected and bilirubin exposure was quantified as the percentage of time above this threshold.[20-21] The fiberoptic probe was calibrated in water before and after monitoring. Records with a bilirubin absorbance drift equal to or greater than 0.15 were discarded. The patients were instructed to follow a special diet, which involved restriction to three meals a day and no food with an absorbance similar to that of bilirubin.[13] Twenty-four-hour bilirubin absorbance data were analyzed with a software program (Gastrosoft, Irving, Tex.) to calculate the total percentage of time the bilirubin absorbance was greater than 0.2 during the total monitored period. Based on the study of 35 healthy volunteers, the upper limit of normal for bilirubin exposure above the absorbance threshold of 0.2 was 1.7% of the total time.[12,20,21] Patients with increased esophageal acid exposure and normal bilirubin exposure were classified as having gastric reflux, and those with an increase in both acid and bilirubin exposure were classified as having duodenogastric reflux.

***Endoscopy.*** Three endoscopic measurements were made in all patients. First was the location of the diaphragmatic crura, identified by having the patient sniff. Second was the location of the gastroesophageal junction, defined by the proximal extent of the gastric rugal folds. Third was the squamocolumnar junction, identified by the change from pink-appearing glandular mucosa to the white, pearly appearing squamous mucosa. Patients with an irregular squamocolumnar junction that coincided with the gastroesophageal junction had biopsies obtained from the pink tongues that extended up into the squamous epithelium. In patients whose squamocolumnar junction was separated from the gastroesophageal junction, biopsies were obtained from four quadrants of the gastroesophageal junction and at every 2 cm interval up to the squamocolumnar junction. The location of each biopsy was recorded. A hiatal hernia was diagnosed when the difference between the position of the crural impression and the gastroesophageal junction was 2 cm or more. The presence of erosive esophagitis was noted.

***Histology.*** All biopsy specimens underwent routine fixation and staining with hematoxylin and eosin. Patients were identified as having Barrett's esophagus by the presence of intestinal metaplasia in an esophagus lined by columnar mucosa. Specialized intestinal metaplasia was identified by the presence of well-defined goblet cells within columnar epithelium.

When there was any doubt, goblet cells were confirmed by Alcian blue staining at pH 2.5. The extent of Barrett's esophagus was defined as the distance from the gastroesophageal junction to the location of the highest point of the squamocolumnar junction.

***Definition of Study Groups.*** The patients were divided into the following groups: (1) patients with an endoscopically normal-appearing esophagus and cardia or those with an irregular squamocolumnar junction in whom no intestinal metaplasia could be found on histolologic examination; (2) patients similar to group 1 except for the presence of erosive esophagitis; (3) patients with columnar lining of the esophagus and intestinal metaplasia on histologic examination, extending less than 3 cm up into the esophagus; and (4) patients with endoscopic evidence of esophageal columnar lining and intestinal metaplasia, extending 3 cm or more into the esophagus.

## Statistics

Fisher's exact test was used to compare proportions between individual groups. Comparisons of proportions between more than two groups were performed using the chi-square test. The Kruskal-Wallis test was used to compare continuous data between more than two groups, and the Mann-Whitney U test was used to compare continuous data between individual groups. Values are expressed as medians and interquartile ranges unless otherwise stated. A $P$ value of less than 0.05 was accepted as significant.

## RESULTS

Demographic data for each of the four study groups are shown in Table I. There was no difference in age distribution, but there was a tendency toward male predominance in all groups with mucosal injury. Thirty (11.5%) of the 262 patients had segments of Barrett's esophagus shorter than 3 cm. The mean length was 1.6 cm and ranged from 1 to 2 cm. Thirty-two patients (12.2%) had segments of Barrett's esophagus longer than 3 cm. Their mean length was 6.2 cm and ranged from 3 to 14 cm. This resulted in an overall prevalence of Barrett's esophagus of 23.7%.

Table II compares the median time and the prevalence of increased esophageal acid and bilirubin exposure. Both progressively increased from patients with no mucosal injury to patients with esophagitis and Barrett's esophagus. Esophageal exposure to acid was significantly higher in patients with short segments of Barrett's esophagus when compared to patients with no mucosal injury, but did not differ from values in the group with esophagitis. Patients with long-segment Barrett's esophagus had the highest acid exposure and were significantly different from all other groups.

**Table I.** Demographic data

| Group | No. of patients | Male : Female ratio | Age (yr) | |
|---|---|---|---|---|
| | | | Median | Range |
| 1—No mucosal injury | 130 | 69:61 | 51 | 18-89 |
| 2—Esophagitis | 70 | 48:22* | 53 | 25-80 |
| 3—Barrett's esophagus <3 cm | 30 | 22:8 | 50 | 22-74 |
| 4—Barrett's esophagus ≥3 cm | 32 | 23:9 | 53 | 33-83 |

*$P$ <0.05 vs. no mucosal injury.

**Table II.** Esophageal acid and bilirubin exposure

| Group | % Time pH <4 (range) | Prevalence of increased acid exposure | % Time bilirubin absorbance >0.2 (range) | Prevalence of increased bilirubin exposure |
|---|---|---|---|---|
| 1—No mucosal injury | 3.0 (0.6-6.0) | 35.4 | 0.1 (0.0-2.6) | 30.0 |
| 2—Esophagitis | 8.0 (6.0-11.6)* | 80.0* | 4.2 (0.2-21.7)* | 61.4* |
| 3—Short-segment Barrett's esophagus | 9.4 (6.1-14.8)* | 93.3* | 7.9 (1.2-18.4)* | 73.3* |
| 4—Long-segment Barrett's esophagus | 27.1 (15.7-41.0)† | 96.9‡ | 15.7 (4.2-30.5)‡ | 84.4‡ |

Values expressed as medians and interquartile ranges.
*$P$ <0.05 vs. group 1.
†$P$ <0.05 vs. all groups.
‡$P$ <0.05 vs. groups 1 and 2.

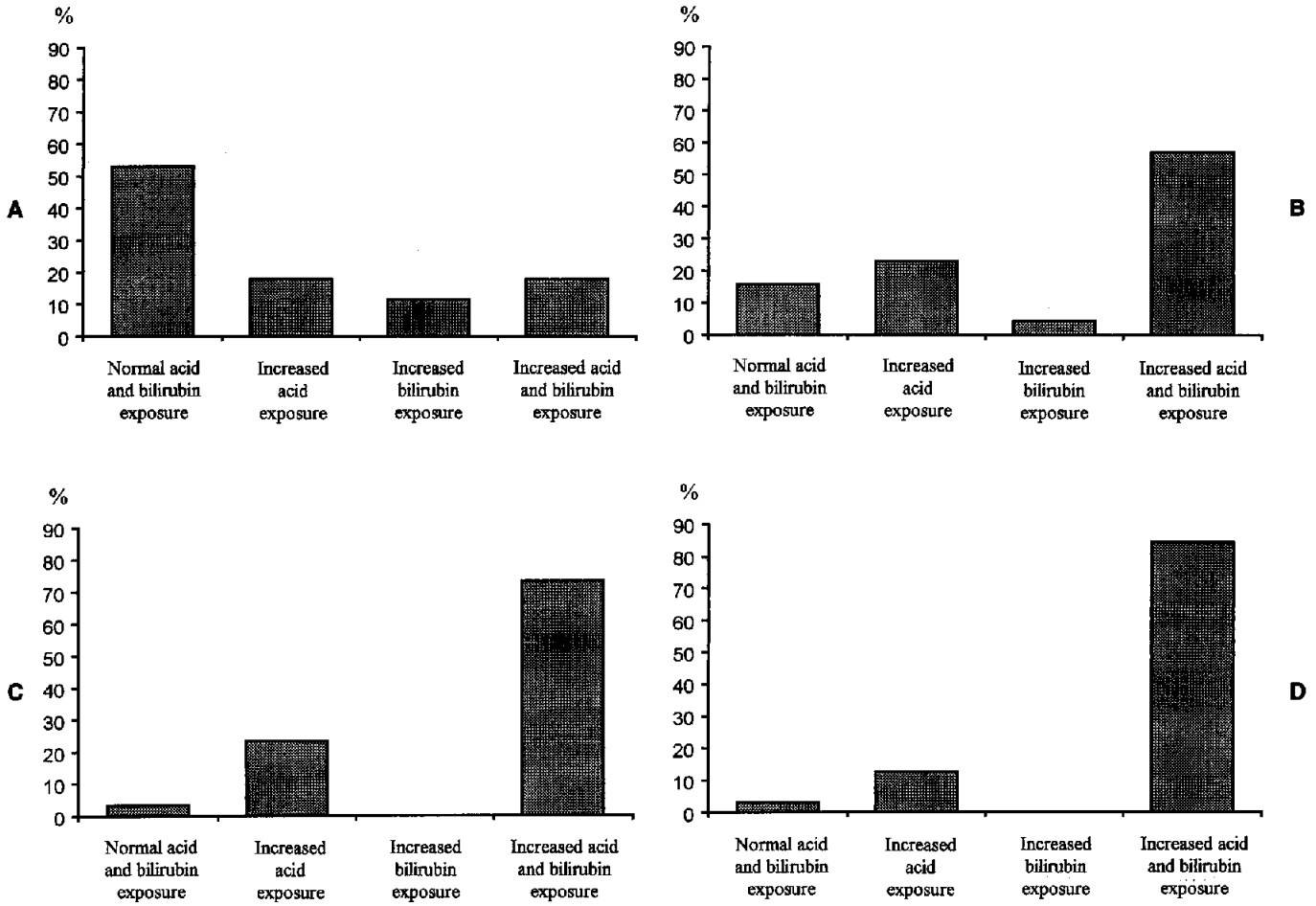


**Fig. 1.** Prevalence of normal esophageal acid and bilirubin exposure, increased esophageal acid exposure only, increased esophageal bilirubin exposure only, and increases in both acid and bilirubin exposure in patients with no mucosal injury **(A)**, erosive esophagitis **(B)**, and short **(C)** and long **(D)** segments of Barrett's esophagus.

**Table III.** Lower esophageal sphincter (LES) characteristics

| Group | LES pressure (mm Hg) | Abdominal length (cm) | Prevalence of defective LES |
|---|---|---|---|
| 1—No mucosal injury | 11.0 (5.6-16.5) | 1.2 (0.6-1.8) | 51.5 |
| 2—Esophagitis | 5.8 (3.4-8.4)* | 0.6 (0.2-1.0)* | 85.7* |
| 3—Short-segment Barrett's esophagus | 5.8 (3.4-10.2)* | 0.8 (0.2-1.4)* | 73.3* |
| 4—Long-segment Barrett's esophagus | 4.7 (1.7-6.7)† | 0.2 (0.0-0.8)‡ | 93.8‡ |

Values expressed as medians and interquartile ranges.
*$P$ <0.05 vs. group 1.
†$P$ <0.05 vs. all groups.
‡$P$ <0.05 vs. groups 1 and 3.

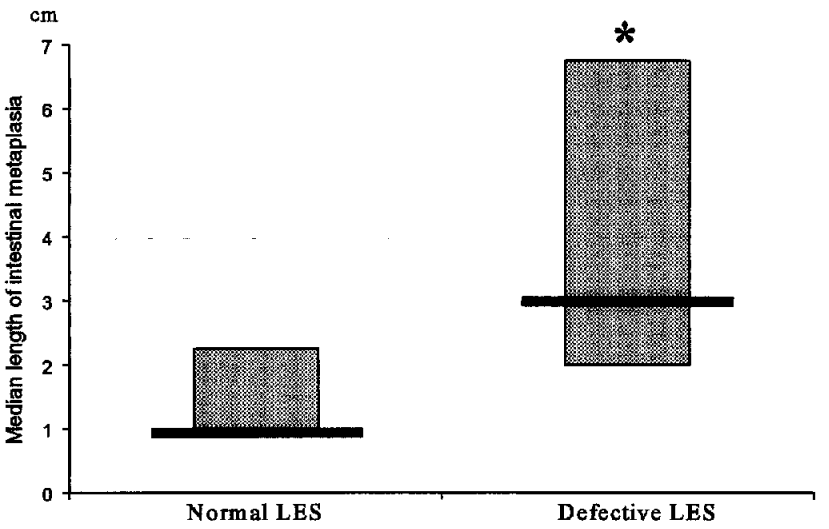


**Fig. 2.** Length of intestinal metaplasia (medians and interquartile ranges) in the presence of a normal and a defective lower esophageal sphincter (LES). * = $P < 0.05$ vs. patients with a normal LES.

There was also a similar progressive increase in the median time of esophageal bilirubin exposure and the prevalence of abnormal bilirubin exposure from patients with no mucosal injury to those with esophagitis and Barrett's esophagus. Patients with short-segment Barrett's esophagus had a significantly higher prevalence of abnormal exposure and a higher median time of bilirubin exposure compared to patients with no mucosal injury but did not differ from those with esophagitis or long-segment Barrett's esophagus.

The composition of the juice refluxed into the esophagus can be acid, bile, or both. These components are related to mucosal injury in Fig. 1. The reflux of bilirubin alone was uncommon. Fifty-three percent of the patients with no mucosal injury had normal esophageal acid and bilirubin exposure suggesting that they did not have gastroesophageal reflux disease. By contrast, in all groups demonstrating mucosal injury, the combination of abnormal esophageal acid and bilirubin exposure had a high prevalence; this was particularly true of patients with long-segment Barrett's esophagus.

Lower esophageal sphincter characteristics are related to mucosal injury in Table III. There was a progressive loss of lower esophageal sphincter pressure and abdominal length as the degree of mucosal injury progressed from no injury to esophagitis, to short- and long-segment Barrett's esophagus. Of interest, when all patients with Barrett's esophagus were classified according to the presence of a normal or a defective sphincter, those with the latter had a significantly greater length of Barrett's mucosa (Fig. 2).

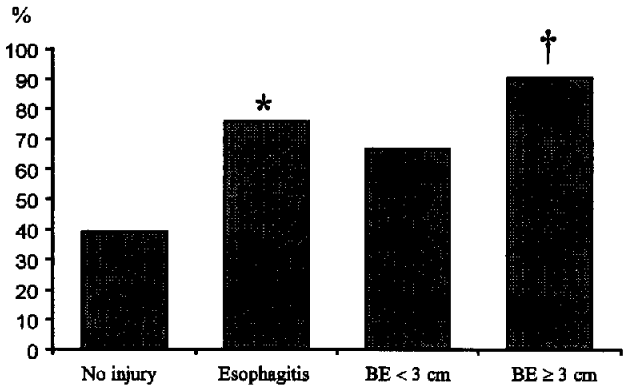


**Fig. 3.** Prevalence of hiatal hernia in patients with no mucosal injury, erosive esophagitis, and short and long segments of Barrett's esophagus. * = $P < 0.05$ vs. patients with no mucosal injury; † = $P < 0.05$ vs. patients with no mucosal injury and esophagitis.

Fig. 3 relates the prevalence of altered anatomy of the cardia, as reflected endoscopically by the presence of a hiatal hernia, to the degree of esophageal mucosal injury. A hiatal hernia was very common in all groups with mucosal injury.

## DISCUSSION

This is the first study of esophageal acid and bilirubin exposure in patients with short segments of Barrett's esophagus. A major observation was that patients with short-segment Barrett's esophagus have increased esophageal exposure not only to acid but

also to duodenal juice. The magnitude of this exposure is comparable to that observed in patients with esophagitis but less than that observed in patients with traditional long-segment Barrett's esophagus. This emphasizes that even a short segment of Barrett's esophagus is a manifestation of severe reflux disease and suggests that its underlying etiology is similar to that of the traditional long-segment Barrett's esophagus.

The mechanism by which duodenal reflux produces injury to esophageal mucosa has been extensively studied both experimentally and clinically. Acid alone, at physiologic concentrations, is relatively harmless but facilitates the action of pepsin.[22-24] Both pepsin and trypsin, in the appropriate pH environment, affect intercellular substances causing shedding of epithelial cells.[24,25] Bile acids affect primarily cell membranes and intracellular organelles.[26] It appears that an acidic environment is needed to augment the ability of bile salts to penetrate into the mucosa.[27] This is consistent with the observation that combined reflux of both acid and duodenal juice results in a high prevalence of esophageal mucosal injury.

In parallel with the abnormalities in esophageal acid and bilirubin exposure found in patients with short-segment Barrett's esophagus, mechanical alterations were also observed. These were manifested anatomically by the presence of hiatal hernias and physiologically by deterioration in the length and resting pressure of the lower esophageal sphincter. The degrees to which both occurred were comparable to the findings in patients with esophagitis but were less profound than what was observed in patients with long-segment Barrett's esophagus. These data, along with the observation that the length of Barrett's mucosa was longer in the presence of a structurally defective lower esophageal sphincter, suggest that short segments of Barrett's mucosa are an intermediate step in the development of longer segments. According to this theory, when the sphincter completely deteriorates, the length of Barrett's mucosa rapidly increases. However, this hypothesis would require a longitudinal study to be tested.

The similarities in the composition of the regurgitated gastric juice and in the lower esophageal sphincter profile in patients with short segments of Barrett's esophagus and those with esophagitis raises the question of why one group develops intestinal metaplasia and the other does not. Possible explanations for the pathogenesis of Barrett's mucosa in this context include the duration of reflux disease, the composition of the refluxate, and/or underlying genetic traits. The development of Barrett's mucosa, in contrast to esophagitis, may require a more prolonged exposure to gastric and duodenal juice than esophagitis. Another possibility is a difference in the composition of the refluxed juice that is not detected by simple pH and bilirubin monitoring. The amount and type of the individual bile acids, pancreatic enzymes, and lysolecithin are not measured by this technology. One important distinction is that erosive esophagitis may heal with treatment, whereas Barrett's esophagus generally persists. Consequently short-segment Barrett's esophagus represents premanent mucosal injury and is a reliable marker of reflux disease.

The propensity for short segments of Barrett's esophagus to undergo malignant transformation is obviously of great relevance. Direct evidence for this possibility comes from individual reports where cancer was seen to develop in persons with short-segment Barrett's esophagus.[4,5] Indirect evidence may be found in the similar epidemiologic characteristics of adenocarcinoma of the esophagus and of the cardia.[7,8] Both predominate in white males and are increasing at the same rate. Although this evidence suggests that the risk of malignant change in short-segment Barrett's esophagus is significant, its magnitude is not known at present.

The recognition that short-segment Barrett's esophagus is a manifestation of the same underlying disease process as long-segment Barrett's esophagus has important epidemiologic implications. One of the most striking observations in this study was that the overall prevalence of Barrett's esophagus almost doubled from 12.2% to 23.7% when patients with short segments were included in the population with Barrett's esophagus. This implies that the incidence of Barrett's esophagus in patients with gastroesophageal reflux disease is far greater than traditionally reported.

We conclude that patients with segments of intestinal metaplasia, regardless of its length, have a high prevalence of structurally defective lower esophageal sphincters and increased esophageal exposure to both gastric and duodenal juices. Both are complications of gastroesophageal reflux disease. Consequently there is no rationale for the arbitrary distinction between long and short segments of Barrett's esophagus based solely on the length of the metaplastic epithelium.

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## *Discussion*

***Dr. J. Hunter*** (Atlanta, Ga.). This draws on much of the superb research from the University of Southern California on the role of bile in the etiology of Barrett's esophagus. Have you made any effort to sort out the role of proton pump inhibitors by examining the effects of long-term acid suppression and determining its role in patients with defective sphincters?

***Dr. S. Öberg.*** We have no data on the role of long-term acid suppression, as most of the patients had antireflux surgery.

***Dr. M. Patti*** (San Francisco, Calif.). You have established a relationship between the length of the lower esophageal sphincter or the contents and the length of the Barrett's metaplasia. Have you tried to establish a similar relationship between the length of metaplasia and esophageal peristalsis or esophageal acid clearance?

***Dr. Öberg.*** No, but we have noted that patients with longer segments of Barrett's esophagus have decreased amplitude of their esophageal contractions.

***Dr. G. Larson*** (Louisville, Ky.). Do you consider Barrett's esophagus to be a progressive disease that worsens over time if left untreated? I ask this because there are data which suggest that neither the duration of symptoms nor the age of the patient seems to correlate with the length of the Barrett's esophagus. Therefore it would be helpful to know how long these patients have been symptomatic and

whether there is a correlation between the duration of symptoms and your findings, and between the age of the patient and the length of the Barrett's esophagus.

***Dr. Öberg.*** We do not have any data on the duration of the disease in the different groups. There is no difference in age among various groups with no injury and with short and long segments of Barrett's esophagus.

There are data to suggest that if the sphincter deteriorates and the exposure reaches further up into the esophagus, the extent of Barrett's disease may increase; however, proof of this would require longitudinal studies and we have not done them.

***Dr. C. Pellegrini (Seattle, Wash.).*** What is the apparent relationship between the use of proton pump inhibitors and the potential for developing esophagitis?

***Dr. Öberg.*** I cannot say how many of these patients were receiving proton pump inhibitors.

# Laparoscopic Fundoplication for Dysphagia and Peptic Esophageal Stricture

*Hadar Spivak, M.D., Timothy M. Farrell, M.D., Ted L. Trus, M.D., Gene D. Branum, M.D., J. Patrick Waring, M.D., John G. Hunter, M.D., F.A.C.S.*

Peptic esophageal stricture with dysphagia is a late manifestation of severe gastroesophageal reflux disease (GERD). Although laparoscopic fundoplication is an effective antireflux operation, its efficacy for persons with peptic esophageal stricture and dysphagia has not been well defined. The aim of this study was to evaluate outcomes after fundoplication in this subgroup of GERD patients. Forty GERD patients with moderate, severe, or incapacitating dysphagia and peptic esophageal stricture were compared to a control group of 121 GERD patients without significant dysphagia or stricture. Reflux symptom severity was scored by each patient preoperatively and at most recent follow-up postoperatively (mean 1.5 years) using a scale ranging from 0 to 4 (0 = symptoms absent; 4 = symptoms incapacitating). Symptom scores were compared by the Wilcoxon rank-sum test. Postoperative redilation and fundoplication failure rates were also determined. At a mean follow-up of 1.5 years after fundoplication, the median dysphagia score had improved from 3 to 0 ($P < 0.001$) in stricture patients and remained low (score 0) in the control group. The median heartburn score also improved from 3 to 0 ($P < 0.001$) in stricture patients, with an identical response in the control group ($P < 0.001$). Among dysphagia/stricture patients, 35 (87.5%) reported overall satisfaction and have not required secondary medical treatment or esophageal dilation. Four patients (10%) have required endoscopic redilation for residual dysphagia and one (2.5%) had reoperation for fundoplication herniation shortly after operation. Laparoscopic fundoplication is an effective therapy for patients with dysphagia and peptic esophageal stricture. (J GASTROINTEST SURG 1998; 2:555-560.)

KEY WORDS: Esophageal stricture, dilation, laparoscopic fundoplication

Peptic esophageal stricture is a consequence of severe gastroesophageal reflux disease (GERD). Chronic exposure of the distal esophagus to gastric refluxate incites inflammation that may manifest as a constricting mucosal band (Schatzki's ring) or, if deeper esophageal erosions or ulcerations develop, a circumferential peptic stricture.

Although laparoscopic fundoplication is an effective treatment for symptomatic GERD,[1] the management of patients with peptic esophageal strictures is controversial. Results of surgical management of peptic strictures have been inferior to those for uncomplicated reflux disease. Periesophagitis and esophageal shortening may place the surgical repair under excessive tension, which may impair esophageal propulsion or increase the likelihood of fundoplication disruption, herniation, or slippage.[2]

Several years ago, "open" antireflux surgery was found to be more effective than antacids and $H_2$-receptor antagonists for controlling GERD in patients with peptic esophageal strictures, because it eliminates duodenogastric reflux and provides more consistent control of esophageal pH than do $H_2$ blockers.[3-6] However, the morbidity, mortality, and discomfort associated with open antireflux surgery limited its widespread application.[7] The development of laparoscopic antireflux procedures and the advent of proton pump inhibitors have redefined the surgical

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and medical management of GERD, and have created an obligation for detailed evaluation of these new therapies to optimize clinical decision making. Our aim was to evaluate the effectiveness of laparoscopic fundoplication for patients with dysphagia and peptic esophageal stricture, and to compare these outcomes to results in GERD patients without stricture or dysphagia undergoing laparoscopic fundoplication by the same surgeon in the same time period.

## METHODS

### Study Design

From 1992 to 1996, 458 patients with GERD underwent laparoscopic fundoplication at Emory University Hospital. Typical symptoms of GERD (heartburn, regurgitation, dysphagia) were scored by all patients at initial surgical evaluation and at postoperative visits using a symptom severity scale (SSS) of 0 to 4. Forty patients (8.7%) with preoperative dysphagia scores of 2, 3, or 4 ("moderate," "severe," or "incapacitating," respectively) and endoscopically confirmed peptic esophageal stricture comprised the study group. The median duration of dysphagia was 5 years (range 0.8 to 30 years).

The control group consisted of *all* patients with uncomplicated GERD (but similar reflux scores) who had no stricture, and preoperative dysphagia scores of 0 or 1 ("none" or "mild"), and who underwent operation during the same time period. One hundred twenty-one patients fulfilled these criteria. Most of the remaining patients, who were not included in the study, had preoperative dysphagia scores of greater than 1 and no stricture.

For both groups, success was defined as significant and meaningful reduction of reflux symptoms including dysphagia, without the need for postoperative esophageal dilation or medical therapy. Continuous normally distributed demographic variables were compared by Student's *t*-test. Nonparametric data, such as pre- and postoperative symptom scores, were compared using the Wilcoxon rank-sum test.

### Diagnosis of GERD/Stricture

Patients with Barrett's esophagus and evidence of severe dysplasia were excluded from the study. The diagnosis of GERD was confirmed by detailed anatomic and physiologic foregut evaluation before operation.[1] Esophagogastroduodenoscopy was performed in all patients to demonstrate structural abnormalities associated with GERD, such as stricture and hiatal hernia, and to allow mucosal survey for esophagitis, unrecognized malignancy, or gastric pathology. A barium swallow test was performed in all patients preoperatively. The diagnosis of stricture or Schatski's ring was derived from this study.

Patients in the study group had either peptic esophageal stricture (n = 34) or Schatzki's ring (n = 6) diagnosed by endoscopy and barium contrast study[7,8] during the preoperative evaluation, and in all cases peptic stricture was confirmed by resistance to dilation at endoscopy or operation. All strictures were less than 3 cm in length, and neoplasm or dysplasia was excluded by biopsy. Preoperatively 19 patients underwent one or two endoscopic dilations, seven had three to five dilations, and 10 required more than five dilations. Four patients did not undergo dilation before operation. Twenty-seven patients underwent dilation during the 4 months prior to operation.

An esophageal motility study[9] was used to characterize lower esophageal sphincter function and to detect unsuspected functional disorders that might hinder propulsion of food through a surgical fundoplication. Among the 40 patients with dysphagia and stricture, mean lower esophageal sphincter pressure was not significantly different from control values (14 ± 11 mm Hg vs. 12 ± 8 mm Hg). Patients with diffuse esophageal spasm, achalasia, or scleroderma were excluded from the study. In the study group, 36 patients (90%) had normal esophageal motility and four patients (10%) had impaired peristalsis (mean esophageal body pressure <30 mm Hg or fewer than 70% of wet swallows induced peristalsis). In the control group, 426 patients (93%) had normal esophageal motility and 32 patients (7%) had mildly impaired peristalsis ($P$ = not significant [NS]). Those with impaired motility underwent Toupet (270-degree) fundoplication.

### Operative Technique

Laparoscopic fundoplications were performed as previously reported.[10] In the dysphagia/stricture group, intraoperative dilation was performed using Maloney dilators. Intraoperative dilation strategy was tailored for each patient. Generally three dilators were passed, starting with the largest size of preoperative dilation and proceeding to 10 Fr larger. In all but one case it was possible to dilate the esophagus to more than 50 Fr. The fundoplication was then created over the dilator. The mean bougie size was 56 Fr (range 46 to 60 Fr). Nissen fundoplication was performed in 34 patients, Toupet fundoplication in four patients, and two patients with esophageal shortening underwent Collis-Nissen fundoplication performed laparoscopically.[11]

## RESULTS

Patients with dysphagia and stricture were, on average, 5 years older than control subjects ($P < 0.01$). Other demographic and perioperative data were similar (Table I). Operative morbidity in the study group consisted of pneumothorax in one patient. One patient developed herniation of the fundoplication after an episode of retching required to relieve early postoperative food impaction. A "redo" laparoscopic fundoplication was performed in this patient 2.5 months postoperatively.

Preoperative heartburn scores were similar in dysphagia/stricture patients and control subjects ($P$ = NS). At median follow-up of 1.5 years (range 0.5 to 4 years), heartburn scores improved significantly in the dysphagia/stricture group ($P < 0.001$) and in the control group ($P < 0.001$) (Fig. 1). Dysphagia scores also improved in the study group ($P < 0.001$) and remained low in the control group ($P$ = NS) (Fig. 2).

In the study group, 27 patients (including the patient requiring early reoperation) reported no residual dysphagia (SSS = 0) and six others reported only rare or mild dysphagia after operation (SSS = 1). Seven patients reported moderate dysphagia (SSS = 2), four of whom (10%) have required at least one redilation. The other three patients who reported residual dysphagia were sufficiently satisfied with their improvement in swallowing to decline further dilations. Excluding the patient with early reoperation (although he was cured of his GERD), and the four patients requiring repeat dilation, 35 patients (87.5%) were free of significant reflux symptoms and required no further dilation after operation. Among GERD patients without dysphagia (control group), 93% had satisfactory postoperative outcome, defined as relief of symptoms and elimination of medication requirements after operation.

On late follow-up, two patients with mild postoperative dysphagia and one patient with moderate postoperative dysphagia were found to have radiologic suggestion of transhiatal fundoplication herniation. None of these patients is sufficiently symptomatic to request or require reoperation.

## DISCUSSION

Peptic esophageal stricture is one of the most morbid and difficult to manage complications of chronic gastroesophageal reflux. Stricture occurs in 1% to 5% of patients with esophagitis, compared to only 0.01% of the overall population.[7] Although aggressive antisecretory therapy lessens stricture recurrence after dilation,[12,13] 30% of patients require repeat dilation within 1 year.[12] A recent study of 58 patients with peptic esophageal stricture reported an average of 4.5 dilations the year after stricture diagnosis and 2.4 dilations per year thereafter, despite ongoing aggressive therapy with proton pump inhibitors.[14] Earlier studies reported similar findings among patients treated with $H_2$ blockers.[12,13,15] Thus patients managed without surgery require regular surveillance and sometimes repeat dilations, in addition to long-term pharmacologic therapy.

Since its development in the early 1990s, laparoscopic fundoplication has proved to be an excellent

**Table I.** Comparison of stricture and control groups

| | Stricture (n = 40) | No stricture (n = 121) | *P* value* |
|---|---|---|---|
| Demographics | | | |
| Mean age (yr) | 52 (range 27-74) | 44 (range 17-79) | <0.01 |
| Males/females | 25/15 | 76/45 | NS |
| Preoperative | | | |
| Mean LES resting pressure (mm Hg) | 14 ± 11 | 12 ± 8 | NS |
| Operative | | | |
| No. of Nissen/Toupet/Collis-Nissen fundoplications | 34/4/2 | 108/13/0 | NS |
| Postoperative | | | |
| Dilations | 4 | — | |
| Reoperations | 1 | 1 | NS |

LES = lower esophageal sphincter; NS = not significant.
*Comparisons performed using Student's *t* test.

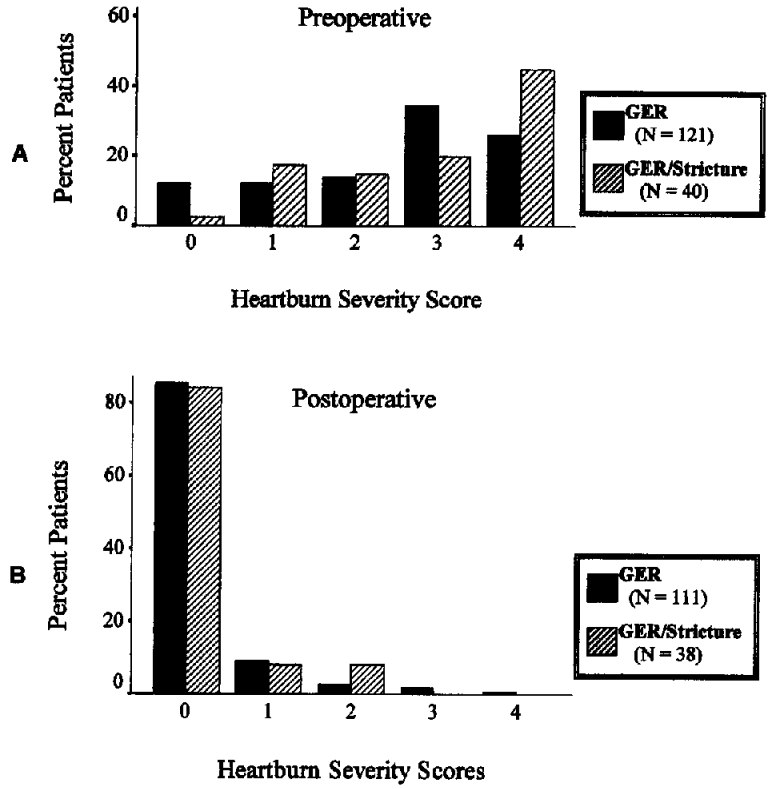


**Fig. 1.** Preoperative **(A)** and postoperative **(B)** comparison of heartburn severity scores in patients with gastroesophageal reflux *(GER)* with and without dysphagia/stricture. Heartburn scores were similar preoperatively ($P = 0.10$), and both dysphagia/stricture patients and GER control subjects showed significant improvement after operation ($P < 0.001$).

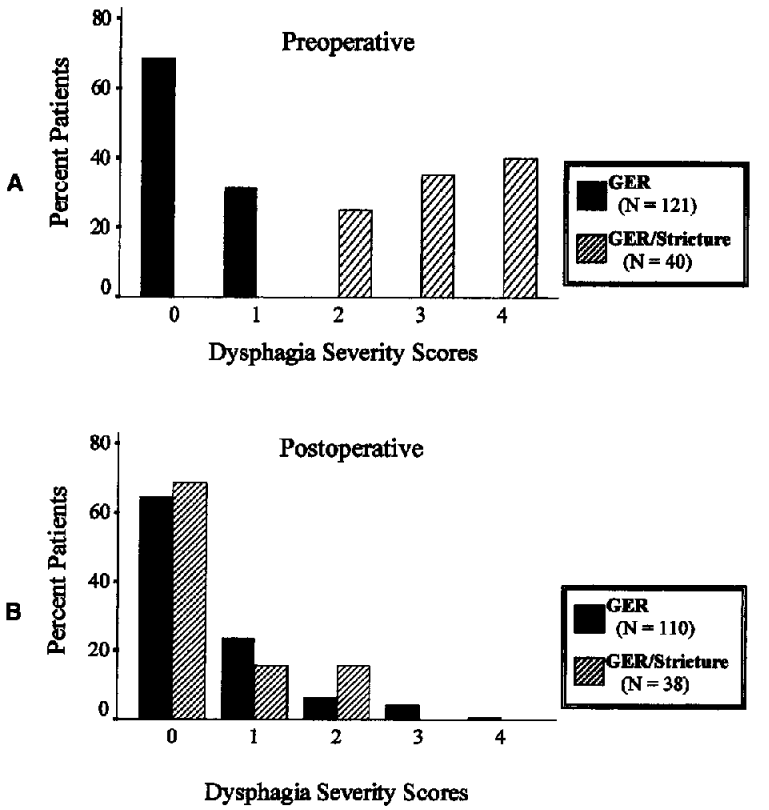


**Fig. 2.** Preoperative **(A)** and postoperative **(B)** comparison of dysphagia severity scores in patients with gastroesophageal reflux *(GER)* with and without stricture. Dysphagia improved significantly in stricture patients ($P < 0.001$) and remained low in GER control subjects.

**Table II.** Treatment of peptic esophageal stricture

| Treatment | Reference | Year | No. | Follow-up (yr) | Effectiveness* | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|
| $H_2$ blockers | Hands et al.[15] | 1989 | 195 | 4.8 | 46% | 3.6% perforation | 0% |
| + dilations | Smith et al.[12] | 1994 | 185 | 1.0 | 54% | — | 0% |
| Omeprazole | Smith et al.[12] | 1994 | 180 | 1.0 | 70% | — | 0% |
| + dilations | Agnew et al.[14] | 1996 | 58 | 5.5 | 84%† | — | — |
| | Mercer et al.[8] | 1986 | 160 | 4.0 | 45%-90% | 10% splenectomy | 2.5% |
| Open surgery | Little et al.[3] | 1988 | 34 | 4.3 | 82% | — | 0% |
| | Vollan et al.[16] | 1992 | 43 | 0.2-12 | 53% | 9% splenectomy | 0% |
| | Bonavina et al.[17] | 1993 | 46 | 2.0 | 75% | 2% leakage | 2% |
| Laparoscopic surgery | Spivak et al. (present study) | 1997 | 40 | 1.5 | 88% | 2.5% pneumothorax | 0% |

*No further dilations after initial treatment except where indicated.
†One year of dilations.

treatment modality for GERD. However, the role of antireflux surgery for patients with advanced esophageal disease, including Barrett's esophagus or peptic esophageal stricture, is more controversial.[16] Our findings suggest that laparoscopic fundoplication and intraoperative esophageal dilation is an effective and durable therapy for GERD patients with dysphagia and stricture, with 87.5% of patients requiring no further intervention at a mean follow-up of 1.5 years. Obviously, longer follow-up is needed but these results are superior to the 1-year primary efficacy of dilation and $H_2$ blockers (54%) or dilation and proton pump inhibitors (70%) in the treatment of peptic esophageal stricture[12] (Table II).

Although the definition of a "true stricture" is debatable, patients were not enrolled in the study group unless a stricture was seen radiographically and esophageal narrowing was confirmed by resistance to dilation. As well, protracted dysphagia relieved with dilation was required for entry to the study group. Six patients who carried a preoperative radiographic or endoscopic diagnosis of Schatzki's ring fulfilled these criteria and were included in the study group. Schatzki's rings are a result of gastroesophageal reflux and frequently progress to circumferential stricture,[7] so their characterization is better defined by the degree of attendant dysphagia and its responsiveness to dilation.

Three patients with residual dysphagia were found to have evidence of fundoplication herniation by barium swallow; however, *none* has incurred sufficient symptoms to warrant reoperation. We speculate that postoperative herniation may be related to the presence of unrecognized esophageal shortening. Although two (5%) of our study patients underwent an esophageal lengthening procedure before fundoplication, the 10% incidence of postoperative wrap herniation may indicate the presence of longitudinal tension on the fundoplication.[17] A short esophagus may produce an abnormally high gastroesophageal junction at endoscopy, a proximally displaced physiologic sphincter at manometry, or dissociation between the gastroesophageal junction and the diaphragm with a straight esophagus on barium swallow. Although the need for esophageal lengthening by Collis gastroplasty is still debated among surgeons,[3,7] we are currently performing the Collis-Nissen procedure if intraoperative esophageal mobilization does not allow at least 2 cm of esophagus to reside in the abdomen without tension. Preoperative discussion of gastroplasty occurs in all patients with Barrett's metaplasia, stricture, or severe esophagitis, but only 16% of these patients require lengthening after thorough esophageal mobilization.[11]

## CONCLUSION

Peptic esophageal stricture is a late complication of GERD. Although pharmacologic therapy and dilation are initially effective, many patients receive only temporary relief. Laparoscopic fundoplication is an effective therapy for patients whose medical therapy is unsuccessful and should be considered as a primary treatment option for patients who are otherwise acceptable surgical candidates. Preoperative treatment with proton pump inhibitors and dilation is recom-

mended. Collis gastroplasty should be used for esophageal shortening, and esophageal resection should be considered for patients with undilatable strictures, especially when associated with poor esophageal peristalsis.

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# Comparison of Thoracoscopic and Laparoscopic Heller Myotomy for Achalasia

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For more than three decades experts have debated the relative merits of thoracoscopic Heller myotomy (no antireflux procedure) vs. laparoscopic Heller myotomy plus Dor fundoplication for treatment of achalasia. The aim of this study was to compare the results of these two methods with respect to (1) relief of dysphagia, (2) incidence of postoperative gastroesophageal reflux, and (3) hospital course. Sixty patients with esophageal achalasia were operated on between 1991 and 1996. Thirty underwent a thoracoscopic Heller myotomy and 30 had a laparoscopic Heller myotomy with a Dor fundoplication. The two groups were similar with respect to demographic characteristics, clinical findings, and extent of manometric abnormalities. Preoperative pH monitoring showed abnormal reflux in two patients in the laparoscopic group. Average hospital stay was 84 hours for the thoracoscopic group and 42 hours for the laparoscopic group. Excellent (no dysphagia) or good (dysphagia less than once a week) results were obtained in 87% of patients in the thoracoscopic group and in 90% of patients in the laparoscopic group. Postoperative pH monitoring showed abnormal reflux in 6 (60%) of 10 patients in the thoracoscopic group and in 1 (10%) of 10 patients in the laparoscopic group. The two patients in the laparoscopic group who had reflux preoperatively had normal reflux scores postoperatively. Laparoscopic Heller myotomy with Dor fundoplication was found to be superior to thoracoscopic Heller myotomy. Both operations relieved dysphagia, but the laparoscopic approach avoided postoperative reflux and even corrected reflux present preoperatively. In addition, the patients were more comfortable and left the hospital earlier following a laparoscopic myotomy. Whether it is truly possible to perform a Heller myotomy without an antireflux procedure in a way that relieves dysphagia and regularly avoids reflux remains questionable. (J GASTROINTEST SURG 1998;2:561-566.)

KEY WORDS: Achalasia, esophageal myotomy, Dor fundoplication, minimally invasive surgery, gastroesophageal reflux

For more than three decades experts have debated the relative merits of two techniques for performing Heller myotomy for achalasia: (1) a myotomy that extends for only a few millimeters onto the stomach, without an antireflux procedure[1,2]; and (2) a myotomy that extends farther (1.5 cm) onto the stomach, accompanied by an antireflux procedure.[3-6] The principal questions have been whether these operations relieved dysphagia and whether a fundoplication was necessary as an adjunct to avoid postoperative gastroesophageal reflux. The debate continues today, at a time when thoracoscopic and laparoscopic techniques have replaced open surgery, and myotomy is now being recommended much more often.

The aim of this study was to compare the results of thoracoscopic Heller myotomy with those of laparoscopic Heller myotomy plus Dor fundoplication in the treatment of esophageal achalasia. We evaluated the following: (1) resolution of dysphagia, (2) incidence of postoperative gastroesophageal reflux, and (3) hospital course.

## PATIENTS AND METHODS

### Thoracoscopic Heller Myotomy

As previously reported, between January 1991 and October 1993, 30 consecutive patients with esophageal achalasia underwent thoracoscopic Heller my-

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otomy at the University of California San Francisco.[7,8] There were 15 men and 15 women whose mean age was 48 years (range 28 to 90 years). The patients had been symptomatic for an average of 81 months (range 4 to 200 months) and had a dysphagia score of 3.5 ± 0.4 (on a scale of 0 to 4). Twenty patients (66%) had undergone pneumatic dilatation (13 patients once; 7 patients twice or more). All patients had the same preoperative workup, which consisted of a barium swallow, endoscopy, esophageal manometry, and ambulatory pH monitoring.

***Operative Technique.*** The operation consisted of a myotomy performed through a left thoracoscopic approach, as previously described.[7,8] The myotomy was 6 to 7 cm long and extended 5 mm onto the gastric wall. Intraoperative endoscopy was used in all patients to facilitate locating the esophagus at the beginning of the mediastinal dissection, and more important, to assess the distal extent of the myotomy.

The patients were examined 2 and 6 weeks postoperatively and were subsequently followed up at 4-month intervals by telephone. The average duration of follow-up was 52 months (range 40 to 70 months). Esophageal manometry and 24-hour pH monitoring were performed 2 to 3 months postoperatively in 10 patients.

## Laparoscopic Heller Myotomy With Dor Fundoplication

Between October 1993 and March 1997, 30 consecutive patients with esophageal achalasia underwent laparoscopic Heller myotomy with Dor fundoplication. There were 15 men and 15 women; the mean age was 47 years (range 15 to 77 years). The patients had been symptomatic for an average of 71 months (range 6 to 300 months) and had a dysphagia score of 3.6 ± 0.6 (on a scale of 0 to 4). Twenty patients (66%) had previously undergone pneumatic dilatation (9 patients once; 11 patients twice or more), and four patients had had intrasphincteric injections of botulinum toxin (3 patients once; one patient three times). The preoperative workup consisted of a barium swallow, endoscopy, esophageal manometry, and ambulatory pH monitoring. Ambulatory pH monitoring showed the presence of abnormal gastroesophageal reflux preoperatively in 2 of the 30 patients: one patient (De Meester score = 49; normal <15) had undergone two pneumatic dilatations, and the other patient (DeMeester score = 50; normal <15) had had three pneumatic dilatations and three intrasphincteric injections of botulinum toxin.

***Operative Technique.*** The patient was placed supine on the operating table with his or her legs in stirrups, and the surgeon stood between the patient's legs. Five 10 mm trocars were used (Fig. 1). Port 1 was for the camera; port 2 for a Babcock clamp and the laparosonic coagulating shears (LCS, Vetracision, Smithfield, R.I.); port 3 for the liver retractor; and ports 4 and 5 for performing the dissection and the myotomy, and for suturing. The dissection was similar to but less extensive than that used for laparoscopic Nissen fundoplication, since only the anterior portion of the right and left crural pillars and the anterior lower 7 cm of the esophagus were exposed (Fig. 2, *A*). The esophagus was not mobilized posteriorly because this is not required for a Dor fundoplication (anterior 180-degree fundoplication).[9,10] The myotomy was performed either at the 2 o'clock (to the left of the anterior vagus nerve) or the 11 o'clock position (to the right of the anterior vagus nerve) in regard to the esophageal circumference. The myotomy was 7 cm long and extended 1.0 to 1.5 cm onto the gastric wall (Fig. 2, *B* and *C*).

A Dor fundoplication was constructed in a manner similar to that described by Rosati et al.[10] In addition, the short gastric vessels were divided with the LCS beginning midway along the greater curvature and extending up to the angle of His. Two rows of sutures were placed, each row consisting of three stitches of 2-0 silk. The first row secured the gastric fundus to the left side of myotomy; the uppermost stitch incorporated the adjacent crus as well as the esophagus (Fig. 2, *D* and *E*). The gastric fundus was then folded over to the right, so that it covered the myotomy, and a second row of sutures was placed between the fundus and the right side of the myotomy; the uppermost stitch also incorporated the right side of the crus (Fig. 2, *F* and *G*). Finally, two sutures were placed between

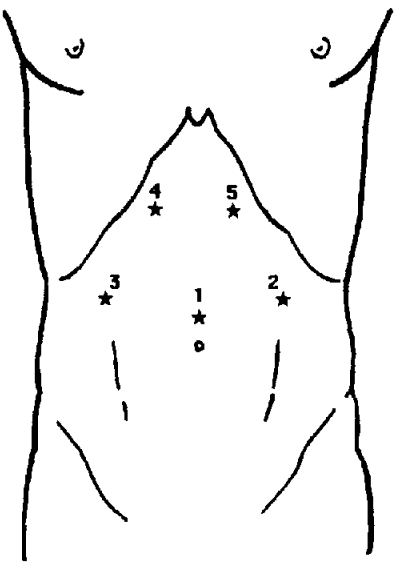


**Fig. 1.** Position of trocars for laparoscopic esophagomyotomy.

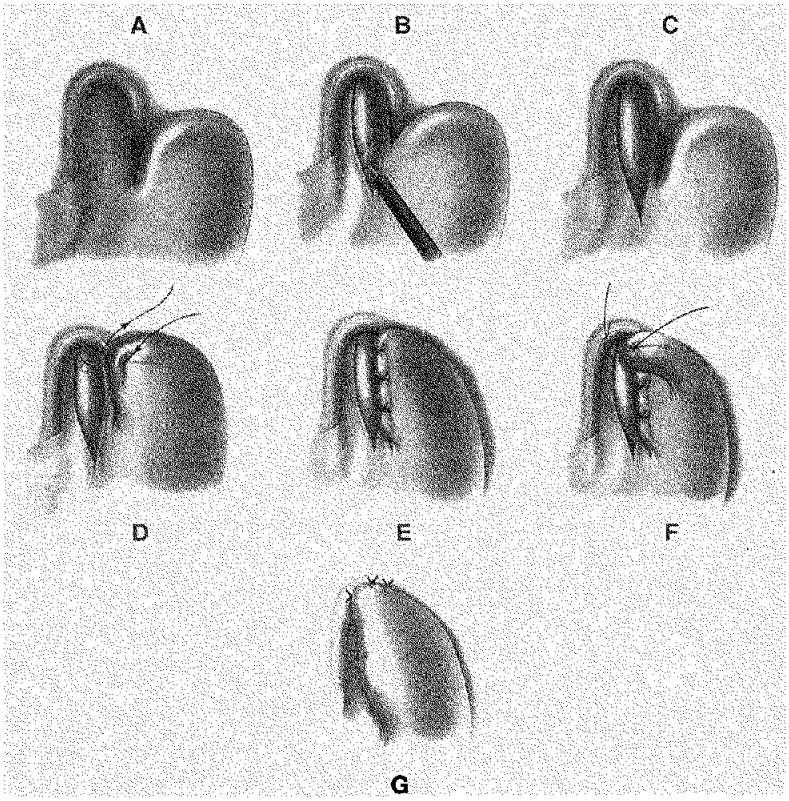


**Fig. 2. A-G,** Laparoscopic Heller myotomy and Dor fundoplication.

the superior aspect of the fundoplication and the anterior rim of the hiatus; these did not include the underlying esophagus.

The follow-up regimen was the same as that for the thoracoscopic procedure. The average duration of follow-up was 13 months (range 1 to 36 months). Ten patients had postoperative manometry and 24-hour pH monitoring performed 2 to 3 months postoperatively.

## RESULTS

### Thoracoscopic Heller Myotomy

***Operation.*** The mean duration of the operation was 150 minutes (range 45 to 210 minutes). Esophageal perforation occurred in three patients, which was managed by converting to a thoracotomy for repair in two; in the third patient the perforation was repaired with an intracorporeal stitch. No complications developed as a result of these repaired perforations.

***Hospital Course.*** The patients were given an unrestricted diet an average of 44 hours postoperatively (range 24 to 96 hours) and left the hospital after an average of 84 hours (range 48 to 140 hours).

***Postoperative Functional Evaluation.*** Esophageal manometry and pH monitoring were repeated postoperatively in 10 patients. Manometry showed that the lower esophageal sphincter (LES) pressure decreased from 30 ± 5 mm Hg preoperatively to 15 ± 2 mm Hg postoperatively. No changes in esophageal body motility were noted. Ambulatory pH monitoring revealed an abnormal reflux score in 6 of 10 patients, all of whom had had normal scores preoperatively. One of these six patients had heartburn, whereas the other five were asymptomatic. In the six patients with gastroesophageal reflux, the LES pressure ranged from 4 to 9 mm Hg. Three of the four patients without gastroesophageal reflux experienced residual dysphagia and had resting LES pressures of 15, 16, and 35 mm Hg, respectively.

***Symptomatic Evaluation.*** The mean ± standard deviation dysphagia score in this group went from 3.5 ± 0.4 preoperatively to 0.6 ± 1.1 postoperatively ($P < 0.05$). Eighty-seven percent of patients had either excellent (70%) or good (17%) results.

A second myotomy was performed laparoscopically in the three patients who had persistent dysphagia. Two obtained complete relief, whereas the third patient who had an advanced megaesophagus eventually underwent a transhiatal esophagectomy. A paraesophageal hernia developed in one patient, which was repaired 6 months following the Heller myotomy. Three of the six patients with postoperative gastro-

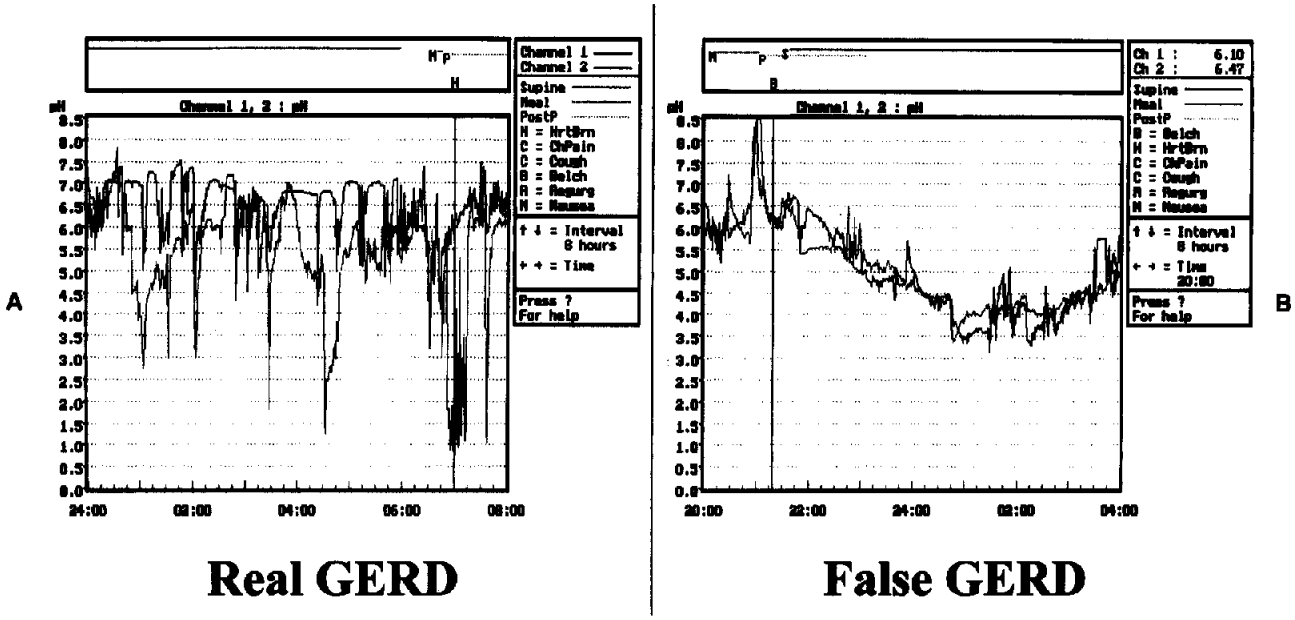


Fig. 3. A, Real gastroesophageal reflux. B, False gastroesophageal reflux.

esophageal reflux are presently being treated with acid-suppressing agents; one of them is being considered for a laparoscopic Dor fundoplication.

## Laparoscopic Heller Myotomy With Dor Fundoplication

***Operation.*** The mean duration of the operation was 166 minutes (range 90 to 300 minutes). Esophageal perforation occurred in three patients and was repaired laparoscopically in all three without complications. Intraoperative endoscopy was used in 15 of the 30 operations, being discontinued as a routine step in the last half of the series. A left pneumothorax developed in one patient, which was treated by tube drainage.

***Hospital Course.*** The patients were given an unrestricted diet after an average of 23 hours (range 7 to 120 hours) and left the hospital after an average of 42 hours (range 23 to 168 hours). Three patients had a prolonged hospital stay: one patient had aspiration of gastric contents at the time of extubation in the operating room (hospital stay 120 hours); one patient with severe coronary artery disease had recurrent episodes of supraventricular tachycardia (hospital stay 96 hours); and one patient required prolonged mechanical ventilation because of preexisting lung disease (hospital stay 7 days). Overall 18 (60%) of the 30 patients left the hospital within 23 hours.

***Postoperative Functional Evaluation.*** Esophageal manometry and pH monitoring were repeated postoperatively in 10 patients. Esophageal manometry showed that LES pressure decreased from 16 ± 8 mm Hg preoperatively to 8 ± 1 mm Hg postoperatively. No changes in esophageal body motility were noted.

Ambulatory pH monitoring revealed an abnormal reflux score (DeMeester score = 19; normal <15) in 1 of the 10 patients. This woman had had a normal score preoperatively. Although asymptomatic, she was given $H_2$-receptor–blocking agents. The postoperative reflux score was normal in the two patients in whom reflux had been present preoperatively.

***Symptomatic Evaluation.*** The mean ± standard deviation dysphagia score in this group went from 3.6 ± 0.6 preoperatively to 0.4 ± 0.7 postoperatively ($P < 0.05$). Ninety percent of the patients had either excellent (77%) or good (13%) results.

## Real Reflux vs. False Reflux

The tracing of each pH monitoring study was carefully reviewed to distinguish between *real* gastroesophageal reflux and *false* reflux due to stasis and fermentation.[11,12] Fig. 3, *A* shows an example of a patient who had gastroesophageal reflux after thoracoscopic myotomy. Each episode of reflux was characterized by a drop in the pH to 2 or 3 followed by acid clearance. Fig. 3, *B* shows the pH recording from a patient with a positive score before a myotomy. In this case, however, it was due to fermentation secondary to stasis. Instead of sharp drops in the pH as seen with reflux, the pH more gradually declines to 4 and remains unchanged for several hours.

## DISCUSSION

The results of this study suggest that a laparoscopic Heller myotomy plus fundoplication should be considered the operation of choice for esophageal achalasia. Even though relief of dysphagia was similar after thoracoscopic and laparoscopic Heller myotomy, the latter offered the following advantages: (1) it was simpler to perform, (2) the hospital course was shorter, (3) the incidence of postoperative gastroesophageal reflux was lower, and (4) the fundoplication corrected reflux that was present preoperatively.

### Technical Aspects

Overall the thoracoscopic approach was slightly more cumbersome for the following reasons: (1) it required the use of a double-lumen endotracheal tube and the lateral decubitus position, and (2) intraoperative endoscopy was necessary to make sure that the myotomy had divided the entire sphincter. The laparoscopic approach had neither of these disadvantages. In addition, the myotomy was simpler to perform laparoscopically, particularly the distal extent on the gastric wall.

We used intraoperative endoscopy routinely during thoracoscopic myotomy to ensure that the LES had been completely divided. As reported previously,[7,13] making this judgment based on the thoracoscopic view alone was incorrect in several of our first few patients, which resulted in an incomplete myotomy and persistent dysphagia requiring another operation. This problem was solved by using endoscopy as an ancillary means of assessing completeness.

On the other hand, intraoperative endoscopy was found to be unnecessary during laparoscopic myotomy. The location of the esophagogastric junction was more obvious, thanks to the better exposure, and the myotomy was deliberately longer and virtually certain to be complete. Although some surgeons use operative esophagoscopy to help look for a suspected mucosal perforation, we prefer to avoid endoscopy in this situation. Even a tiny perforation can be detected when saline solution is forcefully injected through a tube into the esophageal lumen, so any risk of extending the lesion by trauma from an endoscope can be avoided.

### Hospital Course

The hospital course was simpler and recovery was faster after the laparoscopic approach. The patients were allowed an unrestricted diet sooner after laparoscopic myotomy, although this may partly have reflected growing confidence that the patients could actually tolerate immediate feeding. Nevertheless, the patients appeared more comfortable after the laparoscopic operation and they could be discharged earlier, principally because a chest tube was not used. Sixty percent of patients who had a laparoscopic Heller myotomy plus Dor fundoplication were discharged within 23 hours of surgery, and their postoperative course was as simple as that of patients undergoing lap-aroscopic cholecystectomy.

### Relief of Dysphagia

There is no disagreement that a Heller myotomy is the preferred surgical treatment for achalasia, but the details are still disputed. In previous studies the transthoracic and transabdominal approaches have been compared with and without an antireflux procedure. The results have suggested that both methods relieve dysphagia in approximately 80% of patients, and surgical treatment is superior to pneumatic dilatation.[4,14,15] We and others have shown that thoracoscopic and laparoscopic myotomies are equivalent with regard to their ability to relieve dysphagia.[7-10,13,16-20]

### Postoperative Gastroesophageal Reflux

Our study represents the first "head-to-head" comparison of Heller myotomy with and without a fundoplication, not only in relieving dysphagia but also in preventing the development of gastroesophageal reflux. Even though our patients were not assigned randomly to the two procedures, they were similar with respect to demographic characteristics, clinical findings, and extent of manometric abnormalities. Before this series was begun, the surgical team was thoroughly experienced in the surgical treatment of this disease, and the technical steps of the respective open operations were precisely reproduced in the laparoscopic versions.

Postoperative gastroesophageal reflux was assessed by ambulatory pH monitoring because we knew that symptoms are an unreliable index of reflux.[11] The postoperative pH monitoring data showed that reflux was common (60%) after thoracoscopic myotomy, but it was uncommon (10%) when a concomitant fundoplication was used following a laparoscopic myotomy. The gastroesophageal reflux that developed after myotomy was principally subclinical; six (86%) of the seven affected patients were asymptomatic. That only one third of the patients in each group were tested, however, limits somewhat the strength of the conclusions.

Transthoracic myotomy without fundoplication has been recommended by Ellis et al.,[1,2] who reported that dysphagia was improved in 90% of patients, with only a 5% incidence of heartburn. However, in another report, the same group found gastroesophageal reflux postoperatively in 4 (29%) of 14 patients[21] sub-

jected to pH monitoring. Similarly, others found a 25% incidence of gastroesophageal reflux following thoracoscopic Heller myotomy.[12]

The value of an antireflux operation in additon to the esophagomyotomy has been studied by several groups.[6,9,16] For instance, with the use of pH monitoring Bonavina et al.[6] and Ancona et al.[9] found reflux in 9% of patients after open abdominal Heller myotomy plus Dor fundoplication and in 6% of patients after laparoscopic Heller myotomy plus Dor fundoplication, respectively. A Dor fundoplication (anterior 180-degree fundoplication) is the antireflux procedure most commonly used with a Heller myotomy,[6,9,17,18] but a posterior partial (240-degree) or a complete (360-degree) fundoplication has also been tried with success.[16,22] Thus the evidence supports the contention that pH monitoring is required to judge the presence or absence of reflux after these operations and that a fundoplication is essential to prevent reflux.[11,21,22]

This study strongly suggests the need for an antireflux operation in addition to the myotomy. Besides avoiding reflux, fundoplication corrected preexisting reflux when present. This is of genuine importance because many patients come to surgery only after pneumatic dilatation has failed, and reflux has been shown to be present in many such patients.[11]

In conclusion, laparoscopic Heller myotomy with Dor fundoplication was superior to thoracoscopic Heller myotomy in the treatment of achalasia. Both operations relieved dysphagia, but the laparoscopic approach prevented reflux. In addition, the patients were more comfortable and left the hospital sooner after a laparoscopic myotomy.

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# Outcome After Laparoscopic Fundoplication Is Not Dependent on a Structurally Defective Lower Esophageal Sphincter

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With the advent of laparoscopic surgery and the recognition that gastroesophageal reflux disease often requires lifelong medication, patients with normal resting sphincter characteristics are now being considered for surgery. The outcome of these patients after fundoplication is unknown and formed the basis of this study. The study population consisted of 123 patients undergoing laparoscopic Nissen fundoplication between 1992 and 1996. All patients had increased esophageal acid exposure on 24-hour esophageal pH monitoring. Patients were divided into those with a normal (n = 36) and those with a structurally defective (n = 87) lower esophageal sphincter (LES), based on LES resting pressure (normal >6 mm Hg), overall length (normal >2 cm), and abdominal length (normal >1 cm), and their outcomes were assessed. Each group was subsequently divided into patients presenting with a primary symptom that was "typical" (heartburn, regurgitation, or dysphagia) or "atypical" (gastric, respiratory, or chest pain) of gastroesophageal reflux, and outcome was assessed. Median duration of follow-up was 18 months after surgery. Overall, laparoscopic fundoplication was successful in relieving symptoms of gastroesophageal reflux in 90% of patients. Patients with a typical primary symptom had an excellent outcome irrespective of the resting status of the LES (95% and 97%, respectively). Atypical primary symptoms were significantly more common in patients with a normal LES (29%) than in those with a structurally defective LES (10%; $P < 0.05$), and these symptoms were less likely (50%) to be relieved by antireflux surgery. Laparoscopic antireflux surgery is highly successful and not dependent on the status of the resting LES in patients with increased esophageal acid exposure and primary symptoms "typical" of gastroesophageal reflux. Antireflux surgery should be applied cautiously in patients with atypical primary symptoms. (J GASTROINTEST SURG 1998; 2:567-572.)

KEY WORDS: Gastroesophageal reflux, lower esophageal sphincter, laparoscopy, Nissen fundoplication, outcome

Prior to the introduction of laparoscopic fundoplication, surgical treatment of gastroesophageal reflux disease was generally reserved for patients with severe esophagitis, stricture, or those refractory to medical therapy. Physiologic studies of this population demonstrated permanent structural defects of the lower esophageal sphincter (LES) in the vast majority.[1] The presence of a mechanically defective sphincter became a criterion for surgery because of its association with severe disease, the fact that Nissen fundoplication restored normal function in the structurally defective LES, and the fact that it identified patients at a stage of disease that merited open surgery.[2] The introduction and success of minimally invasive antireflux surgery shifted the balance such that patients with less severe disease were considered surgical candidates.[3-5] These patients, characterized by severe symptoms of gastroesophageal reflux and a low prevalence of mucosal injury, often have normal LES characteristics at rest. In this group of patients reflux occurs during temporary loss of the gastroesophageal barrier.[6-9] These shifting referral patterns, together with an im-

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proved understanding of LES failure, led us to reevaluate the traditional concept that antireflux surgery should be reserved for patients with a structurally defective LES.

## METHODS

### Characteristics of the Study Population

The study population consisted of 123 consecutive patients treated with laparoscopic Nissen fundoplication between 1992 and 1996. All patients had increased esophageal acid exposure on 24-hour pH monitoring.[10] There were 91 men and 32 women, with a median age of 49 years (range 18 to 80 years). All patients underwent upper endoscopy, stationary esophageal manometry, and 24-hour esophageal pH monitoring. The most prominent symptom present at the time of surgical referral was taken as the primary symptom for analyses. Heartburn, regurgitation, and dysphagia were considered *typical*, and cough, asthma, chest pain, and any other complaint *atypical* symptoms of gastroesophageal reflux. The majority of patients (85%; 104/123) had a typical primary symptom as the reason for antireflux surgery (Table I).

**Table I.** Primary symptom responsible for surgical treatment

| Symptom | No. of patients (%) |
|---|---|
| Heartburn | 87 (71) |
| Regurgitation | 10 (8.1) |
| Dysphagia | 7 (5.7) |
| Gastric (nausea, vomiting, epigastric pain) | 7 (5.7) |
| Respiratory (cough, asthma, pneumonia) | 6 (4.9) |
| Chest pain | 6 (4.9) |

**Table II.** Symptom grading

Heartburn
- 0 = none
- 1 = minimal, identifiable symptom, occasional episodes, no prior medical visit
- 2 = moderate; primary reason for visit, medical problem
- 3 = severe; constant, daily, disability in activities of daily life

Regurgitation
- 0 = none
- 1 = mild; after straining and/or large meals
- 2 = moderate; predictable with position change, straining, or lying down
- 3 = severe; constant regurgitation, presence of aspiration

Dysphagia
- 0 = none
- 1 = mild; occasionally with coarse foods (meat sandwich, hard roll) lasting a few seconds
- 2 = moderate; requiring clearing with liquids, frequently but not with every meal
- 3 = severe; semiliquid diet, history of meat impaction, difficulty with every meal

### Manometry

Stationary esophageal manometry studies were performed using a single catheter assembly consisting of five polythene tubes bonded together with five lateral openings spaced 5 cm apart from each other and radially oriented around the circumference of the catheter. The catheter was perfused with distilled water at a constant rate of 0.6 ml/min using a pneumohydraulic low-compliance perfusion pump (Arndorfer Medical Specialties, Greendale, Wis.). The three structural characteristics of the LES—resting pressure, intra-abdominal length, and overall length—were measured using a stationary pull-through technique. Based on the structural characteristics of the LES, patients were divided into those with a structurally normal (n = 36) and those with a structurally defective (n = 87) LES. A structurally defective LES was defined in the presence of any one or a combination of the following LES characteristics: resting pressure of less than 6 mm Hg, overall length of less than 2 cm, or intra-abdominal length of less than 1 cm.[1]

### Clinical Outcome

Clinical outcome was obtained from all patients at a median follow-up of 18 months after surgery (range 6 to 58 months). Symptomatic follow-up was complete in 103 (84%) of the 123 patients. A physician other than the surgeon who performed the operation assessed the outcome via telephone or personal interview and completion of a standard questionnaire. The outcome was considered excellent if the patient was completely asymptomatic. Patients whose symptoms were relieved, but who complained of minor gastrointestinal discomfort such as bloating or flatulence, were considered to have a good result. Patients whose symptoms were improved but still required additional therapy were considered to have a fair result. Patients were graded as having a poor outcome if symptoms were not improved or long-term dysphagia developed as a consequence of operative therapy.

**Table III.** Symptomatic outcome in patients with and without a structurally defective lower esophageal sphincter (LES)

| | Structurally defective LES | Structurally normal LES | Total |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| Typical primary symptom | 63/65 (97) | 23/24 (95) | 86/89 (97) |
| Atypical primary symptom | 3/5 (60) | 4/9 (44) | 7/14 (50) |
| TOTAL | 66/70 (94) | 27/33 (82) | 93/103 (90) |

The symptomatic outcome was compared in patients with structurally normal and defective LES, and they were further subdivided depending on the type of primary symptom at presentation (i.e., typical or atypical). Symptoms were scored between zero and three. A symptom score of one signified that the symptom was associated with minimal discomfort, a score of two meant that it caused moderate discomfort, and a score of three indicated that it led to severe discomfort on a daily basis (Table II).

### Statistics

Data are reported as mean ± standard deviation unless otherwise stated. Fisher's exact test was used to compare proportions between two groups. Wilcoxon's rank test was used to compare continuous data. A $P$ value <0.05 was considered significant.

## RESULTS

Symptomatic follow-up was obtained in 103 of the 123 patients. Overall, an excellent or good outcome was achieved in 90% (93/103) of the patients. The LES was structurally defective in 70 (68%) of the 103 patients and normal in 33. Table III shows the prevalence of excellent/good outcome in patients with and without a structurally defective sphincter. Sixty-six (94%) of the 70 patients with a structurally defective sphincter and 27 (82%) of the 33 with a normal resting sphincter had an excellent or good outcome. There was no significant difference between patients with and without a defective sphincter.

Of the 89 patients presenting with a typical primary symptom, 86 (97%) had an excellent or good outcome. There was no difference between patients with typical symptoms and a structurally normal (n = 24) or structurally defective (n = 65) LES (Fig. 1). In contrast, the outcome of patients with atypical primary symptoms was significantly less good than that of patients with a typical primary symptom. This was true irrespective of the status of the sphincter.

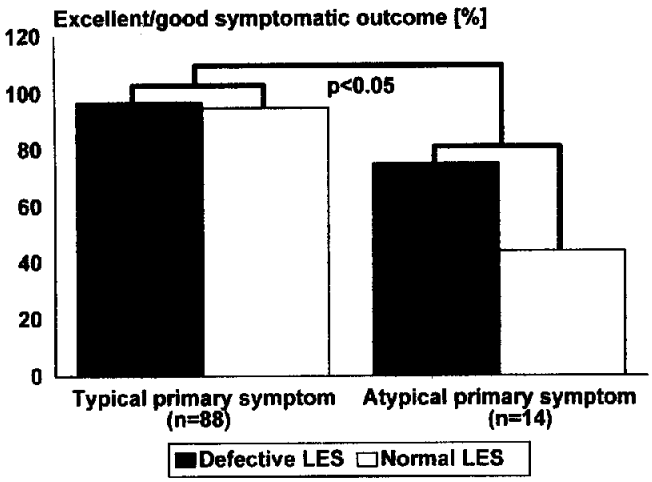


**Fig. 1.** Symptomatic outcome following laparoscopic fundoplication in patients with structurally normal and structurally defective LES in relation to the primary symptom at presentation. The operation was less effective in patients with an atypical primary symptom.

Failure in the majority (70%; 5/7) of these patients was due to the persistence of the atypical primary symptom. The poorest outcome (44% excellent/good) was in the nine patients with a normal sphincter and atypical primary symptoms.

To test whether the excellent/good outcome in patients with typical primary symptoms and normal sphincters was due to a difference in the severity of disease, the pre- and postoperative symptom scores were compared between the two groups. The severity of symptoms in the two groups was identical and the scores were dramatically reduced in both groups (Fig. 2). There was no difference in the prevalence of heartburn, regurgitation, and dysphagia between patients with a structurally normal and defective LES. The prevalence of atypical primary symptoms was higher in patients with a structurally normal LES (28%; 10/36) when compared to patients with a structurally defective LES (10%; 9/87; $P$ <0.05).

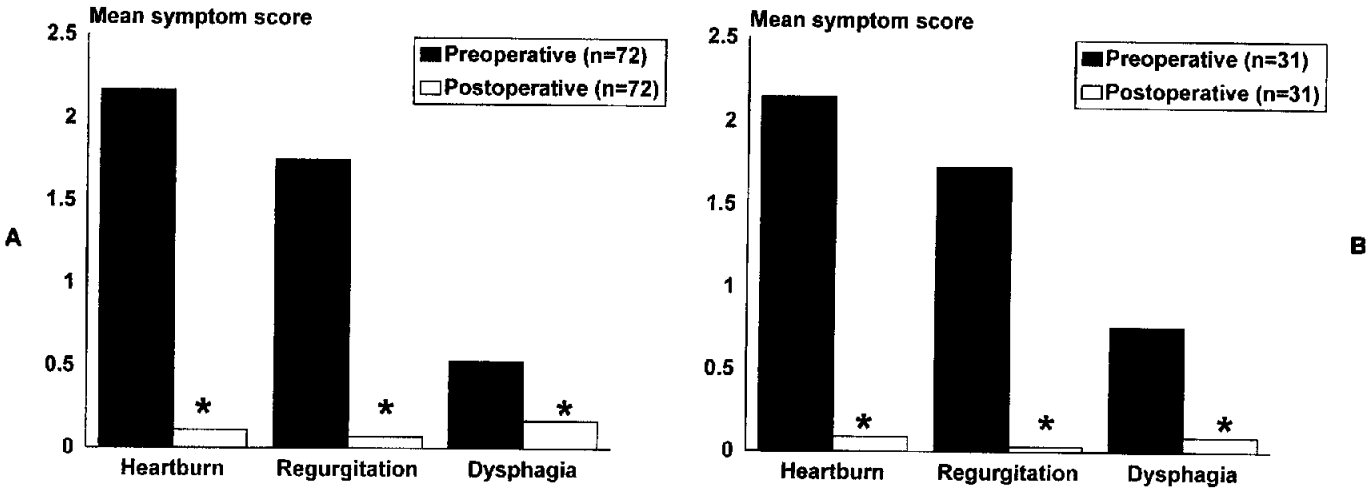


**Fig. 2. A,** Mean pre- and postoperative symptom scores in patients undergoing laparoscopic fundoplication with a structurally defective LES. **B,** Mean pre- and postoperative symptom scores in patients undergoing laparoscopic fundoplication with structurally normal LES. * = $P < 0.01$.

## DISCUSSION

The results of this study show that laparoscopic Nissen fundoplication is highly successful in providing symptomatic relief for patients presenting with the primary symptoms of heartburn, regurgitation, or dysphagia and increased esophageal acid exposure on 24-hour pH monitoring. The success of antireflux surgery in these patients was not dependent on the presence or absence of an abnormal resting LES pressure or length. The outcome was less predictable in patients presenting with atypical primary symptoms, with or without incompetent LES measurements.

Symptomatic gastroesophageal reflux is a very common problem. Prevalence data would indicate that as much as 10% of the population of most Western countries has heartburn on a daily basis. Since the advent of manometric studies, it has become clear that there is a proportion of patients who have severe symptoms but still have a normal LES at rest. Until recently these patients were uncommonly seen in a typical surgical practice, because antireflux surgery was generally reserved for patients with advanced disease in which a defective sphincter was commonly present. With the advent of laparoscopic fundoplication, patients with less severe disease, often with a normal LES, were considered for antireflux surgery. It soon became evident that an excellent outcome could be obtained in these patients as well.

Coinciding with the clinical observations of the benefits of fundoplication in patients with early disease and a normal resting LES, new insights into the possible mechanism of reflux in these patients have emerged. The common denominator for virtually all episodes of gastroesophageal reflux in both patients and normal subjects is the loss of the normal gastroesophageal barrier to reflux. This is usually secondary to low or reduced LES resistance, which may be either permanent or transient. A structurally defective sphincter results in a persistent loss of LES resistance and permits reflux of gastric contents into the esophagus throughout the circadian cycle.[1] This is borne out by the increased prevalence of supine reflux observed in the patients with a defective LES. Transient loss of the gastroesophageal barrier is usually secondary to gastric abnormalities including gastric distention with air or food, increased intragastric or intra-abdominal pressure, and delayed gastric emptying.[6-9] These patients typically have upright or postprandial reflux and less esophageal mucosal injury. Both groups of patients may be equally symptomatic.

In support of these concepts, we have recently shown in animal studies that gastric distention results in progressive shortening of the LES ultimately leading to equalization of esophageal and gastric pressures, that is, reflux.[8,11] Dent et al.[12] have suggested that transient LES relaxation is an important mechanism in symptomatic gastroesophageal reflux and that these short episodes of LES incompetency can be triggered by postprandial gastric distention.[7] Whether LES failure during these episodes is due to neurologically mediated relaxation[13,14] or to mechanical unfolding of the sphincter with resultant loss of cardiac competency is unknown, although we favor the latter. This "dynamic" incompetency of the LES

is of course associated with normal resting LES characteristics when measured under resting conditions.

Constructing a Nissen fundoplication around the lower esophagus is effective in preventing reflux in both groups of patients. It is well documented that a Nissen fundoplication augments the LES pressure and length in patients with a structurally defective LES.[3-5,15,16] Recently studies have also shown that the fundoplication will also prevent both LES unfolding during gastric distention[8,9] and transient LES relaxation.[17,18]

Patients with gastroesophageal reflux can be divided into those with "typical" symptoms of heartburn, regurgitation, and dysphagia and those with "atypical" symptoms such as respiratory or gastric symptoms and noncardiac chest pain. Typical symptoms are a more reliable and precise guide to gastroesophageal reflux as a cause of the patient's symptom. In contrast, it is often more difficult to identify a cause-and-effect relationship between atypical symptoms and gastroesophageal reflux, and the results of surgical therapy have been correspondingly less good.[19] That is not to say that patients with atypical symptoms are not good candidates for antireflux surgery, as many will benefit greatly, but that in these patients it should be applied cautiously. In the present study only half of the patients whose primary presenting symptoms were atypical achieved good or excellent outcome, despite the objective evidence of increased esophageal acid exposure on 24-hour pH monitoring. In the majority of these patients, failure was due to the persistence of the atypical primary symptom. Further testing to improve the understanding of the underlying foregut physiology may be necessary. Patients with primary gastric symptoms may benefit from preoperative gastric emptying studies to detect abnormalities of gastric function. The exact time relation between a reflux event and respiratory symptom may be assessed in patients with primary respiratory symptoms by simultaneous ambulatory motility and esophageal pH studies. Ambulatory motility studies also allow for a detailed assessment of esophageal motor function, which may help to predict the outcome of surgical treatment in this group of patients.[20] Often a trial of high-dose proton pump inhibitors is helpful. Given atypical symptoms, the outcome of antireflux surgery is optimal in patients with a good response to medical treatment rather than in those who fail to respond.

In summary, laparoscopic Nissen fundoplication is highly successful, and is not dependent on the status of the resting LES, in patients presenting with a primary symptom typical for gastroesophageal reflux disease and increased esophageal acid exposure on 24-hour pH monitoring. Antireflux surgery must be applied carefully in patients presenting with an atypical primary symptom. In this group, further diagnostic studies may help to improve the selection of patients for antireflux surgery.

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# Magnetic Resonance Cholangiopancreatography Accurately Predicts the Presence or Absence of Choledocholithiasis

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Accurate common bile duct (CBD) imaging in patients with biliary calculi is an important determinant of specific therapy. Noninvasive methods to evaluate calculi in the CBD have limited accuracy and rely mainly on ultrasonography and computed tomography. Magnetic resonance cholangiopancreatography (MRCP) is a new noninvasive modality available to evaluate the biliary system. This study was undertaken to assess the accuracy of MRCP in predicting the presence or absence of CBD stones in patients at increased risk for choledocholithiasis. The medical records of 48 patients with a final diagnosis of biliary calculous disease undergoing MRCP between November 1995 and April 1997 were retrospectively reviewed. Three groups were identified: choledocholithiasis (n = 19), gallstone pancreatitis (n = 11), and uncomplicated cholelithiasis (n = 18). In all patients the presence or absence of CBD calculi, as determined by MRCP, was correlated with the final diagnosis obtained from endoscopic retrograde cholangiopancreatography (ERCP) (n = 19), intraoperative cholangiography (n = 6), CBD exploration (n = 13), or clinical follow-up (n = 10). Sensitivity, specificity, and accuracy of MRCP were determined. The major clinical indications for MRCP in the 48 patients ware abnormal liver function tests followed by hyperamylasemia. Twenty patients were diagnosed with CBD stones and 28 were not. MRCP correctly predicted the presence of CBD stones in 19 of 20 patients and failed to detect CBD stones in one patient with gallstone pancreatitis. MRCP incorrectly predicted the presence of CBD stones in 3 of 28 patients ultimately found to have gallstones and no CBD stones. MRCP correctly predicted the absence of CBD stones in the other 25 patients including 10 patients with gallstone pancreatitis. Overall, MRCP had a sensitivity of 95%, a specificity of 89%, and an accuracy of 92%. MRCP is an accurate, noninvasive test for evaluating the CBD duct for the presence or absence of calculi in patients suspected of having CBD stones. Our data support the use of MRCP in the preoperative evaluation of these patients as findings may influence therapeutic decisions. (J GASTROINTEST SURG 1998;2:573-579.)

KEY WORDS: MRI, choledocholithiasis, common bile duct, gallstone pancreatitis, ERCP

Calculous disease is the most common surgical disease of the biliary system. Choledocholithiasis is found in a small percentage of patients with uncomplicated, symptomatic cholelithiasis. Certain groups of patients, such as those presenting with abnormal liver function tests, are at much greater risk of having choledocholithiasis.[1,2] The advent of laparoscopic biliary surgery has demanded accurate preoperative bile duct imaging since cholangiography and common bile duct (CBD) exploration may be difficult to perform laparoscopically and operative time is increased with these additional procedures.[3-5] Accurate preoperative biliary imaging is helpful in determining specific therapy.

Among the imaging techniques currently advocated for evaluating the biliary tree, ultrasonography and computed tomography (CT) are the most frequently used in the initial evaluation of patients with symptoms and signs referable to the pancreaticobiliary system. Despite the great sensitivity of ultrasound

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imaging in the detection of gallbladder calculi, choledochal stones may remain undetected in a large percentage of patients.[6-8]

Other techniques for direct visualization of the biliary tree include endoscopic retrograde cholangiopancreatography (ERCP) and, to a lesser extent, percutaneous transhepatic cholangiography (PTC). Advantages of ERCP include the resolution obtained with the technique and the ability to perform therapeutic measures during the procedure. However, ERCP, the current standard of reference for biliary imaging, has a 10% complication rate.[9] For most patients with elevated liver function tests or hyperamylasemia at presentation, results of ERCP will be normal.[10] Improved noninvasive biliary imaging would allow more selective use of therapeutic ERCP and thus decrease the number of unnecessary procedures and associated morbidity.

Magnetic resonance cholangiopancreatography (MRCP) is an emerging radiologic tool for the evaluation of the biliary tree. It was first described in 1991 in a series of patients with obstructive jaundice.[11] Its advantages are that it is a noninvasive technique and no intravenous contrast is necessary. The use of magnetic resonance imaging of the CBD has been reported in several small series of patients with predominantly malignant bile duct obstruction[11-15] and more recently in two small series of patients with choledocholithiasis.[16,17] The clinical utility of MRCP in the management of biliary calculous disease has not been well described. In addition, the role of MRCP in patients with gallstone pancreatitis has not been well documented. Our goal was to evaluate the accuracy of MRCP in patients at increased risk for choledocholithiasis.

## PATIENTS AND METHODS

We retrospectively reviewed the medical records of 48 patients undergoing MRCP for biliary calculous disease at New York University Medical Center between November 1995 and April 1997. During this period a total of 183 MRCP studies were performed. Studies done to evaluate biliary strictures and periampullary or biliary neoplasms were excluded from this analysis. Only patients with a final diagnosis of biliary calculous disease were included in this study. Three groups were identified based on final diagnosis: (1) uncomplicated cholelithiasis (n = 18), consisting of patients with gallstones only; (2) choledocholithiasis (n = 19), consisting of patients with CBD stones either with or without concomitant gallstones; and (3) gallstone pancreatitis (n = 11), consisting of patients with acute presentations of hyperamylasemia and evidence of cholecystitis on pathologic evaluation of their gallbladders.

In 38 patients, findings from MRCP were correlated with other CBD diagnostic studies including ERCP (n = 18), PTC (n = 1), intraoperative cholangiography (n = 6), or operative CBD exploration (n = 13). In the remaining 10 patients, MRCP findings were correlated with clinical follow-up obtained by telephone contact with both patients and their attending physicians. Median follow-up in these 10 patients, from the time of MRCP, was 12 months. The sensitivity, specificity, and accuracy of MRCP in predicting the presence or absence of choledocholithiasis were determined.

A comparison of CBD size between ERCP and MRCP was performed. In 15 patients in which both ERCP and MRCP studies were available for review, caliber measurements of the CBD were taken at the widest point. For ERCP studies, CBD measurements were made directly on the film and magnification effects were accounted for based on the known and measured diameters of the endoscope on the same film. For MRCP studies, CBD measurements were made relative to an electronically calibrated scale incorporated into the side of each image. Correlations of CBD size from ERCP and MRCP studies were determined with Spearman's rank correlation coefficient. In addition, the size of the smallest CBD stone as determined by MRCP was recorded for all cases that were rendered as true positives (n = 19).

### MRCP Technique

All MRCP examinations were performed on a 1.5 Tesla machine (Vision, Siemens Components Inc., Iselin, N.J.), utilizing heavily T2-weighted images and a body phased-array coil. Coronal and axial 4 mm sections were obtained using a **H**alf-Fourier, **A**cquisition **S**ingle-shot **T**urbo spin **E**cho (HASTE) sequence.[18] The matrix size was 160*256 and the field of view was ≥40 cm in all cases. Therefore in-plane spatial resolution was ≤2.5 mm × 1.5 mm. The repetition time was infinite, the echo time was 60 msec, and 160-degree refocusing pulses were used. With these parameters, 20 slices could be obtained in 18 seconds. In patients who could cooperate for a breath hold, an additional coronal projection sequence was used that generates images similar in appearance to conventional cholangiograms. This is a single-shot turbo spin echo with infinite reception time, an echo time of 1100 msec, and a matrix of 240*256. Five 10 mm sections were obtained in a 20-second breath hold. Two separate sets of images were acquired. Both individual sections and maximum intensity projection data were used in the initial interpretations.

Direct cholangiography was performed in 25 patients consisting of either ERCP (n = 18), PTC (n = 1), or intraoperative cholangiography (n = 6).

The initial MRCP interpretations were compared with the initial ERCP and PTC interpretations. These data were obtained from the medical records of patients. Clinical data were obtained from medical records and patient and clinician telephone contact. Chart review was also performed to record findings at intraoperative cholangiography and CBD exploration.

## RESULTS

The median age of 48 patients undergoing MRCP was 53 years (range 20 to 90 years). There were 27 females and 21 males. The clinical indication for MRCP was abnormal liver function tests without the presence of jaundice in 23 patients, hyperamylasemia in 11 patients, clinical jaundice in eight patients, abdominal pain in three patients, and abnormal findings on ultrasound or CT scan in three patients (Table I).

Correlative studies of the CBD were obtained in 38 of 48 patients (Table II). Of 19 patients with a final diagnosis of choledocholithiasis, eight underwent successful CBD exploration, 10 underwent ERCP with stone removal, and one patient had PTC stone extraction. Twelve of 18 patients with uncomplicated cholelithiasis had normal CBD images with ERCP (n = 7) or intraoperative cholangiography (n = 5). In six patients with uncomplicated cholelithiasis, clinical follow-up revealed no evidence of CBD calculi. Of 11 patients with gallstone pancreatitis, five underwent CBD exploration, the results of which were positive in one, one patient underwent ERCP, and one patient underwent intraoperative cholangiography. In four of these patients, no other imaging studies of the CBD were performed, and no evidence of CBD stones became evident with clinical follow-up.

Twenty (42%) of the 48 patients had CBD stones, 19 in the choledocholithiasis group and one in the gallstone pancreatitis group (Table III). MRCP correctly predicted the presence of CBD calculi in 19 of these 20 patients. The one false negative result was in a patient with severe gallstone pancreatitis who had CBD stones found at CBD exploration. Twenty-eight patients (58%) were found not to have CBD stones. MRCP incorrectly predicted the presence of stones in three of these patients. One patient thought to have a single distal stone was found to have a mucosal bulge at ERCP performed the next day. One patient each underwent ERCP and intraoperative cholangiography performed 6 weeks following MRCP. Both of the studies were normal. Although it is possible that CBD stones could have passed in the interim, both cases are being considered as false positives. Results of MRCP were truly normal in 25 of 28 patients,

**Table I.** Demographics and indications for MRCP in 48 patients

| | Uncomplicated cholelithiasis | Choledocholithiasis | Gallstone pancreatitis |
|---|---|---|---|
| Male | 6 | 10 | 5 |
| Female | 12 | 9 | 6 |
| Median age (yr) | 50 (range 22-88) | 61 (range 40-79) | 52 (range 20-90) |
| Indications for MRCP | | | |
| Clinical jaundice | 3 | 5 | 0 |
| Abnormal liver function tests | 11 | 12 | 0 |
| Abdominal pain | 3 | 0 | 0 |
| Abnormal radiologic study | 1 | 2 | 0 |
| Acute pancreatitis | 0 | 0 | 11 |

**Table II.** Correlative studies in patients undergoing MRCP

| | CBDE | ERCP/ PTC | IOC | Clinical follow-up |
|---|---|---|---|---|
| Uncomplicated cholelithiasis | 0 | 7/0 | 5 | 6 |
| Choledocholithiasis | 8 | 10/1 | 0 | 0 |
| Gallstone pancreatitis | 5 | 1/0 | 1 | 4 |

CBDE = Common bile duct exploration; ERCP = endoscopic retrograde cholangiopancreatography; PTC = percutaneous transhepatic cholangiography; IOC = intraoperative cholangiography.

**Table III.** MRCP findings in patient groups

| Common bile duct stones | No. | Uncomplicated cholelithiasis | Choledocholithiasis | Gallstone pancreatitis | MRCP positive | MRCP negative |
|---|---|---|---|---|---|---|
| Positive | 20 | 0 | 19 | 1 | 19 | 1 |
| Negative | 28 | 18 | 0 | 10 | 3 | 25 |

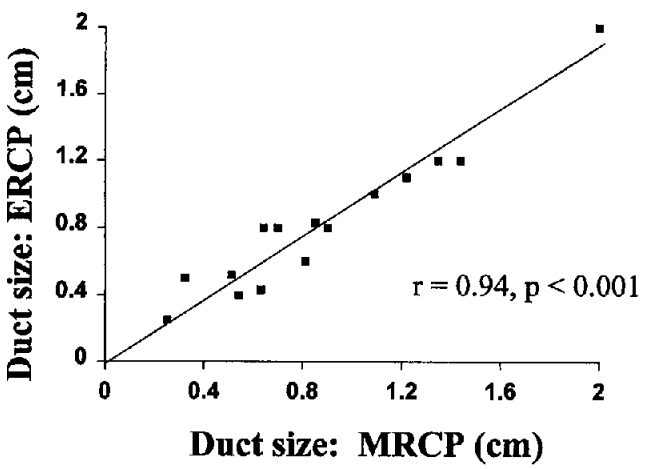


**Fig. 1.** Comparison of common bile duct diameter determined by MRCP and ERCP ($r = 0.94$; $P < 0.001$).

including 10 patients with gallstone pancreatitis who did not have CBD stones. Overall, MRCP had a sensitivity of 95%, a specificity of 89%, and an accuracy of 92% for the detection of CBD stones.

CBD size determined by MRCP was correlated with findings from ERCP. There was a significant positive correlation ($r = 0.94$; $P < 0.001$) between CBD size from MRCP (median 0.80 cm; range 0.25 to 2.0 cm) and from ERCP (median 0.81 cm; range 0.25 to 2.0 cm). An X-Y scatter plot of CBD sizes from ERCP and MRCP is shown in Fig. 1.

For true positive cases, the median size for the smallest stone detected at MRCP was 4.6 mm (range 3.0 to 15.0 mm). In seven patients the smallest stone seen was less than 4 mm.

Representative ERCP and MRCP comparisons are shown in Figs. 2 and 3. The patient represented by Fig. 2 presented with abdominal pain and abnormal liver function tests. MRCP was performed first and revealed a distal CBD stone (Fig. 2, *A*). The same stone is seen on ERCP at the time of endoscopic sphincterotomy and stone extraction (Fig. 2, *B*). The patient represented by Fig. 3 had a history of jaundice that had resolved. MRCP (Fig. 3) revealed multiple CBD stones with duodenal diverticulae. These stones were removed via endoscopic sphincterotomy. Subsequently the patient underwent a laparoscopic cholecystectomy.

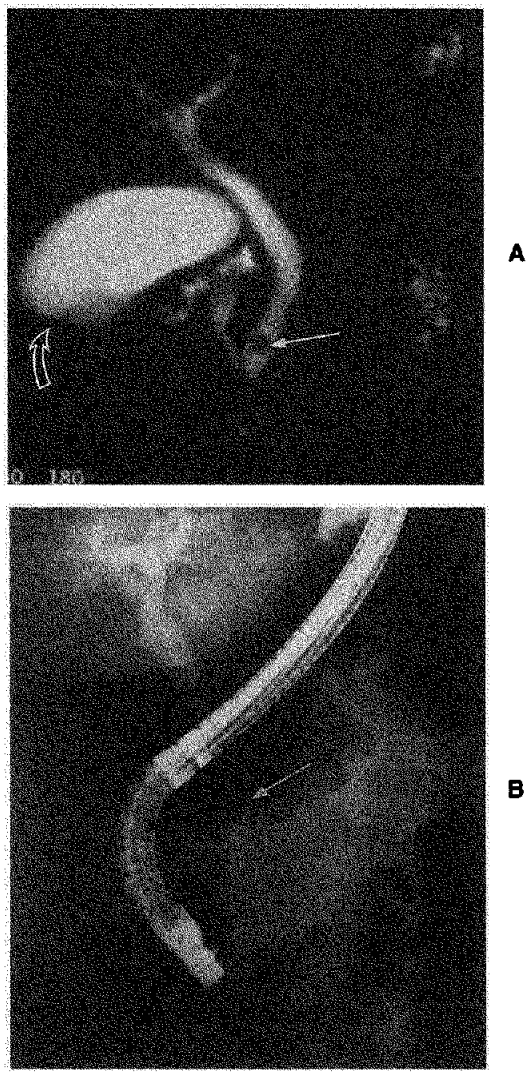


**Fig. 2. A,** MRCP study of a patient with a single common bile duct stone. *Open arrow* indicates gallbladder; *closed arrow* indicates stone in common bile duct. **B,** ERCP study of same patient. *Arrow* indicates stone in common bile duct.

## DISCUSSION

We found that MRCP had a 95% sensitivity and 89% specificity in the diagnosis of CBD stones. In addition, there was an excellent correlation of CBD size between MRCP and ERCP ($r = 0.94$; $P < 0.001$). This study is consistent with the results of previous

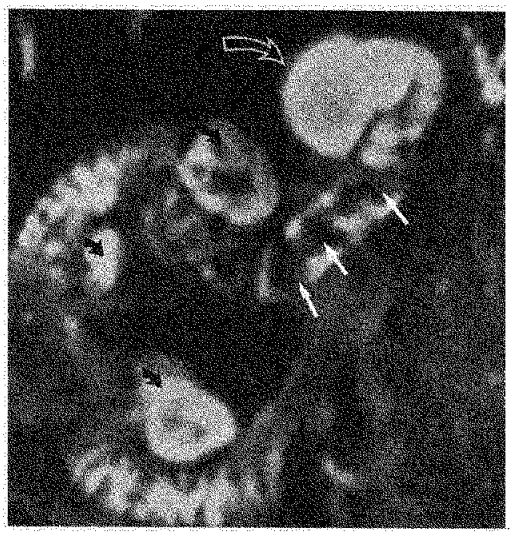

**Fig. 3.** MRCP study of patient with multiple common bile duct stones and duodenal diverticulae. *Open arrow* indicates gallbladder; *long white arrows* indicate stones in common bile duct; *short black arrows* indicate duodenal diverticulae.

studies in the literature, which have revealed excellent correlation between ERCP findings and MRCP. In a prospective comparison of 46 patients undergoing MRCP followed by ERCP, sensitivity for the detection of bile duct dilatation, biliary strictures, and intraductal abnormalities was 96%, 90%, and 100%, respectively.[19] Another study comparing MRCP with ERCP in patients suspected of having choledocholithiasis demonstrated strong agreement between the two studies in regard to the absence or presence of ductal dilatation. In that study MRCP correctly identified 18 of 19 patients with choledocholithiasis and 22 of 26 patients without choledocholithiasis.[17] However, in that study from Hong Kong, recurrent pyogenic cholangitis with jaundice was the predominant clinical presentation. In our series, clinical jaundice was present in only 8 of 48 patients. Most patients in our series had abnormal liver function tests without jaundice or hyperamylasemia, which is more representative of biliary calculous disease in the United States and other Western countries.

There were no complications from MRCP in any of our patients. MRCP is a completely noninvasive modality for evaluating the CBD. MRCP relies on visualizing fluid present in the biliary system, which is seen on heavily T2-weighted images. No contrast is necessary for the study and the only side effect is claustrophobia, which can usually be controlled with pharmacologic sedation. MRCP is safe in pregnant patients, and in those with pancreatitis, previous gastric surgery, or coagulopathy, all relative contraindications to ERCP.

Noninvasive methods for evaluating the CBD have most often relied on ultrasonography and CT. Although both have excellent specificity, these modalities have been demonstrated to be inaccurate because of low sensitivity.[6-8] More invasive techniques for evaluating the CBD include endoscopic ultrasonography, intravenous cholangiography, and ERCP. Endoscopic ultrasonography is a new modality that has been shown to be accurate in the diagnosis of CBD stones.[20] However, it is time consuming, operator dependent, and its usefulness is limited in patients with previous gastric surgery. Since no therapy can be offered with this modality, if it is indicated, ERCP must be performed as an additional procedure. Intravenous cholangiography has been compared to MRCP in the depiction of the biliary tract prior to biliary surgery. Sixty patients with biliary calculi were compared prospectively. All patients with CBD stones had their stones visualized by both MRCP and intravenous cholangiography. The authors concluded that MRCP offered the following advantages: (1) higher rate of bile duct delineation, (2) faster study time, (3) it was not limited by impaired bile excretion, and (4) it did not bear any risk of contrast material–related side effects as compared to intravenous cholangiography.[21]

Laparoscopic cholecystectomy has become the new therapeutic "gold standard" in symptomatic cholelithiasis and at least 80% of all patients are now treated in this manner.[22] Although clinical parameters have been helpful in predicting the presence or absence of choledocholithiasis, imaging modalities increase the accuracy of preoperative assessment.[1] In the laparoscopic era, determining the status of the CBD has a direct impact on specific therapy. Although some surgeons are comfortable clearing the CBD laparoscopically and thus are not as reliant on preoperative assessment, many other surgeons rely on preoperative CBD imaging and subsequent endoscopic clearance if stones are found to be present. Unfortunately many ERCP studies are performed unnecessarily given the current limitations of noninvasive bile duct imaging. It is important to develop accurate, noninvasive techniques for imaging the CBD to decrease the number of unnecessary ERCPs. Endoscopic sphincterotomy and stone extraction carries a 1% mortality rate and approximately 10% of patients will have complications including pancreatitis in 5.4% and hemorrhage in 2%.[9,23] Our study demonstrates that MRCP is a safe, accurate imaging modality to evaluate the CBD duct for the presence or absence of calculi. The determination of CBD size by MRCP correlates well with that determined by ERCP. In addition, MRCP is able to reliably image stones as small as 3 to 4 mm.

MRCP helped guide patient management in our series of 11 patients with gallstone pancreatitis. Six patients in this group underwent laparoscopic cholecystectomy. Among these six patients, one had a preoperative ERCP and one had an intraoperative cholangiogram. Four patients had no diagnostic studies of their CBD other than MRCP. None of these patients have had any findings of CBD stones on follow-up. MRCP was accurate in 10 of these 11 patients. Our only false negative finding occurred early in our experience in a patient with grade E pancreatitis by CT who underwent open cholecystectomy with CBD exploration, at which time innumerable 4 to 5 mm CBD stones were found. MRCP performed the day before surgery revealed a slightly dilated CBD but missed the stones in the CBD.

MRCP also aided in the evaluation of our 18 patients with uncomplicated cholelithiasis. Six of these patients had no other diagnostic studies of the CBD performed. Five of these six patients had abnormal liver function tests. None of these patients have been found to have CBD stones on follow-up. Invasive CBD imaging was avoided in these six patients. There were three false positive MRCP studies within this entire group of 18 patients. The average time delay from MRCP to ERCP in these three patients was 25 days. False positive MRCPs have been attributed to technical artifacts and pneumobilia.[17] A long delay between MRCP and invasive CBD imaging may also result in a false positive MRCP because of spontaneous stone passage. This is difficult to prove unless the passed stone is subsequently retrieved. Nevertheless, we believe that the specificity of MRCP is not as clinically important as the sensitivity, since a positive result can be further evaluated by the same methods that existed prior to the advent of MRCP. Our study demonstrates the strong negative predictive value of MRCP.

According to various investigators, the presence of CBD stones can be predicted to some extent by utilizing clinical, biochemical, and structural criteria.[1,2,24,25] Three levels of relative risk can be distinguished. High risk are those patients with recent acute cholangitis, severe pancreatitis, jaundice, or a very dilated CBD with an elevated serum alkaline phosphatase level. Low risk are those without any of the preceding characteristics and with normal liver function tests. Intermediate risk are those with a history of acute cholangitis or pancreatitis, abnormal liver function tests, or a slightly dilated bile duct.[25]

Management varies depending on risk classification. Patients at low risk may undergo laparoscopic cholecystectomy without preoperative imaging of the CBD. For patients at high risk, several alternatives have been proposed including (1) preoperative ERCP and then laparoscopic cholecystectomy,[26,27] (2) laparoscopic cholecystectomy with either laparoscopic or open CBD exploration,[28] (3) laparoscopic cholecystectomy with intraoperative ERCP,[27] and (4) laparoscopic cholecystectomy with postoperative ERCP.[25] For patients at intermediate risk, similar therapeutic options are available as for high-risk patients; however, the rate of negative ERCPs would be greater than 50%.[10] One commonly applied option is ERCP followed by laparoscopic cholecystectomy for intermediate-risk patients with the understanding that results of most ERCP examinations will be normal.

It is possible that the use of MRCP may lead to lower total cost since the current reimbursement rate based on Medicare's policy for MRCP is $672.00 and for ERCP is $925.00 (hospital charge $400.00, doctor fee $525.00). The small but identifiable risk associated with ERCP entails potential additional costs. The relatively risk-free features of MRCP offer a safety advantage but warrant careful scrutiny. Without risk, the potential for less stringent indications could emerge and eliminate any potential cost savings achieved when MRCP is used in a judicious fashion. Our approach identifies those patients with an intermediate risk for choledocholithiasis, based on symptoms, structure, and blood chemistry, as being appropriate candidates for MRCP. The information obtained by MRCP in these patients can directly influence patient care by improving the therapeutic yield of invasive CBD imaging and stone extraction techniques. Dedicated cost analysis studies will be useful to examine the cost implications in a variety of settings.

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# Detection of Aerosolized Cells During Carbon Dioxide Laparoscopy

*Sayeed Ikramuddin, M.D., Joel Lucas, M.D., E. Christopher Ellison, M.D., William J. Schirmer, M.D., W. Scott Melvin, M.D.*

Laparoscopic surgery for malignancy has been complicated by port-site recurrences. The exact mechanism has yet to be defined. In vitro studies suggest that carbon dioxide–induced tumor cell aerosolization may play a role. We have attempted to document this in a human model. Patients scheduled for elective laparoscopy underwent port placement and abdominal insufflation with carbon dioxide. A suction trap was then filled with 40 cc of normal saline solution and attached to an insufflation site on the port. The carbon dioxide effluent was directed through the saline. The specimen was concentrated, resuspended, and transferred to a slide. A Papanicolaou stain was used. Thirty-five specimens were obtained. Fifteen patients (37%) had malignant disease, which was metastatic in eight. Five patients had carcinomatosis. In two of those with carcinomatosis, staining revealed a large number of malignant cells. Malignant cells were not found in any other patients. In two patients, however, aerosolized mesothelial cells were identified. Follow-up ranged from 2 to 7 months. One patient who displayed cellular aerosolization developed a port-site recurrence. We conclude that malignant cells are aerosolized but only during laparoscopy in the presence of carcinomatosis. It is unlikely that tumor cell aerosolization contributes significantly to port-site metastasis. (J GASTROINTEST SURG 1998;2:580-584.)

KEY WORDS: Laparoscopy, tumor cell, aerosolization, pneumoperitoneum, carbon dioxide

Trocar site recurrences can occur after laparoscopy for malignant disease. At least 152 cases have been reported in the literature.[1,2] To date, there has been no definitive explanation for this type of recurrence. A number of plausible mechanisms have been proposed to explain these observations. First, port-site recurrences may be caused by direct contamination of the fascial defect by instruments and trocars that come in contact with tumor cells. Second, port sites may become impregnated by tumor cells in fluid droplets during the time of desufflation. Third, port sites may be contaminated by viable tumor cells that have been aerosolized in the carbon dioxide ($CO_2$) media. To our knowledge, tumor cell aerosolization in humans has not been directly identified, and the sum of in vitro and in vivo data is equivocal. A technique has been described[3] and validated[4] that allows detection of aerosolized cells during laparoscopy. We used a modification of this system to document the presence of cellular aerosolization in a human model during laparoscopy.

## MATERIAL AND METHODS

Potential subjects were identified by the attending physician either during outpatient workup or at the time of inpatient consultation. Informed consent was obtained. No patients were immunodeficient. Patients undergoing radiation chemotherapy or those with acute inflammatory disorders were excluded. Prior approval was obtained from the institutional review board before the study was conducted. All patients were scheduled for elective laparoscopy. General anesthesia was used in all cases. Prophylaxis against venous stasis and deep venous thrombosis was achieved using pneumatic compression devices. Patients were

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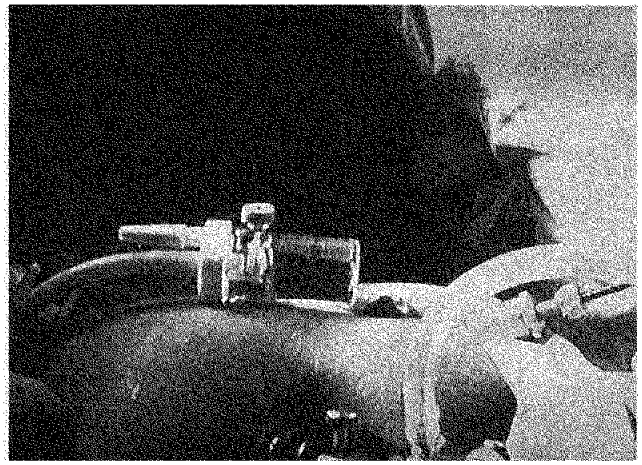

**Fig. 1.** Saline trap filled with 40 cc of saline solution attached to a trocar. The trap is attached to the vent port of the trocar.

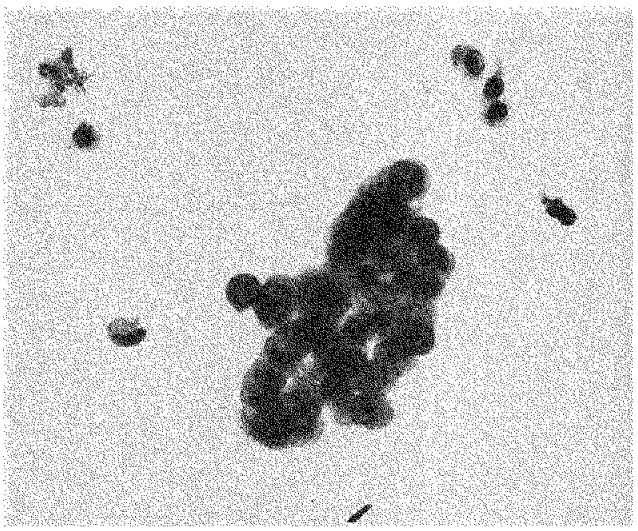

**Fig. 2.** High-power view of aerosolized cells from a patient with carcinomatosis.

divided into a benign and a malignant group based on history and physical examination. Patients underwent port placement with establishment of a pneumoperitoneum, and additional ports were then placed as necessary. Samples were collected into a saline trap connected to an exhaust port on one of the trocars (Fig. 1).

In patients with metastatic lesions, biopsies were performed intraoperatively. The trap was filled with approximately 40 cc of normal saline solution, and $CO_2$ was directed through the saline at a rate at which discrete bubbling was observed. The pneumoperitoneum was maintained at 15 mm Hg. The insufflator was maintained on high flow (10 L/min) for the duration of the procedure. This allowed a continual of egress of $CO_2$ through the trap. Samples were collected for the duration of the procedure. The collection vessel was removed prior to desufflation of the abdomen and taken to the pathology laboratory for processing. Specimens were centrifuged at 600 $\times g$ for approximately 10 minutes. They were then resuspended and washed in Cytolyt (Cytyc Corp., Norwalk, Conn.) solution. After standing for 15 minutes, samples were captured on a slide after being suctioned through a Micropore filter. The filter membrane used was biologically neutral and porous to fluid. The specimens were Papanicolaou stained and then analyzed by a cytopathologist.

## RESULTS

A total of 35 patients were enrolled in the study. Among the 20 patients enrolled in the benign group, the following procedures were performed: laparoscopic cholecystectomy in eight, diagnostic laparoscopy in five, Nissen fundoplication in four, splenectomy in two, and adrenalectomy in one.

There were 15 patients in the malignant group. Seven of them had nonmetastatic disease, which included lymphoma (3), hepatocellular carcinoma (2), and pancreatic tumors (2). There were eight patients in the malignant group who had metastatic disease; in three, the metastases were limited to one organ. The remaining five patients had carcinomatosis secondary to one of the following: pancreatic cancer in two patients, mesothelioma in one, esophageal cancer in one, and gallbladder cancer in one.

The average sampling time was 30 minutes (range 14 to 60 minutes). No malignant disease was found at the time of laparoscopy in the benign group. There were no complications that were a result of the sampling procedure. The pneumoperitoneum was maintained throughout the procedure except during suctioning or suturing.

Cells were detected in four patients (11%). Among these four, a significant number of malignant cells were found in two patients with carcinomatosis (Fig. 2). One patient had an esophageal primary lesion, and the other patient had a pancreatic primary lesion. Two patients exhibited aerosolization of benign reactive mesothelial cells. One patient had hepatocellular carcinoma, and the other had biliary colic. Acellular debris was noted in a number of the remaining specimens.

Follow-up ranged from 2 to 7 months. There was one subcutaneous port-site recurrence in a patient with metastatic esophageal cancer. This patient had demonstrated aerosolization of cells at the time of laparoscopy. The recurrence was detectable both on physical examination and CT scan (Fig. 3).

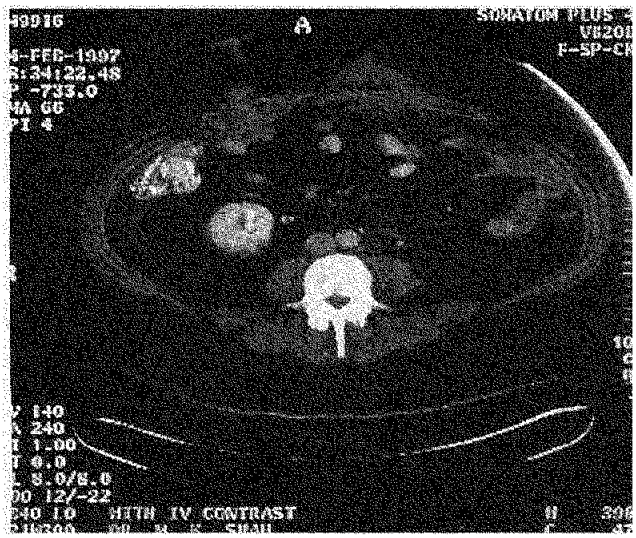


**Fig. 3.** CT scan of the abdomen demonstrating a port-site recurrence.

## DISCUSSION

Recurrence at the wound site after a cancer operation is not a new phenomenon. The incidence of wound recurrence was found to be 1% to 1.5% in a retrospective study of open colectomies for malignancy.[5] Since the advent of laparoscopic surgery, there have been many anecdotal reports linking laparoscopy, pneumoperitoneum, and trocar site recurrences.[2] The incidence of this disease is not truly known but appears to be somewhere between 0.8% and 11% of patients undergoing laparoscopy for malignancy.[5-7] In a recent abstract by Egan et al.[1] reviewing the incidence of port-site metastasis, 152 cases over a 28-year time interval were reported.

Several hypotheses exist to explain the contamination of port sites by tumor cells.[9] First, tumor cells are aerosolized in $CO_2$ gas, which contaminates the port site through leakage around the trocar or following trocar removal. Second, tumor cells can be spread to the open site via contaminated instruments and trocars. Third, tumor cells that have been suspended in droplets of peritoneal fluid, blood, or irrigant may contaminate the open port site at the time of desufflation.

### Aerosolization

Aerosolization is demonstrated by identifying cells collected into a saline bath connected to a port site. Aerosolization of tumor cells during pneumoperitoneum has not been consistently found. An in vitro model devised to detect aerosolization of b16 melanoma cells failed to confirm aerosolization of viable cells.[8] Knolmayer et al.[3] demonstrated in a swine model that during pneumoperitoneum there is a continual egress of epithelial cells into a saline-filled chamber attached to a 14-gauge intravenous catheter. These investigators also demonstrated that aerosolization occurs in a closed plastic environment in which $CO_2$ is allowed to bubble through a solution containing either murine ascites tumor cells or human cecal cancer cells.[4] Both types of cells were found to be aerosolized 38.5% and 50% of the time, respectively. These data validate our use of this technique as it appears to be an effective means of detecting cells if they are aerosolized.

In vivo studies have also been attempted to establish a relationship between $CO_2$ pneumoperitoneum and cellular aerosolization. Hewett et al.[9] reported contamination of a polycarbonate filter attached to an exhaust port, one of the trocars used in a porcine tumor model. This was observed after considerable agitation of the peritoneal contents.[9] Whelan et al.[10] were unable to demonstrate aerosolization of viable tumor cells in either in vivo or in vitro experiments with pressures up to 30 mm Hg.

Detection of aerosolized cells during laparoscopy has been attempted in humans. Redmond et al.[11] examined the effect of pneumoperitoneum on human pancreatic cancer patients. Twelve patients were analyzed who were undergoing staging laparoscopy. The authors collected $CO_2$ into a bath containing culture medium. Polymerase chain reaction was used to look for the presence of mutated k-ras DNA in the samples. The authors reported the sensitivity of polymerase chain reaction to be less than 10 cells. Malignant calls were not directly observed in the $CO_2$ specimens but restriction fragment length polymorphism indicated the presence of mutant DNA in four samples. Bonjer et al.[8] performed a similar experiment in patients with pancreatic cancer. $CO_2$ pneumoperitoneum was created in 25 patients undergoing diagnostic laparoscopy for pancreatic cancer. Eighty liters of $CO_2$ was passed through the collection device. Specimens were analyzed for the presence of cells and carcinoembryonic antigen (CEA). There were no cells in any of the $CO_2$ traps, but the CEA level was elevated in three cases.

### Direct Contamination

In a study of 15 patients undergoing laparoscopic cholecystectomy, cells were found on the instruments in six cases and glandular cells were found on two trocars.[12] In three cases the gallbladder was torn during the dissection. In another experiment designed to evaluate tumor cell distribution in a porcine model, laparoscopic colectomies were performed in the animals after $^{51}Cr$-labeled HeLa cells were injected into

the peritoneal cavity.[13] Tumor cell deposition was recorded at the port sites and on the instruments. The operations were performed using $CO_2$ pneumoperitoneum as well as gasless laparoscopy. Bouvy et al.,[14] in a rat tumor model, documented an increased incidence of tumor recurrence at the port site from which the tumor was removed compared with the other trocar sites. There was no difference in this pattern whether $CO_2$ or gasless techniques were used.

### Desufflation

This theory is based on the premise that tumor cells have been solubilized in fluid droplets, which lodge in the wound during desufflation.[10] The presence of malignant cells in the peritoneal fluid of patients with advanced pancreatic cancer has been well documented. Tumor cells have also been found in blood shed from the surgical field.[15-17] The first group to study this issue in an in vitro model was Whelan et al.[10] A model was devised consisting of a latex balloon insufflated with 1 to 2 liters of $CO_2$. b16 Tumor cells in liquid suspension were placed inside the balloon, which was rapidly decompressed. In one group with maximal tumor cell agitation within the balloon, five of six experiments yielded viable tumor cells, suggesting that rapid desufflation caused dispersion of the tumor cell solution. We did not attempt to compare cytologic findings of peritoneal washings in our patients as this was a preliminary study.

The theory for port-site recurrence is that cells, regardless of the mode by which they arrived at the port site, will become exposed to fibronectin, laminin, and other basement membrane components within trocar sites and bind to these sites.[18] This may provide a new nidus for tumor growth. Local tissue trauma may potentiate this effect. Indirect evidence for this comes from a report by Bonjer et al.,[19] who performed a study comparing tumor recurrence of "crushed" port sites. They found that port sites in rats whose incisions were crushed had a significantly increased mass of tumor deposited. Noteably, in this tumor model there were recurrences at all port sites.

## CONCLUSION

We conclude that port-site recurrence after laparoscopy for malignant disease is a significant problem. Tumor cell aerosolization does occur but has only been associated with carcinomatosis. It is unlikely that tumor cell aerosolization contributes significantly to port-site metastasis. Therefore abandoning the use of laparoscopic techniques for cancer surgery because of tumor aerosolization does not seem warranted at this time.

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## *Discussion*

***Dr. F. Greene*** (Columbia, S.C.). This is a very eloquent way of describing a mechanical process. My one concern is that these cells are being examined on a macroscopic level. There are good data to show that protein fragments, viral particles, especially in HIV patients, may in fact be shed when $CO_2$ is released, so I would urge you to probably switch from the macroscopic to a more microscopic method of studying these cells. The other point to be made here is that tumor biology may be different in the various tumors that you described. You reported positive findings in pancreatic and esophageal cancer. The tumor biology in patients with these two cancers may be very different. I think these differences are multifactorial and that length of time also plays a role. I wonder if you could describe the length of time that these patients were investigated and the length of their operations. I would certainly urge you to continue this work because I think that again the question is should we abandon the use of $CO_2$ or other gases and go to lift techniques? What is your final recommendation at this point given this information?

***Dr. Ikramuddin.*** You have raised a number of interesting points. As far as the time course is concerned, this was a preliminary study so we did not attempt to control for the time period. The mean length of the operations was about 30 minutes, and the range was anywhere from 15 minutes to 1 hour. Your point about different tumors having different tumor biologies is well taken. We plan to expand the study on that basis. Regarding a final recommendation, in my opinion whether $CO_2$ or helium is used is not the critical issue. I think the way the tumor is handled is more important—that is, every effort should be made to avoid direct handling of the tumor and/or crushing of the tumor. Further research needs to be done in analyzing biology at the port site itself in terms of regulation of adhesion molecules. The beta-1 integrins, for example, and potential binding sites that may be provided in this injury model that may potentially be blocked should be considered. I think those are different areas of research, but my final recommendation is that use of $CO_2$ should not be a concern. Paying more attention to tumor handling and careful irrigation of the peritoneal cavity are probably the more important issues.

***Dr. J. Milsom*** (Cleveland, Ohio). I am going to ask a similar question. How did you validate this method of gathering cells? In other words, have you conducted any studies to look for positive controls when you are absolutely certain there would be cells in either a laboratory or a clinical setting.

***Dr. Ikramuddin.*** The three studies we cited speak to that issue. Knolmayer et al. placed tumor cells in a plastic container filled with saline, and they bubbled $CO_2$ into the plastic container and hooked a saline trap up to the port. These were loose nonaggragated cells, and 30.5% to 50% of the time they were, in fact, recovered.

***Dr. Milsom.*** If you are going to continue with this type of study, you might want to consider how, at your own institution, you would validate your test results.

***Dr. Ikramuddin.*** I appreciate your comments. That issue certainly needs to be addressed.

***Dr. W.P. Reed*** (Springfield, Mass.). The thing that makes me curious about this whole issue is that tumor cells are released during open procedures too. We do not seem to encounter the same types of problems with implantation in open wounds that you described with the laparoscopic procedures. Do you think implantation could be related to the relative health of the tissues through which the tumor cells are drawn by the trocar, the small size of the wound, or the inability to irrigate it rather than the fact that cells are simply released? You mentioned earlier that you found that cells were released in the presence of carcinomatosis. When a patient with carcinomatosis undergoes open exploration, cells are scattered all over the wound as well. Perhaps implantation is related more to the relative integrity of the tissues in which those implanted cells are left and the inability to clear the cells out of the tissues at the end of the procedure rather than to some mechanism of release.

***Dr. Ikramuddin.*** That is a very interesting comment. I do not have a direct response, but your point is well taken. Certainly port sites are severely traumatized following laparoscopy. A study by Goldstein in 1993 (J Endurol) examined the effects, in a mouse model, of irrigating the peritoneal cavity with heparin and an RGD peptide to blockade. They found that in the animals irrigated with heparin, there was a decrease in the number and volume of port-site metastases. This was an interesting finding because it suggests that there is something about the biology of the traumatized port site that may have an upregulating effect with certain molecules, and they may create a more accepting environment for tumor cells. Heparin has been known to reconstitute the mucopolysaccharide layer on fibronectin and prevent binding of tumor cells.

# Small-Diameter Prosthetic H-Graft Portacaval Shunt: Definitive Therapy for Variceal Bleeding

*Alexander S. Rosemurgy, M.D., Francesco M. Serafini, M.D., Emmanuel E. Zervos, M.D., Sarah E. Goode, R.N.*

Partial portal decompression has become a popular option in the treatment of complicated portal hypertension. This study was undertaken to report long-term follow-up after partial portal decompression obtained utilizing 8 mm prosthetic H-graft portacaval shunts. A total of 110 consecutive patients underwent H-graft portacaval shunting through a protocol that detailed care and studies from 1988 to 1996. Prospective follow-up recorded efficacy of partial portal decompression, shunt patency, morbidity of shunting, and survival. Seventy males and 40 females, whose average age was 54 ± 12.7 years (standard deviation), underwent shunting. Cirrhosis was due to alcohol abuse in 64%. Fourteen percent were in Child's class A, 55% in Child's class B, and 31% in Child's class C. Shunts were undertaken as emergencies in 20%, urgently in 13%, and electively in 67%. Shunting decreased portal pressure in all patients (30 ± 5.3 mm Hg to 19.9 ± 5.5 mm Hg; $P < 0.001$). Early and late thrombosis was 6.4% and 3.6%, respectively. Late rebleeding occurred in 5.4%. Perioperative (30-day) mortality was 11.8%, and was highest for patients in Child's class C. Three-year survival was 53%. Five-year survival was 41%. Partial portal decompression is achieved with H-graft portacaval shunting. Rebleeding, shunt occlusion, and encephalopathy are uncommon. In this series of unselected older patients with alcoholic cirrhosis, 5-year survival after H-graft portacaval shunting was greater than 40% with minimal intervention. (J GASTROINTEST SURG 1998;2:585-591.)

KEY WORDS: Portacaval shunt, portal hypertension, cirrhosis

Optimal surgical management of variceal hemorrhage due to cirrhosis and portal hypertension remains a topic of debate. The goal of surgery is to relieve hemorrhage through portal decompression while maintaining adequate liver function and avoiding encephalopathy. It is purported that partial portal decompression effectively controls gastrointestinal variceal hemorrhage in patients with cirrhosis and promotes preservation of portal blood flow to the liver, lowering the incidence of postshunt hepatic dysfunction and encephalopathy.[1-3] Because of its efficacy and safety, the partial portacaval shunt has emerged as a valuable tool for the surgeon confronted with a patient with portal hypertension who is bleeding from esophagogastric varices in who nonoperative management has failed.

The concept of partial portal decompression was first introduced by Bismuth et al.[4] in 1967. They constructed a narrow-diameter side-to-side portacaval anastomosis aimed at lowering portal pressure below a threshold sufficient to stop variceal hemorrhage while maintaining prograde hepatic flow. They found no differences, however, in the incidence of encephalopathy and liver failure between patients undergoing total or partial portal decompression and concluded that the size of the shunt stoma did not influence the postshunt portal hemodynamics.[4] On closer analysis of these patients, the authors concluded that these results were related to the widening of the shunt stoma, with equalization of portal and inferior vena caval pressures several months after shunting.[1]

In the early 1980s Rypins et al.[2] reintroduced the concept of partial portal decompression by studying a series of patients undergoing portacaval shunting utilizing a short small-diameter prosthetic graft between the portal vein and the inferior vena cava. Early and late follow-up demonstrated the efficacy of this

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technique in stopping variceal hemorrhage with acceptable rates of encephalopathy and liver failure.[3] Over the past 10 years, several centers have reported on partial portal decompression achieved by means of surgical shunts.[2,3,5,6] Although the techniques of shunting vary from one center to another, the results reported by each center encourage further study and evaluation of partial shunts, particularly in large numbers of patients.

In 1988 our institution began to prospectively evaluate partial protal decompression achieved through a short small-diameter prosthetic H-graft portacaval shunt. We were initially attracted to this approach because of the perceived technical ease of this procedure relative to other shunts and our growing dissatisfaction with conventional surgical shunts including the distal splenorenal shunt. Encouraged by our early results,[7] we continued a large prospective trial to investigate the efficacy of partial portal decompression in controlling variceal bleeding in patients with cirrhosis after failure of sclerotherapy or banding. In undertaking this trial we hypothesized that partial portal decompression would effectively control variceal hemorrhage with low morbidity and mortality. This study reports our experience with 110 consecutive patients who underwent short small-diameter prosthetic H-graft portacaval shunting for bleeding varices not amenable to treatment or after failure of nonoperative therapy.

## PATIENTS AND METHODS

### Prospective Trial

In early 1988 we began a prospective protocol to care for cirrhotic patients with bleeding varices or gastropathy not amenable to or having failed sclerotherapy or banding. Partial portal decompression was achieved with a short small-diameter interposition H-graft portacaval shunt utilizing 8 mm externally reinforced polytetrafluoroethylene (PTFE; W.L. Gore, Flagstaff, Ariz.). In these patients shunting was undertaken as a definitive therapy, never as a bridge to transplantation. For each patient Child's class was determined before shunting. Operations were categorized as follows: elective (hemodynamically stable patients electively scheduled for shunting), urgent (shunting undertaken within 24 hours of determining the need for a shunt), and emergency (shunting undertaken immediately after deciding to place a shunt). Encephalopathy was assessed as nonexistent, mild (well palliated with lactulose and dietary protein restriction), or severe (refractory to aggressive medical management and requiring hospitalization). Ascites was graded as absent (not clinically detectable), mild (controlled with sodium and water restrictions and diuretics), or severe (intractable despite maximum medical management). Patients were not considered candidates for shunting if portal vein thrombosis existed or when chances of survival were considered nil because of profound ill health.

### Construction of H-Graft Shunt

The technique of small-diameter PTFE H-graft portacaval shunt has been described in detail.[8] Briefly, with patients in the 30-degree left lateral decubitus position, all operations were undertaken through a transverse right upper quadrant abdominal incision. Intraoperatively, preshunt and postshunt pressures in the vena cava and portal vein were measured with a 25-gauge needle and a calibrated transducer. Intraoperatively, color-flow Doppler ultrasound assessment (Acuson 128 with linear array 5 MHz probe, Acuson Corp., Mountain View, Calif.) of the direction and velocity of portal vein blood flow was undertaken before and after shunting. After adequate exposure of the vena cava and portal vein, a prosthetic graft was sewn in place using nonabsorbable running monofilament sutures. The graft was an 8 mm externally supported PTFE graft with bevels at both ends oriented at 90 degrees to each other. The graft was never longer than 3 cm toe-to-toe and 1.5 cm heel-to-heel. The graft was sewn near to the bifurcation of the portal vein, so as to minimally compromise any future attempts at liver transplantation. A portion of the caudate lobe was generally resected to facilitate placement of the graft. At the time of shunting, vigorous attempts were not made to ligate collateral vessels arising from the portal vein. We marked the caval end of the graft with radiopaque metal clips to aid postoperative transvenous cannulation.

### Follow-Up

Patency was assessed by venography and pressure measurements on or about postoperative day 5 via transfemoral cannulation of the shunt and portal vein (Fig. 1). Similarly, direction and velocity of portal blood flow were assessed with color-flow Doppler ultrasound. At a minimum, patients were seen in the outpatient clinic within 1 month after discharge and at 6-month intervals thereafter.

### Statistics and Protocol

With full institutional review board approval, written consent was obtained from all patients prior to their enrollment in this trial. Data were entered into a computerized database (dBASE IV, Borland International, Inc., Borland, Tex.), and statistical compar-

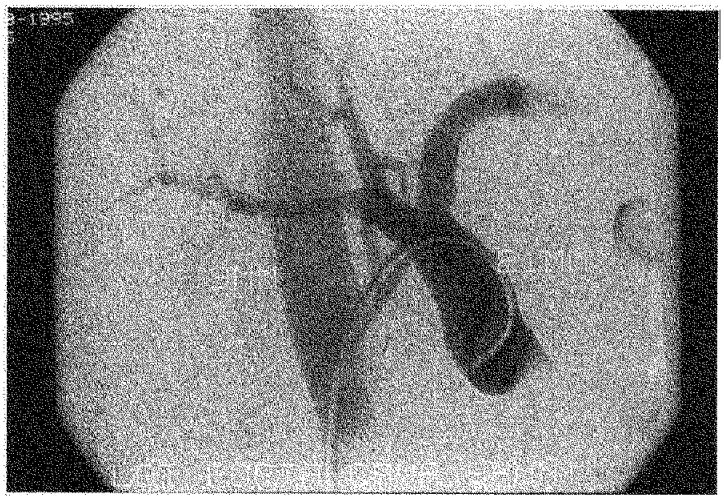

**Fig. 1.** Transfemoral cannulation of a shunt undertaken near postoperative day 5. In this patient the portal vein–vena cava gradient is higher than normal.

isons were made using True Epistat (Epistat Service, Richardson, Tex.). Differences between preshunt and postshunt pressures and flows were compared using the paired Student's *t* test, and significance was accepted with 95% confidence. Early deaths were defined as those occurring within 30 days of shunting; late deaths were those that occurred any time thereafter. Patients undergoing liver transplantation after shunting were considered therapy failures and were thereby considered to have "died" on the date of transplantation. Survival rates are reported at 1, 3, and 5 years after shunting.

## RESULTS

### Patient Demographics

There were 70 males and 40 females who underwent shunting; their mean age was 54 ± 12.7 years (standard deviation) (range 23 to 81 years). All patients had chronic portal hypertension due to cirrhosis. Alcohol abuse was the cause of liver disease in 65% of patients, hepatitis C virus in 12%, alcohol and hepatitis C virus combined in 4.5%, idiopathic causes in 14.5%, methotrexate in 1.8%, biliary cirrhosis in 0.9%, hemochromatosis in 0.9%, and autoimmune causes in 0.9%. Fourteen percent of the patients were designated Child's class A, 55% Child's class B, and 31% Child's class C. Ascites was present in 68% of patients before shunting, and was mild in 80% and severe in 20% of these patients. Encephalopathy was detected in 19% of patients before shunting. Encephalopathy was well palliated with dietary restriction and lactulose in 71% of these patients and was poorly controlled in 29%. Esophageal variceal hemorrhage was the indication for shunting in 48 patients (43.6%), gastric variceal hemorrhage in 12 (11%), esophagogastric variceal hemorrhage in 46 (41.8%), and intestinal variceal hemorrhage in three (2.6%). Portacaval shunts were undertaken as elective procedures in 74 patients (67%), as urgent procedures in 15 (13%), and as emergencies in 21 (20%).

**Table I.** Direction of portal blood flow assessed by color-flow Doppler ultrasound before and after shunting

| | Hepatopetal | Hepatofugal | Mixed |
|---|---|---|---|
| Preshunting | 78 | 6 | 1 |
| Postshunting | 70 | 12 | 3 |

### Direction of Flow

Intraoperative (both preshunt and postshunt) and postoperative color-flow Doppler ultrasound assessment of portal flow was available in 85 patients (77%). The first patients in this series, particularly those operated on as emergencies, were not studied using this technology. Color-flow Doppler ultrasound documented that 8 (10.2%) of the 78 patients studied had reversal of hepatopetal portal flow with shunting (Table I).

### Pressure Measurement

Intraoperatively, preshunt and postshunt portal vein pressures were measured and portal vein to infe-

**Table II.** Portal pressure before and after shunting

| Portal hemodynamics* | Preshunt | Postshunt | *P* value† |
|---|---|---|---|
| PV pressure (mm Hg) | 30 ± 5.3 | 20 ± 5.5 | <0.001 |
| IVC pressure (mm Hg) | 12 ± 5.2 | 14 ± 5.0 | <0.01 |
| PV-IVC gradient (mm Hg) | 18 ± 4.7 | 6 ± 3.5 | <0.001 |

PV = portal vein; IVC = inferior vena cava.
*Data are means ± standard deviation.
†Paired Student's *t* test

rior vena cava pressure gradients were calculated in all patients. Significant reductions in the portal vein pressures and in the portal vein-inferior vena cava pressure gradients were achieved after portacaval shunting in all patients (Table II).

## Shunt Thrombosis

Shunt thrombosis was documented in seven patients (6.4%) during routine postoperative venography. Six of these patients underwent surgical shunt revision after failed thrombectomy and thrombolysis with regional streptokinase. One patient refused reoperation and left the hospital with a clotted shunt. Patency was documented in all after reoperation with transfemoral venography and pressure measurements. All patients discharged from the hospital had patent shunts except the patient who refused reoperation for a clotted shunt.

Four additional shunt thromboses (3.6%) were recorded at various intervals during follow-up. Three patients developed shunt thrombosis within 6 months after shunting. Radiologic thrombectomy restored patency in two patients. Continued patency was documented by venography months later in each. One patient suddenly developed ascites and thrombosis 3 months after shunting and subsequently died of an apparently unrelated pulmonary embolus. The last patient developed thrombosis 3 years after shunting. She had rehemorrhaging from esophageal varices, was noted to have a clotted shunt, and soon thereafter underwent liver transplantation for progressive liver dysfunction. Routine venography at 1, 3, and 5 years detected no unsuspected shunt thrombosis.

## Ascites and Encephalopathy

By the time of discharge, ascites had clinically resolved in 42 (56%) of 75 patients with ascites. The remaining patients demonstrated considerable reduction in ascites and were discharged on lower doses of diuretics or taken off of them altogether. Operative wound reclosure was necessary in five patients to control postoperative ascitic leaks. Additionally, two minor perioperative ascitic leaks were successfully managed with repeated paracentesis and diuretics. Two patients early after shunting and one patient during early follow-up required placement of peritoneovenous shunts for persistence of ascites after failure of aggressive medical therapy.

Six patients (5.4%) developed "new-onset" symptoms of encephalopathy and three patients (2.7%) showed worsening of preexisting dysfunction after shunting. Alcoholic cirrhosis represented the underlying liver disease in eight patients (89%). Preshunt Child's class was A in one, B in four, and C in four. Mean intraoperative portal vein pressure measurements in this subgroup of patients did not differ from those of other patients in this series: 29 mm Hg before shunting and 22 mm Hg after shunting. Follow-up venography and color-flow Doppler ultrasound showed reversal of prograde liver flow in 50% of these patients. Among the nine patients with new onset or worsening of neurologic symptoms after shunting, four died within 3 years of shunting and the other five patients required readmission for adequate control of symptoms related to encephalopathy. All patients with encephalopathy before shunting were adequately managed after shunting with protein restriction (60 g protein/day) and lactulose, and none of them developed encephalopathic coma after shunting.

## Rehemorrhage

No patients had variceal rehemorrhage in the early postoperative period. Seven patients (6.4%) experienced repeat upper gastrointestinal hemorrhage late after shunting. In five patients the cause of late hemorrhage was alcoholic gastritis, which was fatal in four patients at 1, 3, 4, and 5 years, respectively, after shunting. Alcoholic gastritis was easily distinguished from portal gastropathy in each patient with bleeding. In addition, the shunt in each patient was patent with a portal vein–inferior vena cava pressure gradient of less than 10 mm Hg. In an octogenarian bleeding from gastric varices, hemorrhage was successfully

**Table III.** Survival stratified by Child's class

| Child's class | Perioperative (n = 110) | 1 yr (n = 108) | 3 yr (n = 75) | 5 yr (n = 49) |
|---|---|---|---|---|
| A | 94% (15/16) | 88% (14/16) | 57% (4/7) | 75% (3/4) |
| B | 92% (55/60) | 79% (46/58) | 60% (26/43) | 43% (12/28) |
| C | 80% (27/34) | 62% (21/34) | 40% (10/25) | 30% (5/17) |
| *P* value* | 0.17 | 0.08 | 0.26 | 0.23 |

*Log likelihood ratio test.

controlled with splenic artery embolization. Nonetheless, he died 6 months later of old age, progressive liver decompensation, and multiorgan failure. The last patient developed shunt thrombosis at 3 years after shunting and, after rebleeding, she underwent liver transplantation.

## Mortality

Poor hepatic reserve contributed, at least in part, to a number of perioperative deaths. One patient died of a narcotic overdose 5 days after shunting. A second patient died of postoperative respiratory failure related to the development of adult respiratory distress syndrome refractory to aggressive ventilatory support. A third patient died of gastric perforation on the day of planned discharge. This patient had undergone ill-advised sclerotherapy of gastric varices before shunting and had perforation at the site of sclerotherapy. A fourth patient died of toxic epidermal necrolysis, a condition for which he had been treated for years with methotrexate, which was the cause of his cirrhosis. Acute liver failure was the sole cause of death in nine additional patients (8.1%) within 30 days of surgery. In all, there were 13 perioperative deaths (11.8%). Most patients who died had poor functional hepatic reserve before surgery (7 patients in Child's class C, 5 in class B, and 1 in class A).

One hundred ten patients were eligible for 1-year follow-up. Two patients were lost to follow-up. In the remaining 108 patients, documented survival at 1 year was 74%. Thirteen patients (11.8%) died within 30 days of shunting, as previously described, and an additional 14 patients (14.7%) died over the course of the ensuing year. Progressive liver failure was the cause of death in nine patients during the perioperative period and in 8 of 14 additional patients within the first year after shunting. Four of 14 deaths were related to the following (one case of each): hemorrhagic alcoholic gastritis, sepsis, multiorgan failure, and pulmonary embolus. One patient died after liver transplantation and another patient died 3 months after shunting in the angiography suite from splenic artery perforation and massive hemorrhage during elective embolization, undertaken to treat severe thrombocytopenia due to splenic sequestration. Six of 14 deaths occurring within the first year after shunting occurred in patients who were, at the time of shunting, considered Child's class C. Four of these six patients continued to drink alcohol excessively after shunting.

Seventy-seven patients were eligible for 3-year follow-up. Two of these patients were lost to follow-up. Eight patients (10%) died within 30 days of shunting and an additional 13 (17%) died during the 3-year follow-up period, all of them from progressive liver failure. In total, 57% of deaths occurring by 3 years after shunting were related to progressive liver failure. The remaining 12 deaths were due to various other causes: two patients died from ischemic heart disease, two from alcoholic hemorrhagic gastritis, two from trauma, two from cancer, one from a pulmonary embolus, one from complication of diabetes, one from sepsis, and one from multiorgan failure. None of the deaths was due to rebleeding secondary to shunt occlusion. The overall survival at 3 years was 53%.

Fifty-three patients were available for 5-year follow-up. Four of these patients were lost to follow-up. Progressive liver failure was the cause of death in five patients (10%) immediately postoperatively and in 15 patients (30%) during follow-up. Cancer, alcoholic hemorrhagic gastritis, car accidents, sepsis, and encephalopathy were responsible for the deaths of the remaining patients. Overall survival at 5 years was 41%.

Survival stratified by Child's classification at 1, 3, and 5 years is depicted in Table III. Preoperative Child's classification was not a strong predictor of survival during the perioperative period, or at 1, 3, and 5 years (see Table III).

## DISCUSSION

The ideal therapy for variceal hemorrhage in patients with cirrhosis would definitively control variceal

hemorrhage while preserving liver function. With this in mind, partial portal decompression had gained considerable support in the management of complicated portal hypertension. Several techniques of shunting have been employed to achieve partial portal decompression.[2,5,6] Herein we report our experience with partial portal decompression in more than 100 patients using an 8 mm prosthetic interposition H-graft portacaval shunt with follow-up of up to 5 years.

This study portends outcomes to be expected with "all comers" after small-diameter prosthetic H-graft portacaval shunting, as only those patients whose perceived chances of survival were nil because of poor overall medical condition were excluded as candidates for shunting. The patients comprising this study were generally older alcoholic cirrhotic males with an elevated Child's classification. Shunting was undertaken, in general, to treat bleeding gastritis or esophagogastric variceal hemorrhage after failure of sclerotherapy and/or banding. More than half of the patients had ascites. Shunting was undertaken as an emergency or urgently in more than one third.

Despite the preponderance of high-risk patients, we recorded a low incidence of shunt-related morbidity. Early graft thrombosis was approximately 5%, with similar results having been reported by others.[3] Perioperative shunt thrombosis seems to be a result of technical failure. Cutting the graft correctly, keeping the length of the graft less than 3 cm, and avoiding twisting of the graft when placing it represent crucial steps for achieving a favorable early outcome. The latter seems most important, although specific causes of early shunt failure were not identified, leaving explanations of early graft failure open to speculation. In addition, volume depletion and decreases in cardiac output in the early postoperative period may play a role in early shunt failure. We have not found radiologic thrombectomy with thrombolysis to be able to restore more than temporary patency in occluded grafts and we would no longer continue this therapy for extended periods, preferring to promptly reshunt patients with early graft occlusion in whom balloon thrombectomy has failed. The success rates of salvage thrombectomy/thrombolysis vary from center to center, possibly depending on the experience of the interventional radiologists, but more likely depending on the cause of thrombosis. In the series of Collins et al.,[3] successful nonoperative salvage of graft occlusion was likely, whereas all our patients with perioperative graft thrombosis operative shunt revision. In our experience these patients, after reoperation, experienced long-term graft patency rates comparable to those in patients without early graft patency problems. This finding supports our belief that unidentified technical factors are the main causes of perioperative graft occlusion. We found that the best intraoperative predictors of postoperative graft patency are a postshunt portal vein–inferior vena cava pressure gradient of less than 10 mm Hg, a decrease in portal pressure with shunting of at least 10 mm Hg, and a thrill in the inferior vena cava after shunting. Late shunt occlusion was uncommon, with follow-up now approaching 10 years for the first patients in this series. Detectable graft–inferior vena cava anastomotic narrowing has been seen in only a few shuntograms obtained in late (more than 3 years) follow-up. Such narrowing has been remedied by balloon dilatation. Autopsy studies in a small number of patients have not documented notable neointimal hyperplasia.

Early rebleeding after shunting did not occur. Late rebleeding after shunting was uncommon. When rebleeding did occur, it resulted in significant morbidity and mortality. Gastritis due to alcohol recidivism was the most frequent cause of rehemorrhage. This obviously is not a result of shunt malfunction but rather a consequence of social misbehavior in this population of patients. Alcohol recidivism has been a problem in our series of patients, and has had a significant impact on the morbidity and mortality in our patients. This seems to be a problem particularly in patients in Child's C class. Only one patient had bleeding as a result of an occluded shunt. Thankfully, late shunt occlusion was very uncommon.

After shunting, ascites was well palliated. Ascites quickly resolved in more than half of the patients after shunting and at worst was generally well managed with diuretics and dietary restrictions in the remainder. The need for large-volume paracentesis was very infrequent and occurred only in the early postshunt period. Very few patients required placement of peritoneovenous shunts. Similar results were reported by Darling et al.,[9] who noted that most of their patients with ascites postoperatively showed significant improvement by late follow-up.

Although encephalopathy has always been difficult to quantify, the incidence of new onset or worsening of preexisting clinical encephalopathy after shunting was uncommon in our patients. When it did occur, which was generally in the early postoperative period, it was temporary, not severe, and well managed with a diet restricted to 40 to 60 g of protein per day plus lactulose.

Preshunt or postshunt portal vein pressures and portal vein to vena cava pressure gradients did not predict encephalopathy. Encephalopathy in the early postoperative period either resolved by 6 to 8 months or was associated with progressive hepatic deterioration and death by 1 year. Postshunt encephalopathy, even when intermittent, that did not improve over 2 or 3 months was a sign of very poor outcome. If pos-

sible, these patients should undergo liver transplantation. Collins et al.[3] documented postshunt encephalopathy requiring hospitalization in 13% of their patients after placement of 8 mm prosthetic H-graft portacaval shunts, a figure comparable to but higher than ours. In their series 90% of the patients with encephalopathy maintained hepatopetal flow.[3] In a different study, comparing 8 mm vs. 16 mm prosthetic H-graft portacaval shunts, Rypins et al.[10] found that postshunt encephalopathy was far more frequent in patients with total shunts (i.e., 16 mm), and nutrient hepatic flow was better preserved in the patients who underwent partial (i.e., 8 mm) shunting. The etiology of encephalopathy after partial shunting remains unclear. In the experience of Rypins et al.,[10] maintaining adequate nutrient hepatic blood flow was important in avoiding encephalopathy, whereas in our experience maintaining prograde portal flow seems to play a questionable role in avoiding encephalopathy.[10] Possibly maintenance of a certain degree of mesenteric venous hypertension through partial portal decompression limits the absorption of neurotoxic substances from the gut while promoting hepatic perfusion, thereby discouraging postshunt encephalopathy.[11]

Perioperative mortality after partial portal decompression has been reported to range from 6% to 13%,[3,9] and it is usually related to progressive liver failure. Early mortality in our study was 12%. One third of the perioperative deaths were potentially preventable, whereas the remaining patients died of unpreventable progressive liver failure. Child's class and circumstances of shunting correlated best with outcome, as the majority of early deaths were in patients with an elevated Child's classification, and they occurred after shunting under emergency circumstances.

In evaluating the causes of late death, we found that progressive liver failure was responsible for 60% of the deaths occurring after 30 days and before 1 year. Most of the patients dying of progression of liver dysfunction within the first year after shunting continued to drink alcohol postoperatively. After this period, the incidence of liver failure–related mortality decreased substantially, with only 38% of the deaths at 3 years and 19% of those at 5 years after shunting due to progression of liver disease. Alcohol played a role in some of even the most remote deaths through progressive hepatic dysfunction as well as other causes such as trauma. In addition, hemorrhagic alcoholic gastritis was the principal cause of late rebleeding, and was often fatal. Many of the deaths were alcohol related and thereby preventable, mostly being related to social misbehaviors typical of these patients. During a mean follow-up of 24 months, progressive liver decompensation was also the main cause of late death in the study by Johansen.[6] Hepatic deterioration was not a problem in the study by Collins et al.,[3] with no late deaths recorded during a mean follow-up of 43 months.

Small-diameter PTFE H-graft portacaval shunts have proved to be efficacious in managing complications of portal hypertension following failure of emergency medical therapy at our institution. Partial portacaval shunting controls variceal hemorrhage, preserves portal hepatic perfusion, and palliates ascites, with a low incidence of postshunt encephalopathy and acceptable perioperative mortality. Our experience in a large number of patients demonstrates that small-diameter prosthetic H-graft portacaval shunting is a valuable alternative to conventional shunts in the treatment of massively hemorrhaging esophagogastric varices, providing immediate relief of the hemorrhage and an acceptable long-term quality of life.

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