CURRENT LITERATURE

Evidence that tranquilising action of reserpine is associated with change in brain serotonin and not in brain epinephrine *by B.B. Brodie, K.F. Finger, F.B. Orlans, G.P. Quinn and F. Sulser (1960)*: **J. Pharmacol. exp. Ther. 129,** *250.*

A reserpine analogue, dimethylaminobenzoyl methyl reserpate (SU5171) can release half the brain nor-epinephrine in rabbits without releasing significant amounts of brain serotonin and without eliciting sedation. Larger doses release both amines and induce marked sedation. Additional strong evidence that the sedation produced by reserpine itself is not due to the loss of brain nor-epinephrine is provided by experiments in which rats and rabbits subject to stress are not noticeably affected by reserpine. These results suggest that the tranquilising actions of Rauwolfia alkaloids are not related to changes in brain nor-epinephrine level. The implications of these and certain other findings in the role of serotonin in the action of reserpine are discussed.

B N. DHAWAN

Effect of denervation and of cocaine on the action of sympathomimetic amines *by B.C.R. Stromblad (1960)*: **Brit. J. Pharmacol. 15,** *328.*

The secretory effect of sympathomimetic amines on the submaxillary gland of cat was increased after section of the chorda tympani (preganglionic parasympathetic) nerve. After sympathetic denervation, the secretory response to tyramine and phenylethylamine was absent, the response to dopamine and ephedrine decreased and that to adrenaline and nonadrenaline increased. Large doses of cocaine, given locally, produced changes similar to those obtained after sympathetic denervation. The sensitisation towards adrenaline and nor-adrenaline was obtained with smaller doses. Tyramine did not release catecholamines from suprarenal medulla. It is suggested that chromaffine tissue present in the adrenal medulla, or in skin, represents one type of store that can be released by nicotine. The adrenergic neurones, on which tyramine and similar substances might act as releasers, may represent a second ype of store of catechol amines.

B. N. DHAWAN

A series of 2, 6-Disubstituted phenoxyethyl ammonium bromides with true sympatholytic properties *by R.A. Mclean, R.J. Gens, R H. Mohrbacher, P.A. Mattis and G.E. Ullyot (1960)*: **J. Pharmacol. exp. Ther. 129,** *11.*

The original member of this series, compound TM 10, possessed true sympatholytic activity and seemed to have an application in clinical hypertension but for its muscarinic effects. The present study was, therefore, made in an effort to find a close analog which would retain the unique adrenergic blocking action but would lack the undesirable effects. 2, 6-Dimethyl- and 2, 6-dichlorophenoxyethyl trimethyl ammonium bromides together with their alpha and beta methyl analogs were synthesized and studied for autonomic effects. Muscarinic stimulant activity of the unsubstituted compounds was reduced by alpha methylation and eliminated by beta methylation. Sympathetic inhibitor potency revealed by relaxation of the nictitating membrane in unanesthetized cats was reduced by alpha-methylation. Tests with autonomic drugs and nerve action potential recordings indicated that the characteristic inhibition produced by the unsubstituted and the beta-substituted congeners is selective for the terminal sympathetic nerve endings.

G. P. GUPTA

Experimental Diabetes in Rats produced by Parentral Administration of Anti-Insu Slinerum *by Armin, J., Grant, R.T. and Wright, P.H. (1960)*: **J. Physiol., 153,** *146.*

Anti-insulin serum obtained from guinea pigs treated with bovine insulin has been injected intraperitoneally and infused intravenously for 20 hours into conscious rats. Provided the dose is sufficient, such serum induces a diabetic syndrome characterised by hyperglycaemia, glycosuria, polyuria, ketonuria and loss of appetite, leading in some cases to loss of body weight, oliguria, anuria, and death and in others to recovery.

The syndrome is similar to that found in the totally pancreatectomised rat but differs from alloxan diabetes. The authors conclude that the guinea-pig anti-insulin serum provides an useful tool for producing a diabetic state and for studying insulin metabolism.

Their results further suggest that the rat is capable of producing endogenous insulin at a rate of approximately 1.2-2.6 U/kg/ hr and maintains a rapidly secretable store of insulin in the pancreas (5·8 U/kg)

B. N. DHAWAN

Effect of Brain Stem Stimulation on Renal Function *by B.L. Wise and W.F. Ganong (1960)* : **Am. J. Physiol., 193,** *1291.*

The effect of stimulation of the hypothalamus, midbrain, pons and medulla oblongata on renal excretion of water, sodium and potassium and on glomerular filtration rate has been determined in 26 pentobarbitalised dogs with chronically implanted electrodes. Stimulation of 15 points in the dorsal medulla just lateral to the midline led to a rise of blood pressure and an associated fall in creatinine clearance and urine volume. The renal changes were blocked by renal denervation. Stimulation of 6 points in and near area postrema led to a rise in creatinine clearance and urine volume without a significant change in systemic blood pressure. Stimulation of 2 points in pons led to increase in sodium excretion without affecting the glomerular filteration rate. Stimulation of 3 points in the midbrain led to a decrease in creatinine clearance. Stimulation of 39 other points in medulla, pons, midbrain and posterior hypothalamus had no effect on renal function.

B. N. DHAWAN

Scratching Movements Evoked by Drugs Applied to the upper Cervical Cord *by W. Feldberg and K. Fleischhauer (1960)*: **J. Physiol, 151,** *502.*

A restricted region of the upper spinal cord at the level of C-1 is described from which scratching movement of the hind limb can be elicited regularly in pentobarbitalised cats by local application of 0.2% bromophenol blue or of 0.1% tubocurarine to the dorsal surface. These movements are associated with postural changes, the attitude being that of a cat scratching itself behind the ear. The movements could also be recorded myographically from the anterior tibialis muscle. These movements usually occur in bursts. If the drug is applied on one side they occur on the ipsilateral side, if to both, alternately on either side. These movements are not abolished by midcollicular decerebration. However, they could not be elicited in cats under chloralose anaesthesia. The possible mechanism involved is dicussed.

B. N. DHAWAN

Vasopressin stimulation of the isolated adrenal glands : Nature and mechanism of hydrocortisone secretion *by J.G. Hilton, L.F. Scian, C. D. Westermann, J. Nakano and O.R. Kruesi (1960)*: **Endocrinology, 67,** *298.*

By means of direct arterial perfusion of the adrenal glands of the hypophysectomized dog, it has been demonstrated that synthetic lysine, arginine and acetyl arginine vasopressins stimulate the adrenal cortex directly to secrete hydrocortisone. At dose ranges of 100 to 400 milliunits per minute of arginine vasopressin, the response was comparable to that seen following 1 unit per minute of ACTH. The cortisol stimulating activity of vasopressins was highly specific since it was not observed after other polypeptides such as oxytocin, insulin and glucagon or pressor amines such as epinephrine and norepinephrine. ACTH was consistently found to increase aldosterone secretion when perfused through the adrenals. The probable role of arginine vasopressin as a factor in the stress reaction and its ability to activate adrenal phosphorylase are discussed.

G. P. GUPTA

New test for the Biological assay of Oxytocin *by C. Mendex-Bauer, H M. Gabot and R. Caldeyro-Barcia (1960)*: **Science, 132,** *299.*

Lactating rabbits, 15th to 30th following delivery, are anesthetized with a short-acting barbiturate and a strip of mammary gland is removed. The strip is suspended in a bath containing Tyrode solution and the contractions are recorded isometrically. It shows no spontaneous activity and responds with reasonable linearity and stability to oxytocin at concentrations ranging from 0.5 to 10 milliunits per ml.

G. P. GUPTA

Relationship between feeding and satiation centers of the hypothalamus *by W. Wyrwicka and C. Dobrzecka (1960)*: **Science, 131,** *805.*

This study was undertaken to get a better understanding of the relations between feeding and satiation centers situated in the lateral hypothalamic area and ventro-medial nucleus respectively. Electrodes were implanted in the hypothalamus of 5 goats in which an alimentary instrumental conditioned reflex had been previously established. Electrical stimulation of the ventromedial hypothalamus inhibited the conditioned movements and food intake

in hungry goats. This also occurred in those satiated goats in which eating and conditioned movements were elicited by stimulation of the lateral hypothalamic area. Withdrawal of the stimulation of the medial hypothalamus evoked a short after effect in the form of a recovery or increase in the trained movements and food intake.

G. P. GUPTA

A Pharmacological Comparison of Therapeutically Useful Centrally Acting Skeletal Muscle Relaxants *by A.P. Raszkourski (1960)*: **J. Pharmacol. exp. Ther., 129,** *75.*

Six centrally acting skeletal muscle relaxants, chlorzoxazone, mephenesin, mephenesin carbamate, meprobamate, methocarbamol and zoxazolamine have been compared by a series of pharmacological testing procedure for determination of relative potency, duration of action and type of activity. All of these except mephenesin are compounds with relatively long duration of action. The procedure were meant to demonstrate their paralytic activity, acute toxicity, antipentylene-tetrazol and antistrychnine effects and capacity to inhibit polysynaptic reflexes.

Zoxazolamine and chlorzoxazone were most potent in inducing paralysis. Meprobamate also was quite potent where given orally. Chlorzoxazone possesses potent anti-strychnine and little antipentylenetetrazol activity. Meprobamate displayed potent anti-pentylenetrazol activity and relatively weak protective effect against strychnine. No disparity was detected between anti-strychnine activity and polysynaptic reflex blocking activity of the various compounds. The implications of the findings are briefly discussed.

B. N. DHAWAN

Isoproterenol vasomotor reversal by sympathomimetic amines *by D.T. Walz, T. Koppanyi and G.D. Maengwyn-Davies (1960)*: **J. Pharmacol. exp. Ther., 129,** *200.*

A variety of drugs have been reported to produce reversal of the vasodepressor action of isoproterenol. In this investigation the infusion of large doses of sympathomimetic amines of diverse structure were found to produce isoproterenol vasomotor reversal. The inhibitory blocking agent, DCI, neither reversed isoproterenol vasodilator effects nor reduced the effective

doses of active sympathomimetic amines. Hence, it has been concluded that besides possible blockade of inhibitory receptors by large doses of sympathomimetic amines employed, a "Sensitization" of the excitatory receptors must take place. The vasomotor reversal was observed in both cats and dogs, anesthetized with either alpha-chloralose or pentobarbital.

G. P. GUPTA

The Behavioral and other Pharmacodynamic Actions of Methoxypromazine [Tentone (R)], a Tranquilizing Agent *by W. D. Gray, A. C. Osterberg, C. E. Raub and R. T. Hill (1960) :* **Arch. int. Pharmacodyn., 125,** *101.*

The behavioral and other pharmacodynamic actions of phenothiazine derivative Methoxypromazine (1)—which differs from chlorpromazine (2) in having a methoxy group instead of chlorine at the 10 position—are reported in this paper. 1 and 2 were qualitatively similar in the behavioral and other pharmacodynamic actions. Animals treated with 2 were more depressed and less easily aroused than those given 1. Both were equally effective in reducing the spontaneous motor activity of mice and the toxicity of amphetamine in grouped mice. There was no difference in the action of two drugs on the conditioned avoidance behaviour of mice. 1 was more effective than 2 in reducing caffeine hyperactivity.

The hypothermic, antiemetic analgesia potentiating and barbiturate potentiating properties of the two drugs were similar. Increase in the susceptibility of mice to minimal seizures and the rate of passage of a charcoal meal, ulceration and gastric secretion in rats were affected to a similar extent by the two drugs. No important differences were found in hypotensive or adrenergic blocking action. I was more toxic orally while there was no difference in the acute lethality of the two drugs in rats and mice or intraperitoneal administration.

K. N. DHAWAN

Behavioral and Pharmacological Studies of Thiopropazate, A Potent Tranquilizing Agent *by G.C. Stone, B.M. Bernstein, W.E. Hambourger and V.A. Drill (1960)* : **Arch. int. Pharmacodyn ; 127,** *85.*

Thiopropazate dihydrochloride (Dartal) is a phenothiazine derivative which has pharmacological actions which qualitatively resemble those of chlorpromazine. Qunatitatively, thiopropazate was ten times as potent as chlorpromazine in prevention of rats' conditioned avoidance responses, reduction of spontaneous activity of rats and depression of blood pressure in the anesthelozed dog. It is more potent in antagonising the toxic effect of d-amphetamine sulfate in grouped mice, production of depressed state in dogs, depression of rats lever pressing for reward of food, and protecting dogs against apomorphine-induced emesis. It is, however, less potent than chlorpromazine in depressing rectal temperature in the mouse, potentiating hexobarbital narcosis in the mouse, and relaxing spasm in rabbit ileum induced with barium chloride. Chlorpromazine was also more toxic in mice by intravenous and intragastric routes.

R.P.K.

Pentyleneterazol Seizure Activity in Mice as Influenced by Route of Administration, Acute Adrenalecomy and Reserpine *by J. Maxwell Little and Eugena. A. Conard. (1960)* : **J. Pharmacol and Exp. Ther., 129,** *454.*

The effect of reserpine administration, acute adrenalectomy, and combination of both procedures on pentylenethazol (PTZ) doses producing clonic (CnD50) and tonic (TnD50) seizures, as well as the latent periods for onset of seizures, have been studied in mice.

The oral PTZ CnD50 and TnD50 were greater than corresponding values for subcutaneous administration, though the latent period for the onest of convulsions after oral PTZ was shorter. Oral as well parenteral administration of reserpine significantly decreased CnD50 and TnD50 Acute adrenalectomy increased significantly the parenteral PTZ CnD50 and TnD50 and also oral CnD50. The authors have also shown that whereas the adrenal gland is not necessary for the reserpine effect on PTZ threshold, nevertheless the reserpine effect is definitely influenced by the effect of acute adrenalectomy on PTZ seizure threshold.

R.P.K.

The effect of Mescaline on the optic evoked potentials in the unanesthetized Rabbit *by J. R. Smythies, W.P. Koelle and C.K. Levy (1960).* **J. Pharmacol. and Exp Ther. 120,** *462.*

The effect of mescaline on the optic evoked potential of unanesthetized rabbits was determined using quantitative methods with statistical control. These potentials consists of a surface positive negative primary wave followed by three fast waves super-imposed on a slow surface positive negative swing. In general the effect of mescaline is to cause facilitation of the primary wave at all doses used (40,20, 10, and 5 mg/kg) preceded by initial inhibition at the 40—and 20 mg/kg range. These same effects are obtained in the later waves (II, III and IV) except that the inhibition becomes progressively proponderant, the later the wave, and the fecilitation less and more delayed in onset. Changes also occur in the latency of the waves.

R.P.K.

Pharmacological Analysis of the Spinal compression vasomotor Response *by K.P. Bhargava and J.K. Kulsreshta (1960):* **Arch. int. Pharmacodyn., 127,** *67.*

Intrathecal compression of the spinal cord in cats (with the cord ligated at C-7, while still enclosed in the meniges) consistently elicited characteristic rise in blood pressure. Pressure of 100-200 mm Hg for 10-20 seconds was usually necessary for eliciting the response. The vasomotor response consisted of various components—a short latent period, an occasional pre-primary phase, a quick primary rise. and a secondary phase. Agents possessing specific pharmacological actions were studied for their effects on the response in order to analyse the various components.

Central stimulants (strychnine and pentylenetetrazol) potentiated the response and the central depressants (pentobarbital, mephenesin, and meperidine) depressed the response. d-tubocurarine augmented the response in decerebrate unanesthetized cats but depressed it in pentobarbitalized cats. Anticholinergic agents, atropine and hyoscine, potentiated the response. The pre-primary phase was occasionally observed in the control response and has been shown to be due to skeletal muscle effect. Neostigmine usually elicited a pre-primary phase when this was not present in the control. Neuromuscular blocking agents, d-tubo-curarine and succinylcholine, selectively blocked the pre-primary phase.

Thc quick primary component of the response may be ascribed to sympathetic neurogenic discharge and the slow secondary component to neurohumoral discharge from the adrenals. The extent of ganglionic blockade determines the extent of blockade of the SCVR. Since the adrenergic blocking agents (Hydergine, tolazoline and chlorpromazine) completely blocked the response it is evident that the response is finally mediated via the adrenergic effectors. The response has been shown to be independent of the tone of blood vessels.

R.P.K.

Some 2, 3—Disubstituted 3H-4-Quinazolones and 3H-4-Thioquinazolones *by G.B. Jackman, V. Petrow and O. Stephensons (1960)* : **J. Pharm and Pharmacol 12**, *529.*

Some 2-alkyl-3 aryl-3H-4 Quinazolones (1 : x = 0) have been prepared and number of them converted into the thioquinazolones (1 : x = S). A new method for the synthesis of 3-alkyl-3-aryl-3-H-4 quinazolones has been developed and has been employed for the synthesis of represent at the derivatives.

Biological study of the above compounds revealed that some of them, and in particular the 2-alkyl-3-halo-phenyl-3H-4-quinazolones are potent anticonvulsant agents.

R.P.K.