

# THE PATHOLOGY OF THE GALL-BLADDER AND SOME ASSOCIATED LESIONS.

A STUDY OF SPECIMENS FROM 365 CHOLECYSTECTOMIES.\*

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A STUDY of the diseases of the gall-bladder without consideration of the closely associated organs, and without reviewing and compiling the facts regarding the embryology, anatomy and physiology of these organs, would be not only incomplete but apt to lead us to narrow and perhaps fallacious conceptions. In text-books, journals and lectures there is too great a tendency toward an anatomical arrangement of facts—a type of presentation which is incomplete, in that the anatomical boundaries of an organ are of no greater importance than are its functional boundaries and dependencies. Since our partial appreciation of more intimate activities of cells, and the dependency and influence of cells upon other cells, we must add to a study of every organ a consideration of its relation to other organs. Perhaps the oldest recognizable and yet unsolved dependency of organs upon other organs, or cells upon other cells, is seen in the influence upon the mammary glands by stimuli which start in the pelvis during pregnancy. There are organs, however, which are more closely related anatomically and embryologically than these, but which have not been studied correlatively. The close embryological relation of the stomach, duodenum, bile passages, liver and pancreas has not been considered sufficiently from a biological standpoint. The occurrence of such a relationship may be readily seen in the fact that phylogenetically and ontogenetically these

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have evolved from a single tube, the primitive alimentary canal, lined by columnar or cuboidal epithelium, which is present in the amphioxys and in the human embryo. In the simplest forms of animal life possessing an alimentary canal there is no anatomical differentiation into stomach and small and large intestine. The food-stuffs received into such a canal are broken down and assimilated through activities of the lining epithelium. In more highly specialized organisms differentiation into stomach and intestine occurs. There appears at an early stage of this evolution the original liver as a diverticulum of the alimentary tract. It develops from the duodenum; the cells multiply and become the parenchyma of the organ. The pedicle of this mass of cells retains its lumen, or develops a lumen to form the ductus communis. From this diverticulum arises another which becomes the cystic duct and gall-bladder. The pancreas and pancreatic ducts have a similar origin. It may be seen that the functional cells of the liver, gall-bladder, bile ducts, pancreas, pancreatic ducts and duodenum have a close, common ancestry, and are therefore biologically closely related.

One would naturally expect the life unit (that is, the cell) of multicellular organs, such as the liver and pancreas, to retain some of its original sensibilities and activities, although placed in a somewhat different environment. The same blood mechanism which bathes the tissues of the digestive tract in the simpler forms of life exists in the more specialized forms, as may be seen in the anatomical arrangement of the portal system which leads directly to the liver. At least one close physiological instance serves to show that the pancreas and possibly the liver react to stimuli from the duodenum through the blood, as has been shown by Dolinsky,<sup>1</sup> who discovered that acids brought into contact with the mucosa of the duodenum caused prompt secretion of the pancreatic juice. Popielsky,<sup>2</sup> Bayliss and Starling<sup>3</sup> demonstrated this action after severance of the nerves which connected this organ with the pancreas, and therefore concluded that the cells of the duodenum when in contact with a 0.4 per cent. hydrochloric acid

solution gave off something to the blood which acted on the pancreatic cells and possibly on the liver cells.

During specialization and rearrangement of cells of the early upper abdominal alimentary canal nature has twisted the regular nerve supply of the simplest forms until careful study now demonstrates that although the organs are distinct in the higher organisms they are still connected by the same sympathetic, motor and sensory nervous systems. Fibres of the splanchnic nerve reach the walls of the stomach pylorus, bile ducts, gall-bladder, liver and pancreas through the coeliac plexus. The vagus contains branches to and from these organs. Physiologically, a part of this nerve connection has been demonstrated by Pawlow,<sup>4</sup> who showed in animals that gastric secretion was increased by stimulation of the vagus. Hornburg<sup>5</sup> found the same thing true in the human being. Experimental stimulation of the splanchnic nerve diminishes the flow of bile, and section of the same increases the flow. Relationship between these organs may be supplemented and strengthened from the physiological standpoint by a study of the character and distribution of portal blood. In the most simply organized animals products of the activities of the lining cells of the digestive tract are taken up by the underlying blood capillaries and passed into the general system, and in the most highly developed vertebrates this is also true, the products, however, first passing through the liver, which was primarily a part of the digestive tract, thus the liver cells are brought as intimately into contact with and are bathed by the same fluids as the cells out of which the liver grew in the simpler forms of organization. The change in the amount of liver secretion through the influence of absorbed products from the duodenum and through stimulation of the splanchnic nerve has lead Howell<sup>6</sup> to say that we may believe that the quantity of bile secreted varies with the amount and composition of the blood flowing through the liver.

It may be said, therefore, before taking up pathological conditions which arise in the gall-bladder, that the aforesaid organs are embryologically, anatomically, physiologically, and

I shall endeavor to show, pathologically, to be considered a gastro-duodeno-hepatico-pancreatic physiological system, and not functionally separated by arbitrary anatomical boundaries. The questions arising which may have some light thrown upon them by this study are:

First, what are the pathological conditions which arise in the gall-bladder?

Second, what pathological conditions are frequently associated with lesions in the gall-bladder?

Third, what evidence is there for common disturbance in the activity of the duodenum, stomach, liver, and bile passages?

Fourth, what is the relationship between the condition of the stomach and conditions in the duodenum and the function of the liver, gall-bladder and pancreas?

Fifth, is there any relationship between the frequency of pathological conditions of the appendix and disturbances in the stomach, duodenum, liver, gall-bladder and pancreas?

#### MATERIAL.

The material for study in this paper has been furnished by 365 out of 657 cholecystectomies performed by Drs. W. J. and C. H. Mayo, and studies made by the writer at operation in cases in which cholecystostomy for drainage or stones was done.

As soon as the specimens were removed they were examined grossly and microscopically. They were classified into eight groups, which have been verified by examination of fixed specimens just previous to the preparation of this paper.

The normal gall-bladder (Figs. 1 and 2) presents itself at exploration as a bluish, thin-walled receptacle, the contents of which may be gradually expressed. It may be deeply imbedded in the liver substance, it may be double or absent. It varies in size within wide limits.

In classifying the pathological conditions into groups one must bear in mind that one specimen may present the characteristics of the several "types" described. This fact necessitates speaking of specimens as uncomplicated or complicated by

other grades of lesions. The term uncomplicated simply means that grossly the specimen presented practically only one picture.

*Group I: Cholecystitis, Catarrhalis Acuta* (Figs. 3 and 4). There were 65 uncomplicated cases and 9 cases complicated by other stages. Forty-five (69 per cent.) of the uncomplicated cases were associated with gall-stones. In this group may be placed the gall-bladders which retain their general characteristics regarding size and color, both inside and out; in other words, "normal," with the exception that the villi, congested and infiltrated with lymphocytes, are more prominent than normal. The infiltration may extend into the other layers of the wall. The condition occurs with or without stones. My attention was first drawn to this early condition by examination of a resected gall-bladder, which contained stones, but showed grossly no apparent change. Upon microscopical examination, however, the mucosa was infiltrated with lymphocytes and leucocytes. The diagnosis was sometimes made at operation by the thickened viscid bile, which seems to indicate hyperactivity of the glands of the mucosa and partial obstruction to the natural drainage. Other specimens in which no stones were found presented this same condition, and clinically gave a picture of cholecystitis. The stones which occurred in these cases were usually small, and may have been passed through the ducts in the cases in which none were found, or the condition may be the forerunner of stones. This early reaction of the mucosa was seen again in association with further changes, which constitute the second group.

*Group II: Cholecystitis, Catarrhalis Chronica* (Figs. 5 to 14).—Constituting this group were 39 uncomplicated cases and 39 cases associated with other types of inflammatory reaction, 30 (76 per cent.) of the uncomplicated cases contained stones. These specimens vary from Group I only in degree, and one portion of the gall-bladder may belong to the first group and another portion to this group. The principal change grossly consists in an "erosion" of the apices of the villi. These desquamated apices present themselves as yellow

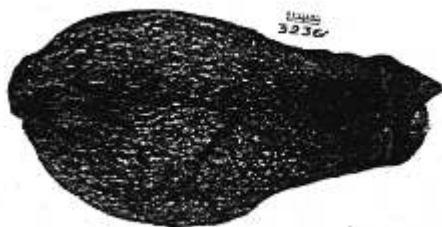
specks scattered over the mucosa (see Plate I.) Otherwise the mucosa may appear normal or congested. This condition we have described as the "strawberry" gall-bladder, on account of the resemblance of the yellow specks to strawberry seeds. These have also been mistaken for fine stones. Microscopically one sees that the epithelium is lost and replaced by scar tissue. Clinically there is nothing to distinguish this group from Group I. It is found with or without stones.

*Group III: Cholecystitis, Catarrhalis Papillomatosa* (Figs. 15 to 17).—In this group there was only one specimen. One of the villi was enlarged and appeared as a papilloma. The condition was associated with stones and an acute catarrhal reaction in the mucosa. The papilloma was 2 mm. long and about 1 mm. in diameter (Fig. 15, a). The cells of the epithelium covering the villi and papilloma were regular in size and shape and possessed nuclei showing no irregularities.

*Group IV: Cholecystitis Papillomatosa Malignum.*—Like papillomata in other portions of the body these often undergo an irregular or perverted hyperplasia, which manifests itself in marked reduplication of the rows of epithelial cells. Upon high power examination of the epithelial cells the chromatin granules are irregularly distributed, the nuclei are irregular in shape and size. These cells may or may not dip below the basement membrane. Such cases have been found during exploration, at which time portions of the gall-bladder were taken for examination. This type does not occur in this series because the cases seen were studied at exploration of inoperable cases.

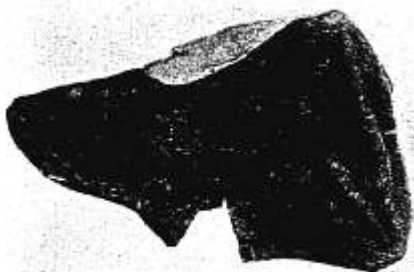
*Group V: Cholecystitis Catarrhalis Carcinomatosa* (Figs. 18 to 25).—There were three cases of cholecystitis catarrhalis chronica which were complicated by carcinoma. The hypertrophy in the least advanced portions of the changed mucosa appears as knob-like outgrowths covered by epithelium which is in a stage of hyperplasia, which differs apparently from simple hyperplasia morphologically in that the nuclei are large, irregular in shape and size and have irregularly distributed

PLATE I.



Cholecystitis catarrhalis chronica. A color photograph showing the fresh appearance of the "strawberry" gall-bladder. (Case 32361.)

FIG. 1.



Gross specimen of a normal gall-bladder, held up to the light to show the thickness and translucency of the wall. (Case 25130.)

FIG. 2.



Section through the wall, showing the shape and regularity of the mucosa. (Case 25130.)



FIG. 3.



Cholecystitis catarrhalis acuta, in which the transparency has disappeared on account of the congestion and swelling of the mucosa. (Case 23219.)

FIG. 4.



Cholecystitis catarrhalis acuta. A section showing the hyperplasia of the epithelium and infiltration of the villi. (Case 23219.)

FIG. 5.



Cholecystitis catarrhalis chronica. The apices of the villi are eroded, leaving points of white or bile-stained connective tissue which cause the "strawberry" appearance against the velvety background. (Case 24225.)

FIG. 6.



Cholecystitis catarrhalis chronica. (Case 17852.)

FIG. 7.



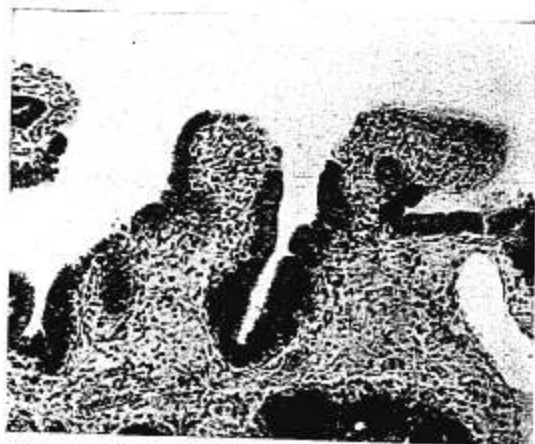
Cholecystitis catarrhalis chronica. (Case 21280.)

FIG. 8.



Cholecystitis catarrhalis chronica. Section through the thickened wall and desquamated apices. (Case 24225.)

FIG. 9.



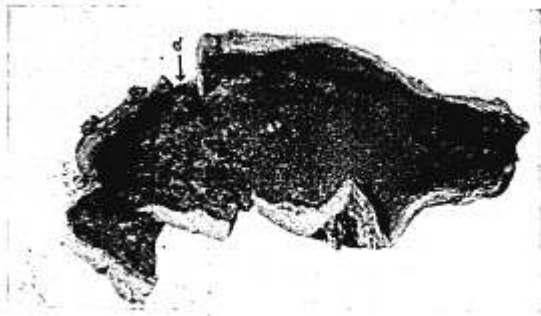
Cholecystitis catarrhalis chronica. (Microphotograph of Case 24225.)

FIG. 10.



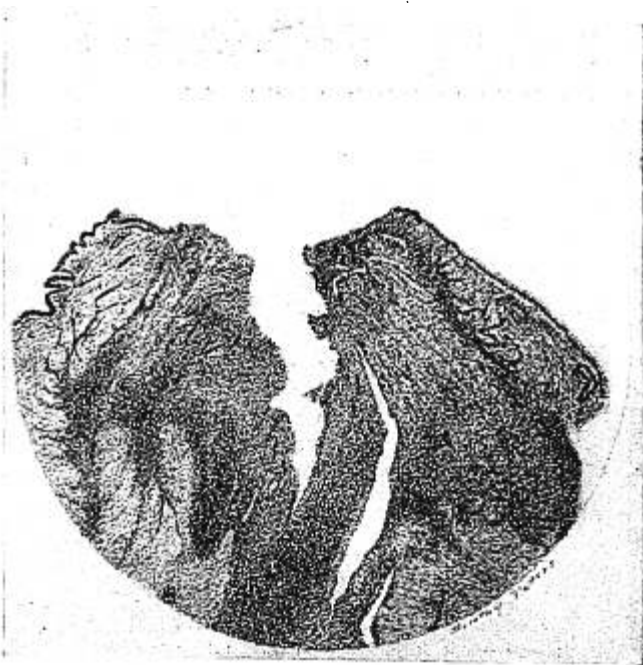
Microphotograph showing the distortion and irregularity of the mucosa.  
(Case 24225.)

FIG. 11.



Cholecystitis purulenta necrotica. (a) Abscesses. (Case 19698.)

FIG. 12.



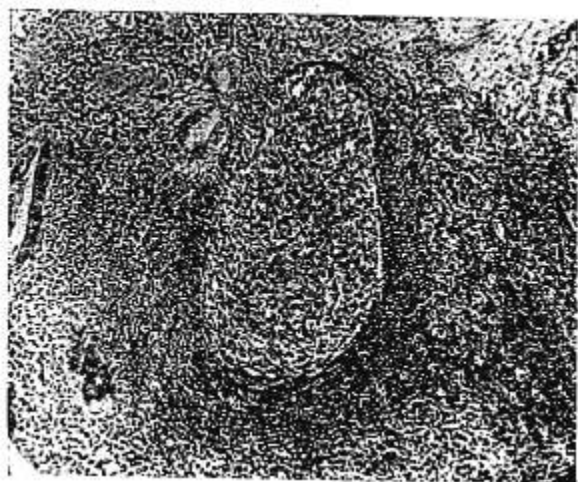
Section through an abscess in the mucosa. (Case 19698.)

FIG. 13



Cholecystitis catarrhalis acuta. Section showing the infiltration of the mucosa and proliferation in a lymph follicle. (Case 20601.)

FIG. 14.



Microphotograph. The germ centre (Fig. 13). (Case 20601.)

FIG. 15.



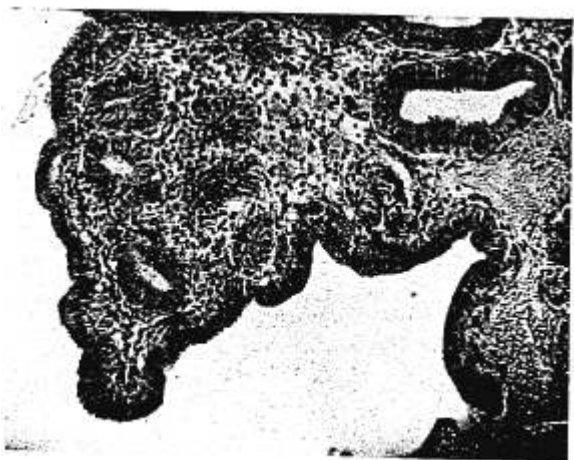
Cholecystitis catarrhalis acuta. Showing a papilloma (a).  
(Case 30267.)

FIG. 16.



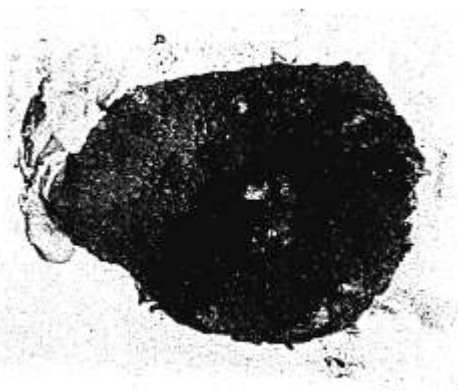
Microphotograph of a section through the papilloma (Fig. 15). (Case 30267.)

FIG. 17.



Microphotograph through FIG. 16 a. (Case 30267.)

FIG. 18.



Cholecystitis calculi carcinoma. (Case 30188.)

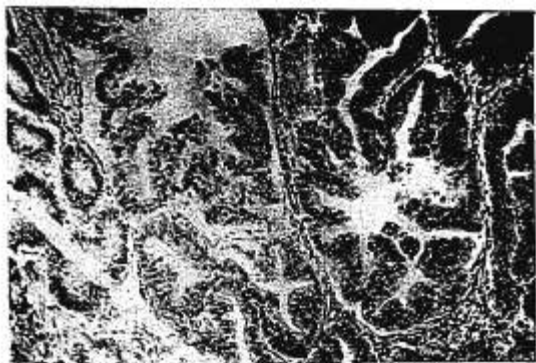


FIG. 19



Microphotograph through the pedicle of portion 5, Fig. 18.  
(Case 30188.)

FIG. 20.



High-power microphotograph of Fig. 19. (Case 30188.)

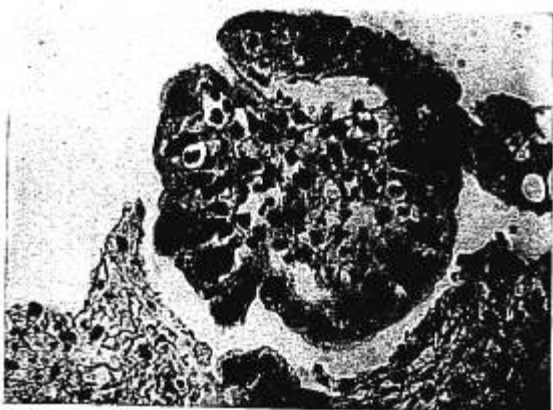
FIG. 21a



FIG. 21b

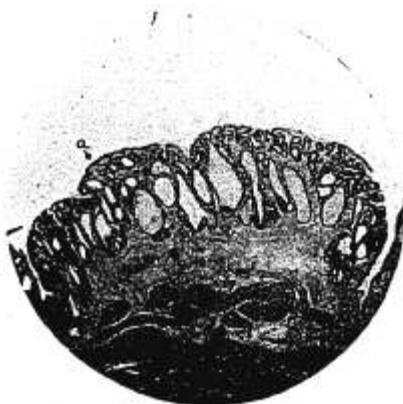


FIG. 21c



Microphotographs showing the irregularity of the cells in portion b, Fig. 18. (Case 30188.)

FIG. 22.



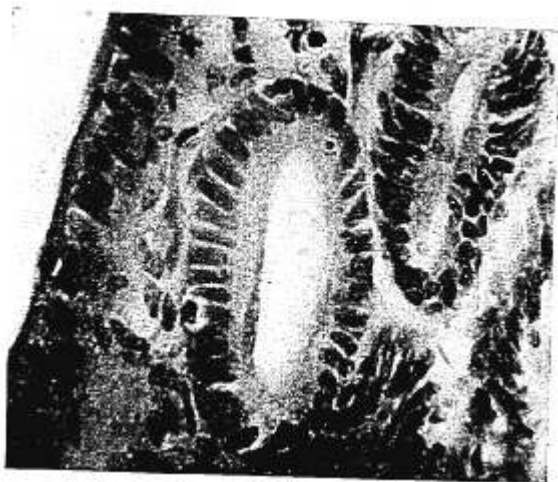
Microphotograph through portion *a*, Fig. 18. (Case 30188.)

FIG. 23.



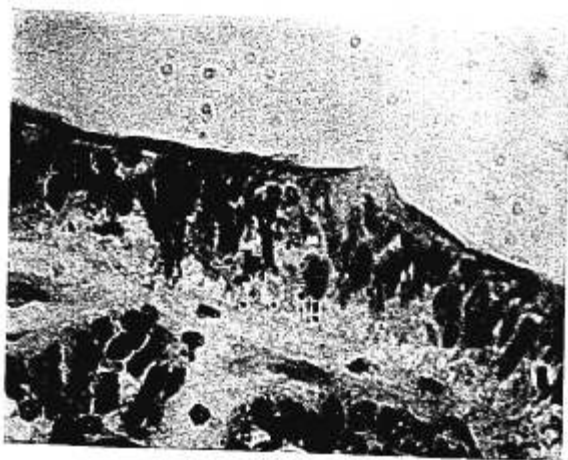
Microphotograph through portion *a*, Fig. 22. (Case 30189.)

FIG. 24.



Microphotograph showing the regularity and irregularity of the cells in Fig. 22.  
(Case 30188.)

FIG. 25.



Microphotograph of the lining epithelium. (Case 30188.)

FIG. 27.



FIG. 26.



Cholecystitis chronica. (Case 25208.)

Cholecystitis chronica, with a stone in the cystic duct. (Case 25504.)

FIG. 28.



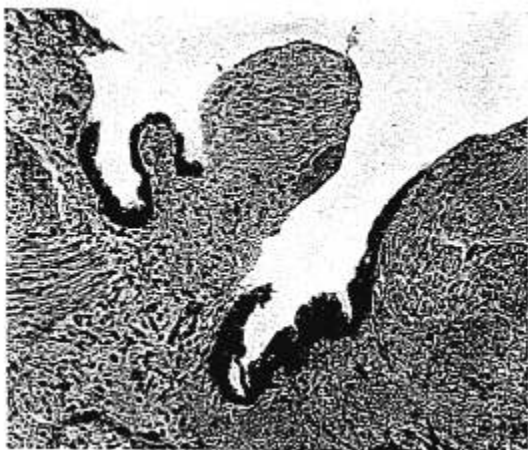
Cholecystitis chronica with almost complete destruction of the mucosa. a, Patches of intact mucosa, b, Scar tissue ridges. (Case 18407.)

FIG. 29.



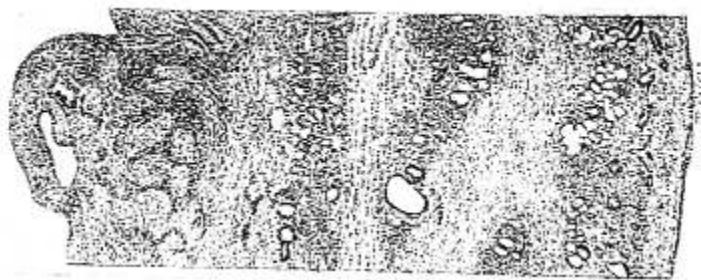
Section through the incompletely destroyed mucosa. (Case 18407.)

FIG. 30.



Microphotograph of Fig. 29.

FIG. 33.



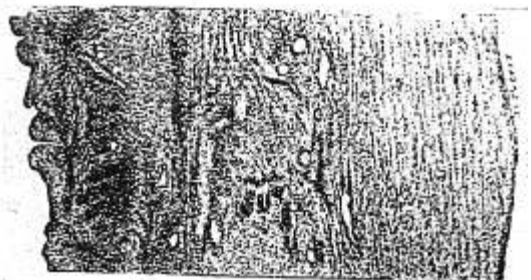
Section through the wall. (Case 26870.)

FIG. 32.



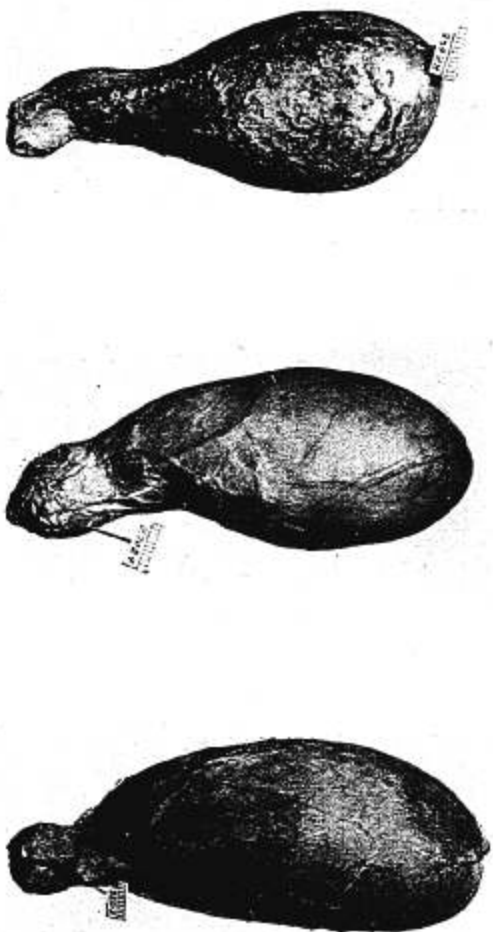
Cholecystitis chronica. (Case 26870.)

FIG. 31.



Section through the wall, showing the complete loss of mucosa. (Case 18407.)

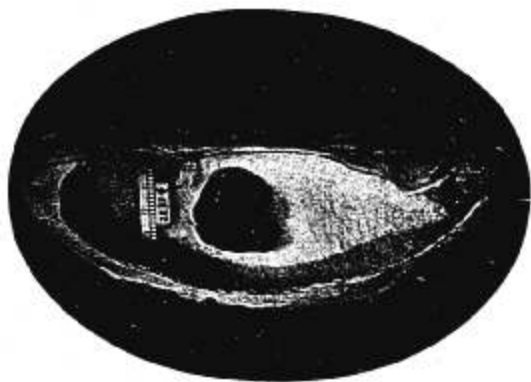
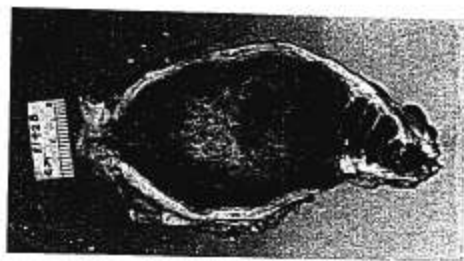
Fig. 31.



*Cholecystitis chronica cysten with a stone in the cystic duct. (Cases 27024, 28925, 28926.)*

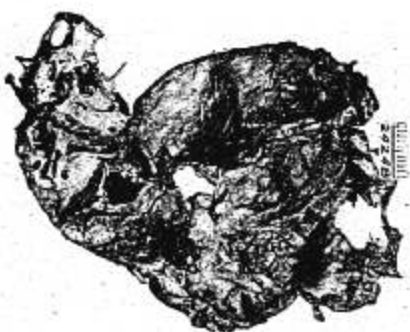


FIG. 35.



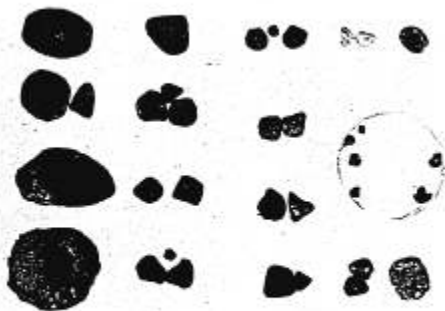
Cholecystitis chronica with a stone in the cystic duct. (Cases 2333, 21425, 22341.)

FIG. 36.



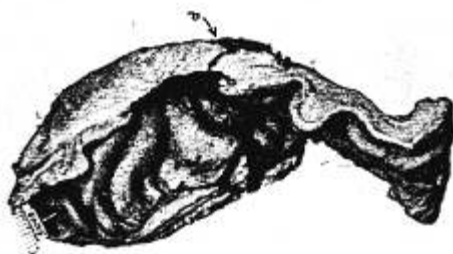
Cholecystitis chronica with stones imbedded in the wall, which gives the specimens the name "Honeycomb gall-bladder." (Cases 28979, 25446, 25448.)

FIG. 37.



Various sizes and shapes of stones found in the series. *a*, A stone which caused intestinal obstruction by ulceration through the gall-bladder wall into the intestine.

FIG. 38.



Ulcer of the duodenum at the papilla of Vater, *a*. The common duct penetrating the base of the ulcer. (Case 31049.)

FIG. 39.



Ulcer of the duodenum associated with cholecystitis catarrhalis chronica and stones. *a.* Papilla of Vater. (Case 31501.)

chromatin (Fig. 21). There are areas however which contain glands, the nuclei of which are regular and indistinguishable from normal or hyperplastic glands (Fig. 24). The more extensive outgrowths (Fig. 18, *b*) arise from the mucosa and possess a base not unlike that seen in the papilloma (Fig. 16). The body of the growth is composed of masses of epithelium (Figs. 19, 20) which, upon high power examination, presents extensive irregularities in the size, shape and distribution of the chromatin granules. Differentiation between this group and Group IV, cholecystitis papillomatosa malignum, must be made with reserve because it is possible that the one is but a stage of the other. No specimens in my series presented sufficient evidence for grouping both conditions under one heading. They present papillomatous outgrowths, differing only in shape. Those under Group VI were knobs, while those in Group IV were filiform and less massive. Earlier stages of carcinoma of the gall-bladder must be found and studied before the life history of such perversions of the epithelium can be accurately pictured.

*Group VI: Cholecystitis Chronica* (Figs. 26 to 33).—There were 78 uncomplicated and 64 complicated cases; of the uncomplicated 73 (93 per cent.) were associated with stones. In this group is placed a condition, gradual stages of which may be seen in specimens of Group II. The continued desquamation of the apices of the villi is associated with proliferation of the connective tissue of the villi and sub-mucosa. The surface, which is normally regular, contracts irregularly and leaves ridges of scar tissue. Upon microscopical examination the inner surface is seen to be void of epithelium and the mucosa has been replaced by scar tissue. The process is not always complete over the whole gall-bladder, as a result of which areas of the condition described in Groups I and II may be seen (Fig. 28). It may occur at operation with or without stones. It has been classified under the term cholecystitis chronica because the mucosa has almost completely disappeared and the process is a chronic one involving the other coats of the wall.

*Group VII: Cholecystitis Chronica Cystica* (Figs. 34, 36).—Seventy-six cases. A stone may become lodged in the cystic duct or in the valves of the neck of the gall-bladder and cause obstruction and distention of the organ. This results in thinning of the wall and destruction of the mucosa or flattening of the scar tissue ridges in the chronic cases. The stone usually is firmly imbedded between the valves and cannot be moved in either direction. Microscopically the wall is a thin layer of connective tissue in which traces of the nuclei of muscle cells may be seen sometimes. Such a gall-bladder attains great size, and is usually the type which presents itself as a large palpable tumor.

*Group VIII: Cholecystitis Purulenta Necrotica* (Figs. 11, 12).—Thirty-three cases. During any stage of inflammation obstruction to the cystic duct may be so great, or the pyogenic infection so virulent that disturbance of the circulation or multiple abscesses in the gall-bladder may occur. The specimens are usually distended, dark blue or black, the contents pus or blood and usually not bile-stained.

*Pericholecystitis Acuta and Chronica* must be considered a sequel of any of the above mentioned degrees of inflammation. Even in the earliest degree of cholecystitis catarrhalis acuta the process may extend to the serosa through the lymphatics, and it is not infrequent to see adhesions, usually to the omentum and transverse colon in this stage.

#### RÉSUMÉ OF THE GROUPS.

It may be seen that the pathology of the gall-bladder reduces itself not to definite pathological lesions, but to stages in a pathological process, which consists of an infection of the mucosa of the gall-bladder, the common or cystic ducts. The elements of disturbance are mechanical and inflammatory. Disregarding the etiology of the condition and whether the infection ascends from the duodenum or descends from the liver, the fact remains that swelling of the mucosa in the ducts at any point in the presence of and aided by some infecting organism causes certain changes or reactions in the wall of

the gall-bladder. The reaction is not unlike inflammation in other parts of the body. To a mild obstruction or infection the first reaction is congestion of the mucosa with slight infiltration. Grossly, the mucosa does not differ perceptibly from the normal mucosa. At this stage the bile at exploration may be of great assistance in making the diagnosis: it may contain an increased amount of "mucin" which gives it greater cohesive quality. Adhesions to the gall-bladder do occur, even with this slight degree of reaction. Congestion and necrosis of the mucosa result in desquamation of the epithelium, thus leaving the tips of the villi bare. These become bile stained and appear as yellow specks, thereby causing the "strawberry" appearance. This condition is only a stage toward further destruction of the epithelium, flattening of the villi and increase in density, due to connective-tissue proliferation, until the velvety appearance of the inside of the gall-bladder disappears and is replaced by a gray, not infrequently, pigmented surface. Externally the wall is seen to be gray and dense. Microscopically, the degrees of the process may be verified.

An obstruction to the outflow of the contents of the organ by a stone in the duct plus a pyogenic infection disturbs the circulation of the wall, causes pus formation and necrosis, which may bring about rupture of the wall and peritonitis, or drainage into neighboring organs. The fact that this complication may occur in gall-bladders in any of the above-mentioned stages results in different pictures of the conditions. The mucosa may be partially intact or completely destroyed. Blocking of the cystic duct alone does not always produce necrosis, at least specimens at operation are often seen in which there is complete obstruction, due to an impacted stone and which present themselves as large, distended, gray-colored, thin-walled cysts. The contents are almost always clear or slightly cloudy and free from bile pigment. The inner surface is usually smooth, or shows only traces of the scar tissue ridges described under *cholecystitis chronica*.

The relation between inflammation and carcinoma has been so constant in many parts of the body, especially demon-

strated in the stomach by Oettinger,<sup>7</sup> Hoche,<sup>8</sup> Graham,<sup>9</sup> Wilson and MacCarty,<sup>10</sup> MacCarty,<sup>11</sup> *et al.* who have shown that a very high percentage of stomach carcinomata occur in the walls of chronic ulcers, that one strongly suspects in the nine cases \* of carcinoma of the gall-bladder in which the average duration of symptoms was nineteen and four-tenths years, that the malignant perversion did not exist over such a long period. This is especially reasonable when one considers that in 280 cases, which were not carcinoma and in which the duration was stated in the histories the average was only six and seven-tenths years.

The question to be asked after a survey of these figures is, can carcinoma exist nineteen and four-tenths years and give symptoms, or were the symptoms inflammatory during this period?

#### CONTENTS OF THE GALL-BLADDER.

From a diagnostic stand-point during operation the fluid contents of the gall-bladder may give much information to the operator.

The bile, which normally is a thin amber-colored fluid containing a small amount of mucus, reveals grossly not infrequently the stages of infection.

An excess of mucus which causes it to be "stringy" is a result of an abnormal activity of the glands of the mucosa, and is almost if not always invariably the result of infection or irritation, occurring with partial obstruction to the natural drainage. Cholesterin crystals which may sometimes be seen grossly in bile which contains no stones, may be taken as indicative of stagnation. Very dark, dirty bile is the result of acute or chronic congestion.

In cases in which there is complete acute obstruction the bile may be bloody or purulent.

The more chronic complete obstructive cases almost invariably contain thin watery or milky fluid.

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\* There were 14 specimens of carcinoma examined, 3 were complete gall-bladders and 11 were portions removed for fresh diagnosis in inoperable cases. In only 9 of these cases was the duration stated in the histories.



*Stones* (Fig. 37).—Two hundred and fifty-two, or 67 per cent. of the 365 cases, were associated with gall-stones, which varied in shape, size and composition, all of which properties bore no apparent relation to the character of the lesion in the gall-bladder.

Interesting, however, is the fact that the percentage of specimens in each group which were uncomplicated by other stages of inflammation and which were associated with stones increased proportionately with the extent of the inflammatory reaction in the gall-bladder, thus 69 per cent. of the specimens which were in an acute catarrhal condition contained gall-stones at operation, although in such cases the possibility of the stones having been passed must be considered.

Of the chronic catarrhal gall-bladders 76 per cent. were associated with stones.

In the more advanced cases of chronic inflammation, in the cases in which practically all of the mucosa was destroyed, the percentage was 93.

From these figures it would seem that the occurrence of gall-stones bore a marked relation to the extent of the lesion and that the early acute catarrhal conditions do not necessarily occur associated with stones.

#### CLINICAL SUMMARY OF CASES.

The histories of these cases were taken by different members of the staff, and the personal equation must be taken into consideration in reviewing the clinical figures.

*Age*.—The youngest patient in this series was a girl (Case 21,610) sixteen years of age, who had suffered attacks of pain under the right costal margin for one and one-half years. This was associated with jaundice and marked tenderness over the right hypochondrium. The gall-bladder was oedematous, distended and contained a stone in the cystic duct. The mucosa was intact, excepting the apices of the villi, the epithelium of some of which was desquamated. The specimen was classed in the groups *cholecystitis catarrhalis chronica*, and *cholecystitis chronica cystica*. The eldest patient in the series was

a male (Case 25,217) aged seventy years who, twenty-five years before operation, had suffered attacks of epigastric pain which radiated to the back. At operation the gall-bladder was filled with stones, and the thickened wall was infiltrated by carcinoma. There was a stone in the cystic duct. This specimen may be grouped as cholecystitis catarrhalis carcinomatosa. Only 25 cases, or 6 per cent. in the series were under twenty-five years of age.

*Sex.*—Out of 365 specimens examined 298 or 81 per cent. were from females and 67 or 19 per cent. were from males, which emphasizes the already recognized predominance of the condition in females.

*Onset of Symptoms.*—It was interesting from a pathological and clinical stand-point to determine how many cases had symptoms in early life, that is, under twenty-five years of age. It was thought that there might be some relationship between appendicitis, which is perhaps more common in this period, and the production of inflammation in the gall-bladder, as was suggested by Ochsner,<sup>12</sup> who thought that the portal of entry for the infecting organism might be the appendix. In the whole series there were only 83 cases with symptoms which began at or under twenty-five years of age. This may be important in distinguishing between the effect of acute and chronic appendicitis on the condition,—that is to say, if the appendix plays a rôle in the etiology of cholecystitis it is strange that such a small number of the cases began under twenty-five years of age. This fact is significant when compared with the percentage of chronically affected appendices associated with cholecystitis. The question arises whether or not the appendix is the portal of entry for the organism, or whether or not stagnation in the stomach and disarrangement of the duodenum, liver and gall-bladder is brought about more commonly reflexly by chronic or subacute lesions in the appendix.

*Pain.*—Pain in cholecystitis seems to vary from mere discomfort to great severity. Practically all of the cases suffered from epigastric pain. Localized pain in the right hypo-

chondrium and under the costal margin occurred in the majority of cases. It was referred to the shoulder in 142 cases. The characteristics of the pain were described as colics, cramps or spasms. The attacks lasted from one to several hours, and were followed by tenderness in the epigastrium or right hypochondrium for two or three days.

*Vomiting.*—Two hundred and ten cases, or 57 per cent. of the series, gave a history of vomiting, although many others suffered from nausea.

*Attacks.*—Attacks of pain usually came on at intervals varying from twenty-four hours to months.

*Jaundice.*—One hundred and sixteen cases gave a history of jaundice, or were jaundiced at the time of examination. The presence of jaundice as a diagnostic sign is very important, but its absence is by no means against cholecystitis.

*Constipation.*—Ninety-one cases gave a history of chronic constipation.

*Relation to Pregnancy.*—Although many of the histories taken in married women did not record any special relation to pregnancy, there seemed to be a great many in whom the symptoms occurred during pregnancy, especially toward the end or shortly after.

*Dyspepsia.*—The question of a dyspepsia history, previous to the onset of definite gall-bladder symptoms, which occurred in 27 per cent. of the cases and might have occurred in more had this point been gone into more thoroughly in the taking of the history allows of speculation, about which at present we are unable to speak positively in a study of the cases presented.

*Appendix History.*—Thirteen per cent. of the histories contained definite reference to pain or soreness in the appendix area.

*Fever and Chills.*—While these were common in many cases it was not noted in the history often enough to be of any value, so far as a percentage was concerned.

*Mortality.*—Since the beginning of the hospital records there have been 657 cholecystectomies and 17 deaths, a percentage of two and a quarter.

## ETIOLOGY.

The etiology of cholecystitis possesses many phases about which we know nothing definite. I shall only attempt to correlate some of the results of other investigations and my own observations in studying the material obtained at operation and postoperative postmortems.

The nature of the infection in the bile passages has been fairly well settled, although more extensive studies would doubtless throw considerably more light upon the subject.

It is fair at present, in view of the work already done on the bacteriology of the condition, to simply state that it must be considered that bacteria play an enormous rôle in the pathological lesions seen in the gall-bladder, liver and bile passages. How these bacteria reach the bile and gall-bladder is still a disputed point and may resolve itself into at least three methods, namely, indirectly through the liver from the portal circulation, as has been emphasized by Adami,<sup>13</sup> through the lymphatics of the intestine or directly by an ascending infection from the duodenum through the common duct. Evidence may be given in favor of all of these methods of infection, although this paper will only deal with conditions which may favor an ascending infection, or make clearer the causes of descending infections. The points worthy of mention are the occurrence of duodenal ulcer in association with cholecystitis, the occasional presence of a duodenal ulcer at the papilla of Vater, and the association of a high percentage of chronic appendicitis with cholecystitis. The first two of these may be seen in two cases in the series herewith presented.

The first case, No. 27,238, was a male aged sixty years, who was operated upon for cholecystitis seventeen months before the last operation. He was improved for five or six months, and again had epigastric pain, jaundice and vomiting. At the second operation, which was performed at St. Mary's Hospital, the gall-bladder was distended, the common duct dilated, and the head of the pancreas very hard. A note at operation stated that, if a third operation should be necessary it should be a cholecystenter-

ostomy. The patient died on the twelfth day after operation. The post-mortem examination revealed a marked cirrhosis of the liver, chronic cholecystitis, chronic pancreatitis, chronic congestion of the spleen, and a chronic ulcer of the duodenum at the papilla of Vater about 1 cm. in diameter. There was almost complete stenosis of the common duct in the base of the ulcer.

The second case, No. 31,049, was a male, aged fifty-eight, who, four years before examination, had attacks of severe epigastric pain which radiated to the back. Seven weeks before the last operation he had similar attacks accompanied by vomiting. At operation the gall-bladder was drained for cholecystitis with one stone, and a hard mass was felt at the end of the common duct, which was thought to be carcinoma of the head of the pancreas. On the fourth day after the operation the patient died from a hemorrhage into the bowel, associated with tarry stools and hæmatemesis. At autopsy a duodenal ulcer 2 cm. in diameter was found. The lumen of the common duct extended apparently unobstructed through the base of the ulcer (Fig. 38).

Both of these cases following upon the experimental work of Maffucci,<sup>14</sup> Charcot,<sup>15</sup> Gombault, Meyer<sup>16</sup> and Tsunoda<sup>17</sup> in which chronic changes in the liver (cirrhosis) were induced by artificial stenosis or partial stenosis of the common duct, must lead us to believe that changes at the papilla of Vater do either allow an infection to ascend the ducts, or through mechanical disturbances in the liver or gall-bladder cause a failure of these organs to prevent or resist infection of the bile from organisms in the portal or general circulation.

The third point, the high percentage of chronic lesions in the appendix in cholecystitis cases, in which both organs were removed at the same operation, is noteworthy from the fact that out of 59 cases in which both organs were removed, 69 per cent. presented definite gross and microscopical lesions, varying from chronic catarrhal conditions to complete obliteration and chronic periappendicitis. It is, however, well known that chronic changes in the appendix are found frequently in individuals who have never given symptoms which were recognized as appendicitis, and that all the chronic lesions which are found at operation have been found in a series of autopsies

made by the writer<sup>18</sup> upon individuals dying of other conditions. The frequency of chronic lesions in otherwise apparently normal individuals arouses the question whether or not 69 per cent. of normal individuals present chronic lesions, or whether this high percentage has any bearing on the lesions in the gall-bladder, in view of the fact that duodenal disturbances are occasionally associated with cholecystitis and knowing that gastric and possibly duodenal disturbances are associated with chronic appendicitis.

It has very often been observed clinically that many patients presenting themselves with marked discomfort and not infrequently sharp pain in the epigastrium, a sensation of fulness, bloating and hyperacidity following eating do not show any changes in the stomach, duodenum or gall-bladder recognizable at operation. An exploration of such cases usually reveals chronic appendicitis. After appendectomy the stomach symptoms disappear.

There is at least one inference to be drawn from a carefully studied series of such cases, and that is that the chronic inflammatory process, or the successive mild acute processes without marked localized symptoms reflexly affect the stomach. This clinical and surgical experience is further strengthened by experimental work. Talma and Clebs<sup>19</sup> produced erosions of the stomach mucosa by continued stimulation of the vagus nerve which causes contraction of the gastric musculature. Litthauer<sup>20</sup> found that artificially produced hyperacidity in the stomach plus trauma to the mucosa produced ulcers which immediately healed. If, however, he produced an anæmia of the part by ligation of the local vessels the ulceration or erosion remained unhealed. These experiments may have some bearing upon the work of Talma and Clebs, who produced an anæmia through contraction of the gastric, especially the pyloric, musculature by stimulating the vagus. They serve here only to bring to mind suggestions regarding known pathological lesions which occur in the stomach, notably the pylorus. The chain of clinical experience regarding chronic appendicitis, gastric and duodenal disturbances may be strengthened by the

experimental work of Roger,<sup>21</sup> who produced gastric hemorrhage by the injection of irritants into the cæcum and by Hedblom and Cannon,<sup>22</sup> who recently have demonstrated a most interesting phenomenon in the muscular rhythm of the stomach and intestines as a result of irritants in the colon. They say, "Not only is the gastric discharge much slower when the colon is irritated but the passage of the food through the small intestine is greatly retarded." This seems to give strength to the fact that there is at least some definite reflex effect upon the stomach and intestine produced by some abnormal conditions in the large intestine. These facts, although they deal largely with the stomach, may throw light upon the disturbances in the duodenum which is so intimately related to, and the functions of which are so closely associated with, the liver and bile passages. The latter are so closely connected with the stomach and duodenum embryologically, anatomically, physiologically and pathologically that disturbance in one might readily be expected to have disturbing influences upon the other.

The points which have come up during this study coupled with the two following cases have strongly aroused a suspicion that possibly the chronic changes in the appendix may reflexly cause disturbances in the stomach and duodenum, which in turn disturb the mechanism of secretion, storage and outflow of the bile, thereby producing conditions favorable for bacterial infection.

Case No. 31,621, a male, aged fifty-five years, who had stomach trouble associated with belching and distress after eating for eighteen years, during the last fifteen of which he had lost forty-five pounds in weight, presented himself for examination complaining of sour eructations, vomiting of bile, belching and diarrhoea. Vomiting always relieved the pain. A posterior gastro-enterostomy had been done elsewhere four years before. The stomach was enormously dilated, but without an ulcer. The patient died of acute dilatation of the stomach and exhaustion, and presented a chronic catarrhal cholecystitis, a strawberry gall-bladder, and an extensive peri-appendicitis chronica.

The second case, No. 31,501, a male, aged fifty-six, had his first attack of pain in the epigastrium three months before examination. It was referred to the right costal arch. A week later he had severe pain in the same region. This was accompanied by slight jaundice, no vomiting, but fever and constipation. He suffered from gas belching, bloating and headaches. At operation a large stone was removed from the neck of the gall-bladder, which it obstructed. The patient had a fatal hemorrhage into the bowel. At autopsy an ulcer of the duodenum was found (Fig. 39).

#### RÉSUMÉ.

1. The gall-bladder, liver, duodenum (pancreas and stomach are embryologically, anatomically, physiologically and pathologically closely related and should be considered a gastro-duodeno-hepatico-pancreatic physiological system.

2. The pathological lesions in the gall-bladder are not definite entities but are degrees in a process of reaction to irritants.

3. They may be divided into the following groups:

I. Cholecystitis catarrhalis acuta (Figs. 3 and 4).

II. Cholecystitis catarrhalis chronica (Figs. 5 to 15).

III. Cholecystitis catarrhalis papillomatosa (Figs. 15 to 17).

IV. Cholecystitis papillomatosa malignum.

V. Cholecystitis catarrhalis carcinomatosa (Figs. 18 to 25).

VI. Cholecystitis chronica (Figs. 26 to 33).

VII. Cholecystitis chronica cystica (Figs. 34 to 36).

VIII. Cholecystitis purulenta necrotica (Figs. 11 and 12).

4. Pericholecystitis acuta and chronica occur as sequels of the above-mentioned degrees in the process of reaction.

5. Pathological conditions in the duodenum are frequently associated with lesions in the gall-bladder and liver.

6. A high percentage of appendices showing chronic and subacute conditions is found associated with cholecystitis and may be an etiological factor in its production.

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