perhaps can give more meaningful results uncomplicated by over-eating and hormonal factors, and can lead to a better understanding of this experimentally produced obesity.

Summary. These experiments demonstrate that hypothalamic obesity can develop in the absence of hyperphagia and of pituitary involvement, and establish that VMM lesions must have caused additional disturbance contributing to this surgically produced obesity.

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Increased Excretion of Fecal Bile Acids by an Oral Hydrophilic Colloid* (32870)

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In a previous paper (1) we reported that the addition of an oral hydrophilic colloid to the mixed or egg-supplemented diets of normal young male medical students lowered the serum cholesterol to a statistically significant extent. We now report additional studies on two normally active young male medical students which confirm the previous finding regarding the lowering of the serum cholesterol of subjects on a self-selected mixed diet and also we report a large concomitant increase in the excretion of fecal bile acids. On the other hand, fecal excretion of neutral sterols was unaffected by the oral hydrophilic colloid.

Materials and Methods. A preparation of hydrophilic colloid derived from the blond psyllium seed (Plantaga ovata-Forsk) available commercially as Metamucil,[1] was used as the bulk-increasing supplement and as supplied was mixed with an equal weight of dextrose. The mucilloid supplement consisted of 6.4 gm of Metamucil taken 3 times daily with meals, making a total of 9.6 gm of hydrophilic colloid ingested each day. All serum cholesterol values were obtained by the method of Zlatkis (2) and were carried out in duplicate. The experimental subjects were 2 normal male medical students (both age 22 years) on mixed self-selected diets. Both subjects maintained their customary activity and neither reported any change in weight during the study. Each subject obtained one 24-hour feces collection each Wednesday of the study. The specimens were stored under 95% alcohol at 4°C until analyzed. Throughout the study the subjects took 0.5 gm of Cr_2O_3 in gelatin capsules with each meal, 1.5 gm total/day. This inert indicator was used to correct for variations in the amount of feces excreted from day to day and also to correct for any incompleteness in fecal collections (3). No corrections for incomplete analytical recoveries of Cr_2O_3 were made in these

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TABLE I. Effect of an Oral Hydrophilic Colloid on Fecal Bile Acid, Fecal Neutral Sterol, and Serum Cholesterol Levels of Young Adult Males.

Subject	Preexperimental period (control)				Experimental period					
Weeks:	1	2	3	4	5	6	7	8	9	10
A										
Total fecal bile acid[a] (mg/24 hr)	245	293	173	178	737	1133	317	866	383	560
Fecal neutral sterol (mg/24 hr)	700	731	523	437	706	438	490	535	395	883
Serum cholesterol (mg/100 ml)	—	220	205	208	160	178	172	188	184	180
B										
Total fecal bile acid[a] (mg/24 hr)	462	556	584	383	1032	744	1617	3375	751	1072
Fecal neutral sterol (mg/24 hr)	536	921	561	500	513	570	568	1326	422	518
Serum cholesterol (mg/100 ml)	—	200	210	194	172	160	158	140	170	178

[a] Mean value of quadruplicate analysis.

calculations. The neutral sterols were determined in duplicate by the method of Abell (4). The total fecal bile acids were determined by the method of Forman (5) which combines solvent extraction, thin-layer chromatography and fluorometry. Two samples were taken for analysis for bile acids from each feces specimen and each sample was analyzed in duplicate. Therefore in the data for fecal bile acid excretion, each of the values given for each week for each subject represents 4 separate and complete determinations (Table I). For statistical purposes and for display in Fig. 1 the mean serum cholesterol values for the control period of the study for each subject was assigned a value of 100%. All subsequent serum cholesterol values for each subject were normalized by converting them to a percentage of this control value. The same normalizing calculations were applied to the fecal bile acid excretion values displayed in Fig. 1, and to the fecal neutral sterol values given in the text. The t test was used in all estimations of the significance of differences between mean values (6,7).

Results and Discussion. Figure 1 shows that lower serum cholesterol values were established in 1 week on the supplement and remained at that level for the duration of the experimental period. The mean serum cholesterol value of weeks 2, 3, and 4 was 206 mg/100 ml which normalized to 100% ± 3.5 (SD) for 6 samples. The mean serum cholesterol value of weeks 5, 6, 7, 8, 9, and 10 was 169 mg/100 ml, which normalized to 83% ± 5.6% for 12 samples. Thus during the 6 weeks of the experimental period there was maintained a 17% average decrease in serum cholesterol values which is equivalent to a decrease of 36 mg/100 ml. This lower level is statistically highly significant ($t = 6.72$, $n = 16$, $p << 0.001$).

Figure 1 also shows that sharply higher values of 24-hour fecal bile acid excretion were established in 1 week on the supplement, and though fluctuating widely remained several-fold above the control period for the 6 weeks on the supplement. The mean fecal bile acid excretion for weeks 1, 2, 3, and 4 was 347 mg/24 hours, which normalized to 100% ± 25.4% (SD). Since 4 complete determinations were made on each specimen, this mean represents 32 determinations of which each average of 4 replicates were used for statistical purposes. The mean fecal bile acid excretion for weeks 5, 6, 7, 8, 9, and 10 was 1024 mg/24 hours, which normalized to 302% ± 172% (SD). Thus during the 6 weeks of the experimental period there was maintained a 202% average *increase* in the total fecal bile acid excretion which is equivalent to an average increase of 677 mg/24 hours. This higher level of excretion is statistically highly significant ($t = 3.275$, $n = 18$, $0.001 < p < 0.005$). The mean of the total neutral sterols excreted for the 4 control weeks was 614 mg/24 hours which normalized to 100% ±

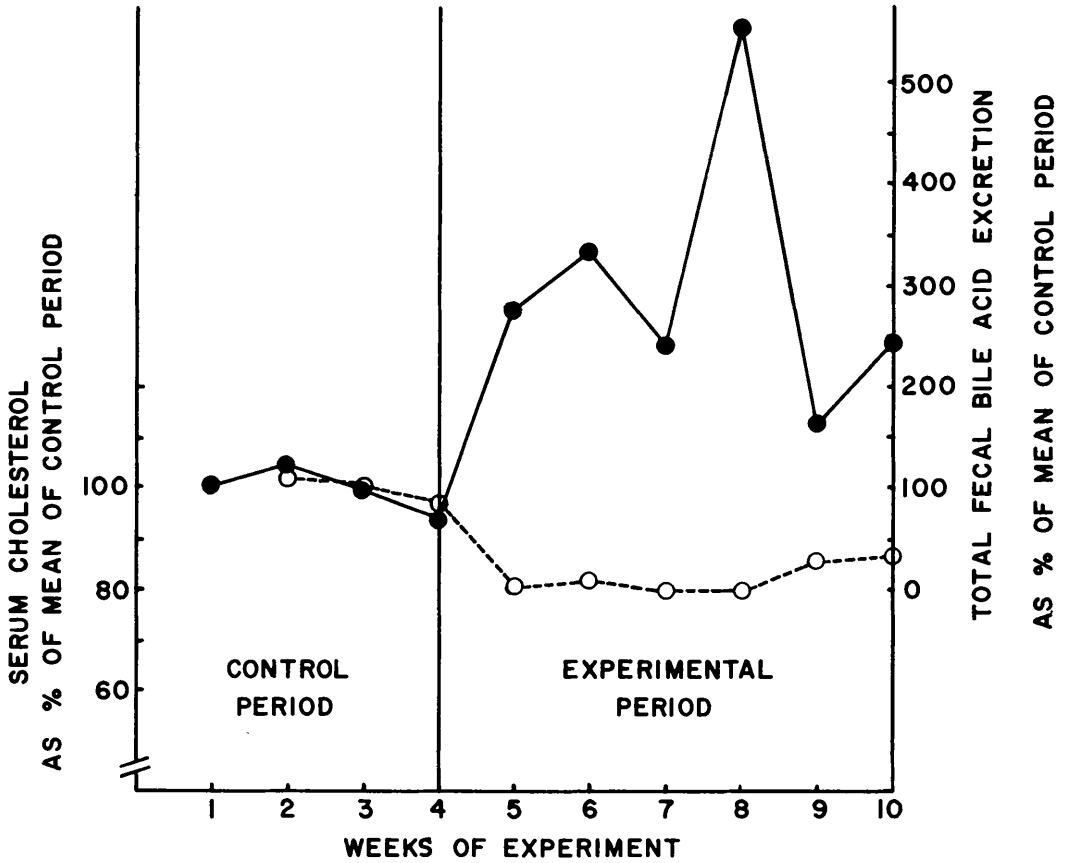

FIG. 1. Effect of an oral hydrophilic colloid on fecal bile acid excretion and serum cholesterol levels of young adult males. Fecal bile acid excretion, (●); serum cholesterol levels, (○).

26% (SD). The neutral sterols for the 6 weeks on the supplement also averaged 594 mg/24 hours, which normalized to 100% ± 48% (SD). Clearly the supplement was without effect on the mean neutral sterol excretion in these two normal subjects.

In view of the well-established fact that excretion of bile acids represents the chief avenue for the loss of cholesterol from the body (8,9), the most direct explanation for the associated reciprocal relationship demonstrated above is that the loss of bile acids in the feces caused the fall in serum cholesterol. It can be argued that the augmented loss of bile acids in the feces causes their increased synthesis from cholesterol thus depleting the body pool of cholesterol. Eventually in the new steady state the increased rate of bile acid synthesis may be compensated for by an increased rate of cholesterol synthesis resulting in stabilization of the serum cholesterol at a lower level. A similar mechanism to explain decreased serum cholesterol associated with increased bile acid excretion has been proposed by others. In studies of hypercholesterolemic patients Van Itallie (10) found increased bile acid excretion in the feces of patients given oral cholestyramine, a bile salt sequestering agent, and he concomitantly observed decreases in serum cholesterol ranging from 20–50%. In follow-up studies of hypercholesterolemic patients subjected to surgical bypass of the ileum, Buchwald (11,12), likewise found decreases in serum cholesterol of about 40%. Similarly in studying patients experiencing acute loss of bile acids from a T-tube in the common bile duct, De Palma (13), reported considerable decreases in serum cholesterol. Sodhi (14) found augmented cholesterol and

cholesterol breakdown products in feces to be responsible for the decrease in serum cholesterol when unsaturation of dietary fat was increased. On the other hand, decreases in serum cholesterol values unaccompanied by significant increase in either fecal bile acid or neutral sterol excretion have been reported by Spritz (15) and Avigan (16), and a redistribution within body cholesterol pools has been proposed (17). Thus although a causal connection between increased excretion of bile acids in the feces and the fall in serum cholesterol appears to be the most likely explanation of our observations, an effect due to redistribution of body cholesterol pools should not be excluded. Altered absorption of cholesterol due to the mucilloid probably does not play a role in our results since no change in neutral sterol excretion was observed.

The means by which the mucilloid increases the fecal excretion of the bile acids is unknown but some effect which restricts the reabsorption of bile salts in the ileum appears likely. Several mechanisms for such a restriction may be proposed: (i) complexing of the bile salts with the mucilloid by some form of ion exchange, such as occurs with cholestyramine, (ii) partition of the bile salts into a gel phase produced by the mucilloid thus lowering their concentration in the phase from which they are normally absorbed, (iii) dilution of the bile salts by increased intraluminal mass due to the mucilloid, and (iv) some effect on the ileal motility such as a reduced transit time. To determine which, if any, of these mechanisms is operative remains of considerable interest, since it is possible that the principle by which mucilloid operates is different from that of any currently known means of lowering human serum cholesterol, and of course its therapeutic application involves no manipulation of diet.

Summary. An oral hydrophilic colloid (9.6 gm/day), after a 4-week preexperimental control period, was fed for a 6-week experimental period to 2 normally active young adult males on a self-selected mixed diet, with the following results: Total fecal bile acids per 24 hours obtained during the experimental period averaged 3 times (302%) the excretion level of the control period. Serum cholesterol levels during the experimental period averaged 17% lower than during the control period. These differences were statistically highly significant by t test ($p < 0.005$). Total neutral sterol excretion per 24 hours in the experimental period was unchanged from the values measured during the control period. The mechanism by which the mucilloid increases fecal bile acid excretion is unknown.

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