from an A2G mouse which had recovered from Ehrlich ascites tumor after viral oncolysis. This fluid precipitated in gel-diffusion assays with aqueous extracts from 3 unspecific tumors and from organs of mice belonging to several inbred strains, but not with similar extracts from other strains. The antigen involved has been provisionally called ϵ-24.

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Comparative Effects of Benzquinamide and P-2565 on Cardiac Rate. (29606)

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The central effects of 2-hydroxy-3-diethylcarbamyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzoquinolizine acetate (benzquinamide) and its alcohol analogue (P-2565) have been described by Weissman and Finger (1), Feldman(2), Smith(3), and Hashkes (4). Chemically both structures are closely related although their potentials to release amines centrally are not parallel(1). Many of the hypotensive agents which release or deplete the brain of norepinephrine (NE) and 5-hydroxytryptamine (5HT) also release or deplete peripheral organs of norepinephrine(5,6,7). The present report describes the effect of benzquinamide and P-2565 on heart rate and on NE levels of the heart.

Materials and methods. Benzquinamide solution was prepared by dissolving 40 mg in 4 ml of water with a drop of glacial acetic acid. P-2565 is readily soluble in water. In the experiments in which the NE levels were determined, the rats were sacrificed by decapitation and the heart tissue was rapidly removed and analyzed by the single extraction method of Shore and Olin(8).

The cardiovascular measurements were carried out on male cats and Sprague-Dawley rats anesthetized with pentobarbital 40 mg/kg i.p. In some experiments rats were anesthetized with a mixture of chloralose 100 mg/kg and urethane 500 mg/kg i.p. Arterial pressure from the carotid artery was recorded by the Statham transducer model 5 Grass Polygraph assembly. Heart rate was taken from the pressure record. The effects of benzquinamide and P-2565 were also tested in adrenal demedullated rats as well as in vagotomized animals. Benzquinamide and P-2565 were administered intraperitoneally. The effect of P-2565 on the isolated cat heart was studied in the Anderson heart perfusion apparatus. A polyethylene tube (No. 50) was introduced into the apparatus through a sidearm to allow drugs to be administered directly into the aorta close to the origin of the coronary arteries. The total volume of the catheter was only 0.1 ml.

Results and discussion. The bradycardia produced in rats treated with P-2565 50 mg/kg i.p. persisted for a longer period than

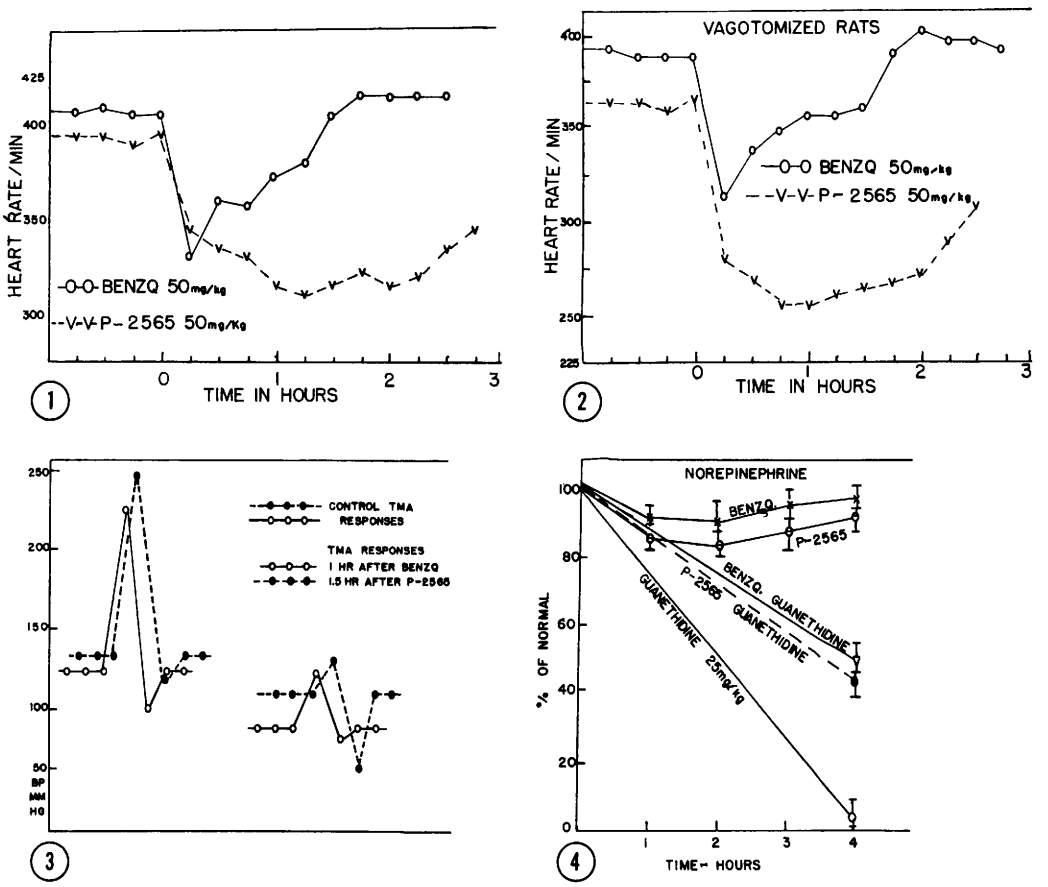

FIG. 1. Effects of benzquinamide (Benzq.) and P-2565 on heart rate of pentobarbitalized rats. Each point is mean of 4 experiments.

FIG. 2. Effect of benzquinamide and P-2565 on heart rate of pentobarbitalized and vagotomized rats. Each point is mean of 4 experiments.

FIG. 3. Blood pressure responses to 0.1 mg/kg of TMA before and after benzquinamide and P-2565 50 mg/kg I.P. Rats were anesthetized with pentobarbital, adrenals were demedullated and 0.1 μg/kg of atropine was given I.V. Each circle on abscissa represents a 15 min time interval. Values are a mean of 4 experiments.

FIG. 4. NE levels of rat heart at various times after benzquinamide 50 mg/kg I.P., P-2565 50 mg/kg I.P., guanethidine 25 mg/kg I.P., benzquinamide + guanethidine and P-2565 + guanethidine. Each value is mean of 16 rats. Normal value for NE is 1.2 μg/g $\pm$.08.

that seen in rats treated with the same dose of benzquinamide (Fig. 1). This bradycardia was not due to central parasympathetic stimulation since vagotomy did not modify this effect (Fig. 2). The bradycardia seen in rats is similar to that observed in earlier work in our laboratory in cats given P-2565 10 to 15 mg/kg i.p. The sudden initial decline in heart rate following administration of both compounds prompted us to test P-2565 on the isolated cat heart. Studies on the isolated cat heart indicated that P-2565 in doses ranging from 1.2 to 1000 μg did not have a direct effect on the isolated myocardium.

The arterial pressure response of rats to tetramethylammonium (TMA) was employed to study the effects of benzquinamide and P-2565 on peripheral ganglia. Since the pressor response to TMA represents a dual action, *i.e.*, a ganglionic stimulating action and a release of NE from the adrenals, the adrenals were demedullated and a small dose of atropine 0.1 μg/kg i.v. was administered to minimize parasympathetic responses. It should be noted in Fig. 3 that the control pressor response to 0.1 mg/kg of TMA

almost doubled the arterial pressure; however, one hour after administration of benzquinamide 50 mg/kg the pressor response to TMA was markedly reduced. The reversal of the TMA response produced by P-2565 (Fig. 3) is similar to that evidenced by reserpine.

Reserpine and a number of reserpine-like compounds, as well as guanethidine, produce a peripheral chemical sympathectomy, Costa (9), Orlans *et al*(10) by depleting peripheral NE stores. Some of the effects of this sympathectomy are bradycardia, decreased arterial pressure, reversal of the TMA response, Carlsson *et al*(5) Brodie *et al*(11), Trendelenburg and Gravenstein(12). On the other hand bretylium, a benzyl quaternary ammonium compound, has been shown to elicit a functional sympathectomy by preventing or blocking the peripheral release of NE induced by reserpine and guanethidine, Boura and Green(13). The final result of this functional sympathectomy is similar to that shown in a chemically sympathectomized animal. In addition, it should be pointed out that Scriabine *et al*(14) have demonstrated that benzquinamide possesses adrenolytic properties.

To determine if the bradycardia induced by P-2565 and benzquinamide was related to cardiac NE depletion, heart tissue was assayed 1, 2, 3 and 4 hours after the rats were treated with each compound. It was found that there was no significant depletion of NE from heart tissue by either drug (Fig. 4). On the other hand guanethidine, a guanidine derivative, 25 mg/kg i.p., depleted the heart of NE in 4 hours; this has been previously shown by numerous investigators. This depletion was interfered with by P-2565 and benzquinamide given one hour earlier; the interference suggests that P-2565 and benzquinamide have some propensity to produce a functional sympathectomy. While initial experiments suggested that the bradycardia was the result of a chemical or functional sympathectomy, the chemical analysis for NE and the guanethidine blockade indicated that these effects are only contributory factors to the bradycardia. It should be noted, moreover, that the ability of these drugs to produce a ganglionic blockade diminished the effect of the functional sympathectomy on the heart.

Summary. The bradycardia produced by benzquinamide or by P-2565 is not related to central parasympathetic stimulation. Studies on the isolated cat heart indicate that P-2565 does not have a direct effect on the isolated myocardium. Benzquinamide and P-2565 have ganglionic blocking properties as indicated by the tetramethylammonium test. In addition, the ability of benzquinamide and P-2565 to antagonize the guanethidine depletion of NE in heart tissue should be considered as a factor influencing the peripheral action of these agents on heart rate.

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