

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 cholesterol is held in solution. It is obvious there-

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fore that the maintenance of the cholesterol in solution is dependent on the concentration of bile salts in the bile and that if it falls below a certain level the cholesterol will be precipitated. The following studies of the differential absorption rate of bile acids and cholesterol seem to show that the gall bladder under certain conditions may play the major part in gall stone formation.

It will be seen that under normal conditions the gall bladder mucosa in its action in concentrating the bile is able to absorb water, of course, rapidly, and the bile salts and cholesterol, if they are absorbed at all, are absorbed at the same rate. In other words the cholesterol content of the bile rises no faster if as fast as the bile salt content, so that there is a wide margin of safety, and no danger that there will not be enough bile salts to hold the cholesterol in solution.

When the gall bladder is diseased a diametrically opposite action takes place. In this series, the cystic duct was ligated which, as we have shown,¹ leads at once to the infection of the gall bladder. Such a gall bladder with the added insult of the insertion of a needle and ligature of the needle hole looks grossly thickened and diseased at the end of 24-48 hours. In some of the experiments it was also traumatized by scraping its mucosa. In this series of experiments an entirely opposite differential absorption took place. In every case samples taken 24 hours later showed an increase in the concentration of cholesterol of 2 to 85%, average + 29% and a lessening in the concentration of the bile salts of 3 to 69%, average — 28%. The ratio of bile salts over cholesterol was 97 for normals, 59 for the 16 experiments. This is of a high enough degree to cause the precipitation of the cholesterol if continued for any length of time. In the traumatized gall bladders this phenomenon was still more marked.

In view of the previously reported precipitation of cholesterol from bile acid solutions by dialysis, it seems reasonable to assume that the gall bladder mucosa has a great absorptive power for bile salts if diseased, and that in the latter case the bile acids are absorbed faster as they would be from any semi-permeable membrane on account of their greater solubility.

¹ Andrews, E., and Hrdina, L., *PROC. SOC. EXP. BIOL. AND MED.*, 1930, **28**, 116.