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Received December 23, 1958. P.S.E.B.M., 1959, v100.

Effect of Digitalis on Potassium Toxicity in Isolated Turtle Heart. (24689)

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It is well accepted that potassium administration can antagonize toxic effects of digitalis(1). Patients receiving digitalis may exhibit digitalis toxicity when their potassium intake is restricted, and patients who are overdigitalized frequently respond to administration of potassium. The converse of these situations has not been satisfactorily investigated. Does digitalis antagonize the effects of potassium toxicity on the myocardium? A perfusion experiment in the isolated turtle heart was devised to study the effects of rapidly acting digitalis preparations on induced potassium intoxication. According to Szent-Gyorgi, the mineraloid hormone of adrenals abolishes "Treppe" in the isolated perfused turtle heart as does digitalis(2,3). The protective action of water soluble desoxycorticosterone glucoside against potassium toxicity was also investigated.

Methods. Hearts were removed from 30 unanesthetized turtles to include 1 cm of the truncus. The dorsal aorta was cannulated and the myocardium perfused through the coronaries, as shown in Fig. 1, with various test solutions(4). The phrenum was attached by suture to metal bar which acted as an isometric lever. Tension developed in the bar was transformed into electrical energy through suitable transducer and recorded on oscillograph. The basic solution (Howell's solution) for perfusion contained the following constituents: NaCl 0.7%, KCl 0.3%, $CaCl_2$ 0.026%, $NaHCO_3$ 0.003%, MgCl 0.01%, glucose 0.1%. Potassium was added to basic solution to augment the final concentrations of potassium by 4, 6, 8, and 12 meq/liter of potassium chloride. The substances to be tested, lanatoside C, acetyl strophanthidin and desoxycorticosterone glucoside were added in varying concentrations to the potassium enriched perfusion medium. Lanatoside C and acetyl strophanthidin were added to the perfusion media to give following concentrations: .4, .8, 1.2, and 1.6 mg/liter. Between each experiment with potassium enriched solution the heart was permitted to return to normal beat by thoroughly perfusing with plain Howell's solution.

Results. A slow infusion of KCl in Howell's solution was capable of producing cardiac arrest in most experiments when the concentration of KCl was augmented by 8 meq/l. There was individual variation, and occasionally arrest was produced with additional 6 meq of potassium/liter. Similarly, some hearts did not arrest even with an additional 10 meq/l. In lower concentrations, KCl impaired development of tension by the myocardium but did not cause arrest. Both amplitude of isometric contraction and rhythmicity were recorded. Potassium solution caused linear decrease in development of tension until asystole occurred (Fig. 2a). Cardiac rate remained constant during perfusion with potassium. Changes in rhythmicity were not progressive as were changes in amplitude of contraction. Rhythmicity was sud-

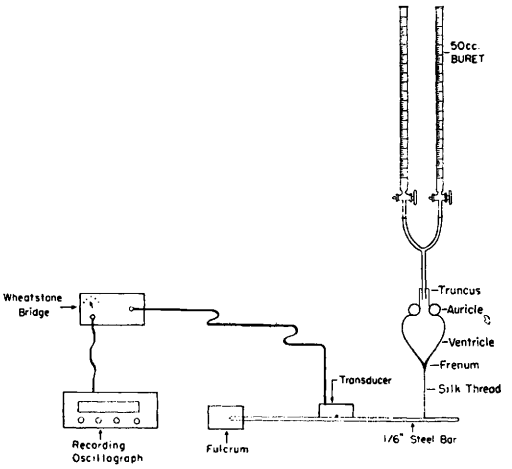

FIG. 1. Schematic diagram of technic used for recording rate and amplitude of contraction in isolated turtle heart.

denly abolished at critical concentration of potassium in the perfusate.

Addition of cardiac glycoside to the potassium containing perfusate usually resulted in sudden abolition of rhythmicity when the amplitude of contraction was not appreciably diminished. Often, complete asystole occurred after 8 or 9 contractions when the concentration of glycoside was greater than .4 mg/liter. Digitalis maintained the strength of contraction even with high concentrations of potassium (Fig. 2b). Rhythmicity was abolished suddenly even when strength of contraction was unimpaired. Increasing the concentra- of glycoside failed to protect against development of potassium asystole and even favored its more rapid development. Use of digitalis as a perfusate prior to perfusion with KCl-digitalis solution did not offer any protection against potassium arrest. However, after perfusion with KCl solution decreased the amplitude of contraction, digitalis was effective in returning the amplitude of contraction to normal. This occurred even though digitalis would cause a sudden cessation in systole. This effect on rhythmicity was partly caused by the production of heart block which could be detected visually. Desoxycorticosterone gluconate was relatively ineffective as compared to digitalis.

Discussion. Perfusion of isolated turtle heart with varying solutions of potassium was effective in first diminishing the strength of isometric contraction and eventually producing asystole. Digitalization of the isolated heart was effective in sustaining development of tension by the myocardium but did not prevent, and even accentuated, the adverse effect of potassium on spontaneous rhythmicity. The adverse effect of digitalis on rhythmicity was partially due to more rapid development of total heart block as observed by persistent auricular rhythmicity with ventricular asystole.

Although conclusions drawn from perfusion experiments in the isolated heart are hazardous, results seem to indicate that digitalis might be effective in protecting against adverse circulatory effects of hyperpotassemia in the intact animal. Digitalis exerts its action by maintaining the strength of myocardial contraction(5). Even though digitalis did not offer protection from development of asystole, the heart block is easily produced in turtles and for this reason, the situation as to rhythmicity may not be analogous to intact mammalian hearts. However, it is difficult to study development of tension in either isolated or intact mammalian hearts, and our study obviates the problem.

Summary and conclusions. Potassium causes diminished strength on isometric contractions in the isolated turtle heart. This decrease in strength of contraction is progressive with increasing concentration of potassium in the perfusate. Digitalis does not protect against development of an asystole in the isolated turtle heart, but does sustain the

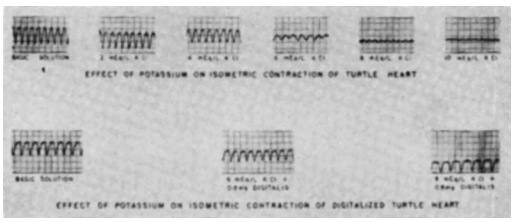

FIG. 2. Development of tension in isometric contraction of turtle heart. Strength of contraction is markedly diminished by addition of potassium to basic solution as shown in upper frames. In the lower frames, the effect of digitalis in preventing this diminution of contraction is demonstrated. At 8 meq/l of additional potassium, digitalis has sustained contraction.

strength of myocardial contraction.

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Received December 29, 1958. P.S.E.B.M., 1959, v100.

Ability of Some Progestational Steroids to Stimulate Male Accessory Glands of Reproduction in the Rat. (24690)

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The principle of multiplicity of actions of steroidal hormones has long been recognized. Steroids thought of as "estrogens" because of ability to stimulate female reproductive tract may also be "androgens" because of ability to stimulate the male tract. Similarly, hormones thought of primarily as adrenal corticoids have ability to produce progestational changes in the uterine endometrium. Progesterone resembles "androgens" because of its property of stimulating the prostate of castrated animals(1). This fact has recently assumed practical significance because of the finding of Wilkins *et al.* that occasionally women treated with progestational substances during pregnancy deliver mildly masculinized female infants(2). Some steroids recently introduced into therapeutic use are remarkably potent in causing glandular proliferation of endometrium, inhibiting ovulation, and to greater or lesser degree maintaining pregnancy in ovariectomized animals(3,4.5). Because of the possible importance of "androgenic" properties of progestins in treatment of pregnant women, a comparison has been made of ability of several of these compounds to stimulate the reproductive tract of castrate male rat. It is not known whether a substance promoting sex gland growth in the male rat will promote differentiation of the human female tract in a male direction, but the data are offered with the belief that a parallelism between the actions on these different end-points may exist.

Methods. Steroids. The drugs, together with some of their synonyms and abbreviations used in this communication, are listed below: 1. 17-α-methyl testosterone, methyltestosterone, (MT), 2. 6α-methyl-17α-acetoxy progesterone, medroxyprogesterone acetate, (MAP)*, 3. 17α-ethinyltestosterone, ethisterone, anhydrohydroxy progesterone, pregneninolone, (ET)†, 4. 17α-ethinyl-19-nortestosterone, norethindrone, (ENT)‡, 5. A mixture of norethynodrel (17α-ethinyl-5, 10-estrene-17β-ol-3-one) and 17α-ethinylestradiol, 3-methyl ether, (EN)§, 6. 17α-acetoxy progesterone, (AP)‖, 7. Progesterone (P), 8. 17α-(2-methallyl) - 19-nortestosterone, SC-9022, (MNT), 9. Testosterone propionate (TP). For administration all compounds were suspended or dissolved in cottonseed oil. *Animals.* Male rats of the Upjohn colony (Sprague-Dawley ancestry) were castrated between 26 and 28 days old. On day following castration steroid treatment began. The rats were divided into groups of 10, each group being treated with single daily oral (0.2 cc) or subcutaneous (0.1 cc) doses of cottonseed

* *Provera,* Registered trademark, The Upjohn Co., Kalamazoo, Mich.

† *Pranone,* Registered trademark, Schering Corp., Bloomfield, N. J.

‡ *Norlutin,* Registered trademark, Parke, Davis & Co., Detroit, Mich.

§ *Enovid,* Registered trademark, G. D. Searle & Co., Chicago, Ill.

‖ *Prodox,* Registered trademark, The Upjohn Co., Kalamazoo, Mich.