digoxin into guinea pigs increases the K content of the ventricles and serum. Toxic doses produce a further rise in serum K whereas the amount of K in the ventricles does not differ significantly from that of untreated animals.

Intravenous infusion into guinea pigs of KCl solution (8·4–134 mM) simultaneously with digoxin (56 μg/ml) fails to influence the lethal dose of digoxin, but with 268 mM solution of the salt the lethal dose of digoxin is decreased ten-fold.

The time of onset of the positive inotropic response of the isolated right ventricle of the guinea pig, stimulated electrically, to a toxic dose of digoxin is not influenced when the KCl concentration of the bathing fluid is raised from 5·6 to 13·5 mM.

The rate of increase of the amplitude of contraction is markedly reduced but the maximum attained is unaltered and the life of the ventricle is greatly prolonged.

The duration of the therapeutic action of digoxin in the failing heart-lung preparation of the guinea pig is increased if the K content of the circulating fluid is increased from 5·6 to 6·1 mM, but considerably decreased when it is raised to 12·1 mM.

These data suggest that: (1) the extracardiac tissues are more sensitive than the myocardium to the action of digoxin on K flux. and (2) that K, depending on its concentration in the heart, can increase or decrease the cardiotoxicity of digoxin.

45 Pharmacology of Chlordiazepoxide (Librium) and Analogues. L. O. Randall and B. Kappell (U.S.A.).

Chlordiazepoxide (Librium) is the first member of a new chemical class of compounds which has shown unique taming effects in animals[1] and powerful anti-anxiety effects in human subjects.[2] Other pharmacological effects first observed in animals and later confirmed in human subjects include anticonvulsant activity and muscle relaxant effects at low doses, with sedative effects and appetite-stimulating effects at high doses. Certain pharmacological effects which were minimal in animal tests were also minimal in human subjects including effects on blood pressure, heart rate and autonomic nervous system.

Analogues of chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3H-1:4-benzodiazepine 4-oxide hydrochloride) showed a similar type of activity in muscle relaxant and anticonvulsant tests. Screening tests include the inclined screen test in mice, the fighting mouse test,[3] the anti-strychnine test and the gross behaviour test in cats. Benzodiazepines having activity of interest include 7-chloro-1-methyl-5-phenyl-3H-1:4-benzodiazepin-2(1H)-one; 7-chloro-2-oxo-5-phenyl-1:2-dihydro-3H-1:4-benzodiazepine 4-oxide; 5-phenyl-7-trifluoro-methyl-3H-1:4-benzodiazepin-2(1H)-one; 7-chloro-2-oxo-5-phenyl-1:2-dihydro-3H-1:4-benzodiazepine; 7-chloro-5-(2-chlorophenyl)-3H-1:4-benzodiazepin-2(1H)-one and 7-nitro-5-phenyl-3H-1:4-benzodiazepin-2(1H)-one.

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46 The Effects of Ethanol and Chlordiazepoxide in Altering Autonomic Responses Evoked by Isocortical and Paleocortical Stimulation. M. N. Carroll, jr., E. C. Hoff, J. F. Kell, jr. and C. G. Suter (U.S.A.).

Unipolar stimulation of the anterior sigmoid gyrus (I), limbic lobe (II), hypothalamus (III), N. Von Bechterew (IV), amygdala (V), and central gray (VI) loci in flaxedilized cats evoked pressor responses, cardiac arrhythmias (nodal and ventricular extrasystoles and ventricular tachycardia with indications of coronary insufficiency), mydriasis and striking inhibition of mobility of the pyloric sphincter and ileum. Salivation was elicited from subcortical loci II, III, IV and VI, and retraction of the nictitating membrane was noted from I, III and VI. Lacrimation was not observed from any of the areas studied.

The intravenous administration of chlordiazepoxide (10–20 mg/kg) elicited a transient hypotention and slight bradycardia whereas 10 per cent ethanol (3 ml/kg, i.v.) produced increased pyloric mobility and slight to marked alterations in the electrocardiogram. Chlordiazepoxide greatly attenuated pressor responses from all brain areas studied whereas ethanol exerted weak anti-pressor effects in areas I, II and strong blocking action against central stimulation of III. Centrally-induced cardiac arrhythmias were completely blocked by chlordiazepoxide in loci II and V whereas ethanol partially attenuated the response only from II. Neither compound showed any activity against centrally evoked salivation, mydriasis or gastrointestinal inhibition.

Inasmuch as chlordiazepoxide lacks the undesirable side effects of ethanol, its prophylactic potential against centrally-induced arrhythmias and pressor responses merits intensive investigation.

47 Effects of Chlordiazapoxide (Librium) and Other Psychopharmacological Agents on "Fixated" Behaviour in Rats. W. T. Liberson, A. Kafka and E. Schwartz (U.S.A.).

Effects of various therapies were investigated on fixation rats[1] with regard to: (1) motor coordination; (2) sensory and symbolic discrimination and speed of their acquisition; (3) reaction times to stimuli during approach, avoidance or escape behaviour; (4) variability of behaviour; (5) compulsive rigidity; and (6) variety of patterns