CURRENT LITERATURE

Comparative effects of various Rauwolfia Alkaloids on centrally evoked Vasopressor responses *by Bhargava, K. P. and Borison, H. L. (1957):* **J. Pharm. & Exper. Therap., 119,** *395.*

Certain Rauwolfia alkaloids (reserpine, rescinnamine, serpentine, ajmaline and ajmalicine) were investigated for their central vasodepressant effects in cats. 5-Hydroxytryptamine was included in this study because it has been implicated as a mediator in the action of reserpine and rescinnamine. Pressor responses were elicited from the medullary vasopressor locus with the steriotaxic technic, and from the spinal cord by spinal fluid (CSF) compression after high spinal ligation. Epinephrine (or norepinephrine) was used to determine peripheral drug effects on vascular reactivity. The results indicate that the alkaloids rescinnamine and reserpinine are to be classed with reserpine because of their mildly depressant effect on electrically induced medullary pressor responses and their lack of effect on pressor responses from spinal compression and from the injection of epinephrine. Similarly, the alkaloids serpentine and ajmaline can be classed with alseroxylon because of their primary depressant effect on pressor responses evoked by spinal compression as well as their potent depressant effect on medullary responses. These two alkaloids, like those in the reserpine group, did not appreciably affect pressor response to epinephrine. Ajmalicine has been demonstrated, by the cross-circulation technic, to possess central depressant activity in addition to its adrenergic blocking activity. 5-HT has been included in the reserpine group because of certain properties which serotonin shares with reserpine, including failure to produce spinal vasomotor depression. Effects of the various alkaloids on the resting blood pressure level are complex and have been discussed in light of the central vaso-depressant influences of these drugs. The results of the investigation indicate that reserpine does not contribute significantly to the pronounced hypotensive activity of alseroxylon.

A peripheral action of reserpine *by Maxwell, R. A., Ross, S. D., Plumer, A. J. and Igg, E. B. (1957):* **J. Pharmacol. & Exper. Therap , 119,** *69.*

Chronic oral administration of reserpine and chlorisondamine chloride to unanesthetised normotensive and hypertensive dogs produced additive depressor effects on arterial blood pressure. However, reserpine when administered

intravenously to anaesthetized dogs after they had received high doses of ganglionic blocking agent, produced a pressor responses of variable magnitude which lasted from 20 minutes to 1 hour. Similar pressor responses could be elicited in unanesthetised dogs treated chronically with reserpine, upon intravenous administration of ganglionic blocking agents. In spinal dog reserpine produced pressor responses and also relaxed transiently the denervated relaxed nictitating membrane of dog and cat. Evidence presented strongly indicates that these unusual effects of reserpine are peripherally evoked and further suggests the involvement of a sympathomimetic humoral mechanism as these effects are blocked by phentolamine.

A method for the biological assay of Reserpine and Reserpine like activity *Chen, G. and Bohner, B. (1957):* **J. Pharmacol. & Exper. Therap., 119,** *559.*

Four procedures are described for the biological assay of reserpine and reserpine like substances in mice: A) the lowering of electrically induced tonic extensor seizure threshold, B) antagonism with Dilantin against electroshock, C) antagonism with Dilantin against metrazol-induced maximal tonic extensor seizures, and D) the reduction of seizure latency between the first clonic and the final maximal tonic-extensor stage of metrazol induced convulsions. The biological activity of rescinnamine was compared with that of reserpine. Advantages and limitations in each procedure are pointed out in discussion of assay results.

Pharmacological effects produced by Intracerebral injection of Drugs in the conscious Mouse *By Haley, T. J. and Mccormick, W. G. (1957):* **Brit. J. Pharmacol., 12,** *12.*

A method has been described for the study of the central effects produced by the intracerebral injection of drugs in unanesthetised mouse. A 3/8 in. 27 gauge hypodermic needle attached to a 0.25 ml. syringe is inserted through the skull into the brain. The site of injection is 2 m.m. from either side of midline on a line drawn through the anterior base of the ears. For ascertaining the areas in the brain ventricular system into which the drugs peneterated indian ink is injected and histological studies made. The

effects observed are in good agreement with those obtained after similar injection in cats, dogs and human beings. After intracerebral injection, drugs of diverse structure produced certain generalised effects like changes in positioning of the tail, stupor, hyperexcitability and tachypnoea. Both acetylcholine and methacwoline produced akinetic seizure and depression. Atropine produced piloerection, increased sensitivity to sound and touch, clonic convulsions and scratching. Hexamethonium caused parkinsonian like muscle tremors and peripheral vasodilatation. After adrenaline hyperexcitability, exopthalmos, stupor and death from pulmonary oedema resulted, but (+) –methylamphetamine produced only piloerection and exaggerated activity in reponse to sound and touch. Ergotamine caused a decreased sensitivity to sound and touch, micturition, and stupor, while ergometrine caused clonic convulsions, piloerection, defaecation and stupor.

A method for evaluation of hypnotic drugs *by Issacs, B. (1957):* **Lancet, 1,** *556.*

A new method for compairing the hypnotic activity of drugs in man depending on the resistance of the sleeping subject to working impulses from the urinary bladder is described. The subject empties his bladder before going to bed and then drinks 500 to 1,000 ml. of water. On awakening the volume of urine voided in ml. (v) and duration of sleep in minutes (t) are recorded. From these data the mean depth of sleep (D) is calculated from the equation: $D = \log t \times \log v$.

Potentiating effect of quinine, I. Analgesics and Hypnotics *by Orahovats, P. D. Lehman, E. G. and Chapin, E. W. (1957):* **Arch. Int. Pharmacodyn., 110,** *245.*

Quinine potentiates the effects of analgesics, narcotics, hypnotics and anaesthetics in animals without increasing their acute toxicity. Quinine, by itself, does not produce analgesia, central nervous system depression or hypnosis. Potentiating effects are obtained only when quinine is administered together with or prior to an analgesic or a hypnotic, not when given after one of these agents. The effective potentiating doses of quinine range between 10 and

100 mgm/kgm. The optimal premedication time with quinine, regardless of the route of administration is 30 to 60 minutes prior to a narcotic or a hypnotic. Morphine, 6-methyl-Delta^{6}-desoxymorphine, methadone, codeine, nalorphine, pentobarbital, hexobarbital, chloral hydrate, chloralose and ethyl alcohal are potentiated by quinine.

Metabolism and metabolic response to electrical pulses in white matter from the central nervous system *by Bollard, B. M. and McIlwain, H. (1957):* **Biochem. J., 66,** *651.*

Subcortical white matter of guineapig, rabbit and man was capable of respiration and glycolysis in ordinary glucose salines at one half to two thirds of the rates found in the cerebral cortex. Under these conditions the guineapig subcortical white matter resynthesised phosphocreatine to a level of about 0.9 M mole/g. In maintaining respiration glucose was replaceable by pyruvate; with succinate and glutamate (but not with acetate and citrate) respiratory rates were greater than in the absence of added substrate, but decreased with time. Glutamate did not, however, support resynthesis of phosphocreatine.

Respirations, glycolysis and phosphocreatine formation maintained by glucose responded to application of electrical pulses to the tissue. Pyruvate also permitted response but other substrates remained ineffective in this respect.

Certain of these characteristics were examined also in tissues from the medulla, thalamus, midbrain and sciatic nerve.

Biosynthesis of cardiotonic sterols from cholesterol in the toad, Bufomarinus *by Siperstein, M. D., Murray, A. W. and Titus, E. (1957)* **Arch. Biochem. Bioph., 67,** *154.*

The synthesis of cardiotonic sterols, marinobufagin and marinobufotoxin has been demonstrated in the toad, Bufomarinus. Approximately 2% of administered cholesterol-4-C^{14} is converted to the sterol lactones in a 75 day period. No incorporation of acetate-C^{14} was detected.

On the release of bradykinin by trypsin and snake venoms *by Hamberg, U. and Roche-Silva, M. (1957)*: **Arch. Int. Pharmacodyn , 110,** *222.*

A comparative study of the bradykinin releasing effects of trypsin and the venoms of B. jararaca and Agk. mokasen is presented. Maximum yield of bradykinin can be obtained from fresh and denatured plasma with an appropriate amount of trypsin. With dry venoms of B. jararaca the yield of bradykinin from fresh plasma is lower. Heat denaturation of venom in boiling water for a few minutes increased considerably its ability to release bradykinin from fresh plasma, owing probably to the disappearance of the bradykinin destroying activity of the dry venom. Upon the denatured plasma, the heated venom could release the maximum bradykinin provided the concentration was high enough and the time of incubation conveniently prolonged, although the proteolytic activity upon casein disappeared. A similar decrease of the proteolytic activity of the venom of Agk. mokasen on casein was obtained after heating, while the bradykinin releasing effect remained unchanged.

The release of bradykinin by these venoms does not bear a direct relationship to their proteolytic activity upon casein. The possibility of its depending upon the esterase activity of both the venoms on BAME (benzoyl-L-arginine) is discussed.

Mechanism of Cardiac slowing by Methoxamine *by Aviado. D.M. and Wnuck, A. L. (1957)* : **J. Pharmacol. & Exper. Therap., 119,** *99.*

Effect of Methoxamine was studied on various Cardiac reflexes in dogs. Epenephrine and norepenephrine were used as prototypes for comparison with methoxamine. The authors conclude that the baroreceptors in the carotid sinus and aortic arch are responsible for the major component of the bradycardiac responses to intravenous injection of methoxamine because selective denervation of both groups of receptors significantly reduce the intensity of response. The rise in arterial pressure brought about by the constrictor action of the drug on systemic vessels activate the baroreceptors in the sinuses and aortic arch. The slight bradycardiac response which presists after carotid-aortic denervation may be due to activation of the stretch receptors in the cardiac wall as a result of rise in auricular and ventricular pressures accompanying the pressor action of methoxamine, although no direct evidence is offered.

Effects of d-lysergic acid diethylamide and its Brom Derivative on Cardiovascular responses to serotonin and on arterial pressure *by Salmoirgaghi, G. C. McCubbin, J. W. and Page, I. H. (1957)*: **J. Pharm. & Exper. Therap., 119,** *241.*

LSD and BOL in larger doses effectively antagonised pressor-depressor responses to serotonin in rats. In cats they showed slight and irregular activity against systemic responses to serotonin and in dogs BOL exhibited weak and inconstant activity. The vaso constrictor responses to serotonin in a perfused extremity were also poorly antagonised by BOL; antagonistic activity when present was non specific. BOL, like ergotamine, failed also to prevent the chemoreceptor stimulat action of serotonin in dogs.

BOL caused sharp and partly sustained fall in arterial pressure when given in quick injection to anaesthetized rats. This effect was less marked in cats and dogs. LSD or BOL given chronically by mouth had no effect on arterial pressure of chronic renal or neurogenic hypertensive dogs.

Effect of temperature on arrhythmia of isolaled rabbit atria *by Beaulnes, A. and Margaret Day (1957):* **J. Physiol., 137,** *86.*

The authors produced arrhythmias in isolated rabbit atria by electrical stimulation in the presence of acetylcholine and 0.5 N K solution. The rhythm varied from 250 to 1440 beats/min. Arrhythmias produced at 37°C diminished in rate on lowering the temperature and often ceased altogether and on raising the temperature the rapid rhythm returned. It was also found that higher temperature (37°C) was more favourable than lower temperature (29°C) for the induction of arrhythmia. Evidence is presented to show that arrhythmia is favoured by conditions which shorten the action potential.

The seperate existence of the Pituitary Erythropoietic Hormone *By Van Dyke D. G., Simpson, M. E., Contoponolos, A. N. and Evans, H. M. (1957):* **Blood., 12,** *539.*

Comparison of the erythropoietic and ACTH activities of boiled and autolycally digested pituitaries of various animals was made on hypophysectomised

female rats. Proportion of these two activities in different preparations varied so greatly as to assure their seperate existence. Autolytic digestion consistently reduces the ATCH activity, while erythropoietic activity is retained. They also found that oxcycellulose is a better adsorbent of ACTH than of erythropoietic harmone. Their observations give added chemical evidence to the accumulated biological evidence establishing the seperate existence of these two pituitary principles.

The part played by LH and FSH in the antiovarial effect as caused by Testosterone propinate in rats *by Gans, E. and DeJongh, S. E.* (*1957*): **Acta Physiol. Pharmacol. Neerl., 5,** *271.*

The antiovarial effect of 50 mg. testosterone propionate daily in adult rats is strongly counteracted by very small amounts of chorionic gonadotrophin and therefore, considered to be due mainly to a fall in circulating LH. Decrease in FSH plays only a minor part in the ovarian atrophy. The alteration in uterine and hypophyseal weights, as observed in these experiments are consistant with the assumption of testosterone propionate enchancing the release of oestrogens by the ovaries as caused by chorionic gonadotrophin.

A series of new compounds inhibiting coenzyme A and cholesterol and Lipid—increasing factors *by Garuttini S., Morpurgo, C., Murelli, B., Paoletti, R. and Passerini, N.* (*1957*): **Arch. int. Pharmacodyn., 109,** *400.*

The above workers found that phenylacetic acid (a substance which is also used clinically for lowering cholestremia) can inhibit coenzyme A. Some compounds were made, similar to phenylethylacetic acid, in which phenyl was substituted by more complex radicals. These compounds also inhibited coenzyme A, sometime very strongly, proportionately with the dose for acetylsulfanilamide synthesis and for acetylcholine synthesis as well. Some of these compounds inhibited the increase of cholesterol in regenerating liver, as well as that caused by Triton experimentally induced hypercholestremia and hyperlipemia.

The Assay of Anti-acethylcholine agents for antagonism of Pilocarpine induced salivation in Rabbits *By Brown, D. M. and Quinton R. M.* (*1957*) **Brit. J Pharmacol., 12,** *53.*

An oral dose of 0.5 to 0.625g/kg. urethane dissolved in 25 ml. saline is employed to sedate the rabbits. It was found that administration of urethane increases the volume of saliva secreted after injection of pilocarpine. 0·5 mg/kg. pilocarpine nitrate is injected subcutaneously 30 to 45 min. after the oral dose of the urethane. In order to standardize conditions they suggest that drugs under investigation be injected 15 minutes before the pilocarpine although the activity displayed under these conditions may not be maximal particularly with compounds containing quarternary nitrogen atom. Atropine Sulphate, Atropine methylnitrate, Benactyzine and Oxyphenonium were tested by this method. It gave results of fair accuracy and reproducibility, permitted a full statistical analysis, and provided an estimate of the error.

On the factors which determine the amplitudes of the 'Miniature End-Plate Potential' *By Katz, B. and Thesleff, S.* (*1957*): **J. Physiol., 137,** *267.*

The miniature end plate potentials were recorded from different frog muscle fiberes and mean amplitude were found to vary over a range of more than 10 : 1. They also determined the 'input conductance of the muscle fiberes (which is related to their diameter) and a highly significant correlation was found (miniature e. p. p and resistance across fibre surface varying in the same direction). They attribute the large differences in the mean amplitudes of miniature potentials to the electrical charges associated with differences in fibre size. The 'quantum' of acetylcholine released is constant even if one compares myoneural junctions from different fibres of evidently varying diameters.

The chemical nature of Darmstoff *by Vogt, W.* (*1957*): **J. Physiol., 137,** *154.*

The chemical nature of Darmstoff was investigated using an extract prepared from horse small intestine. With paper chromatography and mild acidic hydrolysis it could be shown that Darmstoff consist of several acidic phospholipids, one of which is an acetalphosphatidic acid. The chemically prepared acetalphosphatidic acid was shown to have smooth muscle stimulating activity similar to that of natural Darmstoff.

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