COMPARISON OF HYDROCHLOROTHIAZIDE AND QUINETHAZONE IN THE TREATMENT OF NON-AMBULATORY PATIENTS WITH CONGESTIVE HEART FAILURE. R. W. Payne, J. R. E. Valadares* and R. R. Cole.* Univ. of Okla. School of Med., Okla. City, Okla.

The diuretic properties of hydrochlorothiazide, an aromatic disulfonamide, were compared with those of quinethazone (2-ethyl-7-chloro-6-sulfamyl-1,2-dihydro-4-quinazolone), an aromatic monosulfonamide, in 14 bedfast digitalized patients with chronic congestive heart failure. On the basis of urinary and serum Na, K and Cl changes the drugs were equally effective when daily doses of 50 mg. of hydrochlorothiazide were compared with 100 mg. of quinethazone. Electrolyte changes were more prominent than effects on urinary volume. All patients were maintained grossly edema-free with both compounds. While the serum BUN tended to initial slight elevation in the group, no further increase was provoked by either drug. Serum uric acid concentrations were elevated by the agents in 9 of the patients - most marked in one patient with associated gout. Both agents exhibited a comparable mild antihypertensive effect. It is concluded that although both of the diuretic agents show similar qualitative effects, quinethazone is half as potent as hydrochlorothiazide on a mg. basis.

FURTHER LABORATORY STUDIES ON TRIAMTERENE, SK&F 8542. V. D. Wiebelhaus*, J. Weinstock*, F. T. Brennan*, G. Sosnowski*, T. Larsen* and K. Gahagan*. Smith Kline & French Labs., Philadelphia 1, Pa.

Triamterene, SK&F 8542 (2,4,7-triamino-6-phenyl pteridine) antagonizes the effects of aldosterone on both Na^+ and K^+ in the rat and the dog. Triamterene reduces the kaliuretic effects of chlorothiazide in dogs. These observations suggest that the pteridine influences the renal secretion of K^+. This K^+ effect is much more pronounced in the acidotic than in the alkalotic dog. When SK&F 8542 is administered to dogs receiving infusions of KCl, natruresis ensues but there is no evidence of an effect on the excretion of K^+ under these circumstances. This distinguishes the natruresis of the pteridine from that of the cardiac glycosides which do not produce natruresis under these conditions. It also suggests that when plasma levels and/or filtered loads of K^+ are elevated the K^+ effect of the pteridine is essentially nil, suggesting a self-limiting phenomenon. Given to an adrenalectomized dog supported on a high sodium diet but with no steroidal supplements, SK&F 8542 consistently increased sodium outputs, the responses ranging up to 53 per cent increase. While triamterene certainly antagonizes the effects of aldosterone on both Na^+ and K^+ it may be more properly designated as an inhibitor of the renal transfer of Na^+ and K^+, possibly with a distal site of action.

SOME ACID-BASE EFFECTS OF 5,5'-DIMETHYL-2,4-OXAZOLIDINEDIONE (DMO) IN RATS. C. Dean Withrow* and Dixon M. Woodbury. Dept. of Pharmacology, University of Utah, Salt Lake City.

Intraperitoneal administration of 500 mg/kg of DMO to adult Sprague-Dawley rats caused marked changes in tissue and plasma acid-base parameters. Plasma total carbon dioxide concentration was reduced from approximately 23 to 16 mM/L after drug treatment. Decreases of about 3 mM/kg wet weight in total carbon dioxide content of both skeletal muscle and cerebral cortex were observed in the same animals. DMO effects were maximal in approximately 3 hours and had waned in 5 to 6 hours. Treatment of rats with 100 mg/kg DMO also resulted in significant but smaller changes in plasma and tissue carbon dioxide values. These experiments indicate that DMO is not an inert compound insofar as acid-base metabolism is concerned. The use of this drug to estimate cell pH in rat tissues must be cautiously applied if meaningful values for cellular hydrogen ion concentrations are to be obtained. (Supported by grants 2G-153 and B-381, N.I.H., and by National Neurological Research Foundation.)

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ANTAGONISM OF LYSERGIC ACID DIETHYLAMIDE (LSD)-INDUCED HYPERTHERMIA. John T. Elder* and M. Kent Shellenberger*. Dept. of Pharmacology, University of Washington, Seattle 5, Wash.

Various agents have been used in attempts to prevent the pyretogenic response to LSD, 50mcg/kg I.V. as a means of determining the mechanism by which it occurs. Male rabbits were used and temperatures were recorded every 30 min. for 2 hours before and during 5 hours after LSD. Hexamethonium, 10 mg/kg I.V. 30 min. before LSD did not affect the temperature rise. Phenoxybenzamine, 10 mg/kg I.V., 60 min. prior to LSD not only abolished the rise in temperature but reduced it below control levels. The same dose given 23 hours prior to LSD produced significant reduction in the response also. Reserpine, 2 mg/kg I.V. immediately prior to LSD produced a potentiation of the LSD response. Guanethidine, 10 mg/kg I.V. 18 hours before LSD caused significant attenuation of the response. Both reserpine and guanethidine were given on a time schedule intended to produce maximal amine depletion at about the time the peak pyretogenic response to a subsequent dose of LSD occurred. The difference in the effects of these two agents may be due to the relative speed of release of amines; reserpine producing a much more rapid release than guanethidine. Also to be considered are release of peripheral and central catecholamines and serotonin.

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DRINKING INDUCED BY CHOLINERGIC STIMULATION OF HYPOTHALAMUS IS A MUSCARINIC, NOT NICOTINIC, ACTION. Larry Stein* and Joseph Seifter. Basic Medical Sciences Research Division, Wyeth Laboratories, Radnor, Pa.

Grossman (Science 132:301, 1960) has reported that eating or drinking can be elicited by the direct application of crystalline substances into the lateral hypothalamus of the rat. Adrenergic substances (norepinephrine and epinephrine) selectively induced eating, and cholinergic substances (carbachol, acetylcholine capped by physostigmine) selectively induced drinking. We have confirmed and extended the cholinergic findings. Minute quantities (1-5 µg) of crystalline compounds were introduced into the brains of 28 rats through permanently indwelling cannulae. Muscarine had an effect equal to carbachol, producing strong drinking within 5-10 minutes that persisted with variable intensity for almost an hour. Nicotine had the same, small "non-specific" effect as sodium chloride -- about twice as much as no-drug controls, but only 20% of the effect of carbachol or muscarine. (Potassium chloride and sucrose had no effect). The effects of carbachol and muscarine were largely blocked by prior application of atropine. These findings suggest that cholinergically-induced drinking is a muscarinic, not nicotinic, action. We confirmed also that noradrenaline elicits eating, but our adrenergic effects have been smaller and less reliable than the cholinergic ones.