

# Action of Digitalis Glucosides on Isolated Frog Heart<sup>1</sup>

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THE PREVIOUS paper indicated that serum and DOC act on the isolated frog heart by influencing the selective activity of the membrane toward ions and thereby changing the intracellular ionic atmosphere. The characteristic features of this action were its slow development, the decrease or disappearance of the staircase, a characteristic change in the form of contraction, accompanied by an increase in its height and, finally, the development of contracture at higher concentrations. It was also shown that the other substances studied acted in a different way: they developed their action instantaneously, had no marked influence on the staircase or the form of contraction and developed no contracture. It seemed desirable to extend these experiments to other drugs known to act on the heart in order to see into which of the two groups they belong. The methods employed were the same as used in the previous paper.

Glucosides of the digitalis group are known to have a marked and specific action on the frog heart. Figure 1 shows that 350  $\mu$ g. of Digitan (Merck; a digitalis preparation containing the active principle in a low concentration) per ml. abolished the staircase at room temperature. Figure 2 shows the action of 0.25  $\mu$ g./ml. digitoxin, dissolved in Ringer's solution containing one-fourth per cent gelatin. The staircase is practically eliminated, the point of intersection shifted up to 11° C., the angle of crossing made very flat; 350  $\mu$ g./ml. Digitan in a similar experiment made the staircase disappear altogether, up to 21° C., and shifted the maximum of tension to 15° C. (fig. 3). In twice this concentration it abolished the staircase up to 30° C., the highest temperature studied. In all these experiments the force of the heart beat was increased. So far both digitoxin and the cruder digitalis preparations were thus found to act similarly to serum and DOC and the question was whether they also shared the other characteristics of the latter, that is the slow development of action, the change in the form of contraction, and finally the development of contracture at higher concentrations. Figure 4 demonstrates the slow development of the action of Digitan. Figure 5 shows how Digitan changes the shape of the contraction, closely resembling that caused by a reduced potassium, lowered temperature, serum and DOC (compare fig. 10 of preceding paper). The slow development of action is also shown in figure 6.

Like serum and DOC, digitalis glucosides, in higher concentrations, also produce contracture, stopping the heart in systole. As was the case with serum and DOC, the contracture was not due simply to the exaggeration of the symptoms observed at lower concentrations, viz. to the excessive flattening of the curves of contraction; it was more or less a new phenomenon. While the slope of the contraction did not

Received for publication July 25, 1951.

<sup>1</sup> This research was supported by Armour and Company, Chicago, Ill.

flatten appreciably any further the curve of the heart beat did not return to its original base line again, diastole becoming less complete. As the dose was further raised, or the application prolonged, the base line gradually rose until the heart no longer relaxed. As was the case with serum and DOC, contracture was favored by low temper-

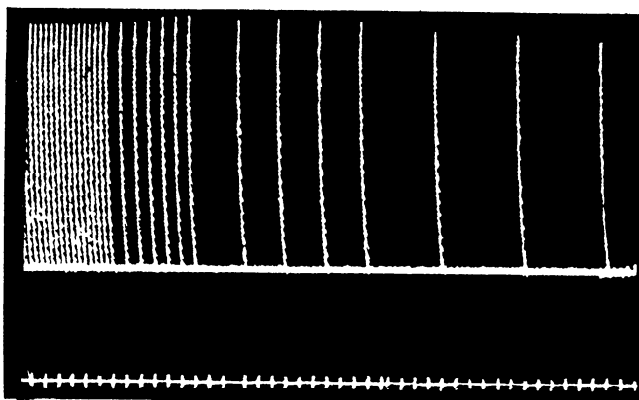


Fig. 1. ACTION OF 350 µg/ml. of Digitan on the frog heart. For explanation see previous paper. Frequencies: one beat/4, 10, 30 and 60 sec.  $T$ : 10 sec.

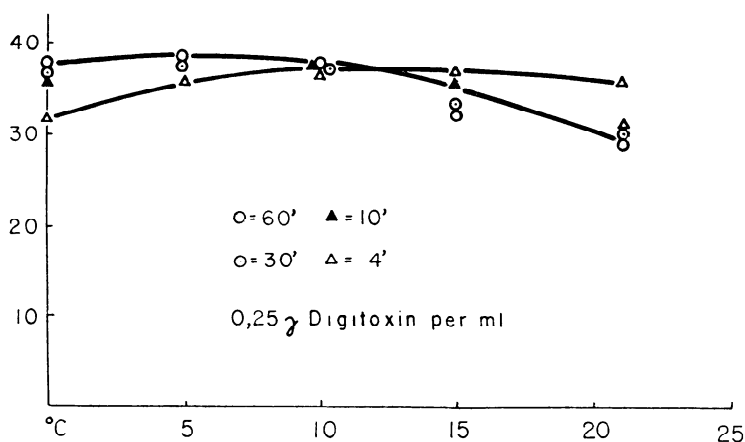


Fig. 2. ACTION OF 0, 25 µg/ml. of digitoxin.

ature. This was very convenient. While the contracture developed at room temperature was no longer reversible, the contracture which began to develop at 0° C. disappeared if the temperature was raised to 21° C., where the drug could be washed out of the heart, thus allowing the use of the same heart in repeated tests. Related substances such as those of the strophantus group showed similar action.

It can thus be concluded that digitalis glucosides and related substances have the same mechanism of action as DOC when acting on the isolated frog heart. This con-

clusion, which has been suggested by earlier investigators (1, 2), is supported by the close chemical relation of both substances.

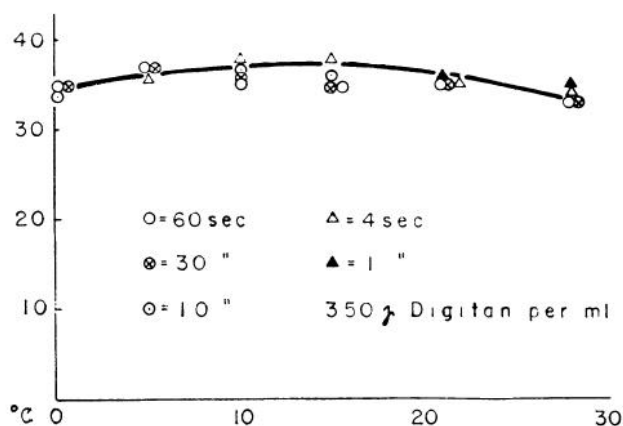


Fig. 3. ACTION OF 350 µg/ml. of Digitan on the staircase. For explanation see previous paper.

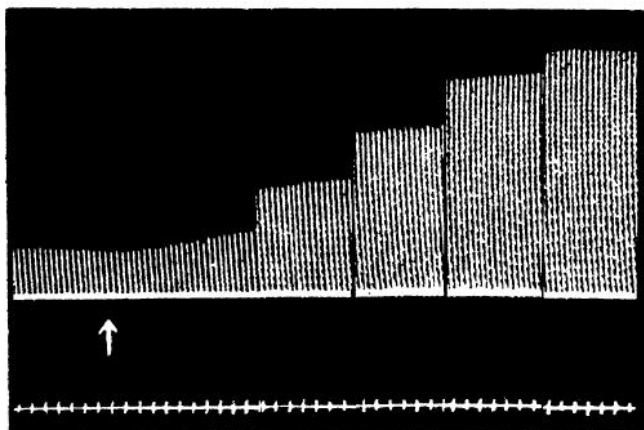


Fig. 4. DEVELOPMENT OF THE ACTION OF DIGITAN. At arrow, 350 µg/ml. of Digitan were added. Five minutes elapsed between each section; one beat every 4 sec. At this frequency the tension developed is low. The increase in tension is connected with the disappearance of the staircase. *T*: 10 sec.

#### DISCUSSION

Changes in the function of the heart associated with the abolition of the staircase influence the function favorably, while systolic contracture must be termed a toxic effect. Comparison of various digitalis and strophantus preparations showed that the relative concentrations at which these abolished the staircase, and at which they induced contracture, varied within wide limits. If the concentrations of a preparation

needed to abolish the staircase at room temperature and the concentrations necessary to develop contracture at  $0^{\circ}\text{C}$ . were united in a quotient, this quotient would be found to vary in the different preparations from 0 to 2.5, a further evidence of the

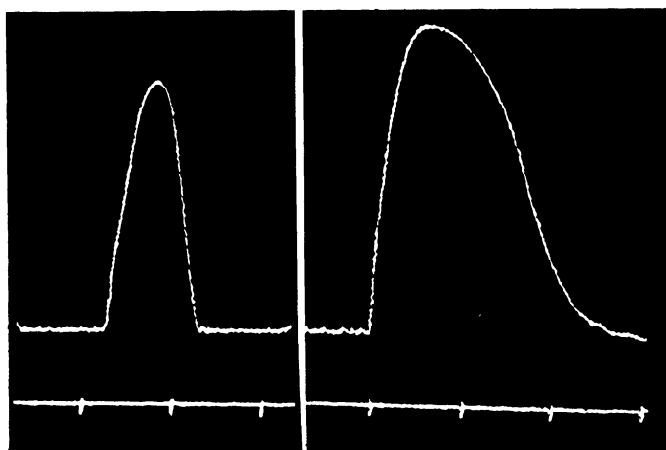
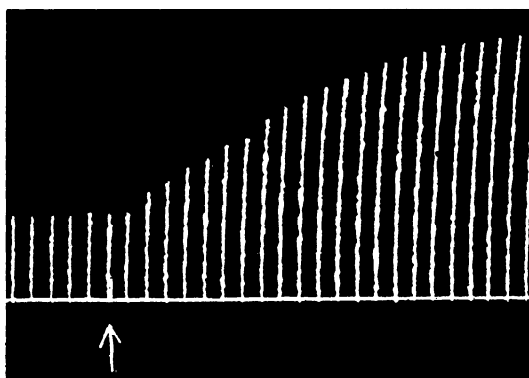


Fig. 5. ACTION OF  $400\text{ }\mu\text{g/ml.}$  of Digitan on the single heart beat. Temperature,  $21^{\circ}\text{C}$ . T: 1 sec.

Fig. 6. THE SLOWLY DEVELOPING ACTION of  $500\text{ }\mu\text{g.}$  of Digitan added at *arrow*. Heart was beating once per minute. (Compare fig. 9 of previous paper.)



relative independence of both actions.<sup>2</sup> The activity of digitalis preparations is mostly measured by their ability to produce contracture, thus by a toxic or undesirable action. The authors believe that their observations not only promise a better understanding of the therapeutic action of these substances but also open the way to the establishment of better and simpler assays of activity. An ideal digitalis preparation

<sup>2</sup> Saponins cause contracture without abolishing the staircase. Their presence may be responsible for quotient 0. Possibly, this complication drops out in the whole animal where the saponins may be bound by constituents of the blood.

should abolish the staircase without producing contracture at all. Such a substance would be overlooked altogether with present assays.

#### SUMMARY

Digitalis glucosides and related substances act on the isolated frog heart similarly to DOC and serum, which suggests a similar mechanism of action. The merit of digitalis assays is discussed briefly.

#### REFERENCES

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