

Inhibition of Ileal Water Absorption by Intraluminal Fatty Acids INFLUENCE OF CHAIN LENGTH, HYDROXYLATION, AND CONJUGATION OF FATTY ACIDS

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Research Article

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Inhibition of Ileal Water Absorption by Intraluminal Fatty Acids

INFLUENCE OF CHAIN LENGTH, HYDROXYLATION, AND CONJUGATION OF FATTY ACIDS

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ABSTRACT The influence of fatty acids on ileal absorption of water, electrolytes, glucose, and taurocholate was examined in Thiry-Vella fistulas in five mongrel dogs. Fatty acid absorption also was measured. Segments of terminal ileum were perfused at steady state with isotonic electrolyte solutions containing 11.2 mM glucose, 4.5 mM taurocholate, and 0.1–5.0 mM fatty acid. Three C_{18} fatty acids, oleic acid, 10(9)-hydroxystearic acid, and ricinoleic acid, completely inhibited water absorption at 5 mM. Sodium, chloride, and potassium absorptions were inhibited in parallel with absorption of water. Differences between the potencies of C_{18} fatty acids were apparent when lesser concentrations were perfused. Dodecanoic and decanoic acids were as effective as C_{18} fatty acids at 5 mM but octanoic and hexanoic acids were ineffective. The polar group of C_{18} fatty acids was modified by conjugating oleic and ricinoleic acids with taurine. When these compounds and a substituted C_{10} fatty acid, *p*-*n*-decylbenzenesulfonate, were perfused, water absorption was also inhibited. Short-chain fatty acids (C_8 and C_4) and their hydroxylated derivatives were ineffective at 5 mM. When water absorption was inhibited, absorption of glucose and taurocholate was decreased. We speculate that the phenomenon of inhibition of water and electrolyte absorption by fatty acids may be relevant to steatorrhea and diarrhea in man.

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INTRODUCTION

In steatorrhea, the ileum and colon are exposed to excess quantities of fatty acids. Long-chain fatty acids impair electrolyte and water absorption in the colon (1),¹ and this effect is thought to contribute to the diarrhea that can accompany steatorrhea (2). Oleic acid (Δ^9 -octadecenoic acid) and ricinoleic acid (12-hydroxy- Δ^9 -octadecenoic acid, the active principle of castor oil) also modify water transport in the human jejunum (3), where they can provoke fluid secretion, suggesting that modification of intestinal water transport may be a general characteristic of long-chain fatty acids. However, the influence of fatty acids on ileal absorption and the secretory properties of medium- and short-chain fatty acids have not been reported.

The molecular characteristics necessary for a fatty acid to inhibit water absorption are not known. Hydroxylated fatty acids have been implicated specifically in diarrhea, mainly on the basis of chemical similarities between ricinoleic acid and the major hydroxy fatty acid of steatorrheal stools, 10-hydroxystearic acid (4). However, in the human jejunum, oleic and ricinoleic acids have comparable effects on water absorption (3).

Here we describe the influence of fatty acids on ileal absorption in chronic canine Thiry-Vella fistulas. Long-chain fatty acids inhibited electrolyte and water absorption in this model. In association with decreased water absorption, absorptions of glucose and taurocholate were decreased. The influence of fatty acid chain length, hydroxylation, and conjugation (with taurine) on the inhibition of ileal water absorption was also evaluated.

¹ Ammon, H. V., and S. F. Phillips. Inhibition of colonic water and electrolyte absorption by fatty acids in man. *Gastroenterology*. In press.

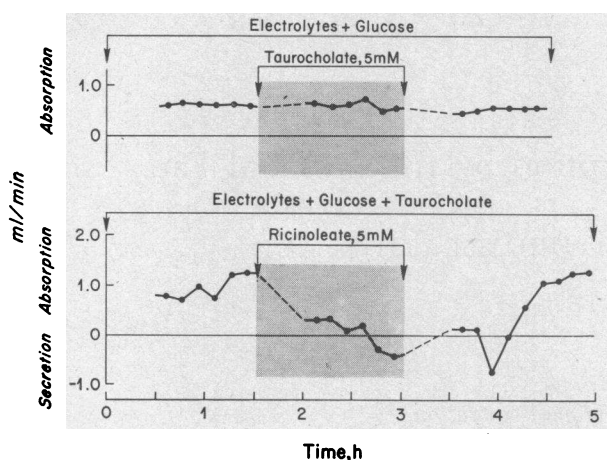


FIGURE 1 Water absorption during perfusion of canine Thiry-Vella loop of ileum with balanced isotonic electrolyte solution. Each point represents one 10-min collection period (see Methods). Above, stability of water absorption during 4½ h of perfusion and failure of taurocholate to influence water absorption. Below, inhibition of water absorption by 5 mM ricinoleic acid with delayed return to base-line absorption when control solution was reinstated.

METHODS

Animal model. Thirty-Vella fistulas were constructed under sterile surgical conditions in one male and four female mongrel dogs (body wt, 9–16 kg). The loops comprised approximately 35 cm of ileum and terminated 15 cm proximal to the ileocecal valve. 2 wk were allowed for the dogs to recover from the operation. They maintained their body weight for 8 mo and had no diarrhea. Loops were irrigated with 154 mM NaCl three times weekly if experiments were not performed. The experiments were conducted with the dogs under light anesthesia with pentobarbital sodium. Foley catheters (16 F) were placed in both ostia, and solutions were perfused at 37°C and 2.5 ml/min in isoperistaltic direction (Harvard Model 1201, Harvard Apparatus Co., Inc., Millis, Mass.). Sampling was by gravity drainage into a graduated cylinder. Control and test solutions were perfused for 90 min. The first 30 min were used for equilibration; six sequential 10-min collections were then made and their mean was considered to represent one experimental period. Steady-state conditions were verified by subsequent measurement of a non-absorbable marker, polyethylene glycol (PEG).²

Experimental design. We tested initially the stability of water absorption during more than 3 h of perfusion, the influence of taurocholate on water absorption, and the reversibility of changes in water absorption induced by 5 mM ricinoleic acid in each loop (Fig. 1). Control water absorption was stable and uninfluenced by taurocholate. The fatty acid-induced inhibition of water absorption was fully reversible only after 90 min of control perfusion. Therefore, water and electrolyte absorptions were compared in each animal during perfusion with a control solution before perfusion with an identical solution containing fatty acids. The effects of the following compounds were examined:

² Abbreviation used in this paper: PEG, polyethylene glycol.

C₁₈ fatty acids (oleic acid, 10(9)-hydroxystearic acid, and ricinoleic acid) in concentrations of 0.1–5 mM; short- and medium-chain fatty acids at 5 mM; taurine conjugates of oleic and ricinoleic acid at 5 mM; and a synthetic anionic detergent, *p*-*n*-decylbenzenesulfonate at 5 mM. Each compound was tested in four animals on 1 or more days.

Composition of perfusates. Control and test solutions were isotonic electrolyte solutions and were identical except for the fatty acid content (Table I); sodium chloride content of test solutions was reduced by up to 5 mM to preserve isotonicity. Long-chain fatty acids were used as sodium salts and were 99% pure by gas-liquid chromatography. Ricinoleic acid was prepared by serial solvent extraction in petroleum ether-methanol after saponification of castor oil; 10(9)-hydroxystearic acid was prepared as a mixture of 9- and 10-hydroxystearic acid according to the method of Knight, Koos, and Swern (5). Oleic acid and medium- and short-chain fatty acids were obtained from commercial sources (Nu-Chek Prep, Elysian, Minn.). Taurocholate was synthesized according to the method of Norman (6) and purified by solvent extraction (7); taurine conjugates of oleic and ricinoleic acid were synthesized and purified in an analogous way. These compounds were greater than 95% pure by thin-layer chromatography.

Analytical methods. Taurocholate was measured by the steroid dehydrogenase enzyme assay (8), sodium and potassium by flame photometry (IL Model 143, Instrumentation Laboratory, Inc., Lexington, Mass.), and chloride by electrotitration (Buchler Instruments Div., Nuclear-Chicago Corp., Fort Lee, N. J.). [¹⁴C]PEG was counted, in a dioxane-based cocktail, by liquid scintillation spectrometry (Liquimat, Picker International Corp., White Plains, N. Y.) with an efficiency of 65–75%. Glucose was determined by the glucose oxidase method (Boehringer Mannheim Corp., New York) on aliquots placed into separate vials containing sodium fluoride. C₁₈ fatty acids were extracted (9) from acidified solution into toluene-ethanol (2:1, vol/vol), after addition of heptadecanoic acid as an internal standard, and were measured by gas chromatography of their methyl esters. Dodecanoic acid was analyzed in a similar way with tridecanoic acid as internal standard. The fatty acids were methylated with freshly prepared diazomethane. Decanoic or octanoic acid was methylated, together with nonanoic acid as an internal standard, according to a modification of Drucker's method (10), with boron trichloromethanol (Applied Science Labs, Inc., State College, Pa.).

For the analysis of oleyltaurine (or ricinoleyltaurine) we used ricinoleyltaurine (or oleyltaurine) as internal

TABLE I
Composition of Perfusates

Sodium	120 mEq/liter
Potassium	20 mEq/liter
Chloride	90 mEq/liter
Bicarbonate	50 mEq/liter
Glucose	11.2 mM
Taurocholate	4.5 mM
Fatty acids*	0–5 mM

pH 8.0; osmolality, 280 mosmol/kg; PEG, 5 g/liter, with [¹⁴C]PEG, 5 μCi/liter.

* In test solutions only.

standard. Samples (1 ml) were mixed with 1 ml of a 5 mM methanolic solution of the internal standard, and 6 ml of 2.67 N sodium hydroxide in methanol was added, resulting in a final NaOH concentration of 2 M. After vigorous saponification (16 h, 115°C) in a nickel bomb (Parr Instrument Co., Moline, Ill.), 2 ml of the hydrolysate was acidified with hydrochloric acid and extracted (9) into 9 ml of toluene-ethanol (2:1). Aliquots (4 ml) of the upper phase were evaporated and methylated with diazomethane. The methyl esters were measured by gas chromatography.

The methyl esters of fatty acids were chromatographed on 4.3% OV 17 (Applied Science Labs, Inc.) in a 183-cm column. Column temperature was 210°C for the C₁₈ fatty acids, 120°C for the C₁₂ compound, and 110°C for the C₈ and C₁₀ compounds.

Calculations and statistical analysis. Net absorptions of water in milliliters per minute, electrolytes in microequivalents per minute, and fatty acids, glucose, and taurocholate in micromoles per minute by the entire loop were calculated, relative to changes in the concentration of PEG, by using standard formulas. For statistical analysis we used paired *t* tests and Dunnett's test for multiple comparisons (11). Linear regressions were calculated by the method of least squares. To permit comparison between studies on different days, mean water absorption during each control period was designated as 100% absorption, and zero net water movement was designated as 100% inhibition of absorption. Since the magnitude of net fluid secretion induced in these studies was usually small, secretion was also designated as 100% inhibition. This analysis facilitated comparisons between individual experiments but has no implications as to the mechanism by which net fluid movement is altered.

TABLE II
Effects of C₁₈ Fatty Acids on Water Absorption

Concentration	n	H ₂ O absorption*		P, control vs. test
		Control	Test	
mM		ml/min		
Ricinoleic acid				
5	14	0.71 ± 0.09	-0.17 ± 0.03	<0.001
2	3	0.80 ± 0.11	-0.02 ± 0.05	<0.05
1	8	0.70 ± 0.13	-0.05 ± 0.05	<0.005
0.1	4	0.81 ± 0.16	0.39 ± 0.17	NS
10(9)-Hydroxystearic acid				
5	4	0.36 ± 0.13	-0.14 ± 0.06	<0.025
2	6	0.71 ± 0.19	-0.08 ± 0.12	<0.02
1	15	0.62 ± 0.09	0.21 ± 0.06	<0.005
0.1	4	0.68 ± 0.11	0.68 ± 0.11	NS
Oleic acid				
5	8	0.75 ± 0.09	-0.05 ± 0.05	<0.001
2	4	1.08 ± 0.26	0.40 ± 0.18	<0.05
1	16	0.49 ± 0.08	0.22 ± 0.06	<0.005

* Mean ± SE.

TABLE III
Effects of Fatty Acids and Fatty Acid Derivatives on Water Absorption

Compound	n	H ₂ O absorption*		P, control vs. test
		Control	Test	
ml/min				
C ₁₂	4	0.37 ± 0.11	-0.17 ± 0.05	<0.001
C ₁₀	3	0.37 ± 0.10	0.03 ± 0.14	<0.001
C ₈	3	0.55 ± 0.24	0.43 ± 0.10	NS
C ₆	3	0.62 ± 0.15	0.59 ± 0.17	NS
C ₄	4	0.64 ± 0.16	0.57 ± 1.10	NS
C ₂	3	0.56 ± 0.03	0.58 ± 0.12	NS
Lactic acid	4	0.51 ± 0.10	0.70 ± 0.15	NS
γ-hydroxybutyric acid	3	0.47 ± 0.25	0.68 ± 0.21	NS
Oleyltaurine	3	0.50 ± 0.14	-0.06 ± 0.04	<0.05
Ricinoleyltaurine	4	0.66 ± 0.22	0.05 ± 0.11	<0.01
PDB‡	4	0.54 ± 0.17	0.11 ± 0.08	<0.01

* Mean ± SE. Test substance was present at 5 mM.

‡ *p*-*n*-decylbenzenesulfonate.

RESULTS

Control water absorption. Control water absorption varied from day to day and from animal to animal. These fluctuations displayed no pattern except in one dog in which control absorption appeared to decrease after 3 mo; no further experiments were performed in this animal. Occasionally, water was secreted during control observations. These experiments were not used for analysis, although the changes induced by test perfusates were always in the same direction as in the other animals.

Effect of C₁₈ fatty acids on water absorption. At 5 mM concentration, the three C₁₈ fatty acids inhibited water absorption completely and usually induced water secretion (Table II). The change induced by 10(9)-hydroxystearic acid was slightly but significantly (*P* < 0.05) less than that induced by oleic or ricinoleic acid. However, this difference may be due to lower control water absorption values during experiments in which 10(9)-hydroxystearic acid was used (*P* < 0.05). No differences between the three fatty acids could be detected at 2 mM concentration. At 1 mM, ricinoleic acid was significantly more potent than oleic acid (*P* < 0.05). The effect of 1 mM 10(9)-hydroxystearic acid was intermediate and did not differ significantly from that of either ricinoleic or oleic acid.

Effect of medium- and short-chain fatty acids. The effects of medium- and short-chain fatty acids were measured at 5 mM concentrations only (Table III). Dodecanoic acid (C₁₂) inhibited water absorption completely and usually induced secretion; decanoic acid (C₁₀) inhibited water absorption significantly (*P* < 0.001). The changes induced by octanoic acid (C₈) and fatty acids of lesser chain-length were not significant.

TABLE IV
Absorption of Fatty Acids and Intraluminal Concentration*

Fatty acid*	n	Absorption rate‡	Intraluminal concn‡
		$\mu\text{mol}/\text{min}$	mM
Oleic	4	6.93 ± 0.45	3.61 ± 0.10
10(9)-hydroxystearic	4	3.52 ± 0.37	4.70 ± 0.03
Ricinoleic	4	0.79 ± 0.31	4.20 ± 0.03
C ₁₂	4	9.06 ± 1.38	3.14 ± 0.26
C ₁₀	3	9.87 ± 0.53	3.02 ± 0.08
C ₈	3	11.01 ± 0.42	2.86 ± 0.09
Oleyltaurine	3	1.22 ± 0.44	4.71 ± 0.04
Ricinoleyltaurine	4	0.94 ± 0.15	4.87 ± 0.11

* Mean \pm SE.

‡ Initial concentration in perfusate, 5 mM; mean concentration is arithmetic mean of initial and recovery concentrations. Infusion rate of fatty acids was 12.5 $\mu\text{mol}/\text{min}$.

Two hydroxylated short-chain fatty acids, γ -hydroxybutyric acid and lactic acid, had no effect.

The anionic detergent, *p*-*n*-decylbenzenesulfonate, at 5 mM also inhibited water absorption.

Effect of taurine-conjugated C₁₈ fatty acids. To determine whether the presence of a carboxyl group is necessary for the secretory effect of C₁₈ fatty acids, oleyltaurine and ricinoleyltaurine were tested at 5 mM. Both inhibited water absorption to the same degree as did the parent compounds (Table III).

Effects on electrolyte movements. Absorption of sodium, potassium, and chloride, determined in all experiments, corresponded closely to that of water: $r = 0.919$ for sodium and water, $r = 0.837$ for potassium and water, and $r = 0.984$ for chloride and water.

Effects on absorption of glucose and bile acids. Absorption of glucose and bile acids was determined in 16 control perfusions and 16 test perfusions (5 mM ricinoleic acid in 8, 5 mM 10(9)-hydroxystearic acid in 4, and 5 mM ricinoleyltaurine in 4) in which water absorption was completely inhibited. Since the movements of water, glucose, and bile acids did not differ among these three groups of studies, the results are combined. Mean \pm SE water absorption decreased from 0.49 ± 0.10 ml/min during the control observations to -0.10 ± 0.04 ml/min (secretion) during the test perfusions. Glucose absorption in the control periods was 19.4 ± 1.4 $\mu\text{mol}/\text{min}$ ($69.3 \pm 5.0\%$ of the infused amount) and decreased to 4.4 ± 0.4 $\mu\text{mol}/\text{min}$ ($15.7 \pm 1.4\%$; $P < 0.001$). Bile acid absorption in the controls was 7.1 ± 0.4 $\mu\text{mol}/\text{min}$ ($63.1 \pm 4.4\%$) and decreased to 0.88 ± 0.15 $\mu\text{mol}/\text{min}$ ($7.8 \pm 1.3\%$; $P < 0.001$).

Water movement correlated well with the movement of glucose ($r = 0.784$) and bile acids ($r = 0.714$). The

closest correlation, however, was observed between the movements of taurocholate and glucose ($r = 0.918$).

Absorption of fatty acids. Among the C₁₈ fatty acids, oleic acid was best absorbed and ricinoleic acid was least absorbed (Table IV). The differences between the absorption rates of the three C₁₈ fatty acids were significant ($P < 0.01$). Medium-chain fatty acids were more rapidly absorbed. Table IV also shows differences in recovery and mean intraluminal concentrations of fatty acids, which resulted largely from their different rates of absorption.

Recovery of PEG. Mean PEG recoveries in control and test periods were $97.4 \pm 1.6\%$ and $101.2 \pm 0.8\%$, respectively ($P < 0.05$).

DISCUSSION

Experimental model. The effect of fatty acids on intestinal water absorption has been studied in man (3),¹ but the present model permitted a large number of compounds to be tested in the ileum, a segment of intestine not easily accessible in man. These isolated loops were a suitable model in that control water absorption was stable for more than 3 h and most loops maintained their absorptive capacity for 8 mo. However, control absorption varied between animals and from day to day, so it was necessary to use each animal as its own control in every experiment. Because changes in water absorption induced by 5 mM fatty acids lasted for up to 90 min, our design required that control perfusions be followed by test perfusions.

As judged by recovery rates, PEG was a valid non-absorbable marker for the model. The small but statistically significant increase in PEG recovery during perfusion with fatty acids may have been due to changes in intestinal transit which, however, were not measured.

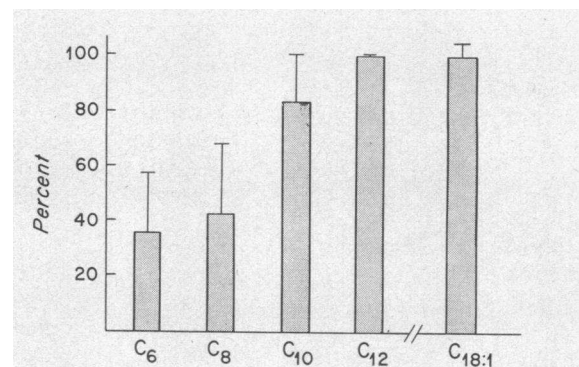


FIGURE 2 Comparison of inhibitory effects of different fatty acids on water absorption in canine ileal Thiry-Vella fistulas. Results have been normalized by expressing them as percentage inhibition of control absorption, thereby allowing direct comparisons of fatty acids (see Discussion). Mean (\pm SE) inhibition of water absorption for at least three dogs is shown in each column.

But changes in water absorption produced by fatty acids could not have been the result of changes in marker recovery, because the marker recovery was greater under test conditions.

Effects of fatty acids on water absorption. Together with previous studies demonstrating an effect of C₁₈ fatty acids in the colon (1)¹ and the jejunum (3), the present results suggest that C₁₈ fatty acids influence water absorption in the entire intestine. It is clear that this potential is not limited to C₁₈ compounds. The inhibitory effect of fatty acids was related to their concentration in the perfusates and to their chain length, with C₁₈, C₁₂, and C₁₀ compounds being most effective.

In regard to these effects *in vivo*, rates of fatty acid absorption may be important determinants, because slower absorption may enhance the effective intraluminal concentration. Thus, at the higher concentrations, the three C₁₈ fatty acids had similar effects. But at 1 mM, differences were apparent and the most rapidly absorbed compound was the least effective. Although the secretory potentials of various fatty acids *in vivo* are probably modified primarily by differences in rates of absorption, we cannot exclude a potentiating effect of the additional hydroxyl group in ricinoleic and 10-hydroxystearic acids.

When the inhibitory effects of fatty acids of different chain length are compared (Fig. 2), a range of activity is seen. Two influences of decreasing chain length can be predicted, both of which should reduce secretory potential. When perfused at the same concentrations, medium-chain fatty acids were less potent than long-chain compounds and, because they are absorbed more rapidly than C₁₈ fatty acids, their intraluminal concentration is lower. Thus, even C₈ and C₆ compounds might have decreased water absorption if perfused at higher concentrations; however, 40 mM hexanoic acid does not produce water secretion in the jejunum (12).

Short-chain fatty acids are produced in the distal intestine by bacterial fermentation of carbohydrates (13). They are less well absorbed than medium-chain fatty acids (14). They have a low pK and, at the pH of the distal bowel, they should be mainly ionized. In addition, the fraction that is un-ionized should traverse lipid cell membranes more slowly than higher fatty acids, which have greater lipid solubility. They have been implicated in osmotic diarrhea (2, 15), but in low concentrations (5 mM), the compounds tested here had no specific effects on water absorption comparable to those of long-chain fatty acids.

When oleic and ricinoleic acids are conjugated with taurine, the polar end becomes a sulfonate rather than a carboxylate group. Furthermore, in *p-n*-decylbenzenesulfonate, a benzene ring is positioned close to the sulfonate polar end and the constituent fatty acid is C₁₀.

These derivatives had effects on water absorption similar to those of the component fatty acids. Thus, the nature of the polar group seems to be unimportant. A common denominator for all active compounds is their ability to decrease surface tension. This general statement also applies to the secretory effect of dihydroxy bile acids in the human colon (16), jejunum (17), and ileum (18). However, additional factors must play a role since trihydroxy bile acids are also surface-active but have no secretory effects (16–18).

The present experiments cannot define the mechanism of altered water movement. Electrolyte movement, specifically sodium and chloride transport, was altered in parallel with that of water. In fact, it is likely that reduced absorption or secretion of sodium and chloride is the primary influence of fatty acids and that changes in water movement are secondary phenomena. Bright-Asare and Binder (1) have examined possible mechanisms for fatty acid-induced secretion in the rat colon and found that, in association with electrolyte and water secretion, mucosal permeability to inulin increased and the transmucosal potential difference decreased.

Absorption of fatty acids. Relative rates of fatty acid absorption are in agreement with previous observations that absorption increases with decreasing chain length (19), provided no double bonds or polar groups are introduced into the molecule. We found no previous comparisons of the absorption rates of oleic and hydroxylated C₁₈ fatty acids. The differences observed here are consistent with the concept that fat absorption can be characterized as passive transport across lipid membranes. The addition of a hydroxyl group or a double bond decreases the oil/water partition of the lipid, makes the molecule more polar, and thereby decreases its rate of transport across a lipid membrane (20). Thus, ricinoleic acid, which contains both a double bond and a hydroxyl group, was absorbed less well than either hydroxystearic or oleic acid.

Clinical significance. Together with earlier observations, the present results indicate that long-chain fatty acids can influence fluid transport in the entire gut. This phenomenon can be related to two common clinical circumstances: the cathartic effect of castor oil, and the increased fecal water excretion in steatorrhea.

When in health the intestine is exposed to a poorly absorbed fatty acid such as ricinoleic acid or when in disease the intestine is exposed to unabsorbed dietary fatty acids, water absorption in the jejunum and ileum should be impaired. The result will be an increased fluid load to the colon which may produce diarrhea, if the absorptive potential of the colon is exceeded. In addition, fatty acids decrease the capacity of the colon to absorb water (1).¹ Bacterial transformation (21) of oleic acid to 10-hydroxystearic acid may enhance the

"cathartic effect" of fatty acids in the colon but this conversion does not appear to be a prerequisite (1).¹ In fact, hydration of the double bond of oleic acid in this process should decrease the aqueous solubility of the fatty acid. The physical state and concentration of the fatty acids in the intestine should be decisive because presumably they must be in the aqueous phase to block water absorption. Solubility may be influenced by other factors, including pH and presence of calcium ions and bile acids in the lumen. Intraluminal concentrations of fatty acids in the ileum in steatorrheal diseases have not been reported. In a recent abstract, concentrations of fatty acids in the aqueous phase of steatorrheal stools were measured and were found to be above those used in the present studies; however, stool fatty acid concentration could not be related to the presence or absence of diarrhea (22). The relationships between fecal concentrations of fatty acids and concentrations in the intestinal lumen are uncertain.

The possibility that water secretion, induced by fatty acids, might induce secondary malabsorption of other substances warrants further study. Glucose and bile acid absorption was reduced here; in the human jejunum,³ fatty acid-induced water secretion impaired absorption of glucose, xylose, L-leucine, L-lysine, and folic acid. This phenomenon might be nonspecific, because the absorption of all compounds showed similar declines, and the effect was rapidly reversible.

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³ Ammon, H. V., and S. F. Phillips. Unpublished data.