BLOOD PHOSPHATASE AND THE VAN DEN BERGH REACTION IN THE DIFFERENTIATION OF THE SEVERAL TYPES OF JAUNDICE

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When icterus, unaccompanied by other definite signs or symptoms, develops in an elderly patient, it is frequently a matter of difficulty to decide whether obstruction of the extrahepatic bile ducts—more particularly by malignant disease of the pancreas—is present, or whether the case is one of simple catarrhal jaundice. It may be that the diagnosis is made with certainty only after an interval of several weeks, by observation of the general progress of the case and of the jaundice. Again, to distinguish an obstructive from a toxic jaundice may be a troublesome problem in the early stages of the condition, since the onset and symptoms may be alike, and in both there may be pale stools, biliuria, and a direct van den Bergh reaction.

It was claimed for the van den Bergh reaction, on its introduction, that it distinguished obstructive jaundice on the one hand, from catarrhal, toxic, and infective jaundice on the other—the obstructive variety giving a "direct" reaction, the others a "biphasic" or an "indirect." Extensive clinical trial has shown that while the reaction is useful in other ways this particular claim is untenable, since any type of reaction may be obtained in catarrhal and toxic jaundice, the direct reaction being the most frequent finding in the author's experience. In these circumstances it seems that the use of another method of distinguishing gross obstructive jaundice from the other varieties is desirable. The main purpose of this paper is to describe a method which has been found to be very reliable in the examination of fifty-two consecutive cases of jaundice. In addition, some relevant constructive criticism of the modern theory of icterus and of the van den Bergh reaction is offered. The van den Bergh reaction was carried out on all the cases of the series, and the results are shown in the table.

THE VAN DEN BERGH REACTION

It is convenient at this point to make some observations on the subject of the reaction itself. The "direct" reaction was described by van den Bergh,¹ and has passed into a number of textbooks, as characterized by a blue-violet colour, maximal in thirty seconds, resulting from mixing equal parts of icteric serum and reagent. In actual practice a result answering this description is seldom met with; the author has not yet seen one in the course of several hundred tests. The usual finding with "direct-action serums" is that a colour change begins at once on the addition of the reagent and progresses through a reddish shade to a red-violet or violet. It is probably owing to this that the colour is described in other textbooks as violet, red-violet, red, pink, and rose. Moreover, the colour change takes up to half an hour to reach its final shade, as can be readily demonstrated by putting on a second test half an hour after the first and noting the time taken for the colours to become equal. These remarks apply to serums tested as soon as possible after collection. If the serums are allowed to stand for some time the reaction takes place more slowly. The direct reaction in its usual form, therefore, would be more correctly described as a change of colour from the original yellow, through red, to a

red-violet or violet, beginning at once on addition of the reagent, the whole process taking several minutes and sometimes as long as half an hour. But this is essentially the description of a "biphasic" reaction as given by van den Bergh—namely, "a red colour appearing at once and gradually deepening to violet." This is unfortunate, since the significance of a biphasic reaction may be very different from that of a direct reaction.

In order to avoid this difficulty, the author now makes use of the following facts:

(1) The pigment in obstructive jaundice serums is insoluble in chloroform.

(2) The pigment in indirect reaction serums is soluble in chloroform.

(3) The biphasic reaction is thought, on good experimental grounds, to be a combination of the other two types.

The reaction is said to be *direct*, therefore, when the colour change begins on the addition of the reagent, whilst not more than a trace of the total pigment is extracted when another sample of the serum is shaken with an equal volume of chloroform (judged by the colour of the chloroform layer as compared with the colour of the serum). The reaction is said to be *biphasic* when the colour change begins on the addition of the reagent, whilst an appreciable proportion of the pigment is extracted by the chloroform. This was found to be more satisfactory in practice than endeavouring to name the type of reaction solely from the final colour obtained and the time occupied in reaching it, and it is in this sense that the terms "direct" and "biphasic" are used in the table. An *indirect* reaction is one in which no change of colour occurs with the reagent until after the addition of alcohol to the serum. Hence there is no difficulty in recognizing this type, and the fact that the pigment may be completely extracted by chloroform is not made use of.

It will be observed on reference to the table that not only did all the cases of obstructive jaundice give a direct reaction, but most of the toxic and all the catarrhal cases reacted in a like manner. It would not have been possible to classify these cases by the colour obtained in the van den Bergh test, as in every one the final shade was more or less violet. This accords with the view already widely held, that the reaction gives little assistance in differentiating obstructive jaundice from the other varieties, with the exception of the haemolytic type, which gives the indirect reaction.

The quantity of bilirubin in the serum was estimated in every case by van den Bergh's method, but this method suffers from the disadvantage that varying quantities of pigment are carried down with the protein precipitate on the addition of alcohol, and so are not included in the final estimation. This is more particularly the case in serums giving a direct reaction. In addition, the adsorption in different serums is not proportional to the total pigment present. On this account Thannhauser and Andersen's modified method, in which the whole of the bilirubin is estimated, was also carried out. The figures for both methods are given for purposes of comparison and reference. The bilirubin content of normal serum is 0.2 to 0.5 unit.

BLOOD PHOSPHATASE

The property possessed by certain body tissues and organs of hydrolysing phosphoric esters into the free alcohol and phosphoric acid is attributed to the presence of enzymes, to which the name of phosphatases has been given. One or more of such enzymes are normally present in blood, and the ability of the blood to split phosphoric esters in the above way is referred to as the phosphatase

activity of the blood. Experimental evidence has been brought forward by Robison and his associates² to show that phosphatase plays an important part in the formation of bone, and it appears that this enzyme may also be a factor in carbohydrate metabolism.

It was found by Kay³ and by Roberts,⁴ working independently, that the phosphatase activity of the blood is greatly increased in osteitis deformans, and Kay showed further that a marked increase also occurs in other conditions in which extensive bony changes are taking place. In the varied series of cases investigated by Roberts were included two cases of obstructive jaundice and one case of catarrhal jaundice. The two cases of obstructive jaundice showed an increase in blood phosphatase activity as great as that noticed in some of the cases of osteitis deformans, whereas the catarrhal jaundice figure was only slightly raised above the normal. This difference between the two forms of jaundice seemed to merit further investigation, the result of which has been to establish the fact that in cases of gross obstructive jaundice, such as may result from a gall-stone in the common bile duct or a pancreatic carcinoma, the blood phosphatase figure is invariably high, whereas in all other varieties of jaundice the figure is but slightly raised, and may even be normal, though the patient may be deeply jaundiced. The results on which this statement is based are shown in the table, and the method used in obtaining these results will now be described.

TECHNIQUE AND PRESENT INVESTIGATION

About 10 c.cm. of blood was removed from the patient's arm vein in the usual way. Of this 5 c.cm. was allowed to clot to yield serum for the van den Bergh test, and 5 c.cm. was oxalated for the phosphatase determination. Should it be preferred to use plasma for the van den Bergh test, the whole of the blood can be oxalated, and, after the removal of the 4 c.cm. required for the phosphatase, the remainder can be centrifuged for plasma.

The phosphatase activity was estimated by the author's method,⁴ which consists in determining the increase in inorganic phosphorus (that is, the amount of hydrolysis) on incubating the blood with excess of sodium beta-glycerophosphate for two hours at 38–40° C., at pH 8.9. The phosphorus is determined before and after incubation by Benedict's colorimetric method, as described in Myer's *Practical Chemical Analysis of Blood*. The results are expressed in units of phosphatase per 100 c.cm. blood, one unit being the amount of enzyme that will liberate 1 mg. phosphorus in two hours under the above conditions. The method sacrifices a certain amount of accuracy in order to be easily applicable and to diminish time consumption, so that the exact limits of normality are not precise, but a result not exceeding 5.5 units may be taken as normal.

In the description of the method in the original paper it was stated that the minimal quantity of oxalate should be used to prevent clotting, as it was noticed that excess of oxalate led to lower results for the blood phosphatase. It has since been found that this is because the oxalate interferes with the determination of the phosphorus, though it does not appear to affect the activity of the enzyme. This was shown by carrying out the phosphatase procedure on three portions of blood under identical conditions, except that a little additional powdered oxalate was added to portion 2 before incubation. After incubation and protein precipitation had been carried out on the three specimens, an amount of oxalate was added to specimen 3 equal to that previously added to specimen 2. The inorganic phosphorus was then determined in each, the results being: (1) 15.4 mg.; (2) 14.6 mg.; (3) 14.6 mg. Thus the effect of oxalate is produced during the phosphorus determination, not during the incubation. When excess of oxalate is used, the

effect is more noticeable the greater the concentration of phosphorus, so that the error does not vanish in computing the increase in phosphorus concentration, but leads to a lower value for the phosphatase. If a great excess of oxalate is added no colour at all develops in the phosphorus determination, but the small quantity necessary to inhibit clotting makes no essential difference to the result.

Although the phosphatase figure is often alone sufficient to distinguish the obstructive nature of a jaundice, it is an advantage to carry out a quantitative bilirubin estimation at the same time, in order to obtain a numerical expression of the jaundice to compare with the phosphatase figure. The degree of skin pigmentation is not a reliable index of the bilirubin content of the blood, and it is on the relation between this content and the phosphatase activity that the differentiation really depends. Thus, a phosphatase figure which would indicate toxic jaundice if the bilirubin content of the serum was high might favour a diagnosis of obstructive jaundice if the serum bilirubin was low. (Compare Cases 6 and 24.)

REMARKS ON CASES

The cases are arranged in the table into obstructive, toxic and infective, catarrhal, and haemolytic jaundice, and a small unclassified group. With the exception of one or two of the last-named, the diagnosis in every instance was clearly established either on clinical grounds or as a result of operation or necropsy.

It is obvious from a perusal of the figures that the cases fall definitely into obstructive or non-obstructive groups. Only one case in the obstructive group shows a phosphatase figure of less than 10 units, and in this case the jaundice was relatively slight (2.7 units of bilirubin). On the other hand, none of the toxic and catarrhal cases has a phosphatase figure above 10, with the exception of Case 37, which will be referred to later. The fact that several of the toxic cases were deeply jaundiced emphasizes the distinction. The essentially obstructive nature of the icterus in Cases 3 and 7 was apparent from the macroscopical and microscopical findings at necropsy.

No.	Diagnosis	Units of phosphatase	Type of van den Bergh reaction	Units of Bilirubin	
				v.d.B. method	T. & A. method
Obstructive					
1	Carcinoma pancreas	18.5	Direct	12.0	—
2	„ stomach with jaundice	19.6	„	12.5	16.4
3	Miliary tuberculosis with jaundice	10.9	„	10.7	15.0
4	Stone in common bile duct and ruptured cystic duct	11.8	„	6.5	7.0
5	Pancreatic cirrhosis—cholecystotomy	20.4	„	12.0	18.3
6	Carcinoma bile duct—six days after operation	9.4	„	2.5	2.7
7	Hodgkin's disease with jaundice...	18.4	„	11.6	14.9
8	Cholelithiasis	14.6	„	11.3	15.5
9	Carcinoma pancreas	16.0	„	13.8	19.4
10	„ „	12.6	„	5.0	5.5
11	Obstructive jaundice	22.9	„	12.2	19.8
12	Cholelithiasis	14.7	„	1.5	2.0
13	Carcinoma stomach with jaundice	13.6	„	15.3	19.1
14	Carcinoma pancreas	12.1	„	6.7	9.3
15	„ „	16.8	„	17.4	23.4
16	„ „	17.8	„	15.8	21.5
17	Cholelithiasis	20.3	„	13.9	25.0
18	Carcinoma bile ducts... ..	17.0	„	11.3	18.6
19	„ stomach with jaundice	18.6	„	10.0	14.1
20	Cholelithiasis	16.5	„	8.2	11.1
21	Carcinoma pancreas	21.3	„	14.1	19.9

No.	Diagnosis	Units of phosphatase	Type of van den Bergh reaction	Units of Bilirubin	
				v.d.B. method	T. & A. method
Toxic and Infective					
22	Toxic jaundice—patient died ...	8.7	Biphasic	17.0	—
23	Jaundice following N.A.B. ...	5.0	Direct	13.5	17.6
24	" " " 5th day " 10 days later " 7 " "	6.6	"	9.8	16.0
		9.4		21.7	30.0
		7.9		18.5	25.5
25	Toxic jaundice	8.9	"	28.0	35.0
26	Jaundice following N.A.B., 21st day	5.5	"	13.2	20.3
27	Suppurative cholangitis	7.5	"	55.0	—
28	Infective cholangitis—ten days after laparotomy, jaundice fading	7.7	"	3.6	5.0
29	Infective jaundice following cholecystectomy for gall-stones	8.1	Biphasic	14.6	19.2
30	Jaundice following N.A.B.	5.1	Direct	6.2	10.2
31	Subacute yellow atrophy	8.2	Biphasic	18.0	20.6
32	Jaundice following N.A.B.	6.9	Direct	21.0	26.5
Catarrhal					
33	Catarrhal jaundice	4.7	Direct	17.5	20.3
34	" "	4.2	"	2.5	6.9
35	" "	5.0	"	5.0	7.3
36	" "	3.7	"	3.7	5.1
37	" " (patient aged 3)	13.9	"	2.7	—
38	" "	4.8	"	10.0	13.9
39	" " 1 week after onset " 3 weeks "	6.6	"	23.9	27.7
		8.9		17.4	23.8
40	" "	5.2	"	13.7	17.9
Haemolytic					
41	Pernicious anaemia	2.7	Indirect	5.0	—
42	Severe secondary anaemia	5.5	Delayed direct	1.6	—
43	Secondary anaemia	2.2	"	1.9	1.7
44	Acholic jaundice	3.2	Indirect	6.8	7.0
45	Pernicious anaemia	3.3	"	3.0	—
Unclassified Cases					
46	Portal cirrhosis... ..	21.9	Biphasic	1.2	1.6
47	" "	6.0	"	1.3	1.5
48	Cirrhosis or carcinoma liver ...	7.6	"	0.9	1.2
49	Chronic hepatitis	9.1	Direct	0.5	0.5
50	Catarrhal jaundice (?)	6.7	"	5.0	7.3
51	Acute onset infective endocarditis in case of Graves's disease	6.8	Biphasic	2.7	2.9
52	? (Enlarged spleen—positive W.R.)	7.4	Direct	1.4	2.0

Case 11 was clinically one of obstructive jaundice, but the patient left the hospital before the nature of the obstruction had been ascertained. In Cases 22 and 25 there was again no question as to the nature of the jaundice, though the actual "toxin" was not discovered. It will be noted that five cases of so-called "haemolytic" jaundice are included (Cases 41 to 45), in each of which the phosphatase figure is normal. The unclassified cases are so grouped either because the clinical diagnosis was in doubt or because the class into which the jaundice should be put on pathological grounds is open to dispute!

Case 46.—Male, aged 31, with enlarged liver and spleen. There was a lack of unanimity of opinion in the diagnosis of this case, as it closely resembled the mythical Hanot's cirrhosis. The phosphatase figure is exceptionally high in comparison with the slight degree of the jaundice, and it is probable that some factor other than gross biliary obstruction is involved. This case was encountered at the outset of the research, and when later its exceptional nature was recognized an attempt was made to get into touch with the patient in order that a more thorough investigation might be made. This proved impossible, as the patient had died in the interval.

Case 47.—Male. Portal cirrhosis, with hob-nail liver and history of ascites and Talma-Morrison operation. Kay⁵ found a slightly increased blood phosphatase in a case of portal cirrhosis, but he does not mention the presence or absence of jaundice.

Case 48.—Male. An obscure case with a greatly enlarged liver, diagnosed provisionally as carcinoma liver or cirrhosis.

Case 49.—A woman, aged 43, who had had "catarrhal jaundice" four months previously, and who still showed an icteric tint and an enlarged liver.

Case 50.—A woman, aged 25, diagnosed as catarrhal jaundice at the time of the test (with which diagnosis the figures are in agreement), but as the jaundice was still present several weeks later the case has been left unclassified.

Case 51.—A girl, aged 20, who had been under observation and treatment for some months for thyrotoxicosis, and who then became suddenly worse, with intense pain in the legs, vomiting, and jaundice. This proved to be the onset of infective endocarditis, which ended fatally a few weeks later. It is probable that such a jaundice would be toxic in nature, but the case is complicated by the fact that the blood phosphatase is liable to be slightly increased in Graves's disease.

Case 52.—Another obscure case. A woman, aged 43, with an enlarged spleen and a positive Wassermann reaction, who left the hospital before a satisfactory diagnosis had been made.

In several of the cases in the main groups the method described was of value in establishing the diagnosis, and it is perhaps permissible to refer to one such case as an example. A man, aged 67, was admitted to hospital complaining of increasing jaundice of three weeks' duration. No symptoms of any significance were present. On examination there was nothing abnormal found except the jaundice. The stools were pale, biliuria was marked, and the van den Bergh test was direct, the serum containing 20.3 units of bilirubin. A diagnosis of carcinoma pancreas was made. Against this was the fact that the phosphatase activity of the blood was normal. On further investigation of the case the Wassermann reaction was found to be positive, whereupon the patient admitted that he had been having "injections" on this account. When he was seen two months later the jaundice had cleared up and the serum gave an indirect reaction (0.4 unit bilirubin). The case is No. 26 in the table.

The cases of catarrhal jaundice are shown in the table separately from other jaundices of toxic and infective nature. At first sight Case 37 would appear from its phosphatase figure to belong to the obstructive group, but this is not necessarily so, since the patient was a child of 3 years of age, and the normal blood phosphatase in children is nearly double that for an adult, though the actual limits of variation have not been worked out by the author's method. A blood phosphatase estimation on a child of 5, convalescent after pneumonia, carried out at the same time as the above, gave a value of 8.2 units. Nevertheless catarrhal jaundice of an obstructive nature cannot be excluded in this case. In this connexion it may be mentioned that it is probably a mistake to regard catarrhal jaundice as a pathological entity. Klemperer, Killian, and Heyd⁶ divide it into three classes:

- (1) Due to obstruction of the ostium of the common bile duct from gastro-intestinal catarrh.
- (2) By degeneration of the liver with multiple necrosis—a sort of mild yellow atrophy.
- (3) Due to cholangitis.

Cases of the first class would show the objective signs of an obstructive jaundice, and the phosphatase method would presumably fail to differentiate such a jaundice from that due to other forms of obstruction, but apart from the doubtful case referred to above the difficulty was not met with in this investigation. The fact that the phosphatase value was low in all the other cases supports the view widely held at the present time that most cases of catarrhal jaundice are of the nature of a hepatitis.

DISCUSSION

Although the reason for the relation between the phosphatase activity of the blood and the type of jaundice is not as yet altogether manifest, there are a few points bearing on the matter which may be discussed at this

stage. In the first place, the differences observed in the phosphatase are not due to any variation of hydrogen-ion concentration in the incubation mixtures. This point was disposed of at once by incubating several well-buffered specimens of icteric bloods at different pH values, when the distinction between the two main types of blood was maintained. Nor is there any reason for postulating the presence of phosphatase-inhibitory substances in toxic jaundice blood, since a mixture of equal parts of such blood and high phosphatase blood from a case of osteitis deformans gave the exactly average value of its two components.

It was thought that the explanation might be found in the fact that bile contains phosphatase, so that on the occurrence of biliary obstruction the entry of bile into the blood would increase the phosphatase activity of the latter as well as its bilirubin content. There are, however, two reasons why this alone will not explain the facts. In the first place, on testing the point experimentally it was found that the phosphatase activity of bile is in itself insufficient to account for the high figures obtained. Several tests were carried out in which cadaver bile, or bile draining from the gall-bladder or from the bile ducts after operation, was added to normal blood, of which the following will serve as a typical example.

Normal blood was mixed with fresh bile in the proportion of 3 to 1. A van den Bergh test on the mixture was direct, and 13.3 units of bilirubin were present as estimated by van den Bergh's method (colour comparison was impossible when Thannhauser and Andersen's method was used). The phosphatase activity of the original blood was 2.8 units, and of the mixture 3.6 units (estimated at optimum pH by a slight modification of the method used for blood), from which it may be deduced mathematically that the activity of the bile was about 6 units. Direct determination of the bile phosphatase could not be accomplished as turbidity developed during the phosphorus determination. Thus an artificial obstructive jaundice serum of 13.3 units showed the blood phosphatase activity of a toxic jaundice. In one case a small proportion of dark viscous cadaver bile from the gall-bladder was used, which resulted in a phosphatase value for the mixture of 12.2 units, but the bilirubin figure was far in excess of any likely to occur in practice.

The second reason against the bile phosphatase hypothesis is that it is inconsistent with the low phosphatase figures found in toxic jaundice if the modern view of this condition be accepted—namely, that the jaundice is in part due to biliary obstruction or to necrosis of liver cells by which free passage of bile constituents into the blood is made possible, thus accounting for the direct or biphasic van den Bergh reaction, the frequently pale stools, and the biliuria. According to van den Bergh, biliuria is always indicative of obstruction.

The modern explanation of the van den Bergh reaction and jaundice has, however, never appeared entirely satisfactory to the author, but with the slight modification about to be tentatively put forward, it seems to fit the facts better and to allow of an explanation of the phosphatase figures. It is at present thought that indirect-reaction pigment is produced from haemoglobin by the cells of the reticulo-endothelial system, is conveyed to the liver in the blood, where it is taken up by the polygonal cells and converted into direct-reaction pigment, in which form it is excreted into the bile. When bile is reabsorbed into the blood in obstructive jaundice a direct van den Bergh reaction is therefore obtained: If for any reason the liver cells are unable to deal with all the pigment produced by the reticulo-endothelial cells this will accumulate in the blood and result in an indirect reaction. In toxic jaundice both these factors are supposed to be at work, with the result that the blood contains both types of pigment and so gives a biphasic reaction.

A MODIFICATION OF EXISTING VAN DEN BERGH THEORY

The suggested amendment is that indirect-reaction pigment is converted into direct-reaction pigment, not in the polygonal cells, but in the blood, in, or even outside, the liver, so that the function of the polygonal cells is simply to transfer the direct-reaction pigment from the blood into the bile. Some support is afforded to this view by the fact that direct-reaction pigment is readily dialysable, whereas indirect-reaction pigment, which is probably present in the colloidal form, will not dialyse.^{7, 8} Accumulation of direct-reaction pigment in the blood could then occur in one of two ways: (1) by obstruction to the bile ducts, so that the liver no longer removes bilirubin from the blood; (2) by functional inefficiency of the liver cells, such as occurs in toxic or catarrhal jaundice.

In either of these eventualities the blood would show a direct reaction, which is what actually occurs in practice. The idea of the "circular tour" undergone by the bile pigment in obstructive jaundice—that is, from the blood through the liver cells and back into the blood via the lymphatics or the hepatic capillaries—may be retained in addition if desired. The explanation of the biphasic reaction and of its occurrence from time to time in toxic jaundice remains essentially as before, the accumulation of the indirect-reaction component being due to an insufficiency of the agent in the blood necessary for its conversion to direct-reaction pigment, which suggests that this agent originates mainly or entirely in the liver. This amended explanation gets over an awkward point in Mann's work on bile-pigment formation, which does not appear to have been noticed. Mann⁹ found that when the liver was removed in dogs jaundice developed after an interval of six hours, the blood showing, first, an indirect reaction, and, later, a biphasic. This would clearly be impossible on current theories—that a biphasic reaction indicates direct-plus indirect-reaction pigment, and that direct-reaction pigment is due to the passage of the indirect-reaction type through the liver cells.

The modified theory also makes it possible to explain the relation between blood bilirubin and blood phosphatase in jaundice. This will differ according as the phosphatase be assumed to originate in the liver cells or elsewhere. If it originates in the liver cells, then in obstructive jaundice it either passes into the blood instead of into the bile, when the biliary secretion ceases, or it joins the "circular tour" with the bilirubin, and in this manner reaches the blood. In toxic jaundice it passes into the bile in the normal way, whereas the bilirubin is held back in the blood in varying degree by the functional incapacity of the liver cells. If, on the other hand, we assume that the phosphatase originates outside the liver and reaches it in the blood stream, its accumulation in the blood in biliary obstruction is accounted for in the same way as the rise in pigment content, whilst in toxic jaundice the liver must be supposed to excrete phosphatase more readily than pigment. From a biochemical investigation into bile and jaundice serums, which it is hoped to publish in due course, it would appear that the actual details of bile-pigment metabolism are more complex than this account suggests, but the latter offers a solution of the present problems without contravening any of the established facts.

The point which remains for explanation is why the blood phosphatase figures in obstructive jaundice should exceed those found for bile. This may be accounted for by noting that whereas bile pigment is readily excreted in the urine, phosphatase is not; hence, the phosphatase figure will soon rise relatively and absolutely. Kay⁵ has shown that the urinary phosphatase excretion is not greatly increased above the normal in Paget's disease with high blood phosphatase, and the author has

confirmed this observation and has noted further that the phosphatase excretion in all types of jaundice is also but slightly increased. This implies that an early case of obstructive jaundice would show a relatively low phosphatase figure, but no case of obstructive jaundice of less than a week's duration has been met with in the course of the work. The point might be settled by ligature of the common bile duct in animals, but opportunity to do this has not occurred. At the same time, the idea that the whole of the differences observed may be accounted for solely on the duration of the jaundice is untenable, since several of the toxic cases were of long duration. The optimum pH for the blood phosphatase in jaundice is the same as that for the phosphatase in osteitis deformans, and it may well be that the same enzyme is concerned in the two conditions, being produced in the liver and concentrated at the site of bone formation. In this connexion it is interesting to recall the observation of Buchbinder and Kern,¹⁰ who found that a low blood calcium and osteoporosis followed the ligature of the common bile duct in dogs, which findings have been attributed to inefficient absorption of calcium from the intestine owing to the absence of bile. Reasons are given by Kay⁵ for thinking that in bony diseases the high blood phosphatase is a result, not a cause, but in obstructive jaundice the high blood phosphatase precedes any bony change, so that it is possible that in these cases the increased blood phosphatase leads to some disturbance of calcium-phosphorus metabolism.

Finally, it is necessary to draw attention to two classes of case in which the phosphatase activity of the blood may not elucidate the cause of jaundice.

1. When the patient is already suffering from a disease in which the phosphatase is raised, as in Case 51, already discussed, in which jaundice developed during the course of Graves's disease. Apart from obstructive jaundice, however, the phosphatase is considerably raised only in conditions in which extensive bony changes are occurring.^{4 5}

2. Cases in which the jaundice is slight, where there may be difficulty in deciding whether the phosphatase figure is raised or not, owing to the fact that the method of phosphatase estimation has a fair margin of error. The accurate but more elaborate method described by Kay¹¹ might be of use in such cases. Further, the final phosphatase figure depends to some extent on the initial figure before the onset of jaundice, so that a low initial phosphatase and a trifling obstructive jaundice might leave the figure within normal limits. This, however, is not the class of case in which the type of jaundice is of great practical importance, whilst it is clear that the method is capable of differentiating correctly most of the cases ordinarily met with. On this account it seemed worth while reporting it at this stage, in order that it might be applied and further tested by others interested in the subject.

SUMMARY

1. The current description of the direct and biphasic van den Bergh reactions is criticized and suggestions made for its improvement. The results of the reaction in a series of cases of jaundice are presented as evidence in support of the view that the reaction fails to differentiate obstructive from toxic and catarrhal jaundice.

2. The obstructive nature of a jaundice can be recognized by the increased phosphatase activity of the blood, which occurs strikingly in this type alone. The procedure adopted to recognize this increase is outlined, and the results obtained in a series of fifty-two consecutive cases reported. These results demonstrate that, by the method described, toxic, infective, and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type.

3. The relation between the phosphatase activity of the blood and its bilirubin content is discussed. A modification of the modern theory of jaundice and the van den Bergh reaction is proposed, which appears to explain the facts better than the present view, and to allow also of an explanation of the above relationship.

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RELATION OF EXCESSIVE CARBOHYDRATE INGESTION TO CATARRHS AND OTHER DISEASES *

BY

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Elsewhere¹ attention has been drawn to the fact that in a large boarding school for girls the incidence of cases of catarrhal illness of more than seven days' duration was greatly reduced during the war years. The following table shows the average incidence of such illness in the ten years 1904-13 and in the four years 1914-17.

	1904-13	1914-17
	Per cent.	Per cent.
Spring terms	4.15	0.6
Summer terms	1.1	0.5
Autumn terms	2.05	1.3
Average per annum	2.6	0.8

This suggests that perhaps the duration of catarrhal illness is affected by some article of diet the consumption of which was reduced during the war. Do we know of any foodstuffs which in excess aggravate this condition? Many observers believe that children who have a low tolerance for carbohydrates are especially prone to catarrhal affections. H. C. Cameron² has described the catarrhal child as having an excess of water in the body, and has attributed the tendency to lymphoid hyperplasia in all situations and to catarrhal inflammation of the "swollen and oedematous mucous membranes" to this cause. He finds that evident and permanent improvement follows restriction of carbohydrate food.

McClendon^{3 4} has demonstrated water retention after high glucose feeding both in man and in animals. Ramsay⁵ has described the occurrence of visible congestion and exudate in the retinas of patients whose carbohydrate intake is in excess of what they can tolerate, and has pointed out that this is an index of the state of the capillaries elsewhere in the body. Occasional albuminuria (so

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