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**Bilirubinemia and Bromsulphalein Retention.**

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We have previously reported<sup>1</sup> that reticulo-endothelial blockade produced by the intravenous injection of India ink or saccharated iron oxide leads to a retention of intravenously injected bromsulphalein. That bromsulphalein disappears from the blood in normal animals faster than it is excreted in the bile has been recognized by various workers. This observation is in harmony with the occurrence of retention after reticulo-endothelial blockade. Theoretically therefore, bromsulphalein retention may be due to either a dysfunction of the reticulo-endothelial system or a defective hepatic excretion or both. In some experiments designed to study this relationship it was considered necessary to determine whether there is any mutual interference between bilirubin and bromsulphalein with respect to their rates of elimination from the blood stream. The present report is concerned with the effect of injected bilirubin on bromsulphalein elimination.

The experiments were performed upon dogs, both normal and anesthetized. Pure bilirubin (Eastman Kodak Company) dissolved in distilled water with the aid of a few drops of 10% sodium hydroxide solution was used. Bromsulphalein tests were performed in the usual way, using 2 mg. per kilo of dye and determining the dye concentration in plasma samples obtained at 5 minutes and at 30 minutes, the reported figures for each test indicating the percentage of dye in a 5-minute sample and in a 30-minute sample respectively. Five mg. per kilo was given to 4 normal dogs. In one dog a bromsulphalein test was run immediately and showed no retention (10-0). In the other 3 the bromsulphalein was injected 30 to 180 minutes after the bilirubin. Very slight retentions occurred (20-0, 30-5, 15-0 respectively). Ten mg. per kilo was given to 3 normal dogs. Thirty to 180 minutes later the bromsulphalein tests showed retentions of 40-10, 20-0, and 40-10 respectively. In one dog the test was repeated—injecting the bromsulphalein immediately after the bilirubin. Normal figures (10-0)

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<sup>1</sup> Mills, M. A., and Dragstedt, C. A., *PROC. SOC. EXP. BIOL. AND MED.*, 1936, **34**, 228.

were obtained. Five mg. per kilo of bilirubin produced but a slight and transient bilirubinemia, the plasma concentrations decreasing from a range of 3.3 to 4.3 mg. per 100 cc. at 5 minutes to non-recognizable amounts in 90 minutes. After 10 mg. per kilo the plasma concentrations of bilirubin declined from a 5-minute range of 7.2 to 10 mg. per 100 cc. to nonrecognizable amounts in 120 minutes. In order to maintain a more persistent bilirubinemia 2 injections of 10 mg. each at an interval of 30 minutes were made into a normal dog. Thirty minutes after the second injection this animal showed a dye retention of 50-15. In 2 other animals 10 mg. of bilirubin was injected while they were under ether anesthesia. This definitely prolongs the bilirubinemia. These animals showed dye retentions of 60-30 and 70-50 respectively. Short periods of ether anesthesia in our experience have had no effect on the bromsulphalein test. Anesthesia of 2 to 4 hours causes a very slight retention<sup>2</sup> but has never in our experience resulted in such marked retention as this.

These experiments have been limited on account of the cost of the bilirubin, but we believe that they definitely show that an artificially induced bilirubinemia causes a retention of bromsulphalein. It has been recognized by various workers<sup>3, 4</sup> that after experimental obstruction of the bile duct, there is no appreciable dye retention until a definite bilirubinemia develops and that the degree of dye retention then increases somewhat proportionately with the bilirubinemia. Rosenthal<sup>3</sup> interpreted the failure to obtain dye retention immediately after experimental obstruction as indicating that the liver cells, if uninjured, can take up the dye, even though they cannot excrete through the biliary channels in the normal way. Our observations suggest a different interpretation, namely that the dye retention is secondary and related to the bilirubinemia. The further implication of this would be that while dye retention might occur without jaundice, marked jaundice could not occur without dye retention. As far as we know this is in accord with the reports in the clinical literature.

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<sup>2</sup> Rosenthal, S. M., and Bourne, W., *J. A. M. A.*, 1928, **90**, 377.

<sup>3</sup> Rosenthal, S. M., *J. A. M. A.*, 1924, **83**, 1049.

<sup>4</sup> Snell, A. M., Greene, C. H., and Rowntree, L. G., *Arch. Int. Med.*, 1925, **86**, 273.