

Formal Discussion of "Cancers of the Pancreas and Biliary Tract: Epidemiological Considerations"¹

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The formation of gallstones has been attributed to changes in bile composition that disrupt the balance between the components that maintain the solubility level of cholesterol. Ternary diagrams showing the exact concentrations of cholesterol, bile salts, and lecithin that result in nonlithogenic bile have been published (1, 9, 16, 18).

Gallstone formation can be induced in hamsters by feeding a fat-free diet high in cholesterol and sucrose (5). The type of carbohydrate in the diet is of importance, glucose giving 100% cholesterol stones (6). Mice fed diets containing glucose, lard, cholesterol, and cholic acid develop gallstones (19). Cholesterol gallstones can also be produced by diet in rabbits (2) and possibly in dogs (7). When rabbits are fed cholesterol (dihydrocholesterol), they develop gallstones rich in this sterol (4, 14).

The foregoing discussion illustrates the importance of diet and dietary components in the production of gallbladder disease. The need for a fine balance in sterol-bile salt-lecithin composition is emphasized by the data of Schoenfield and Sjövall (15), who observed gallstones in guinea pigs fed a diet containing a bile acid sequestrant, cholestyramine. The gallstone formation was attributed, in part, to the depletion of the bile salt pool by cholestyramine. Recently, there has been an upsurge in interest in the dietary effects of nonnutritive fiber. Data have been presented to support the claim that populations subsisting on high-fiber diets are less prone to gallbladder disease (3, 20). We have some recent data bearing on this point.

In the course of an experiment designed to induce atherosclerosis in baboons, we noted that the ratio of the primary biliary bile acids (cholic and chenodeoxycholic) to the secondary bile acids (deoxycholic and lithocholic) was higher in the control animals (10). We also found that the specific activity of bile salts in the gallbladders of the test animals (after injection of [³H]mevalonic acid) was lower than that of the controls. The data suggested a reduced synthesis of primary bile acids. The test diets contained 40% carbohydrate, 25% casein, 14% hydrogenated coconut oil, and 15% cellulose and were fed for 1 year. The carbohydrates used were fructose, sucrose, starch, and glucose. The control baboons were fed bread, fruit, and vegetables. The

data are summarized in Table 1. Serum cholesterol levels rose about 25 to 34% in the test groups. Serum triglyceride levels were elevated (over starting levels) by 72 and 55% in the fructose and sucrose groups and by 44 and 40% in the starch and glucose groups. A similar experiment in rabbits in which the effect of a semipurified diet was compared with laboratory ration showed the biliary cholic/deoxycholic acid ratio to be lower in the test group (13).

These findings caused us to speculate on the possibility that bile salts might be bound by various dietary constituents, especially by dietary fiber. In 1 experiment (Table 2), we compared binding *in vitro* of sodium taurocholate to cholestyramine, cellulose, cellophane spangles, wheat straw, bran, and alfalfa (11). As expected, cholestyramine bound most of the substrate. Cellulose and cellophane spangles, 2 substances often used as bulking agents in semipurified diets, bound practically no substrate. Alfalfa bound 21% as much sodium taurocholate as did cholestyramine.

Since human bile contains 2.5 to 6.0 times as much glycocholate as taurocholate (8), we carried out an experiment in which the binding of both bile salts was assessed (12). The results are summarized in Table 3. It may be seen that cholestyramine and Colestipol, 2 substances designed to bind bile acids and bile salts, bound significantly more of the taurine conjugate of cholic acid. Three "natural" substances (alfalfa, wheat straw, and sugar beet pulp) bound significantly more glycocholate. We also observed

Table 1
Effect of semipurified diets^a on aspects of lipid metabolism in baboons

Diet	Serum lipids (mg/dl)		Bile	
	Cholesterol	Triglycerides	P/S ratio ^b	Specific activity of bile salts
Fructose	162 ± 10 ^c	129 ± 11	0.56	0.16
Sucrose	152 ± 9	116 ± 8	0.61	0.16
Starch	156 ± 8	108 ± 5	1.33	0.17
Glucose	151 ± 11	105 ± 7	0.81	0.14
Control	113 ± 3	78 ± 4	1.67	1.00

^a Forty % carbohydrate, 25% casein, 14% hydrogenated coconut oil, and 15% cellulose fed for 1 year.

^b Ratio of primary (cholic and chenodeoxycholic) to secondary (deoxycholic and lithocholic) bile acids.

^c Mean ± S.E.

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that alfalfa bound similar levels of cholic and chenodeoxycholic acids but significantly less (70% less) deoxycholic acid. These findings suggest that different bile acids and bile salts are unique with regard to binding by any specific substance. These differences should be ascertained and borne in mind when working with any particular material.

Since different types of nonnutritive fiber showed a spectrum of binding properties, we thought that it would be of interest to test certain condiments. Some of the materials tested are present almost daily in the diets of various populations. A summary of our data (17) (Table 4) shows that curry powder binds almost twice as much sodium taurocholate as does alfalfa, whereas green pepper binds only one-seventh as much.

In view of the developing interest in the effects of diet in the etiology of cancer and the insistence by some that fiber may prevent colon cancer, it is important to learn more

about possible mechanisms by which fibers (or other dietary components) affect lipid metabolism and also how they might affect the development of some types of cancer.

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Table 2

Binding *in vitro* of sodium taurocholate^a (average of 3 determinations)

Substance	% bound
Cholestyramine	81.5 ± 0.2 ^b
Cellulose	0.5 ± 0.5
Cellophane spangles	0.4 ± 0.7
Wheat straw	1.8 ± 0.8
Bran	0.7 ± 0.7
Alfalfa	16.9 ± 0.7

^a Forty mg of substance incubated for 60 min at 37° with 5 ml of 0.15 M NaCl containing 100 μ moles of bile salt.

^b Mean ± S.E.

Table 3

Comparison of binding of sodium tauro- and glycocholate^a

Binding substance	Taurocholate (T)	Glycocholate (G)	T/G
Cholestyramine	87.7 ± 0.22	73.2 ± 0.6	1.20
Colestipol	75.1 ± 0.2	66.2 ± 0.3	1.13
Alfalfa	25.3 ± 0.31	28.6 ± 0.46	0.88
Wheat straw	2.6 ± 0.52	6.1 ± 0.40	0.43
Sugar beet pulp	2.7 ± 0.26	3.9 ± 0.95	0.69

^a Eighty mg of binder and 100 μ moles of bile salt incubated at 37° for 1 hr. Average of 3 experiments.

Table 4

Binding of sodium taurocholate by selected comestibles^a (alfalfa = 1.00)

Curry powder	1.96
Cloves	1.49
Oregano	1.30
Chili powder	1.10
Thyme	0.90
Sage	0.37
Ginger	0.30
Nutmeg	0.29
Rosemary	0.24
Green pepper	0.13

^a Binding substance, 100 mg, and 100 μ moles of sodium taurocholate incubated in 0.15 M NaCl for 1 hr at 37°

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