THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Kinsley Renshaw final oral examination for the degree of

Master of Science in Surgery

We recommend that the degree of

Master of Science in Surgery

be conferred upon the candidate.

W. E. Lee
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REPORT

OF

COMMITTEE ON THESIS

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Kinsley Renshaw, for the degree of Master of Science in Surgery. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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4-21 6M

THESIS

MALIGNANT NEOPLASIA OF THE EXTRAHEPATIC BILIARY TRACT

Kinsley Renshaw, B.A., M.D.

Submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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MALIGNANT NEOPLASIA OF THE EXTRAHEPATIC BILIARY TRACT

Kinsley Renshaw, B.A., M.D.

Notwithstanding the fact that malignant conditions of the biliary tract have been well described in the literature, recent contributions concerning the treatment of jaundice seems to justify a review of the subject. It seems advantageous in order to avoid confusion, to consider this subject under two main heads.

1. Neoplasia of the gall-bladder. (60)

2. Neoplasia of the hepatic, cystic, and common ducts, with those of the ampulla and papilla.

PART I NEOPLASIA OF THE GALL BLADDER

A REVIEW OF THE LITERATURE

Three cases of cancer of the gall-bladder were reported before 1800; two by de Stoll in 1777 and one by Halle' in 1786. Baillie reported a case in 1794, but the diagnosis was questioned because the lesion resembled tuberculosis. From 1800 to 1850 seven cases were reported. Durand-Fardel, in 1840, were the first to describe the condition fully. In the latter half of the nineteenth century many contributions to the subject were made by English, French, German, and American writers, among the most important of which may be mentioned those of Rolleston, Villard, Courvoisier, Zenker, Futterer, Musser, Ames, and Smithies, representing the medical aspect of the subject, and of those of Mayo-Robson, Moynihan, Quenu, Kehr, Erdman, Deaver, and W.J. Mayo from the surgical and prognostic aspects.

Pawcett and Rippmann, in 592 necropsies in cases of gall-stone, found malignant conditions of the gall-bladder in forty-eight cases. Dr. W.J.Mayo has stated that cancer occurred in eighty-five of 3908 operations on the gall-bladder and biliary passages in the Mayo Clinic. Erdman found the incidence of cancer in this organ to be 6.7 per cent in 224 cases of cholecystitis in which he operated from 1917 to 1919. Deaver found 1.6 per cent malignancy in 1000 operations for gall-stones, and Smithies has reported 2.3 per cent malignancy in 1000 operations on the gall-bladder.

PATHOLOGY

Ziegler believes that carcinoma of the gall-bladder is of the cylindrical epitheliomatous type which takes the form of a papillary or fungous tumor, or of a cancerous ulcer. MacCallum believes that the malignancy takes the form of adenocarcinoma or epithelioma. Rolleston has found the condition to

consist chiefly of carcinoma, which may be of the columnar or spheroidal-cell variety and the cells may undergo colloid degeneration. The tumor may be papillomatous or invasive. Through metaplasia a squamous-cell carcinoma may occur. He cites references to twenty-two cases of the squamous-cell type. Primary sarcoma is considered exceedingly rare; Rolleston cites only fourteen references to this type of growth. It is believed that the growth originates in the glands in the wall of the gall-bladder or in its mucous membrane. MacCarty and Rolleston believe that both carcinoma and epithelioma arise from the mucous membrane which lines the gall-bladder.

Rolleston states: "It may be concluded that carcinoma, whatever its form, arises from the mucous membrane as a whole, and no statement that either form of carcinoma arises exclusively from the surface epithelium of the gall-bladder or from the epithelium lining the glands is justified. . . . The growth is found most commonly in the fundus, although it may occur in the neck of the organ, or be diffuse in form." Futterer classifies his cases as follows: Seventeen in the fundus, thirteen in the neck, eight in the anterior wall, and seven in the posterior wall.

ETIOLOGY

Malignancy of the gall-bladder is shrouded in the same cloak of mystery as is cancer in general. Many writers believe that the chief causal factor is the local irritation of gall-stones, which are present in a large percentage of the reported cases. Musser found stones in primary malignant disease of this organ in 69 per cent of cases, Futterer in 70 per cent, Winton in 81 per cent, Zenker in 85 per cent, Courvoisier in 91 per cent, Siegert in 95 per cent, Janowski in 100 per cent, and Deaver in 89 per cent. Beadles found sixty-four cases of secondary malignancy, with stones in two instances. Siegert found stones in 15 per cent of secondary malignancy. Whether the stones are the cause or the result of the growth has been widely discussed.

Lutton, Lancereaux, Lang-Heinrich, and Forster favored the view that the growth precedes the stones. It was suggested that the neoplastic condition causes stagnation and inspissation of the bile with a resultant formation of stones. It is now generally conceded that the stones precede the growth. Various English writers claim heredity as a factor in from 11 to 17 per cent. Schueppel denies this. In Smithies' series a history of heredity was found only once.

AGE AND SEX INCIDENCE

Cancer of the gall-bladder shows a predilection for females; Zenker found 72.9 per cent in women; Naunyn 83 per cent; Musser seventy-five females to twenty-three males. Smithies, on the other hand, reported sixteen males to seven females. The condition is usually observed between the ages of fifty and seventy. Sherrill gives the average age as fifty-four and five-tenths years, Smithies as fifty-nine years, and in Musser's cases the ages were as follows:

YEARS	PATIENTS
1 - 10	1
11 - 20	0
21 - 30	1
31 - 40	9
41 - 50	19
51 - 60	29
61 - 70	19
71 - 80	14
81 - 90	1

Ames reported the case of a boy aged four.

The clinical picture in our cases does not differ from that described in the literature. Lancereaux divided malignancy of the gall-bladder into a

biliary form characterized by belching, abdominal cramps, dyspepsia, jaundice, abdominal mass, and fever; and an hepatic form with an insidious onset, short duration, vague abdominal pains, weakness, diarrhea, or constipation, rapid enlargement of the liver, and occasional slight jaundice. Guyot added three other groups, chiefly dependent on the symptoms produced by adhesions of the malignant gall-bladder to other organs: pseudopyloric symptoms, intestinal symptoms, or symptoms due to perforative peritonitis. Rolleston divides the cases into those in which the symptoms are associated with preexisting cholelithiasis, those in which the symptoms are due to the local effects of the disease, and those in which they are due to invasions of the adjacent parts by the growth and to metastasis in the liver, peritoneum, or elsewhere. W. J. Mayo mentions the following diagnostic clinical points in connection with the diagnosis: A hard tumor in the region of the gall-bladder, absence of rigidity unless the peritoneum is involved, progressive loss of flesh and cachexia, a nodular tumor if the liver is involved, and jaundice if the ducts are involved.

SURGICAL TREATMENT

Bardenheuer was probably the first to extirpate the gall-bladder for cancer. Hochenegg next performed the operation; his patient had not had a relapse at the end of eight months. When the tumor is confined to the gall-bladder cholecystectomy is generally conceded to be the operation of choice. In some cases a portion of the liver may be removed, as was first advised by Mayo-Robson, although when it is necessary to remove a large portion, poor results may be expected. Cotte speaks of palliative and radical operations, that is, cholecystostomy, which should be reserved for the badly infected cases, or for those in which there is considerable retention in the gall-bladder, and cholecystectomy with the removal of the neighboring lymphatic glands and the excision of adjacent liver tissue. The results of surgical

treatment of malignancy of the gall-bladder as gleaned from the literature are far from satisfactory. W. J. Mayo, in 1910, reported five patients alive after two years. In these a preoperative diagnosis of malignancy was not made. One patient whose diagnosis was made preoperatively lived more than one year. Smithies reported the cases of two patients who have remained well more than four years; all the other patients in his series died within eight months. Quenu, in ninety-three collected cases, reported results as follows: Death in less than three months, seventeen; death between three and four months, seven; death between four and six months, six; death between six and eight months, eight; death between eight and twelve months, one; death at the end of one year, three.

Friedham reported a patient alive and without relapse after four and one-half years; Worner, after three years; Kortze, after two years and two months; Mayo-Robson, after two years; Friedham, after three years, but dead after four years; Hochenegg, dead after three years; and Patel, dead after two and one-half years. Quenu gives the immediate mortality as being due to hemorrhage, syncope, septicaemia, peritonitis, and shock.

From January, 1907, to January, 1921, 7878 operations were performed for gall-stones at the Mayo Clinic. Within this period primary malignancy of the gall-bladder (confirmed by pathologic examination) occurred in eighty-four cases (carcinoma eighty-two cases; epithelioma one; and lymphosarcoma one). The carcinomas were divided into the adenomatous and the colloid types, the adenomatous type being much more frequent and taking the form of papillary or ulcerative growths, with a general thickening of the walls. Thirty-four gall-bladder specimens were available. In twenty-three the condition was a diffuse form of carcinoma with a general thickening of the walls of the gall-bladder. The fundus was no more frequently involved than the pelvis. In four the cancer was of the fundus, in three the condition was the flat

ulcerative type, and one was of the papillary type. There was one papilloma of the middle portion, one of the pelvis, and three flat ulcerative growths at the neck of the organ. The epithelioma was situated at the fundus; the lymphosarcoma involved both the fundus and the pelvis.

In the series of eighty-four cases there were thirty-eight cholecystectomies and forty-six explorations. Stones were found in thirty-seven of the thirty-eight cholecystectomies. Stones were definitely present in thirty-three cases in which explorations were performed; they were undetermined in twelve and absent in one. The epithelioma was unaccompanied by stones, while the lymphosarcoma was associated with them. In a number of instances the growth was situated so that there could be no interference with bile drainage, thus probably disproving in these cases the hypothesis that the neoplastic obstruction produced the stones.

In only nine cases was there a history of hereditary or family cancer. Sixty-eight of the patients were females; sixteen were males. The ages were as follows:

YEARS	PATIENTS
1-10	0
11-20	0
21-30	2
31-40	2
41-50	12
51-60	37
61-70	27
71-80	3

SYMPTOMATOLOGY

The average duration of symptoms was from ten to thirty years, the longest duration was more than forty years. One patient had felt perfectly well until one month before operation; an inoperable carcinoma was found.

The average loss of weight was fifteen pounds. One patient had lost fifty pounds; another had gained weight.

Sixty patients gave a definite history of gall-stone colic. Thirty-two complained of a dull pain either with or without colic. The pain was situated in the epigastrium in forty-three cases; in the right hypochondrium in forty-four; in the upper left abdomen in six; and in the lower abdomen, back or precordial region each in one. The pain radiated to the back in thirty-eight cases; to the right shoulder in eleven; to the left shoulder in four, and to the right iliac fossa in two. Eusterman has called attention to the frequency of pain in the back in cases of malignancy of the gall-bladder. Thirty patients had pain so severe as to require morphia for relief. One patient was given chloroform.

Forty patients had varying degrees of jaundice. Forty-seven had vomited and fifty had been nauseated; forty-three had been constipated, and one had had diarrhea.

Twenty-three patients gave a history of fever.

Forty-nine patients complained of tenderness on palpation; in forty the tenderness was in the right hypochondrium, in nine in the epigastrium, A mass was palpated in thirty-seven; in thirty-two in the right upper abdomen; in three in the epigastrium; in one in the middle abdomen; and in one in the lower abdomen. The liver was definitely palpable in seven patients; one only had physical signs of ascites.

Test meals were given to thirty-three patients and achlorhydria was found in one, subacidity in nineteen, normal acidity in twelve, and hyperacidity in one.

DIAGNOSIS

It is extremely difficult to diagnose malignant conditions of the gall-bladder early enough to obtain favorable results from surgical treatment.

Usually the chief symptoms are those of gall-stones, and there does not seem to be any additional chain of symptoms whereby the onset of malignancy can be foretold. Rapid loss of weight and strenth, pain referred to the back, and a mass with or without jaundice, indicate advanced malignancy in some cases. Malignancy in the bile ducts or in the pancreas can scarcely be differentiated. Severe cholangitis with or without stones in which there is a rapid loss of weight may be confused with neoplasia. Empyema of the gall-bladder may simulate malignancy.

In the thirty-eight cases of cholecystectomy a diagnosis of gall-bladder disease with or without stones was made in twenty-five; in five a questionable diagnosis of cancer of the gall-bladder was mentioned, while in one, cancer of the liver was diagnosed.

In the forty-six explorations, gall-bladder disease was diagnosed in twenty-two cases, malignancy of the gall-bladder in twelve, and of the liver in three.

TYPE OF OPERATION

Cholecystectomies were performed in thirty-eight of the eighty-four cases. In six of these a portion of the liver was also removed, and in one three-fourths of the common duct was resected. Choledochotomy was performed in five. In forty-six cases the condition was considered inoperable from a radical point of view. A partial cholecystectomy was performed in four, cholecystostomy in ten, and choledochotomy, appendectomy and posterior gastro-enterostomy each in one case. In the cases in which the gall-bladders were removed the growth had extended to the liver in nine, to the biliary ducts in four, to the pancreas, in three, and to the lymph-glands in five. Explorations showed that the growths had extended to the liver in thirty-seven, to the bile ducts in two, to the lymph-glands in thirteen, to the pancreas in three, to the stomach in three, to the colon in four, to the duodenum in two, to the small

intestine in four, to the operative incision in one, to the peritoneum in three, to the omentum in two, to the pleura in one (necropsy), to the left lung in one (necropsy), and to the pelvis in one.

PROGNOSIS

The operative mortality in the series reported was not exceedingly large. One patient died within the two weeks following cholecystectomy. Seven died within the two weeks following exploration; a total of eighty-four patients.

TABLE I.

Results of Operation.

Exploration		Cholecystectomy	
Duration of Life	Patients	Duration of Life	Patients
		Years	
1 week	5	1	1*
2 weeks	2	2 (Three still alive)	5
3 weeks	1	3	1
1 to 2 months	9	4	1
2 to 3 months	6	5	0
3 to 4 months	2	6	1
4 to 5 months	2	7	1
5 to 6 months	4	8 (One still alive)	2
7 to 8 months	2	9 (Still alive)	1
8 to 9 months	0	10	1
9 to 10 months	1	11 (Still alive)	1
10 to 11 months	1	12	0
Alive 11 to 12 months	2		
Alive 2 years after operation	1	Months	
Alive 1 year after operation.	1	1	3
Seven patients could not be traced.		2	1
		3	0
		4	3
		5	0
		6	2
		7	2
			26
		Twelve patients could not be traced.	

*Patient alive one year after operation; not heard from since.

The cases are divided into three groups:

Group 1. - Cases in which after symptoms of gall-stone colic for years there is a sudden change; the patient begins rapidly to lose weight and strenth,

the pain becomes continuous; jaundice, fever, and a tumor may or may not be present.

Group 2. - Cases similar to those in Group 1 with the exception that instead of symptoms of gall-stone colic there are symptoms of gall-bladder dyspepsia.

Group 3. - Cases in which there are no symptoms up to one year before operation, then a sudden development of symptoms of malignancy, rapid loss of weight and strength, cachexia, and tumor. Jaundice may or may not be present. Some of these patients may have pain, either of a dull boring character, or that of gall-stones; others may not have pain.

The forty-six cases in which exploratory operations were performed are divided into three groups: thirty cases in Group 1, five cases in Group 2, and eleven cases in Group 3.

DISCUSSION

Twenty-nine of the thirty-eight patients on whom cholecystectomies were performed had had symptoms referable to the gall-bladder for more than one year; nine had had symptoms for less than one year.

If the condition is operable cholecystectomy should be performed; cholecystostomy should only be performed when besides the tumor there is a severe infection of the gall-bladder, or as a path for the introduction of radium (W.J.Mayo[64]). Cholecystostomy for stones had been performed elsewhere in five of the eighty-four cases, indicating that malignancy may develop in gall-bladders that have been drained.

W. J. Mayo[61] considers jaundice a contraindication to operation when a definite diagnosis of malignancy of the gall-bladder has been made.

Complications may be due to perforation of the gall-bladder, as happened in one case in the series, to empyema, or to extension to the neighboring viscus by continuity, contiguity, or metastasis.

Seven patients on whom a cholecystectomy had been performed were alive six years after operation, a percentage of 8.3 cures. The diagnoses in these cases were: Gall-stones in three, gall-bladder disease in three, and gastric carcinoma in one (in this case adhesions had developed between the gall-bladder and the pylorus). The operative procedures were: Cholecystectomy in five; cholecystectomy, excision of adjacent liver tissue, and choledochotomy in one; cholecystectomy and gastroenterostomy in one (besides the malignancy there were gastric and duodenal ulcers).

CONCLUSIONS

1. Malignancy of the gall-bladder is not an uncommon occurrence.

2. Carcinoma is the most common type of neoplasia found; sarcoma is exceedingly rare.

3. Gall-stones are complications in a very large number of cases.

4. Heredity seems to have little influence in the development of malignancy in this organ.

5. Females and males are afflicted in the ratio of about four to one.

6. Seventy-five per cent of cases occur between the ages of fifty and seventy.

7. In most cases there has been a history of gall-stones for some time.

8. Early cholecystectomy for stones will either prevent the development of malignancy or find the condition in its incipiency.

9. Late operation is of little value except as a diagnostic procedure.

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PART II NEOPLASIA OF THE HEPATIC, CYSTIC AND COMMON DUCTS, WITH THOSE OF THE AMPULLA AND PAPILLA.

A REVIEW OF THE LITERATURE.

Cancer of the bile ducts as a clinical and pathological entity, is of more recent interest than Cancer of the Gall-Bladder. According to Devic and Gallivardin it was not recognized previously to the middle of the 19th century.

Rokitansky, in his Anatomical Pathology, considers their involvement by secondary growths from nearby organs as the only possibility and the majority of the authors of that time agreed with his views. Schueppel in an article published in 1878 describes the first cancer of the hepatic canal and he believes that this with the lower part of the common duct, is the place of election for biliary neoplasms[14]. Durand-Fardel published the first case of cancer of the common duct and according to Mayo-Robson, cancer of the ampulla was first described by McNeal in 1835.

Musser in 1889 collected eighteen cases of duct carcinoma. Buson collected eleven cases, mainly of the ampulla. Claisse tabulated fifty. Devic and Gallivardin after eliminating doubtful cases, analyzed fifty-six. Rolleston reports fifty cases. Outerbridge analyzed 110 cases, fifty-one of which were cases previously collected by Geiser.

In 4578 autopsies Kellynack[63] found eight cases of carcinoma of the gall-bladder and only two of the ducts. While in 511 operations on the gall-bladder and bile ducts done at The Mayo Clinic up to March 1903, twenty-two cases were for malignant disease, and of this number it was thought that six were primary in the bile ducts. (Mayo, W. J. 62)

Geiser reports a series of 5865 autopsies on cancer patients in which the duodenum was affected but twenty-three times, or in 0.4 per cent; 70 per cent of these being at the ampulla. Sears in 1904 reported a case of carcinoma

confined to the papilla of the common duct as being the first instance of that kind ever found at the Boston City Hospital.

PATHOLOGY

Ziegler believes that carcinoma of the bile ducts is usually of the columnar celled bype. MacCallum and Ewing are of a similar opinion. According to the latter, these are usually of the adenomatous form associated with some mucus production, the alveoli varying in size and being lined accordingly with either columnar, cuboidal or small spheroidal cells and grossly being of the villous, nodular or diffuse type.

Rolleston is seemingly of the opinion that the great majority of the carcinomata of the bile ducts are derived from the surface epithelium although he says, "It is possible that spheroidal-celled carcinoma of the bile duct may be derived from the mucus glands in its wall." In his analysis of forty-three cases, thirty-seven are columnar, five spheroidal and one of the colloid type. Mucoid degeneration of columnar cells or transition from columnar to spheroidal cells may take place. Metaplasia may result in the formation of squamous celled [illegible] carcinoma as in the gall-bladder. A micro-photograph of such a metaplasia with columnar celled cancer in one part and squamous celled cancer in another is shown(Rolleston). Duval describes a case of primary melanoma of the ampulla. Mayo-Robson and Rolleston both say that cancer of the head of the pancreas is spheroidal celled while cancer of the ducts is almost always of the columnar type. 56 The truth of this statement according to MacCarty depends on the stage of cellular differentiation but from a practical point of view the distinction seems to be of little value. The exact location of the tumors in the region of the papilla are according to Ewing difficult if not impossible of determination arising as they do from either the intestinal, pancreatic or biliary tracts. According to Geiser's figures previously quoted a majority of them would have their origin in the ampulla. We found no mention in the literature of sarcoma.

The growth most frequently occurs in the common duct. Rolleston's ninety cases were divided as follows: Common bile duct thirty-four, (lower end twenty-

three, upper end eleven); junction cystic, common and common hepatic duct twenty-seven; common hepatic duct nineteen; right and left hepatic ducts three; cystic duct six; cystic and lower end of common duct one each. Devic and Gallivardin's fifty-three cases were divided as follows: Twenty common duct (supra duodenal); fifteen junction cystic, common and hepatic ducts(juxto or sub-hepatic) and sixteen hepatic. The cystic duct is only credited with a few cases as probably a majority of them are either classed as cancer of the gall-bladder, or having spread to the common, or common and hepatic ducts, are classified with the sub-hepatic group.

Lecene writing in 1911, credits his case with being the third cancer of the cystic duct on record. The growth is usually confined within the walls of the bile ducts and may (1) project into the lumen, (2) form an annular stricture or (3) spread along the tube in a diffuse manner producing obstruction, sooner or later, in all.

Extension is usually limited to the walls of the bile duct. By infiltration papillary tumors may invade the liver through the bile ducts but usually this takes place by the portal lymphatics(Ewing).

Metastases are infrequent, according to Devic and Gallivardin they occur in one-fifth of the cases, Outerbridge reported 22 per cent, Shuller 15 per cent. In Mussers eighteen cases metastases occured as follows: Liver seven, mesenteric glands one, peritoneum one, pancreas one. Rarely are distant metastases found. Paynton reports a case of cancer of the common duct, with rapid distant metastases and death without jaundice.

On exploration small nodules in the liver produced by peripheral dilation of the small intra-hepatic bile ducts may be mistaken for metastases. Courvoisier[27] mentions one case in the literature in which superficial branches of the intra-hepatic bile ducts presented a varicose condition and four cases in which superficial terminal bile ducts were transformed into small cysts, the size

of a cherry, protruding from the liver. Below the growth the caliber of the ducts remains normal, while above, the ducts are dilated. In Mussers eighteen cases the ducts were dilated in nine instances. In cases with hepatic or juxto-hepatic portions of the ducts involved, the gall-bladder is as a rule small; exceptionally however, it is found distended with mucus or in an empyematous condition, while with tumors involving the common duct or the ampulla the gall-bladder is dilated, unless previously bound down or retracted by infection and stones. In a report of fourteen cases of cancer of the hepatic, common and cystic duct by Devic and Gallivardin, the gall-bladder was dilated seven times, normal three, and retracted four, while in ten cases of cancer of hepatic duct observed at autopsy the gall-bladder was not mentioned (probably retracted) three , retracted four, normal one, and dilated two. According to Courvoiser[96] the gall-bladder is enlarged in 84 per cent of bile duct cancers. The liver is either enlarged or smaller than normal with dilated ducts filled either with bile or clear mucus-like material. Futterer describes an icteric necrosis occuring in the central zone of the liver lobule with the rest of the structure remaining comparatively normal, this he explains by a reversal of flow of bile to the lymph chanels, and Herring and Simpson in experiments on bile pressure have described a similar reversal of the bile stream.

ETIOLOGY

Zenker is of the opinion that primary cancer of the ducts begins as a papilloma and Rolleston reports one case which seems to support the same sequence. Mayo-Robson recognizes the possible association of malignancy of the ducts with papilloma but believes that gall-stones are a greater etiological factor in duct malignancy than is generally conceded. Rolleston says, "It is conceivable that carcinoma of the bile ducts may supervene on an old ulcer as it does in gastric carcinoma".[57] MacCarty in an article on "Gall-Bladder and Some Associated Lesions" presents two cases with reports and photographs of specimens

showing duodenal ulcers located at the papilla with definite involvement of the ampulla. In both cases the outstanding symptomatic features are those of gall-bladder disease with associated obstructive symptoms.

In Rolleston's series gall-stones were present in about one-third of the cases of primary cancer of the ducts, which is in marked contrast with the cancer of the gall-bladder where they occur in about 70 per cent of the cases. Of Devic and Gallivardin's forty cases only nine showed stones, and Outerbridge found stones in only about 20 per cent of 110 cases. Keen is of the opinion that cancer arising in the excretory ducts of the liver is seldom associated with stones. McGlinn on the other hand in 9000 autopsies found eleven cases of cancer of the gall-bladder, eight of which were associated with gall-stones and five cases of cancer of the bile duct, associated with stones in each case. Conradi[27] in a series of necropsies found stones present in the common duct in nearly 15 per cent of cases of cholelithiasis and Dr. Hale White concluded that 20 per cent of all people that have gall-stones ultimately develop cancer of the biliary passages. Heredity as an etiological factor is apparently of little importance.

AGE AND SEX INCIDENCE

Cancer of the bile ducts in marked contrast to cancer of the gall-bladder shows a predilecition for males. Rolleston notes fifty-five males, thirty-five females; Devic and Gallivardin thirty males and sixteen females; Miodowski twenty-six males and fourteen females, while in Mussers cases they were equally divided.

Like cancer of the gall-bladder, cancer of the ducts occurs most frequently between the age of fifty and seventy. Of Rolleston's eighty-three cases, fifty-eight averaged over fifty years with practically no difference shown in the two sexes. In Musser's series the average age was fifty-six and six tenths, (oldest eighty-one, youngest twenty-nine). Miodowski's series was divided as follows:

YEARS	PATIENTS
30 - 40	3
40 - 50	8
50 - 60	9
60 - 70	14
Over 70	5

The clinical picture in cases of malignancy of the ducts, is as a rule, that of an obstructive jaundice, the picture varying in different cases, depending upon the location of the growth and the various associated conditions as infection, stones or pancreatitis.

Devic and Gallivardin classify their cases as follows:

1.- Those accompanied by-
1-Hypertrophy of the liver.
2-Enlarged gall-bladder due especially to cancer of the supra-duodenal portion of bile duct or segment of hepatic duct under liver.

2.- Those atypical with or without hypertrophy of the liver and atrophy of the gall-bladder due to cancer of hepatic duct.

3.- Those simulating biliary hypertrophic cirrhosis.

4.- Those which they call "An-Icteric".

These are characterized by chronic progressive jaundice of insidious onset, accompanied or not by digestive disturbances or pain, cachexia and increasing weakness followed by death in from two to six months.

According to Upcutt the most striking features of the clinical picture are the absence of pain, intensity of the jaundice and the extreme emaciation.

According to Rolleston they may be classified clinically as follows:

1.- Those with insidious onset and generally the first symptom noticed is jaundice.

2.- Acute onset of gastro-intestinal symptoms followed by jaundice suggesting the ordinary catarrhal jaundice.

3.- Somewhat vague dyspeptic symptoms may exist for some time preceding onset of obstructive jaundice.

4.- In a few cases sudden onset of colicky pain similating impaction of stone.

SURGICAL TREATMENT

The surgical treatment of these cases is either palliative or radical. The pancreatic duct is not susceptible to radical treatment and we have a choice of (1) hepato-cholangiostomy with all the objections of a skin fistula and the consequent loss of bile, or (2) hepato cholangio-enterostomy(first suggested by Baudouim[18] in 1896).

Cotte advises doing this as a hepato cholangio-jejunostomy in Y, the anastamosis being made to the anterior portion of the left lobe of the liver, because in this part the hepatic duct takes a direct course throughout and has only a short branch, which anatomical fact would be more apt to lead to a fistulous connection. The jejunostomy is done in Y with a view of lessening the amount of the ascending infection(Cotte).

Separate consideration of the cystic duct is not necessary because to all intents and purposes its treatment is the same as in confluent type, ie.-cancer of cystic, common and hepatic ducts.

The radical treatment of cancer of confluent type may be divided in two parts. (1) Resection of the involved parts. (2) Reestablishment of biliary continuity.

Quenu and Tuffier[12] place the cut end of the duct in the stomach while Kehr,[12] Terrier and Vautrin[12] place it in the duodenum. Mayo and Jaboulay[12] advise end to end suture of the common and hepatic ducts. Cotte advises use of T. tube because he believes it saves time. Sullivan in experimental work on dogs describes the formation of a new duct. He places a one-fourth inch pure rubber tubing into the pancreatic duct fastening it there with permanent

suture, passing the other end through the duodenum according to the method of Witzel, the tube is finally covered by omental graft. (In his experimental work the tube was finally passed off through the bowel.)

Palliative operation in the confluent type(cancer of cystic, common and hepatic duct)consists of: (1) In the presence of infection a cholecystostomy with the idea of relieving the infection and with the hope that constriction in the duct below may be lessened by lessening of spasm(comparable to gastrostomy with stricture of the oesophagus in which sounds may be passed following a gastrostomy)(Cotte). (2) In cancer of confluent type with little or no infection, we can utilize some form of anastomosis between the biliary tract and intestine. We are limited in this depending upon the site and extent of lesion to some form of anastomosis between either the gall-bladder or hepatic duct and the intestinal tract. If the gall-bladder can be used then a cholecyst-gastrostomy, colostomy or enterostomy may be done. Mayo-Robson prefers an anastomosis with colon as it is easier and W. J. Mayo[62] says, "From my experience I see no reason why colon cannot be used as well as any part of the intestinal tract", and again "We have joined the gall-bladder to the colon five times for chronic pancreatitis and these cases did fully as well as five cases where duodenum was used. One case living five years after operation".[62] In Winiwarter's original works cholecyst-colostomy was the method of choice.

Cholecyst-gastrostomy may be used and according to experimental work of Oddi and the clinical experience of many later surgeons, the presence of bile in the stomach before and during the period of digestion in no way diminishes the power of digestion. In the performance of the cholecyst-enterostomy type of operation we have the choice of two methods (1) Murphy Button anastomosis, (2) Some form of suture anastomosis. Moynihan, writing in 1905 in his book on gall-stones and their surgical treatment, says he has only found it necessary to do a cholecystenterostomy once and that time he did a suture

anastomosis.

Similar palliative operations may be utilized for cancer of ampulla and papilla as in other parts of the biliary tract. Types of radical operations available in cancer of the ampulla and papilla:

12

1.-Circular excision of Korte.
2.-Transduodenal excision of Halsted.
3.-Transduodenal excision of cauterization of papilla and part of duodenal wall.

Halsted reports what he believes to be the first case of transduodenal excision for cancer of the ampulla with transplantation of the ducts. (Patient died six months later.) But to McBurney belongs the credit for first adopting the method of transduodenal exploration previously suggested by Langenbach in 1884.

Cuneo reports a case similar to Halsted's in which marsupialization of the pancreas was practiced(patient died second day).

Retro-duodenal resection of the common duct may be done.

Occasionally these operations are followed by posterior gastro-enterostomy, but Hartman believes that this is only occasionally necessary and that the big danger is from ascending infection rather than duodenal obstruction. According to Hartman and others this infection may be overcome by draining the common duct or gall-bladder. Coffey from experimental work on bile duct transplantation in dogs and similar experience with the ureter, believes it can be overcome by his method of transplantation.

Kausch devised and carried out successfully a very radical two stage operation designed for use in cases with extensive cancer of the ampulla and duodenal papilla.

The steps of Kausch's operation are: (1) Murphy Button cholecystenterostomy followed in an interval of two months by (2)-a-resection of part of the duodenum along with the tumor (b) division and ligation of the common duct (c) di-

vision of the head of the pancreas (d) gastro-enterostomy (e) marsupialization of the stump of the pancreas in the open end of the duodenum. Patient made good recovery(Kausch)[12]. Korte advises similar operation.

Brewer is of the opinion that cholecyst-enterostomy is dangerous and carries with it a mortality of 75 per cent.

Quenu[80] reports eighteen collected cases in which a radical operation was done with twelve deaths or an operative mortality of 66.6 per cent. Of the remaining six cases two were excluded because of metastasis, leaving four cases with an average reported length of life of fifteen months, (longest two and one-half years, shortest six months).

Lewis reports a case operated on by Howard Kelly, well eight and one-half years after radical extirpation of cancer of the ampulla.

A rather extensive summary of the various types of operations reported, with their mortality, is included in the second volume of Deaver and Ashurst's Surgery of the Upper Abdomen.

Upcutt believes the greater percentage of deaths are due to hemorrhage. Hepatic inefficiency, cholemia and shock are undoubtedly contributary causes.

From January 1907 to January 1921 there occurred at the Mayo Clinic twenty cases of primary malignancy of the bile ducts(confirmed by pathological examination)all being carcinoma, eight of the adenomatous type, two of the papillary type and all consisting of either columnar, cuboidal or spheroidal type of cells. Grossly they varied from the annular constricting to the flat diffuse and occasionally villous type.

The common duct was most frequently involved. In twelve the growth was in the common duct, four being at the junction of the common with the cystic duct, two junction common, cystic, and hepatic, one at the upper end of common duct and one at the lower end. In one postmortem specimen the common duct was involved throughout the lower one-third. The hepatic was involved once, being

associated with a disseminated cancer of the intra-hepatic bile ducts(probably direct extension). The cystic duct was involved twice, the ampulla and papilla five times(one obstructing annular type in the ampulla, one involving the head of the pancreas).

In this series of twenty cases all but two were operated on, (specimens from autopsy) three cases were explored, palliative operations were done in eleven cases, and radical operations in four.

Stones were found in eight cases (two just stony material). Stones were only present in one of the five cases located at the ampulla. The cancer of the hepatic duct was not associated with stones while in both cases of cancer of the cystic duct stones were present.

In the common duct cases stones were present in five, negative in six.

In only two cases was there a history of heredity. Thirteen patients were males and seven females. The oldest seventy-eight, the youngest twenty-five.

YEARS	CASES
21 - 30	1
31 - 40	3
41 - 50	2
51 - 60	7
61 - 70	5
71 - 80	2

SYMPTOMS

The average duration of obstructive symptoms was five months, the longest fourteen months, (cancer of ampulla) shortest one month. (Exploration showed metastases in the liver.) Eleven of the cases gave a history of gall-bladder or gall-stone trouble preceding the onset of obstructive symptoms, for an average period of five years, (longest nine years) while nine of the cases gave no history previous to the present trouble. The average loss of weight for

fifteen patients was twenty-five and five tenths pounds, associated in the majority of cases with considerable loss of strength. Twelve of the cases had pain varying from a soreness or dull ache in the epigastrium or right hypochondrium to a severe typical gall-stone colic, with radiation to back and shoulders in eight cases. Four cases in which stone were noted as not present had typical colicky pains.

All of the twenty cases were jaundiced. In eleven cases the jaundice was constant, eight intermittant. From the history one could not determine the nature of the jaundice, (whether of yellow or green type). Pruritus was definitely present and associated with the jaundice in eleven instances, while in five it preceded the jaundice. Seventeen cases had clay stools, two diarrhea, and in one the stools were normal. In fifteen cases the urine was noted as containing bile, with albumin (two on a bases of four) in a majority of cases.

Hemorrhage as evidenced by petechiae, purpura or ecchymosis was noted five times, one patient had ecchymotic spots over entire body and another patient not operated on, had copious hemorrhage from the bowel the day before death.

Courvoisier[27] warns us to search the history of the patient and make careful examination over the entire body in order to ascertain whether or not a predisposition to hemorrhage exists and says, "Operation may be fatal from hemorrhage not associated with the wound."

In sixteen cases the coagulation time averaged eight (four being ten). The liver was palpable in ten, gall-bladder in six and spleen in four cases. Ascites was present in three cases. Chills and fever was noted seven times. Nausea and vomiting was not of frequent occurence after the onset of obstructive jaundice.

DIAGNOSIS

The diagnosis of malignant conditions of the bile ducts is as difficult, if not more so, than that of malignant conditions of the gall-bladder. Usually the chief symptoms are those of a preceeding or accompanying gall-bladder or gall-stone disease with insidious or sudden development of obstructive jaundice symptoms. The obstructive symptoms may appear alone without any previous history of trouble, and may or may not be associated with pain or colic, chills and fever. Occasionly the important features are a diarrhea with pasty stools, followed later on by jaundice. Jaundice is the one almost constant feature and may be preceeded or followed by a distressing pruritus. Loss of weight and strength is as a rule marked. A tumor may or may not be felt and with the possibility of numerous extra-hepatic conditions producing the obstruction, a diagnosis outside of obstructive jaundice is well nigh impossible. But in a male during the fifth or sixth decade of life with a history of obstructive jaundice, especially of insidious type, which persists, malignancy of the ducts is always a possibility.

Moynihan[23] says, "No one living is infallible in the differential diagnosis of obstructive jaundice, the diagnosis is always difficult and the chance of life saved is so important, that however positive the evidence of malignancy may be, I have advised operation in all cases".

In this series of twenty cases the diagnosis was as follows:

	Cases
Obstructive jaundice, malignancy questionable	9
Obstructive jaundice, stones or malignancy	8
Cholangitis	1
Disease of the gall-bladder	1
Cirrhosis or malignancy	1

TYPES OF OPERATION

Of eighteen operative cases, three were explored, palliative operations were done in eleven cases, and four were treated radically. Metastases were found in four cases, two cancers of the ampulla with metastasis of the liver,

one cancer of the ampulla involved the head of the pancreas by direct extension, one cancer of the hepatic duct metastasized to the liver (at necropsy this appeared to be by direct extension along the ducts). Pancreatitis was noted seven times, cirrhosis seven times. In three cases the ducts contained white bile.

PROGNOSIS

The operative mortality of this series of cases (33 1/3 per cent) compares favorably with those previously reported. The average postoperative length of life of thirteen patients of the series being a little more than five months, one patient living fifteen months and another a little more than three years.

OPERATION

Number	Location	Exploratory	Duration of Life
1-a115806	Common duct	Abdominal incision with closure (Spec. for diagnosis)	Six weeks.
2-a45192	Common duct	Abdominal incision (Spec. for diagnosis)	?(left the Hosp. Seventh day.)
3-a208988	Ampulla	Exploration	Ten days.
		Palliative	
4-a197147	Hepatic duct	Cholecystostomy liver puncture and drainage.	Forty-eight hours.
5-a91510	Cystic duct	Cholecystostomy (Spec. from cystic duct)	Dead (time?)
6- a253416	Common duct	Cholecystostomy (Spec. for diagnosis)	Seven days.
7-a207955	Common duct	Cholecystostomy (Spec. for diagnosis)	Dead(time?)
8-a163919	Common duct	Cholecystostomy and choledochostomy with T tube extending through common duct into pancreatic duct and duodenum.	Five months.
9-a66344	Common duct	Choledochostomy with T tube drainage	Five months.
10-a62646	Common duct	Cholecystduodenostomy Cholecystostomy previously(elsewhere)	Two months.
11-a137890	Common duct	Cholecystgastrostomy	Twenty-four hours.
12-a74038	Common duct	Cholecystectomy with removal of part of the anterior wall of the common duct, Robson hepaticus drain	Two months.
13-a226626	Ampulla	Choledochostomy with transduodenal exploration(Spec. from papilla)	Fifteen months.
14-a180037	Ampulla	Cholecystgastrostomy(note-returned with pyloric obstruction, posterior gastro-enterostomy-Death).	Three years.
		Radical	
15-a120992	Cystic duct	Cholecystectomy resection of cystic duct with involved parts of common and hepatic ducts, anastomosis over T tube.	Three months.
16-a35861	Common duct	Choledochotomy, cholecystectomy with removal of all the cystic duct and part	?

Number	Location	Operation	Duration of life
		Radical	
		of the common duct. Plastic on common duct.	
17-a253761	Common duct	Excision of growth of common duct with end-to-end anastomosis; interrrupted sutures.	?
18-a269833	Ampulla	Choledochotomy, transduodenal excision (knife and cautery) cholecystduodenostomy.	Nine days

Note: Two cases of the series were not operated on. Specimens obtained at autopsy.

1st case a118598 Came to the clinic with fourteen months history diarrhea, jaundice, weakness and anemia, gradual increasing pain in right costal margin, with periods of remission. Cholecystostomy elsewhere about two months previously, persistent biliary fistula, forty pound weight lost, hemoglobin 25 per cent. Death eighteen months following onset of symptoms. Postmortem primary cancer of the ampulla with involvement of head of pancreas.

2nd case a340400 Well until five months ago, following a big dinner, indigestion with very loose mushy stools; two weeks later jaundice; no history of colic, chills or fever; no hemorrhage; liver and gall-bladder enlarged; intense pruritus; blood urea 106, urea nitrogen fifty, phthalein 35 per cent; hemoglobin 60 per cent, coagulation time nine minutes; weight loss 35 pounds. While under observation developed petechial hemoorhages with marked bleeding from the bowel the day before death. Death about six months after onset of symptoms. Postmortem carcinoma common duct, chronic pancreatitis.

The cases are divided into four groups.

Group 1. Cases with a history of gall-stone disease for a variable period, later associated with or followed by symptoms of obstructive jaundice.

Group 2. Cases with history of gall-bladder disease for a variable period

of years, later associated with or followed by symptoms of obstructive jaundice.

Group 3. Cases with development of obstructive jaundice symptoms, either of the insidious painless variety or associated with pain.

Group 4. Cases with history of diarrhea and pasty stools, of the pancreatitis type, followed later by symptoms of obstructive jaundice.

DISCUSSION

It would seem that the surgery dealing with malignant conditions of the biliary tract has not advanced proportionately with the surgery of other parts of the upper abdomen. Technical difficulties themselves do not seem to be responsible.

Apparently the element preventing operation or causing disaster when tried, in a large percentage of cases, is hemorrhage. Recent clinical investigations by Walters of the Mayo Clinic, dealing with the control of hemorrhage in jaundiced patients by the intravenous administration of calcium seems to advance some hope for better results in these cases; as do certain preoperative and postoperative principles designed to conserve and stimulate liver cell activity, recently reiterated and emphasized by Crile.

If it were not for the above factors, malignancy of the biliary ducts, being as a rule small, limited within the walls of the bile ducts and not metastsizing until late, should lend themselves readily to surgery.

CONCLUSIONS

1. Malignancy of the bile ducts while less frequent than in the gall-bladder (ratio in this series one to four) is not uncommon.

2. Carcinoma is the most common type of neoplasia found.

3. Gallstones would seem to be of greater etiologic importance than is generally considered.

4. Heredity seems to have little influence.

5. Males and females are affected in this series in the ratio of about two to one.

6. About two-thirds of the cases occur between the ages of fifty and seventy.

7. The diagnosis of malignancy of the ducts is uncertain.

8. The diagnosis of obstructive jaundice being made, an exploration as a rule is advisable.

9. From the standpoint of slowness of growth and rarity of metastasis their surgical treatment should be favorable.

10. Early treatment of disease of the gall-bladder may occasionally prevent their development.

11. Operation after development of jaundice carries a high mortality.

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ILLUSTRATIONS---NEOPLASIA OF THE GALL-BLADDER

Fig. I 47799 Papillary Carcinoma of the Fundus of the Gall-Bladder.

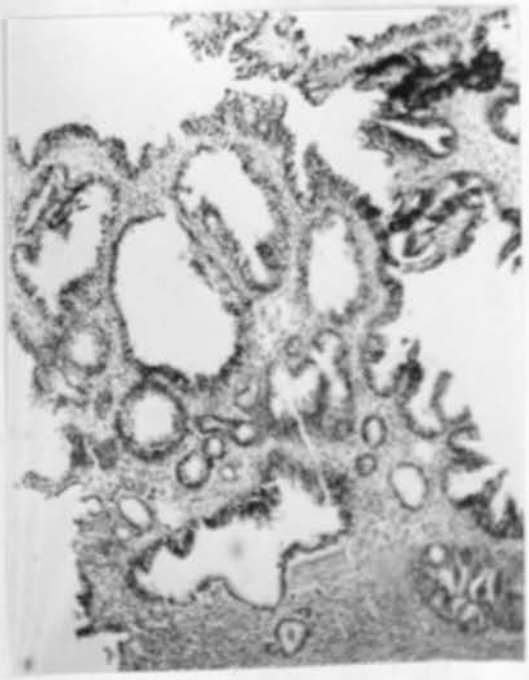

Fig. 2 47799 Carcinoma shown in Figure I X50.

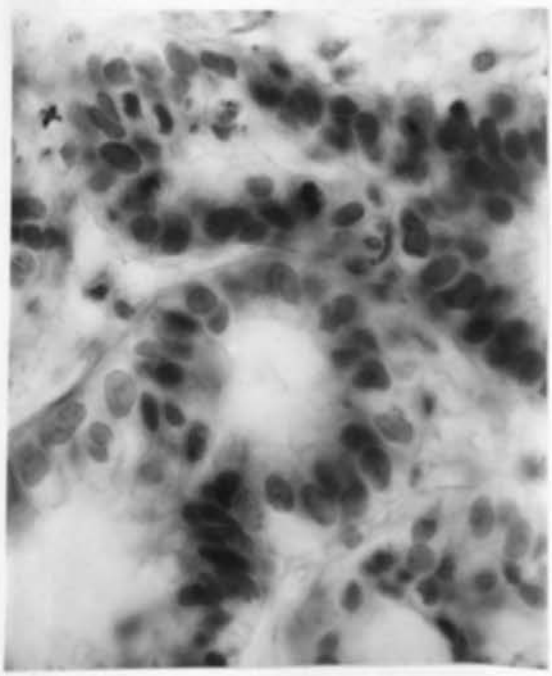

Fig. 3 47799 Carcinoma shown in Figure 1 X500.

Fig. 4 233246 Papillary Carcinoma of the Gall-Bladder.

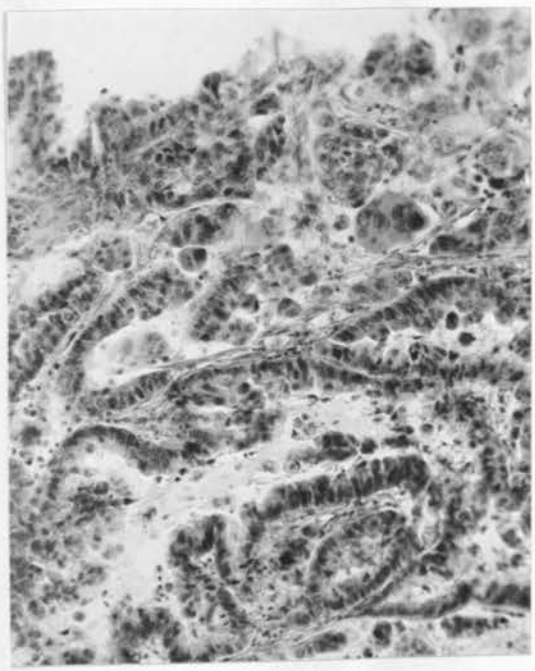

Fig. 5 233446 Carcinoma shown in Figure 4 X50.

Fig. 6 197859 Colloid Carcinoma of the Gall-Bladder.

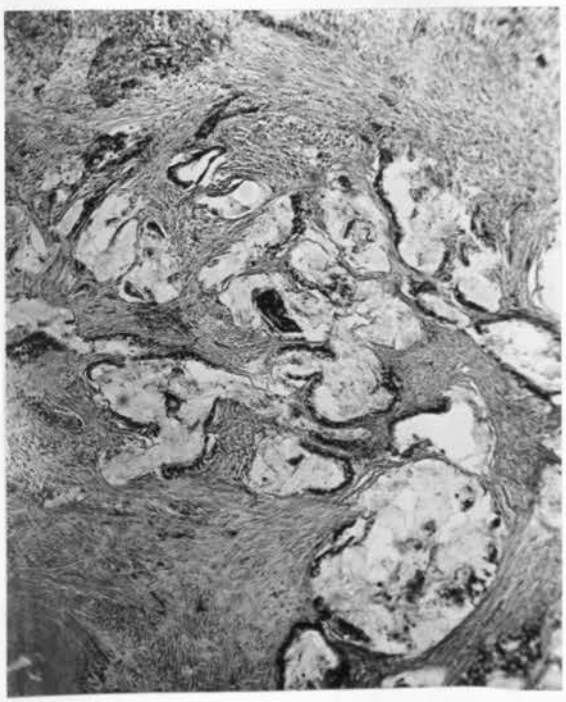

Fig. 7 197895 Carcinoma shown in Figure 6 X50.

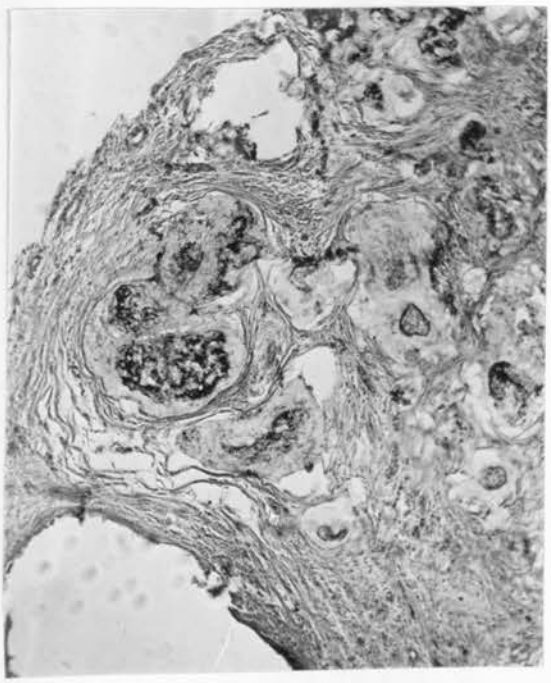

Fig. 8 197895 Carcinoma shown in Figure 6 X50.

Fig. 9 181245 Diffuse Carcinoma of the Gall-Bladder.

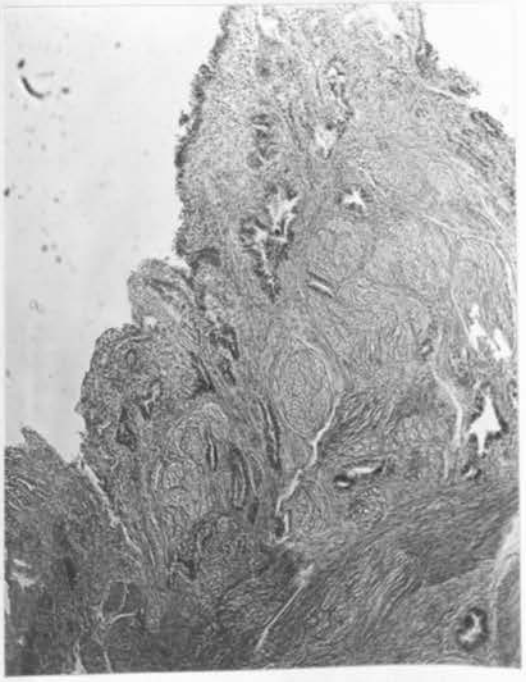

Fig. 10 181245 Carcinoma shown in Figure 9 X50.

Fig. 11 35874 Diffuse Carcinoma of the Gall-Bladder with Adjacent Liver Tissue.

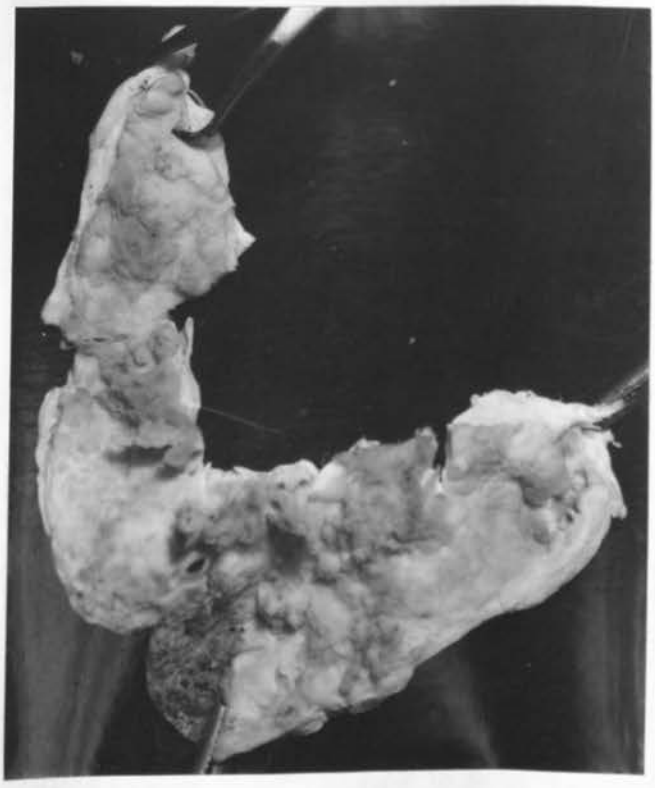

Fig. 12 314451 Diffuse Carcinoma of the Gall-Bladder.

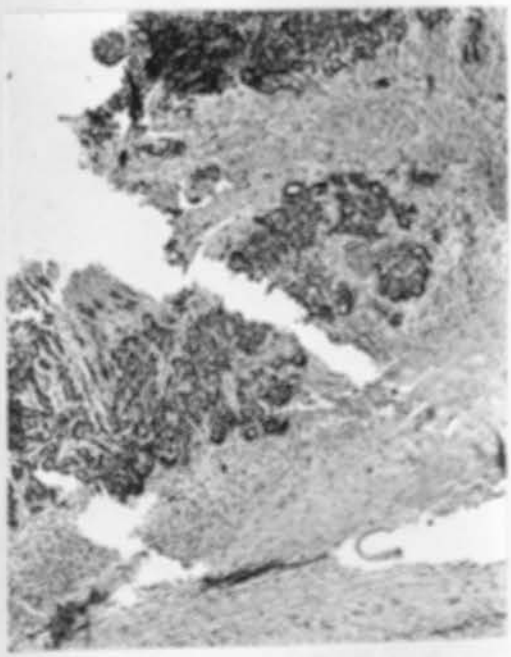

Fig. 13 314451 Carcinoma shown in Figure 12 X50.

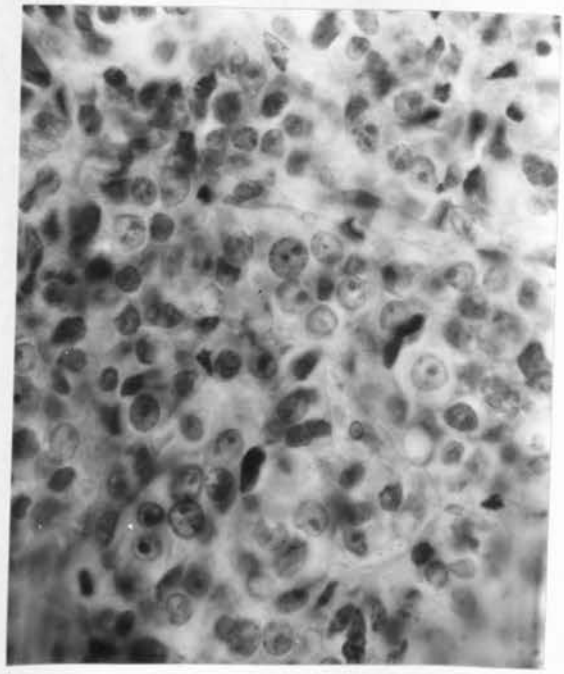

Fig. 14 314451 Carcinoma shown in Figure 12 X500.

Fig. 15 27259 "Innocent" Gall-Stones.

Fig. 16 163101 Epithelioma of the Gall-Bladder.

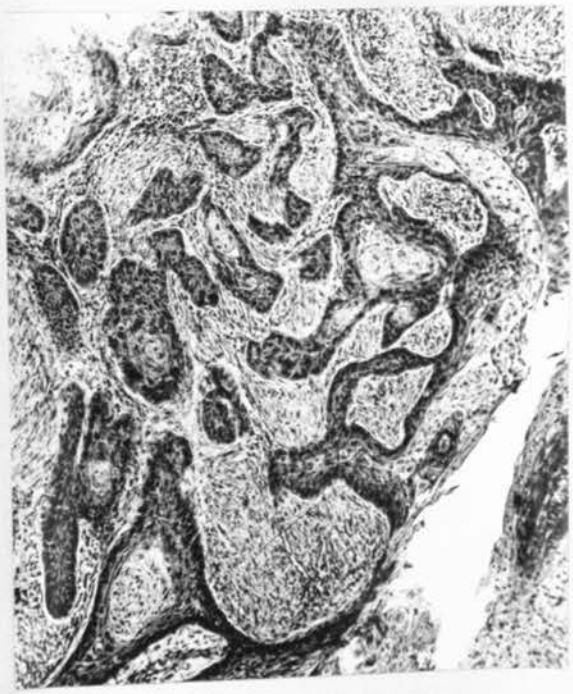

Fig. 17 163101 Epithelioma shown in Figure 16 X50.

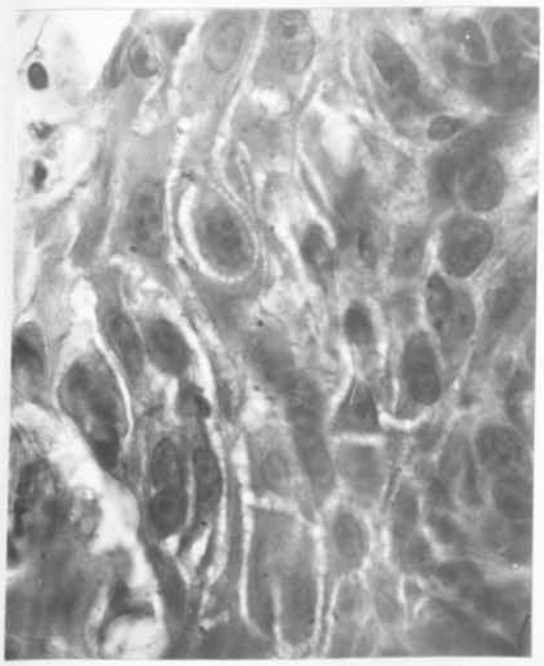

Fig. 18 163101 Epithelioma shown in Figure 16 X1000.

Fig. 19 342964 Lymphosarcoma of the Gall-Bladder, with Adjacent Liver Tissue.

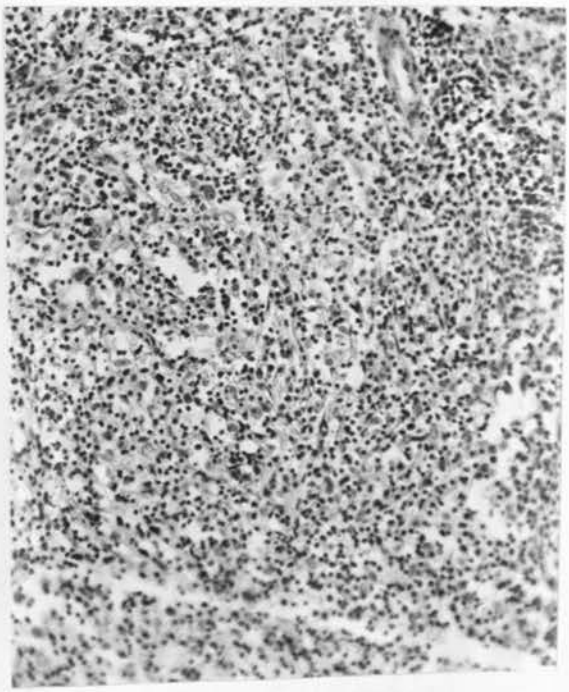

Fig. 20 342964 Lymphosarcoma shown in Figure 19 X50.

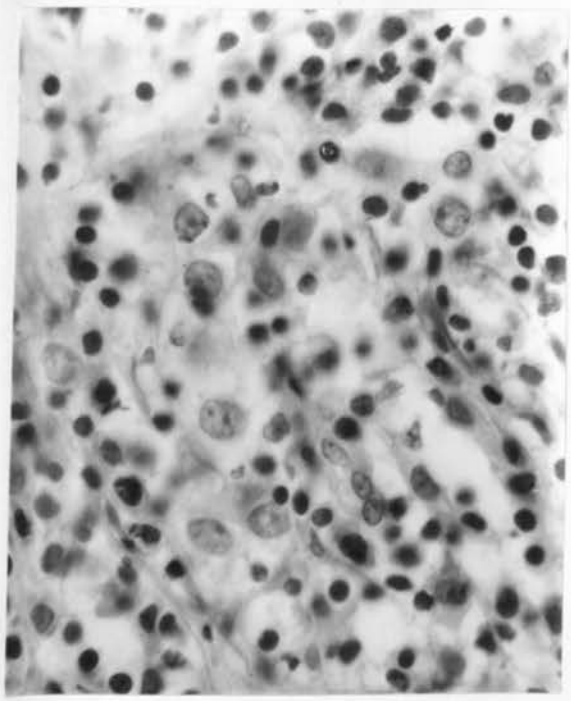

Fig. 21 342964 Lymphosarcoma shown in Figure 19 X500.

ILLUSTRATIONS---NEOPLASIA OF BILE DUCTS.

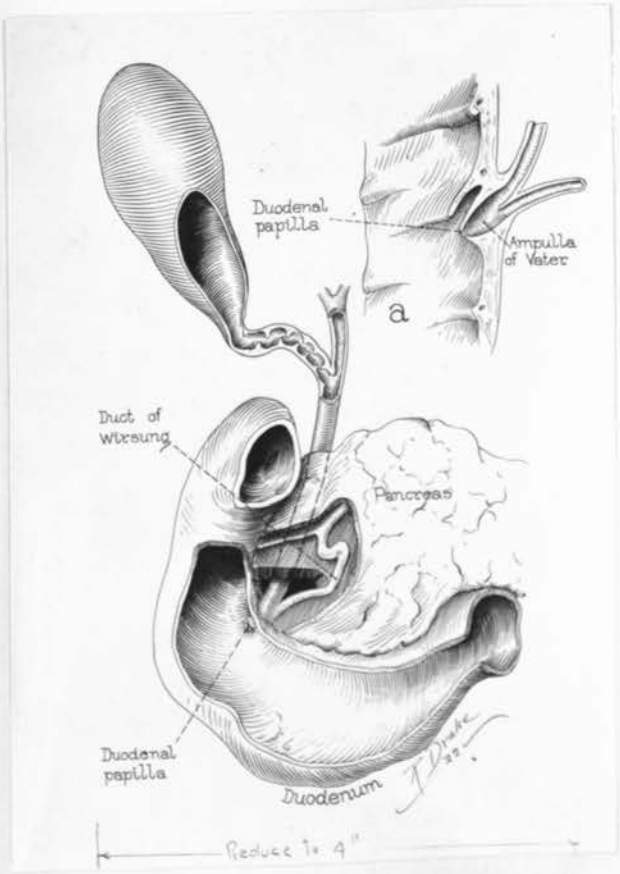

Fig. 22 Schematic Representation of the Biliary Tract.

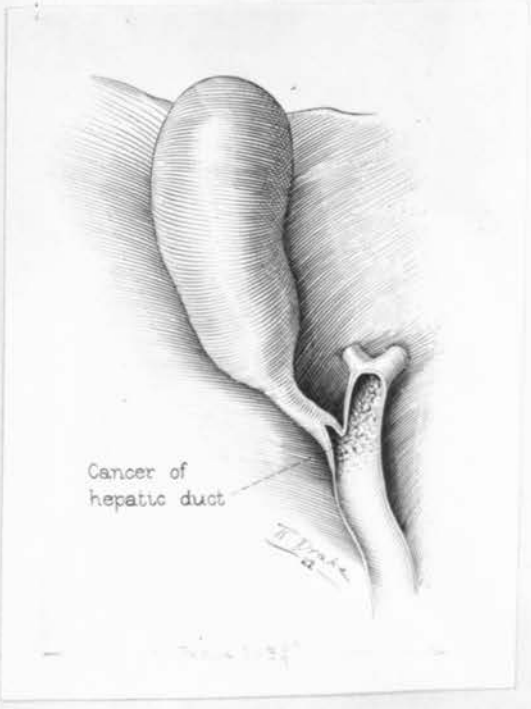

Fig 23 a253416 Cancer of the Hepatic Duct, probably originating at Junction of Hepatic and Cystic Duct.

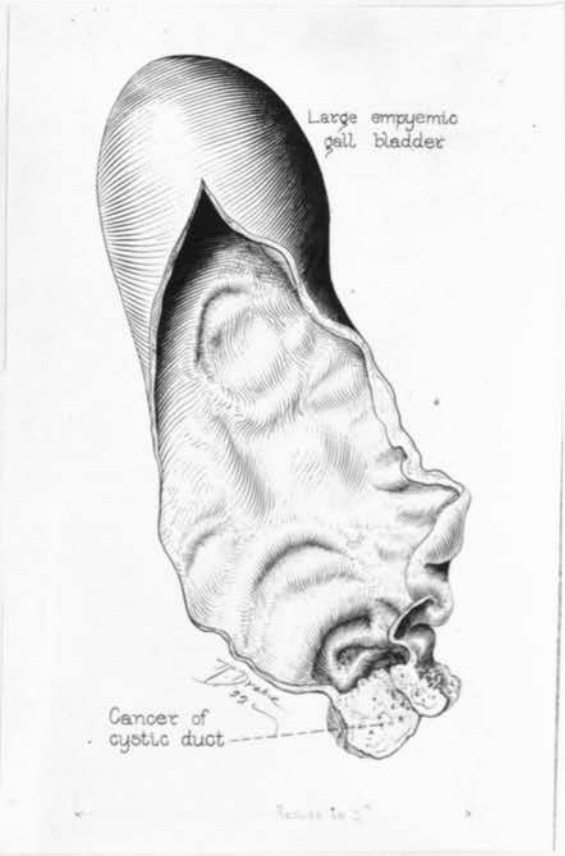

Fig. 24 a120992 Cancer of the Cystic Duct with a large Empyematous Gall-Bladder.

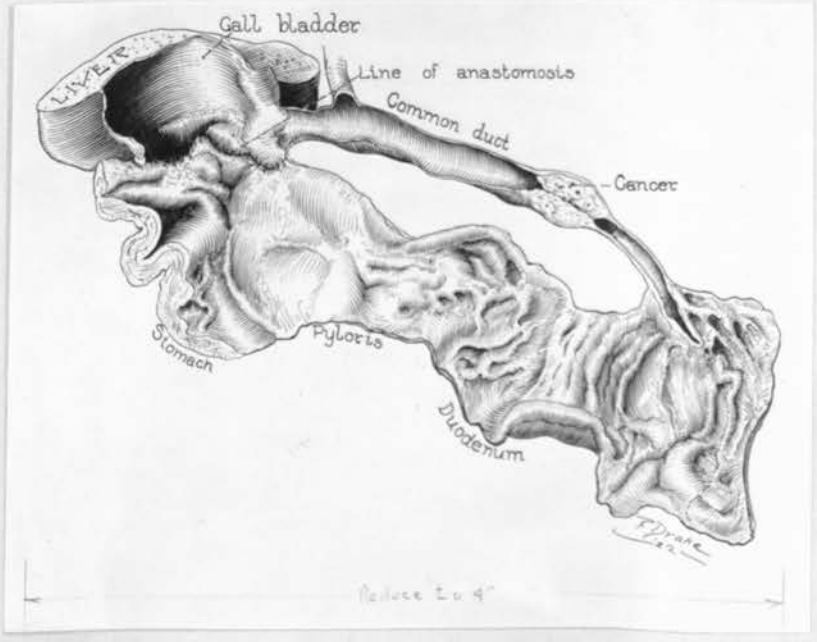

Fig. 25 a137890 Cancer of the Common Duct; Ducts dilated above. Cholecystgastrostomy.

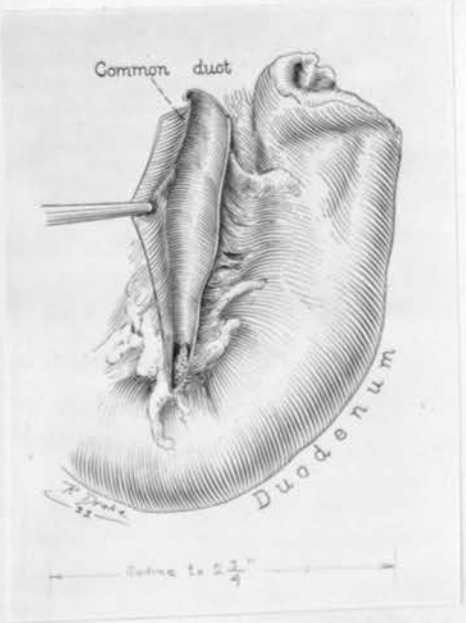

Fig. 26 a118598 Extension of Cancer of the Ampulla and Papilla, up into the Common Duct, Duct dilated.

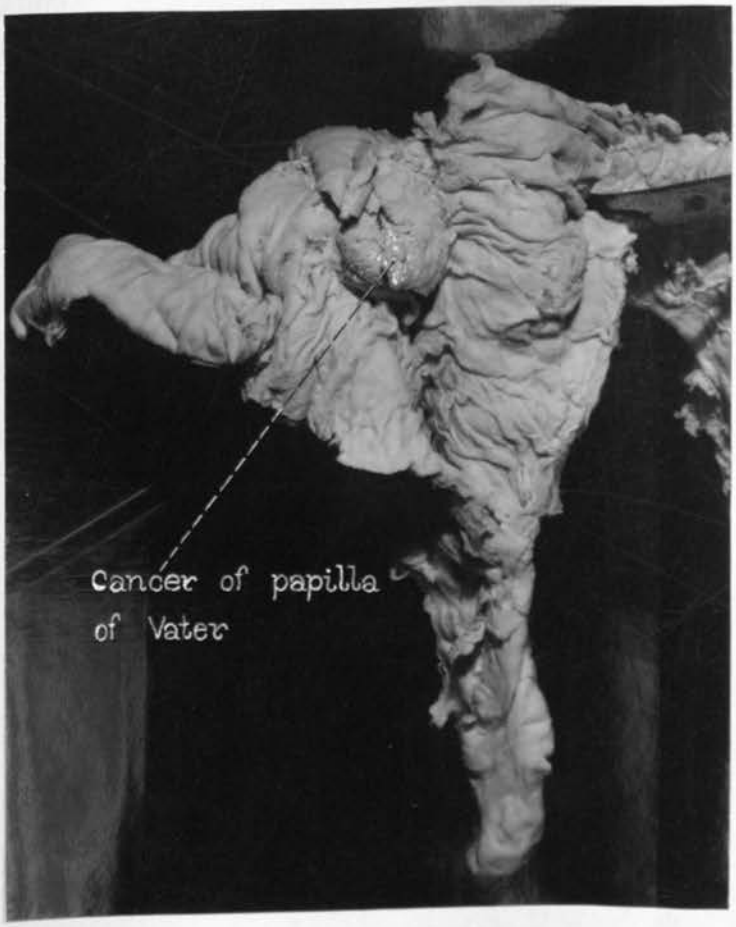

Fig. 27 a118598 Cancer of the Ampulla and Papilla.

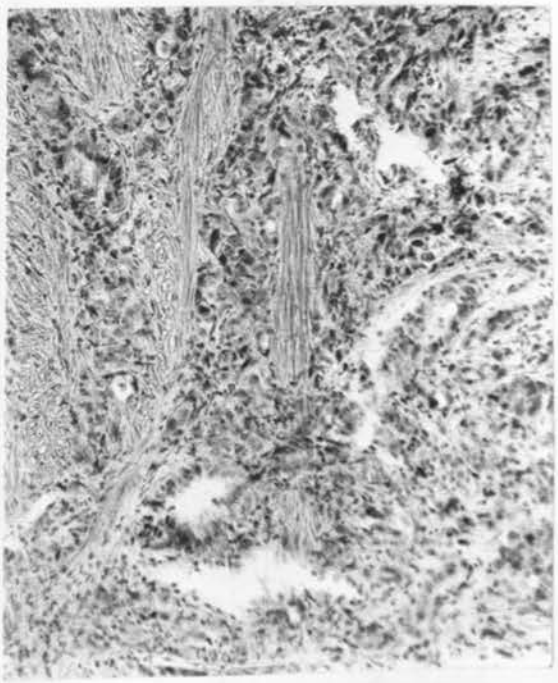

Fig. 28 a207955 Carcinoma of the Common Duct, mainly Cuboidal Cells with a tendency to acinus formation. X100.

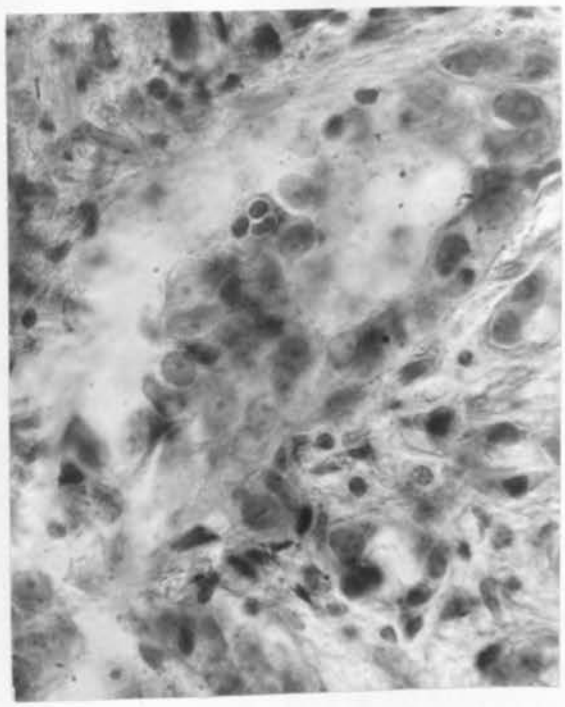

Fig. 29 a207955 Carcinoma shown in Figure 28 X500.

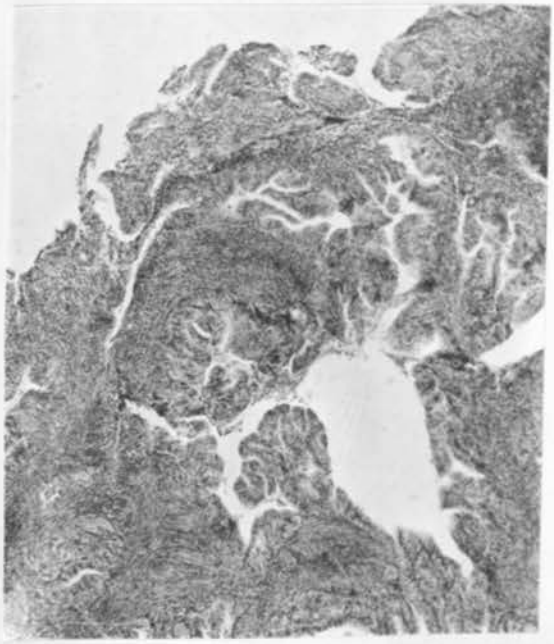

Fig. 30 a253416 Adenocarcinoma Common Duct. Tendency to Papillary formation. X50.

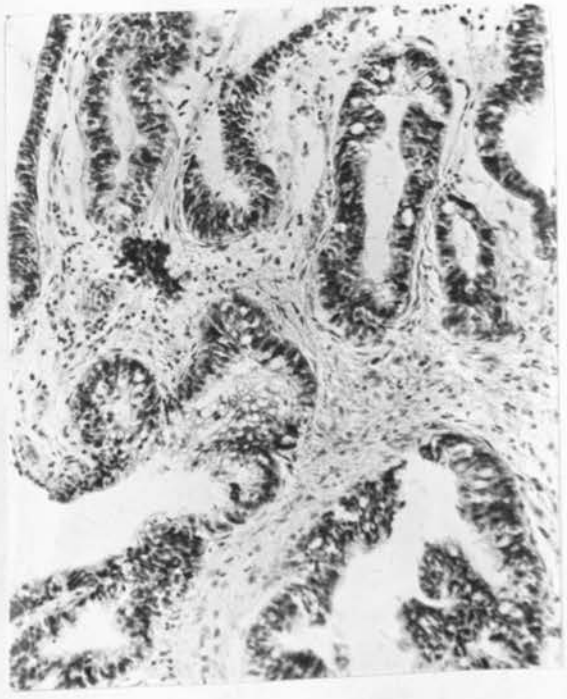

Fig. 31 a253416 Adenocarcinoma shown in Figure 30 X100.

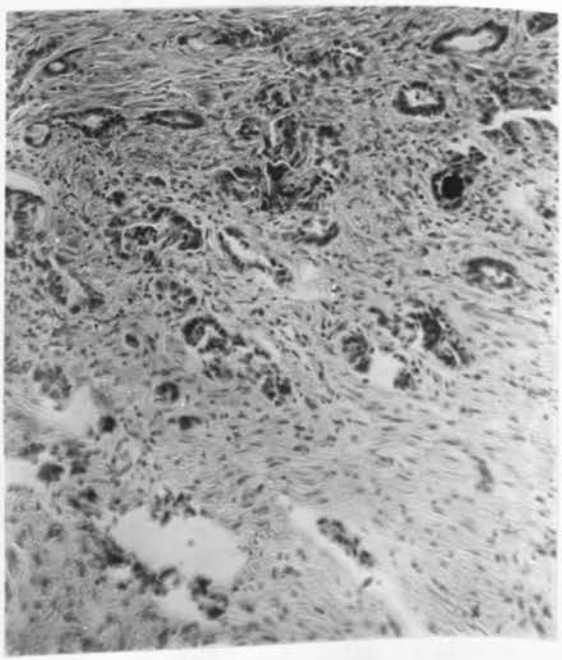

Fig. 32 a137890 Adenocarcinoma (Law Cuboidal Cell) of the Common Duct. X100.

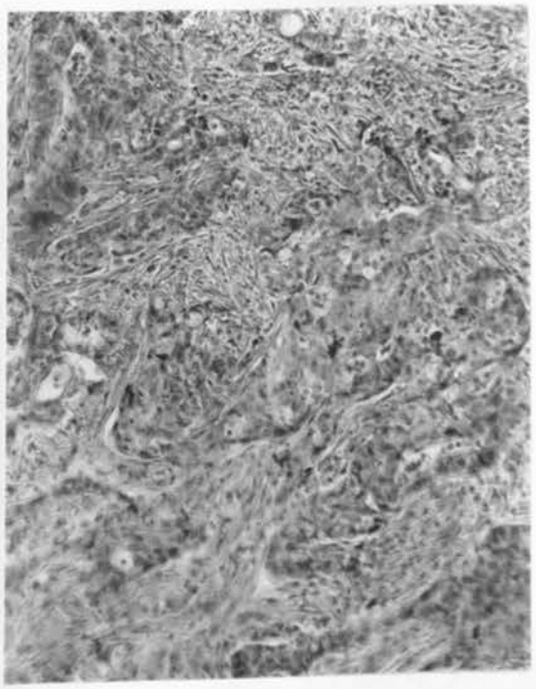

Fig. 33 a253761 Adenocarcinoma of the Common Duct X100.

Fig. 34 a226626 Papillary Carcinoma of the Ampulla of Vater. X100.

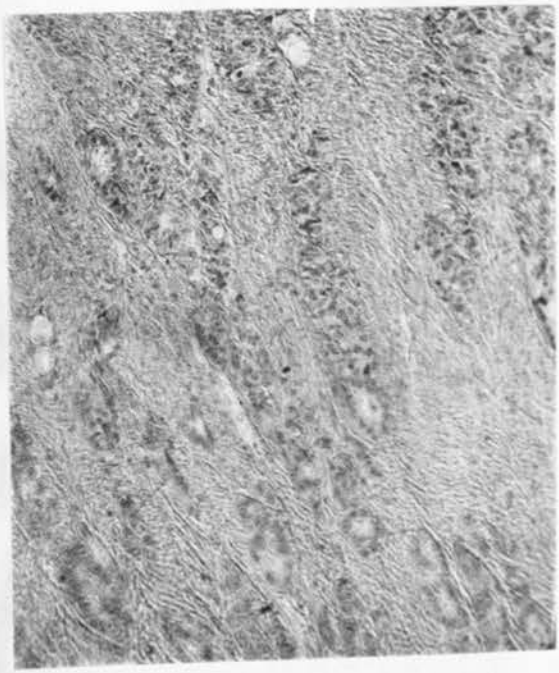

Fig. 35 a180037 Carcinoma of the ampulla X100.