

Title: Malabsorption Due to Paramomycin

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Paramomycin (Humatin<sup>R</sup>) is a non-absorbable antibiotic structurally related to neomycin. The antibacterial spectrum of the two drugs is similar and their clinical applications are generally the same.

Neomycin is known to produce reversible malabsorption in man (1). We have recently shown that malabsorption of xylose and sucrose begins within 6 hours of a single small dose of neomycin in Thai people (2). Histologic and enzyme histochemical abnormalities of the small bowel epithelium occur. Bacteria-like bodies accumulate within macrophages in the lamina propria with continued drug administration. All changes revert to normal when neomycin is stopped.

The present study was undertaken to evaluate the potential of paramomycin to induce functional and structural abnormalities of the small bowel in man. Malabsorption due to paramomycin administration is, to our knowledge, previously unreported.

#### Material and Methods:

Subjects-Seven normal Thai females, mean age 19.1 (16-29) years, with no history of recent antibiotic ingestion gave informed consent for the studies described below. Subjects were hospitalized and given 2 grams of paramomycin\* (approximately 50 mg/kg) daily.

Five hour urinary xylose excretion and 2 hour serum xylose concentration were measured (3) after an oral dose of 25 grams of d-xylose. Sucrose tolerance tests were performed as previously described (2) and the rise in blood total reducing substance (hereafter termed blood sugar) determined by a modification of the Hoffman method adapted to the autoanalyzer (4). Fecal fat content in 4-6 day collections marked by carmine red dye was measured by the method of van de Kamer et al (5). During the study period the usual low fat Thai diet (6) was supplemented with 75 grams of butter daily.

Jejunal biopsies were obtained with the Crosby-Kugler capsule (7) from the region of the ligament of Treitz. Biopsies were taken after a 12-14 hour fast, the morning after a 30-40 gm fat meal. Specimens were oriented on monofilament plastic mesh, placed in Bouin's picroformol acetic fixative and examined with a stereoscopic dissecting microscope. Cryostat sections were stained with Oil-red-O for neutral fat. Paraffin sections were cut at 5 microns and stained with hematoxylin and eosin. Mac Callum-Goodpasture and Feulgen stains were employed on selected material.

\* Paramomycin sulfate was a gift of Parke, Davis, and Co.

## RESULTS

### Absorption Tests:

D-Xylose: Table 1 and figures 1 and 2 show the effect of paramomycin on urinary xylose excretion and serum xylose concentration. No effect was apparent for the first 2 days on drug. Thereafter, there was a significant decrease in both urinary excretion and serum concentration.

Sucrose Tolerance Test: Figure 3 shows the effect of paramomycin on the maximum rise in blood sugar during a sucrose tolerance test. There was considerable variability in the maximum rise during the control period, however, no subject had a flat response (rise in blood sugar of less than 20 mg%). During administration of the drug, 5 of the 7 subjects had a flat response and the maximum rise was blunted in another (PT). No effect occurred in the remaining subject (SW).

Fecal Fat Excretion: There was no effect of the antibiotic on fecal fat excretion (figure 4). In fact, fecal fat content during drug administration was lower than the control value in 4 subjects.

Tissue Examination: Control biopsies conformed to the previously described Thai norm (2). In 6 hour biopsies the epithelial layer contained many polymorphonuclear leucocytes and round cells. There were numerous intracytoplasmic basophilic particles and bacteria-like structures within columnar epithelial cells near the villus tips (figure 5). There was nuclear shrinkage and cytoplasmic clumping, but these changes were quite variable from patient to patient. There were many mitoses in the crypts. The lamina was edematous.

In biopsies obtained on the 7th day of drug administration (figure 6) the villus tips appeared blunt and were crowded with mononuclear phagocytes containing bodies similar to these previously described in neomycin induced malabsorption (2). The alteration in columnar cell morphology described above was present but to a lesser extent.

The columnar epithelial cells appeared normal in biopsies obtained 7 days after the final dose of drug. Phagocytes in the lamina propria were much less conspicuous.

### DISCUSSION:

Paramomycin is one of the group of amino-glycoside antibiotics and has structural similarities to neomycin, streptomycin, and kanamycin (9). In its antibacterial spectrum, clinical application, and potential toxicity it most resembles neomycin. It is strange that malabsorption due to paramomycin is not previously reported while several groups of workers have shown the potential of neomycin in inducing malabsorption (1, 10-11). Messinger and Samet (12) did show that paramomycin administration resulted in lowering of serum cholesterol as does neomycin, however, no investigation of intestinal function was conducted,

The present report demonstrates that paramomycin administration causes malabsorption of xylose and sucrose. At the dosage used, no effect on fecal fat excretion was noted. Since diarrhea is not uncommon in subjects receiving more than 3 gm per day of paramomycin (13), it would not be surprising to find steatorrhea with higher doses of drug. This would be consistent with the dose dependent effect of neomycin on fecal fat excretion (10, 13). Neomycin, however, even in doses of 1-2 grams per day in Thais may cause increased fecal fat excretion (2).

In comparison to our previous data on the effects of neomycin in Thai subjects (2), paramomycin administration causes less disruption of function. Malabsorption within hours of a single dose of paramomycin was not observed. Histologic changes were qualitatively similar but quantitatively less striking than observed with neomycin. Figure 7 shows the effect of the two drugs, administered 4 months apart, in a single patient. It is clear that neomycin produces more profound abnormalities of function.

The mechanism by which neomycin and paramomycin cause malabsorption is not known. The fact that 2 structurally related drugs with the same mechanism of action (15), cause intestinal malfunction suggests that an idiosyncratic reaction is not involved. Suppression of bacterial flora or overgrowth of non-susceptible organisms is unlikely since neomycin induced malabsorption is detectable within hours. Further more, 2-4 grams of tetracycline daily did not produce similar abnormalities of function or structure in Thai subjects (unpublished data). Although other mechanisms, such as alteration of bile salts (16) or abnormal lipolysis (17) have been proposed, it seems probable that these drugs directly affect protein synthesis in human intestinal epithelial cells as they affect sensitive bacterial organisms (2).

The clinical significance of drug-induced malabsorption is uncertain. The relative importance of suppression of nitrogen-forming bacteria and induced azotorrhea by neomycin or paramomycin in the therapy of hepatic coma has not been established. If the latter factor is of importance, neomycin might be the drug of choice since it appears to cause more profound malabsorption. On the other hand, if antibacterial activity is of greater significance, absorption of sugar and fat would probably be less effected by paramomycin and general nutrition less disturbed. This would be of major importance in poorly nourished cirrhotic patients.

The exact nature and significance of the intercellular bacteria-like bodies which accumulate in macrophages in the lamina propria of the Thai bowel during the administration of either neomycin or paramomycin is unknown. If these are truly bacteria, some breakdown of the normal defenses of the intestinal mucosa would appear to take place. Whether or not this invasion of the lamina propria would increase susceptibility to infection is undetermined. In the short term studies reported here, no serious complications occurred. The effects of long term antibiotic administration, however, in relation to infection and the reversibility of the induced functional defects remain to be studied.

#### SUMMARY:

The effects of 2 gm per day of paramomycin on intestinal function and structure in 7 normal Thai females was studied. Both xylose and sucrose were malabsorped after 2 days on drug, whereas no effect on fecal fat excretion was found. Histologic abnormalities of the villus epithelial cells, and the appearance of many bacteria-like structures within macrophages in the lamina propria were observed during drug administration. These functional and structural changes were similar, but less profound than those found in neomycin-induced malabsorption in Thais. All effects were transient and disappeared following cessation of drug administration.

Table I  
Effect of Paramomycin on the 25 gram D.Xylose Tolerance Test

Subject	Urine Xylose, grams per 5 Hours			2 Hour Serum Xylose, mg per 100 ml		
	Control	Paramomycin*	Recovery	Control	Paramomycin*	Recovery
BU	7.05,7.41,5.42	5.21,3.19	1.36	42.9,48,39.4	26.5,23.1	13.1
NO	4.32	1.36	2.48,2.52	37.7	14.3	18.2,25
PN	7.37,6.78,7.78	4.97,5.18	6.76,7.34	56.7,37.8,41.8	31.7,31.7	40.7,51.7
PT	7.35,7.17	4.74	4.64,6.06,4.94	55.4,66	50	50.46,9,49.2
RA	4.63	3.23,3.02	5.91,5.67,6.03	27.7	28.2,26.1	28.3,39.6,4 0.6
SI	4.80,3.41	3.36,2.47	2.95,4.39	37.3,29.0	22.5,22.5	27.0,33.6
SW	6.94	2.54	4.30	53.6	31	32
Mean	5.88 ± 1.10+	3.42 ± 1.24	4.28 ± 1.52	43 ± 10.8	28.8 ± 3.4	33.1 ± 12.2
"P" value ‡	< 0.01	0.02	< 0.01	NS§		

\* Day 3-5 on Drug

+ 1 S.D.

‡ Significance of difference between groups compared

§ Not significant at .05 level

FIG. 1. EFFECT OF PAROMOMYCIN ON URINARY EXCRETION OF D-XYLOSE, MEAN AND RANGE  
 25 gram Xylose Test, 5 HOUR URINE COLLECTION

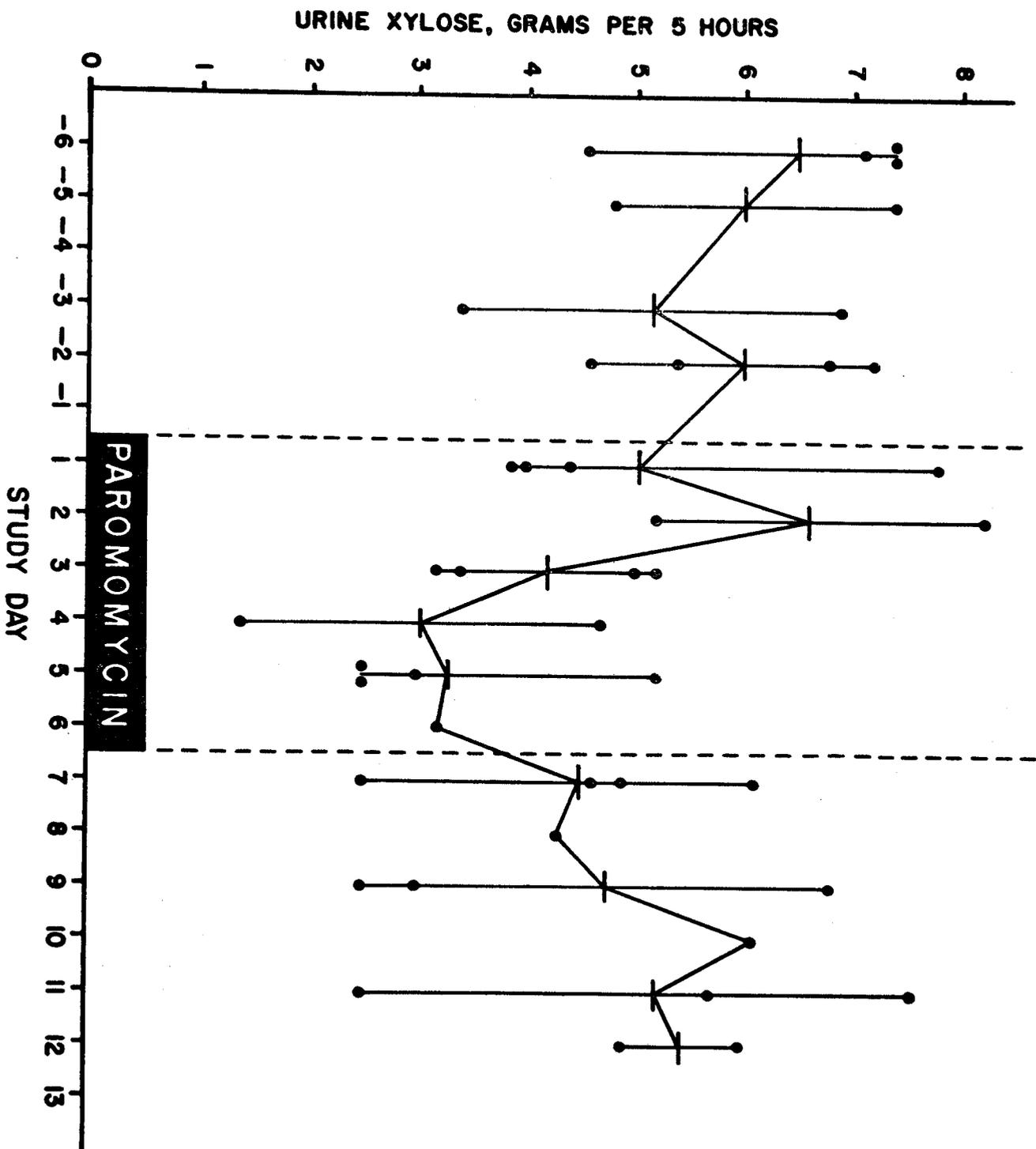


FIG. 2. EFFECT OF PAROMOMYCIN ON SERUM XYLOSE CONCENTRATION 2 HOURS AFTER ORAL ADMINISTRATION OF 25 GRAMS OF D-XYLOSE

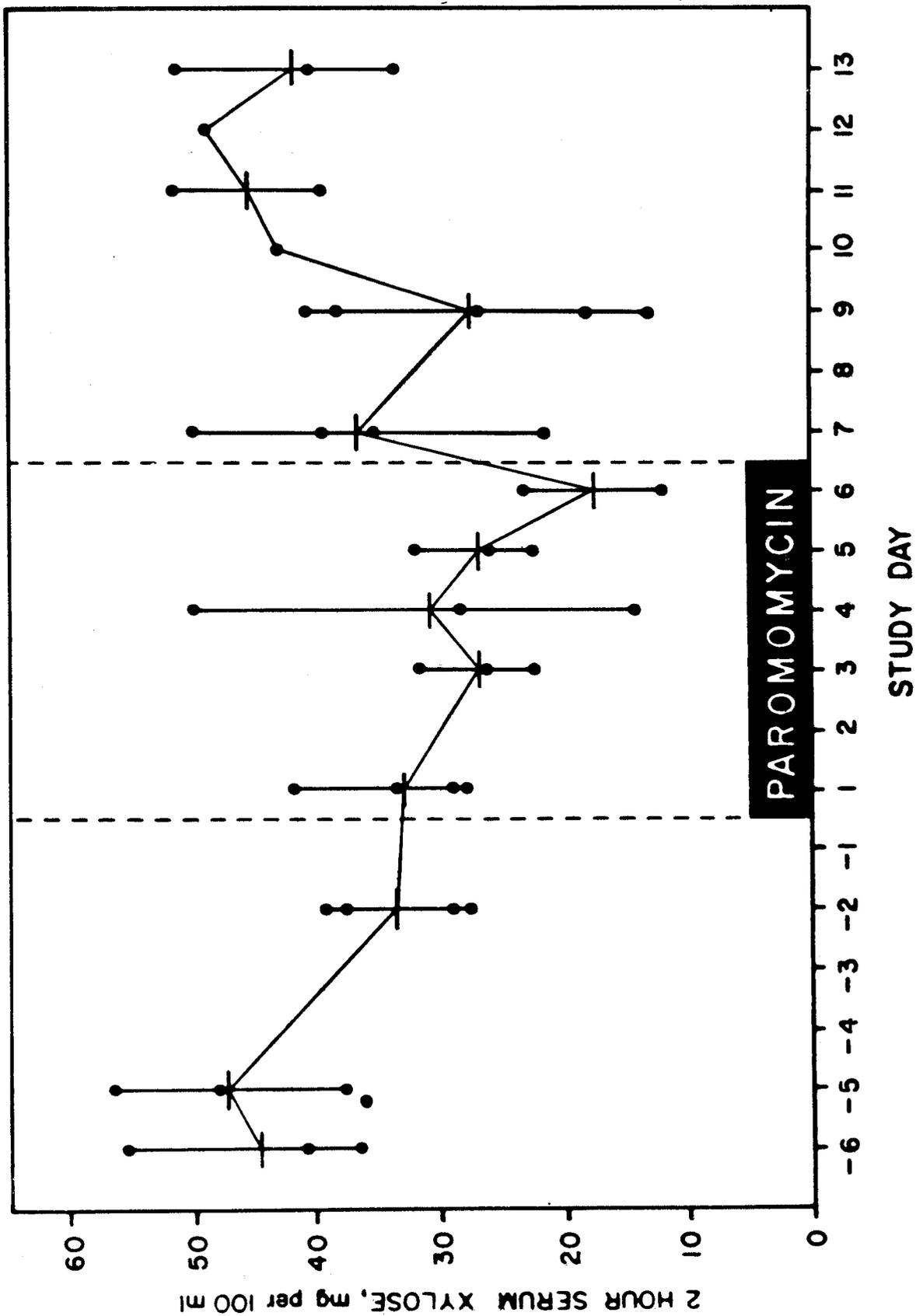


FIG. 3. EFFECT OF PAROMOMYCIN ON THE SUCROSE TOLERANCE TEST. MAXIMUM RISE OF BLOOD SUGAR FOLLOWING SUCROSE, 1.5 gm./KBW, DURING A 90 MINUTE TOLERANCE TEST

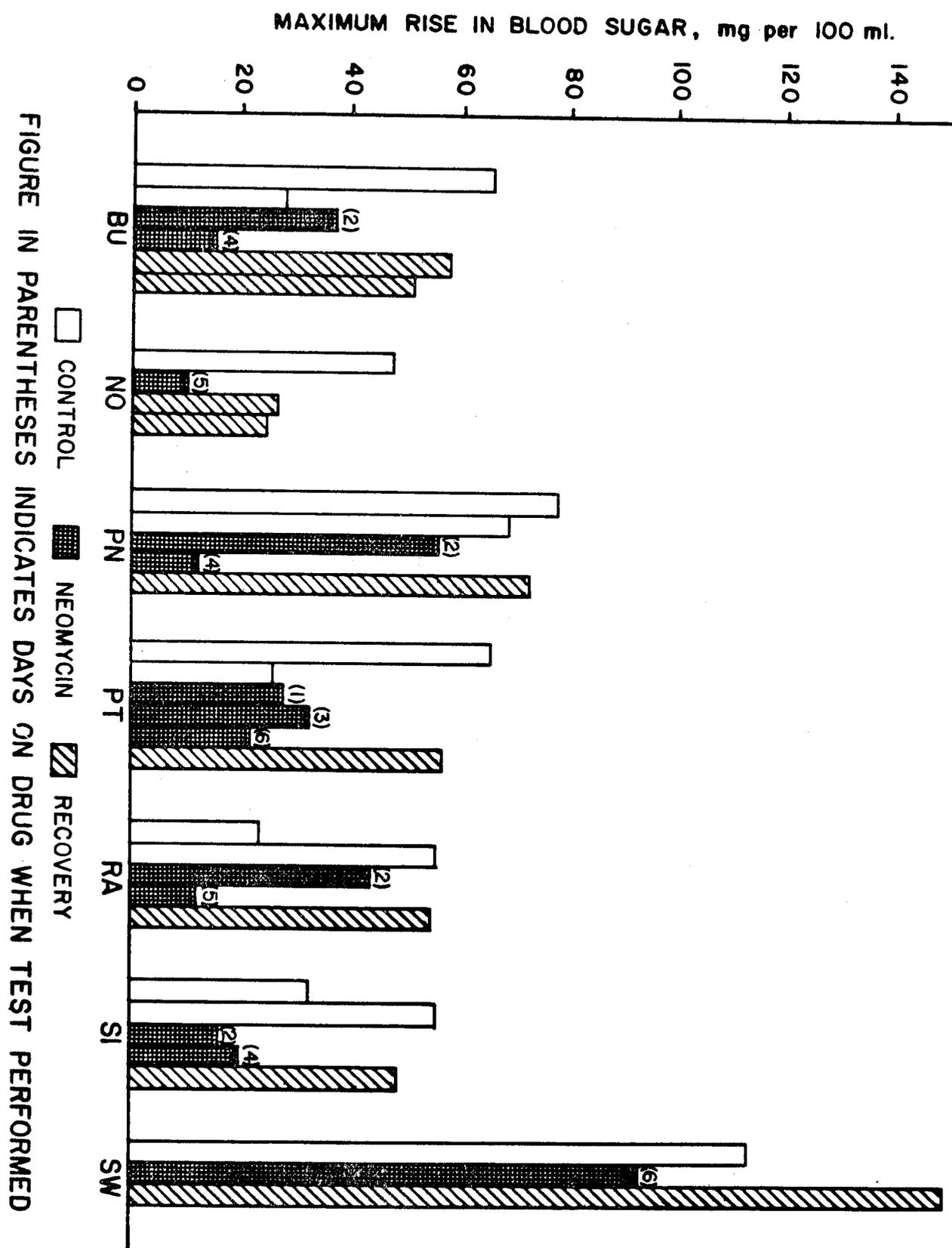


FIG. 4. EFFECT OF PAROMOMYCIN ON FECAL FAT EXCRETION

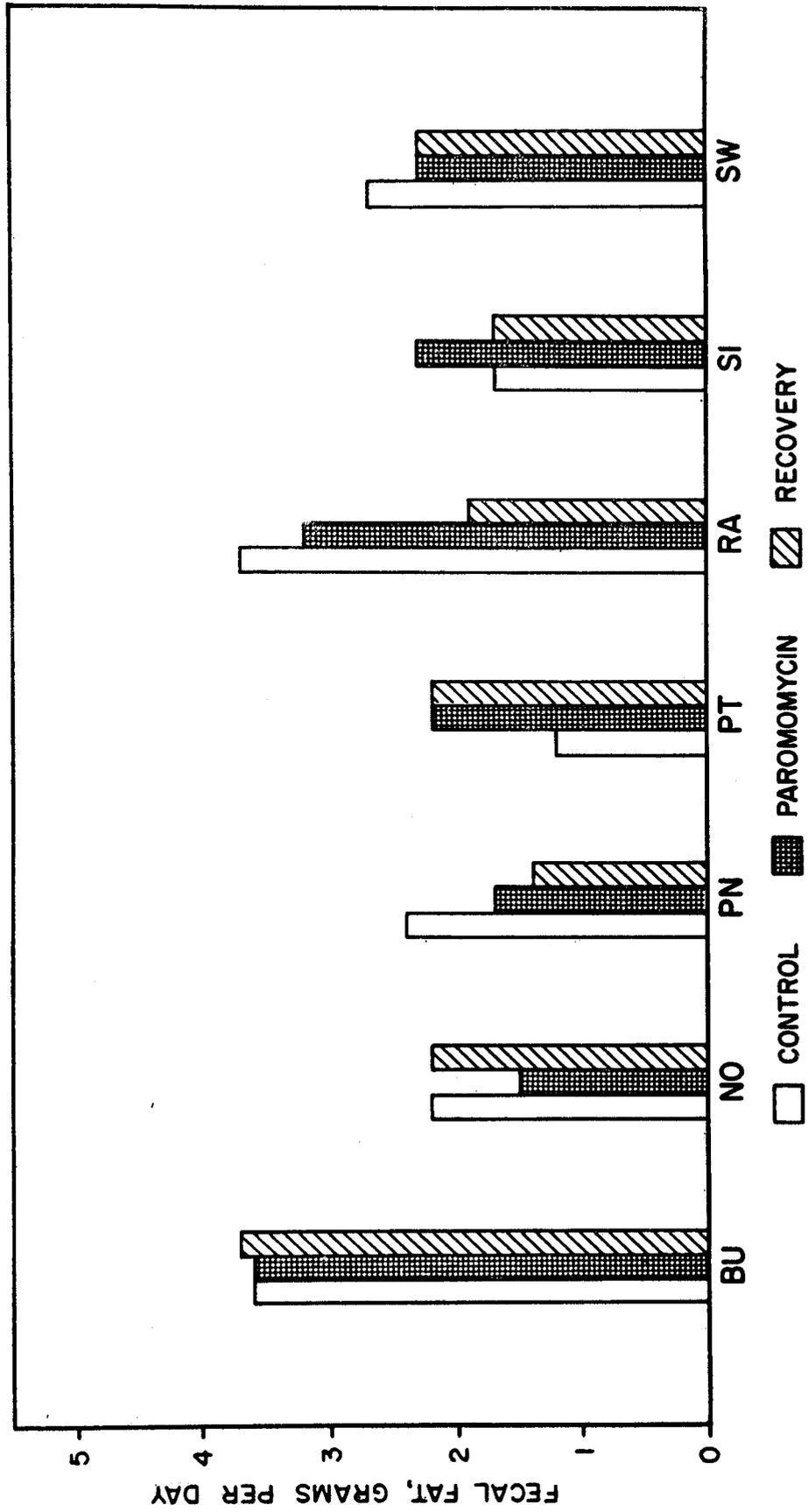


Figure 5. Hematoxylin and eosin, xl, 1000. Control biopsy showing normal jejunal epithelium on left. Biopsy on right taken 6 hours after oral paramomycin administration. Note disruption of epithelial pattern and cellular debris and intracellular bacteria-like structures.

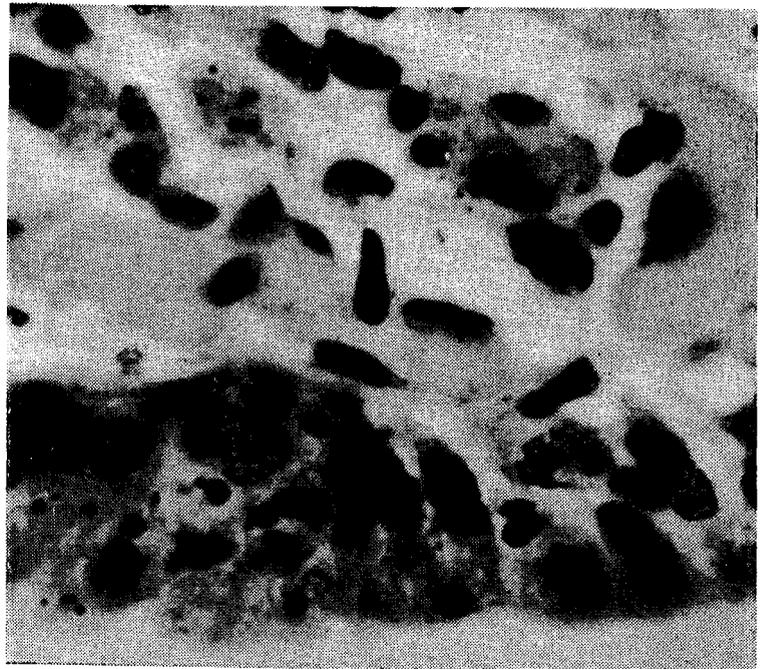
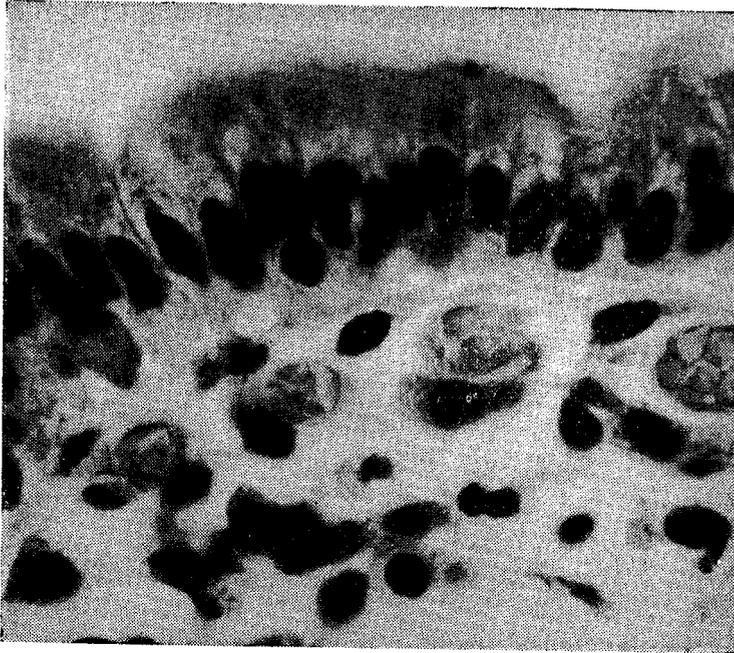


Figure 6. Hematoxylin and eosin, x1,000. Jejunal biopsy taken 7 day after cessation of paramomycin administration. Note return of epithelial pattern toward normal.

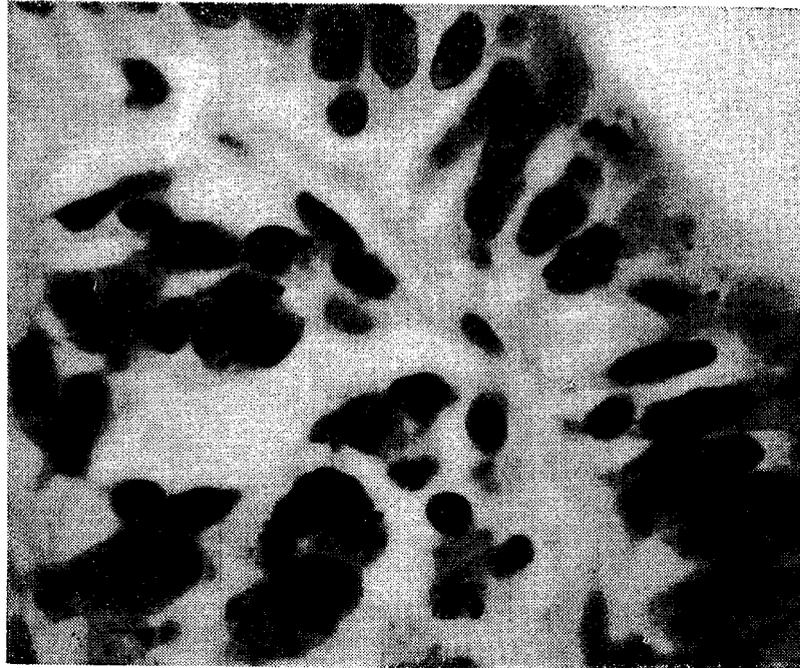
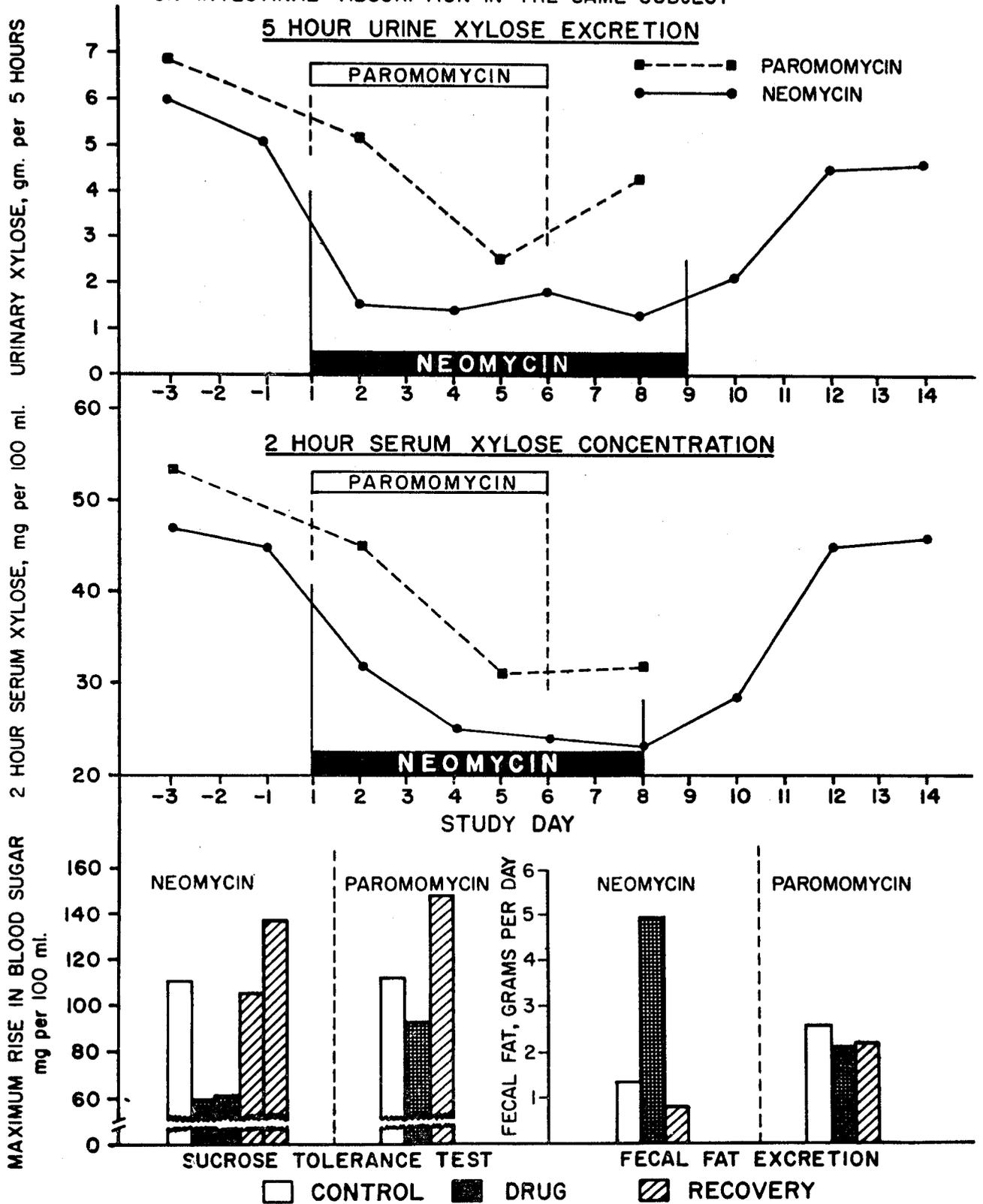


FIG. 7. COMPARISON OF THE EFFECT OF NEOMYCIN AND PAROMOMYCIN ON INTESTINAL ABSORPTION IN THE SAME SUBJECT



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