The results of this study are summarized in Table 1. It is evident that in the reserpine treated eye, the average pupillary diameter was 5.90 ± 0.12 mm as compared to the control eye (7.38 ± 0.21 mm). Absence of any change in the pupillary size of the control eye in all these rabbits rules out the possibility of central or systemic action. Conjunctival or corneal irritation can be excluded since there was no lacrymation or redness of the conjunctiva upon local application of reserpine. The mechanism of the local miotic action of reserpine is open to speculation. Reserpine has been shown to decrease the catecholamine contents of the iris (6). It could be that depletion of catecholamines by reserpine may lead to sympathetic inactivity and this may be responsible for the parasympathetic preponderance. The relative importance of the peripheral action of reserpine in comparison to the centrally induced miosis by systemic administration of reserpine cannot be stated.

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ACCUMULATION OF DIGITOXIN BY THE HEART AND "THE CUMULATIVE EFFECT OF DIGITALIS"

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There exists a considerable literature (1-4) on "the cumulative effect of digitalis", but the mechanism involved in the appearance of "the cumulative effect" is still a matter of speculation. The present work was designed to know whether "the cumulative effect of digitalis" occurs as a result of the real accumulation of digitalis or is due to digitalis-induced change in the heart tissue. Experiment was carried out with cats and guinea pigs. At various times after a single intravenous injection of 0.132 mg/kg digitoxin in cats or of 0.750 mg/kg digitoxin in guinea pigs, the following observations were made; 1) determination of lethal dose of digitoxin by Hatcher's method, 2) measurement of glycosides (digitoxin and its metabolites) content in the heart by Repke's method (5), 3) patho-histological examination of the heart tissue.

The lethal dose of digitoxin in cats decreased markedly 24 hours after the administration of the drug, reaching the half of the control value 48 hours later. The significant decrease in the lethal dose was still recognized about 10 days after the drug administration. Thus, it can be said that, in cats, the cumulative effect of digitoxin is quite remarkable. In guinea pigs, however, "the cumulative effect of digitoxin" could

FIG. 1. Glycoside content in the heart after a single intravenous injection of 0.132 mg/kg digitoxin in cats or of 0.750 mg/kg digitoxin in guinea pigs. The results are expressed as the means of values obtained from 8-10 animals. The standard error of mean is shown by the vertical line.

not be observed; namely the decrease in the lethal dose of digitoxin did not appear at any time after the drug administration.

The content of glycosides (digitoxin and its metabolites) in the cat heart, as shown Fig. 1, was still in high level even 48 hours after the injection of digitoxin. However, the content of glycosides in the guinea pig heart was only a half of that in cats 24 hours after the drug administration. After 48 hours no glycosides could be detected in the heart of guinea pig. The patho-histological examination of the heart revealed that, only in guinea pigs which gave no cumulative effect, changes such as degeneration and vacuolation were demonstrated. The data obtained indicate that the real accumulation of digitoxin by the heart plays a predominant role in the appearance of the cumulative effect of digitoxin.

As a fact supporting this concept, the following experiment could be cited. The cats with interrupted entero-hepatic circulation, i.e. biliary fistula cats, failed to show the hypersensitivity to digitoxin. It is very noteworthy that the disappearance of cumulative effect by interrupting enteron-hepatic circulation is accompanied by the reduced content of glycosides in the heart. This decrease in glycosides content occurred rapidly in the very similar manner to the case of guinea pigs, in which the cumulative effect of digitoxin could not be observed (Fig. 1).

On the basis of these results, it would be concluded that in the appearance of "the cumulative effect of digitalis" the real accumulation of digitalis in the heart plays a predominant role and the accumulation in the heart, as far as cats are concerned, is related intimately with the entero-hepatic circulation of digitalis.

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