On October 3, 1997, the University of California, Davis, under the leadership of James E. Goodnight, Jr, MD, chair of the Department of Surgery, gathered together 5 distinguished authorities in surgical pancreatic disease to present a symposium in honor of the retiring professor of 21 years, Charles F. Frey, MD. The atmosphere was one of informality and “give and take,” and the result was not only a thorough and up-to-date review of many aspects of pancreatic disease but a wonderful tribute to a colleague who has spent a lifetime in this area of endeavor. Dr Frey has been a leader in this field, both scientifically in refining and extending our treatment of severe acute pancreatitis and administratively in organizing the Pancreas Club and promoting the concept that one could manage the pancreas, not in fear, but with confidence of success.

After words of welcome, Charles F. Frey, MD, introduced each of the guests with poignant comments and anecdotes relating to their individual idiosyncrasies. There followed the presentations summarized in this article.

PATHOGENESIS OF ACUTE EXPERIMENTAL PANCREATITIS

Andrew L. Warshaw, MD, Massachusetts General Hospital, Boston: Dr Warshaw reviewed the animal procedures used in producing a model of acute pancreatitis. Levels of the trypsinogen activation peptide, measurable by the enzyme-linked immunosorbent assay, rise within minutes of the onset of acute pancreatitis and continue to be elevated, making this peptide an excellent marker for observing the inflammatory process. The microcirculation of the pancreas suffers from diminished perfusion during inflammation, and this ischemia and the hypercalcemia accompanying it represent the only significant variables in the production of pancreatitis (calcium increases trypsin activity). Administering contrast material, as in early dynamic computed tomography, appears to make pancreatitis worse by reducing capillary flow and oxygenation to the pancreas, but nitric oxide has a protective effect by reducing trypsinogen activation peptide levels. Dr Warshaw speculated regarding the role of alcohol on the pancreas, indicating that a nonoxidative pathway through fatty acid ethyl esters produced ectopic trypsinogen activation.

ROLE OF CYTOKINES IN ACUTE PANCREATITIS

Howard A. Reber, MD, University of California, Los Angeles (UCLA): In addition to local acinar enzyme activation and release with the autodigestion of the pancreas, the secondary production of inflammatory mediators (cytokines spewed from macrophages) also plays a role in the systemic response in acute pancreatitis. Using a choline-deficient diet to produce experimental pancreatitis, Dr Reber’s group used interleukin 10 (an up-regulator of interleukin 1α, which inhibits cytokine synthesis and release) both prophylactically and after the establishment of disease to reduce the mortality of pancreatitis (compared with that in control subjects), while decreasing circulating levels of cytokines. Furthermore, the liver, rather than the pancreas, seems to be the source of cytokines; by blocking the Kupffer cells of the liver with gadolinium, the levels of cytokines were lowered and mortality improved. This opens a new area of pharmaceutical approaches to the management of pancreatitis.
NECROTIZING PANCREATITIS: ROLE OF OPEN PACKING

Edward L. Bradley III, MD, State University of New York at Buffalo: Pancreatic necrosis is the principal determinant of death in patients with pancreatitis, and trypsinogen activation peptide is a candidate serum marker of necrotizing pancreatitis. The indications for surgical intervention in cases of necrotizing pancreatitis include recognition, extension, the failure to respond to nonoperative therapy, and evidence of infection. Dr Bradley reviewed the problem of sterile necrosis, indicating that the operative approach has a slightly higher mortality and more organ failure. Thus, in general, an operative intervention is warranted only occasionally. Transendoscopic drainage of sterile necrosis was commented on favorably. Eighty percent of deaths in acute pancreatitis are due to sepsis. Needle aspiration of any necrotic area is a rapid way of determining the presence of infection so as to initiate early treatment. Thus, the questions that need to be resolved are the timing of the operation and the technique of surgical clearance. Evidence now favors late intervention (second or third week) and open packing initially, with the placement of large-bore catheters (for lavage) after a number of necrosectomies, and secondary wound closure. With this technique, the time in a surgical intensive care unit is reduced and mortality should approximate 15%. The real indication for open packing remains extensive necrosis involving the area under the colon and lateral to it, as well as in the lesser sac.

USEFULNESS OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) IN MANAGING PSEUDOCYSTS

William Nealon, MD, University of Texas, Galveston: Dr Nealon reviewed the natural history of pseudocysts, including maturation time (4-6 weeks), the role of expectant management (40%-50% of patients managed without immediate operation), and the spontaneous resolution of asymptomatic lesions (>60% of nonoperative cases associated with acute pancreatitis, whereas no regression occurs with those associated with chronic disease). He also discussed the role of spiral computed tomography and ERCP in diagnosing, defining, and planning the treatment of pseudocysts by determining communication of the cyst with the pancreatic ductal structure and the nature of the pseudocyst. The type of drainage, when needed, can be based on this information and the best results for the patient predetermined.

PATHOPHYSIOLOGY OF PAIN IN CHRONIC PANCREATITIS

Dr Reber: From his animal studies, Dr Reber suggested that ductal and interstitial pressures are elevated in chronic pancreatitis and that, as a result, vascular perfusion pressure is less than that needed to overcome the high tissue pressure. This results in a degree of ischemia manifested by low tissue pH, low tissue PO2, and low blood flow. As an example, secretin stimulation in chronic pancreatitis decreases blood flow and further diminishes the interstitial pH and PO2—all opposite to secretin’s effect in normal healthy persons (the basis for pain?). With duct decompression (Puestow procedure), however, there is a prompt increase in the interstitial pH, PO2, and blood flow with secretin administration (a reason for pain relief?). Thus, Dr Reber postulates that pancreatic pain is the result of ischemia, and measures aimed at correcting this problem of flow can relieve pain. Dr Reber has confirmed the diminished blood flow by endoscopic measurements in 12 patients with chronic pancreatitis (an average reduction of 50%).

CHRONIC PANCREATITIS: CAN WE PRESERVE PANCREATIC FUNCTION BY DECOMPRESSION OF THE PANCREATIC DUCT?

Dr Nealon: From the literature, 70% to 90% pain relief followed the Puestow procedure, 60% to 80% relief followed a Whipple operation, and short-term 50% relief occurred with stent placement in patients with chronic pancreatitis. Dr Nealon reviewed his institution’s series of 205 patients (188 with alcoholic pancreatitis) who had surgical intervention for pain, whose pancreatic duct was at least 7 mm, and who exhibited some degree of pancreatic function. In this series, 95% of patients had pain, 60% pancreatic calcification, 100% ERCP changes of the ductal system, 30% steatorrhea, and most (60%) had glucose intolerance or diabetes mellitus. After extensive preoperative testing and selection, all had Puestow procedures; 80% had relief of pain, and 94% had weight gain. There was a definite delay in further pancreatic deterioration and, in some, an improvement of function. Recurrence was not necessarily related to pressure in the ducts. Data from longer follow-up are awaited.

NEW APPROACHES TO PAIN MANAGEMENT IN CHRONIC PANCREATITIS: SPLANCHNICECTOMY

Dr Bradley: After reviewing studies of the somatic distribution of pain from electrode stimulation of the head, body, and tail of the pancreas, Dr Bradley analyzed a group of 22 patients he had studied—all with “small duct” (<7 mm) chronic pancreatitis—who presented with substantial pain. They were divided into 3 treatment groups. The first received a placebo; the second, sympathetic block; and the third, somatic nerve block. The group given preoperative sympathetic block had an overall impressive response in pain relief, and when those patients underwent thorascopic splanchnecctomy, that relief was sustained for up to 2 years of follow-up. Dr Bradley offered this as a measure of last resort in patients with small-duct pancreatitis who have persistent pain.

MOLECULAR BIOLOGY OF PANCREATIC CANCER

Charles J. Yeo, MD, The Johns Hopkins University, Baltimore, Md: Dr Yeo reviewed the risk factors for pancreatic cancer, noting that 1 of them is genetic. He then characterized the chromosomal deletions (chromosomes 18, 17, 13, 12, and 6) and the gains of chromatin (gene amplification) associated with this cancer. Furthermore, he
defined the fractional allelic losses, pointing out that the p16 gene, the p53 gene, and the DPC4 loss are all at least 50% altered in cancer of the pancreas. He alluded to the K-ras and her-2/neu oncogenes and their possible role and finally affirmed that 5% to 10% of all pancreatic cancer is familial. All of this led to the conclusions that this disease is one of acquired somatic mutations and that continuing genetic study may lead to important gains in identifying and eventually treating patients.

WORKUP OF PANCREATIC HEAD MASS AND STAGING OF PATIENTS WITH PANCREATIC CANCER: MASSACHUSETTS GENERAL HOSPITAL APPROACH

Dr Warshaw: The Massachusetts General Hospital experience with all comers—primarily patients with no early screening tests who present at a late stage in their disease—is a 17% survival rate after 1 year and 5% after 5 years. Thus, there is a need for both an earlier detection technique and better staging to avoid unnecessary operations. At that institution, spiral computed tomography with intravenous contrast material and laparoscopy (including peritoneal cytologic tests and an appropriate biopsy specimen) are the mainstays for staging. Endoscopic ultrasonography has not proved successful. Laparoscopy has shown that about 30% of patients have metastases undetected on computed tomography and, when peritoneal cytologic study was added, an additional 16 of 94 patients were found to have tumor cells in the washings and fluid specimens. All of these positive test findings, including peritoneal cytologic tests, stopped resective therapy and avoided debilitating and costly hospitalization time. At this institution, the savings from using laparoscopy was $3500 per patient. Dr Warshaw implied that the next step was to look for tumor cells in the bone marrow preoperatively and to study the implications of such findings.

DOWNSTAGING PANCREATIC CANCER THROUGH CHEMOTHERAPY, MAKING PANcreatoduodenectomy FEASIBLE: UCLA EXPERIENCE

Dr Reber: Forty percent of patients with pancreatic cancer have locally advanced disease (major vascular involvement) that, when recognized, results in palliative treatment with fluorouracil and irradiation (mean survival about 1 year). In recent years, a 4-drug program has been instituted (continuous rather than bolus fluorouracil, leucovorin calcium, mitomycin, and dipyridamole) in 44 patients for a minimum of 6 months; they were then reexamined and surgical treatment considered. Of this group, 17 (39%) responded to therapy by at least a 50% reduction in measurable tumor with relatively modest adverse effects. Seven of this group seemed to be candidates for resection after treatment, and 5 of these patients underwent an operation for cure. Two patients are alive at 22 and 54 months. Overall, whether or not reoperation was needed, the survival rate has improved, especially in responders. The protocol has been adopted as a Southwestern Oncology Group multicenter study.

ADVANCES IN SURGICAL MANAGEMENT OF PANCREATIC CANCER AND CLINICAL TRIALS: THE JOHNS HOPKINS UNIVERSITY EXPERIENCE

Dr Yeo: The Johns Hopkins University series is now up to 650 patients who had pancreatoduodenectomy, with a 1.4% mortality and a 41% complication rate (delayed gastric emptying, 19%; fistula, 14%; and wound infection, 10%). Of the overall group, 68% (443 patients) had periampullary disease. The postoperative hospital stay averaged 13 days. A pylorus-preserving procedure and partial pancreatectomy were being used whenever possible. Erythromycin lactabionate was given routinely, and in a series of 118 patients, the drug appeared to help gastric emptying as seen on a scan and perhaps less so clinically. The group studied the use of pancreatecto-gastrostomy in 145 patients to determine if this hookup afforded less opportunity for leakage, but they found no advantage over pancreateojunostomy. One hundred seventy-three patients have been studied to determine whether postoperative chemotherapy and x-irradiation therapy are helpful in prolonging survival regardless of tumor size, margins, or nodal involvement. Dr Yeo and colleagues confirmed that intensive treatment with both modalities is best. The group is currently studying the use of immunotherapy. In the resectable cases, the results have been a 20% survival rate after 5 years.

CYSTIC NEOPLASMS OF THE PANCREAS

Dr Warshaw: His experience with 175 patients with cystic neoplasms of the pancreas was reviewed. The patients were categorized by the malignant potential of the neoplasms: pseudocysts, nonmalignant; serous, rarely malignant; mucinous, often malignant; and papillary cystadenocarcinoma. Dr Warshaw noted that pancreatic ductal obstruction seen on ERCP was always associated with cancer and warned that physicians should be wary of a cystic lesion of the pancreas when there is no history of pancreatitis or alcoholism or when the lesion is asymptomatic. Of the diagnostic tests available, needle aspiration is most helpful. Characteristic markers of aspirated fluid included carcinoembryonic antigen as useful, values of which are high in patients with mucinous masses, and CA-15-3, which is even more specific for cancer in those with mucinous neoplasms. All mucinous tumors should be surgically treated, but for serous lesions, various treatment options are available.

Between each group of presentations—acute pancreatitis, chronic pancreatitis, and pancreatic cancer—cases were presented by University of California, Davis, residents for discussion by the panel. Many valuable points were made, and there seemed to be almost unanimity in views about the major issues of the diagnosis and treatment of pancreatic disease.

At a reception, Dr Frey was presented with a university-embossed chair and a plaque of distinction.

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