stimulating effect of B_{12} is more marked in females on high carbohydrate diets than in littermate sisters on diets of like protein content but with the calories provided by fat or a mixture of fat and carbohydrate.

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Suppression of Vasomotor Reflexes in Man Following L-Hydrazinophthalozine (C-5968).* (18085)

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A recent paper by Reubi(1) indicates that L-hydrazinophthalozine (C-5968), produces an increase in renal blood flow in hypertensive patients as well as a variable reduction in arterial pressure. Since no other hypotensive agent thus far studied possesses such properties(2) it seems of interest to attempt to localize further the site of action of C-5968 in man.

Method and results. L-hydrazinophthalozine was administered intravenously to 12 normotensive and 3 hypertensive patients in doses of 0.30 to 0.35 mg per kg. Sympathetic vasopressor responses, digital plethysmography, and skin temperature recordings were carried out according to methods previously described(3). Following intravenous injection of the phthalazine derivative all of the changes described below began to develop after 10 minutes, reached a maximum in 20 to 40 minutes, and then slowly receded over a period of several hours. The reduction in mean $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ arterial pressure ranged from 0 to 24% (average 8.5%) in the normotensive subjects and from 0 to 23% (average 8.6%) in the hypertensive patients. In both groups the percentile reduction of diastolic pressure was greater than the percentile fall in systolic pressure. In all patients the visible precordial and carotid pulsations appeared more prominent and forceful. A moderate tachycardia appeared in all patients (pulse rate increase 4 to 32 beats per minute) except 2 of the hypertensive patients who developed bradycardia. Transient inversion of the T waves particularly in leads V2 to V5 frequently were observed in the electrocardiogram.

After C-5968 there usually occurred marked inhibition or abolition of the vasopressor "overshoot" following the Valsalva maneuver, the tiltback "overshoot" and the cold pressor response. Postural hypotension occurred frequently but not invariably. Significant changes in digital skin temperature were not observed in a room maintained at 70°F. However, in environmental temperatures of 75° and higher, flushing of the hands frequently was seen, and there was an increase in pulse volume of both fingers and toes. The reflex vasoconstrictor responses to "noxious" stimuli in the digits were significantly inhibited.

Preparation C-5968 in the dosages used in the present studies in man did not prevent or reverse the hypertension produced by commercial epinephrine infused intravenously at rates of 0.11 to 0.23 μg per kg per min. Also, the tachycardia produced by epinephrine was not prevented. However, in 3 of 3 patients studied when norepinephrine was

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given intravenously at rates varying between 0.15 and 0.30 μg per kg per min. there was a moderate reduction of the pressor response varying between 12 to 45% (mean 31%). In addition there was a consistent and marked (approximately 80%) inhibition of the bradycardia induced by norepinephrine. In one instance, following C-5968, the infusion rate of norepinephrine was raised to twice that given in the control period. This resulted in a 31% increase in mean arterial pressure without, however, significant change in heart rate. Thus, after C-5968, blockade of norepinephrine bradycardia appeared to be far more complete than the inhibition of the pressor response induced by norepinephrine.

The side effects were palpitation, frequently observed, headaches, complained of in three subjects and dyspnea, which was noted by 2 hypertensive patients. The headaches were of a severe "pounding" type usually located in the occipital area, and were observed more frequently in patients receiving prolonged oral medication than in the present series given single intravenous injections of the drug.

Discussion. The significant although incomplete inhibition of sympathetic reflexes following C-5968 indicates that the drug has autonomic blocking action. The site of inhibition may be central, ganglionic or peripheral. The absence of epinephrine reversal and nasal congestion suggest that this compound in the dosages used does not act at the peripheral nerve endings. These observations in man are opposite to those achieved with higher dosage levels in animals by Gross and his co-workers(4). Others(5,6) have observed diminution in the epinephrine pressor response in animals but only in doses higher than those used in the present studies in man. There have been no reports of epinephrine reversal. Thus, preparation C-5968 does not appear to be adrenolytic in the same sense as Dibenamine or Priscoline. However, the slight inhibition of the norepinephrine pressor response observed in the present study as well as the inhibition of both epinephrine and norepinephrine hypertension following larger doses of C-5968 in animals(4-6) suggest that the drug may have an unusual type of peripheral action.

The failure to produce potentiation of the epinephrine and norepinephrine pressor responses, and the absence of changes either in pupillary size or visual accommodation suggests that the drug does not block ganglionic transmission. The other possible sites of action are in the central nervous system including the hypothalamus, the medulla and/or the spinal cord. Central inhibition of vasomotor reflexes is suggested by the ability of C-5968 to block almost completely the bradycardia following norepinephrine since the latter response probably is due to activation of the carotid sinus and aortic arch reflexes secondary to the hypertension produced by norepinephrine. Compound C-5968 differs, however, from other drugs which inhibit vasomotor reflexes centrally such as dihydroergocornine(6) and pentaquine(7) in that it also produces palpitation and tachycardia to a degree almost as marked as that observed after epinephrine.

Like DHO, preparation C-5968 did not act immediately after intravenous injection but required a latent period of 10 to 15 minutes. This suggests that the drug either is converted to an active compound in the body, or that the central mechanism which it affects responds slowly or else is acted upon secondarily through a chain reaction affecting unknown intermediary organs.

Summary and conclusions. The administration of L-hydrazinophthalozine results in inhibition of sympathetic vasoconstrictor reflexes in man. In addition it has epinephrine-like effects on the heart. C-5968 differs from other "sympatholytic" drugs studied thus far in man.

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