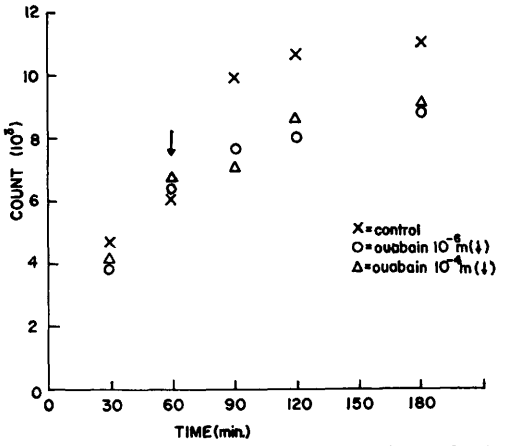

FIG. 1. Effect of ouabain on Fe^{59} uptake by rabbit reticulocytes.

tained in 10 experiments. Consequently, it is concluded that the Na-K ATPase system is probably involved in iron transport in rabbit reticulocytes, thus providing further evidence of the widespread function of this system in transport processes.

Summary. Uptake of Fe^{59} by rabbit reticulocytes in the presence of ouabain was inhibited. From such evidence it is concluded that the Na-K ATPase system is probably involved to some degree in iron transport in rabbit reticulocytes.

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Serum Cholesterol Reduction by Para-Aminosalicylates in Man. I-131 Triolein Absorption Studies.* (29931)

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It has been reported from this laboratory that oral administration of neomycin reduced significantly the concentration of serum cholesterol in man(1,2,3). Following this finding, the effect of 17 additional antibacterial drugs on the serum cholesterol level of patients has been studied. Several antibacterial drugs were found to affect serum cholesterol to varying degrees(3,4). Of these, oral administration of para-aminosalicylic acid at daily doses of 8 to 12 g was most effective, and reduced serum cholesterol concentrations significantly (average fall: 25%) in each of 15 patients(3). Similar results from other laboratories have been published(5,6,7), and Tygstrup, Winkler and Jorgensen reported that oral administration of para-aminosalicylates resulted in significantly lower serum cholesterol levels than intravenous administration of the drug in 9 patients(7,8). They also noted a moderate increase of fecal triglyceride excretion following oral administration of the drug. The possibility that the serum cholesterol-lowering effect of PAS may depend on its local action in the gastrointestinal tract had to be considered, particularly in the context of evidence reported earlier from this laboratory, showing that the cholesterol-reducing effect of neomycin depends exclusively on its activity within the gut(3).

Oral administration of para-aminosalicylic acid (acid PAS) has been reported to cause more severe gastrointestinal symptoms than sodium para-aminosalicylate (sodium PAS) (9), and it has been shown that absorption of the acid compound is slower than that of the sodium salt(9). In the present study the effect of acid and sodium PAS on serum cholesterol concentration of a group of patients is reported. The effect of administration of

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these compounds on the absorption and fecal excretion of I-131 labeled triolein was also studied.

Comparative effect of acid and sodium PAS on serum cholesterol concentrations. Material and methods. Fourteen hospitalized patients were studied in 23 experimental periods of 5 to 19 weeks duration. Six male and 8 female patients ranged in age from 19 to 63 years. All of the patients had pulmonary tuberculosis and were hospitalized in a tuberculosis hospital. At the time of the study they were afebrile, out of bed, and had normal liver and kidney function tests. They consumed a regular hospital diet, in which about 38 to 45% of the total calories were derived from fat. They were given 300 mg of oral isoniazid daily and 1 g of intramuscular streptomycin twice weekly throughout the study, including control periods. This medication has no effect on the concentration of serum cholesterol, either solely or in association with PAS administration(3). Medications known to influence serum cholesterol levels, or other antibacterial drugs were not given. Only those patients who previously showed a good tolerance to administration of PAS were selected for the study. At the beginning of the experiments, the patients had been maintained on oral PAS for periods varying between 2 and 8 months. Total serum cholesterol concentrations were determined once a week in the fasting state by the method of Abell *et al*(10). Control serum cholesterol levels were determined for 8 weeks or longer, after the interruption of PAS administration. Patients were weighed weekly and blood counts, tests of urine, blood urea nitrogen, serum bilirubin and cephalin flocculation were carried out periodically.

Twelve g of sodium PAS was given orally to 14 patients daily for 5 to 14 weeks. Nine g of acid PAS, whose PAS content is approximately equivalent to 12 g of the sodium salt, was given to 4 patients for 6 to 19 weeks, and 5 subjects were given 12 g of acid PAS for periods varying between 9 and 12 weeks. Each patient who was given acid PAS was subsequently maintained on the sodium salt, to compare the effect of the two compounds. The medication was given in 3 equal daily doses either as tablets or as weighed powder.

Results. The results of administration of PAS are included in Table I. In 9 experiments, following oral administration of the acid compound, average total serum cholesterol concentrations fell in each patient by 15 to 35% (average fall: 29%), which is in agreement with previous results(2,3). However, following the daily oral administration of 12 g of sodium PAS, only 7 of the 14 patients showed a significant decrease of the average total serum cholesterol level by 11 to 26% (average fall: 19%), whereas in the remaining 7 patients the change was not statistically significant. Fig. 1 shows the comparative effect of the acid and sodium compounds, suggesting that at equimolar doses acid PAS had a more marked reducing effect on serum cholesterol levels than the sodium salt.

No serious side effects were observed, although the change to acid from sodium PAS

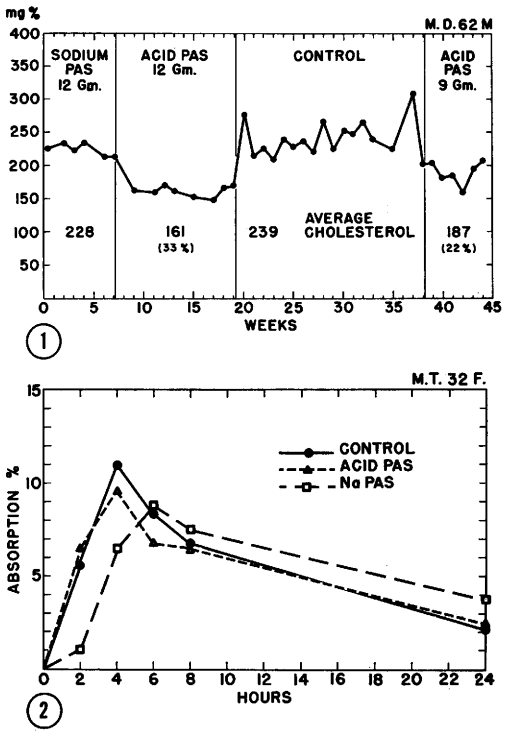

FIG. 1. Effect of oral administration of sodium (12 g daily) and acid PAS (9 and 12 g daily) on serum cholesterol concentrations of M. D. 62 ♂.

FIG. 2. Absorption of I-131 triolein (whole blood activity in % of dose given) during control period and following oral administration of acid and sodium PAS, in M. T. 32 ♀.

TABLE I. Effect of Oral Administration of Acid and Sodium PAS on Average Total Serum Cholesterol Concentration (and standard deviation) of 14 Patients.

Patient			Control	Sodium PAS 12 g				Acid PAS 9 g				Acid PAS 12 g			
Age	Sex		Average total serum cholest	Wk*	Average total serum cholest	% fall	p	Wk*	Avg total serum cholest	% fall	p	Wk*	Avg total serum cholest	% fall	p
			(mg %)		(mg %)				(mg %)				(mg %)		
43	♂		294 ± 16	13	218 ± 25	26	<.001	19	251 ± 21	15	<.001	9	204 ± 15	31	<.001
63	♂		239 ± 26	7	228 ± 14	—	>.05	6	187 ± 16	22	<.001	12	161 ± 8	33	<.001
19	♀		219 ± 8	8	240 ± 8	18	<.001	9	198 ± 13	32	<.001				
27	♀		175 ± 15	13	155 ± 15	11	<.01	8	113 ± 9	35	<.001				
40	♀		191 ± 20	7	141 ± 16	26	<.001					9	129 ± 13	32	<.001
39	♂		289 ± 32	8	242 ± 10	16	<.001					11	196 ± 25	32	<.001
37	♀		199 ± 11	8	188 ± 8	—	>.025					10	136 ± 18	32	<.001
50	♂		270 ± 34	14	211 ± 22	22	<.001								
23	♂		285 ± 19	9	241 ± 49	—	>.05								
38	♀		195 ± 17	6	167 ± 17	—	>.025								
50	♀		278 ± 10	6	261 ± 11	—	>.025								
30	♀		207 ± 5	6	180 ± 18	13	<.01								
32	♂		286 ± 21	5	261 ± 13	—	>.05								
52	♀		148 ± 11	6	143 ± 14	—	>.5								

*Weeks on PAS.

initiated somewhat more frequent minor gastrointestinal complaints. The weight of the patients remained within 3 lb variation throughout the study, except in 3 subjects whose weight increased by 5 to 9 lb with no apparent relationship to the level of serum cholesterol or to the effect of PAS. Hematopoietic, hepatic and renal functions were not altered.

I-131 Triolein absorption studies. Material and methods. Nine patients were studied, all of whom were included in the previous study group. A total of twenty I-131 triolein absorption tests were carried out. The study was repeated twice in 7 patients and 3 times in 2 patients, each test during different experimental periods. The following experimental program was carried out: a test was done after at least 4 weeks of oral sodium PAS administration in 7 patients and acid PAS administration in 4; repeat absorption tests were done subsequently during control periods when the patient's cholesterol concentration had returned to pre-treatment levels.

The patients were given 10 drops of Lugol's solution USP on the day preceding the test, and once each day thereafter for 72 hours. After an overnight fast a capsule containing 50 to 100 microcuries of I-131 triolein was given orally and regular feeding and medication schedules were resumed. Blood was collected serially during 24 hours, and stool was obtained in 24-hour periods in separate containers for 72 hours after the beginning of the experiment. Whole blood radioactivity was read against standards in 4 ml aliquots, and per cent absorption was calculated from standard blood-volume charts. Total fecal radioactivity was determined on a measured aliquot from each of the 24-hour stool specimens, homogenized in a blender.

Results. The results of the I-131 triolein absorption tests are shown in Table II. In 6 instances the tests were carried out after a significant fall of serum cholesterol levels had occurred following administration of oral PAS. The average absorption of radioactivity in these cases was 9.5 and 8.3% during control and PAS periods respectively, whereas the total 72-hour fecal elimination was 5.6% of the administered dose during both control and PAS periods. The difference in absorp-

TABLE II. Results of I-131 Triolein Absorption Tests in 6 Patients After Significant Reduction of Serum Cholesterol Levels, and in 5 Patients with no Change in Serum Cholesterol Concentrations, as Compared to Control Periods.

	Average % absorption (and range)		Average 72 hr stool activity (and range)	
	Control	PAS	Control	PAS
Serum cholesterol reduced	9.5 (5.5–14.5)	8.3 (6.8–10.2)	5.6 (1.3–11.0)	5.6 (1.4–11.3)
	$p > .2$		$p > .5$	
Serum cholesterol not reduced	10.9 (7.0–15.2)	11.9 (7.5–17.2)	2.2 (0.1– 4.3)	8.1 (2.6–19.5)
	$p > .4$		$p > .05$	

tion was not statistically significant. In an additional 5 experiments the tests were carried out during the administration of sodium PAS with no significant alteration of serum cholesterol levels, and were compared to control results. In these cases the average radioactivity absorptions were 10.9 and 11.9% and fecal eliminations were 2.2 and 8.1% respectively during control and PAS periods. The differences were not statistically significant. Fig. 2 shows absorption curves in patient M.T. 32 F.

Discussion. There is no evidence available to explain the mechanism of the serum cholesterol-reducing effect of PAS, or the reason for the difference between the activity of the acid and sodium compounds. It has been reported(7,8) that the fall of serum cholesterol levels was slower and less pronounced during intravenous than during oral administration of the drug. This suggests that, as in the case with neomycin(3), the serum cholesterol reducing effect of PAS may depend on its activity within the gastrointestinal tract. Acid PAS being less readily absorbed than the sodium salt(9), this theory may possibly explain the difference in the activity of the two compounds.

Nonetheless, the possibility that the effect of PAS on serum cholesterol is due to its presence in the systemic circulation cannot be ruled out. However, the knowledge accumulated on the effect of the drug on serum cholesterol seems to indicate that it may be dependent on its presence within the gastrointestinal tract, rather than in the systemic circulation.

Tygstrup, Winkler and Jorgensen reported the occurrence of a slight degree of steatorrhea during oral PAS administration(7,8). They stated, however, that it was of such mild intensity that it probably played no role in the cholesterol reducing activity of the drug. In the present report it is clear that absorption and fecal excretion as measured by I-131 triolein were not different during PAS and control periods, therefore, it seems highly unlikely that the mild degree of steatorrhea occasionally occurring could be responsible for the activity of PAS on serum cholesterol levels. The accuracy of the I-131 triolein absorption test has been criticized (11,12). It is, however, generally accepted that the fecal elimination of the label is a reasonably reliable indicator of fat absorption and checks well with chemical controls (13,14).

One of the working theories in this laboratory is that neomycin lowers serum cholesterol levels by modifying the character of the intestinal bacterial flora, as has been reported previously(3). There is reason to believe that a number of other antibacterial substances may act alike(3,4). If PAS can ultimately be proven to act on serum cholesterol by a similar mechanism, one may then deal with a group of chemically unrelated compounds, which would possibly include other substances as well, influencing serum cholesterol levels possibly through their action upon the intestinal bacterial flora. If the intestinal flora then is of importance in regulating serum cholesterol levels, it is possible that the character and the changes of the flora are the direct mediator of the effect of a group of factors on serum cholesterol designated as "environment." The well known epidemiologic data, concerning differences of serum cholesterol levels among different populations of various parts of the earth, may then be due,

in part, to environmentally induced differences in the character of the intestinal bacterial flora.

Summary. Daily oral administration of 9 and 12 g of acid PAS to 7 patients in 9 experimental periods of 6 to 19 weeks duration resulted in significant reductions of the average total serum cholesterol concentration in each subject by 15 to 35%. The average fall for the group was 29%. Daily oral administration of 12 g of sodium PAS to 14 patients for 5 to 14 weeks was followed by a significant fall of average total serum cholesterol levels in only 7 patients by 11 to 26%. The average fall for these subjects was 19%. The remaining 7 patients showed no statistically significant variation of serum cholesterol following administration of oral sodium PAS. The absorption and fecal elimination of I-131 triolein was studied during the administration of PAS in a total of 20 experiments. In 6 patients I-131 triolein absorption tests were carried out during control periods and after the reduction of serum cholesterol levels by the administration of PAS. Five patients, in whom oral administration of sodium PAS failed to alter the concentration of serum cholesterol, were subjected to I-131 triolein absorption tests during control periods and following oral administration of sodium PAS. There was no significant difference between control and PAS periods in the average whole blood radioactivity and in the 72-hour fecal elimination of radioactivity in either of the two groups. It was thus concluded that the absorption of dietary triglycerides was not significantly altered by oral administration of the drug. The possible mechanisms by which administration of PAS lowered the concentration of serum cholesterol were discussed.

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Effects of X-Irradiation on Susceptibility of Neonatal Rat Brain and Muscle to Coxsackie B1 Virus Infection.* (29932)

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Unlike adult mouse or rat brain, the immature neural tissues of the newborn animal are highly sensitive to ionizing radiation and susceptible to Coxsackie B virus infection. Susceptibility of mature brain is increased following ionizing radiation. This increase

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