severe as that found within the same time period in control mice injected with equal volumes of saline. Malonate injections in the same mice also reduce survival time, apparently because of the fulminating infection which results. The increased severity of the bacteremia accompanying the malonate injections could be due to a) an impairment of the mouse's defense against bacterial infection, b) the establishment of an internal environment within the mouse which favors bacterial reproduction along the lines postulated by Lewis(6), or c) a combination of (a) and (b). The need for additional experiments thus becomes evident.

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Effect of Glycol Mesylates on Mouse Sarcoma 180.* (20833)

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Haddow and Timmis(1) recently reported on the inhibition of growth of Walker carcinoma 256 in rats by a series of α,ω-dimethanesulfonyloxyalkanes, $CH_3SO_2O(CH_2)_nOSO_2CH_3$. Growth inhibiting activity was found to be greatest when $n = 4$ or 5. Galton (2) tested Myleran, the compound corresponding to $n = 4$, and found it to be of value in the treatment of chronic myeloid leukemia. We are reporting on the ability of a series of methanesulfonyl ("mesyl") esters of primary, secondary and tertiary aliphatic diols and triols, and the mesylates of polyglycols, to inhibit the growth of Crocker sarcoma 180 in white mice.

Materials and methods. Both Carworth Farms and Taconic white mice were employed. Drugs were injected intraperitoneally in normal saline or peanut oil both in the determination of single-dose LD_{50} values and in the evaluation of tumor inhibitory activity. A 7- to 10-day-old tumor was dissected in penicillin-Ringer-Locke solution, and approximately 20 mg portions transplanted subcutaneously into the axillary region of anesthetized mice, groups of 5 experimental and 5 control animals being used with each drug at each dose level. Treatment was begun 24 hours after transplantation, and was continued daily or on alternate days dependent on the reaction of the mice to the drug. Initially the compounds were administered at a level $\frac{1}{3}$ to $\frac{1}{2}$ that of the single-dose LD_{50} value, the level subsequently being reduced if toxic effects became marked. The experiments usually were terminated eight days after transplantation, and the mean weights of the control and treated tumors determined. The compounds were compared on the basis of the mean per cent change in body weight in the experimental and control animals, and the mean per cent inhibition of tumor weight. As a control, mice were treated with 2:4:6-tris-ethyleneimino-1:3:5 triazine (TEM), a known inhibitor of sarcoma 180. In the case of several of the more active compounds, hematoxylin and eosin stained slides were prepared from tumors recovered from treated animals, and compared with tumors from control animals.

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TABLE I. Inhibition of Growth of Sarcoma 180 in Mice by Methanesulfonyl Esters of Aliphatic Diols, Triols and Polyglycols.

	Hydroxy compounds from which mesyl esters were derived	LD_{50}, mg/kg	Treatment level, mg/kg	Mean % change in body wt: Treated mice	Mean % change in body wt: Control mice	Mean % inhibition of tumor wt
	Diols	CH_3SO_2-O-$(CR_2)_n$-O-SO_2CH_3 (R=H or alkyl groups)				
	n=2					
1	Ethylene glycol	250	85	— 3.0	+ 3.0	26
2	Propylene "	500	170	— 7.8	— 5.3	4
3	Butanediol-2,3	800	235	— 3.8	— 5.1	41
4	Pinacol	30	17*	— 1.3	— 3.1	15
	n=3					
5	Trimethylene glycol	500	235	— 8.2	+ 2.2	37
6	Butanediol-1,3	500	150	— 2.2	+ 7.4	53
7	2,2-Diethyl propanediol-1,3	1800	800*	+ 5.1	+10.8	0
8	2-Butyl-2-ethylpropanediol-1,3	500	100*	+10.5	+20.2	0
9	2-Methyl-pentanediol-2,4	1000	500	—23.0	+ 9.5	79
10	2-Ethyl-hexanediol-1,3	800	400	— 7.4	— 3.2	40
	n=4					
11	Butanediol-1,4	250	40*	—19.9	+ 3.7	92
12	2-Butynediol-1,4	15	5*	— 4.6	— .5	0
13	2,5-Dimethyl-3-hexyne-diol-2,5	200	80*	— 6.4	— 3.0	0
14	3,6-Dimethyl-4-octynediol-3,6	1200	333*	— 6.6	— 3.1	26
	n=5					
15	Pentanediol-1,5	2000	500	— 9.8	+ 5.9	42
16	2-Methoxymethyl-2,4-dimethyl-pentanediol-1,5	300	100*	— 2.8	— 1.2	31
	Triols					
17	Hexanetriol-1,2,6	1500	300*	—11.0	+ 6.2	89
18	Triol 230†	1200	400*	— .5	+ 5.0	35
	Polyglycols	CH_3-SO_2-O-$(CH_2CH_2$-O$)_n$-CH_2CH_2-O-SO_2CH_3				
19	Diethylene glycol	500	165*	+ 2.0	+ 6.0	62
20	Dipropylene "	1000	300*	—31.2	+ 1.0	95
			150*	—25.9	+ 1.6	64
	n=2					
21	Triethylene glycol	1500	700	—12.6	— .6	61
			1000	—25.0	+10.2	78
	n=21					
22	Polyglycol E-1000	2000	666	+ 1.2	+ 7.7	14
	n=44					
23	*idem* -2000	5000	2000	—11.7	— 9.5	15
	n=90					
24	*idem* -4000	10000	3000	— 5.9	— 6.4	0
	n=135					
25	*idem* -6000	10000	5000	— .5	+ 2.0	38
	n=200					
26	*idem* -9000	10000	1000*	— 3.3	+ 9.2	57
			5000*	+ 4.1	+ 9.0	46
27	TEM	2.8(3)	.5*	—21.1	+ 1.6	90
—	Starvation‡	—	—	—28.3	+ 6.9	30

* Treatment on alternate days. † 90% 2-hydroxyethoxymethyl-2,4-dimethyl-pentanediol-1,5.
‡ See text.

Results. The results obtained in screening this series of methanesulfonyl esters of glycols and polyglycols are presented in Table I. Among the alkylene diols, the activity reported by Haddow and Timmis(1) for the mesylate of butanediol-1,4 was confirmed. The introduction of unsaturation into the carbon chain reduced tumor inhibitory ac-

tivity, usually with an increase in toxicity. Variations in the degree of branching in the carbon chain, or in the degree of substitution on the carbon atoms bearing OH groups, did not have a uniform effect on either toxicity or tumor inhibition. Of the 2 triols investigated, the trimesylate of hexanetriol-1,2,6 was especially effective. The mesylates of the polyglycols were studied to determine the effect of the introduction of oxygen into the carbon chain, and because of the increased water solubility of these compounds. As a group, these compounds exhibited a low order of toxicity, but significant inhibition of tumor growth was observed only when they were administered at levels causing definite reduction in body weight.

Because compounds are known which inhibit tumor development mainly as a result of the inanition resulting from administration of the drugs, the effect of starvation on the growth of sarcoma 180 in mice was determined. During an 8-day experimental period, mice were permitted free access to water but food was withheld except for one Purina pellet per animal on the fourth day. Such caloric restriction was found to result in a mean loss in body weight of 28.3%, accompanied by a 30% inhibition in tumor weight. The reduction in tumor weight caused by compounds such as number 9, 11, 17 and 20 thus is considerably in excess of that caused by caloric restriction alone.

The dimesylate of triethylene glycol (No. 21) caused a toxic reaction not observed with the other drugs in this series. Following injection of this compound the animals became convulsant within 5 to 10 minutes with full extension of all extremities and with the body in an opisthotonic position. Sections for microscopic study were prepared from 7-day control tumors, and 7-day tumors from animals treated with compounds 11, 17, 20 and 21. In comparison with the control tumors, the treated tumors were characterized by a scarcity of mitotic figures and an increase in fat and intercellular tissue.

Summary. Methanesulfonyl esters of a series of aliphatic diols, triols and polyglycols were prepared and tested for an ability to inhibit the growth of sarcoma 180 in white mice. Variations in the degree of branching in the carbon chain, or in the degree of substitution at the carbon atoms bearing hydroxyl groups, did not have a uniform effect on either toxicity or tumor inhibitory activity. Significant inhibition of tumor growth could be demonstrated for 5 of the drugs when they were administered at levels causing definite reduction in body weight.

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