mary glands from control rats. Rats treated during late pregnancy also showed no change in DNA, but an increase in cellular RNA content was observed. These results are interpreted as indicating that a preparturient increase in corticosteroid activity may be involved in the normal initiation of lactation, but does not appear to be related to the increase in mammary DNA normally associated with the initiation of lactation.

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Effect of Reserpine on Sympathetic Vasoconstrictor Responses (33758)

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The majority of the antihypertensive agents in common usage today impair sympathetic reflex activity to a greater or lesser extent. Investigations of the effects of reserpine on vasoconstrictor responses have produced variable results. While some studies reported partial or complete inhibition of the Valsalva overshoot (1, 2) and mild orthostatic hypotension (3) this has not been confirmed by other investigators (4–6). The present study was undertaken to assess the extent of inhibition of therapeutic doses of reserpine in man to a variety of tests for sympathetic vasomotor activity.

Methods. Ten male patients on the general medical wards or from the Hypertension Clinic of the Veterans Administration Hospital were studied before and at the end of a period of reserpine administration. All subjects except two were hypertensive. Five patients received 0.5 mg of reserpine daily for at least 5 weeks and the other 5 received 2.0 mg for 6–10 days. All studies were performed in the hemodynamic laboratory. Arterial pressure was monitored by means of a Teflon "long dwell" needle inserted into the brachial artery and connected to a Statham P23Db Strain gauge transducer. The digital plethysmograph, which consisted of a plastic cup sealed around the finger with silicone grease, was connected to a Statham PM5 pressure transducer. Sanborn carrier preamplifiers and multichannel direct writing recorder were used for amplification and recording.

The following tests of reflex sympathetic activity were carried out. The Valsalva maneuver was performed by asking the subjects to take a deep breath and then to expel the air forcefully into a closed system for 10 sec. The blowing pressure, which was maintained at approximately 40 mm Hg, was recorded via a Statham P23AA pressure transducer. The highest intra-arterial pressure recorded within a few seconds after release of the expiratory effort was taken as the overshoot. The pressor response to cold was determined by immersion of one hand in ice water for 1 min. The orthostatic effect on the arterial pressure of quiet standing at 90° tilt for 5 min was recorded. An intravenous in-

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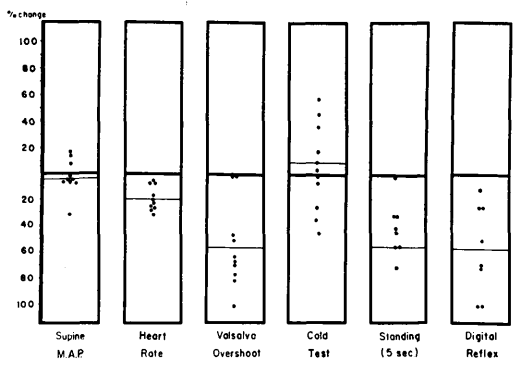

FIG. 1. Summary of changes following reserpine in the various parameters shown: the points indicate the individual changes while the thin horizontal lines indicate the means.

fusion of tyramine hydrochloride at a rate of 2 mg/min was administered in order to achieve an elevation of mean arterial pressure of approximately 30 mm Hg in the supine position or to a maximum dose of 10 mg. The amount required to achieve the desired effect during the control period was repeated after reserpine administration. Mean arterial pressure was determined by the sum of the diastolic pressure plus one-third of the pulse pressure.

Results. The administration of reserpine was associated with an average decrease of supine mean arterial pressure from 113 to 109 mm Hg (p = NS). Heart rate fell from 77 to 62.2 beats/min ($p < .01$). A reduction of the Valsalva overshoot occurred after reserpine, the overshoot in the control averaging 21 mm Hg which fell to 7.2 mm Hg after drug administration ($p < .01$) (Figs. 1–3). This effect was uniform in all subjects except 2 who had no overshoot even in the control period. The overshoot was completely blocked in 2 patients. During the control period a reflex bradycardia accompanied the Valsalva overshoot, the heart rate averaging 7.6 beats/min less than during the pre-Valsalva state. After reserpine there was no change in heart rate associated with the attenuated arterial pressure response to the Valsalva maneuver.

The average pressor and heart rate response to the immersion of the hand in ice water was not altered by reserpine even when the Valsalva overshoot was blocked (Figs. 1 and 3). During control period tyramine (av. total dose, 6 mg) led to a rise in mean arterial pressure of 30 mm Hg associated with a decrease in heart rate of 8.9 beats/

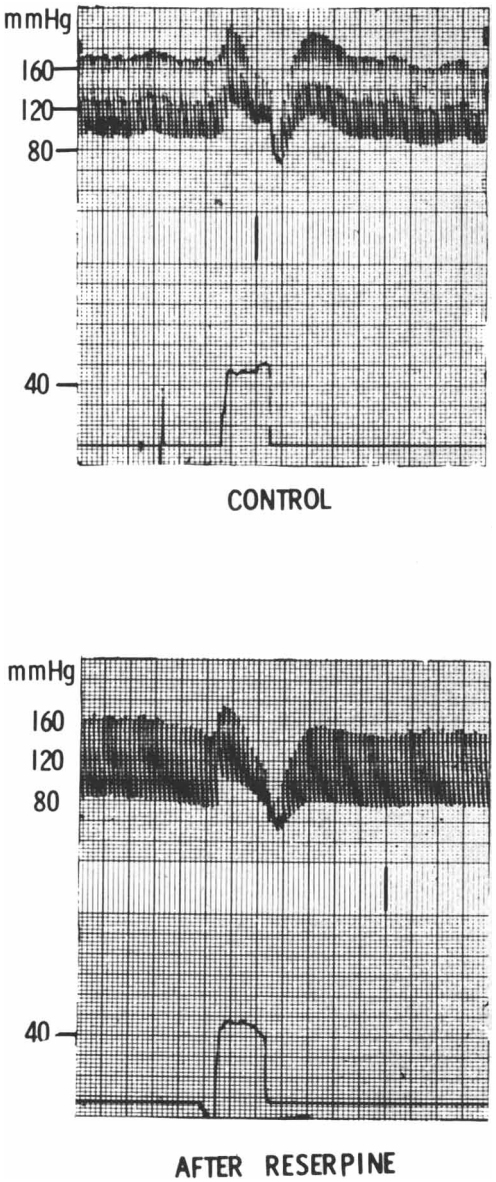

FIG. 2. Recordings of intra-arterial pressure (above), and blowing pressure (below) during the Valsalva maneuver in a 52-year-old hypertensive patient given 2 mg of reserpine daily for 10 days: after reserpine, note inhibition of the overshoot following release of the expiratory effort.

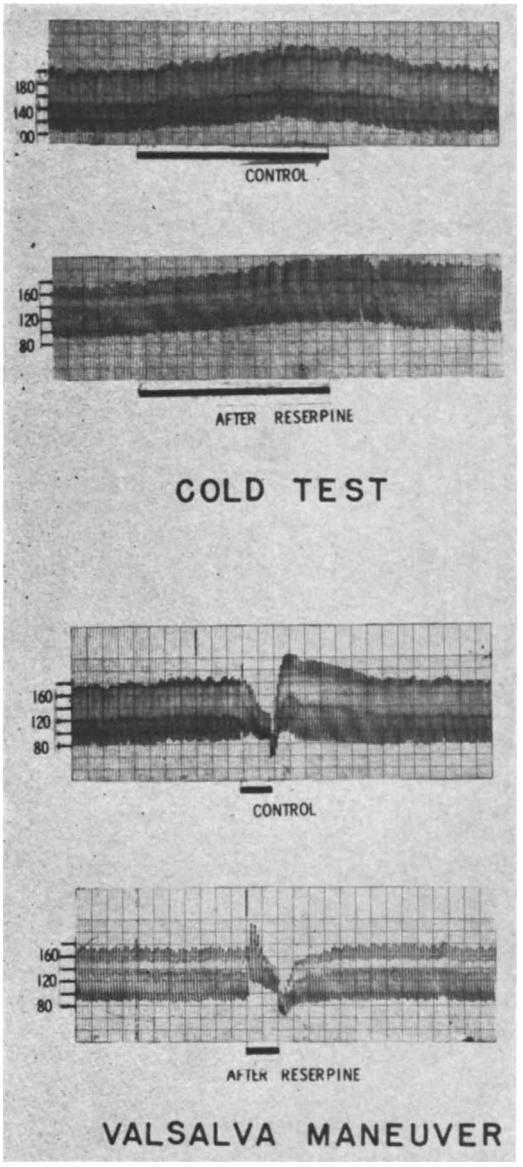

FIG. 3. Recordings of intra-arterial pressure during the cold pressor test (above), and Valsalva maneuver (below) in a 36-year-old patient with essential hypertension given 0.5 mg reserpine daily for 6 weeks: after reserpine, note failure of inhibition of the cold pressor response at the same time that the Valsalva overshoot is blocked.

min. Reserpine significantly reduced the tyramine effect with a rise in mean arterial pressure of only 10.7 mm Hg ($p<.05$) and practically unchanged heart rate response.

The orthostatic response of the arterial pressure during the control period was biphasic with an initial drop followed usually within 5 seconds by a rise to levels above supine. After reserpine the initial fall in standing pressure was significantly enhanced with a decrease of 20.4 mm Hg compared to 12.6 mm Hg during the control period ($p <$ 0.5). With further standing during control the mean arterial pressure continued to rise above the supine base line. After reserpine this elevation above the supine level did not take place (Figs. 1 and 4).

The digital vasoconstrictor reflex following a deep breath was blocked after reserpine in 6 of 8 patients in whom it could be adequately tested (Fig. 5) and was inhibited in the remaining 2 subjects (Fig. 1).

Discussion. The mild blood pressure lowering effect of reserpine in this study was expected since significant reduction is seen only in large series and is not great (7). The presence of an adequate reserpine effect in six patients was manifested by a significant reduction in heart rate and a reduced effect of infused tyramine. The decreased response to tyramine after reserpine has been well demonstrated previously in man (1) and experimental animals (8) and has been at-

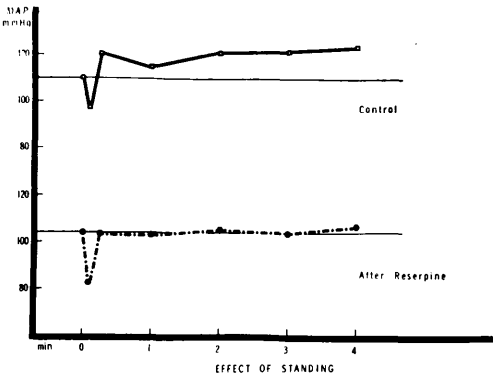

FIG. 4. Average change in mean arterial pressure of 10 subjects during the first 4 min following assumption of the erect position: the first points represent the mean arterial pressure in the supine position. Following reserpine, note the greater fall in mean arterial pressure immediately following the tilt and impaired recovery of the blood pressure as compared to the control.

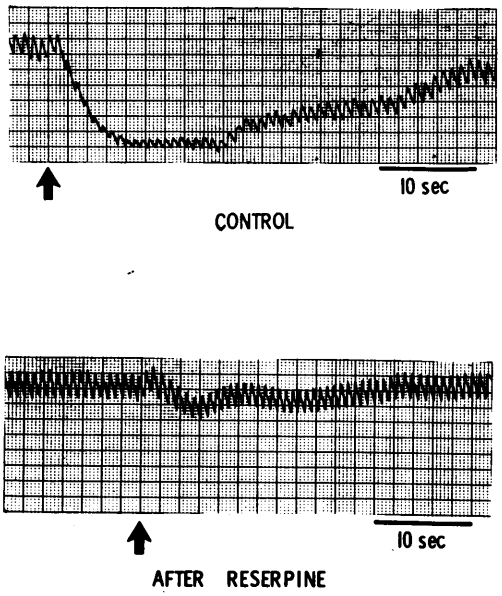

FIG. 5. Recordings of the digital plethysmogram illustrating the vasoconstrictor response following a deep breath (indicated by arrows) in a 42-year-old hypertensive patient given reserpine, 0.5 mg daily, for 5 weeks: note marked diminution in pulse and digital volumes in the control tracing which are completely blocked after reserpine.

tributed to the catecholamine depleting effect of the drug.

The inhibition of the digital vasoconstrictor reflex by oral reserpine is in agreement with other studies. Winsor in 1954 showed that small doses of reserpine (0.39 mg/day) produced slight inhibition of the digital vasoconstrictor reflex while large doses (2.8 mg/day) greatly inhibited or abolished the response (5). Ruttkay-Nedecky (9), on the other hand produced significant depression of the reflex in all 21 subjects after 7 days of 0.25 mg/day and the inhibition was evident after the first 2 days.

Reports on the effect of reserpine on the orthostatic response of the blood pressure have been variable. Some authors describe mild orthostatic hypotension (3) while others do not consistently find such an effect even after parenteral administration of the drug (4, 10). Smulyan and his associates (11) studied subjects before and 4 hr after 2.5 mg of reserpine intramuscularly. Following 60° head-up tilt there was a 6% rise in mean blood pressure during control and a 2% rise after reserpine. The present results indicate a mild orthostatic effect with a more prominent fall in blood pressure immediately after standing and a tendency to a slowed return to base line without complete recovery or overshoot as seen normally. This mild orthostatic hypotension is in contrast to that seen after ganglionic blockade (12) or guanethidine (13) which produce considerable falls of pressure on standing without any tendency to return to base line.

The absence of alteration of the cold pressor response is surprising but is in agreement with other investigations (4, 5). Shapiro (14) studied 10 patients on reserpine alone and 10 on reserpine plus thiazide. He found that reserpine did not affect the pressor response to the cold test or to noxious stimuli such as mental arithmetic or confusing color charts. The major pressor stimulus during the cold test probably is associated with the development of pain rather than the temperature change per se (15, 16). Pain produces a discharge of catecholamines from the adrenal medulla (17). At lower doses reserpine inhibits the synthesis of epinephrine and norepinephrine in sympathetic nerves and other tissues to a greater extent than in the adrenal medulla (18). This effect is similar to that seen with bretylium tosylate which does not block adrenal discharge of catecholamines following sympathetic stimulation (19) and only partially inhibits the cold pressor test (20). Furthermore, infusion of norepinephrine in the reserpinized subjects produces a normal or enhanced response (1, 2, 21). It appears that reserpine will inhibit neurogenically transmitted vasoconstrictor reflexes without significantly affecting adrenal release or the pressor response to circulating catecholamines. It is also possible that reserpine does not affect pressor responses produced by the cold test or noxious stimuli involving the cortex or thalamus. Finally, it is possible that the pain associated with the cold pressor test provides a more potent stimulus of the sympathetic nervous system than does posture or the Valsalva maneuver and this completely breaks

through the moderate inhibition produced by reserpine.

The overall results indicate that reserpine does produce mild inhibition of sympathetic reflex activity as exemplified by inhibition of the Valsalva overshoot and the digital vasoconstrictor reflex response to a deep breath and by a mild orthostatic hypotension. However, the pressor response to a painful stimulus such as the cold pressor test is not inhibited.

Summary. The effects of reserpine on the responsiveness of the sympathetic nervous sytem was assessed in 10 subjects. The Valsalva overshoot was significantly inhibited and the digital reflex vasoconstrictor response to a deep breath was blocked in the majority of the subjects tested. On assuming the upright position recovery of blood pressure was moderately impaired following reserpine although symptomatic orthostatic hypotension did not occur. These results indicate mild impairment of sympathetic reflex vasoconstrictor responses. By contrast, the cold pressor response was not inhibited. The latter effect may be due to failure of the drug to inhibit adrenal release of catecholamines or to the fact that the cold test is a more potent stimulus to the sympathetic nervous system.

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