THE EXPERIMENTAL PRODUCTION OF HEPATIC CIRRHOSIS.[1]

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(PLATES XIII.–XVI.)

AN extended series of investigations on metabolism, which has been carried on for some years past in this laboratory, has necessitated many collateral studies, not always of a chemical nature, of which the present work is an example.

In a previous communication[2] we described the artificial production of cirrhosis of the liver by means of ligature of the left hepatic duct in cats, the animals being killed at the end of from five to six months. This investigation has since been carried a stage further, the changes obtained in the liver being considerably more advanced than those observed in the course of the preceding work, and ending in atrophy of the affected liver area. In addition to cats, dogs have been used for experiment, and the period during which the animals have been kept alive has been extended up to sixteen months. In the present paper we give for the first time illustrations of the changes in the liver, macroscopic and microscopic, resulting from ligature of the left bile duct.

METHOD.

Concerning the operative procedure, which consists in ligature of the left hepatic duct, little need be added to what has already been stated in the communication referred to above. The operation is far more easily carried out in cats than in dogs, owing to the pendulous abdomen and yielding chest wall of the former animal. Occasionally much difficulty is experienced in isolating the left hepatic duct, and sometimes, in spite of much care, the cystic duct is mistaken for the left hepatic duct. The operation does

[1] Towards the expenses of this research a grant was received from the British Medical Association, on the recommendation of the Scientific Grants Committee of the Association.

[2] *Brit. Med. Journ.*, London, 1898, vol. ii. pp. 1743, 1744.

not interfere with the general health of the animals; they usually gain weight, and do not suffer from jaundice or ascites, and the colour of the motions remains unchanged.

In all the experiments referred to in this paper there was complete absence of sepsis.

It is of importance to keep the animals alive for several months after ligature, in order that easily recognisable changes may develop. If no change is visible to the naked eye, a microscopic examination is necessary, in order to ascertain the presence or absence of interstitial change. In all cases portions of the ligatured and non-ligatured areas should be sectioned and compared. In the absence of these precautions, changes of slight degree may easily be overlooked.

The Naked-Eye Appearance of the Liver after Ligature of the Left Bile Duct.

Of four dogs operated upon successfully, none were kept alive more than six months. In all the liver presented but little visible alteration. Up to about four months no change could be asserted with confidence. At the end of about six months, in two of the dogs, the peritoneal surface of the left lobe of the liver exhibited, in the fresh state, the outlines of the lobules in some situations with much more distinctness than was the case over the surface of the right lobe, but the contrast between the two was not at all obtrusive, and upon cutting into the liver no marked difference between the right and left portions of the liver was observed. No change was evident on inspection of the remaining two livers. In the hardened livers of all four animals the lobules became everywhere more distinct in the left portion of the liver, but no further difference between the ligatured and non-ligatured areas was rendered manifest to the naked eye. The microscopic characters of these livers are described in the next section.

Of ten cats operated upon successfully, several were kept alive for twelve months or more, and one for sixteen months. These experiments furnish ample material for studying the changes induced by ligature. During the first four to six months the difference between the peritoneal aspect of the right and left portions of the liver is usually not at all marked, and consists in a slightly more pronounced outlining of the hepatic lobules on the left side. At the end of twelve to fifteen months the naked-eye change may become very obtrusive, as in the cat's liver shown in Plate XIII. Fig. 1, and in Plate XIV. Fig. 4. Thus, in the liver shown in Fig. 1 for example, twelve months after ligature, there is on the left side slight but distinct shrinking, especially towards the anterior border, which is irregularly thinned, and presents an irregular outline. A further striking feature of the left portion of this liver was the appearance on the peritoneal surface of yellowish-white irregular areas, resembling wash-leather, some of the larger ones being distinctly raised. Between these areas the liver retained to some extent its normal dark brown aspect, and the outlines of the lobules, which were considerably smaller than elsewhere, could often be made out, and were especially conspicuous at the junction with the surrounding healthy liver. The area affected, however, appeared to be distinctly less than might be expected as the result of the ligature. These changes were most marked towards the left free border, and gradually disappeared as the attachment of the triangular ligament was approached. On the under surface of the liver the left duct was seen as a short, tortuous tube, with a thin, whitish wall of about the diameter of a lead pencil, filled with clear, somewhat viscid, contents of a light brownish-yellow colour, stopping suddenly close to the portal fissure, where the ligature was applied, and bifurcating at its opposite

extremity. On section of the left portion of the liver it was found to be channelled out by tortuous dilated bile ducts, the largest of the size of a goose-quill, filled with viscid yellowish contents, which, on hardening the tissue in Müller's fluid, became converted into a soft clot. As these dilated ducts communicated freely with one another, when one was incised, the fluid contained in the others could readily be expressed through the opening thus made.[1] When the cavernous character of the affected portion of the liver, due to these dilated channels, is considered, as also the overgrowth of fibroid tissue, it is readily understood how marked is the wasting of the liver parenchyma. Thus, in the section exhibited in Plate XIV. Fig. 4 for example, it will be noted that the linear wasting of the parenchyma amounts to between a quarter and half the width of the section. Assuming the average disappearance of the liver substance in any linear direction in the area corresponding to the ligatured left duct to be three-eighths, the extent of liver tissue actually remaining in this area would be reduced to $(\frac{5}{8})^3 = \frac{125}{512}$, or about one-quarter of its original amount, and in some places the degree of destruction was obviously greater than this.

The changes thus described as occurring in the cat at the end of twelve months were not found in all cases, though the operation was always performed in every detail in exactly the same manner. Thus, another cat presented at the end of thirteen months considerably less change; the left portion of the liver was almost normal in its aspect, and only on close examination were the lobules seen to be smaller (in some places markedly so) than over the rest of the liver, while here and there they were indistinct. There was a small depressed scar on the surface, and the left bile duct beyond the ligature was distended; it did not, however, reach the diameter of a crow-quill; while no yellowish-white areas were to be seen. After hardening in Müller's fluid the left portion became irregularly shrunken and indistinctly pitted on the surface, in contrast to the rest of the liver, which had a smooth surface. On microscopic examination the changes present were similar to those about to be described, as occurring twelve months after ligature, in the animal whose liver is shown in Plate XIII. Fig. 1, but were far less advanced. Similar differences were noted in other animals killed at nearly equal periods after ligature.

Thus it was found in our experiments that the amount of change caused by ligature of the left bile duct in a given period of time was not constant; but that the livers reacted, as in the two cases just described, very differently towards the same injury; sometimes considerable destruction of liver substance occurring rapidly, sometimes a much less marked change developing with corresponding slowness. A suggested explanation of this difference will be given later. It may here be observed that the extreme diversity of the response to ligature may perhaps explain the discordant results obtained by different observers. As already mentioned, when the change is slight, it cannot always be recognised on simple inspection in the fresh state, though perfectly distinct in section under the microscope.

The Microscopical Characters of the Liver after Ligature of the Left Bile Duct.

The alteration in structure of the portion of the liver towards which the ligatured duct runs is seen on microscopical examination to depend, in

[1] It was in consequence of a small portion of the affected area of this liver being excised for hardening in alcohol that, in the section shown in Plate XIV. Fig. 2, the biliary passages are collapsed, with the exception of one extremely dilated duct seen below, which has, however, become partly contracted, so that its epithelial lining is corrugated.

addition to a distension of the larger biliary passages and an increase in the number of the smaller ducts seen in section between the lobules, upon the production of fibrous tissue separating the lobules, which soon become markedly atrophied.

Of the four dogs operated upon successfully, one showed at the end of four months a moderate degree of interstitial fibrosis affecting the larger radicles of the portal vein in the affected area. This case is unusual in this respect, that the hepatic lobules are not surrounded by new tissue as is usually the case after ligature. It does not, however, appear that this type of reaction is usual in the dog, for the remaining three animals showed on the left side a general interlobular fibrosis, which was in two cases rather more marked than that shown in Plate XIV. Fig. 2, and in the remaining case was almost as marked as that shown in Plate XIV. Fig. 4, and attended with considerable atrophy of the hepatic lobules. The characters of the interstitial tissue are identical with those about to be described as occurring in cats. The right portion of the liver was in all cases unaffected.

In the cats in which the left bile duct was ligatured, the changes in the left portion of the liver at the end of four to six months (or longer, if the reaction to ligature was slight) were generally of the same type (Plate XIV. Fig. 2), though differing in degree, and exhibiting some variation, both in their microscopical characters and also in their naked-eye appearance. The morbid process induced consists in the appearance of richly nucleated fibroid tissue around the lobules, so that the lobules are mapped out into polygonal areas, and the appearance of the section is thus strikingly altered. The newly formed connective tissue, however, does not extend into the lobules, but is sharply limited to their periphery. The interlobular change is not always so regular as in Fig. 2, some of the lobules not being completely outlined; but in none of the cats was the change markedly irregular. In both cats and dogs distension of the largest bile ducts is also present at the end of from four to six months.

At a later period, when marked reaction to ligature has occurred (*i.e.* at the end of twelve to fourteen months), the affected area of the liver shows a considerable alteration in structure (Plate XIV. Fig. 4). The hepatic lobules become atrophied, sometimes almost to extinction; the larger bile ducts become markedly dilated, while the smaller biliary passages become increased in number; and finally there is an abundant interlobular development of fibrous tissue.

The size of the lobules in the area supplied by the ligatured duct varies considerably, the diminution in size being sometimes extreme, sometimes apparently inconsiderable, even in situations in which the development of fibroid tissue is greatest. The striking feature of the liver parenchyma in advanced cirrhosis from ligature is always, however, the lobular atrophy. The question arises, How does this atrophy occur; is it general or partial? When the liver is treated by Marchi's method, it is found that the peripheral zone of fatty infiltration, which is a striking feature on the right side of the liver, has disappeared from the cirrhotic area on the left side, where, however, some fatty change is noted in the large mononucleated cells containing blood pigment, which are sparsely and irregularly distributed between the capillaries of the lobules and the cell columns (Plate XVI. Figs. 8 and 9). From this absence of fatty change in the outer region of the lobules, it is to be inferred that the atrophy of the lobules progresses from without inwards, the periphery being the first to be destroyed. This conclusion is further supported by the circumstance that no marked atrophy of liver cells is observable; in fact, the cells of the liver parenchyma in the cirrhosed area are indistinguishable from those in the unaffected area, no definite changes being recognisable in the cytoplasm or nuclei by the staining methods employed (van Gieson's

stain, methylene-blue, osmic acid, etc.). No vitreous degeneration of the liver parenchyma is met with.

The appearance of the biliary passages in the affected area of the liver varies according to their size. The larger ducts are relatively enormously dilated, some which normally are hardly larger than a horse-hair being expanded perhaps to the diameter of a goose-quill. Accompanying this dilatation there is much tortuosity, and there may be also some varicosity present. The epithelial cells lining the distended bile ducts are flattened and stretched. When incised the dilated ducts collapse, and their epithelial lining is sometimes corrugated (Plate XIV. Fig. 4); sometimes, again, the enlarged ducts are simply flattened, their walls coming in contact with little or no puckering. The appearance of the smaller biliary passages lying at the periphery of the lobules in the cirrhosed area generally differs from that of the larger bile ducts, in the absence of any considerable degree of dilatation; their lumen is usually small, often exceedingly minute and difficult to recognise. The smaller biliary ducts, which are present in very large numbers, are very tortuous, exhibit a well-developed epithelial lining, consisting of a single layer of closely packed cubical cells, and form striking objects in the stained section (Plate XV. Fig. 7). Occasionally more than a single layer of epithelial cells appears to be present; but such an appearance is unusual. Most of these ducts exhibit a well-defined lumen, the small size of which may perhaps be explained in part by the support afforded by the surrounding fibrous tissue, which is present in great abundance. Every transition is met with between the smaller biliary passages and the large, much dilated ducts visible to the naked eye. On the other hand, much difficulty is experienced in the attempt to trace out the connection between the smallest bile ducts and the bile canaliculi. This point, upon which our investigation is still proceeding, has, up to the present, remained obscure by the methods we have hitherto employed.

The development of interlobular fibrous tissue is irregular in its distribution. Even in the earlier change, three to five months after ligature, in cases in which there is fairly general perilobular change, such as is shown in Plate XIV. Fig. 2, it will be noted that some of the lobules are not completely surrounded; and the same feature is shown again in Plate XIV. Fig. 4, where the changes following ligature are far more advanced. The collagen bundles are well formed (Plate XV. Fig. 7), and readily separate into exceedingly delicate fibrils. Lying among the connective tissue strands are elongated and flattened nuclei, which are often curved in adaptation to the wavy outlines of the connective tissue bundles. These nuclei are more abundant, and are slightly larger than those seen in fibrous tissue whose development has long been completed, as in the fasciculate layer of the *cutis vera*. The relation of the biliary tubules to the connective tissue lying between the lobules varies much. In some cases the former are, bulk for bulk, as abundant as the latter; sometimes the new fibrous tissue is, for a short distance, devoid of bile ductlets.

Occasionally a strand of connective tissue passes into a lobule, as in Plate XV. Fig. 7, but such an appearance is not common.

Blood vessels are present in the interlobular fibroid tissue in the ligatured area in fair abundance. Lymph spaces are also recognisable, but are usually of small size. Here and there cells containing blood pigment are recognisable. A small number of such cells are occasionally seen scattered through the lobules.

Lying embedded in the connective tissue between the lobules in the area of the ligature, small collections of multinucleated cells are met with occasionally, but on the whole rarely (Plate XV. Fig. 7). Possibly these collections may be caused by the rupture of one of the smallest bile ducts.

Where sulphindigotate of sodium is administered subcutaneously, it is

found that the bile canaliculi are injected both in the lobules of the affected area on the left side of the liver and in the perfectly healthy lobules on the right side, and that no definite difference in the aspect of the injected canaliculi can be recognised on either side, even though the interstitial change is advanced (Plate XV. Figs. 5 and 6). It thus appears that this secretory function of the liver still persists in the ligatured area.

In all the animals operated upon the right portion of the liver remained unaffected when the left bile duct was ligatured.

Glisson's capsule was not specially affected in the ligatured area. No necrotic patches were observed in the liver after ligature. The peritoneal cavity was free from fluid. There was no evidence of jaundice. The fæces were unchanged in colour.

Elastic tissue is found in fair abundance in the walls of the larger interlobular vessels.

The Mode in which, after Ligature of a Single Bile Duct, Cirrhosis is brought about in the Corresponding Liver Area.

Before attempting to interpret the structural changes resulting from ligature, the following facts must be borne in mind:—

1. In spite of the ligature, bile continues to be secreted in the area of the ligature. That the functions of the lobules involved are not abolished is shown—(*a*) by the elimination of sodium sulphindigotate by these lobules, even when cirrhosis is advanced; (*b*) by the presence of bile, somewhat altered in composition, in the larger bile ducts, even as long as from twelve to fourteen months after ligature; and (*c*) by the absence of any conspicuous change in the aspect of the hepatic cells in the ligatured area. In the human subject, as is well known, when the common bile duct is completely obstructed by a calculus, bile pigments find their way into the circulation, at the same time disappearing from the fæces.

2. The bile secreted by the affected lobules can leave the biliary passages in two ways: by osmosis and by rupture.[1] That the former occurs not only in the case of bile, but also in the case of various saline fluids, is a matter of common knowledge, so that it is not necessary here to dwell further upon the fact that the walls of the smaller bile ducts are permeable membranes in respect of bile.[2] How far the second process—rupture—occurs, it is not easy to speak with confidence. Possibly the occasional presence of small collections of leucocytes in the interlobular tissue may be due to this cause. The infrequency of focal areas of tissue change, however, suggests that rupture is probably not an effective factor in the production of cirrhosis, while the diffuse character of the change in its earlier

[1] Cp. "On the Effect of Injecting Dilute Sulphuric Acid into the Common Bile Duct," Wakelin Barratt, *Journ. Path. and Bacteriol.*, Edinburgh and London, 1898, vol. v. pp. 340–347.

[2] Secretion of bile takes place in the guinea-pig at a pressure of 200 mm. of bile. Resorption occurs in the dog under a pressure of 275 mm. of a column of bile; when this occurs the lymphatics at the portal fissure can be seen to contain yellow-coloured lymph.

stages is in favour of osmosis, which would be general in its distribution, occurring throughout all the bile ducts of the affected area. Both processes would take place in the smallest ducts more readily than in those of larger size.

3. Bile acts as a feeble irritant. Its irritant action is insufficient to produce any inflammatory reaction in the mucous membrane of the gall bladder or duodenum; but, on the other hand, when it mixes with the lymph in the lymph spaces of the liver, it cannot be supposed to be without effect upon the nutrition of the tissues with which it comes into such intimate contact.

The structural changes resulting from ligature of a bile duct are threefold: interlobular development of fibroid tissue; changes in the bile ducts; and atrophy of hepatic lobules.

The interlobular development of fibroid tissue is readily explicable as the result of the continuous slight irritation resulting from the constant presence of bile in small amount outside the biliary passages. It is indeed impossible to imagine that bile could find its way by osmosis (or rupture) into the interlobular lymph spaces, as occurs when a duct is completely occluded, without causing disturbance of nutrition; and of all the nutritional disturbances caused by slight degrees of irritation, the most common and most general is increased formation of fibrous tissue. That this explanation of the interlobular fibrosis is probably correct, is further indicated by the fact that this process is earliest developed and is always most advanced at the periphery of the lobules (Plate XIV. Fig. 2). The increased pressure in the bile ducts may also help to determine fibrosis; but there is no reason to suppose that the influence of this factor is other than slight.

We have next to consider the great increase in the number of the smaller bile ducts which are seen in section in the interlobular tissue of the affected area. This is, we believe, in great part explicable as resulting from the distension and elongation, both extreme in degree, of pre-existing ductlets, which subsequently become crowded together, as the hepatic lobules atrophy from without inwards, sometimes probably to complete disappearance. It is doubtful if it is necessary in order to explain the increase in number of the smaller biliary passages to assume that a new formation of bile ducts takes place, such as occurs in the course of development for example, but rather that such elongation and enlargement of pre-existing structures takes place as the result of the mechanical obstruction of the ligature, as occurs, for instance, in the veins in extreme cases of varix of the lower limbs, or of varicocele. At the periphery of the lobules in the affected area the small interlobular bile ducts are usually quite distinct from the adjoining lobules, being separated by strands of fibrous tissue. Occasionally, however, very fine ducts are seen running towards the columns of liver cells, and it is perhaps this appearance which has given rise to

the view that the interlobular bile ducts are developed from these columns, but a careful study of sections of cirrhosis produced experimentally fails to lend support to this view, or to the somewhat allied hypothesis of Cornil that the bile canaliculi, becoming laid bare by the recession of the lobule when atrophy occurs, an ingrowth of epithelium from the extra-lobular bile ducts occurs, which thus affords a lining to the basement membrane, of which the canaliculi are formed. While the occurrence of some such process cannot perhaps be denied, a study of sections from the cirrhotic area has not afforded any proof that new bile ducts can be formed in this manner. The point cannot be settled until staining methods are worked out which will satisfactorily display the termination of the bile canaliculi and the commencement of the smallest ducts. At present, we regard the hyperplasia of bile ducts as in great measure due to the mechanical effect of the contained bile, leaving open for the present the question as to whether other processes may not also occur.

The atrophy of the hepatic lobules, as has been already remarked, appears to commence at the periphery, and to proceed from without inwards. Careful observation fails to reveal any general atrophy of lobules. The cell columns of the affected lobules are of exactly the same size and aspect as those of the healthy lobules outside the area of ligature. The most natural explanation of this progressive disappearance of liver cells from the periphery inwards is that it is the result of the toxic influence of the bile which passes out of the smallest bile ducts. It has already been pointed out that osmosis of bile through the walls of the bile ducts due to increased pressure of the contained bile would naturally be most marked at the periphery of the lobules, where the smallest, and therefore most thin-walled, ducts are met with. This circumstance explains the disappearance of the hepatic lobules from without inwards, as it does also the earliest appearance of fibrosis at the periphery of the lobules. It must, however, be conceded that no alteration of the liver cells is observable at the periphery of the lobules in the cirrhosed area. The fact that the canaliculi of the lobule apparently still retain their connection with the bile ducts in the interlobular tissue after the disappearance of the marginal zone of the lobule, is probably due to the fact that the canaliculi are formed of basement membrane continuous with that of the bile ducts. A similar, but not a parallel, case is observed in the kidney in hydronephrosis when atrophy of the pyramids occurs.

It is difficult to estimate the influence which any pressure exercised by the newly formed fibrous tissue may have in bringing about atrophy of the lobules. The absence of any evidence of compression of the liver parenchyma must, however, be regarded as proof that such an effect must be very small.

The fact that the reaction of the liver to ligature varies in degree in different cases has been already mentioned. This variation in

response may be conceived as due to a lowering of the functions of the affected liver area, varying in different livers. Again, the condition of the smaller ducts in respect of the osmosis of bile under increased pressure may also vary in different animals. Again, conditions connected with the operation may also be effective. Thus it may happen that the ligature, though effective at first, may not, as time goes on, continue to completely close the lumen of the bile duct to which it is applied. In fact, there is no difficulty in suggesting causes for variation in the degree of cirrhosis following ligature, but it is difficult in any given case to produce satisfactory evidence of the cause of such variation.

SUMMARY.

When a single bile duct is ligatured, the portion of the liver remaining outside the area of ligature remains unaffected, while the following changes occur in the ligatured area :—

1. A development of interlobular fibroid tissue occurs. In this tissue small collections of multipartite nuclei are occasionally met with, but such collections form but a small fraction of the interlobular tissue.

2. The larger bile ducts become dilated, and there is a marked hyperplasia of the smaller bile ducts lying between the lobules, which become tortuous and appear considerably increased in number.

3. The hepatic lobules atrophy; the atrophy commencing at the periphery, and proceeding from without inwards.

4. The rapidity with which these changes develop, and their intensity vary considerably in different animals of the same species, though the operative procedure is the same in all cases.

5. The functions of the liver cells in the atrophied lobules still continue, as is shown: by the elimination of sodium sulphindigotate; by the presence of bile in the larger bile ducts; and by the unaltered aspect of the liver cells. All these facts are observable when extreme cirrhosis has occurred.

The mode of production of cirrhosis after ligature of a single bile duct appears to be as follows :—

1. The interlobular fibrosis is attributable to the continued slight irritation set up by bile which passes through the walls of the smaller bile ducts by osmosis, caused by the increased pressure of the bile resulting from ligature. Rupture of the smaller bile ducts probably is not an effective factor in experimentally induced cirrhosis.

2. The dilatation of the larger bile ducts and the marked increase of the smaller ones is, in part, at any rate, directly due to the ligature, and is comparable to the extreme elongation and increase in size of the veins and venules, which is seen in considerable degrees of varix of the lower extremities and in varicocele. Our observations have so far

failed to afford proof of other modes of formation of the interlobular bile ducts.

3. The atrophy of the lobules is due chiefly to the irritant effect of bile which has passed out of the bile ducts, and which acts principally, if not almost exclusively, upon the peripheral portion of the lobule. It does not appear that pressure upon the lobules caused by the newly formed interlobular fibrous tissue is an effective factor in causing atrophy.

DESCRIPTION OF PLATES XIII.-XVI.

PLATE XIII.

FIG. 1.—Anterior surface of liver of cat twelve months after ligature of the left bile duct. *Natural size.* The portion of the liver to the left, in part of its extent, fails to exhibit the outlines of the hepatic lobules, and presents instead a surface which is in places nearly smooth, in other places finely granular, with here and there mammillary eminences of the size of hempseeds or larger, which are paler than the adjoining tissue. At the junction of this altered tissue with the rest of the liver the hepatic lobules are seen to be considerably atrophied. The extreme left border below, where the change is greatest, is seen to have an irregular outline instead of the unbroken curve which it normally presents. The specimen has been hardened in Müller's fluid ; in the fresh state the outlines of the lobules are less distinct, while the mammillary areas of the left portion of the liver, which are of a light yellow colour, form a striking contrast to the deep brown colour present elsewhere, and the fine pitting of the surface seen after hardening is absent. Sections of the right and left portions of this liver are given in Plate XIV. Figs. 3 and 4. (Nat. size.)

PLATE XIV.

FIG. 2.—Section of the left portion of the liver of the cat five months after ligature of the left bile duct. A growth of interstitial fibroid tissue containing numerous nuclei has outlined the hepatic lobules in a very striking manner. The intralobular veins, from which the columns of liver cells radiate, can be readily recognised. In several places the larger branches of the portal vein, together with lymph spaces, can be seen as white clefts. The section of the right portion of this liver is identical with that shown in Fig. 3. Methylene-blue. (× 25.)

FIG. 3.—Section of the right portion of the liver of a cat twelve months after ligature of the left bile duct. This portion of the liver is quite normal in aspect, and is represented so that a comparison may be made with the left portion of the liver in the area of ligature. The interlobular veins are dilated, and the junctions of the lobule are indicated here and there by a few darkly stained interlobular vessels. This, and the succeeding section, Fig. 4, are taken respectively from the right and left portions of the liver represented in Plate XIII. Fig. 1. Methylene-blue. (× 25.)

FIG. 4.—Section of the left portion of the liver of a cat twelve months after ligature of the left bile duct. The hepatic lobules, which are conspicuously atrophied, are separated by a considerable amount of fibroid tissue containing enlarged bile ducts and blood vessels. This tissue, which is irregularly distributed, surrounds the lobules, sometimes completely, sometimes only partially. Some of the interlobular veins are to be recognised, two of them appearing markedly dilated. Below is seen a dilated hepatic duct, which has, however, undergone some contraction, so that its wall has become corrugated. Elsewhere the numerous enlarged hepatic ducts, which the interstitial tissue contains, have

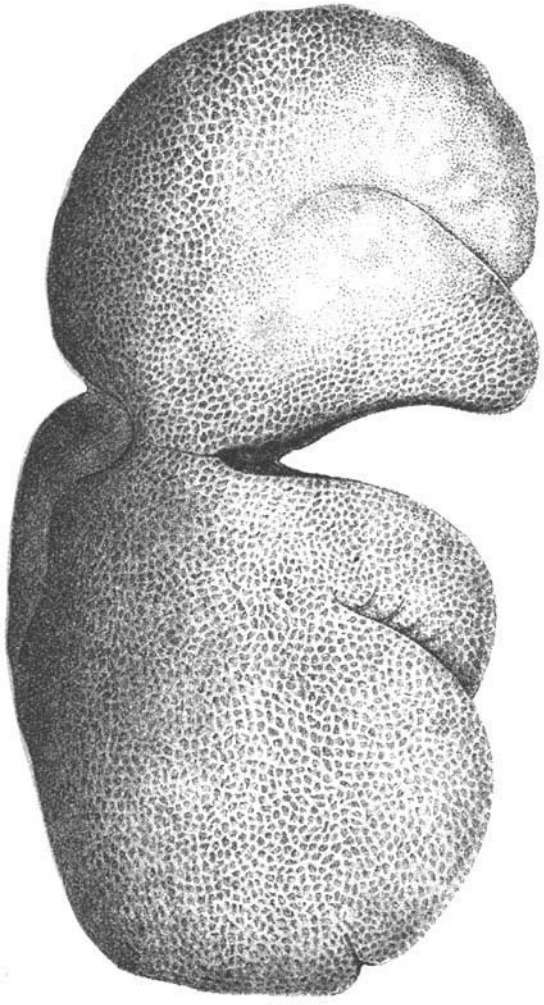

Fig 1

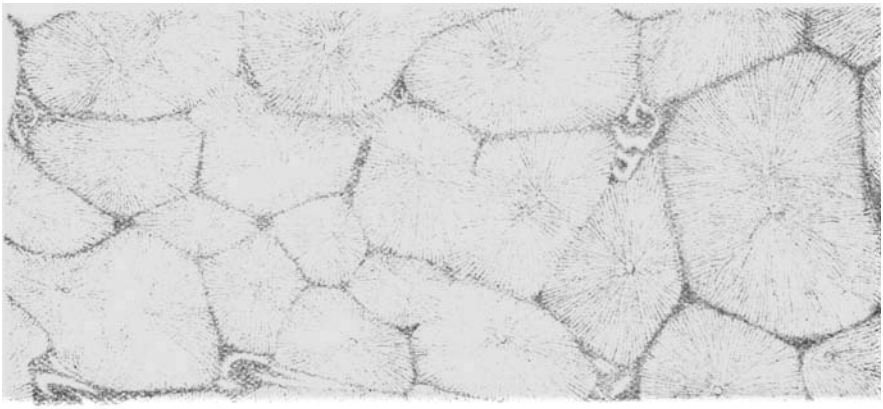

Fig. 2.

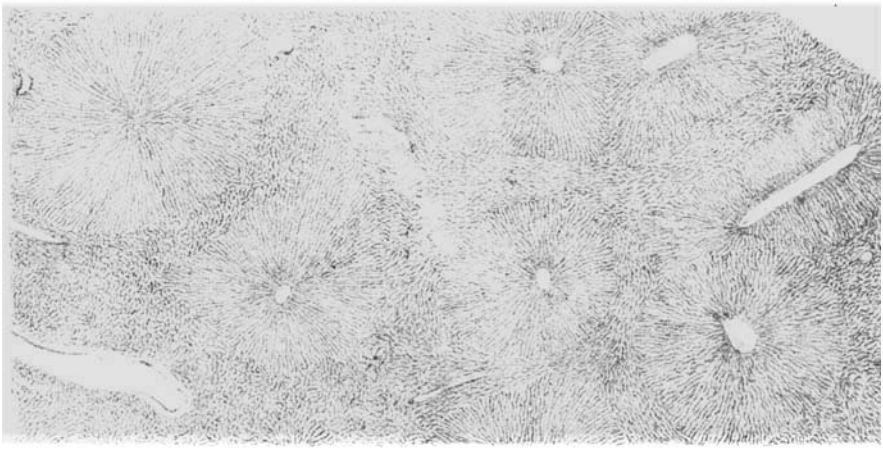

Fig. 3.

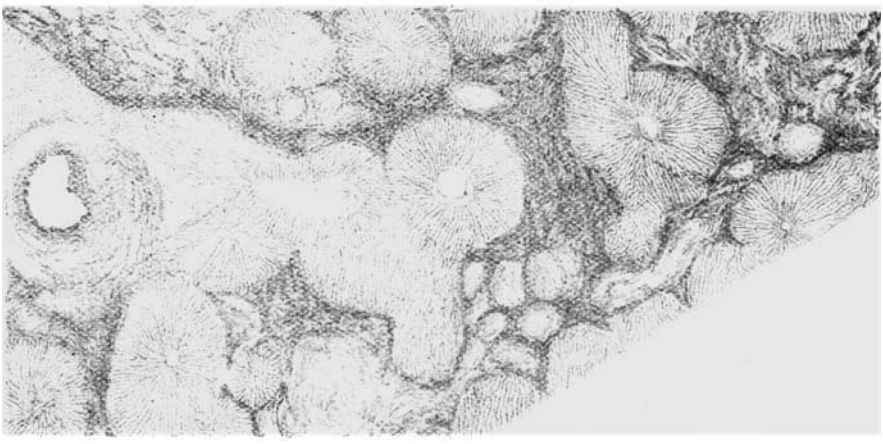

Fig. 4.

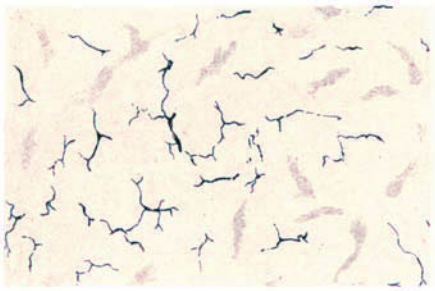

Fig. 5.

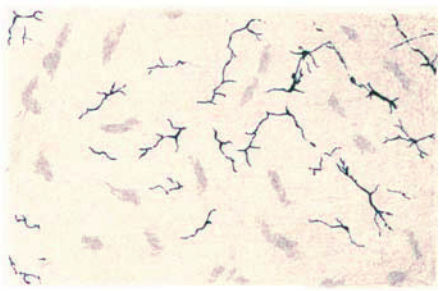

Fig. 6.

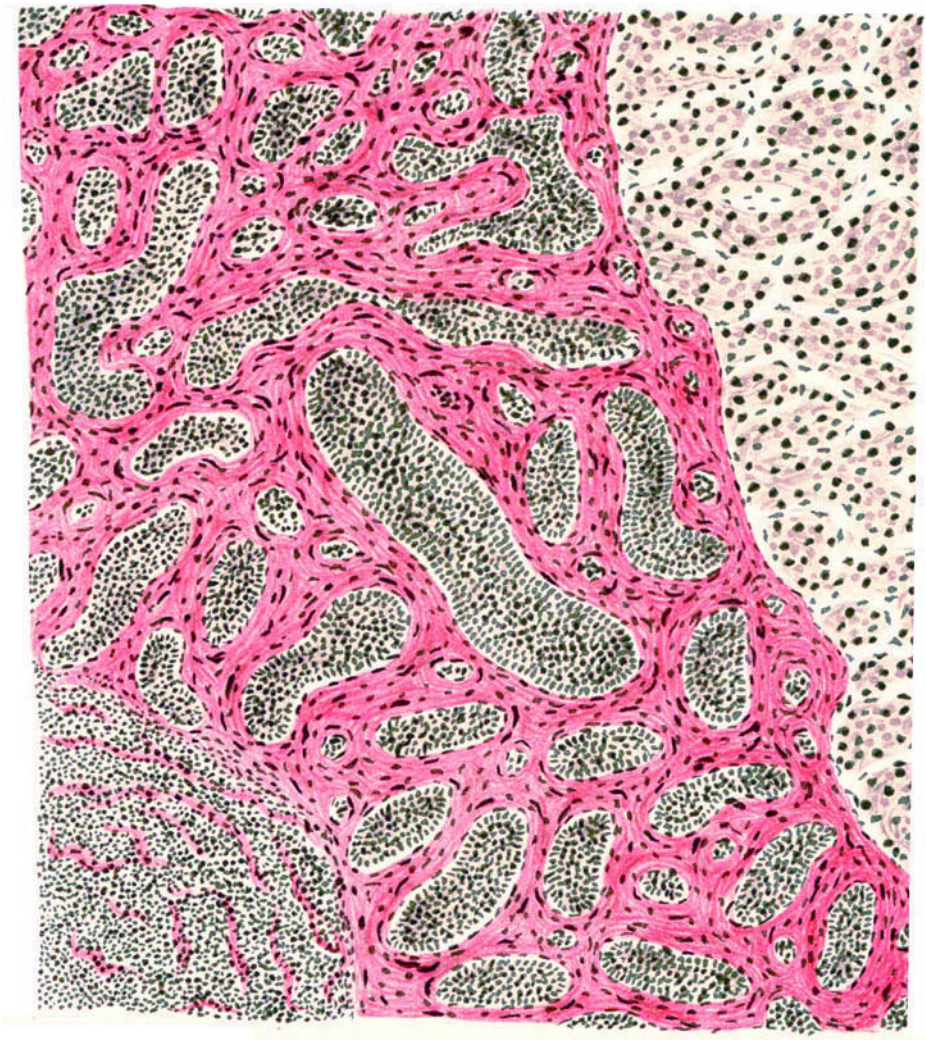

Fig. 7.

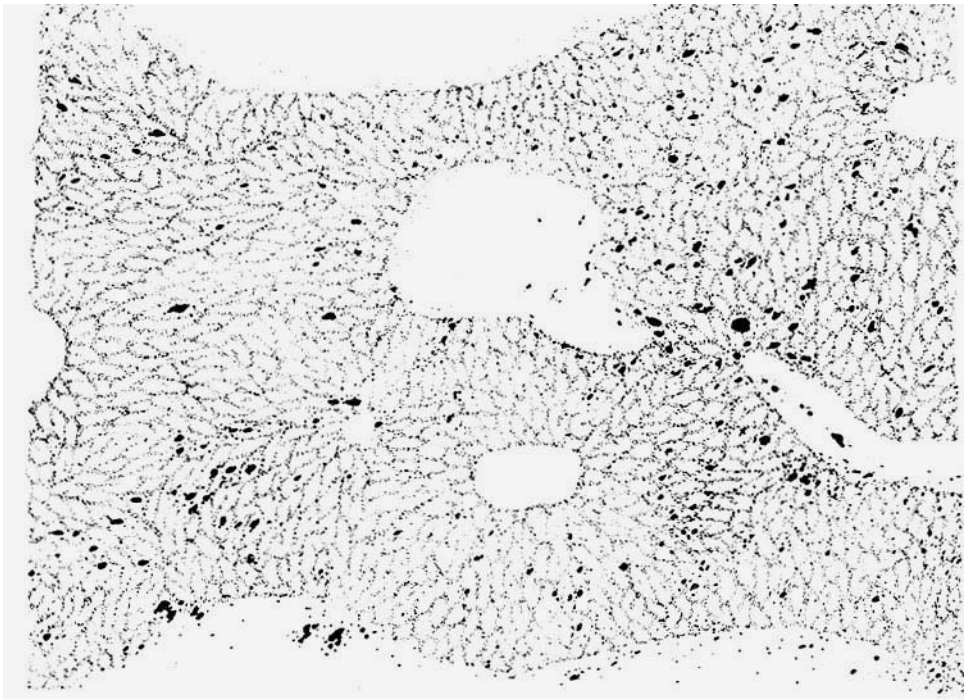

Fig 8

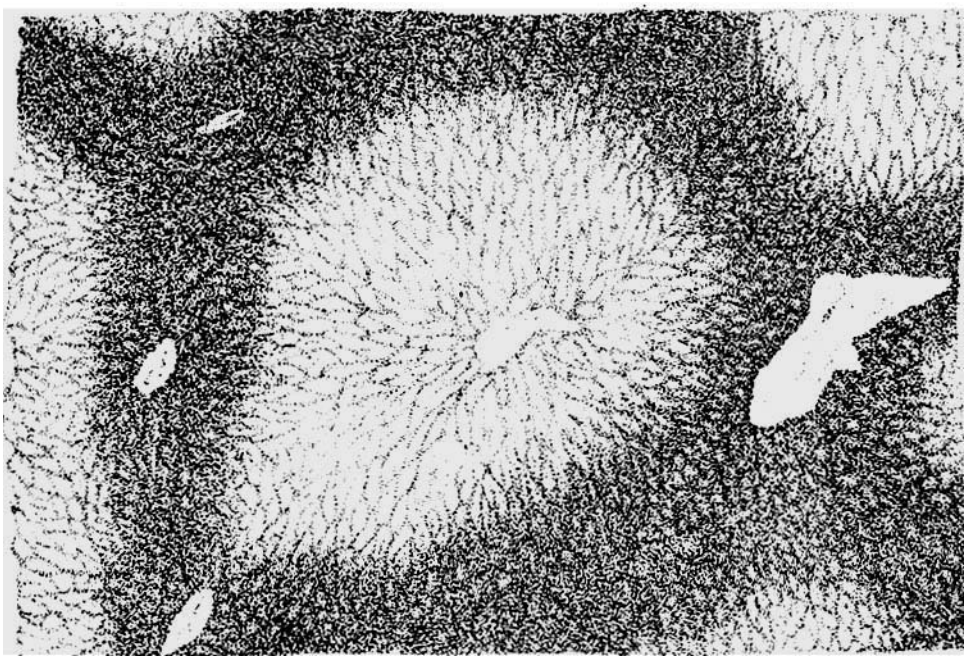

Fig 9

become wholly collapsed during the preparation of the tissue. The peritoneal coat seen above and to the left does not exhibit any change. Methylene-blue. (× 25.)

PLATE XV.

Sections of the liver of a cat twelve months after ligature of the left bile duct.

FIGS. 5 and 6 correspond to the ligatured and healthy areas respectively. The bile canaliculi are injected with sodium sulphindigotate. Unstained. (× 360.)

FIG. 7 is taken from the area corresponding to the ligature. Above and to the right is seen a portion of an hepatic lobule, the cells of which are healthy in aspect. In two places a strand of connective tissue is seen in the lobule, lying by the side of the cell columns. The rest of the section is made up of newly developed interlobular tissue, consisting of well-formed collagen bundles, more or less wavy in outline, and exhibiting numerous flattened, elongated nuclei lying parallel to the connective tissue strands. Embedded in the fibrous tissue are numerous bile ducts running a tortuous course. These ducts are lined by a single layer of closely packed cubical epithelial cells. In the section the lumen of the ducts is not clearly seen, the biliary passages being everywhere collapsed. Below and to the left is seen a small collection of multinucleated leucocytes; such collections are met with occasionally in the fibroid interlobular tissue, but are, on the whole, rarely met with. Stained by van Gieson's method. (× 210.)

PLATE XVI.

FIGS. 8 and 9.—Sections of liver of cat twelve months after ligature of the left bile duct. (The liver is the same as that represented in Plate XIII. Fig. 1, Plate XIV. Figs. 3 and 4, and Plate XV. Figs. 5, 6, and 7.) Fig. 8 represents the area drained by the ligatured left bile duct; Fig. 9 is taken from the right lobe, the ducts of which are free. Both sections show fatty change. In Fig. 8 the atrophied lobules show here and there cells lying by the side of the liver columns which are loaded with fat; similar cells containing fatty material are also seen in the interlobular tissue. The hepatic cells exhibit a fine stippling. In Fig 9 the periphery of the lobules is the seat of an abundant cell infiltration, while elsewhere the cells of the parenchyma exhibit only very fine black dots, as in Fig. 8. The large black collections seen in Fig. 8 are noted in sections unstained by osmic acid to represent mononucleated cells containing abundant reddish-brown material, presumably derived from red blood corpuscles. It is this pigment which takes the osmic acid stain. Osmic acid staining. (× 70.)