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This Week's Citation Classic

Odell G B. The dissociation of bilirubin from albumin and its clinical implications. *J. Pediat.* 55:268-79, 1959.

The cytoxicity of bilirubin cannot be accurately assessed from its total concentration in plasma, because bilirubin is bound to albumin. The current studies demonstrate the ability of albumin to bind bilirubin is significantly reduced when other organic anions (e.g. sulfisoxazole, benzoate, and hematin, which also bind to albumin) coexist in the plasma of neonatal infants with hyper-bilirubinemia. The results indicate that the pathogenesis of bilirubin toxicity is more closely related to that fraction of the circulating bilirubin which is dissociated from albumin or indirectly to the relative saturation of the albumin with bilirubin. [The *SCI*® indicates that this paper has been cited over 205 times since 1961.]

Gerard B. Odell
Department of Pediatrics
University of Wisconsin School of Medicine
Madison, WI 53706

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"The genesis *of* these studies can be appropriately ascribed to 'undisciplined' thinking about the chemophysiology of bilirubin. I use the term 'undisciplined,' for most investigators in clinical medicine who study bilirubin metabolism have been trained in either gastroenterology or hematology. My research interests and training were in electrolyte physiology and maturation of renal function. This was interrupted by two years of military service and a year as Chief Resident.The research for this paper took place at the Harriet Lane Home at the Johns Hopkins School *of* Medicine. When i got back to the laboratory bench, I found the major aspects of salt and water homeostasis had been well described. The forbearance of my mentors, R E. Cooke and H. H. Cordon, allowed me to switch directions, and I decided to study organic anion secretion by the kidney.

"I selected bilirubin as a clinically important anion, particularly during the period of neonatal jaundice. The molecule has two propionic acid side-chains, and I reasoned that by non-ionic diffusion, one should be able to promote its renal excretion during neonatal jaundice. On an alkaline ash diet the unconjugated anion of bilirubin was not excreted in significant amounts in the urine! Invitro ultrafiltration experiments demonstrated it would not be filtered at the glomerulus; but why was it not subject, like other protein-bound anions to tubular secretory processes, such as those for para-aminohippuric acid or salicylate?

"It was at that juncture that I was motivated to study the albumin-binding of bilirubin. While working for the chemistry department during college, I was allowed to take, a certain number of courses tuition-free and for fun I took colloidal chemistry. When thinking about the protein-binding *of* bilirubin, a highly apolar molecule, to the macromolecule of albumin with apolar binding sites, I realized my undergraduate education might prove useful. Thus I read with renewed interest about Freundlich and Langmuir adsorption isotherms, Scatchard plots and Klotz's classic analysis of the binding of small molecular anions to albumin.

"I was also taught and believed that even a lead pipe has a vapor pressure of lead around it. It was in the latter context that I viewed the equilibrium of bilirubin between albumin and its aqueous environment, and thus described it in terms of the chemical laws of mass action, even though the concentration of bilirubin in plasma water had at the time never been measured.

"I suspect this paper has been frequently quoted because it appealed to the scientific training of its readers. The application of the principles of colloidal and physical chemistry to a clinical problem provided an explanation whereby some infants with the same extravascular concentrations of bilirubin could in one instance suffer no injury, while others either died of bilirubin toxicity or exhibited chronic morbidity. The reported observations in this paper demonstrated how the administration of drugs to prevent infection in jaundiced neonates could result in higher mortality and morbidity from bilirubin toxicity because the drugs reduced the albumin, binding capacity for bilirubin."