CURRENT LITERATURE

Modification of Maximal Audiogenic and Electroshock Seizures in Mice by Psychopharmacological Drugs *by G.B. Fink and E.A. Swinyard (1959)* : **J. Pharmacol. exp. Ther., 127,** *318.*

The duration of the components of maximal seizures induced in mice by sound and electroshock were measured and the two seizure patterns have been compared. Seven psychopharmacological agents and two anti-convulsant drugs were tested for their ability to prevent the running component of maximal audiogenic seizures (MAS), to prevent the tonic-extensor component of both MAS and maximal electroshock seizures (MES) and to prolong the latency of MAS and MES.

The tonic convulsion is the major feature in both types of seizures. MAS differs from MES in that appreciable latency, wild running and clonus precede the tonic component. A period of clonus follows both MAS and MES.

Chlorpromazine, promazine, trifluprornazine and hydroxyzine prevent the tonic extensor component of MAS in nearly or slightly above neurotoxic doses. Neurotoxic doses of these four drugs are also required to increase MAS and MES latency. Reserpine actually increases seizure severity and decreases MES latency. In nontoxic doses meprobamate, phenylglycodol, phenobarbital and diphenylhydantoin prevent MAS running and MAS and MES tonic extension. These four drugs are most effective by the MAS tonic extension test.

R.P. KOHLI

Adrenergic Receptive Mechanism of Canine Ileum *by R.P. Ahlquist and B. Levy (1959)* : **J. Pharmacol. exp. Ther., 127,** *146.*

According to Ahlquist's classification of adrenergic receptors, the *alpha* receptors were assigned to the smooth muscle of the intestine. This was anamolus since *alpha* receptors elsewhere are related to smooth muscle contraction rather than relaxation. In this study an attempt has been made to block intestinal inhibitory effect of some sympathomimetic amines in the intact anesthetized dog with dibenamine, dibenzyline, dibozane and dichloroisoproterenol (DCI). The inhibitory effect of phenylephrine is

not modified by amotriphene. Amotriphene produced reduction in auricular and ventricular rate and reversion to a normal rhythm. Amotriphene appears to have greater effect on refractory period and relatively smaller effect on conduction velocity as compared to quinidine and procainamide.

R.P. KOHLI

The Influence of Benactyzine on Learning in Cats *by I. Reventlow (1959)* : **Acta Pharmacol. Toxicol., 16,** *136.*

Experimental neurosis was induced in cats by using a modified Masserman's technique. The cat was taught to obtain food from the box when the bell rang and then to press the pedal to ring the bell. The time taken by the cat, after having eaten a pellet of food, to fetch the next one was recorded in seconds and designated "feeding-cycle". Then the cat was exposed to air blasts every 10th time it put its head into a box from which it had learned to extract food. The number of feeding cycles and the duration of each was found to be increased by the development of experimental neurosis which is assumed to be due to a conflict between a drive to obtain food and a drive to avoid the blast of air.

The cats which were hesitant to open food box benefited from the treatment with benactyzine. Benactyzine did not affect the learning process, but it seemed to facilitate learning when the behaviour suggested the presence of emotional factors that inhibit learning. It apparently benefits both "insightful" and "conditioned" reactions when they are inhibited by emotional factors.

N. MISRA

Sympathetic Post-ganglionic Cholinergic Fibres *by J.H. Burn, and M.J. Rand (1960)* : **Brit. J. Pharmacol., 15,** *56.*

The usual conception about adrenergic fibres is that they are fibres directly liberating noradrenaline. However, the observations of these authors suggest that fibres liberating acetylcholine may, by doing so, discharge noradernaline from the stores located in the fine nerve terminals or in the near-by tissues.

Cholinergic fibres were known to occur in sympathetic nerves supplying the sweat glands, the vessels of the hindleg of a dog, the nictitating membrane of a cat and the tongue of a dog. In the present experiments, using

reserpine to deplete the extractable noradernaline from the stores, evidence has been obtained for the presence of cholinergic fibres in many more sympathetic nerves—namely the sympathetic nerves supplying the vessels of the rabbit ear, the atrium of the heart, piloerector muscles of the cats tail, isolated uterus of virgin bitch and cat, and the spleen.

In reserpine treated cats sympathetic stimulation produced a contraction of the nictitating membrane but this action was abolished by atropine. After this action was abolished by atropine, a slow infusion of noradernaline restored it. It seems that the infusion of noradernaline restored these actions by restoring the depleted stores in the reserpine treated animals.

Thus cholinergic fibres seem to be present wherever they are looked for in sympathetic fibres. The authors explain that sympathetic fibres were originally cholinergic, but in the process of evolution they came to innervate a store of noradrenaline (resembling the innervation of adernal medulla). Some fibres developed further and chromaffine tissue formed in them. The true adrenergic fibres were thus formed.

N. MISRA

Pharmacological Actions of Thalidomide (L-Phthalimidoglutarimide), A new Sedative Hypnotic Drug *by G.F. Somers (1960)* : **Brit. J. Pharmacol., 15,** *111.*

The results show that this sedative hypnotic drug differs from barbiturates in that there was absence of initial excitation in mice and it did not produce motor incoordination, respiratory or cardiac depression and narcosis. The LD50 in mice was more than 5 g./kg. as compared to 0.27 g./kg. for phenobarbitone. The lack of toxicity may be due to a limited absorption. Like phenobarbitone and glutethimide, it showed no analgesic action but potentiated the analgesic action of morphine and pethidine. It increased the duration of catatonia produced in mice by chlorpromazine and reserpine and increased the potentiating effect of these drugs on hexobarbitone induced narcosis in mice. Central stimulants like methylphenidate and methamphetamine antagonised the CNS depressant action of Thalidomide. It seems to have distinct advantages over barbiturates as a sedative hypnotic drug.

N. MISRA

The Decarboxylation of Amino Acids Related to Tyrosine and their Awakening Action in Reserpine Treated Mice *by H. Blaschko, and T.L. Chrusciel (1960)* : **J. Physiol., 151,** *272,*

A number of aminoacids related to 3:4-DOPA were tested for their awakening action in mice tranquillized with reserpine. The aminoacids used were L-DOPA, D-DOPA, metatyrosine, 2:3-DOPA, 2:5-DOPA and 3:4-dihydroxyphenylserine.

The results showed that in normal animals, L-DOPA and metatyrosine caused an increase in motor activity in mice, more so after iproniazid, but D-DOPA, 2:3-DOPA and 2.5-DOPA were without effect on motor activity.

In animals treated with reserpine, L-DOPA and m-tyrosine exhibited awakening effect but D-DOPA, 2:3-DOPA, 2:5-DOPA and dihydroxyphenylserine did not have any awakening effect, even after iproniazid in the reserpinised animals. Dopamine and noradrenaline also had awakening effect in the reserpine treated mice but the onset was delayed. This suggested that the amino-acids, which were able to awaken the mice treated with reserpine, acted after being converted to the corresponding amines.

N. MISRA

The Pharmacological Actions of (m-hydroxy phenethyl) Trimethyl Ammonium (Leptodactyline) *by V. Erspamer and A. Glasser (1960)* : **Brit. J. Pharmacol. 15,** *14,*

Leptodactyline occurs naturally in the skin of some amphibian species of the genus Leptodactylus in South America. It is the first m-hydroxy phenyl alkylamine so far discovered in a living organism. m-Tyrosine, hitherto unknown in nature, may represent the parent aminoacid of the substance.

The available experimental evidence suggests that leptodactyline causes a powerful nicotinic stimulation at the autonomic ganglia and the myoneural junction and a considerable neuro-muscular block, preceded and accompanied by short lived polypnoea and by muscular twitches all over the body, and lacks muscarinic effects. It may be classed among muscle relaxants producing neuro-muscular block by depolarisation.

The presence of an OH group at meta position seems to be of decisive importance for the intensity of pharmacological effects. Thus it is 10-20 times more powerful than its p-hydroxy isomer, candicine. Something similar has been observed with regard to the sympathomimetic pressor activities of the

three isomers of hydroxy phenyl-2-methyl amino ethanol. The meta-isomer (Synephrine) is 6 and 18 times more pressor than the para and ortho isomers respectively.

The physiological significance of leptodactyline is obscure. It seems probable that, in common with other amphibian extracts, extracts of the leptodactylus skin have also been used by the natives of South America in the preparations of some "Curares".

N. MISRA

Norepinephrine Depletion as a Possible Mechanism of Action of Guanethidine (SU 5864), a New Hypotensive Agent *by R. Cass, R. Kuntzman and B. B. Brodie (1960)* : **Proc. Soc. exper. Biol. & Med., 103,** *871.*

Guanethidine [2-(Octahydro-1-azocinyl)-ethyl-guanidine sulfate] produces a variety of sympatholytic effects of prolonged duration, including fall of arterial pressure. The drug acts by making the peripheral sympathetic system unresponsive to stimuli. This can not be attributed to interference with the conduction of nerve impulses on transmission across ganglia or to blocking the action of norepinephrine. It has been suggested that guanethidine may interfere with release and/or normal distribution subsequent to release of the transmitter at the sympathetic neuro-muscular junction. This study shows that it decreases level of norepinephrine in heart and spleen without lowering norepinephrine level in the brain in rabbits and cats. It is suggested that it lowers blood pressure by producing chemical sympathectomy through depletion of norepinephrine from peripheral nerve endings.

G. P. GUPTA

Site of Action of Hydralazine and Dihydralazine in Man *by B. Ablad (1959)* : **Acta. Pharmacol. Toxicol. 16,** *113.*

The effects of hydralazine and dihydralazine on the human circulation were studied with the aim of ascertaining whether the hypotensive action of these drugs is attributable to a central or to a peripheral site of action. Animal experiments suggested that hydralazine compounds administered intravenously were rapidly eliminated from the blood stream. It should therefore be assumed that, by occluding the circulation of one arm for 10 minutes and injecting the compound intravenously into circulating blood at the beginning of that period, only minute amounts of it would be distributed in that arm compared with other tissues.

Comparison of the changes in blood flow in that arm after administration of the drug and the changes occurring in the other arm, should afford the possibility of localizing the site of action.

With the two drugs, the blood flow tended to increase somewhat in the hand and forearm whose circulation had not been occluded, during and after injection of the drug. On the contrary, in the hand and forearm which had been occluded, a pronounced decrease in blood flow occurred when the reactive hyperaemia had subsided. This decrease was much less if the sympathetic innervation of the arm had been blocked. The results suggest that hydralazine and dihydralazine have a vasodilator effect *via* a site of action localized in the vascular bed.

G. P. GUPTA

Benzmalecene : Inhibition of Cholesterol Biosynthesis and Hypocholesteremic Effect in rats *by J. W. Huff and J. L. Gilfillan (1960)* : **Proc. Soc. exper. Biol. & Med. 103,** *41.*

An agent capable of inhibiting biosynthesis of cholesterol by mammalian system, would be of possible clinical interest in various hypercholesteremic states. The discovery that 2-C^{14} mevalonic acid is utilized by rat liver preparations for biosynthesis of cholesterol with an effeciency far greater than any previously tried precursor, has made possible the study of a number of compounds which would inhibit this system. The paper describes the results obtained with benzmalecene, a potent inhibitor of cholesterol biosynthesis. It inhibits *in vitro* incorporation of 2-C^{14}—mevalonic acid into cholesterol by liver homogenates. The inhibition is non-competitive. Oral administration of this compound to normal rats resulted in significant reduction in plasma cholesterol.

G. P. GUPTA

The Effects of Coronary Occlusion in Dogs Treated with Reserpine and in Dogs Treated with Phenoxybenzamine *by H. M. Maling, V. H. Corn Jr. and B. Highman (1959)* : **J. Pharmacol. exp. Ther., 127,** *229.*

It has been suggested that the ventricular tachycardia resulting from myocardial infraction in dogs is due, at least in part, to epinephrine and norepinephrine which are liberated from the necrotic myocardium and which may act upon the functional cells bordering the infarct. The present paper

reports experiments in which this concept has been tested by producing infarcts in dogs after the administration of reserpine to deplete the myocardium of norepinephrine. The effect of coronary occlusion in dogs under the influence of adrenergic blocking agent, phenoxybenzamine has also been studied. The experiments show that spontaneous ventricular ectopic activity and prolonged myocardial hypersensitivity occur after infarction in hearts depleted of norepinephrine by reserpine or pretreated with phenoxybenzamine. It is unlikely that the release of norepinephrine from the infarcted area has a significant role either in usual development of spontaneous arrhythmias and myocardial hypersensitivity or in the deposition of neutral fat around the boundary.

G. P. GUPTA