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-

promazine and chlorprothixene were the same as those which caused ataxia.

A suggestion is offered according to which the ratio of effective doses of a compound in different tests may be indicative of its therapeutic effectiveness. Recently, Freed (1960) reported a clinical investigation of amitriptyline which showed its antidepressant properties in depressed patients.

80 Differentiation of Central Depressants by Means of the Veratramine Excitation. W. SCHOETENSACK and G. HALLMANN (Germany).

Veratramine in small doses evokes tremors, in higher subletal doses convulsive-like excitation phenomena.

Studies in rats and mice have shown the following results: (1) Tremor and convulsions are only suppressed by a few centrally acting muscle relaxants such as mephenesin, zoxazolamine, 2-aminobenzthiazole, chlormezanone and carisoprodol, whereas meprobamate and 2-(γ-methoxypropylaminomethyl)-1:4-benzodioxane-HCl fail to block the veratramine excitation; (2) A number of unsaturated tertiary alcohols, urethane, chloral hydrate and phenylacetylurea abolish the veratramine convulsions but not the tremor.

Hypnotics and anticonvulsants such as phenobarbital, hexobarbital, phenytoin, and troxidone, also a number of tranquillizers, ganglionic blocking-, sympathicolytic-, and anticholinergic agents are ineffective against tremor and convulsions up to the level of lethal doses.

The two excitation phenomena induced by veratramine differ completely in their unusual resistance against most of the investigated drugs from the excitations produced by leptazol, strychnine or by harmine and tremorine.

Transections of brain in rat suggest that structures within the lower brain stem are responsible for initiating the veratramine excitation.

Transections in the higher brain levels including the diencephalon do not change fundamentally the reactions after application of veratramine. After removal of the cerebellum convulsions appear but not tremor.

Decerebrate rigidity in rat is intensified by the central excitants mentioned above, including harmine and tremorine; veratramine, however, completely prevents the hyperactivity of the extensors and after cessation of the veratramine excitation the decerebrate rigidity appears unchanged.

Since the veratramine excitation is completely inhibited only by a limited number of centrally-acting muscle relaxants, these findings seem to be of considerably value for evaluation and differentiation of central muscle relaxants.

The nervous mechanisms probably responsible for the initiation and evidently specific inhibition of the two stages of the veratramine excitation are discussed.

81 Three Types of Artificially Induced Tremors and the Effect of Some Antiparkinsonian Agents upon Them. I. L. BONTA and H. M. GREVEN (Holland).

Usually antiparkinsonian drugs are pharmacologically evaluated by testing them against varying types of tremors produced by surgical methods (tremor-monkey) or chemical means (nicotine, Tremorine). In the course of our investigation of the effect of intracerebral drug injections, we observed that a new compound, Gre-1248, induced a type of hyperkinesia (running fits and hind-limb tremor), which reminded us of certain motor disturbances occurring in extrapyramidal syndromes. The effect of nicotine, Tremorine and Gre-1248 on mice will be demonstrated by a short film.

Antagonistical studies with several antiparkinsonian drugs (atropine, caramiphen, trihexyphenidyl, orphenadrine, diethazine, etc.) have shown that the various compounds induced different degrees of protection against the three types of tremors. The question of parallelism between experimentally-induced tremors and Parkinson's disease or related extrapyramidal disorders will be briefly discussed.

82 A Contribution to the Pharmacology of Tremorine-induced Tremor. P. STERN and J. GAŠPAROVIC (Yugoslavia).

The onset of tremorine-induced tremor (TT) in mice is delayed by application of iproniazid or PIH 20 hr prior to tremorine (T); similarly applied hydralazine or α-methyl DOPA have the opposite effect. Since iproniazid and PIH increase dopamine, serotonin (S) and GABA in the CNS, the three precursors, DOPA, 5-hydroxytryptophan (5-HTP) and glutamic acid were examined. Only 5-HTP delayed TT and harmine-induced tremor, but not that induced by 3-amino-1:1:3-triphenylpropan-1-ol or diethylcysteamine. DOPA and glutamic acid did not act on either kind of tremor. When T was preceded by iproniazid (20 hr) and 5-HTP (2 hr) TT was delayed considerably further than by action of either substance alone. Consequently, an increase of S in the CNS delays TT, although T itself has no influence upon the S-level. The fact that hydralazine and α-methyl DOPA, two inhibitors of amino-acid decarboxylases, are capable of inducing tremor, favours this assumption. S-antagonists, harmine and LSD also induce tremors. Reserpine and chloropromazine-induced Parkinsonism is interpreted on the basis of these facts. In contrast to chloropromazine, reserpine reduces the level of dopamine, the concentration of which is particularly high in the corpus striatum. The latter contains, in addition, much S, substance P and choline acetylase. We have found that S potentiates this enzyme, but so does T alone. It is open to discussion whether accumulation of S in definite regions, e.g. the corpus striatum, can lead to an inhibition of TT. The present results pre-