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**THE FORMATION AND DISSOLUTION
OF CALCIUM BILIRUBINATE.
A CHEMICAL MODEL SYSTEM
SIMULATING THE FORMATION
AND DISSOLUTION
OF CALCIUM-CONTAINING PIGMENT
GALLSTONES**

The nature of the formation of calcium-containing gallstones is the formation of a specially constructed solid phase of calcium bilirubinate in the presence of bile acids and mucoproteins. As a model, the kinetic and thermodynamic behaviors of the Ca-Bilirubin-Taurocholate-Chondroitin sulphate system were studied by monitoring the variations of the concentrations of calcium and bilirubin with time. The solid phase separated was studied by means of X-ray diffraction, SEM, IR etc. In the absence of bile acids and mucoprotein, calcium ions react instantly with bilirubin (pH 7.9) giving aggregates of fine particles. No further growth or aggregation is observed. Taurocholate (TC) inhibits the reaction to some extent depending on the concentration of TC. The initial reaction stage is of first order, with $\log k = a - bC_{TC}$ ($r = 0.9934$). The conditional solubility products of calcium bilirubinate decrease with the increasing of the concentration of TC. SEM shows that, differing from the case without TC, the primary aggregates may aggregate further to clusters of various shapes. The addition of chondroitin sulphate compensates the inhibitory effect of TC and a number of particular shaped particles were obser-

ved, which support the idea that the calcium bilirubinate binds to the polysaccharide.

The differential UV spectra of the solutions containing TC and bilirubin and the potentiometric studies of the solutions containing calcium and TC show that both Ca and bilirubin tend to bind to TC micelles. Thus, it is proposed that the reactions of calcium ion and bilirubin proceed in a special mode in the micellar background. The TC micelles, with the bilirubin molecules in their hydrophobic cores, catch calcium ions rapidly from the solution. The calcium ions are likely to be bound to the negative charged micellar surface. And then, calcium ions react with bilirubin in the micelle. Fluorescence studies give some evidence supporting this proposal.

The dissolution of calcium bilirubinate pellets with some chelating agents were studied by monitoring the concentration of calcium and bilirubin at different time intervals in the presence or absence of bile acids. The calcium and bilirubin dissolve nonsynchronously. Thus a two step process is suggested. This process includes a rapid dissolution of calcium leaving the sparingly soluble, polymerized bilirubin in the solid. As the second step, bilirubin dissolves slowly and to a much smaller extent than calcium. A significant cooperative dissolving effect was observed between the chelating agents and the bile acids. For different chelating agents, the limits of dissolution (Ca concentration) are parallel with the conditional stability constants of the calcium chelates.



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INTERACTION OF CADMIUM AND BOVINE SERUM ALBUMIN AND THE MOBILIZATION OF CADMIUM FROM BOVINE SERUM ALBUMIN WITH CHELATING AGENTS

The binding of cadmium to Bovine Serum Albumin (BSA) was studied by means of the potential recovery method with a Cd selective electrode as the monitor. The average number of moles of Cd bound to each mole of BSA (\bar{N}) was determined as the function of Cd concentration at different pH values. $\log \bar{N}$ vs $\log [Cd]$ profiles are linear provided the pH is kept constant. If both $[Cd]$ and $[H^+]$ are introduced as variables, a general equation $\bar{N} = K[Cd]^m$ may be obtained to fit the experimental data. Both K and m are functions of pH. The \bar{N} values under different conditions may be calculated by means of this equation. From Scatchard plots of the experimental data, it is suggested that there are two strong and ten weak binding sites (from pH 5.28 to 7.92) and the binding constants for these sites were determined. The results of competitive gel chromatographic studies show that cadmium ions can hardly displace the BSA-bound zinc ions, but zinc ions can displace BSA-bound cadmium ions readily. It is supposed that the strong binding sites for cadmium may be the same ones as for zinc, the zinc binding being stronger than the cadmium binding, while the

weak binding sites bind cadmium only. Fluorescence studies support this supposition. Surfactants (SDS and Tween 80) change the fluorescence spectra of BSA and Cd-BSA solutions and influence significantly the binding capacity of BSA for Cd. The mobilizing ability of chelating agents to BSA-bound cadmium was determined by gel chromatography and the results are expressed as a parameter F , which is the ratio of BSA-bound cadmium in the presence and absence of chelating agent. The relative mobilizing abilities are: $DTPA > EDTA > EGTA > NTA > TRIEN > PEN > CYS > HIS > SA$.

The $\log F$ values vary linearly with $\log K'_{CdL}$. Dimercapto chelating agents are anomalous in this respect. DMPS and DMS increase the binding capacity of BSA. These results are in accord with the *in vivo* experiments reported in ref. [1].

REFERENCES

- [1] A.B. MARK, *J. Inorg. Nucl. Chem.*, **43**, 3039 (1981).