THE BILIARY OBSTRUCTION REQUIRED TO PRODUCE JAUNDICE.

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In a recent paper from this laboratory[1] observations were reported proving that a part of the rabbit's liver can function for the whole as regards bile elimination. A good instance in point is furnished by an experiment performed with another end in view. In a series of rabbits the ducts from three-fourths of the hepatic tissue were ligated and the portal branch to the remaining fourth was tied at the same operation, thus increasing the portal flow and by consequence bile formation in the mass with obstructed ducts. Under such circumstances the entire burden of bile elimination was laid on a mere quarter of the parenchyma, and this supplied with blood only by the hepatic artery, a source furnishing approximately two-fifths of the normal quantity if one may judge from data obtained in dogs.[2] Yet the rabbits remained unjaundiced and healthy. More recent observations upon dogs have convinced us that the experiment will yield a similar result with them. And it has been a surprise to discover on a search of the literature that no general recognition exists of the large margin of safety of the liver in bile elimination. On the contrary, frequent categorical statements may be found to the effect that, in man at least, jaundice is often caused by lesions affecting only a small proportion of the hepatic parenchyma.

Quincke and Hoppe-Seyler[3] state that transient obstruction of a small duct branch may bring about the absorption of sufficient bile to lead to a clinical

[1] Rous, P., and Larimore, L. D., *J. Exp. Med.*, 1920, xxxi, 609.

[2] Macleod, J. J. R., and Pearce, R. G., *Am. J. Physiol.*, 1914, xxxv, 87.

[3] Quincke, H. I., and Hoppe-Seyler, G., in Nothnagel, N., Specielle Pathologie und Therapie, Vienna and Leipsic, 2nd edition, 1912, xviii.

jaundice. The obstruction may be difficult to find at autopsy and the small ducts should be carefully searched for it. According to Eppinger[4] icterus is roughly proportional in intensity to the size of the occluded ducts, and localized inflammatory processes may cause it. Rolleston[5] believes that it follows the occlusion of one branch of the hepatic duct although the other continues to pour bile into the intestine; but not so according to Naunyn[6] who asserts that icterus under these circumstances fails to develop save when there is a complicating *Cholangie*. Krehl[7] holds that icterus occurs in many diseases through local stagnation and resorption. Recently van der Bergh and Snapper[8] have called attention to the fact that intrahepatic tumors of considerable size, and manifestly occluding many ducts, are often unaccompanied by jaundice, whence it follows in their opinion that local lesions in general must frequently exist without causing an accumulation of bile pigment in the organism.

The divergence of opinion illustrated by these specimen citations is obviously the result, first, of a lack of experimental evidence on the essential point at issue—the ability of a part of the liver to act for the whole as concerns bile elimination—and, second, of conclusions from clinical instances complicated by many factors.

For the work here to be described dogs and monkeys have been employed. Rabbits could not be used because their bile pigment fails to react satisfactorily to the ordinary tests.

Criteria of Bile Retention.

The clinician as a rule is first apprized of deficient bile elimination in his patient by the development of bilirubinuria with or without a tissue icterus. As our prime aim has been to determine how much biliary obstruction may exist without clinical manifestations, the tests in current use have been adopted for the work.

These tests as applied to the blood are very unsatisfactory. The Gmelin reaction with blood serum, so strongly advocated by French workers,[9] is yielded only when bilirubinemia is obvious to the eye, while furthermore lutein gives a

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[4] Eppinger, H., *Ergebn. inn. Med.*, 1908, i, 107.

[5] Rolleston, H. D., Diseases of the liver, London, 2nd edition, 1912.

[6] Naunyn, B., *Mitt. Grenzgeb. Med. u. Chir.*, 1919, xxxi, 537.

[7] Krehl, L., Pathologische Physiologie, Leipsic, 9th edition, 1918, 571.

[8] van der Bergh, A. A. H., and Snapper, J., *Berl. klin. Woch.*, 1914, i, 1109.

[9] Gilbert, A., Herscher, M., and Posternak, S., *Compt. rend. Soc. biol.*, 1903, lv, 530; 1905, lvii, 250.

positive reaction; and the intensity of color of the plasma itself, save in outspoken cases, is trustworthy only in the absence of hemolysis and of extraneous pigments such as carotin. The reactions of Obermeyer and Popper[10] have proved in our hands little more sensitive than that of Gmelin. The diazo test recently advocated by van der Bergh and Snapper[11] is delicate, and promises to be of great clinical value, but its use has been limited as yet and it is not entirely specific.[12] We have employed it in the present work in its negative aspect, as the criterion wherewith to rule out bilirubinemia, for which it would seem highly suitable. None of many dog sera obviously stained with bile has failed to give the test, and the unstained sera have regularly proved negative.

The diazo reagent is a mixture, made fresh each day, of the following stock solutions. (*a*) 5 gm. of sulfanilic acid and 50 cc. of hydrochloric acid in 1,000 cc. of distilled water. (*b*) 0.5 per cent solution of sodium nitrite in distilled water. For use 1 part of (*b*) is added to 50 of (*a*).

The oxalated or citrated plasma to be tested is first shaken briefly with two volumes of 95 to 96 per cent alcohol and centrifuged to throw out the precipitate that forms. The supernatant fluid will now contain all of the bilirubin unless the plasma held very large quantities, in which case some will be carried down with the precipitate and must be extracted with 64 per cent alcohol if a quantitative result is to be obtained. On the addition of the diazo reagent to the fluid containing bilirubin, in the proportion of 1 part to 4, the beautiful violet tint of azobilirubin appears after a few minutes. To determine its amount a colorimeter is used and a solution of pure bilirubin in chloroform (5 mg. per 100 cc.) to give with the reagent a standard tint.

The Gmelin reaction has been used to detect bilirubinuria, and to quantitate it Hooper and Whipple's[13] modification of Salkowski's method has been employed as routine. The sodium nitrite-nitric acid solution recommended by Gilbert, Herscher, and Posternak[9] has been found to yield a better Gmelin response than the ordinary fuming nitric acid.

In contrast with the tests just mentioned, those for bile salts in the urine are none of them satisfactory. Pettenkofer's reaction was employed for one series of dogs, but Hay's sulfur reaction was adopted for most of the animals as less open to technical error and relatively specific.[14] Attempts to detect cholates in the blood were after many trials abandoned. The method recently described by Hoover and Blankenhorn[15] whereby the salts are separated out by dialysis and

[10] Obermeyer, F., and Popper, H., *Wien. med. Woch.*, 1910, lx, 2592.

[11] van der Bergh, A. A. H., and Snapper, J., *Deutsch. Arch. klin. Med.*, 1913, cx, 540.

[12] Koessler, K. K., and Hanke, M. T., *J. Biol. Chem.*, 1919, xxxix, 497.

[13] Hooper, C. W., and Whipple, G. H., *Am. J. Physiol.*, 1916, xl, 332.

[14] Lyon-Caen, L., *J. physiol. et path. gén.*, 1910, xii, 526.

[15] Hoover, C. F., and Blankenhorn, M. A., *Arch. Int. Med.*, 1916, xviii, 289.

TABLE I.

Bilirubinuria in the Absence of Bilirubinemia in Dogs.

Normal dogs.				Operated dogs.				
Dog No.	Procedure.	Urine.	Blood.	Dog No.	Operation.	Time of observation.	Urine.	Blood.
16	Normal dog. Fasting on 6th and 9th to 12th days inclusive.	Bile pigment present on 6th and 8th to 14th days inclusive.	Negative.	19	All ducts ligated but those to lateral liver mass; 71 per cent of liver obstructed.	Before operation. After operation.	Bile pigment present for 3 days. Bile pigment present on 1st to 8th, and on the 10th day after operation.	Negative. Pigment in plasma on 6th, 7th, and 8th days after operation.
17	Normal dog. Fasting on 6th and 9th to 14th days inclusive.	Bile pigment present on 6th, 7th, 9th, and 11th days.	"	8	Ducts to lateral mass left free; 71 per cent of liver obstructed.	Before operation. After operation.	Bile pigment present for 5 days. Bile pigment present on 2nd, 3rd, and 12th days.	Negative. "
18	Normal dog. Fasting on 6th day only.	Bile pigment present on 6th and 7th days.	"	10	Ducts to left lateral lobe left free; 72.4 per cent of liver obstructed.	Before operation. After operation.	Negative. Bile pigment present on 4th, 5th, 10th, and 12th days.	" "

				12	Duct to right lateral lobe left free; 82 per cent of liver obstructed.	Before operation.	Negative.	Negative.
						After operation.	Bile pigment present on 4th, 9th, and 11th days.	" until 11th day, then faintly positive.
				11	Duct to right lateral lobe left free; 82 per cent of liver obstructed.	Before operation.	Negative.	Negative.
						After operation.	Bile pigment present on 6th day.	"

concentrated failed regularly in our hands to give positive results with the plasmas of jaundiced dogs excreting cholates through the kidneys. This may have been due to the lack in the dog of a renal threshold for bile salts such as in man leads to their accumulation in the circulation.

The Renal Threshold for Bilirubin.

In man, as is well known, the normal blood plasma has a yellow color owing to the presence of bilirubin; and a considerable increase in the pigment may occur without the passage of any into the urine, much less the appearance of a tissue icterus.[15] According to van der Bergh and Snapper[11,16] the plasma of healthy dogs is colorless and this has been our own finding except in animals with "physiological jaundice" induced by fasting. The plasma of normal monkeys is also in our experience practically colorless and fails to give the diazo reaction. We have further noted that in both dogs and monkeys bilirubinemia never occurs without bilirubinuria, while in dogs, at least, bile pigment is frequently to be found in the urine when it cannot be demonstrated in the circulation (Table I).

The state of the urine, then, furnishes a more delicate criterion of icterus in the dog than does that of the blood. The conditions are very different in man. In man, owing to the high renal threshold for bilirubin a considerable accumulation of pigment takes place in the blood before any escapes into the urine, and consequently one must reckon from a base-line of normal pigment retention in work upon defective bile elimination. This complicating factor does not exist in the dog and monkey. Such a renal threshold as is present in these animals—and *a priori* one would be expected on grounds of biological relationship—has so slight an elevation as to produce no evidence in the blood of its presence.

Method.

The animals were kept in metabolism cages and the 24 hour urines were examined for a number of days prior to operation, as regards their general character and the presence of bile salts and pigments. The monkeys were males, but most of the dogs chosen were females and with one exception (No. 10) none was taken which

[16] van der Bergh, A. A. H., and Snapper, J., *Berl. klin. Woch.*, 1914, li, 1109.

showed spontaneous icterus, so called. Throughout the work the routine tests were carried out upon cage urines, but positive findings were controlled by catheterization. At more or less frequent intervals, as occasion warranted, the blood was examined for bilirubin. The monkeys were fed on bananas, the dogs on bread and meat.

The biliary obstruction was induced by ligating and, where possible, cutting various branches of the hepatic duct under ether anesthesia. Asepsis was maintained, and the wound in the abdominal wall closed in three layers. When the free portion of the duct to be obstructed was too short to be doubly tied and cut, several stout ligatures were laid upon it, a procedure which in the dog generally served to close the duct throughout the term of experiment. Indeed, we have been but little troubled with the restoration of the duct channels by the cutting through of ligatures, possibly because of the large caliber of the silk used. In monkeys, on the other hand, even coarse ligatures were found to work through the duct walls within 10 days to 2 weeks, and either the continuity of the channel was reestablished, or a leak from it led to death. Needless to say, at every autopsy a careful study was made of the final results of operation and cultures were taken from the liver and the stasis bile. The animals were killed with chloroform. Instances in which infection existed were ruled from consideration.

Arrangement of the Dog and Monkey Livers.

The main liver mass of the dog consists of the left lateral and central and right central lobes with the ill defined quadrate lobe as an essential part of the last which also bears the gall bladder on its under surface.[17] There is another mass, separate both by contour and tissue cleavage, the lateral mass as we shall term it, which lies just above and to the right of the pylorus and is made up of the right lateral and caudate lobes. The main liver contains on the average about six-tenths of the parenchyma, the lateral mass about three-tenths. The remaining one-tenth consists of the papillary, or Spigelian, lobe placed below the main liver and separated from the lateral mass by the gastrohepatic omentum, but connected with both by tissue bridges. The course of the bile ducts falls in roughly with the anatomical arrangement of the tissue which they drain. A large branch coming from the left lateral and central lobes joins another from the right central and caudate lobes,—into which, by the way, the cystic duct opens,—and thus there is formed a large main channel into which the small papillary branch empties, and, lower down, within a few centimeters of the intestine, the considerable duct from the lobe mass. Frequent marked variations from this typical arrangement are encountered. Thus, for example, the branch from the lobe mass may course toward the main liver to join that from the right central and caudate lobes. Or the branch which appears to spring from the whole left central and

[17] Bradley, O. C., A guide to the dissection of the dog, London, New York, Bombay, and Calcutta, 1912.

TABLE II.

Weight of the Lobes of the Normal Dog Liver, Expressed in Percentages of the Total Organ.

Dog No.	Body weight.	Sex.	Liver weight.	Papillary lobe.	Lateral mass.		Entire lateral mass.	Main liver.			Entire main liver.
					Right lateral.	Caudate.		Left lateral.	Left central.	Right central.	
	kg.		*gm.*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1	10	M.	315.2	5.8			29.0				65.2
2			181.5	7.3	19.5	9.8	29.3	25.4	11.5	26.5	63.4
3	$7\frac{3}{4}$	M.	226.0	5.1	14.8	8.7	23.5	32.9	16.4	22.1	71.4
4	11	F.	330.5	6.1	16.8	14.8	31.6	24.5	13.6	24.2	62.3
5	15	M.	545.0	4.6	22.8	13.2	36.0	27.1	12.1	20.2	59.4
6	11		305.5	5.4	12.4	8.6	21.0	30.1	15.8	27.7	73.6
7	7	F.	212.5	4.7			34.0			19.1	61.3
8	$11\frac{3}{4}$	M.	505.0				40.0				60.0
9	8	"	279.0				27.0				73.0
10	$9\frac{1}{4}$	F.	288.0				22.7				77.3
11	11	M.	337.0	6.2			23.4			28.4	70.4
12	$11\frac{1}{4}$	"	423.0				27.1				72.9
13	8	"	253.5				21.0	37.0			79.0
14	9	F.	333.5				25.8	27.2			74.2
15	7	M.	242.0				31.0				69.0
16	7	F.	335.0				20.0			21.8	80.0
17	8	M.	359.0	5.0			33.2				61.8
18	$10\frac{1}{4}$	F.	359.5	4.6			32.0				63.4
19	9	"	351.0	6.0			27.1	25.0			66.9
20	$8\frac{3}{4}$	"	335.0	4.9			25.3	27.7			69.8
21	7	"	231.5	4.1			21.6	28.5	18.6	27.2	74.3
22	$12\frac{3}{4}$	M.	472.0	4.9			32.6	25.8			62.5
23	6	F.	285.0	4.6			36.8	24.5			58.6
24	8	"	252.5	3.9	21.6	14.5	36.1	27.7	11.7	20.6	60.0
25	$6\frac{1}{2}$	"	235.7	4.4	19.5	9.5	29.0	29.7	11.0	25.9	66.6

26	$6\frac{1}{2}$	F.	193.0	5.2	18.1	12.5	30.6	26.4	11.9	25.9	64.2
27	$7\frac{3}{4}$	M.	261.5	4.6	22.8	14.7	37.5	26.8	11.1	20.0	57.9
28	$8\frac{1}{2}$	"	311.0	5.8	15.4	12.2	27.6	25.0	9.5	32.1	66.6
29	$4\frac{1}{2}$	F.	138.5	5.1	15.8	13.8	29.6	25.9	13.1	26.3	65.3
Average				5.1 (21 cases).	18.1 (11 cases).	12.0 (11 cases).	29.0 (29 cases).	27.6 (18 cases).	13.0 (12 cases).	24.5 (15 cases).	67.3 (29 cases).
Variation				3.9–7.3	12.4–22.8	8.6–16.9	20.0–40.0	24.5–37.0	9.5–18.6	19.1–32.1	57.9–80.0

lateral lobes may in reality drain but a small portion of these, their bile emptying for the most part into the just mentioned duct from the right central and caudate lobes. Large vasa aberrantia are frequent. They may be patent and filled with bile for several centimeters above their junction with the common duct, but stop short of the liver tissue or cease thereabouts to be patulous. A mistaken dependence upon such vessels for bile elimination has in some of our experiments led to the development of total obstruction when a partial one had been projected.

The liver lobes are in general defined by a cleavage of the parenchyma nearly to the hilum of the organ; and when there is but one duct from a lobe or group of lobes its obstruction leads to stasis throughout the tributary region. The proportion of the total liver affected can be readily determined under such circumstances. Potentially, at least, the case is different when there are two ducts or more to a lobe and one is left open. Under such circumstances relief may perhaps come to the area in stasis through newly opened channels into the unobstructed neighboring tissue. For it is well known that the bile canaliculi anastomose freely within the lobules. That no relief comes of a magnitude meriting consideration will be shown further on. The main difficulty lies in determining the exact amount of tissue in stasis.

Table II gives the weights of the liver lobes of twenty-nine normal dogs, expressed in percentages of the organ. In all cases the liver was removed before the blood had clotted. It will be seen that there is a rather large individual variation in the tissue distribution.

The monkey liver is divided into five lobes, much as in the rabbit, and these are grouped into a main liver and a lateral mass, which are connected at the base by a broad tissue bridge, as are the individual lobes also. A single short duct comes from each of the masses mentioned, and these unite to form an hepatic duct into which the cystic duct enters lower down, as in human beings. None of the ducts from the individual lobes save that from the caudate is accessible to ligation. This circumstance like that of the early cutting through of the ligatures has much hampered our observations.

"Physiological Jaundice."

Investigators upon icterus in the dog agree that it is frequently encountered in mild form in animals that appear normal. Naunyn[18] showed, as far back as 1869, that fasting for 24 hours regularly leads in most dogs to the appearance of bile pigment and salts in the urine. The icterus is not dependent on increased concentration of the urine, though it is made more evident thereby. A bilirubinuria from fasting was a frequent complicating factor in our early experiments, occurring

[18] Naunyn, B., *Arch. Anat., Physiol. u. wissensch. Med.*, 1869, 579.

regularly in the Sunday to Monday 24 hour specimen of unoperated animals as a result of the small ration of the day first mentioned. When a full diet was provided on Sundays intercurrent icterus became rare and often was traceable to disease. It was never found as the result of anesthesia or of the trauma of operation. In monkeys a fasting icterus was not noted, although it is said to develop occasionally in human beings.[3]

In view of these facts it seemed wise to keep several normal animals under observation with the operated ones as a control to intercurrent manifestations, and this was accordingly done.

Results of Total Obstruction in the Dog.

In sixteen dogs total obstruction was produced, sometimes by ligating and severing the common duct, but more frequently by cutting its large tributaries after their individual ligation. The tissue icterus that followed was never as pronounced as in human beings under similar conditions but in all cases was easily recognizable, while, in all, bile pigment became abundant in the blood and urine.[19] The tissue icterus was first visible on the 5th to 10th day, as yellowed scleras. The results in four of the sixteen dogs which were followed with special care have been tabulated (Table III).

The first sign of biliary obstruction was the appearance, as a rule, of pigment in the urine during the second or third 24 hours after operation but sometimes earlier. The delay is due, as Affanassiew showed,[20] to bile accumulation in the gall bladder and distended ducts: when he filled these reservoirs with wax at the time of operation icterus developed very much more promptly. Bilirubinemia was usually noted within 24 hours after bilirubinuria, and cholates were recognizable in the urine on the 3rd or 4th day. At autopsy of the dogs, after 9 to 46 days of obstruction, a general tissue jaundice was regularly found, the liver being especially affected.

[19] We have since autopsied an animal in which after 9 days of total obstruction no tissue icterus was discoverable. Urine and plasma were markedly tinted with bilirubin. There is little doubt that tissue pigmentation would have occurred in a day or so more.

[20] Affanassiew, M., *Z. klin. Med.*, 1883, vi, 281.

TABLE III.

Results of Total and Partial Obstruction in Dogs.

Dog No.	Sex.	Findings prior to operation.	Observed after operation for	Weight of animal.		Liver portion and per cent obstructed.	Postoperative findings.		Remarks.
				Initial.	Final.		Bilirubinemia.	Urine.	
			days	*kg.*	*kg.*				
1	F.	Negative for 9 days.	26	$10\frac{3}{4}$	11	Total obstruction.	Positive on 3rd day and after.	Pigment on and after 2nd day; salts on 3rd day and thereafter.	Scleral jaundice appeared on 8th day.
2	"	Negative for 10 days.	15	$9\frac{1}{2}$	$9\frac{1}{2}$	" "	Positive on 2nd day and after.	Pigment on and after 2nd day; salts on 5th day and thereafter.	Scleral jaundice appeared on 5th day.
3	"	Negative for 7 days.	20	$3\frac{3}{4}$	$2\frac{1}{2}$	" "	Positive on 4th day and after.	Pigment and salts positive on 3rd day and after.	Scleral jaundice appeared on 8th day.
4	"	Negative for 4 days.	13	$8\frac{3}{4}$	$8\frac{1}{2}$	" "	Positive on 3rd day and after.	Pigment and salts on 3rd day and after.	Scleral jaundice appeared on 9th day.
5	"	Negative for 3 days.	26	$10\frac{1}{4}$	$10\frac{3}{4}$	All except lateral mass; 71 per cent.	None.	Negative.	
6	"	Negative for 4 days.	10	$9\frac{1}{2}$	$9\frac{1}{2}$	" "	"	" save for salts on 3rd day.	
7	"	Negative for 7 days.	37	$7\frac{1}{2}$	$6\frac{1}{4}$	" "	"	Negative.	
8	"	Slight bilirubinuria of unknown cause during 5 days.	36	$7\frac{1}{4}$	$8\frac{1}{4}$	" "	"	Pigment and salts faintly positive on 2nd and 3rd days; salts positive on 16th, 20th, and 21st days.	Unoperated control animals showed pigment and salts likewise.

9	F.	Negative for 6 days.	23	$5\frac{3}{4}$	$5\frac{1}{4}$	All except left lateral lobe; 72.4 per cent.	None.	Pigment dubiously positive on two occasions.	Unoperated control animals showed pigment and salts likewise.
10	M.	Negative for 7 days.	34	17	16	" "	"	Pigment occasionally throughout.	
11	"	Negative for 6 days.	36	$14\frac{3}{4}$	$16\frac{1}{4}$	All except right lateral lobe; 82 per cent.	"	Salts from 7th to 14th days; thereafter, like pigment, negative.	Pigment once dubiously positive in urine.
12	F.	Negative for 7 days.	45	$15\frac{3}{4}$	$14\frac{1}{2}$	" "	"	Salts from 8th to 37th days; pigment on 4th, 9th, and 42nd days.	
13	"	Negative for 7 days.	15	$9\frac{1}{2}$	$9\frac{1}{2}$	All except papillary lobe; 95 per cent.	Positive on 11th day and after.	Pigment on 2nd, 3rd, and 4th days; salts and pigment on 11th day and thereafter.	
14	"	Negative for 7 days.	15	$6\frac{3}{4}$		" "	Positive on 2nd day and after.	Pigment on 2nd day and after; salts on 1st day and after.	
15	F.	Negative for 8 days.	28			Control animal.	None.	Pigment on 18th and 20th days; pigment and salts on 22nd, 24th, and 25th days.	
16	"	Negative for 4 days.	33			" "	"	Negative throughout.	
17	"	Negative for 5 days.	32			" "	"	Pigment on 11th, 12th, 13th, and 14th days; salts on 14th day.	
18	"	Negative for 5 days.	30			" "	"	Pigment and salts on 6th day and pigment on 19th day.	Pigment once dubiously positive in urine.

Results of Partial Obstruction in the Dog.

Partial obstruction was produced in ten dogs. Bile accumulation within these animals would presumably take place more slowly than on total obstruction, owing to the smaller amount of tissue in stasis and to the eliminative activities of the unobstructed portion. For these reasons no animal was considered to have given negative results as regards icterus until at least 10 days after operation and most were kept under observation for several weeks. As we shall point out further on, the unobstructed liver portion undergoes some hypertrophy within 10 days, while that in stasis atrophies, and thus the tendency to bile retention must soon be counteracted by lessened secretion in the region of stasis combined with increased facilities for elimination.

In four dogs approximately seven-tenths of the liver parenchyma was placed in stasis, in two others about three-fourths, in two, four-fifths, and in two about nineteen-twentieths. Table III summarizes the findings. Tissue icterus is not recorded because it was never observed, even when the eliminative burden had been thrown abruptly upon a mere twentieth of the liver.

In the four animals in which the duct from the lateral mass, draining on the average 29 per cent of the whole organ, was alone left open, bile pigment and salts were never demonstrable in blood or urine save on days when they were also present in control animals from the same intercurrent cause, namely, fasting. This was the case too when the free duct was that from the left lateral lobe containing 27.6 per cent of the tissue. A slightly greater degree of obstruction, produced by tying and cutting all the ducts except that to the right lateral lobe, or 18 per cent of the liver, resulted in the appearance of bile salts in the urine during the 2nd week after operation, occasionally accompanied in one animal by bile pigment as shown with the Gmelin test. The amount of pigment was always too slight to be quantitated, and bilirubinemia was not observed. Finally, when all the ducts were closed except that from the little papillary lobe, which holds from 3.8 to 7.3 per cent of the liver tissue, or on the average 5.1 per cent, pigment and cholates did indeed appear regularly in both blood and urine, and almost as rapidly as when total obstruction had been produced. In the two instances studied a sufficient bile elimination took place, however, to prevent tissue icterus during the 15 days of observation, and in view of the papillary hypertrophy found at the end of this period there is but slight reason to suppose that a greater retention would have occurred later.

The four normal dogs that shared the general conditions of the operated animals and were followed in the same way yielded findings that were several times of great value, disclosing that bilirubinuria and choluria noted in the operated animals were "physiological," from food deprivation. In this connection it seemed of interest to determine whether animals with seven-tenths of the liver in bile stasis would show fasting icterus more readily than normal controls. Accordingly during a period of 6 days several animals of each sort were fed only a thin bouillon. This they took in quantity with result that the urinary output remained large. The experiment will be set forth in detail in a later paper on the physiology of jaundice. Here we shall merely state that while icterus appeared in most of the animals, it developed no sooner and was no more marked in the operated individuals than in the controls.

Liver Adaptation.

In dogs with total biliary obstruction jaundice of the liver parenchyma is outspoken after a few days. By contrast, when obstruction is partial, even when it affects nineteen-twentieths of the organ, an hepatic icterus is not observed. From this it is evident that vicarious bile elimination becomes effective very close to the source, so to speak, a fact which is not surprising when one considers that the hepatic cells lie in the midst of copious blood and lymph streams, which, if kept free of bile, should keep them free also.

Long continued obstruction to the ducts from a part of the canine liver results in noteworthy changes in the whole organ, just as in the rabbit[21] and in man.[22] The portion in stasis gradually becomes sclerotic by an interlobular proliferation of the connective tissue, and the parenchymal cells undergo a gradual simple atrophy, and may

[21] Nasse, *Verhandl. deutsch. Ges. Chir.*, 1894, xxiii, pt. 2, 525.

[22] Carnot, P., and Harvier, P., *Arch. méd. exp. et anat. path.*, 1907, xix, 76.

TABLE IV.

Results of Total and Partial Obstruction in Monkeys.

Monkey No.	Previous findings.	Observed after operation for	Weight of animal.		Liver portion and per cent obstructed.	Postoperative findings.		Remarks.
			Initial.	Final.		Bilirubinemia.	Bilirubinuria.	
		days	*gm.*	*gm.*				
1	Negative for 13 days.	7	1,900	1,900	Total obstruction.	Positive on 1st day and after.	Positive on 1st day and after.	Tissue icterus on 4th day and after.
2	Negative for 1 day.	8	2,375	2,300	" "	Positive on 1st day and after.	Positive on 1st day and after.	Tissue icterus on 3rd day and after.
3	Negative for 1 day.	11	2,300	2,375	" "	Positive on 2nd day and after.	Positive on 2nd day and after.	Tissue icterus on 3rd day and after.
4	Negative for 1 day.	12	3,100	2,900	" "	Positive on 5th day and after.	Positive on 5th day and after.	At operation a pathological dilatation of the bile passages was noted. Tissue icterus on 8th day and after.
5	Negative for 5 days.	12	2,300	2,325	All except lateral mass and papillary lobe; 75 per cent.	None.	None.	Duct continuity restored toward end of experiment.
6	Negative for 21 days.	11	1,975	2,025	All except lateral mass; 80 per cent.	"	"	Questionable restoration of duct's continuity toward end of experiment.
7	Negative for 5 days.	11	2,650	3,225	" "	"	"	Obstruction maintained.

ultimately disappear. Meanwhile, the tissue with duct unobstructed gradually hypertrophies. The underlying causes for these alterations have been analyzed in a previous paper from this laboratory.[1] In the dog they take place far more slowly than in the rabbit. A parenchymal shift is usually not discernible in less than 10 days, but after a month may be very marked. At this time the mass in stasis may be much shrunken, with finely hobnailed surface. Needless to say, instances free of infection are here alone referred to. The region with obstructed bile channels is now sharply demarcated from the adjacent hypertrophic tissue, and has been found to correspond closely in extent with the ramifications of these channels, thus proving that during stasis no important connections open between the blocked ducts and the neighboring free ones.

The shifting of tissue caused by local obstruction renders it impossible to determine exactly from the weights of the liver portions at autopsy how much of the parenchyma was originally placed in stasis. But the anatomical relations and a knowledge of the normal proportions of the liver lobes, such as Table II affords, enable one to reach an approximate conclusion on this point.

Results of Biliary Obstruction in the Monkey.

Seven monkeys were used (Table IV). They yielded results essentially similar to those in the dog. As in this animal, total obstruction was well tolerated, but bilirubinuria appeared more rapidly, developing in two out of four instances within the first 24 hours after operation. What would seem to be an interesting illustration of delay in its appearance owing to accumulation of bile in the ducts and gall bladder is afforded by Monkey 4. At operation a note was made that the bile passages of this animal, though undistended, were about three times the usual diameter. Despite the production of total obstruction, pigment failed to appear in urine or blood until the 5th day and tissue icterus was not seen until the 8th day. At autopsy all of the bile passages were enormously distended.

The plasma of monkeys subsisting on a banana diet is colorless and the urine nearly so. Bilirubinemia appears at approximately the same time as bilirubinuria, on the 1st or 2nd day of total obstruction, and tissue icterus follows on the 3rd or 4th day. Cholates were never demonstrable in the urine by Hay's method. Further work would seem desirable on this point.

In three monkeys 75 to 80 per cent of the liver was placed in stasis. Owing to the rapidity with which ligatures cut through the ducts it was deemed best to terminate the experiments 11 and 12 days after operation. Even then in one instance there had been partial restoration of the duct continuity with some escape of bile into the intestine, though the well defined anatomical changes in the liver indicated that this was recent. At no time did the blood or urine of any of the animals contain bilirubin. That this would have continued to be the case is shown by the autopsy findings. For the livers, even in so brief a time, had undergone marked alterations in the direction of a functional readjustment. The unobstructed tissue was notably hypertrophied, and that in stasis shrunken and sclerotic. The changes had taken place almost as rapidly as in the rabbit, far more so than in the dog.

DISCUSSION.

The ability of a small portion of the liver to function for the whole as regards bile elimination when there is local obstruction depends without doubt upon several factors. That the parenchymal cells can rapidly excrete bile pigment and salts coming to them in large amount on the blood stream is proven by the promptness with which these substances pass into the bile when thrown into the circulation for experimental purposes.[23] Bile constituents formed by the tissue in stasis, and carried away from it by the blood and lymph, will of course be treated similarly. But the conditions of stasis themselves tend to lessen the amount of bile formed. For the obstructed ducts, dilating under pressure, interfere with the local portal flow[24] and divert a portion of the blood and with it the functional activities, to the more normal hepatic regions. There follows in due course a pa-

[23] Wertheimer, E., *Arch. physiol. norm. et path.*, 1892, iv, series 5, 577. Stadelmann, E., *Deutsch. med. Woch.*, 1896, xxii, 785.

[24] Betz, W., *Sitzungsber. k. Akad. Wissensch. Math.-naturw. Cl., Wien.*, 1862, xlvi, 238.

renchymal shifting from the region in stasis,[1] which, as time passes, tends to become complete. It is possible, furthermore, that stasis directly influences the liver cells to form less bile, but this cannot be profitably discussed.

Attempts should be made to determine in human beings the margin of safety in bile elimination. Quantitative studies on the rate of disappearance of jaundice after the surgical relief of total biliary obstruction should provide interesting figures on the ability of the liver to excrete pigment in excess. Injections post mortem into the bile ducts to determine the degree of obstruction in congenitally cystic livers and livers with widespread carcinomatosis ought, in connection with the clinical findings, to yield data of value. Perhaps the most direct evidence, though, is to be had from cases of local obstruction by intrahepatic calculi.

Beer,[25] who described many instances of stones within the liver, remarks on the fact that even when numerous and widely distributed they often cause no symptoms during life. Lewisohn[26] tells of finding at operation a liver studded with fibrous nodules in each of which was one or more gall stones. Yet the patient had for a long time been in good health and unjaundiced. Carnot and Harvier[22] report the complete atrophy of a liver lobe as result of an intrahepatic calculus occurring in a patient who was never jaundiced. Such instances, as well as those more frequent ones of disseminated hepatic carcinomatosis without jaundice, which come under clinical observation, give good reason for the belief that the human liver possesses a margin of safety in bile elimination not inferior to that of the dog and monkey.

There is a point of immediate practical import in the demonstration that the biliary obstruction required to produce jaundice is one affecting the greater portion of the liver. Jaundice is not infrequently seen in association with abscesses and other less discrete inflammatory changes occupying but a small portion of the hepatic tissue. The inference from such observations has been that the jaundice results from local bile resorption. But in view of our

[25] Beer, E., *Med. News*, 1904, lxxxv, 202.
[26] Lewisohn, R., *Ann. Surg.*, 1916, lxiii, 535.

findings this would seem highly unlikely. Rather should one think in such instances of a general injury either to the liver parenchyma or ducts, or else to the blood corpuscles.

SUMMARY.

The bile ducts from three-quarters of the liver substance in dogs and monkeys can be obstructed without any clinical evidence developing of pigment or cholate accumulation in the organism. And in the dog nineteen-twentieths of the liver substance can be placed in stasis without the occurrence of tissue icterus such as regularly follows total obstruction in this animal. There is no reason to suppose that this will not be found true in the monkey as well. Always a local obstruction results sooner or later in atrophy of the affected tissue with compensatory hypertrophy elsewhere. Thus as time passes the derangement of function produced by the sudden stasis is progressively lessened.

The plasma of the dog and monkey, unlike that of man, is normally free from bilirubin, and this pigment so readily escapes from the blood into the urine that bilirubinuria is often to be found in the dog in the absence of bilirubinemia, while the latter is never met with alone in either animal. It follows that in both species the renal threshold for bilirubin is much lower than in man,—if indeed one can be said to exist at all.

The amount of biliary obstruction required to produce jaundice in human beings is probably as great as in the experimental animals with which we have dealt. The clinical jaundice encountered in association with local liver lesions should be viewed not as the result of local bile resorption, but as due to a general injury to the hepatic parenchyma or ducts, or to blood destruction.