Effect of Aminopterin and Antibiotics on Disaccharidase Activity of the Rat Small Bowel

Since 1961 we were able to reproduce an experimental enteropathy by treating rats with antifolic drugs or antibiotics, in order to study the anatomical, functional and histochemical disorders that these drugs may cause in the small bowel. Anyway, in the assessment of this so-called 'therapeutic or jatrogenic enteropathy', the study of intestinal disaccharidases, although possibly interesting, received slight attention.

The purpose of this investigation is to determine whether or not intestinal disaccharidases can undergo some changes in course of administration of antifolic drugs or antibiotics.

Material and methods. 110 rats of the same age and sex, were divided into 5 groups and treated as summarized in Table I. At the end of the treatment the rats were sacrificed, and the disaccharidases determined. A fragment of intestinal mucosa was frozen for histochemical studies. The technique of DAHLQUIST and BRAUN[1], modified by Jos et al.[2], was used. The homogenate obtained by scratching the mucosa was adequately diluted and incubated with the substrate. The released glucose was determined by the glucose-oxydase method (AURICCHIO et al.[3], DAHLQUIST[4]).

Results. (1) After 7 days' treatment, both antibiotics and aminopterine caused a marked decrease of all disaccharidases which have been searched. (2) The prolonged treatment produced changes mainly in the lactase; highly indicative was the lactase deficiency after 60 days' antibiotic therapy. (3) The results obtained with both methods (chemical analysis and histochemical technique) were overlapping. (4) The antibiotics used, tetracycline sulphate and neomycine, caused the same lesions.

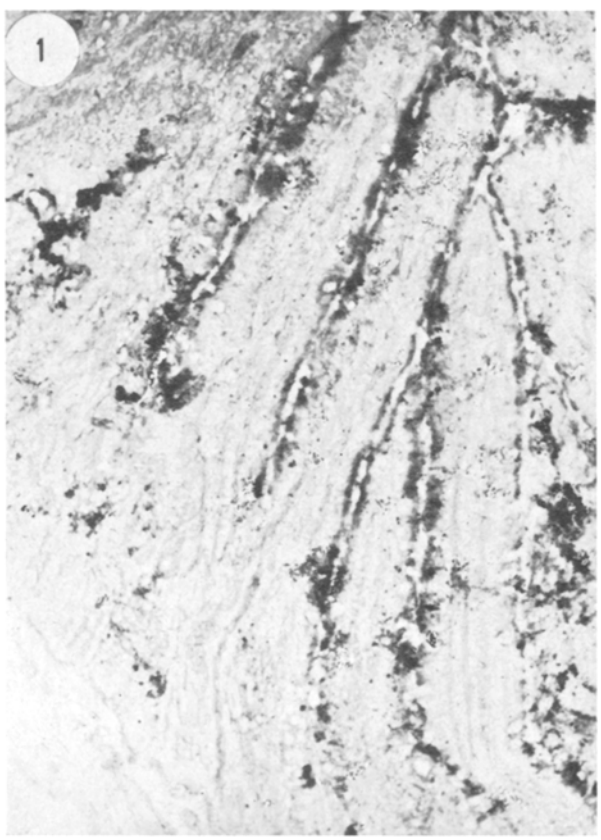
Table 1. Antibiotic and Aminopterin treatment in 5 groups of rats

Group	No. of rats treated	Dose mg/kg body wt.	Drug administered	Duration of treatment (days)
I	25	0.2	Aminopterin	7
II	25	0.04	Aminopterin	60
III	25	50	Antibiotic	7
IV	25	5	Antibiotic	60
V	10	2 ml	Saline	7 or 60

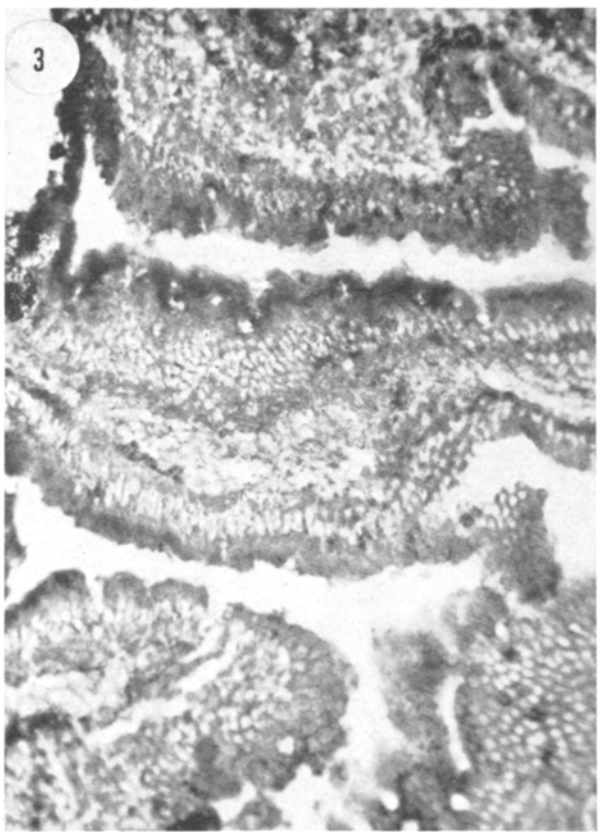
Table II. Disaccharidase activity of mucose homogenates[a]

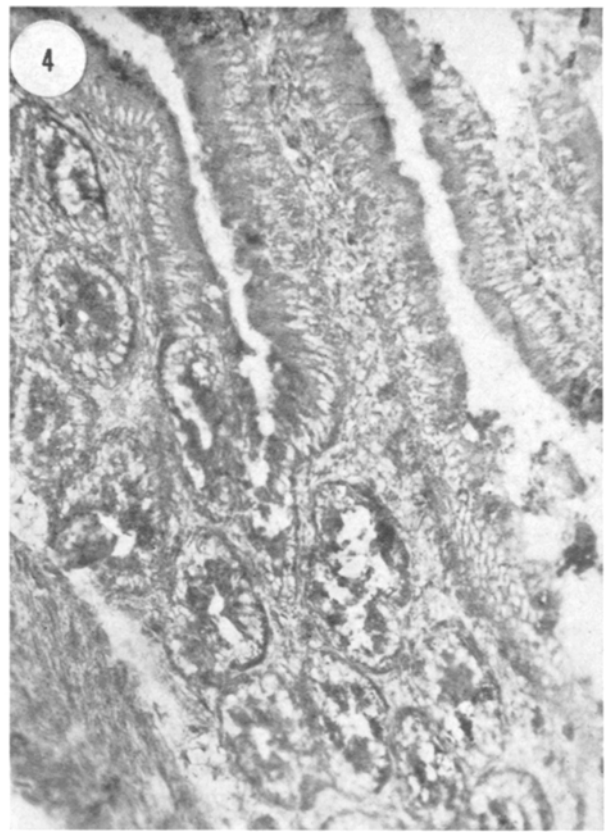
Aminopterin	Day 7[b]	P	Day 60[b]	P
Lactose	0.096 ± 0.08	>0.05	0.343 ± 0.115	>0.05
Sucrose	0.097 ± 0.340	>0.05	2.390 ± 0.316	N.S.
Maltose	1.664 ± 0.392	0.001	3.539 ± 1.686	N.S.
Antibiotic				
Lactose	0.216 ± 0.031	<0.001	0.440 ± 0.020	<0.001
Sucrose	1.353 ± 0.093	>0.01	2.841 ± 1.414	N.S.
Maltose	1.778 ± 0.031	0.001	2.907 ± 0.118	>0.05
Control rats[c]				
Lactose	0.956 ± 0.054			
Sucrose	2.610 ± 0.024			
Maltose	3.352 ± 0.077			

[a] Results expressed as mean ± S.E. Units are μmole of disaccharide hydrolysed per min per g (wet wt.) of mucosa. Comparison by Student's *t*-test. [b] Results of 10 experiments. [c] Results of 6 experiments.



Figs. 1 and 2. Small bowel of rats of the control group. Histochemical demonstration of sucrose activity (black staining). × 90.





Figs. 3 and 4. Small bowel of rats treated with aminopterine for 60 days. There is no obvious difference to the picture of the control group. × 160.

The results, reported in the Table II, are in full agreement with the observations of others; actually it has been demonstrated that antibiotics (especially neomycine and kanamicyne) and antifolic drugs can be responsible for a deficit of intestinal disaccharidases.

The histological changes observed in the course of the drug enteropathy make easier the assessment of the results: the massive treatment for 7 days caused a severe damage of the intestinal mucosa, with a complete upsetting of its normal picture; on the contrary, the chronic treatment for 60 days brings about slighter anatomical lesions. The high dose treatment gives rise to a marked decrease of the whole disaccharidase, whilst the chronic therapy results in an impairment of the single lactase, which is the most unstable intestinal disaccharidase.

However, we have previously observed various degrees of mucosal damage in the same experimental condition, while studying some enzymatic activities closely related to the respiratory function. The degree of damage and the number of impaired enzymes obviously depend on the type of drug used and on the doses given (SCHIRALDI, MARANO et al.[5,6]). It has been stated that both antibiotics and antivitamins interfere in the cycle of the cellular life, since they can block some vital enzymatic processes of the cell which seeks a new suitable condition, by compensating the deficit with other enzymes. This behaviour, previously observed for the phosphatases, has been demonstrated in the course of chronic treatment with antibiotics; sometimes the saccharidase content is higher than in the control group (Figures 1–4).

Moving from the experimental field to human pathology, this research can provide a further explanation of the pathogenesis of the 'therapeutic enteropathy', which resembles, to a certain extent, the experimental enteropathy of the rat. Moreover, the lactase deficiency due to a prolonged antibiotic treatment may suggest a new explanation of the lactase deficit oberved in human pathology, either isolated or associated to a sprue-like syndrome (SCHIRALDI et al.[7]).

Riassunto. Sono state studiate, con tecnica istochimica e con dosaggio enzimatico, alcune disaccaridasi (lattasi, saccarasi, maltasi) nell'intestino di ratto trattato con dosi scalari di antibiotici e antifolici (aminopterina). Si è osservato che il trattamento massivo con tali farmaci altera tutti gli enzimi studiati; il trattamento refratto, in dosi più basse ma per lungo tempo, determina deficit solo della lattasi.

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[1] A. DAHLQUIST and A. BRUN, J. Histochem. Cytochem. *10*, 294 (1962).
[2] J. JOS, J. FREZAL, J. REY, M. LAMY and R. WEGMANN, Ann. Histochem. *12*, 53 (1967).
[3] S. AURICCHIO, A. RUBINO, R. TOSI, G. SEMENZA M. LANDOPT, M. KISTLER and A. PRADER, Enzym. Biol. Clin. *3*, 193 (1963).
[4] A. DAHLQUIST, J. clin. Invest. *41*, 463 (1962).
[5] O. SCHIRALDI, N. GRIMALDI and R. MARANO, Archo. ital. Anat. Istol. patol. *36*, 274 (1962).
[6] O. SCHIRALDI, R. MARANO, N. GRIMALDI and A. CAPURSO, Archo. ital. Anat. Istol. patol. *37*, 180 (1963).
[7] O. SCHIRALDI, G. PASTORE, O. MANGHISI and R. MARANO, Policlinico, Sez. Prat. *46*, 343 (1969).