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DISEASES OF THE GALL-BLADDER*

BY

CECIL P. G. WAKELEY, D.Sc., F.R.C.S.,
F.R.S.E.

FELLOW OF KING'S COLLEGE, LONDON; SENIOR SURGEON AND DIRECTOR OF SURGICAL STUDIES, KING'S COLLEGE HOSPITAL; CONSULTING SURGEON TO THE MAUDSLEY HOSPITAL AND TO THE ROYAL NAVY

It is a curious fact that although the gall-bladder is not essential to health it is very rarely absent in man. In those animals in which there is no gall-bladder, such as the horse, deer, pigeon, and rat, the sphincter of Oddi is often very well developed.

Double Gall-bladder

From the developmental standpoint one would expect a larger percentage of abnormalities, as the gall-bladder is developed as an outgrowth from the primary hepatic diverticulum; this outgrowth is sometimes bifid, giving rise to complete division into two, or the subdivision of the fundus. The first recorded case in which a double

gall-bladder was removed at operation was that of Sherren, who in 1910 operated upon a woman aged 52, and removed the specimen (No. 561/31) which is now in the Royal College of Surgeons of England. Schachner, in 1914, operated upon a woman of 52 for cholecystitis, discovered a double gall-bladder, and drained both sacs. A case which came under my care in 1923 at King's College Hospital was that of a woman, aged 56, who had definite signs of chronic cholecystitis with gall-stones. At operation I removed a double gall-bladder, one sac containing stones and the other containing bile and mucus only (Fig. 1).

FIG. 1.—Drawing of double gall-bladder removed at operation. One sac contained gall-stones, but the other contained only bile.

With the advent of cholecystography and the submission of innumerable gall-bladders to x-ray examination each year, only a very few cases of double gall-bladders are discovered. In fact, Graham was not able to find a single example in 1,218 cases examined by cholecystography. However, Cave has reported two cases of double gall-bladder which were discovered by means of cholecystography, but confirmation by laparotomy was not forthcoming.

The gall-bladder during embryonic life is embedded in the substance of the liver, and occasionally this condition persists throughout life, and may cause the surgeon some trouble if cholecystitis should supervene. Although intrahepatic gall-bladders are found in such animals as the stoat, shark, ferret, pig, wart-hog, and many marsupials,

they must be looked upon as very rare occurrences in adult human beings. During the second month of human foetal development the gall-bladder is quite buried in hepatic tissue, and at birth a small proportion of infants

FIG. 2.—Various positions of the gall-bladder in relation to the under surface of the liver. (a) Normal position as seen in the infant. (b) to (e), Different types of intrahepatic gall-bladders. (f) Normal position as seen in adult life.

are found to have complete or partial intrahepatic gall-bladders. However, during the first six months of post-natal life the gall-bladder becomes more prominent and tends to leave the liver bed (Fig. 2).

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Torsion

Passing from an intrahepatic gall-bladder at one end of the scale we find a gall-bladder with a well-marked mesentery at the other, and this condition predisposes to torsion (Fig. 3). A well-formed mesentery is seen in

FIG. 3.—Diagram showing a freely mobile gall-bladder possessing a long mesentery. Such a case as this would be liable to torsion of the gall-bladder.

4 to 8 per cent. of gall-bladders, and yet only a very few of these are free, because the fundus of the gall-bladder becomes adherent to the omentum or the duodenum. Probably a partial rotation of the gall-bladder takes place in some of these cases, leading to congestion and even inflammation, so that adhesions are formed between the gall-bladder and neighbouring structures.

Another factor predisposing to torsion is a long cystic duct. The cystic duct is normally $1\frac{1}{2}$ inches in length, but variations are common, and cases are on record in which the cystic duct was fully $3\frac{1}{2}$ inches long. The presence, or absence, of gall-stones does not seem to have any definite bearing on the condition, as in some recorded cases stones have been found while in others they have been absent. In the case I described in the *Clinical Journal* in 1927 the gall-bladder contained six faceted stones.

Cases of torsion or volvulus of the gall-bladder are rarely diagnosed, and cases are still reported in which the condition has been recognized only at necropsy. Ormos records a case in a woman, aged 71, who died with symptoms of haemorrhagic colitis. When the abdominal cavity was opened at the necropsy a very enlarged gall-bladder was found with a pedicle, which originated at the junction of its middle and lateral thirds; the gall-bladder was twisted round the pedicle and was necrotic. It is curious that torsion of the gall-bladder has been recorded in females only, and the majority of these have been aged.

There is often a history of previous pain in the abdomen, generally right-sided. A tumour is usually present. Unlike volvulus of the intestine which has gone on to gangrene, necessitating enterostomy, with a high mortality, torsion of the gall-bladder has no operative mortality, because usually the mobility of the gall-bladder renders the operation easy.

Traumatic Lesions

During recent years, with the ever-increasing motor traffic, transport has been responsible for the greater number of traumatic abdominal lesions.

Pure bile is sterile, but if any inflammation of the biliary passages has occurred, organisms will be present. If a considerable quantity of bile escapes suddenly into the peritoneal sac, acute peritonitis is certain to follow sooner or later, whether organisms are present or not; slight jaundice arises from absorption of bile by the peritoneum, and this may also be found in the urine. A more gradual escape of the secretion will probably lead to the formation of a localized intraperitoneal abscess or collection of fluid associated with jaundice, and possibly clay-coloured stools. In the case of a penetrating wound, bile and blood will escape on the surface, and septic peritonitis is almost sure to follow. Exploratory laparotomy should always be carried out in these cases when

the initial shock has passed off. Removal of the gall-bladder, when damaged, is not difficult as a rule. However, damage to the liver or bile ducts may be a factor which mitigates against success.

Cholecystitis

Inflammation of the gall-bladder is responsible for the greater proportion of diseases of that organ. For convenience, inflammations of the gall-bladder may be divided into: (a) acute cholecystitis, and (b) chronic cholecystitis. In the main it may be said that cholecystitis is a chronic progressive disease, which begins with infection of the gall-bladder in early life, quite often gives rise to biliary colic in middle life, and if not treated by surgical means will cause serious complications in later life.

It cannot be stressed too forcibly that infection of the gall-bladder is frequently the precursor of such crippling conditions as chronic arthritis, toxic myocarditis, toxic nephritis, toxic hepatic cirrhosis, and even of toxic mental derangement. During the last ten years the Surgical Research Laboratory in Edinburgh, under the able direction of Professor D. P. D. Wilkie, has done much to elucidate the pathology of chronic cholecystitis, and to place this clinical condition on a sound scientific foundation.

ACUTE CHOLECYSTITIS

The question as to the best form of treatment in cases of acute cholecystitis still gives rise to controversy, and no consensus of opinion has been forthcoming in this country or among American or Continental surgeons. It is useless to postulate hard-and-fast rules governing the treatment of such an important surgical condition, as each case must be treated on its merits, but nevertheless there are certain facts which have become established and crystallized during the last ten years. Perforation of the gall-bladder calls for immediate operation, and it is the prodromal signs which precede perforation that are so important if we wish to lessen the mortality of this acute abdominal condition. Personal experience is always a help in coming to a conclusion as to the best form of treatment in surgical procedure.

During the last twenty years I have operated upon twenty-six cases of acute cholecystitis; in six of these the patient died—a mortality rate of 23.1 per cent. This is, to my mind, much too high a mortality rate, and I am convinced that acute cholecystitis calls for conservative surgery; in my cases some of the patients died because too much was done in the acute stage of the disease. A similar mortality rate is recorded for acute cholecystitis in some of the American clinics, and yet immediate operation is advocated. These cases require careful and constant supervision on the part of the surgeon, as immediate operation may be necessary at any period during the first three weeks of the illness. In general it may be said that when the patient is seen the first day of the illness, unless perforation is considered imminent, conservative measures may be adopted. During the first week a waiting policy may be pursued. If, however, the patient is not progressing, or the temperature remains elevated and the pain persists, or the gall-bladder increases in size, then operation should be performed. It is always advisable to remove the gall-bladder after an acute attack of cholecystitis, and a month after the disappearance of all symptoms is a useful time to allow.

CHRONIC CHOLECYSTITIS

If it is an accepted fact that chronic cholecystitis frequently begins early in life and causes toxic manifestations during middle and later life, then surely the rational form of treatment is removal of the gall-bladder. Yet how often one finds patients with chronic

disease of the gall-bladder being treated with hexamine, with the idea of disinfecting this diverticulum. In my opinion hexamine by the mouth is useless, and even huge doses given intravenously have had no effect, in my hands, in causing any disinfection of the gall-bladder.

The question of diagnosis is an important one, because it must not be thought that before chronic cholecystitis is diagnosed jaundice or colic must have been recorded. Nor are we to assume that the typical case is the "fair, fat, fertile, flatulent female of forty." There is a tendency to-day to belittle clinical history and clinical examination, and to allow the biochemist or the radiologist to make the diagnosis of gall-bladder disease. How often the patient is told that the gall-bladder is quite normal because the cholecystogram does not show any abnormality, or that there cannot be any stones in the gall-bladder because biliary drainage by means of a duodenal tube and the administration of magnesium sulphate does not reveal any cholesterol crystals or calcium bilirubin. It is wise always to consider the gall-bladder "suspect" in middle-aged persons who have some manifestations of chronic toxæmia, unless some other focus of infection is discovered.

Chronic appendicitis may be the forerunner of a similar disease in the gall-bladder, and the same type of organisms may be discovered in the wall of both these structures. Chronic cholecystitis is due to a blood-borne streptococcal infection which is situated in the wall of the gall-bladder, and plays a definite, yet very important, part as a focus of infection. To my mind the gall-bladder is still belittled and unconsidered, and is often passed over without comment when medical men are trying to discover the possible source of septic infection in these middle-aged patients.

The treatment of chronic cholecystitis is complete removal of the chronically infected gall-bladder—namely, cholecystectomy. As a disease chronic cholecystitis has been known from time immemorial, for gall-stones have been found in the most ancient of mummies. Medical treatment and diet can do a certain amount of good, but cannot cure the condition and cannot prevent complications from occurring. Perhaps the most satisfactory of the bile-salt preparations is dehydrocholic acid, which can be given to patients twice a day for a period before and after operation. It acts by causing a thinning of the bile, but has no action whatsoever on the evacuation of the bile in the gall-bladder.

Gall-stones may ulcerate into various viscera, such as the stomach, duodenum, colon, or pelvis of the kidney. The commonest by far is ulceration into the duodenum, owing to its anatomical proximity. However, the duodenum is the widest part of the small intestine, and impaction and obstruction do not occur in it. It is in the narrowest part of the small bowel, the distal ileum, that acute obstruction arises. Acute intestinal obstructions due to gall-stones are not common, but they are well known and are found in aged patients, the majority of patients being over 70 years of age. The gall-stones illustrated in Fig. 5 were removed from the ileum of an elderly patient who was admitted to hospital with acute intestinal obstruction which was thought to be due to a growth of the colon.

There can be no doubt that cholecystography can be of great value in the diagnosis of organic disease of the gall-bladder, but it only tells us that the gall-bladder does or does not concentrate well in general terms. Probably, in the future, when better technique both in the administration by mouth or intravenous injection of a suitable dose of sodium tetra-iodophenolphthalein has been attained, we may obtain results which are far more valuable to the clinician in the interpretation of gall-bladder disease.

Gall-stones contain a certain amount of calcium salts, and although this is usually a low percentage, it accounts for the fact that radiographic examination gives positive results in some cases. It is a wise procedure to take a skiagram of the gall-bladder area prior to undertaking cholecystography, since, in quite a number of cases, gall-stones will be demonstrated and the latter investigation will not be necessary.

A barium meal may give the practitioner considerable help in cases of vague dyspepsia in which the clinical history and examination reveal nothing. In some cases the duodenal cap is indented by an enlarged and adherent gall-bladder (Fig. 4).

FIG. 4.—Barium meal showing the deformed duodenal cap due to pressure of an enlarged adherent gall-bladder.

There is bound to be a small proportion of cases in which the gall-bladder is "suspect," and yet there is no definite evidence to go upon. It may be that all sources of infection have been eliminated in chronic rheumatoid manifestations, and yet the patients are no better; in such cases it is justifiable to explore the gall-bladder. In several cases of chronic rheumatoid arthritis in which I have performed cholecystectomy the results have been most gratifying.

The so-called "strawberry gall-bladder" is not a disease in itself, but is a condition in which the epithelium and stroma of the gall-bladder have become infiltrated with lipoids and cholesterol, and in the stroma large foamy cells of quite characteristic appearance occur. The condition is associated with cholecystitis, and gall-stones are quite often present. It is interesting to note that the strawberry gall-bladder, or, as it is sometimes called, "cholesterosis," can be produced experimentally in rabbits by feeding the animals on cholesterol and injecting streptococci into the gall-bladder wall. There seems very little doubt that this condition, to which so much attention has been given of late, is in reality the aftermath of chronic infection of the gall-bladder.

The operation of cholecystectomy for chronic cholecystitis must not be looked upon as a serious one provided adequate pre-operative and post-operative treat-

ment is carried out. Modern operative technique only gives a low mortality, and in 467 cases which have come under my supervision during the twenty-year period 1915-1935, I have lost twenty-six, a mortality of 5.5 per cent. This corresponds almost exactly with some American statistics, for Fowler of Brooklyn has reported a mortality of 5.9 per cent. in 1,206 cases, while Erdmann of New York reports a record of 525 operations with a mortality of fifteen cases, equalling 2.85 per cent. Thus this operation, which had a high mortality thirty years ago, may be said to have an extremely low one at the present time.

Analysis of 505 Cases of Cholecystectomy, 1915-35

Total Mortality: 7.3 per cent.

Diagnosis	Number of Cases	Sex	Deaths	Per-centage	Total
Acute cholecystitis ...	26	Females 21 Males, 5	5 1	23.8 20.0	23 %
Chronic cholecystitis ...	467	Females, 386 Males, 81	21 5	5.4 6.2	5.5 %
Malignant cholecystitis	10	Females, 8 Males 2	4 1	50.0 50.0	50.0 %
Torsion of gall-bladder...	1	Female	0	Nil	Nil
Double gall-bladder ...	1	Female	0	Nil	Nil

Malignant Disease of the Gall-bladder

Carcinoma of the gall-bladder is in itself a rare disease, but it would be excessively rare if patients with chronic cholecystitis were more often submitted to operation, for fully 95 per cent. of cases of malignant disease of the gall-bladder are produced by calculi. Ten cases of malignant disease of the gall-bladder have come under my care, and in all these calculi were present. Most of these were operated upon under the mistaken diagnosis of chronic cholecystitis with gall-stones, and it is a curious fact that the operation is usually quite easy, and there is no suspicion of malignant disease until the gall-bladder is opened and submitted to histological examination. We shall only come to know the true incidence of carcinoma of the gall-bladder when every operation specimen is submitted to full histological examination.

FIG. 5.—Gall-stones which had ulcerated through the gall-bladder wall into the duodenum and become impacted in the lower ileum.

Diseases of the gall-bladder, which in the main are due to infection, are quite common, and can only be cured by surgical measures. Radical operation gives a low mortality rate and results in a cure of the condition in most cases; it prevents innumerable complications and sequelae in later life, not to mention malignant disease.

BIBLIOGRAPHY

- Cave, P.: *Lancet*, 1931, i, 751.
 Erdmann, J. F.: *Ann. of Surg.*, 1935, ci, No. 5, 1139.
 Fowler, R. S.: *Amer. Journ. Surg.*, October, 1933, p. 53.
 Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S.: *Diseases of the Gall-bladder and Bile Ducts*, 1928.
 Illingworth, C. F. W.: *Brit. Journ. Surg.*, 1929-30, xvii, 203.
 Newman, C.: *Lancet*, 1933, i, 785.
 Ormos, P.: *Gyogyazat*, 1922, xii, 484.
 Wakeley, Cecil P. G.: *Brit. Journ. Surg.*, 1927, xv, No. 58, 334.
 Idem.: *Clin. Journ.*, June 1st, 1927, p. 257.
 Wilkie, D. P. D.: *British Medical Journal*, 1929, ii, 37.

**SOME IMMUNOLOGICAL ASPECTS OF
THE CURE AND PREVENTION
OF DIPHTHERIA ***

BY

J. MENTON

BACTERIOLOGIST TO THE COUNTY OF STAFFORD

From the clinical point of view this subject can be limited to the consideration of passive and active immunization and the immunological accidents attending these procedures. In passive immunization ready-made antitoxin is introduced into the patient's circulation. In active immunization the patient manufactures his own antitoxin as the result of natural or arranged antigenic stimuli. Passive immunization is of short duration, and is used for treatment. Active immunization stimulates a tissue habit which lasts for years, and is the ideal prophylactic.

The theme of this address centres round a patient who died of acute anaphylaxis nearly a quarter of a century ago. A boy, aged 9 years, suffering from scarlet fever, was admitted to an institution. As cross-infection was prevalent he was given on admission 500 units of diphtheria antitoxin intramuscularly. The acute course of the scarlet fever was uneventful. Three weeks later he was allowed up and was transferred to a convalescent ward. A week later he developed acute faucial diphtheria. He was then ordered 2,000 units of diphtheria antitoxin. Immediately after the injection he showed symptoms of acute respiratory distress and collapsed and died in fifteen minutes.

Active and Passive Immunization

The prophylactic use of antitoxin was more prevalent then than now. Many years previously attention had been drawn to the temporary nature of passive immunization. Globulin solution remains slightly longer in the blood than unconcentrated serum, but it is doubtful if any form of antitoxin is retained in sufficient quantity to prevent infection three weeks after administration. Its use for this purpose merely gives a false sense of security; sensitizes the patient and increases the risk of unpleasant reactions if he should afterwards need serum treatment; may lead to a higher carrier rate; and may delay the development of natural active immunity. Some people recommend during an epidemic an initial dose of 1,000 units of antitoxin followed by active immunization fourteen days later, but there are scientific objections to this procedure. As one antigen now available can produce a good response in fourteen days it is better to segregate and actively immunize the susceptibles at once if their swabs are negative. Those showing positive swabs may be virulent carriers—if so, they are already immune; or they may be incubating the disease—if so, clinical signs will soon appear and antitoxin can then be injected. The old objections to active immunization during an epidemic do not hold if toxoid preparations are used. A small number may develop the disease before protection is established, and parents should be warned of this possibility.

* Read before the North Staffordshire Medical Society, June 6th, 1935.