Effect of an Anion Exchange Resin on Serum Cholesterol in Man.* (25358)

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It is well known that bile acids are a major end product of cholesterol metabolism and that cholesterol is probably the only precursor of bile acids(1-3). Rate of oxidation of cholesterol to bile acids is believed to be regulated by need for bile acids for digestive purposes, cholesterol normally being oxidized at a rate sufficient to replace the bile acid that escapes reabsorption and is lost in the feces (4,5). If an agent could be found that would sequester bile acids and thereby promote their excretion in the feces, 2 consequences of clinical interest might be anticipated: (1) increase in rate of oxidative degradation of cholesterol, and (2) decrease in serum cholesterol level. Tennent(6) described lowering of serum cholesterol levels in animals fed the chloride salt of a basic anion exchange resin. This material (MK 135) has marked affinity for bile acids *in vitro* and is believed to exert its serum cholesterol-lowering effect by virtue of this property(6). The present report summarizes results obtained when MK 135 was administered to 26 patients, many with elevated serum cholesterol levels.

Procedure. Twenty-six patients were studied for 2 to 34 weeks. Fifteen patients had coronary artery disease; 3 essential hypercholesteremia; 4 normocholesteremia; and 4 moderately elevated serum cholesterol associated with mild, well-regulated diabetes mellitus. Four patients were studied while under treatment with acenocoumarin (Sintrom®). Patients ranged in age from 34 to 80 years. All except 3 were studied initially while in the hospital. Each patient continued with his previous diet and medications except that concurrent use of niacin (in pharmacologic amounts), sitosterols, estrogenic substances, and polyunsaturated fatty acid supplements was prohibited. Prior to administration of MK 135, at least 2 control measurements of concentration of serum total cholesterol and cholesterol esters were obtained. Subsequently, MK 135 was given to each patient in one of two forms: (1) as a liquid suspension containing 0.25 g of resin/ml, or (2) as a powder containing 0.83 g of resin/g of powder. Fifteen patients received 15 ml of the liquid 4 times a day (15 g of resin), and in 3 of this group, the dose was doubled during treatment. Eleven patients received 5 g of the powder 3 times a day (13 g of resin). The material was taken with or immediately after each meal and, when 4 doses were prescribed, at bed time. Serum total cholesterol and cholesterol ester levels were determined three times a week while patients were in the hospital and at weekly intervals as out-patients. Levels of total cholesterol and cholesterol esters were determined by the Schoenheimer-Sperry method(7). Patients were weighed frequently and a record was kept of dietary intake.

Results. In only 3 of the 26 patients were serum total cholesterol levels lowered by less than 10% (Table I). Average control levels for each individual ranged from 133 to 400 mg %, with average for group of 273 mg %. In terms of individual responses, average decrease in serum total cholesterol during treatment varied from 6.2 to 38.2%; in terms of the group, average decrease was 20.0 ± 8.0%‡. This was highly significant ($p < 0.001$). Multiple covariance analysis indicated that the patients with highest initial cholesterol levels tended to have greatest decreases ($p < 0.05$). In terms of clinical groups, average % decreases in level of serum cholesterol were as follows: familial hypercholes-

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‡ S.D. $= \sqrt{\frac{\Sigma (x-x)^2}{n-1}}$.

TABLE I. Changes in Serum Total Cholesterol during Administration of MK 135.

Diagnostic group	Avg initial serum total cholesterol (mg %)	Duration of treatment (days)	Avg % decrease in serum total cholesterol	Lowest level during treatment (mg %)
Coronary heart disease	324	28	17.9	239
	270	21	19.1	207
	368	112	38.2	202
	320	22	28.3	198
	227	21	13.7	159
	254	49	9.5	207
	280	18	21.4	191
	259	16	26.6	185
	328	16	29.7	177
	243	28	14.4	160
	327	94	18.3	231
	209	14	7.7	172
	310	35	18.7	202
	272	14	22.1	170
	267	63	32.3	162
Familial hypercholesteremia	400	236	25.3	262
	352	32	25.0	264
	363	28	20.1	259
Diabetes mellitus (mild)	302	14	12.6	227
	232	18	10.3	191
	230	22	17.4	174
	307	21	20.8	200
Normocholesteremic patients	133	20	6.2	106
	208	16	11.3	174
	141	24	24.4	95
	168	20	29.3	91

terolemia 23.5%; coronary heart disease 21.2%; diabetics 15.3%; and "normocholesteremia" 18.1%. Serum cholesterol responses of representative members of each group to administration of MK 135 are shown in Fig. 1.

Six patients receiving MK 135 had only a slight decrease in serum total cholesterol while on the usual dose of 15 g of resin/day. When the dose was doubled 5 of these patients showed appreciable lowering in cholesterol level.

Three patients had complaints during MK 135 administration attributable to the medication. These included nausea and vomiting in one, nausea and constipation in one, and fecal impaction in one elderly, bed-ridden patient. Four additional patients volunteered the information that they had become moderately constipated while on the powder. No effect was noted upon appetite or weight nor was there impaired digestion as manifested by distention, diarrhea or bulky stools. Among the diabetic group and patients on acenocoumarin there were no changes in diabetic control or anticoagulant status.

Fifteen patients were followed after termination of MK 135 treatment. Eight showed a prompt rebound to levels ranging from 4.6

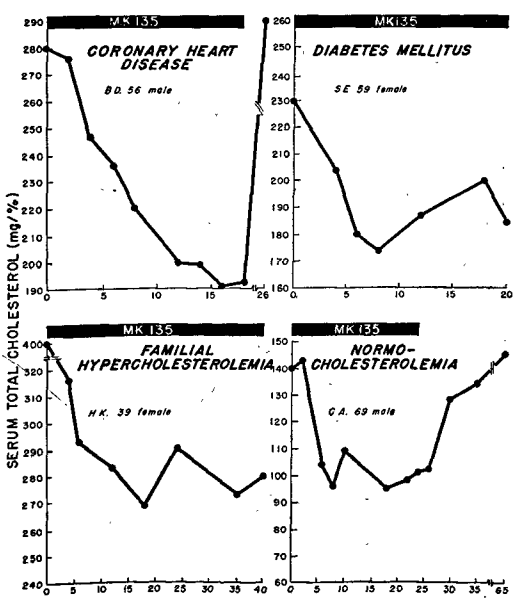

FIG. 1. Representative serum cholesterol responses to MK 135.

to 30.6% above control values. After 2 weeks, this "rebound" group returned to control levels.

Changes in esterified fraction of serum cholesterol always paralleled changes in serum total cholesterol.

Discussion. Although direct proof is lacking that the mechanism whereby MK 135 lowers cholesterol involves sequestration of bile acids, with increased cholesterol catabolism, animal experiments suggest that this is the most likely explanation(6). It was not possible in the present studies to assess rate of cholesterol catabolism or extent of fecal excretion of bile acids and other catabolic end products of cholesterol metabolism. Such studies are in progress.

The drop in serum total cholesterol levels after MK 135 treatment was begun usually was prompt, dramatic and sustained. Appreciable decreases in cholesterol level occurred within 4 days following MK 135 administration. Although the largest decrement occurred during first week of therapy, continued treatment was associated with further decreases during subsequent weeks. Six subjects were studied for 6 weeks or longer; all maintained lowered values of serum total cholesterol throughout the entire study period without evidence of "escape." Mean decrease of 20% was calculated by averaging cholesterol levels obtained in each subject at regular intervals following initiation of treatment and then using this value to determine mean decrease for the entire group. The lowest levels of serum cholesterol during treatment are shown for each subject in Table I.

Effectiveness of MK 135 is also indicated by its rate of success. Of 26 patients who were followed for a sufficient period, only 3 (or 11.6%) had a fall in serum total cholesterol of less than 10%. These 3 showed decreases of 6.2%, 7.7% and 9.5%. Hence, MK 135 was successful in reducing serum total cholesterol levels by more than 10% in approximately 88% of the series. This figure, as well as extent of decreases in cholesterol, compares favorably with results reported for other hypocholesteremic agents(8-10). It is also noteworthy that MK 135 was effective in lowering cholesterol in patients whose control levels of serum total cholsterol were already low by American standards.

Although analysis of dose-response curves was not done, there was an indication, within limits, of a direct relationship between amount of resin ingested and degree of depression of cholesterol levels.

In almost every case, MK 135 was well tolerated. Minor complaints such as constipation and nausea occurred in 6 patients (5 of whom were on the powder) and these disappeared promptly following discontinuance of treatment.

Following cessation of MK 135 administration cholesterol levels rose promptly. Of 15 subjects studied after termination of MK 135 treatment, 8 showed rises in cholesterol levels that transiently exceeded control values. Such an overshoot could have been anticipated on theoretical grounds since an enforced increase in the rate of cholesterol oxidation might be expected to result in some degree of increase in cholesterol synthesis.

Summary. Preliminary results of administering a resin with bile acid sequestering properties are reported. The preparation was administered to 26 patients for periods of 2 to 34 weeks. Serum total cholesterol levels were lowered by more than 10% in 23 of 26 patients. Average decrease in serum total cholesterol for all subjects was 20% ($p<0.001$). No systemic side-effects were observed. Six subjects treated for 6 weeks or longer maintained lowered values of serum total cholesterol without escape.

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