

likely to replace the well-tried Graham test, but it is an additional means of investigation which may be helpful after cholecystectomy or where a gallbladder has not been visualized. Our results do not suggest that the technique will necessarily give reliable information regarding the functional efficiency of the liver. It is interesting that the excretion may test a separate liver function from that of most of the routine tests.

SUMMARY

Examination with Cholografin was helpful in six of 30 cases studied, supplying information not obtainable by oral methods of investigation. The test is recommended as an adjunct to oral methods, but it is not believed that at present it can

displace the well-tried Graham method. The manufacturer's instructions regarding the timing of the x-ray exposures and the rate of intravenous injection may usefully be modified. The skin test for sensitivity has been unhelpful. As an index of liver function it does not seem to parallel the usual laboratory tests.

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DISEASES OF THE GALLBLADDER: THEIR NATURE AND CLASSIFICATION*

MURRAY R. ABELL, M.D., Ph.D.,†
Ann Arbor, Mich.

NO OTHER VISCUS responds to inflammation with such diversity of morphological reaction as does the gallbladder. Even the superfluous appendix cannot compete with the wide range of tissue changes which occur in the gallbladder. The different responses may be attributed to injury by bacterial, chemical, metabolic, or physical agents, or to combinations of these.

All cases of cholecystitis were considered until fairly recently to be due to infection with streptococci, *Bacillus coli* (*Escherichia coli*) or *Bacillus welchii* (*Clostridium welchii*).^{1, 2, 3} Experimental evidence, however, as well as clinical observations, indicates that in most instances chemical factors are of greater importance than infection, the latter being purely of secondary significance. This cannot, of course, be considered true for *Salmonella* infections or for organisms of great virulence. Womack and Bricker⁴ have demonstrated the irritant effect of stagnant and concentrated bile, and have induced lesions in dogs

that were identical with those observed in human subjects by occluding the cystic duct and/or injecting concentrated bile. Bile salts and cholesterol are considered the most potent irritants, the other constituents being of minor importance. Bisgard and Baker⁵ stressed the possible etiological significance of pancreatic enzymes which, in certain circumstances, may be diverted into the gallbladder. Needless to say, calculi are intimately related to cholecystitis, not only as sequelæ, but also as important factors in recurrent or persistent inflammation.

Table I lists the different types of cholecystitis. Some of the subtypes are used solely in a descriptive sense and cannot be considered necessarily as distinct entities. Acute cholecystitis in a pure form is seen infrequently by the pathologist and most cases which are so labelled by the clinician are actually examples of a new process superimposed on chronic cholecystitis, or are acute exacerbations of chronic cholecystitis. Both true acute cholecystitis and the impure forms are manifested by congestion, œdema, and polymorphonuclear leukocytic infiltration, but an example of the latter type gives evidence of old or healed inflammation in its scar tissue, and calculi are usually present. Bacteria can rarely be demonstrated in the tissues or in the exudate. Non-suppurative inflammation is the rule. Suppurative inflammation, that is, extensive liquefactive necrosis with pus formation and intramural abscess, is the exception. If hæmorrhage is severe or if the mucosa

*From the Department of Pathology, University of Michigan, Ann Arbor, Mich.

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†Assistant Professor of Pathology, University of Michigan.

TABLE I.

A CLASSIFICATION OF CHOLECYSTITIS	
I.	Acute cholecystitis
a.	Acute purulent
b.	Acute suppurative
c.	Acute hæmorrhagic
d.	Acute ulcerative
e.	Acute gangrenous (necrogenic)
II.	Subchronic (subacute, subsiding acute) cholecystitis
III.	Chronic cholecystitis
a.	Chronic proliferative
b.	Chronic productive
c.	Chronic purulent (empyema)
d.	Chronic lipogranulomatous
e.	Chronic lymphofollicular (typhoidal or paratyphoidal)
f.	Chronic calcific ("porcelain" gallbladder)
g.	Chronic cholecystitis with hydrops or mucocele
h.	Chronic cholecystitis with cholesterosis
IV.	Recurrent cholecystitis (acute on chronic, or acute exacerbation of chronic cholecystitis)
V.	Miscellaneous types of cholecystitis
a.	Tuberculous
b.	Mycotic
c.	Parasitic
d.	Polyarteritis nodosa

is ulcerated extensively, the adjectives hæmorrhagic or ulcerative are applicable. The inflammatory reaction is sometimes extreme with extensive necrosis and often with thrombosis, although the latter is not an integral part of the process. The gallbladder is greenish black or brown and very friable, accounting for its frequent perforation. In such instances the process can truly be called gangrenous or necrotizing.

Subchronic (subacute or subsiding acute) cholecystitis is characterized by young fibroblastic tissue and by a polymorphous inflammatory cell response with numerous eosinophils and plasma cells. Neutrophils, lymphocytes, and histiocytic macrophages are present also.

Chronic cholecystitis is even more variable than the acute form. Calculi are practically

always present and are more frequently of mixed pigment and cholesterol type. Chronic cholecystitis in conjunction with the metabolic disorder cholesterosis is of mild degree and usually limited to scattered foci of lymphocytes and plasma cells throughout the wall. There is always some fibrosis of the wall in chronic inflammation. This interrupts the muscularis propria and extends into the perimuscular tissues. Lymphocytes and plasmacytes predominate but there are inflammatory cells of other types. Robertson and Ferguson⁶ have drawn attention to the increased size and number of Rokitansky-Aschoff sinuses or Luschka crypts, which they consider synonymous, in chronic disease. These epithelium-lined diverticula extend through the muscularis propria into the perimuscular and subserosal tissues (Fig. 1). They provide niduses for the formation of calculi (Fig. 2) and of abscesses, and may rupture with resultant bile peritonitis. In persistent low-grade inflammation, mucosal proliferation is sometimes marked, accounting for the terms "proliferative cholecystitis" and "cholecystitis glandularis proliferans." This exuberant overgrowth must be distinguished from early, well-differentiated adenocarcinoma. As a result of a predominantly productive inflammation, the wall of the gallbladder may be almost completely replaced by hyaline fibrous connective tissue in which are foci of chronic inflammatory cells. The gallbladder is literally a fibrous sac and the entity is called chronic productive cholecystitis.

Chronic purulent cholecystitis can be considered synonymous with empyema of the gallbladder, in which the lumen is distended with purulent exudate. Andrews⁷ has pointed out that many examples termed empyema on naked-eye

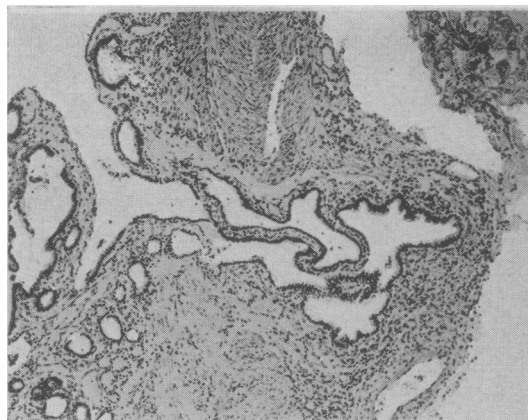


Fig. 1

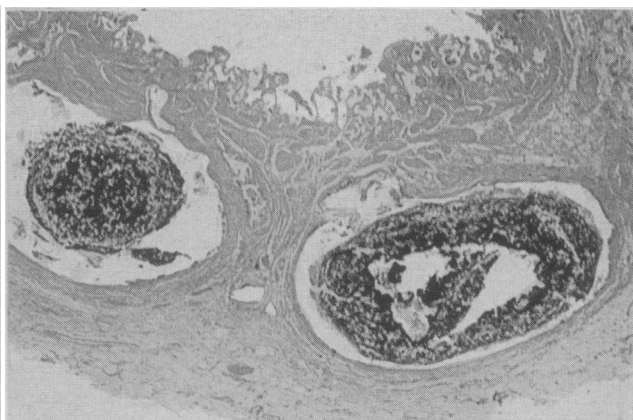


Fig. 2

Fig. 1.—Rokitansky-Aschoff sinus in gallbladder with chronic cholecystitis, extending through the entire thickness of the muscularis into the subserosa. X 45. Fig. 2.—Calculi in Rokitansky-Aschoff sinuses outside the muscularis in the subserosa. X 25.

inspection are not truly such, for the milky fluid distending the lumen is not pus but an emulsion of calcium carbonate or cholesterol. Although frequently mentioned, true empyema is a rare occurrence.

An interesting type of inflammation of the gallbladder results in the formation of intramural lipogranulomas. These areas consist of granulation tissue with abundant fibroblastic proliferation, numerous lipid-containing macrophages, and sometimes cholesterol clefts and multinucleated foreign body giant cells. Weismann and McDonald⁸ have shown by chemical analysis that such gallbladders contain increased amounts of cholesterol and cholesterol esters. The authors concluded that the lipids, especially cholesterol, are etiologically responsible for the granulomatous inflammatory reaction. It is possible that the Rokitansky-Aschoff sinuses play a part in the development of this interstitial reaction.

Another histologically distinctive type of chronic cholecystitis is termed lymphofollicular and is characterized by aggregates of lymphocytes and plasma cells in the substantia propria, sometimes with the formation of lymph follicles. These aggregates or follicles cause a nodular protrusion of the mucosa into the lumen (Fig. 3). Whenever such a histological pattern is observed, the possibility of the patient's being a typhoid or a paratyphoid carrier must be considered, as response of this particular type has been shown to occur in such infections.⁹ Lymphofollicular cholecystitis cannot, however, be considered pathognomonic of Salmonella infection.

The extensive deposition of lime salts over the inner surface and in the wall of the gallbladder which results in a viscus of eggshell consistency is termed calcific cholecystitis or "porcelain" gallbladder (Fig. 4).¹⁰ Hydrops and mucocœle of the gallbladder are special manifestations of mild chronic cholecystitis with obstruction of the cystic duct in the absence of significant infection. Theoretically, in hydrops the lumen is distended with a serous fluid, whereas in mucocœle it is filled with mucin. From the practical aspect such a distinction is not always possible.

There are other inflammatory lesions of the gallbladder which are uncommon and which are part of a systemic infection or are secondary to inflammation of an adjacent viscus. The chronic infective granulomas such as tuberculosis or actinomycosis are unusual, the former occurring more often than the latter. Polyarteritis with focal necrosis and inflammation is sometimes seen. Some of these cases show vascular lesions as part of the syndrome of periarteritis nodosa whereas in others the characteristic arteritis appears to be restricted to the gallbladder. There is, as yet, no adequate explanation for the latter group.

A classification of neoplasms and neoplasm-like lesions is given in Table II. Benign neoplasms are uncommon, of little practical significance, and of interest mainly to the pathologist. Hamartomas and choristomas are recognized occasionally. Hamartomas are neoplasm-like masses of adult tissue, the result of faulty development. They consist of tissues that normally make up the viscus in which they are located. Choristomas

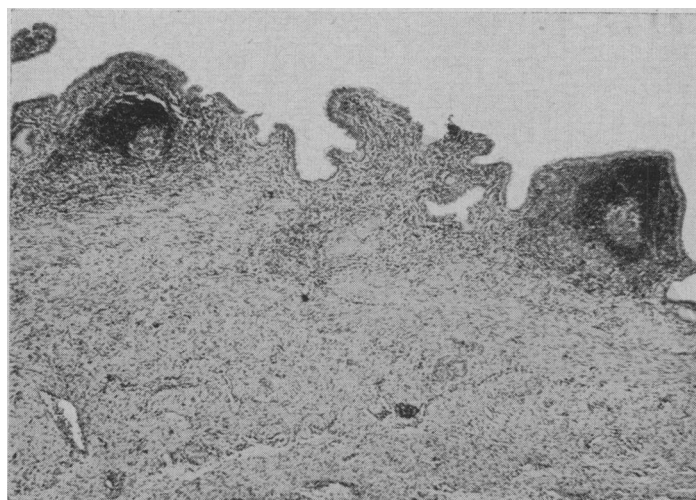


Fig. 3

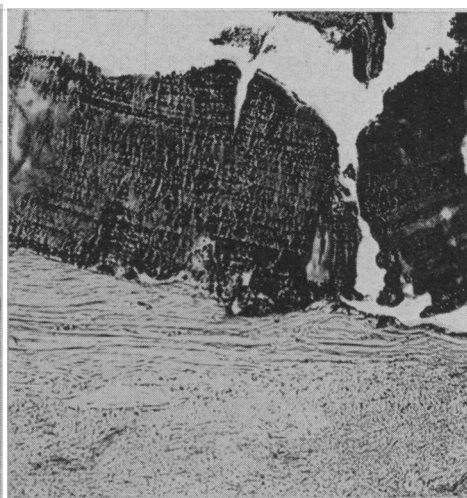


Fig. 4

Fig. 3.—Lymphofollicular typhoidal cholecystitis in a patient who had typhoid fever many years before. Such patients are carriers. Lymphoid aggregates and follicles lie immediately beneath the mucosal epithelium. X 75. Fig. 4.—Chronic calcific cholecystitis or "porcelain" gallbladder. Calcium carbonate covering the inner surface. Similar deposits were present throughout the wall. X 80.

TABLE II.

PRIMARY NEOPLASMS OF GALLBLADDER	
I.	Hamartomas and choristomas
a.	Adenomyomatous
b.	Hepatic
c.	Gastric
d.	Intestinal
e.	Pancreatic
II.	Benign Neoplasms
a.	Papilloma
b.	Adenoma
c.	Leiomyoma
d.	Fibroma
e.	Lipoma
f.	Angioma
g.	"Amputation neuroma"
h.	Hæmangiopericytoma
i.	Neurofibroma
j.	Myxoma
k.	Chondroma
l.	Myoblastic myoma (granular cell myoblastoma or neurofibroma)
III.	Malignant neoplasms
a.	Carcinomas
1.	Intramucosal ("in-situ") carcinoma
2.	Adenocarcinoma
	Adenocarcinoma simplex
	Adenocarcinoma papilliferum
	Adenocarcinoma mucosum
	Acantho-adenocarcinoma
3.	Scirrhus carcinoma
	Linitis plastica
4.	Medullary carcinoma
	Signet-ring cell carcinoma
5.	Squamous cell carcinoma
6.	Carcinoid tumour, argentaffin carcinoma(?)
b.	Sarcomas
1.	Leiomyosarcoma
2.	Fibrosarcoma
3.	Hæmangiosarcoma
c.	Lymphoblastoma

are similar to hamartomas except that they represent adult tissues misplaced from some adjacent viscus. The adenomyoma of the gallbladder may be considered a hamartoma. It consists of a mass of glandular and leiomyomatous elements, either embedded in the wall or projecting into the lumen as a polyp. This was the most common benign tumour in the series reported by Shepard, Walters, and Dockerty.¹¹ A number of interesting choristomas have been reported, but

they are rarities. Probably the most common are the accessory lobes or nodules of adult liver tissue usually projecting from the serosal surface of the fundus. They have no connection with the liver and the small bile ducts penetrate the muscularis to empty into the lumen of the gallbladder. Kerr and Lendrum¹² reported a very interesting mucosal polyp of the gallbladder which was composed of intestinal epithelium with Paneth and enterochromaffin cells and which secreted large quantities of sodium chloride and water. Two rare choristomas are shown in Figures 5 and 6.

True papillomas and adenomas are uncommon.¹¹ Possibly many of the so-called adenomas are actually adenomyomas. Kane, Brown, and Hoerr¹³ found eight examples of papilloma in approximately 2,000 gallbladders. It is logical to assume that some papillomas can undergo a malignant transformation. However, most carcinomas of the gallbladder are not preceded by papillomas. Certainly such papillomas do not play the role in the subsequent development of carcinoma that colonic and rectal polypi do. The other benign neoplasms listed in Table II are even less frequent than those mentioned. One lesion, usually classified as neoplastic but not a true neoplasm, is the "amputation neuroma" which may follow either cholecystectomy or cholecystostomy.

Essentially all malignant neoplasms of the gallbladder are carcinomas. A total of 114 cases of carcinoma of the extrahepatic biliary system, including the gallbladder, were found in 12,838 necropsies performed at the University Hospital (Michigan). As is shown in Table III, eight of these were so extensive that the primary site could not be determined with certainty, but was considered definitely to be either the gallbladder or the extrahepatic ducts. There were 48 cases

TABLE III.

CARCINOMA OF GALLBLADDER AND EXTRAHEPATIC BILE DUCTS (12,838 NECROPSIES, UNIVERSITY OF MICHIGAN)							
Primary site	No. of cases	M.	F.	Percentage of total necropsies	Percentage of necropsies on patients over 21 years	Percentage of necropsies with malignant neoplasia	Percentage of necropsies with carcinomas
Gallbladder.....	48	16	32	0.37	0.53	1.30	2.14
Bile ducts.....	58	41	17	0.45	0.63	1.57	2.59
Extrahepatic							
biliary system*.....	8			0.07	0.08	0.21	0.36
Totals.....	114			0.89	1.24	3.08	5.09

*These cases were considered to be of either gallbladder or extrahepatic duct origin but the neoplasm was too extensive to be certain of the exact origin.

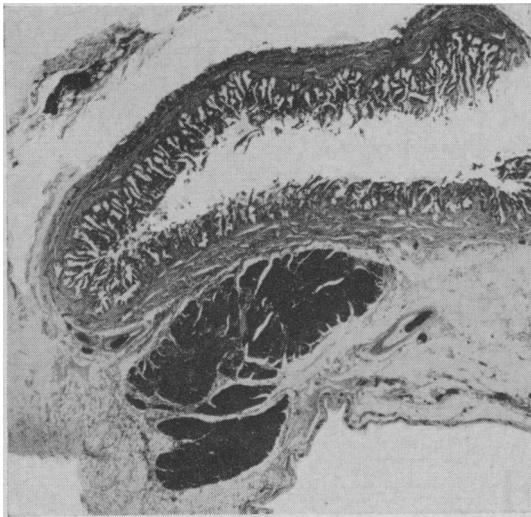


Fig. 5

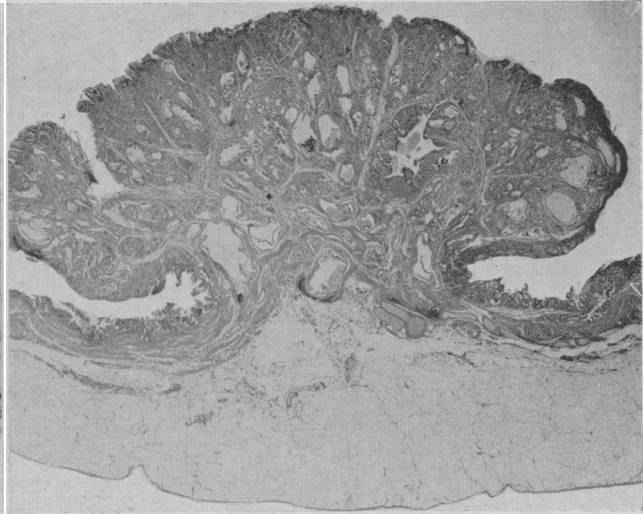


Fig. 6

Fig. 5.—Pancreatic choristoma. The dark lobulated mass in the subserosa beneath the muscularis is pancreatic tissue. X 10. Fig. 6.—Gastric choristoma of the gallbladder. The polypoid mass of tissue projecting from the mucosal surface is composed of gastric glands. X 10.

of primary carcinoma of the gallbladder and 58 cases of carcinoma of bile ducts, including the ampulla of Vater. The incidences of these carcinomas as percentages of total necropsies performed, of necropsies on patients 21 years of age or older, of necropsies manifesting malignant lesions and of necropsies revealing carcinomas are listed in the table. The figures are similar to those of Kirshbaum and Kozoll¹⁴ and of Jones.¹⁵ The incidence of carcinoma in gallbladders removed surgically is approximately the same, 1 to 2%.^{15, 16}

Carcinoma of the gallbladder is more common in women and in this series was in proportion of two women to one male (Tables III and IV). Many series show even a higher incidence in women. Carcinoma of the extrahepatic bile ducts is significantly more common in men. The incidence of calculi in cases of carcinoma of the gallbladder varies in different series from 60 to 100%. In this series calculi were found in 73% (Table IV). This close association with calculi is not seen with carcinoma of the bile ducts. It is known that in most cases cholelithiasis precedes the development of carcinoma. The sequence of events is probably cholecystitis, chole-

lithiasis, then carcinoma. However, this does not imply a specific carcinogenic activity on the part of the calculi and, although this has been suggested, there is no proof of such action.

It is interesting to note that there were two synchronous primary carcinomas in five of the 48 patients. Four of these cases were unassociated with cholelithiasis. The other primary carcinomas were located in colon, cervix, breast, prostate and stomach. This finding suggests an intrinsic tendency or predisposition to the formation of malignant epithelial neoplasms. Of interest also is one case of carcinoma of the biliary ducts in which multiple autochthonous foci were demonstrated throughout both extrahepatic and intrahepatic bile ducts. This occurrence, as well as a diffuse "cancerization" of the biliary mucosa, is probably far more common than is generally realized and has been stressed by Willis.¹⁷

The various malignant neoplasms that may involve the gallbladder are listed in Table II. Intramucosal carcinoma or "carcinoma *in situ*" is observed in surgical specimens solely as an incidental finding. Its incidence is not definitely known and little attention has been paid to it because as yet there is no practical means whereby it can be diagnosed before operation. It is safe to presume that it probably precedes a high percentage of infiltrative carcinomas. An example is illustrated in Figure 7. Sections from many blocks of this gallbladder revealed a diffuse malignant transformation of the mucosa without infiltration. The cytological features were obviously those of malignant neoplasia.

TABLE IV.

CARCINOMA OF GALLBLADDER*					
	No. of cases	Average age	Age range	Calculi present	Percentage with calculi
Male.....	15	59	(34 - 73)	19	63
Female.....	32	61	(39 - 80)	25	78
Totals.....	48	61	(34 - 80)	35	73

*Multiple primary synchronous cancers in 5 cases; in 4 of these there were no calculi.

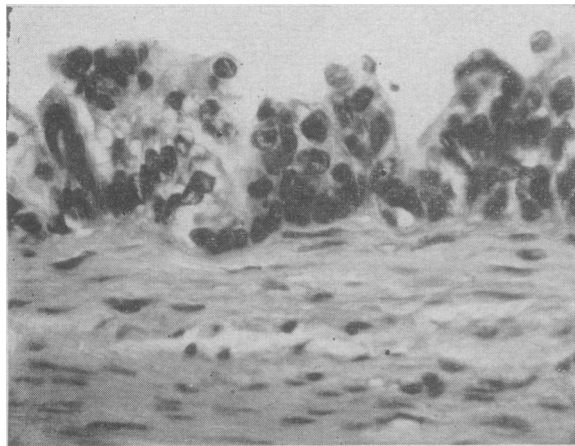


Fig. 7.—Intramucosal carcinoma of the gallbladder. There is a diffuse malignant transformation of the mucosa with no infiltration of the substantia propria. The atypical cells possess large, irregular, hyperchromatic nuclei. There is one division figure near the centre of the field. X 600.

Adenocarcinoma of a moderately well differentiated form comprises the bulk of carcinomas of the gallbladder. The different histological patterns cited under adenocarcinoma (Table II) cannot be considered as distinctive entities, in that two or more patterns may be found in the same neoplasm. However, when one pattern is dominant, the use of the corresponding descriptive term is justified. The term adenocarcinoma mucosum refers to a well-differentiated carcinoma characterized by the production of abundant epithelial mucin. It is similar to lesions in the gastro-intestinal tract. Acantho-adenocarcinoma is

a rather distinctive histological type, so named because of areas of squamous transformation associated with the glandular elements. This term is used in preference to adeno-acanthoma because the neoplasm is basically an adenocarcinoma (Fig. 8). The prefix acantho is used purely in a descriptive capacity.

Scirrhus carcinoma is probably next in frequency to adenocarcinoma and by some authors is considered as a type of adenocarcinoma. When it involves the entire viscus and results in a contracted thick-walled tube, it can be likened to linitis plastica of the stomach or colon. Undifferentiated medullary or encephaloid carcinoma, including the signet-ring cell type, is uncommon, as is pure squamous cell carcinoma. The latter comprises approximately 1% of all carcinomas of the gallbladder and must be differentiated from acantho-adenocarcinoma. Sarcoma of the gallbladder is a curiosity.

Carcinomas of the extrahepatic bile ducts are histologically similar to those of the gallbladder. Scirrhus carcinomas are more frequent and most of the adenocarcinomas show production of mucin.

SUMMARY

The etiological role of chemical irritants in the production of cholecystitis is considered of

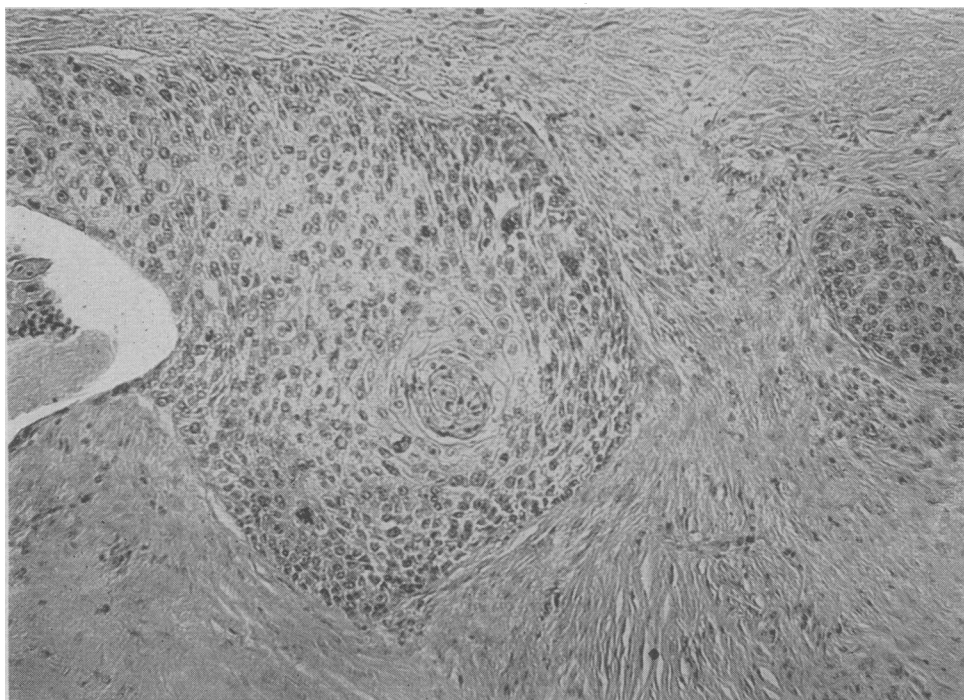


Fig. 8.—Acantho-adenocarcinoma. A solid nest of atypical squamous cells with a central whorl and slight keratin formation. At other levels the neoplasm reproduced glandular structures. X 225.

greater importance than that of bacteria, although the latter cannot be completely dismissed. The histological criteria for the different types of inflammation are cited. Of interest is chronic lymphofollicular cholecystitis which may indicate that the patient is a typhoid or paratyphoid carrier. Most clinical examples of acute cholecystitis actually represent acute exacerbations of a chronic or recurrent cholecystitis.

Benign neoplasms and neoplasm-like lesions of the gallbladder are uncommon. Hepatic, pancreatic, gastric, and intestinal choristomas are rare developmental abnormalities of interest primarily to the pathologist. Cases of carcinoma of the gallbladder and the extrahepatic bile ducts comprised 0.89% of 12,838 necropsies performed at University Hospital, 3.08% of necropsies disclosing malignant neoplasms, and 5.09% of all necropsies with carcinomas. Carcinoma of the bile ducts was more frequent than of the gallbladder. The histological features of the

various malignant neoplasms are discussed briefly and some of the more interesting types illustrated.

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CAROTID ANGIOGRAPHY A CLINICAL EVALUATION OF 200 CONSECUTIVE CASES

DWIGHT PARKINSON, M.D.* and
A. E. CHILDE, M.D.,† *Winnipeg, Man.*

INNUMERABLE ARTICLES on this subject with excellent reviews of the literature have appeared from centres all over the world. It is not our intention to attempt an additional review. This study was undertaken merely to evaluate cerebral angiography as it is currently used as a diagnostic procedure in a neurosurgical service at the Winnipeg General Hospital.

MATERIAL

Two hundred consecutive cases, from the same neurosurgical service at the Winnipeg General Hospital, in which cerebral angiography was carried out, were chosen in the 1950-53 period. Forty-six of these patients had bilateral carotid angiography and 20 others had repeated angiography, so that in all there were 266 angio-

grams on these 200 patients. All injections were given by the same operator. The patients ranged in age from two months to 80 years. There were 12 in each of the first two decades, 34 in the third decade, 56 in the fourth, 44 in the fifth, 22 in the sixth and 20 over 60 years of age. Thus about 30% were below the age of 30, 50% between 30 and 50 and 20% over 50.

TECHNIQUE

Skin, conjunctival and intravenous testing have been abandoned as they have proved quite unreliable. Some of the most marked reactions to angiography have occurred in patients who had given negative responses to one or more of the above tests. The percutaneous route has been used in all but two patients, one an obese, aged female and the other a two-month-old infant. Local anaesthesia only has been employed in all but 16 patients.

The common carotid artery is palpated between the trachea and the sternocleidomastoid at the level of the thyroid cartilage. A wheal is raised here with 2% procaine, and following this 6 to 8 c.c. of the same solution is injected about the carotid sheath and 3 to 4 c.c. behind it. It has been noted that it is often easier to puncture

*From the Department of Surgery, University of Manitoba Medical School and Winnipeg General Hospital.
†From the Department of Radiology, University of Manitoba Medical School and Winnipeg General Hospital.