The Pressure of Bile Secretion and the Mechanism of Bile Absorption in Obstruction of the Bile Duct.

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In the course of a series of experiments which were made for the purpose of determining the mode of entry of bile into the lymphatics of the liver during obstruction of the common bile duct we had occasion to measure the pressure of bile secretion in several animals. Our results were so different from the figures generally given that we have ascertained the maximum pressure of bile secretion in a number of dogs, cats, and rabbits, in two guinea-pigs, and in two monkeys. The first part of the present paper deals with the pressure of bile secretion; in the second part the mechanism and site of bile absorption are discussed.

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Part I.—The Pressure of Bile Secretion.

Previous Observations.

Estimations of bile-pressure were first recorded by Friedländer and Barisch (5). These observers found that the maximum pressure attained by the bile in guinea-pigs varies between 184 and 212 mm., measured in terms of the height of a column of bile and water. Their method of procedure consisted in ligaturing the common bile duct near the duodenum, and tying a cannula into the fundus of the gall bladder which was then brought forward into the abdominal wall. A vertical glass tube was connected to the cannula by rubber tubing, the animal placed on its side and a millimetre scale affixed to the vertical tube so that the zero mark was opposite the fundus of the gall bladder. The bile mounts in the tube at first rapidly, then with decreasing speed until a maximum is reached. The column of fluid moves up and down with the respirations of the animal, and sinks again after a maximum is attained.

Heidenhain (8) in 1868 published the results of a number of experiments on bile secretion, and among them were several in which the bile-pressure

was recorded. In a curarised dog the maximum pressure attained was 146 mm. bile. In a rabbit a pressure of from 163 to 168 mm. bile was recorded, in another rabbit 115 mm. bile was the maximum, while in a third rabbit a maximum pressure of 242 mm. bile was reached.

In Hermann's 'Handbuch der Physiologie,' Heidenhain (9) gives the secretion pressure of bile in five dogs as varying from 110 to 220 mm. of a solution of sodium carbonate. A simultaneous measurement of blood-pressure in a branch of the superior mesenteric vein in each of these animals gave figures varying from 50 to 90 mm. of a solution of sodium carbonate. From these figures and those of Friedländer and Barisch, Heidenhain concluded that secretion of bile is not a mechanical effect of blood-pressure in the liver, but a vital act, and that the pressure of secretion is produced by the activity of the liver cells. Heidenhain showed, moreover, that the maximum pressure reached in any case is not an absolute measurement of the force that the liver cells can exert in secretion, but is rather the pressure at which bile secretion is balanced exactly by bile absorption.

Most text-books of physiology give Heidenhain's figures. Afanassiew (1) is stated to have recorded the maximum pressure in dogs as 275 mm. bile.

Richet (15) gives the maximum pressure in cats as varying between 158 and 264 mm. bile. These figures appear to be taken from the results of experiments by Kowalewsky (12), who finds the pressure varies from 12 to 20 mm. Hg. in curarised cats.

In 1905, Freese (3) measured the force of contraction of the gall bladder in dogs. He introduced a cannula into the gall bladder through the common bile duct and cystic duct, then tied a ligature round the common duct near the duodenum. Stimulation of the splanchnic nerve caused contraction of the gall bladder sufficient to support a column of Ringer's solution 214·5 to 313 mm. high. The method does not appear to have excluded the secretion pressure of bile. Ligature of the common bile duct near the duodenum must have brought about a rapid rise of pressure in the bile passages which would be transmitted to the interior of the gall bladder. It is possible that some of the pressure changes in Freese's experiments, ascribed by him to the musculature of the gall bladder, may have been due to changes in the rate of secretion and absorption of bile in the liver.

Methods employed in the Present Research.

The animals were anæsthetised with chloroform. Tracheotomy was then performed, and the anæsthetic subsequently continued by a tracheal tube. In some cases ether was employed after the chloroform. In all experiments the animals were kept deeply under the anæsthetic and killed by an overdose,

or by opening the inferior vena cava in the thorax. After anæsthesia was complete, the animal was partially immersed in the supine position in a large bath of 0·9 per cent. salt solution kept at a constant temperature of 37° C. The abdomen was opened and the cystic duct clamped by a small strong clip near the gall bladder. A silver cannula was inserted into the common bile duct and tied in position there. A fine piece of rubber tubing was slipped over the end of the cannula and attached to the lower end of a vertical piece of glass tubing 1 mm. in internal diameter. A millimetre scale was attached behind it, and so arranged that it and the glass tube could be raised or lowered to adjust the zero mark. The rubber tubing had in it a T-piece, from the third limb of which another piece of tubing led off to the side of the bath, and was so arranged that when open the drops of bile fell on an electric marker, by means of which the rate of secretion at zero pressure could be recorded on a slowly moving drum. The abdomen was freely opened, so that movements of the diaphragm affected the pressure as little as possible; in this way the respiratory spring of the column of bile was diminished and rarely exceeded 1 or 2 mm. The opening in the abdomen was covered with a sheet of cotton wool, and the animal was then entirely immersed, with the exception of the head and neck, in the warm salt solution. The vertical glass tube was adjusted so that the zero mark was at the level of the hepatic duct at the portal fissure. Part of the liver was thus above the level of the zero mark, but the greater part of it was at a lower level. This we believe to be as exact a method as that adopted by Friedländer and Barisch. It is certainly advantageous to maintain the temperature of the animal by warm saline when the abdomen is open, seeing that the experiment may be of some considerable duration.

In some animals we also determined the blood pressure in the splenic vein as near the portal vein as possible. The pressure was recorded by means of an apparatus similar to that described for recording the bile pressure. In this case a T-tube led to a pressure bottle containing a saturated solution of sodium carbonate, and the apparatus was filled and the pressure recorded in terms of a column of that solution. Before removing the clip from the vein after insertion of the cannula, the fluid was allowed to fill the vertical tube to a height approximating to the probable blood pressure; the pressure bottle was then shut off by a clip, and the clip on the splenic vein removed. The method was found to give good results.

Occasionally we made intravenous injections of extract of duodenal mucosa or of bile into a jugular vein.

In beginning an observation we usually recorded the rate of flow of bile secretion at zero pressure by the marking of drops in the way described on

a slowly moving drum. After a time the tube leading to the dropper was clamped, the bile began to rise in the vertical tube and the height reached was recorded every five minutes, and in some cases every minute. Readings were continued for some time after a maximum pressure had been registered. We frequently allowed the bile to flow again at zero pressure, and after a time recorded the rate of secretion again. In some animals several estimations of the maximum pressure were made with intervals between of secretion at zero pressure. In a few cases we took simultaneous records of bile and pancreatic pressures; the latter we intend to deal with in a subsequent paper.

Results Obtained.

The bile pressure was measured in 19 cats. One of these was unhealthy and suffering from diarrhœa. The maximum bile pressure in this cat was 210 mm. bile, and was the lowest of the series. The lowest maximum of the other 18 was 240 mm., and the highest pressure of any we recorded was 373 mm. The average maximum pressure for 19 cats was 304·4 mm. bile. The subjoined table gives the figures for each animal.

Cat.	Sex.	Weight.	Maximum pressure of bile.
		grammes.	mm.
A	Male	3300	366
C	,,	2850	330
D	Male (castrated)	2900	280
E	Female	2650	373
F	Male	2600	310
G	,,	2950	335
H	Female	2500	321
I	Male	3200	336
J	,,	2750	282
L	Female	2430	289
M	Male	3100	210
N	Male (castrated)	3720	310
O	Female	2500	325
P	Male	3200	315
Q	,,	2850	319
R	,,	3850	240
S	Female	2600	272
T	,,	2900	244
U	,,	2300	327

Measurements of bile pressure were made in eight dogs. The lowest maximum recorded was 243 mm. bile; the highest was 342 mm., figures considerably in excess of those given by Heidenhain. The lowness of the readings obtained by Heidenhain in the dog may possibly be due to his having employed curari. The average pressure in the eight dogs we

experimented on was 300 mm. bile. The table presents the figures for each animal.

Dog.	Sex.	Weight.	Maximum pressure of bile.
		kilos.	mm.
A	Male	10·5	328
B	,,	13·0	295
C	,,	12·6	243
D	Female	11·5	285
E	Male	12·2	342
F	,,	11·0	285
G	,,	9·25	304
H	,,	10·5	315

Four ordinary rabbits gave us maximum bile pressures ranging from 181 to 204 mm. bile. The average pressure was 197 mm.

In two Belgian hares pressures of 225 mm. and 306 mm. bile respectively were recorded. The latter animal was a large one, and the rate of bile secretion was rapid.

The subjoined table gives the details.

Animal.	Sex.	Weight.	Maximum pressure of bile.
		grammes.	mm.
Belgian hare A	Female	2800	225
Ordinary rabbit B	Male	2100	203
Ordinary rabbit C	Female	1900	181
Belgian hare D	Male	3300	306
Ordinary rabbit E	Female	2700	200
Ordinary rabbit F	,,	2250	204

We made two estimations in guinea-pigs, but found these animals difficult to work with. A male guinea-pig, weighing 480 grammes, gave us a maximum bile pressure of 122 mm.; a female, weighing 650 grammes, gave a maximum of 154 mm. bile. These figures are less than those given by Friedländer and Barisch. Both guinea-pigs took the anæsthetic badly, and died before many observations had been made. Our figures are for this reason in all probability lower than the average.

In one monkey (*Macacus rhesus*) the maximum bile pressure was found not to exceed 220 mm. bile. This animal was unhealthy, and had suffered for some time from diarrhœa. In another monkey (*Macacus rhesus*) the bile pressure rose to 321 mm. bile.

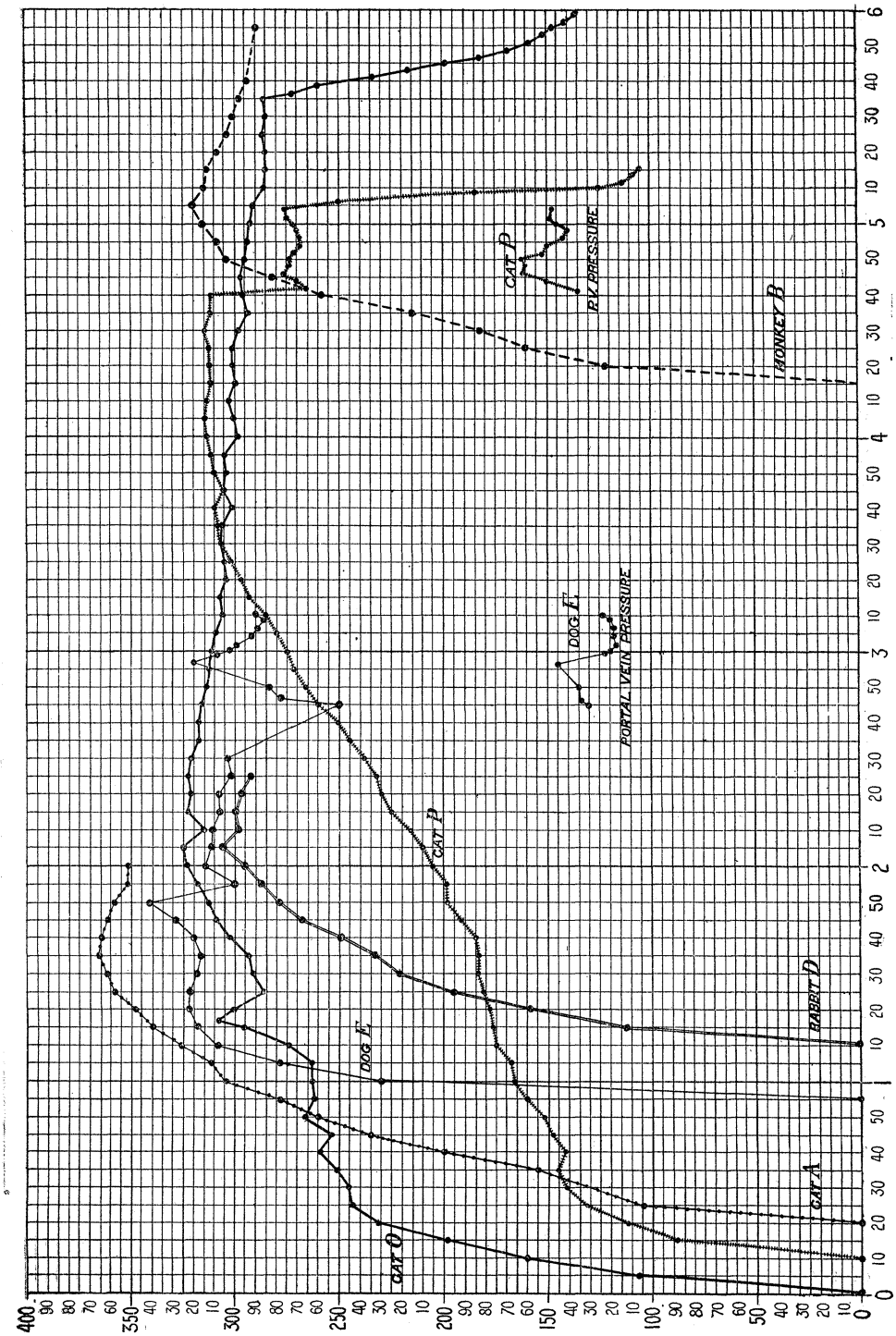
The highest bile pressures were recorded in cats, 373 mm. bile in Cat D

being the greatest. The average maximum for cats, 304·4 mm., in our series corresponds closely with the average maximum for dogs, 300 mm. Rabbits have a lower pressure, in round numbers about 200 mm. bile. In a healthy monkey the maximum pressure was 321 mm. Bile pressure in the monkey probably averages about the same as that in the cat and dog.

In all our experiments the pressures recorded are measurements of the pressure in the common bile duct in terms of a vertical column of bile. The gall bladder was occluded in every case, so that its contractions could have no influence on the pressure; that the occlusion was complete was verified in every animal after death. The free opening of the abdomen under warm normal saline prevented extraneous pressure on the liver by abdominal and diaphragmatic movements; consequently, little oscillation of the column of bile ever occurred, and the readings may be accepted as indicating a true secretion pressure.

Graphic representations of the rise of bile pressure and its time relations are interesting. The accompanying chart gives several examples of pressure curves. In it the figures on the left-hand side denote the pressure in terms of millimetres of bile, while the figures below the chart represent time in five-minute intervals.

As a general rule, the bile pressure rises rapidly at first, the rate depending chiefly on the rate of bile secretion. After reaching a pressure of 100 mm. or thereabouts, the rise of pressure begins to slow down. Cat A, Dog E, and Rabbit D (see chart) gave typical pressure curves. In these animals the bile pressure rose rapidly, but the amount of rise diminished at every reading until a maximum was reached, after which the pressure began to fall. The curve of pressure in Cat P represents another type in which, after attaining a certain height, the pressure remains stationary or even falls, but only temporarily, afterwards rising gradually, but slowly. In this cat the maximum pressure, 315 mm., was attained 3 hours 55 minutes after commencement of the experiment. We had several examples of this slow rise to a maximum. In the chart is also placed a short record of the height of portal vein pressure of Cat P; the large drop in bile pressure was due to interference with the portal circulation in putting the cannula into the splenic vein; some of the sodium carbonate solution also entered the circulation. A short record of portal vein pressure in Dog E is also given. A simultaneous reading of bile pressure and portal vein pressure shows that the two coincide in their variations. Rise of blood pressure is accompanied by a rise of bile pressure; fall of blood pressure by a fall of bile pressure. Changes in blood pressure in the portal vein at once show themselves in the rise or fall of bile pressure. The rapid


CAT A
RABBIT D
CAT D
PV. PRESSURE
MONKEY B
DOG F
PORTAL VEIN PRESSURE
DOG F
CAT D
DOG F
CAT D

variations thus brought about point to a mechanical explanation of their occurrence. Heidenhain argued that bile absorption took place with greater rapidity at a low blood pressure, while the rate of secretion by the liver cells was also diminished. No doubt this is a potent factor in the long run, yet the slight and rapid changes in pressure that occur must be mechanical. Stimulation of the vagus nerve, for instance, causes a rapid and simultaneous fall of both bile pressure and portal vein pressure. In Dog C, with bile pressure 204 mm., and portal vein pressure 107 mm., stimulation of left vagus by faradic current for five seconds caused an immediate fall of bile pressure to 195 mm. and blood pressure to 95 mm. One minute later bile pressure had risen to 214 mm. and blood pressure to 115 mm.

Injection of extract of duodenal mucous membrane into a vein frequently caused a rise of bile pressure, and was found to increase the rate of secretion at zero pressure. It was not always successful, and often, while found to be very active on pancreatic secretion, had no effect on bile secretion or pressure.

The injection of bile into a vein was invariably attended by increased rate of secretion. It usually brings about an increase of bile pressure; but if the latter is high at the time of injection very little effect is noticed.

The animals we experimented on were, with a few exceptions, well nourished, and had been fed in the morning some hours before being anæsthetised. The rate of bile flow as determined before estimation of bile pressure was found to be very variable. A rapid rate of secretion is not essential to the production of a high pressure, but it influences the form of the pressure curve. The size and weight of the animal does not appear to influence bile pressure, provided the animals are of the same species.

We did not take many subsequent records of bile pressure in the same animal. The rate of secretion of bile is usually diminished after the bile duct has been obstructed for some time, but not invariably; we have obtained records of bile flow in which the rate has been increased. Subsequent records of bile pressure give as a rule lower readings than the first, as was pointed out by Friedländer and Barisch. An exception may be quoted. In dog D a maximum pressure of bile of 285 mm. was recorded. After release of the bile from the bile duct a record of bile flow was taken, and, half an hour later, secretion was more rapid than it had been prior to the first experiment. A second record of bile pressure, taken an hour after the first, reached a maximum of 305 mm. bile, an increase of 20 mm. pressure. A lower second reading is not therefore essential, and with an increased rate of secretion by the liver cells there may be, as in this case, a higher pressure reached.

Part II.—Absorption of Bile from the Bile Passages in the Liver.—Previous Observations.

Ligature of the common bile duct in the living animal is followed sooner or later by the presence of the constituents of bile in the blood. It was at one time believed that the bile enters the blood directly in the liver. Haller (6) stated that communications exist in the liver between the hepatic veins and bile ducts, and in support of this adduced the fact that injection of the bile ducts with fluid is followed by its escape into the veins. Saunders (16), in 1795, published the results of experiments performed on dogs. In a living dog he ligatured the common bile duct and killed the animal two hours afterwards. He found the lymphatics of the liver distended with bilious fluid and the thoracic duct filled with moderately diluted bile. There was no appearance of jaundice as indicated by the conjunctiva, and he stated that it was probable that bile was only just beginning to enter the blood vessels.

Tiedemann and Gmelin (17), in 1827, recognised that most of the observations of Saunders were correct. They found jaundice appeared not earlier than the third day after ligature. Frerichs (4) noted a yellow tinge of the conjunctiva first appearing between the 60th and 70th hour after ligature. He challenged the statement of Saunders that bile is found in the blood after two hours.

That the bile is absorbed by the lymphatics of the liver in obstructive jaundice has received abundant confirmation from the works of V. Fleischl (2), Heidenhain, Vaughan Harley (7), and many other observers. Heidenhain determined experimentally the site of the escape of bile from the bile channels into the lymphatics. He injected a solution of indigo-sulphate of soda into the bile ducts and found that the skin, mucous membranes, and urine were rapidly coloured blue. Examination of sections of the liver showed him that there was no coloration of the interior of the lobules, the blue was present in the interlobular bile ducts, but not in the bile capillaries. Secretion of bile must have been going on while absorption was taking place. Heidenhain concluded that the bile escapes from the interlobular bile ducts into connective-tissue spaces and is carried away by the lymphatics.

Most observers, and especially Vaughan Harley, have insisted that in obstructive jaundice the bile reaches the blood solely by the lymphatics. Nauwerck (14), on the other hand, denies this and believes that the bile enters the blood directly through fine channels in the liver cells.

Mall (13) has recently stated that when the lymphatics of the liver are injected from the bile duct there is always an extravasation in the centre of

the "portal unit." Extravasation does not take place from the bile capillaries, but only from the duct as it communicates with the capillaries, as well as from the larger bile ducts. Mall finds that the lymphatics of the liver do not drain all portions of the liver, but only those parts formed by the centres of the "portal units." He states that there are no lymphatics in the centres of the lobules, nor at the nodal points.

In a paper (11) published last summer we gave reasons for concluding that there are no lymphatics in the liver lobules at all; they are confined to the portal spaces, *i.e.*, to the centres of the "portal units" of Mall.

The question of bile absorption resolves itself into that of the mode of formation of lymph in the liver. If there are no lymphatics in the lobules of the liver, and the production of liver lymph is to be regarded as purely mechanical, its source must be confined to the portal spaces. In this case the interlobular veins must be extraordinarily permeable to allow the passage outwards into the lymphatics of so large an amount of concentrated lymph. On the other hand, if the liver cells take part in its formation, the lymph must be secreted at the periphery of the lobules, and if all the cells in the lobule participate there must be something of the nature of a communication from cell to cell throughout the lobule. Given such a mechanism, the secretion of lymph may be regarded as a vital act on the part of the liver cells. We hoped that we might by our experiments throw some light upon this question.

Methods Employed.

After determining in the manner already indicated the maximum pressure of bile secretion in an animal we allowed the obstructed bile to escape from the bile passages. A piece of rubber tubing leading from a reservoir containing carmine gelatine was then slipped over the cannula in the common bile duct, and the bile passages were injected with carmine gelatine at pressures varying in different animals. We made use of an apparatus by means of which we could inject at pressures measured in terms of the height in millimetres of a vertical column of water. The difference in pressure between similar heights of a column of bile and a column of water being practically negligible, the pressures may be regarded as sufficiently alike. In most cases we employed a pressure of injection not exceeding the maximum of bile pressure previously recorded in the animal. In some cases the injection was continued and the bile duct ligatured before the animal was killed. In others the injection was made *post mortem*, the animal being killed by an overdose of chloroform, or by opening the inferior vena cava above the diaphragm so as to avoid a rise of blood pressure in the liver. Sometimes we used an injection pressure higher than the maximum bile

pressure, in other cases a lower pressure was employed. Injection was continued for periods of time varying from one to six hours.

On completion of the experiment, the bile duct was ligatured and the liver removed and placed in cold 10-per-cent. formalin. After a time it was cut up, fixation completed in formalin, and pieces cut in paraffin. Sections were lightly stained with hæmatoxylin and examined.

Results Obtained.

Injection of the bile duct at the maximum pressure of bile secretion was in every case sufficient to fill the larger bile ducts with carmine gelatine. Where the animal was living throughout the experiment the secretion of bile continued, the lymph vessels in the portal fissure were distended with bile-stained lymph, and the yellow colour could in some cases be seen extending into the thoracic duct. In several experiments both in the cat and dog carmine gelatine was found in the lymph trunks of the liver and in the portal lymph glands. Whenever injection mass appeared in the lymph trunks outside the liver the injection had been at a comparatively high pressure or had been continued for some time. In Cat A, the maximum bile pressure of which was 366 mm., the injection pressure was 410 mm. for 40 minutes, and was then raised to 520 mm. water for 30 minutes longer. The animal was living throughout the time of injection, and carmine gelatine was freely mixed with lymph both in the portal lymphatics and thoracic duct. In Dog A, maximum bile pressure 328 mm., the injection was at a pressure of 400 mm. water for three hours (dog living). In this case also carmine gelatine was present in portal lymphatics and thoracic duct. Cat L, maximum bile pressure 289 mm., was injected for six hours at a pressure of 120 mm. water. The animal was dead before injection began, but the inferior vena cava had been ligatured above the diaphragm; carmine gelatine was found in the portal lymphatics on completion of the experiment.

We attempted to ascertain the time at which bile appears in the portal lymph trunks after ligature of the bile duct. For this purpose we clamped the cystic and common bile ducts in a cat, opened a lymph trunk near the portal fissure and gathered the lymph every two minutes by pieces of blotting paper which had previously been soaked in a solution of cane sugar and dried. After drying the lymph-filled pieces we tested them with strong sulphuric acid for bile acids. We were not satisfied with the reaction, but the lymph trunks issuing from the liver were strongly bile-stained one hour after obstruction of the bile duct. Heidenhain found indigo-sulphate of soda to appear in the lymph very soon after its injection into the bile ducts, but in such an experiment there is no guarantee that the entry has not been

made by rupture of the interlobular ducts. Heidenhain indeed explained its occurrence on this supposition. It is difficult to show the presence of small quantities of bile in the blood, but in many of our experiments the urine contained bile acids. Dr. Cramer kindly tested the urine for us; Gmelin's test for bile pigment gave negative results, but bile acids were readily demonstrable. Bile acids were found in the urine two hours after the beginning of a record of bile pressure.

In animals which were kept alive during injection of the bile ducts at a pressure lower than or not exceeding the maximum bile pressure attained, sections of the liver show little injection. The larger bile ducts are filled with carmine gelatine and the injection passes into the smaller interlobular ducts. In the dog and cat very few of the bile capillaries are injected, a few are filled at the periphery of the lobules, but the injection does not extend more than one or two cells inwards. The adjoining liver cells are frequently filled with a lighter coloured (diluted) carmine gelatine. These cells appear to have been injected from the bile capillaries. The rabbit's liver shows the same appearance, but more of the bile capillaries are injected. Hering (10) noted the filling of liver cells from the bile duct. He stated that Berlin blue, when injected into the bile duct under so small a pressure that no extravasation takes place, fills only the bile capillary network in the periphery of the lobule. Higher pressure produces extravasation first into the liver cells in the form of small round drops, later irregular large drops, lastly, the whole liver cell appears blue. Further injection bursts the cell wall, and the injection flows into masses or escapes into the blood capillaries. We have noticed a similar appearance in sections of the livers examined. Injection of the bile ducts at a pressure near to or exceeding slightly the maximum bile pressure almost invariably causes extravasation into the blood vessels, and this is especially liable to occur when the injection is carried out in the dead animal. The extravasation appears to take place in the manner described by Hering by a filling of the cells at the periphery of the lobule and escape of the injection from them into the neighbouring sinusoids. In livers injected after death this filling of liver cells and escape into blood vessels renders the interpretation of the appearance produced a difficult one. The injection undoubtedly gets into the blood vessels at the periphery of the lobule. In an animal injected during life the appearance is somewhat different. In Cat E, which was injected during life for 55 minutes only at a pressure of 443 mm. water (maximum bile pressure, 373 mm.), the lymph of the portal lymphatics and thoracic duct contained carmine at the end of that period. Sections show extravasation of carmine gelatine into the cells at the periphery of the lobules, but no injection of the blood vessels as

in the other livers. There has been escape into the blood vessels at the periphery of some of the lobules, and the carmine gelatine has been taken up by Kupffer's cells, and appears in them in the form of small round drops. Kupffer's cells are greatly distended with drops near the periphery of the lobule, and contain carmine gelatine in decreasing amounts towards the central vein, in the neighbourhood of which they are generally free.

The most valuable injections are those in which the bile duct has been injected at comparatively low pressures so as to avoid extravasation, and yet fill the interlobular bile ducts. If the pressure is higher, rupture occurs as stated, but there is also the appearance of injection mass having passed out of the finer interlobular ducts into connective-tissue spaces. It is probable that with a high pressure of injection most of the fluid passes out in this manner and so reaches the lymphatics. Heidenhain was undoubtedly right in assigning the site of rupture to the fine interlobular ducts leading from the lobules. When a low pressure is employed there is no trace of such rupture, although the ducts are filled, yet in this case bile is escaping from the liver by the lymphatics. In the rabbit's liver, where injection penetrates along the bile capillaries further into the lobules, one often sees a number of cells in a column suffused with diluted injection mass, as though the material were passing through them in the direction of the periphery of the lobule.

The readiness with which obstruction of the bile duct is recovered from, the bile again following its natural course when the obstruction is removed, and the observations of Heidenhain that the bile secreted after removal of the obstruction contains the same relative proportions of solids to fluid, show that no permanent damage is caused by the leakage, assuming it to be a leakage. One would hardly expect so complete a recovery were there a mechanical rupture of the wall of the bile ducts. One must rather assume that there is some physiological explanation of the absorption of bile. It is possible that the walls of the interlobular ducts are capable of allowing bile to pass out without any physical damage resulting, and that such passage cannot occur when the internal pressure is reduced, thus acting as a kind of safety valve allowing escape into the lymphatics when required. Carmine gelatine, however, does not appear capable of passing out in this way when injected at pressures too low to produce extravasation, but high enough to turn the flow of bile into the lymphatics.

Escape of bile into the lymphatics, if it occurs from the liver cells directly, can only be from the cells at the peripheral part of the lobule. Inside the lobule the only escape possible is by the natural channels, the bile capillaries, or into the fine plasmatic channels which permeate the liver

cells. It is remarkable that the protoplasm of the liver cell, containing as it does the plasmatic channels and the origin of the bile capillaries, should be able to sustain so great a difference of pressure without bile passing from the bile capillaries into the blood sinusoids. That the liver cells should be capable of injection in much the same manner both from the blood vessels and from the bile ducts is a fact of extreme importance. The pressure necessary in either case is a comparatively small one. In none of our experiments on the injection of intracellular canals in the liver from the blood vessels did we find any escape of injection material from the cells into the bile passages. On the other hand, injection of the bile ducts in the dead animal appears to be invariably attended with filling of a few of the cells at the periphery of the lobule and escape into the blood vessels.

The intracellular plasmatic channels are in direct communication with the blood vessels, but when injected from the latter it is often difficult to make out in every cell the mode of entrance of the injection. It is probable that the liver cell exerts a controlling influence on the amount of plasma which passes in from the blood. We found it difficult to wash the injection mass out of the channels by a subsequent perfusion through the blood vessels of normal saline.

We suggested in our previous paper that the intracellular plasmatic channels of the liver act as an intermediate system, linking the blood vessels in the lobules to the lymphatics outside, and that the lymph passes from cell to cell on its way to the periphery of the lobule. The absorption of bile by the lymphatics in obstructive jaundice seems to us to favour this view. The mechanism of bile absorption appears to be in the liver cell. When the passage of bile is obstructed, the pressure in the bile ducts and capillaries rapidly rises, secretion continues, but is diverted in the peripheral cells of the lobules into the lymph stream; when obstruction is removed, the bile again follows its normal course. The amount of pressure which the liver cell has to sustain, and which is exerted on it when the bile duct is occluded, is comparatively low, and does not materially affect its vitality. An example of this is furnished by Dog D, already instanced, in which a maximum bile pressure of 285 mm. bile was recorded in the first experiment. The obstruction was then removed, and a record of the rate of bile flow taken. The rate of secretion half an hour later was more rapid than it had been prior to the experiment. A second record of bile pressure taken an hour after the first gave a maximum pressure of 305 mm. bile. That subsequent estimations of bile pressure are not as a rule as high as the first may quite well be explained by a diminution of activity of the liver cell, due to the length of time the animal is under the anæsthetic.

The form of the curves of bile pressure shows that there is not much absorption until the pressure has reached about 100 mm. bile. The rate of rise of pressure then begins to diminish more rapidly in some cases than in others. Absorption is at first slow, but gradually increases until its rate is as rapid as the rate of secretion when the column of bile becomes stationary.

On the death of the animal, the bile pressure, if high, sinks rapidly at first, but on approaching a pressure of about 100 mm. falls much more slowly and becomes almost stationary. The same thing occurs even if death has been caused by opening the inferior vena cava above the diaphragm. Blood pressure in the liver rapidly falls to zero, but the bile pressure falls slowly. The curve of fall of bile pressure after death is given on the chart. In Cat O, the sudden fall of bile pressure near the end of the tracing is due to death from an overdose of chloroform. When the pressure had fallen to 149 mm. bile, the inferior vena cava was divided above the diaphragm; bile pressure fell very slowly, and six minutes later was 134 mm. In Cat P, death was brought about by division of the inferior vena cava, and the pressure of bile secretion, which was 276 mm. at the time, fell rapidly at first, then at a decreasing rate. Ten minutes after the vein had been opened the bile pressure was 108 mm., and falling very slowly. If the bile had been escaping from ruptured bile ducts into the lymphatics or into the blood vessels, it is improbable that this slowing of the fall of pressure would have taken place.

The absorption of bile seems to us to be bound up with the formation of lymph in the liver, and while we advance no definite proofs in favour of Asher's view, we are inclined to think that the phenomena observed in the absorption of bile can best be explained on the hypothesis that lymph is a product of the activity of the liver cells, and that in obstructive jaundice the bile secreted leaves the liver cells with the lymph, instead of by its proper channels, the bile canaliculi.

Summary.

The maximum pressure reached by the bile in obstruction of the bile duct exceeds the figures originally given by Heidenhain. In the dog, cat, and monkey the average maximum pressure is about 300 mm., measured in terms of a vertical column of bile. The highest pressure recorded was 373 mm. bile in a cat. In the ordinary rabbit the pressure reaches about 200 mm. bile, but may exceed 300 mm. in the case of the Belgian hare.

After obstruction of the common bile duct and cystic duct, the pressure in the bile passages rises rapidly at first, but slows as a maximum is reached. Subsequent records of bile pressure after temporary release of the bile may exceed the first maximum, but are usually lower. After death the bile

pressure falls rapidly until it has reached about 100 mm. bile, after which the fall is comparatively slow, even when the blood pressure in the liver is at zero.

The height of bile pressure attained is, as Heidenhain showed, the pressure at which as much bile is secreted every moment as is taken up from the bile paths by re-absorption. The obstructed bile leaves the liver by the portal lymphatics. Injection of the bile ducts with carmine gelatine at a pressure not exceeding the maximum bile pressure is also followed by the appearance of the injected material in the liver lymphatics. The examination of sections of livers thus injected reveals the presence of the injection in the liver cells at the periphery of the lobules. Appearances suggest that the bile escapes from the liver cells through the intracellular plasmatic channels described by Schäfer, and that these channels are to be regarded as an intermediate system linking the blood vessels of the liver with the lymphatics at the periphery of the lobules.

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