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Duodenoscopy and Endoscopic Retrograde Choledochopancreatography: Present Position in Relation to Periampullary and Pancreatic Cancer

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Duodenoscopy and endoscopic retrograde choledochopancreatography represent a major advance in the diagnosis of periampullary and pancreatic lesions. Instruments, techniques and complications are reviewed. A combination of endoscopy and ERCP will yield diagnosis in a high proportion of patients suspected of pancreatic or ampullary carcinomata. Information is obtained which is not only of diagnostic value but is important in the surgical treatment of such patients.

KEY WORDS: endoscopic retrograde choledochopancreatography, periampullary and pancreatic cancer

The introduction of fiberoptics into endoscopy (Hirschowitz et al., 1958) has revolutionized diagnostic methods, particularly in the gastrointestinal tract. The maneuverability, flexibility, and excellent optical systems of modern fiberscopes have brought an ever increasing area of the gastrointestinal tract within the range of direct examination. Recent refinements in instrumentation allow duodenoscopy (Takagi, 1969; Hara and Ogoshi, 1970; Shindo et al., 1970) cannulation of the papilla of Vater under direct vision and the performance of endoscopic retrograde choledochopancreatography (ERCP) (Oi et al., 1969; Ogoshi et al., 1970; Classen, 1971; Cotton, Salmon, Blumgart, et al., 1972; Blumgart et al., 1972; Blumgart and Salmon, 1973; Burwood et al., 1973). These techniques have opened a welcome new dimension in the investigation of duodenal disease (Cotton, 1972) and in the diagnosis of jaundice (Blumgart et al., 1974). Retrograde choledochopancreatography has also made possible the examination of the pancreatic ductal system, allowing accurate investigation of patients with known or suspected pancreatic disease. The relevance of these new methods in relation to pancreatic cancer is as yet unclear.

The purpose of this paper will be to review the impact of endoscopy and endoscopic retrograde choledochopancreatography on the diagnosis, management, and prognosis of pancreatic and periampullary carcinomata.

INSTRUMENTS AND TECHNIQUE

Forward-viewing panendoscopes are necessary for routine esophagogastroduodenosocopy

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but do not allow reliable views of the descending duodenum or of the papilla of Vater. It is essential to employ a lateral-viewing flexible duodenoscope with a channel for the passage of biopsy forceps or teflon cannulae (1.6 mm diameter) which may then be passed through the instrument into the field of view over a small controllable bridge (Fig. 1). These instruments allow automatic insufflation of air, and suction and photography can be carried out easily.

Metal-tipped cannulae are not generally available, but their use facilitates cannulation and their radio-opacity is useful. More recently, cannulae have been developed using radio-opaque materials with distance markers and small cytology brushes, which can be passed down the length of the instrument and introduced at the orifice of the papilla of Vater; these instruments are now under trial.

Our studies have been carried out using the Olympus JFB I and Olympus JFB II instruments.* Lateral-viewing endoscopes suitable for papillary cannulation are also produced by Machida** and by the American Cystoscope Makers, Inc.† Adequate facilities and staff are necessary for good results. Successful ERCP depends on cooperation between an experienced endoscopist and radiologist, and it is also preferable to have at least one technical assistant and one nurse present during examination.

A recent history of acute pancreatitis (within two weeks) and Australia antigenemia appear to be the only absolute contraindications to examination. We admit patients for examination and maintain observation for at least 36 hr afterwards. The patients are examined in the X-ray department with fluoroscopic screening available. The entire procedure is conducted under local pharyngeal anaesthesia (topical lignocaine 4%). Premedication is carried out using intramuscular atropine (0.6 mg) and intramuscular Diazepam (10 mg), with usually a further intravenous injection of Diazepam (5–10 mg) immediately before intubation (Main, 1967). During duodenoscopy and cannulation of the papilla of Vater, it is essential to maintain duodenal ileus. Hyoscine n-butyl bromide (Buscopan) is given at this stage in increments of 40 mg to maintain duodenal ileus. Buscopan is not available in the USA; as a substitute, probanthine or atropine and dicyclamine hydrochloride (Bentyl) (Gregg, 1972; Vennes and Silvis, 1972) give an adequate duodenal ileus. General anaesthesia is not necessary and in any event is undesirable since patients cannot complain of pain due to inexpert use of the instruments or excessive injection of contrast material into the pancreatic duct. For the same reason, we do not employ pethidine in our premedication regime. With the patient in the left lateral or semiprone position, the endoscope is passed into the esophagus. Panendoscopy is desirable in most cases, but esophageal examination can be omitted, particularly if there is an adequate barium meal examination and if the main site of interest is the duodenum and pancreas.

With side-viewing instruments, intubation is performed with the distal end facing anteriorly. The esophagus is not usually visualized but the stomach is examined and the instrument then advanced through the pylorus to the duodenum. The presence or absence of bile in the duodenal loop is noted, and a full examination is carried out for distortion, mucosal ulceration, infiltration, or diverticulae. Biopsy and cytology specimens and photographs are taken as necessary.

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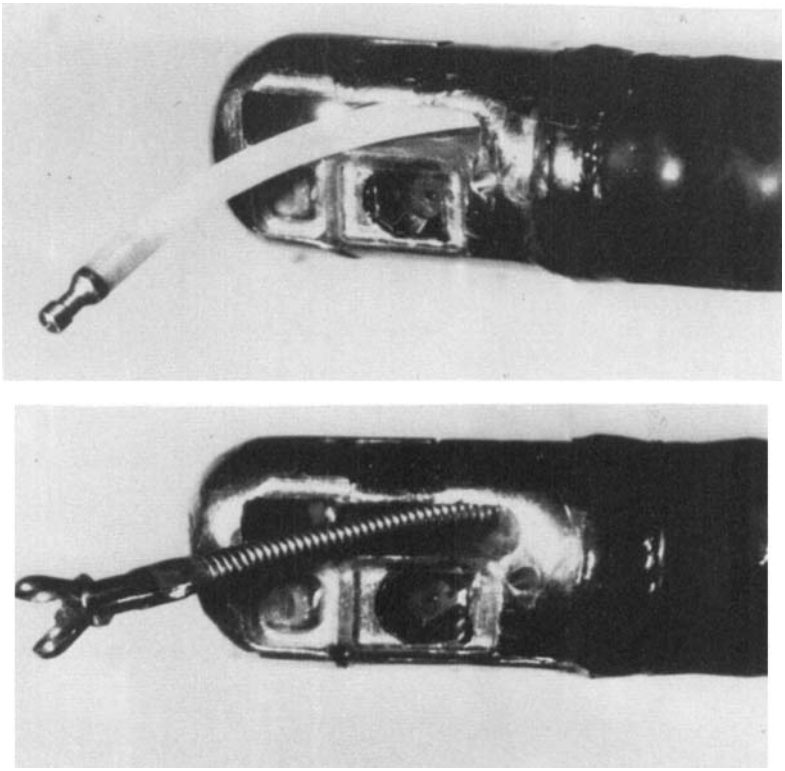

Fig. 1. Distal end of Olympus JFB 1 instrument showing polythene cannula and biopsy forceps protruding from the working channel of the instrument. Both these may be moved independent of the tip of the instrument by means of a bridge controllable from the proximal end.

The papilla of Vater is sought, lying usually slightly posteriorly halfway down the medial wall of the descending duodenum. It is characterized by a longitudinal fold or folds running down the medial wall for some centimeters and terminating in a semicircular rather hooded fold and a small glans (Fig. 2). The shape of the papilla may vary during examination, and bile or blood may be observed draining from its orifice. With experience, the duodenum is entered in a very high proportion of patients and the papilla located. Thus, we have examined 145 patients, entered the duodenum in 144, and located the papilla in 140 (Blumgart et al., 1974). Failure to find the papilla is usually due to gross distortion occasioned by previous surgery or by pancreatic disease. Small accessory papillae can be seen in over 24% of patients (Cotton, 1972).

The papilla is cannulated by obtaining a close face-on view; the teflon cannula filled with contrast is then passed through the instrument and guided into the papillary orifice. Contrast medium is then introduced slowly under fluoroscopic control. Thorough radiological examination is necessary, and the techniques and management have been described (Burwood et al., 1973). It should be noted that the pancreatic duct should not be overfilled, and injection should cease when the fine pancreatic radicles are visualized.

Successful cannulation can be carried out in a high proportion of patients, although the success rate will vary with the experience of the operator, the indications and criteria for the examination, and, of course, duodenal distortion due to disease. While high success rates (75% or more) for opacification of a duct are reported (Ogoshi et al., 1970; Oi et al.,

Fig. 2. Typical view of the papilla of Vater as seen at duodenoscopy.

1970; Blumgart et al., 1972; Cotton, Salmon, Blumgart, Burwood, Davies, Lawrie, Pierce, and Read, 1972; Burwood et al., 1973; Blumgart et al., 1974), the most useful figures are those for selective cannulation of a clinically relevant duct or ducts. Filling the bile duct in a patient suspected of pancreatic disease may be a diagnostic failure. Most operators have found that it is easier to fill the pancreatic duct rather than the biliary system. Selective cannulation is, therefore, more often a problem of changing from the pancreatic duct to the biliary system, although both may fill simultaneously. Selective success rates for the pancreatic or biliary ductal system have been reviewed by Cotton (1972) and vary from 64% to 78%. This is in line with our experience, and we have filled both biliary and pancreatic ductal systems in 18 of 20 consecutive examinations.

RETROGRADE PANCREATOGRAPHY

The main pancreatic duct and its branches are usually outlined by the injection of 2–5 ml of contrast medium. If the cannula is withdrawn, rapid emptying results and is

usually complete within 5 min. This time period may be somewhat delayed in the elderly. The main duct is frequently pistol shaped with an acute bend between the head and the body, although so many normal variations have been described (Kasugai et al., 1972) that it is impossible to diagnose pathological displacement. Indeed, pancreatograms are as yet relatively unfamiliar and are easier to obtain than to interpret.

The main pancreatic duct tapers from head to tail, and measurements have been made and corrected for size by comparison with the overlying instrument. The mean normal diameter increases with age, and the mean greatest normal diameters have been found to be less than 4 mm before the age of 40 and between 4 and 6 mm after that age. Kasugai and his colleagues (1972) measured the maximum diameters of the normal duct in the head, body, and tail of the pancreas. In 68 patients the mean (± 1 SD) maximum diameter of the duct in the head of the pancreas was 3.5 mm, in the body 2.67 mm, and in the tail 1.7 mm. The degree of filling of branch ducts depends largely on the volume and pressure of contrast injection and varies considerably. However, it may be difficult to diagnose pathological lack of filling of even a major branch such as that to the uncinate process. Much further careful study is necessary, and at the moment interpretation of retrograde pancreatograms must rely on major changes in the main ductal system. It should be noted that the main pancreatic duct may appear entirely normal despite pancreatic disease. This particularly applies to pancreatitis where, although great variations in caliber and localized stenosis are the most common abnormal findings, up to 30% of ducts may appear normal (Cotton, 1972; Kasugai et al., 1972).

The ERCP appearances of carcinoma vary, and since pancreatic tumors do not necessarily involve the main duct, this somewhat restricts the technique as a diagnostic tool. There may be an inability to perform retrograde pancreatography despite adequate papillary cannulation. This is found with neoplastic infiltration at or near the papilla. Similarly, carcinoma of the pancreas located high in the head or a common bile duct neoplasm in this situation may allow pancreatography to be carried out but prevent opacification of the common bile duct or allow identification of only its lower end. In a proportion of patients, there are strictures of both the pancreatic and common bile ducts with adequate filling beyond these points. Such stricture of the common bile duct with compression is diagnostic of pancreatic cancer, particularly if associated with concomitant compression of the pancreatic duct (Fig. 3a and b). We have recently noted that the pattern of incomplete ductal obstruction may be indicative of the extent of tumor and give some guidance to likely operability. Stenosis in the main pancreatic ducts may be comparatively localized, and at the site of the stenosis there are frequently no fine pancreatic radicles demonstrable. The ducts distal to the stenosis might show dilatation, and we have noted in several patients that this occurs in association with severe pancreatic pain. The duct may, however, narrow rather irregularly before being interrupted.

COMPLICATIONS

Endoscopy and retrograde choledochopancreatography can be practiced with acceptable risks. The hazards of endoscopy itself are rare (Schiller et al., 1972), but there may be reactions to medication (anticholinergic drugs), occasional damage caused by the cannula to the papilla of Vater or the ducts, transmission of hepatitis, cholangitis and septicemia, and pancreatitis.

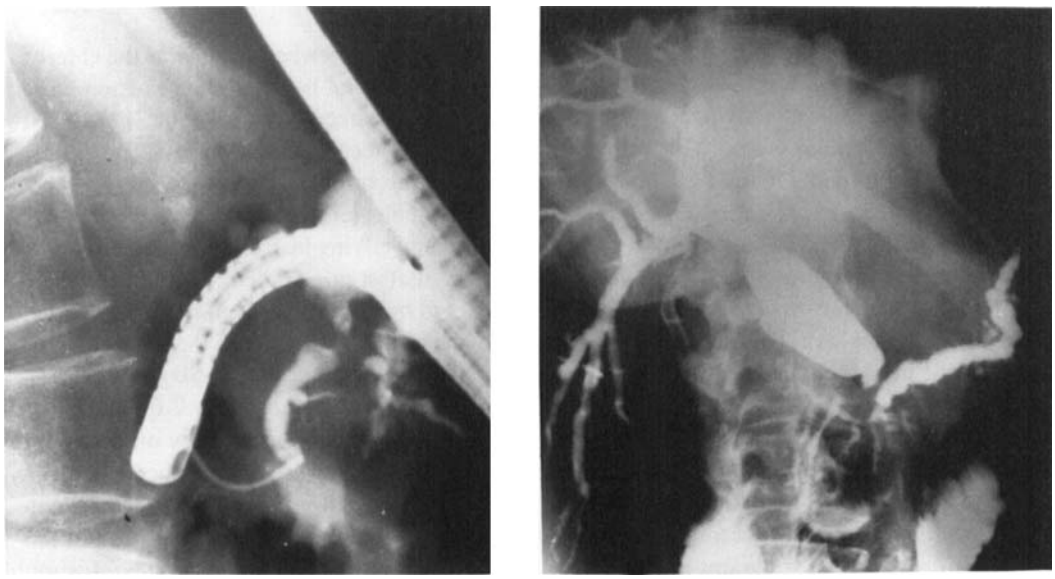

Fig. 3. a and b. Endoscopic retrograde choledochopancreatogram. The distal end of the instrument and the cannula can be clearly seen. There is a stricture both of the common bile duct in its lowermost intrapancreatic portion and of the pancreatic duct. Both the common bile duct and the pancreatic duct are dilated distal to the stricture. Case of pancreatic carcinoma subsequently proven at laparotomy.

Febrile reactions, cholangitis, or bacteremia following ERCP have been reported (Cotton, Salmon, Burwood, and Pierce, 1972; Gulbis et al., 1972; Ogoshi and Hara, 1972; Oi, 1972; Blumgart et al., 1974). Such infection, however, has only been described following cholangiography, especially when contrast has been injected past an incomplete stricture. In such circumstances, close observation for at least 24 hr is essential. The infection seems to be similar to that which can follow percutaneous and transjugular cholangiography and is probably caused by dissemination of bacteria already present in a stagnant biliary system.

Transmission of infectious hepatitis from patient to patient via gastrointestinal endoscopes has not been described but deserves mention. All jaundiced patients should be tested for hepatitis associated antigen, and patients who have a positive test should be refused examination.

The area of the papilla can be damaged, especially if forcible attempts at injection of contrast material are made with the cannula incorrectly placed. We have experienced submucosal injection of contrast in one patient, and this has been recorded by other observers (Oi, 1972). The cannula has been thought to have perforated the common bile duct at the site of a ductal neoplasm (Cotton, Salmon, Blumgart, Burwood, Davies, Lawrie, Pierce, and Read, 1972). In addition, the metal tips can be detached from cannulae (Heully and Laurent, 1972), but this has not resulted in retention within the ductal system.

The serum and urinary amylase levels often rise significantly following successful retrograde filling of the pancreatic duct. The peak levels are achieved within a few hours and return to normal in one to four days. Serum amylase levels have been serially measured in 52 patients by Cotton (1972), and a pathological rise occurred in 38 cases in which pancreatograms were achieved. Very occasionally, these rises in serum amylase are accompanied by a clinical illness consisting of pain and fever. Such episodes are not common and have occurred only twice in 145 examinations that we have recently conducted

(Blumgart et al., 1974). However, during 1972 there have been reports suggestive of acute pancreatitis in eight patients (Ogoshi and Hara, 1972; Gregg, 1972; Fujita et al., 1972; Galvan and Klotz, 1972), and one death has been recorded (Stadelmann et al., 1972). This gives a total incidence of pancreatitis of 1–2% (Cotton, 1972).

It should be pointed out, however, that although such complications do occur, the incidence is in fact very low.

REVELANCE TO PERIAMPULLARY AND PANCREATIC CARCINOMA DIAGNOSTIC ACCURACY

There is now no doubt that endoscopy and ERCP can yield accurate diagnosis in a high proportion of patients with pancreatic or periampullary carcinomata. Thus, in a study of 146 jaundiced patients, duodenoscopy was carried out in 144, and the papilla cannulated in 80%. Diagnostic information was obtained in 109 (75%) of the patients, and useful information in a further 11. Of these patients, 25 had pancreatic or bile duct cancer diagnosed by means of ERCP, and five had pancreatic or ampullary carcinomata in whom a biopsy positive endoscopic diagnosis was made (Blumgart et al., 1974). Ninety-six of these patients had further investigations carried out, including the use of hypotonic duodenography. Barium meal and hypotonic duodenograms suggested pancreatic cancer in eight patients, and in six this diagnosis was confirmed. The presence of an ampullary carcinoma was suspected in three patients after barium studies, but this diagnosis was not confirmed at endoscopy in two. In two further patients, endoscopy and biopsy confirmed the presence of a well differentiated ampullary carcinoma, and in one of these, the lesion had not been shown at a previous barium meal examination. These results for endoscopy and ERCP are similar to the experience of others (Ogoshi et al., 1970; Oi et al., 1970; Kasugai et al., 1972; Ogoshi et al., 1973).

Most reports, however, have dealt with the diagnostic accuracy of these new methods but have not assessed their potential in relation to many other factors of importance. Thus, whether diagnosis and early resection will influence longevity remains to be seen. The value of preoperative information and the influence of such information on operative decisions is difficult to assess, and the influence on operative morbidity and mortality is conjectural. Indeed, while many studies compare the accuracy of endoscopic diagnoses to subsequent findings at laparotomy, the results are seldom argued in the terms mentioned above.

It is important to examine the success of the method in the diagnosis of pancreatic and periampullary lesions and attempt to separate these figures from the overall success rates which have been reported. Thus, in a recent report of 270 attempted examinations, 74% were successful (Kasugai et al., 1972), but in this large series, only nine carcinomata of the pancreas were diagnosed, including five of the head and four of the tail or body of the pancreas. Similarly, only 21 of 252 patients examined by Ogoshi and his colleagues (1973) had a diagnosis of pancreatic carcinoma. In these and other reports there is scanty information as to misdiagnoses, follow-up data, and the impact of the method on treatment. In recent correspondence, it has been ascertained that only four patients with operable carcinoma of the pancreas have been diagnosed by endoscopy or endoscopic retrograde choledochopancreatography in three centers by examiners with an extensive experience of the method (Classen, 1974; Salmon, 1974; Cotton, 1974).

In a personal experience of 26 patients in whom a diagnosis of pancreatic or

periampullary cancer was suspected on clinical grounds (Table I), a correct diagnosis was made by means of endoscopy and ERCP in 25. Of these 26 patients, 22 were jaundiced, and intermittent jaundice was present in five cases. Four patients were examined because of undiagnosed upper abdominal pain; in one patient this pain was accompanied by recurrent attacks of unexplained pancreatitis and in another by peripheral venous thrombosis. In one patient, the procedure was terminated at gastroscopy since an unsuspected carcinoma, not demonstrated at previous barium meal studies, was discovered in the antrum of the stomach. In the remaining 25 patients, the duodenum was entered, and in 21 the papilla was seen. In two patients, ampullary carcinomata were visualized (Fig. 4) and proven at biopsy. Cannulation of the papilla of Vater was attempted in the remaining 19, and was successful on 15 occasions. This success rate for cannulation (60%) is less than our reported success rate (80%) for the diagnosis of a variety of lesions causing jaundice; this difference probably reflects the known difficulty in visualizing the duodenum and the papilla of Vater and the difficulty in carrying out cannulation in cases with distortion of the duodenum consequent on pancreatic carcinoma. Of the 15 patients successfully cannulated, the relevant ducts were shown in 14 (Table I). In one patient, a pancreatogram only was successfully obtained. Repeated attempts at retrograde cholangiography in this case failed, but it was thought on screening that the terminal portion of the common bile duct filled but then rapidly emptied. A correct diagnosis of distal ductal carcinoma was made in this case. Of the remaining 14 patients, four were shown to have carcinoma of the pancreas. Of these four, three were jaundiced, and one was examined for undiagnosed upper abdominal pain. Two of the patients who were jaundiced and one who proved to have a carcinoma of the midbody of the pancreas were operable. The endoscopic method had yielded an early enough diagnosis for resection in this latter patient, and in one of the jaundiced cases the information available at ERCP suggested possible operability since the stricture demonstrated involved only incomplete compression of the common bile duct at its lower end. The presence of a stone within the common bile duct was diagnosed in six patients, five of whom presented with painless progressive obstructive jaundice, and in four further patients a perfectly normal pancreatic and biliary tree was demonstrated. Of these, one had been jaundiced and was subsequently shown to have cholestatic jaundice, and the remaining three had been examined for undiagnosed upper abdominal pain. It should be noted, however, that only one of the latter three patients has since been submitted to laparotomy. This patient proved to have peritoneal and liver metastases from an occult malignant melanoma. Thus, of the 15 patients in whom cannulation was successful, a positive diagnosis of pancreatic or ductal cancer was obtained in five, and of these four proved operable. A diagnosis of pancreatic carcinoma was excluded in seven patients, and the endoscopic methods allowed precise planning of operation in those patients subsequently submitted to laparotomy. It is of some interest that in this small series patients examined and successfully cannulated had earlier, more manageable lesions that those in whom cannulation was unsuccessful. Thus, of the 11 patients in whom cannulation failed or was not attempted (Table II), two were noted to have carcinoma of the papilla of Vater, which was proven at biopsy in both instances. However, carcinoma of the pancreas was diagnosed in seven instances by endoscopy (positive biopsy obtained in three of these), and none were operable. One patient proved to have a carcinoma of the stomach with secondary deposits in the liver, and an erroneous diagnosis of pancreatic carcinoma was made in a patient with a large common bile duct filled with calculi, producing distortion of the duodenal wall.

There were only four patients with periampullary carcinomata in this small series.

TABLE I. Endoscopy and ERCP: Suspected Pancreatic and Periampullary Cancer

No. of cases	26
Duodenum entered	25 (1 carcinoma of stomach)
Papilla seen	21
Cannulation attempted	19 (2 ampullary tumours)
Cannulation successful	15
Relevant ducts shown	14
Diagnosis correct ERCP	15
Correct endoscopic diagnosis	10 (6 biopsy positive)
Incorrect endoscopic diagnosis	1

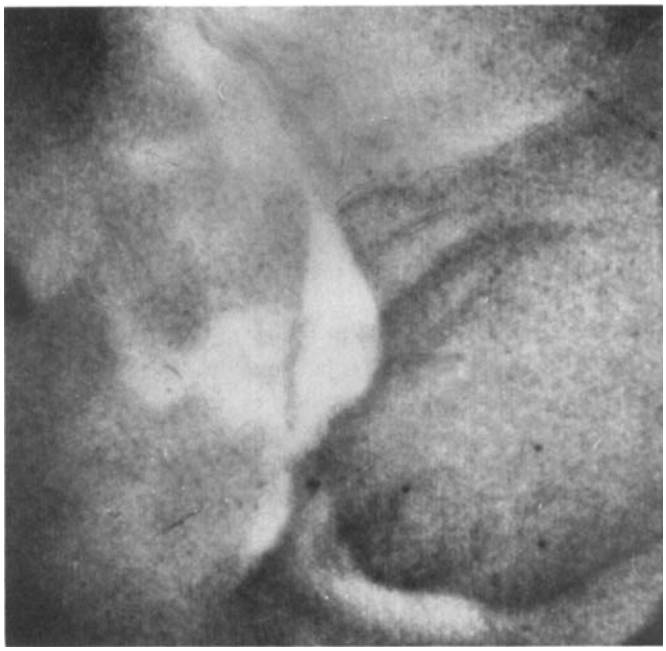

Fig. 4. Duodenoscopic view of carcinoma of ampulla of Vater.

TABLE II. Suspected Pancreatic and Periampullary Cancer

Cannulation Unsuccessful or not Attempted (11 Cases)

	No.	Operable
Carcinoma ampulla	2*	2
Carcinoma pancreas	7	0
Carcinoma stomach	1	palliative
Stones in bile duct	1	1

*Cannulation not attempted

However, it should be noted that barium meal together with hypotonic duodenography suggested the subsequently proven endoscopic diagnosis in only one case (Table III). Both ampullary carcinomata were of the papillary, well differentiated variety (Fig. 5); positive biopsies were obtained at endoscopy. Such information has been suggested to be of value in planning operations in patients with ampullary cancer (Crile et al., 1970; Blumgart and Kennedy, 1973).

EFFECTS ON MANAGEMENT

There is no doubt that endoscopy and ERCP allow precision of diagnosis in a large number of patients with pancreatic or periampullary cancer. Indeed, the advent of these methods permits of preoperative differentiation between ampullary lesions and lesions of the lower common bile duct or periampullary pancreas. The difficulty in making this differentiation in the jaundiced patient or in separating these conditions from carcinoma of the duodenum, impacted stone, peptic duodenal ulcer, and chronic relapsing pancreatitis is well known (Warren et al., 1968).

The value of endoscopy and ERCP, particularly in the jaundiced patient, to provide early precise information should not be underestimated. Such information is of great value in planning operative procedures and indeed may spare laparotomy in a proportion of patients (Blumgart et al., 1974).

The difficulties of open biopsy or needle biopsy at operation and the dangers of these procedures may also be spared by the precise information available after endoscopic examination. Indeed, future developments in the field of perendoscopic needle biopsy of the pancreas and better cytological methods should improve diagnostic accuracy.

Not only is precise diagnosis provided by endoscopic methods but further study may show that the method yields some preoperative index of operability. In addition, for inoperable cases, information may be available which is of value in guiding palliative surgery.

THE FUTURE

It has been pointed out (Warren et al., 1968) that there are many false assumptions that may lead to tragedy in the treatment of cancer of the pancreas or periampullary lesions. The patient may be treated medically for an inordinately long time before operation is advised, which is due to a diagnosis of hepatitis or cholestatic jaundice. The vast difference in the prognosis of cancer of the head of the pancreas on the one hand and carcinoma of the ampulla of Vater, the distal common bile duct, and the duodenal mucosa might not be appreciated, and it may be thought that the mortality of pancreaticoduodenectomy is prohibitive. Finally, exploratory operations may fail to establish a diagnosis, and second operations are difficult.

There is no doubt that in all these areas endoscopic methods have a great deal to offer, and because of the improvement in diagnosis, there may well be significant improvements in mortality and morbidity for surgical procedures for these diseases. Although early diagnosis has been made only in very few patients so far examined by means of ERCP, future developments in endoscopic methods, combined with other diagnostic techniques such as selective coeliac axis angiography, radioisotopic scanning, and

TABLE III. Periampullary Carcinomata

	No.	Endoscopy + Biopsy	ERCP
Ampullary carcinoma	2*	2	–
Carcinoma bile duct	1	0	1**
Carcinoma pancreas	1	0	1

*Hypotonic duodenography suspected in 5 cases; correct in 1.
**Only pancreatic duct shown.

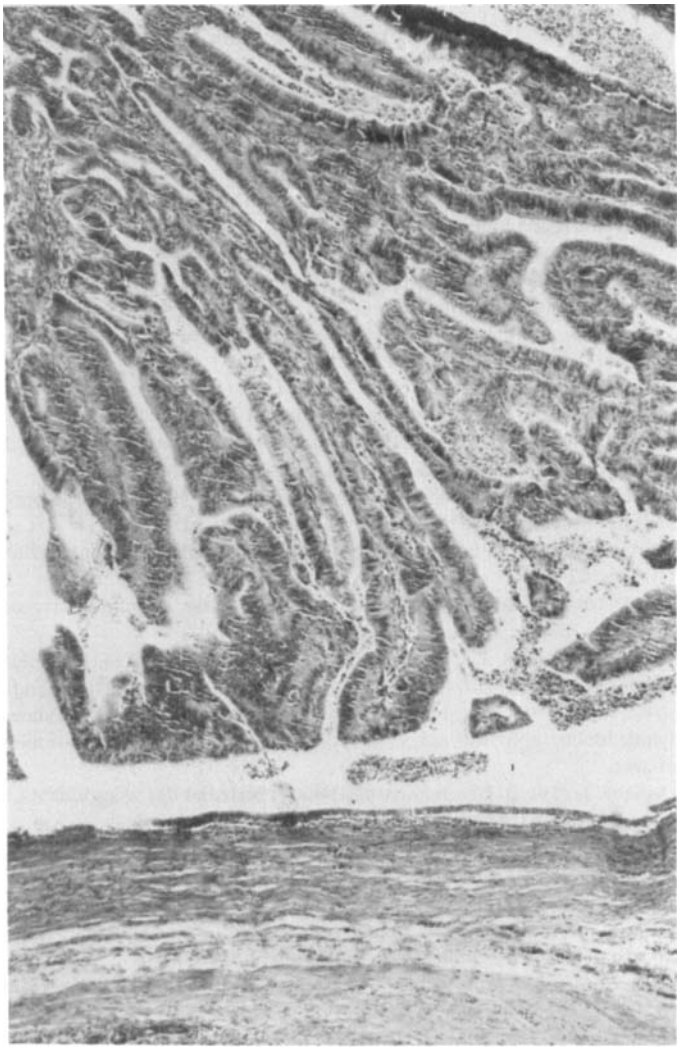

Fig. 5. Papillary well-differentiated ampullary carcinoma. This form has a better prognosis than the ulcerating less well-differentiated variety of ampullary tumor. (Photomicropraph H and E 20X).

pancreatic function tests, may allow more cases to be recognized earlier and thus influence survival in cancer of the pancreas.

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