Summary. 1. Quinidine sulfate at a concentration of 1 x 10^{-3} M strongly inhibits the uptake of glucose and fructose by intact rat diaphragm under anaerobic conditions. 2. Quinidine is without effect on endogenous anaerobic lactic acid production by rat diaphragm. 3. Glucose at a concentration of 1 mg/ml or 4 mg/ml markedly stimulates anaerobic glycolysis while fructose at a concentration of 5 mg/ml produces only a slight stimulation. 4. Stimulation of glycolysis by glucose or fructose is abolished by 1 x 10^{-3} M quinidine and partially inhibited by 5 x 10^{-4} M quinidine. 5. It is suggested that quinidine inhibits glucose or fructose uptake prior to the step at which these sugars and glycogen share a common metabolic pathway.

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In vitro Effect of Two Pantheine Analogues on Co-Enzyme A Requiring Systems.* (22704)

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The use of metabolic analogues in the study of intermediary metabolism is a method of long standing. That an antagonist of a metabolite active in a multitude of systems would affect each system to varying degrees is predictable in view of the variation in physical constants pertaining to substrate-enzyme, apo-enzyme—co-factor relationships. In the field of vitamin metabolism, experimental data supporting this prediction has only recently been forthcoming(1-4). Analogues have been found which have a very striking antagonizing effect on one or more pathways dependent on the normal metabolite. The same concentration of drug, however, has little effect on other such dependent systems (3,4). These extremes in affinity of metabolic analogues for various systems in which the normal metabolite participates are of great importance in regard to chemotherapy. The present communication extends these observations to analogues affecting pantothenic acid metabolism.

Experimental studies pertaining to the *in vitro* effect of 2 pantethine analogues, omega-methylpantethine and bis (beta-pantoyl-aminoethyl) disulfide on the ability of pigeon liver homogenates to acetylate sulfanilamide and to synthesize citrate from fumarate and pyruvate are presented in the Table. Although omega-methylpantethine inhibited sulfanilamide acetylation, a similar concentration of this compound was without activity against citrate formation. Increasing the concentration of omega-methylpantethine did, however, have some inhibiting effect on the ability of pigeon liver to synthesize citrate from pyruvate and fumarate. The addition of bis (beta-pantoylaminoethyl) disulfide to an aliquot of the same homogenate inhibited citrate formation. At this same concentration little effect was observed on sulfanilamide acetylation. Increasing the level of bis (beta-

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TABLE I. Effect of Omega-Methylpantethine and Bis (beta-Pantoylaminoethyl) Disulfide on Sulfanilamide Acetylation and Citrate Formation in Tissue Homogenates.*

Treatment		% original activity† Sulfanilamide disappearance‡	Citrate formation‡
None		100	100
Omega-methylpantethine	1.8×10^{-3}M	52	96
	5.5×10^{-3}M	46	86
Bis-(β-pantoyl) disulfide	1.8×10^{-3}M	91	51
	5.5×10^{-3}M	68	15

* All values are avg of 2 separate experiments run in duplicate.

† Control values were 2.68 μM sulfanilamide acetylated/hr/g wet wt in the case of sulfanilamide studies and 28.4 μM citrate formed 50 min./g tissue wet wt in the case of the citrate studies.

‡ Each reaction vessel contained: 250 mg pigeon liver, 0.01 M Mg^{++}, 0.154 M K^{+}, 0.02 M phosphate, 0.003 M ATP, 4.8×10^{-3}M L-cysteine, 0.03 M acetate, 5.8×10^{-6}M sulfanilamide and pantothenic acid analog as indicated, in a final vol of 2.9 ml. All components were adjusted to pH 7.4.

Each reaction vessel contained 40 mg pigeon liver, 0.01 M Mg^{++}, 0.154 M K^{+}, 0.02 M phosphate, 0.003 M ATP, 2.4×10^{-3}M L-cysteine, 0.03 M pyruvate, 0.03 M fumarate, 3.5×10^{-3}M sodium monofluoroacetate and pantothenic acid analog as indicated in a final vol of 2.9 ml. All components were adjusted to pH 7.4.

pantoylaminoethyl) disulfide produced inhibition in the acetylation process. Thus, with 2 analogues at the proper concentration, a striking inhibitory effect on one Co-enzyme A dependent system is observed with only slight interference with another Co-enzyme A dependent system.

Co-enzyme A competitively protects transacetylase from inhibition by high concentration of bis (beta-pantoylaminoethyl) disulfide (1). We have confirmed these findings and have extended them by showing that Co-enzyme A protects both this system and that concerned with citrate formation against antagonism by either omega-methylpantethine or bis (beta-pantoylaminoethyl) disulfide (unpublished data). Thus, the mechanism of *in vitro* inhibition observed in the above cases, may be attributed to competition between the normal mercaptan, Co-enzymes A, and the related compounds, omega-methylpantethine and bis (beta-pantoylaminoethyl) disulfide.

It must be pointed out that the *in vitro* studies reported probably bear little relationship to the mechanism of carcinostasis observed with both of these compounds(5), since tumor inhibition is obtained with drug concentrations far below the levels used *in vitro*.

Summary. Omega-methylpantethine was observed markedly to inhibit sulfanilamide acetylation at concentrations which were ineffective against citrate formation in pigeon liver homogenates. With aliquots of the same homogenate, bis-(beta-pantoylaminoethyl) disulfide was observed to inhibit citrate formation at concentrations which were ineffective against sulfanilamide acetylation. In either case, higher concentrations of these compounds were effective in inhibiting both systems.

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