

PHYSIOLOGICAL CAUSES FOR THE VARIED CHARACTER OF STASIS BILE.

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PLATE 4.

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The fluid encountered at operation in the obstructed bile passages of human beings is of notably various character. Even in cases free of infection all gradations may be found between a black, tarry material and the watery, colorless "white bile" that has long puzzled surgeons. The causes for this diversity are not immediately evident in clinical instances because of the numerous complicating factors which give to each an almost individual peculiarity. One looks in vain for a clue to them in such a book as that of Kehr¹ which describes in detail the findings in many hundred operations upon diseased bile passages. But they are readily ascertained through experiment. The different, and in general opposed, functions of the gall bladder and ducts are principally responsible—infection aside—for the protean character of stasis bile.

Method.

Dogs have been mostly employed for the work, with some cats and *rhesus* monkeys. Many animals used for concurrent observations on other themes were available. Obstruction to the bile ducts was produced by tying and cutting, with the excision, where possible, of a piece, and at difficult points by ligatures laid on in series. In dogs and cats the danger of a restoration of continuity by cutting through of the silk thread was found to be negligible when that used was of large caliber. The operations were performed aseptically under ether anesthesia, and the abdominal wound was closed in three layers. Infection and other complications were rare. Save where specifically mentioned, instances showing them have been ruled from consideration. After some days or weeks

¹ Kehr, H., *Drei Jahre Gallensteinchirurgie. Bericht über 312 Laparotomien am Gallensystem aus den Jahren 1904–06*, Munich, 1908.

the animals were chloroformed and the ducts, their contents, the liver, and the hepatic vessels were carefully studied. Bits of the tissue and drops of the stasis bile were placed on agar and in bouillon, and the hepatic tissue was examined histologically.

The common duct of the dog and cat is formed from three or more main hepatic branches, high up into one of which the gall bladder empties. The arrangement varies greatly from animal to animal, and by taking advantage of special instances one may obstruct every large duct in turn, now in connection with the gall bladder and again separately, in association with a total obstruction, or with a local one so small as to be insignificant for the organism. In this way it is possible to test whether any duct has functions peculiar to itself. There is, properly speaking, no cystic duct in the dog or cat, owing to the entrance just below the bladder neck of a tributary from the right side of the right central lobe, but in the monkey there is a slender one, which, like that of man, empties into the common duct, an arrangement which much limits the obstructive permutations possible to the experimenter.

When the material was sufficient, quantitative estimations were made of the pigment and cholates in the stasis bile. In our opinion the results so obtained are not to be accepted without reservation because bilirubin, at least, undergoes changes on incubation in the gall bladder;² but they suffice to indicate the trend of affairs. Hooper and Whipple's³ modification of the Salkowski test was used to estimate pigment. The method has been discussed at some length in a preceding paper.⁴ For bile salts, the Foster and Hooper's⁵ amino nitrogen method was employed when the material was sufficient, and Hay's sulfur test when it was not. The amino-acid determinations were carried out for us in Dr. Van Slyke's laboratory. The Pettenkofer test for bile salts could not be used because it yields a positive result with cholesterol. To disclose the presence of the latter the Liebermann-Burchard method was employed.

Contrasting Types of Stasis Bile.

Whenever an obstructed bile duct was left in communication with the gall bladder the stasis bile later found proved to be heavily pigmented, and syrupy, ropy, or even tarry, according to whether the period of obstruction had been short or long.

Experiment 1.—In sixteen dogs, two cats, and one monkey obstruction of the common duct was produced, or of one or more of its hepatic tributaries in such wise that the gall bladder still communicated with the channels in stasis.

² Hammarsten, O., *Lehrbuch der physiologischen Chemie*, Wiesbaden, 8th edition, 1914.

³ Hooper, C. W., and Whipple, G. H., *Am. J. Physiol.*, 1916, xl, 332.

⁴ Rous, P., and McMaster, P. D., *J. Exp. Med.*, 1921, xxxiv, 47.

⁵ Foster, M. G., and Hooper, C. W., *J. Biol. Chem.*, 1919, xxxviii, 355.

The changes that took place in the stasis bile were the same, whether total obstruction had been produced or not. In animals killed after 2 to 4 days the gall bladder and the ligated ducts connecting with it were tensely, though not greatly, distended with a syrupy, dark brown bile. 2 or 3 days later the color of the fluid was noted to be definitely green-brown, and after 10 days to 2 weeks of stasis it was a green-black, and the contents of the gall bladder was mucinous or even tarry, while that of the connecting ducts was a heavy syrup. In the next 3 or 4 weeks the bladder bile underwent no important change but the fluid in the ducts gradually thickened to a jelly which gave Hay's reaction for bile salts in high dilution. Further our observations did not go.

The contents of ducts separately ligated and of the obstructed common duct blocked off from the gall bladder was entirely different.

Experiment 2.—In nineteen dogs, three cats, and four monkeys, the common duct was obstructed and the gall bladder neck as well, or else one or more large hepatic ducts separately tied and cut.

The stasis fluid in these instances was at first brown, then green but definitely less pigmented, and finally, after 10 days or more of stasis, clear, often completely colorless, even in jaundiced animals, or at most of a pale yellow, and usually without sufficient cholates to give Hay's or Udranszky's test. That from the cat was syrupy and in one case a tenacious jelly, but the yield of the dog and monkey was watery with a slight, translucent, glairy admixture. No greater contrast to the inspissated biles of Experiment 1 could have been devised. Yet both types of stasis fluid were frequently obtained at one time from the same animal (Figs. 1 and 2).

Experiment 3.—Obstructions were so placed on the bile channels of twenty-one dogs, three cats, and two monkeys that some of the large ducts in stasis were deprived of their connection with the gall bladder, while others still possessed it.

At autopsy both sets of ducts were equally distended, the one with a heavy, green bile giving Hay's test in high dilution, the other with the colorless or lightly tinted fluid above described (Fig. 1). In the contents of the finest duct ramifications visible to the eye on section of the liver tissue, like differences were discernible. Several apparent exceptions in which a green bile was found where a colorless fluid had been expected served to emphasize the invariable nature of the rule.

On search, a communication with the gall bladder was discovered in every such instance, either by way of a fistula or through reestablishment of the old connection.

Causes for the Differing Types.

It is clearly evident how the contents of a green system, as we may call one connected with the gall bladder during stasis because of the characteristic hue, comes to be highly pigmented and at last tarry. In a companion paper we have demonstrated that the normal gall bladder effects a great and rapid concentration of the bile. One has only to suppose that the organ still functions in some measure during stasis to explain the heaping up of pigment in it and the connecting ducts. The change from brown to green is, for the most part at least, a simple oxidation of bilirubin to biliverdin.² The thickening to a heavy syrup and eventually to a tar or jelly occurs through the gradual accumulation of a mucinous nucleoprotein which is a normal product of the bladder mucosa.²

What, now, is the derivation of the colorless material distending a "white system," one obstructed out of connection with the gall bladder? There are several possibilities, but a discussion of them is unnecessary since our findings point in a single direction. The thin, colorless fluid is not bile at all but a product of the duct wall that has gradually replaced the small amount of hepatic secretion originally pent up.

Experiment 4.—A greater or less portion of the common duct with, in some instances, the trunks of the larger hepatic ducts was isolated in five dogs by ligating and cutting it above and below. After various periods up to 12 days the animals were chloroformed and examined. The isolated duct segment was found uninflamed but greatly distended in every case—up to a diameter of about 1 cm. on the average—and held several cubic centimeters of colorless and watery, or thinly mucinous, fluid, identical in its obvious characters with that of a white system of ducts as above described. All of the animals had become jaundiced as result of the total obstruction, yet none of the duct fluids was bile-stained and the two that were submitted to Hay's test gave a negative response. Cultures attested their sterility.

Experiment 5.—In a female dog of 11.5 kilos a segment of common duct was isolated and connected by means of a glass cannula and flexible rubber tube with a small, empty rubber balloon, which was left in the abdominal cavity when the abdominal wound was closed. Recovery from the operation was prompt, and the

animal remained in excellent condition during the 6 days prior to reexamination. The bag now held 8.5 cc. of a clear, sterile, watery fluid, slightly alkaline to litmus, and with a specific gravity of 1.011. The mucosa of the duct was not inflamed. A few degenerating epithelial cells separated from the fluid on standing, and when looked at in long column the latter had a faintly greenish cast, doubtless as result of changes in the bile pigment originally left in the duct. Hay's test for cholates was negative. The dog had not yet developed a tissue icterus.

These experiments demonstrate that the mucosa of the duct secretes a fluid of its own and is not prevented from so doing by a pressure sufficient to stretch considerably the tough and rather inelastic duct wall. The degree of distension observed was about equal to that in the closed ducts above the isolated segment. In this relation it is interesting to remember that the pressure within the ducts rises during stasis in the dog to equal that of a column of bile approximately 300 mm. high.^{6,7} The amount of fluid produced in Experiment 5 in the absence of such a pressure obstacle was no negligible one—8.5 cc. in 6 days from a strip of mucosa about 2 cm. long and 0.7 to 0.8 cm. broad when the duct was laid open longitudinally.

Histological Changes.

The hepatic tissue in connection with obstructed ducts filled with colorless bile does not differ in the least in appearance, even after weeks of stasis, from that giving into a green system in the same animal. When the ducts from part of the liver have been left open there will be noted a general dilatation of the blocked channels, a slowly developing, orderly, interlobular cirrhosis, a few pigment thrombi between the parenchymal cords, and a more or less marked parenchymal atrophy in the region of stasis with compensatory hypertrophy elsewhere. When obstruction is total and jaundice has been present for some weeks one will find in addition marked parenchymal icterus and many intralobular bile thrombi, but still no differences referable to the green and white systems. Coursing beside the distended colorless ducts of the latter, and away from the liver, may be seen lymphatics turgid with

⁶ Herring, P. T., and Simpson, S., *Proc. Roy. Soc. London, Series B*, 1907, lxxix, 517.

⁷ Mitchell, W. T., Jr., and Stifel, R. E., *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 78.

fluid colored a bright yellow with bilirubin, and yielding a positive Hay's reaction. It is clear that the liver must be forming bile which is somehow prevented from entering the usual channels. The preventive agent can scarcely be other than the colorless secretion of the duct walls which has gradually backed up within them.

Development of a White System.

A systematic study has been made by us of the various steps in the development of a white system in the dog. During the first few days of obstruction the duct contents is still pigmented, appearing indeed somewhat more so than normal bile, owing to the conversion of part or all of its bilirubin into the much darker biliverdin. After about a week, as a rule, the pigment has become much less in amount, though in the lack of any criterion as to its original quantity, which varies greatly, of course, from animal to animal, examples cannot be given.

By the 10th or 11th day the duct contains a practically colorless fluid. In eleven dogs with total obstruction lasting from 8 to 27 days and icterus in varying degree, it was completely colorless, and devoid of cholates. So too in three cats with pronounced jaundice after 11 to 14 days of obstruction. Many instances could be cited of perfect white systems in animals with a partial obstruction, but these have less interest, owing to the fact that the occurrence of icterus was prevented in their case through a vicarious elimination of bile by the unobstructed liver portions. We have said that very few formed elements are present in the duct fluid. Cholesterol is practically absent as shown by the Liebermann-Burchard test which is occasionally negative and at most weakly positive. All these facts are as true for the contents of branches from single lobes, separately obstructed, as for that of the large channels.

Authorities are not agreed as to the precise point of escape of the bile from obstructed ducts but it is known to be close to the margin of the lobuli. According to Heidenhain⁸ and most workers it is situated at the junction of the intralobular bile capillaries with the collecting channels of Glisson's capsule. Bürker⁹ places it within the lobuli but

⁸ Heidenhain, R., *Studien des physiologischen Instituts zu Breslau, Leipsic*, 1868, No. 4, 234.

⁹ Bürker, K., *Arch. ges. Physiol.*, 1900-01, lxxxiii, 241.

near to their periphery. However this may be, one can suppose that in the gradual formation of a white system the fluid that accumulates in the ducts, diluting and replacing their original content, escapes at the same point as the bile. Certainly it must escape far back toward the lobuli, else the ducts in Glisson's capsule would be observed to contain bile, not colorless fluid when the liver is cut open. One may vision a slow upward current of duct secretion meeting and opposing a more rapid one downwards of bile in the region of the duct radicles, and the escape of both together through the walls.

In the monkey a "white bile" completely devoid of pigment and cholates is not obtainable, owing to the great distensibility of the ducts, so that relatively large amounts of stasis bile collect in them; to the short period during which they remain obstructed when cut between ligatures; and finally to one of several factors now to be discussed, which, acting likewise in the dog, often prevent the elaboration of a perfect "white bile." These are: (1) derivation of the white system from an hepatic lobe having another outlet which is patent; (2) the presence of gall bladder mucosa in the white system; (3) long continued obstruction.

In another connection¹⁰ we have furnished evidence that the bile radicles which unite to form each primary hepatic duct fail in the dog to anastomose in any significant degree with those of other ducts. Each drains what may be termed a separate watershed, and when its outlet is blocked, as when the duct is tied, the tributary region suffers to its outermost limits, as is shown by the eventual sharp line of demarcation between normal liver parenchyma and that of the region in stasis, a line which follows closely the anatomical limit of the obstructed ducts. But physiologically the separation is not quite absolute, as the present work shows. Repeatedly in the course of it we have had opportunity to note the influence of a free duct on the contents of a white system, having its ramifications in the same tissue mass. Under such circumstances the fluid of the white system is regularly yellow with bilirubin and contains cholates, although other white systems deriving from entire lobes of the same liver have contents colorless and negative for bile salts. The fact that the pigment

¹⁰ McMaster, P. D., and Rous, P., *J. Exp. Med.*, 1921, xxxiii, 731.

in the affected white system is bilirubin, not biliverdin as in old stasis biles, argues its recent production. The most reasonable explanation of its presence would seem to be a constant slight secretion of bile into the ducts as result of a lowering of pressure in them consequent in turn upon a slight continual leakage from the white system over into the adjoining unobstructed region. How and where this leakage occurs cannot be said. In the monkey there is evidence for a considerable amount of it in the development regularly of a broad zone of transition between the liver tissue that is atrophic as the result of transmitted pressure from obstructed ducts and the adjoining normal parenchyma.

We have called attention in another paper to a difficulty encountered in attempts to block off completely the gall bladder of the dog without encroachment on the duct. The bladder mucosa often extends below the neck of the organ, to or beyond the entrance of the first channels from the liver, as is readily seen when the duct is laid open. The development of a new gall bladder after cholecystectomy is probably traceable to this arrangement, for it never occurs when the segment of duct in question immediately next the bladder has been ablated.¹¹ So great is the concentrating activity of the bladder upon the bile that when a ligature is laid on the neck of the organ the small residual portion left below may suffice, as we have shown, to effect a considerable reduction in the fluid bulk of the secretion.⁴ It is to such a reduction in fluid bulk, whereby a little bile is enabled to enter a white system, that some of our anomalous instances should be attributed. In these cases when the duct distended with pale yellow bile was slit open a still more distended segment of characteristically thin walled bladder mucosa disclosed itself below the ligature which had been supposed to exclude it entirely. The neighboring ducts which had been separately obstructed held by contrast a colorless fluid.

Finally, in several dogs in which a white system and a general jaundice had existed for 6 weeks or more the stasis fluid was yellow and contained cholates in the absence of the factors just mentioned. The duct wall was now stretched very thin. Lessened secretion from it, or seepage through it, may have occurred.

¹¹ Haberer, H., and Clairmont, P., *Verhandl. deutsch. Ges. Chir.*, 1904, xxxiii, pt. 2, 81.

The Changes in a Green System.

The activities of the gall bladder during stasis merit special attention because they perhaps have no small share in the production of gall stones. The changes that occur within a white system are all in the direction of dilution and replacement of the bile. Those in a green system on the other hand seem at first view to be wholly the result of progressive biliary concentration. Within the first few days the bladder contents turns greenish black and as weeks elapse it thickens to a tar or jelly, while similar though less marked alterations occur in the fluid of the connecting ducts. It has required quantitative observations to show that here is no gradual accumulation of pigment; and in a preliminary note we have expressed this erroneous view.¹² What really happens is a progressive conversion of bilirubin to the greatly darker biliverdin, whereby a gradual disappearance of much of the pigment is masked. The point can be readily demonstrated by diluting out the bladder bile with water. The bile obtained after a week or 10 days of obstruction, though colored a green-black, dilutes out through the yellow-brown of bilirubin, to a bright yellow which only disappears in relatively large quantities of water. After another week the green persists to a higher dilution, but the proportion of water required to bring about a total disappearance of color is not so great. Finally after 5 weeks or more in the dog, and much sooner in the monkey, the yellow tint is missing when water is added to the bile and only a clear green is got which fails to survive much dilution. The disappearance of pigment thus indicated is also shown by titrations carried out according to Hooper and Whipple's method. At the latest period of stasis that we have studied—44 days, in the dog—the bladder contents still reacts characteristically with acid alcohol, and colorimetric readings against a bilirubin standard can be made. The amount of pigment found per cubic centimeter is now not more than twice that of many normal biles, instead of six to ten times the quantity as during the first 10 days.

How soon after the production of a green system does the concentrating activity of the gall bladder cease, and what are the maximum alterations effected by it? These questions are not readily answered.

¹² Rous, P., and McMaster, P. D., *Proc. Soc. Exp. Biol. and Med.*, 1920, xvii, 143.

STASIS BILE

TABLE I.
Character of Stasis Bile from the Gall Bladder.

Dog No.	Dura- tion of obstruc- tion.	Contributing liver lobes.	Liver per cent.	Jaundice.	Character of stasis fluid.	Diluting to.	Pigment per cc.	Sodium tauro- cholate per cc.	Hay's test + at dilution of.	Remarks.
1	2	Right and left central; pa- pillary.	43	0	Dark brown, syrupy.	Yellow.	2.7	32.2	1 in 80	Other lobes unob- structed.
2	4	All except cau- date and pa- pillary.	83	Slight.	Brown-black, syrupy.	"	5.9	35.0	1 " 64	Other lobes unob- structed. No tissue jaundice but bilirubin in blood and urine.
3	9	Caudate, right lateral; half of right central.	42	0	Thick olive- black, syrupy.	"	2.8	36.7	1 " 64	Other lobes unob- structed.
4	9	All except cau- date.	88	0	Thick olive- black, syrupy.	Greenish yellow.	4.3	34.0	1 " 40	Other lobes unob- structed.
5	9	Right central; papillary.	32	+	Viscid, green- black.	"	3.2		1 " 20	Other lobes ob- structed.
6	9	Main liver mass.	73	+	Viscid, green- black.	"	5.7		1 " 40	Other lobes ob- structed.
7	10	Right and left central; pa- pillary.	43	0	Thick greenish black syrup.	"	3.8	10.2	1 " 64	All other lobes ex- cept caudate ob- structed.
8	12	Right and left central.	38	+	Thick greenish black syrup.	Yellow-green.	3.0		1 " 32	Other lobes ob- structed.

9	34	Right central and papillary.	31	0	Thick green-black syrup.	Green.	1.9	63.1	1 in 192	Caudate and right lateral also obstructed.
10	36	Right half of right central.	12	0	Tarry, dark green.	Yellow.	1.0	16.4	1 " 128	Other lobes save caudate and right lateral are also obstructed.
11	36	Right central and papillary.	26	0	Tarry, dark green.	Green.	0.9	56.6	1 " 64	Other lobes excepting right lateral and a part of caudate are obstructed.
12	44	Main liver mass and papillary.	65	0	Tarry, green-black.	Yellowish green.	1.2	8.5	1 " 256	Part of caudate lobe also obstructed.

The inspissatory changes come about entirely through osmosis and diffusion, and are limited by the Δ of the blood.¹³ After the first few days the bladder and ducts undergo no further dilatation, their capacity when they are taken together being now only twice to four times the normal. It follows that the stasis bile will be mostly a derivative of that purveyed by the liver during the first few days of obstruction. And since the constitution of ordinary bile in substances of large molecule varies much, it follows that the small space available for its accumulation may in some individuals come to be occupied largely by substances of one sort to which the bladder wall is impermeable, and again by those of another. This fact is reflected in the irregularities of Table I.

In none of the fluids recovered after 2 days or more of stasis was so great a concentration of pigment found as in some bladder biles acted upon by the normal organ for 24 hours.⁴ After 9 days of stasis the pigment is still unincreased, and later there is a gradual diminution in it. One may conclude that the maximum pigment concentration is effected during the first day or two of obstruction, and that thereafter the activity of the gall bladder in this regard practically ceases.

Quantitative observations on cholesterol were not made because the bladder mucosa itself is recognized to be a source of the substance. Cholates though were estimated in two ways, as already stated,—by Foster and Hooper's amino-acid method and by Hay's sulfur test carried out on progressive dilutions of the bile.

Both of these methods as used in connection with stasis bile are open to criticism. An inspissated bile long kept at body temperature may very well come to contain other substances besides salts of taurocholic acid that fail to come down in boiling alcohol and will yield amino-acids on hydrolysis. Derivatives of the abundant nucleoprotein in special might well do this. Hay's sulfur test is not only given positively by any substance that lessens surface tension, but the lessening ordinarily caused by cholates may be hindered by other bile constituents. Thus, for example, we have several times found that a watery solution of sodium taurocholate which yielded a positive Hay's test when mixed with a given amount of water, failed to do so in the presence of a very slight trace of bile although the latter itself contained cholate but not in quantity sufficient to elicit a reaction in the dilution employed. There are then several possible explanations for the differences in result of the two methods (Table I).

¹³ Brand, J., *Arch. ges. Physiol.*, 1902, xc, 491.

The general indications obtained by both methods are that bile salts, unlike pigment, may increase in concentration as stasis progresses.

The gradual viscid thickening is the result of the persistent elaboration by the bladder wall of a mucinous material identified by Hammarsten as a nucleoprotein.² This is not produced in any quantity by the ducts. At first only the contents of the receptaculum chyli are thickened with it, but later it extends into the larger and smaller passages, and finally the most minute ones visible to the unaided eye are distended with tiny plugs of green jelly. In this connection it is noteworthy that the distribution of pigment and cholates throughout the green system eventually becomes an approximately even one. At first these are principally massed in the gall bladder, as would follow from the localization of the concentrating activity to this latter.

Experiment 6.—In thirteen dogs, one cat, and one monkey, with green stasis systems of 2 to 36 days duration a clamp was placed upon one of the tributary ducts at autopsy and the fluid obtained from above was compared with the bladder contents as regards pigment and cholates. So little material was yielded by the duct that Hay's test of graduated watery dilutions, and a direct color comparison with similar dilutions of the bladder contents, were the best methods available. They regularly indicated at first marked differences between the two biles, which tended to disappear later. Thus after 4, 9, and 10 days of obstruction, respectively, in three dogs the pigment was only 54, 25, and 30 per cent as strong in the duct fluid as in the gall bladder, whereas in three other dogs kept for 34, 36, and 36 days, its relative strength was 80, 86, and 100 per cent.

More factors influence the changes in a green stasis system than in a white one. The differing permeability of the bladder wall for different substances, and the eventual clogging of the mucosa which will vary in its effects with the substance; the continued production of mucus; the activity of the ducts to dilute the bile; these and doubtless other moments interact to alter the stasis fluid. The eventual tendency is toward replacement of the bile with duct secretion and mucinous material from the bladder.

The Pressure in Green and White Systems.

The fluid in obstructed bile ducts is pent under a day-to-day pressure averaging about 300 mm. of bile in the dog,⁷ a sufficient evidence that there are considerable barriers to its escape. These barriers would appear to be equally effective for the green and white systems. The distension of the ducts is the same in both when present in a single liver, and, what is perhaps more significant, the hepatic regions pertaining to the two show no noteworthy differences. We have pointed out in a previous paper¹⁰ that the pressure in regions of stasis has effect in a diversion of the portal stream with local parenchymal atrophy and a compensatory hypertrophy elsewhere. The changes may be readily followed in the dog liver, where they are marked after but a few weeks. Now were the duct pressure in a green or a white system much greater than in its fellow there should be a reflection of this in differing degrees of parenchymal change. Such are not found. The activity of the gall bladder, while sufficient to determine the character of the stasis bile, is, then, without enduring influence on the stasis pressure. The fact that the pressure developing when ducts are suddenly obstructed is the same as that on their continued stasis^{4,7} suggests that the prime moment in its maintenance is the secretory activity of the liver.

Some Results of Infection.

Consideration has been given thus far only to happenings in the absence of infection. The entrance of this latter may bring with it innumerable complexities. Two that have come under our eye will be put on record, since they throw light upon the problem of obstruction in man.

The fluid elaborated by infected ducts is sometimes no longer thin but so viscid as practically to occlude the ducts. In a dog from which we were making day-to-day collections of the bile from different portions of the liver, infection occurred of one of the duct systems drained by rubber tubes. Almost at once its output became thickly mucinous and practically lost the biliary character, being but faintly tinted with bilirubin whereas the companion bile that served as control was still thin and dark. At autopsy the liver

proved to be normal; and portions of the control bile when incubated with organisms from the infected ducts failed to thicken. There is little doubt that here we had to do with cholangitis rendered obstructive by a thick secretion from the duct walls; that is to say, just such a condition of affairs as is supposed to be operative in the catarrhal jaundice of human beings.

Infection may so change the gall bladder that a white system develops where a green is expected. In one of our dogs chronic infection led to a thickening of the bladder wall, and this organ and all of the obstructed ducts connected with it were found distended with a colorless, syrupy fluid that failed to give Hay's reaction but contained small ropes of old pus and numerous micrococci. There is good reason to suppose that in this instance the infection prevented an inspissation of bile by the bladder.

DISCUSSION.

It has long been taken for granted that the walls of the ducts influence the bile as do those of the gall bladder, and this view has colored the interpretation of pathological findings. That it is incorrect the present observations show. The activities of ducts and bladder are opposite in nature, but of such different magnitude that those of the bladder determine the picture when the bile is submitted to both. It is a curious fact that the duct walls, though intimately related to the tissue forming the bile, themselves secrete a fluid that is colorless even when the animal is heavily jaundiced. The glands of the wall behave in this respect like those forming the tears and saliva and those of the gastric mucous membrane,¹⁴ as contrasted with the sweat glands and kidneys which put out bilirubin during icterus. It is true that the fluid in a white system with walls stretched thin after long standing total obstruction may be lightly tinted with bilirubin and contain cholates; but these substances not improbably come from the liver under such circumstances. The fact may be recalled in this relation that mucous surfaces in general become permeable to bile pigment when inflamed.¹⁴

¹⁴ Krehl, L., *Pathologische Physiologie*, Leipsic, 9th edition, 1918.

“White biles” have been obtained from human beings with extreme fatty degeneration of the liver¹⁵ as well as after duct obstruction. The instances on record leave little doubt that a liver with injured parenchyma sometimes yields a colorless fluid having scarcely any resemblance to true bile. Our present findings warrant the suggestion that the fluid is derived from the duct walls, while the liver cells proper have practically ceased secreting. However this may be, there is no doubt that the ducts are the source of “white bile” in obstructive instances. In them the integrity of the parenchyma is attested by the resumption of secretion into the old channels when the impediment has been removed.¹⁶ The condition of affairs while the obstruction holds is essentially similar to that studied by Heidenhain⁸ in his classic experiments on the introduction under pressure of sodium indigotate into the ducts. The strange fluid, whether indigotate or white bile, fills all the extralobular passages, preventing any bile from entering them, and its surplus escapes with the bile itself through the walls of the duct radicles at or near the margins of the liver lobuli. When pressure is relieved the bile once more takes its way into the proper channels, flushing out ahead of it the strange fluid. Secretion by the liver is never inhibited, only diverted, a fact abundantly proven by the jaundice that ensues when the obstruction has been total.

In many instances in man of white bile from obstructive causes the hepatic duct or a branch of it has alone been blocked, but in others the common duct is occluded and the gall bladder and all the passages fill with a colorless fluid.¹⁶ Here is an apparent contradiction to our rule on the origin of green and white systems. But a green system can only be produced when the gall bladder is capable of concentrating bile during stasis. Lacking this ability the organ becomes a mere diverticulum in a white system. And it is with such incapable gall bladders that one has to do in these anomalous instances. Aschoff and Bacmeister¹⁷ have emphasized the fact in

¹⁵ Ritter, E., *Compt. rend. Acad.*, 1872, lxxiv, 813. Robin, A., *Compt. rend. Soc. biol.*, 1884, xxxvi, 115.

¹⁶ Kausch, W., *Mitt. Grenzgeb. Med. u. Chir.*, 1911, xxiii, 138. Fischler, F., *Physiologie und Pathologie der Leber, nach ihrem heutigen Stande mit einem Anhang über das Urobilin*, Berlin, 1916.

¹⁷ Aschoff, L., and Bacmeister, A., *Die Cholelithiasis*, Jena, 1909.

connection with hydrops that the normal gall bladder does not distend with fluid when tied off at the neck but draws gradually down into a small, thick walled globe containing a little mucous jelly. This happens even during the jaundice of total obstruction, as we have had occasion to note. Hydrops, as Aschoff and Bacmeister rightly say, is the expression of a change in the bladder wall such that fluid is elaborated by it instead of withdrawn through it. When an organ pathologically active in this way, or one merely indifferent to the bile, stands in connection with an obstructed duct system there will inevitably occur a gradual replacement of the original stasis bile with a secretion derived from the duct walls. We have furnished a specific instance in the animal already mentioned that was operated upon for the production of a green system, but in which a white developed instead, in connection with a bladder thick walled from chronic infection. Kölliker and Müller¹⁸ noted as far back as 1856 in a dog with an ill cared for gall bladder fistula that a glairy, colorless fluid collected when the fistulous opening closed for a day or two, which was replaced by bile after some hours of drainage.

A recognition of the physiological influences which make for the production of green and white stasis systems should bring some order into the chaos of observations on stasis bile. One is enabled to say with certainty that here the concentrating activity of the gall bladder is mainly responsible for the character of the fluid found, and that there it is the product of the ducts and in certain instances of an hydropic bladder. But the diverse infections to which the biliary passages are liable bring with them innumerable complexities. One we have recorded in the sudden mucinous thickening of duct bile, with obstruction as a result.

The differing activities of the bladder and ducts bear directly upon the problem of cholelithiasis. Our observations leave little ground for surprise over the fact that stones of the hepatic duct or its branches are relatively infrequent and give but little trouble clinically. A greater or less degree of obstruction of these channels must often occur: it is inevitable to inflammatory or neoplastic changes in the liver tissue. But such local stasis as may thus be caused is followed,

¹⁸ Kölliker, A., and Müller, H., *Verhandl. physik.-med. Ges. Würzburg*, 1856, vi, 435.

as the present experiments show, not by a concentration of the stagnating bile, but by its dilution and replacement with a fluid from which one of the principal substances forming stones, bilirubin, is often completely absent and the other, cholesterol, sometimes practically so. The fluid is thin, like the liver bile itself, and both will readily find a way around stones that only partially occlude a duct.

The participation of the gall bladder completely changes the conditions and the ultimate prospect. We have shown how rapidly the organ acts to inspissate the bile, even in the absence of stasis.⁴ Aschoff and Bacmeister bring evidence that most stones have their beginning in an uninfected and approximately normal gall bladder. In their view cholesterol falls out of the incubated bile in crystalline form and deposition takes place thereon; while Naunyn¹⁹ and many others believe that bacteria and cellular debris constitute the nuclei of formation. Whatever the true case, this much at least is certain, that the enlargement of stones is by a deposition out of solution or suspension. The activity of the gall bladder to concentrate the bile cannot but be of profound importance in this connection. Indeed, if one accept the cholesterol hypothesis of stone origin it assumes primary significance. The very rapid "growth" of stones that have passed into the common duct and cause partial obstruction, as described by Naunyn, and the secondary formation in such cases of stones just above, are alike attributable in large part to the influence of the bladder upon repeated fresh increments of bile. And the danger of total obstruction under such circumstances is rendered greater by the thickening of the bile with bladder mucus.

We have already pointed out that the upper portion of the cystic duct often has the physical characters of the bladder wall and with them its concentrating ability.⁴ This latter fact will go far to explain the development of stones in the duct after cholecystectomy, an occurrence not infrequent in the days before duct ablation was practised.

Aschoff has an aphorism to the effect that the essential and common cause of all gall stones is biliary stasis. One might say for many

¹⁹ Naunyn, B., A treatise on cholelithiasis, Sydenham Society translation, London, 1896.

cases, as coming nearer to the actual event, that it is biliary inspissation.

Stones rarely develop as a result of continuous obstruction. Under such circumstances, as we have shown, bile soon ceases to come from the liver into the closed passages, and that which at first assembles becomes thickened with mucus from the bladder and gradually diluted with the secretion of the duct walls. In none of our old bladder biles was any particulate matter found except desquamated cells.

How do these facts bear on the present vogue of cholecystectomy? It is evident from them that the concentrating activity of the gall bladder renders it a menace during intermittent stasis and whenever the bile itself is of such kind that stones readily form out of it. The more normal the organ, or to speak precisely, the more of the concentrating faculty it retains, the greater is the danger. On the other hand, the surgeon should realize that the removal of a normal gall bladder entails, as we have pointed out in a companion paper,⁴ functional disturbances that are none the less significant because the body adjusts itself to them. Furthermore, as Oddi originally showed, cholecystectomy is often followed by a marked and permanent dilatation of all the ducts so that they come to hold much bile. The accumulated secretion is separated from the intestine only by a weakened sphincter, and ascending infection of the ducts has been noted to occur.

In patients with a tendency to stone formation it would seem wise to prevent, so far as possible, concentration of bile by the gall bladder. A simple expedient suggests itself to this end, namely frequent feeding. During fasting periods not only is bile stored in quantity and concentrated by the bladder but the secretion as it comes from the liver is rich in solids.²⁰ The passage of chyme through the duodenum is accompanied by an expulsion of the bladder contents²¹

²⁰ Stadelmann, E., *Der Icterus und seiner verschiedenen Formen*, Stuttgart, 1891.

²¹ Bruno, G. G., *Dissertation*, St. Petersburg, 1898, and Klodnizki, *Dissertation*, St. Petersburg, 1898; cited by Babkin, B. P., *Die äussere Sekretion der Verdauungsdrüsen*, Berlin, 1914, 344. Bruno, G. G., *Arch. sc. biol. St. Pétersbourg*, 1899, vii, 87.

and its replacement with an abundant, thin flow from the liver. Viewed as prophylaxis, the oftener this can happen the better.

SUMMARY.

The gall bladder and ducts exert opposite influences upon the bile. The ducts fail to concentrate and thicken it with mucus as the bladder does, but dilute it slightly with a thin secretion of their own that is colorless and devoid of cholates even when the organism is heavily jaundiced. The fluid may readily be collected into a rubber bag connected with an isolated duct segment. It continues to be formed against a considerable pressure, and, in the dog, is slightly alkaline to litmus, clear, almost watery, practically devoid of cholesterol, and of low specific gravity to judge from the one specimen tested. In obstructed ducts separated from the gall bladder, or connecting with one so changed pathologically that the concentrating faculty has been lost, such fluid gradually replaces the small amount of bile originally pent up. It is the so called "white bile" of surgeons.

When obstructed ducts connect with an approximately normal gall bladder the stasis fluid is entirely different, owing to the bladder activity. At first there accumulates in quantity a true bile much inspissated by loss of fluid through the bladder wall, darkened by a change in the pigment, and progressively thickened with bladder mucus. As time passes duct secretion mingles with the tarry accumulation and very gradually replaces it. The inspissation of the bile, as indicated by the pigment content, is at its greatest after only a day or two of stasis.

The differing influences of the ducts and bladder upon the bile must obviously have much to do with the site of origin of calculi and their clinical consequences. The concentrating activity of the bladder cannot but be a potent element in the formation of stones. We have discussed these matters at some length. Intermittent biliary stasis is admittedly the principal predisposing cause of cholelithiasis; and the stasis is to be thought of as effective, in many instances at least, through the excessive biliary inspissation for which it gives opportunity. In this way a normal gall bladder can become,

merely through functional activity, a menace to the organism. In patients with the tendency to stones frequent feedings may lessen the danger of their formation.

EXPLANATION OF PLATE 4.

FIG. 1. White and green stasis systems after 11 days of total obstruction with jaundice. Retouched photograph. The gall bladder and connecting ducts, *A, A, A*, are dark with heavily pigmented green bile, while the branches, *B, B*, of a separately ligated duct distended with "white bile" are translucent and practically colorless.

FIG. 2. "White bile" and green from the same animals. The contrasting specimens, *A* and *B*, were obtained after 22 days of obstruction in a dog with one large duct left open, and consequently no icterus; and *A'* and *B'*, after 26 days of total obstruction with icterus.



FIG. 1.

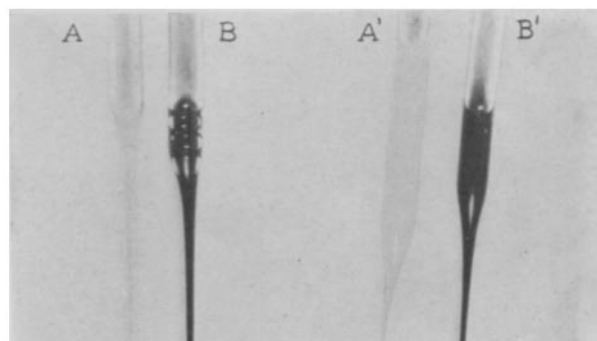


FIG. 2.

(Rous and McMaster: Stasis bile.)