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Quantitative Studies of Direct Serum Bilirubin.

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In the presence of hyperbilirubinemia, little or no clinical significance is attached at the present time to the qualitative van den Bergh reaction, except in the diagnosis of hemolytic forms of jaundice. However, an immediate direct reaction is obtained at times in patients with cirrhosis and hepatocellular damage, and following relief of biliary obstruction, in the presence of serum bilirubin concentrations within normal limits. The introduction, by Malloy and Evelyn,¹ of a photoelectric method for the exact quantitative determination of "direct" bilirubin raised the possibility that some light might be thrown upon the significance of the direct van den Bergh reaction and the pathogenesis of hyperbilirubinemia in such cases.

Material and Methods. Determinations were made of total and direct bilirubin, readings being made in the case of the latter at 5 and 30 minutes, employing the photoelectric method of Malloy and Evelyn.¹ In addition, the usual qualitative direct van den Bergh reaction was performed in each instance, development of the characteristic color within 30 seconds being regarded as constituting a positive direct reaction. Data reported here include observations made in the following types of cases: (a) 35 subjects with no evidence of hepatic or biliary tract disease; (b) 107 determinations in 40 patients with hepatocellular damage; 33 determinations in 7 cases of cirrhosis of the liver; 19 determinations during periods of complete biliary obstruction in 8 cases.

Results and Comment. The findings are presented in detail in Table 1. In the normal group, with serum biliary concentrations of 0.1-0.8 mg%, the 5 minute direct bilirubin constituted 0-50% and the 30 minute direct bilirubin 0-75% of the total. Excluding the few instances in which there was no direct bilirubin (total bilirubin 0.1-0.2 mg), the ranges of these values were 12-50% and 25-75% of the total, respectively. These values are in substantial agreement with those reported by Malloy and Evelyn in normal subjects (30 minute direct bilirubin, 35-70% of total).

In the patients with cirrhosis, the proportion of direct bilirubin

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¹ Malloy, H. T., and Evelyn, K. A., *J. Biol. Chem.*, 1937, **119**, 481.

TABLE I.

Total bilirubin mg	Normal						Cirrhosis						Hepatocellular						Obstructive						
	Direct bilirubin			Direct bilirubin			Direct bilirubin			Direct bilirubin			Direct bilirubin			Direct bilirubin			Direct bilirubin			Direct bilirubin			
	5 min	30 min		5 min	30 min		5 min	30 min		5 min	30 min		5 min	30 min		5 min	30 min		5 min	30 min		5 min	30 min		
.1	0	.0	0-50																						
.2	.0	.05	0-25	.0	.15	0-75																			
.3	.05	.1	17-33	.1	.2	33-67																			
.4	.05	.2	12-50	.1	.25	25-62	.3	.75	0.4	100															
.5	.15	.25	30-50	.2	.3	40-60	.15	0.4	30-60	.35	.5	70-100													
.6	.1	.2	17-33	.2	.3	33-50	.2	0.4	33-67	.4	.5	67-83	.1	.3	20-60	.2	.5	40-100							
.7	.15	.2	21-29	.25	.35	36-50	.2	0.6	62-75	.6	.8	75-100	.4	.67		.5	.83								
.8	.2	.25	25-31	.35	.44		.5	0.6	62-75	.6	.8	75-100	.1	.5	12-62	.4	.6	50-75							
.81-1.0													.1	.5	11-50	.4	.8	44-80							
1.1-2.0							.7	1.0	54-71	.4	1.5	33-86	.2	1.1	17-73	.5	1.4	37-100							
2.1-5.0										1.8	2.3	75-100	4	3.8	14-77	7	4.2	19-85							
5.1-10.0										4.7	69		2.1	6.5	36-81	2.6	6.9	51-86							
10.1-20													5.5	12.8	54-69	6.0	13.8	59-85	7.6	11.0	56-71	8.3	11.9	60-75	
20+																				11.5	20.4	57-79	13.2	22.4	66-81

was rather consistently higher than normal (5 minutes, 30-75% ; 30 minutes, 33-100%) throughout the range of values for total bilirubin (0.4-10.0 mg %). This was particularly true with total bilirubin values within the limits of normal (30 minute direct, 67-100%). In the patients with hepatocellular damage there was greater variation in the proportion of direct bilirubin (5 minute, 11-81% ; 30 minutes, 19-100%). In those with total bile stasis the 5 minute direct bilirubin constituted 56-79% and the 30 minute 60-87% of the total. These data suggest that in the presence of a serum bilirubin concentration within the limits of normal (0.1-0.8 mg) a direct bilirubin content constituting more than 50% of the total at 5 minutes and more than 70-75% at 30 minutes is indicative of hepatic functional impairment.

An attempt was made to ascertain possible differences in the proportion of direct bilirubin in the sera of patients with normal total bilirubin concentrations giving negative direct van den Bergh reactions and those giving positive direct reactions. The data bearing on this point are presented in Table II. There appears to be no significant difference between either the proportions or the absolute amounts of direct bilirubin in the two groups which could account for the striking difference in behavior of the sera in the qualitative van den Bergh reaction. It must be remembered, however, that the latter is read at the end of 30 seconds, whereas the quantitative direct readings are made at 5 and 30 minutes. The absence of significant relationship between the production of the positive direct van den Bergh reaction and either the total bilirubin concentration, the concentration of direct bilirubin or the proportion which the latter constitutes of

TABLE II.

Total bilirubin mg	Positive direct van den Bergh Direct bilirubin				Negative direct van den Bergh Direct bilirubin			
	5 min		30 min		5 min		30 min	
	mg	%	mg	%	mg	%	mg	%
	Cirrhosis.							
.4	.3	75	.4	100				
.5	.15-.4	30-60	.35-.5	70-100				
.6	.2-.4	33-67	.4-.5	67-83	.4	67	.5	83
.7								
.8	.5-.6	62-75	.6-.8	75-100	.5	62	.6	75
	Hepatocellular Damage.							
.4					.1	25	.3	75
.5					.1-.3	20-60	.2-.5	40-100
.6	.4	67	.5	83				
.7			.4-.6	57-86	.1	14	.4	57
.8	.2-.5	25-62	.4-.6	50-75	.1-.2	12-25	.4-.5	50-62

TABLE III.
Jaundice Following Sulfanilamide.

Days	1	3	4	5	6	8	10	12
Total bilirubin	5.9	4.6	2.9	1.6	1.1	0.8	1.0	0.4
Direct bilirubin (30 min)	.5	.5	.7	.8	.5	.5	.5	.2
Direct van den Bergh Reaction	—	—	+	+	+	+	+	—

the total is illustrated also by data obtained in a patient with jaundice following administration of sulfanilamide.

Conclusions. The chief clinical value of the quantitative determination of direct serum bilirubin appears to lie in the detection of hepatic functional impairment in the presence of a normal serum bilirubin concentration. Values constituting more than 50% of the total with readings at 5 minutes or more than 70-75% with readings at 30 minutes are probably abnormal. There is no apparent significant relationship between the amount or proportion of direct bilirubin and the production of a positive direct van den Bergh reaction in sera with normal total bilirubin content.

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Response of *Sulfapyridine-fast* Pneumococci to Sulfathiazole and Sulfamethylthiazole.

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Our experimental studies,¹ as well as those of MacLeod,² have shown that inadequate treatment of pneumococcal infections with sulfapyridine leads to development of organisms which are resistant or *fast* to that drug. Whether these *sulfapyridine-fast* pneumococci are equally *fast* to other sulfanilamide derivatives, such as sulfathiazole and sulfamethylthiazole, is a matter of theoretical and practical interest. Consequently, we have studied the reactions of 2 of our *sulfapyridine-fast* strains to these latter drugs.

Essentially identical experiments have been performed with each *fast* strain and with the parent strains from which these *fast* organ-

¹ Schmidt, L. H., and Dettwiler, H. A., in press.

² MacLeod, C. M., *J. A. M. A.*, 1939, **113**, 1405.