

## THE TENDENCY OF CARCINOMA OF THE PANCREAS TO SPREAD BY BLOOD-VASCULAR INVASION \*

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Although carcinoma of the pancreas is a relatively uncommon disease, four cases of this condition have been found at necropsy at the Peter Bent Brigham Hospital during a six months' period, including last winter. These cases represent one-half the number of such cases coming to necropsy in this laboratory since the opening of the hospital in 1913, the total being only eight cases. Study of the series shows that in three cases the head was involved primarily; in one case the head and body was involved, in three cases the cancer was diffuse throughout the organ, and in one case it was limited to the tail. Two of the carcinomas were of the scirrhus type, five were adenocarcinomas and one, composed of atypical cells, was interpreted as having arisen from the islands of Langerhans rather than from ducts or parenchyma.

Extensive metastasis occurred in six of the eight cases, a relatively high percentage, judging from the figures obtainable from the literature. In the standard works metastases to the liver and retroperitoneal lymph nodes are usually mentioned, and by some authors they are stated to be common, but there appears to have been little reported concerning more distant secondary growths, and no emphasis has been placed on the notable tendency of these tumors to spread by way of the blood stream.

Baldwin,<sup>1</sup> in a review of fifty cases collected from the Index Medicus up to 1900, finds that scirrhus carcinoma is the most common carcinoma of the pancreas and that metastases are not common, except in the liver. He gives the following figures relative to the frequency of secondary growths in his series:

Metastases: None in 10 cases; liver, 11; neighboring lymph nodes, 11; duodenum, 5; lungs, 3; kidneys, 3 (once in the right kidney and once in the left kidney alone); spleen, 3; capsule of spleen, 1; opening of common duct into duodenum, 2; omentum, 2; pleura, 2; colon, 2; solar plexus and nerves, 2; mesocolon, 1; muscular coat of intestine, 1; abdominal wall, 1; pyloric wall, 1; opening of cystic duct from gall-bladder, 1; psoas muscle, 1; no statement concerning metastases, 8.

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\* From the Pathologic Laboratory of the Peter Bent Brigham Hospital, Boston.

1. Baldwin, F. A.: Phila. M. J., 6:1195, 1900.

He does not state, however, in how many instances lesions in various organs were associated in the same person or what combinations were found.

In connection with blood-vascular invasions, Baldwin describes the following condition found in the primary growth in one of his own cases:

Some of the vessels have their lumen completely obliterated by growth into it of tumor cells and others have their lumen partially or wholly closed by laminated thrombi and when these are examined one finds places where two, four, or six cells are seen which are entirely surrounded by fibrin and blood cells of thrombus. If one follows back along the vessel wall, one sees a place where the wall has been involved by tumor from without. First there has been an invasion of the adventitia. From this coat, tumor cells have proceeded along lymph spaces into media and intima. Then points are seen where tumor cells have broken through into the intima and grown into the lumen. It is in these vessels that the laminated thrombi are found in which the loosened cells are noted.

In the series studied in this laboratory, the two cases which on microscopic examination proved to be scirrhus carcinoma showed no metastases, but in the remaining six cases, secondary involvement of the liver was present in all, and regional lymph nodes were affected in all but one.

The lungs of five of the six patients were involved, the stomach was involved in four and the duodenum in four cases, the two latter organs apparently by direct invasion rather than by metastasis, although it was frequently impossible to determine definitely which type of extension had occurred. In three cases there were metastatic foci in the suprarenals and in a fourth case direct invasion of the left suprarenal occurred. The brain was examined in only two cases; secondary growths were found in both. In these two cases, which will be described more in detail later, there was a generalized carcinomatosis, involving almost every organ.

The features on which it is desired to lay emphasis are: (1) the tendency of these tumors to invade the blood stream locally; (2) the occurrence of generalized carcinomatosis by blood dissemination, and (3) the signs caused by secondary growths in two patients which obscured the clinical picture. There was definite evidence of dissemination by way of the blood stream in two cases of adenocarcinoma, and in two others there was invasion of the portal vein or its branches, in which, however, no generalized distribution of tumor foci occurred.

#### REPORT OF CASES

The following extracts from the protocols serve to illustrate the invasion of the venous system:

CASE 1.—L. K., male, aged 33. Necropsy by Dr. S. B. Wolbach. Carcinoma of head of pancreas. "On opening the portal vein it is found to be surrounded by tumor (primary) for a distance of 6 to 7 cm. At the lower margin of the tumor at the level of the entrance of the superior mesenteric vein it has a plaque-like thrombus of friable whitish material and upon removal of this thrombus the intima is found roughened, elevated and firm, and it is evident that tumor has extended into the vein at this point."

CASE 2.—O. S., male, aged 75. Necropsy by Dr. S. B. Wolbach. Carcinoma of tail of pancreas. "Dissection of the extrahepatic portion of the portal vein shows nothing unusual, but a probe introduced into the splenic vein meets resistance where it enters the tumor and here it is completely occluded. The splenic vein is picked up at the hilus of the spleen and two branches of large size are found running in the gastro-splenic omentum to the greater curvature of the stomach, while the splenic vein itself enters the tumor where it is compressed and occluded by the firm growth. Further dissection of the portal vein shows the branches going to the left lobe to be normal. The main branch going to the right lobe is completely occluded by a tumor nodule. The occluded portion is preceded by a short distance of vein which is flattened by surrounding tumor. The large branches of the hepatic vein opening into the vena cava from the right are compressed and a few small yellowish nodules from 1 to 2 mm. in diameter are present in the intima. Such vessels when followed into the

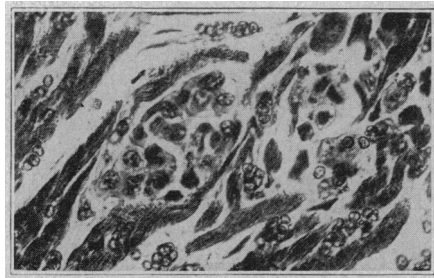


Fig. 1.—Metastatic focus in myocardium. High power.

substance of the liver appear to be occluded completely where they enter the tumor nodules." This man also showed occlusion of the hepatic duct within the liver substance.

In the patients in whom more generalized distribution occurred, invasion of larger vessels was not demonstrated but there seems little doubt that the process by which the tumor spread is similar in the two types, and that secondary growths at more distant points owe their origin to invasion of the venous system either at the seat of the primary growth or in the liver.

Of the two cases in which secondary tumors were numerous, the first showed metastases in the liver, lungs, suprarenals and brain. In the liver there were the usual large umbilicated nodules and in the suprarenals there was practically complete replacement of parenchyma by tumor growth. Both lungs presented typical small plaques on their pleural surfaces and within the substance of the organs, and in addition the left lung showed a rather unusual picture.

CASE 3.—W. D., male, aged 50. Necropsy by Dr. F. D. Adams. Carcinoma of head of pancreas. "The upper lobe of the left lung is firm, collapsed, contracted, and about one fourth of the normal size. It is drawn over toward midline and is adherent to adjacent pericardium. On tracing the upper branches of the pulmonary artery and vein and the bronchus into this lobe they are all found to be completely occluded by the firm mass of tissue. The pulmonary artery on the medial side of the obstruction contains within its lumen, posteriorly, a raised reddish mass, adherent to wall and which on section has a yellowish center, giving the appearance of tumor metastasis with superimposed thrombus. The firm upper lobe on section shows a dark greenish blue anthracotic surface with scattered areas of greenish yellow fading into surrounding tissue. Microscopic examination showed practically complete destruction of lung tissue, the architecture being in places entirely destroyed by tumor cells having a tendency toward alveolar formation, but with a dense fibrous tissue stroma. In this mass, as well as in other foci in the lung, there were found areas in which cells were smaller than the typical tumor cells and were surrounded by homogeneous, structureless material interpreted as being colloid.

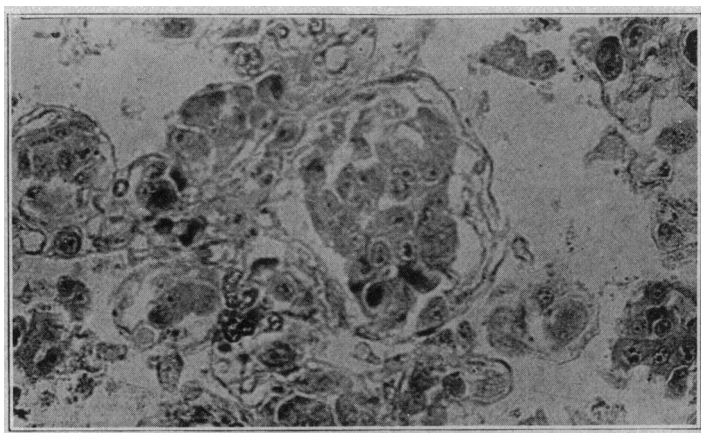


Fig. 2.—Metastatic focus in alveoli of lung. High power.

This material was also found free in irregular spaces in the stroma without relation to tumor cells which had probably been present previously but had degenerated. Other places in the lungs showed invasion by small masses of tumor tissue which followed outlines of the pulmonary alveoli, but tumor cells could not be demonstrated within the alveolar capillaries.

Foci of tumor growth were found scattered through the cortex and white matter of the brain in this patient, being described as small irregular areas of discoloration, brownish, somewhat gelatinous, irregularly outlined and poorly demarcated. They proved to be, on microscopic study, metastases involving brain tissue and in places overlying meninges as well. Here there were frequently found blood vessels filled completely or partially with clumps of tumors cells and sometimes lying a short distance apart from the tumor focus. Colloid change was prominent in all the foci examined in this brain.

Colloid was found also in one other case, but in the latter it was present in the primary growth as well as in the metastases, whereas

in the instance just discussed the tumor in the pancreas was a pure adeno-carcinoma.

The most unusual case of the series is one in which a diffuse carcinomatosis occurred with widely distributed metastases.

CASE 4.—M. Ca., female, aged 47. Necropsy by Doctor F. D. Adams.

Body: Obesity. Pallor suggesting quite severe anemia. Edema about left eye. Swelling of deeper tissues in region of angle of jaw, extending well down into the neck. Beneath, a hard irregular nodular mass is palpable, which appears to be a tumor involving the parotid gland and regional nodes as well.

Peritoneal Cavity: Numerous small white, slightly raised tumor nodules scattered at irregular points on the intestinal surfaces, averaging from 2 to 3 mm. in diameter. Mesenteric lymph nodes enlarged and show evidence of invasion.

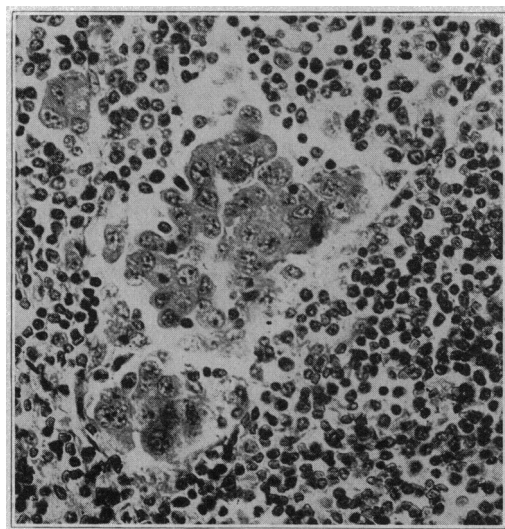


Fig. 3.—Metastatic focus in malpighian body of spleen. High power.

Pleural Cavities: Tumor nodules on diaphragmatic surface.

Mediastinum: Nodules present in the fatty tissue surrounding the pericardium and on external surface of pericardium, but none on its inner surface.

Heart: Normal size. Nodules averaging from 3 to 4 mm. in diameter on the epicardial surface. Endocardium shows a number of tumor plaques and nodules in right auricle and ventricle. Valves and myocardium not remarkable.

Lungs: Tumor nodules present on pleural surfaces and within substance of the organs.

Spleen: No gross evidence of tumor invasion.

Gastro-intestinal Tract: Nodules on peritoneal surfaces as noted. Similar nodules scattered through mucosa of stomach, small and large intestines.

Pancreas: Enlarged, firm, hard and nodular. Outer surface studded throughout with closely packed tumor nodules, raised over surface from 1 to 5 mm. Involvement of peripancreatic tissue by tumor nodules as well. On section, gland is largely replaced by tumor throughout, but small areas of normal appearance are seen lying between nodules.

Liver: A few small and large (about 1 cm. in diameter) nodules are present.

Gallbladder and ducts: Not remarkable.

Kidneys: Both organs show tumor nodules in cortex and medulla, varying from 1 to 3 mm. in diameter. Passive congestion. Both pelves bright red in color, showing extreme degree of hemorrhage into mucosa.

Suprarenals: Not remarkable.

Bladder: Not remarkable.

Uterus: Tumor nodules within mucosa.

Ovary: Not remarkable.

Neck: Piece of tissue removed from region of left parotid gland shows tumor infiltration.

Brain: No evidence of tumor externally or on section after fixation.

*Microscopic Examination.*—Heart: Several small nests of epithelial cells of tumor type are seen in the myocardium, particularly in capillaries and small blood vessels.

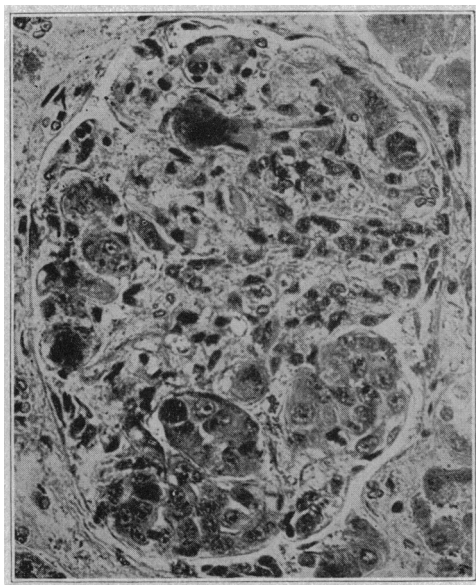


Fig. 4. Metastatic focus in glomerulus of kidney. High power.

Lungs: Alveolar capillaries show tumor emboli varying from single cells to small clumps. They are included within the capillaries but many have invaded surrounding tissue, and lie free in the alveoli. In some sections they form long cords of cells outlining alveoli. In one section there are large tumor masses, the largest measuring 4 mm. in diameter, of typical cells arranged in alveoli and cords. Mitoses are numerous. There is quite marked edema.

Spleen: Isolated small clumps of tumor cells are found in the malpighian bodies, as well as in the pulp.

Stomach: There is one section which shows high elevation of mucosa due to infiltration of submucosa and portions of mucosa by tumor cells.

Small Intestine: An occasional group of tumor cells is seen in the mucosa.

Large Intestine: Tumor cells are present singly and in small groups.

Pancreas: Two sections contain tumor nodules, some of them as wide as 3 mm. Nodules are composed of epithelial cells staining typically and arranged in alveolar form. There is attempted encapsulation with considerable interstitial pancreatitis resulting in atrophy of alveolar parenchyma. Mitotic figures are numerous.

**Liver:** In one section there is a large tumor nodule 14 mm. wide composed of alveoli of epithelial cells surrounded by a fine fibrous stroma. There is also dissemination through the liver substance, the capillaries containing tumor cells in varying numbers.

**Kidneys:** A large number of glomeruli contain a few tumor cells in the capillary tufts, in most instances the cells lying entirely within the lumina of the vessels. Larger areas of tumor invasion are also present.

**Suprarenals:** A few groups of tumor cells present in capillaries of medulla.

**Bladder:** A few tumor cells in occasional capillaries are found in the muscularis.

**Uterus:** Negative, except for marked obliterative endarteritis.

**Ovaries:** Numerous tumor nodules are present in vascular spaces, apparently lymphatics.

**Bone Marrow:** Tumor cells are present in large numbers.

**Mesenteric Lymph Nodes:** Show almost complete replacement by tumor growth.

**Brain:** Foci of tumor metastasis are found in the brain cortex. For the most part these foci consist of tumor cells situated in perivascular spaces, although in some parts cerebral tissue has been invaded, the center of growth being apparently a perivascular space.

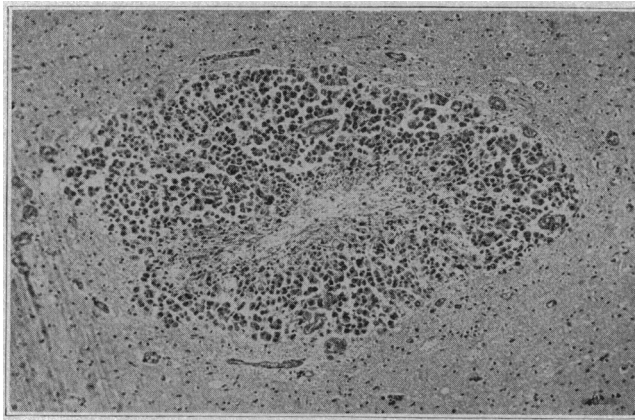


Fig. 5.—Metastatic focus in brain showing perivascular growth. Low power.

In this group of cases the carcinoma of the pancreas showed a definite tendency to invade local blood vessels and to disseminate metastases to the liver and lungs, and in some instances to other parts of the body. The type of tumor in which this occurs is the adenocarcinoma. While the primary tumor may be essentially of adenocarcinoma type, colloid change may occur in primary or secondary growths.

It is of interest from the clinical standpoint to note that in the two cases showing the widest dissemination there were signs due to secondary invasions which were of such a nature as to obscure the diagnosis. One patient (W. D., Case 3) showed a mass of collapsed lung and tumor in the upper left chest and a lesion in this region was demonstrated on physical examination and by roentgen ray. (Pulsation of the mass was observed under the fluoroscope.) These facts,

taken into consideration with a systolic murmur at the apex and a diastolic murmur in the third interspace on the left, pupillary signs, abnormalities of the deep reflexes and a positive Wassermann reaction in the blood serum, caused several observers to record a diagnosis of syphilis, aneurysm and syphilis of the liver. There was no evidence of syphilis at the necropsy, the jaundice being due to biliary obstruction just above the ampulla, the central nervous system signs probably being due to areas of softening in the brain, and the heart murmurs possibly to pressure on the vessels by the growth in the lungs. The presence of tumor metastases in the brain, and the demonstration of tumor cells within capillaries, make it seem probable that the infarctions were due to invasion of cerebral vessels by tumor or their occlusion by tumor emboli.

## PATHOLOGIC ANALYSIS OF EIGHT CASES OF MALIGNANT TUMORS OF PANCREAS

Name	Location	Liver	Regional Lymph Nodes	Lungs	Parietal Pleura	Stomach	Duodenum	Kidneys	Suprarenals	Venous Invasion	Biliary Obstruction	Type
M. R.	Head	—	—	—	—	—	—	—	—	—	+	Scirrhus
G. P.	Diffuse	—	—	—	—	—	—	—	—	—	+	Scirrbus
C. M.	Diffuse	+	+	+	+	+	+	—	+	—	—	Adenocarcinoma with colloid
M. Ch.	Head	+	+	+	+	+	—	—	—	—	—	Islands of Langerhans
L. K.	Head	+	+	—	—	+	+	—	—	Portal	—	Adenocarcinoma
O. S.	Tail	+	—	+	+	—	—	—	Left (extension)	Splenic hepatic portal	Intra-hepatic	Adenocarcinoma
W. D.	Head and body	+	+	+	—	—	+	—	+	Pulmonary cerebral	+	Adenocarcinoma with colloid
M. Ca.	Diffuse	+	+	+	+	+	+	+	+	Diffuse	—	Adenocarcinoma
Total.....		6	5	5	4	4	4	1	4	4	4	

In the case of M. Ca. (Case 4) there was a history of profuse bleeding per urethra for five days prior to admission to the hospital. Cystoscopic examination revealed a normal bladder and a normal urethral orifice on the right with a normally clear efflux. On the left, however, the orifice was pouty and there was no efflux during prolonged observation. The patient passed almost pure blood per urethra while in the hospital, but further study was impossible because of her poor condition. The genito-urinary findings, however, taken in conjunction with general signs of malignant disease, pointed toward a diagnosis of hypernephroma.

On microscopic examination, the most unusual feature of this case is the presence of extensive metastases within glomerular tufts. About half the number of tufts in each kidney contain groups of tumor cells.



Often one can see only two or three tumor cells plugging a capillary channel; in other cases the glomeruli are almost completely filled with them. Occasionally, tumor crescents fill and distend the capsular spaces. Mitotic figures are numerous in these secondary growths. Larger branches of the renal veins show areas of thrombosis, some fresh, others older, with beginning organization. Occlusion of these vessels does not appear to be complete. No tumor cells have been demonstrated in these thrombi. The disturbances of circulation in the kidney due to these glomerular metastases and to thrombosis probably account, in part, at least, for the extensive pelvic hemorrhages leading to hematuria.

Persistent jaundice, due to obstruction of bile ducts, is regarded as one of the most important signs of pancreatic carcinoma, and it has been estimated that it occurs in about three fourths of such cases.<sup>2</sup> In the series of eight cases under discussion, this feature was present in only four instances. There was obstruction at the ampulla in the two scirrhus cases, just above the ampulla in a third case, and of the intrahepatic portion of the hepatic duct in a fourth case. In the latter instance, occlusion was caused by a metastatic growth and not by primary tumor, which was in the tail. Four patients, in two of whom the head was involved primarily, showed no obstruction, despite the fact that in three of them there was extensive involvement of portions of the duodenum.

Clinically, carcinoma of the pancreas was strongly considered in three of the four cases with jaundice, but received practically no attention in the cases where this factor was not present. However, on reviewing the clinical records of the latter patients, after the necropsies, it was found that no features had been overlooked which should have given a key to the correct diagnosis.

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2. Osler and McCrae: *Modern Medicine*, Ed. 2, New York, Wm. Wood & Co., 1914, Vol. 3, p. 652.