Toxic Effects of Fluid from the Coagulating Gland of the Guinea Pig* (22941)

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During a study of the antigenic properties of the genital organs of the guinea pig, it was unexpectedly observed that the fluid from the coagulating glands produced toxic symptoms and death in rabbits and in guinea pigs.

Methods. These glands are attached to the seminal vesicles(1,2); they were removed with eye forceps from guinea pigs that were exsanguinated under ether anesthesia. The fluid from the coagulating gland (FCG) was obtained, as a rule, by pressing the cut glands and clearing the fluid by centrifugation. Occasionally, the fluid was drawn from the glands *in situ* into a small syringe through a 27 gauge needle.

Results—Action of FCG in the rabbit. Following intravenous, intraperitoneal, intramuscular or subcutaneous injections, the symptoms included: miosis, salivation, cyanosis of the ears and lips, dyspnea, urination and defecation. The blood pressure was lowered and there was a variable drop in body temperature. The rabbits became prostrated and died within a few hours after injection. The first symptom was miosis which appeared in 2 to 5 minutes after injection and often lasted about one-half hour. Rabbits recovering from a sublethal dose were again susceptible. The minimal intravenous lethal dose was about 0.002 ml of FCG. Male and female rabbits showed about the same susceptibility. Pathological findings included dilation of the right heart, petechial hemorrhages on the surface of the thymus; the spleen and the liver were dark red, the large veins of the abdominal cavity were distended. Histological sections of the abdominal organs showed that the capillaries and venules, as well as the sinuses of the liver and spleen, were dilated and contained clumped red cells. Extracts of other organs of guinea pigs, such as prostate, testis, epididymis, spleen, and liver did not produce parasympatomimetic effects.

Action in guinea pigs, cats, rats and mice. FCG from guinea pigs injected into guinea pigs intravenously caused urination, defecation, dyspnea and prostration, but no miosis was noted. Death occurred in one to 2 hours after injection. The lungs were not inflated. When 0.2 to 0.5 ml of FCG was injected subcutaneously regional clonus occurred lasting for a few minutes. Some of the guinea pigs developed rigidity of one or both hind legs several hours or one day after subcutaneous or intramuscular injection given regions distant from the hind legs. Of 3 cats injected intravenously with 1 ml of guinea pig FCG, 2 showed miosis and 3 intense salivation; one died and 2 recovered following a period of prostration. While large doses of guinea pig FCG produced systemic symptoms and death in rats, mice were not susceptible. FCG from rats, hamsters or mice failed to produce similar effects in rabbits, guinea pigs and rats. Extracts from prostates of the rabbit, bull, dog, or man produced no similar symptoms in the rabbit.

Instillation of a drop of guinea pig FCG diluted 1:10 into the eyes of rabbits caused no miosis but induced congestion of blood vessels and swelling of the conjunctiva and the nictating membranes. This condition lasted for one day.

It is of significance that strips of uterus and ileum of rabbits reacted with contraction to a 1:200 dilution of rabbit FCG in Tyrode solution.

The active agent of FCG is non-dialyzable, stable at 55° for 30′ but destroyed by heating at 80° for 20′. It can be precipitated by half saturated $(NH)_2SO_4$. Incubation at 37°

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for 30′ with fresh rabbit serum does not destroy the active agent. Preservatives such as formaldehyde (0.1%), phenol (0.5%) and merthiolate (1:10,000) do not affect it. It can be freeze-dried with little loss of its activity.

Summary. Fluid from the coagulating gland of the guinea pig injected intravenously or intramuscularly produced toxic effects (miosis, urination, defecation, salivation) and death in rabbits, recalling the parasympatomimetic action of certain drugs. When it was injected into guinea pigs intravenously, it caused urination, defecation, prostration and death in about one hour. In guinea pigs, the intramuscular injection of this material caused regional clonus. Fluid from the coagulating glands of rats and mice injected into rabbits did not produce a similar effect.

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Comparative Effects of Ouabain Upon Contractile Force of Guinea Pig Diaphragm and Heart.* (22942)

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The positive inotropic action of cardiac glycosides upon heart muscle has been well established in studies with isolated papillary muscles(1) and ventricle strips(2) and with intact heart preparations(3-5). The effect of these drugs upon the force of contraction of skeletal muscle is less clear, however. For example, no significant positive inotropic action was observed in a variety of skeletal muscle preparations(6-10). On the other hand, a number of investigations using different preparations or experimental conditions have revealed an increased force of contraction(6,7,9-16). Similarly, negative inotropic actions have been reported (7,9,15-17) as well as failure to observe such an effect with other preparations or conditions(6,8,9). The conflicting results obtained above are in part inexplicable. It might be noted, however, that in much of the work (with *in situ* as well as isolated preparations) the experimental conditions were not defined precisely, nor were concentration-action relationships explored fully. In addition, direct comparisons of the action on skeletal and cardiac muscle of the same animal have not been made.

The effects of these drugs assumes an especial importance in view of recent work on their mechanism of action, in which skeletal muscle and contractile protein preparations from skeletal muscle have been used(18-21). The significance of such investigations is in large dependent upon demonstration that cardiac glycosides produce a positive inotropic action upon skeletal muscle. We have therefore investigated the problem in simple skeletal and cardiac muscle preparations of guinea pig *in vitro,* using well-defined conditions and a wide range of concentrations.

Methods. The isolated left phrenic nerve-diaphragm preparation of the guinea pig (150-200 g males) was used. Preparation of the strip from the diaphragm was carried out as described originally in the rat by Bülbring (22), and the muscle stimulated with a Grass stimulator (Model S-4-B) with square wave shocks. The muscle was stimulated either directly (the base of the muscle wedge rested upon a platinum electrode of the same length as the muscle base) with a stimulus of 1 millisecond duration and 40 volts, or indirectly

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