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Effect of Certain Drugs on Properties of the Human Atrioventricular Node.

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In reciprocal rhythm an impulse originating in the atrioventricular junctional tissue passes to the ventricle, and in addition by retrograde conduction stimulates the atrium. If the retrograde conduction has been rapid, the cycle terminates; however, if conduction has been slowed, the impulse may find the junctional tissue responsive, and after traversing part of the auricle again stimulate the A-V node and ventricle, producing a reciprocal beat, or "Umkehr-Extrasystole." Clinical examples of such a mechanism were first described by White,[1] who based his concept of the physiological processes present on the circus mechanism observed earlier by Mines.[2] Reciprocal rhythm has been reported by others, and has been discussed most recently by Scherf.[3]

We have recently studied a patient who manifested this type of disturbance, and have taken the opportunity to study the effect of several drugs on the properties of the junctional tissue, presumably in the neighborhood of the A-V node. The clinical features of the case will be described elsewhere, together with certain electrocardiographic findings that may be of theoretical importance. The possibility suggested by Luten and Jensen[4] that some of the reported cases represent a parasystole rather than a reciprocal rhythm, has in this instance been definitely excluded.

By measuring the RP intervals of a large number of complexes, we have determined the retrograde conduction time below which reciprocal stimulation of the ventricle did not occur, but above which reciprocal beats were seen. This value we have taken to represent the refractory period of the junctional tissue. The mean value of the RP interval has been taken as a measure of retrograde conduction; the corresponding PR interval for a given RP time (0.40 sec.) has been taken as a measure of forward conduction. Curves relating RP and PR intervals have shown recovery of the conduction tissue;[5] this recovery time has been regarded also as the time of relative refractoriness.[6]

The effects of drugs, and of nervous influences, on the physiological properties of cardiac tissues have been studied extensively since the early studies of Lewis and his associates; the most modern studies are those of Macleod[7] and of Wedd *et al.*[8] It seems superfluous to review them here.

Method. Electrocardiograms were taken first by means of an esophageal electrode, since the clear-cut P waves obtained in this fashion facilitated the measurement of the RP and PR intervals. Since passage of the esophageal electrode sometimes appeared to influence reflexly the rate and the site of the pacemaker, a CF lead was used routinely, with the chest electrode placed in the third interspace at the right sternal border; this lead gave satisfactorily sharp P waves. The records were taken for a period of 5 to 8 minutes. After a control curve, a drug was administered; at the estimated time of full effect, indicated in Table II, further tracings were recorded. Measurements were made with a hand lens.

Results. In Table I we show the changes with varying amounts of *digitalis* studied over a period of 25 days. The quantity of digitalis accumulated has been estimated in

1 White, P. D., *Arch. Int. Med.*, 1915, **16**, 517.

2 Mines, G. R., *J. Physiol.*, 1913, **46**, 370.

3 Scherf, D., *Arch. Int. Med.*, 1941, **67**, 372.

4 Luten, D., and Jensen, J., *Am. Ht. J.*, 1931-32, **7**, 593.

5 Lewis, T., and Master, A. M., *Heart*, 1925, **12**, 209.

6 Ashman, R., *Am. J. Physiol.*, 1925, **74**, 121.

7 Macleod, A. G., *Am. Ht. J.*, 1939, **17**, 294, 305.

8 Wedd, A. M., Blair, H. A., and Gosselin, R. E., *J. Pharm. and Exp. Therap.*, 1942, **75**, 251.

TABLE I.
Digitalis Action on A-V Node.

Date	Digitalis cumulation, cat units	Rate, per min	Refractory period, sec	Forward conduction, sec	Retrograde conduction, sec	Recovery
Feb. 16	0	50	0.26	0.185	0.30	Complete in 0.45 sec.
25	3	48	.285	.195	.18	Complete in 0.45 sec.
Mar. 4	5	45	.37	.255	.18	Delayed and incomplete.
5	5	48	.375	.27	.25	More delayed.
6	5	50	.36	.255	.40	
9	5	50	.36	.27	.41	Further delayed and least complete.
11	7	48	.40	.285	.38	Less delay and more complete.
12	6	52	.32	.25	.22	Very slight delay; almost complete.
13	5	51	.29	.205	.15	Normal again.

TABLE II.
Drug Action on A-V Node.

Date		Time after drug	Rate per min	Refractory period, sec	Forward conduction	Retrograde conduction	Recovery
Mar. 5	Control		48	0.375	0.27	0.25	
	Prostigmin	10 min.	45	.47	.34	.36	Delayed and incomplete
	Atropine	1 ''	53	.32	.245	.21	Return to control curve
6	Control		50	.36	.255	.35	
	Atropine	1 ''	50	.36	.275	.27	No definite change
11	Control		48	.40	.285	.38	
	Epinephrine	8 ''	50	.39	.28	.44	Slightly more complete
	Neosynephrine	17 ''	47	.39	.285	.27	No change
12	Control		52	.32	.25	.22	
	Quinidine	1 hour	46	.46	—	.49	Marked delay; never complete
		2 ''	44	.41	.315	.35	Less delay; finally complete
13	Control		51	.29	.205	.15	
	Mecholyl and atropine	2 min	33	*.48-.76	—	.50	Marked delay; not quite complete
		7 ''	50	.36	.24	.30	Less delay; not quite complete
		20 ''	52	.31	.23	.23	Return almost to control curve

* All retrograde conduction times of 0.48 sec or less showed no reciprocal beats; all above 0.76 showed reciprocal beat; none between these figures.

the usual fashion, and must be regarded as approximate only. The refractory period of the junctional tissue, and forward conduction time through this area, vary in a manner which closely parallels the estimated digitalis saturation. Retrograde conduction shows first an acceleration with smaller doses, and then a delay with larger doses of digitalis. This is similar to the findings of Clark and Mines[9] in their study of the effects of digitalis on the frog heart.

[9] Clark, A. J., and Mines, G. R., *J. Physiol.*, 1913-14, **47**, vii.

Recovery curves after digitalization show delay, *i.e.* longer PR intervals for given RP intervals, and failure to become complete, *i.e.*, longer PR intervals even with the longest RP periods. These changes seem to follow closely the prolongation of the refractory period, which suggests that changes in relative refractoriness parallel the effective refractory period. This appeared to be true of digitalis effect, as well as of the effects produced by the other drugs employed.

We could detect no phase of supernormal conduction.

In Table II are summarized the effects of other drugs. Prostigmine (1 mg., i.m.) prolonged the refractory period and slowed both retrograde and forward conduction. This effect was more than neutralized by the subsequent injection of atropine (1/50 grain i.v.), though atropine alone on the following day showed a less conspicuous effect.

Epinephrine (0.5 cc, subcu.) showed a definite effect only by slowing retrograde conduction, while neosynephrin (5 mg. subcu.) did little more than accelerate it. Both produced very slight shortening of the refractory period.

Quinidine (5 grains, p.o.) markedly prolonged the refractory period and slowed A-V conduction in both directions. One hour after administration, forward conduction could not be tabulated since the refractory period exceeded the time (0.40 sec.) selected as the constant RP interval at which the PR time was measured.

An uncomplicated mecholyl (acetyl-B-methyl choline 20 mg subcu.) effect was not obtained since the reaction following its injection necessitated the immediate administration of atropine. From the curves taken, however, there may be made out easily the marked prolongation of refractoriness and delay in conduction, which gradually regress under the influence of atropine.

Further studies were prevented by the spontaneous disappearance of the reciprocal mechanism, which we were unable to reproduce.

Comment. We consider that the indicated changes in the refractory period are the result of medication, and that the rate change contributes no important part of this effect. The rate change was trivial in most instances; at the slow rates observed the refractory period changes relatively little with change in rate; and finally, we could measure the refractory period of the ventricle—that is, the QT interval with varying Q-Q periods—and found virtually no change due to slight variations at the slower rates.

The effective refractory period of the junctional tissue is definitely prolonged by digitalization; this is in agreement with Lewis' earlier work,[10] but must be interpreted in the light of the later studies of Drury,[11] Macleod,[8] and Wedd,[12] in which they conclude that the local absolute refractory period of heart muscle is shortened by digitalis glucosides. The delay of A-V conduction is commonly recognized clinically, though the initial acceleration of retrograde conduction finds it parallel only in animal experiments.

The depressant action on heart muscle of quinidine is illustrated by its effect on conduction, on recovery, and on refractoriness. Prolongation of the latter is in agreement with views long held, but which have not been confirmed in the latest study of Wedd *et al.*;[12] however, in the intact heart of our subject we cannot clearly divorce refractoriness from conduction effects, and are measuring the effective, rather than the absolute local refractoriness.

Carotid sinus stimulation was ineffective in our patient, but mecholyl and prostigmine produced the striking effects noted above. We note the total effect and do not feel justified in attempting the separation of direct effects from those mediated through the vagus, if indeed such a distinction is valid.

It is noteworthy that the susceptibility to change, and the magnitude of change, is in every instance much greater for retrograde conduction than for forward conduction.

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10 Lewis, T., Drury, A. N., and Iliescu, C. C., *Heart*, 1921-22, **9**, 21.

11 Drury, A. N., and Love, W. S., *Heart*, 1926, **13**, 77.

12 Wedd, A. M., Blair, H. A., and Dwyer, G. K., *J. Pharm. and Exp. Therap.*, 1941, **72**, 394.