THE PATHOGENESIS OF EARLY OBSTRUCTIVE JAUNDICE.

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INTRODUCTION.

For many years investigators have been concerned with the question of the mechanism of early obstructive jaundice, some studying the process as a whole, others limiting themselves to certain aspects of the problem.

In cases of complete obstructive jaundice of long standing, the mechanism is fairly well understood. As shown by Eppinger (1) for the first time, and confirmed by Abramow and Samoilowicz (2), the bile canaliculi in these cases are distended and tortuous and their walls frequently ruptured, the bile emptying into the pericapillary lymph spaces. These observations lead to the theory of increased tension of the bile capillaries due to bile continually flowing from the liver cells but unable to reach the duodenum. As a result of increased tension the vessel walls rupture and the extravasated bile is absorbed either by the blood capillaries or by the lymphatics. It then finds its way into the blood stream and is partly excreted in the urine and partly deposited in the tissues. This theory however, especially in the initial stage of the process, has found many opponents.

Minkowski, as early as 1892 (3) and again in 1904 (4), emphasizes the importance of alterations of the liver cells in causing jaundice and proposes his theory of "*paracholie*" or the passage of bile from the pathological liver cells directly into the perilymphatic spaces, rather than into the bile capillaries. Sterling (5) some years later arrived at the same conclusion. He was not able to observe rupture of the bile capillaries after biliary obstruction and laid emphasis on early changes in the liver cells themselves.

Ogata (6) says that before the rupture of the bile capillaries there is a dilatation due to increased pressure. He believes that a necrosis of liver cells appears in the first stages of biliary obstruction. Browicz (7), Jagie (8), Kodama (9) and Hiyeda (10) have confirmed these findings. They were unable to observe any rupture of bile capillaries in early obstructive jaundice. The last two investigators, studying liver sections from 7 to 11 hours after ligation of the ductus choledochus, could

observe only a dilatation of bile capillaries, and in some cases the formation of bile thrombi (*"Gallenthromben"*).

We must discard the early observations regarding the time of first appearance of bile in the blood stream because of faulty technique. Either the Gmelin test was used to detect the bile pigments or else the investigators tested for bile salts. We know now that the Gmelin test is the least sensitive of all bilirubin reactions, and even as yet we have no method sensitive enough to detect small traces of bile salts in blood or urine.

Eppinger (11) in 1920 stated that 24 hours after obstruction one can notice an increase in the bilirubin content of the blood. Lepehne (12) in 1921, experimenting with rabbits and employing the Van den Bergh test to detect bilirubin, observed in 3 out of 5 animals an increase of blood bilirubin from 0.4 to 6.5 units within 24 hours. Bloom (13), using dogs previously nephrectomised, noticed the presence of the indirect Van den Bergh reaction from 1 hour and 19 minutes to 4 hours after ligation of the bile ducts. Kodama (9) in 1925 observed, in rabbits and dogs, the appearance of the indirect reaction 7 hours after ligation of the ductus choledochus, the direct reaction appearing 10 hours after obstruction. More recently Bollmann, Sheard and Mann (14) employing the Keuffel and Esser spectrophotometer to detect the bilirubin showed that the increase of bilirubin in the blood begins 5 minutes after ligation of the bile ducts. They further studied the pressure within the bile ducts and they observed that it was raised from 14 mm. water pressure to 270 or 300 mm. after obstruction. In conclusion they state: "As soon as the pressure in the biliary ducts has risen to 250 or 300 mm. of water, the hepatic cells become impervious to bilirubin so that bile pigment is neither excreted into the bile capillaries nor is it absorbed from the blood by the hepatic cell."

Report of Experiments.

I. First Appearance of Bile in the Blood Stream after Biliary Obstruction.

In all of our experiments we have employed dogs previously kept in metabolic cages and known not to show the so called physiologic bilirubinuria.

The method employed to detect bilirubin in the blood and lymph has been the well known Van den Bergh test, the reactions obtained being divided into three groups:

Direct Reaction.—Instantaneous appearance of the colour reaction after the addition of the reagent, reaching its maximal intensity in from 20 to 30 seconds.

Biphasic Reaction.—(Combination of direct and indirect reaction) in which the colour reaction begins within the first 30 seconds but does not reach its maximum intensity until from 1 to 30 minutes later.

Indirect Reaction.—In which the colour reaction begins from 1 to 3 minutes or more after the addition of the reagent, requiring sometimes the addition of alcohol. The maximum intensity is reacted after a variable time and the action of alcohol is essential to produce the maximum colour.

We used according to Lepehne's technique (15) 0.25 cc. of lymph or serum to which was added 0.20 cc. of freshly prepared reagent. The quantitative estimation was made with the Bausch and Lomb microcolorimeter, with, as standard, a solution of crystallised cobalt sulfate[1] previously checked against a solution of pure bilirubin. The determinations in serum giving the indirect Van den Bergh reactions were made according to Van den Bergh's technique, and the quantitative estimations in those giving biphasic or direct reactions were made by the modification of Thannhauser and Andersen (16).

The operative technique was the same as that employed by Bloom. All the dogs were given a preparatory injection of morphine followed in 30 minutes by ether anesthesia and were kept lightly under the anesthetic until the end of the experiment.

In this series of experiments, both kidneys were removed and the ductus choledochus and cystic duct ligated through a midline abdominal incision. Samples of blood were taken every 15 minutes from the carotid artery into which a cannula had been previously introduced. When the direct Van den Bergh reaction appeared in the blood the dogs were killed with ether. At necropsy the ligatures were verified and samples of liver taken for microscopic examination.

Five experiments were performed; all gave concordant results. The following protocol gives the details in one experiment; the results of the series have been summarised in Table II.

Protocol of Experiment on Dog 8.

Female, weight 11.5 kilos. At 10 a.m. a hypodermic injection of morphine was given. At 10:30 a.m. anesthesia with ether. At 10:50 a.m. a cannula was put in the carotid artery and a sample of blood taken. At 11:15 a.m. midline abdominal incision and transperitoneal double nephrectomy. At 11:30 a.m. ligation of ductus choledochus and cystic duct. Samples of liver were taken every 15 minutes.

The experiment lasted 6 hours and 20 minutes. The dog was killed with ether and a necropsy performed. The ligatures were well placed; there was no blood in the abdominal cavity. The liver was slightly hyperemic; on section, the portal and interlobular veins were found to be full of blood; the bile ducts were full of bile. The lymph vessels looked distended and greenish in colour. The spleen was

[1] 3.915 gm. of $CoSO_4 \cdot 7H_2O$ in 100 cc. distilled water is equivalent to 0.005 mg. per cc.

full of blood but not swollen. Samples of liver were taken for microscopical sections.

At 1 p.m., that is 1 hour and 30 minutes after biliary obstruction, the blood serum gave the indirect Van den Bergh reaction, which remained until 2:15. At this time, that is 2 hours and 45 minutes after obstruction, the Van den Bergh reaction became biphasic. At 4:15 p.m. or 4 hours and 45 minutes after obstruction, the reaction became direct rising steadily until the animal was killed.

TABLE I.

Dog 8. Experimental Obstructive Jaundice in Dogs Previously Nephrectomised. Van den Bergh Reaction and Bilirubin Estimation in the Blood Serum, Withdrawn Every 15 Minutes from the Carotid Artery.

Blood	Van den Bergh reaction			Time after obstruction	Quantitative estimation of bilirubin
Time	Direct	Biphasic	Indirect		
a.m.					*mg. per liter*
10:50	−	−	−		
11:30	Ligation of common and cystic bile ducts				
11:45	−	−	−		
12 m.	−	−	−		
p.m.					
12:15	−	−	−		
12:30	−	−	−		
12:45	−	−	−		
1	−	−	+	1 hr., 30 min.	Traces
1:15	−	−	+		"
1:30	−	−	+		"
1:50	−	−	+		"
2:15	−	+		2 hrs., 45 min.	1.50
2:35	−	+			2.00
2:55	−	+			2.50
3:15	−	+			3.50
3:35	−	+			3.75
4:15	+			4 hrs., 45 min.	4.00
4:35	+				4.50
4:55	+				5.50

In Table II we summarise the five experiments performed. We see that in the early hours after biliary obstruction in dogs, the time of appearance of bilirubin in the blood is quite constant. The indirect reaction appears during the 2nd hour after obstruction is performed and persists from 1 hour to 1 hour and 45 minutes. The biphasic reac-

tion then appears and lasts from 1 hour and 10 minutes to 2 hours and 10 minutes. Finally the direct reaction appears 4 to 5 hours after obstruction and will last as long as the obstruction persists.

The behaviour of the biphasic reaction was not always the same. Thus in Dog 7 the biphasic reaction first appeared 2 hours and 30 minutes after obstruction; in the following sample, 15 minutes later, the reaction was indirect; in the sample collected 30 minutes later it had become biphasic again.

In Fig. 1 we give the results of the quantitative estimations of bilirubin made in the five experiments. The rise in the bilirubin content of the blood, after it is first detected, is regular until the end of the

TABLE II.

Experimental Obstructive Jaundice in Nephrectomised Dogs. Summary of Experiments Showing the Time of Appearance of Van den Bergh Reaction in the Blood Serum.

Dog No.	Sex	Weight	Time of appearance of the Van den Bergh reaction in the blood serum, after total biliary obstruction		
			Indirect	Biphasic	Direct
		kg.			
3	F.	8	1 hr., 25 min.	2 hrs., 15 min.	4 hrs., 23 min.
4	F.	12.2	1 hr., 15 min.	3 hrs.	4 hrs., 10 min.
6	M.	10	1 hr., 20 min.	2 hrs., 40 min.	4 hrs.
7	F.	5.4	1 hr., 20 min.	2 hrs., 30 min.	4 hrs., 55 min.
8	F.	11.5	1 hr., 30 min.	2 hrs., 45 min.	4 hrs., 45 min.

experiment. We may add that another series of experiments now being performed indicates that the rise is continuous and slow until 40 hours after total biliary obstruction. Then a sudden rise occurs which is maintained at more or less the same level until relief of the obstruction or until death. We take from these experiments, one shown in Fig. 2, which indicates the bilirubin content in the blood during the whole period of obstruction until relieved by a biliary fistula. The blood bilirubin after relieving the biliary obstruction, behaves, as we see in this figure, in a manner exactly the reverse of that noted in early obstructive jaundice. The 3rd day after relief of the obstruction the blood bilirubin, besides diminishing in quantity, has become

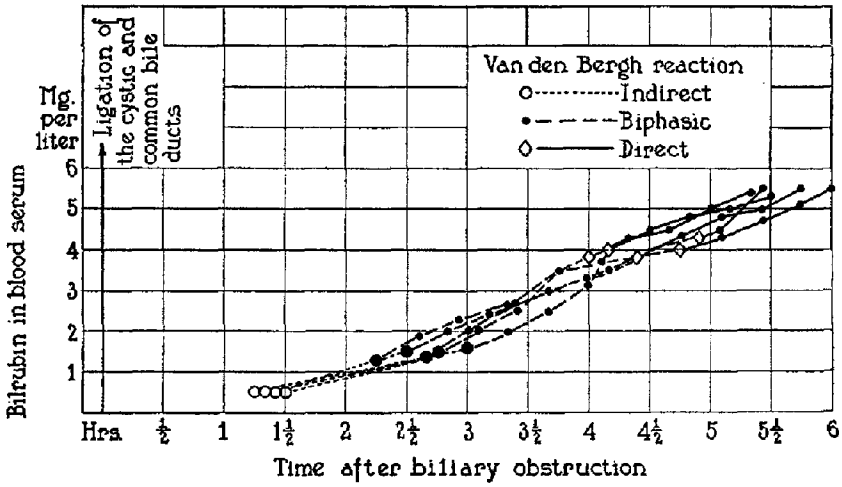

FIG. 1. Experimental obstructive jaundice in nephrectomised dogs. Curve of blood bilirubin and Van den Bergh reaction in early obstructive jaundice.

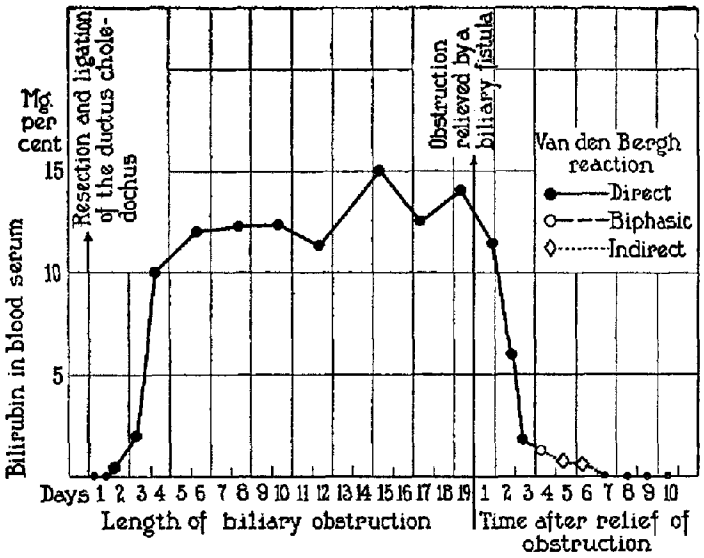

FIG. 2. Experimental obstructive jaundice in dogs. Curve of blood bilirubin during the whole period of obstruction till 7 days after relief of obstruction by a biliary fistula.

biphasic in type; on the 5th day the Van den Bergh reaction has changed into an indirect type. On the 7th day after relief of the obstruction, the bilirubin had disappeared from the blood.

II. Route Taken by the Bile to Reach the Blood Stream after Biliary Obstruction.

The question of the route taken by the bile to reach the blood stream after complete biliary obstruction has also attracted considerable attention. Many investigators have supposed the escape of bile from the liver in obstructive jaundice to be due to the activity of the lymphatic apparatus, while others uphold the view that this process is essentially an absorption of bile from the liver by the activity of the blood capillaries.

Fleischl (17) after ligating the ductus choledochus collected the lymph through a fistula made in the thoracic duct and found it charged with bile, while after 5 hours he could not detect any bile in the blood stream. Kunkel (18) and Kufferath (19) reached the same conclusion from determinations of the bile salts. Harley (20) ligated the common bile duct of two dogs, and in one in addition closed the thoracic duct. He observed in the dog with thoracic duct intact, that bile appeared in the urine in the course of a few hours after biliary obstruction, while in the dog with thoracic duct closed as long a period as 8 days elapsed before there was any such discharge. Wertheimer and Lépage (21) performed a series of experiments on dogs with a fistula of the thoracic duct and ligation of the ductus choledochus. They injected ox bile into the bile duct of the right hepatic lobe, and after a certain time could observe the presence of the cholohematin spectrum in the bile coming from the left hepatic lobe, but in these experiments they could not look for the presence of cholohematin in lymph, because, "quand le spectre de la cholohematine commençait à se montrer dans la bile du chien, la lymphe était devenue rouge." They then injected solutions of pure bilirubin under pressure and observed the appearance of the Gmelin reaction in the lymph 1 hour after the injection and its appearance in the urine 2 hours and 30 minutes after the injection. They conclude: "La verité est que les deux ordres des vaisseaux contribuent à leur resorbtion et. . . . . Le rôle des lymphatiques n'en reste pas moins important." But 1 year later (22) these same investigators performed simultaneous ligations of the ductus choledochus and thoracic duct and observed the appearance of bile in the urine. They considered the lymphatic route to be of secondary importance because they observed that bile pigment also appeared in the urine in a like manner when they ligated the ductus choledochus only. Mendel and Underhill (23) injected indigo carmine, KI, K ferrocyanide, milk and I, and milk into the common bile duct, and observed that these foreign substances appeared first in the urine

and then in the lymph with the exception of the milk-iodine mixture, which was detected 65 minutes after the injection in the lymph but not in the urine. They concluded that the hepatic capillaries are the important factor in this absorption. Whipple and King (24) ligated the common bile duct, exposed the thoracic duct and placed a ligature at its junction with the jugular vein. They detected the bile pigments in urine and lymph by the use of the Salkowski test. From their experiments they concluded that in obstructive jaundice the bile which escapes from the

TABLE III.

Dog 11. Experimental Obstructive Jaundice in Nephrectomised Dogs. Van den Bergh Reaction and Bilirubin Estimation in Samples of Lymph Withdrawn Every 20 Minutes from a Thoracic Duct Fistula, Previously Performed.

Lymph	Van den Bergh reaction			Time after obstruction	Quantitative estimation of bilirubin
Time	Direct	Biphasic	Indirect		
					mg. per liter
12:30	−	−	−		
12:40	Ligation of common and cystic bile ducts				
1:00	−	−	−		
1:20	−	−	−		
1:40	−	−	+	1 hr.	Traces
2:00	−	−	+		0.5
2:20	−	−	+		0.8
2:40	−	−	+		0.80
3:00	−	−	+		0.85
3:20	−	+		2 hrs., 40 min.	1.25
3:40	−	+			1.20
4:00	−	+			1.30
4:20	−	+			1.30
4:40	−	+			2.00
5:00	−	+			2.50
5:20	−	+		4 hrs., 40 min.	3.25
5:40	+				3.25
6:00	+				3.50
6:15	+				4.00

liver is absorbed by the blood capillaries and carried by the blood to the kidneys: "at best the lymphatic system is a secondary factor in the mechanism of jaundice." Bloom in the paper previously mentioned (13) detected bilirubin in blood and lymph by the Van den Bergh technique and observed that a positive test for bilirubin was obtained in the lymph while the blood was still pigment-free. He concluded that "during the first hours after obstruction of the common bile duct, the bile pigments are carried from the liver by the lymph stream and by it are emptied into the general circulation."

Report of Experiments.

The purpose of our second series of experiments was to study the route taken by the direct bilirubin found some hours after obstruction, to reach the blood stream.

The protocol of one experiment is given in detail; the results of the series of experiments have been summarised in Tables III and IV.

TABLE IV.

Dog 11. Experimental Obstructive Jaundice in Nephrectomised Dogs. Van den Bergh Reaction and Bilirubin Estimations in Samples of Blood Serum Withdrawn Every 20 Minutes from the Carotid Artery.

Blood	Van den Bergh reaction			Time after obstruction	Quantitative estimation of bilirubin
Time	Direct	Biphasic	Indirect		
					mg. per liter
12:20	−	−	−		
12:40	Ligation of common and cystic bile ducts				
1:05	−	−	−		
1:20	−	−	−		
1:40	−	−	−		
2:00	−	−	−		
2:20	−	−	−		
2:40	−	−	−		
3:00	−	−	−		
3:20	−	−	+	2 hrs., 40 min.	Traces
3:40	−	−	+		Traces
4:00	−	−	+		0.5
4:20	−	−	+		0.8
4:40	−	+		4 hrs.	1.00
5:00	−	+			1.30
5:20	−	+			1.50
5:40	−	+			1.50
6:00	+			5 hrs., 20 min.	2.00
6:15	+				2.00

Dog 11.—Male, weight 16 kilos. An injection of 3 cg. of morphine was given 39 minutes before ether anesthesia was begun. All the veins entering the left external jugular vein at its junction with the thoracic duct were ligated and a cannula placed in the jugular vein, at 12:15 p.m. The lymph flow was regular at a rate of 20 cc. to 30 cc. per hour. At 12:20 p.m. a cannula was inserted in the right carotid artery and a sample of blood withdrawn. At 12:32 p.m. midline incision and transperitoneal double nephrectomy. At 12:40 p.m. ligation of common and

cystic bile ducts. Samples of blood were withdrawn every 20 minutes, the lymph being examined at the same time. The indirect Van den Bergh reaction appeared first in the lymph 1 hour after the obstruction. 2 hours and 40 minutes after the obstruction the Van den Bergh reaction in the lymph became biphasic, while the indirect reaction appeared in the blood serum. 4 hours and 40 minutes after obstruction the Van den Bergh became direct in the lymph, and 40 minutes later, that is 5 hours and 20 minutes after biliary obstruction, the blood serum showed also the direct Van den Bergh reaction. The dog was killed at 6:20 p.m. with ether. At necropsy the ligatures of bile ducts were well placed. The liver appeared hyperemic. On section the bile ducts were distended with bile. The lymphatics were distended and greenish in colour. Samples of liver were taken for microscopic examinations.

TABLE V.

Experimental Obstructive Jaundice in Dogs Previously Nephrectomised. Ligation of Bile Ducts and Thoracic Duct Fistula.

Dog No.	Sex	Weight	Time of appearance of the Van den Bergh reaction after biliary obstruction in dogs with thoracic duct fistula					
			Lymph			Blood		
			Direct	Indirect	Biphasic	Direct	Indirect	Biphasic
		kg.						
11	M.	16	4 hrs., 40 min.	1 hr.	2 hrs., 40 min.	5 hrs., 20 min.	2 hrs., 40 min.	4 hrs.
14	F.	12.2	4 hrs., 20 min.	50 min.	2 hrs., 25 min.	5 hrs., 15 min.	2 hrs. 30 min.	4 hrs., 15 min.
17	F.	14.4	4 hrs., 50 min.	1 hr.	2 hrs., 50 min.	5 hrs., 45 min.	2 hrs., 55 min.	4 hrs., 30 min.

In one additional experiment the thoracic duct was ligated accidentally. We proceeded as previously, taking samples of blood every 15 minutes. In this dog, the indirect Van den Bergh first appeared in the blood 2 hours and 45 minutes after obstruction. The biphasic reaction appeared 4 hours and 30 minutes and the direct reaction 5 hours and 30 minutes after obstruction. The Van den Bergh reaction in this case behaved as it did in the experiments with thoracic duct fistula.

We summarise in Table V the results of our three experiments, which are in close agreement.

We see from these experiments that after complete biliary obstruc-

tion associated with a thoracic duct fistula, the bile appears first in the thoracic duct before it is detectable in the blood, but that 1 hour later it is present in the blood, not only when the lymph is being drained from the thoracic duct, but even when the duct has been ligated.

Microscopic Examinations of the Liver of These Dogs, 5 to 6 Hours after Total Biliary Obstruction.

It is generally agreed that rupture of bile capillaries appears only in the late stages of biliary obstruction. We made microscopical examinations of the liver of the dogs reported in our experiments. Hematoxylin and eosin sections showed no atrophy or necrosis of the liver cells which appeared quite normal. The bile ducts were not noticeably distended and no bile thrombi were observed. The Kupffer cells in the liver of Dog 8 (whose protocol has been given) contained a moderate amount of brown pigment which could be stained for iron. No such pigment was found in any of the others. Frozen sections stained with Scharlach R revealed only a slight amount of finely divided fat in the liver cells. The cells lining the smaller bile ducts consistently contained fat droplets of various size. Sections were fixed and stained by the method described by Vance (25) for the demonstration of bile canaliculi. The canaliculi were well stained, prominent and slightly distended but the most careful search failed to reveal the rupture of any of them into adjacent lymph spaces.

DISCUSSION.

Taking first in consideration the behaviour of the Van den Bergh reaction in early obstructive jaundice, we see from our experiments that the indirect reaction appears first, then the biphasic and some hours later the direct reaction, which remains during the whole period of obstruction. In spite of the many investigations carried out concerning the nature of the Van den Bergh reaction, it still remains an unsettled problem. Nevertheless from McNee's (26) and Van den Bergh's (27) researches corroborated by Andrews' important work (28), it is clear that the bilirubin normally present in the circulating blood gives only the indirect reaction, and that on passing through the liver cell during excretion, it is changed in some as yet undeter-

mined manner into a form which gives the direct reaction.[2] What is the significance of the indirect reaction which uniformly appears in the plasma of this animal soon after obstruction, and lasts a short time? It seems to us that a possible explanation for this phenomenon would be that as a consequence of the biliary obstruction a nervous reflex may occur which would lead to sudden paralysis of the function of the liver cells and as a result the circulating bilirubin would remain in the blood stream. This would be analogous to the temporary reflex paralysis of the excretory function of the kidney after ligation of the ureters, which is a well known phenomenon. As the process of bilirubin formation goes on, the bilirubin would soon reach a level sufficient to give a positive test with the diazo reagent. This reflex phenomenon would not last very long. Some hours after obstruction the liver cells would resume their function and the bilirubin giving the indirect reaction would be changed by them into bilirubin giving the direct reaction. We are at present engaged in a study of this possibility.

Another difficult aspect of the problem now presents itself. If in the first hours of obstructive jaundice there is no rupture of bile canaliculi, by what process does the direct reacting bile appear in the blood? In short what is the intimate mechanism of early obstructive jaundice? This is a field in which suggestions only can be made. Must we return to Minkowski's theory as offering the only plausible explanation? The double polarization of the liver cells has been known since Claude Bernard's memorable discovery of the glycogenic function of the liver (29). We know that the epithelial liver cell can function in two different ways: as a gland of internal secretion expelling its products into the blood stream and as a gland of external secretion excreting bile into the bile canaliculi. But it is extremely difficult to comprehend by what mechanism the excretion of bile can shift from an external to an internal secretion.

A close examination of the microscopic sections of the liver in early obstructive jaundice, stained by Vance's technique, shows the bile canaliculi dilated and extending between the liver cells in small distended pouches, the blind end of these lying in contact with the

[2] In the dog, bilirubin is present in the plasma normally in amounts too small to be detected by the Van den Bergh test.

pericapillary spaces. It would be quite easy to believe that bile might diffuse from these thin walled pouches into the tissue spaces without any actual rupture of the bile canaliculi. This diffusion would be favored by the mounting pressure inside the bile ducts, which rises rapidly according to Bollmann, Sheard and Mann (14).

Regarding the second question, that of the route taken by the bile to reach the blood, since, as we have seen in the thoracic duct fistula experiments, direct reacting bilirubin soon finds its way into the perivascular lymph spaces which surround the hepatic capillaries, bile may diffuse into these capillaries and thus directly enter the blood stream, as we have observed in our experiments.

We think our experiments explain the contradictory results of other investigators concerning the route by which bilirubin reaches the blood in obstructive jaundice. We feel justified in concluding as Wertheimer and Lépage did after their first observations: "La verité est que les deux ordres des vaisseaux contribuent à leur resorbtion et . . . . Le rôle des lymphatiques n'en reste pas moins important."

CONCLUSIONS.

1. After experimental ligation of the bile ducts in dogs, two distinct processes are clearly manifested: first, the accumulation of the normally circulating bilirubin in the blood with its characteristic indirect Van den Bergh reaction for a period of several hours, and second, the subsequent appearance of the bile bilirubin giving the direct Van den Bergh reaction. It is possible that the first process may be due to a temporary reflex inhibition of the function of the liver cells due to ligation of the duct and comparable to the same phenomenon which usually occurs in the kidney when the ureter is ligated. The second process begins before any rupture of the bile capillaries is visible. Liver sections made 6 to 7 hours after obstruction show these bile capillaries dilated and extending between the liver cells in small distended pouches the blind end of these lying in contact with the pericapillary spaces. It is possible that bile may diffuse from these thin walled pouches into the perivascular lymph spaces, this diffusion being favored by the mounting pressure inside the bile ducts.

2. In early obstructive jaundice bile first appears in the lymph, but exclusion of the thoracic duct from the circulation by drainage causes

a delay of only a few hours in the appearance of bile bilirubin in the blood stream. We must therefore conclude that after biliary obstruction bile enters the circulation both by way of the blood capillaries and the lymphatics, although the latter route is the more important.

We wish to express our thanks to Dr. Arnold R. Rich for his constant assistance and many valuable suggestions.

BIBLIOGRAPHY.

1. Eppinger, H., *Beitr. path. Anat. u. allg. Path.*, 1902, xxxi, 230; 1903, xxxiii, 123.
2. Abramow and Samoilowicz, *Virchows Arch. path. Anat.*, 1904, clxxvi, 199.
3. Minkowski, Diskusion über Lebercirrhose, *Verhandl. XI Kong. inn. Med.*, Leipsic, 1892.
4. Minkowski, *Z. klin. Med.*, 1904, lv, 34.
5. Sterling, *Arch. exp. Path. u. Pharmakol.*, 1911, lxiv, 468.
6. Ogata, *Beitr. path. Anat. u. allg. Path.*, 1913, lv, 236.
7. Browicz, *Wien. klin. Woch.*, 1900, xiii, 785.
8. Jagie, *Beitr. path. Anat. u. allg. Path.*, 1903, xxxiii, 302.
9. Kodama, *Beitr. path. Anat. u. allg. Path.*, 1925, lxxiii, 187.
10. Hiyeda, *Beitr. path. Anat. u. allg. Path.*, 1925, lxxiii, 541.
11. Eppinger, H., in Kraus and Brugs, Handbuch der spezielle Pathologie und Therapie, Berlin, 1920, vi, 97.
12. Lepehne, *Deutsch. Arch. klin. Med.*, 1921, cxxxv, 79.
13. Bloom, W., *Bull. Johns Hopkins Hosp.*, 1923, xxxiv, 316.
14. Bollmann, Sheard, and Mann, *Am. J. Physiol.*, 1927, lxxxi, 461.
15. Lepehne, G., *Ergebn. inn. Med. u. Kinderheilk*, 1921, xx, 221.
16. Thannhauser and Andersen, *Arch. klin. Med.*, 1921, cxxxvii, 179.
17. Fleischl, *Ber. Ges. Wissensch.*, Leipsic, 1874, ix, 42.
18. Kunkel, *Ber. Ges. Wissensch.*, Leipsic, 1875, x, 232.
19. Kufferath, *Arch. Physiol.*, 1880, xxiii, 291.
20. Harley, *Arch. Anat. u. Physiol., Physiol. Abt.*, 1893, xxxi, 290.
21. Wertheimer and Lépage, *Arch. physiol. norm. et path.*, 1898, x, 339.
22. Wertheimer and Lépage, *J. physiol. et path. gén.*, 1899, i, 259.
23. Mendel and Underhill, *Am. J. Physiol.*, 1905, xiv, 252.
24. Whipple and King, *J. Exp. Med.*, 1911, xiii, 115.
25. Vance, *Anat. Anz.*, 1913, xliv, 412.
26. McNee, J. W., *Quart. J. Med.* 1923, lxiv, 390.
27. Van den Bergh, H., Die Gallenfarbstoff in Blute, Leipsic and Leyden, 1918.
28. Andrews, C. H., *Brit. J. Exp. Path.*, 1924, v, 213.
29. Bernard, Claude, Leçons de physiologie expérimental, Paris, 1855, 89.