to the importance of the spleen in the hematopoietic system of each strain.

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Salicylates and Experimental Beryllium Poisoning. (19482)

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Acute beryllium poisoning in mice, readily produced by the intravenous injection of soluble beryllium salts, usually terminates fatally in 3 days(1,2). Death results from acute liver failure following hepatic focal and mid-zonal necrosis(1,3). Additional pathological changes in the kidney and spleen have also been described. Recently, aurintricarboxylic acid, a substance of relatively low toxicity, was found to be an effective antidote when it was administered to mice up to 8 hours after they had received LD_{95} amounts of $BeSO_4$ intravenously(2). This protection was attributed to its chelating and lake-forming properties. The present study was undertaken to ascertain if the salicylic acid portion of the aurintricarboxylic acid molecule would be as effective in reversing experimental beryllium intoxication.

Experimental. $BeSO_4$ was injected intravenously into young adult female CF#1 mice in an aqueous solution containing 0.07 mg Be per ml at a pH of 3.6-3.7. The animals were injected with 0.7 mg Be per kg, an amount which kills approximately 95% of the mice within 2 weeks. Compounds tested for antidotal properties were administered intravenously one hour later, except as otherwise noted. Control animals given only beryllium showed a 2.2% survival after 14 days with a 50% mortality time of 2.4 days.

Sodium salicylate was studied at various dose levels and the results, summarized in Table I, show this compound to be effective as an antidote when given in adequate doses either intravenously or intraperitoneally. Of the sodium salts of various analogues of salicylic acid tried, those without the ortho-hydroxy, carboxylic acid structure were uniformly ineffective. However, not all compounds with this grouping showed protective properties. Sodium *p*-aminosalicylate gave only equivocal results. Sodium gentisate, a product of salicylate metabolism(4), and its analogue, sodium 2,4-dihydroxybenzoate, were ineffective.

Disodium catechol disulfonate, which has been found to be effective in the treatment of experimental uranium poisoning(6), was partially successful.

Sodium salicylate afforded protection when treatment with 400 mg per kg was delayed 8 hours but not when treatment was postponed 24 hours. Pretreatment 8 hours before the beryllium was administered was ineffective, probably because of metabolism and excretion of salicylate during this period.

Discussion. The toxicity of beryllium to tissues has been ascribed by several investigators to its soluble, ionized form(1,5). Among the factors believed to be involved in effective antidotal action against beryllium ions is the chelating action of the ortho-hydroxy, carboxylic acid structure, which reduces the availability of the toxic ionized beryllium(7). Such chelation is presumed to occur with salicylate as well as with aurintricarboxylic acid, which in addition forms a stable lake. Undoubtedly, factors other than chelation are involved in successful protection against acute experimental beryllium poisoning. For example, on a molar basis about 35

TABLE I. Effect of Salicylate and Salicylate Analogs on Experimental Beryllium Poisoning in Mice.

Compound*	Dose level, mg/kg	No. mice	% survival at 14 days	Time to 50% death in days
Beryllium controls	—	90	2.2	2.4†
Sodium salicylate (Na *o*-hydroxybenzoate)	600	20	100‡	—
	400	39	79	—
	200	10	60	—
	40	10	0	2.5
Sodium salicylate (intraper.)	600	10	100	—
" *p*-aminosalicylate	660	10	20	2.9
	400	30	57	—
" *m*-hydroxybenzoate	600	10	40	2.4
" *p*-hydroxybenzoate	600	10	0	2.4
" *o*-chlorobenzoate	600	10	0	2.8
" gentisate (Na 2,5-dihydroxybenzoate)	660	10	0	2.4
	330	10	10	1.9
Sodium β-resorcylate (Na 2,4-dihydroxybenzoate)	660	10	0	1.4
Disodium catechol disulfonate (Na_2 1,2-dihydroxybenzene-3,5-disulfonic acid)	800	10	50	8.4
	400	10	50	13.4
	200	9	33	4.3
	80	10	20	2.4

* All compounds administered intrav. except as noted.
† Mean value of 9 experiments.
‡ No deaths after 60 days and 132 days, respectively, in 2 groups of 10 mice each.

times as much salicylic acid is required for antidotal action than aurintricarboxylic acid. Moreover, the amount of salicylic acid used (600 mg per kg) is roughly 75% of the median lethal dose while the comparable effective dose of aurintricarboxylic acid is about 11% of its LD_{50}. Whether suitable chelating compounds with or without lake-forming properties will be effective in the treatment of acute beryllium poisoning in man and further in the therapy of chronic beryllium granulomatosis needs to be established.

Although the ortho-hydroxy, carboxylic acid grouping is present in the dihydroxybenzoates, in the compounds tested the presence of the second hydroxyl group nullifies the antidotal action toward beryllium. To the extent that gentisic acid is a metabolite of salicylic acid (4 to 8% in humans(4)), the protective properties of the latter are diminished by salicylate degradation. The major metabolic products of salicylic acid are the conjugates with glycine and glucuronic acid, and the rates at which these are formed from beryllium-salicylate chelates are not known. Consequently, it cannot be predicted whether sodium salicylate would be therapeutically useful in human beryllium poisoning or whether it would be a hazard because of the translocation and possible release of toxic beryllium ions in more susceptible tissues.

Summary. Intravenously or intraperitoneally administered sodium salicylate in dose levels of 600 mg per kg is an effective antidote for acute beryllium poisoning in mice when given up to 8 hours after the administration of intravenous beryllium sulfate in LD_{95} amounts. Salicylate analogues without the ortho-hydroxy, carboxylic acid grouping were generally ineffective as were 2 dihydroxybenzoates.

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