prefrontal cortex was made on this animal, the lesion including all tissue anterior to a plane 5 mm in front of the arcuate sulcus on the dorsal surface and about 2 cm in front of the optic chiasm on the orbital surface. Recovery was uneventful. In the three days immediately following operation, the remarkable increase in locomotor progression characteristic of prefrontal macaque preparations developed gradually to its peak. Tests given 10–14 days postoperatively showed perfect retention of the auditory discrimination habit, but only chance scores on the visual and auditory delay problems. Considerable formal training in the subsequent months did not improve his performance. The monkey was kept under observation and almost daily trained and tested for 14 months following the operation. Throughout this period the activity level remained high, but no behavior suggestive of Jacksonian fits or epileptoid seizures was observed.

On July 19, 1948, at 10: 00 A.M., he was given 6 mg of benzedrine by subcutaneous injection (his weight at this time was 8 lbs). Activity continued as before dosage, but food given was not swallowed, remaining in the food pouch. Twenty minutes later he was given 4 mg additional (the total amount given being about half the minimum lethal dosage, *1*). During the next 40 min greatly increased activity, muscular incoordination, attacks on the cage walls, and general violence, but no convulsions, were noted. This condition was followed by prostration. He was then given 30 mg of Nembutal intraperitoneally. In the afternoon he was sitting up and moving about quietly. Partial paralysis of the left limbs, affecting the arm more than the leg, was observed. The right limbs appeared weak and uncoordinated. At 6: 30 P.M. he was again prostrate and started having Jacksonian-type seizures, beginning with the corner of the mouth and spreading to the hand, arm, trunk, and leg of the left side. At no time in any convulsion did the clonic movements spread to the right side of the body. Later the convulsions started from the ear and were followed by adversive head movements and progressive involvement of the left limbs and trunk. At 7: 15 P.M. the convulsions were starting with the adversive head movements. Each seizure lasted about 40 sec with about a 5-min interval between seizures. This interval gradually decreased until at about 8: 00 P.M. the convulsions were coming every 2 min. In all, about 30–40 convulsions were observed. At 8: 20 P.M. he was given 60 mg of Nembutal intraperitoneally, and the convulsions stopped within 5 min. Twenty minutes later convulsions again started, and he was given another 60 mg of Nembutal in two doses in the next hour and 105 mg more at 11: 30 P.M. At 3: 30 A.M. the animal was awake, prostrate, and quiet, and remained this way until evening. During the morning following he was given saline solution subcutaneously, and in the afternoon he drank a cup of orange juice and ate two pieces of fruit. That night he was sitting up, capable of movement but quiet and unresponsive. The paralysis and weakness were somewhat alleviated, but the left side was still less efficient than the right. The next morning he had regurgitated all the food previously eaten and appeared very weak and stuporous, lying down much of the time. Late that afternoon he was sacrificed and perfused with 10% formalin. The brain was removed 48 hrs later. There was no hemorrhage or other gross abnormality which could account for the severe symptoms following the administration of benzedrine. There was scar tissue of about 2–3 mm in extent in the anterior part of the remaining frontal cortex on both sides.

It has been suggested by Hebb and Penfield (*2*) that maximum physiological and behavioral dysfunction may result from pathologically functioning tissue rather than from lack of tissue *per se*. Further, Penfield and Erickson (*4*) have localized adversive seizures, similar to the type described here, in the cortex of the frontal lobe immediately in front of the sensorimotor area. Kopeloff, *et al.* (*3*) have shown that a focus of irritation in the cortex produced by local application of a disc containing certain inactive materials may fail to cause seizures until sensitizing agents such as alumina cream are introduced parenterally. Our findings indicate that (a) irritative lesions, though insufficient to produce epileptic discharge, may be present after cerebral excisions; (b) benzedrine may increase sensitivity to these irritative effects; and (c) observed abnormalities of behavior, such as hyperactivity and failure in the delayed response test, following brain lesions may be due to the irritative action of pathological tissue which is subliminal for fits.

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The Pharmacological Properties of Some 2-Substituted-4-hydroxymethyl-1,3-dioxolanes[1]

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Certain simple monoethers of glycerol were recently shown to cause a transient paralysis of the voluntary skeletal muscles without embarrassment of respiration (*2*). In smaller doses these substances had a controlling influence on various types of tremors and other involuntary movements, as well as a relaxing effect on spasm, spasticity, and rigidity (*1*, *3–6*). The purpose of this

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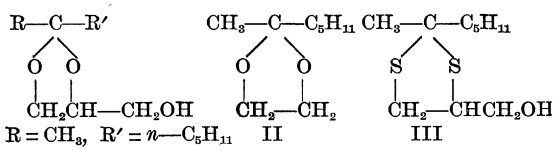
note is to show that these characteristic effects of the glycerol ethers on the central nervous system are also present in another series of compounds of quite different structure, the 2-substituted-4-hydroxymethyl-1,3-dioxolanes (e.g. I).



I, $R = CH_3$, $R' = n\text{—}C_5H_{11}$ II III

Preliminary examination of over 50 compounds (most of them new[2]) in this series showed that the type of physiological action obtained was markedly influenced by the groups in position 2. Some of the 2-alkyl and 2,2-dialkyl derivatives possessed a type of action similar to that of the monoethers of glycerol. Large doses of the active compounds caused complete muscular paralysis with a decrease of muscle tone. Spontaneous respiration and certain reflexes such as the knee jerk and wink reflex were maintained, even during profound paralysis. Small doses, which did not cause any detectable changes in the behavior and appearance of the animals, protected them from the effect of lethal doses of strychnine and Metrazol.

This paralyzing action appeared to be optimal if a total of 6–8 carbons was attached at position 2; the lower, water-soluble members of the series, and the higher, virtually water-insoluble members, were almost completely inactive. The compounds where R was methyl and R′ a straight-chain alkyl group of 5–7 carbon atoms were found definitely superior to those with a different combination of groups, even when the total number of carbons on the 2-position was constant. It is interesting to note that the substitution of a cyclohexyl group for the *n*-amyl or *n*-hexyl (I, $R = CH_3$, R′ = cyclohexyl) group decreased the activity sharply. Compounds in which R and R′ were part of a carbocyclic ring, *i.e.* derivatives of cyclopentanone and cyclohexanone, showed some paralyzing activity, but less than those in which R and R′ were alkyl groups.

The presence of the free hydroxyl group seemed to be essential for activity. The removal of the hydroxyl, as in II, or the acetylation of the hydroxyl of I abolished, or very markedly decreased, the paralyzing activity. The dithiolane III, analogous to I, was also inactive, as were the two examples of 2-substituted-4-hydroxymethyl-1,3-dioxolanes examined which contained a basic nitrogen atom. Compounds of formula I where R was alkyl and R′ was aryl or heterocyclic also possessed interesting pharmacological properties. Some of these compounds caused paralysis, whereas other closely related compounds caused tremors, hyperexcitability, and convulsions.

The dependence of the activity and toxicity on the size and nature of the alkyl groups in position 2 is illustrated in Table 1, which gives the mean paralytic and mean lethal doses of a few of the alkyl substituted compounds examined. (The dose which caused a loss of the righting reflex in 50% of the animals was taken as a measure of the relative activity of the compounds and was called the mean paralytic dose.) The table also gives the comparable values for myanesin (*o*-toloxy-1,2-propanediol), the best compound of the glycerol ether series. It will be noted that certain members of the dioxolane series possessed greater activity and a greater margin of safety than myanesin.

TABLE 1

MEAN PARALYZING AND MEAN LETHAL DOSES OF CERTAIN 2-SUBSTITUTED-4-HYDROXYMETHYL-1,3-DIOXOLANES AFTER INTRAPERITONEAL ADMINISTRATION TO WHITE MICE

Formula I R	Formula I R′	$PD_{50} \pm SE$* (mg/kg)	$LD_{50} \pm SE$* (mg/kg)	$\frac{LD_{50}}{PD_{50}}$
$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	205 ± 24	730 ± 69	3.6
$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	155 ± 33	730 ± 73	4.7
$n\text{-}C_6H_{13}$	H†	153 ± 23	430 ± 53	2.9
CH_3	$n\text{-}C_5H_{11}$	105 ± 24	500 ± 31	4.8
CH_3	$s\text{-}C_5H_{11}$	190 ± 30	475 ± 56	2.5
Myanesin		180 ± 20	500 ± 43	2.8

* PD_{50} = mean paralyzing dose; LD_{50} = mean lethal dose; SE = standard error.

† This compound may have the 1,3-dioxan structure, which is a 6-ring isomeric with structure I. This structure has been excluded for the other compounds.

Certain compounds mentioned in this preliminary communication may be useful as tools in neurophysiological research; others have potential therapeutic application.

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A New Treatment of Viscosimetric Data[1]

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An interesting relationship exists in flow data secured from capillary-tube viscometers. To illustrate, Fig. 1 contains the flow data for several liquids obtained with a capillary-tube viscometer in which driving pressures were accurately controlled and expressed in millimeters of water. No kinetic energy corrections were applied. All of the flow lines look like those to be expected from such a study: they are logarithmic in type.

When two fixed pressures are chosen, as was done for Fig. 2—namely, at 100 and 500 mm of water pressure—and the two points for each liquid joined to form "two-

[2] We are indebted to J. Figueras, C. G. Krespan, L. Libermann, and F. C. Pennington for their work on the synthesis of these compounds. We are also indebted to R. Plato Schwartz, M.D., for his interest in this work.

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