Why Another Journal?

Tom R. DeMeester, M.D., President, The Society for Surgery of the Alimentary Tract

The long-awaited JOURNAL OF GASTROINTESTINAL SURGERY has begun publication. Co-Editors John Cameron and Keith Kelly have done an excellent job. As you read it, and hopefully enjoy it, I can imagine many of you asking: "What, another journal, or do we really need another journal to read?" Allow me to respond. To begin with, it is necessary to make a distinction between our new journal and most others devoted to surgery. Our journal is owned and produced by our Society—that is, The Society for Surgery of the Alimentary Tract (SSAT). Most other journals are owned and produced by private publishers. It is important to differentiate between the two. A society is defined as a group of persons who come together for the purpose of advancing a shared interest. The key components are the persons and the purpose. The purpose is pursued through the persons acting together. A business is a commercial activity established for the purpose of providing a livelihood. The key components are the activity and the livelihood. The livelihood is pursued through a corporate structure directed by a chief executive officer. Consequently a society self-corrects for professional reasons, whereas a business self-corrects for financial reasons.

In our Society the persons are surgeons with a special interest in the gastrointestinal tract. The purpose of our Society is to "stimulate, foster, and provide surgical leadership in the art and science of patient care; teach and research the diseases and functions of the alimentary tract; provide a forum for the presentation of such knowledge; and encourage training opportunities, funding, and scientific publications supporting the foregoing activities."

It is on the latter of the four preceding objectives that our Society is currently focused. We have evaluated the possibility of establishing a gastrointestinal surgical fellowship to improve training in the care of complex gastrointestinal illnesses, we have investigated new sources of funding to support research and training opportunities, and we have reviewed new ways of publicizing our activities and disseminating the knowledge gained from them. What have we accomplished to date? The Education Committee chaired by Dr. Carlos Pellegrini will soon submit to the Society a document entitled, "Fellowship in Gastrointestinal Surgery," which describes the details of our proposed fellowship. A committee of the Board of Trustees will report on the possibility of the SSAT joining forces with the American Digestive Health Foundation, the purpose of which is to raise monies collectively to support research. The Board of Trustees of the SSAT, after several years of discussion, has decided to proceed with establishing and producing its own journal.

Having our own journal will provide the following benefits to the Society: (1) It will allow us direct capability and maximum flexibility in communicating with members of the Society. (2) It will provide an avenue for publishing the proceedings from our annual meeting of the consensus panel organized by our research committee and the Conjoint Clinical Symposia organized by our program committee. (3) It will allow for publication of the abstracts submitted to the program committee for review and the full scientific manuscripts of those selected for oral or poster presentations at our annual meeting. (4) It will establish a surgical journal that is focused solely on the gastrointestinal tract and comes under the scrutiny of a Society that values professional ethics over business ethics. (5) It will provide an avenue, monitored by the Society, for entering the age of CD-ROM and disseminating information by means of this route. (6) It will allow the control of the economic resources that flow from the publishing effort to remain within the Society and be used for its purposes. In short, it is hoped that the JOURNAL will become the major organ for relaying information on new and existing surgical techniques and developments pertaining to diseases of the gastrointestinal tract, not only in the United States but worldwide.

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Good communication is essential if we are to work successfully with our colleagues toward achieving the objectives of our Society. Written communication is fundamental. It is characterized by its precision and its ever-present availability. It can be read and reread, talked about and thought about, copied and stored. It is so basic to the well-being of our Society that it must be considered an integral part of our organization. Taking all these considerations into account, I hear myself say: "Yes, we do need another journal to read!"

Our New Journal

John L. Cameron, M.D., Keith A. Kelly, M.D., Co-Editors

For The Society for Surgery of the Alimentary Tract (SSAT), and we think for gastrointestinal surgery at large, 1997 is a landmark year. This year marks the establishment of our new journal, the JOURNAL OF GASTROINTESTINAL SURGERY.

The SSAT was founded in 1960. Through the efforts of its many members, the organization has helped elevate the practice of gastrointestinal surgery, has promulgated the training of gastrointestinal surgeons, and has supported research in digestive diseases. Over the past 25 years the Society has established itself as a scholarly organization and a major force in alimentary tract surgery. It serves as the surgical arm of Digestive Disease Week, the largest annual digestive disease meeting in the world.

Digestive diseases affect one out of every four Americans and account for more lost days from work than any other category of disease. Surgery is key in managing many digestive disorders, and the public needs and wants surgeons who are up-to-date in the field. Keeping up-to-date on the latest advances in gastrointestinal surgery has not been easy. Reports of state-of-the-art management and new advances are scattered throughout numerous journals and in a variety of forums. After several years of research and intensive discussion, the SSAT has decided that reports in our field should be concentrated in a single journal devoted exclusively to surgery of the alimentary tract. This will make the material much more accessible to the many physicians and surgeons who care for patients with gastrointestinal diseases. The American College of Surgeons has assembled research reports in gastrointestinal surgery into a special section of the *Surgical Forum* for years, but no American journal has devoted itself exclusively to this important field of surgery.

The aim of our new journal is to bring state-of-the-art discussion of and advances in gastrointestinal surgery to the profession in a single journal, so as to provide a ready source of material in the field. We believe the convenience of this approach will enhance dissemination of new ideas and expedite the application of new advances. Moreover, we hope the JOURNAL OF GASTROINTESTINAL SURGERY will attract young people to the field, and into our Society, and stimulate interest and research in digestive diseases. Finally, the formation of the JOURNAL should be an important step in the recognition of gastrointestinal surgery as a unique field of surgery. Gastrointestinal surgery is clearly part of the field of general surgery, but it is also an important subspecialty, as are vascular surgery and surgical oncology.

The JOURNAL will emphasize high-quality original papers in our field, scholarly reviews, instructive case reports, innovative advances in surgical techniques, instructive letters to the editor, book reviews, comments by leading experts in the field of surgery with a broad perspective on special topics, as well as papers presented at the annual meeting of the SSAT. The Co-Editors will be aided by an Editorial Board comprised of distinguished colleagues from the United States and abroad. We expect that our new journal will reach across national boundaries and bring together from around the world those with an interest in digestive surgery.

The SSAT and the Co-Editors invite active participation in the JOURNAL from all who have an interest in gastrointestinal surgery, in its teaching and its research. We expect the JOURNAL to attract a broad readership that includes medical students, residents, and physicians and surgeons in private practice, as well as those associated with government and academic institutions. We promise a responsive journal—one that will continue to change and evolve over time. This is an exciting new venture for the SSAT, and we invite your comments and input so that we might make this new journal the premier source worldwide for information on surgical gastroenterology.

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Portal Hypertension: A Surgical Hepatologist's View of Current Management

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Current strategies for management of acute esophageal variceal bleeding and for long-term treatment after an episode of variceal bleeding are outlined. Acute variceal bleeding is best managed by means of endoscopic therapy (sclerotherapy, band ligation, or "superglue"), whereas the role of pharmacologic agents remains controversial. In cases of failure of endoscopic therapy, a transjugular intrahepatic portosystemic shunt (TIPS) procedure, an emergency shunt, or a transection operation should be performed. Patients who experience an acute variceal bleeding episode require long-term management to prevent recurrent bleeding. Endoscopic treatment is preferred using either sclerotherapy or banding. The principal alternative is long-term pharmacologic therapy with beta-adrenergic receptor blocking agents. Major surgical procedures should be reserved for failures of endoscopic or pharmacologic therapy. The distal splenorenal shunt or the new narrow-diameter polytetrafluoroethylene portacaval shunt is preferred. All patients who are first seen with acute variceal bleeding should be considered for a liver transplant, although few will ultimately become transplant candidates. Patients with end-stage liver disease who are not transplant candidates should be identified and major high-cost therapy discontinued. Prophylactic therapy prior to variceal bleeding should be considered in selected patients. At present, only pharmacologic therapy is justified. The major problem remains identification of those patients at high risk for a first episode of variceal bleeding. (J GASTROINTEST SURG 1997;1:4-12.)

Patients who have portal hypertension and esophageal varices present for management of acute variceal bleeding or for long-term management to prevent recurrent bleeding after a proved variceal bleed. Patients may also present for possible prophylactic management prior to a first episode of variceal bleeding. Prophylactic therapy remains a topic of considerable controversy. My current views are presented herein, with emphasis on the controversies surrounding this issue.[1-3] A recent meta-analytic review has helped to provide insight into these controversies.[4]

At the present time, the principal primary forms of therapy for patients either with acute variceal bleeding or after repeated instances of variceal bleeding are endoscopic treatment and pharmacologic management. Surgical procedures, including portosystemic shunts and devascularization and transection operations, as well as the radiologically performed transjugular intrahepatic portosystemic shunt (TIPS) procedure, should be reserved for patients who fail endoscopic or pharmacologic therapy. All patients should be considered for a liver transplant, although few will become transplant candidates. Patients with end-stage liver disease who are not transplant candidates should be carefully evaluated to determine whether any form of definitive treatment is justified.

This article is concerned with the management of esophageal varices. The management of much less common gastric and intestinal variceal bleeding, as well as bleeding from portal hypertensive gastropathy[5] and intestinal vasculopathy, is also important but beyond the scope of this report.

MANAGEMENT STRATEGIES

Management of Acute Variceal Bleeding

Each episode of acute major variceal bleeding is associated with a high mortality rate, particularly in

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those patients who have severe underlying liver disease. The mortality rate is much lower when the patient is managed in a specialized hepatology unit with expertise in a wide variety of available management options. Patients with suspected acute variceal bleeding must be admitted to the hospital, preferably to a specialized hepatology unit, or be transferred to such a unit as soon as possible. These patients should be treated in an intensive care unit whenever possible and carefully resuscitated.[1-3]

The use of vasoactive drugs, either alone or in combination with endoscopic management, is controversial.[4,6] The current controversies are presented in the relevant sections that follow. The most widely used drug at present is somatostatin or its synthetic analogue, octreotide, although glypressin may be as effective. An intravenous infusion of vasopressin, with or without nitroglycerin, was widely used in the past but has been largely superseded by the other agents. Metoclopramide has also been shown to be effective[7] but requires further evaluation.

Emergency diagnostic endoscopy is mandatory to confirm that the patient does indeed have varices and that these varices are bleeding. Patients with varices and suspected variceal bleeding can usually be divided into the following three groups: those with active variceal bleeding, those with variceal bleeding that has stopped, and those who have varices but who are bleeding from another lesion.[8,9] Clearly in the latter group, the other condition, and not the varices, should be treated on its own merits.

I firmly believe that emergency endoscopic therapy should be undertaken at the time of the initial diagnostic endoscopy. Delay may be associated with additional major bleeding, which may be fatal.[2] Furthermore, this policy has an added benefit in that definitive therapy is begun immediately. The emergency endoscopic therapy options include emergency sclerotherapy, emergency variceal band ligation, and the use of superglue (cyanoacrylate). Sclerotherapy remains the most commonly used treatment, although it may be supplanted by banding in the future. Superglue is of particular value in patients in whom acute esophageal variceal bleeding is difficult to control and in those being treated for bleeding gastric varices.

Emergency endoscopic therapy may fail either because an adequate view cannot be obtained or because the endoscopist has insufficient experience. Balloon tube tamponade is indicated in these instances. A carefully inserted Sengstaken-Blakemore balloon tube will invariably achieve tamponade of variceal bleeding if correctly inserted and positioned. This will allow time for further attempts at resuscitation in an intensive care unit, with repeat endoscopy and endoscopic therapy being performed by an expert several hours later. If bleeding continues or recurs in a patient after a balloon tube has been inserted, the tube should be checked by an expert and if it is found to be correctly placed, the patient should undergo repeat endoscopy to determine the cause of bleeding. A cause other than varices, which was missed at the initial diagnostic endoscopy, will usually be found.[2]

Failure of emergency endoscopic therapy has been defined as further variceal bleeding that occurs after two endoscopic treatments during a single hospital admission for an acute bleeding episode.[3,10] Such patients should have a balloon tube inserted and then undergo either a TIPS procedure, placement of an emergency shunt, or an esophageal transection procedure. Our group has shifted from emergency surgery to the use of the TIPS procedure in this emergency situation despite the long-term disadvantages of the TIPS procedure, which are discussed below. Our group has also noted that with modern available therapy including variceal banding, the failure rate for emergency endoscopic therapy has declined considerably. We previously reported a 70% success rate after a single sclerotherapy injection and a success rate of greater than 90% after a second treatment.[8,9] The success rate is now well over 95%.

All patients who have had acute variceal bleeding should immediately be entered into a definitive management program, usually repeated endoscopic therapy, because at least 70% of these patients will have a recurrence of variceal bleeding, particularly early, with a high attendant mortality rate.[1]

Long-Term Management After Variceal Bleeding

The mainstay of long-term management is endoscopic therapy, usually injection sclerotherapy, although endoscopic variceal band ligation is gaining favor and may replace sclerotherapy. There may also be a limited role for superglue injected into the varix. The principal alternative is long-term pharmacologic therapy, the disadvantages of which are outlined below.

Once a patient has had endoscopically proved esophageal variceal bleeding, endoscopic therapy, either sclerotherapy or variceal banding, should be instituted and administered at weekly intervals until the varices are eradicated. The patient should then undergo endoscopic examination at 3 months, to confirm eradication, and subsequently at 6-month or 1-year intervals. Whenever recurrent varices are diagnosed, either during routine endoscopic evaluation or because of recurrent variceal bleeding, patients should be subjected to the same weekly endoscopic therapy regimen until all varices have been re-eradicated.[11]

Failure of long-term endoscopic therapy has been defined as either recurrent bleeding despite adequate endoscopic therapy or esophageal varices that are difficult to eradicate by means of endoscopic therapy.[2,11] Such patients should be subjected to elective surgical shunt placement or a devascularization and transection operation, or they should be considered for a TIPS procedure. We prefer the Warren distal splenorenal shunt at present. Long-term management problems associated with the TIPS procedure are detailed below.

Prophylactic Management

Prophylactic management is defined as treatment of patients who are known to have esophageal varices prior to their first variceal bleeding episode. When all patients with varices without previous bleeding are evaluated, only 30% will eventually have variceal bleeding during their lifetime.[12] Therefore treatment of all patients would result in 70% of the patients receiving unnecessary treatment. The real problem has been the identification of high-risk patients. The endoscopic criteria of large varices with "cherry red" spots and other criteria set forth by Beppu et al.[13] have been widely used, although their ability to predict bleeding has proved disappointing.[14] The newer North Italian Endoscopic Club criteria include both the endoscopic appearance of the varices and indices of liver function.[15] Predictions based on these criteria are claimed to be more accurate.[15] However, this remains to be confirmed in a major prospective study. A group from Bologna, Italy, has added the Doppler ultrasound congestion index to the endoscopic and liver function criteria and claims to have devised a better predictive index.[16] This, too, remains to be confirmed in a prospective evaluation.

The most widely used prophylactic management has been pharmacologic therapy, particularly with propranolol.[4,17] I believe this is justified in some high-risk patients, especially if they live a great distance from a specialized hepatology center. Prophylactic surgical shunts were abandoned several decades ago because patients with shunts had a higher mortality rate than those treated expectantly. The use of prophylactic sclerotherapy and prophylactic devascularization and transection operations is currently being widely reported, particularly in Japan, but in my view this practice cannot be justified until truly high-risk patients can be better identified.[1-3]

MANAGEMENT CONTROVERSIES

Conservative Management

Poor-risk patients presenting with acute variceal bleeding, who do not respond to standard emergency treatment including endoscopic therapy and who are not candidates for a liver transplant, should be carefully evaluated for expectant treatment. Once a decision is made, no further high-cost therapy should be instituted. Clearly this raises difficult moral and ethical issues, but it is the only realistic option in today's cost-conscious environment.

The same philosophy applies to patients undergoing long-term management. If the patient has end-stage liver disease and is not a candidate for a liver transplant, then treatment, which is not only expensive but uses medical manpower that is often in short supply, should not be undertaken when the situation is hopeless.

Liver Transplantation

Liver transplantation is the only treatment that offers a permanent cure for both the underlying liver disease and the portal hypertension. We believe that all patients presenting with acute variceal bleeding should be considered for a liver transplant, and those deemed likely candidates should be managed with endoscopic therapy. Patients who fail endoscopic therapy should undergo an emergency TIPS procedure early in their management before they reach the point where a transplant is no longer an option because the risk has become prohibitive.

After emergency measures are taken to control the bleeding, the patient should undergo a rapid diagnostic workup and, if the patient is accepted into a transplant program, an early liver transplant should be performed because of the danger of further variceal bleeding, which could prove fatal.

The fact that a patient has had variceal bleeding is not an indication of the need for a liver transplant.[18] The indication for a transplant is based on the patient's underlying liver disease, as would be the case in patients without varices. The majority of our patients have alcoholic cirrhosis and continue to drink; therefore few of them are candidates for a transplant. The same applies to the majority of patients with variceal bleeding in North America. Patients with good liver function who have failed endoscopic therapy should undergo shunt placement, preferably a distal splenorenal shunt, rather than a transplant.[18]

Endoscopic Management

Injection sclerotherapy has been the mainstay of emergency and long-term management of esophageal varices for several decades. The recent introduction of variceal band ligation and the outcome of several controlled clinical trials suggest that variceal band ligation might be a superior form of management,

particularly when banding is combined with low-dose sclerotherapy. The use of cyanoacrylate monomer (superglue) has probably been underemphasized in the past and requires further evaluation, particularly when combined with subsequent sclerotherapy when variceal bleeding has been difficult to control.

Injection Sclerotherapy. There are three main techniques of injection sclerotherapy.[2,3] One is intravariceal injection with the aim of thrombosing the varix, thereby controlling acute variceal bleeding and subsequently also preventing further variceal bleeding. The second technique, widely used in Europe, is paravariceal sclerotherapy, whereby multiple small injections are introduced into the submucosa circumferentially around the lower third of the esophagus. Paravariceal injection adjacent to a bleeding varix controls the acute bleeding by compression and subsequently repeat injections thicken the mucosa over the varices, thereby preventing recurrent bleeding. Both intravariceal and paravariceal injections become less accurate and most likely end up as a combined technique, particularly as varices become smaller. Our group has employed a predominantly intravariceal technique that uses 5% ethanolamine oleate for long-term management, but we prefer a combination of intravariceal and paravariceal injections of 5% ethanolamine oleate for the management of acute variceal bleeding. Our technique, as is true of others, is continually being refined and is described in detail elsewhere.[19]

A major disadvantage of sclerotherapy, unlike other treatments for portal hypertension, is that it has not yet been standardized. The only standard aspects are the use of a fiberoptic endoscope, usually as a free-hand technique without an oversheath. The three techniques described previously are used differently by different investigators with a wide variety of sclerosing agents. Ethanolamine oleate, sodium tetradecyl sulphate, and sodium morrhuate have been the agents most commonly used for intravariceal injections, and polidocanol and ethanolamine oleate have been used for paravariceal injections. The timing of the injection, the volume of sclerosant, and the site of injection also vary enormously from one center to another, as does the skill of the sclerotherapist. It is therefore not surprising that the published results have been conflicting, which makes it difficult to compare findings from different centers.[1-4]

Our group, similar to others, has demonstrated that acute variceal bleeding can be controlled in 70% of patients with a single injection. This means that in 30% bleeding recurs, necessitating another injection. A second injection has been shown to control variceal bleeding in more than 90% of patients.[8,9] Patients in whom sclerotherapy failed (more than two treatments)[3,10] were subjected to additional major procedures, usually surgical, in the past but are now most often treated with a TIPS procedure in our unit. However, failure to control acute variceal bleeding endoscopically is becoming increasingly rare.

Repeated injection sclerotherapy has proved highly effective in managing patients long term after variceal bleeding. Injections must be performed at weekly intervals until the varices have been eradicated. In the first controlled trial comparing endoscopic sclerotherapy with conservative management, our group demonstrated that varices could be eradicated and that once varices were eradicated, further variceal bleeding was prevented.[20] However, we failed to show a survival advantage. This differed from some other studies.[3,11] The reason, in my view, is that we treated all patients who presented with subsequent episodes of acute variceal bleeding with the best available therapy at that time, namely, sclerotherapy. We did not allow the control patients who presented with later acute variceal bleeding to continue bleeding with associated mortality. Disadvantages are that repeated sclerotherapy management requires lifelong follow-up. Varices will recur in time and will need to be reinjected. Complications are also cumulative over time.[11,21] Furthermore, patients need to have access to a major medical center for follow-up. Repeated injection sclerotherapy remains the most widely used form of therapy, although it may well be superseded by esophageal variceal band ligation in the future.[22]

Patients who have failed long-term endoscopic sclerotherapy have been treated with major surgical procedures in our unit, as described below. The combination of sclerotherapy and pharmacologic therapy has theoretical advantages, but the published results have been conflicting.[4]

Esophageal Variceal Band Ligation. The concept of esophageal variceal band ligation was devised by Stiegmann et al.[23,24] The technique is similar in principle to the rubber band ligation procedure that is widely used to treat internal hemorrhoids. The four initially completed prospective randomized controlled clinical trials comparing this technique with repeated sclerotherapy showed that the two techniques were equally effective in controlling acute variceal bleeding and eradicating varices.[23,25-27] However, variceal band ligation eradicates esophageal varices with fewer treatment sessions and with fewer complications compared to sclerotherapy. The initial trial conducted by Stiegmann et al.[23] showed a survival advantage. Additional trials have been published recently with similar results, although there have been some differences.[28-30] There is a good theoretical reason for combining banding with low-dose sclerotherapy.[31] Banding is easy to accomplish when varices are large but becomes increasingly more

difficult as the varices diminish in size. The Cape Town group is currently evaluating a combination of banding and low-dose sclerotherapy as compared with our technique of injection sclerotherapy in a prospective randomized controlled trial.

Several trials have yielded conflicting results with combined sclerotherapy and vasoactive drugs for the management of acute variceal bleeding. Banding and vasoactive drugs are currently being evaluated. In one trial it was concluded that octreotide may well be useful in combination with banding.[32] Results of trials combining banding with beta-adrenergic receptor blockade with propranolol in long-term management have yet to be presented.

Despite enthusiastic endorsements by some investigators, banding as currently practiced has a number of disadvantages. Band ligation becomes more difficult to accomplish as the varices become smaller with repeated treatments. Banding requires an overtube and the endoscope must be removed and reloaded for each ligation, which is inconvenient. The overtube has given rise to complications, although most have occurred outside the controlled trials. These complications include esophageal perforation, pinching of the mucosa between the overtube and the endoscope, and even rupture of esophageal varices due to an increase in pressure caused by compression by the overtube in the upper esophagus. It has been reported that "multiple-fire" devices, which will eliminate the need for reloading and might even make it possible to perform banding without an overtube, are currently being developed.

Some believe that variceal band ligation will probably supersede sclerotherapy as the mainstay of long-term management of patients after variceal bleeding.[22] It is likely that a combination of banding and low-dose sclerotherapy will prove best.

Cyanoacrylate Monomer (Superglue). Superglue (cyanoacrylate long-chain monomer) has probably been underutilized in the past. Among the major proponents of superglue are Binmoeller and Soehendra[33] from Germany. Their group has recently pointed out the advantages and disadvantages of this glue. Cyanoacrylate is particularly valuable for managing acute bleeding varices when they have been difficult to control because the glue immediately thromboses the varix and plugs the varix lumen. The bolus of glue is eventually extruded into the esophageal lumen. Cyanoacrylate glue has also been very effective in the management of gastric varices. Cyanoacrylate is mixed with lipiodol to facilitate the injection and it also enables the injection to be visualized fluoroscopically. Superglue should be combined with sclerotherapy in long-term management[33-35] because the rate of rebleeding has been high when the glue is used alone and because varices are difficult to treat as they become smaller with treatment because the superglue must be accurately placed within the varix lumen. The dangers of cyanoacrylate include spillover, with isolated case reports of portal vein thrombosis, cerebral thrombosis, and pulmonary problems. The agent is potentially carcinogenic but this has not been documented in clinical studies. There is also a danger that the endoscope could be damaged. The use of silicone oil, both on the end of the endoscope and in the working channel, together with other specific precautions makes this less likely. Additional trials with superglue in patients with esophageal varices are needed before its ultimate role can be defined.

Pharmacologic Management

Pharmacologic therapy has been used alone or in combination with endoscopic therapy for treatment of acute variceal bleeding and for long-term management after variceal bleeding. Vasoactive drugs aimed at controlling acute variceal bleeding have been used for decades. Nevertheless, their efficacy remains debatable. Multiple controlled trials have compared the various vasoactive drugs used either alone or in combination with endoscopic management for acute variceal bleeding.[4,6] The findings remain contradictory.

The previously used infusions of vasopressin with or without nitroglycerin have been largely replaced by glypressin and somatostatin. However, the cost of somatostatin and glypressin is a consideration. Glypressin (Terlipressin) is a synthetic analogue of vasopressin. It has the distinct advantage of being effective when given as intravenous bolus doses. Usually 2 mg is administered every 4 to 6 hours. A recent report has demonstrated its value when it is administered early before the patient is transported to the hospital.[36] Terlipressin has been effective in controlling acute bleeding in 60% to 80% of patients.[6] Currently, the most widely used agent is somatostatin or its analogue, octreotide. The results remain contradictory but the overall impression is that somatostatin is of value. Somatostatin is usually administered as a continuous intravenous infusion of 250 μg/hr after an initial bolus dose of 250 μg. Somatostatin has been shown to be effective in controlling acute bleeding in 80% of patients.[6] Its synthetic analogue, octreotide, has been the subject of several recent controlled trials showing its efficacy[37-39] but the results have not been uniform. These agents have also been used in combination with endoscopic therapy.[37-41] Combined therapy may prove to be superior. Metoclopramide, which constricts the lower esophageal sphincter, has also been shown to arrest variceal hemorrhage[7] but confirmatory trials will still be required.

The theoretical advantage of using vasoactive agents prior to the initial endoscopy is that if the patient's variceal bleeding is controlled with these agents, the endoscopic therapy that is undertaken at the time of the first diagnostic endoscopy will be easier to administer. The ultimate role of pharmacologic therapy in the management of acute variceal bleeding requires further evaluation.[6] The high rate of success currently being achieved with the use of endoscopic sclerotherapy or banding may make the addition of these agents, which are costly and not without side effects, unnecessary.

Pharmacologic agents have also been widely used as the sole treatment in long-term management. Beta-adrenergic receptor blockade with propranolol has been studied the most.[1,3,4,42-48] More recently the use of nitrites has been evaluated.[48] The use of beta blockade in association with sclerotherapy has also been evaluated and may be superior to the use of either alone, although the results have not been uniform.[4,43-46] If propranolol therapy could lower the incidence of acute bleeding prior to endoscopic eradication of varices, this would be an advantage. Many groups use beta blockade with propranolol as the first-line therapy in long-term management. It is not effective in all patients. For the approximately 20% in whom it fails and who then present with subsequent variceal bleeding, endoscopic therapy can be used. It is our view that endoscopic therapy is the preferred first-line treatment in the majority of patients.

The problems of long-term propranolol treatment include compliance with lifelong therapy, particularly in patients with alcoholic cirrhosis. Propranolol is also not without side effects, and not all patients respond to propranolol therapy. The nonresponders can only be identified by invasive investigations to determine whether the reduction in portal pressure has been inadequate. With time, patients on propranolol continue to experience bleeding, whereas patients successfully treated with endoscopic therapy only have variceal bleeding before their varices are eradicated or when varices subsequently recur.[47] There is also the theoretical danger that the sudden discontinuation of propranolol could result in an increase in portal pressure with the potential for variceal rupture.

In those patients who are likely to be compliant, long-term propranolol therapy is a viable option.[48] Its true role compared to endoscopic therapy should become evident with further studies. Whether nitrites will prove to be better will also require additional studies.[48] Propranolol therapy is the most acceptable form of prophylactic therapy for patients who have not yet experienced variceal bleeding but who are at high risk for such an occurrence.[4,17,42] It is used by our group for prophylaxis in selected patients.

Surgical Management

The use of major surgical procedures to salvage patients who do not respond to conventional therapy for acute variceal bleeding has diminished significantly since the advent of sclerotherapy and, more recently, variceal band ligation and the TIPS procedure. Surgery remains the treatment of choice when endoscopic therapy fails in long-term management after variceal bleeding.

Portosystemic Shunts. Although most groups do not advocate emergency portacaval shunting for control of acute variceal bleeding, Orloff et al.[49] have achieved consistently good results with portacaval shunts placed within 8 hours of the patient's admission. In a recent randomized controlled trial, Orloff et al.[50] have shown that an emergency portacaval shunt is more effective with a highly significant survival advantage when compared with initial conservative management followed by a subsequent elective portacaval shunt. Others have not achieved such good results,[51] but Orloff's persistent reporting of excellent data in the management of acute variceal bleeding requires further evaluation with the use of his protocol.

Shunting remains the principal treatment for failures of endoscopic therapy in long-term management. Here, currently, the preferred shunt is the Warren distal splenorenal shunt, which in theory preserves prograde mesenteric flow to the liver while decompressing the esophagogastric area, the site of esophagogastric variceal bleeding.[52,53] An interesting new narrow-diameter shunt that also preserves prograde flow to the liver has been devised by Sarfeh and Rypins.[54] In a controlled trial their group has shown that a narrow-diameter (8 mm) reinforced polytetrafluoroethylene synthetic portacaval graft is more effective than the standard wide-diameter graft that was used in the past.[54] Further evaluation of this narrow-diameter shunt should determine whether it is better than the distal splenorenal shunt. The Sarfeh shunt is a simpler procedure to perform. The narrow-diameter shunt has also been used in the mesocaval position.[55] The use of the original end-to-side and side-to-side portacaval shunts for long-term management has diminished since the advent of these newer procedures. The portacaval shunt has, however, been the "gold standard" by which other therapy has been judged in the past.[1-3] An end-to-side shunt effectively prevents subsequent variceal bleeding but the major disadvantage has been unpredictable side effects, particularly portosystemic encephalopathy. The Warren and Sarfeh shunts are associated with a lower incidence of encephalopathy in most published controlled trials.[53-56]

In my view, the Warren and possibly the Sarfeh shunts are the best options currently available for managing failures of long-term endoscopic therapy. These

shunts can also be considered when pharmacologic therapy fails and should be used in selected patients who are likely to be compliance problems or live a great distance from the endoscopic management center.[56]

The distal splenorenal shunt has been compared with sclerotherapy in several trials,[57] but the consensus remains that injection sclerotherapy is the best primary therapy in long-term management after variceal bleeding.[52,56]

Devascularization and Transection Operations. A simple esophageal transection using a staple gun has been shown to be a highly effective form of treatment when sclerotherapy fails in the management of acute variceal bleeding[58] and has been used in the past by our group. However, it has recently been replaced by the TIPS procedure in the rare instances when current endoscopic therapy fails.

Our group has used an extensive esophagogastric devascularization and esophageal transection procedure performed entirely through the abdomen, leaving the spleen in situ, for long-term management. This has been compared with repeated sclerotherapy in an unpublished controlled trial from Cape Town. The conclusion was that both repeated sclerotherapy and devascularization and transection were equally effective in long-term management after variceal bleeding, but repeated sclerotherapy was a simpler procedure that was less expensive and used fewer hospital resources. We therefore recommend repeated sclerotherapy (or other endoscopic therapy) as the primary long-term treatment and have reverted to using shunts when endoscopic therapy fails. Our data are similar to those from a multicenter study in Great Britain.[59]

TIPS Procedure. Until recently, major surgery was the only method for placing a portosystemic shunt. The TIPS procedure is a new, relatively simple, nonoperative interventional radiologic technique by which a portacaval shunt can be placed percutaneously. The TIPS procedure is demanding but has proved to be simple when performed by experts, with a high rate of technical success. The procedure has been very widely adopted prior to adequate controlled trials.

The TIPS procedure has proved to be highly effective in the management of acute variceal bleeding when endoscopic therapy has failed.[60,61] This procedure was initially used as a bridge to liver transplantation but is now widely used in other patients, particularly those who were initially in good physical condition but deteriorated rapidly because of ongoing bleeding.[62]

The TIPS procedure is also being used with increasing frequency for long-term management, but major problems have become evident with time.[60,61,63,64] The incidence of encephalopathy is as high as that for a standard portacaval shunt when patients are followed for a long enough period. More important has been the high rate of stenosis or occlusion over time, which rises to approximately 50% at 1 to 2 years. Another problem is cost. The cost of a single Wallstent used for a TIPS procedure is approximately 1000 dollars. This doubles if more than one Wallstent is required. Because of subsequent stenosis and occlusion, there is the added cost of repeated investigation and the cost of subsequent TIPS procedures when the prosthesis becomes occluded and the patient presents with further variceal bleeding.

Taking these problems into account, we believe that the TIPS procedure should be restricted to use as an emergency measure after endoscopic treatment of bleeding varices has failed. Such patients can always be subjected to another definitive management procedure later after the emergency is over. With the introduction of newer lined TIPS prostheses, this situation may change in the future.

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Duodenum-Preserving Pancreatic Head Resection: Long-Term Results

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Early and late results from 298 patients with chronic pancreatitis who were surgically treated by means of duodenum-preserving pancreatic head resection (DPPHR) were prospectively analyzed. The aim of this operative procedure is to treat complications of chronic pancreatitis caused by inflammatory enlargement of the pancreatic head by decompressing the common bile duct, the pancreatic duct, the duodenum, and the retropancreatic intestinal vessels. End points of the study were early and late postoperative outcome. The follow-up period ranged from 1 to 22 years with a median follow-up of 6 years. In-hospital mortality was 1%, postoperative morbidity was 28.5%, and the rate of repeat laparotomy was 5.7%. Diabetes mellitus developed early in the postoperative period in six patients (2%). After a median follow-up of 6 years, late mortality was 8.9%. In the late follow-up period 88% of our patients were completely free of pain or had infrequent episodes and 63% were able to return to work. DPPHR might be considered as an alternative surgical technique in the treatment of chronic pancreatitis if the dominant lesion is in the pancreatic head. (J GASTROINTEST SURG 1997;1:13-19.)

Chronic pancreatitis is a painful and often long-lasting disease for which surgery is frequently the best therapy. As many as 50% of all patients with chronic pancreatitis will ultimately require surgical treatment.[1-4] Therefore the type and quality of the operative procedure are major factors that should be considered in the treatment of these patients.[5-12]

Indications for surgery in chronic pancreatitis are intractable pain accompanied by complications, for example, common bile duct obstruction, duodenal stenosis, pancreatic duct obstruction, and involvement of major retropancreatic intestinal vessels.[4,7,8,13-16] Complications caused by lesions of the pancreatic head have, to date, usually been treated either by modifications of the Whipple procedure[4,16-19] or by some type of bypass operation such as the Puestow/Partington-Rochelle procedure.[20]

We present herein data from 298 patients who have undergone a new operation—duodenum-preserving pancreatic head resection (DPPHR)—for the treatment of chronic pancreatitis. This procedure offers the advantage of treating the complications of this disease that are related to the pancreatic head including pain.

OPERATIVE PROCEDURE

The operation has been described in detail elsewhere.[21-23] Briefly, the primary goal of the procedure is subtotal resection of the head of the pancreas, thereby preserving the body and tail of the pancreas. To guarantee the blood supply to the remaining duodenum, a small rim of pancreas dorsal and close to the duodenum is also preserved (Figs. 1 to 3). The result of this operation is decompression of the major retropancreatic intestinal vessels, as well as decompression and drainage of the pancreatic duct, the common bile duct, and the duodenum. This is achieved without partial resection of the stomach, duodenum, or extrahepatic common bile duct.

PATIENTS

Between 1972 and 1993, a total of 298 patients underwent DPPHR for chronic pancreatitis. Preoperatively, a standardized diagnostic workup was performed including endoscopic retrograde cholangiopancreatography (ERCP), contrast-enhanced CT scanning, an oral glucose loading test, and a pancreolauryl test[24] to evaluate exocrine pancreatic function. Angiography of

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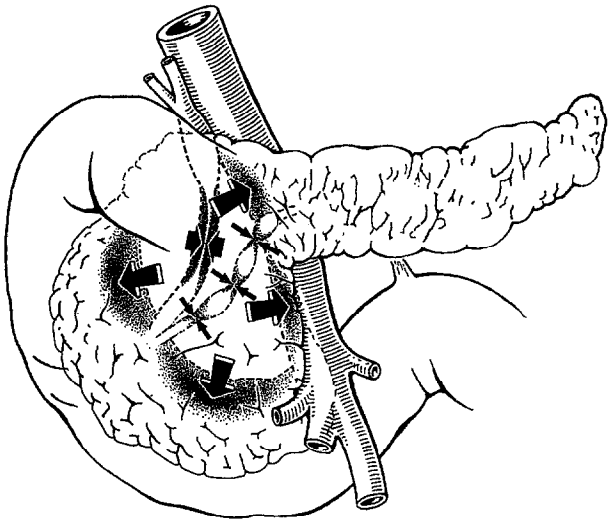

Fig. 1. Diagram illustrating chronic pancreatitis with complications attributed to enlargement of the pancreatic head. Indications for DPPHR are obstruction of the common bile duct (medium-sized arrows), pancreatic duct (small arrows), duodenum (large arrows), and retropancreatic intestinal vessels (large arrows).

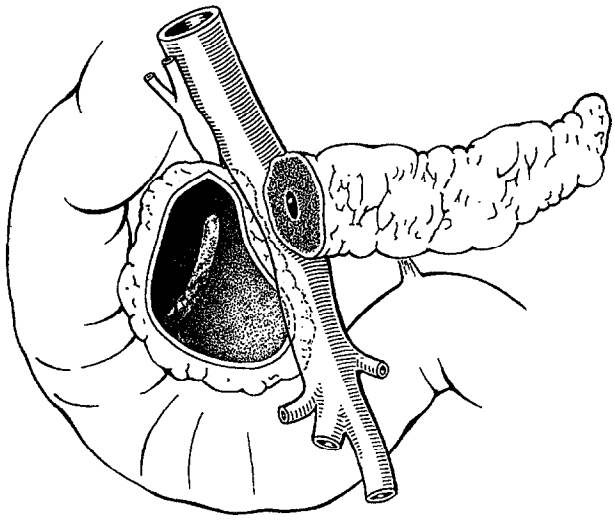

Fig. 2. Operative view following DPPHR. Decompression and drainage of the pancreatic duct, common bile duct, the duodenum, and retropancreatic intestinal vessels have been achieved.

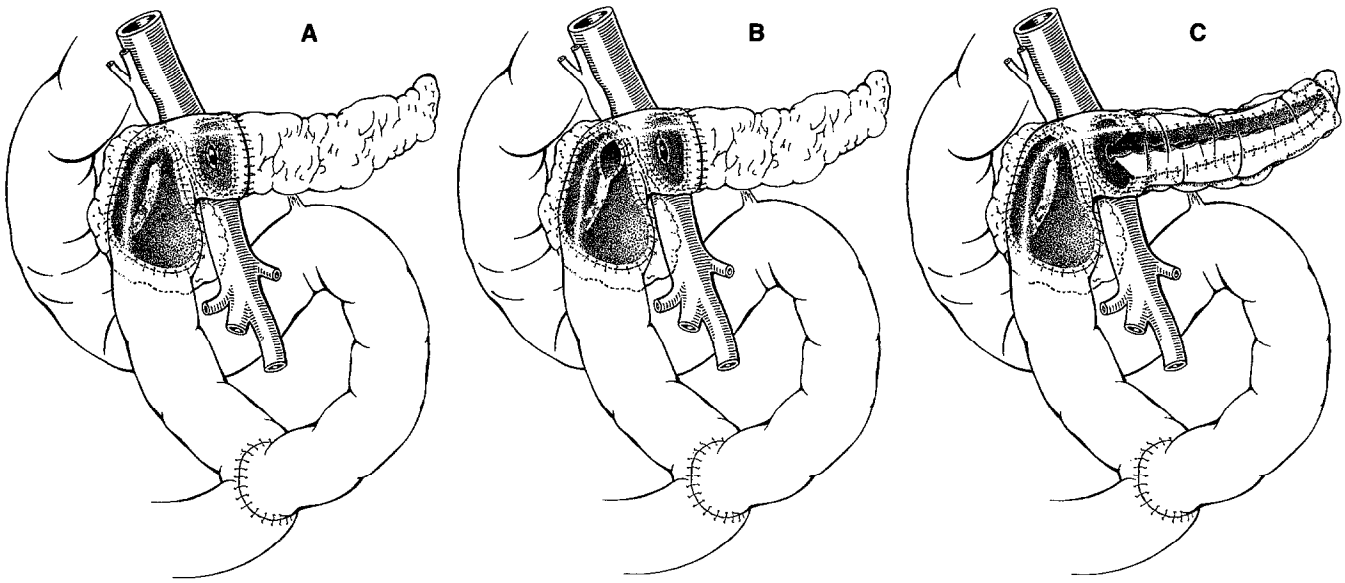

Fig. 3. Reconstruction following DPPHR. **A,** Standard reconstruction in which an end-to-end anastomosis with the left pancreas and a side-to-side anastomosis with the remaining pancreatic head are performed. **B,** In 49 of 298 patients additional decompression of the common bile duct was achieved by creating an inner anastomosis with the interposed jejunal loop. **C,** Puestow modification in which a side-to-side anastomosis between the left pancreas and the interposed jejunal loop is performed. This reconstruction was performed in 21 of 298 patients.

Table I. Characteristics of 298 patients undergoing duodenum-preserving pancreatic head resection

Characteristics	
Male	250 (84%)
Female	48 (16%)
Mean age (yr)	44 (range 22-74)
Duration of pain (mo)	62 ± 55
Etiology	
Alcohol	265 (89%)
Other	34 (11%)

Table II. Indications for surgery in 298 patients undergoing duodenum-preserving pancreatic head resection

Indications	No.	Percent
Abdominal pain	279	94
Intractable*	214	72
Pancreatic head enlargement†	248	83
Pancreatic duct obstruction‡	185	62
Common bile duct obstruction‡	144	48
Jaundice§	43	14
Duodenal obstruction‖	95	32
Symptomatic	20	7
Vascular obstruction/portal hypertension¶	52	17

* Pain requiring analgesics at regular intervals.
† CT (contrast-enhanced)/ultrasonography ≥4 cm in diameter.
‡ Endoscopic retrograde cholangiopancreatography.
§ Serum bilirubin >40 mol/L
‖ Hypotonic duodenography (barium).
¶ CT/angiography.

Table III. Additional surgical procedures in 298 patients undergoing duodenum-preserving pancreatic head resection

Procedure	No.	Percent
Cholecystectomy	82	28
Common bile duct anastomosis	49	16
Portal vein decompression		
Closed	49	16
Open	3	1
Puestow procedure	21	7
Additional pseudocyst anastomosis	3	1
Splenectomy	3	1
Left/tail resection	2	0.7

the celiac trunk and mesenteric artery including a venous phase was carried out in patients with suspected vascular stenosis with collateral circulation (based on clinical signs and CT scan).

Patient characteristics and the indications for surgery are listed in Tables I and II. The patient population was 84% male (mean age 44 years [range 22 to 74 years]), 89% of whom were alcohol abusers; this was similar to the makeup of other study groups in the United States and Europe.[4,8,18,25,26] Abdominal pain (94%), inflammatory enlargement of the pancreatic head (83%), and common bile duct (48%) and pancreatic duct obstruction (62%) were the predominant indications for surgery. Preoperatively 52% of our patients had normal blood glucose levels, whereas 23% and 25% showed signs of subclinical or insulin-dependent diabetes mellitus, respectively.

RESULTS

Surgical Procedure

As is shown in Figs. 1 to 3, the objective of DPPHR is to treat complications arising from the inflammatory tumor (Figs. 1 and 2) including the common bile duct, the pancreatic duct, and duodenal stenosis and compression of the major retropancreatic intestinal vessels. In addition to the standard reconstruction after DPPHR (Fig. 3, *A*), open decompression of the common bile duct was required in 49 patients (16%) (Table III). This was achieved by creating an inner anastomosis with the interposed jejunal loop (Fig. 3, *B*). In another 21 patients (7%) the phenomenon known as "chain of lakes" was encountered in the main pancreatic duct. As a result the entire duct was longitudinally incised and a Puestow modification of the side-to-side anastomosis was performed between the left pancreas and the jejunal interponate (Fig. 3, *C*).

Early Postoperative Results, Morbidity, and Mortality

Three (1.01%) of 298 patients died in the hospital (Table IV). There were 85 early postoperative complications (28.5%), and 17 patients (5.7%) required a repeat laparotomy, mainly because of anastomotic leakage (n = 5), intra-abdominal abscess (n = 3), or bleeding (n = 3) (Table V). Six patients (2%) developed insulin-dependent diabetes mellitus in the early postoperative period (Table VI). The median duration of postoperative hospitalization was 13 days (range 7 to 59 days).

Late Postoperative Follow-up Results

A follow-up investigation was conducted in December 1994, which included a questionnaire and a standardized interview. If the patient did not respond to our request for follow-up information, the family physician was asked to complete the questionnaire. The follow-up period ranged from 1 to 22 years with a median follow-up of 6 years. Forty patients (13%) were definitively lost to follow-up (Table VII), but information was available from 258 (87%).

Late mortality after a median period of 6 years was 9% (23 of 255 patients). Eighty-eight percent of the patients either had no pain or rare occurrences (Table VIII); 81% showed a mean increase in body weight of 10.7 kg (± 5.8 kg), and 63% of our patients resumed their former occupations.

Table IV. Early and late mortality

In-hospital mortality (3/298 patients)	1.01%
Pulmonary embolism (n = 1)	day 9
Sepsis (n = 1)	day 10
Leakage of pancreatic anastomosis (n = 1)	day 12
Late mortality (23/255 patients; 1-22 year follow-up)	8.9%

DISCUSSION

The procedure known as DPPHR was introduced in 1972.[21-23] Since then several pancreatology centers have adopted this procedure and additional techniques of pancreatic head resection for treatment of chronic pancreatitis have been developed.[27-35] Having performed the procedure in almost 300 patients with chronic pancreatitis, we feel justified in stating that DPPHR can be carried out with low postoperative mortality and morbidity and that the early postoperative complication rate compares favorably with those of other standard surgical procedures used to treat chronic pancreatitis, such as resection or drainage.[4,7,8,12,20] It should also be noted that the late mortality rate of 9% after DPPHR seems to be within the range of or lower than the 20% to 30% late mortality rate after pancreaticoduodenectomy for the Whipple procedure.[8,36-39] A major drawback of our

Table V. Postoperative morbidity

Complications	No.	Percent	No. of repeat laparotomies
Bleeding*	17	5.7	3
Intra-abdominal abscess	9	3.0	3
Anastomotic leakage	6	2.0	5
Pancreatic fistula†	8	2.7	—
Septic shock	4	1.3	1
Small bowel obstruction	3	1.0	2
Ischemia of duodenum	1	0.3	1
Common bile duct stenosis	1	0.3	1
Ulcer perforation	1	0.3	1
Medical complications‡	35	11.7	—
TOTAL	85 (28.5%)		17 (5.7%)

*Patients requiring more than 3 units of blood later than 24 hours after the operation or reoperation.
†More than 50 ml/day of drainage fluid (high amylase concentration) later than 10 days after surgery.
‡Pulmonary failure, pneumonia, cardiocirculatory failure, and/or renal failure.

Table VI. Endocrine function before and after duodenum-preserving pancreatic head resection

	No. of patients	Normal	Diabetes mellitus	
			Subclinical	Insulin-dependent
Preoperative	281	146 (52%)	65 (23%)	70 (25%)
Early postoperative	298	6 patients with newly developed insulin-dependent diabetes mellitus (2%)		

*Oral glucose tolerance or serial blood glucose test results were available for 281 patients.

study is the fact that 13% of our patients were lost to follow-up. This is due to the nature of the disease and to the length of follow-up (up to 22 years).

The standard procedure used to treat pancreatic head complications in chronic pancreatitis is the Whipple operation and its major modification, the pylorus-preserving pancreaticoduodenectomy.[40,41] In three randomized controlled trials the superiority of the duodenum-preserving technique over pylorus-preserving resection in chronic pancreatitis has been demonstrated.[42-44]

It is not surprising that preservation of the duodenum is superior to resection of the organ, because the duodenum has been shown to be the central organ for glucose metabolism in experimental studies in animals, in healthy human beings, and in patients suffering from chronic pancreatitis.[45-47] Operation-induced diabetes occurs in up to 20% of patients after Whipple resection[8,18,39,48] in contrast to a rate of 2% in our patients. Late death in these patients with chronic pancreatitis is often influenced by the presence or absence of intact glucose metabolism. Thus procedures in which glucose tolerance is preserved postoperatively might have an advantage in that the long-term prospects for a good quality of life would be increased.

Pain is the crucial symptom in patients with chronic pancreatitis. Recently other mechanisms of pain generation have been identified[49-51] in addition to commonly accepted causes of pain such as duct obstruction. These theories of chronic inflammatory entrapment of pancreatic nerves can better explain why 88% of patients experience long-lasting pain relief following DPPHR. This percentage of patients who are free of pain compares favorably with long-term outcome following the Whipple procedure. In contrast, long-term pain relief after bypass procedures in these patients would appear to be inferior.[52-58]

Table VII. Group designations for patient follow-up

Patients undergoing surgery	298
In-hospital deaths	3
Lost to follow-up	40
Late deaths	23
Available for late follow-up	232

Table VIII. Late follow-up results (median 6 years) in 232 patients after duodenum-preserving pancreatic head resection

Results	No.	Percent	
Rehospitalization	23	10	
Abdominal pain			
None	143	62	88
Rare*	61	26	
Frequent†	28	12	
Resumption of former occupation			
Complete	147	63	
Unemployed	11	5	
Retired‡	74	32	
Body weight increase	187	81	
Consumption of alcohol			
Yes	104	45	
No	128	55	

*Pain occurring once a month or less; no need for regular medication.
†Pain occurring weekly or daily requiring medication.
‡Retired because of advanced age or disease.

CONCLUSION

In the future, surgery for chronic pancreatitis might be recommended more often for the following reasons: (1) the incidence of this disease is rising in Western countries[59,60]; (2) earlier surgical intervention is beneficial to the patient with regard to the natural course of the disease[6,61,62]; (3) a significant association between chronic alcoholic pancreatitis and pancreatic cancer has recently been demonstrated[63-68]; and (4) perioperative mortality following pancreatic head resection has decreased in recent years.[69-74] For these reasons we believe that organ-preserving procedures aimed at treating complications and pain without causing additional illness in the patient (e.g., diabetes mellitus) should be adopted in the future when contemplating any type of surgical treatment of chronic pancreatitis. Among the operations currently available, procedures aimed at preserving the duodenum best meet these prerequisites[21,31,34,75] and as such might be considered valuable alternatives in the treatment of chronic pancreatitis.

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Laparoscopic Pancreatic Resection: Is It Worthwhile?

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A series of 23 patients who had undergone an attempted laparoscopic Whipple (n = 10) or laparoscopic distal pancreatectomy (n = 9) or laparoscopic enucleation (n = 4) since January 1992 were retrospectively reviewed. In the laparoscopic Whipple group (6 women and 4 men; mean age 71 [range 33 to 82] years), eight had malignant periampullary tumors and two had chronic pancreatitis. The rate of conversion to an open procedure was 40%, and complications were seen in the nonconverted group. The average operative time was 8.5 hours, and the hospital stay was 22.3 days. However, in the laparoscopic distal pancreatectomy and enucleation groups, there were seven women and six men (mean age 46.5 [range 27 to 75] years). Of these, nine patients had a planned laparoscopic distal pancreatectomy (8 for islet cell tumors and 1 for chronic pancreatitis) and four had a planned laparoscopic enucleation (all 4 for islet cell tumors). The conversion rate for these patients was 36%, and the mean operative time was 4.5 hours for laparoscopic distal pancreatectomy and 3 hours for laparoscopic enucleation. The hospital stay was 5 days and 4 days, respectively. Although this series was small, no benefit seemed to be derived from the use of a complete laparoscopic Whipple procedure. Laparoscopic distal pancreatectomy and enucleation were technically easier to perform and seemed to benefit patients by shortening their hospital stay with no recurrence of disease. (J GASTROINTEST SURG 1997;1:20-26.)

The increasing use of laparoscopy for staging of lesions permits a progressive ease of dissection around the pancreas. Exposure of the body of the pancreas through a window in the gastrocolic omentum followed by a laparoscopic Kocher maneuver is a logical first step toward successful laparoscopic resection. Also, the increased use of diagnostic laparoscopic ultrasonography permits the localization of small pancreatic lesions and improves tactile sensation. Limited and anecdotal experience with laparoscopic pancreatic resection has been reported.[1-3] The aim of this study was to retrospectively review the collected series of laparoscopic pancreatic resections for benign and malignant disease and to determine the feasibility, morbidity, and rate of recurrent disease associated with this procedure.

PATIENTS AND METHODS

We retrospectively reviewed the record of 23 patients who had undergone a laparoscopic resection of the pancreas between January 1992 and May 1996 at The Cleveland Clinic Foundation (Cleveland, Ohio), the Hotel-Dieu de Montreal (Montreal, Quebec), and the Instituto Nacional de la Nutricion Salvador, Zubiran (Mexico City) (one case of enucleation was managed with the assistance of Dr. Miguel F. Herrera).

Variables studied included age, sex, localization studies, type and location of the tumor, size, type of procedure, operative time, blood transfusions, nodal status, postoperative stay, morbidity, use of laparoscopic ultrasonography, and follow-up period for recurrence.

TECHNIQUE

Patients selected for a possible laparoscopic resection are subjected to a laparoscopic staging procedure. This includes a three-trocar procedure (two 11 mm and one 5 mm trocars) with a 30-degree angled 10 mm laparoscope to view all aspects of the pancreatic gland. First the body and tail are exposed anteriorly through a window in the gastrocolic ligament by lifting the greater curvature of the stomach using a laparoscopic Babcock forceps from an epigastric trocar. The window may be created using a scissors with electrocautery

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or by ligating transverse branches from the gastroepiploic arcade with medium to large titanium clips. The window must be large enough (>8 cm) to allow inspection beyond the gastroduodenal artery to the hilum of the spleen anteriorly and inferiorly. A laparoscopic ultrasonographic probe, 10 mm in diameter, with a frequency of 7.5 MHz (Aloka, Tokyo, Japan) may be inserted through any port and placed anteriorly directly onto the neck, body, and tail of the pancreas. The image can be transmitted directly to the main laparoscopic monitor and be split with a video mixer to provide the operator with both views (laparoscopic and ultrasonographic). The head of the pancreas can also be scanned with the probe making contact directly over the head of the gland around the duodenal loop. Furthermore, a laparoscopic Kocher maneuver can be performed with an additional trocar inserted in the right paramedian area at least 15 cm away from the umbilicus to obtain a lateral view of the second and third portions of the duodenum. The retroperitoneum is entered with a 5 mm scissors between the right kidney and the lateral view of the second portion of the duodenum. Once the dissection has been extended beyond the vena cava and the duodenum, these structures can be elevated with a laparoscopic Babcock forceps. The laparoscopic probe can again be positioned behind the uncinate process to evaluate this blind area, as well as the posterior pancreas.

The laparoscopic Whipple technique used is, in fact, a pylorus-preserving procedure with a modification for the pylorojejunostomy, which is end to end. The peritoneum covering the common bile duct is opened anteriorly and laterally so it can be dissected with a laparoscopic right-angled dissector from the portal vein and the right hepatic artery. The bile duct can be suspended with a 2-0 nylon suture or umbilical tape introduced through one of the trocar sites. A total of six trocars (11 mm) are used in the subcostal area and the periumbilical area. In the last two laparoscopic Whipple procedures, an 8 cm mini-incision was made initially in the right subcostal area for the introduction of the nondominant (left) hand with a special plastic sleeve attached that maintains the pressure of the pneumoperitoneum (Dexterity Pneumosleeve, Pilling-Weck, Research Triangle Park, N.C.). With a combination of trocars in the epigastric, umbilical, and periumbilical areas, the dissection, transection, and reconstruction are carried out with laparoscopic instruments under laparoscopic vision with the dominant (right) hand. The hand inside the area is useful for gentle retraction, completion of the Kocher maneuver, palpation of tumor extension, and evaluation of tumor resectability; in addition, bleeding can be controlled with finger compression and suturing is also facilitated. This mini-incision is usually necessary anyway for extraction of the specimen.

The bile duct is transected with a 30 mm Endo-GIA stapler (U.S. Surgical Corp., Norwalk, Conn.) approximately 2 to 3 cm above the superior pancreatic border. The stapling device keeps the bile duct closed to prevent spillage of bile during the operation. The first portion of the duodenum is then divided approximately 1 cm distal to the pylorus using the same stapler, which requires a 12 cm trocar in the umbilicus. The gastrocolic omentum has been divided using electrocautery, titanium clips, and lately ultrasonic energy (10 mm Endoshears, Ultracision Inc., Smithfield, R.I.). In addition, the fourth portion of the duodenum, medial to the mesenteric vessels, is transected with the stapler. The gastroduodenal artery is double clipped with titanium or divided using the stapler with a vascular cartridge. The neck of the pancreas is cleared from the portal vein using a 5 mm irrigation-suction probe, and gentle blunt dissection is used to push away the portal vein until it is completely cleared from the neck of the pancreas. The pancreas is then transected with scissors, beginning inferiorly and moving toward the superior border anterior to the portal vein. The ultrasonic dissector is extremely useful to achieve this goal with minimal blood loss. The uncinate process is then cleared from the mesenteric artery and vein, again using the ultrasonic dissector or an endoscopic linear stapler. The resected specimen is placed in a sterile plastic bag for later extraction or pulled through the Pneumosleeve if one has been used.

Three anastomoses are created by means of intracorporeal techniques, the proximal jejunal loop is pulled behind the mesenteric vessels, and its antimesenteric side will be approximated to the pancreatic duct in two layers. A 5 F pediatric tube will serve as a stent and need only be 5 cm in length. One half of the stent is inserted into the pancreatic duct and sutured to the duct and jejunal opening with 4-0 monofilament absorbable sutures. A layer of 3-0 silk interrupted sutures is first applied between the posterior capsule of the pancreas and the serosal side of the jejunal loop. The duct itself with the stent in place requires four to six 4-0 monofilament absorbable sutures. Another layer of 3-0 silk interrupted sutures is then applied between the anterior capsule of the pancreas and the serosal side of the jejunal loop. The second anastomosis, the hepaticojejunostomy, is now performed without tubes with a running posterior and running anterior 3-0 monofilament absorbable suture. Finally, the third anastomosis is performed with the same suture between the pylorus and the jejunum end to end. A feeding jejunostomy (T-tube, 14 F) is in-

serted through one of the trocar sites, and two large Jackson-Pratt drains are left anterior and posterior to these anastomosis.

For laparoscopic distal pancreatectomy, the patient is rotated laterally 45 degrees so that the left side is up or in a full lateral and reverse Trendelenburg position. If the gastrocolic window is not wide enough, the mobilization is carried out until the lower short gastric vessels are divided. This will greatly enhance the anterior view of the tail of the pancreas. Four trocars (three 11 mm and one 12 mm) are needed to perform the dissection and transection. The inferior border of the pancreas is dissected from the retroperitoneal fat using a 5 mm hook with cautery until the gland is mobile and the splenic vein is reached posteriorly and superiorly. The tail is then grasped with a 5 mm atraumatic forceps. Traction is applied anteriorly and inferiorly to expose, under tension, the transverse branches of the splenic artery and vein, for a spleen-preserving caudal pancreatectomy. The branches are ligated with medium titanium clips until the desired length has been attained. Mobilization of the tail and body, up to the portal vein, can be achieved in this manner. The pancreas is then transversely transected with an endoscopic linear stapler (30 mm in length and 12 mm in diameter [U.S. Surgical Corp.] or 60 mm in length and 18 mm in diameter [Ethicon Endo-Surgery, Cincinnati, Ohio]). This provides adequate closure of the pancreatic duct and partial ligation of pancreatic arterial arcades. These arcades may need to be ligated with clips or cauterized. The specimen is then extracted using a rigid (8 × 12 cm) plastic bag (Cook Inc., Bloomington, Ind.) through a minimally enlarged umbilical incision. All fascial incisions are closed and a Jackson-Pratt drain is left in place near the transection plane.

For enucleation, the exposure is similar to that used for distal pancreatectomy. Once the islet cell tumor has been localized, the dissection is usually carried out with a 5 mm hook with cautery between the normal parenchyma and the tumor itself. The pancreatic vessels feeding the tumor are ligated with medium to large titanium clips. Extraction is performed by placing the insulinoma into a sterile plastic bag through one of the ports (10 mm), which is enlarged to the diameter of the lesion. A Jackson-Pratt drain is left in place over the enucleation in the lesser sac.

RESULTS

Ten patients (6 women and 4 men; mean age 71 [range 33 to 82] years) underwent an attempted laparoscopic Whipple pylorus-preserving procedure. The presenting symptoms were painless jaundice in eight and chronic pain requiring constant narcotics in two. The diagnosis and indications for an attempted laparoscopic Whipple procedure are listed in Table I. Eight patients were operated on for a malignant tumor and two for chronic pancreatitis. Forty percent required conversion to an open procedure; two patients were converted early on because there was not enough space to perform an adequate mobilization (bowel distension), and in two cases the opening was inadequate for insertion of a suspensory device through a mini-incision. The operative time required for a laparoscopic Whipple procedure averaged 8.5 (5.5 to 12) hours compared to 4.6 (3.5 to 6.0) hours for conversion to an open procedure; the hospital stay was 22.3 (7 to 62) days vs. 20.1 (14 to 36) days, respectively.

An average of 2.0 (0 to 6) units of packed red blood cells was transfused perioperatively in the laparoscopic Whipple group and 1.5 (0 to 4) units in the converted group. Complications were seen in three patients who had a laparoscopic Whipple procedure and none in the converted group. These included delayed gastric emptying in one, splenic hemorrhage in one, and a pancreatic leak in one. The delay in gastric emptying was managed with total parenteral nutrition for 2 additional weeks, the splenic hemorrhage necessitated a splenectomy 24 hours after the initial operation, and the pancreatic leak, which was minor, was contained with the Jackson-Pratt drains and stopped by the second postoperative week. Among patients undergoing resection for malignant disease, there were three with positive nodes in the laparoscopic group and two with positive nodes in the converted group. There was no difference in the average number of nodes retrieved (7 [3 to 14] vs. 8 [6 to 11]). During the 19-month follow-up period (range 1 to 36 months), one patient in South America was lost to follow-up. There was no evidence of tumor recurrence in the laparoscopic group and one patient in the converted group was alive with disease after 12 months. One of the two patients operated on for chronic pancreatitis had a recurrence of pain, which necessitated reoperation for recurrent small bowel obstruction.

Among the patients in the laparoscopic distal pancreatectomy and enucleation groups, seven women and five men were operated on for a presumed islet cell tumor of the pancreas, the diagnosis of which was based on clinical findings and/or preoperative radiologic or nuclear localization; in addition, one male patient who had chronic pancreatitis was treated for localized dilatation of the pancreatic duct and pancreatolithiasis to the tail of the pancreas. The mean age of the patients was 46.5 (29 to 74) years. The mean size of the resected lesions was 3 (2 to 6) cm.

Table I. Indications for attempted laparoscopic Whipple procedure

Indication	No.
Pancreatic adenocarcinoma	4
Ampullary adenocarcinoma	3
Chronic pancreatitis	2
Cholangiocarcinoma	1

Table II. Preoperative localization

	Distal		Enucleation	
	No.	+Loc.	No.	+Loc.
CT scan	8	4	4	2
MRI	4	0	—	—
Octreotide scan	7	2	2	0
Angiography	7	3	3	1
Portal venous sampling	4	2	—	—

Table III. Planned laparoscopic distal pancreatectomies

Preoperative diagnosis	Postoperative diagnosis	Conversion
Insulinoma	Insulinoma	—
Insulinoma	Insulinoma (body-tail)	—
Insulinoma	Insulinoma (neck)	+ (retroportal)
Insulinoma	Malignant mixed insulinoma-gastrinoma	+
Gastrinoma	Malignant gastrinoma	+
Insulinoma	Insulinoma	—
Unknown	Cystadenocarcinoma	—
Chronic pancreatitis	Same	

Preoperative localization consisted of multiple series of radiologic examinations including CT scan of the abdomen with contrast, MRI, abdominal angiography and/or portal venous sampling, and octreotide nuclear scan (Table II). In spite of attempts at preoperative localization in all cases, 36% of tumors were not identified prior to laparoscopy. The best results (50%) have been achieved using CT scans, angiography, or portal venous sampling. Endoscopic ultrasonography has not been available at our institution.

During the laparoscopic staging procedure, results of laparoscopic ultrasonography were available in 9 (69%) of 13 patients. Interestingly, two insulinomas (2 and 2.5 cm) were not seen, one was located in the retroportal neck and one in the body. Also excluded were two lesions that were thought to be artifacts on CT scan in one women with hypoglycemia without hyperinsulinism and another with presumed vasoactive plasmatic substances. Ultrasound also helped to localize the site of the proximal resection line in the patient with chronic pancreatitis. Laparoscopic distal pancreatectomies were planned in eight patients because of an islet cell tumor, the presence of which was confirmed in seven (Table III). One lesion was, in fact, a 3 cm serous cystadenocarcinoma. In three cases in this group, conversion to an open procedure became necessary. In addition, enucleation was planned in four patients and performed in one case with conversion (Table IV). The procedure performed during conversion was a pancreatotomy with enucleation of an insulinoma, which was retroportal in the neck but not visible anteriorly. This lesion was missed by laparoscopic ultrasonography but detected by open ultrasonography. Also, preoperative localization with portal venous sampling revealed an area in the body of the pancreas.

Table IV. Planned laparoscopic enucleation

Preoperative diagnosis	Postoperative diagnosis	Conversion
Insulinoma (tail)	Insulinoma (body)	—
Unknown	Nesidioblastoma	+ (Whipple)
Vasoactive secreting tumor?	Normal pancreas	—
Hypoglycemia	Normal pancreas	—

Two patients with malignant gastrinomas were converted after diagnostic laparoscopy in view of the extensive intra-abdominal disease. One required a distal pancreatectomy (body and tail) with splenectomy, left

adrenalectomy, partial gastrectomy (greater curvature), transverse colectomy, and hepatic segmentectomy II-III. The other patient also underwent a distal pancreatectomy (tail), splenectomy, partial gastrectomy, and hepatic metastasectomy. In one patient enucleation of a nonsecreting islet cell tumor of the head of the pancreas was planned. This was performed because at laparoscopy it was discovered that the tumor was too deep in the pancreatic parenchyma to be removed. Therefore she underwent an open pylorus-preserving Whipple procedure for nesidioblastoma (3 cm) with positive antibodies to somatostatin and glucagon.

Operative time was shorter in the nonconverted distal pancreatectomy and enucleation groups (Table V). Only two complications were seen in the laparoscopic group, significant intraoperative bleeding from an inferior tear of the transplenic vein requiring multiple titanium clips. The patient who underwent resection for a cystadenocarcinoma was elderly (74 years of age) and required readmission for a small infected collection area near the pancreatic bed, which was percutaneously drained. The hospital stay was prolonged in the converted group (Table VI) because of multiple complications (delayed gastric emptying, pneumonia, and pancreatic leak). During the mean follow-up period of 27 months (range 15 to 28 months), no recurrences were seen in any of the patients who had undergone insulinoma resection or laparoscopic enucleation. However, three subsequent reoperations were performed in the converted group because of multiple metastases in the right lobe of the liver from malignant gastrinomas in two patients requiring debulking and metastasectomy. The laparoscopic distal pancreatectomy for chronic pancreatitis took only 2.5 hours, and the patient did well and was discharged on postoperative day 4 with no complications.

Table V. Operative time

Procedure	Hours (range)
Distal pancreatectomy	
Converted	6.3 (4-8)
Nonconverted	4.5 (4-5)
Enucleation	
Converted	4.5
Nonconverted	3.0
Diagnostic	1.3 (1-1.5)

Table VI. Postoperative stay

Procedure	Days (range)
Distal pancreatectomy	
Converted	21 (16-33)
Nonconverted	5.0 (4-7)
Enucleation	
Converted	14.0
Nonconverted	4.0
Diagnostic	1.5 (1-2)

DISCUSSION

This small series demonstrates that not only is laparoscopic pancreatic resection feasible and safe, but it can duplicate the open operation (Whipple, distal and enucleation). Two questions remain, however: (1) Is there any short- or long-term benefit, and (2) is it worth it to subject the patient to a more difficult operation? At this point in time, the advantages of a complete laparoscopic Whipple procedure are questionable, but in recent cases performed in an assisted fashion using a sleeve with the hand inside, the operative time has been cut in half, which seems to translate into a shortened hospital stay. From an oncologic viewpoint, certain questions remain unanswered. Recent laboratory data have shown a decrease in immunosuppression normally seen after laparotomy, which may be of benefit to cancer patients.

Clearly, there is a benefit for patients undergoing laparoscopic distal pancreatectomy or enucleation for benign pancreatic disease, despite a longer operating time. Preoperative localization becomes more important with the laparoscopic technique. According to Yeo et al.[4] preoperative CT correctly localized the tumor in 59% of patients, which is no different from the findings in our series. However, angiography seemed to have a better yield (75%). This puts the surgeon in a difficult situation because in one third of all cases the tumor must be localized during the surgical intervention.[5]

Aside from examining the dissectable pancreatic surfaces, the laparoscopic surgeon has a tactile sensation that is somewhat diminished by compression of the pancreatic tissue with a 10 mm palpation probe. Laparoscopic ultrasonography did not identify all lesions during the staging procedure, and it is expected to reproduce the results of open surgery where the best strategy is to combine palpation and ultrasonography.[6] However, laparoscopic ultrasonography can be useful in questionable cases where artifacts appear on radiologic images. Unnecessary laparotomy can thus be avoided. The technique may be especially useful in nonfunctioning islet cell tumors. As we showed in our patients, we do not hesitate to convert to an open Whipple procedure, since these lesions may develop into nonfunctioning islet cell carcinomas if they cannot be enucleated or resected laparoscopically.[7,8]

Among nonconverted patients, very little morbidity was encountered and the postoperative stay was shortened, presumably because there was less trauma to the abdominal wall and less exposure to ambient air. No pancreatic leaks were encountered despite the use of an endoscopic stapler. Also, patients remained free of recurrences after a reasonable follow-up, thus confirming that a true successful enucleation and resection can be achieved using the laparoscopic method. In a recent series in which open resection was used to treat insulinomas in 34 patients, 31 of them were symptom free at a mean follow-up of 16 months.[9] It can therefore be concluded from this small series that laparaoscopic enucleation and resection of islet cell tumors are feasible. Initially this procedure should be reserved for benign lesions of the tail or body of the pancreas, especially anteriorly. it requires the expertise of highly skilled laparoscopic surgeons with experience in digestive diseases, who have facilities for intraoperative laparoscopic ultrasonography available to them. These surgeons should also be proficient in the open operation and open intraoperative ultrasonography of the pancreas.

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Discussion

Dr. J. Roslyn (Philadelphia, Pa.). I would ask you to qualify some of the figures you presented in your study. You mention that the length of stay was 22 days for patients who had Whipple procedures, yet the morbidity you encountered seems minimal. Why was your length of stay so long, including patients who were hospitalized for up to 60 days? Similarly, for distal pancreatectomy, the length of stay appeared to be close to 3 weeks. Finally, do you have any data concerning cost? What do you think really are the true benefits of performing these complicated procedures laparoscopically?

Dr. M. Gagner. We have not examined the cost itself with regard to this procedure. Concerning the length of stay, I think that the 22-day length of stay is related to complications. We have seen some morbidity; that is, half of the patients in the laparoscopic group had complications such as delayed gastric emptying and pancreatic leaks, which led to the prolonged hospital stay. There was also an elderly patient who, for lack of family support, had to remain in the hospital for 62 days, which really skewed the data for average length of stay.

With respect to distal pancreatectomy and enucleation, there is no question about the benefit right now. The laparoscopic Whipple procedure, which is the completed Whipple operation that requires six trocars, needs an operating room time that ranges from 10 to 12 hours.

There is a learning curve. As my ability to perform the procedure has improved, the operative time has decreased to between 5½ and 7 hours, which is much more reasonable. There is also a potential benefit of less immunosuppression.

Dr. J. Hoffman (Philadelphia, Pa.). You mentioned that there were six adenocarcinomas among the 10 patients in whom Whipple procedures were attempted, and you completed six of these operations. Which of those six patients actually had pancreatic adenocarcinomas? It seems to me that the most dangerous aspect of this is that you are less effectively excising the tissue along the superior mesenteric vessels. You are running a stapler across the mesopancreas, leaving a fair amount of tissue that normally would be resected in the open technique. If any of the pancreatic cancers were in the group undergoing resections, what was the status of the histologic margins? Were there any recurrences along these margins?

Dr. Gagner. There were four pancreatic adenocarcinomas among the eight patients with malignant disease who underwent resections. The margins appeared normal in all of them, even though we had used a laparoscopic stapler earlier in our experience to perform the uncinate process resection. Lately we have been more delicate in the dissection of the uncinate process from the superior mesenteric vein and the superior mesenteric artery when using the ultrasonic dissector. I truly believe that this operation is the same as an open technique.

As you know, there were patients who had positive nodes, and those positive nodes were identified postoperatively. This was the case in more than half the patients.

Dr. D. Evans (Houston, Tex.). You had no fistulas in your insulinoma enucleations. Could you comment on how you closed the pancreas? Could you also briefly touch on how difficult it was to obtain approval from your Institutional

Review Board for the phase I study of operating on patients with cancer of the periampullary region and how you handled informed consent?

Dr. Gagner. We encountered no fistulas in the groups undergoing distal pancreatectomy and enucleation. In the distal pancreatectomy the pancreatic duct is closed with three rows of staples. Thus there is no need to suture the duct itself. For the enucleation we did not use any sutures. Clips were applied to the vessels, and drainage tubes were always placed next to the transected plane or the enucleated plane.

If you can perform the same operation applying the same principles, I do not believe there is any ethical dilemma. Obviously the patients are informed of our intention to treat them laparoscopically. They are also advised that in the event of any difficult problem, we will convert to an open approach.

Duodenogastric Reflux Potentiates the Injurious Effects of Gastroesophageal Reflux

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Experimental studies have shown that the severity of esophageal mucosal injury in gastroesophageal reflux disease is related to the reflux of both gastric and duodenal juice. The purpose of this study was to determine whether duodenal juice potentiates esophageal injury in patients with reflux disease or, in fact, causes no harm allowing acid and pepsin to do the damage. A total of 148 consecutive patients who had no previous gastric or esophageal surgery underwent endoscopy and biopsy, manometry, and 24-hour esophageal pH and bilirubin monitoring. Esophageal injury was defined by the presence of erosive esophagitis, stricture, or biopsy-proved Barrett's esophagus. Exposure to duodenal juice, identified by the absorbance of bilirubin, was defined as an exposure time exceeding the ninety-fifth percentile measured in 35 volunteers. To separate the effects of gastric and duodenal juice, patients were stratified according to their acid exposure time. One hundred patients had documented acid reflux on pH monitoring, and in 63 of them it was combined with reflux of duodenal juice. Patients with combined reflux (50 of 63) were more likely to have injury than patients without combined reflux (22 of 37; $P < 0.05$). When the acid exposure time was greater than 10%, patients with injury (n = 40) had a greater exposure to duodenal juice (median exposure time 17.2% vs. 1.1%, $P = 0.006$) than patients without injury (n = 5), but there was no difference in their acid exposure (16.9% vs. 13.4%). Patients with dysplasia of Barrett's epithelium (n = 9) had a greater exposure to duodenal juice (median exposure time 30.2% vs. 7.2%, $P = 0.04$) compared to patients without complications (n = 25), whereas acid exposure was the same (16.4% vs. 15%). Duodenal juice adds a noxious component to the refluxed gastric juice and potentiates the injurious effects of gastric juice on the esophageal mucosa. (J GASTROINTEST SURG 1997;1:27-33.)

Gastroesophageal reflux disease is the most common disease of the foregut in the Western world. Barrett's esophagus, identified by the presence of specialized intestinal epithelium, develops in approximately 18% of patients with chronic reflux disease.[1] Longitudinal studies have shown a sequence evolving from esophagitis to metaplasia to dysplasia to adenocarcinoma, thereby linking gastroesophageal reflux disease to the development of esophageal adenocarcinoma.[2]

The potential injurious components that reflux into the esophagus include gastric secretions such as acid and pepsin, as well as biliary and pancreatic secretions that regurgitate from the duodenum into the stomach. In vitro studies have shown that acid alone does minimal damage to the esophageal mucosa but the combination of acid and pepsin is highly deleterious.[3] Experimental studies in animals have shown that the reflux of duodenal contents into the esophagus aggravates inflammation,[3,4] increases the prevalence of Barrett's esophagus,[5,6] and results in the development of esophageal adenocarcinoma.[5,7-9] Clinical studies have documented the presence of duodenal juice in the esophagus of patients with reflux disease, particularly in those with advanced disease.[10-17]

The aim of the present study was to determine whether duodenal juice potentiates esophageal injury in patients with gastroesophageal reflux disease or is an innocent bystander while acid and pepsin do the damage.

PATIENTS AND METHODS

Study Population

Thirty-five asymptomatic volunteers (male:female ratio 24:11, mean age 30.4 years, range 19 to 48 years), who had a manometrically normal lower

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esophageal sphincter and a normal esophageal acid exposure were studied to identify normal values for esophageal exposure to duodenal juice.

A total of 186 consecutive patients with symptoms of reflux disease were investigated by means of endoscopy and biopsy, stationary esophageal manometry, and combined 24-hour esophageal pH and bilirubin monitoring. Patients with named motility disorders or a history of previous surgery on the esophagus or stomach were excluded (n = 25). Another 13 patients were excluded on completion of the studies because of a technical problem with bilirubin monitoring. Of the remaining patients, 110 had increased esophageal exposure to acid and/or bilirubin (male:female ratio 77:43, mean age 51 years, range 17 to 77 years). Fifteen of these patients had a previous cholecystectomy. The studies on volunteers and patients were approved by the Institutional Review Board of the University of Southern California.

Endoscopy

Upper gastrointestinal endoscopy with biopsy of the gastroesophageal junction and the esophagus was performed in all patients. Esophageal injury was defined as either erosive esophagitis (i.e., linear or circumferential erosions), stricture, or Barrett's esophagus. The latter was defined by the presence of specialized intestinal epithelium on a biopsy specimen taken from above the gastroesophageal junction. Complicated Barrett's esophagus was defined as the presence of stricture, ulcer, or dysplasia that coincided with the presence of specialized intestinal epithelium.

Combined 24-Hour pH and Bilirubin Monitoring

Twenty-four hour monitoring of bilirubin levels was performed simultaneously with pH monitoring as previously described.[15] In short, the pH and fiberoptic probes (Bilitec 2000, Synectics Medical, Inc., Irving, Texas) were placed 5 cm above the manometrically determined upper border of the lower esophageal sphincter. Medications were discontinued 2 days before testing (2 weeks for omeprazole), and diet was restricted to food with a pH greater than 5 and a low absorbance.[13] After the study, the fiberoptic probe was placed under water in a light-sealed container. If the absorbance was greater than 0.15, the recording was discarded. Analysis was done with a commercially available software program (Synectics Medical, Inc.). The time during which the esophageal pH was less than 4 was measured and expressed as the total percentage time and as a composite pH score.[18] The composite score indicated increased exposure to acid, if the value exceeded 14.7. A threshold of 0.2 absorbance was used to calculate the esophageal exposure to bilirubin,[15] a marker for the presence of duodenal juice. Patients were considered to have abnormal esophageal exposure to duodenal juice if the percentage time of exposure exceeded the ninety-fifth percentile level of asymptomatic volunteers.

Stratification of Acid Exposure

The time of esophageal exposure to acid was stratified to examine the effects of duodenal juice exposure over various durations of acid exposure. Based on the total percentage of time that the esophageal pH was below 4, patients were divided into the following four groups: less than 6%, 6% to 8%, 8% to 10%, and greater than 10%. The prevalence of injury was determined for each of these groups.

Statistics

Data are expressed as the median and interquartile range unless otherwise stated. Fisher's exact test was used to compare proportions between two groups. The Mann-Whitney U test was used to compare continuous data. A P value <0.05 was considered significant.

RESULTS

Normal Values for Esophageal Exposure to Bilirubin

The percentage time at an absorbance greater than 0.2 was plotted for each of the 35 healthy volunteers (Fig. 1). The median percentage time with absorbance greater than 0.2 was 0%, the seventy-fifth percentile 0.1%, the ninety-fifth percentile 1.7%, and the ninety-ninth percentile 6.7%. Based on these studies, increased esophageal exposure to duodenal juice was identified when the total percentage exposure time to bilirubin exceeded the ninety-fifth percentile level.

Relationship of Gastric and Duodenal Juice Exposure to Esophageal Injury

Thirty-seven patients had only increased esophageal exposure to acid (i.e., reflux of only gastric juice) and 63 patients had both increased acid and bilirubin exposure (i.e., reflux of gastroduodenal juice). Increased esophageal exposure to duodenal juice without increased exposure to gastric juice was uncommon (n = 10), and only one of these patients had esophageal injury. Because the latter composition of the esophageal reflux can be caused by an alteration of the pH of gastric juice either by duodenal juice or other causes, these patients were excluded from fur-

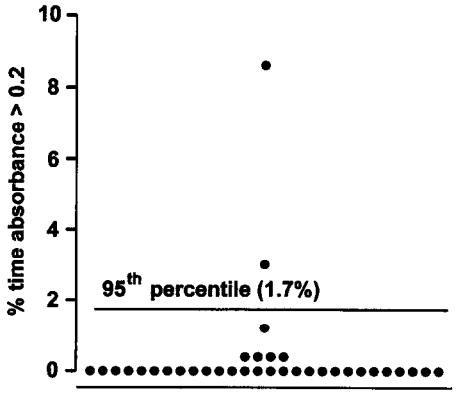

Fig. 1. Total percentage time of bilirubin exposure with an absorbance greater than 0.2 in 35 asymptomatic volunteers with normal acid scores and a manometrically normal lower esophageal sphincter. Note that increased bilirubin exposure in healthy persons is very uncommon.

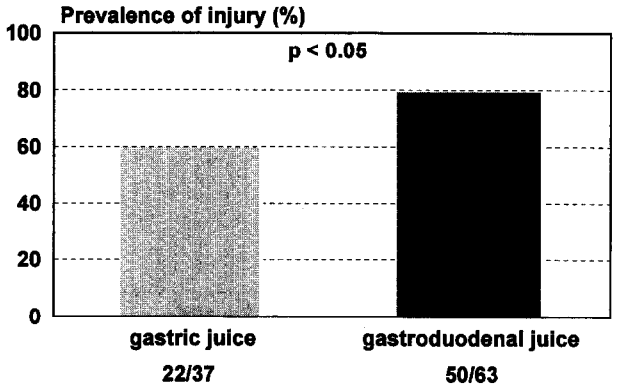

Fig. 2. Prevalence of esophageal injury in patients with reflux of gastric juice only compared to those with reflux of both gastric and duodenal juice.

Table I. Relationship between the type of reflux and injury

Injury	Gastric reflux	Gastroduodenal reflux	Total
No injury	15 (54%)	13 (46%)	28
Esophagitis	13 (38%)	21 (62%)	34
Barrett's esophagus without complications	8 (32%)	17 (68%)	25
Barrett's esophagus with stricture, ulcer, or dysplasia	1 (8%)	12 (92%)	13
TOTAL	37	63	100

ther analysis. Table I shows the relationship between the finding on endoscopy and the type of reflux. Fifty-nine percent of patients with gastric reflux had esophageal injury compared to 79% with gastroduodenal reflux ($P < 0.05$; Fig. 2). Of interest, 46% of patients with gastroduodenal reflux had Barrett's esophagus, whereas only 24% of those with gastric reflux alone had Barrett's esophagus ($P < 0.05$). When analyzed from the perspective of esophageal injury, reflux of gastroduodenal juice occurred in 46% of patients with no mucosal injury, in 62% of patients with esophagitis, in 68% of patients with uncomplicated Barrett's esophagus, and in 92% of patients with Barrett's esophagus and stricture, ulcer, and dysplasia.

Stratification of Acid Exposure

Fig. 3 relates the prevalence of esophageal injury to the length of time the esophagus was exposed to acid with and without the presence of duodenal juice. As expected, the prevalence of injury initially increased as the time of acid exposure increased for both groups. However, patients with gastroduodenal reflux continued to have a higher prevalence of injury with a higher acid exposure, whereas the prevalence of injury was approximately 60% to 70%, even with increasing acid exposure in patients who had reflux of gastric juice alone. In patients with an acid exposure time greater than 10%, the presence of duodenal juice resulted in significantly more injury ($P < 0.005$). Thirty-five (97%) of 36 patients with an acid exposure time greater than 10% and the presence of duodenal juice had esophageal mucosal injury, whereas only five (56%) of nine patients with gastric reflux alone and an acid exposure time greater than 10% had esophageal injury. The importance of duodenal juice is underscored in the 45 patients with high acid exposure (>10%) by a comparison of their acid and bilirubin exposure times (Fig. 4). Patients with injury had a significantly higher bilirubin exposure than those without injury ($P = 0.006$), whereas the difference in acid exposure was not significant.

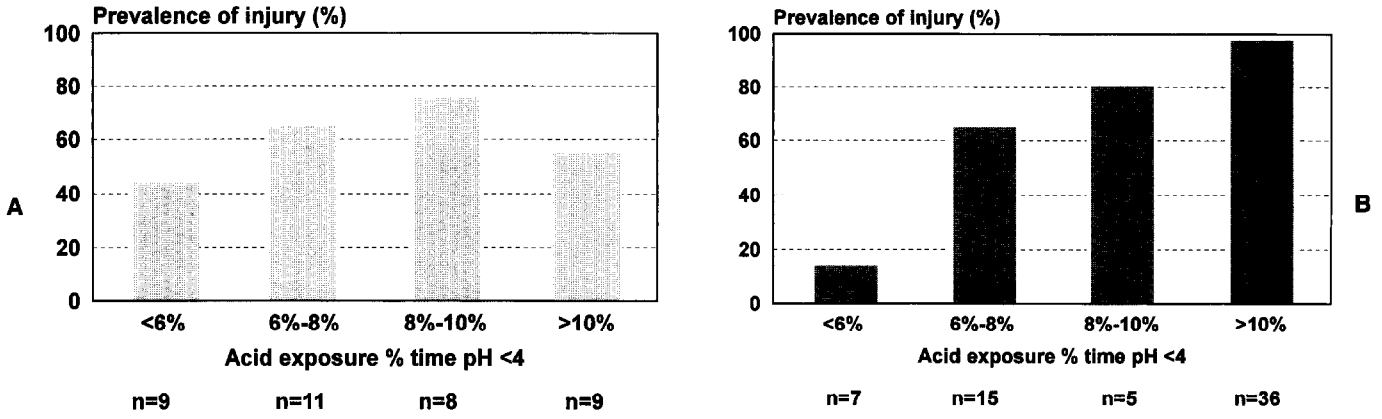

Fig. 3. Relationship between the prevalence of injury and the amount of acid exposure in patients with gastric reflux **(A)** and gastroduodenal reflux **(B).** There were no significant differences in the prevalence of injury in patients with gastric reflux alone. Patients with gastroduodenal reflux and an acid exposure time greater than 10% had a significantly higher prevalence of injury ($P < 0.001$) compared to those with gastroduodenal reflux and an acid exposure time less than 10%. The prevalence of injury between the two types of reflux differs significantly ($P < 0.005$) in patients with an acid exposure time greater than 10%.

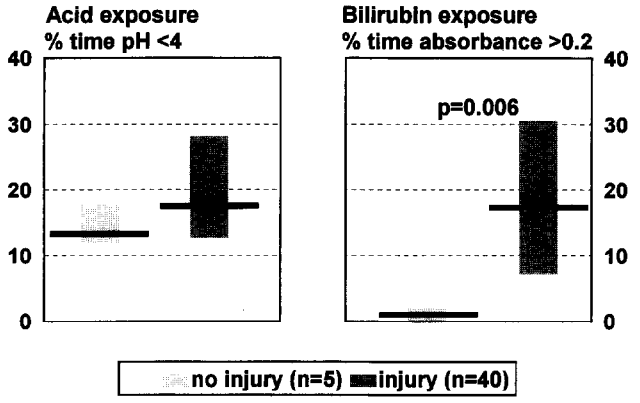

Fig. 4. Evaluation of the subgroup of patients with an acid exposure time greater than 10%. Acid and bilirubin exposure times are plotted for patients with and without injury. The median is indicated by a line, the interquartile range by a box.

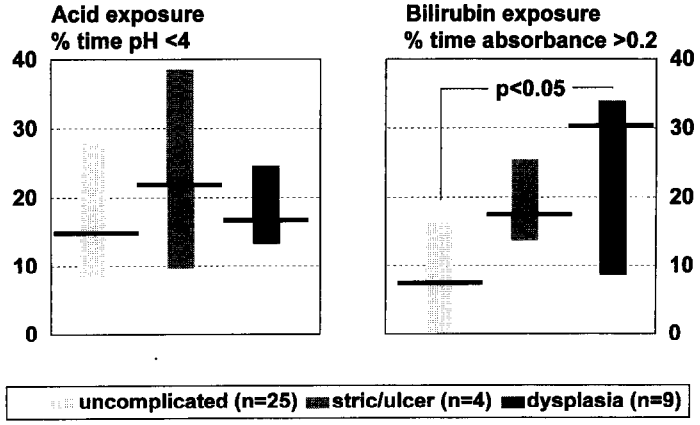

Fig. 5. Acid and bilirubin exposure times for patients with Barrett's esophagus with and without complications. Patients with complications included two with strictures, two with ulcers, seven with low-grade dysplasia, and two with high-grade dysplasia. The median is indicated by a line, the interquartile range by a box.

Composition of Esophageal Reflux in Patients With and Without Complications of Barrett's Esophagus

Thirteen of the 38 patients with Barrett's esophagus had complications; two had strictures, two had ulcers, two had high-grade dysplasia, and seven had low-grade dysplasia. A comparison of the acid and bilirubin exposure times was made between patients with uncomplicated Barrett's esophagus, Barrett's complicated by stricture or ulceration, or Barrett's complicated by dysplasia. Patients with dysplasia had a significantly higher bilirubin exposure when compared to patients with uncomplicated Barrett's esophagus ($P = 0.04$), whereas the acid exposure time in all three groups was similar (Fig. 5).

DISCUSSION

This study demonstrates that duodenal juice adds a noxious component to gastric juice refluxing into the esophagus and potentiates the injurious effects of gastroesophageal reflux resulting in esophagitis, Barrett's metaplasia, and complicated Barrett's esophagus.

Patients who had reflux of both gastric and duodenal juice had a higher prevalence of esophagitis and Barrett's esophagus than patients who had reflux of gastric juice alone. The injurious effect of duodenal juice is more apparent when a subgroup of patients with an acid exposure greater than 10% was analyzed (Fig. 3). In these patients exposure to duodenal juice, not gastric juice, was the main factor associated with injury (Fig. 4). Based on results in patients undergoing gastrectomy, Sears et al.[17] concluded that "acid rather than duodenogastric reflux is the main culprit in gastroesophageal reflux disease." Our results show the opposite, particularly when patients were stratified according to acid exposure time. In patients whose esophageal acid exposure time exceeded 10%, the presence of duodenal juice was associated with esophageal injury. The highest exposure to duodenal juice was found in patients with Barrett's esophagus, particularly in those with dysplasia (Fig. 5). Consequently, complications of Barrett's esophagus may be related to exposure to duodenal juice and not to acid exposure. Supporting this concept is the fact that gastric aspiration studies in patients with and without complications of Barrett's esophagus showed higher levels of bile salts in patients with complicated Barrett's esophagus,[10,16] again emphasizing the crucial role of duodenal juice.

The results of this study are in agreement with findings in animal models, which demonstrate a synergistic effect of duodenoesophageal reflux in an acidic environment on esophageal mucosal injury.[19,20] In a rat model reflux of duodenal juice, not gastric juice, was a prerequisite for the development of adenocarcinoma.[5,7-9] These findings in animal models, in conjunction with the previously cited clinical reports and the present study, show a relationship between esophageal exposure to gastroduodenal juice and the occurrence of Barrett's esophagus, dysplasia, and adenocarcinoma. This encourages the effective reduction of esophageal exposure to all noxious components in the treatment of gastroesophageal reflux disease.

Medical therapy is aimed primarily at reducing esophageal acid exposure and does not correct the underlying abnormality of a defective lower esophageal sphincter. As a consequence, practically all patients with reflux disease treated medically require lifelong therapy. Surgical therapy can correct the underlying defect in reflux disease (i.e., an incompetence of the lower esophageal sphincter) and abolish esophageal exposure to all noxious components.

The spectrum of patients presenting with gastroesophageal reflux disease ranges from patients with episodic symptoms without esophagitis to those with severe esophageal injury, such as peptic stricture or Barrett's esophagus. Patients with minor disease can be managed adequately with conservative treatment. However, there is a substantial cohort of patients who suffer from recurrent or progressive disease despite maintenance therapy.[21,22]

Well-recognized risk factors for the progression of gastroesophageal reflux disease are a defective lower esophageal sphincter,[23] increased esophageal acid exposure in the upright and supine positions on 24-hour pH monitoring,[24] and severe esophagitis.[22] The results of the present study indicate that reflux of duodenal juice is an additional risk factor for progressive disease.

Questions arise concerning the effects of gastroduodenal reflux in patients receiving acid suppression therapy. Champion et al.[12] showed that 20 mg of omeprazole taken twice daily suppressed esophageal acid reflux, but reflux of duodenal contents, although reduced, continued to exceed the normal range in four of nine patients. Alleviation of symptoms alone is inadequate for the treatment of these patients, because even without symptoms, reflux and injury to the esophageal mucosa may continue. Furthermore, these patients appear to require lifelong treatment with proton pump inhibitors. Recent clinical studies have raised serious concerns about long-term acid suppression and the development of atrophic gastritis with its premalignant potential.[25] In addition, findings in animal studies have raised the issue of whether reflux of duodenal juice prompts progression to esophageal adenocarcinoma.[26]

CONCLUSION

Patients with gastroesophageal reflux disease and reflux of duodenal juice combined with high acid exposure are at higher risk for the development of esophagitis, Barrett's metaplasia, and dysplasia with its premalignant potential. This should encourage consideration of antireflux surgery, which in most cases can be performed laparoscopically. Surgical therapy enables construction of an effective lower esophageal sphincter that prevents reflux of both gastric and gastroduodenal juice and has been shown to yield superior results compared to medical therapy in controlling the complications of reflux disease.[27,28]

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Discussion

Dr. J. Harmon (Washington, D.C.). Your report of duodenal esophageal reflux is interesting to me because Dr. Lillemoe, who is now at Johns Hopkins, and I, about 10 years ago, did a lot of work with a rabbit model of esophagitis characterizing what causes the injury in gastroesophageal reflux disease. I think what we found is very consistent with the results of your study—that is, acid and pepsin are very damaging, that if bile is added acid and pepsin are more damaging, and that acid combined with bile is damaging.

What is most interesting is that even alkaline bile, which does not create an erosive esophagitis, nonetheless has impressive effects. It reduces the electrical potential difference, it increases the permeability to the hydrogen ion, and it causes edema. Now that H_2 blockers can be obtained over the counter and proton pump inhibitors are widely available, we are getting rid of the acid, we are getting rid of the pepsin because pepsin only works in an acid environment, and we are left with bile acids in an alkaline environment. Meanwhile, as we are doing this, we are seeing an epidemic of Barrett's esophagus and adenocarcinoma of the lower esophagus.

So, are they related? I think we are going to have to address this. My question is, how are we going to address this? In looking ahead to your next year's presentation, are you looking at expression of proto-oncogenes as a link between this alkaline reflux and the increased incidence of Barrett's esophagus and adenocarcinoma.

Dr. M. Fein. Basically you are asking what are the consequences of medical therapy in these patients? It is important to remember that all of these patients were studied off therapy, so we cannot exactly predict bilirubin exposure in them.

It is likely that by decreasing acid exposure we are also decreasing the injury in the esophagus. The problem is that medical treatment must be continued for the rest of the patient's life.

We need to study patients whose injuries progress or recur while they are receiving medical treatment and we must measure the amount of acid and bilirubin present. You also suggest studying mutations in the mucosa. At present, we are trying to link genetic alterations to the nature of the refluxed juice.

Dr. J. P. Shoenut (Winnipeg, Canada). I noticed on the first slide that there were no reflux events that exceeded a pH of 7. We have commonly thought that the combination of acid reflux and alkaline reflux was most damaging to esophageal mucosa. What is the reproducibility of this bilirubin reflux in these patients who have esophageal damage. Also, is there treatment for this other than surgery?

Dr. Fein. You noticed correctly that mostly the duodenal reflux occurs together with acid reflux. Only rarely does combined reflux have a pH greater than 7.0. We did not conduct studies on reproducibility. Other investigators have already shown that the results are reproducible. I addressed the consequences of treatment in my answer to the previous question. The amount of reflux needs to be reduced dramatically. This can be achieved by using very high doses of proton pump inhibitors or, more practically, by means of antireflux surgery.

Dr. B. Bass (Baltimore, Md.). The damaging effects of bile salts are, in fact, concentration dependent, so that 5 mmol/L of bile, which is a concentration that is found in the gastric lumen, is quite damaging, whereas 1 mmol/L is less damaging. Can you tell us anything about the concentration of bile salts in the lumen of the esophagus of these patients? Did higher concentrations of bile salts correlate with greater degrees of injury or can the Bilitec device not provide any quantitative assessment?

Dr. Fein. The main disadvantage of the Bilitec device is that it is not quantitative. Absorbance values correlate only roughly with the concentration of bile salts.

Dr Bass. Have you sampled the bile in this well-characterized set of patients and saved it for later high-performance liquid chromatography analysis?

Dr. Fein. Not in these patients.

Dr. T. DeMeester. We have conducted esophageal aspiration studies of bile salts, and the concentrations range from 100 to 200 mmol/L. Equivalent concentrations have been shown to cause cell death in cytotoxicity studies.

Outcome After Failed Initial Therapy for Rupture of the Esophagus or Intrathoracic Stomach

Mark K. Ferguson, M.D., Laurie B. Reeder, M.D., Jemi Olak, M.D.

Survival after rupture of the esophagus or intrathoracic stomach is improving, but continued leakage after initial therapy remains a problem. We retrospectively reviewed patients with rupture of the esophagus or intrathoracic stomach to determine the prevalence of continued leakage after initial therapy and how this complication affects outcome. Our review included 58 patients, 38 (66%) of whom had preexisting esophageal disease. The etiology of perforation was spontaneous rupture in 17, penetrating trauma in four, and iatrogenic injury in 35; two patients had perforation from other causes. Initial therapy consisted of drainage in eight, primary repair in 24, resection in 18, bypass in two, and observation in six. The overall mortality rate was 12% (7 of 58 patients) and continuing leaks were identified in 21% (12 of 58 patients). These leaks were unrelated to patient age, existence of prior disease, or delay in therapy but were more common after initial treatment by primary repair with or without pleural flap coverage compared to other management strategies (6 of 9 vs. 6 of 49; $P < 0.001$). Salvage therapy with survival was possible in 10 (83%) of 12 patients by means of esophagectomy in four, exclusion in one, drainage in two, or observation in three. Continuing leaks can be avoided by providing soft tissue coverage other than pleura over a primary repair and by not leaving an intrathoracic esophageal stump. Aggressive management of continuing leaks results in survival in more than 80% of patients. (J GASTROINTEST SURG 1997;1:34-39.)

Perforation of the esophagus or intrathoracic stomach remains a therapeutic challenge. Recent results of outcomes following therapy for esophageal perforation suggest that the overall mortality rate is decreasing.[1] This is likely the result of improved medical management as well as refinements in the selection of therapy for individual patients. Clinical judgment is one of the most important factors determining the outcome of this problem. Despite reductions in overall mortality, the morbidity associated with this entity remains high, and a substantial number of patients fail initial therapy and have continued leakage from the site of perforation. We sought to determine what the underlying causes were for failure of initial therapy, how failed initial therapy affects overall outcome, and what methods are available for use in the salvage of patients who fail initial therapy.

PATIENTS AND METHODS

We retrospectively reviewed the hospital records of 58 patients treated at The University of Chicago Hospitals for perforation of the esophagus or intrathoracic stomach from January 1980 through March 1996. Five of the patients were diagnosed with esophageal perforation at other hospitals and were immediately transferred to The University of Chicago Hospitals for treatment. Seven patients underwent initial therapy at outside hospitals and were transferred in a septic condition with ongoing leakage for salvage therapy. Information was collected concerning history of prior esophageal disease; etiology and diagnosis of perforation; timing, method, and outcome of treatment; incidence of continuing leaks; and management of failed initial therapy.

The classification and analysis of data were carried out in a manner similar to that previously described.[1] The time interval from the occurrence of perforation to the diagnosis and treatment was classified as either early (<24 hours) or late (>24 hours). Subgroups for analysis were created based on the presence of preexisting esophageal disease, cause of perforation (spontaneous, traumatic, or iatrogenic), timing of treatment

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(early or late), mode of treatment, and whether or not initial therapy failed. Outcome was broadly classified based on the incidence of postoperative morbidity and mortality. Mortality refers to operative mortality and includes death within 30 days of surgery and/or during the same hospitalization. Morbidity refers to the incidence of nonfatal complications.

Analysis was performed using chi-square analysis for categorical data and Student's t test for continuous data. Continuous data are expressed as mean ± standard error of the mean. A P value <0.05 was accepted as being statistically significant.

RESULTS

The 58 patients included 36 men and 22 women who had a mean age of 53 ± 2 years (median 52 years, range 16 to 84 years). Thirty-eight patients (66%) had preexisting esophageal disease (Table I). The etiology of perforation was iatrogenic in 35 (60%), spontaneous in 17 (29%), and traumatic in four (7%); two patients (4%) had perforation from other causes. The diagnosis was made by esophagram in 31 (53%), by endoscopy in seven (12%), and by other means (CT scan, clinical diagnosis) in 14 (24%); the method of diagnosis was not recorded in six patients.

Thirty-six patients (62%) were diagnosed and treated within 24 hours of perforation and 20 (34%) had a delay in treatment; the timing of therapy was not recorded in two patients. Initial management included primary repair in 24 patients (with or without an added pleural flap in 9 and reinforced with a muscle flap or gastric wrap in 15), resection with delayed reconstruction in 15, surgical drainage in eight, observation alone in six, resection and primary reconstruction in three, and bypass in two.

Overall nonfatal morbidity and mortality rates were 50% and 12%, respectively. All seven patients who died had preexisting esophageal disease including carcinoma in four and benign stricture, eso-

Table I. Morbidity, mortality, and continuing leaks associated with treatment of esophageal perforation

Group	Patients No. (%)	Mortality No. (%)	Nonfatal morbidity No. (%)	Continuing leaks No. (%)
All patients	58 (100)	7 (12)	28 (48)	12 (21)
Underlying disease				
None	20 (34)	1 (5)	13 (65)	5 (25)
Disease	38 (66)	6 (16)	15 (39)	7 (18)
Stricture	7 (12)	1 (14)	3 (43)	1 (14)
Achalasia	10 (17)	0 (0)	4 (40)	0 (0)
Cancer	8 (14)	4 (50)	1 (13)	1 (13)
Varices	5 (9)	1 (20)	2 (40)	1 (20)
Other	8 (14)	0 (0)	5 (63)	4 (50)
Etiology				
Traumatic	4 (7)	0 (0)	2 (50)	1 (25)
Spontaneous	17 (29)	1 (6)	12 (71)	6 (35)
Iatrogenic	35 (60)	6 (17)	12 (34)	4 (11)
Operative	9 (15)	0 (0)	6 (67)	2 (22)
Endoscopy	19 (33)	3 (16)	5 (26)	1 (5)
Instrumentation	7 (12)	3 (43)	1 (14)	1 (14)
Other	2 (4)	0 (0)	2 (100)	1 (50)
Timing of treatment				
Early	36 (62)	4 (11)	16 (44)	7 (19)
Late	20 (35)	3 (15)	11 (55)	4 (20)
Unrecorded	2 (3)	0 (0)	1 (50)	1 (50)
Treatment				
Observation	6 (10)	1 (17)	2 (33)	2 (33)
Closure ± pleural flap	9 (16)	1 (11)	7 (78)	6 (67)*
Closure with muscle/stomach	15 (26)	0 (0)	7 (47)	1 (7)
Bypass	2 (3)	2 (100)	0 (0)	0 (0)
Resection only	15 (26)	2 (13)	10 (67)	3 (20)
Resection + reconstruction	3 (5)	1 (33)	1 (33)	0 (0)
Drainage only	8 (14)	0 (0)	2 (25)	0 (0)

*$P < 0.001$ compared to closure with muscle/stomach and compared to all other treatments combined.

phageal varices, and a connective tissue disorder in one each. Three of the four patients with esophageal carcinoma underwent stent placement for malignant stricture with unresectable disease. Two of these patients were treated with esophageal exclusion and bypass and had early sepsis, which resulted in withdrawal of therapy. The third patient who underwent stent placement was observed only and was classified as having a continuing leak. In the final patient with esophageal cancer, perforation occurred during dilatation; this patient underwent immediate resection and reconstruction, which was complicated by a massive cerebrovascular accident and withdrawal of supportive measures. The patient with a benign stricture had a perforation resulting from dilatation and underwent resection and reconstruction complicated by sepsis leading to death. The patient with esophageal varices had a perforation that was associated with the use of a Sengstaken-Blakemore tube; this patient underwent drainage and cervical diversion and died of sepsis. The patient with a connective tissue disorder had a spontaneous perforation that was diagnosed late. Esophageal repair was attempted but resulted in a continuing leak necessitating resection followed by death from multisystem organ failure. Thus two of seven deaths were associated with continuing leaks.

Salvage therapy with survival was possible in 10 of 12 patients with continuing leaks (Table II). Five had sepsis and underwent esophagectomy (n = 4) or exclusion (n = 1), and five were stable and were managed with drainage or observation (2 patients with continuing cervical leaks are included in this group). The presence of continuing leaks was unrelated to the existence of prior disease or the etiology of the leak. Initial treatment failure was associated with a mortality rate of 17% (2 of 12 patients) compared to a rate of

Table II. Management of continuing leaks

Patient	Prior disease	Etiology	Initial therapy	Salvage therapy	Outcome
1	None	Trauma	Repair	Observation	Survived
2	None	Spontaneous	Repair	Resection	Died
3	Stricture	Endoscopy	Observation	Resection	Survived
4	Cancer	Stent placement	Observation	Observation	Died
5	Varices	Endoscopy	Repair	Observation	Survived
6	None	Spontaneous	Partial resection	Resection	Survived
7	None	Spontaneous	Repair	Resection	Survived
8	Motility disorder	Spontaneous	Drainage	Exclusion	Survived
9	Hiatal hernia	Spontaneous	Repair	Resection	Survived
10	Hiatal hernia	Spontaneous	Partial resection	Drainage	Survived
11	Radiation injury	Intraoperative	Repair	Observation	Survived
12	None	Spontaneous	Partial resection	Drainage	Survived

Table III. Recent utilization of options for management of esophageal perforation

Reference	Interval	No. of patients	Available treatment options and outcome					
			Observation	Mortality	Drainage	Mortality	Stent	Mortality
Goldstein and Thompson[4] (1982)	1966-1980	44	12	4	0	0	0	0
Bladergroen et al.[5] (1986)	1937-1984	114	23	—	32	—	0	0
Nesbitt and Sawyers[6] (1987)	1975-1984	51	6	1	5	3	0	0
Wilde and Mullany[7] (1987)	1976-1986	37	19	7	1	0	9	4
Flynn et al.[8] (1989)	1977-1988	68	14	2	3	0	1	1
Pillay et al.[9] (1989)	1972-1987	23	12	4	1	0	0	0
Attar et al.[10] (1990)	1958-1989	64	2	1	17	6	0	0
Tilanus et al.[11] (1991)	1972-1989	59	17	—	10	—	0	0
Kim-Deobald and Kozarek[12] (1992)	1983-1991	23	11	7	0	0	2	2
White and Morris[13] (1992)	1975-1990	52	0	0	12	4	2	0
Current study (1997)	1980-1996	58	6	1	8	0	0	0
TOTAL		593	122 (21%)	33%	89 (15%)	28%	14 (2%)	50%

11% (5 of 46 patients) in those without initial failure. In patients who had a delay in therapy, the mortality rate was only slightly increased compared to those treated early (15% vs. 11%). Continuing leaks were more common after initial treatment by repair with or without pleural flap coverage compared to repair combined with muscle wrap or fundoplication (6 of 9 [67%] vs. 1 of 15 [7%]; $P < 0.001$) and compared to all other therapies (6 of 49 [12%]; $P < 0.001$).

All three patients who underwent partial esophagectomy, that is, a blind stump of esophagus was left in the mediastinum, had continuing leaks. One patient was managed with completion esophagectomy and staged reconstruction. The other two patients underwent drainage with a surgically established esophagopleurocutaneous fistula and subsequently underwent staged reconstruction.

DISCUSSION

Perforation of the esophagus or intrathoracic stomach remains a serious clinical problem. The primary precepts of therapy, early diagnosis and intervention, although they still apply, have been supplanted somewhat by improvements in antibiotic efficacy and critical care techniques that have led to substantial improvement in survival rates among patients in whom diagnosis is delayed. Although reports from earlier series of patients indicate that there is decreased survival in patients who experience a delay in diagnosis and therapy (42% vs. 12% of patients treated <24 hours after injury), our review, which includes more recent data, indicates that the disparity in survival rates between the early and late treatment groups is narrowing.[1,2] Our report also suggests that the overall mortality rate is declining somewhat relative to what has been reported in prior reviews.[2,3]

Although overall survival remains the principal criterion for determining success in the management of perforation of the esophagus and intrathoracic stomach, the focus of attention has recently begun moving toward the more controversial area of appropriate selection of therapy. Selection of therapy has a direct and profound impact on morbidity. The recent upsurge of interest in the use of primary repair of perforation, even in patients who experience a delay in diagnosis, has led to increasingly frequent reports of continued leakage following initial intervention. The recognition of this problem led us to review our experience with failed initial therapy after treatment of perforation of the esophagus or intrathoracic stomach.

Our findings are similar to those of recently published reports on management of esophageal perforation. The overall mortality rate, even when patients with end-stage carcinoma are considered, is acceptable at 12% and likely reflects not only improvements in medical management but also an increasing knowledge of how to individualize the selection of surgical management techniques. A review of institutional series dealing with esophageal perforation published since 1980 shows the variety of techniques available for managing esophageal perforation (Table III).[4-13] The frequent use of primary repair reflects an increasing interest in esophageal preservation in patients with perforation in the absence of an underlying malignancy. A higher than average mortality rate occurred in some groups, such as patients undergoing observation and drainage, which likely reflects the presence of underlying disease such as end-stage cancer for which minimally aggressive therapy is instituted after the perforation is recognized. The relative

Available treatment options and outcome							
Primary repair	Mortality	Exclusion	Mortality	Resection	Mortality	Total mortality	Overall mortality rate
23	4	9	6	0	0	14	32
49	—	0	0	10	—	24	21
31	3	7	1	2	0	8	16
7	0	1	0	0	0	11	30
44	2	2	1	4	0	6	9
8	2	0	0	2	0	6	26
30	5	5	4	9	2	18	28
13	4	0	0	19	4	17	29
9	—	1	—	3	1	11	48
28	4	5	3	5	0	11	21
24	1	0	0	18	3	7	12
266 (45%)	12%	30 (5%)	52%	72 (12%)	16%	133	23%

frequency of use of the techniques listed in Table III cannot be extrapolated to selections made for management of patients with failed initial therapy and continuing leaks. With ongoing sepsis, more aggressive therapy is necessary than when a patient is otherwise healthy. This more aggressive approach is reflected in Table II and is likely responsible for the relatively good outcomes among our patients with continuing leaks.

There is controversy regarding recent recommendations advocating the widespread use of primary repair in most patients with esophageal perforation, including those patients who experience a delay in therapy and intervention. Proponents of this technique demonstrate that it can be used with good overall survival, but they report an appreciable incidence of continuing leaks following primary repair, regardless of whether such repair is performed early or late following perforation.[14] A review of publications from 1980 demonstrates an overall prevalence of continuing leaks of 23% among 311 patients with esophageal perforation managed with primary repair (Table IV).[4,6-8,14-22] Interestingly, despite the prevalence of continuing leaks in this patient population, the overall mortality rate was low. There is no way of discerning how many of the patients who died had associated continued leakage, but the results suggest that the technique can be used in a large percentage of patients with esophageal perforation with good long-term results.

There are patients, however, in whom primary repair should not be the only treatment option. Patients with extensive loss of esophageal tissue, those with underlying end-stage motility disorders, and of course those with carcinoma of the esophagus are not candidates for esophageal preservation. The likelihood of a persistent, symptomatic chronic stricture is high in the first group of patients, and ongoing therapy is often necessary.[23] Patients with motility disorders, including many of those in whom perforation occurs spontaneously with no prior diagnosis of esophageal disease, often have symptoms of dysphagia after successful management of the perforation.[24] Some patients even have a second spontaneous perforation.[23,25] Although we are not suggesting that most patients who have a spontaneous perforation should be managed by means other than primary repair, we believe that careful consideration of both short- and long-term expectations is appropriate before therapy is selected.

In contrast to the recommendations for the widespread use of initial primary repair with the objective of esophageal preservation, our initial management group included a substantial number of patients who underwent esophageal resection because of underlying cancer, severe preexisting esophageal disease, or sepsis due to delayed diagnosis. Techniques that preserve the esophagus often have considerable attendant morbidity often leading to a prolonged hospital stay, whereas resection in selected patients eliminates the source of sepsis and, when appropriate, the underlying esophageal disease.[26] Resection, as can be seen from Tables I and III, carries an acceptable associated mortality rate (17% and 16%, respectively). Esophageal resection is also appropriate for managing selected patients with continued esophageal leakage, particularly in the presence of sepsis.[27] Staged reconstruction, usually with stomach pull-up and cervical esophagogastrostomy, restores these patients to a near-

Table IV. Incidence of continued leakage and death after primary repair of esophageal perforation

Reference	Interval	No. of patients	Continued leakage	Died
Goldstein and Thompson[4] (1982)	1966-1980	23	6	4
Larsen et al.[15] (1983)	1963-1982	43	4	8
Walker et al.[16] (1985)	1963-1983	12	5	3
Nesbitt and Sawyers[6] (1987)	1975-1984	31	10	3
Wilde and Mullany[7] (1987)	1976-1986	7	1	0
Flynn et al.[8] (1989)	1977-1988	44	5	2
Gouge et al.[17] (1989)	1975-1988	14	2	0
Pate et al.[18] (1989)	1958-1988	26	6	6
Gayet et al.[19] (1991)	1976-1988	13	2	1
Ohri et al.[20] (1993)	1989-1991	9	3	1
Whyte et al.[21] (1995)	1976-1993	22	4	1
Wright et al.[22] (1995)	1979-1994	28	9	4
Wang et al.[14] (1996)	1986-1994	18	9	3
Current study (1997)	1980-1996	21	7	1
TOTAL		311	73 (23%)	37 (12%)

normal functional status and obviates the need for ongoing treatment of underlying esophageal disease.

Our findings illustrate important points concerning surgical techniques in these patients. Primary repair, especially when there has been a delay in diagnosis and intervention, should be supplemented with reinforcement using a well-vascularized pedicle of tissue. Pleura, intercostal muscle, other skeletal muscles, stomach, and pericardial fat all serve this purpose well. What is generally not recognized, however, is the relative lack of utility of the pleural wrap in the management of an acute esophageal perforation. In the presence of chronic inflammation, the pleura becomes thickened and more vascularized. However, when the perforation is acute, this tissue is too thin and too poorly vascularized to provide any true benefit in most patients.

In patients in whom resection is necessary for management of esophageal perforation, the blind stump of the esophagus should never be left in a mediastinal location, regardless of whether a sump-type drain is placed within it. Esophageal peristalsis will recanalize the oversewn or stapled end, resulting in mediastinal sepsis, empyema, or enterocutaneous fistula. For many years we have used the technique described by Orringer and Stirling[26] of transposition of the remaining esophagus to a subcutaneous location on the chest wall. This has the advantage of preserving esophageal length and providing a suitable place for fitting an ostomy appliance, which is often a difficult task in the cervical region where end esophagostomies are usually brought out.

Our findings support the use of aggressive therapy in the management of perforations of the esophagus and intrathoracic stomach. Definitive initial therapy is successful in the majority of patients with perforation. Continuing leaks can be avoided by providing soft tissue coverage other than pleura over a primary repair and by not leaving an intrathoracic esophageal stump. Aggressive management of continuing leaks results in survival in more than 80% of patients.

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Glutamine Stabilizes Intestinal Permeability and Reduces Pancreatic Infection in Acute Experimental Pancreatitis

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Intestinal barrier failure and subsequent translocation of bacteria from the gut play a decisive role in the development of systemic infections in severe acute pancreatitis. Glutamine (GLN) has been shown to stabilize gut barrier function and to reduce bacterial translocation in various experimental settings. The aim of this study was to evaluate whether GLN reduces gut permeability and bacterial infection in a model of acute necrotizing pancreatitis. Acute necrotizing pancreatitis was induced in 50 rats under sterile conditions by intraductal infusion of glycodeoxycholic acid and intravenous infusion of cerulein. Six hours after the induction of pancreatitis, animals were randomly assigned to one of two groups: standard total parental nutrition (TPN) or TPN combined with GLN (0.5 $g/kg^{-1}/day^{-1}$). After 96 hours, the animals were killed. The pancreas was prepared for bacteriologic examination, and the ascending colon was mounted in a Ussing chamber for determination of transmucosal resistance and mannitol flux as indicators of intestinal permeability. Transmucosal resistance was 31% higher in the animals treated with GLN-supplemented TPN compared to the animals given standard TPN. Mannitol flux through the epithelium was decreased by 40%. The prevalence of pancreatic infections was 33% in animals given GLN-enriched TPN as compared to 86% in animals receiving standard TPN ($P < 0.05$). Adding GLN to standard TPN not only reduces the permeability of the colon but decreases pancreatic infections in acute necrotizing pancreatitis in the rat. This confirms previous reports that GLN decreases bacterial translocation by stabilizing the intestinal mucosal barrier. The present findings provide the first evidence suggesting that stabilizing the intestinal barrier can reduce the prevalence of pancreatic infection in acute pancreatitis and that GLN may be useful in preventing septic complications in clinical pancreatitis. (J GASTROINTEST SURG 1997;1:40-47.)

As advances in critical care have largely reduced the once prevalent early death from cardiorespiratory complications and renal failure in severe acute pancreatitis, secondary infection and sepsis are now the major causes of illness and death in this disease.[1,2] Clinical experience has shown that the risk of developing local or systemic complications from acute pancreatitis is increased in patients with infected pancreatic and peripancreatic necrosis.[3,4] The microorganisms that can be isolated from the infected tissue resemble common intestinal flora implying that translocation of bacteria from the gut plays a major role in the pathogenesis of pancreatic infection.[5] Consequently three ways of reducing bacterial infection in acute pancreatitis have been suggested: (1) elimination of bacteria in the gut; (2) prevention of bacterial translocation; and (3) extermination of bacteria after migration through the bowel wall on the way to the pancreas or in the pancreas itself. Experimental and clinical studies have already demonstrated that the prevalence of pancreatic infections and subsequent septic complications can be reduced by oral antibiotics selectively eliminating gram-negative bacteria from the gut and by intravenous antibiotics covering the intestinal microorganisms and concentrated

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in the pancreas.[6,7] Thus we were looking for ways to reduce translocation of bacteria from the gut. In initial trials we tested the effect of glutamine, which has previously been shown to improve the integrity of the gut mucosa and to reduce bacterial translocation in other experimental settings.[8] The same rodent model of acute necrotizing pancreatitis (ANP) previously used to demonstrate the efficacy of selective gut decontamination and intravenous antibiotic therapy with imipenem in decreasing the prevalence of bacterial infection in the pancreas was employed in this study.[9] Besides investigating the effect of glutamine on secondary pancreatic infection, we also measured its effect on increased gut permeability associated with acute pancreatitis, which is believed to be one of the decisive promoters of bacterial translocation.[10] Our results not only confirm previous reports that glutamine reduces bacterial translocation but also provide the first evidence that stabilizing the intestinal barrier can reduce apparent secondary infection.

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.

Acute necrotizing pancreatitis was induced under sterile conditions in 50 male Sprague-Dawley rats (330 to 390 g) by intravenous infusion of 5 $\mu g/kg^{-1}/hr^{-1}$ cerulein (Farmitalia, Freiburg, Germany) over a 6-hour period superimposed on a standardized infusion of 10 mmol/L glycodeoxycholic acid (Sigma Chemical Co., St. Louis, Mo.) into the common biliopancreatic duct after clamping of the main hepatic ducts as previously described.[11] As an improvement of this technique, a special infusion pump (IVAC 770, Lilly Medizintechnik, Giessen, Germany) was used for volume- , pressure- , and time-controlled intraductal infusion. All infused substances were processed through a sterilization filter (Nalgene, 0.2 μm; Nalge Ltd., Hereford, England), and bacteriologic tests were repeatedly performed to ensure the sterility of each step of the procedure.

After induction of ANP, animals were randomly allocated to one of two groups: group A (n = 25) was given a standard solution for total parenteral nutrition (TPN) without glutamine, and group B (n = 25) was given the same solution with the addition of 0.5 $g/kg^{-1}/day^{-1}$ glutamine (TPN + GLN).

For comparison of disease severity in the two groups, plasma trypsinogen activation peptide (TAP) levels were determined at 6 hours (before the start of therapy) as previously described.[12] Elevation of TAP levels in the early course of acute pancreatitis has been shown to parallel the development of acinar cell necrosis and to correlate with death in this pancreatitis model.[13] Therefore it can be used to confirm disease severity and to stratify experimental groups.

Infusions were prepared under sterile conditions using a commercially available amino acid solution (Amino Mix, Fresenius, Bad Homburg, Germany) and hypertonic dextrose (Glucosteril, Fresenius) from the hospital pharmacy. Alanyl-glutamine (Dipeptamin, Fresenius) was added to one diet (group B) and alanine plus glycine to the other (group A) in such amounts that both solutions were isocaloric and isonitrogeneous. Therapy was begun 6 hours after the induction of pancreatitis and solutions were administered continuously for 96 hours by means of Harvard infusion pumps at a rate of 6.25 $ml/kg^{-1}/hr^{-1}$. This time point was chosen because by then significant necrosis is already present.[11] Initiation of treatment at 6 hours therefore mimics the delay in therapy until patients present with established acute pancreatitis. Animals were kept in single metabolic cages cleaned once a day; they were maintained on a regular light-dark cycle and were not given any food or water besides the infusions.

At 96 hours the surviving animals were killed by an intracardiac injection of pentobarbital (200 mg/kg). Animals that died before the designated end point were excluded from further analysis because including them might have biased the bacteriologic findings as a result of an increase in gut permeability during cardiocirculatory derangement prior to death and postmortem overgrowth of bacteria. Autopsies were performed under sterile conditions. The duodenal segment of the pancreas was fixed in 10% formalin for histologic scoring of acinar cell necrosis according to previously described criteria[11]; the splenic segment was harvested, weighed, and immediately processed for bacteriologic examination. In addition, cecal stool samples from seven to nine animals per group were prepared for quantitative culture of aerobic and anaerobic organisms using standardized methods.[14,15] Briefly, specimens were placed in an aerobic chamber (Coy Laboratory Products, Inc., Grass Lake, Mich.) containing 80% nitrogen, 10% hydrogen, and 10% carbon dioxide. Two milliliters of phosphate-buffered saline–gelatin dilution medium (PBS-GD) was added. After homogenization, serial $\log_{10}$ dilutions (10^0 to 10^{-11}) were made in PBS-GD; 100 ml of the undiluted specimen and each serial dilution were inoculated onto plates of Centers for Disease Control (CDC) anaerobic blood agar, CDC anaerobic agar with phenylethyl alcohol, and CDC anaerobic laked blood agar with kanamycin and vancomycin (all purchased from Becton Dickinson Microbiology

Systems, Cockeysville, Md.). The plates were then incubated in the anaerobic chamber at 35° to 37° C for 5 days. Furthermore, 0.1 ml of each dilution was used to inoculate plates of *Brucella* agar with 5% horse blood, phenyl alcohol agar with 5% sheep blood, and MacConkey agar (all purchased from Becton Dickinson Microbiology Systems), which were incubated in an ambient atmosphere at 35° C. Aerobic cultures were examined after 48 hours of incubation; anaerobic cultures were studied after 2 and 5 days. Bacterial counts are presented as colony-forming units (CFU). More than 10^3 CFU per gram of tissue was considered an infection.

Electrophysiologic experiments to determine the barrier function of the epithelium were performed in vitro employing modified Ussing chambers.[16] In brief, 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, Braun, Melsungen, Germany) on a plastic ring (inner diameter 9 mm, outer diameter 11 mm) and inserted between the two halves of the Ussing-type chamber. Sealing was achieved at a diameter of 6 mm with soft silicone rubber seals.[17] Effective chamber area was 0.28 cm^2.

The bathing solution 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^- 2.4, $H_2PO_4^-$ 0.6, D-glucose 10, β-hydroxy-butyrate 0.5, glutamine 2.5, and D(+)-mannose 10.[16,18] A combination of 50 mg/L azlocillin (Securopen, Bayer, Leverkusen, Munich, Germany) and 10 mg/L imipenem (Zienam, MSD Sharp & Dohme) was added to the bathing solution after it had been determined to be most effective against bacterial growth during the time of this study; it did not affect short circuit current in the concentrations used. The solutions were gassed with a mixture of 95% oxgen and 5% carbon dioxide and had a pH of 7.4. All Ussing chamber experiments were performed at 37° C.

Transtissue impedance measurements were carried out as described in earlier reports.[17,18] Briefly, sine wave alternating currents (1 Hz to 65 kHz) were applied across the tissue, and the voltage responses were detected by a frequency response analyzer (Solartron Schlumberger, Farnborough, Great Britain). Resulting complex impedance data were corrected for the resistance of the bathing solution. A semicircle was fitted to the measured impedance locus plot by least-squares analysis. From this semicircle three parameters of an electrical equivalent circuit were obtained: a resistor (R^e) and a capacitor in parallel with each other representing the epithelium, and a resistor (R^{sub}) in series to this unit representing the subepithelium. Thus the impedance technique discriminates between the epithelial (R^e) and the subepithelial (R^{sub}) contribution to the total tissue resistance (R^t).

Unidirectional ^{3}H-mannitol flux studies from mucosa to serosa were performed under short circuit conditions. Mannitol fluxes were calculated using standard formula. An adjacent segment of the colon was removed and fixed in 10% formalin for light microscopy in a blinded manner.

The incidence of bacterial infection in pancreata from animals in both experimental groups was compared by chi-square test, comparison of TAP (log-transformed), bacterial counts and indicators of gut permeability by one-way analysis of variance. Values less than 0.05 were considered significant. All data are expressed as mean ± standard error of the mean unless otherwise specified.

RESULTS

Plasma TAP levels 6 hours after the start of pancreatitis induction were similar in both experimental groups (2.9 ± 0.6 vs. 2.7 ± 0.5 nmol/L), indicating equally severe pancreatitis before the start of therapy. Death occurred within 96 hours in 48% of the group receiving standard TPN and in 34% of the group given glutamine-supplemented TPN (NS). No significant differences in the extent of pancreatic necrosis were found between the groups at the end of the experiment (1.8 ± 0.3 vs. 1.6 ± 0.2).

Cecal flora determined at autopsy consisted of a mixed flora of gram-positive and gram-negative microorganisms and anaerobes characteristic of small rodents held in laboratories. These results were consistent with the bacteriologic findings in our previous studies in which the same model was used.[19] Again there was no difference between the two treatment groups (10^9 vs. 10^9 CFU/g; median).

The potential difference across the colon specimens (data not shown) assessed in the Ussing chamber indicated the viability of all but one specimen (which was subsequently excluded from further analysis).

The total resistance of the colonic wall (R^t), which reflected its ability to resist the passive movement of small ions, was 70 ± 4.5 Ω·cm^2 (n = 9) in the group given standard TPN and was increased to 92 ± 3 Ω·cm^2 (n = 10) in animals given glutamine-supplemented TPN ($P < 0.001$; Fig. 1). If R^t was subgrouped into epithelial (R^e) and subepithelial (R^{sub}) resistance, it turned out that the change in total tissue resistance was predominantly due to a change in epithelial resistance. Epithelial resistance (R^e) was 39 ± 4 Ω·cm^2 with standard TPN and increased to 55 ± 3 Ω·cm^2 after TPN + GLN ($P < 0.01$). The resistance of the subepithelial layers (R^{sub}) was not significantly altered; it was 31 ± 3 Ω·cm^2

with standard TPN and 37 ± 3 Ω·cm^2 after TPN + GLN.

The flux of mannitol across the tissue, reflecting (reciprocally) the passive permeability of this sugar, was decreased from 190 ± 20 nmol/hr^{-1}/cm^{-2} after standard TPN to 114 ± 14 nmol/hr^{-1}/cm^{-2} after TPN + GLN ($P < 0.01$; Fig. 2).

Histologic examination of colon segments adjacent to those subjected to electrophysiologic measurements showed no evidence of enterocyte cell damage. There was no cellular vacuolization, cuboidalization, or loss of brush border and no disruption of the basement membrane. Minor leukocyte infiltration and submucosal edema were seen in a few specimens; the muscularis propria and serosa were normal. Comparison of the light microscopic appearance, as described by a pathologist blinded to the treatment groups, revealed no difference between animals given standard TPN and those given glutamine-enriched TPN.

The prevalence of bacteria in the pancreatic specimens obtained from the surviving animals treated with standard TPN was 86% (Fig. 3). The flora were polymicrobial with *Escherichia coli*, enterococci, and *Staphylococcus aureus* as the predominant organisms. The median number of microorganisms found in the infected pancreata was 10^7 CFU/g. These findings paralleled those of our previous studies with the same model of ANP. In contrast to this high prevalence of bacterial infections in the standard TPN group, only 5 of 15 animals treated with the glutamine-enriched TPN had significant pancreatic infection ($P < 0.05$). The bacteria isolated from the pancreata of these animals were also polymicrobial, and the median number of microorganisms in the positive cultures was 10^4 CFU/g ($P < 0.05$).

DISCUSSION

Local and systemic septic complications are presently the major determinant of morbidity and mortality in acute pancreatitis.[3,4] Research has suggested that septic sequela of acute pancreatitis are commonly associated with infection of devitalized pancreatic and peripancreatic tissue by bacteria resembling the gastrointestinal flora.[5] The phenomenon of enteric bacteria crossing the intestinal wall and subsequently invading extraintestinal tissue has been defined as bacterial translocation.[20] Concern that bacterial translocation may only be a laboratory phenomenon has been dispelled by a recent clinical trial, the results of which showed that selective decontamination of the gut significantly reduced pancreatic infections and subsequent morbidity and mortality from septic complications in patients with severe acute pancreatitis.[6]

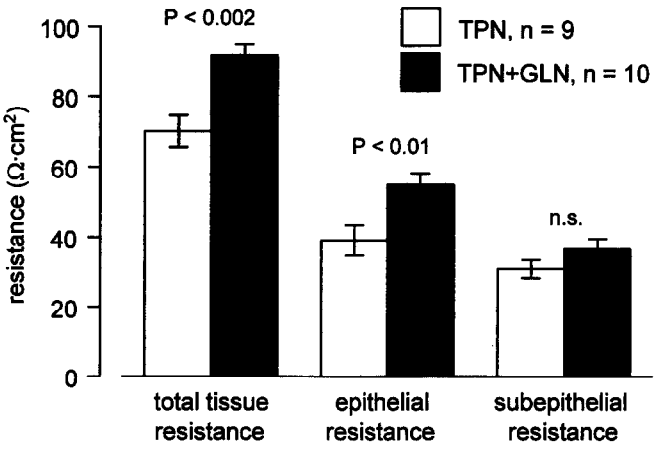

Fig. 1. Electrical resistance of the colon in vitro. Using impedance analysis, the total tissue resistance was subdivided into epithelial resistance and subepithelial resistance. The barrier for small ions between the lumen and the capillaries in vivo is reflected by the epithelial resistance.

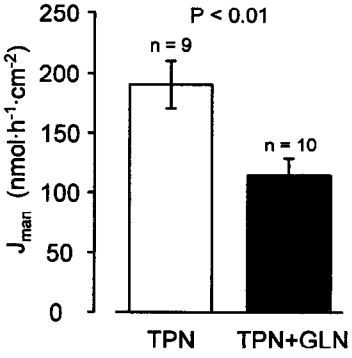

Fig. 2. Mannitol flux through the colon. Since no cellular mannitol transporters exist, mannitol flux is an indicator (reciprocal) of paracellular permeability

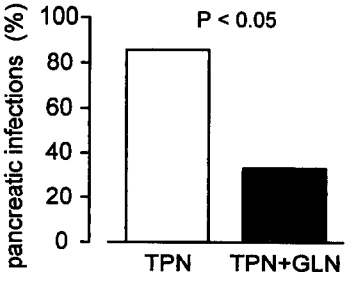

Fig. 3. Prevalence of pancreatic infections.

In view of this information, it is conceivable that prevention of bacterial translocation from the gut (rather than elimination of the bacteria in the gut) is another promising way to reduce pancreatic infections in acute pancreatitis. The factors leading to bacterial translocation are not completely understood and are believed to be promoted by three major factors: (1) disruption of the ecologic balance of the normal intestinal microflora, resulting in an overgrowth of certain (facultative pathogenic) bacteria; (2) impaired integrity of the gut mucosal barrier; and (3) a deficient host immune defense.[10] In severe acute pancreatitis all of these factors are present, and there is increasing evidence that therapeutic efforts aimed at stabilizing these disorders, such as bolstering the host immune defense,[21] improve outcome.

Increased gut permeability as one factor responsible for intestinal barrier failure in acute pancreatitis has often been suspected based on intraoperative findings and was first demonstrated in our rodent model of ANP by Ryan et al.,[22] who found increased gut permeability for polyethylene glycol in the absence of light and electron microscopic changes. The reason for impaired gut permeability in acute pancreatitis is unknown; it may be secondary to decreased blood supply and impaired intestinal microcirculation or the result of inflammatory mediators released during acute pancreatitis.[23] Restoration of impaired mucosal integrity may be hampered by the lack of enteral alimentation, which has been shown to play a decisive role in preserving the intestinal barrier function.[10,20]

In severe acute pancreatitis, however, early enteral nutrition is often delayed by gut paralysis and recurrent episodes of pain and hyperamylasemia. Thus attention must be focused on alternative ways of accelerating the repair or preventing and limiting disruption of the intestinal mucosal in patients receiving TPN for a prolonged period because they are at increased risk for acquiring gut-derived sepsis.

There is evidence to suggest that the use of growth factors, trophic gut hormones, and specific nutrients such as glutamine can be effective.[10,24] Current information on glutamine attests to its importance as the principal fuel for the intestinal epithelium and its decisive role in maintaining intestinal function and structure, especially in stress-related situations when glutamine synthesis and metabolism are disturbed.[8,10,24,25] This knowledge together with data demonstrating decreased intracellular glutamine levels in critically ill patients (including those with severe acute pancreatitis[26]) has supported the concept that glutamine may be conditionally indispensable in times of stress and injury and should therefore be supplemented in these patients.

Commercially available amino acid solutions for parenteral nutrition do not contain glutamine because of its unfavorable chemical properties, which include limited water solubility and instability during heat sterilization and storage. These drawbacks have only recently been overcome with the development of glutamine-containing dipeptides such as ananyl-glutamine, which are more stable and become rapidly hydrolyzed after intravenous infusion.[27] Experimental studies as well as preliminary clinical evidence have demonstrated that the addition of these dipetides to the standard TPN regimen results in improved nitrogen homeostasis, conservation of skeletal muscle, accelerated wound healing, maintenance of intestinal function and morphology, and enhanced gut barrier function.[8]

In light of all this information, we questioned whether glutamine would also stabilize impaired intestinal barrier function in acute pancreatitis and thereby reduce bacterial translocation and subsequent infection of pancreatic tissue. To evaluate this possibility, we assessed the prevalence of pancreatic infection in rats with ANP on a regimen of TPN with and without the addition of glutamine; gut permeability in these animals was determined in order to further elucidate the way in which glutamine might stabilize the intestinal barrier. The suitability of our model, which closely resembles severe pancreatitis in humans, for evaluating antimicrobial therapy has been demonstrated in numerous studies.[9,28] Its attractive features with regard to the present investigation include increased gut permeability,[9] a high prevalence of early infections of the pancreas with enteric microorganisms,[22] and the possibility of reducing these infections with appropriate therapy.[19]

Our results clearly demonstrate that the addition of glutamine to standard TPN enhances the resistance to small ions and decreases the flux rate of mannitol through the bowel wall; in addition, improvement in these indicators of gut permeability is associated with a significant decrease in the prevalence of pancreatic infections in this model of ANP. The significance of these observations is underlined by the fact that the protocol excluded other major factors besides gluramine that may possibly influence gut permeability and bacterial infection. Groups treated with and without glutamine did not differ with respect to the severity of ANP either before the start of the therapy (as assessed by TAP levels) or at the end of the experiment (as indicated by the amount of acinar cell necrosis). The bacteria isolated from the stool resembled the typical intestinal microflora and did not differ between the two experimental groups. All measurements were performed in a blinded fashion using standard procedures including determination of the

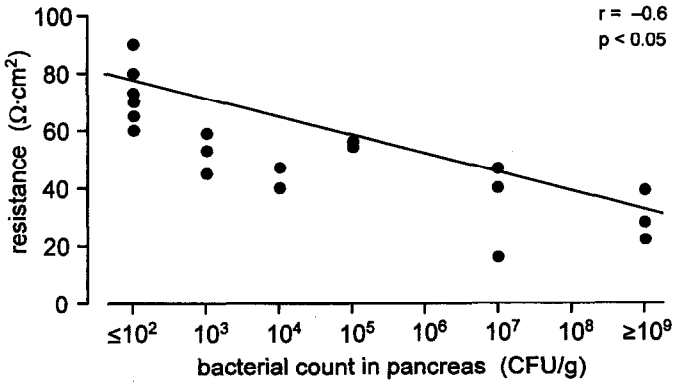

Fig. 4. Correlation between gut resistance and bacterial count in the pancreas. Regression is calculated using least-squares analysis.

indicators of gut permeability in the Ussing chamber together with impedance analysis, which are well-established methods for studying transport and barrier function of epithelia.[16-18]

The mechanism by which glutamine (as a single amino acid nutrient) exerts its effect on the gut is unclear and may include supplying the metabolic energy and the nucleotide bases required for cell division and replication. Glutamine may also serve as a secretagogue stimulating the release of trophic hormones, which themselves play a role in several metabolic pathways in the intestine.[29,30] More important than the effect of glutamine on increased permeability, which has recently been confirmed in other experimental and clinical settings, is the observation that stabilization of gut permeability is associated with decreased bacterial infection of the pancreas. The hypothesis that increased gut permeability at the mucosal level contributes to increased bacterial translocation has recently been advocated by Go et al.,[31] who found a close correlation between the two phenomena when comparing gut permeability in vitro and bacterial translocation in vivo in endotoxin-treated rats. The relationship found in the present study (Fig. 4) between gut resistance and bacterial count in the pancreas of animals with pancreatic infections furthers this concept and suggests that stabilization of increased gut permeability in ANP reduces not only bacterial translocation but apparent pancreatic infection as well.

The reduction in the prevalence of pancreatic infection from 86% in animals given TPN without glutamine to 33% in the animals given TPN supplemented with glutamine is comparable to the improvement seen with selective gut decontamination and intravenous imipenem in the same model.[9] The mortality rate at 96 hours was not significantly reduced, which is not surprising; it intrinsically belongs to this level of acute pancreatitis and results from the combination of the acute inflammatory process with volume sequestration and secondary renal and cardiorespiratory failure that cannot be altered by antimicrobial therapy. Proper antibiotic treatment does, however, prevent septic sequela and improves survival in the later course of the disease,[28] which confirms the clinical experience that pancreatic infections, although acquired within the first days of the disease, have an important bearing on late septic complications and mortality.[3] Since this has been demonstrated both in our model of ANP[28] and in severe human pancreatitis,[6] we did not repeat our experiments within a longer time frame but plan to test the effect of glutamine on the outcome of severe acute pancreatitis in a randomized clinical trial.

The underlying hypothesis that glutamine may reduce gut-derived infections by stabilizing the intestinal barrier is the most important finding in this study and warrants further evaluation including assessment of immunologic defense mechanisms, which may also influence bacterial translocation.

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Discussion

Dr. H. Freund (Jerusalem, Israel). Glutamine is usually claimed to be the fuel for the enterocyte and is effective in the small bowel. Your entire experiment basically deals with the colon. So how do you reconcile this discrepancy and explain the effects of glutamine in the colon?

Dr. T. Foitzik. We studied the colon because it is the major locale for bacterial translocation. Glutamine is the principal fuel for both the small bowel and the large bowel, at least in stress-related situations.

Dr. E.C. Opara (Durham, N.C.). There is a great deal of evidence in the literature to suggest that the integrity of the gut is somehow related to the glutathione content. Have you studied the gut content of glutathione in these experimental and control animals?

Dr. Foitzik. No, we have not.

Dr. K. Lee (Pittsburgh, Pa.). We have conducted a similar study and our preliminary results also show changes in permeability in the Ussing chamber. Have you studied the passage of live bacteria across the membrane since the Ussing chamber is well suited for these experiments. Did the passage of mannitol across the membrane correlate with that in the animals in which you saw evidence of bacterial translocation to the lymph nodes or other sites?

Dr. Foitzik. We are conducting experiments with live bacteria right now. There was a positive correlation between gut resistance and mannitol flux in the Ussing chamber and bacterial counts in the pancreata of the same animals.

Dr. S. Ashley (Los Angeles, Calif.). In the Ussing chamber studies, when you measure electrical resistance, what you are really looking at is the pericellular pathway. I think

most of the studies on translocation have suggested that it is transcellular. Although you observed an increase in the number of bacteria translocating, do you think this was related to the resistance change? If glutamine is given intraluminally, sodium-nutrient cotransporters are activated, which is how glutamine traverses cell membranes. How do you think these two occurrences are interrelated? Other studies have shown that glutamine as a fuel is probably better given through the lumen rather than parenterally.

Dr. Foitzik. We administered glutamine intravenously because we were attempting to mimic the clinical situation. Because patients with severe acute pancreatitis are kept on TPN, glutamine should be given intravenously. Since glutamine solutions are now commercially available for intravenous use in patients, it was reasonable to test intravenous glutamine in our experimental model.

Dr. H. Reber (Los Angeles, Calif.). You describe what you did to reduce pancreatic infection, but I am not sure your animals really did have pancreatic infection at all. In other words, you noted that bacteria were present in the pancreas, but in order to prove that infection is really occurring, I think you need to show that the presence of the bacteria is actually causing cellular necrosis and damage. Did you show a certain amount of necrosis in the animals that had bacteria present, and is that more necrosis than would be found if no bacteria were present in the acute pancreatitis model? Since there was no difference in necrosis between the treated and nontreated groups, you may have decreased the number of bacteria but I do not think you decreased the infection rate.

Dr. A.L. Warshaw (Boston, Mass.). To respond to Dr. Reber's point that the index being measured at this 96-hour point is the number of colony-forming units of bacteria present in the pancreas—this is essentially correct. We know that the 96-hour indices are, in fact, valid markers for true infection, that is, the development of abscesses and infected necrosis, and ultimately the death of the animal. The 96-hour time is thus a convenient and accurate point at which to look at the effect of an intervention. Infection appears to require necrotic tissue as a culture medium, but infection does not seem to increase the amount of necrosis in this model.

Dr. R. Prinz (Chicago, Ill.). We have used a model in which bile salts were injected into the pancreatic duct of rats to study translocation, and we have found that there is ischemic damage to the small intestine, which at the time of our observations appeared to be more profound or more evident than that in the colon. I would be interested to know whether you could continue your studies and examine the small intestine using the same chamber. I also question whether your number of groups is complete. You used TPN as one group and TPN supplemented with glutamine as the other group. TPN has profound effects on the gut including atrophy, and I would like to see what the effects of pancreatitis alone, with no nutritional support, would be in your model.

Dr. Foitzik. We plan to study the small intestine in the future. We have obtained measurements from healthy animals and animals with pancreatitis given regular chow from day 2 onward. Gut permeability is increased in the animals with pancreatitis, even with regular chow, as compared to healthy controls. Animals with pancreatitis that were given glutamine had almost normal gut permeability despite pancreatitis and despite TPN.

Laparoscopic Cholecystectomy During Pregnancy Is Safe for Both Mother and Fetus

Sabas F. Abuabara, M.D., Glenn W.W. Gross, M.D., Kenneth R. Sirinek, M.D., Ph.D.

The use of laparoscopic cholecystectomy in pregnant women has been slow to gain wide acceptance for two reasons: one is the potential for mechanical problems related to the pregnant uterus and the other is fear of fetal injury resulting from instrumentation or the pneumoperitoneum. To assess the effects of laparoscopic cholecystectomy on both the mother and the unborn fetus, we reviewed our surgical experience over a 5-year period analyzing indications for the procedure along with complications and outcome. During this 5-year period, 22 patients ranging in age from 17 to 31 years underwent laparoscopic cholecystectomy during pregnancy. Gestational ages ranged from 5 to 31 weeks with two patients being in the first trimester, 16 in the second, and four in the third. The primary indications for surgical intervention were persistent nausea, vomiting, pain, and inability to eat in 17 patients, acute cholecystitis in three, and choledocholithiasis in two. In all patients a pneumoperitoneum was established by means of a closed technique starting in the right upper quadrant of the abdomen. Two of the 22 patients also underwent successful transcystic common bile duct exploration with removal of common duct stones. All 22 patients survived the surgical procedure without complications, and there were no fetal deaths or premature births related to the procedure. Based on the preceding results, it would appear that laparoscopic cholecystectomy during pregnancy is safe for both the mother and the unborn fetus. Indications for this procedure should include stringent criteria such as unrelenting biliary tract symptoms or the complications of cholelithiasis. If at all possible, when laparoscopic cholecystectomy is indicated, it should be performed either in the second trimester or early in the third. (J GASTROINTEST SURG 1997;1:48-52.)

Laparoscopic cholecystectomy has become the procedure of choice for patients with symptomatic cholelithiasis and its complications.[1,2] However, use of this technique in the pregnant patient with acutely symptomatic biliary tract disease has been slow to gain wide clinical acceptance, despite the fact that laparoscopic procedures have been used during pregnancy to treat other intra-abdominal problems.[3-5] This attitude has been based on fear of either fetal injury or precipitation of a miscarriage. Evidence of fetal acidosis in an experimental animal model[6] has not translated into untoward side effects in humans in the limited number of case reports published.[7-36] Only a single report advises against laparoscopic cholecystectomy in the pregnant patient.[34]

Prompted by early reports that laparoscopic cholecystectomy was safe for both mother and fetus,[7,8] we have been using this approach since November 1991. This report presents our experience with 22 consecutive patients who have undergone laparoscopic cholecystectomy during pregnancy.

MATERIAL AND METHODS

All pregnant patients who were referred for treatment of acutely symptomatic cholelithiasis or its complications were considered candidates for the laparoscopic approach. Each patient was informed that this was not the standard approach and that experience with it was limited. Information was collected from each patient regarding age, parity, previous operations, symptoms, gestational age, operative time, surgical complications, and outcome of pregnancy. After giving fully informed written consent, each patient had an endotracheal tube placed for induction of general anesthesia. The Veress needle technique was used to establish a pneumoperitoneum in all patients. The needle was inserted in the right upper quadrant of the

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abdomen, away from the uterine fundus. A 5 mm trocar was then introduced in the same site as the needle insertion, and through it a 5 mm laparoscope was passed. Under direct vision, two 10 mm trocars were introduced, one in the epigastrium and the other one supra- or infraumbilically, depending on the body habitus of the patient and the gestational age. A fourth trocar was used only in patients who required exploration of the common bile duct. Intra-abdominal pressure was maintained at 10 to 14 mm Hg and patients were placed in the reverse Trendelenburg position with a tilt to the left. Every patient underwent sequential pneumatic compression of the lower extremities, as well as placement of a transvaginal Doppler cardiac fetal monitor when appropriate for the gestational age. Dissection of the gallbladder was performed with scissors, which were connected to electrocautery for simultaneous hemostasis. The cystic duct stump and the cystic artery were handled with the double laparoscopic clip technique. Intraoperative cholangiography was not performed and common bile duct exploration was carried out through the cystic duct. Tocolytic agents were not used in this group of patients.

RESULTS

During a 5-year period, 22 pregnant patients underwent laparoscopic cholecystectomy. Two of these patients also underwent simultaneous transcystic common bile duct exploration and choledocholithotomy using a 3 mm choledochoscope and a Dormia or Segura basket (Table I). Four patients were operated on during the third trimester of pregnancy (at 28, 29, 30, and 31 weeks' gestation), 15 were in the second trimester, and three were in the first trimester. There were 17 multiparous patients and four of them had had previous abdominal operations, which included three cesarean sections and one ovarian cystectomy. There were no conversions to the open cholecystectomy technique. Mean operative time was 59 minutes (range 40 to 128 minutes). The longest operative times (120 and 128 minutes, respectively) occurred in the two patients who underwent common bile duct exploration. Seventeen of the 22 patients presented with persistent right upper quadrant abdominal pain, nausea, and vomiting. Following documentation of gallstones by ultrasonography, each patient was maintained on intravenous fluids and given nothing by mouth for several days. All 17 patients be-

Table I. Review of 22 pregnant patients undergoing laparoscopic cholecystectomy

Patient	Age (yr)	Obstetric history	Operative time (min)	Gestational age (wk)	Surgical history	Symptoms
1	24	G4 P3 Ab0	48	21	C-section Ovarian cystectomy	Pain, N/V
2*†	23	G3 P2 Ab0	120	5	—	Pain, N/V, fever
3	19	G1 P0 Ab0	60	30	—	Pain, N/V, fever
4	23	G3 P2 Ab0	45	31	C-section ×2	Pain, N/V
5	27	G2 P1 Ab0	55	19	—	Pain, N/V
6	19	G2 P1 Ab0	48	18	—	Pain, N/V
7	24	G3 P2 Ab0	56	20	—	Pain, N/V
8	21	G2 P1 Ab0	50	19	—	Pain, N/V
9*	23	G3 P2 Ab1	65	28	—	Pain, N/V
10	21	G2 P1 Ab0	45	22	—	Pain, N/V
11	22	G1 P0 Ab0	56	21	—	Pain, N/V
12	18	G2 P1 Ab0	55	29	C-section	Pain, N/V
13	20	G2 P0 Ab1	50	22	—	Pain, N/V
14	23	G3 P1 Ab1	60	8	—	Pain, N/V
15*	21	G2 P1 Ab0	70	19	—	Pain, N/V, fever
16*	25	G2 P1 Ab0	40	15	—	Pain, N/V
17*†	22	G5 P5 Ab0	128	25	—	Pain, N/V
18‡	18	G1 P0 Ab0	55	16	—	Pain, N/V
19	21	G1 P0 Ab0	40	19	—	Pain, N/V
20	17	G2 P1 Ab0	50	14	C-section	Pain, N/V
21	29	G3 P2 Ab0	45	11	—	Pain, N/V
22	31	G2 P0 Ab1	40	17	—	Pain, N/V

G = gravida; P = para; Ab = abortion; N/V = nausea/vomiting.
*Acute cholecystitis.
†Common bile duct exploration.
‡Peutz-Jeghers syndrome.

came acutely symptomatic after ingesting food, which prompted surgical intervention. Three patients had acute cholecystitis and another two had biliary pancreatitis. These latter two patients underwent successful transcystic common bile duct exploration, choledochoscopy, and stone extraction.

All 22 patients tolerated the surgical procedure well, with no precipitation of labor or fetal death. Twenty-one patients became asymptomatic following laparoscopic cholecystectomy. One patient with Peutz-Jeghers syndrome continued to have nausea and vomiting for 2 weeks after the operation. She subsequently developed a small bowel obstruction and underwent multiple (12) resections of small bowel polyps. She was delivered of an immature male infant 1 month after this operation, which was 2 months after she had undergone laparoscopic cholecystectomy. All of the other patients, with the exception of two who are still pregnant at 18 and 30 weeks' gestation, have been delivered of healthy infants with no evidence of developmental abnormalities to date. Seventeen patients were discharged on postoperative day 1, two on day 2, one on day 3, and two on day 4. The patients who required the longest hospital stays were those who had acute cholecystitis or biliary pancreatitis and the one patient with Peutz-Jeghers syndrome.

DISCUSSION

In the early developmental stages of laparoscopic cholecystectomy, pregnancy was an absolute contraindication for the procedure.[37] However, as early as 1972 there were reports in the obstetric literature of laparoscopic procedures being performed in pregnant patients for the diagnosis of ectopic pregnancy.[3] These procedures were associated with a very low rate of fetal loss in those patients who were found to have a normal intrauterine pregnancy, and there appeared to be no long-term ill effects on the fetus. Use of laparoscopic procedures in pregnant patients was then extended to management of the acute problems of ovarian torsion and appendicitis.[4,5] The first reports in the English literature of successful laparoscopic cholecystectomy in pregnant patients appeared as isolated case reports in 1991.[7-9] On the basis of these reports and the previous literature demonstrating the safety of laparoscopy in this situation, we decided to use the laparoscopic approach for all pregnant patients who required an urgent or emergency cholecystectomy. Most patients who were referred with symptomatic cholelithiasis were managed nonoperatively with changes in their diets and/or administration of minimal doses of pain medication. Only those patients who had persistent abdominal pain and were unable to eat, those with persistent nausea or vomiting, and those who had acute cholecystitis or biliary pancreatitis were considered to be candidates for surgery.

Since those initial reports a total of 76 cases of successful laparoscopic cholecystectomy during pregnancy have been published.[10-36] Only one study has concluded that laparoscopic cholecystectomy is contraindicated in the pregnant patient.[34] In that report there were four fetal deaths among seven patients who underwent the procedure, three within 1 week of the operation and one 4 weeks postoperatively. This difference in fetal outcome compared to other reports is not clear. However, one contributing factor may have been the mean operative time of 106 minutes, which is approximately twice as long as our operations. When our 22 patients are added to the previously published series, for a total experience of 98 procedures, the four fetal deaths (4.1%) among our patients compares favorably with the 5% loss rate associated with the open procedure.[38]

The pregnant uterus reaches the umbilicus at approximately 20 weeks' gestation, and from that point on displacement of the abdominal viscera superiorly in the abdomen limits the space available for both trocar placement and laparoscopic manipulations. If a 5 mm trocar is first introduced into one of the upper abdominal quadrants, then the two other trocars can be safely inserted and appropriately positioned under direct vision. The operation should be limited to only three trocars because of the decreased intra-abdominal space available for performing a cholecystectomy. In the present series a fourth trocar was placed in those patients who required common bile duct exploration.

The method of establishing a pneumoperitoneum (open vs. closed) does not appear to play a role with regard to the risk to the fetus. However, two issues have been raised concerning the pneumoperitoneum in the pregnant patient. The first is the potential for gas embolism, a complication that has been reported in patients who have undergone termination of a pregnancy followed by laparoscopic tubal ligation.[39] This is thought to occur secondary to the entrance of gas through the uterine sinusoids by direct uterine puncture or via the Fallopian tubes. The same pathophysiology could be operational in the pregnant uterus. This catastrophe has not materialized to date.

The second concern is the development of fetal acidosis secondary to establishing a pneumoperitoneum with carbon dioxide.[34] This has been attributed to an increase in $PaCO_2$ in the maternal circulation. Others have speculated that this acidosis may be compounded by the mechanical effect of increased intra-abdominal pressure adversely altering placental circulation. In one animal experiment[6] the maternal $PaCO_2$ was 15 mm Hg higher than the end-tidal PCO_2 ($ETCO_2$), also with an $ETCO_2$ lag time of 30 to 40 minutes for any

change in the $PaCO_2$. This reinforces the need to maintain the $ETCO_2$ between 25 and 30 mm Hg by changing the minute ventilation, or by means of controlled ventilation, which may then induce further adverse hemodynamic responses. The significance of these physiologic changes with regard to the end result of the pregnancy is unclear because of the acute nature of the experiment. In any case this underscores the need to maintain the maternal $ETCO_2$ in the 25 to 30 mm Hg range, which was attempted in each of our patients. In the nonpregnant patient the increase in $PaCO_2$ has correlated with the total time that a pneumoperitoneum with carbon dioxide is maintained.[40] Therefore it is important to keep the operative time to a minimum to ensure safety. In addition, intra-abdominal pressure should be kept at the lowest possible level that will still allow the surgeon to achieve adequate exposure. In the present study the average operating time was 52 minutes (excluding two patients who underwent common bile duct exploration), and intra-abdominal pressure was kept at 10 to 14 mm Hg. Laparoscopic cholecystectomy in the pregnant patient, in which a gasless technique is used, has been reported but needs further investigation.[33]

Numerous series published within the past 10 years have demonstrated that open cholecystectomy during pregnancy should be reserved for acutely symptomatic patients or for those with complications of gallstones.[41-43] It can be performed safely, preferably during the second trimester, with an overall fetal death rate of 5%[38] and with no congenital malformations attributed to the procedure. In 1996 laparoscopic cholecystectomy is the procedure of choice for patients requiring either elective or acute removal of the gallbladder. Based on reports in the literature and on our own results, we believe that laparoscopic cholecystectomy should also be the procedure of choice under similar circumstances in pregnant patients. We have performed this procedure during all three trimesters, with no fetal deaths related to it and no congenital abnormalities; only two of our patients have not yet given birth. Two patients who had pancreatitis secondary to choledocholithiasis underwent successful laparoscopic common bile duct exploration and stone removal. Liberman et al,[30] reported a similar successful experience. It is our belief that with the new 3 mm choledochoscope and adequate training this is a better alternative to either pre- or postoperative endoscopic retrograde cholangiopancreatography with its attendant exposure of the fetus to irradiation.

We have performed the procedure in pregnant patients up to 31 weeks' gestation and have not encountered any problems from a technical standpoint. The three-trocar approach is more appropriate because there is less available operating space, and this approach should be used routinely. The latest gestational age at which laparoscopic cholecystectomy should be performed remains controversial. Patients who are beyond 34 weeks' gestation have been controlled with medication alone. After 36 weeks' gestation, usually the fetus engages the pelvis and the uterine fundus descends, theoretically providing the same amount of available intra-abdominal operating space as in the patient at 32 to 34 weeks' gestation. Uterine irritability is increased, however, at this late gestational stage and labor may be more easily induced. To date we have not encountered this problem.

CONCLUSION

We believe that laparoscopic cholecystectomy is the procedure of choice in the pregnant patient. Although it would appear that laparoscopic cholecystectomy is safe at all gestational ages, if possible it should be performed after the period of organogenesis (12 weeks). The only absolute contraindications would be the absolute lack of space for manipulation of the instruments, unclear anatomy at the moment the procedure is being performed, or a lack of adequate training and/or experience of the surgeon.

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Discussion

Dr. J. Hunter (Atlanta, Ga.). Why do you use three trocars? What is the advantage of using one less 5 mm trocar in pregnant patients? There are now close to 100 reported cases of laparoscopy in midpregnancy, with only one series showing poor outcomes. Is this technique safe and, if it is, why were there so many poor outcomes reported by Amos et al.[34] from Jackson, Mississippi?

Dr. S. Abuabara. One reason for using only three trocars is that during pregnancy there is less space available to perform a cholecystectomy, and we consider three trocars to be the standard right now. At 30 weeks' gestation, in a normal intrauterine pregnancy, there is not much intraperitoneal space. We believe this procedure can be performed up to 31 to 32 weeks. Regarding the series from Jackson, Mississippi, we really do not know why the outcome was so different, but the mean operative time reported in that series was 109 minutes. Our mean operative time is 52 minutes, and we think that has something to do with the difference. In a report from St. Louis published in 1991, Kaminsky showed how in some patients with chronic pulmonary disease the P_{CO_2} increased dramatically with production of acidosis and hypercarbia. This may translate into acidosis in the fetuses of those patients who undergo a procedure that lasts longer than 1 hour. This may account for the poor outcome in the Jackson series. In our series we had 98 patients with four fetal deaths, which is a 4.1% loss rate compared to the 5% rate with the open technique.

Laparoscopic Treatment of Liver Cysts

Paul Hansen, M.D., Sunil Bhoyrul, M.D., Prithvi Legha, M.D., Albert Wetter, M.D., Lawrence W. Way, M.D.

Symptomatic simple liver cysts should be treated. In this report we describe the results of a straightforward, well-tolerated laparoscopic operation for this condition. Between 1990 and 1996 we performed 19 laparoscopic liver cyst excisions. The exposed portion of the cyst wall was excised and a piece of omentum was secured into the remaining cyst cavity to prevent recurrence. The average age of the patients was 65 years (range 30 to 81 years). Eight patients (42%) had single simple cysts, nine patients (47%) had multiple simple cysts, and two patients (11%) had polycystic liver disease. Fifty-three percent of the patients had previous abdominal operations, 47% had undergone previous needle aspirations, and one had previously undergone unsuccessful laparoscopic cyst decompression elsewhere. The indications for surgery included abdominal pain, mass, early satiety, malaise, bloating, and shortness of breath. Two patients underwent concurrent cholecystectomies, and one patient underwent concurrent laparoscopic Nissen fundoplication. Follow-up, which averaged 32 months (range 3 to 68 months), is complete in all patients. There was one treatment failure among the patients with simple cysts. Both patients with polycystic liver disease have had recurrent symptoms. The laparoscopic approach to simple liver cysts is relatively straightforward, and if certain technical principles are adhered to, the success rate is very high. (J GASTROINTEST SURG 1997;1:53-60.)

Most simple cysts of the liver are small and asymptomatic and of no clinical significance. An occasional one, however, becomes large enough to produce abdominal discomfort or gastrointestinal symptoms, and a question arises as to what should be done. A variety of options have been proposed, some considerably more invasive than others. For more than two decades our approach has been to perform a wide unroofing of the cyst and to allow the small daily secretion of fluid from the remaining cyst lining to drain into the peritoneal cavity where it is readily absorbed. Other methods that have been advocated include percutaneous aspiration with or without intracystic sclerotherapy,[1,2] excision of the entire cyst from the liver,[3] partial hepatectomy encompassing the cyst,[3] and Roux-en-Y drainage of the cyst.[4,5]

Shortly after the rapid expansion of laparoscopic surgery that began in 1989, we realized it should be technically feasible to perform the same type of unroofing procedure laparoscopically that we had been performing up to that point by means of open laparotomy. We describe herein our subsequent experience with the laparoscopic treatment of liver cysts.

METHODS

Data from 19 consecutive patients undergoing laparoscopic treatment of benign, nonparasitic liver cysts at the University of California, San Francisco (UCSF), between October 1990 and February 1996 were collected prospectively and analyzed. Follow-up, which is complete in all patients, ranged from 3 to 68 months (average 32 months).

There were 16 women (84%) and three men (16%). The average age was 65 years (range 30 to 81 years). Eight patients (42%) had single cysts, nine patients (47%) had multiple cysts, and two patients (11%) had polycystic liver disease.

Single cysts averaged 15 cm in diameter (by CT scan) and ranged from 7 to 25 cm. Patients with multiple simple cysts usually had two or three dominant cysts and occasionally a smaller one. The dominant cysts (the ones treated surgically) averaged 9 cm in diameter and ranged from 6 to 16 cm.

Four patients (22%) had at least one previous upper abdominal operation, and 10 patients (53%) had at least one previous lower abdominal operation. Nine patients (47%) had undergone from one to nine cyst

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aspirations, and one patient had an inadequate laparoscopic operation for a large liver cyst at another hospital before being referred to UCSF with a recurrence. The indications for surgical treatment are listed in Table I.

Two patients with gallstone disease underwent concurrent cholecystectomies. In each the principal symptoms (e.g., abdominal mass, early satiety) were caused by the liver cyst. In one patient with symptomatic gastroesophageal reflux, a large solitary hepatic cyst of the left lobe was unroofed to facilitate a laparoscopic fundoplication.

Table I. Distribution of symptoms in 19 patients with laparoscopically treated liver cysts (most patients had more than one indication for the operation)

Symptoms	No. of patients	Percent
Pain	17	89
Mass	8	42
Possible neoplasm	3	16
Early satiety	3	16
Dyspnea	1	6
Malaise	1	6
Bloating	1	6
Total patients	19	

OPERATIVE TECHNIQUE

The operations were all performed using standard laparoscopic methods. Three to five ports were used depending on anatomic details such as the number and location of the cysts.

The objectives of the operation were to remove as much of the exposed cyst wall as possible and to take steps to ensure that omentum or other viscera completely filled the residual cyst cavity. No attempts were made to excise cyst wall that was encased in hepatic parenchyma.

The operation can be described as involving five steps (Fig. 1). The first step, which should be accomplished before puncturing and draining the cyst, is to obtain exposure of the entire surface of the cyst. This may be simple in the case of cysts that present on the anterior surface of the liver, but those on the inferior, lateral, or posterior surfaces are often partly concealed by inflammatory adhesions to nearby viscera or by peritoneum. It is far easier to determine the margins of the cyst before it is decompressed than afterward, so adhesions should be taken down before proceeding to the next step.

Next the line of resection of the cyst wall should be determined and marked on the tissue with electrocautery. It should be 0.5 to 1.0 cm to the cyst side of the margin between the cyst wall and normal hepatic parenchyma. This too should be accomplished before the cyst is drained, because afterward the cyst wall tends to collapse in folds, making the desired pathway harder to visualize.

Excision of the cyst wall can then begin, starting at the most dependent point of the circle previously marked by electrocautery. Starting low avoids the problem of blood from the cut margins of the cyst dripping into the area to be dissected, where it may obscure the intended line of transection. When the cyst is entered, its fluid should be suctioned out. After a flap of cyst wall has been raised, the interior of the cyst can be inspected for any signs of neoplastic tissue (e.g., papillary growth) and a biopsy specimen may be obtained as indicated.

The dissection should proceed to excise the entire piece of cyst wall mapped out for removal. This only takes a few moments with thin-walled cysts, but a thick (e.g., 1 cm) cyst wall contains more blood vessels that must be cauterized and the greater bulk of tissue requires more time. We have not encountered bleeding that could not be controlled with the standard monopolar electrocautery. A considerable amount of smoke is produced when excising a piece of thick-walled cyst, and in these cases we connected two insufflators to separate ports and allowed gas to leak from a third port, which created a continuous exchange of the pneumoperitoneum.

Large cysts (>9 cm) have a greater proportion of their wall exposed than do smaller ones. It is often possible to remove a circular piece of cyst wall from these large lesions that equals approximately 80% of the full diameter of the cyst, and when this has been accomplished, the cyst remnant resembles a dinner plate more than a decapitated sphere. Consequently there is less chance of the edges coming together to produce a recurrent cyst. Furthermore, since these giant cysts are usually at the inferior surface of the liver, neighboring viscera and omentum automatically come into contact with (i.e., fill) the remaining cyst.

Small cysts (5 to 9 cm), especially those located high on the liver, may reside deeper in the liver substance and have a smaller proportion of their wall exposed. It may be impossible to excise a piece that constitutes more than approximately 25% of the full diameter of the cyst, and at the completion of the dissection a distinct cavity remains. To prevent apposition of the cut margins and recurrence of these cysts,

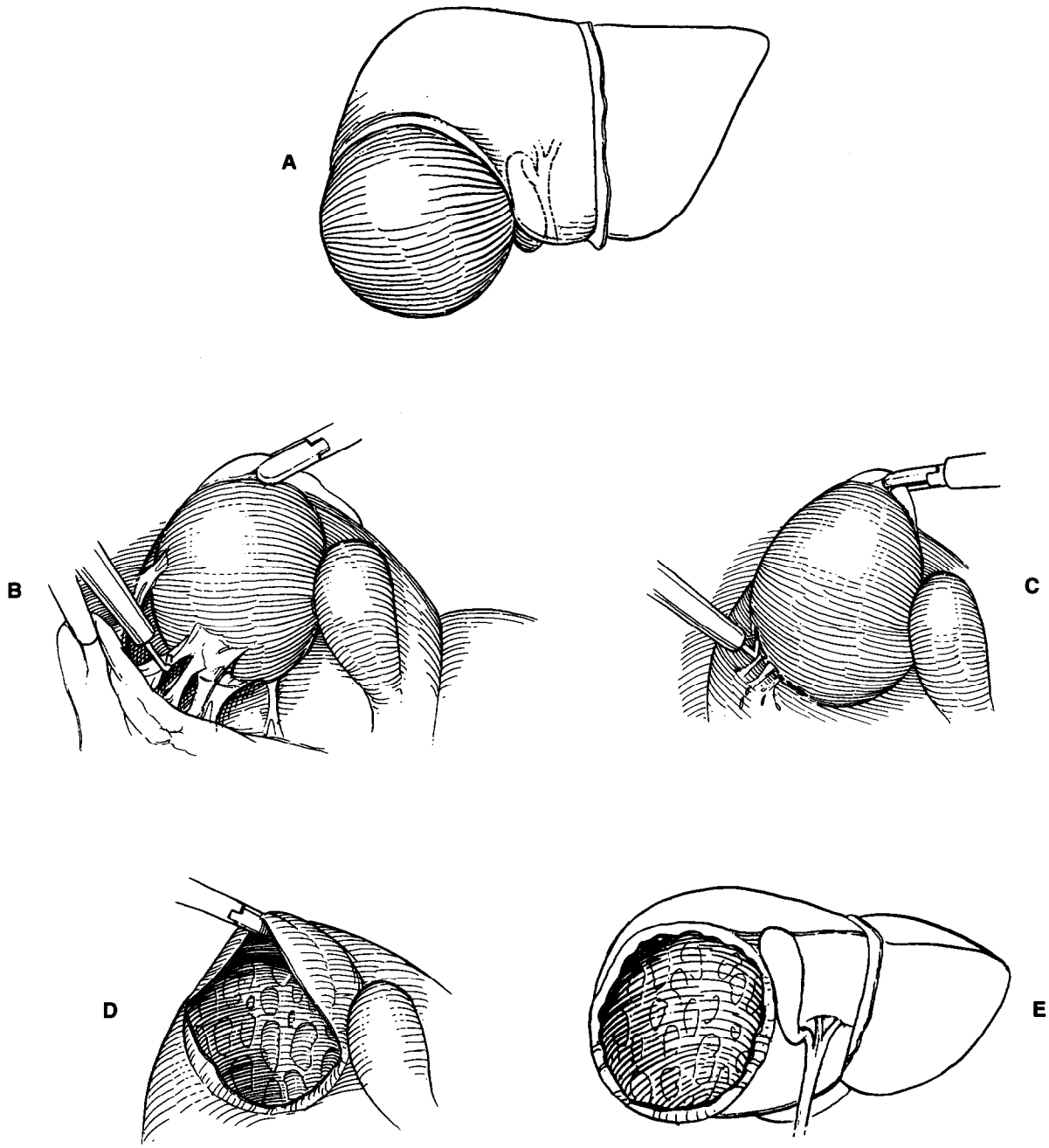

Fig. 1. A, Large simple liver cyst. **B,** All adhesions are taken down before opening the cyst. **C,** The cyst wall–hepatic parenchyma margin is scored before opening the cyst. **D,** The cyst cavity is inspected and a biospy specimen obtained if desired. **E,** All exposed cyst wall is excised.

it is essential to fill this cavity with omentum and to secure it in place (Fig. 2). There is no ideal instrument for this latter maneuver, but the standard medium-large metal clips have been adequate. The staples designed for use in laparoscopic hernia repair are unsatisfactory because they cut through the soft liver tissue and pull out. Sutures would undoubtedly work well, but they are more time consuming to place than clips.

Thus the fifth step is to make sure that the residual cavity is filled with viscera or omentum.

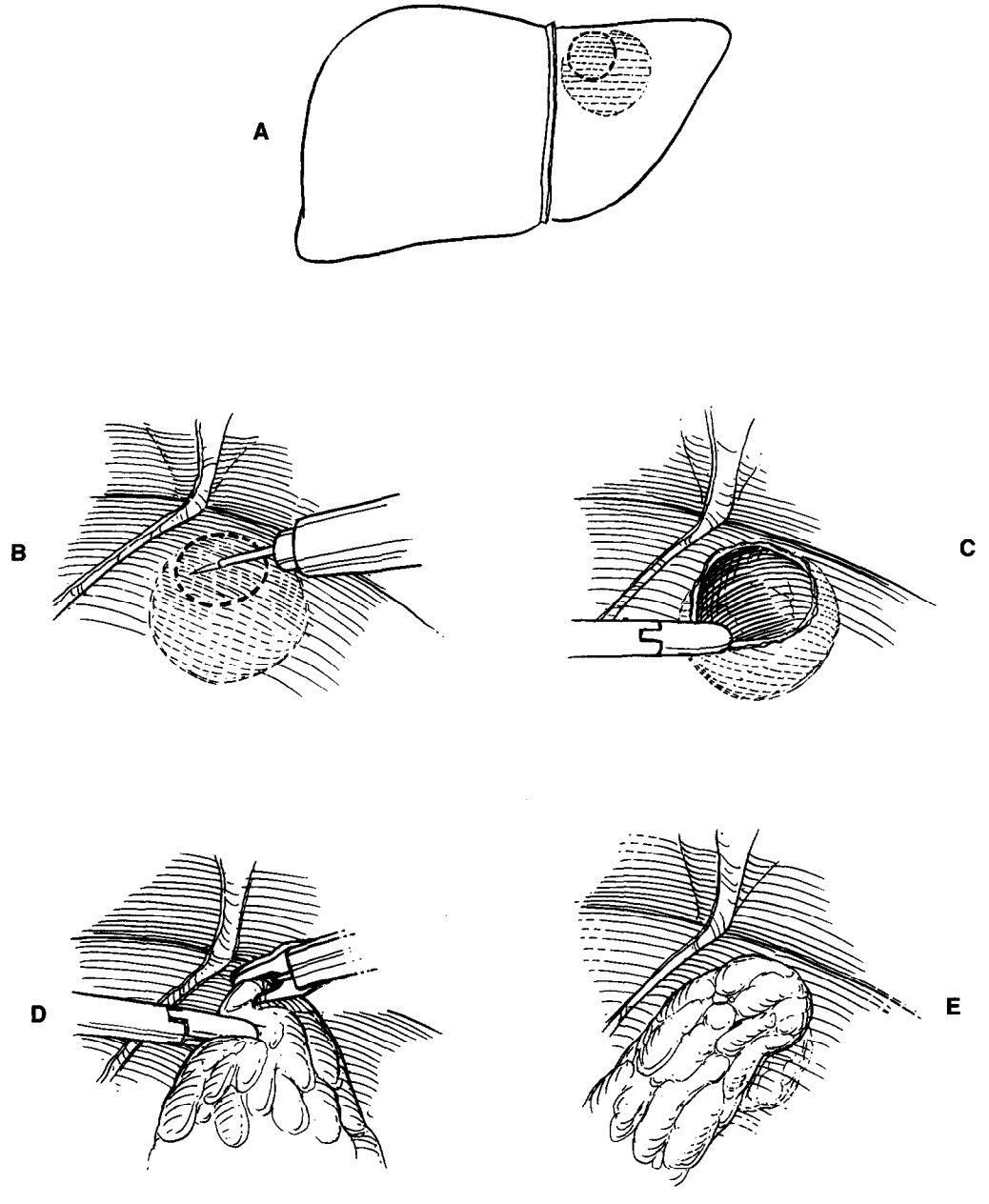

Fig. 2. A, Intraparenchymal cyst. **B,** Adhesions are divided and the cyst is identified by visual appearance, ballottment with forceps, or needle aspiration. **C,** All exposed cyst wall is excised. **D** and **E,** The remaining cavity is filled with omentum.

RESULTS

The operating time for the 16 cases that consisted exclusively of liver cyst excision averaged 150 minutes (range 90 to 253 minutes). In the two patients undergoing concurrent cholecystectomy, the operations lasted 130 and 177 minutes, respectively. The combined liver cyst excision and fundoplication took 375 minutes.

Postoperative hospital stay averaged 2.5 days (range 1 to 8 days). No patient was lost to follow-up. Follow-up CT scans were obtained 6 months postoperatively in the first 10 patients who remained asymptomatic, but when they all demonstrated permanent resolution of the cysts (Figs. 3 and 4), this practice was discontinued.

Sixteen of the 17 patients who did not have polycystic disease have remained symptom free, with no evidence of recurrence at 3 to 68 months (average 30 months). There were three complications (18%) and one treatment failure (6%). The complications included a trocar injury to the liver, which required a small subcostal incision to control bleeding; a postoperative bile leak from a small bile duct in the cut margin of the cyst, which required percutaneous drainage of a small subhepatic collection of bile and endoscopic placement of a temporary stent in the bile duct; and a trocar site hernia 2 years postoperatively. In each of the patients who was thought possibly to have a septated neoplastic cyst, the lesion turned out to be two

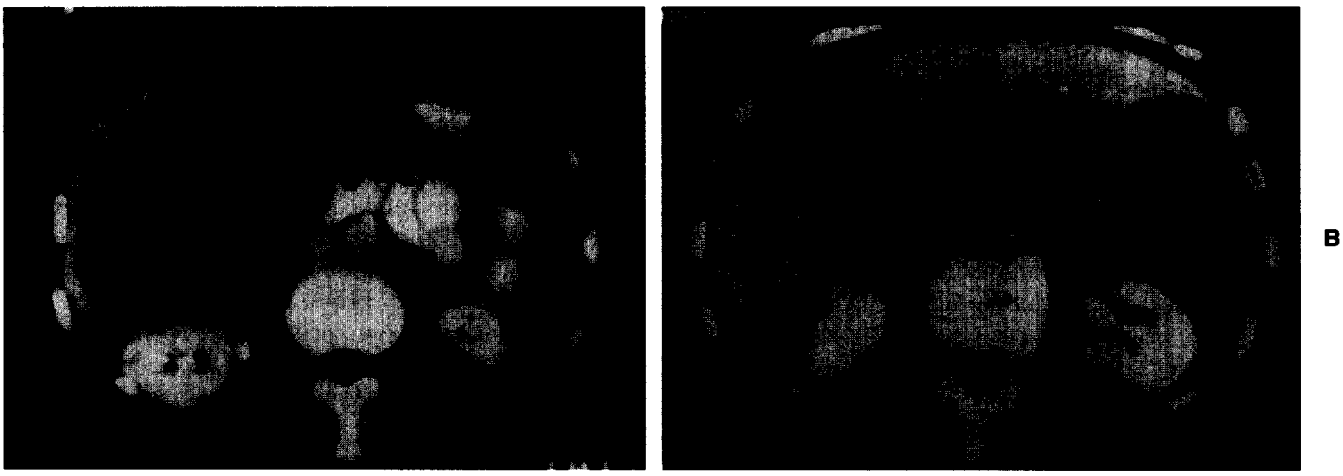

Fig. 3. A, Large simple cyst before surgery. **B,** Appearance in the same patient 6 months after surgery, demonstrating permanent resolution of the cyst.

Fig. 4. A, Intraparenchymal simple cyst. **B,** Appearance in the same patient 6 months after surgery, demonstrating the omentum-filled cavity.

juxtaposed simple cysts, the contact surfaces of which gave the appearance on CT scans of a septum within a single cyst. We encountered no neoplastic liver cysts during the period of this study.

The first patient was the only treatment failure. This woman, who had undergone a cholecystectomy in the distant past, had two large cysts in the right lobe of the liver. Adequate exposure of the lesions proved difficult and the excision was suboptimal. Portions of the cysts were removed, but symptoms returned and x-ray films showed that the cysts had recurred. Another more thorough operation was performed through a laparotomy, and the patient has been symptom free for 3 years. Both patients with polycystic liver disease have persistent cysts and recurrent symptoms.

DISCUSSION

Benign liver cysts occur in approximately 5% of the general population, but no more than 5% of these lesions cause symptoms.[3] The principal clinical manifestations are abdominal pain, abdominal mass, and early satiety. Less common findings include shortness of breath, bloating, rupture, torsion, bleeding, infection, and biliary obstruction.[3] Once they become symptomatic, liver cysts should usually be treated.

Differentiating between simple hepatic cysts, on the one hand, and neoplastic and echinococcal cysts, on the other, is usually possible based on preoperative findings.[6-8] Although they may resemble simple cysts on CT scans, neoplastic cysts (e.g., cystadenoma) often demonstrate a buildup of tissue along one wall, hypervascularity of the cyst wall, or internal septation. An appearance of septation, the most common finding, can also result from two simple cysts that are in contact with each other. Although neoplastic cysts that are difficult to distinguish from simple cysts are quite uncommon, we assume at the start of an operation that any solitary cyst could be neoplastic, so even in the absence of preoperative clues, we routinely look for neoplastic tissue within the interior of the lesion early in the operation. If a neoplastic cyst is diagnosed at this point, the abdomen should be opened and the lesion excised. Finally, the surgeon is at no disadvantage in making this distinction during laparoscopy compared to open surgery.

Echinococcal cysts have even less chance of causing confusion. In adult patients, CT scans of echinococcal cysts rarely show the same type of homogeneous fluid-filled interior as is seen with simple cysts.[8] With few exceptions the lumen of an echinococcal cyst in adults contains daughter cysts and considerable amounts of solid debris, and the picture is quite different from that of a simple hepatic cyst. Furthermore, the patient will almost always have a history of having spent a long period, usually during childhood, in an endemic area—usually in an environment where sheep farming was prevalent. We encountered no cases during the period of this study in which a preoperative diagnosis of simple cyst was changed to one of these alternatives, either during surgery or after the specimen had been examined microscopically.

Although not life-threatening, some simple cysts of the liver are huge and profoundly affect the patient's quality of life. Primary care physicians and gastroenterologists often assume, however, that surgical treatment must involve a lengthy, risky procedure that includes substantial blood loss. Consequently either no treatment or aspiration may be recommended, particularly in elderly patients. These assumptions, which stem from the striking appearance of these lesions on x-ray films, are incorrect because surgical therapy is well tolerated and blood transfusions are rarely necessary (there were none in our patients).

Therefore the main points of this report should be kept in mind. Unroofing is a definitive and safe treatment for liver cysts. With few exceptions the operation can be performed laparoscopically, so the patient obtains the desired benefits of the laparoscopic approach—minimal discomfort, shortened hospital stay, and rapid resumption of normal activities. The success of the laparoscopic procedure depends on strict adherence to specific technical precepts.

Our experience demonstrates that with the type of laparoscopic operation performed in these patients, the desired clinical objectives can be achieved. The only unsatisfactory result among those without polycystic disease occurred in the first patient, where the operation did not achieve the technical goal of obliterating the cyst cavity by the combined effects of excising the wall and filling the residual space with viscera. The greater the amount of cyst wall that is removed, the smaller the remaining cavity and the less arduous the filling step.

A few words of caution are in order regarding alternative treatments. Complete excision of the cyst, which is an operation of considerably greater magnitude and one that is poorly tolerated by elderly patients, is unnecessary.[3] For similar reasons partial hepatectomy is also considered excessive. Roux-en-Y drainage was once thought to be indicated for cysts with a connection to the bile duct, but biliary connections are either very rare or nonexistent, and complications have been frequent in the few reported instances in which this procedure was attempted.[9] Although communications with the bile duct are seen in echinococcal disease, we have never encountered this with a simple hepatic cyst, even in instances where the cyst fluid was pigmented.

Aspiration alone cannot succeed because the cyst refills promptly. Aspiration combined with catheter drainage has a similar outcome after the catheter is removed, and since the catheter often incompletely drains the lesion, cyst infection is a potential complication. Aspiration and sclerotherapy is a more sensible treatment but its results are also poor. For the sclerotherapy to be successful, the cyst must be thoroughly collapsed by the aspiration so that the cyst walls come together. With large, thick-walled cysts the type of collapse that is physically possible more closely resembles what takes place when air is let out of a basketball rather than a balloon; that is, the wall develops folds that contain residual spaces. Before being referred to us, one of our patients underwent aspiration and sclerotherapy of a large (25 cm) cyst, which was followed by severe pain, hypotension, and a week in the hospital—with no permanent effect on the cyst.

We were dissatisfied with the technical and clinical results in the patients with polycystic liver disease and would be hesitant to recommend laparoscopic treatment of this condition, even though we believe there is a role for unroofing of cysts in some cases.[10-13] The difficulty here is the presence of fairly large cysts on the posterior aspect of the liver, an area that is awkward to expose laparoscopically. The laparoscopic operation can be used to treat anterior and lateral cysts, but posterior cysts cannot be managed as effectively with this approach. Our current belief is that the outcome in polycystic disease depends so heavily on achieving a thorough decompression of all cysts larger than 6 to 7 cm, that if surgery is indicated, the procedure should be a laparotomy.

CONCLUSION

The key elements of treatment of simple cysts of the liver are good exposure, wide excision of the cyst wall, and omental packing to prevent reapposition of the cyst wall. These objectives can usually be achieved laparoscopically, which means that surgical therapy is well tolerated and predictably successful.

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Discussion

Dr. W. Meyers (Worcester, Mass.). My main question really relates to the pathology. Having treated a number of liver cysts laparoscopically, we now believe there are more true neoplasms among patients with large liver cysts than was formerly appreciated. We have used ultrasound in an effort to identify the neoplastic cysts, and for these cysts we have performed liver resections laparoscopically.

What do you recommend in terms of where this type of procedure should be performed? Because it appears to be so easy for a laparoscopic surgeon to simply "pop" a liver cyst, it would be tempting for surgeons who see few such lesions to do so. Is that what you recommend?

Dr. P. Hansen. In the past we have usually been able to identify neoplastic cysts on the basis of preoperative findings. The three lesions that we did have some question about turned out to be simple cysts that were lying adjacent to each other. Once we opened and decompressed the cyst cavity, we inspected the inside for signs of neoplastic disease.

We believe that a number of relatively uncommon laparoscopic procedures are best confined to centers where there is a high level of expertise. Although this is a fairly straightforward operation, we encountered one patient whose laparoscopic operation had been performed elsewhere and proved inadequate. That fits your description. Still, we

have enumerated the essential steps of the operation, so others will know what is required for a successful outcome.

Dr. J. Svanvik (Linkoping, Sweden). I wonder about the extent of the follow-up and the recurrence rate. Did you check all patients with ultrasound or CT scans?

Dr. Hansen. In our first 10 asymptomatic patients, CT scans were obtained 6 months postoperatively. There were no recurrences among those patients so we subsequently discontinued routine postoperative imaging because we considered it unnecessary or, at the very least, an unjustified expense. We continue to follow the patients clinically.

Dr. Svanvik. I am still concerned about recurrence because liver cysts are lined with epithelium that resembles biliary epithelium. I believe the epithelium has to be destroyed to avoid recurrence. We have been using the argon beam coagulator to coagulate the epithelial lining in simple liver cysts that we have treated. I suspect there is a risk of late recurrence if the epithelium is left intact.

Dr. Hansen. That has not been our experience thus far, although our follow-up has only lasted a few years. The lining of simple cysts consists of cuboidal epithelium. We expect the residual cyst wall to continue to secrete a small amount of fluid, but it is readily reabsorbed by the peritoneum. The key is to make sure that this residual secretion cannot become compartmentalized.

Dr. J. Hunter (Atlanta, Ga.). I agree with your comments regarding polycystic liver disease. Another technical problem in that condition is that deep cysts often have large vessels in their walls, which have been compressed by the pneumoperitoneum. There is a risk that one of these vessels could be cut, and if bleeding did occur, it could be quite difficult to control.

Did you notice any bile staining of the cyst fluid, and if so did you manage those cysts any differently? Second, did you find anything of significance on histologic examination of the specimens? We discovered a couple of unsuspected biliary cystadenomas; one was subsequently resected and the other one is being followed. Third, did you ever find it necessary to "pedicalize" the omentum to obtain a sufficient amount to fill the cyst?

Dr. Hansen. An occasional cyst did contain bile-stained fluid, but it was not treated any differently from the others. There were no abdominal bile collections postoperatively, except for the patient who had leakage from a small duct in the cut wall of the cyst. This particular patient did not have bile-stained fluid in her cyst. Mobilizing the omentum may be difficult in patients who have had prior abdominal operations. In one patient we had to expend a moderate amount of extra effort to obtain an adequate tongue of omentum that would reach and fill a cyst high on the surface of the liver, but the end result was good.

Dr. B. Launois (Rennes, France). I see that one of your complications was a bile leak; we too have encountered this type of problem. Have you tried using an intraoperative technique that offers more systematic visualization of the biliary tree, for example, blue dye, to see whether there was a leak in the bottom or on the edge of the cyst, especially in patients with symptomatic cysts?

Dr. Hansen. Our practice has been to incise the cyst wall 0.5 to 1.0 cm from its border with the parenchyma. We have not used anything to test for a bile leak, but if there had been an accurate method, it might have been helpful in our one patient who required percutaneous placement of a drain postoperatively.

Dr. A. Warshaw (Boston, Mass.). Most of your patients presented with pain, which emphasizes that these cysts really can cause pain, a fact that has been disputed. With small cysts, where the association with the symptoms may not be so clear, would you recommend or did you use preoperative aspiration to see if the symptoms could be relieved before deciding to operate?

Dr. Hansen. No, that has not been our practice. If we were confident that the clinical response to aspiration could truly predict the results of surgery, that would be worthwhile. Although the idea is plausible, we are not aware of any data that prove it. For the type of cysts you are referring to—intermediate-sized lesions—establishing a relationship between the lesion and the symptoms has largely been a diagnosis of exclusion. Although this approach seems less satisfying than having more positive evidence, it has been successful.

Dr. Launois. We were disappointed with the results of laparoscopic treatment of liver cysts because most of these cysts recurred. For this reason we now use percutaneous puncture with injection of ethanol, and we have achieved more satisfactory results.

Dr. Hansen. Injection of ethanol into large cysts, especially thick-walled cysts, is often unsuccessful, as was seen in a number of our patients before they were referred to us for surgery. The success of laparoscopic therapy depends on whether the principles outlined in this presentation are followed. If they are, the procedure should be completed quickly and it should be well tolerated, and the therapy should be definitive.

Beneficial Effect of Enteral Glycine in Intestinal Ischemia/Reperfusion Injury

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It has been shown in vitro that glycine can protect renal tubules and hepatocytes from hypoxic injury. Glycine also attenuates ischemic injury in transplanted livers. The present study investigated the effect of enteral glycine in a murine model of ischemia/reperfusion injury of the small intestine. Mice (n = 12 in each group) were randomized to receive two gastric gavages of either a 20% glycine (Gly) or 23% balanced amino acid (AA) solution with a 6-hour interval between each gavage. One hour after the second gavage, mice underwent superior mesenteric artery clamping for 20 minutes. The clamp was then released for reperfusion. Another group of mice (n = 8) underwent a sham operation and served as additional control animals. Six hours after ischemia/reperfusion, the mice were killed in order to assess the intestinal injury (intestinal protein content, mucosal disaccharidase activity, and intestinal histologic findings) and the systemic consequences (bacterial translocation, serum interleukin-6, and lung myeloperoxidase activity). A second set of mice (n = 55) underwent identical gavages and ischemia/reperfusion and they were followed for survival. Compared to AA, enteral glycine administered prior to intestinal ischemia/reperfusion injury significantly preserved mucosal indices and intestinal histology and decreased lung myeloperoxidase activity. Survival was also significantly increased in animals receiving glycine compared to AA control mice. These data suggest that enteral glycine supplementation may be beneficial in attenuating intestinal ischemia/reperfusion injury and its related systemic effects in this murine model. (J GASTROINTEST SURG 1997;1:61-68.)

Several in vitro studies have demonstrated that supplementation of glycine in the culture media can protect renal tubules,[1-4] hepatocytes,[5-7] and endothelial cells[8] from hypoxia-induced cell injury. When administered to subjects in a liver transplantation animal model, glycine significantly decreased hepatocellular injury of the transplanted liver and improved host survival.[9] Glycine has also been shown to minimize ischemic injury in a low-flow, reflow liver perfusion animal model.[10] These results suggest that glycine can significantly attenuate hypoxia-induced tissue injuries.

Intestinal ischemia/reperfusion (I/R) injury is a clinical event with a high rate of complications in surgical and trauma patients. Intestinal blood flow is seriously reduced not only by occlusion of mesenteric vessels but also during shock associated with sepsis or hemorrhage. Among the internal organs, the intestine is probably the most sensitive to I/R injury. Damage at the mucosal layer allows enhanced uptake of bacteria and endotoxin from the intestinal lumen to systemic circulation.[11] In addition, the intestine is the richest source of xanthine oxidase,[12] which is the initial source of free radicals that can cause further tissue damage.[13] Intestinal ischemia/reperfusion injury also causes pulmonary infiltration of neutrophils, which contributes to the development of adult respiratory distress syndrome.

The aim of this study was to determine, using a murine model, whether enteral administration of glycine could protect intestinal tissues from I/R-induced injury of the small intestine and attenuate the systemic effects of this injury.

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MATERIAL AND METHODS

Animals

Six- to 8-week-old Swiss-Webster CFW female mice (body weight 19 to 22 g) were purchased from Charles River Laboratories, Wilmington, Mass. Animals were housed in plastic cages, allowed free access to food and water, and acclimatized for at least 4 days in the animal facility before experiments were begun. The room was maintained on 12-hour cycles of light and dark. The animal facility has been approved by the American Association for Accreditation of Laboratory Animal Care, and the animal protocols were approved by the Institutional Animal Care and Use Committee.

Experimental Design

Twenty-four mice were randomized to receive two gavages of either a 20% glycine solution (Gly) (n = 12) or an isonitrogenous 23% balanced amino acid mixture (AA) (n = 12) separated by 6-hour intervals. One hour after the second gavage, animals were anesthetized with methoxyflurane (Pitman-Moore, Inc., Mundelein, Ill.) and a 1 cm midline laparotomy was performed. The superior mesenteric artery and vein were exposed. Intestinal ischemia was produced by placing a curved vascular clamp (Fine Science Tools, Inc., Foster City, Calif.) around the superior mesenteric vessels for 20 minutes. Intestinal ischemia was verified by the observation of a change in the color of the intestine and cessation of arterial flow in the mesentery. The clamp was then released for reperfusion, and 1 ml of saline solution was injected subcutaneously in the flank for fluid resuscitation. Reperfusion of the small intestine was confirmed by the prompt return of normal intestinal color. The peritoneal cavity was then closed with 3-0 silk sutures. Another group of mice (n = 8) received gavages of 0.2 ml saline solution and underwent anesthesia, laparotomy, and manipulation of the intestine to serve as sham operation control subjects. Animals were killed by carbon dioxide asphyxiation at 6 hours following surgery. Samples of small intestine, mesenteric lymph nodes, spleen, blood, and lung were collected and assayed as described below. In the second set of animals (Gly, n = 28; AA, n = 22; and Sham, n = 5), the same intestinal I/R procedures were carried out. Animals were then monitored for 72 hours and the percentage of surviving animals was calculated.

To determine whether appropriate serum concentrations of glycine were generated by the gastric gavages, the following study was performed. Six groups of mice (n = 3 per group) were fasted with free access to water for 12 hours and then given a 0.2 ml gavage of either a 20% Gly solution or an isonitrogenous 23% balanced AA mixture. Mice were killed and blood was obtained by heart puncture at 1, 3, and 6 hours after the gavage. Serum samples were kept frozen at −20° C until glycine concentrations were determined by means of high-performance liquid chromatography (Waters Chromatography, Marlborough, Mass.) using the OPA method.[14]

A 12 cm segment of small intestine from the ligament of Treitz was promptly isolated and freed of its mesenteric fat. Under a fixed tension (5 g), a 5 cm segment was obtained for intestinal indices and enzymatic analysis. The remaining 5 cm segment was turned inside out, rinsed in ice-cold saline solution, blotted dry, and weighed. The mucosa was completely scraped away with a glass slide, weighed, and stored at −70° C until assayed. A 1 cm segment of intestine obtained from the distal portion of the jejunum was submitted for standard histologic examination.

Analysis of Mucosal Protein and Enzymatic Activities of the Jejunum

Mucosal protein (%; mg/mg mucosa^{-1}) was determined with the use of bicinchoninic acid protein assay reagent (Pierce Chemical Co., Rockford, Ill.).[15] To study villous enzymatic function, mucosal disaccharidase activities (nmol/min^{-1}/mg protein^{-1}) were assayed using the method of Nesser and Dahlqvist[16] with sucrose and maltose as substrates.

Morphologic Examination

Intestinal samples were fixed in 10% formalin and then subjected to standard sectioning and staining with hematoxylin and eosin. Slides were coded and examined by a pathologist (Hai T. Ngugen, V.M.D., Cornell University Medical College, New York, N.Y.)

Table I. Histologic grading scale

Grade	Description
0	Normal villi
1	Apical villous edema
2	Mild fusion of the villi
3	Prominent fusion of villi
4	Apical villous sloughing (ulceration) involving <1/3 villous height
5	Apical villous sloughing involving 1/3 to 2/3 villous height
6	Apical villous sloughing (ulceration) involving >2/3 villous height
7	Focal necrosis of muscularis propria
8	Transmural necrosis

who was blinded to the code. Specimens were graded according to the scale shown in Table I as described in a previous report.[17]

Samples of mesenteric lymph nodes, spleen, and liver were obtained in an aseptic fashion, weighed, and each was placed in a sterile tube containing 1 ml of phosphate-buffered saline (PBS). The procedures for tissue bacterial cultures have been described previously.[18] Tissues were homogenized in PBS. Serial dilutions were carried out and 0.2 ml of each dilution was plated onto blood agar (Difco Laboratories, Inc., Detroit, Mich.) and incubated at 37° C for 48 hours. A positive culture was defined as more than 10 colony-forming units per plate.

The right lobe of the lung was isolated and washed thoroughly with cold (4° C) saline solution. After the specimen was blotted dry, lung wet weight was measured and the tissue was stored at −70° C until myeloperoxidase activities were assayed.

Determination of Myeloperoxidase Activity

Myeloperoxidase activity was assessed as an index of neutrophil infiltration. Samples of lung or intestine were homogenized in 4 ml of 50 mmol/L potassium phosphate buffer, pH 6.0, and centrifuged at 16,000 *g*, 4° C, for 30 minutes. Pellets were resuspended in 1.5 ml potassium phosphate buffer containing 0.5 g/dl exadecyltrimethylammonium bromide and sonicated for 90 seconds on ice. Samples were incubated at 60° C for 120 minutes and centrifuged at 35,000 *g*, 4° C, for 30 minutes. The supernate, 10 µl, were added to 190 µl of 50 mmol/L potassium phosphate buffer, pH 6.0, containing 0.167 mg/ml O-dianisidine with 0.0005% hydrogen peroxide, and absorbances at 450 nm were measured (UV maxKinetic Microplate Reader, Molecular Devices Corp., Menlo Park, Calif.). Values were calculated as change per minute in absorbance between 1 and 3 minutes per milligram of tissue.

Blood was obtained by heart puncture. Serum was separated and kept frozen at −20° C until interleukin-6 levels were measured by enzyme-linked immunosorbent assay as previously described.[19]

Statistical Analysis

All results are expressed as mean ± standard error of the mean, and the data were analyzed using a statistical computer program (InStat, version 2.00, GraphPad Software, San Diego, Calif.) on a Macintosh computer system. Analysis of variance was employed followed by Newman-Keuls test to identify the differences between individual groups. The difference in survival between groups was compared by means of 2 × 2 contingency test (Fisher's exact test). A P value of <0.05 was considered significant.

RESULTS

Serum Concentrations of Glycine After Gavage

Serum concentrations of glycine in mice gavaged with 0.2 ml of 20% glycine solution were increased approximately twofold at 1 and 3 hours compared to control mice gavaged with a balanced AA solution (Fig. 1). However, by 6 hours after the gavage there was no significant difference between the Gly and AA groups.

Intestinal Indices and Histologic Findings

Results of intestinal mucosal protein content and brush border membrane enzyme activities (disaccharidase: sucrase and maltase) are shown in Table II. Compared to the Sham group, at 6 hours after I/R injury the mucosal protein content and brush border membrane enzyme activity were significantly reduced in the AA group. However, in the Gly group there was no significant decrease in any of these markers.

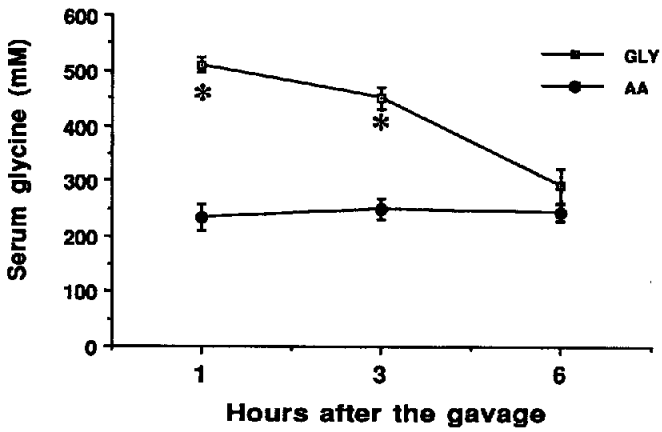

Fig. 1. Mean serum concentrations of glycine in mice receiving a gavage (0.2 ml each) of 20% glycine (Gly) solution were significantly increased at 1 and 3 hours after the gavage as compared to mice receiving a balanced AA solution (*$P > 0.05$).

Table II. Intestinal mucosal indices and enzymatic activity of the jejunum 6 hours after intestinal I/R injury in mice

	Sham (n = 8)	Gly (n = 12)	AA (n = 12)
Protein (%:mg/100 mg tissue)	20.4 ± 1.8	21.3 ± 1.0	16.8 ± 1.1*
Disaccharidase (nmol/min/mg protein)			
Sucrase	23.8 ± 1.2	24.1 ± 1.0	19.6 ± 1.4*
Maltase	124.6 ± 9.4	123.8 ± 6.2	91.75 ± 11*

Values are mean ± SEM.
*$P < 0.05$ vs. Sham and Gly groups by analysis of variance.

Histologic examination showed that the normal tissue structures of intestinal mucosa were generally preserved 6 hours after I/R injury. However, villous edema, prominent villous fusion, and apical villous sloughing involving the tip of the villus were observed in the AA group (grade 3 to 4). In the Gly group there was only slight edema and mild fusion of the villi (grade 1 to 2). In addition, it was noted that many of the mucosal crypts contained necrotic cells. Therefore 50 crypts per specimen were randomly counted and the percentages of crypts with cellular necrosis were calculated. The Gly group had a significantly lower percentage of necrotic crypts compared to the AA group (Fig. 2; Gly 25% ± 2% vs. AA 57% ± 7%, $P < 0.05$).

Bacterial Translocation

The results of bacterial culture of mesenteric lymph nodes, spleen, and liver 6 hours after I/R injury are shown in Fig. 3. There were no positive cultures found in the Sham group. Six hours after intestinal I/R injury, the percentage of positive bacterial cultures of mesenteric lymph nodes, spleen, and liver were relative low. The Gly group did have a lower incidence of positive cultures of mesenteric lymph nodes and spleen than the AA group, but this was not statistically significant.

Interleukin-6 and Lung Myeloperoxidase

Serum interleukin-6 levels were undetectable in the Sham group. There were elevated levels of serum interleukin-6 six hours after small intestinal I/R injury. The group given enteral glycine had a lower mean serum level of interleukin-6 (13.0 ± 3.0 ng/ml) compared to the AA group (18.4 ± 2.4 ng/ml), but the difference was not statistically significant.

Although the mean wet lung weight was elevated in the AA group and remained normal in the Gly group, the mean wet lung weights were not statistically different among the three groups (Gly = 99.7 ± 3.1 mg; AA = 110.3 ± 3.9 mg; and Sham = 95.1 ± 12.8 mg). Mean lung myeloperoxidase activity at 6 hours after I/R injury was significantly increased in comparison to the Sham group (Fig. 4). The supplementation of enteral glycine significantly reduced the mean lung myeloperoxidase activity at 6 hours after I/R compared to values in control mice receiving AA ($P < 0.05$).

Survival

Among the mice given enteral AA, survival rates were approximately 91% and 60% at 6 hours and 24 hours, respectively, after reperfusion. Survival was significantly improved in mice receiving enteral glycine after I/R injury compared to the AA control group (Fig. 5; $P < 0.05$).

DISCUSSION

Many studies have characterized the physiologic and pathologic events of small intestinal I/R injury.[20-24] Tissue edema can be observed shortly after I/R injury of the small intestine.[22] As the injury progresses, apical villous enterocytes degenerate and slough, resulting in diminished brush border membrane enzymes. Focal mucosal necrosis then occurs. These tissue injuries result in impairment of the mucosal barrier leading to intestinal bacterial or endotoxin translocation.[11] Pulmonary neutrophil infiltration[23,24] and adult respiratory distress syndrome can also develop. Myeloperoxidase is one of the main enzymes in neutrophil granules, and tissue myeloperoxidase activity is a widely used marker for the neutrophil infiltration. The mechanisms of I/R injury–induced pulmonary neutrophil infiltration are not fully understood. There is evidence to suggest that neutrophils are activated by the ischemic intestine during reperfusion, and a number of cytokines released by injured tissue may facilitate this activation. Although small intestinal I/R injury–induced neutrophil infiltration of the lungs can occur without bacteria/endotoxin involvement,[25]

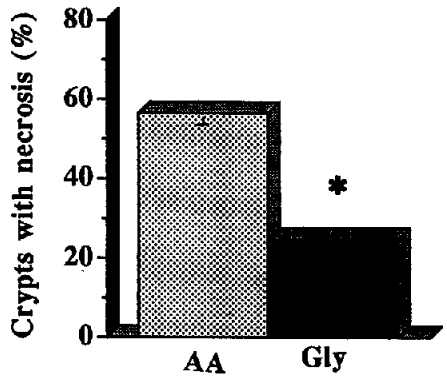

Fig. 2. Intestinal histologic findings 6 hours after small intestinal I/R injury. Fifty crypts per histologic specimen were randomly counted and the percentages of crypts with cell necrosis were calculated. The Gly group had a significantly lower percentage of necrotic crypts compared to the AA group (*$P < 0.05$).

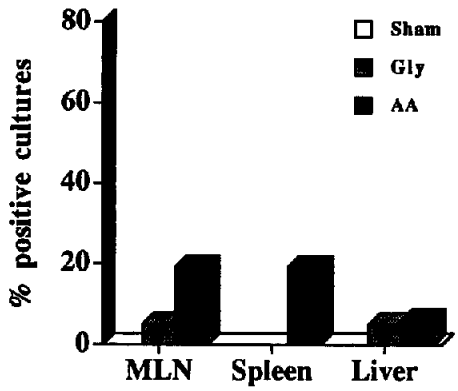

Fig. 3. Bacterial translocation 6 hours after small intestinal I/R injury. Bacterial cultures of mesentric lymph nodes, spleen, and liver were positive although the rates were relatively low. The incidence of positive bacterial cultures of mesenteric lymph nodes and spleen in the Gly group was lower than that in the AA group, but the difference was not statistically significant ($P > 0.05$).

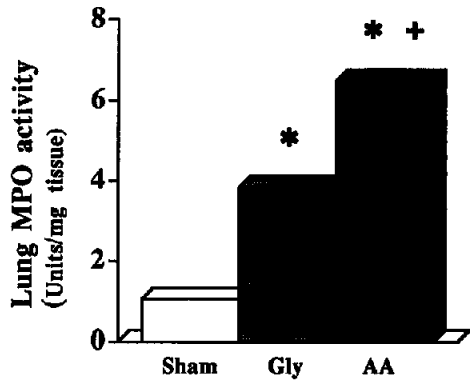

Fig. 4. Lung myeloperoxidase (MPO) activity 6 hours after small intestinal I/R injury. Mean lung MPO activity in mice subjected to I/R injury was significantly elevated compared to values in the Sham group. Mice in the Gly group had significantly decreased mean MPO activity compared to mice in the AA group (*$P > 0.05$ vs. Sham; †$P > 0.05$ vs. Gly; analysis of variance).

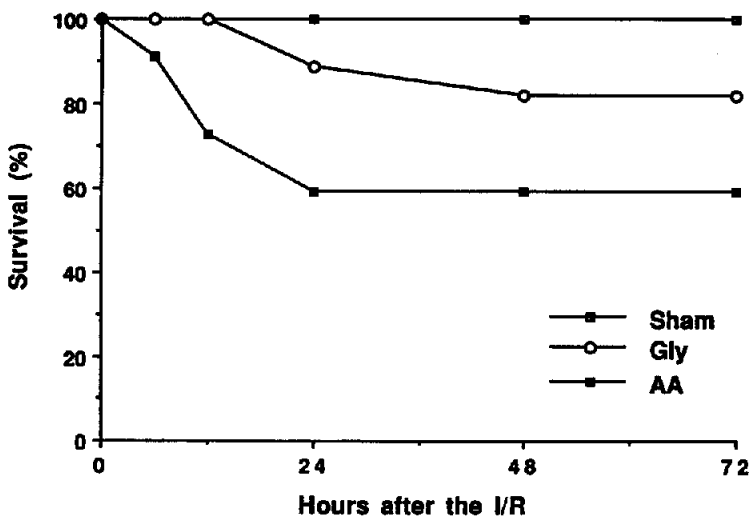

Fig. 5. Survival after small intestinal I/R injury. Survival after I/R injury was significantly improved in the Gly group compared to the AA group ($P > 0.05$, Gly vs. AA).

translocated bacteria or endotoxin can certainly accelerate neutrophil activation.

Glycine is the simplest amino acid but it has considerable physiologic significance. It is a basic element in creatine and glutathione synthesis. It can be metabolized to pyruvate, a key molecule in glucose metabolism. Glycine is also a main precursor of purine and porphyrin synthesis. Previous reports have demonstrated that glycine can protect cells and tissues of the kidney and liver[5,7,10] from ischemic and hypoxic injury in a dose-dependent manner both in vitro[5,7] and in vivo.[10] Because intestinal I/R injury is a complication of surgery and/or trauma and can result in severe systemic consequences such as adult respiratory distress syndrome, we investigated the effect of enteral glycine in a murine model of small intestinal I/R injury. Our hypothesis was that enteral glycine could attenuate the intestinal tissue damage during I/R injury of the small intestine, thereby preserving the intestinal barrier to microbes and endotoxin. In addition, detrimental systemic effects such as pulmonary injury caused by neutrophil infiltration would also be diminished by the administration of enteral glycine.

Glycine is one of the most absorbable amino acids.[26] Enteral absorption of glycine through the brush border membrane is thought to be a combination of simple diffusion, facilitated diffusion, and active transport,[27] the latter by two major Na^+-dependent transport systems (system GLY and ASC)[26] for glycine in the enterocyte. The data in this study indicate that enteral feeding of 0.2 ml of a 20% glycine solution can cause a significant increase (approximately twofold) in the serum glycine level. Thus this dose of glycine was used throughout.

This study demonstrates for the first time that enteral glycine has a beneficial effect on the small intestine after I/R injury of this organ in mice. In this model 20 minutes of small intestinal I/R injury causes a significant decrease in the intestinal protein content and decreased brush border membrane enzymes. The incidence of bacterial growth in the spleen was increased and pulmonary myeloperoxidase was significantly elevated after I/R injury. Furthermore, these events were associated with a 40% mortality rate in this model. Glycine supplementation was demonstrated to diminish intestinal damage after I/R injury in comparison to the AA control group. Enteral glycine appeared to preserve the mucosal protein content and brush border membrane enzyme activities at near-normal levels compared to values in mice in the AA control group. In addition, glycine significantly attenuated the increase in the pulmonary myeloperoxidase activity associated with I/R injury. Finally, enteral glycine resulted in improved survival after I/R injury as compared to AA control mice.

The mechanism of the protective effect of glycine in the intestine is not yet clear, but there are suggestions based on other studies. Weinberg et al.[3] reported that glycine blocked the increase in cytosolic free calcium of Kupffer cells in response to activating stimuli. There is evidence indicating that glycine may affect calcium flux by decreasing the efficiency of chloride channels in the cell membrane.[3] This would interfere with chloride-calcium exchange resulting in insufficient calcium influx. Changes in cytosolic free calcium levels are ubiquitous intracellular signals associated with cellular activation.[28] Uncontrolled increases in cytosolic free calcium, therefore, might mediate excessive activation resulting in the formation of membrane blebs and cell death,[29] a possible mechanism of I/R-induced injury. Nichols et al.[7] reported that glycine inhibits nonlysosomal calcium-dependent proteolysis, which is stimulated by calcium influx. Finally, glycine supplementation may directly decrease free radical production in ischemia by inhibiting cellular lipid peroxidase activity and/or it may inhibit immune responses by blocking intracellular signaling through reduction of calcium influx.

In summary, we have demonstrated that mean serum concentrations of glycine were increased after enteral supplementation. Enteral glycine attenuated I/R-induced intestinal injury and pulmonary neutrophil infiltration after intestinal I/R in mice. This was further associated with improved host survival after this injury.

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Discussion

Dr. B. Schirmer (Charlottesville, Va.). Have you tried giving the glycine intravenously. Is an oral route of administration specifically required to achieve these benefits?

Dr. J. Shou. We are currently trying intravenous injections. The problem is that after intravenous injection, there is a very high glycine level, but it clears quickly. Within an hour glycine appeared in the urine. Now we are trying to change to a rat model in which we can continuously perfuse glycine.

Dr. Schirmer. Another obvious amino acid to study would be glutamine, which is the preferred fuel of the enterocyte. Have you tried this same study with glutamine?

Dr. Shou. We have not yet tried glutamine, but we have tried a number of other amino acids that have a similar molecular structure.

Dr. L. Cicalese (Pittsburgh, Pa.). You are using total protein content as an index of mucosal injury but you also describe edema, so perhaps that is not the best way to go. Second, as you stated at the beginning of your presentation, glycine can be converted to pyruvate. We have found that pyruvate can prevent I/R injury. Did you try to inhibit the conversion of glycine to pyruvate to see if this effect is mediated by pyruvate?

Dr. Shou. Edema does occur after ischemic injury, so this might be contributing to the decrease in the protein content of the mucosa. We realize there is a possibility that glycine is converted to pyruvate. Pyruvate has some similar effects on I/R injury.

Dr. N.E.P. Deutz (The Netherlands). One of the obvious mechanisms could be stimulation of the glutathione synthesis in the gut. That was one of your hypotheses. Did you measure the concentration?

Dr. Shou. We have not measured that yet. Glycine is not a rate-limiting factor for glutathione synthesis. A super-high dose of glycine might not alter glycine synthesis.

Dr. D. Mailman (Houston, Tex.). I was uncertain about one aspect of your experimental design. Did your sham-operated animals undergo I/R?

Dr. Shou. No. They just received anesthesia for the laparotomy. We manipulated the intestine a bit and then closed the incision.

Dr. Mailman. So you are not really sure whether in the presence of I/R glycine would actually help.

Dr. Shou. We found there was little difference regardless of whether the animals were given saline solution, water, or an amino acid solution.

Dr. Schirmer. Can you speculate on the actual mechanism of this protection? Is this a localized cytoprotective effect? Does it affect regional blood flow? Does it affect free radicals? Is there anaerobic energy conferred to the cell by the glycine? How is it working?

Dr. Shou. If you examine the I/R mechanism of the tissue injury, you will find there are some data suggesting that glycine can stop the calcium influx in a number of cells. Also, calcium influx is a common pathway that is involved in cell activation.

A Functional In Vitro Model to Examine Signaling Mechanisms in Gastrin-Mediated Human Cell Growth

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Gastrin (G-17) is a trophic hormone with a high affinity for the cholecystokinin-B receptor (CCK-BR); the mechanisms linking receptor binding and activation of downstream events to cell growth are not known, and these studies have been hampered by the lack of a cell model. We have established a pancreatic carcinoid cell line, BON, which produces a number of gut hormones; however, these cells lack native CCK-BR. The purpose of our study was to develop a model cell line containing the CCK-BR and to characterize the cellular mechanisms involved in gastrin regulation of human cell growth. BON cells were transfected with an expression plasmid containing the human CCK-BR, and stable clones were selected using G418. Functional CCK-BR was confirmed by reverse transcriptase–polymerase chain reaction, ^{125}I-gastrin binding, and mobilization of intracellular calcium ($[Ca^{2+}]_i$) in response to G-17. Stable transfectants were treated with G-17 (±) the CCK-BR antagonist, L365,260 (L-60); growth was assessed using a Coulter counter. G-17 stimulated the growth of the stable clones, whereas the selective CCK-BR antagonist, L-60, abolished this G-17–mediated trophic effect. We have shown that G-17, acting through the CCK-BR, mobilizes $[Ca^{2+}]_i$ as a second messenger and stimulates cell growth. Our unique BON cell line, stably transfected with the human CCK-BR, provides a novel paradigm to further delineate signaling mechanisms in gastrin regulation of human cell growth. (J GASTROINTEST SURG 1997;1:69-77.)

The peptide hormone, gastrin (G-17), is a known trophic factor for normal gastrointestinal mucosa and numerous gut neoplasms.[1-4] Patients with Zollinger-Ellison syndrome, which is characterized by hypergastrinemia, have massive mucosal hyperplasia of the gastric fundus.[5] In addition, gastrin stimulates both the in vivo and in vitro growth of a number of gastric and colon cancer cell lines[6-10]; the precise signal transduction mechanisms involved in gastrin-mediated regulation of human cell growth has not been clearly elucidated.

Gastrin and cholecystokinin (CCK) are structurally related peptides that share an identical carboxyl pentapeptide, which appears to be involved in the physiologic action of both hormones. The receptors for gastrin/CCK are cell surface receptors, structurally related to the larger superfamily of seven transmembrane-spanning, G-protein–coupled receptors. Three subtypes of gastrin/CCK receptors have been identified based on pharmacologic and structural differences: the CCK-preferring CCK-A receptor (CCK-AR), the gastrin-preferring CCK-B receptor (CCK-BR), and the less well-characterized CCK-C receptor. The CCK-BR has been detected in gastric parietal cells, pancreatic acinar cells, gut smooth muscle cells, and in numerous gut neoplasms.[11,12] Gastrin binds to the CCK-BR, activates G-proteins, and initiates a complex cascade of downstream intracellular events including activation of adenylyl cyclase, hydrolysis of phosphatidyl inositol, mobilization of intracellular calcium, activation of protein kinases, and induction of certain nuclear transcription factors (e.g., members of the AP-1 gene family).[13-15] L365,260 (L-60), a nonpeptide antagonist specific for CCK-BR, ef-

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fectively blocks gastrin-mediated growth of gastric and colonic neoplasms, suggesting a direct receptor-mediated effect.[16,17] Although these antagonists have been useful in correlating each receptor type with its physiologic function, the presence of multiple CCK receptor subtypes in the existing in vitro models has complicated the delineation of the cellular mechanisms involved in gastrin-mediated regulation of human cell growth.

We have established a functioning endocrine cell line, BON, derived from a human pancreatic carcinoid tumor.[18,19] This unique cell line contains no native receptors for the gastrin/CCK family of peptides and exhibits no physiologic responses to G-17 or CCK octapeptide (CCK-8). Transfection of BON with an intact human CCK-BR and selection of stable clones that express a functional receptor for gastrin would provide a novel in vitro model to examine the signaling mechanisms involved in gastrin-mediated cell growth. Using this novel human in vitro model, the purpose of our study was to characterize the cellular mechanisms involved in gastrin-mediated regulation of human cell growth.

MATERIAL AND METHODS

Materials and Reagents

The CCK-BR primers were synthesized by Genosys Biotechnologies, Inc. (The Woodlands, Tex.), and the reverse transcriptase-polymerase chain reaction (RT-PCR) systems were purchased from Promega Corp. (Madison, Wisc). Fura-2 was obtained from Molecular Probes, Inc. (Eugene, Ore.). The selective CCK-AR (L364,218; L-18) and CCK-BR (L365,260; L-60) antagonists were gifts from Merck & Co., Inc. (Rahway, N.J.); CAM1028-T-013 (CAM1028), a selective CCK-BR antagonist, was a generous gift from Parke-Davis Neuroscience Research Center (Cambridge, U.K.). RNAzol was obtained from Biotecx Laboratories, Inc. (Houston, Tex.), and oligo(dT)-cellulose was purchased from Collaborative Biomedical Products (Bedford, Mass.). Zeta-Probe (Bio-Rad Laboratories, Life Science Group, Hercules, Calif.) nylon membranes were hybridized with AP-1 (c-*jun*, *jun*-B, *jun*-D, c-*fos*) cDNA probes (American Type Tissue Collection, Rockville, Md.) labeled with α-^{32}P-deoxyadenosine triphosphate (Du Pont NEN Medical Products, Wilmington, Del.) using the Random Prime-It II kit (Stratagene, La Jolla, Calif.).

Tissue Culture

The human pancreatic carcinoid cell line, BON, was established in our laboratory[18] and cultured as described previously.[19] Briefly, these cells are maintained in Dulbecco's modified Eagle's medium (DMEM) and F12K (1:1) supplemented with 10% fetal calf serum. Cells were cultured in a humidified incubator with 5% carbon dioxide, at 37° C, and routinely passaged at 85% confluence. Passages 10 to 15 were used for all studies.

Transfection of Human CCK-BR

The 1.35 kb human CCK-BR cDNA, a generous gift of Dr. Alan S. Kopin of the New England Medical Center,[20] was ligated into the *Eco*RI/*Hind*III site of the eukaryotic expression vector, pcDNA3 (Invitrogen Corp., San Diego, Calif.). BON cells were transfected with the human CCK-BR expression plasmid using the calcium phosphate method. Isolated clones were selected in the presence of 800 μg/ml of G418 (Gibco, Grand Island, N.Y.), and stable transfectants were maintained in DMEM:F12K media with 400 μg/ml of G418.[21] Passages 15 to 22 of the stable clones were used for all experiments.

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

Total RNA was isolated by the method of Chomczynski and Sacchi[22] using RNAzol, and polyadenylated (poly [A]$^+$) mRNA was isolated through oligo-dT cellulose column chromatography. Parental BON cells and normal human antral tissue served as negative and positive control specimens, respectively. Poly[A]$^+$ mRNA (1 to 2 μg) was reverse transcribed using 1 mmol/L deoxynucleotide triphosphate mix, 0.5 μg oligo(dT) primer, and avian myeloblastosis virus reverse transcriptase (Promega Corp.) at 42° C for 1 hour; 10 μl of the reverse transcriptase reaction was used as a template for polymerase chain reaction, using 5 units of *Taq* DNA polymerase and 0.1 μg of the CCK-BR specific primers. These primers flank the coding regions of the human CCK-BR (5′ sense primer: 5′-TCACCAATGCCTTCCTCCTCT-CACTGGCAG-3′; 3′ antisense primer: 5′-TTG-GCTGTCGCTGTCACTGTCGCCGTCAAA-3′). The reaction was cycled 35 times at 94° C for 30 seconds, 60° C for 1 minute, and 72° C for 1 minute; the 575 base-pair band was detected by agarose gel (1.2%) electrophoresis and ethidium bromide staining.[23]

^{125}I-Gastrin Binding Studies

Exponentially growing cells (2-3 × 10^6 cells/assay) were incubated with unlabeled ligand (G-17, CCK-8, L-60, L-18 [10^{-13} to 5 × 10^{-5} mol/L)] for 15 minutes at room temperature; ^{125}I-gastrin (2200 Ci/mmol) (Du Pont NEN Medical Products) was added at

a concentration of 25 to 50 fmol/tube for a final volume of 1 ml, and the cells were incubated for an additional 1 hour at room temperature. After incubation, the cell pellet was washed and specific binding determined as previously described.[24]

Measurement of Intracellular Calcium ($[Ca^{2+}]_i$)

Real-time recording of $[Ca^{2+}]_i$ was performed using fura-2 fluorescence as described previously.[25] Cells were loaded with 2 μmol/L Fura-2 acetoxymethyl ester (50 minutes at 25° C) and imaged using a Nikon Diaphot inverted microscope (Nikon Inc., Instrument Group, Melville, N.Y.) coupled to a dual monochrometer system (Photon Technology International, Inc., South Brunswick, N.J.). $[Ca^{2+}]_i$ mobilization was calculated by the method of Grynkiewicz et al.[26] For the photometry studies cells were pretreated with the CCK-BK antagonist (L-365,260 [10^{-7} mol/L]; CAM1028 [10^{-7} mol/L]) was given prior to stimulation with G-17 (10^{-8} mol/L).

RNA Extraction and Northern Blot Analysis

Poly $[A]^+$ mRNA was extracted from control and treatment groups (G-17 [10^{-8} mol/L]: 0.5 hour, 1 hour, 4 hour), loaded onto standard 1.2% agarose-formaldehyde gel, transferred to a nylon membrane, and hybridized with a specific ^{32}P-labeled cDNA probe (c-*jun*, *jun*-B, *jun*-D, and c-*fos*). Hybridization and washing conditions have been described previously.[27,28] Blots were stripped and reprobed with a β-actin gene to ensure intact RNA samples and equality of loading. Specific hybridization was visualized (at −80° C) and analyzed by standard densitometry.

Growth Studies

Stable transfectants (1.5×10^4 cells) were grown in 12-well plates in DMEM:F12K supplemented with 10% fetal calf serum. After 24 hours, the medium was replaced with fresh medium containing 0.1% fetal calf serum; human G-17 (10^{-10} to 10^{-6} mol/L) or other test agents were added at this time. Cells were collected daily by trypsinization, and total cell count was determined using a Coulter counter (Coulter Electronics, Inc., Hialeah, Fla.).

Statistical Analysis

All $[Ca^{2+}]_i$ studies were performed in triplicate and representative findings are shown. Growth studies and Northern blot analyses were performed in triplicate. Statistical significance was assessed at $P < 0.05$ using analysis of variance and subsequent Newman-Keuls multivariate analysis.

RESULTS

Stable Transfection of Human CCK-BR Into BON Cells

To confirm expression of the CCK-BR transcript in the transfected BON cell clones, RT-PCR was performed using primers that flank the coding regions of the human CCK-BR (Fig. 1). BON-CCK-BR expressed the correct 575 base-pair RT-PCR product; parental (wild type) BON cells, which lack a native CCK-BR, served as a negative control and normal human antrum served as a positive control. Furthermore, the BON-CCK-BR transfectants are capable of binding gastrin with high affinity, as shown in the competitive binding assays and Scatchard analysis (Fig. 2). The transfected human CCK-BR has a high

Fig. 1. BON-CCK-BR stable clones express the correct 575 base-pair RT-PCR product; parental (wild type) BON cells serve as a negative control and normal human antrum serves as a positive control.

binding affinity for both G-17 and CCK-8 (Fig. 2, *A*); in addition, competition with the receptor antagonists revealed a significantly greater affinity for the selective CCK-BR antagonist (L-60) than the CCK-AR antagonist (L-18). Scatchard analysis identified two high-affinity binding sites for ^{125}I-gastrin (Fig. 2, *B*). The first binding site expresses approximately 5.7 × 10^3 sites/cell with a K_d of 0.2 nmol/L, whereas the second binding site expresses approximately 2.1 × 10^5 sites/cell with a K_d of 17 nmol/L. These affinity constants are of the same order of magnitude as the constitutively expressed gastrin receptors found in rat and guinea pig gastric parietal cells, as well as in other human gut neoplasms.[11,12,29]

Functional Responses of Stably Transfected CCK-BR in BON Cells

To determine whether the human CCK-BR was functional when stably transfected into BON cells, intracellular calcium mobilization in response to varying concentrations of G-17 and CCK-8 were measured by fura-2 spectrofluorometry (Fig. 3). Several of the BON-CCK-BR stable clones were tested to determine $[Ca^{2+}]_i$ mobilization in response to G-17; we have selected BON-CCK-BR clone No. 2 (BON-CCK-BR #2) to further characterize the physiologic and functional properties of the human CCK-BR in the BON cell line. The photometry tracings in Fig. 3, *A* demonstrate $[Ca^{2+}]_i$ mobilization in response to

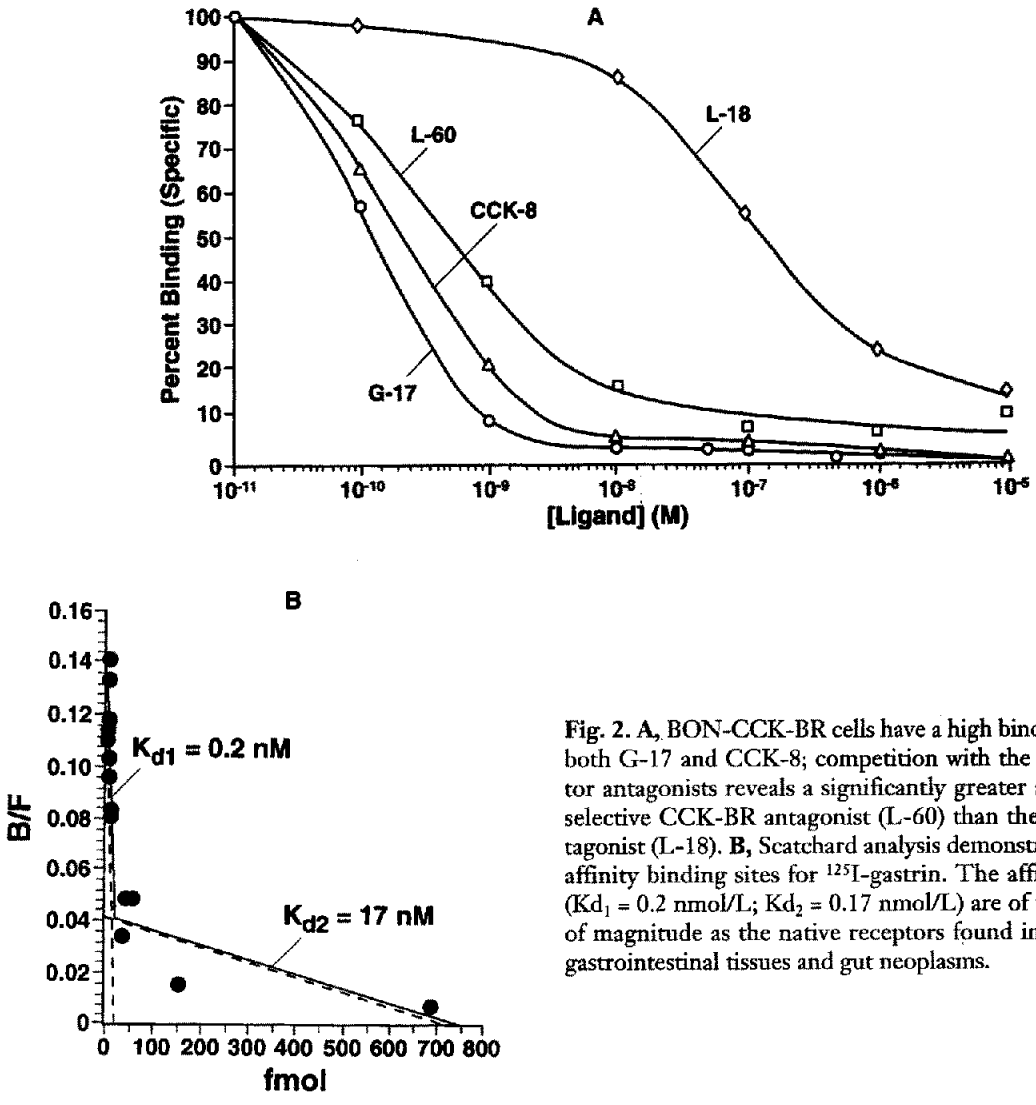

Fig. 2. **A**, BON-CCK-BR cells have a high binding affinity for both G-17 and CCK-8; competition with the specific receptor antagonists reveals a significantly greater affinity for the selective CCK-BR antagonist (L-60) than the CCK-AR antagonist (L-18). **B**, Scatchard analysis demonstrates two high-affinity binding sites for ^{125}I-gastrin. The affinity constants (Kd_1 = 0.2 nmol/L; Kd_2 = 0.17 nmol/L) are of the same order of magnitude as the native receptors found in other normal gastrointestinal tissues and gut neoplasms.

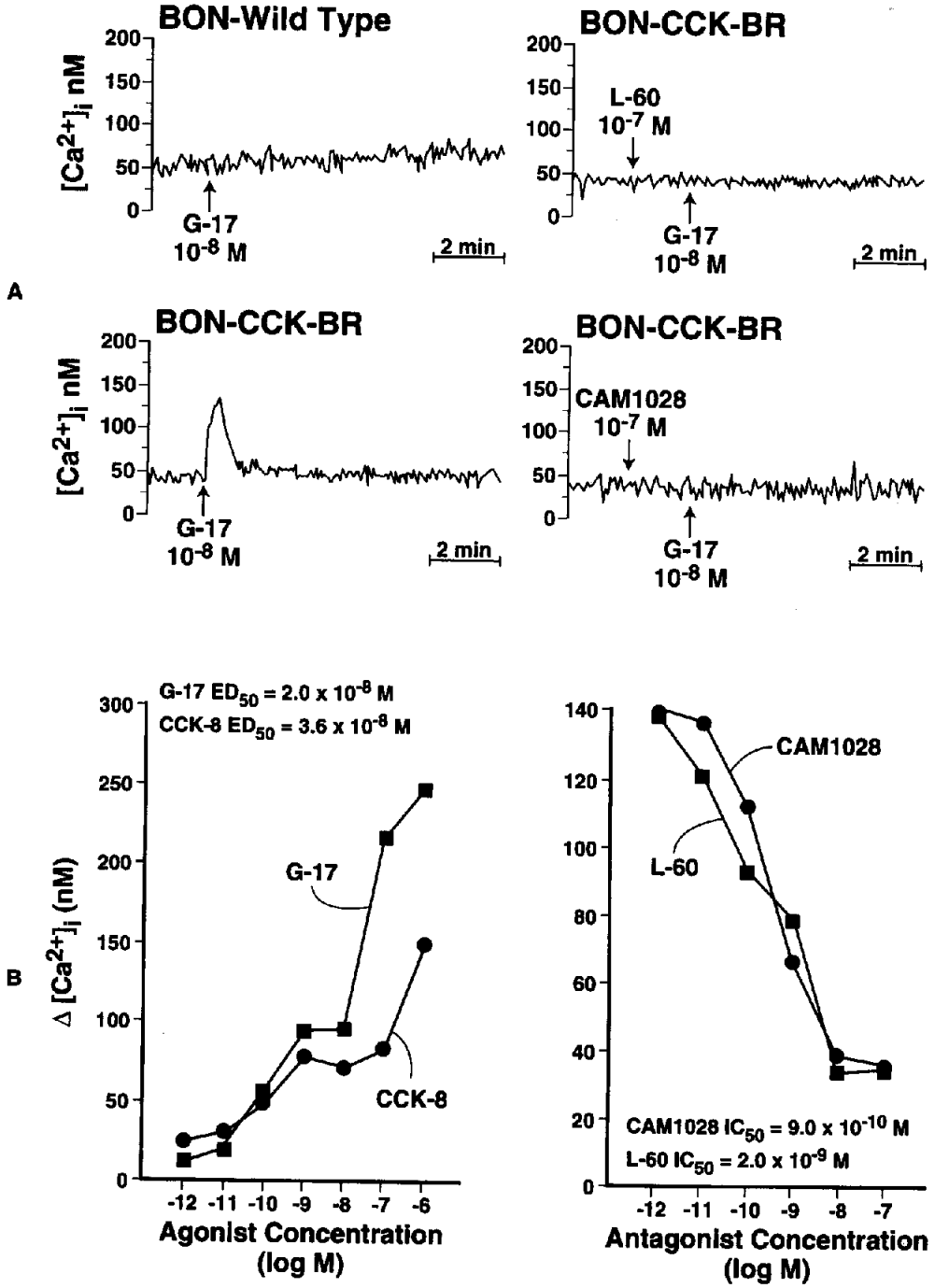

Fig. 3. A, Intracellular calcium ($[Ca^{2+}]_i$) mobilization in response to G-17 (10^{-8} mol/L) in parental (wild type) BON cells and BON-CCK-BR stable clones. Parental BON cells (top left) do not mobilize $[Ca^{2+}]_i$ in response to G-17; in contrast, treatment of BON-CCK-BR (bottom left) with G-17 results in rapid mobilization of $[Ca^{2+}]_i$, demonstrating a functional CCK-BR. Treatment of the stable clones with the CCK-BR antagonists L-60 (10^{-7} mol/L; top right) and CAM1028 (10^{-7} mol/L; bottom right) inhibits $[Ca^{2+}]_i$ mobilization in response to G-17 (10^{-8} mol/L). B, Dose-response curves of $[Ca^{2+}]_i$ mobilization in response to G-17 and CCK-8 are summarized on the left, with ED_{50} values of 2.0×10^{-8} mol/L and 3.6×10^{-8} mol/L, respectively. Similarly, the inhibition curves for L-60 and CAM1028 (selective CCK-BR antagonists) are shown on the right, with IC_{50} doses of 2.0×10^{-9} mol/L and 9.0×10^{-10} mol/L, respectively.

G-17 (10^{-8} mol/L); the top left tracing confirms that there are no functional CCK-BRs in parental BON cells; the bottom left tracing demonstrates a functional CCK-BR in our stable clone No. 2 capable of mobilizing $[Ca^{2+}]_i$ as a second messenger; and the two right images demonstrate that this mobilization of $[Ca^{2+}]_i$ can be completely inhibited by the selective CCK-BR antagonists, L-60 and CAM1028. Treatment of the stable clones with the CCK-AR antagonist, L-18, revealed no inhibition of the $[Ca^{2+}]_i$ mobilization in response to G-17 (data not shown). The dose-response curves of $[Ca^{2+}]_i$ mobilization in response to G-17 and CCK-8 are summarized in Fig. 3, *B* (left), with ED_{50} values of 2.0×10^{-8} mol/L and 3.6×10^{-8} mol/L, respectively. Likewise, the inhibition curves for CAM1028 and L-60 in the BON-CCK-BR #2 clone are summarized to the right and reveal IC_{50} doses of 9.0×10^{-10} mol/L and 2.0×10^{-9} mol/L, respectively. Collectively, these studies demonstrate that we have established a novel in vitro model of a human endocrine cell line stably transfected with the human CCK-BR; in addition, the BON-CCK-BR #2 stable clone possesses a functional CCK-BR with high binding affinity that is correctly coupled to the calcium second messenger.

Gastrin Activates Expression of AP-1 Transcription Factors c-*jun* and c-*fos*

To determine whether G-17 increases AP-1 gene expression, BON-CCK-BR #2 cells were treated with G-17 (10^{-8} mol/L: 0.5 hour, 1 hour, and 4 hours) and RNA was extracted for Northern blot analysis (Fig. 4). Increases in the expression of both c-*jun* (187%) and c-*fos* (346%) are noted by 0.5 hour and 1 hour after G-17 treatment; the expression of these immediate early genes returned to near-baseline levels by 4 hours. In contrast, the expression of *jun*-B and *jun*-D does not appear to be altered by treatment with G-17. The β-actin gene was used as an invariant control for RNA loading and demonstrates relatively equal loading in all lanes. Taken together, BON-CCK-BR #2 cells demonstrate an early induction of both c-*jun* and c-*fos* expression in response to G-17, suggesting a possible role of the AP-1 transcription factors in gastrin-mediated cell growth.

G-17 Stimulates Growth of BON-CCK-BR Transfectants

To determine whether the BON cells stably transfected with the human CCK-BR had a physiologic response to G-17, growth studies were performed and cell proliferation was assessed using a Coulter

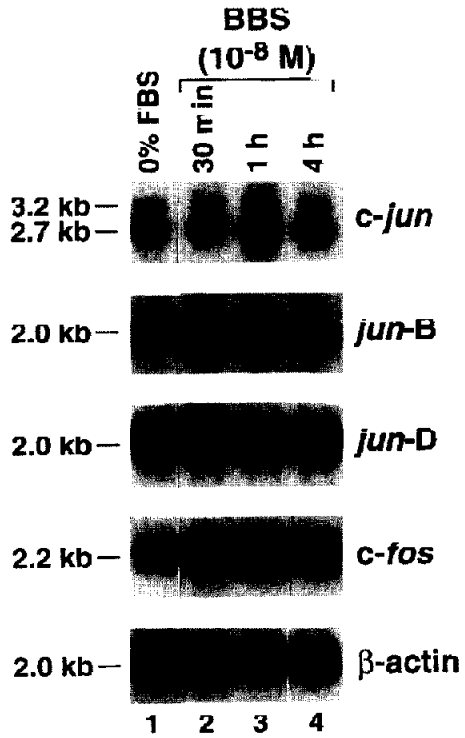

Fig. 4. Increases in the expression of c-*jun* and c-*fos* are noted by 0.5 hour and 1 hour after treatment with G-17 (10^{-8} mol/L), and values return to baseline by 4 hours; *jun*-B and *jun*-D do not appear to be significantly induced by G-17. The β-actin gene served as an invariant control for RNA loading.

counter. BON-CCK-BR #2 cells treated with physiologic doses of G-17 (10^{-8} mol/L) demonstrated a 20% increase in growth by day 8 (Fig. 5). In correlation with the binding and intracellular calcium studies, the addition of L-60 resulted in complete inhibition of the trophic effects of G-17 (Fig. 5). These growth studies confirm that BON-CCK-BR #2 cells not only possess a functional CCK-BR but also demonstrate a physiologic response to gastrin; BON-CCK-BR #2 may provide a useful endocrine model to delineate the cellular mechanisms involved in gastrin-mediated cell growth.

DISCUSSION

Gastrin is a potent trophic factor for both normal and neoplastic gut tissues; the binding of gastrin to the CCK-BR at the cell surface initiates a complex cascade of intracellular events leading to the nucleus and eventually resulting in cell growth. The signal transduction pathways involved in gastrin-mediated regulation of this cellular process have been difficult to elucidate, partly because most of the available in

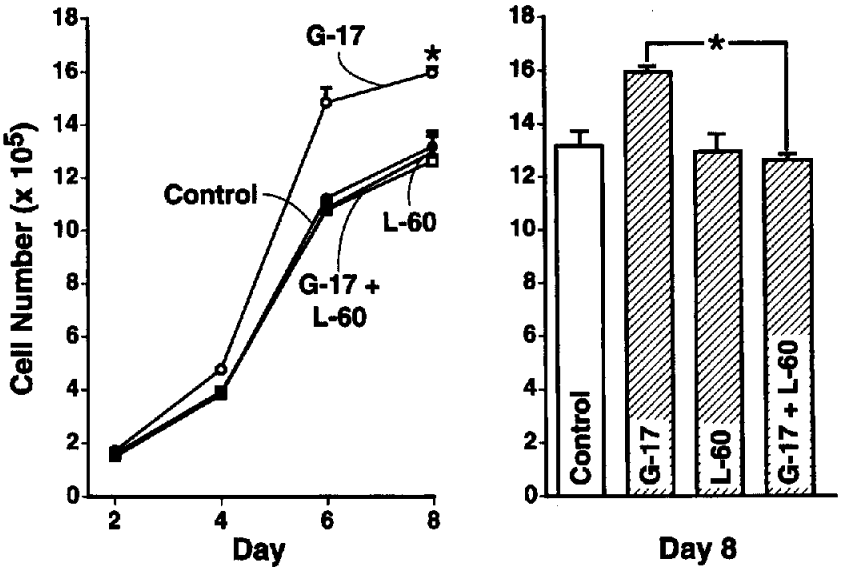

Fig. 5. Growth curves are shown on the left, with day 8 cell counts shown on the right as a bar graph. G-17 (10^{-8} mol/L) stimulated the growth (~20%) of BON-CCK-BR cells by day 8 as compared with controls; the addition of L-60 resulted in complete inhibition of the trophic effects of G-17. Treatment with vehicle or L-60 alone had no effect as compared with controls.

vitro models express more than one CCK receptor subtype or lack a significant physiologic response.

We have transfected the human CCK-BR into a human carcinoid cell line, BON, which possesses many functional and morphologic characteristics of gut enteroendocrine cells.[30] BON cells stably transfected with the CCK-BR express functional receptors, which bind gastrin with high affinity and mobilize intracellular calcium as a second messenger. The pharmacologic properties of the CCK-BR in our stable clones are similar, in terms of binding affinities and selectivity to agonists/antagonists, to other in vivo and in vitro models that express native gastrin receptors.[11,12,29] Gastrin-stimulated mobilization of $[Ca^{2+}]_i$ is specific to the CCK-BR transfected cells; parental BON cells lacking the CCK-BR do not respond to either gastrin or CCK-8. Furthermore, gastrin-induced mobilization of $[Ca^{2+}]_i$ in the transfected BON cells is competitively inhibited by the selective CCK-BR antagonists, L-60 and CAM1028.

The BON-CCK-BR #2 clone has a significant growth response to G-17; in correlation to the binding and calcium studies, this trophic response can be competitively inhibited with known CCK-BR antagonists. We have characterized the CCK-BR transfected in BON cells; gastrin is bound at the cell surface with high affinity and $[Ca^{2+}]_i$ is mobilized as a second messenger. In addition, gastrin significantly stimulates the growth of this in vitro model; what remains unknown are the complex intermediate steps leading to the nucleus and to cell growth. AP-1 nuclear transcription factors have been implicated as possible mediators of cell growth; treatment of BON-CCK-BR cells with gastrin activates the expression of two of the AP-1 transcription factors, c-*jun* and c-*fos*, suggesting that these immediate early genes may play a role in gastrin-mediated mitogenesis.[31,32] The expression of c-*jun* and c-*fos* is increased within 30 minutes after treatment with G-17, with peak increases noted at 1 hour; induction of these nuclear transcription factors is transient and they are restored to baseline levels by 4 hours. Future studies will begin to examine the role of various protein kinases in the activation of the AP-1 transcription factors. Furthermore, with the use of this model system we will begin to delineate, in a stepwise fashion, the precise signal transduction pathways involved in gastrin regulation of human cell growth. In addition, these clonal cell lines will allow us to examine other physiologic roles (peptide secretion, gene activation) of gastrin, as well as the proforms of gastrin (glycine-extended gastrin).

CONCLUSION

We have established a unique in vitro model by the stable transfection of the human CCK-BR into the gut endocrine cell line, BON. Our data demonstrate

that the human CCK-BR is highly expressed in our BON-CCK-BR stable clones and coupled to the regulation of intracellular calcium. Furthermore, gastrin acts through the human CCK-BR to stimulate human cell growth; the selective CCK-BR antagonists inhibit receptor binding, calcium mobilization, and the trophic effects of gastrin. The neuroendocrine cell line, BON, stably transfected with the human CCK-BR, provides a novel in vitro model to further delineate the signaling mechanisms in gastrin-mediated growth of human gut neoplasms.

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Discussion

Dr. M. Mulholland (Ann Arbor, Mich.). Do your cells manufacture cyclic adenosine monophosphate (cAMP)? Does the dose-response curve for cAMP parallel that for calcium? You show that calcium is mobilized and early-response transcription factors are activated. Does the calcium mobilization cause growth? Have you conducted experiments to block calcium mobilization to see if the growth is blocked?

With your calcium experiments and your other experiments, you see a very rapid onset of action. The growth action is very slow and significant only after 6 days and was only about 20% above your control values. How do you interpret that?

Dr. H.J. Kim. We have just begun to use this model to measure cAMP, and we are beginning to examine that second messenger. The cAMP second messenger has been implicated in the trophic effects of gastrin in other cell systems, and it is imperative that we study it after initially characterizing the receptor with intracellular calcium mobilization.

We have not yet directly linked intracellular calcium mobilization to growth. We will need to determine whether we can inhibit intracellular calcium mobilization and, in turn, inhibit growth of the cell model in order to directly link those two pathways. Also, we have begun to examine other nuclear transcription factors to see if there is an intermediary in the nucleus for delineating the signal transduction pathway between receptor binding and activation of second messengers to the growth response.

The 20% increase in growth has been seen typically in numerous cancer models, and growth responses in our colon cancer cell lines have been typically approximately 20% to 40% at best. Treatment with the agonist on day 1 seems to demonstrate its trophic effect by day 6, and I am not quite sure why the effect does not show up until later.

Dr. M.E. Zenilman (Bronx, N.Y.). This was a very good study on cell transfection, proving that what you did was, in fact, true and then using your results as a model for physiologic measurement. The question I have is a bit like Dr. Mulholland's in terms of cell growth. You were measuring cell number as a monitor of cell growth and it did take a fair number of days for you to achieve your desired effect. Did you change the media every day with the gastrin to make sure that there was no destruction of the gastrin in the medium you were testing? Did you measure other parameters of cell growth, such as thymidine incorporation or bromodeoxyuridine incorporation, which are typically a bit more sensitive?

Dr. Kim. These are very interesting questions. I have taken these cell lines and evaluated them in several different ways prior to presenting the composite data. Daily treatment of the agonist, because there are peptidases in the serum and in the media that break down these gut hormones, results in no difference in treatment of the cells at day 1. In addition, washing the cells every day and adding fresh media with fresh gastrin also did not alter these growth characteristics. We did just look at cell number. Our next step is to study 3-[4,5-Dimethylthiozol-2-yl]-2,5-diphenyltetrazolium bromide assays and thymidine incorporation, but we have not yet carried out those experiments.

Fungal Hepatic Abscesses: Characterization and Management

Pamela A. Lipsett, M.D., Chih-Jen Huang, M.D., Keith D. Lillemoe, M.D., John L. Cameron, M.D., Henry A. Pitt, M.D.

Hepatic abscesses are being recognized with increasing frequency in immunocompromised patients and those with malignant diseases. Risk factors and treatment for patients with pure fungal abscesses and mixed fungal and pyogenic abscesses have not been well described. A retrospective review of patients with hepatic abscesses was undertaken at The Johns Hopkins Hospital from 1973 through 1993. Eight patients with pure fungal hepatic abscesses and 34 patients with mixed fungal/pyogenic abscesses were identified. Clinical presentation, diagnosis, management, and outcome were analyzed. In the group with pure fungal abscesses, fungemia was predictive of death; four patients in this group died, whereas the remaining four patients who received amphotericin B treatment before the onset of fungemia all survived. In the group with mixed fungal/pyogenic abscesses, 11 patients received amphotericin B, whereas 23 did not. Ten (43%) of these 23 patients died. However, only one of five patients who received more than 1000 mg of amphotericin B died. In patients with hematologic malignancies, who are known to be at risk for fungal infections, amphotericin B treatment should be instituted early. In patients with mixed fungal/pyogenic hepatic abscesses who fail to improve after drainage and broad-spectrum antibiotics, antimycotic therapy should be considered early, before the onset of fungemia. (J GASTROINTEST SURG 1997;1:78-84.)

Hepatic abscesses have been recognized since the time of Hippocrates; however, the etiology, microbiology, diagnosis, and treatment of these abscesses continue to evolve.[1-3] In their classic paper published in 1938, Ochsner et al.[2] reported that the major causal factors leading to liver abscesses were bacteria from appendicitis and amebiasis. Bacteria and parasites continue to account for the majority of pathogens recovered from hepatic abscesses. However, fungal hepatic abscesses have recently been recognized with increased frequency in various subgroups of patients. An immunosuppressed state secondary to chemotherapy and infection with the human immunodeficiency virus (HIV) have both been associated with fungal hepatic abscesses.[4-6] On the other hand, a limited number of mixed fungal and pyogenic infections in liver abscess have been reported.[7-9] To define the importance of fungal hepatic infections, the medical records of 42 patients identified as having a fungal hepatic abscess over a 21-year period were reviewed, focusing on clinical presentation, risk factors, diagnosis, and the role of antimycotic therapy.

MATERIAL AND METHODS

The medical records of 161 patients managed at The Johns Hopkins Hospital with a diagnosis of a hepatic abscess from January 1973 through December 1993 were reviewed. The 153 patients with a bacterial infection are described in detail elsewhere.[10] Thirty-four of these 153 patients also had fungal growth from their hepatic abscesses. Eight additional patients were identified with pure fungal hepatic abscesses. To be included in this study patients had to have at least one of the following criteria: (1) fungal growth from the abscess (n = 34), (2) abnormal CT or ultrasound scans and blood cultures that were positive for fungal growth (n = 2) or abnormal radiographs and a serologic test showing growth of *Cryptococcus* (n = 1), or (3) evidence of fungal hepatic infection found at autopsy (n = 5).

A retrospective review of the medical records yielded information on clinical presentation, laboratory results, radiologic evaluation, treatment, and outcome for all 42 patients. Associated medical conditions were carefully assessed, as were specific radiologic characteristics of the hepatic abscess. The type and timing of

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surgical, percutaneous, and antimicrobial drug treatments were recorded, and each was analyzed for its effect on outcome.

The group of patients with pure fungal hepatic abscesses was compared with those patients who had mixed fungal/pyogenic abscesses to identify factors that might aid in clinical diagnosis, identification of predisposing factors, and management of this difficult disease. Differences between the groups were determined by means of Fisher's exact test or the Wilcoxon test as appropriate. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Over the past 21 years 161 patients with a hepatic abscess have been identified. Forty-two patients (26%) were identified with a positive fungal culture. Pure fungal abscesses were seen in eight patients (4.9%), whereas an additional 34 patients (21.1%) had mixed fungal and hepatic abscesses. As shown in Table I, patients with pure fungal abscesses were statistically younger, with a mean age of 34 years compared to 56 years for those with mixed fungal abscesses.

The etiology of hepatic abscesses in the two groups is shown in Fig. 1. The etiology of the hepatic abscesses could be determined in all pure fungal abscesses. In 2 of the 34 patients with a mixed fungal/pyogenic infection, the etiology of the infection remained idiopathic. Biliary tract disease, either benign or malignant, was significantly less common in patients with a pure fungal vs. a mixed fungal/pyogenic infection (13% vs. 71%, $P < 0.05$). As expected, because of the presence of biliary tract disease in the group with mixed fungal/pyogenic hepatic abscesses, 25 (74%) of 34 patients had a history of prior biliary surgery and/or an indwelling stent.

All patients in the group with pure fungal abscesses could be considered to be immunosuppressed because of recent chemotherapy for leukemia (n = 7) or hepatobiliary disease (n = 1). Six of the eight patients in this group were diagnosed as having a hepatic abscess just after recovery from a neutropenic state. Four of the five immunosuppressed patients in the mixed group were receiving steroids either for asthma (n = 2) or arthritis (n = 2). One additional patient was infected with HIV. Other notable risk factors for the development of a mixed fungal/pyogenic infection were the presence of active diverticulitis (n = 1) or an in-

Table I. Patient population

	Pure fungal abscess (n = 8)	Mixed fungal/ pyogenic abscess (n = 34)
Age (yr)		
Mean	34	56*
Range	3-68	25-83
Sex		
Male	5	19
Female	3	15

*$P < 0.05$ vs. pure fungal abscesses.

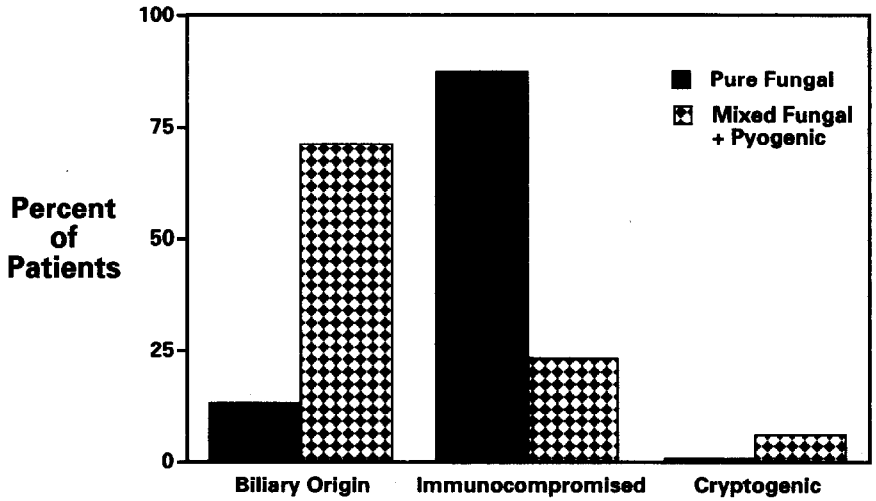

Fig. 1. Etiology of fungal hepatic abscesses. Etiology of patients with pure fungal vs. mixed fungal/pyogenic abscesses is shown. Leukemia and associated treatment was the most common cause in patients with pure fungal abscesses, whereas biliary tract disease accounted for the vast majority of all mixed fungal/pyogenic abscesses.

Table II. Presenting symptoms

Symptoms	Pure fungal abscess (n = 8) (% of patients)	Mixed fungal/ pyogenic abscess (n = 34) (% of patients)
Fever	100	97
Chills	63	48
Diarrhea	38	6
Nausea/vomiting	13	19
Malaise	13	29
Anorexia	13	26
Weight loss	13	23
Respiratorydistress	13	10
Mental status changes	13	10

Table III. Presenting signs

Signs	Pure fungal abscess (n = 8) (% of patients)	Mixed fungal/ pyogenic abscess (n = 34) (% of patients)
Jaundice	63	71
Hepatomegaly	25	44
Right upper quadrant abdominal tenderness	25	58
Diffuse abdominal tenderness	0	3
Ascites	0	10
Hypotension	0	29
Basilar rales	0	13

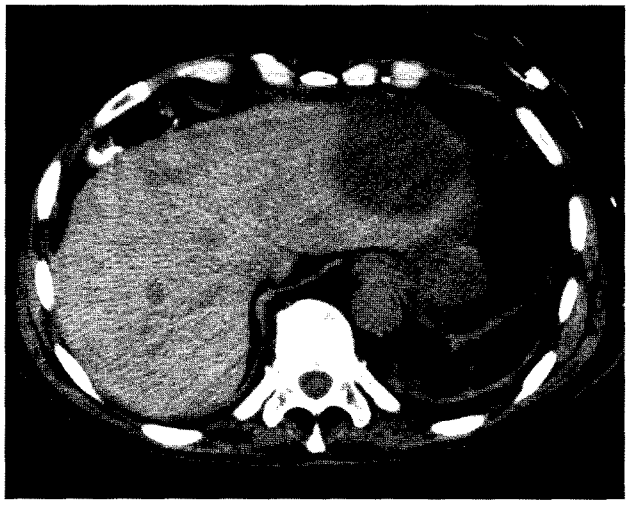

Fig. 2. CT scan of a patient with a benign biliary stricture and a large left hepatic abscess that was successfully treated with percutaneous drainage.

tra-abdominal abscess (n = 1). Diabetes mellitus was found to be the only associated medical condition in two patients with a mixed fungal infection.

The use of broad-spectrum antibiotics preempted the development of fungal abscesses almost uniformly in both groups, including 91% of the patients in the mixed fungal/pyogenic group and 100% of those in the pure fungal group. The majority of patients in both groups received these antibiotics for longer than 2 weeks.

Clinical Presentation

The clinical presentation of patients in each of the groups is shown in Table II. Fever was the most common presenting symptom in both groups, whereas jaundice was the most common presenting physical finding. Nausea was present in a minority of patients in both groups, whereas malaise, weight loss, respiratory distress, and changes in mental status represented systemic signs of infection in both patient groups. On physical examination, patients in both groups were found to have hepatomegaly or abdominal tenderness (Table III). Hypotension (blood pressure <90 mm Hg) was present in the mixed fungal/pyogenic group, whereas none of the patients in the pure fungal abscess group were hypotensive. Leukocytosis (>10,000/mm^3) was present in 75% of the mixed fungal/pyogenic group, whereas an additional 9% of the patients in this group had a leukocyte count of less than 1000/mm^3. Since the majority of patients in the pure fungal group had hematologic malignancies and were treated with chemotherapy, the leukocyte count was not helpful in identifying an infectious process. Results of liver function tests and bilirubin, transaminase, and alkaline phosphatase values were commonly abnormal, and there were no significant differences between the two groups. Bilirubin was usually three times the normal value, whereas transaminases were two and alkaline phosphatase three times the normal values, respectively.

Diagnostic Evaluation

The most valuable roentgenographic study for establishing the diagnosis of hepatic abscess in both groups of patients was the CT scan (Fig. 2). In patients with pure fungal abscesses, five (63%) of eight scans were abnormal. In this pure fungal abscess group the diagnosis of a liver abscess was confirmed by needle aspiration or by open biopsy in six of eight patients. One patient had an abnormal CT scan and serologic tests showed growth of *Cryptococcus* but needle aspiration was not performed, and in one addi-

tional patient the diagnosis of a pure fungal abscess was confirmed only at autopsy.

In the mixed fungal/pyogenic group, abnormal CT liver scans were found in 25 patients (74%), whereas sonograms were abnormal in 22 patients (65%). Cholangiography demonstrated a variety of abnormalities with a malignant stricture (60%) or a benign stricture (36%) when performed in patients with structural hepatobiliary disease.

Characteristics of Hepatic Abscesses

In the group with pure fungal abscesses, multiple abscesses in both lobes of the liver were seen in six of eight patients, with five patients having more than 10 abscesses identified (Table IV). Pure fungal abscesses were small with seven (88%) of the eight patients having abscesses that were less than 2 cm. A single focus of hepatic infection was seen in two of eight patients with a pure fungal abscess. In patients with mixed fungal/pyogenic hepatic abscesses, bilateral multiple foci were seen in 74% of patients. However, only 24% had more than 10 identifiable abscesses. Eleven (32%) of 34 patients with a mixed hepatic infection had a single source of infection (Table IV). Patients with a mixed fungal/pyogenic hepatic infection had significantly larger abscess cavities when compared to those with a pure fungal abscess ($P < 0.05$) (Table IV). No direct communication between the hepatic abscess and the bile duct was present in any of those with pure fungal abscess, but 14 (41%) of 34 patients with a mixed abscess had a direct communication between the bile duct and the cavity of the hepatic abscess. The coexistence with splenic abscess was found significantly more often in those with pure fungal abscesses (71%), whereas a splenic abscess was seen in only 12% of the mixed pyogenic group ($P < 0.01$).

Microbiology of Hepatic Abscesses

Direct cultures were obtained from the abscess cavity in 34 patients. In the overall group *Candida* species were found in 28 patients (82%). In the pure fungal abscess group, however, *Aspergillus* was seen in two patients, one of whom also had *Candida*. All remaining patients in the pure fungal abscess group had *Candida* identified in the abscess cavity. In the mixed fungal/pyogenic group, *Aspergillus* and *Candida* were seen in one patient, whereas two additional patients had both *Candida* and *Cryptococcus*. All remaining patients with a positive abscess culture from percutaneous or surgical drainage had *Candida* species identified. Multiple bacteria were also identified in 28 patients (82%) in the mixed abscess group. Twenty-one of these patients (65%) had bacteremia and in eight of these patients there were multiple organisms. None of the patients in the pure fungal abscess group had bacteremia, whereas four of eight patients had fungemia. In the mixed pyogenic group seven patients had fungemia, all of whom had simultaneous bacteremia.

Table IV. Characteristics of fungal hepatic abscess

	Pure fungal abscess (n = 8)	Mixed fungal/ pyogenic abscess (n = 34)
No. of abscesses		
Single	2	11
Multiple (>10)	1	15
Diffuse (>10)	5	8
Size		
≤ 2 cm	7	9
> 2cm	1	25*

*$P < 0.05$ vs. pure fungal abscesses.

Table V. Antimycotic therapy and outcome*

	Pure fungal abscess (n = 8)	Mixed fungal/ pyogenic abscess (n = 34)
Without fungemia	n = 4 (0)	n = 27 (11)
No therapy	0 (0)	20 (7)
>500 mg amphotericin B	0 (0)	3 (3)
>1000 mg amphotericin B	4 (0)	4 (1)
With fungemia	n = 4 (4)	n = 7 (6)
No therapy	0 (0)	3 (3)
>500 mg amphotericin B	3 (3)	3 (3)
>1000 mg amphotericin B	1 (1)	1 (0)

*Numbers in parentheses represent number of deaths in each group.

Therapy and Outcome

All identified hepatic fungal abscesses were drained for either diagnosis or therapy. Drainage of the hepatic abscess was performed either percutaneously in 58% of patients or by operative drainage in 24%. Percutaneous aspiration of the abscess alone was performed in 8% of all patients. No significant differences were seen in mortality rates based on the type of drainage procedure employed; percutaneous drainage was associated with 30% mortality, operative drainage with 38% mortality, and aspiration with 33% mortality. All patients in the pure fungal group received amphotericin B (Table V). Four of eight patients in this group survived.

All four patients who died had fungemia, with antimycotic therapy initiated only after the onset of fungemia in each case. All surviving patients were treated with doses of amphotericin B in excess of 1000 mg.

In the mixed pyogenic group only 11 patients (32%) were treated with amphotericin B. Five of these 11 patients received at least 1000 mg of amphotericin B. In six of seven patients with fungemia, amphotericin B therapy was initiated only after the development of fungemia. All six of these patients died, with the one patient who survived fungemia completing a full course of amphotericin B. The overall mortality rate for patients in the mixed fungal/pyogenic group was 50%, with patients who received a full course of amphotericin B having a significantly lower mortality rate in comparison to those patients who received less than 500 mg (20% vs. 62%; $P < 0.05$). Fewer deaths were also seen with amphotericin therapy when patients with fungemia were excluded, but this difference did not achieve statistical significance (25% vs. 43%).

Multivariate analysis of the risk factors associated with death are shown in Table VI. A direct complication of the hepatic abscess was considered if bleeding occurred, jaundice increased, or increased sepsis and hypotension developed immediately following drainage of the abscess. In the overall group of 42 patients, fungemia and a direct complication from the hepatic abscess were predictive of death. In the pure fungal abscess group, jaundice also influenced mortality, whereas in the mixed fungal/pyogenic abscess group the presence of malignancy had a negative impact on survival.

DISCUSSION

Pure fungal hepatic abscesses have been recognized with increasing frequency in recent years. Factors associated with this development have been aggressive chemotherapy for hematologic diseases, aggressive treatment of malignant hepatobiliary diseases, long-term indwelling biliary catheters, prolonged use of broad-spectrum antibiotics, parenteral nutrition support, and long hospitalizations.[7,8,11,12] At Johns Hopkins 20% of all patients with a hepatic abscess have positive fungal cultures, with the majority of patients having a mixed fungal/pyogenic infection.[10]

Patients with a mixed fungal/pyogenic abscess are more likely to be older and have biliary obstruction when compared to patients with a pure fungal abscess.

Table VI. Factors influencing mortality in fungal hepatic abscess

	Pure fungal abscess (n = 8)	Mixed fungal/ pyogenic abscess (n = 34)	Total patients (n = 42)
White blood cells (/mm³)			
<1000	0	3 (2)	3 (2)
1000-10,000	3 (1)	5 (2)	8 (3)
10,000-20,000	1 (0)	13 (4)	14 (4)
>20,000	1 (1)	12 (8)	13 (9)
Albumin (gm/dl)			
<2.5	1 (1)	11 (8)	12 (9)
≥2.5	5 (1)	21 (9)	26 (10)
Total bilirubin (mg/dl)			
≥1.5	4 (3)*	26 (13)	30 (16)
<1.5	5 (0)	8 (4)	13 (4)
Fungemia	4 (4)*	7 (6)	11 (10)†
No fungemia	4 (0)	27 (11)	31 (11)
Shock (blood pressure <90 mm Hg)	0	9 (6)	9 (6)
No shock	8 (4)	22 (10)	30 (14)
Complications	4 (4)*	26 (17)‡	33 (21)†
No complications	4 (0)	8 (0)	12 (0)
Multiple abscesses	6 (3)	23 (11)	29 (14)
Single abscess	2 (1)	11 (6)	13 (2)
Malignancy	7 (3)	21 (14)‡	28 (17)
No malignancy	1 (1)	13 (3)	14 (4)

Numbers in parentheses represent number of deaths in each group.
*$P < 0.05$ within the pure fungal group.
†$P < 0.05$ within the total group.
‡$P < 0.05$ within the mixed fungal group.

Although both groups are likely to have a malignancy, patients with a mixed fungal/pyogenic abscess are more likely to have a biliary or pancreatic malignancy, whereas patients with pure fungal abscesses almost uniformly were being treated for a hematologic malignancy. Patients with pure fungal hepatic abscesses were younger (33 vs. 56 years of age; $P < 0.05$) and were immunosuppressed by chemotherapy and steroids.

The diagnosis of pure fungal hepatic abscesses after intensive chemotherapy is difficult because of the small size and poor histologic definition of these abscesses during neutropenia. Only after granulocytes recover do these foci of fungal infection in the liver show characteristic histologic and roentgenographic patterns. In this series the diagnosis of pure fungal abscesses was established after recovery from the neutropenic state in six of eight patients. The diagnosis in the remaining two patients, who were neutropenic at the time, was established only at autopsy. In this patient population early treatment with amphotericin B was clearly linked to survival. Four of eight patients died of their fungal hepatic abscesses and sepsis, with all four of these patients having documented fungemia prior to the initiation of amtimycotic therapy. Since amphotericin B acts on the fungal cell wall with a cumulative total dose effect, improved survival from fungal infections can only occur when treatment is begun early in the disease process.[13,14] In other patient populations treatment of fungal infections after the onset of fungemia is also associated with a poor outcome with an overall mortality rate of 50%.[15]

The clinical presentation and diagnostic evaluation for patients with a mixed fungal/pyogenic infection is similar to that for patients with a pyogenic hepatic abscess.[10] The presence of a combined fungal/pyogenic hepatic abscess can only be distinguished by blood culture or tissue diagnosis. Although bacterial infection may be more predominant and influential in the clinical presentation of patients with mixed fungal/pyogenic hepatic abscess, the coexistence of the fungus increases the death rate significantly.[6] The reasons for this difference are multifactorial. These patients are chronically ill with a malignancy and have been managed with multiple courses of broad-spectrum antibiotics. The increased mortality associated with the presence of a fungal pathogen suggests that fungal involvement represents infection rather than colonization. Furthermore, the development of fungemia can be predictive of death, whereas early treatment of fungal pathogens is associated with improved survival. In a pyogenic abscess features considered predictive of death include multiple abscesses, bilateral abscesses, leukocytosis, jaundice, bacteremia, and septic shock.[9,10,16] However, these factors are not predictive of death in the presence of combined fungal/pyogenic hepatic infection. In this series factors associated with a decrease in mortality included treatment with amphotericin B prior to the onset of fungemia. On the other hand, direct complications of hepatic abscess such as bleeding and jaundice were associated with an increase in mortality.

Treatment of a hepatic abscess, irrespective of microbiologic findings, includes drainage and appropriate antimicrobial therapy. In this series drainage, whether accomplished percutaneously by aspiration or by catheter, or by a surgical drainage procedure, did not alter outcome. Antimycotic therapy, however, was essential for survival in immunosuppressed patients with a hematologic malignancy. Amphotericin B has been the agent of choice for these patients. Fluconazole, an azole antimycotic agent useful in patients with esophageal candidiasis, has not been widely used in the treatment of critically ill patients with life-threatening fungal infections. Fluconazole is available in both an intravenous and an oral form, but the oral form has not been studied in patients who are ill with altered gastrointestinal absorption.

In patients with a mixed fungal/pyogenic abscess, drainage of large cavities (<5 cm) is often required but antibacterial therapy is also mandatory. In patients who are being treated with broad-spectrum antibiotics, in whom a continuing infectious process is present, antimycotic therapy is warranted. It has been suggested that topical irrigation therapy with nystatin, imidazole derivatives, or amphotericin B might be effective in terminating local colonization of fungus in the abscess cavity.[12] However, local treatment has never been proved to be effective in critically ill patients with a systemic fungal infection. Critically ill patients with a mixed fungal/pyogenic infection should be treated empirically for both bacterial and fungal pathogens.

Based on this retrospective review, and considering the difficulty in establishing a diagnosis of disseminated fungal infection, we recommend early treatment with a systemic antimycotic agent if the patient remains ill in spite of drainage and appropriate antibacterial coverage. Positive fungal blood cultures are associated with a high mortality rate (8 of 11 patients), particularly when fungemia is not related to an intravenous catheter infection. Moreover, not all invasive fungal infections are associated with or have documented fungemia.[17] No currently available laboratory test will assist the clinician in solidifying the diagnosis of an invasive fungal infection. Thus an aggressive treatment algorithm that includes early antimycotic therapy may result in improved survival of patients with pure fungal and mixed fungal/pyogenic hepatic infections.

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Long-Term Consequences of Intraoperative Spillage of Bile and Gallstones During Laparoscopic Cholecystectomy

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Laparoscopic cholecystectomy is associated with a higher incidence of iatrogenic perforation of the gallbladder than open cholecystectomy. The long-term consequences of spilled bile and gallstones are unknown. Data were collected prospectively from 1059 consecutive patients undergoing laparoscopic cholecystectomy over a 3-year period. Details of the operative procedures and postoperative course of patients in whom gallbladder perforation occurred were reviewed. Long-term follow-up (range 24 to 59 months) was available for 92% of patients. Intraoperative perforation of the gallbladder occurred in 306 patients (29%); it was more common in men and was associated with increasing age, body weight, and the presence of omental adhesions (each $P < 0.001$). There was no increased risk in patients with acute cholecystitis ($P = 0.13$). Postoperatively pyrexia was more common in patients with spillage of gallbladder contents (18% vs. 9%; $P < 0.001$). Of the patients with long-term follow-up, intra-abdominal abscess developed in 1 (0.6%) of 177 with spillage of only bile, and in 3 (2.9%) of 103 patients with spillage of both bile and gallstones, whereas no intra-abdominal abscesses occurred in the 697 patients in whom the gallbladder was removed intact ($P < 0.001$). Intraperitoneal spillage of gallbladder contents during laparoscopic cholecystectomy is associated with an increased risk of intra-abdominal abscess. Attempts should be made to irrigate the operative field to evacuate spilled bile and to retrieve all gallstones spilled during the operative procedure. (J GASTROINTEST SURG 1997;1:85-91.)

Laparoscopic cholecystectomy has become the "gold standard" for the surgical management of symptomatic cholelithiasis, and has replaced traditional open cholecystectomy. Although laparoscopic cholecystectomy is associated with a slightly higher incidence of iatrogenic injury to the biliary tract compared to open techniques, overall complication rates appear to be similar for the two procedures. We and others have noted that iatrogenic perforation of the gallbladder occurs more frequently during laparoscopic cholecystectomy, leading to intraperitoneal spillage of bile and gallstones.[1,2] Although some authors initially suggested that intraoperative perforation of the gallbladder should prompt conversion to an open procedure,[3] the current practice at most institutions is to retrieve as many stones as possible and to irrigate the peritoneal cavity to evacuate the spilled bile.

Although spillage of gallbladder contents is thought to be relatively innocuous, the long-term consequences of intraperitoneal spillage of bile and gallstones are undefined. Results of experimental studies in animals have been contradictory. Several studies showed a minimal fibrotic reaction to intraperitoneal stones,[2,4,5] whereas others demonstrated abscess formation.[6] Furthermore, there are numerous case reports of complications arising from spilled bile and gallstones.[7-15] The aim of this study was to determine the factors predisposing to intraoperative perforation of the gallbladder and the incidence and spectrum of adverse sequelae related to spillage of bile and gallstones.

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MATERIAL AND METHODS

Between July 1990 and August 1993, 1139 consecutive patients underwent attempted laparoscopic cholecystectomy for symptomatic cholelithiasis. Clinical, diagnostic, therapeutic, and follow-up data were collected prospectively. Excluded from analysis were 80 patients (7.0%) who were converted to open cholecystectomy because of the presence of dense adhesions (n = 26), severe inflammatory changes (n = 22), extensive spillage of bile or gallstones (n = 10), or for miscellaneous reasons (n = 22). Of the 1059 patients who underwent successful laparoscopic cholecystectomy, the gallbladder was removed intact in 753 (71%), whereas in 306 patients (29%) the gallbladder was perforated during the course of the operation. In these patients the specific details of the operative procedure were reviewed.

Short-term follow-up was based on a clinic visit 2 to 3 weeks postoperatively, and long-term follow-up was achieved by questionnaire or telephone conversation in 977 patients (92%) at a mean of 3.3 years (range 2.1 to 5 years). Of the 82 patients without satisfactory follow-up, 26 had died, nine were incarcerated (Federal Medical Center prisoners), eight no longer resided within the United States, and 39 declined to answer questionnaires. Hospital records of these patient subsets were carefully reviewed to exclude selection bias. The incidence of gallbladder perforation was similar between patients with and without satisfactory follow-up data (29% vs. 32%). No major early complications were identified in patients with intact gallbladders, but among those in whom intraoperative gallbladder perforation occurred, two developed perihepatic abscesses and two had superficial wound infections. The incidences of postoperative complications in the results to follow are based only on patients in whom long-term follow-up was completed.

Operative Technique

Laparoscopy was performed by either an attending surgeon or resident under direct staff supervision. Both elective and emergency cases were included in the study. A four-trocar technique with a 30-degree angled laparoscopic video camera was used.[16] Dissection of the gallbladder was performed using a combination of electrocautery and blunt dissection with fine graspers, and the cystic artery and cystic duct were ligated with titanium clips. The gallbladder was removed through either the umbilical or epigastric port. When perforation of the gallbladder occurred, attempts were made to retrieve all spilled stones, and the peritoneal cavity was irrigated with saline solution to evacuate the spilled bile. Patients typically received one preoperative and one postoperative dose of antibiotic, most commonly a cephalosporin. In patients with acute cholecystitis, especially when the bile culture was positive, broad-spectrum antibiotics were administered for a longer period depending on the clinical situation.

Statistical Analysis

Statistical comparisons of proportions were performed by means of either the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared by means of the Wilcoxon rank-sum test. P values <0.05 were considered statistically significant. Summary parameters within the text are expressed as mean ± standard deviation.

RESULTS

A total of 1059 patients underwent successful laparoscopic cholecystectomy between July 1990 and August 1993. Iatrogenic perforation of the gallbladder occurred in 306 patients (29%, with a 95% confidence interval ranging from 26% to 32%), of whom 191 (62%) had spillage of only bile detected, and 115 (38%) in whom spillage of both bile and gallstones was noted (Table I). There was a higher proportion of male patients in the perforated gallbladder group compared to the intact group (43% vs. 28%; $P < 0.001$). The mean age of the perforated gallbladder group was greater than that of the intact group (56 ± 15 years vs. 52 ± 16 years; $P < 0.001$), and patients in the perforated gallbladder group weighed more (81 ± 18 kg vs. 77 ± 17 kg; $P < 0.001$). A history of abdominal surgery was not associated with an increased incidence of intraoperative gallbladder perforation. Adhesions between the gallbladder and the omentum conferred a greater risk of gallbladder perforation (42% vs. 30%; $P < 0.001$). Although patients in the perforated group had a slightly higher incidence of acute cholecystitis compared to the intact group (11% vs. 8.5%), this difference was not statistically significant.

Iatrogenic perforation of the gallbladder was higher in the first year (1990) of our experience with laparoscopic cholecystectomy (40%), but the incidence decreased progressively each year thereafter to 24% in 1993. Perforation of the gallbladder occurred during dissection of the gallbladder from the liver in 47% of patients, during extraction through the abdominal wall in 21%, and as a result of intraoperative retraction in 14%. The operative time for patients in the perforated group was slightly longer (100 ± 38 minutes vs. 106 ± 38 minutes; $P < 0.01$) but of little clinical significance. Similar numbers of laparoscopic cholecystectomies were performed by surgical residents in both patient groups (26% vs. 24%; $P = 0.573$).

Postoperative Complications

There were no perioperative deaths and no bile duct injuries. Ten patients (1%) required reoperation for postoperative complications, including two patients in the intact group (0.3%) for closure of persistent cystic duct stump leaks, and eight in the perforated gallbladder group (3%), with three for drainage of intra-abdominal abscesses, two for decortication of empyema, two for repair of an iatrogenic cautery injury to the duodenum, and one for persistent postoperative hemorrhage.

No differences between groups were found in the incidence of postoperative wound infection, pulmonary complications, ileus, or bile leakage (Table II). Postoperative pyrexia occurred in 54 patients (18%) in the perforated gallbladder group and in 67 (9%) in the intact group ($P < 0.001$). There were no clinically significant differences in the preoperative white blood cell count, although the postoperative white blood cell count tended to be higher in the perforated gallbladder group (9800 ± 3200 vs. 9200 ± 3400; $P = 0.02$, a difference of no clinical relevance). Similarly there were no differences in the postoperative use of parenteral or oral analgesics administered to the two patient groups or in the need for an antiemetic. Mean hospital stay was longer in the perforated gallbladder group (2.1 ± 3.2 days vs. 1.6 ± 1.3 days; $P < 0.01$); however, there was no statistical difference in the mean time for each group to return to work (13.6 ± 10.7 days vs. 17.0 ± 31.8 days; $P = 0.3$). The majority of patients in both groups were satisfied with their operative procedures (92% vs. 96%; $P = 0.29$).

Among the 977 patients for whom long-term follow-up information was available, four (0.4%) developed intra-abdominal infections. All belonged to the perforated gallbladder group ($P = 0.001$). Two additional patients in the perforated gallbladder group, with no long-term follow-up, were identified as having developed intra-abdominal abscesses. One patient died of prostate cancer prior to the follow-up survey, and the other declined to complete the follow-up questionnaire. Of these six patients, four had spillage of both bile and gallstones and two had spillage of bile only. A perihepatic abscess occurred in three of the six patients, two of whom also had right-sided empyema. A subhepatic abscess developed in the other three patients.

Only one patient in whom an intra-abdominal ab-

Table I. Patient and operative characteristics

	Gallbladder status		
	Intact	Perforated	*P* value
Patients	753 (71%)	306 (29%)	
Bile only		191 (62%)	
Gallstones and bile		115 (38%)	
Sex			
Male	214 (28%)	132 (43%)	<0.001
Female	539 (72%)	174 (57%)	
Mean age (yr)	52 ± 16	56 ± 15	<0.001
Mean weight (kg)	77 ± 17	81 ± 18	<0.001
Acute cholecystitis	64 (8.5%)	35 (11%)	NS
Omental adhesions	226 (30%)	127 (42%)	<0.001
Mean surgical time (min)	100 ± 38	106 ± 38	0.008
Operation performed by surgical trainee	182 (24%)	79 (26%)	NS

Table II. Complications: Intact vs. perforated gallbladder (long-term follow-up)

Complication	Intact (%)	Perforated (%)	*P* value
Intra-abdominal infection	0 (0)	4 (1.4)	0.001
Ileus	9 (1.3)	4 (1.4)	NS
Pulmonary infection	1 (0.1)	2 (0.7)	NS
Bile leakage	2 (0.3)	1 (0.4)	NS
Hemorrhage	2 (0.3)	2 (0.7)	NS
Wound infection	17 (2.4)	3 (1.1)	NS
Residual gallstone symptoms	72 (10.9)	30 (11.1)	NS

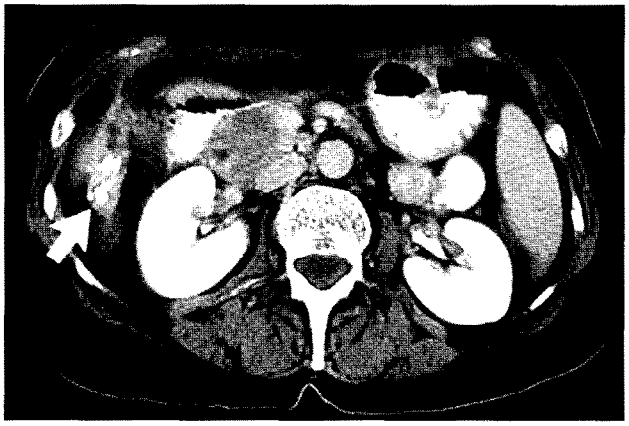
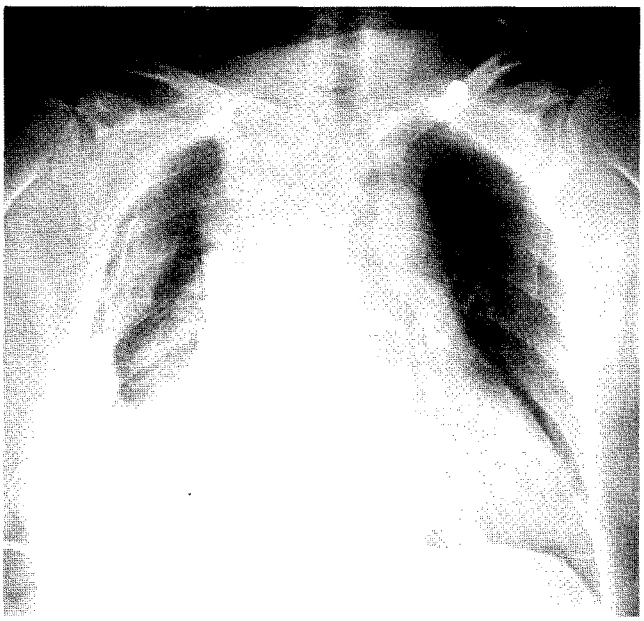


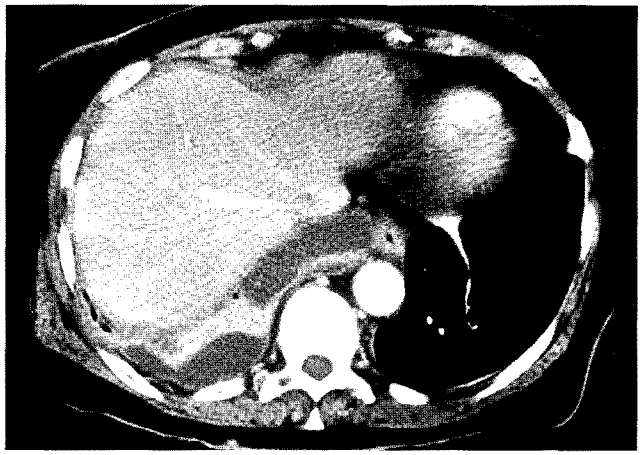
Fig 1. CT scan demonstrating intraperitoneal gallstones (arrow) with surrounding inflammatory reaction and fluid collection.

scess developed was known to have residual gallstones remaining at the completion of the procedure. These were not removed because of their inaccessibility laparoscopically. Signs of intra-abdominal infection occurred within 10 days of laparoscopic cholecystectomy in four patients; however, one patient presented with infection 28 days after the operation and another patient after 34 months.

Four patients had their intra-abdominal abscesses drained percutaneously under CT guidance, but three of them subsequently required operative intervention (Table III). In one patient symptoms resolved after CT drainage, but persistent right upper quadrant pain developed 6 months later and the patient underwent laparotomy. A small chronic subhepatic abscess was found, which contained three large, mixed stones (Fig. 1), and the symptoms resolved thereafter.

A





B

Fig. 2. A, Right-sided empyema secondary to perihepatic abscess resulting from retained gallstones. Thoracocentesis was performed, followed by right thoracotomy and decortication. **B,** CT scan of patient in *A*, showing subhepatic abscess, which required surgical drainage.

Table III. Major infective complications secondary to spilled bile and gallstones

Patient	Spillage	Site of infection	Percutaneous CT drainage	Operative intervention
1	Bile	Perihepatic	Successful	None
2	Bile	Perihepatic, right chest	Unsuccessful	Right thoracotomy and decortication of empyema, drainage of perihepatic abscess
3	Bile + gallstones	Subhepatic	Not attempted	Laparotomy, removal of intraperitoneal gallstones; postoperative pulmonary embolus
4	Bile + gallstones	Subhepatic	Unsuccessful	Laparotomy, drainage of abscess
5	Bile + gallstones	Subhepatic	Unsuccessful	Laparotomy, drainage of abscess
6	Bile + gallstones	Perihepatic, right chest	Not attempted	Right thoracotomy and decortication of empyema, removal of gallstones and drainage of perihepatic abscess

Laparotomy was performed in two other patients for drainage of an intra-abdominal abscess. Two patients required a transthoracic decortication for empyema secondary to perihepatic abscess formation (Fig. 2).

DISCUSSION

Since it was first reported in 1989, laparoscopic cholecystectomy has rapidly become the standard treatment for symptomatic cholelithiasis.[17] The procedure, however, is not without complications, most notably a higher incidence of biliary tract injuries compared to open cholecystectomy.[18-21] Nevertheless, 5 years of clinical experience and numerous prospective[22-25] and retrospective[26-28] trials have established laparoscopic cholecystectomy to be a safe procedure with a low incidence of major complications. Although a large number of studies have examined clinical outcomes of laparoscopic cholecystectomy, few have directly addressed the consequences of spillage of bile and gallstones within the peritoneal cavity, an event that occurs more frequently with laparoscopic than with open cholecystectomy.[1,2] There are case reports of gallstones lost at the time of surgery subsequently causing intra-abdominal abscesses,[7-10] empyema,[9] abdominal wall abscesses,[1,11,12] cutaneous sinus tracts,[13,14] and bladder fistulas.[15] Although these complications appear to be rare, their actual incidences are unknown.

Of 1059 patients who underwent laparoscopic cholecystectomy, 306 (29%) had spillage of bile alone or spillage of bile and gallstones into the peritoneal cavity. This incidence is similar to the 32% incidence of gallbladder perforation reported by Jones et al.[29] but is considerably greater than the perforation rate described in a Canadian multicenter study (9%).[30] Variables associated with greater risk of intraoperative gallbladder perforation were male sex, increasing age, and weight. Similar associations were noted by Jones et al. It is likely that a combination of factors makes the operation more technically challenging in heavier male patients, including the presence of increased abdominal wall adipose tissue, increased liver mass and friability (often fatty infiltration), which puts greater tension on the gallbladder during cephalad retraction, and a greater amount of fat around the cystic duct. In our study the most common timing of iatrogenic gallbladder perforation was during dissection of the gallbladder from the liver. All but 11 of our 1059 cholecystectomies were performed using electrocautery. Because only a few patients had the operation performed with laser dissection, we cannot draw any conclusions about the relative risk of perforation by other methods of dissection. The second most common time of iatrogenic gallbladder perforation was during removal of the gallbladder through the abdominal wall. To prevent bile and gallstone spillage when a large gallstone burden prevents ready extraction of the gallbladder through one of the ports, the gallbladder can be placed in a specimen bag before crushing or extracting stones with a stone forceps, or the fascial incision at the port site can be enlarged. These steps should minimize the incidence of gallbladder perforation and its subsequent infective complications.

It is noteworthy that the incidence of acute cholecystitis was similar in the intact and nonintact patient groups, a finding also reported by others.[2] Although an acutely inflamed gallbladder might be more friable superficially, the edematous and thickened gallbladder wall may also protect against inadvertent perforation during the different aspects of the operative procedure. In our early experience there was a low threshold for conversion to open cholecystectomy when the gallbladder was severely inflamed, which likely contributes to the low incidence of gallbladder perforation in these patients. As might be expected, there was a higher incidence of gallbladder perforation during the first year that laparoscopic cholecystectomy was performed at our institution; thereafter, however, the iatrogenic perforation rate stabilized at approximately 25%.

Despite the frequency of intraoperative perforation of the gallbladder, spillage of bile or gallstones did not lead to serious adverse sequelae in most patients. Surprisingly the incidence of wound infection was similar for both patients with an intact and perforated gallbladder. Even when spillage into the port site was analyzed separately, no significant correlation with subsequent wound problems was noted. Overall only six patients in the group with a perforated gallbladder had intra-abdominal abscesses; in two patients an empyema developed and required decortication. Empyema presumably developed from spilled gallstones that caused perihepatic abscess formation with subsequent erosion through the diaphragm into the right pleural cavity. This complication has been reported previously.[9] Although percutaneous CT-guided drainage was attempted in four patients, three still required surgical intervention because of inadequate drainage, probably because of the inability to remove the inciting gallstones.

Intraperitoneal gallstones plus bile have been shown to cause a predisposion to abscess formation in animal studies,[6] whereas sterile gallstones incite only a mild inflammatory reaction.[5] In our study, four of six patients who developed intra-abdominal abscesses had known spillage of both bile and gallstones. Brown pigmented stones theoretically may be more problematic when left within the abdomen because of their frequent association with bacterobilia.[31] Bile culture or stone analysis was not routinely performed; therefore no conclusions

can be drawn regarding the effects of spillage of infected bile or the type of gallstones spilled.

CONCLUSION

The overall risk of serious complications after intraoperative spillage of gallbladder contents during laparoscopic cholecystectomy is low. Intra-abdominal abscess formation after laparoscopic cholecystectomy occurred only in patients in whom bile and/or gallstones were spilled (1.4%). No intra-abdominal abscesses occurred in the 753 patients in whom gallbladder was removed intact. It therefore seems prudent to irrigate the peritoneal cavity with a large (>1 liter) quantity of saline solution if iatrogenic perforation of the gallbladder with spillage of bile or gallstones occurs. Whether topical antibiotics are important is unknown. If gallstones are knowingly spilled within the abdominal cavity, every attempt should be made to remove all gallstones. Because infective complications are rare following gallbladder perforation, conversion to laparotomy is not routinely indicated. However, conversion to an open procedure should be considered in patients in whom it is not possible to retrieve the majority of the gallstones laparoscopically, especially when bacterobilia is suspected or confirmed by Gram stain of the bile. Furthermore, if intra-abdominal abscess formation occurs, percutaneous drainage is likely to be ineffective unless the inciting gallstones can be removed.

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Discussion

Dr. L.W. Traverso (Seattle, Wash.). Since these data were not obtained prospectively, do you believe that the incidence of bile leakage is higher? Do you believe that the incidence of lost gallstones may also be higher? The incidence of bile leakage from the gallbladder at your institution was 29%, and you showed six patients in this group to have intra-abdominal abscesses giving an incidence for all patients of approximately 1.5% to 2%.

If you consider only the group that had bile leakage, or gallstone spillage, the incidence would be about 2%. If you just look at the subgroup in which gallstones were known to have contaminated the peritoneal cavity, the incidence of intra-abdominal abscess is approaching 4%.

Based on these data, I think you would have to inform your patients that there is an 11% chance that the gallbladder could be perforated and that stones could spill into the abdomen. Should this occur, the risk of intra-abdominal infection would be almost 4%. Have you examined the subgroup of patients for risk factors in this group that had only stone spillage? Were these stones spilled during retraction, during removal of the gallbladder from the abdomen, or during removal of the gallbladder from the gallbladder bed?

Dr. D.C. Rice. The clinical, therapeutic, and diagnostic follow-up data were collected in a prospective fashion in that the data base was prospectively generated in those patients who had spillage of gallbladder contents. We then went back and reviewed those patients' charts for further details of the intraoperative events such as the timing of gallbladder perforation. The overall perforation rate would remain 29%.

As was seen from the slides, bile spillage alone accounted for only two cases of intra-abdominal abscess. It is always difficult to know whether or not there may have been some small stones, or perhaps sludge that was not noted at the time of surgery, that could have accounted for a higher incidence or could have predisposed to abscess in those patients. I agree that gallstone spillage is significantly more likely to lead to abscess formation.

Dr. L. Way. (San Francisco, Calif.). Can you define the terms more precisely? What do you mean by spillage of bile? Do a few drops of bile suffice, or is there a specific threshold amount? In a retrospective study, can you obtain reliable information on the amount of bile and the number of stones, and can you get a sense of just how vigorous an effort was made to "tidy up" the peritoneal cavity?

Dr. Rice. It is difficult to quantify the amount of bile spillage. If the surgeon noted that there was light spillage of bile during cholangiography, we did not regard that as bile spillage. Only in cases where there was noted laceration or perforation of the gallbladder did we look on that as significant bile spillage.

Dr. N. Soper (St. Louis, Mo.). We too have examined our incidence of gallbladder perforation during laparoscopic cholecystectomy and it is remarkably similar at 30%. In our experience perforation did not lead to any untoward complications postoperatively, except for the fact that the operations took about 10 minutes longer because of the extra time needed to "clean up" the operative field. There was no increased incidence of abscess or other infectious complications. Do you proceed any differently once a perforation occurs? Do you culture the bile or administer a longer course of antibiotics? If in fact there was pus or an empyema of the gallbladder and you perforated it, would you recommend doing anything different at that time?

You stated that 10 patients were converted to open cholecystectomy because of perforation, yet your recommendation is that conversion is not required. What would cause you to convert to an open procedure at the time of surgery if a perforation of the gallbladder were to occur?

The other difference was that in the patients who suffered a perforation intraoperatively, the postoperative length of stay was longer than in those who did not, and I wonder why that was. Did it have to do with the patients who needed reoperation early on?

Would you make any other recommendations as to what should be done in the event of a perforation, such as placing the gallbladder in a bag? Do you think that because the initial incision is larger with an open entry there is less likelihood that the gallbladder will be perforated?

Dr. Rice. There was no difference in the amount of antibiotics given to patients who had perforation of the gallbladder and those who did not. Most patients did not develop intra-abdominal abscesses. Of those who did, four of the six presented within 10 days of surgery. They received a longer course of antibiotics.

The reason for the longer hospital stay could perhaps be attributed to the irritative effect of spillage of bile in the peritoneal cavity, which causes greater pain. Although when we analyzed narcotic pain medication used, comparing patients who suffered perforation with those who did not, we did not identify any difference. I am not quite sure why those patients stayed longer in the hospital.

Regarding prophylaxis in the case of a perforation, I think that sealing the perforation either with clips or with an Endoloop is something that should be done. Also, if the gallbladder is distended, prophylactic decompression can sometimes make it easier to manage.

If a large stone burden makes it difficult to remove the gallbladder through the fascial incision, we enlarge the fascial incision or use a stone crusher to try and break up the stones. Also, a laparoscopic specimen bag might be used if the gallbladder has been perforated.

Commitment and Fulfillment: The Life of John H.C. Ranson

Charles F. Frey, M.D.

John H.C. Ranson, M.D.
October 28, 1938–November 30, 1995

It was a time of sadness and mourning for all of us in The Society for Surgery of the Alimentary Tract when we heard that our President, John Ranson, S. Arthur Localio Professor of Surgery, had died on November 30, 1995, while undergoing treatment of multiple myeloma in Little Rock, Arkansas. It was to have been my honor to introduce him at our Annual Meeting. Instead I am here today to talk about his accomplishments and commitment to his profession, patients, and family.

In hope of giving as accurate a characterization of John as possible, I have spoken with his loyal assistant Helena Logan, his colleague and friend Kenneth Eng, his chairman and friend Frank Spencer, his student Bill Nealon, other pancreatic surgeons including Edward Bradley, John Cameron, Howard Reber, Andrew Warshaw, and—most important—his sister, K. Anne Ranson, and his beloved wife, Patricia, who are here with us today and to whom I am greatly indebted for much of the information about John's early life, education, and significant events in his life. As those of you who attended the President's Dinner last night know, Patricia has faced the aftermath of John's death with grace, courage, and strength. Her gallantry and presence in the face of adversity were an inspiration to us. I have also reread some of John's landmark papers, which are as valid today as when they were published 22 years ago.

Chronology

John was born on the eve of World War II, October 28, 1938, in Bangalore, India, the son of missionaries—the Reverend Dr. Charles Wesley Ranson and Jesse Grace Margaret Gibb. John's father, Charles, was a tall, charming, jovial Irishman. He dominated every room he entered by his presence and conversation. He lived to be nearly 85 and took great pride in John's accomplishments. John's father was held in high regard by the Indian government, which awarded him a medal for public service. John's mother, a quiet, self-effacing woman, also achieved distinction. A professor of history, she was commissioned to write a history of England for Indian students. Grace Ranson was also a champion tennis player and played with the Royal Family when they visited India. The Ranson family left India and returned to England in 1945, when John was 6 years old. Then, when John was 9, the family moved to the United States, where his father worked for an international missionary organization based in New York City. At age 11, in the English tradition, John went

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away to boarding school, but not in England. He attended the Groton School in Massachusetts. He maintained throughout his life many of the friendships developed during these formative years at Groton. Two years later, when John was 13, his family returned to England. John continued his studies at Groton and commuted back and forth across the Atlantic during his summer holidays on the Queen Mary. On graduation from Groton, he faced the choice of attending undergraduate school at Harvard or returning to England, where his family now resided, and attending Oriel College, Oxford, which was his father's alma mater. He chose Oxford. Shortly after John's return to England, tragedy struck. His beloved mother was killed in a car accident on New Year's Eve 1957. She was only 50; John was 18.

A few years after his wife's death, John's father returned to the United States as a professor and dean of the Theological Seminary of Drew University in New Jersey. He was to live in the United States for the rest of his life. John had two sisters. His older sister, to whom he was very close, lived in Scotland, where she was a high school teacher of French and Spanish. Mary, who had three children, died prematurely of a brain tumor at age 48. John's younger sister, Anne, lives in New Milford, Connecticut, and is Editor-in-Chief of the *Academic American Encyclopedia*. Anne donated her bone marrow to John during his multiple myeloma therapy. John's Uncle Fred may have influenced John's choice of profession. Fred was a surgeon in Shanghai before World War II. He was interned by the Japanese, during which time he contracted tuberculosis. No longer able to perform surgery after the war, he retrained as an ophthalmologist.

John obtained his undergraduate and graduate degrees from Oxford University in England, an M.A. in physiology, B.M., B.Ch., and then trained at St. Bartholomew's Hospital in London, England. He completed his surgical residency training at Bellevue Hospital and New York University Medical Center. He then joined the faculty of New York University, where he prospered under the leadership of Frank Spencer and S. Arthur Localio. He became Director of the Division of General Surgery and Director of the Residency Training Program at the New York University Department of Surgery, the S. Arthur Localio Professor of Surgery, and Chairman of the House Staff Committee.

John met his bride-to-be, Patricia Vignolo, in New York. She was a native of California and a graduate of Northwestern University. She worked in advertising and marketing and by the time they met, she had achieved distinction as an account supervisor in a large advertising agency in New York City. Their attraction was mutual and romantic. They were married in 1982. She and John were devoted to their two children, Elizabeth, now age 12, and Gibb, age 9, and derived much joy from their joint activities. John never missed a conference with his children's teachers.

Professional Achievements

John's clinical and research interests were in gastrointestinal surgery and focused on the liver, biliary tract, and pancreas. He was the author and coauthor of 79 original publications, eight selected summaries in gastroenterology, 47 book chapters, two books and one film in the American College of Surgeons library. His skills as a surgeon and surgical educator were recognized by Dr. Spencer. Only 10 years after joining the faculty, he was appointed a full professor. He was the recipient of many honors. He was an Alpha Omega Alpha fellow, treasurer of the James the IV Association of Surgeons, and served successive terms as Secretary and President of The Society for Surgery of the Alimentary Tract. He received the Hammond Citation for Distinguished Service from the New York State Medical Society and the Rousing-Tschering Medal of the Danish Medical Society. He was a vestryman and lay reader of St. James' Church of New York and a Knight of the Order of St. John of Jerusalem. Over a period of 20 years, he touched the lives of many surgeons. He was in great demand as a guest lecturer, as an invited speaker at symposia, and as a member of various postgraduate course faculties. He was a member of every important surgical society in the United States, including the American Surgical Association, the Southern Surgical Association, and The Society for Surgery of the Alimentary Tract, as well as the Royal Society of Medicine in London. He was on the editorial board of the *American Journal of Surgery*, the *British Journal of Surgery*, *Pancreas*, and the *International Journal of Pancreatology*.

John made many original contributions to our knowledge of gastrointestinal disease. He was a pioneer in our understanding of severe pancreatitis. In clinical studies he noted the frequency and severity of pulmonary insufficiency, the incidence and nature of coagulation deficiencies, the optimal timing of biliary surgery, and the role of the CT scan in managing pancreatitis. In the research laboratory he and his colleagues studied complement metabolism and chemotaxis. Additionally, he examined the relationship of pseudocysts, splenic vein thrombosis, and portal hypertension.

Although John made many other contributions to the management of gastrointestinal disease, his best-known contributions relate to long-term therapeutic

peritoneal lavage in patients with severe pancreatitis, which reduced the incidence of infection and death, and the grave prognostic signs of pancreatitis, better known as the Ranson signs. There is a belief that in all matters of scientific achievement, we stand on the shoulders of those who preceded us. In the case of therapeutic lavage, there is an unresolved issue for someone in this audience to take up—an issue that John and I discussed on more than one occasion. Does the benefit of long-term therapeutic lavage derive from the removal of noxious substances from the abdominal cavity or is therapeutic lavage simply an improved form of fluid resuscitation?

The Ranson signs of severity applicable to patients with acute pancreatitis constituted a remarkable achievement. Twenty-two years after their publication in 1974, the Ranson signs are still in use around the world and are still valid. Ed Bradley described an experience he had while making ward rounds in a remote third world country years ago. He was asked by one of the few English-speaking physicians if he knew Dr. Criteria. "Dr. Criteria?" he questioned. "Yes," was the reply, "Dr. Ranson Criteria." Based on astute clinical observations and later validated statistically in 1977, the Ranson signs stand as a monument to John's brilliance as a clinical investigator.

In the context of the early 1970s, there was little precedent for the development of grave signs for acute pancreatitis or any other disease, with the exception of the New York Heart Association classification of heart disease developed in the 1950s and the Child classification for patients with cirrhosis of the liver in the 1960s. However, John was faced with a large number of patients with acute pancreatitis in whom the clinical assessment of severity was often inaccurate. He saw the need for a tool that could predict severity within hours of the onset of acute pancreatitis. Identifying the physiologic and laboratory tests that could be used to indicate severity required many observations, hard work, and sophisticated knowledge of statistical methodology. John was far ahead of his time. In developing the Ranson grave signs of acute pancreatitis, he developed a tool that was helpful in patient triage, allocation of scarce resources, evaluation of the quality of care, interhospital comparisons, assessment of alternative therapies, and a predictor of death.

While John influenced surgical practice of pancreatic disease throughout the world with his publications and research, he was a very effective teacher and educator and role model for house staff and medical students at New York University. John did not have to shout, stamp his feet, threaten, or use other histrionics to gain the attention of the medical students and house staff. His intellectual curiosity and the enjoyment he derived from teaching were conveyed to his listeners. He was always helpful and always responsive to questions. He taught by the Socratic method. His remarks were expressed quietly, they were pithy and cogent, and were often based on his own observations in which he demonstrated the relationship between function and structural abnormalities of gastrointestinal disease. A simple raising of the eyebrow or a wry smile could express his disdain for a foolish notion. Sometime John's colleagues found it hard to emulate their teacher. Kenneth Eng, John's partner for many years, described his experience on becoming a faculty member at New York University and trying to arrange an on-call schedule with John. John was said to have replied, "Oh, that's not necessary. I'm around all the time." Dr. Eng felt if John was around all the time, then he ought to be too. Mercifully, for Dr. Eng, after 3 years of both of them being on call every night, weekend, and holidays, a call schedule was established when Tom Gouge joined the group.

John was a master surgeon with good judgment and technical virtuosity. The house staff turned to him for help with the most difficult gastrointestinal procedures. They say power corrupts and absolute power corrupts absolutely. John never corrupted the authority he derived from his position as Chief of General Surgery. The power he had in the operating room stemmed from the knowledge that he was a master surgeon. He was not arrogant, he was not a bully, he was not obnoxious or aggressive, he did not cast blame on others when problems arose—unfortunate traits we may recognize in ourselves or other surgeons lacking in self-esteem and talent. Instead John whistled while he worked: he enjoyed being in the operating room. He was unflappable and imperturbable in the face of surgical peril and adversity not infrequently associated with some operations on the pancreas.

At surgical meetings when John and I met with his colleagues, he was quiet and reserved. When disagreements arose during a discussion, he never personalized the discussion; he never used hyperbole or discredited those who disagreed with him. In fact, those who disagreed with John held him in high regard because he dignified his adversaries by listening carefully to their views and incorporating their concerns into his reply. John's equanimity and focus on the issues and his scholarly approach brought reason to heated debates or controversial issues.

Character

I turn from what John achieved to the factors in his life that were instrumental in developing his character. I confess this is speculation, although I have had

guidance from Patricia Ranson, Anne Ranson, and others. The influences I see were his religious background, his parents and their surrogates, his commutes across the Atlantic, and his mother's untimely death.

John's commitment to surgery was, I believe, more than that to a profession. Surgery to John was a vocation—a calling to which he would dedicate his life and energy. Surgery is a noble cause to which a Christian could give himself fully and in good conscience, much as his father had given himself to missionary work. John's long hours in the hospital and on call, along with his dedication to patient care, research, and education, support the view that John believed surgery was his vocation. John gave a talk on ethics in medicine to the laity at St. James' Episcopal Church in New York in which he revealed some of his feelings about his chosen vocation. His address on the topic of being a surgeon and a Christian left an extraordinary impression on his audience. Several of them wrote to Patricia after his death to express their feeling that they had seen God in man—this man who was a surgeon.

As devoted as John was to his vocation, he never allowed ambition to be his master. He never allowed the end (the goal of being a professor or Chief of General Surgery) to justify the means. The demands of academic surgery, particularly early in one's career when we are in what Joe Fischer describes as the "academic tunnel," can be overwhelming and destructive to family life. Perhaps John knew this and made a conscious decision not to marry until he was in his forties, or at least until he found Patricia. Once married, John was a devoted husband and father to his children, Elizabeth and Gibb. Patricia and John shared many common interests including travel, antiques, gardening, theater, religion, and paintings.

John grew up in a religious family accustomed to having to make personal sacrifices for the greater good. His mother, steady and serene, was a woman of uncompromising character who expected the best from her son and supported him in achieving it. Quiet and reserved though John was, he was unflinching when it came to principles. Patricia relates that John had asked to meet with black medical students while on a visit to South Africa. His request was ignored. He insisted until his hosts were reluctantly coerced into meeting his demands.

Influential Events

Family moves from one continent to the next, consistent with his father's role as a missionary, left John in the care of surrogates as well as his own parents during his formative years. While John was at Groton and his family primarily in England, he spent many school holidays with a family, close friends of his parents, in Chatham, New Jersey. Later, a family of old friends in Belfast, Northern Ireland, provided yet another home. There the man of the house was a physician, a recognized pioneer in industrial medicine. John could not help but be changed by this variety of experience. He became accustomed to differences in living styles. When we see something done differently from what we are used to, the contrast forces reflection.

The summer commutes from the United States to England and back on the Queen Mary were quite different from our experience of flying to Europe today in which the time is measured in hours rather than days. The days spent rocking to the rhythm of the waves, the seemingly limitless exposure of blue water encourage contemplation and provide a time for sorting things out, making decisions, resolutions, and commitments.

The untimely death of his mother—with whom he shared so many qualities—must have been an immense shock to an 18-year-old, and perhaps a time of rededication and commitment in her memory.

Accomplishments

How do we measure John's accomplishments? Certainly in the world's eyes he was a remarkable man of great talent, superior intellect, and technical ability, with a penchant for hard work.

He was a preeminent surgeon, a member of all the important surgical societies, on the editorial board of many journals, acknowledged master of pancreatic disease, father of severity assessment of acute pancreatitis, and President of The Society for Surgery of the Alimentary Tract, the most prestigious society in the world devoted to the study of diseases of the alimentary tract.

He was a good friend with a wry sense of humor, a good conversationalist, and a fun person to be with while traveling, in meetings, or in the operating room. He touched many lives. His funeral at St. James' Episcopal Church was officiated by 14 vested clergy and attended by close to 1000 persons. Patricia received hundreds of letters of condolence, for which she is most grateful.

Fulfillment

How did John feel about his life and accomplishments? Did he feel fulfilled as he faced his disease and the risks of the treatment for it? John was working on adding the final touches to the program for this year's meeting of the SSAT. He had already organized the entire postgraduate course, a labor of love, for which we are grateful, and which proved to be such a suc-

cess this past Sunday. He was concerned about an upcoming visit of the Residency Review Committee to New York University to review the surgical program, about which he had discussions with Frank Spencer. From Arkansas he had done much of the paperwork in preparation for the Residency Review Committee visit. He was looking forward to working in the new surgical research unit that he had fostered and brought to fruition at New York University. He was in the throes of preparing his presidential address. His topic, based on the information he had gathered in preparation for the talk, likely would have dealt with the need for quality assurance in the managed care environment. Perhaps, if he had lived, we would have heard about a new set of Ranson criteria to audit the quality of surgical care. He was reveling in a happy marriage and watching his children grow up. All this was cut off by his untimely death.

However, I believe John felt he had fulfilled his commitment to his wife and family and vocation in the sense that he had given full measure of himself to them. His goodness, exemplified in the way he lived his life, and his unwavering faith that good will prevail have affected his family and all of us, and we are the better for it.

I know in my heart that John made a commitment to do good and be of service to others. He made it early in life before he was 20 years of age. He died, as we all know, with much more to offer. But he had fulfilled his commitment and knew that his example would light the way for his family and the rest of us.