when stained by the Feulgen and by the Van Kossa methods. These latter technics indicate the protein, mineral (phosphate, probably calcium phosphate) and nuclear debris content of the casts. The lesions are similar in appearance from 3 to 10 days following the injection of spermine although at 10 days large lakes of mineral deposits (probably calcium phosphate) are noted within the lumina of the tubules of the distal nephron.

In all sections studied no glomerular, vascular or stromal changes were evident and lesions in the kidney as described above were similar in sacrificed animals to those observed in animals dying after the injection of spermine.

Other tissues failed to reveal significant morphologic change except for the presence of rare foci of necrosis in the liver of several animals surviving for 4 days after the spermine injection.

Animals injected with spermidine, putrescine and cadaverine failed to reveal any morphologic changes in the viscera.

Conclusions. Spermine administered parenterally is highly active in producing renal injury in mice, rats, and rabbits. This property was not observed for spermidine, putrescine, or cadaverine.

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Studies on Nicotinamide Inhibitors. (19648)

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Pyrazinoic acid was reported to be active in the cure of human pellagra(1). This compound, however, was later found to have no nicotinic acid activity for increasing the V-factor of human blood(2). Other investigators reported pyrazinoic acid and, in some cases, the corresponding amide to be inactive for the cure of canine blacktongue(3), growth of isolated pea roots(4), and for the growth of various microorganisms, for example, *Leuconostoc*(5), *Pasteurella*(6), *B. dysenteriae*(6), and *Proteus vulgaris*(7). These compounds have not been reported as nicotinamide antagonists for microorganisms.

Of a series of pyrazine and pyridine derivatives which were assayed for antinicotinamide activity with *Lactobacillus arabinosus*, strain 17-5, pyrazinoic acid, pyrazinamide and 2 sulfanilamido-5-nitropyridine are shown to be reversible inhibitors of nicotinamide. Experiments with pyrazinamide on rats and chicks are also reported.

Experimental methods. The details of the microbiological assays and the animal tests are given in a previous publication(8). The compounds tested for inhibitory activity with *L. arabinosus* were initially assayed at levels of 0.5, 1.0, 3.0, and 5.0 mg per ml alone and in the presence of 0.02 μg per ml of nicotinamide. This level of nicotinamide alone gives approximately half-maximum growth. The compounds showing inhibition were retested at 7 levels from 0.5 to 15 mg per ml against 7 levels of nicotinamide ranging from 0.005 to 0.2 μg per ml. An inhibition index was then calculated, which represents the ratio of inhibitor to vitamin producing a 50% inhibition of growth. The compounds were ad-

TABLE I. Inhibition of Nicotinamide Response of *L. arabinosus*.

Compound	Nicotinamide conc., γ/ml	Inhibition index × 1000
Pyrazinamide	.005	200
	.010	200
	.020	250
Pyrazinoic acid	.005	100
	.010	100
	.020	150
2-sulfanilamido-5-nitropyridine	.005	250
	.010	200
	.020	250

TABLE II. Reversibility of Pyrazinamide Inhibition of Nicotinamide.

Pyrazinamide conc., γ/ml × 1000	Nicotinamide conc., γ/ml	ml of .1 N NaOH A	ml of .1 N NaOH B
	.005	2.24	2.26
1	.005	1.91	1.87
1	.010	2.40	2.36
2	.010	3.83	3.80
2	.010	2.00	2.01
	.020	4.15	4.13
5	.020	5.90	5.92
5	.020	2.92	2.87
	.040	7.98	7.90

TABLE III. Effect of Pyrazinamide on Nicotinamide Growth Response in Rats.

Treatment	Initial wt and No. ( )	Avg gain and No. alive ( ) 2 wk	4 wk
Basal diet	40(9)	14(9)	18(7)
+50 γ Nicotinamide daily	40(9)	25(9)	53(9)
+100 γ " "	43(9)	36(4)	84(4)
+200 γ Pyrazinamide "	40(9)	15(9)	23(9)
+10 mg " "	40(9)	17(9)	30(9)
+10 mg Pyrazinamide +50 γ Nicotinamide	41(9)	21(9)	50(9)

ministered orally once each day to the rats and chicks in aqueous or 25% ethanol solutions at the levels indicated in the tables.

Results. The following 34 compounds were found to be without anti-nicotinamide activity: Pyridine-3,5-dicarboxylic acid, Pyrazine-2,3-dicarboxylic acid, 4-Methylpyridine-2,3-dicarboxylic acid, Pyrazine-2,3-dicarboxamide, 3-Bromopyridine, 2-Methyl-3-amino-4,5 bis (aminomethyl) pyridine • 3 HCl, N-Thiazolylpyrazinamide, N, N Dimethylpyrazinamide, N-Methylpyrazinamide, N-Pyrazinylthiourea, N-Methylolpyrazinamide, N-Diethyl pyraiznoylaspartate, N-Pyrazinoylpiperidine, N-Isobutylpyrazinamide, N-(2-pyridyl) pyrazinamide, N (3-pyridyl) pyrazinamide, N-Phenylpyrazinamide, N-Hexadecylpyrazinamide, 3-Pyrazinoylamidoquinoline, N-(β-hydroxyethyl)N′ - pyrazinoylethylenediamine, 3-Hydroxypyridazine-6-carboxamide, 2-Pyrrolidone-5-carboxamide, 2-Chloroquinoxaline-3-carboxamide, 1-Thiazolylpyrrole-α-carboxamide, N-Thiazolylthiophene-α-carboxamide, Desoxypyridoxine HCl, Salicylamide, Furoic acid, Furanilide, Pyrazinohydrazide, 1-Carbethoxy-4(α,β-dicarbethoxyethyl) piperazine HCl, N-(p-Methoxybenzyl) pyrazinamide, Pyrazinohydroxamic acid, Ethyl N-pyrazinoyl-β-alanate. None of the compounds showed any growth stimulating activity for *L. arabinosus*.

Three compounds, pyrazinamide, pyrazinoic acid and 2-sulfanilamido-5-nitropyridine reversibly inhibited nicotinamide for this microorganism. The inhibition index for each compound was constant over a 4-fold range of concentration of the vitamin as shown in Table I. Extension of the range was not feasible because of the insolubility at higher concentrations of the compounds. Table II gives some typical data illustrating the reversibility of the inhibitions, using pyrazinamide as the example.

The effects of pyrazinamide on the response of rats and chicks to nicotinamide are shown in Tables III and IV. No clear-cut inhibition in these species by the use of this compound could be demonstrated. A slight, probably non-specific interference, in the response of the chick to nicotinamide was observed.

Discussion. The early work, previously mentioned, on the lack of nicotinamide activity of pyrazinamide and pyrazinoic acid for several species of bacteria and animals, has been confirmed and extended. It appears that these compounds, under the conditions described for *L. arabinosus*, are relatively weak inhibitors, which can be readily reversed by small amounts of nicotinamide. A number of closely related compounds were found to be inactive in this respect.

The animal tests would indicate that pyrazinamide is not an antagonist for rats or chicks. It was not found to be toxic for dogs at the levels used by Waisman *et al.*(3). It

TABLE IV. Effect of Pyrazinamide on Nicotinamide Growth Response in Chicks.

Level of nicotinamide, γ daily	Level of pyrazinamide, γ daily	Initial wt and No.	Avg gain and No. alive ( ) 2 wk	4 wk
50		40 (27)	17 (22)	41 (14)
50		42 (10)	40 (10)	80 (9)
100		40 (28)	35 (25)	99 (21)
200		39 (37)	45 (37)	166 (30)
	200	40 (8)	4 (6)	— (0)
	1 mg	39 (9)	25 (8)	44 (6)
	10	40 (19)	19 (15)	35 (7)
	100	38 (10)	9 (8)	40 (7)
200	1	39 (9)	37 (8)	111 (7)
50	10	42 (10)	28 (10)	57 (9)
100	10	42 (10)	38 (8)	82 (8)
200	10	40 (19)	46 (18)	119 (17)
100	100	38 (10)	28 (9)	96 (9)
200	100	38 (10)	30 (10)	126 (10)

is improbable that large enough doses could be given to animals to induce pellagra, if its inhibition index for *L. arabinosus* is an indication of the amount required.

Summary. 1. Of a series of 37 compounds tested, pyrazinamide, pyrazinoic acid and 2-sulfanilamide-5-nitropyridine were found to be nicotinamide antagonists for *L. arabinosus*. 2. Pyrazinamide was not an antagonist for rats or chicks.

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Changes in Glucose Tolerance as an Index of Improvement after Electroshock Therapy. (19649)

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Impairment of glucose tolerance in many patients with manic-depressive, involutional and schizophrenic psychoses is well known. An attempt was made to evaluate the possible use of changes in glucose tolerance after electroshock therapy as an objective index of clinical improvement.

Material and methods. Twelve patients, ranging in age from 32 to 73 years, were the subjects; 10 were women. One of the patients was known to have had diabetes mellitus for a decade; the disease was discovered here in 2 others. The patients were given 3 electroshock treatments weekly in the numbers indicated (Table I). All patients were much improved following treatment. Studies of the blood sugar were made after oral administration of 100 g of dextrose before the first and again 5 to 10 days after the last treatment; the method of Folin and Wu(1) was used.