for their failure to take the usual stains.

These giant-cell inclusions are therefore considered to be a byproduct of granulomatous inflammation in cicatrizing enteritis.

Summary. Inclusion bodies in the giant cells of 2 cases of cicatrizing enteritis (regional ileitis) were investigated. By physical and chemical methods they were found to be inorganic calcium salts. The anions were not identified. Their origin is attributed to focal abnormalities of the cytoplasm of giant cells found in this type of granulomatous inflammation, which attract calcium salts. In their development they somewhat resemble psammoma bodies.

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Effect of Strophanthin and Quinidine upon Conduction and Electrical Systole (Q-T Interval) of the Rabbit Heart.*

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Previous studies from this laboratory[1,2] noted the effects on conduction of varying rates of stimulation, and of the use of strophanthin and quinidine, upon the isolated rabbit ventricles. Intraventricular conduction times (QRS widths) increased markedly at extremely high (300 and over) rates of stimulation. Strophanthin, and particularly quinidine, prolonged the QRS intervals at all rates of ventricular contraction.[1] The electrical systole or Q-T interval showed a more gradual decrease with increasing ventricular contraction rates. Small doses of strophanthin, of the order of 0.006 mg/kg, in general prolonged the Q-T interval; larger doses, *e.g.* 0.018 mg/kg, uniformly shortened it,[2] in line with its known clinical effect. Quinidine consistently prolonged the ventricular electrical systole or the Q-T interval, as it delayed intraventricular conduction.

The isolated rabbit ventricles were a useful instrument of study for two reasons. First, they could be driven at much faster rates than the whole heart. Secondly, we were able to elicit the effects of various drugs upon the ventricular musculature without the complicating interconnected influences upon the atria and the A-V junctional tissues. The following presentation is of similar studies made with the isolated whole rabbit heart.

Method. The procedure was essentially the same as in the previous experiments. The perfusion fluid best adapted for the whole heart we found to be the one used by Calder[3] under similar conditions. The atria were left on and the electrodes of the thyrotron stimulator applied usually to the right atrium. The electrocardiographic records were made as before, approximately at 10 minute intervals after the introduction of the drugs into the rubber tube leading to the aortic cannula. Control measurements similarly spaced and rest periods between salvos of rapid stimulation excluded the effects of fatigue. Oxygenation and a constant 37°C temperature of the perfusing fluid were provided as before by means of continuous bubbling of 5% CO_2 in oxygen and a heated water jacket respectively.

Results. Effect of varying rates. Lengthening of the P-R interval occurred, gradually as a rule, at increasingly fast rates of stim-

* Supported, in part, by a grant from the Sandoz Chemical Works, Inc.

1 Decherd, G., and Ruskin, A., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 114.

2 Ruskin, A., and Decherd, G., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 117.

3 Calder, R. M., PROC. SOC. EXP. BIOL. AND MED., 1947, **65**, 76.

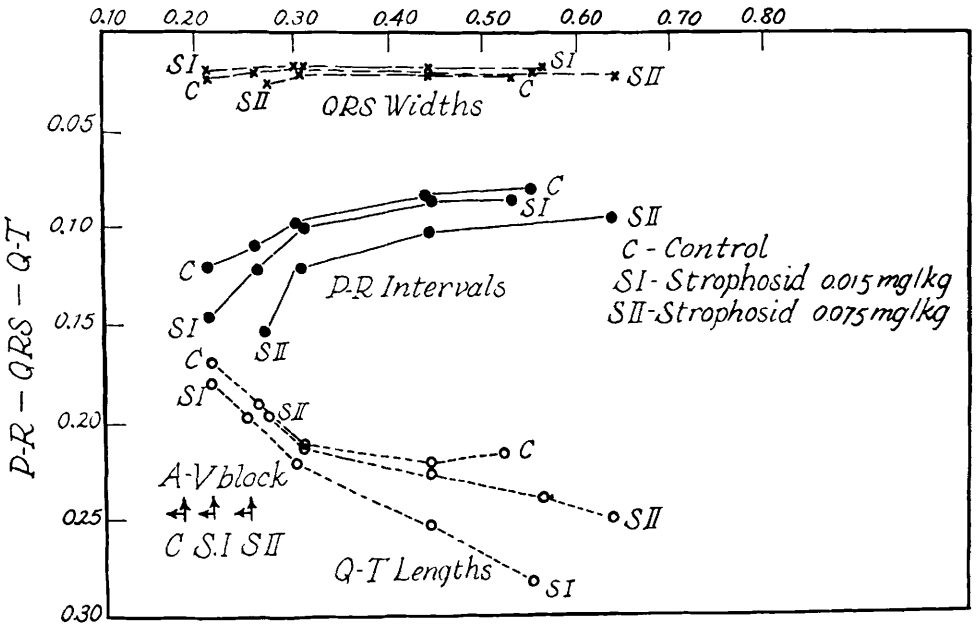

FIG. 1.

Effects of a small, and later a larger, dose of strophanthin upon the P-R, QRS, and Q-T intervals of the electrocardiogram of the isolated rabbit heart at various cycle lengths (R-R intervals (abscissae in seconds)).

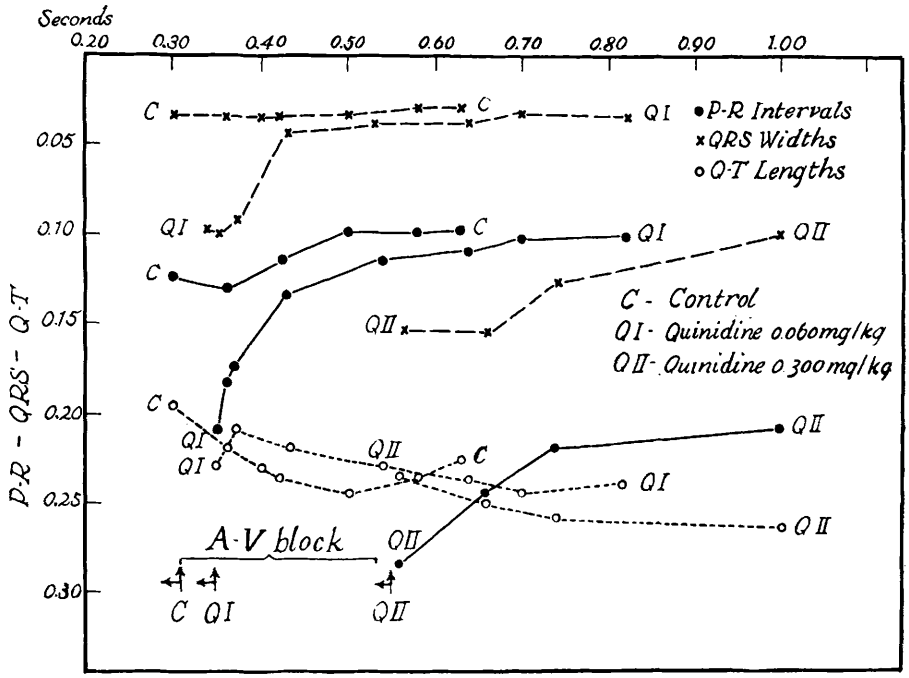

FIG. 2.

Effects of a small, and later a larger, dose of quinidine upon the P-R, QRS, and Q-T intervals of the electrocardiogram of the isolated rabbit heart at various cycle lengths (R-R intervals (abscissae)).

ulation. Great prolongation of the P-R interval at rapid rates of stimulation before second degree A-V block intervened was noted infrequently. The QRS width decreased very slightly before dropped beats occurred under similar circumstances of increasingly rapid stimulation (Fig. 1 and 2). These results contrast with the much steeper recovery curves of intraventricular conduction when ventricles are directly stimulated at much faster rates.[1] Nor did we usually observe any transient improvement in A-V conduction over a short range of rapid rates, causing a notch in the recovery curves, such as we observed in our previous studies of intraventricular conduction.[1] That the QRS widths likewise failed to shorten and then increase markedly at rapid rates of stimulation may be explained on the basis of the strongly limiting factor of A-V block upon these rates. QRS widening and aberration was again noted in the second, third and sometimes fourth complexes of groups produced by sudden rapid rates of stimulation, provided these rates approached those possible by direct ventricular stimulation.[1] Corresponding widening of P-R intervals, even to dropped beats, occurred at the beginning of groups of complexes produced by a series of rapid stimuli with relatively short rest periods in between. This phenomenon, presumably dependent on fatigue and increased relative refractoriness, has been noted in experimental A-V Wenckebach block by Scherf[4] and in patients with paroxysmal tachycardia by Decherd *et al.*[5]

The generally inverse relations of the Q-T interval to cycle length were seen in this (Fig. 1 and 2) as in our previous study.[1] That they deviate from the straight line relations predicated by Robb,[6] and by Schlamowitz,[7] may be explained on the bases of the special conditions of our experiments, involving very slow as well as very fast cardiac rates, at times beyond physiological limits, and elimination of extracardiac reflex nervous factors.

Effects of Strophanthin (Strophosid, Sandoz). The well-known slowing of A-V conduction by digitalis and strophanthin glucosides was substantiated by our study (Fig. 1). P-R intervals were prolonged at all rates of stimulation in proportion to the dose employed. QRS prolongation was noted especially at rapid rates of stimulation and with the larger doses of the drug (Fig. 1). These effects were more marked in our previous study, employing the ventricles only and at faster rates. Small doses of strophanthin caused prolongation of the Q-T interval and this was usually reversed by larger doses (Fig. 1); this latter shortening is comparable to its characteristic clinical effect[9]; prolongation with small doses has been noted in the isolated frog heart.[8] We have been able to demonstrate similar effects employing other glucosides (Cedilanid (Sandoz), Scillaren-B (Sandoz), and digitoxin). The usual effects upon the S-T segments were also seen.

Effects of quinidine. The effects on conduction upon addition of quinidine to the perfusate were classical, *i.e.* A-V and I-V conduction were both slowed at all rates of stimulation in proportion to the dose administered (Fig. 2). The effects upon the Q-T interval were not clear-cut, however. Slight prolongation, at most, was noted with larger doses (Fig. 2). At times paradoxical shortening was obtained despite definite delays in conduction as well as in the absolute refractory period. This contrasts sharply with the prolongation noted in the ventricular preparations[1] and in clinical usage of the drug.

Comment. The recovery curves of A-V and intraventricular conduction parallel closely those previously published for the two loci of conductivity by Lewis and Master[10] and by us[1] respectively. Beyond a certain rate

[4] Scherf, D., *Wien. Arch. inn. Med.*, 1939, **18**, 403.

[5] Decherd, G. M., Herrmann, G. R., and Schwab, E. H., *Am. Heart J.*, 1943, **26**, 446.

[6] Robb, J. S., and Turman, W. G., *Am. J. Med. Sc.*, 1947, **214**, 180.

[7] Schlamowitz, I., *Am. Heart J.*, 1946, **31**, 329.

[8] Clark, A. J., and Mines, G. R., *J. Physiol.*, 1913, **47**, VII.

[9] Kisch, B., *Strophanthin*, Brooklyn Medical Press, 1944.

[10] Lewis, T., and Master, A. M., *Heart*, 1925, **12**, 209.

of cardiac beating the conduction time is more and more prolonged as the recovery period shortens.

The results are in general confirmatory of what is known about the cardiac effects of strophanthin and quinidine, with the possible exception of the Q-T interval modifications by quinidine. Both drugs, especially quinidine, prolong atrio-ventricular, as well as intraventricular conduction, more so at rapid rates of cardiac beating. These are presumably direct muscular effects in our experiments, unless the amputated nerve endings are also affected (?). The recovery curves are markedly depressed downward and to the right, indicating prolongation of the relative and absolute refractoriness of the atrio-ventricular as well as the ventricular musculature. The slower the recovery of conductivity, the longer the period of relative refractoriness, the greater the incidence of partial A-V and Wenckebach types of block. This is our theoretical prediction[11] as well as the actual occurrence in our data.[12] Both strophanthin and quinidine, thus, predispose to Wenckebach (and Mobitz) types of A-V block, though they are found also frequently enough in our control curves at rapid cardiac rates. These findings substantiate the known clinical effects of the two drugs.

Rapid rates of stimulation of the auricles, up to 300 per minute, usually failed to elicit paroxysmal ventricular tachycardia or fibrillation, seen in the faster stimulated ventricular preparations,[1] typically after marked QRS aberration. Ventricular ectopic beats, with bigeminy, occurred not infrequently, but runs of them were rare, nor were they apparently influenced by strophanthin or quinidine in these, as in the ventricular,[1] preparations of rabbit hearts.

Summary. Recovery curves of conductivity of the A-V node and ventricles for the isolated rabbit heart driven at various rates followed the usual logarithmic pattern. Strophanthin, and especially quinidine, caused delayed recovery and more prolonged refractoriness of both regions of the heart. Strophanthin prolonged the Q-T interval in small doses and usually shortened it in larger doses. Quinidine effects upon the Q-T interval were unexpectedly variable, contrary to the usual prolongation in thyrotron driven ventricles and in clinical cases.

[11] Decherd, G. M., and Ruskin, A., *Brit. Heart J.*, 1946, **8**, 6.

[12] Ruskin, A., and Decherd, G. M., unpublished data.

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Hemochromogens and Related Compounds in Liquid Ammonia.*

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A study of the reactions and reaction products of hemin and coordinating substances in liquid ammonia by means of spectroscopy and bio-assay has not been made previously. However, the senior author[1-5] has made various studies on the reactions of ammonolyzed and ammonated proteins, protein derivatives and hemin. Some of the reactions in liquid

* The authors wish to thank Armour and Company and the Wellcome Research Laboratories for their generous gifts of dried blood proteins, and the Illinois Department of Public Health for the supplies of desiccated plasma and liquid globulin.

[1] Roberts, R. G., and Miller, C. O., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 821.

[2] Roberts, R. G., and Miller, C. O., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 522.

[3] Roberts, R. G., Tweedy, W. R., and Smullen, C. H., *J. Biol. Chem.*, 1935, **112**, 209.

[4] Roberts, R. G., and Miller, C. O., *J. Am. Chem. Soc.*, 1936, **58**, 309.

[5] Roberts, R. G., *J. Biol. Chem.*, 1939, **128**, 597.