76 On the Activity of γ-amino-butyric-acid Derivatives on Central Nervous System Excitability. A. BERTELLI and G. GAVAZZI (Italy).

The action of γ-amino-butyric acid and β-hydroxy-γ-amino-butyric acid intraperitonally administered to rats, on the nervous stimulation caused by many exciting and convulsing drugs (strychnine, cardiazol, amphetamine, morphine, NH_4Cl, etc.) was studied.

It was observed that with regard to β-hydroxy-γ-amino-butyric acid and to the greater absorption of the molecule, β-hydroxy-γ-amino-butyric acid exerts a remarkable antagonistic action against the above-mentioned exciting drugs.

77 The Effect of Certain Glutarimides on Brain Metabolism. P. J. NICHOLLS (United Kingdom).

The convulsants, β-methyl-β-ethyl- and β-methyl-β-*iso*propyl-glutarimides and the hypnotics, β, β-, di-*n* propyl- and α-ethyl- α-phenylglutarimides were examined using rat brain brei. Cholinesterase and amine oxidase were not affected by any of the compounds but there was a slight inhibition of choline-acetylase activity by concentrations of 10^{-3} M of the hypnotic glutarimides. When glucose or glutamate were substrates, the oxygen uptake was inhibited by the convulsant and hypnotic glutarimides in concentrations of 10^{-2} and 10^{-3} M. respectively. This inhibition was reversed by methylene blue. In rat liver mitochondria, concentrations of the drugs inhibiting oxygen uptake had no effect on oxidative phosphorylation. The oxidation of succinate and *p*-phenylenediamine by rat brain was unaffected by the glutarimides. Concentrations of the drugs inhibiting oxidation of lactate caused no appreciable accumulation of co-enzyme neither did they affect the transfer of hydrogen from reduced coenzyme to flavoprotein. With yeast, which does not require coenzyme for oxidation of lactate, the glutarimides inhibited the oxygen uptake in the presence of lactate but they had no action on yeast lactic dehydrogenase.

From these results it is concluded that the glutarimides act at the flavoprotein level. While the convulsant glutarimides are effective only at doses which would be lethal *in vivo*, such an effect may explain the mechanism of action of the hypnotic glutarimides. A similar site of action has been proposed for the oxybarbiturates.[1, 2]

1. ALDRIDGE, W. N. and PARKER, V. H. (1960), *Biochem. J.*, **76,** 47.
2. GRIEG, M. E. (1946), *J. Pharmacol.*, **87,** 185.

78 The Mechanism of the Antagonistic Action of Reserpine on the Anticonvulsant Effect of an Inhibitor of Carbonic Anhydrase. W. D. GRAY, C. E. RAUH and R. W. SHANAHAN (U.S.A.).

Treatment of mice with reserpine abolishes the anticonvulsant action of methazolamide, an inhibitor of carbonic anhydrase; in contrast, the action of diphenylhydantoin is only slightly affected. Possible modes of action of reserpine are actions on: (1) the absorption and fate of the inhibitor; (2) its penetration into the central nervous system; (3) interference by reserpine on the interaction of the enzyme and the inhibitor; or (4) a functional antagonism, since reserpine is known to enhance the susceptibility of mice to electroshock seizures. Mice treated with reserpine 24 hr before the oral or the intravenous administration of methazolamide showed increased concentrations of inhibitor in plasma, erythrocytes, and in brain. Treatment with reserpine had no action on the localization of carbonic anhydrase and carbonic anhydrase inhibitor following differential centrifugation of homogenates of the brains of mice. Both appear to be localized in the soluble fraction. Three of the suggested possible modes of action do not appear to be involved; the antagonistic action of reserpine possibly operates at a functional (physiological) level or levels within the central nervous system.

79 Tranquilizers and Antidepressants: A Pharmacological Comparison. F. HERR, J. STEWART and M. P. CHAREST (Canada).

The actions of chlorpromazine and chlorprothixene on a battery of pharmacological tests were compared with those of imipramine in an attempt to discover in animals properties which might correlate with the clinical effects of these drugs. On the basis of these tests, a series of compounds of unknown pharmacological properties was investigated. One of these compounds, amitriptyline, synthesized independently by this and another laboratory, has been studied in detail and is compared with those mentioned above.

The differences in the pharmacological activities of chlorpromazine, chlorprothixene, imipramine, and amitriptyline were quantitative rather than qualitative. All potentiated hexobarbital and alcohol narcosis, decreased body temperature, and caused ataxia. They decreased spontaneous motility, impaired performance of learned responses, and also delayed the learning of these responses. In these tests, in order to obtain a given degree of effect, larger doses were required of imipramine and amitriptyline than of chlorpromazine and chlorprothixene. In spite of the fact that higher doses of imipramine and amitriptyline were required to influence, for example, a conditioned runway response, these effective runway doses were about a fifth of the doses which caused ataxia. On the other hand, the effective runway doses of chlor-