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CARCINOMA OF THE PANCREAS AND CARCINOMA OF THE AMPULLA OF VATER: A RE-EVALUATION*

The L. Duncan Bulkley Lecture

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THE late L. Duncan Bulkley, whose memory is honored by this lecture, was particularly interested in malignant neoplasms, so it is appropriate that this afternoon's discussion should be on some type of malignant disease even though he, not being a surgeon, had not dealt with carcinoma of the pancreas. Inasmuch as ampullary tumors, those of the terminal common duct, and those arising in the head of the pancreas near the ampulla of Vater are all eventually associated with obstructive jaundice they will be grouped together for the purposes of this discussion, and tumors of the body and tail of the pancreas will merely be referred to incidentally. The reason for this is that jaundice appearing early in the development of the tumor is the one hopeful element in an otherwise rather gloomy picture. Unfortunately malignant tumors in the body and tail, with the exception of malignant cystadenomata,

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seldom give meaningful symptoms early enough to allow for successful extirpation. Moreover the long accepted view that carcinoma of the pancreas is slow to metastasize has not been borne out in our experience, as several of our cases which seemed highly hopeful at operation were shown by pathological examination of the specimen removed at operation to have spread to small apparently uninvolved lymph glands, or up the wall of the common duct, and others succumbed later to metastases not appreciable at the time of operation.

Surgeons have been intrigued by carcinoma of the pancreas and ampullary region since Halsted[1] in 1898 did the first successful transduodenal resection of a carcinoma of the ampulla of Vater. Although his patient survived for only about seven months, such interest was stimulated by this experience that thirty years later, in 1927, Cohen and Colp[2] were able to collect fifty-eight cases of operative attack in this area. In February 1935, we[3] presented before the joint meeting of the Philadelphia Academy of Surgery with the New York Surgical Society a patient who had undergone six months previously what we believe to be the first attempt at partial pancreatectomy with duodenectomy. This case and two others formed the basis for the article by Whipple, Parsons and Mullins[4] read before the American Surgical Association in May of the same year. This report stimulated such interest that in 1941 Hunt[5] was able to report on 124 cases including those reported by Cohen and Colp[2] and others, and since then many papers have been published suggesting changes in technique and other details of management.

Koerte in 1905 did a transduodenal resection on a patient who survived at least twenty-two years. This feat and long term successful follow-ups on operations by Kelly for nine years, Cabot for eight years, Clar for five years and one by Muller dying nearly five years later as well as others for shorter periods were reported by Hunt[5] as successes out of seventy-nine attempted. We must assume that in these instances the patients were to say the least fortunate in that their tumors were at the moment of operation still localized to the superficial zone of the ampulla without extension up the common duct or elsewhere. This seems a reasonable assumption because local excision can hardly be considered as proper cancer surgery where the limits of the tumor are in doubt and cannot be compared to the excision of a polyp of the colon with malignant change only at its apex. Tumors of the ampullary region cause early jaundice. If jaundice is caused early enough the malignant process

may still be localized but we cannot be sure exactly how well localized. It seems clear that once the barrier of the capsule of the pancreas has been breached and lymph glands or perineural lymphatics have been invaded, a wide spread dissemination to liver and to other lymph gland areas is rapid although perhaps microscopic for an unknown period of time. The application of this concept will be referred to later in this discussion.

The first operation was performed before Vitamin K was available, and consisted in a palliative cholecystogastrostomy as the first stage. Dr. Clinton R. Mullins was Surgical Resident at that time and persuaded us to attempt resection of the tumor. We therefore proceeded, with some trepidation, to do a partial duodenectomy and partial pancreatectomy as the second stage. We anastomosed the cut ends of the duodenum because of its simplicity, but this resulted in duodenal obstruction necessitating a subsequent gastroenterostomy. Therefore the plan was formulated[4] to divide the operation into two stages, the first including gastroenterostomy, cholecystogastrostomy and ligation of the common duct, and in the second stage removal of the duodenum with part of the pancreas.

The development of various changes in details of the operation that have been added since that first case in August 1934 is of some interest, showing as it does how errors can be corrected and new ideas used constructively. Some of the original theories have been substantiated, whereas others have proved erroneous. For example, it was assumed that the external secretion of the pancreas was not necessary to life. This was borne out in our first two cases, but subsequently even when the operation was changed to include anastomosis of the pancreas to the intestinal tract we have had a certain number of individuals who have had steatorrhea. We have not been able to explain this variation between individuals. Moreover we assumed that sufficient atrophy of the acinar cells would have occurred to make the development of a pancreatic fistula unlikely. Soon, however, the development of pancreatic fistula was reported from several sources, and various methods of effecting successful anastomosis of the pancreas to the intestinal tract were developed. This step is now generally practiced not only to prevent the formation of pancreatic fistulae but of equal importance to make available for the purposes of digestion whatever external secretion may be available.

One of the first changes in technique was suggested by Eliason's[6] report of a high incidence of ascending cholangitis following cholecystogastrostomy and our experience of losing our first case eight months after

operation because of liver abscesses. Whipple[7] castigated this operation as a bad procedure and suggested the Roux Y method of conducting the bile to the intestinal tract first using the gall bladder, and later the common duct to avoid biliary fistula and of course when no gall bladder was available. The most important changes in technique followed the introduction of Vitamin K which reduced the danger of postoperative hemorrhage to trivial proportions and made a one-stage operation desirable for many obvious reasons. Quite independently in 1940, Whipple,[8] early in March, Hunt later in March, and Trimble[9] in April, performed one-stage resections of the head of the pancreas with the duodenum. Their results definitely established the one-stage operation as the procedure of choice except in certain bad risk cases with marked impairment of liver function. Cases since then have been reported from all parts of the country with many slight variations in technique but all involving relatively wide excision. Two of such ideas are of real interest. Pearse[10] showed the importance of a 25 cm. limb of jejunum between the biliary and gastric anastomoses in order to prevent reflux, and this we now incorporate in our operation. Cattell and Pyrtek[11] reported that Cole observed the presence of cancer cells floating in the fluid in the distended pancreatic duct, a finding that we have confirmed, and suggested the advisability of a total pancreatectomy in those cases where the lesion is in the head of the organ and a dilated duct is identifiable, particularly in the diabetic who withstands total pancreatectomy extremely well.

Tumors arising in the body or tail, except for the malignant papillary cystadenomata which present a smooth rounded tumor and are readily removable, seldom give symptoms before the growth has penetrated beyond the capsule or has metastasized, and therefore present a nearly hopeless problem. The adenocarcinomata that arise in the head at a distance from the ampullary region likewise seldom call attention to themselves early enough to fall into the favorable category. This leaves us with ampullary tumors, arising in either duodenal or terminal common duct epithelium, and true pancreatic tumors close enough to the ampulla to cause jaundice early in their development. These two types are indistinguishable from one another diagnostically and therapeutically.

As one sees these cases clinically, a jaundiced patient presents himself with or without pain. The diagnostic problem is quite simply to determine whether the jaundice is due to an intra or an extrahepatic

lesion, and if the latter whether due to stricture, stone, tumor or inflammation. We believe that on admission to hospital all cases of jaundice should be considered as possible, if not probable candidates for surgery, and that in addition to the usual diagnostic procedures many of the elements of a preoperative regime should be instituted in order to save much valuable time. Moreover an accurate diagnosis cannot always be arrived at and in a few instances operation will be required even for intrahepatic conditions.

There are two important elements in the differential diagnosis of jaundice, first the history and physical, and secondly, various laboratory tests. From the history one may get significant data such as previous attacks of gall bladder disease or acute pancreatitis, exposure to hepatotoxins, or the administration of blood or plasma. In spite of the usually accepted textbook statement that carcinoma of the head of the pancreas is associated with painless jaundice, our experience has been that roughly 30 per cent will complain of vague upper abdominal pain or pain in the back. It is worth noting that one should not rely too heavily on a history of previous attacks of biliary colic as ruling out neoplastic disease, because gall stones have been found in a fair number of cases with carcinoma of the ampullary region. The finding of an enlarged gall bladder is of real significance according to Courvoisier's law, which holds true in 80 per cent of the cases. Enlargement or not of the liver is of no diagnostic significance, nor are the depth and the tint of jaundice or the presence or absence of itching, all of which vary so markedly that they often fail to be of much importance in the individual case.

The laboratory tests can be roughly divided into two categories, first those to furnish data needed in the differential diagnosis and secondly those that will indicate the general condition of the individual and the deficiencies that require correction not only as part of preoperative preparation but often as an important element in any medical regime of therapy. If we can demonstrate that the pathological condition is intrahepatic we as surgeons do not have to differentiate between toxic hepatitis, cirrhosis, viral or homologous serum jaundice, cholangiolitic hepatitis or any of the non-surgical conditions associated with jaundice. The tests we rely on are the alkaline phosphatase, cephalin flocculation and thymol turbidity as the most reliable first screening tests. The alkaline phosphatase is almost regularly elevated in obstructive jaundice and is seldom elevated in the early phase of hepatitis, to use an inclusive term.

whereas the cephalin flocculation and thymol turbidity tests usually are strongly positive with hepatitis and do not rise following obstruction until liver damage has occurred. Confusion of course will arise in the obstructive case who already has suffered from some liver disease such as cirrhosis. Study of the fluid obtained from duodenal drainage will reveal: bile with hepatitis, none in obstruction of the duct; crystals are usually present with stone; blood may be present with superficial ulceration of a tumor; and finally the pancreatic ferments are usually altered in carcinoma, but we seldom study the ferments now because of time and technical difficulties and the fact that other evidence is sufficient. The Papanicolaou test on the centrifuged specimen may reveal cancer cells when there is an ulcerated lesion and if positive is of the greatest importance. It will not be positive probably in tumors in the head that have blocked the duct and are not ulcerated and therefore if negative is not significant. With barium in the duodenum there will not be enlargement of the duodenal loop except with large palpable tumors, but there may be evidence of external pressure, and one occasionally sees the so-called reverse three defect caused by an ulcerated tumor in the ampulla.

The table below indicates in a simplified form the positive and negative results in the tests now used in the differential diagnosis of jaundice.

To assay the general condition of the individual one is interested in the renal, cardiac and liver functions and the status of the circulating blood. The simpler tests for renal function together with electrocardi-

TABLE I—POSITIVE AND NEGATIVE RESULTS IN TESTS IN DIFFERENTIAL DIAGNOSIS OF JAUNDICE

	Hepatitis	*Stone*	*Tumor*
Alkaline Phosphatase	—	+	+
Cephalin Flocculation Thymol Turbidity	+	—	—
Duodenal Drainage			
Bile	+	—	—
Crystals	—	+	—
Blood	—	—	±
Ferments	+	+	abnormal

ography and x-ray of the heart should suffice. Determination of the bromsulfalein clearance and the A/G ratio will give adequate information to assess liver function, which is of particular importance in the debilitated patient with impaired liver function where a two-stage procedure with a few weeks between stages may seem to be less risky than a one-stage operation.

Rather complete blood studies will give the base line on which all pre- and postoperative therapy is predicated. A complete count, hematocrit, clotting time and grouping furnish certain basic data. We know the patient is jaundiced but the level of bilirubin in the serum is determined for later comparison. We seldom employ the van den Bergh test as we feel that other tests are more helpful. The blood volume and the blood levels of sodium, potassium, chlorides and CO_2 will indicate the most important deficiencies. Commonly in these cases the plasma volume is increased and the red cell mass is diminished even though the red cell count and hematocrit may be within normal limits. An electrolyte imbalance is uncommon before operation but is very common after operation particularly in reference to sodium and potassium. All these tests will indicate the deficiencies to be corrected so that the patient may come to operation in reasonably good equilibrium. Vitamin K will be indicated for prothrombin deficiency, whole blood for diminished red cell mass, and dietary measures supplemented if needed by parenteral amino acids for hypoproteinemia. All of this series of procedures is time consuming, which emphasizes the point previously made as to the importance of, firstly, considering on admitting an adult with jaundice to hospital that operation may be necessary, and, secondly, of instituting a program of tests which can help in preparing for operation with the minimal loss of time.

There does not seem to me to be any point in going into the technical details of the operation in this paper. There are however certain points that do deserve mention with emphasis. The operation, which consists of partial gastrectomy, partial or total pancreatectomy, with removal of the duodenum and lower common duct and perhaps the spleen, and then a rather complicated reconstruction of the gastrointestinal tract with implantation of the common bile and pancreatic ducts, is by definition of the greatest magnitude. No surgeon should attempt it unless he is fully familiar with the anatomy of the region, which knowledge had better be refreshed in the anatomical laboratory as the pos-

terior aspect of the head and neck of the pancreas are in intimate relationship with several extremely important blood vessels. Moreover the postoperative care involves a thorough understanding of fluid balance, so that the principle of having a team, consisting of surgeons who work together with highly trained laboratory workers available, to handle these cases has seemed to us basically sound and our experience has been that it contributes to safety as shown by a significant reduction in operative mortality.

In the actual performance of the operation certain vascular landmarks are identified and one proceeds methodically step by step protecting and preserving vital structures but yet removing en bloc the structures mentioned above. In the reconstruction phase of the operation the cut end of the common duct is anastomosed to the jejunum just below its closed end which has been brought up behind the superior mesenteric vessels where the duodenum lay previously. The common duct or preferably the common hepatic above the entrance of the cystic duct is employed in order to remove as long a segment of lower duct as is possible. Moreover if the gall bladder is used there is some danger of a biliary fistula from the tied end of the duct. The cut end of the pancreas, except of course when total excision has been done, is anastomosed to the jejunum just below the bile duct anastomosis with a small tube in the pancreatic duct passed through a small stab wound in the gut wall with suture of the pancreatic capsule to the jejunal serosa. The objective of this anastomosis is to obviate pancreatic fistula and also to conserve for digestive purposes any ferments that may be present. This has been found worth while as pancreatic fistula is now rare and comparatively few patients indicate pancreatic deficiency during their period of survival. The third and last anastomosis, the gastrojejunostomy, is done at least 25 cm. distal to the pancreatic jejunostomy in order to prevent reflux. We have found it convenient to employ a retrocolic Hofmeister type as one would in an ordinary partial gastrectomy.

These are shocking operations involving prolonged operating time, much dissection and handling of viscera, and are usually associated with considerable blood loss. Two liters of blood during the operation do only a little more than replace the blood lost, so an additional 2000 cc. of fluid will be required in the first twenty-four hours. This may consist partly of blood, the balance being dextrose in water and dextrose in saline. The great danger in the postoperative period is over-hydration

and in particular the over-administration of sodium, therefore the intake should be limited to the neighborhood of 3000 cc. including not over 500 cc. of sodium salt solution. Even with a reasonably limited salt intake a storage of sodium may occur with a loss of potassium. This aspect of fluid and electrolyte balance was discussed by Lockwood and Randall[12] before this Academy in December 1948. The loss in potassium may be from wound drainage, from nasogastric or intestinal drainage, and thirdly because potassium is excreted during the period when the patient is taking nothing by mouth meanwhile maintaining urinary excretion of potassium. Even in the absence of dehydration cellular potassium may be replaced by sodium and this interchange will be more marked if an excess of sodium is administered resulting in cellular edema because of the greater osmotic tension of sodium. The clinical manifestations of potassium deficiency are asthenia, listlessness and even myasthenia with electrocardiographic changes, all of which respond at times dramatically to administration of potassium. In order to be aware of shifts in the circulating electrolytes one should maintain a chart showing the daily intake and output of fluid by each and every route, and the daily estimation of the blood levels of sodium, potassium and chlorides. If the blood potassium drops to 3.0 m.eq/l or lower one should add 30 m.eq/l of potassium chloride to the intravenous fluid. If the sodium level falls sodium lactate should be used and conversely ammonium chloride will raise the chloride level without adding more sodium. In the years before we had a flame photometer and a well trained team to handle these insidious shifts in electrolytes it is certain that many deaths occurred roughly ten days after operation that were directly due to faulty fluid and electrolyte management, rather than to assumed delayed shock and furthermore that some of the instances of peritonitis were due to poor wound healing at anastomotic sites based on local edema.

In March 1947 a team was organized consisting of the late John Lockwood and myself with Milton R. Porter and Henry T. Randall at that time surgical residents. This report is based on the experiences of this team and a few cases done by other members of the attending staff in the past four years and consists of twenty-four radical operations including one for pancreatolithiasis and one transduodenal resection of the papilla. This latter case, not done by the team, succumbed. This operation is not advisable as it carries a high risk as shown by a recent report

by Miller et al.[13] and as was indicated many years ago by Hunt.[5] These twenty-four cases at operation were considered favorable. During this same period 103 other cases were explored, were found inoperable and a biopsy or short-circuiting procedure performed. Roughly one-fifth of the cases explored have been considered operable, and as will be shown a number of the twenty-four had metastatic spread that was not appreciable at the operating table. Our criteria for non-resectability is based on any spread beyond the pancreatic capsule, into lymph glands, subperitoneal tissue such as the root of the mesentery, or the portal vein. The finding on microscopical study of perineural extensions not appreciable in the gross specimen is a bad prognostic sign.

The life expectancy with palliation varied markedly. One patient who had merely a biopsy done survived for one year. The patients with a non-functioning islet cell carcinoma may live a long time, as shown by Dr. Whipple's first one-stage case that lived for ten years, and one of ours living just under three years in whom only a short-circuiting operation was performed. Three others with palliative procedures survived eleven, fourteen and sixteen months but the vast majority succumbed before six months had passed. The survival rate in those considered operable in our series conforms with the experience of Miller et al.[13] and of Cattell and Pyrtek[11] that those arising in the pancreas itself have a far less favorable outlook than those with ampullary lesions. Miller et al. also point out that invasion of the portal vein, which of course is not discovered until almost the last moment before removal of the specimen, is a potent factor in immediate postoperative mortality.

Out of the twenty-four radical resections, among them one for pancreaticolithiasis, there are 11 survivors, and of these one will die shortly at a little over 18 months post operation. Four died in the immediate postoperative period making a total operative mortality of 16 per cent although in this same period our team operated on seventeen patients with one death which occurred in a total pancreatectomy, a mortality rate of 5.8 per cent. Five total pancreatectomies were done for reasons to be discussed later with two operative deaths, a mortality of 40 per cent in this small series, but the others died within a year of recurrence. Those that have died since discharge from hospital lived from five to eighteen months but only two have survived over a year, the balance succumbing in from five to eight months, which indicates the high incidence of unsuspected metastases. The nine operated on for carcinoma

that are still living without recurrence as far as is known are 48, 36, 30, 28, 27, 20 and 14 months, and two others under twelve months since operation. The one patient with lithiasis having a radical operation is living at nearly 4 years but has developed diabetes.

The site of origin of the tumor has had a definite significance as to postoperative longevity. Without exception those that have died at various intervals following operation had lesions arising in the pancreatic tissue proper and exhibited microscopical lymph gland or perineural extension as the two most important unrecognizable features in the gross examination of the specimen.

Those that still survive had lesions classified as follows:

1. Duodenum or ampullary region without spread: 4 cases, 1 at 4 years, 1 at 3 years, 2 under 1 year.
2. Duodenum or ampulla with extension: 4 cases, 1 at 2-1/2 years, 1 at 28 months, 1 at 27 months, 1 at 14 months.
3. Head of pancreas with spread: 1 living at 20 months, 1 on the point of death at 18 months.

It is worth noting that we have had no cases arising in the head without microscopical evidence of spread. We have noted that some of the lesions in the head have extended into the body on microscopical study of the specimens either directly through the tissue or along the duct without evidence of extrapancreatic extension. This finding has led us to attempt total pancreatectomy in lesions in the head because of the difficulty in knowing just where to transect the body and because of the possibility of cancer cells being present in the duct fluid. Five such operations have been done with disappointing results. Two died in the immediate postoperative period, one of them perhaps because of a coronary occlusion. The others survived less than eight months.

The following conclusions seem inescapable:

1. Carcinoma in this area tends to disseminate early.

(a) Those that arise in pancreatic tissue proper extend along perineural and perivascular lymphatics, to lymph glands and directly through the capsule to the peripancreatic fat. Also they spread impalpably within the gland and can extend along a dilated duct by flotation in the dammed up secretion.

(b) Carcinomas arising in the terminal common duct, or on the surface of the ampulla may be a little slower to spread up the common duct or through the duodenal wall but this difference is perhaps more ap-

parent than real because jaundice will appear so early.

2. All cases of jaundice in the adult should be considered on admission to hospital as possible candidates for surgery so that no time may be wasted in preparation for operation if this is decided upon.

3. Palliative short-circuiting operations are indicated in all cases exhibiting palpable, or visible extension, as this will furnish just about equal comfort and longevity as compared with the radical operation.

4. Total pancreatectomy is worth the attempt in lesions starting in the head without evidence of spread, although a considerably larger series must be collected before the value of this more radical operation is established.

5. Radical operation holds real hope for those individuals with lesions localized to the ampulla as shown by this and other series.

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