THE ASSOCIATION BETWEEN GALL-BLADDER LESIONS AND HEPATITIS IN THE HUMAN SUBJECT.*

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(With Special Plate.)

SINCE E. A. Graham published his paper entitled "Hepatitis, a constant accompaniment of cholecystitis" in *Surgery, Gynecology, and Obstetrics*, in 1918, articles have been written by others corroborating his contention.

The present investigation was begun about three years ago to determine, if possible, the extent of the hepatitis, the type, and the route by which the liver becomes affected. My method has been much the same as that used by others—namely, to obtain segments of liver at operation and to subject them to microscopic and bacteriological scrutiny—but I think my investigation has this advantage over any other within my knowledge, that sections have always been taken from both lobes of the liver, in the case of the right lobe at a distance of at least 1 inch from the gall-bladder fossa, so that the whole liver should not be judged from the condition of that part of it in the immediate neighbourhood of an inflamed gall-bladder.

The method employed to obtain the liver sections was as follows: A triangular piece with a base of about half an inch and sides rather longer was taken from the anterior edge of the right lobe under strictly aseptic precautions and placed in a sterile tube; the sides of the gap were brought together by one or more mattress sutures of fine catgut and tied with just sufficient tension to stop bleeding. A similar proceeding was conducted on the left side. In most of the cases the gall-bladder was sent for examination, care being taken to prevent bile coming in contact with the exterior. In many cases the cystic gland was also separately removed. A fresh set of instruments was used for each proceeding, each specimen being placed in a separate sterile tube; all were sent immediately to the laboratory for culture and later for histological examination. There was never any difficulty in arresting haemorrhage, and the procedure did not seem to disturb the progress of the patients in the least.

There are 50 cases in this series, but for various reasons it has been possible to get a complete histological report of only 34. Of the 34 cases the gall-bladder was pathological in 20 and normal in 14. These 14 cases were regarded as controls, and were operated on for the following conditions: 1 for subacute appendicitis, 2 for chronic appendicitis, 2 for visceroptosis, 4 for duodenal ulcer, 3 for jejunal ulcer, 1 for gastric ulcer, and 1 for a condition needing laparotomy.

THE EVIDENCE OF HEPATITIS: ITS CHARACTER AND EXTENT.

Investigation into the state of the liver was made in three ways: (1) macroscopic—at operation; (2) microscopic; (3) certain liver tests were made before operation and the results placed side by side with those furnished by examination of the liver sections.

Macroscopic Evidence.

There is ample evidence of hepatitis in that part of the liver in contact with an inflamed gall-bladder, but when one attempts to assess the condition of the liver as a whole from naked-eye appearances I think one is on very uncertain ground. In acute infections of the gall-bladder and other organs, such as the appendix, one gets the impression that the liver is large, soft, and succulent, as though it were oedematous, and the rounded edge of the liver lends support; it is difficult to prove, because if oedema is present it is not of sufficient intensity to show in the sections. As regards the more numerous chronic cases I came to mistrust macroscopic observations con-

cerned with thickness and enlargement as evidence of hepatitis, for in many cases these disagreed with microscopic conclusions. In fact, only the latter give reliable evidence; moreover, the information obtained by this simple procedure may be of considerable value in certain cases in connexion with their subsequent progress, when taken in conjunction with liver tests.

Microscopic Evidence.

Under the microscope these cases of hepatitis show round-celled infiltration in the portal tracts and between the liver lobules (Figs. 1 and 2). Fatty infiltration is common, and occasionally degenerative changes suggesting necrosis are seen. The portal tracts often show fibrosis. Polymorphs can be seen in some of the sections, but for the most part the cellular infiltration is caused by lymphocytes. Figure 3 shows a section of normal liver from a case of so-called visceroptosis; the difference between this and Figures 1 and 2 is very noticeable. Two further points are very evident in these sections: (1) the appearances are always of the same character, but differ in degree in different cases; (2) in any one case these characteristics are always the same in degree and kind in the two lobes of the liver; in fact, they are widespread.

As regards the gall-bladder, there is lymphocytic infiltration in most of the coats, sometimes polymorphs, and, as a rule, fibrosis replacing in many cases the muscular coat in part. Strawberry gall-bladders I have referred to as pathological rather than instances of cholecystitis, since the evidence of inflammation is sometimes exceedingly scanty. An analysis of the 34 cases is given in Table I.

TABLE I.

Hepatitis.	State of Gall-bladder.	
	Normal.	Pathological.
None	3	1
Slight	5	7
Moderate	5	2
Marked	1	10
	14	20

There was hepatitis in 30; in 4 the liver sections were normal. Of these 4 cases one had a pathological gall-bladder in which there were no stones, but moderate fibrosis with round cells here and there. The other 3 had normal gall-bladders; one was a case of chronic appendicitis, another of jejunal ulcer, and a third of visceroptosis. At the other end of the table we find 11 cases showing marked hepatitis; there were 10 with pathological gall-bladders, and one was normal; this was a case of duodenal ulcer in which the degree of hepatitis was quite well marked. In the groups showing slight or moderate hepatitis there are 9 cases with a pathological gall-bladder, and 10 in which the gall-bladder was normal—practically an equal number in each class. The most striking features of this table are, I think, the preponderance of pathological gall-bladders in the group with marked hepatitis, and the prevalence of hepatitis whether the gall-bladder is diseased or not.

Of the exact relation of the round-celled infiltration to the structures in the liver, I am uncertain whether it begins in connexion with the bile ducts, lymphatics, or blood vessels; obviously it must be one or more of the three. It seems to me that as a general rule the area near the blood vessels is less involved by round cells, and I think the same may be said of the larger bile ducts. The smaller bile ducts, however, appear to be very definitely placed in close relation to the areas of maximum infiltration, and it is difficult to escape the conclusion that they are in some way concerned; in fact, the condition seems to be a pericholangitis of the smaller bile ducts at the periphery of the lobules in the first place (see Fig. 4). I think a careful examination of the sections shows that the lumen of the bile ducts is free from epithelial debris or other sign of inflammation, and the walls too, though they appear to be pressed against one another, do not show any inflammatory change. It is not easy to be sure of this, because in many sections the ducts are to a great extent obscured by the round cells; but in the clearer parts of the fields it seems to be as just stated. The infiltration surrounding the smaller bile ducts appears to be quite sufficient in many

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places to produce pressure and obstruction; the significance of this will be discussed after reviewing the results obtained with the liver tests.

If it is true that the bile ducts are not actually inflamed, it seems likely that the lymphatics are the real centre of the infiltration and that they run in close relation to the small bile ducts at the periphery of the lobules, and that it is in virtue of this close relationship that the bile ducts are seemingly so much concerned in the infiltration. Practically nothing is known of the lymphatics in the liver: it is therefore only possible to speculate about the position they occupy; but if we compare the lymphatic arrangements in the spleen and lymph glands we find a marked similarity of general plan of structure. In these the reticulo-endothelial tissue sifts out what is not acceptable to the blood, and by means of masses of round cells—in reality the same thing as the solitary glands of the intestine—such foreign matter as bacteria is rendered harmless, and a great proliferation of round cells may occur in and around these masses during the performance of this task. It is therefore suggested as a reasonable inference from what is seen in my sections showing hepatitis that the Kupffer cells, the reticulo-endothelial tissue of the liver, extract harmful material from the blood and pass it out to lymphatics lying alongside the hepatic cells and small bile ducts; thence it is carried to larger lymphatics in the portal sheaths where these abut on the periphery of the liver lobules. If this explanation is correct the masses of round cells seen in my cases of hepatitis may be a reactive proliferation of lymph follicles normally lying diffusely scattered through the liver in a similar though not so well-defined arrangement as that of the lymphatic glands and spleen. In Hodgkin's disease such lymphatic collections become very apparent in the liver.

My series does not provide sufficient material from which to form conclusions as to the route by which the liver and gall-bladder became infected. There are, however, interesting bits of evidence. For example, in one case the liver showed the usual round-celled infiltration, and from both lobes a few colonies of a coliform bacillus were grown; the appendix showed signs of a recent inflammation, and from it was grown a similar coliform bacillus. The patient was a boy of 15, who had recently had an attack of undoubted clinical acute appendicitis, which was subsiding. This would appear to be infection of the liver from the appendix, more especially as the organism, which was identical from the two sources, was not the usual *B. coli*, so that coincident infection of the liver from some other source does not seem a reasonable assumption. There is every reason, too, to suppose that the organisms had been carried in the portal blood. I profoundly mistrust any theory which seeks to explain infection by the lymphatics if it involves the supposition of retrograde flow in the absence of obstruction to the normal forward movement; and so far as the liver is concerned all the lymph normally flows out of it and none whatever into it.

Another case suggests infection of the gall-bladder via the hepatic artery.

This patient was a woman, aged 28, who, until she had an attack of acute tonsillitis, had enjoyed good health. During this attack she was seized with sudden severe pain in the epigastrium, which radiated to the back; there was tenderness over the gall-bladder region; but there was no jaundice. She had several attacks of typical biliary colic later; no indigestion was present in the intervals. At the operation, which was performed two years after the initial attack of pain, she was found to have a thick-walled gall-bladder, shrunken and recently inflamed, which contained a single mixed cholesterol stone. Under the microscope the gall-bladder showed extensive lymphatic infiltration of its wall, the muscles replaced to a large extent by fibrous tissue, and in places large collections of leucocytes. The liver sections showed slight lymphocytic infiltration.

It is reasonable to suppose that the reaction in the liver which we are calling hepatitis results from infection carried by the hepatic artery or the portal vein. As I shall show presently it is unusual to be able to grow organisms from the liver sections; this may be explained partly by the phagocytic activity of the Kupffer cells rapidly weakening and destroying the bacteria, partly by the probability that the noxious material is often toxin and not bacteria, and

partly by the surgical habit of delaying operation on acute gall-bladder conditions as a general rule, so permitting time for the lessening of bacterial virulence.

I have already stated that hepatitis is commonly present in many intra-abdominal lesions; it is not quite clear why it should be more marked in patients with pathological gall-bladders than in others. I think that it is, and there are several possible explanations.

1. It may be that the greater degree of hepatitis is primary, and an associated alteration of biliary secretion, in the presence of some metabolic change—as, for example, increased cholesterol in the blood—favours the deposition of aseptic stones, which subsequently, in one way or another, induce cholecystitis and attendant mixed stones.

2. The blood from the gall-bladder is poured into the portal vein close to the liver, whereas that from the appendix, for example, has to travel some distance in a fairly sluggish stream with some 10,000 leucocytes to the cubic centimetre (there may be many more in an acute attack), where there would be opportunity for bacterial virulence to be diminished before the liver is reached.

3. The size of the gall-bladder as compared with the appendix would presumably mean more noxious material entering the liver during a state of inflammation.

These explanations are contingent on infection entering the liver by the portal vein.

4. The hepatic artery may be the portal of entry, the site of infection being a distant focus, and a selective affinity determining the intensity of the attack falling on the gall-bladder as is now generally held. This receives support from the experimental side, but I doubt if we are reproducing human etiological conditions by massive intravenous injection of organisms. Moreover, the supposition would be that the gall-bladder so infected produced the hepatitis; but the degree of pathological change in the gall-bladder does not seem to be the only determining factor in the degree of hepatitis, for examination of 21 cases shows that in 11 a marked degree of cholecystitis and hepatitis coincided, whereas in 10 no such similarity of pathological change was observed—in about half the gall-bladder was grossly changed and the liver little affected, while in the other half the liver showed marked hepatitis and the gall-bladder only a slight degree of inflammation (Figs. 5 and 6). This suggests that sometimes, at any rate, hepatitis is primary.

5. Infection might pass into the liver up the bile ducts; but as the larger bile ducts certainly, and I think also the smaller ones, show no evidence in the lumen or wall of infection it does not seem probable that this is the route by which infection enters and becomes effective, apart from those cases which present partial or complete obstruction of the common duct.

In 32 cases the condition of the pancreas was noted. It is easier to assess the state of this organ by palpation, I think, than in the case of the liver. In 20 patients, 12 of whom had pathological gall-bladders, the pancreas was normal. In 12 others it was decidedly hard, the hardness in most cases being confined to the head; in one of these the hardness was associated with a strawberry gall-bladder, in 2 with very slight cholecystitis, in 2 others with acute cholecystitis, and in 7 with definite chronic cholecystitis; of these 6 were cases of stone in the common duct. It seems probable from recent work on pancreatitis that cases associated with stone in the common duct receive the infection directly up the duct of Wirsung. If we subtract the common duct cases in my series there are 6 left showing pancreatitis out of 24 cases with pathological gall-bladders, exactly 25 per cent., and although the degree of pancreatitis, estimated by palpation, does not tally case by case exactly with the degree of hepatitis estimated by microscopic examination, yet there is a close parallelism. The blood supply to the head of the pancreas comes via the gastro-duodenal artery from the hepatic, which makes this coincidence of hepatitis and pancreatitis an interesting one, and possibly suggests that at least in 25 per cent. of cases infection of the liver arrives by the hepatic artery. Of course this is pure speculation stimulated by the figures and observations recorded above, but it suggests lines on which further investigation might prove profitable.

BACTERIOLOGY OF THE LIVER, BILE, AND GALL-BLADDER WALL.

The results are shown in Table II.

TABLE II.—Result of Cultures from the Gall-bladder Wall, Bile, and Liver Sections.

State of Gall-bladder.	Gall-bladder Wall.	Bile.	Liver.
Pathological	Negative	Negative	<i>B. welchii</i>
"	"	"	Negative
"	<i>B. coli</i>	<i>B. coli</i>	" —
"	Negative	Negative	Negative
"	<i>Streptococcus</i>	<i>B. coli</i>	"
"	<i>Staphylococcus</i>	Negative	"
"	Negative	"	"
"	"	<i>Staphylococcus</i>	"
"	"	Negative	"
"	"	"	"
"	"	"	"
"	<i>Staphylococcus</i>	<i>B. coli</i> and <i>staphylococcus</i>	<i>B. coli</i> and <i>staphylococcus</i>
"	Negative	<i>B. coli</i>	—
Normal	—	—	Negative
Pathological	—	—	"
Normal	—	—	"
Pathological	<i>B. coli</i>	<i>B. coli</i>	—
Normal	—	—	Negative
"	—	—	"
Pathological	<i>B. coli</i>	<i>B. coli</i>	"
"	Negative	Negative	<i>Staphylococcus</i> and diphtheroid
"	Negative	<i>B. coli</i>	"
Normal	—	—	<i>Streptococcus</i> (virulent)
Pathological	Negative	<i>B. coli</i>	<i>Staphylococcus</i>
Normal	—	—	Negative
"	—	—	<i>Staphylococcus</i> and <i>B. welchii</i>
"	—	—	Negative
"	—	—	<i>Coliform bacillus</i>
Pathological	Negative	Negative	—
"	<i>B. coli, staphylococcus</i> and diphtheroid	<i>B. coli</i>	—
Normal	—	—	Negative
"	—	—	"

The outstanding features of this table are: (1) The large number of negative results in all the material examined. (2) In the few cases where the findings were positive the liver sections and bile showed the same organisms only once—a case in which *B. coli* and *staphylococcus* were cultured from both sources. (3) When positive results were obtained the organisms in the majority of cases were those which normally grow in the intestines.

The simultaneous presence of *B. coli* in the bile and gall-bladder wall in several cases suggests infection of the latter from the bile, for in five out of eight cases of acute cholecystitis *B. coli* were cultured from both, whereas in only four out of thirteen chronic cases were cultures of this organism obtained. There is a strong suggestion here that the infecting organism is *B. coli*, and that it readily dies out; whether it gains access to the bile and the gall-bladder from the liver or up the common duct cannot be decided. The infrequency of positive cultures from the liver suggests the latter route; and further, that if hepatitis is related to cholecystitis in a primary capacity it is so by virtue of inefficiency of the bile to hold its constituents in solution, thereby facilitating the formation of gall-stones and ultimately cholecystitis. But there is the possibility that, although the liver rapidly destroys the virility of the organisms, yet in the presence of inefficient liver cells (shown by liver tests, as we shall see later) active organisms are allowed to go through these cells instead of being rejected by them and passed into the lymphatics.

On several occasions cultures were made from the cystic gland in cases of pathological gall-bladder; only twice did any organism grow—once a *staphylococcus* and once a *streptococcus* which conformed to the type described by A. L. Wilkie. This was a case of acute cholecystitis with a stone impacted in the neck of the gall-bladder. In another

case in which a man was operated on for a subacute attack of cholecystitis with stones, the cystic gland was about the size of a moderate-sized broad bean. No growth was obtained either from it or from the gall-bladder, although one would think that a gland of this size examined during the actual attack would be an ideal one from which to culture an organism.

The marked pathological changes found in the liver and gall-bladder, combined with the number of negative bacteriological findings, suggest a readiness for the infecting organisms to die out, or it may be that we are apt to place too strong an emphasis on the infection theory of gall-bladder disease. It seems reasonable to infer from these results that it is unlikely that the gall-bladder can be a chronic focus of bacterial infection for more distant parts, as the organisms disappear very quickly after they have stimulated the gall-bladder into an inflammatory state.

The media used for culture purposes were: (1) glucose agar—deep tubes; (2) surface smears on blood agar (heated); (3) deep tubes of agar containing 0.1 per cent. sodium sulphide—giving anaerobic conditions.

CERTAIN LIVER TESTS IN RELATION TO HEPATITIS.

For this part of my subject I chose the van den Bergh test, because it is generally considered to give reasonably accurate information about bilirubin and the processes involved in its production, etc., and the laevulose test because it has been well recommended by some and thoroughly condemned by others, and it seemed a good opportunity to find out, if possible, which opinion was justified.

Van den Bergh Test.

The results of this test depend on the quality and quantity of bilirubin in the blood. In obstructive jaundice there is a prompt direct reaction; in haemolytic jaundice a positive indirect reaction only; and in toxic jaundice a biphasic result—that is, a positive indirect and also usually a delayed direct.

There was only one case of clinical jaundice at the time of operation included in my series, as I did not feel justified in taking sections in this type of case as a rule; this case gave a prompt direct reaction. There were three which gave a delayed direct and positive indirect reaction; two of these were common duct cases without clinical jaundice. All the other positive results were of the indirect kind and of varied degree. I have attempted to give the results of the test side by side with the degree of hepatitis as shown by the microscope. For this purpose I have put into one class the cases showing marked or moderate (that is, definite) hepatitis, and into another those showing slight hepatitis or normal liver (see Table III). From this table it will be seen that in the first group the reaction is definitely more pronounced.

TABLE III.

Hepatitis Marked or Moderate.		Hepatitis Slight or Nil.	
Condition of Gall-bladder.	Van den Bergh Test.	Condition of Gall-bladder.	Van den Bergh Test.
Pathological ...	D.N.; I.N.	Pathological ...	D.N.; I.N.
"	D.N.; I.P. (s)	"	D.N.; I.P. (s)
Control case ...	D.N.; I.P. (s)	"	D.N.; I.P. (s)
Pathological ...	D.N.; I.P.	"	D.N.; I.P. (vs)
"	D.N.; I.P.	Control case ...	D.N.; I.N.
"	D.N.; I.N.	"	D.N.; I.P. (s)
"	D.N.; I.P.	"	D.N.; I.P. (vs)
"	D.N.; I.N.	"	D.N.; I.N.
"	D.P.; I.P.	"	D.P. (s); I.P.
"	D.N.; I.N.	"	D.N.; I.P. (s)
"	D.N.; I.P.		
"	D.P.; I.P.		

D.N. = Direct van den Bergh, negative. D.P. = Direct van den Bergh, positive. I.N. = Indirect van den Bergh, negative. I.P. = Indirect van den Bergh, positive. (s) = Slight reaction. (vs) = Very slight reaction.

It is a little difficult to interpret these results, but there are some significant features. In describing the microscopic sections I have already said that one gets the impression that some of the smaller bile ducts are compressed; this is supported by the delayed direct reaction seen in three of

the cases. Moreover, in some of the sections the liver cells show bile staining; and there are appearances of the same kind as those seen in cases of toxic jaundice. These features suggest that the increase of bilirubin in the blood is due to interference with the polygonal cells, sometimes by poisoning, sometimes by damming back of the bile in the smaller bile ducts, and sometimes by both. The increase of bilirubin shown constitutes latent jaundice. In the few cases in which the fragility of the red cells was examined it was found to be normal; this strengthens the view that the jaundice is due to something in the liver and not to haemolysis.

Laevulose Test.

The basis of this test is that laevulose given to a normal person does not increase the blood sugar, whereas when the liver is functioning deficiently there is a characteristic increase in blood sugar. The dose of laevulose is given on an empty stomach, and the blood sugar estimated half-hourly for two hours.

I have divided the cases into two classes (Table IV) as in the van den Bergh test. In Tables V and VI, dealing

TABLE IV.

Hepatitis Marked or Moderate.		Hepatitis Slight or Nil.	
Condition of Gall-bladder.	Laevulose Test (Liver Function).	Condition of Gall-bladder.	Laevulose Test (Liver Function).
Pathological ...	Deficient	Pathological ...	Not deficient.
" ...	Deficient	" ...	Not deficient.
Control case ...	Deficient	" ...	Deficient.
Pathological ...	Deficient	" ...	Deficient.
" ...	Deficient	Control case ...	Not deficient.
" ...	Deficient	" ...	Not deficient.
" ...	Deficient	" ...	Not deficient.
" ...	Deficient	" ...	Deficient.
" ...	Deficient	" ...	Not deficient.
" ...	No! deficient	" ...	Not deficient.

TABLE V.—Cases in which Hepatitis was Marked or Moderate.

Type of Case.	Van den Bergh Test.	Laevulose Test (Liver Function).
Pathological gall-bladder ...	D.N.; I.P. (s)	Deficient.
Pathological gall-bladder ...	D.N.; I.P.	Deficient.
Control ...	D.N.; I.P. (s)	Deficient.
Pathological gall-bladder ...	D.N.; I.P.	Deficient.
Pathological gall-bladder ...	D.N.; I.P.	Deficient.
Pathological gall-bladder ...	D.N.; I.N.	Deficient.
Pathological common duct ...	D.P.; I.P.	Deficient.
Pathological gall-bladder ...	D.N.; I.N.	Not deficient.
Pathological common duct ...	D.P.; I.P.	Deficient.
Pathological common duct ...	D.N.; I.P.	Deficient.

See Table III for explanation of letters in Tables V and VI.

TABLE VI.—Cases in which Hepatitis was Slight or Nil.

Type of Case.	Van den Bergh Test.	Laevulose Test (Liver Function).
Pathological gall-bladder ...	D.N.; I.N.	Not deficient.
Pathological gall-bladder ...	D.N.; I.P. (s)	Not deficient.
Pathological gall-bladder ...	D.N.; I.P. (s)	Deficient.
Pathological gall-bladder ...	D.N.; I.P. (vs)	Probably deficient.
Control ...	D.N.; I.N.	Not deficient.
Control ...	D.N.; I.P. (vs)	Not deficient.
Control ...	D.N.; I.P. (vs)	Not deficient.
Control ...	D.N.; I.N.	Deficient.
Control ...	D.P. (s); I.P.	Not deficient (haemochromatosis)
Control ...	D.N.; I.P. (vs)	Not deficient.

respectively with cases in which hepatitis was marked or moderate and others in which it was slight or nil, the results of both tests are placed side by side. One case, which was thought to be an instance of haemochromatosis, should be omitted. It will be observed that there is a close

parallelism between the results given by the two tests; on the whole the state of the liver is shown more accurately by the laevulose test. This came rather as a surprise. I do not wish to stress these findings unduly, because the number of cases is small. So far as I know neither of these tests has been checked by microscopic liver examinations prior to this series, and it may be that the condemnation which the laevulose test has suffered is due, not so much to it being an unreliable test of the state of the liver, as to the fact that a result which indicates hepatic deficiency does not necessarily receive clinical support. This may be because our present knowledge of what is going on in the liver purely from clinical observation is depressingly deficient, and not because the laevulose test is at fault.

I feel that some explanation is due for presenting so few cases; I would point out that it is extremely difficult for a single investigator to produce a large series; the work involved is very time-consuming, and it is not always easy to get the necessary collaboration at the time the material comes to hand; moreover, the patient has to be considered primarily, and in many cases I did not feel justified in prolonging the operation beyond the period that was absolutely essential, nor in subjecting the jaundiced patients to a possible risk of oozing from the cut liver, and so on. However, every series adds to the total contribution to this subject, and a sufficient number of cases have been reported, I think, to warrant the conclusion that hepatitis is associated in some way with cholecystitis, and also with many other intra-abdominal lesions. In regard to the existence and type of the hepatitis, my findings agree very closely with those of Graham; on the other hand, the bacteriology of my series differs from his in degree rather than in kind; on both these points they are quite different from what A. L. Wilkie describes.

The correlation of functional tests of the liver with microscopic examinations has opened up a new field so far as I am aware; with such a few cases at one's disposal any explanation of the observed phenomena must to a large extent be speculative. Nevertheless, the results seem sufficiently interesting and uniform on the whole to make it worth while extending this method of research.

I should like to thank Dr. A. L. Taylor and Miss Hickman, who did the microscopic part of this work; Professor McLeod and Miss Wheatley, who are responsible for the bacteriology; and Dr. Fowweather, who determined the liver function tests. Without their help it would have been impossible for me to have obtained the reliable laboratory information so essential to this kind of investigation.

CARCINOGENIC SUBSTANCES AND THEIR FLUORESCENCE SPECTRA.

BY

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(With Special Plate.)

THE results described here are the latest obtained in an investigation of the carcinogenic action of coal tar. It has been known for many years that cancer could be produced by certain industrial products (gas-works tar, shale oil) which had been exposed to high temperatures, and this process of formation of carcinogenic materials has been extended in the laboratory of the Cancer Hospital Research Institute by heating a variety of substances (acetylene, isoprene, cholesterol; human skin, muscle, and hair; yeast) of which every one yielded products which caused cancer when applied to mice. An attempt was then made to obtain cancer-producing substances at body temperature by reactions which might resemble more closely those occurring in the tissues, when cancer develops naturally, than do changes in a red-hot tube at 700° to 900°.

Schroeter¹ in 1920 described a mixture of high-boiling compounds formed when aluminium chloride acted upon tetralin (commercial tetrahydronaphthalene) at 30° to 40° C. We found that this material was carcinogenic; one of the earliest experiments with it yielded 8 cancers and 3 papillomas from 20 mice in 256 days. This mixture of high-boiling compounds will be referred to as "Schroeter" for the sake of brevity. In some preparations

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FIG. 1.—Section of right lobe of liver, showing round-celled infiltration surrounding many apparently normal bile ducts.

FIG. 2.—Section of left lobe from the same case as Fig. 1. Same appearances with well-marked fatty infiltration.

FIG. 3.—Section of normal liver.

FIG. 4.—Zone of (?) early infiltration at junction of portal tract and liver lobules.

FIG. 5.—Section from liver. Note marked round-celled infiltration around a number of small bile ducts, some of which seem to be compressed.

FIG. 6.—Gall-bladder wall—practically normal. Section from same case as Fig. 5.