activity of these agents is not dependent upon the increased ATP phosphohydrolase, since the inflammatory reaction *per se* did not influence the hepatic ATP phosphohydrolase activity.

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Potentiation of the anticonvulsant action of acetazolamide

SIR,—Certain α- or β-adrenergic blocking agents antagonize the anticonvulsant action of acetazolamide (Rudzik & Mennear, 1966a), but dichloroisoprenaline enhances it. Since the anticonvulsant action of acetazolamide is mediated through a catecholamine mechanism (Gray, Rauh & Shanahan, 1963; Rudzik & Mennear, 1966b), the enhancement of acetazolamide by dichloroisoprenaline may be related to its ability to produce adrenergic stimulation before blockade. We now report the effects of several central nervous system stimulants as well as amine-releasing agents on the anticonvulsant action of acetazolamide.

Male albino mice (Harlan Industries), 18–26 g were dosed with the various agents under investigation 30 min before the intraperitoneal injection of acetazolamide. The ED 50 value (Litchfield & Wilcoxon, 1949) for the anticonvulsant effect of acetazolamide was determined 30 min after the injection of acetazolamide. Maximal electroshock siezures were given (Swinyard, Brown & Goodman, 1952) and the criterion for protection against the seizure was abolition of hind leg extension. The results are in Table 1.

As reported earlier (Rudzik & Mennear, 1966b) dichloroisoprenaline potentiated the anticonvulsant effect of acetazolamide while MJ-1999 [4′-(1-hydroxy-2-isopropylamino) methanesulphonanilide] antagonized it. Dichloroisoprenaline has also been reported to produce a stimulant effect upon the grossly observed behaviour of rats (Randrup, Munkvad & Udsen, 1963), to antagonize reserpine-induced ptosis in mice (Aceto & Harris, 1963) and to enhance the lethal effect of amphetamine in aggregated mice (Mennear & Rudzik, 1965). Intrinsic (adrenergic stimulatory) activity has not been reported for MJ-1999 (Dugan & Lish, 1964).

Since amine-depleting agents have been reported to antagonize the action of

TABLE 1. EFFECTS OF SEVERAL PHARMACOLOGIC AGENTS ON THE ANTICONVULSANT ACTION OF ACETAZOLAMIDE IN MICE

Treatment	Intraperitoneal dose (mg/kg)	Change from control ED50
Dichloroisoprenaline ..	10	−40*
MJ-1999	30	+192*
Metaraminol	10	−77*
(+)-Amphetamine ..	2·0	−52*
Ephedrine	5·0	−70*
Caffeine	5·0	−58*
Imipramine	5·0	−51*
Desipramine	5·0	−40*
Tranylcypromine ..	10	−52*
Cocaine	5·0	−32

* Significantly different from control value ($P > 0.05$).

acetazolamide (Rudzik & Mennear, 1966a) it was interesting to find that metaraminol, when administered 30 min before acetazolamide, produced potentiation. This, however, may be a reflection of the release of catecholamines by metaraminol. In support of this hypothesis is our finding that after 4 hr of pretreatment with metaraminol the anticonvulsant action of acetazolamide is significantly antagonized (control ED 50 23 mg/kg *vs.* treated ED 50 74 mg/kg).

The potentiation of acetazolamide by amphetamine, imipramine, desipramine and tranylcypromine, each of which is known to influence the disposition of catecholamines, lends support to the hypothesis that acetazolamide produces its anticonvulsant action through a catecholamine mechanism. The failure of cocaine to produce significant potentiation of acetazolamide may be related to its biphasic effect on tissue levels of catecholamines (Potter, Axelrod & Kopin, 1962).

A number of pharmacologic agents were found to be without effect on the anticonvulsant action of acetazolamide. These agents include: tyramine, mepyramine, morphine, and SKF-6890 [2-(2,6-dimethylphenoxy)ethyltrimethylammonium bromide].

It seems that a catecholamine mechanism may be involved in the potentiation of the anticonvulsant action of acetazolamide as well as its anticonvulsant effect *per se*.

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