PANCREATIC CANCER AND ITS TREATMENT BY IMPLANTED RADIUM

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My object in this paper is to state the result of the attempts I have made by means of implanted radium to bring into the field of therapeutics a form of cancer in which only rare surgical successes have been won by ablatory operations, attended by a very high degree of risk. Let me say at the beginning that I use the expression "pancreatic" cancer in a clinical rather than a strictly pathological sense to cover not only primary pancreatic cancer, but also those cases where a carcinoma, primary in the ampulla of Vater or the common bile-duct, or the main pancreatic ducts, extends into the substance of the pancreas, and so simulates a primary pancreatic growth.

It is but rarely, even during operation, that a clear distinction can be drawn between primary carcinoma of the pancreas and a secondary invasion of the pancreas by a growth starting in the common bile-duct, but fortunately for purposes of treatment while the distinction is difficult it is not important.

If the crater of an ulcer can be palpated through the anterior wall of the descending duodenum, it is almost certain that the growth is a true Vaterian one, but by the time such an ulcer can be felt the pancreas will certainly be involved, and the treatment is that for pancreatic carcinoma.

Early Carcinoma of the Bile Papilla and Ampulla.—According to Lauwers true ampullary carcinoma has little tendency to spread or to invade the glands. A cancer of this type, detected early, presents itself as a small firm nodule at the end of the common duct. For a case of this kind the right treatment is to open the duodenum, to excise the papilla with the growth by diathermy without penetrating through the outer coat of the duodenum, and to complete the operation by sewing up the incision in the duodenum. In the absence of jaundice cholecyst-enterostomy may be deferred.

These cases form a well-defined group in which excision seems the treatment of choice. They do not come within the ambit of this paper, and its conclusions do not apply to them.

It would prolong this paper unduly to give an account of the very difficult surgical problems presented by Vaterian cancer and of the attempts which have been made to deal with them by operative measures, especially as this branch of the subject has been recently dealt with by Dr. E. Lauwers, of Courtrai, in his paper "Traitement chirurgical du Cancer Vaterien" (Journal de Chirurgie, December, 1933).

I will now describe the seven cases upon which this paper is based, and will afterwards discuss the conclusions to be drawn from them.

CASE I.—*Carcinoma of the pancreas with obstructed common duct. Interstitial radium treatment. Cholecystduodenostomy. Complete temporary relief and restoration of health. Subsequent pyloric stenosis. Abdomen reopened by Mr. R. P. Rowlands and no sign of carcinoma found. Gastroenterostomy. Temporary restoration to health. Second laparotomy by Mr. Rowlands. Large carcinoma of the pancreas obstructing the portal and splenic veins. Death twenty-six months after the first operation.*

Captain B. C. H. was sent to me by Doctor Steen, of Ilford, October 19, 1925. The story of his case is a very interesting one, and is best told by means largely of original documents since both before and after radium treatment it came under the notice of skilled independent observers.

The first of these documents is a letter dated October 1, 1925, from Dr. J. F. Weir, of The Mayo Clinic, to the patient.

My dear Mr. H.:

Pursuant to your request I am writing at this time to outline our findings in your case. These are as follows:

When you registered, you gave a history of about six weeks' duration of painless, gradually deepening jaundice, associated with marked pruritus. During that time your appetite had been good and you had eaten well. However, you had lost between twenty and thirty pounds in weight. For the preceding six months you had noticed some impairment in your strength and ambition. Since the onset of the jaundice your bowels had a tendency to become somewhat loose at times but this became quite a marked feature while under our observation at the clinic.

Physical examination showed a marked jaundice. There was an evident weight loss. There was a mass in the right upper quadrant extending below the slightly enlarged liver which we interpreted as being a distended gall-bladder. The urine was negative except for the presence of bile. The blood count and the differential count were normal. The blood Wassermann and blood culture were negative. The gastric analysis showed a total acidity of 70, free hydrochloric 56, and a total quantity recovered at the end of one hour of seventy-five centimetres. Three stool examinations showed no parasites or ova, but oil or fat was present in excess. An X-ray examination of the chest was negative.

This investigation was made during the course of a journey to England. October 20, 1925, I saw Captain H. in London and wrote as follows to his medical adviser, Doctor Steen:

I saw yesterday your patient, Captain H. I found a deep resistance in the epigastric region level with the pancreas. The liver is rather down but its edges soft. I suspect, however, that its surface is nodular.

In my opinion the symptoms point to a malignant growth of the pancreas or of the biliary papilla of the duodenum. It is, however, possible that he is suffering from a chronic pancreatitis, and if that is the case he will certainly benefit by operation. I do not think that any further examination short of an exploratory incision is likely to clear up the diagnosis, and as he is a comparatively young man and has not lost his vigor I think it is worth while exploring the abdomen. The odds are, however, that the condition is a malignant one and I would not like to press the operation unduly, though it is the only chance.

October 21, 1925, I operated on the patient at the Ilford Emergency Hospital The following are my notes at the time.

Usual gall-bladder incision showed a smooth normal liver with a very distended gall-bladder on the verge of necrosis. In the head of the pancreas behind

and adjoining the pylorus was found a puckered mass about the size of a chestnut, evidently a carcinoma. The bile-duct was greatly distended from below the pylorus. Three tubes of radium 25, 12.5 and 12.5 mg. element were placed in the substance of the mass and left for twenty-four hours. Cholecyst-jejunostomy was performed. Patient stood the operation well. *Diagnosis.*—Carcinoma of the pancreas.

Captain H. made a good recovery and subsequently came under the care of Dr. A. M. Mitchell, of Guildford, who, October 5, 1926, wrote as follows:

History August 16, 1925.—Consulted doctor in Canada; he had jaundice, slight, and cutaneous irritation. *Diagnosis.*—Hemolytic jaundice. Liver and spleen not enlarged.

September 8, 1925.—At Mayo Clinic three weeks. No operation. Fractional test meals; X-ray; stools examined; *etc.* Mass in right upper quadrant of abdomen. Losing a pound a day.

October 17, 1925.—In England. Mr. Sampson Handley operated on October 22. Cholecystenterostomy. Three tubes of radium inserted over pancreas for twenty-four hours. Healed quickly. Pretty well, but some indigestion; resumed taking fats soon after operation and digested them.

April 30, 1926.—Returned to Canada. Fairly healthy state; ordinary meals.

Early August.—Acute indigestion and vomiting. Returned to England. Vomiting still persisting intermittently and losing flesh but I am doubtful if more than can be accounted for by the vomiting. No tumor felt and the X-rays show definite pyloric obstruction.

Mr. Sampson Handley does not return until November 10 and my feeling is that he should not wait until then, but should have his pylorus investigated and probably some sort of short circuit done for him.

October 8, 1926.—Mr. Rowlands saw patient and confirmed my opinion that something should be done immediately.

October 15, 1926.—Operation at a nursing home in Guildford. The stomach was large, œdematous and friable, obstructed near the pylorus probably as the result of adhesions. No ulcer was found and no sign of growth, but the whole of the pancreas was a little harder, but no larger, than normal. No evidence of malignant disease at present. Extensive adhesions on the right side of the abdomen. Posterior gastro-jejunostomy performed.

November 30, 1926.—Dr. Mitchell writes to Mr. Rowlands:

I ought to have let you know before this what a complete success your operation on Captain H. was. He has made an uninterrupted recovery and is slowly but steadily putting on flesh.

Next comes a letter from the patient himself.

January 8, 1927.

You will no doubt recall performing an operation cholecyst-jejunostomy upon me in about October 23, 1925, and will have your records of my condition at that time.

I returned to Canada in April of last year feeling very well indeed—my weight being 244 pounds.

About the beginning of August my health began to fail again with bad indigestion, vomiting and loss of weight. Under the impression that cancer was developing I returned to London in early September, and found that you were then in the United States.

After a preliminary period I was operated upon by Mr. Rowlands, of Guys, the operation being a short circuit of the stomach—the trouble being due to adhesions. Mr. Rowlands' report of my present condition is very cheering to me,

as he could find no trace of cancer development at the time of the operation, October 15, 1926.

My present weight is nine stone and ten pounds, showing a steady increase all the time, and I feel remarkably well.

The story is completed in the following letter from the late Mr. R. P. Rowlands, whose recent loss British surgery has to deplore:

December 21, 1927.—I am sure that you will be interested to know the further history of Captain H., for whom you performed cholecyst-duodenostomy some years ago. I performed gastro-jejunostomy a little over a year ago for duodenal stenosis, when you were away in America. Since then I have opened a posterior subdiaphragmatic abscess in August this year. He went on having rigors occasionally, and lately these became much more frequent and severe, and a little jaundice developed. Lord Dawson saw him again and it was ultimately decided to explore the abdomen in the hope of finding a stone, or other removable obstruction, in the common bile-duct.

I explored him yesterday at Guildford. I am sorry to say that there was a large growth in the head of the pancreas, completely obstructing the portal vein, the common bile-duct and the duodenum. The liver was normal, but the spleen was enlarged from obstruction of the splenic vein. The body of the pancreas was similarly enlarged from obstruction of the pancreatic duct, but the cholecyst-duodenostomy was patent, and the gastro-jejunostomy was normal. The veins in the great omentum, falciform ligament and especially those running from the duodenum to the gall-bladder, over the old anastomosis, were enormously enlarged to establish a collateral circulation. The anastomosis between the great omentum and the anterior abdominal wall was similarly dilated. I fear the outlook is very bad.

I think your original diagnosis of growth at the head of the pancreas, or of the common bile-duct, must have been correct, and that probably the radium treatment delayed the progress of the disease.

Captain H. died shortly after this operation.

This case supplies irrefutable evidence of the temporary disappearance following radium treatment of all signs of carcinoma when the pancreas was palpated during a second laparotomy. The subsequent recrudescence of the growth excludes the possibility that my original diagnosis might have been erroneous.

From an evidential point of view the case is thus more important than the cases where no return of the growth has taken place.

CASE II.—*Vaterian carcinoma with nodular extensions into the pancreas, associated with gall-stones. Radium treatment of the carcinoma, removal of gall-stones. Cholecyst-duodenostomy. Patient well nearly fourteen years later.*

Jane B., a married woman of fifty-five, was sent into my ward at the Middlesex Hospital September 25, 1920, by Dr. H. Campbell Thomson. For five or six years she had been subject to sudden acute attacks of right hypochondriac pain, passing round to the back, and occurring on the average about every three weeks, and lasting from a few hours to a whole day. The attacks were generally accompanied by vomiting and shivering. During the attacks she had noticed that the urine was dark, though her motions were unaltered in color.

The last severe attack occurred three weeks before admission, but there had been two subsequent mild ones.

She had never suffered from jaundice, and was not jaundiced on admission—a rather important fact, since it negatives the suggestion of impacted calculus in the common duct which might otherwise be made.

September 27, 1920, I opened the abdomen by a right paramedian incision about six inches in length. The gall-bladder was found to contain stones.

Upon feeling the surface of the pancreas a number of hard nodules like secondary nodules of carcinoma were felt, and further search revealed a primary growth in the posterior wall of the second part of the duodenum in the situation of the orifice of the common bile-duct.

The fundus of the gall-bladder was incised and about fifty gall-stones were removed with a spoon. A cholecystduodenostomy was then performed so that later if the duodenal growth occluded the bile-duct, bile should still be able to reach the duodenum.

A tube of radium, 45-mg. element, with a 1-mm. platinum screen, fixed on the end of a stout silver wire was introduced behind the duodenal growth after mobilization of the duodenum by a vertical incision through the peritoneum at the right margin of the viscus. The wire of the radium tube projected from the sutured incision, and the tube was removed in fifteen hours.

The patient made a good convalescence and was discharged twenty-three days after the operation. For two and one-half years she remained quite well, but about March, 1923, she again began to suffer from pain in the right hypochondriac region, passing round to the right scapula, coming on gradually, becoming acute, associated with vomiting, and passing off in about two and one-half hours though shivery feelings lasted another hour. In May, 1925, she noted pain in the back, passing down to the legs, during the attacks. The attacks became more severe and frequent, and November 24, 1925, she was again admitted under my care. She was stated to have recently lost forty-two pounds in weight. Morphia injections had been necessary during the attacks. During an attack six weeks before readmission she had noticed herself yellow and the stools light in color.

It was thought that the attacks indicated temporary obstruction of the cholecystduodenostomy opening, and operation was considered unnecessary. She was discharged December 16, 1925. She was again admitted May 19, 1926, almost in a state of collapse, and for the first time the notes record jaundice. Nothing was done surgically, and she left the hospital June 12, 1926.

March 29, 1928, I saw her again. She was perfectly well, free from pain, and putting on weight, having gained twenty and one-half pounds during the previous twelve months. She remains well at the present date (March, 1934).

CASE III.—*Carcinoma of pancreas with distention of gall-bladder. Radium and cholecystgastrostomy. Death.*

Mr. R., aged about seventy, failed in health in September, 1929. Vomiting, abdominal pain and jaundice were the principal symptoms, with pyrexia up to 102. The liver was unduly palpable. Occult blood and free fatty acid were present in the stools, and a provisional diagnosis of cancer of the pancreas was made. October 29 I explored the abdomen and found a distended gall-bladder and a large hard mass in the head of the pancreas. There was a scarred and contracted area of peritoneum on the under side of the transverse mesocolon, so that evidently the growth had infiltrated widely. Cholecystgastrostomy. Two 25-mg. tubes of radium were introduced into the substance of the tumor from below the mesocolon for twenty-four hours. The condition of the patient did not permit of a gastroenterostomy. Death from asthenia in forty-eight hours.

CASE IV.—*Carcinoma of bile papilla. Exploration. Radium treatment. Death.*

Mr. B., aged eighty-two, first seen January 7, 1928, had suffered for some weeks from severe epigastric pain, with tenderness and a doubtful thickening in the duodenal region. The diagnosis was cholecystitis, but abdominal fat precluded effective palpation. An exploratory operation showed a lump one inch in diameter at the end of the common bile-duct, and involving the pancreas. Through the anterior wall of the duodenum the crater of the ulcer could be felt in the situation of the bile-papilla. After division

of the posterior parietal peritoneum to the right of the duodenum a drainage tube was introduced into contact with the outer aspect of the lump. Two 25-mg. radium tubes were left in the drainage tube for twenty-four hours. A very cautious prognosis was given in view of the age and condition of the patient. Three days after operation the patient died "for no apparent reason." A necropsy confirmed the diagnosis of carcinoma. The pathologist reported as follows: The two portions of tissue removed from the pancreas were sectioned. Histologically the features are those of a carcinoma. The growth is composed of hyperchromatic cells which resemble the parenchyma of the pancreas but the nuclei take up a relatively large proportion of the cell and the alveoli are irregular. There is some hyperplasia of the islets.

CASE V.—*Carcinoma of head of pancreas. Operation. Radium treatment. Death ten days later.*

James N., aged fifty-eight, was admitted to the Middlesex Hospital under my care in March, 1930, with a history of two month's jaundice. Upper paramedian laparotomy disclosed a localized hard mass in the head of the pancreas. Tubes of radium totalling 21 mg. were inserted in the end of a drainage tube which was placed in contact with the mass. A cholecystgastrostomy was then performed. The patient died ten days later without any symptoms except increasing weakness. A necropsy showed a carcinoma of the pancreas invading the duodenum and occluding the bile-duct.

CASE VI.—*Carcinoma of pancreas. Laparotomy. Insertion of radium tubes. Twenty-five days later gastroenterostomy for pyloric obstruction. Death two days later.*

William H., aged fifty-four, was admitted to the Middlesex Hospital under my care in November, 1928. For two years he had suffered from pain in the epigastrium with loss of appetite and weight. Upper paramedian laparotomy. A hard mass was felt in the head of the pancreas. A portion removed for section showed only chronic inflammatory changes. Three 25-mg. tubes of radium were pushed into the mass and were left for twenty-four hours. Twenty-five days later signs of pyloric obstruction necessitated a gastroenterostomy, but the operation proved too much for the patient's strength and he died in forty-eight hours. Post-mortem, a large ulcer three-quarters inch in diameter was felt in the first part of the duodenum. The second part of the duodenum was involved in a large polypoid colloid growth infiltrating the head of the pancreas.

CASE VII.—*Carcinoma near end of common bile-duct, with wasting and epigastric pain. Radium operation. Patient at work and free from symptoms ten months later.*

Mr. D. S. N., aged sixty-four, was first seen in June, 1933, complaining of loss of weight for a month with spasmodic pain in the epigastrium, not definitely related to the ingestion of food. Vomiting, constipation and jaundice absent. On X-ray examination the stomach was large with marked intermittent pyloric spasm and considerable delay in emptying. Six and three-quarter hours after ingestion of barium a residue remained in the stomach and a well-marked fleck residue still later.

June 22, 1933, the abdomen was opened by diathermy through a right paramedian supra-umbilical incision. The stomach was normal, but the first and second parts of the duodenum were dilated. The gall-bladder was not distended. A cystico-omental band crossed the duodenum and was divided. The pylorus was normal and no sign of an ulcer was found either above or below it. Three inches below the pylorus and behind the duodenum was a puckered hard mass, about two and one-half inches in diameter, evidently a carcinoma originating at the end of the common bile-duct. The duodenum was mobilized by an incision through the peritoneum at its right border, and nine 2-mg. tubes of radium element enclosed in a glove finger were inserted on the posterior aspect of the growth and in contact with it and were left for fifty hours.

The question of a cholecyst-gastrostomy and a gastroenterostomy was considered, but the anæsthetist reported that the patient's general condition was bad, and neither operation appeared necessary at the moment. It was thought that one or both operations

would be required later after a period of improvement which might last two or three years.

Mr. N. was seen again in January, 1934. He states that he feels very well and that his only trouble is constant flatulency, but this is no worse than it has always been through his life. He can take any food in reason and is sleeping well. Since the operation he has gained fifteen pounds. Pulse soft and regular, perhaps rather deficient in volume. Patient had much pain before the operation but now has none and feels well and able to do a full day's work. On examination his stomach was perhaps a little splashy, but is high up and not dilated. There is no present indication for a gastro-jejunostomy (January 6, 1934).

This patient's medical man, Doctor Farquharson, reports as follows on April 8, 1934:

I saw Mr. N. a few days ago and as far as I could judge he is going on very well. He has put on weight and the only trouble seems to be marked flatulence; some of this I think is due to his leaving off his alkaline powder. He has no glands and I cannot feel his liver, his color is good and he is carrying on his work.

The flatulence which at present is the patient's only symptom may indicate that some stenosis is developing in the duodenum and that a gastroenterostomy will be necessary later on.

Results of Radium Treatment.—Of the seven cases of carcinoma of the pancreas recorded in this paper one remains cured after a period of nearly fourteen years. The presence of isolated nodular deposits outside the main mass at the time of operation made the diagnosis in this case as certain as it could be without a biopsy. The removal of a piece of the growth for section involves a grave additional risk which in this case, and as a rule, appears unjustifiable.

In a second case life was prolonged for over two years, although according to Robson and Moynihan the whole clinical course of pancreatic carcinoma is run as a rule within twelve months. Furthermore, at a second laparotomy, necessitated by pyloric obstruction, all signs of carcinoma had disappeared, following the radium treatment. The growth later resumed its activity and was found at the necropsy.

In a third case the patient remains well ten months after radium treatment, a period long enough to justify the assertion that radium has imposed a definite check to the growth, but too short to justify any confident hope that the growth is cured.

In the remaining four cases death occurred within a short period of the laparotomy, apparently from simple asthenia, a mortality of 57 per cent. It must be admitted that this is a high and discouraging mortality. These patients are generally advanced in years, and have been suffering perhaps for months from malnutrition, the result of vomiting and frequently from jaundice. I do not think that radiation has anything to do with the mortality, though it might be advisable in future cases to screen the right suprarenal capsule by a lead screen covering the posterior aspect of each of the radium tubes.

A comparison between the results of palliative operations in which no radium is used, and my own results, confirms the conclusion that the high mortality is due to the unsatisfactory general condition of the patients and

not to radiation. According to Gosset the mortality of simple cholecystostomy for pancreatic carcinoma is 70 per cent., and of cholecystenterostomy 75 per cent.

Under all the circumstances it may I think be claimed that my results are encouraging. Interstitial radium in pancreatic carcinoma appears to hold out a one in seven chance of permanent cure, and a three in seven chance of prolonged relief.

Conclusions.—It is one of the difficulties of the surgery of relatively rare conditions that the individual's experience, even in a lifetime, may be too limited to warrant the expression of firm conclusions. My essays in the radium treatment of carcinoma of the pancreas, though they extend over thirteen years, leave me in this unsatisfactory position.

My material is of suggestive rather than demonstrative value. The conclusions I have arrived at are provisional and subject to correction by further collective experience but they will serve to define the outline of an unexplored subject and to form a baseline from which other workers may start. Owing to difficulties of diagnosis and the comparative rarity of pancreatic carcinoma, the subject is essentially one for collective investigation, preceded, if possible by the general adoption of an agreed plan of action. With these qualifications I shall state my personal conclusions in dogmatic form.

Carcinoma starting in the ampulla of Vater if detected early as a small nodule at the outlet of the bile-duct may be dealt with by opening the duodenum and doing a limited intraduodenal ablation of the growth by diathermy. It will usually be wise to do a cholecyst-duodenostomy to avoid cicatricial stenosis at the orifice of the common duct.

All other forms of Vaterian cancer can be more hopefully treated by implanted radium than by ablational operation. Although ablational operations may win a rare and splendid triumph as in a case of my colleague Gordon-Taylor they lie at the limits of the patient's endurance and the surgeon's skill, and their mortality will always remain very high. Moreover, they are only exceptionally practicable.

In using implantation radium treatment it must be recognized that even if the growth be completely fibrosed by radiation its obstructive effects upon the bile-duct and upon the duodenum may be actually aggravated by cicatrization. After the surgeon has divided the posterior parietal peritoneum to the right of the duodenum, mobilized the duodenum, and introduced radium tubes into close contact with the posterior aspect of the growth, logic demands with an eye to the future that he should anastomose the gall-bladder to the duodenum and then should do a gastroenterostomy. I say logic demands this, but the general condition of the patient may make it advisable to postpone the gastroenterostomy, or even (in the absence of jaundice) also the cholecyst-duodenostomy.

What is the optimum dose of radium in pancreatic cancer? Provisionally I would put it at 700 to 1000 mg. hours. This statement is ambiguous since

it gives no time-intensity ratio. Should a large quantity of radium be used for a short time, or a small quantity for a longer time? Experience in cancer of the tongue has shown that the employment of small power tubes inserted for a week is far more effective than the use of large tubes for a day. In using a group of 2-mg. or 3-mg. tubes in the retroperitoneal tissues there might be a risk of a persistent sinus if the tubes were left as long as a week. Nevertheless, it is, I think, in this direction that hope for the future lies. I propose in future cases to use perhaps three tubes each of 2-mg. element, and to remove them after five days, giving a total dose of 720 mg. hours.

In any case I prefer to use radium rather than radon. The intensity of radon tubes is initially uncertain, dependent as it is upon the hurried observation of a laboratory technician. The rapid fall in intensity of a radon tube appears in any case to be an undesirable factor.

In conclusion my experience justifies the statement that a surgeon who on opening the abdomen finds an irremovable pancreatic cancer is not doing his duty to the patient unless he subjects the growth to interstitial irradiation.