administered by continuous infusion to guinea-pigs by a method similar to one used by Sekiya and Vaughan Williams (3). Guinea-pigs of both sexes weighing between 250 and 600 g were used. The animals were anaesthetized with 25% urethan solution in a dose of 0.7 ml/100 g of both weight. A polyethylene catheter was introduced into the jugular vein and ouabain was administered by infusion through the canula with the help of a continuous infusion machine at a rate of 5 mcg at every 1.5 minutes with a gap of one minute in between each infusion. Occurrence of ventricular fibrillation or cardiac arrest was taken as the end point.

The observations are depicted in Table 1.

In the experiments, it has been seen that when the animals were treated with 5 mg/kg of reserpine 24 hours before, they died of cardiac arrest instead of ventricular fibrillation. However, this effect was not observed when the animals were treated with reserpine just at the start of ouabain infusion or when reserpine was administered after 40% lethal dose of ouabain. From these it may be concluded that the modification of the cause of digitalis intoxication seen after 24 hours of treatment with reserpine, was due to depletion of cardiac catecholamines. This confirms the earlier observations of Erlij and Mendez (4) but is in variance with those of Takagi *et al.* (5).

The *beta*-adrenergic blocking agent propranolol but not INPEA, modified the mode of death after ouabain. It is thus logical to assume that the absence of ventricular fibrillation induced by propranolol is not due to its *beta* adrenergic blocking activity. However, neither it could be attributed to a 'quinidine like' effect since quinidine itself did not modify the mode of death after ouabain. It is, therefore, likely that propranolol affected ouabain induced ventricular fibrillation via some mechanism other than *beta*-adrenergic blockade or non-specific 'quinidine like' effect. In this context reference may be made to i) the local anaesthetic action of propranolol (Sekiya and Vaughan Williams (3)), ii) the proposed neural action (Standaert *et al.* (6)) or iii) the possibility of direct pharmacological antagonism to ouabain (Tuttle and Innes (7)).

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INTERACTION BETWEEN EXTRACELLULAR SODIUM AND THE EXCITATORY EFFECT OF ACETYLCHOLINE ON THE NON- PACEMAKER POTENTIAL ARRESTED BY PROPRANOLOL IN THE ISOLATED RABBIT'S ATRIA

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An excitatory effect of acetylcholine (ACh) on the non-pacemaker potential arrested by high doses of the adrenolytics was observed previously in the isolated rabbit's atria (1). In present experiments, interaction

between extracellular sodium (Na) concentration and the excitatory effect of ACh was investigated in the isolated rabbit's atria.

Rabbits of either sex weighing from 2.0 to 3.0 kg were used. Isolated atria were maintained in Ringer-Locke's solution bubbled with 95% O₂ and 5% CO₂ at 30°C. Non-pacemaker potentials of spontaneously beating atria were recorded intracellularly in almost the same manner as previously described (1).

Propranolol (10⁻⁵ g/ml) decreased gradually the resting potential, the rate of rise of depolarization phase and the height of overshoot, and prolonged the repolarization time of the action potential, and arrested the non-pacemaker action potential about 60 minutes after its application (Fig. 1A, A-C). ACh (10⁻⁶) could

FIG. 1A. Effect of propranolol (A-C) and the evoking effect of ACh in the presence of propranolol (D-G) on the non-pacemaker transmembrane potential of the rabbit's atria.

A : before, B : 40 minutes after propranolol (10⁻⁵), C : 60 minutes after, D : 1 minute after the first addition of ACh (10⁻⁶), E : 3 minutes after, F : 1 minute after the addition of ACh (10⁻⁶) and NaCl (30 mM), G : 15 minutes after.

B. Effect of ACh on the rabbit's atria in low sodium Ringer-Locke solution.

a. The non-pacemaker potentials.

A : before, B : 30 minutes after the replacement of 60 percent of NaCl in Ringer-Locke solution by sucrose, C : 8 minutes after ACh (10⁻⁷), D : 1 minute after atropine (10⁻⁶) in the presence of ACh.

b. The contractile amplitude.

Numerals below the record show atrial frequencies (beats/min). Each recording of the transmembrane potentials in Fig. 1A, A-G and Fig. 1B, B-D was performed in the same single cell.

temporarily evoke the action potentials arrested by propranolol, but in the normal nutrient solution (154 mm external Na) the complete recovery in both the rate of rise and amplitude of the action potential could not be obtained even by repetitive additions of ACh (Fig. 1A, D-E). However, simultaneous addition of the same single dose of ACh and 30 mm of external Na (totally 184 mm) could result in the more complete recovery of these parameters and moreover continuous firing of the action potentials (Fig. 1A, F-G). On the other hand, contraction of rabbit atria arrested by propranolol (10^{-5}) was partially recovered by the addition of ACh (10^{-6}) or/and 77 mm NaCl (totally 231 mm).

When sixty percent of the external NaCl was replaced by an isoosmotic amount of sucrose in untreated atria, action potential showed a decrease in both the rate of rise and the height of overshoot without markedly changing the resting potential (Fig. 1Ba, A-B). The decrease in both the heart-rate and the contractile amplitude was also observed. ACh (10^{-7}), applied 30 minutes after changing the solution, could restore completely these parameters without marked changing of the resting potential (Fig. 1Ba, C). The contractile amplitude, in both spontaneously beating atria and electrically driven atria (40 beats/min), was also recovered by ACh (10^{-7}) (Fig. 1Bb), the effect of which was blocked by the addition of atropine (10^{-6}) (Fig. 1Ba, D).

Morales-Aguilera and Vaughan Williams (2) have shown that propranolol reduced the rate of entry of depolarizing current. Johnson and Robertson (3) proposed the following hypothesis that ACh restarted an atrium arrested by quinidine by the direct effect on the "sodium carrying system". Further evidence for these hypotheses was presented by this experiment. The excitatory effect of ACh might be due to a direct improvement on the "sodium carrying system" in the condition of low sodium availability in addition to the indirect recovery resulted from the slight restoration of the resting potential by increasing permeability to potassium.

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ANTAGONISM OF IMIPRAMINE INDUCED FATAL HYPERPYREXIA IN MAO INHIBITOR TREATED RABBITS

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Extensive use of monoamine oxidase inhibitors and imipramine in psychiatric practice has revealed serious toxic reactions. It has been observed that combination of monoamine oxidase inhibitor and imipramine produces a symptom complex characterized by hyperexcitement, motor restlessness and hyperpyrexia (1-6). Furthermore, hypertensive crisis, subarachnoid haemorrhage and pulmonary oedema has been reported to occur in patients who were maintained on monoamine oxidase inhibitor and took cheese or broad beans (7, 8). High contents of tyramine in cheese and 3-4 dihydroxyphenylalanine (dopa) in broad beans have been suggested to be responsible for the above mentioned serious side effects. Since it is known that in MAO inhibitor pretreated animals administration of both, tyramine and dopa increase circulating catecholamine content