Effects of Psyllium Hydrocolloid on Bile Acid Metabolism in Normal and Hypophysectomized Rats[1] (35239)

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Although there have been relatively few studies of the effects of dietary bulk on cholesterol and bile acid metabolism, those that have appeared indicate that bulk can have important effects. Portman and Murphy (1) showed that feeding rats synthetic diets low in bulk resulted in slow bile acid turnover rates. When these diets were supplemented with cellulose, greatly increased rates were noted. Although Keys *et al.* (2) could find no effect of dietary cellulose supplements on human serum cholesterol levels, they did note a significant lowering when the diets were supplemented with pectin. Papers have subsequently appeared (3, 4) which indicate that pectin is an effective cholesterol-lowering agent, and that it acts by increasing the rate of bile acid excretion.

Recently two studies have appeared (5, 6) which show that another source of dietary bulk, psyllium hydrocolloid (Metamucil[2]), is an effective serum cholesterol-lowering agent in man, and that it also increases bile acid excretion. Since increased bile acid excretion could result from a shift in relative bile acid concentrations (7), from decreased bile acid half-lives, or from increased bile acid pool sizes, we have studied the mechanism of the effect. Normal and hypophysectomized rats were the subjects used in this study.

Methods and Procedures. Groups of 8 rats were used as follows: 2 groups of normal controls, 2 groups of normal treated rats, 1 group of hypophysectomized controls, and 1 group of hypophysectomized treated rats. The basic food was Rockland rat diet containing (%): protein, 24.27; fat, 4.15; fiber, 4.86; carbohydrate, 56.23; and ash, 7.78. The 3 control groups were maintained *ad libitum* on unsupplemented diet throughout the experiments. The diet of the 3 treated groups was supplemented with 4% Metamucil for 3 weeks. In order to study turnover rates, 5 μCi (57.6 mCi/mmole) of cholic acid-24-^{14}C was then injected intraperitoneally into the rats of one of the normal control and one of the normal treated groups, and the rats of both hypophysectomized groups. The other group of normal control and normal treated rats were injected intraperitoneally with 5 μCi (30.4 mCi/mmole) chenodeoxycholic acid-24-^{14}C. After injection, all animals were placed in individual metabolism cages and feces were collected daily for 8 days. The animals were then killed, and small intestine, large intestine, and cecums (all plus contents) and livers were removed and quick frozen until analyzed.

Tissue and feces bile acids were extracted with chloroform:methanol, 2:1, and assayed for ^{14}C activity and small intestine bile acid concentration as previously described (7). Bile acid half-lives were calculated according to Lindstedt and Norman (8). Bile acid pool sizes were calculated as described by Strand (9).

Results and Discussion. The effects of diets supplemented with 4% Metamucil on bile acid half-lives are shown in Figs. 1 and 2. In Figs. 1 and 2, the time in days after injection of ^{14}C bile acids is plotted on the ordinate against $-\log (1-u^t/u^{max})$ on the abscissa. u^t = fecal biles acid-24-^{14}C excretion (cpm) up to and including a given day; u^{max} = total bile acid-24-^{14}C recovered in the feces and tissues of a given animal. In each case a

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[2] Generous gift of G. D. Searle & Co., Chicago, Ill.

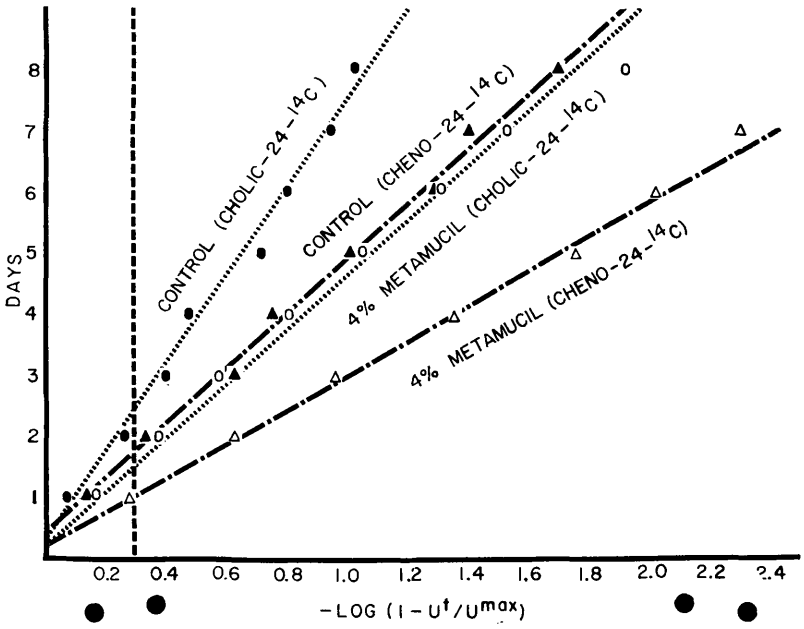

FIG. 1. Rate of elimination of pool bile acids in control rats and rats fed a diet supplemented with 4% Metamucil. The bile acid in parentheses is the bile acid determined. The vertical line cuts the curves at the half-lives of the bile acids.

straight line was obtained, which indicates that bile acid excretion is governed by first order kinetics. The half-life of the bile acid pool can be read from the curves at the point where $u^t/u^{max} = 0.5$. The broken vertical line intersects the curves at the half-life of the bile acid pool.

In normal rats the cholic and chenodeoxycholic acid half-lives for controls were 2.5 ± 0.3 and 1.73 ± 0.4 days, respectively. When the diet was supplemented with 4% Metamucil, the half-lives dropped to 1.5 ± 0.5 and 1.05 ± 0.2 days, respectively. Thus, Metamucil is an effective agent for increasing the turnover rate of bile acids in normal rats.

Since bile acid excretion rates depend not only on bile acid half-lives but also on pool sizes, it was necessary to determine this parameter. The results are shown in Table I. In normal rats, Metamucil supplement had little effect on cholic acid pool size but significantly increased the size of the chenodeoxycholic acid pool. The results indicate that Metamucil effectively increases bile acid excretion in normal rats not only by decreasing the half-lives of the bile acids in their recirculating pools, but also by increasing the size of the chenodeoxycholic acid pool.

When rats are hypophysectomized they exhibit greatly increased bile acid half-lives, and greatly decreased bile acid excretion rates (10). This has been shown to be a factor contributing to the easy accumulation of cholesterol in these animals. It was therefore of interest to see whether Metamucil would increase bile acid excretion in these animals. The turnover data are shown in Fig. 2. The half-life of cholic acid was 7.00 ± 1.02 in the hypophysectomized controls, indicating a turnover rate about one-third that of normal rats. When the diet of these rats was supplemented with Metamucil, the half-life dropped to 4.6 ± 0.94 days. This decrease in the half-life is comparable to that seen in normal rats, that is about 40%. It would thus appear that the effect of Metamucil is independent of hormonal factors. The effect of Metamucil on chenodeoxycholic half-lives was not determined in these animals, since this acid is usually present in very small amounts in the hypophysectomized rat pool.

The results of the pool size determinations

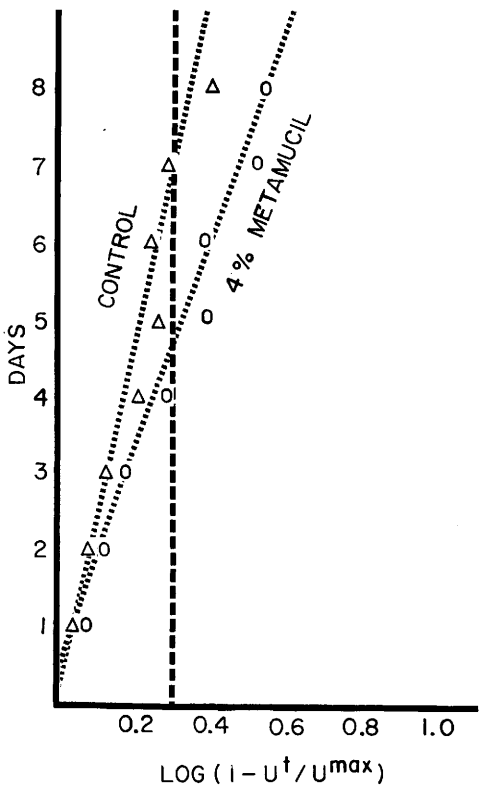

FIG. 2. The rate of elimination of cholic acid in hypophysectomized rats on a control diet or a diet supplemented with 4% Metamucil. The vertical line cuts the curves at the half-life of cholic acid.

are shown in Table I. As in the normal rat, Metamucil had little effect on the size of the hypophysectomized rat cholic acid pool but significantly increased its chenodeoxycholic acid pool size. It therefore appears that Metamucil supplements have almost identical effects on bile acid metabolism in normal and hypophysectomized rats, and effect increased bile acid excretion by both pool size increases and half-life decreases.

The data show that hypophysectomized rats, as well as normal ones, are capable not only of maintaining but also of significantly increasing bile acid pool sizes in the face of increased turnover rates under these circumstances. It is apparent that the hypophysectomized rat has no defect in its ability to convert cholesterol to bile acids. Work with the bile acid sequestering agent, cholestyramine, is in agreement with this finding (11).

Just how Metamucil decreases bile acid

TABLE I. Effect of Metamucil (4%) on Size of the Cholic and Chenodeoxycholic Acid Pools of Normal and Hypophysectomized Rats.

Diet	Cholic acid (mg/100 g rat)	Chenodeoxycholic (mg/100 g rat)
	Normal rat	
Control	9.78 ± 1.12	1.16 ± 0.38
Metamucil (4%)	10.6 ± 1.68	2.59 ± 0.87
	Hypophysectomized rat	
Control	8.16 ± 0.57	0.78 ± 0.23
Metamucil (4%)	9.88 ± 1.99	1.10 ± 0.12

[a] ± values are standard deviations.

pool half-lives has not been determined. It is probable that it decreases the reabsorption of bile acids from the small gut. Leveille and Sauberlich have demonstrated (4) *in vitro* that pectin decreases taurocholic acid transport across the small intestinal wall by 50%, and a similar effect by Metamucil is probable. The mechanism by which Metamucil could effect such a decrease in intestinal transport is uncertain, but there are several possibilities, such as: (a) the mucilloid could alter the composition of the micelles from which bile acids are absorbed in the small intestine; (b) it could alter the transit time of bile acid through the small gut lumen; or (c) it could alter the intestinal microflora, which have been shown to have important effects on bile acid turnover rates.

Summary. A study was made of the effects of diets supplemented with psyllium hydrocolloid (Metamucil) on bile acid half-lives and pool sizes in normal and hypophysectomized rats. Metamucil decreased bile acid half-lives by about 40% in both normal and hypophysectomized rats. The mucilloid also effected small but significant increases in the size of the bile acid pools. It was demonstrated that Metamucil increases bile acid excretion in rats by increasing the turnover rate and size of the bile acid pool. Pituitary and target gland hormones have little or no effect on the drug's ability to effect these changes.

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