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The Mitchell Banks Memorial Lecture ON THE GALL BLADDER AND ITS INFECTIONS.

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BY

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(With Special Plate.)

THE art of the surgeon which strives to rescue the life or restore the health of patients must serve, wherever possible, as the handmaid of science. When, by one device or another, we remove diseased organs, or parts of organs, or alter the mechanical or physiological processes which they fulfil, we must no longer rest content merely by the means by which we effect these changes—we must seek to know by what process the pathological state has been produced, what are its relations, if any, to other morbid conditions, near at hand or far away, and what modulations in function or in action are the result. Surgery does not complete its high mission by healing the individual patient, though in this must always lie its chief importance. It now seeks to advance the science of Medicine; and it may claim to have done so in a manner exclusively its own.

The application of this general principle to the particular instance of cholelithiasis is interesting. Before the surgeon became competent to inspect the gall bladder little was known of cholelithiasis but its catastrophes. The symptoms caused by stones within the gall bladder were referred to the stomach, and it was among the descriptions of functional diseases of this organ that the clinical history of the earlier stages of this condition was to be found. In consequence there started the fallacy, which is being so reluctantly abandoned, that gall stones as a rule cause no symptoms, and may often be regarded as "silent" or "innocent."

During the last forty years, in consequence of the knowledge gained during operations, there has steadily grown up a clear apprehension of the clinical symptoms caused by cholelithiasis. The various problems of differential diagnosis also have engaged attention, and a conception of the clinical and pathological relations between this disease and other morbid changes within the abdomen has now been established. Of this relationship we know little as yet; its existence has, however, clearly been established by direct research, and it is for analogical research to pursue to their birthplace the individual elements in a very complex pattern of pathological changes. Though we have learnt much as to the physiological activities of various organs within the abdomen, we know little of the correlation of normal functions as between one of these organs and another, or between one organ and many others. We know even less of the effect of morbid changes in one organ upon other organs; we are only beginning to realize their existence and their significance. May I to-day endeavour to interest you in some of the problems regarding the gall bladder as they present themselves to the surgeon?

THE PHYSIOLOGY OF THE GALL BLADDER.

[Sir Berkeley Moynihan then discussed the evidence, obtained by direct and by analogical research, upon which our knowledge of the functions of the gall bladder is based; and concluded as follows:

1. The chief function of the gall bladder is excretory.
2. The mucosa of the gall bladder absorbs fluid, and other substances, from the hepatic bile, which it reduces to one-sixth or less of its original bulk.
3. Fluids and other substances absorbed are carried off by the lymphatics and by the capillary circulation.
4. The mechanism by which the gall bladder is emptied is complex; muscular contraction, variations in abdominal pressure, milking of the common duct by duodenal peristalsis, the "Sprengel air pump" action of bile as it descends from the liver, flowing past the opening of the cystic duct, elastic recoil, may all play a part in this act.
5. The quantity of bile leaving the gall bladder in the course of twenty-four hours is very small.
6. The functions of the gall bladder as an adjuvant of alimentary digestion are slight; and operative experience suggests that they are almost negligible.
7. The part played by the gall bladder in the general economy, by virtue of its powers of absorption, is unknown. There is suggestive evidence that it is concerned with the movements or the metabolism of cholesterol.]

INFECTION OF THE GALL BLADDER.

Infection of the gall bladder may be primary or secondary.

Primary infection is rare. The cause is connected with the solitary cholesterol stone, formed aseptically, as Aschoff¹ asserts, within the gall bladder. Such a stone is said to own a different origin from all other stones; they are dependent upon infection, this one arises from causes other than infection. When once formed the stone may at length become temporarily or permanently engaged in the cystic duct, whose obstruction starts a primary inflammatory change both in the walls of the gall bladder and in the contents. The stone, by its constant friction against the walls of the gall bladder, may in this way also initiate inflammatory changes.

Secondary infections of the gall bladder are far more frequent. The paths by which infection may reach the gall bladder are many. Organisms may be carried in the blood stream, in the bile, in the lymph stream, or may invade the walls of the viscus by direct extension from neighbouring parts—the liver, the stomach, the duodenum, colon, or kidney.

1. Infection through the Blood Stream.

(a) *Arterial Route.*—The gall bladder derives its blood supply through the cystic arteries from the hepatic artery. This route is followed only in cases of general septicaemia.

(b) *Venous Route.*—The veins of the gall bladder empty directly into the portal vein. Infection arises through this channel only by a process of thrombosis or thrombophlebitis. No example of this has occurred in my series of cases.

We owe our knowledge of haematogenous cholecystitis to Rosenow.² He found that organisms removed from the gall bladder, from the bile, from the centre of gall stones, or from the cystic gland of patients treated by cholecystectomy, contained organisms, chiefly streptococci, which, when injected intravenously into animals, produced lesions of the gall bladder, of the bile ducts, and sometimes of

the stomach or duodenum. He suggested that such organisms have an "elective affinity" for tissues like those from which they were originally derived. Such organisms reach the gall bladder of the animal by the blood stream, and in the gall bladder produce lesions exactly comparable to those in the organs from which they were taken. Whether it is the micro-organism which selects the tissue in this "elective affinity," or whether it is the soil which alone provides the food necessary for the growth of the germs—the soil selecting the germ—is not a matter of importance. The truth is well established by Rosenow's experiments and by clinical and pathological research in man that micro-organisms attacking the gall bladder may reach it through the blood stream.

The question has been closely studied in connexion with typhoid fever, but the results of experimental work appear very conflicting. J. Koch,³ in a patient who died of enteric fever, found inflammatory changes in the mucous and submucous layers of the gall bladder. Just beneath the epithelial layer of the villi he found masses or clumps of organisms, apparently those of typhoid fever. No organisms were found on the surface of the mucosa. He therefore drew the conclusion that it was not from the bile that the gall bladder was infected, but by a process of embolism. In the nests of organisms in the wall of the gall bladder propagation took place, liberated organisms escaping through the mucosa into the gall bladder, there to infect the bile. Chiarolanza⁴ injected typhoid bacilli into the veins and beneath the skin of rabbits, and described the organisms as forming emboli in the capillaries of the submucous layer of the folds of the gall bladder. Other observers have, however, recovered organisms injected into the veins from the bile descending from the liver. It is interesting to note that the injection of Dakin's fluid into the blood stream is apt to cause acute cholecystitis.

2. Infection by the Lymphatic Route.

From our knowledge of the development of the gall bladder we should expect to find few lymphatic communications between it and the liver. In some situations, however, and notably at the splenic flexure, it seems possible for an organ to appropriate the peritoneal vessels which may come into relation with it. Professor Jamieson tells me that there is great traffic of vessels, especially from the under surface of the right lobe of the liver, with those of the gall bladder as together they pass inwards on their way to the lesser omentum. Winkerden,⁵ investigating the gall bladder of the cat, failed to demonstrate any communication between its lymphatics and those of the liver. This is a contradiction of Sudler's⁶ earlier observations, which showed an intimate connexion between the surface lymphatics of the liver and those of the gall bladder in man. Dr. A. L. Taylor, examining my cases of cholecystectomy in which a piece of the liver was removed, found evidence of hepatitis, of a thickened liver capsule, of dilated lymphatics beneath it, and of dilated lymphatics in the outer coat of the gall bladder.

The "hepato-lymphatic route" of invasion of the gall bladder, if it exists, would therefore appear to depend upon the following series of events: hepatitis—infection of intrahepatic lymphatics—extension of infection to the freely anastomosing surface lymphatics of the liver—involvement of communicating lymph vessels in the outer wall of the gall bladder. If this sequence is followed then the occurrence of hepatitis should be frequent, and invasion of the serosa and subserosa of the gall bladder be demonstrable in an early stage of gall-bladder infection. Everts Graham⁷ was the first to suggest the invariable existence of hepatitis in cases of cholecystitis and of cholelithiasis. Many surgeons had been familiar with the fact that infection of the liver and early and localized cirrhosis were observed both in cases in which stones were present in the gall bladder and in cases where, although calculi were not found, the gall bladder showed evidence of chronic inflammation. Our observations, carried on since Graham indicated the methods of inquiry, fully support his contention; and no doubt now remains that hepatitis, if not the invariable, is yet the very frequent, antecedent of cholecystitis. A further point concerns the condition of the gall-bladder wall. As to this the answer is unequivocal.

The outer coats are in a large proportion of cases more seriously affected than the inner. In this series of 81 cases there were only 18 in which inflammatory changes were more marked in the inner coats.

The wall of the gall bladder contains organisms more frequently than the bile. In 33 out of 81 cases active micro-organisms were found; in 30 cases in the wall, in 25 in the bile. A further observation made in my cases is relevant to this issue. The lymphatic vessels in the outer coat were grossly dilated in 20 cases out of the 81. The vessels were mostly free of cells, but some contained lymphocytes. In 16 of the 20 cases the lymphatics of the subserous coat were dilated, and there was frequently evidence of infection in and around them. The lymphatic appears, therefore, to be a very probable route by which infection may reach the gall bladder.

Further evidence of the early involvement of the lymphatic system in cases of cholecystitis is afforded by the condition of the cystic gland. C. H. Mayo was the first surgeon to call attention to the significance of this observation. Among the signs which we now accept as indicating early though definite infection of the gall bladder, proved later on by microscopic and bacteriological examination of its walls, is the enlargement of the gland which lies in close relation to the cystic duct. Indeed, its enlargement not only demonstrates the existence of an infection, but is an indication of the necessity for the removal of the gall bladder.

3. Infection through the Bile Stream.

If infection is to reach the gall bladder through the bile stream it may either descend from the liver or ascend from the duodenum. That retrograde infection from the intestine is possible is clearly indicated by the presence, as the nucleus of a stone, of foreign bodies which, in the absence of a fistula between the gall bladder and the intestine or the surface of the body, could reach the lumen of the gall bladder in no other way. Such a nucleus as a piece of cotton fibre, or a tiny flake of copper from a cooking utensil, must ascend from the duodenum. C. J. Bond's⁸ experiments lend conclusive support to this view. He found that coloured fluids introduced into the rectum could be recognized in the discharge from the gall bladder after the operation of cholecystotomy. We know that after the operation of typhlotomy the coloured fluids can be recognized in the intestinal discharge a few minutes after their introduction into the rectum. Bond showed that retrograde currents extend throughout the entire length of the alimentary canal. What alone is doubtful is, therefore, the frequency with which this ascending path of infection is followed. The following facts elicited from my cases are relevant.

As stated above, in 33 cases out of 81 active infection was present; in 30 cases organisms were cultivated from the wall, in 25 cases from the bile. In 8 cases in this series the bile was extracted from the duodenum by Lyon's method.⁹ In 2 cases only were organisms present which proved identical with those found in the gall bladder.

HYPOCHLORHYDRIA AND ACHLORHYDRIA.

The influence of hypochlorhydria and of achlorhydria is perhaps important. The duodenal contents are usually sterile, and are made and kept so by the antiseptic action of the gastric juice, which depends upon the presence of hydrochloric acid. In over 300 of my cases, including this series, it was found (by Dr. Aileen Wilson) that 22 per cent. of patients showed complete achlorhydria, the ordinary incidence of the condition being not more than 5 per cent. Achlorhydria, in cases in which afterwards gastro-entérostomy or gastrectomy is done and the mucous membrane examined, is sometimes associated with, and is perhaps dependent upon, chronic gastritis. We do not know at what period of life achlorhydria first occurs, whether it is a congenital condition, or whether it follows upon some acute or sustained infection in early years. But it appears very probable, and Knott's¹⁰ work would confirm this view, that when free hydrochloric acid is absent the "gastric germicidal barrier" is removed; the pylorus then is relaxed, and organisms escape unharmed into the duodenum, whence (if there is also relaxation of the sphincter of Oddi, as seems

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FIG. 1.—A generation of large translucent pure cholesterol stones.

FIG. 2.—Cholesterol stones: on the largest one, displaced during operation from the cystic duct, calcium is being deposited.

FIG. 3.—Two small stones with calcium nucleus. Large stone showing layers of calcium and layers of cholesterol.

FIG. 4.—Cholesterol stones with early laminar deposit of calcium.

FIG. 5.—Calculi with calcium nucleus, surrounded by cholesterol.

Series of x-ray photographs of the gall bladder immediately after removal to show the constitution of stones, by Dr. L. A. Rowden.

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FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

Photomicrographs by Dr. A. L. Taylor, showing the condition of the gall bladder in chronic cholecystitis.

probable) they may ascend to the gall bladder. It is significant also that achlorhydria is perhaps responsible for lesions of the appendix, which may, through the portal system, themselves be the precursors, or possibly the causes, of an infection of the bile as it descends from the liver. My cases showed that when achlorhydria was present the bile in the gall bladder was infected in 66 per cent., as compared with 28 per cent. in cases where the acid content was normal or increased—the incidence, that is, of biliary infection is more than twice as high. Judd,¹¹ in an examination of 100 consecutive cases, found that the gall-bladder wall showed organisms in 29; in 7 cases only did the bile contain them.

Hyperchlorhydria was present in 16 of my 81 cases, and 6 of these patients had duodenal ulcer as well as cholecystitis. The evidence, therefore, appears to show that infection of the bile through the duodenum does certainly occur, and that it is more likely to develop when achlorhydria is present. When achlorhydria was found the radiological examination often showed a pyloric relaxation and a quicker escape of gastric contents into the duodenum. The associated relaxation of the sphincter of Oddi, though possible, is not demonstrable.

THE LIVER, PORTAL SYSTEM, AND APPENDIX.

Infection may also reach the interior of the gall bladder through bile descending from the liver. The sequence of events in this "hepato-biliary route" will therefore be: infection of liver cell—hepatitis—destruction of parenchyma—infection of bile—contact infection of gall-bladder mucosa. If this path were followed we should expect to find that when a piece of the liver is taken for microscopic examination inflammatory changes are present. In three cases in this series a definite hepatitis, most marked in the portal tracts, was found. The number is too small to have any value greater than this—that it does show that this type of hepatitis definitely occurs in association with cholecystitis.

The infective agent which reaches the gall bladder in this way is derived from the portal system. In this are two streams—the one derived from the alimentary canal, the other from the spleen. So far as the alimentary stream is concerned the main source of origin (of any infection) is most frequently the appendix. We know, from the clinical experience of a multitude of observers, that the appendix shows evidence of disease in a large proportion of cases in which cholecystitis or gastric or duodenal ulcers are present. Indeed, it is rare to find solitary inflammatory affections of the stomach, duodenum, pancreas, liver, gall bladder, or appendix. When one of these shows evidence of disease one or more of the others is likely also to be implicated. Whether the disease starts in one and spreads thence to the others, and if so in which one it begins, is doubtful. All of these viscera may possibly derive their infection from an outside source. There is a constant stream of bacteria from the intestinal lumen into the blood. The organisms may be arrested in the glands of the mesentery or in the endothelium of the liver sinuses. So long as they remain within leucocytes no signs of infection arise. The destruction of organisms by the Kupffer cells leads to a filling of the perivascular spaces by leucocytes, and finally to hepatitis. The bactericidal power of the liver is known to be considerable; the hepatic cells are indeed formidable "destructors." Some few organisms from time to time, by happy chance for them, escape with their lives, perhaps at a time when the liver is momentarily overwhelmed by a flood of unusually viru-

lent microbes. Those which so escape descend in the bile to the gall bladder, and contact with bile may cause the organisms (especially if they are of the *Bacillus coli* group), to clump in the concentrated bile and so to become the nuclei for stones. If hepatitis is incidentally caused it by no means necessarily follows that the gall bladder suffers later, whether through the lymphatics or through the bile stream; for multiple or solitary abscesses of the liver, or such conditions as syphilitic hepatitis, may be very advanced, yet the gall bladder remains normal.

THE SPLEEN.

But remembrance should also be given to the possibility that organisms within the portal current may be derived from the spleen. The association of diseases of the liver, and of gall stones, with diseases which seem to have their origin or their chief development in the spleen, has recently become clearer. In cases of haemolytic jaundice 60 per cent. of the patients suffer also from cholelithiasis. With splenic anaemia both cirrhosis of the liver and gall stones are associated. Enlargement of the spleen is noticed

in cases of stones in the gall bladder and the duct, but sufficient regard has not been paid to the possibility that it is from the spleen that the infective agent is immediately derived. There are cases in which a large number of small stones are found throughout the substance of the liver, not only in cases of cirrhosis, but in cases where the liver appears little if at all changed from the normal. And every surgeon is familiar with cases of recurrent gall stones in which the common duct and all the ducts of the liver within reach are filled with mud and fine stones, which may be washed down in almost unending quantities. In

such cases I pass several tubes up into the liver, and apply the Carrel method of intermittent irrigation for several weeks. Splenectomy for recurrent cholelithiasis may be found necessary in such cases. One of the functions of the spleen is to filter out micro-organisms and toxic substances from the blood stream, and to send them to the liver for destruction. It may sometimes harbour them as well as transmit them. Its capacity to do so in syphilis has been shown by W. J. Mayo. Possibly in other infections micro-organisms or toxic materials are held up and passed on only from time to time to the liver, which in this way receives the material, chiefly bilirubin and calcium, upon which the gall stones are deposited. It seems possible that stones with a bilirubin calcium nucleus may owe their origin to increased destruction of red cells in the spleen.

DIRECT EXTENSION.

Infection may reach the gall bladder from any viscus to which it adheres. If, for example, a duodenal ulcer, or even a gastric ulcer, is about to perforate, the gall bladder may become adherent to the inflamed area; and if the wall of the intestine is then completely destroyed, the gall-bladder wall may form the basis of the ulcer and so prevent perforation. Infection in this way may be spread from the outer coats to the lumen of the gall bladder. When so close an attachment of duodenum and gall bladder occurs it almost invariably has its origin in the latter. A stone seeks to escape from the gall bladder, which, becoming inflamed, adheres to the duodenum. A fistula forms, and a large stone escapes, perhaps to become impacted in the intestine and to cause acute obstruction. In only one case in my series of 81 did it seem possible that the gall bladder was infected in this way.

DESCRIPTION OF PLATE.

FIG. 6.—Gall-bladder wall from a typical case of chronic cholecystitis. The mucous membrane is relatively intact and the muscular coat of healthy appearance. The subserous coat is greatly thickened.

FIG. 7.—Peritoneal and subserous coats of a gall-bladder wall in chronic cholecystitis. This shows again the great fibrotic thickening and congestion and the ubiquitous infiltration by chronic inflammatory cells. The large spaces have contained fat. The mucosa and muscularis are almost intact.

FIG. 8.—Section from the inflammatory fibrous tissue immediately beneath the serous coat. In the middle of the field is a greatly dilated lymphatic vessel. The mucous membrane in this case is practically normal.

FIG. 9.—Section of liver from a case of chronic cholecystitis. A portal sheath is shown containing a vein, an arteriole, and a small bile duct. The sheath is considerably fibrosed and thickened, and contains numerous chronic inflammatory cells. These are particularly prominent surrounding the bile duct in the large tract and round the smaller ducts in the left-hand top corner of the slide.

FIG. 10.—A portion of liver including a portal tract, from a case of subacute cholecystitis. There is a good deal of fatty infiltration of the liver parenchyma and a widespread inflammatory infiltration of the tract by small lymphocytes. The situation of greatest infiltration is round the small bile ducts in the bottom right-hand corner.

FIG. 11.—Centrifuged deposit from the bile in chronic cholecystitis. The deposit consists almost entirely of desquamated mucosal epithelium with very few inflammatory cells. None of these is seen in this slide. In cases either with or without stones the scantiness of inflammatory cells in the bile is a noteworthy feature and is some evidence against mucosal infection.

CONCLUSIONS AS TO INFECTION.

An examination of the gall-bladder wall in my series of 81 consecutive cases shows clearly that infection began in the outer coats in 63. In 18 cases the inner coats were more seriously affected, but in some at least of these it appears possible that infection, beginning in the outer coats, attacked the inner coats more severely only because impaction of a stone in the cystic duct caused an obstruction which was quickly followed by inflammatory changes which fell upon the mucosa first. Infection may reach the outer coat by direct extension from the liver, by lymphatic infection from the liver, or by implication of the peritoneal surface as a consequence of disease in an adjacent organ, such as the appendix. In those cases in which infection begins from within, the ascending route appears to be followed more frequently than I had realized. Cholecystitis seems as a rule to be a part only of an infection which has its origin elsewhere; hepatitis is very commonly, if not always, present, and is almost certainly of earlier origin than the inflammation of the gall bladder.

PATHOGENESIS OF CALCULI.

In the series of cases upon which this paper is based the blood cholesterol and the blood calcium were measured before operation. The gall bladder after removal was at once examined by the radiologist as it lay in sterile wrappings. The cholesterol and the calcium content of the bile in the gall bladder was taken and the bile and the gall-bladder wall examined for micro-organisms. Sections of the wall were taken in order to study the degree of inflammation in the several coats.

When a gall bladder containing stones is removed by operation and examined at once with x rays a very interesting discovery is made. As a rule, with few exceptions, the composition of the stone is dependent upon its size. The smaller stones are translucent; they consist of cholesterolin without admixture or addition of any other substance. As the stones grow larger a thin deposit of calcium may be found upon the surface; the x-ray picture shows a thin crescent, the "new moon" appearance, or a smattering of black spots upon a translucent stone. When the stone is still larger a complete covering of calcium may be found, and the "wedding ring" stone is seen in the x-ray photograph. As the calcium deposit becomes heavier the shadow grows increasingly opaque, and finally a dense black appearance is presented. The inference is clear, I think, that not only the solitary stone, but the multiple stones, are, as a rule, built around a nucleus of cholesterol crystals deposited from concentrated bile.

The deposition of calcium undoubtedly occurs more rapidly upon an impacted stone. When, for example, there are a number of cholesterolin stones of medium size in the gall bladder, and one becomes wedged in the opening of the cystic duct, or in a pocket at the fundus, calcium is soon found upon the surface. When the gall bladder is opened such a stone may be wrenched from its lodgement only with difficulty, and may tear away a piece of the gall bladder as it becomes free. In such conditions the mucosa is always destroyed, perhaps by pressure, and the stone is then in contact with a fibrosed muscular coat, an adventitious inflammatory coat, or the tissue of a neighbouring organ (liver, omentum, or intestine) in which it is buried. Calcium here, as elsewhere, seems to be deposited as the result of a long-continued irritation. When the cholesterolin stone is becoming coated by calcium we may expect to see changes in the mucosa of the gall bladder, inflammation, fibrosis, ulceration, and finally complete destruction. We must not, however, be betrayed into supposing that these are primary changes which in their earlier stages have been responsible for the origin of the stones. It seems quite clear, from the examination of my cases, that the changes are induced by the stones, and are therefore not primary but consequential.

There are, however, stones which are differently formed. From the first the stone is impenetrably opaque, the shadow is quite black, and it is obvious that calcium alone or in a very large proportion is present. Other stones show on x-ray examination a tiny speck of blackest calcium, doubtless derived from the liver, surrounded by a mass of trans-

lucent cholesterolin. An examination of the interior of the gall bladders from which stones have been removed shows that during the months or years when cholesterolin alone is found in the stones the changes in the mucosa of the gall bladder are slight. The membrane may be thickened, coarsened; its reticulation, at first exaggerated, may later be diminished or destroyed; ulcers may be found here and there, and papillomata may grow from any part. But the calcium deposit upon stones shows increase, the mucosa is found to have changed and soon to be completely destroyed, perhaps together with the submucosa, until at last nothing remains but a dense wall of fibrous tissue. No trace of elastic or muscular coat remains. This varying condition of the mucosa seems in some measure to correspond to the change in the blood cholesterol, which seems to be high when the mucosa is active and low when it is lacking or fibrosed. It is interesting to note that when foreign material forms the nucleus of stones (3 cases with copper nucleus and 1 with cotton fibre) the calcium content of the stones is higher than usual—1 per cent. to 6.4 per cent., compared with 0.1 per cent. in the cholesterol stones.

The conclusion of the matter as to the pathogeny of stones in the gall bladder appears to be this:

Infection reaches the gall bladder, the outer coats as a rule being first affected. As a result the activities of this little viscus are at first enhanced; the lymphatics are engorged and the activity of the excretory or osmotic functions of the mucosa augmented. During this period the "cholesterol flood" is at its highest; increased absorption of cholesterol and its transmission to the general circulation cause hypercholesterolaemia. If the lymphatics in a further stage of inflammation become blocked and the mucosal activity continues, a deposit of lipid or crystals of cholesterol occurs in the mucosa, oedema being prevented or reduced by means of the activity of the capillary circulation. The condition develops which I first described as "a disease of the gall bladder requiring cholecystectomy."¹² To this disease MacCarty¹³ later gave the name "strawberry gall bladder." It is now generally described as "cholesterosis." This condition, it is interesting to observe, never occurs unless the cystic duct is patent and bile can freely enter the gall bladder. The best description of it is given by Boyd: the "graceful fragile gossamer folds of mucosa are completely altered, being weighted down by dense yellow opaque masses much as a delicate birch tree might be weighted down by a load of snow." The yellow material is lipid in nature, and displays the properties of an ester of cholesterol. Sections of the gall bladder often show long bloated villi filled with this material, and pendent only by the narrow pedicle. If this pedicle is torn the villus will soon form the nucleus of a stone, and crystals of cholesterol will make haste to envelop it. What has happened in one villus has perhaps at the same time happened in many. And so a generation of stones is formed. Cholesterosis may, of course, be a primary condition of the gall-bladder mucosa, a too heavy saturation of bile by cholesterolin resulting in the deposit of lipid in the villi. Such a condition existed among some of the 18 cases in my series in which the disease probably began in the mucosa.

When the stones begin to grow, as they may so rapidly do, they begin to be themselves the cause of material changes in the gall-bladder wall, by reason of the irritation they cause, or when obstruction of the cystic duct occurs. Secondary changes in the entire thickness of the gall bladder then result; the muscular coat and the elastic coats are fibrosed, and disappear; the outer coats become thickened, a deposit of fat occurs in the walls, adhesions form, and all the changes with which we are so familiar in advanced cases make their appearance. Concomitantly, blood changes in respect of cholesterolin and calcium content are observed. While the mucosa is overactive hypercholesterolaemia is as a rule found; when the mucosa is destroyed we may expect to find hypocholesterolaemia.

The importance of all these considerations, both to the physician and to the surgeon, is obviously considerable. If, on the one hand, infections of the gall bladder begin from within then medical treatment in the early stages by the methods suggested by Lyon, and advanced by Hurst,

may not only bring immediate relief but may interrupt an impending and otherwise inevitable series of changes, leading at last to irremediable conditions, in which the aid of the surgeon would be necessary. It is, in my judgement, not the least of the functions of the surgeon in this present, and I hope passing, phase of his activities, to help the physician to recognize stages in disease earlier than those with which *post-mortem* experience made us familiar; and in this way to do something to prevent disease from drifting until the surgeon alone can offer help. The business of the surgeon is to diminish surgery.

If, on the other hand, the gall-bladder infections begin from without, and are merely part of an infection which spreads widely, involving first the liver, then a far wider view is necessary, and a multitude of other most relevant questions arise. Prevention of the disease of cholelithiasis must then be sought in a study of changes earlier than any with which we are yet familiar. The relief of symptoms of the disease, however, when once established in the gall bladder, is hardly to be permanently obtained except by its removal, for if the outer coats are involved first, Lyon's method must, I think, lose much of its value. Our immediate inquiry must accordingly be directed not only to the clinical manifestations of early infections of the liver and gall bladder and their antecedents, but also to a study of early pathological changes in the liver and gall bladder, as revealed by inspection during operation. The microscopic, chemical, and bacteriological examination of any parts removed must be correlated with the knowledge so obtained.

SYMPTOMS OF EARLY CHOLECYSTITIS.

The symptoms which my inquiries indicate as being those of cholecystitis in its earlier stage are fundamentally those which I described some years ago as the "inaugural symptoms of cholelithiasis."¹⁴ They are as follows: Flatulence and fullness after meals, amounting sometimes to so great distress that a woman takes off her corsets or loosens them; great epigastric discomfort which may involve the right side also or pierce through to the back; early satiety during a meal, a feeling that when a small meal is taken the stomach is overfull; a sudden unaccountable sensation of intolerable nausea, described very often as "sea-sickness," sometimes accompanied by faintness and often by salivation; a feeling of cold associated with slight shuddering, often coming on with great regularity; acidity and "water-brash." None of these symptoms is severe and none striking. It is in association and persistence rather than in individual character that their importance lies. The complexion of patients is often altered, although they do not realize it. After removal of the infected gall bladder a patient will often comment upon an improvement in the complexion, and remark that it is "as it used to be many years ago." Now and again in such patients a more acute disturbance of health is noticed; pain and distress in the upper part of the abdomen are associated with local tenderness, with swelling of the liver—whose edge becomes more easily palpable—and with a slight increase of tenderness. It is as though the whole liver were affected by a slight but transient inflammation. Some months or years later an attack of hepatic colic occurs, not with the agony associated with the passage of a calculus, but with a rather more subdued but still sufficiently acute pain which radiates to the right side and presses through to the shoulder. In an intelligent patient these several steps may all be traced.

INDICATIONS FOR OPERATION.

The criticisms which may properly be urged against this description are that it is vague and that many of the symptoms are of great frequency, occurring even in those who consider their health quite satisfactory. I am not quite sure that vagueness, however applicable as a quality of any individual symptom, can truthfully be made to apply to their conjunction. It is the presence of all, or most of them, over periods of weeks or months, their consistency as well as their character, which is significant. As to the charge concerning their frequency I would say that infections of the gall bladder are in truth very common. Indeed, I think the statement that of all forms of dyspepsia that

dependent upon the gall bladder is the commonest, is unassailable. We use the word "functional" in connexion with dyspepsia far too easily. If we look back to the great teachers of medicine two or three centuries ago—and it is well worth while to do so—we shall see that Trousseau, Thomas Watson, and others described many of the dyspepsias we now know to be dependent upon gross organic disease as "functional."

The exact description of the clinical manifestations of gastric ulcer, the recognition of duodenal ulcer in its full character and frequency, the discovery of "gall-bladder dyspepsia," the demonstration of chronic appendicitis and of visceral prolapse as causes of indigestion, have all led to a diminution in the number of "functional affections of the stomach." A still further contraction, perhaps the greatest of all, will occur when we are able fully and clearly to recognize the effect upon the health for which infections of the gall bladder, its antecedents and its consequences, are solely responsible. The uncertainty which may attach to the clinical history is relieved or removed by the Graham-Cole method of cholecystography. The value of this method does not attach itself so much to the diagnosis of cholelithiasis, in which the proportion of errors is always small, but to the study of normal physiology, and of pathological changes in the gall bladder. Dr. Rowden pointed out to me almost at the beginning of our investigation of cases by this method, how likely it seemed that the negative evidence would prove to be most valuable in those early cases of gall-bladder disease in which our interest was then chiefly engaged. In a few cases diagnosed as early cholecystitis either no shadow of the gall bladder was seen or perhaps only a faint shadow after a long interval. When an operation was performed we sometimes hesitated to remove a gall bladder which showed only a slight degree of structural change. But its subsequent examination, and especially the after-history of the patient, showed that cholecystectomy had indeed been necessary. It soon became evident that one of the main functions of the gall bladder, concentration of bile, was checked at a time when the external appearances of the viscus were only slightly altered; and further, that in this precocious stage the "inaugural symptoms" were clearly elicited.

If, therefore, "inaugural symptoms" are present, and if a cholecystographic shadow is absent, diminished in opacity, or delayed in appearance, the integrity of the gall bladder may safely be impugned, and operation for its removal be performed.

The appearances presented by the early pathological gall bladder vary. There is often a lack of the usual lustre, the walls, normally deep blue in colour, are a little paler, and perhaps a little thinner; there is apt to be a deposit of fat, especially towards the pelvis or along vessels. Adhesions are present, and the cystic gland is enlarged, while in later stages the wall becomes thickened and fibrous in texture. The changed appearance is often so slight that reluctance to remove the gall bladder may naturally be felt. But the subsequent examination of the wall will convince both pathologist and surgeon that the extent of the involvement justifies ablation. In such examinations attention has hitherto been chiefly centred on the mucosa; it is, however, the outer coats which will call for the most careful scrutiny.

I have no doubt that until we are able clearly to understand and to control the earlier symptoms of cholecystitis and its foregoing conditions, removal of the gall bladder should be performed more frequently than is now the custom. In cases of inveterate mild dyspepsia I have many times hesitated whether to extirpate a gall bladder which did not seem much changed. Yet when I have not removed it I have found symptoms unrelieved, and have been compelled to operate again, with great satisfaction to my patient. I am happy to find this experience corroborated by one of the shrewdest and sanest of my surgical friends, Starr Judd of Rochester.¹¹ Advance in this direction must be slow and wary, and any case dealt with should receive the most exhaustive inquiry beforehand, and the parts removed—the gall bladder and perhaps a tiny fragment of the liver—should be examined with care and completeness; examinations of the blood and bile, in respect at least of the cholesterol content, may be made concurrently. I know

no department of medicine which so much requires that the physician and the surgeon and all laboratory workers should be in league together.

Note.—This address is based upon an experience of many hundreds of cases of cholecystitis operated upon in recent years, but more particularly upon a series of 81 cases, in which the following examinations were made. Before operation the cholesterol and calcium contents of the blood were estimated, in many cases a Reyfuss test meal was given, and in a few a duodenal intubation was made. The gall bladders removed were first examined by Dr. L. A. Rowden and were then opened; cultures of the bile and of the gall-bladder wall were made; the calcium and cholesterol content of the bile was estimated; and sections were made of the gall-bladder wall. In some cases the blood was examined for cholesterol at varying periods after the operation.

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THE PREVENTIVE FRAME OF MIND IN MIDWIFERY.*

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OBSTETRICS has, I think, always suffered by being unfairly compared with the two great sister branches of our practical work, medicine and surgery, for there is really no proper basis of comparison. Medicine and surgery are in practice concerned with conditions which are wholly pathological. In so far as they deal with the preservation of the physiological they come under the heading of preventive medicine. The functions with which the science and art of obstetrics deal partake of both physiological and pathological characters. Obstetrics is thus in a somewhat equivocal position, and, as Mahomet's coffin was believed to be suspended between heaven and earth, so it lies midway between the heaven of the purely physiological and the lower earth of the pathological. On the earthly side we have distinguished obstetricians—as, for example, Professor De Lee in America—who would have us believe that the function of parturition is becoming more and more pathological under the influence of the increasing artificiality of modern life. Our own friend Dr. C. E. Douglas had certainly one foot firmly on the earth when he propounded the suggestion that possibly there was something inherent in the condition of pregnancy which made a woman more prone to death—some diminished power of resistance to disease, call it what you will, some sacrifice which the individual woman offers to the race. On the other side you have the optimists who regard parturition as a purely normal physiological function, regardless of the false analogy which such an expression implies. As has been pointed out again and again, parturition differs from all other physiological functions in that it is performed in the interests of the race, while all others are performed in the interests of the individual only. The truth is that the proper place of obstetrics is partly on the earth and partly in the heavens, and our business is to keep it as far as possible on the higher physiological levels. This, I maintain, can only be done by deliberately adopting and practising a preventive frame of mind.

When we come to think of it in rather more detail, the functions of the modern obstetrician are most pronouncedly

bound up with preventive medicine. I submit that these functions may be summed up as follows:

1. To watch over the health of the expectant mother, and, as far as may be possible, of the unborn child during the period of utero-gestation.
2. To foresee conditions calculated to create difficulty or danger in childbirth, and to take steps either to remove them if possible, or to arrange for the birth to take place in circumstances in which the best obstetric skill may be available.
3. To conduct the delivery so that both mother and child are exposed to the minimum of risk and injury.
4. To restore the mother to her ordinary vocation in life with health and vigour as far as possible unimpaired.
5. To foster her capacity to nurse her child.
6. To see to it that the mother's reproductive organs return to a healthy normal condition fit for further normal functioning.
7. To watch over the health of the infant and thus begin the ante-natal care of the succeeding generation.

Could any programme well be more preventive than this?

The problem of the persistent maternal mortality rate seems to me to offer three sides upon which it is susceptible to attack and to some degree of remedy. The first of these is in regard to the methods of practice, the second is in regard to the conditions of practice, and the third is in regard to the teaching of midwifery.

THE METHODS OF PRACTICE.

How does the general principle of prevention apply to the methods of practice? The first part of the answer is obvious—to wit, that the routine and universal practice of ante-natal examination and supervision promises an immediate improvement in maternal mortality. To recall in detail the benefits to be obtained by ante-natal care would be to go over ground already familiar. But what we have to keep in view and to emphasize in our advocacy is that the benefits are not theoretical or merely possible, but certain. To avert difficulties by foresight and foreknowledge, or to prepare in advance for unavoidable difficulties, is bound in the long run to produce better results than follow from trusting to one's ability to treat unexpected complications as and when they arise. The general public requires education on this point, and I earnestly suggest that one of the duties devolving on each member of such a society as ours is to preach this gospel of ante-natal supervision amongst the public until it becomes universally understood. That the profession also needs to be educated on this point is not so generally appreciated, but it is a fact. In one sense ante-natal care is nothing new, but in another sense—in the sense of the general routine exercise of such supervision—it is a new doctrine to the great majority of present-day practitioners. It is only graduates of the last dozen years or so who have had the doctrine hammered into them as students. To all the older practitioners the teaching that such supervision is an integral part of the obstetrician's duty is new, and it is always a difficult thing to arrest the attention of the profession to new teaching except it be accompanied by some striking discovery—such as, for example, insulin. I am speaking of what I know when I say that our young graduates are sometimes actually discouraged in their efforts to practise ante-natal supervision by seniors who are not alive to its importance.

The methods of ante-natal supervision are simple. A very little practice will produce a reasonable degree of skill in estimating the relative sizes of the head and the pelvis, and in other respects the ante-natal examination is along ordinary medical lines. Another great point is that the means to carry out this principle are already to hand. Financial assistance is offered by the Government to every municipality which starts an ante-natal centre. But it is not enough to establish centres. The women must be got to go to the centres. Our experience in Edinburgh certainly encourages us to believe that, if the centres are established and well run, the patients will be forthcoming in increasing numbers. Furthermore, the practice must be adopted in private by the profession throughout the whole country; the rural districts are the most difficult in this respect. When this is done we shall be making a gallant effort, and infallibly a fruitful effort, to attack our problem. At present in Scotland not more than 9 per cent. of the

* Being part of the valedictory presidential address to the Edinburgh Obstetrical Society.