the secretory response of the stomach to blood borne stimuli. However, both Harries (1957) using conscious dogs with gastric fistulae and Jacobson, Linford & Grossman (1966) using conscious dogs with separated gastric pouches found that isoprenaline [(0·75–2·75 μg/kg)/min] either decreased histamine induced secretion or had no effect. We have repeated the experiments on dogs with separated gastric pouches and have extended the observations to anaesthetized dogs and by using a wider dose range.

In thirteen experiments on dogs anaesthetized with pentobarbitone, isoprenaline [(0·125–8·0 μg/kg)/min] increased histamine induced gastric acid secretion (HIGAS) on every occasion, although in four of these experiments (in which the gastric secretion was collected through the cannulated pylorus) the increase was apparently preceded by a decrease. The decrease was probably an artefact due to relaxation of the stomach wall which would have produced a temporary change in the drainage of gastric juice.

Two dogs with separated pouches were used. In the first dog isoprenaline [(0·125–4 μg/kg)/min] increased HIGAS in seven experiments. In one experiment with isoprenaline [(4 μg/kg)/min] there was no clear effect. In the second dog increased HIGAS was observed on four occasions with (0·06–0·25 μg isoprenaline/kg)/min and decreased HIGAS on three occasions with (0·5–1 μg isoprenaline/kg)/minute. The inhibitory effect of isoprenaline in this dog was analysed in a further series of experiments. It was not abolished by light pentobarbitone anaesthesia, by pharmacologically effective doses of guanethidine or hexamethonium or by bilateral section of the splanchnic nerves but was abolished both by phentolamine and by propranolol.

We conclude that suitable doses of isoprenaline increase HIGAS in both anaesthetized and conscious dogs. In conscious dogs large doses of isoprenaline decrease the secretory response. The mechanism of this effect is not yet fully understood.

This work was supported by the Medical Research Council.

REFERENCES

HARRIES, E. H. L. (1957). The mode of action of sympathomimetic amines in inhibiting gastric secretion. *J. Physiol., Lond.*, **138**, 48P.

JACOBSON, E. D., LINFORD, R. H. & GROSSMAN, M. I. (1966). Gastric secretion in relation to mucosal blood flow studied by a clearance technic. *J. clin. Invest.*, **45**, 1–13.

Explanation for the discrepancy in reported cardiac electrophysiological actions of diphenylhydantoin and lignocaine

B. N. SINGH (introduced by E. M. VAUGHAN WILLIAMS), *Department of Pharmacology, University of Oxford, Oxford*

Although diphenylhydantoin (DPH) and lignocaine have now gained widespread acceptance as effective drugs in the therapy of cardiac arrhythmias some controversy has been aroused concerning their fundamental mechanism of action.

In contrast to many other anti-arrhythmic drugs, concentrations of DPH and lignocaine corresponding to therapeutic concentrations in man have recently been reported to cause no significant depression of the maximal rate of depolarization (MRD) of the cardiac action potential (Strauss, Bigger, Bassett & Hoffman, 1968; Bigger, Bassett & Hoffman, 1968; Davis & Temte, 1969; Bigger & Mandel, 1970;

Mandel & Bigger, 1970). Our preliminary data with both drugs, however, were at variance with these findings. In their studies, Davis & Temte used a perfusion medium containing 2·7 mM concentration of potassium and Bigger and his colleagues, 3 mM. These concentrations are very much lower than the generally accepted physiological range of 5·0–5·5 mM (Spector, 1956). The effects of DPH and lignocaine on electrical and mechanical functions of isolated rabbit atrial and ventricular muscle in normal (5·6 mM) and low (3·0 mM) potassium solutions have therefore been compared. Since both drugs equilibrated rapidly in the tissue bath, several concentrations of each drug per preparation could be tested, and control values obtained after, as well as before, exposure to the drug in both normal and low potassium solutions.

In isolated rabbit atria DPH ($1{\cdot}81\times10^{-5}$M–$1{\cdot}45\times10^{-4}$M) produced a dose dependent decrease (28–66%) in MRD in 5·6 mM potassium solution. In 3·0 mM potassium solution, the initial decrease occurred at $7{\cdot}25\times10^{-5}$M (12·7%) and was still not striking at $1{\cdot}45\times10^{-4}$M (22·5%). In ventricular muscle the MRD was reduced by 10–46% with DPH ($1{\cdot}81\times10^{-5}$M–$7{\cdot}25\times10^{-5}$M) in normal solution but only by 6% in low potassium medium with $7{\cdot}25\times10^{-5}$ M. Lignocaine ($1{\cdot}12\times10^{-5}$M–$3{\cdot}73\times10^{-5}$M) depressed the MRD by 34–70% in atrial muscle and by 29–67% in ventricular muscle in normal potassium solution. In low potassium solution, the initial depression was at $3{\cdot}73\times10^{-5}$M (15·4%) in atria but no change was found in ventricular muscle at this concentration. In therapeutic concentrations, neither drug altered the resting potential voltages but they produced slight acceleration of repolarization in ventricular, but not in atrial, muscle perfused in both normal and in low potassium solutions. The effects of DPH and lignocaine on the spontaneous and maximum driven frequencies, conduction velocity, contraction amplitude and electrical threshold in normal potassium solution also resembled those for quinidine (Vaughan Williams & Szekeres, 1961). In low potassium medium these effects were either absent or small.

The results thus indicate that the direct electrophysiological actions of DPH and lignocaine are similar to those of quinidine and, like those of quinidine (Watanabe, Dreyfus & Likoff, 1963), are potassium dependent. *In vivo* actions, therefore, which cannot be explained by such direct or Class I (Singh & Vaughan Williams, 1970) cardiac effects, suggest that extracardiac effects may be involved which merit further investigation.

REFERENCES

BIGGER, J. T., BASSETT, A. L. & HOFFMAN, B. F. (1968). Electrophysiological effects of diphenylhydantoin on canine Purkinje fibers. *Circulation Res.*, **22**, 221–236.

BIGGER, J. T. & MANDEL, W. J. (1970). Effects of lidocaine on the electrophysiological properties of ventricular muscle and Purkinje fibers. *J. clin. Inv.*, **49**, 63–77.

DAVIS, L. D. & TEMTE, J. V. (1969). Electrophysiological actions of lidocaine on canine ventricular muscle and Purkinje fibers. *Circulation Res.*, **24**, 639–655.

MANDEL, W. J. & BIGGER, J. T. (1970). Effects of lidocaine on sino-atrial node and atrial fibers. *Am. J. Cardiol.*, **25**, 113–114.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1970). A third class of anti-arrhythmic action. Effects on atrial and ventricular ultracellular potentials, and other pharmacological actions on cardiac muscle of MJ 1999 and AH 3474. *Br. J. Pharmac.*, **39**, 675–687.

SPECTOR, W. S. (1956). Editor. *Handbook of Biological Data*, p. 53. Philadelphia: W. B. Saunders Company.

STRAUSS, H. C., BIGGER, J. T., BASSETT, A. L. & HOFFMAN, B. F. (1968). Actions of diphenylhydantoin on the electrical properties of isolated rabbit and canine atria. *Circulation Res.*, **23**, 463–477.

VAUGHAN WILLIAMS, E. M. & SZEKERES, L. (1961). A comparison of tests for antifibrillatory action. *Br. J. Pharmac. Chemother.*, **17**, 424–432.

WATANABE, Y., DREIFUS, L. S. & LIKOFF, W. (1963). Electrophysiological antagonism and synergism of potassium and anti-arrhythmic agents. *Am. J. Cardiol.*, **12**, 702–710.