

## JAUNDICE AS AN EXPRESSION OF THE PHYSIOLOGICAL WASTAGE OF CORPUSCLES.

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(Received for publication, February 21, 1925.)

The coloring matter responsible for jaundice is derived from blood pigment and, to all appearance, from that alone.<sup>1</sup> The amount of bilirubin present from day to day in the bile yielded by animals with intubated common duct constitutes an immediate if not entirely accurate index to the amount of blood destruction, whether this be in part the consequence of pathological influences, or merely the result of ordinary corpuscular wear and tear.<sup>2</sup> In view of this relationship, one may assume that, other things being equal, jaundice arising from bile retention will be to some extent conditioned in its degree by the amount of blood destruction that takes place. The purpose of the present paper is to bring out the fact that during obstructive jaundice the daily variations in ordinary corpuscular wastage find a direct expression in like variations in the bilirubinemia. This could scarcely be the case were the bile pigment distributed throughout the jaundiced organism as rapidly as formed; for the intercurrent variations in amount of bilirubin elaborated in the absence of a pathological blood destruction are far too small to be registered in terms of a general icterus. As our observations will show, the pigment is largely confined to the vascular pool, even in cases of long-standing jaundice, the staining of the tissues which attracts clinical attention being but the highly imperfect secondary manifestation of a blood condition.

### *Technique.*

Biliary obstruction was produced in a series of robust dogs by cutting the common duct between ligatures. The cystic duct was also severed to rule out the

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<sup>1</sup> Rous, P., Broun, G. O., and McMaster, P. D., *J. Exp. Med.*, 1923, xxxvii, 421. Broun, G. O., McMaster, P. D., and Rous, P., *J. Exp. Med.*, 1923, xxxvii, 733.

<sup>2</sup> Broun, McMaster, and Rous,<sup>1</sup> p. 733.

influence of the gall bladder to delay jaundice.<sup>3</sup> The operations were conducted aseptically under ether anesthesia; and healing by first intention was the rule. The hemoglobin percentage of the blood, as obtained from an ear vein, and its content of bilirubin were followed from day to day, the hemoglobin by Newcomer's method, and the bilirubin by that of Meulengracht,<sup>4</sup> with accessory determinations by the indirect diazo method.<sup>5</sup> It might be thought that the so called direct diazo would have been more to the purpose, since much of the bilirubin accumulating in the plasma on obstruction is brought down and lost in the precipitation with alcohol incident to the indirect test,<sup>5</sup> an occurrence responsible in the present instance for a notable and consistent underestimation

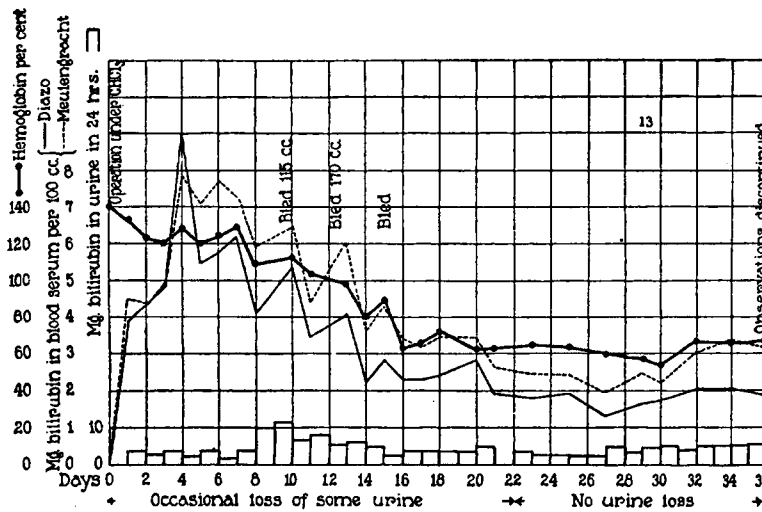


CHART 1. The concurrent variations in hemoglobin percentage and bilirubinemia during biliary obstruction.

of the bilirubinemia, as comparison with the Meulengracht quantitation clearly shows (Charts 1 and 2). But the indirect diazo had one great advantage, that it served as a check upon the character of the jaundice; for any pronounced hemolytic icterus, superimposed upon that due to the obstruction, would, presumably, have given evidence of itself in a disproportionate increase in the bilirubinemia, as measured by the diazo test. For the bilirubin deriving from hemolysis comes down to a much less extent on alcohol precipitation than does that accumulating as result of obstruction. No complication of the sort was encountered.

<sup>3</sup> Afanassiew, M., *Z. klin. Med.*, 1883, vi, 281.

<sup>4</sup> Meulengracht, E., *Deutsch. Arch. klin. Med.*, 1921, cxxxvii, 38.

<sup>5</sup> van den Bergh, A.-A. H., *Presse Med.*, 1921, xxix, 441.

The bilirubin excreted in the urine was quantitated daily;<sup>6</sup> and routine examinations were made for evidence of kidney injury (casts, albumin). There was at most only the slight disturbance that is not uncommon in the first weeks of jaundice.<sup>6</sup> During the early part of the work some portion of the 24 hour urine specimen was lost at times in the transfer of the animal from metabolism cage to laboratory. Later this was avoided by avoiding the transfer. Catheterization was not done, whence it follows that the 24 hour output of bilirubin, as recorded, must have frequently been in some part that of the period immediately preceding.

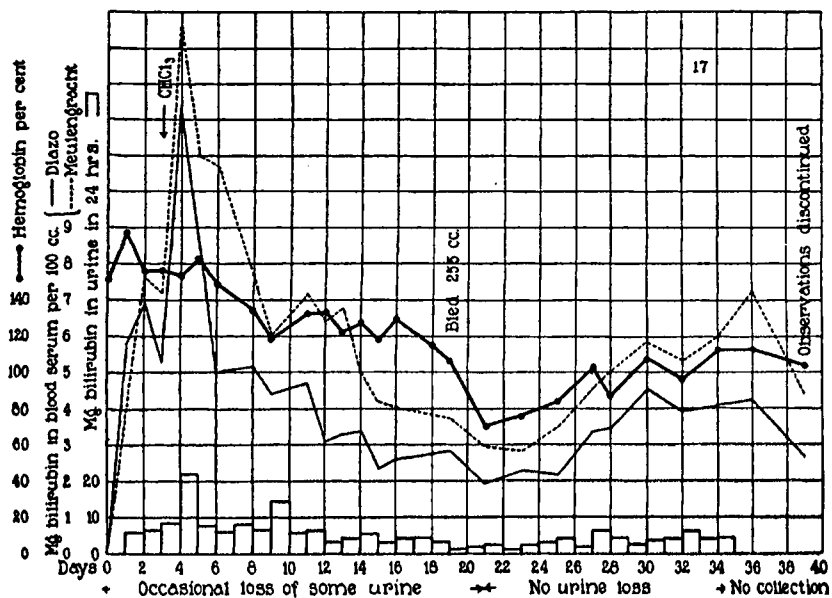


CHART 2. The concurrent variations in hemoglobin percentage and bilirubinemia during biliary obstruction.

The blood-letting was accomplished by aspiration from a jugular vein. An occasional animal showed from time to time a little blood in the stool as result of hemorrhoids; the dogs remained in good condition, despite the jaundice. Since some of the animals were to be utilized for other purposes, to which the observations on the jaundice formed a necessary preliminary, a considerable group were studied.

<sup>6</sup> Haessler, H., Rous, P., and Broun, G. O., *J. Exp. Med.*, 1922, xxxv, 533.

*Concurrent Variations in Hemoglobin Percentage and Bilirubinemia.*

In Charts 1 and 2 typical findings, as obtained in individual dogs, are depicted. It will be seen that, following an initial period of bilirubin accumulation in the blood, during which the curve of the concentration mounted steeply, this curve tended to level off and fall. The course of events found irregular expression in the output of bilirubin through the urine. Chloroform anesthesia provided an early cause of complication in both the instances recorded, but its influence on the long-time phenomena can be disregarded. The changes in bilirubinemia corresponded notably in time and degree with like variations in the hemoglobin percentage of the blood. Some of the minor concurrent variations in the two may well have been due to alterations in blood volume; but this cannot have been the responsible cause for the marked and sustained parallelism. Furthermore, the removal of a portion of the circulating blood pigment by bleeding was found to have result in a corresponding, or even more than corresponding, reduction in the bilirubinemia. And as long as the hemoglobin percentage remained at a low figure, just so long was the bilirubinemia relatively mild. With recovery from the anemia, the bilirubinemia curve mounted with that of the hemoglobin (Chart 2).

Even under the conditions that obtain immediately after an obstruction has been produced by operation, when the amount of bilirubin accumulating within the organism is temporarily increased by that derived from the destruction of blood which has escaped into the traumatized tissues<sup>7</sup> or been injured, perhaps, by the anesthetic,<sup>8</sup> there is to be perceived a relationship between the curve of the developing bilirubinemia and the amount of circulating hemoglobin. A chart which will illustrate the fact is published in an accompanying paper.<sup>9</sup>

Needless to remark, findings such as those described can only be expected in the absence of complication. A pathological breaking down of blood superimposed upon biliary obstruction would, of course,

<sup>7</sup> McMaster, P. D., Broun, G. O., and Rous, P., *J. Exp. Med.*, 1923, xxxvii, 395.

<sup>8</sup> Drury, D. R., and Rous, P., *J. Exp. Med.*, 1925, xli, 611.

<sup>9</sup> Drury and Rous,<sup>7</sup> Chart 2.

tend to increase bilirubinemia while at the same time lessening the hemoglobin percentage. In the course of some unpublished work one of us, with Dr. McMaster, has made repeated injections, at short intervals, of dog hemoglobin into animals already icteric as result of obstruction. It proved possible in this way to increase jaundice greatly within a few hours. But the changed condition is impermanent; by the next day as a rule the dogs have largely rid themselves of the unusual accumulation of pigment. During the period of adjustment the animals put forth urine containing great quantities of bilirubin. An instance of another sort, one in which the production of bilirubin underwent a lasting increase, is to be found in the companion paper just referred to. It will there be seen that, following a chloroform anesthesia such as ordinarily produces only transient effects,<sup>10</sup> there was not only an intensified bilirubinemia but an increased elimination of bile pigment by the kidneys, both enduring for weeks, together with a lowered hemoglobin percentage. The diazo tests on the blood plasma gave no indications of a special hemolysis. The animal was sacrificed while the phenomena were still manifest, and search made for a liver lesion and, by culture, for infection. Neither was found.

Incidental mention has already been made of the fact that when the circulating hemoglobin of the dogs with biliary obstruction was depleted by bleeding, there was sometimes a more than corresponding reduction in the bilirubinemia (Charts 1 and 2). This overreduction is permanent with the alteration in the hemoglobin percentage, and hence it cannot be referred merely to the loss of bilirubin involved in removal of the blood. A similar overreduction takes place in the bilirubin output of bile fistula animals in association with intercurrent reductions in the hemoglobin, conservation of the latter pigment within the organism being presumably responsible therefor.<sup>2</sup> Whether this explanation will hold in the present case is not certain from the data thus far assembled. In such relation the fact has interest that the rise in the curve of bilirubinemia during recovery from the anemia outstrips the rise in hemoglobin percentage just as does that of the output of bilirubin under similar circumstances in intubated dogs.

<sup>10</sup> Drury and Rous,<sup>7</sup> Chart 3.

That the distribution of retained bile pigment throughout the body takes place slowly is evident from the disparity in the tissue icterus and blood icterus following obstruction to the common duct. Coloration of the tissues follows upon a mounting bilirubinemia more tardily in dogs than in human beings, often not being evident for nearly a week. There have been claims that it sometimes does not occur at all; and certainly it varies much from individual to individual, as, for that matter, one may suppose the corpuscular wastage to do. We have made an attempt to prevent any development of jaundice by rendering animals markedly anemic prior to the tying of the common duct; but it always put in appearance after a time.

*The Distribution of the Pigment Causing Jaundice.*

The bilirubinemia present at any special moment in a jaundiced creature must be thought of as an expression not only of blood destruction but of a balance between the rate of bile pigment formation and the rates of its distribution and ultimate disposition. Not impossibly some of it may be converted to other substances within the tissues,<sup>10</sup> but since nothing positive is known of such a happening, it must of necessity be dismissed from attention. Of excretion this much can be said, that when the hepatic outlet for bilirubin has been blocked the main path for it is the renal, though there is an escape, quantitatively negligible, into some of the other secretions and into the intestinal tract. While large quantities of bilirubin may, on occasion, be voided through the kidneys, under the best of circumstances the organism cannot be freed of it in this way, even in an animal such as the dog in which the renal threshold for the pigment, to all practical purposes, does not exist. In general the intensity of bilirubinemia varies directly with bilirubinuria, though expressing the latter ineffectually.<sup>6</sup> This rule will be observed to hold in the instances charted for the present paper.

The relationship between bilirubinemia and tissue icterus is not yet clearly understood. Our findings give good reason for the supposition that a barrier to the distribution of bilirubin must exist somewhere between the blood and tissues. How else can one account for the

detailed parallelism between the hemoglobin and the bilirubinemia curves—a parallelism which could never exist if the way to the tissues were open? That bile pigment from hemolytic sources fails to pass into the urine with the ease of that accumulating as the result of frank obstruction is recognized; but during the present series of experiments we had to do with pigment of the latter sort. Though of relatively diffusible type, this passes with great difficulty into the lymph, as our tests have shown. Animals with an established and practically unvarying tissue icterus, as result of long continued biliary obstruction, were etherized, and specimens of lymph from mesenteric lacteals and from retroperitoneal lymphatics were collected directly into sharp-pointed, curved pipettes by direct puncture of the thin walled vessels. Limpid specimens sufficient in bulk for a comparison with the blood plasma were readily to be obtained in this way. No quantitative estimations were made because none was necessary, the amount of bilirubin in the pale yellow lymph being evidently far less than that in the deep yellow plasma. The findings in dogs injected intravenously a few minutes beforehand with sodium indigotate provided an enlightening contrast, the concentration of this highly diffusible dyestuff being the same in the lymph specimens as in the blood.

Such observations enable one to comprehend the character of the pigment distribution during jaundice. As result of a normal and, often, of a pathological, wastage of red cells bilirubin is formed into the blood stream, from which it passes only with great difficulty to the tissue fluids. That portion of it which is not retained in the tissues eventually finds a way back to the blood through the lymph channels. Thus both by an initial and by a secondary accumulation the pigment tends to be confined in the vascular pool. The development of tissue icterus after obstruction is gradual, not only because bilirubin accumulates gradually, but because there is an effective barrier to a general distribution of the pigment from blood to tissues. Its disappearance is swift when the obstruction has been relieved, both in consequence of a special liver activity<sup>7</sup> and because there is no barrier to the passage from tissues and blood, the thoracic duct providing an open road.

All this being true one might suppose that injury to the blood vessels would lead to an increased tissue icterus by facilitating the escape of bilirubin. This is the actual case. In dogs jaundiced as the result

of obstruction there may be seen a local intensification of the icterus where the skin is inflamed, and a similar occurrence has often been reported in human beings. The evidence provided by such instances is not unequivocal, however, for the damaged tissues might well have taken up more pigment than usual out of a lymph of similar content to that at normal situations. The yellow urticaria sometimes occurring during jaundice to which Schürer<sup>11</sup> gave the name "icteric skin writing" provides a better example. Jadassohn<sup>12</sup> has recently surveyed the literature of the phenomenon. While in some instances it would seem to result merely from local accumulations of lymph holding bile pigment in the same quantity as elsewhere, in others one must suppose that the blood vessels have been so affected locally as to let bile pigment through. The possibility that a fulminant general icterus may sometimes be consequent, in part, on an abnormal permeability of the vessels for the accumulating bile pigment is worth consideration.

#### SUMMARY.

The jaundice that develops after obstruction of the common duct in the absence of complications, expresses the physiological wastage of corpuscles occurring from day to day; and the intensity of the bilirubinemia varies as does the total of functioning hemoglobin-containing tissue from which this wastage takes place. There is to be observed a constantly readjusted direct relationship between hemoglobin percentage, bilirubinemia, and, by corollary, bilirubinuria. Induced losses of red cells find expression at once in a lessened accumulation and excretion of bile pigment; and as the regeneration of hemoglobin takes place the amount of bile pigment increases *pari passu* both in plasma and urine. The jaundice of bile retention is far less pronounced during secondary anemia than when the individual is full blooded, other things being equal.

During uncomplicated obstructive jaundice the intercurrent changes in bilirubinemia correspond closely with those in circulating hemoglobin even when tissue icterus is of long standing. The fact indi-

<sup>11</sup> Schürer, J., *Deutsch. med. Woch.*, 1922, xlviii, 593.

<sup>12</sup> Jadassohn, J., *Deutsch. med. Woch.*, 1923, xlix, 1544.



cates the presence of a barrier to the distribution of bile pigment from the blood, and such a barrier is to be found in the walls of the vessels. Its influence is at once evident on comparing lymph specimens and blood specimens from the long jaundiced animal. The amount of bile pigment in the lymph is then seen to be negligible, relatively speaking. Tissue icterus should be thought of as, ordinarily, the highly imperfect secondary expression of a condition which tends to be localized to the blood pool. On occasion more pigment than usual may escape from this pool, as for example into the wheals of the yellow urticaria described by clinicians.