

THE EARLY SIGNS AND SYMPTOMS OF CHOLELITHIASIS.

By SIR BERKELEY MOYNIHAN, BART., K.C.M.G., C.B., LEEDS.

It has probably been the experience of many surgeons to operate upon cases in which a diagnosis of cholelithiasis has been made, and to fail to find any stones within the gall-bladder.

In such cases, many years ago, I was content to drain the gall-bladder, and I found in a disturbing number of occasions that the bile was sterile. The gall-bladder looked normal in many of them ; but many presented those early signs of disease which I now recognize at a glance. In the cases which had been drained, a temporary abeyance of symptoms was almost constantly observed, but a recurrence rarely failed. A second operation was performed and the gall-bladder removed. In 1909 I described "A Disease of the Gall-bladder requiring Cholecystectomy", a disease unrelieved by cholecystotomy, in which the gall-bladder wall itself presented the evidences of chronic or subacute inflammation. There was a denudation or destruction of the villi, with a deposit of lipoid material, especially cholesterin esters, in the stroma of the mucous membrane. To this condition MacCarthy later gave the very appropriate descriptive name of the 'strawberry gall-bladder'. The appearance of the living membrane exactly resembles that of a ripe strawberry, the congested mucosa being studded with brighter yellow dots which end abruptly at the cystic duct.

There are more types of 'strawberry gall-bladder' than one, and the differences probably represent stages of gradual development. In its earliest, but quite definite, form, the mucosa is a little redder than the normal, and the slightly yellow specks show nothing but lipoid material. It is possible, as Professor M. Stewart has suggested to me, that in this stage the gall-bladder merely represents a local phase of the general condition hypercholesterolaemia, and that infection has not yet developed in its walls. In later stages the villi may become denuded of epithelium, and tiny ulcers soon develop upon the surface ; or cholesterin crystals, like fine grains of sand, may firmly adhere to, or be embedded in, its walls. In the latest stage the gall-bladder becomes thickened throughout, a firm and copious deposit of fibrous tissue is found in its walls, and calculi are often present.

This experience led to a closer study of the gall-bladder walls, and of the bacterial content of the bile in cases in which cholelithiasis was present, or was suspected ; and, as more and more cases have come under review, it has by degrees become clear that there are conditions of the gall-bladder, apart from calculous disease, which cause a close mimicry of the symptoms of gall-stones, and which can be successfully treated only by cholecystectomy. The diagnoses we make of abdominal diseases are often inferences only, and not certainties, however much we may be tempted so to regard them. If a patient suffers from repeated attacks of pain in the upper abdomen associated with a rigor, which is indicated upon the 'steep' temperature chart ; if jaundice, which is always present, deepens after the attack and gradually subsides until the next attack ; and if there is a progressive loss of weight : we do not hesitate to diagnose a floating stone in the common bile-duct. But the symptoms are not those of stone, but those of a cholangitis, which may be and usually is provoked by a stone, but which may be provoked by other conditions also, such as a series of hydatid cysts escaping down from the liver (as I have seen twice), or a pancreatic calculus in the ampulla, or a subacute or chronic pancreatitis. So it is, I think, with the diagnosis of stones in the gall-bladder. The condition that provokes the symptoms is an infection of the gall-bladder, set up it may be by stones, but not seldom existing in an early or advanced degree in the absence of stones. The

whole course of these diseases of the gall-bladder or of the liver, associated with gall-stones, is not yet by any means clear to us ; but our knowledge is widening little by little, and a broad conception of the whole problem is now possible.

By what means and through what channels is the gall-bladder infected ?

There are several possible avenues which may be traversed by invading micro-organisms.

1. INFECTION MAY ASCEND FROM THE DUODENUM, along the common and cystic ducts to the gall-bladder, or along the common and hepatic ducts to the liver.—This mode of infection, if it exists at all, is probably very rare. Bond's experiments have shown that pigments introduced into the rectum can soon be recognized in the discharge from the gall-bladder after cholecystotomy. It is certain, therefore, that organisms can travel directly upwards in these reflux currents. But they probably do not, because the duodenum is, as a rule, sterile, and is very rarely infected heavily. The downward current of bile flushes the common duct with a certain regularity.

2. INFECTION MAY DESCEND FROM THE LIVER.—Organisms reach the liver by way of the portal stream. As the blood passes round the liver lobules its organisms are caught up by the hepatic cells, which are the great 'destructors', and are rendered inert or killed. Some few may escape with their lives, perhaps at a time when the liver is momentarily overwhelmed by large numbers of organisms. Those which so escape gain access to the gall-bladder, and may form the nucleus of stones, which make haste to develop round them. The portal blood consists of two main streams, one from the alimentary canal and one from the spleen. The view has been generally held that the former is the current along which most of the micro-organisms travel ; and this no doubt is true. But remembrance should also be given to the possibility that organisms may be derived from the spleen. The association of diseases of the liver, and of gall-stones, with diseases that seem to have their origin or their chief development in the spleen, has recently become clearer. In cases of hæmolytic jaundice, 60 per cent of the patients suffer also from cholelithiasis ; with splenic anæmia, cirrhosis of the liver and gall-stones are both 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. About ten months ago I operated on such a case in which seven operations had been performed. I dealt with the bile-ducts as I have described, and then removed a spleen that was enlarged to approximately thrice the normal size. Since that time no attacks of pain or jaundice have returned, and as this is by far the longest interval of freedom the patient has had for some years, I am hoping that we may have cut off the source of supply of the infecting organisms to the liver. Splenectomy for recurrent cholelithiasis may be found necessary in similar 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, rather than 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 upon which gall-stones are deposited.

3. INFECTION MAY BE DERIVED FROM THE BLOOD.—We owe our knowledge on this subject to Rosenow.¹ 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, the bile-ducts, and some-

times of the stomach or duodenum. He suggested that such organisms have an 'elective affinity' for the tissues of the like kind to 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 that selects the tissue in this 'elective affinity', or whether it is the soil that alone provides the culture medium necessary for the growth of the germs which are scattered everywhere in the blood-stream—the soil selecting the germ—is not a matter of importance. The truth is well established by Rose-now's experiments and by clinical and pathological research in man, that micro-orga-nisms attacking the gall-bladder may reach it through the blood-stream.

The question has been most closely studied in connection with typhoid fever, but the results of the experimental work appear very conflicting. J. Koch,² in a patient who had 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; organisms being liberated and escaping through the mucosa into the gall-bladder to infect the bile. Chiarolanza³ 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, among them Girode, have however recovered organisms injected into the veins from the bile descending from the liver.

The investigations of Gosset, Loevy and Magrow⁴ show that calculi may originate inside the villi of the mucous membrane as minute collections of cells surrounded by cholesterol. As they grow they detach themselves from the wall of the gall-bladder, and becoming free within its cavity, they increase in size, and press upon each other until they become faceted. In any large collection of stones in the gall-bladder two or more generations may be recognized, groups created in the same period of infection being of almost equal size: the larger the stones the longer their existence. The conveyance of organisms by the blood-stream to the gall-bladder probably accounts for those cases (examples are not very infrequent) in which an acute cholecystitis or appendicitis follows rapidly upon such infections as tonsillitis and influenza; or pancreatitis or orchitis upon an attack of mumps.

4. INFECTION MAY REACH THE GALL-BLADDER FROM THE LIVER BY WAY OF THE LYMPHATICS.—The lymphatics of the gall-bladder communicate freely with those of the liver. Affections of the liver, changes in size and changes in the cells, have been noticed very irregularly by most surgeons. It would be well if a note of the size and condition of the liver could be embodied in all accounts of operations for gall-stones. If, along with the gall-bladder, a piece of the liver is removed, it should be submitted to microscopic examination. E. A. Graham⁵ noticed in a series of 30 cases that the liver was enlarged in 26. In the remaining four there was definite gross evidence of a previous or existing pathological change in the liver other than an enlargement. Inflammatory changes, chiefly of the nature of pericholangitis, were constantly observed in cases of acute and subacute cholecystitis. Graham suggests that an involvement of the liver is "so frequently an accompaniment of cholecystitis that the association must be practically a constant one."

Sudler⁶ has shown the intimate connection which exists between the surface lymphatics of the liver and the lymphatics of the gall-bladder through the attachments of the latter to the fossa in which it lies. The view is held that it is through these lymphatics that the gall-bladder may be infected from the liver, that cholecystitis is secondary to hepatitis. My own experience gives support to this hypothesis. Gross affections of the liver which could conceivably be regarded as antecedent to the gall-bladder infections found at operation are present in less than one-fourth of the total number of cases submitted to operation, and among these must be included all those cases where a splenic

condition could have been responsible for the hepatic enlargement or disease, and those in which these conditions were probably secondary to the gall-bladder disease. But the history of attacks in which enlargement of the liver has temporarily occurred (a sort of œdema or phlegmon) is occasionally to be obtained. In the examination of specimens by the microscope, cases are seen in which the peritoneal and subperitoneal coats are invaded by infection when the mucous and submucous coats are normal. In these cases infection must reach the gall-bladder either by the lymphatics, which is most probable, or possibly by the blood-vessels. When the infection arrives through the blood-vessels, it is the submucosa that is first affected in almost every instance.

The view has also been taken that the pancreatic inflammations which are found associated with cholelithiasis are due to a pancreatic lymphangitis. It is difficult to say with certainty how often the pancreas is affected in cases of cholelithiasis. Conditions such as swelling of the head of the pancreas, or hardening or fibrosis, are very difficult to assess, and mere palpation exposes an opinion based upon it to many errors. My estimate, a conservative one, I think, places the frequency of pancreatic implication in cholelithiasis at 12 per cent. The removal of a tiny portion of the pancreas gives valuable information, but it is not as often practised as it might be. Thiroloix and others have suggested that the free communications of the lymphatics of the gall-bladder and the bile-ducts with those of the pancreas, the whole forming one plexus, explain the origin of pancreatic inflammation secondary to cholecystitis and cholangitis; and they discredited the previously accepted view that the infection travels by way of the cystic and common ducts. And Deaver has added the weight of his great authority to this teaching. He writes that "most cases classed together under the general term of chronic pancreatitis are at first really cases of pancreatic lymphangitis, the infection being propagated from the gall-bladder and bile-ducts or from the pyloric region of the intestine along their efferent lymph channels, which come into intimate relation with those surrounding and embedded in the head of the pancreas."

We do not know, however, that the infection of the pancreas usually spreads from its surface inwards, rather than from the duct outwards to the body of the gland.

It is true that in cholecystitis the cystic gland is always enlarged, and that in cholangitis the glands along the duct may be so large and so hard as to make the discrimination between them and stones very difficult. In such cases the supra-pancreatic glands may also be enlarged. Nordmann's experiments seem, however, to controvert the view that invasion of the pancreas is primarily lymphatic. If in the dog a ligature is placed around the opening of the ampulla of Vater into the duodenum, the common bile-duct and the upper duct of the pancreas are then directly continuous one with the other. If, after this ligature, a virulent culture is introduced into the gall-bladder, acute pancreatitis develops. If the same culture is introduced and the cystic duct at once ligatured, no pancreatitis develops. In these experiments at least the conveyance of the infection from the gall-bladder to the pancreas is by the way of the ducts, and not through the lymphatics. And probably this is often, if not generally, true of the acute condition in man also.

5. INFECTION MAY REACH THE GALL-BLADDER BY DIRECT CONTINUITY.—This method is rare. Gastric and duodenal ulcers—especially the latter—may have the gall-bladder adherent to them. The duodenum is sometimes saved from perforation by having the gall-bladder soldered on to its outer surface. I have on many occasions found an inflamed appendix either adherent to the gall-bladder or in closest contiguity to it. Infection may penetrate the gall-bladder from its serous surface inwards in such cases; but in the aggregate they may be very few in number, and from the point of view of the development of gall-stones they are negligible.

The examination of a large number of gall-bladders shows that infection begins with almost equal frequency on the mucous surface and on the peritoneal coat. From the mucosa it penetrates by degrees deeper and deeper until the elastic coat has disappeared and the muscular coats are at last destroyed. An interesting observation that we have made shows that even an early invasion of the submucosa is often indicated by the develop-

ment beneath the peritoneum of the gall-bladder of a considerable deposit of fat. It would seem as though a warning had reached the serous covering that it must protect the general peritoneal cavity from the impending perforation of the coats of the gall-bladder. A fat deposit fulfilling the like purpose is often seen elsewhere. A gastric ulcer lying on the lesser curvature has often a large mass of fat developed around it; a septic kidney is swathed in thick masses of fat; a chronically infected appendix has a grossly thickened mesentery; diverticula of the left colon are covered with fat; and so on. The deposit of fat in the walls of the gall-bladder, at first along the line of the vessels, but later covering the whole organ, is often the most obvious sign of infection of the walls.

Gall-stones are found only in the later stages of an infection of the gall-bladder. It is not yet certain exactly where they are formed, whether within the cavity of the gall-bladder or in the mucosa. In the majority of cases they are probably formed within the cavity of the gall-bladder, being due to the clumping of organisms in the bile, and to the protective covering of these organisms by deposits of cholesterol. To impress upon students this truth, I told them long ago that "every gall-stone is a tombstone erected to the memory of the organisms dead within it." But the organisms are sometimes buried alive. Llewellys Barker, of Johns Hopkins, records the case of a patient who, at the age of 8, suffered from typhoid fever; at the age of 43 he was operated upon for gall-stones; from the interior of the stones living active typhoid organisms were recovered.

Much has been written of the 'latency' or the 'innocence' of gall-stones, but with one single exception I believe it to be true to say that gall-stones invariably cause symptoms. Not, it is true, those symptoms of advanced disease which alone were described in the text-books of medicine until the present day, but symptoms which are nevertheless sufficiently characteristic.

The one exception to the above rule is concerned with the solitary cholesterolin stone which often becomes impacted in the cystic duct. The cause of the formation of this single stone is not yet fully known; but it is I think certain that it is not due, as all other stones are, to infection. Such single stones are found in gall-bladders which show no sign of bacillary invasion, and the bile is constantly sterile; nor can any organisms be found in the centre of the stone. In the later stages, after many severe attacks of pain, the gall-bladder walls may become altered; but such changes are consecutive and not primary. The relationship between this type of stone, and indeed all forms of gall-stone, and the cholesterol content of the blood is not referred to here. It is a matter of the greatest interest and importance, but not immediately relevant to the points I wish to raise.

A single cholesterolin stone is an ovoid stone rarely larger than a nutmeg. Its surface is finely granulated; on section it presents a number of radiating marks, like the spokes of a wheel. It contains no organisms, and no other constituent than cholesterolin. It is apt to be caught in the pelvis of the gall-bladder at the entrance to the cystic duct, and is sometimes found just beyond the first segment of the valves of Heister. It causes no symptoms until it obstructs the duct, and that is the chief feature which clinically distinguishes it from all other forms of gall-stones. In all of these dyspeptic symptoms are aroused, and may be present for months or years before any obstructive symptom develop.

The first indication of the presence of a single cholesterolin stone is always a sudden attack of most agonizing pain, beginning in the epigastrium, spreading across the abdomen, and through to the tip of the shoulder-blade. The patient feels as though transfixed by a knife. The agony is terrible; the patient, unable to breathe (the diaphragm being in spasm), feels as though he would burst owing to the great and intolerable distention. Vomiting may bring relief. Relief, however it comes, comes in an instant. This absolutely abrupt onset and absolutely abrupt cessation of agony are quite characteristic of cystic duct obstruction, and are never seen so plainly in any other condition. When the pain persists for a few hours the gall-bladder may be palpable; the area over it remains tender and feels sore for many days afterwards. These typical symptoms, in the absence of an antecedent dyspepsia, enable a diagnosis of a solitary cholesterolin stone to be made with a considerable degree of confidence.

All other stones than this are due to infection, and infection, being present before stone formation, may give rise to symptoms which it is slowly becoming within our power to recognize. They are at present, however, suggestive rather than decisive. They are wholly referable to the stomach. Flatulence and fullness after meals, amounting sometimes to so great distress that a woman takes off her corsets or loosens them; 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; and 'acidity' and 'water-brash' are often mentioned by the patients.

None of these symptoms is severe, and none striking. It is rather in the association and persistence of them than in their 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 the 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 noted; 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 the rather more subdued but still sufficiently acute pain that probably indicates the passage of bile which is inspissated by thick mucus. In an intelligent patient these several steps may all be traced.

The first cause of these symptoms is uncertain. In recent years inquiry has been made into the association of cholecystitis and hepatitis. E. A. Graham examined portions of the liver removed with the gall-bladder in the operation of cholecystectomy, and found definite changes therein in 87 per cent of the cases. Now and again a fragment of the liver comes away with an adherent gall-bladder. In all such pieces we have found changes—advanced or slight—in the liver substance, and have attributed them to an extension to the liver from the gall-bladder. But it appears to be not unlikely that in many cases it is the liver that is first involved in the inflammatory process, and that the gall-bladder is attacked later by invasion of its lymphatics or by direct extension. The inaugural symptoms of cholecystitis may be due to lesions in the appendix, the liver, the gall-bladder, or all of these organs. Our present knowledge does not allow us to decide, but it is the stomach that is always blamed.

Pathology.—The changes produced in the gall-bladder by infections which reach it through the bile, the blood, or the lymphatics, produce changes that are slight but easily recognizable by the practised eye. Among the earliest of such changes is a loss of lustre and of colour. The surface is dimmed and whiter, the normal blue colour being lost everywhere except perhaps at the fundus; and the texture of the walls is a little thicker, and suppleness is lost, the elastic layer—as we know by examination of sections—being soon destroyed. A deposit of fat is found beneath the serous surface extending upwards along the vessels first, from the cystic duct. The whole gall-bladder is cedematous, and the fundus may show a patch of thickened and reddened opacity which feels almost like a tumour. The cystic gland is enlarged, and sometimes the glands along the common duct also. The pancreas may be enlarged, more especially towards the head.

The gall-bladder may be adherent to the stomach, or duodenum, or colon. There is, however, an 'adhesion' of the gall-bladder that is normal; it is in the form of a mesentery attaching the organ to the duodenum on the inner side and to the colon below. It is probably an extension of the mesogastrium to the right. It is easily recognized. Adhesions which bind the gall-bladder to any neighbouring structure are always evidences of an infection which, wherever originating, has spread at last to the parts around. It is probably true to say that every gall-bladder adherent in this manner has pathological changes so advanced within its walls as to warrant its removal.

When the gall-bladder is opened the bile is thicker in consistency and darker in colour than usual. The mucosa may be oedematous and turgid, and deep red or purple in colour. The villi at first are swollen and sodden, but later are smoothed away. The 'strawberry' appearance is commonly seen. In the later stage erosions, ulcers, and diverticula may appear, and little abscesses are sometimes found within the walls. Small shaggy papillomata are not infrequent. I have many times found them so placed that it was possible they had been washed into the cystic duct, and had obstructed it. These papillomata are frequently of a bright yellow colour from the presence of deposited lipid; they often possess an extremely tenuous attachment to the mucosa, and must often become detached. It is reasonable to suppose that under suitable conditions they may become the starting-point of calculi. In still later stages cicatricial tissue is found, and the walls appear thick, hard, and sclerosed. So advanced a change almost invariably depends, however, upon the long-continued irritation of gall-stones.

NOTE ON THE HISTOLOGY OF GALL-BLADDER DISEASE, BY DR. O. GRUNER.—A histological study of the walls of the gall-bladder which has been made in 100 cases, has shown that the lesions to be found may be grouped according to their relation to the muscular coat: (1) *Cases showing the chief changes in the mucosa and submucosa*; (2) *Cases in which the chief lesions appear in the subperitoneal tissues*.

When considered in this way, the channel of infection may be readily seen in the microscopic sections as being either by way of the mucosa or the peritoneum—in the former case presumably through the blood-stream, and in the latter through the lymphatics. In the cases in which the infiltration is all through the coats, that layer which shows the most intense infiltration is presumably the one in which the infection began; and the *peritoneal* infiltration in these cases is due to the fact that the organisms are making their way through from the mucosa into the subperitoneal layers by means of lymphatic channels. And furthermore, when the whole thickness of the wall is involved in this way, it appears probable that the infection has not been a single event, but has been repeated at least once, and very likely many times. This constitutes 'recurrent cholecystitis'.

1. *Mucosal Infections*.—In these cases the early changes noted are oedema of the folds or 'villi' and the appearance of a certain number of inflammatory cells. As the process increases in severity, the oedema spreads through the muscular wall into the subperitoneal layers, and at the same time there is a gradual accumulation of inflammatory cells in the same direction, and fat spaces make their appearance in the subperitoneal tissue.

Should the inflammation subside at this stage, the gall-bladder may return to normal, regaining its flaccidity and elasticity, though always retaining the tell-tale deposit of fat. But if the process does not come to an end—either because the circulation in the walls is hindered by the presence of stones, or because the invading organisms are of greater virulence—hæmorrhages occur from time to time, and a well-marked cellular infiltration becomes evident, so that the mucosa becomes very thick. Superficial hæmorrhages accompany the formation of ulcers, and the extension of organisms into the walls is accompanied by an interruption in the continuity of the muscle bundles, and a loss of elastic tissue. Once this stage has been reached the viscus can no longer retract, and the damaged muscle cannot attempt to expel its contents. Moreover, the sogginess of the walls makes them incapable of changing their shape; they can only be distended more and more if bile should happen to enter the bladder still further, or contract by reason of cicatrization.

A still later stage, with yet more advanced tissue changes, is reached when the mucosa is converted into a granulation tissue, all the normal structures having been lost. This is sometimes the effect of double infections of the walls, as for instance by streptococci combined with *B. coli*, or by anaerobic organisms associated with *B. coli*. Sometimes it is the effect of repeated infections by similar organisms each time. This stage may subside by a natural process of organization of the granulation tissue, in which case all structures of the normal wall are absent, and the gall-bladder is composed of a mass of fibrous tissue more or less laminated, and enveloped in dense pericholecystitic adhesions.

2. *Peritoneal Infections*.—The peritoneum becomes thickened by the intense engorgement of the vessels as well as by oedema, and these changes may involve the subperitoneal tissue also as far as the muscularis. In this case the elastic fibres are damaged in an early stage, and a number of changes affecting the mucosa become possible owing to a secondary disturbance of the conditions within the gall-bladder lumen. As the acute phase subsides, a fibrosis and permanent oedema of the outer coats becomes evident. Even here a re-infection may occur and lead to the formation of an extensive granulation tissue replacing the original wall, although the mucosa is still relatively unimpaired. The natural result in such a case would also be the formation of a chronic cicatricial contracted gall-bladder.

In this brief paper I am considering the question of infection alone. But before we can come to any final conclusions with regard to the formation of gall-stones, other

factors concerned are in need of discussion. Among these the most important is that of the cholesterol content of the blood. Dr. McAdam has been working upon this question in connection with some of my cases, and the following note which he has kindly written for me will serve to introduce the subject.

In the course of an investigation into the cholesterol content of the blood in various pathological conditions carried out by Miss C. Shiskin, M.B., and myself, a series of cases of cholelithiasis have been examined, before and after operation. Sixty per cent showed a hypercholesterolaemia, while the remainder gave normal values. The latter cases have doubtless shown an excess of blood cholesterol at one time or another, the gall-stones present being perhaps the relics of a former hypercholesterolaemia.

A subnormal value was found in a number of cases clinically diagnosed as cholelithiasis not included in the above list, since at operation no calculi were found. Although the presence of infection always tends to reduce the cholesterol of the blood, yet a chronic cholecystitis does not appear to reduce the cholesterol content in conditions of cholelithiasis, and a frankly low pre-operative value should make one suspect some other condition than cholelithiasis except in conditions of acute infection.

The immediate result of operative treatment is a marked fall in the cholesterol of the blood. This is most marked in cases of drainage of the biliary passages. The effects of the anaesthesia doubtless also play a part, while we have observed in all the conditions investigated, other than cholelithiasis, that operative procedures seem invariably to lead to an immediate loss of cholesterol in the blood.

But it is the cholesterol value of the blood some months after operation that appears to be of practical importance. Rothschild and Rosenthal⁷ have distinguished two types of hypercholesterolaemia in cases of cholelithiasis.

1. *Obstructive hypercholesterolaemia*, which is temporary, the cholesterol content of the blood returning to normal with the removal of the obstruction.

2. *Diathetic hypercholesterolaemia*, in which the excess of cholesterol is more or less continuously present. This condition may be intensified by the additional presence in the bile-passages of an obstruction to the completion of the metabolic cycle of the cholesterol. When there is this diathesis, the hypercholesterolaemia persists, even after the removal of the obstruction. Most of the cases, so far examined by us, belong to *Group 1*; a few, however, had a markedly high cholesterol content several months after cholecystectomy. These findings suggest that, in cases which show a distinct hypercholesterolaemia before operation, provision should be made for drainage of the bile in order to deplete the body of the retained lipoids. If a later examination should reveal a persistently high cholesterol content, then further accumulation of cholesterol may be controlled by dietetic measures.

Recent work has shown conclusively that there is no synthesis of cholesterol in the body, and that any addition to the total cholesterol content of the blood and tissues is derived from that present in the food. Free cholesterol is converted into cholesterol esters in the intestinal canal, from which they are absorbed and are distributed by the blood-stream to the body cells. As the result of metabolic activity in the cells, cholesterol is again liberated, carried by the blood-stream to the liver, and excreted into the bile, to be again re-esterized and re-absorbed from the intestinal tract. Thus an interference with this constant cholesterol metabolic cycle through drainage of the bile, in cases of diathetic hypercholesterolaemia, may be of considerable surgical importance.

REFERENCES.

- ¹ROSENOW, *Mayo Clinic*, 1916, 222.
- ²KOCH, J., *Zeits. f. Hyg. u. Infektionskrankh.*, 1909, lxxii, 1.
- ³CHIAROLANZA, *Ibid.*
- ⁴GOSSET, LOEVY, AND MAGROW, *Bull. Soc. Biol.*, 1920, i, 1207.
- ⁵GRAHAM, E. A., *Arch. of Surg.*, 1921, ii, 92.
- ⁶SUDLER, *Johns Hop. Hosp. Bull.*, 1901, xii, 126.
- ⁷ROTHSCHILD AND ROSENTHAL, *Amer. Jour. Med. Sci.*, 1916, clii, 394.