rise to stomach trouble, not by reducing the original daily dose, but by introducing after every two days, later every second day, a free day—that is, a day without digitalis.

Of course, regular observation of the patient must determine which scheme we adopt in each individual case. Once we reach a frequency of 80 in the recumbent position it may be wise to reduce the daily dose from, let us say, 3 decigrams to 2, but not less. With further improvement we may even find it possible to give the full dose every third day only; and, curious to say, this method allows us to keep the patient and his heart continuously under a fully active dose of digitalis without any signs of intoxication. This treatment may be continued for an indefinite number of relatively healthy years.

Clinical experimental proof of the excellent success of this simple scheme is easily obtained in this category of patients. By carefully gauging the ventricular rate and the pulse deficit, and especially by making graphic records, it will be found that in regularly living patients both values are lower on the free days than on the days of digitalis administration. It is quite clear that the dose works most actively on the second day. If the patient is well you can introduce a second free day, and find out by counting the pulse whether digitalis action is still operative. This objective evidence will give the decision of how long intervals may be allowed. The same very simple tactics may have the same beneficial effect in treating other forms of heart trouble which require continuous digitalis treatment.

The only real difficulty to overcome is the opposition of the doctor, who has been taught, and found out for himself, that digitalis treatment should not be pushed for too long a period. In such cases it is the doctor who has to be treated, and his opposition may be overcome by making it clear that although this may involve treatment continued for years, as a matter of fact it is really intermittent treatment, which differs from the routine methods only in respect of shortness of the intermissions.

There are two important advantages in this scheme. First, the free days can be used for carrying out another treatment—for instance, with diuretics. The stomach is thus not overburdened by drugs, and we are assisted in this other treatment by the fact that it also is being prosecuted every second or third day. The other advantage is that after having stabilized the heart rate and having found out with what dosage this success was attained, we can send the patient home and tell the doctor, and even the patient, that the treatment should be continued until the next visit of the patient, and that the daily dose should never be altered, but longer intervals should be introduced when the pulse becomes too slow. On the other hand, the intervals should be shortened or the drug be given day by day continuously if signs of a worse condition begin to appear.

Ladies and gentlemen, it would have been very pleasant, at least to me, to illustrate what I have said with the histories of a great number of convincing cases. But this would be completely out of place, and every physician has the means to provide himself with proof at the bedside. On the other hand, I must be prepared to hear that I have not brought any news to you, but only that which you all knew and did already. In this case I can only state that what I have been saying is concordant, even almost identical, with the conclusions William Withering gave us out of his own experience. At any rate, I am in the very best company.

Perhaps one word more may be added. I wish to impress again upon my audience, particularly upon the students present, that I do not despise scientific research in the field of medicine. On the contrary, anyone who has watched my work must know that I have dived deeply into pure biology to get to an understanding of the intimate nature of certain clinical phenomena. But, as I said, medicine has two faces, and asks for two sorts of faithful servants: the pure scientist, and he who is solely the practitioner. You need not leave your own country to find the most wonderful examples. There is William Harvey, the thinker and the first experimenter, the author of *De Motu Cordis*, the tercentenary of the publication of which was celebrated less than two years ago; there is also William Withering,

whose digitalis work was purely clinical, and whose name is now celebrated here, where he worked out his problems. Let us try to follow both of these men, to the benefit of mankind; but be pure and careful scientists in all your theoretical work, and whole-hearted physicians at the bedside. To the physician I say, never forget Withering, who, knowing nothing at all about the intimate action of digitalis on the heart, nevertheless gave the profession a work of undying value in his account of the foxglove.

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An Address

ON

CHOLECYSTITIS AND GALL-STONES.*

BY

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CHOLECYSTITIS due to infection of the gall-bladder is one of the commonest of abdominal affections. In the course of time it often leads to the formation of gall-stones, from which about 10 per cent. of the population suffer. The causes of gall-stones may be considered under three headings.

(A) Infection.

This may be derived from any septic source anywhere in the body. The most important sources are the mouth, nose, throat, intestines, and especially the appendix. The most common organisms found in the walls of the gall-bladder are the streptococcus and the *Bacillus coli*; the staphylococcus, pneumococcus, *Bacillus pyocyaneus*, *Bacillus welchii*, and *Bacillus typhosus* are also sometimes discovered in the walls or contents of the gall-bladder.

1. The organisms may reach the gall-bladder through the blood, either by the cystic artery direct to the gall-bladder, or through the portal vein to the liver. The former is probably the most common, and carries organisms from distant parts, such as the mouth and throat, whereas the portal vein carries infection from the intestines. The organisms are then excreted by the liver into the bile, and thus reach the gall-bladder. *B. coli communis* infection of the urinary organs is very common in women, especially during pregnancy and after labour. This condition is frequently associated with cholecystitis, probably due to vascular spread of the infection.

2. The infection may spread through the lymphatics, especially from the liver, pancreas, or appendix.

3. It may invade the gall-bladder directly from any inflamed organ in contact with or adherent to it, such as an inflamed appendix or duodenal ulcer.

4. Infection may spread up from the duodenum along the bile ducts, especially if there is achlorhydria, as there is in about 40 per cent. of gall-stones. The absence of free hydrochloric acid allows the *Bacillus coli* to flourish in the duodenum.

It is very doubtful if gall-stones ever form in the absence of infection, which generally lurks deeply in the walls of the gall-bladder; but it is commonly believed that the single cholesterol stone forms in an aseptic gall-bladder, for there may be little sign of inflammation. It is probable, however, that the inflammation which may cause the stone to form subsequently disappears.

The stones generally form round a nucleus made of agglutinated bacteria, precipitated mucus, or debris from the epithelial walls, and above all from broken off papillae, perhaps laden with cholesterol. The crystalline deposits of cholesterol, calcium salts, or pigment are held together by an organic matrix derived from the inflamed gall-bladder.

(B) Cholesteræmia.

An excess of cholesterol in the blood may be due to obesity, pregnancy, menstruation, or a diet too rich in

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fats. This may lead to deposition of cholesterol crystals from the bile and to the formation of gall-stones in an inflamed gall-bladder.

(C) *Stasis.*

Stasis of bile in the gall-bladder or elsewhere naturally tends to infection, concentration of bile, and the deposition of stones. Stasis may be due to lack of exercise; to obstruction of the cystic duct, which is less than one-tenth of an inch in diameter, by a swollen mucous membrane due to cholecystitis; by valvulation, kinking, or torsion of the neck of the gall-bladder; and frequently stones are associated with new growths, such as adenoma, papilloma, and primary or secondary carcinoma of the gall-bladder.

SYMPTOMS AND SIGNS.

In 1918 Moynihan described the inaugural symptoms of cholecystitis. It is difficult to say when gall-stones begin to form in an inflamed gall-bladder. The following are the most important symptoms of cholecystitis: flatulent dyspepsia of an irregular and most intractable type; a feeling of fullness, weight, oppression, or sinking in the epigastrium and right hypochondrium; attacks of chilliness, with gooseflesh; pain over the right hypochondrium, passing through to the lower part of the right shoulder-blade. Later, belching, nausea, and vomiting. Flatulence may be so troublesome that the patient frequently has to loosen her garments. There is often a distaste for eggs and fatty and acid foods.

During the presence of symptoms, there may be cutaneous and deep tenderness in the right hypochondrium and epigastrium, and, as pointed out by Ryle, superficial tenderness over the third to the tenth dorsal spine. An enlarged gall-bladder may be felt, especially on deep inspiration.

The above symptoms are, in the main, due to cholecystitis. When gall-stones have formed, and especially when they tend to invade and travel along the ducts, more severe and striking symptoms develop, such as biliary colic. This is very severe, comes on quite suddenly, lasts from a few minutes to several hours, and then it disappears as suddenly as it came. When it is not accompanied or followed by jaundice, it is due to a stone blocking the orifice or channel of the cystic duct. Relief may come by the stone falling back into the gall-bladder, or occasionally passing into the common bile duct. Later in the disease biliary colic may be associated with jaundice, and then indicates obstruction of the common bile duct. As the orifice of this duct at the duodenal papilla is very small (less than 1/12 inch in diameter), quite small stones may fatally obstruct it. More commonly, however, stones of larger size, having passed through a dilated cystic duct, become impacted in the upper reaches of the common bile duct. Stones may lurk in the common bile duct for years without causing jaundice, because they may not obstruct for a sufficient length of time.

DIAGNOSIS.

A careful study of the clinical history, symptoms, and signs generally enables us to make a correct diagnosis of cholecystitis or of gall-stones, but as the two conditions merge into each other it is not always easy to tell when gall-stones have actually formed.

An enlarged gall-bladder, or persistent or recurrent tenderness under the right costal margin, is very suggestive of inflammation of the gall-bladder. The tenderness is higher and further out than that over a duodenal ulcer; but there may be considerable difficulty in distinguishing these two conditions, especially when there is hunger pain and hyperchlorhydria. When severe colic, with or without jaundice, develops it is much in favour of gall-bladder disease, but sometimes the pains associated with duodenal ulcer may be very severe and due to pylorospasm. Radiography after an opaque meal, and the examination of the faeces for blood, are then invaluable.

Appendicitis may be easily confused with cholecystitis, especially when the appendix or gall-bladder is misplaced. For instance, the inflamed appendix may be high up and in contact with the gall-bladder, or lying high up behind the ascending colon, and give local signs closely

resembling those of cholecystitis. Similarly, the gall-bladder may be very low down, and give local signs closely resembling those of appendicitis. Sometimes right renal colic closely resembles biliary colic; radiography, cystoscopy, pyelography, and cholecystography are then invaluable.

In doubtful cases simple radiography should always be tried first, for this may show opaque gall-stones, renal calculi, or other characteristic opacities, which may or may not make an opaque meal or cholecystography superfluous. The shadow of an opaque meal in the stomach, duodenum, or colon may be distorted and indicate pressure or traction of the gall-bladder upon the stomach, duodenum, or colon.

The discovery of cholecystography by Graham and Cole¹ in 1923 was a great advance; it has already borne much fruit, and promises more to come when its merits and possibilities are more widely appreciated. Whereas simple radiography, even with the aid of opaque meals, rarely gives any indication of cholecystitis or of small or non-opaque gall-stones, Graham's method helps us to an early diagnosis of all these. It is particularly valuable in demonstrating obstruction of the bile ducts before cholecystitis has developed or become recognizable. Obstruction of the cystic duct by a stone too small to cast a shadow, by torsion, valvulation, or bands, can thus be recognized and radically treated at an early stage. It also estimates the power of the gall-bladder to concentrate and to expel bile, and of the liver to secrete it. These add much to the range and value of diagnosis and prognosis.

Graham's method is invaluable in the differential diagnosis of diseases of the gall-bladder from those of the alimentary and urinary tracts. The pure dye,* given with care and in suitable doses, rarely does any harm, but it ought not to be given to patients suffering from heart disease, atheroma, abnormal blood pressure, or to those affected with chronic jaundice, cholangitis, or threatened with uraemia or hepatic insufficiency. The test is a little more accurate when the drug is given intravenously, but it is more convenient, and is often considered safer, when given by the mouth. Various writers estimate the accuracy of this method of diagnosis as from 80 to 97 per cent.

Gastric analysis, and an examination of the duodenal bile, sometimes help considerably in the diagnosis of diseases of the stomach and duodenum from those of the gall-bladder. The discovery of abnormalities, such as bacteria, pus cells, or cholesterol crystals, in the bile withdrawn through the duodenal tube points strongly to disease of the biliary tract.

When jaundice is associated with biliary colic the diagnosis becomes much easier, for these symptoms always indicate obstruction of the common bile duct by stone or other foreign body.

In over 80 per cent. of cases of calculous obstruction of the common bile duct the gall-bladder is not enlarged, as pointed out many years ago by Courvoisier and Murchison; but occasionally there may be coincident obstruction of the cystic duct, and then the gall-bladder may be palpable.

So far, cholecystography has rarely been successful in showing the smaller stones that commonly obstruct the common bile duct.

When the obstruction is due to pancreatitis or growth the gall-bladder is usually enlarged and palpable, and typical biliary colic is absent. These facts, and the absence of colic, serve to distinguish these forms of obstruction from that due to gall-stones.

INDICATIONS FOR OPERATION.

If the symptoms of cholecystitis or of gall-stones fail to subside, or recur after careful medical treatment, it is generally wise to operate early in order to prevent serious complications. Early operations have a mortality of under 2 per cent., whereas late ones, especially for perforative cholecystitis or for stones impacted in the common bile duct, with infective cholangitis, may have a very high mortality.

The mere demonstration of gall-stones or of cholecystitis is not always a sufficient indication for operation. In

* Graham and Cole (*Diseases of the Gall-bladder and Bile-ducts*, 1929, pp. 262 and 264) prefer the intravenous administration of 2.5 grams of phenoltetraiodophthalein. For oral administration they use 4 to 5 grams of tetraiodophenolphthalein.

many people gall-stones cause no appreciable discomfort, or only such as can be relieved by medical treatment. But we have no medical means of dissolving or evacuating gall-stones; and although they sometimes pass spontaneously along the ducts, or escape through fistulae into the gastro-intestinal tract, they are very rarely completely evacuated in either of these ways.

The following are some of the serious consequences of delay before operating for the removal of gall-stones.

1. Suppuration, perforation, peritonitis, acute and chronic septicaemia, osteo-arthritis.
2. Jaundice and cholangitis, with risk of cholaemia and haemorrhage.
3. Cancer of the gall-bladder, which develops, according to Rolleston and others, in at least 5 per cent. of all cases of gall-stones. The danger of this complication is greater than that of operation.
4. Intestinal obstruction by gall-stones which have ulcerated into the bowel.
5. Pancreatitis.
6. Hepatic insufficiency.
7. Cardiac degeneration.

When possible, it is safer to wait for a quiet interval before operating, so as to allow thorough investigation and preparation of the patient. Fortunately, the acute symptoms, such as colic, jaundice, and fever, generally subside under careful medical treatment; for, unlike the appendix, the gall-bladder rarely perforates or sets up spreading peritonitis.

When signs of spreading peritonitis do develop, or an enlarged, tender gall-bladder can be felt, and symptoms such as vomiting, fever, and rigors do not abate, or signs of acute pancreatitis develop, an immediate operation is necessary. Similarly, when jaundice, associated with fever, fails to clear up under medical treatment, an early operation offers the best hope.

These emergency operations should be limited to simple drainage of the gall-bladder or common bile duct. Radical operations can be carried out later when the patient is better, the liver function is restored, and sepsis has subsided.

OPERATION.

Medical treatment having failed, operation for cholecystitis and gall-stones should be carried out before the disease has spread beyond the gall-bladder and cystic duct, so that the disease can be eradicated by cholecystectomy at a comparatively small risk. In later cases drainage of the gall-bladder or common bile duct may have to be established in order to save life. These delayed operations have a much higher mortality, and are more often followed by recurrence of symptoms, often demanding secondary operation.

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SOME RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE NERVOUS SYSTEM.*

BY

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NEUROLOGY is a branch of medicine which I often have to defend, because I am told that, although it is a most interesting exercise in applied physiology, what treatment is possible in organic diseases of the nervous system? We maintain, however, that therapeutics in neurology compares very favourably with that of other organic medical diseases—of the heart, kidney, and liver, for instance. I propose, therefore, to review some of the more recent developments not only in the diagnosis of nervous system diseases, but also in their treatment.

One of the most important advances of recent years is the procedure known as "cisterna puncture"—that is, the insertion of a needle into the cisterna magna, that large

portion of the subarachnoid space which lies between the inferior surface of the cerebellum and the posterior aspect of the medulla. The puncture consists in penetrating the tissues between the occipital bone and the atlas vertebra, and withdrawing cerebro-spinal fluid. This may sound rather heroic, but is really quite as simple as lumbar puncture. The needle used should be graduated in centimetres, a depth of from 5 to 6 cm. being the maximum distance that the needle can be safely introduced in the adult before the medulla is reached. The surface point taken is the spine of the axis vertebra; the needle is inserted just above this and directed upwards at an angle of 30 degrees from the horizontal. After penetration of the skin it is advisable to remove the stylet from the needle before the latter is pushed onwards into the cisterna magna: then, as soon as the subarachnoid space is reached, a drop of cerebro-spinal fluid appears.

As regards the practical application of cisterna puncture, it may be mentioned that, apart from its use for the withdrawal of cerebro-spinal fluid for diagnostic purposes, it is of great value in the treatment of various forms of meningitis. In meningococcal and pneumococcal meningitis, for instance, the therapeutic serum can be introduced through the cisterna puncture needle and the serum thus brought into close contact with the site of maximum inflammation, which is invariably at the base of the brain. It thus replaces the older method of introducing the serum through a lumbar puncture needle. The puncture can also be used for injecting salvarsanized or mercurialized serum in the treatment of various forms of neurosyphilis. Further, it is of great value for the introduction of lipiodol in the localization of spinal cord tumours—a subject which I shall consider later.

A great deal may be learned from the pathological examination of the cerebro-spinal fluid. It is quite possible by this means to confirm a clinical diagnosis of compression of the spinal cord by tumour or abscess. In this condition the cerebro-spinal fluid shows fairly its characteristic reactions, which include a considerable increase in the amount of total protein present as compared with the normal of 0.02 to 0.04 per cent., but no increase in the normal number of cells (2 to 4 per cubic millimetre) and no alteration in the glucose and chlorides. This phenomenon has been termed "dissociation albumino-cytologique" by French physicians. Occasionally, in addition to the excess of protein, the cerebro-spinal fluid may be yellow in colour (xanthochromia) and may even coagulate spontaneously on standing; to this latter condition the term "Froin's syndrome" is applied, but the essential feature is the excess of protein with no increase in the number of cells. In addition to spinal cord tumour, dissociation albumino-cytologique may occur in cases of meningitis and certain forms of polyneuritis; and I have also seen it in cerebro-spinal arterio-sclerosis.

Another useful cerebro-spinal fluid test is Lange's colloidal gold reaction. The exact physio-chemical changes are complicated, but, briefly, the procedure consists of the application of the protective action of colloids on the precipitation of gold suspensions by sodium chloride to the protein in the cerebro-spinal fluid. Lange found that normal cerebro-spinal fluid, when diluted with 0.4 per cent. of sodium chloride, does not affect a solution of colloidal gold, whereas pathological fluid produces changes often characteristic for various diseases. Dilutions of cerebro-spinal fluid with salt solution, ranging from 1 in 10 to 1 in 5,120, are put up in a series of ten test tubes, each successive tube containing a higher dilution. A measured quantity of colloidal gold solution giving a purple coloration is added to each tube, and the series is examined after an interval of twenty-four hours for any colour changes that may have occurred. With normal cerebro-spinal fluid the purple colour is unchanged in each of the tubes. In abnormal reactions the colour changes range from blue to white in different tubes of the series. According to the resulting tints we can plot out a graph—the horizontal representing the series of tubes and the vertical the colour changes. Certain neurological conditions are indicated by typical curves. In general paralysis, for instance, we find what is known as a "paretic" curve. The first three or four tubes of the series undergo almost complete

* An address delivered to the City Division (Metropolitan Counties Branch) of the British Medical Association.