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The Etiology of Gall Stones. I. Chemical Factors.*

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(Introduced by Edmund Andrews.)
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The problem of gall stone formation is the problem of the precipitation of cholesterol out of the bile. An explanation is only possible when we know how the cholesterol is held in solution in the bile. The bile differs from all the other body fluids in that it contains large amounts of bile salts which, for a long time, have been known to have the power to hold many ordinarily insoluble substances in solution. Long ago Wieland and Sorge[1] showed that desoxycholic acid, a split product of the glyco- and taurodesoxycholic acids occurring in bile formed with various substances, insoluble in water, a soluble addition compound. We have investigated the question as to whether one certain bile acid or all bile acids are responsible for the solubility of the cholesterol in the bile.

We have found that when bile acids are precipitated from human gall bladder or fistula bile by $FeCl_3$, lead acetate by acidification, or by any other means there is a simultaneous precipitation of cholesterol. This can easily be proved by dissolving the bile acid fraction in alcohol and adding digitonin, which brings down a precipitate of cholesterol-digitonid. The complex of bile acids and cholesterol is readily soluble in water and may be purified by various methods without lessening the cholesterol content. These substances have about the same cholesterol content, 6-9%, without regard to the form of bile acids from which they are made.

These same products may be prepared from pure bile acids. We have made these complexes from cholic, desoxycholic acid, glycocholic and taurocholic acids. The properties of these substances are very similar. The bond between the cholesterol and the bile acid is a very loose one and even in the preparation there is very often a slight loss of cholesterol. The bond is considerably looser than in the complex between fatty acids and desoxycholic acid described by Wieland and Sorge.[1] Splitting is brought about for example by digitonin and by many organic solvents (e.g. ether, chloro-

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[1] Wieland, H., and Sorge, H., *Z. f. physiol. Chem.*, 1919, **97**, 1976.

form, etc.) Further investigations are necessary to show whether this is a chemical combination or simply a phenomenon of simultaneous solution. Part of the bile acids yield this complex only in salt form; others, the taurocholic acid, as acids as well.

Large amounts of these complexes have been isolated from human bile. It appears that all or nearly all of the cholesterol is bound to the bile acids in this form. On the contrary in dog or ox bile, enormous volumes yielded but small amounts of the complex, most of the bile acids being in a combination with fatty acids.

The importance of this for human gall stone formation is shown by the slight influences which bring about a breaking up of this complex. If the watery solutions of the Na-glycotholic-acid complex are dialysed, the bile salts pass through the membrane and the cholesterol is retained quantitatively. As there is no longer sufficient bile salts within the membrane to hold the cholesterol in solution it is precipitated. We have demonstrated this phenomenon not only in substances prepared from liver and gall bladder bile but in many complexes of bile salts and cholesterol synthetically prepared.

All these experiments show that as soon as the bile acids are got out of the solution, the cholesterol must be precipitated. Any time that the organism by any pathological changes, brings about a significant lowering of the bile acids in the gall bladder in relation to the amount of cholesterol in it, cholesterol precipitation is bound to ensue. The fact that dog and ox bile contain very small amounts of this complex offers an explanation of why cholesterol containing gall stones are never found in animals.

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The Etiology of Gall Stones. II. Rôle of the Gall Bladder.*

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In the preceding paper it was shown that the greater content of cholesterol in human bile than in that of animals was associated with the formation of a water soluble complex with bile salts. By this means more cholesterin is held in solution. It is obvious there-

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