THE FALLIBILITY OF PANCREATIC BIOPSY*

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THERE IS NO more difficult clinical problem in abdominal surgery today than that presented by a mass in the head of the pancreas.[3, 6, 12, 14] In contrast to masses of uncertain nature elsewhere in the human body, where biopsy is properly and effectively employed, biopsy of a mass in the head of the pancreas is unsatisfactory. There is danger of troublesome bleeding immediately, and of pancreatic fistula subsequently. Even when successfully accomplished, biopsy is often non-informative or frankly erroneous.

Neither the consistency, size, shape, nor degree of fixation of the suspect mass is of aid in differentiating a neoplastic lesion from an inflammatory one. Two situations are encountered in which the correct diagnosis may, with reasonable certainty, be made by gross findings. The first is that presented by a mass in the head of the pancreas with associated diffuse hepatic or peritoneal carcinomatous metastases. In this situation the diagnosis of incurable cancer of the pancreas with metastases can quite safely be made. The second is that in which the mass in the head of the pancreas is associated with findings of chronic cholecystitis and cholelithiasis, with evidence of common duct dilatation and inflammation, and with evidence of old fat necrosis in mesentery and omentum, especially in the lesser omental sac. In this situation the diagnosis of chronic pancreatitis can probably be made with relative assurance, particularly if the patient, in addition, gives a history of recurring episodes of abdominal pain, nausea and vomiting, and transient jaundice going back over several years. In other situations in which a tumefaction in the head of the pancreas is found without associated findings, the problem of accurate diagnosis at the time of surgery is baffling.

Kirtland[9] has proposed the use of the Silverman needle for aspiration biopsy of pancreatic masses at the time of exploration. Although we have had no personal experience with this method of biopsy for pancreatic lesions, we suspect that, as with all other methods of biopsy, it is of absolute value only when a biopsy positive for cancer is obtained.

HISTOPATHOLOGICAL CONSIDERATIONS

The histological changes in the pancreas secondary to acute ligation of the pancreatic duct have been previously described.[1] Grauer[7] and Haunz, and Baggenstoss[8] have more recently described the changes in the pancreas found at autopsy in patients with cancer of the head of the pancreas. The latter state that "in neoplastic obstruction of the pancreatic ducts the earliest changes are distention of the ducts and flattening of the epithelial lining. . . . Dilatation and occasional rupture of acini probably occur during the active stage of secretion, and it is considered that most of the focal areas of pancreatitis and fat necrosis are initiated in a similar manner. Later in the process nearly all acinar tissue is replaced by fibrous change, and this replacement becomes the most conspicuous change in the entire organ." The occurrence of pancreatitis in association with

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pancreatic carcinoma is occasionally mentioned by others,[3, 9, 14] but its surgical significance has never been emphasized.

Figure 1 demonstrates the rather dense fibrosis surrounding pancreatic cancer, the compression, dilatation, distortion and dissolution of pancreatic lobules with replacement by fibrous tissue, and the infiltration

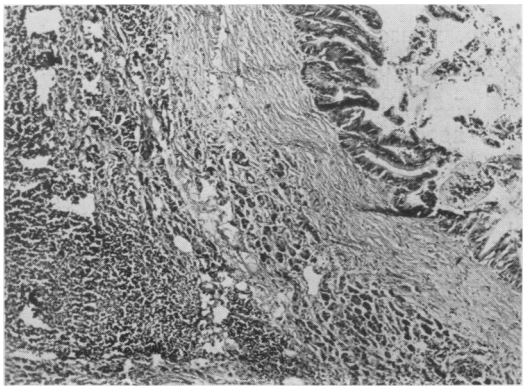

FIG. 1. (M. H. Pancreas x 22.) Well differentiated adenocarcinoma in the right upper corner borders on dense fibrous tissue. Acinar tissue in center is decreased in quantity, distorted, and is undergoing dissolution. Massive infiltration of inflammatory cells is seen to the left.

of leukocytes throughout. The striking juxtaposition of pancreatitis and pancreatic cancer is well shown.

Figure 2 is a representative section of pancreas taken a few millimeters distal to cancer, and Figure 3 is a representative section of subacute and chronic pancreatitis from a surgical specimen in which no cancer was present. The similarity between the two sections is evident, both showing comparable degrees of acinar dilatation, distortion and atrophy, with extensive fibrosis, infiltration of leukocytes and focal collections of inflammatory cells resembling early abscesses.

Figures 4 and 5 are representative sections from surgical margins of resection in two different individuals undergoing pancreatoduodenectomy for cancer. Neither show the presence of cancer in these planes. Figure 4 demonstrates considerable distortion of lobules, with increase of intra-acinar connective tissue, infiltration of leukocytes, and dilatation of ducts. Figure 5 represents what is believed to be more advanced changes of similar nature. There is here almost complete absence of acinar tissue, the dense fibrous tissue being broken only by occasional normal-appearing islets of Langerhans, and by markedly dilated pancreatic ducts.

That pancreatic cancer is associated with varying degrees of pancreatitis seems thus substantiated. Neoplastic invasion of pancreatic ducts results in obstruction, distention, inflammation, necrosis and fibrosis of pancreatic tissue distal to the area of invasion. This "distal pancreatitis" surrounds the cancer in varying degree, but necessarily forms the outermost layer of the gross tumefaction, which is the portion accessible to the surgeon's palpating hand or biopsy knife (Fig. 6). The implication of this fact is self-evident. The high incidence of falsely negative biopsies is thus quite understandable.

ANALYSIS OF CLINICAL MATERIAL

Thirty-one patients consecutively treated for cancer of the pancreas form the basis for this report. Nine patients in this group had had exploratory laparotomy performed elsewhere three to nine months prior to admission to Memorial Hospital, and had been considered to have benign pancreatitis on the basis of a pancreatic biopsy performed at that time. Of these nine patients, only two were found at secondary operation by the writer to be suitable for pancreatoduodenectomy, which was performed. The remaining seven patients all had evidence of disseminated cancer for which no active treatment could be given. These seven patients, as well as the two operative cases, are now dead of cancer. Nine of 31 patients, or 29 per cent of this series (26.5 per cent of 34 patients), therefore were denied the opportunity of surgical cure by pancreato-duodenal resection at

the time of their first exploration because of the surgeon's reliance on a "negative" pancreatic biopsy.

During the same interval three additional patients believed to have cancer of the pancreas were explored, found to have a localized mass in the head of the pancreas, and subjected to pancreatoduodenectomy. The tumefaction in these cases was subsequently proved by histological study to be benign. Fortunately all three patients survived their radical surgery and are living and well 3 years, 18 months* and 5 months following their resection. Two of the three appear economically and socially rehabilitated. Adding these three patients with benign disease to the 31 patients with cancer provides a total of 34 patients having, or believed to have, cancer of the pancreas. Unnecessary surgery was performed in 8.8 per cent of this group of 34 patients.

Fraser,[6] in analyzing 1035 cases of obstructive jaundice due to pancreatic disease, found that 7 per cent of simple lesions were mistaken for malignant neoplasms, and that 16 per cent of malignant lesions were mistaken for simple disease. Fraser's 7 per cent incidence of mistaking benign for malignant lesions is comparable to the 8.8 per cent of this series. The 26.5 per cent incidence of mistaking malignant for benign lesions in this small series as compared with Fraser's figure of 16 per cent is doubtless explained by the inevitable preponderance of patients with cancer in any series reported from a cancer hospital.

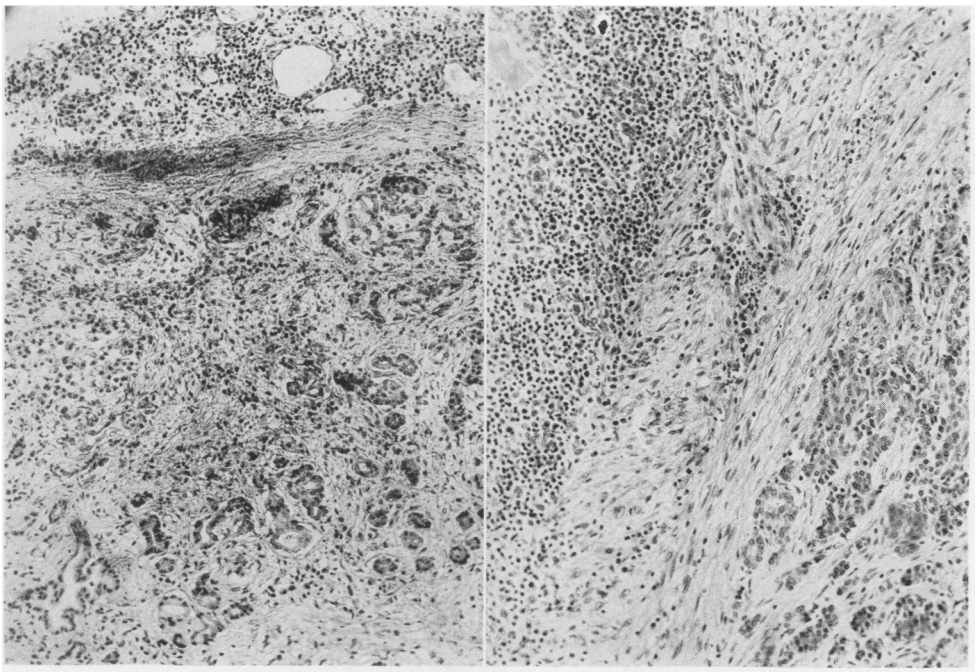

FIG. 2 FIG. 3

FIG. 2. (J. B., pancreas x 57.) Section taken a few millimeters distal to cancer, demonstrating distortion and disruption of pancreatic lobules, infiltration of leukocytes, dilatation of ducts, and proliferation of dense fibrous tissue, all typical of subacute pancreatitis.

FIG. 3. (A. D., pancreas x 57.) Findings similar to those in Figure 2. Pancreatoduodenectomy was performed in this instance in the belief that cancer was present. Fibrosis, lobular disruption, and massive inflammatory infiltrate are evident, typical of benign subacute pancreatitis. No cancer was found on histologic study.

* Patient died on November 17, 1953, 22 months following pancreatoduodenectomy. Cause of death: Biliary cirrhosis which antedated, but no doubt was aggravated by, the surgery performed.

DISCUSSION

Since occasional case reports are now appearing indicating five-year clinical cures in cancer of the head of the pancreas following pancreatoduodenectomy,[2, 5, 10, 11, 15] this hitherto hopeless lesion must now be regarded as potentially curable by radical surgery. In the 31 patients with cancer under discussion none has been observed for as long as five years, and no statement concerning cure in the surviving members of this group is warranted. It can definitely be stated, however, that no one in this group is at present living, unless he has undergone pancreatoduodenectomy.

Pancreatoduodenectomy is a major surgical undertaking, characterized by significant morbidity and mortality. In the 34 patients of this series, 12 pancreatoduodenectomies were performed with a surgical mortality of 25 per cent. Other surgeons are reporting steadily improving mortality figures for this operation, and in certain clinics the mortality rate is now around 10 per cent.[4, 13, 16] With increasing experience and with improved preoperative and postoperative care, it is believed that a 10 per cent operative mortality is a goal well within reach of all surgeons performing pancreatoduodenectomy.

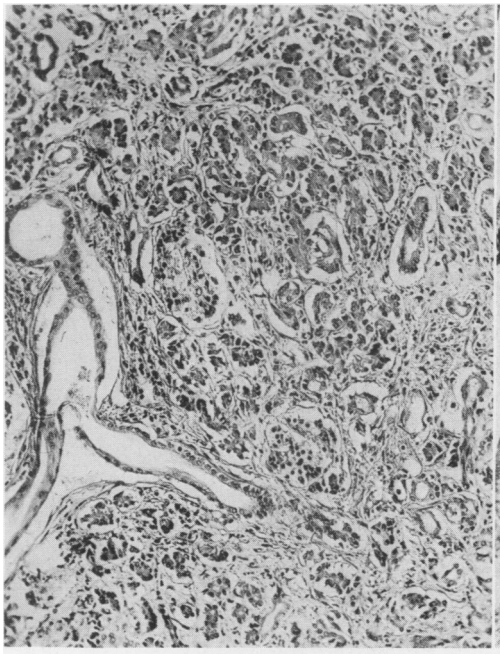

FIG. 4

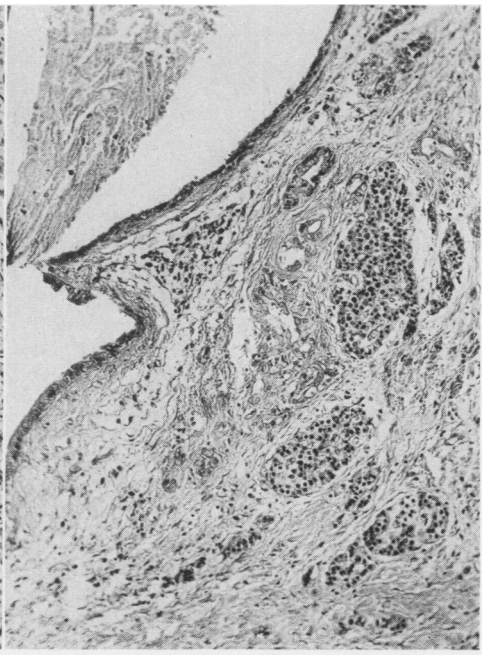

FIG. 5

FIG. 4. (A. A., pancreas x 57.) Section taken at surgical margin of resection performed for cancer of the head of the pancreas. No carcinoma present in this plane. Acini are dilated, distorted, diminished in number, and separated by fibrous tissue. Leukocytic infiltration is present, and a dilated pancreatic duct in tangential section is evident.

FIG. 5. (J. L., pancreas x 57.) Section taken at surgical margin of resection performed for cancer of the head of the pancreas. No carcinoma present in this plane. There has been almost complete replacement of acini by fibrous tissue. One edge of a markedly dilated pancreatic duct is shown at the left in tangential section, as well as several normal-appearing islets of Langerhans. These findings are believed to exemplify a progression of changes already seen in Figure 4.

In this series of 34 patients, in which there was one surgical death in every four pancreatoduodenectomies performed, there was also a 26.5 per cent incidence of pancreatic cancer mistaken for benign disease because of misleading biopsy material, with death from cancer in all these patients. This means that slightly more than one

death in four occurred where pancreatoduodenectomy might have been, *but was not,* performed.

The implication of this statement is obvious and worthy of thought; namely, that as many patients were consigned to certain death from pancreatic cancer by unwarranted conservatism as experienced operative death from aggressive surgical ablation of their pancreatic neoplasm. Inferential support of this idea is supplied by reference again to the large series of patients reported by Fraser. Unrecognized malignant lesions of the pancreas were present in 16 per cent of his 1035 cases of obstructive jaundice due to pancreatic disease, meaning that one patient in six died from cancer perhaps unnecessarily, because of failure to perform definitive excisional surgery. If one assumes a 20 per cent operative mortality for pancreatoduodenectomy as being representative of the general performance of this operation throughout the surgical world, then one will have for comparison one fatality in every five pancreatoduodenectomies performed.

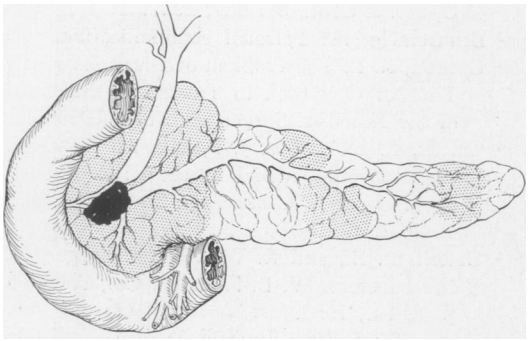

FIG. 6. Diagrammatic representation of pancreas and associated structures. A relatively small cancer in the head of the pancreas is obstructing both the common bile duct and the major pancreatic duct of Wirsung, and is completely surrounded by a large, bulky area of pancreatitis. Other foci of pancreatitis, secondary to ductal obstruction, are depicted in the body and tail of the pancreas.

It would seem, therefore, that, given a patient with a suspicious mass in the head of the pancreas, his chances of surviving pancreatoduodenectomy are only slightly worse than his chances of *not* having cancer if the head of the pancreas is left *in situ.* And for the surgeon who has reduced his operative mortality to 15 per cent or less, the patient's chances of surviving pancreatoduodenectomy are better than his chances of not having cancer.

If this be so, the surgeon whose philosophy toward cancer is aggressive rather than defeatist is forced to conclude that pancreatoduodenectomy should be undertaken when he finds on exploration a tumefaction of unknown nature in the head of the pancreas that is technically resectable. This resolution should be uninfluenced by biopsy, performance of which is considered superfluous. Cattell and Warren,[5] in their recent monograph, state, "With few exceptions in our experience, it was necessary to proceed with resection without positive histologic diagnosis, but it should be emphasized that resection is not proceeded with unless dilatation of either the pancreatic duct or biliary tract can be demonstrated."

The surgeon committed to such a course must be prepared to accept a final benign diagnosis in a certain group of these patients (probably about 7 per cent), being assured that only by such aggressive surgery is the patient with early pancreatic cancer offered the chance for cure. Furthermore, again assuming an operative mortality of 20 per cent for this procedure, he must be prepared to accept an occasional fatality in a patient with benign pancreatic disease, but from the standpoint of mathematical probability this should occur only once in every 71 pancreatic resections.* If

* Probability of X happening [Pr(X)] = $\frac{\text{No. ways X can happen}}{\text{No. ways all events can happen}}$

Probability of X and Y happening = Pr(X) x Pr(Y)

The probability of an operative fatality in a person with benign pancreatic disease is therefore 0.20 x 0.07 = 0.014. A probability of 0.014 is approximately the same as 1 chance in 71 occurrences.

a surgeon's operative mortality falls to 10 per cent, then he runs the mathematical probability of losing a patient with benign disease only once in every 143 resections.

CONCLUSIONS

If biopsy of a pancreatic mass were reasonably accurate, all tumefactions in the pancreas would be thus diagnosed in spite of troublesome complications that might arise. Pancreatic biopsy, however, is often misleading or frankly inaccurate. This is due to the high incidence of associated pancreatitis resulting from neoplastic invasion of pancreatic ducts with secondary dilatation, inflammation, and fibrosis of tissue distal to the area of invasion. This "distal pancreatitis" surrounds the cancer in varying degree, but necessarily forms the outermost layer of the gross tumefaction, which is the portion accessible to the biopsy knife. In the interest of curing more patients with cancer of the head of the pancreas, it is proposed that pancreatoduodenal resection, when technically feasible, be undertaken for all masses of uncertain nature in the head of the pancreas without recourse to biopsy.

On the basis of discussion herein contained it would appear that a patient with a mass of unknown nature in the head of the pancreas has a chance of surviving pancreatoduodenectomy only slightly less than his chance of *not* having cancer of the pancreas if the suspect mass is left undisturbed. While surviving pancreatoduodenectomy is no assurance of cure of pancreatic carcinoma, nevertheless the antithesis is invariably true; namely, that all patients with cancer of the head of the pancreas succumb to this disease with or without any other method of treatment.

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