transfused with compatible hemophilic plasma. No effect on the hemostatic mechanism of normal subjects was demonstrated following the transfusion, nor did the ability of the recipient's plasma to correct the clotting defect of known hemophilic plasma change following this procedure.

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Anticonvulsant Activity of 2,2-Disubstituted-1,3-Propanediols in Electroshock Seizures. (19045)

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It has been recently shown that certain 2,2-disubstituted-1,3-propanediols possess marked anticonvulsant properties against convulsions produced by pentylenetetrazole (metrazol) (1,2). One compound of this series, 2,2-diethyl-1,3-propanediol (DEP) which received a more thorough pharmacological investigation(1-4) proved very effective against convulsions produced by chemical agents such as strychnine, pentylenetetrazole and picrotoxin, but was relatively weak in preventing electroshock seizures(1,4). It was of interest to investigate whether all 2,2-disubstituted-1,3-propanediols would show stronger anticonvulsant activity in chemoshock convulsions than in electroshock convulsions or whether this property was peculiar to DEP. In view of the close chemical relationship of certain 2,2-disubstituted-1,3-propanediols to barbiturates, the possibility that each of these compounds may be converted in the body to the same anticonvulsant substance was considered.

Experimental. White male mice of the CF-1 strain weighing between 18-24 g were used. Seizures were produced by applying through corneal electrodes 60 cycle current from a Hans-Tech electroshock apparatus with a current intensity of 50 milliamperes and 0.2 second duration. With the machine used the current delivered was independent of the external resistance. Experiments have shown that with a stimulus of 12.5 milliamperes and duration of 0.2 second about 50% of mice convulse; thus 50 milliamperes represents about 4 times the convulsive threshold dose. Most mice survived repeated shocks of 50 milliamperes administered at hourly intervals without showing marked changes in sensitivity to electroshock seizures. Drugs were administered orally in a 5% suspension of gum acacia. Groups of 10 mice were treated at dose levels increasing in geometrical progression by a factor of approximately 1.5 and shocked 30, 90 and 150 minutes after the administration of the drug. The number of animals protected at each dose level was noted. A mouse was considered to convulse if it showed the extensor tonic phase of the convulsion as described by Toman *et al.*(5). Mice showing only clonic seizures are considered non-reactors. The results were obtained graphically(6) and are expressed as the dose protecting 50% of the animals from the tonic extensor phase of electroshock convulsions. The compounds used in these studies were prepared by Dr. B. J. Ludwig and his associates of these Laboratories.

Results. The table gives the doses in mM/kg protecting 50% of animals from the extensor tonic phase of electroshock seizures, applied 30 minutes after administration of

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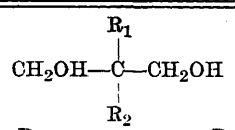
TABLE I. Mean Protective Doses of Substituted Propanediols in Electroshock Seizures and Pentylenetetrazol Convulsions in Mice.



No.	R_1	R_2	Molecular wt	Electroshock, protective dose, oral, mM/kg	Metrazol, protective dose, intraperitoneal, mM/kg
1	methyl	methyl	104	>20.6	>2.5
2	ethyl	ethyl	132	2.8 ± .08	.3
3	*n*-propyl	*n*-propyl	160	2.6 ± .17	.55
4	*n*-butyl	*n*-butyl	188	2.9 ± .19	>1.3
5	methyl	ethyl	118	5.8 ± .41	1.35
6	"	*n*-propyl	132	2 ± .1	.53
7	"	iso-propyl	132	3.2 ± .28	.67
8	H	*n*-butyl	132	5.8 ± .3	—
9	methyl	"	146	3.2 ± .21	1.44
10	ethyl	"	160	3.4 ± .23	—
11	"	ethoxy	148	8.7 ± .22	>1.7
12	phenyl	H	152	3.2 ± .18	>1.6
13	"	ethyl	180	1.2 ± .04	.67
14	phenoxy	"	196	4.5 ± .31	>1.3
15	phenyl	phenyl	228	1 ± .04	—
16	benzyl	benzyl	256	3.1 ± .3	—
17	phenobarbital sod.		254	.16 ± .008	.15
18	mephenesin		182	2.3 ± .12	.44

the compound. With the exception of phenobarbital, all compounds were ineffective 90 and 150 minutes after administration. The doses protecting animals from death caused by pentylenetetrazole 100 mg/kg as previously found(1) are also given.

Compounds with aliphatic substituents on the C_2 atom did not show outstanding anticonvulsant activity. The dimethyl substituted compound was inactive and the methyl ethyl compound had only slight activity. Compounds with 2 aliphatic substituent groups having a total of 4 or more carbons showed anticonvulsant activity of a comparable degree; it appeared to be of little importance whether the substituent groups were placed symmetrically or asymmetrically around the central carbon atom. Anticonvulsant action was decreased when one of the substituents was H or an alkoxy group as in compounds No. 8 and 11. It was of interest to note that DEP (No. 2) which on a weight basis possessed a similar protective action as phenobarbital against convulsions produced by pentylenetetrazole, was about 10 times less effective than phenobarbital when tested by the electroshock procedure. The methyl propyl isomer (No. 6), which was less effective in chemoshock appeared significantly more active in the electroshock procedure. The methyl isopropyl isomer (No. 7) was of somewhat lower efficacy than DEP in both electroshock and chemoshock tests. The *n*-butyl isomer (No. 8) had only weak anticonvulsant action.

Among the compounds with aromatic substituents the phenyl ethyl and the diphenyl propanediol possessed an anticonvulsant activity almost 3 times that of DEP in preventing electroshock seizures. Compounds where one of the substituents was an H or aryloxy group (No. 12 and 14) showed less activity. The dibenzyl propanediol had also a relatively weak anticonvulsant action.

Discussion. A study of Table I indicates that all compounds possessing anticonvulsant activity of some magnitude possess in common a carbon atom to which four other carbon atoms are directly attached (a quaternary carbon atom). This is a common feature of anticonvulsant drugs of both the barbiturate and propanediol series. Compounds with a tertiary carbon atom such as No. 8, 11, 12 and 14 are less anticonvulsive than comparable compounds possessing a quaternary carbon. Thus 2-*n*-butyl-1,3-propanediol (No. 8) is considerably less potent as an anticonvulsant than the 3 isomers possessing quaternary car-

bon atoms. Similarly the phenyl ethyl propanediol is more effective than the phenoxy ethyl analogue. However, propanediols possessing a quaternary carbon are not necessarily anticonvulsant as is witnessed by the lack of activity of the 2,2-dimethyl-1,3-propanediol (No. 1).

Putnam and Merritt(7) have stated that practically all substances with marked anticonvulsant properties contain at least one phenyl nucleus in a terminal position. If two phenyl nuclei are present they are both attached to the same carbon atom. It is of interest that in conformity with this rule the propanediols containing one or two phenyl nuclei show strongest anticonvulsant activity.

The propanediols differ from other anticonvulsants of the barbiturate, hydantoin, and oxazolidine-2,4-dione series in possessing a very short duration of action. When animals were repeatedly subjected to electroshock seizures, propanediols were effective 30 minutes after administration of the drug but gave no protection 90 or 150 minutes after administration. Mephenesin showed a similarly short duration of action. Phenobarbital on the other hand had a long duration of action and full activity came on slowly.

It is of interest to speculate whether compounds related to substituted 1,3-propanediols occur as degradation products of certain barbiturates in the body. It may be that for instance phenobarbital is broken down in the body to urea and a product related to 2-ethyl-2-phenyl-1,3-propanediol. Goodman and Toman(8) have pointed out that no unequivocal proof has ever been advanced to indicate that antiepileptic drugs act *per se* to prevent seizures and it is within the realm of possibility that a compound derived from 2-ethyl-2-phenyl-1,3-propanediol is the effective anticonvulsant agent of phenobarbital. The effectiveness of the barbiturates and the propanediols in both electroshock and chemoshock convulsions certainly appears to point in this direction.

Summary. 2,2-Disubstituted-1,3-propanediols in suitable dosage prevent electroshock convulsive seizures in mice. The molecular configuration favorable for maximal anticonvulsant activity is the presence of a quaternary carbon atom to which one or two phenyl radicals are attached. The possibility is pointed out that derivatives of propanediols occur in the body as degradation products of certain barbiturates and they may constitute the effective anticonvulsant substances.

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Effect of Intratracheally Administered Wulfenite on Lungs of Mice. (19046)

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Evans(1-3) reported that the introduction of piezo-electrically active materials into the tracheae and peritoneal cavities of rats and of rabbits resulted in extensive proliferation of fibrous tissue in the lungs and in the abdomen. This reaction was thought to result from the electromotive charges given off by the dusts when exposed to stresses and strains in the body tissues. Evans felt that this property might explain the pathogenesis of pneumoconiosis, since Lanza's data(4) indicated that

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