18 to 10 g daily, and the next 2 insulin sensitivity measurements were made after the animals had consumed 10 g food/day for 4 weeks (Fig. 1, D) and 9 weeks (Fig. 1, E) respectively.

Results. Prolonged undernutrition led to relatively high fasting blood sugar levels and increased insulin sensitivity (Fig. 1, A). Nutritional rehabilitation was accompanied by progressive lowering of fasting blood sugar titers and gradual return of normal insulin sensitivity (Fig. 1, B and C). A second period of underfeeding at first did not lead to any change (cf. Fig. 1, C and D). However, upon further prolongation of undernutrition marked insulin sensitivity returned, although it was not accompanied by fasting blood sugar levels higher than those found in *ad libitum* fed rats (cf. Fig. 1, A and E).

Discussion. These findings demonstrated that *ad libitum* feeding abolished both the relative hyperglycemia and hypersensitivity to insulin in the fasted state which are characteristic of underfed rats, and that return of normal insulin resistance was not due to immunity to insulin which had arisen because of its repeated administration, since during a second period of underfeeding excessive insulin sensitivity again developed, although less rapidly than in the course of initial undernutrition. Systematic studies of the influence of age on fasting glycemia and insulin sensitivity and on the effects of underfeeding on these aspects of carbohydrate metabolism remain to be done. However, in our previous study(1) we have not noted any consistent differences in these regards among rats whose weight ranged from 180 to 350 g at the inception of underfeeding or, if the animals were fed *ad libitum,* at the time of determination of insulin sensitivity.

Summary. The characteristic fasting insulin hypersensitivity of chronically underfed rats is gradually abolished by subsequent prolonged *ad libitum* feeding and slowly returns during repeated undernutrition.

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Influence of Adrenergic Blockade and an Amine Oxidase Inhibitor on Reserpine Hypotension. (23281)

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The hypotensive effect of intravenous reserpine in anesthetized dogs requires 2 hours to become significant(1). Recent evidence which indicates that reserpine releases a sympathetic neurohumoral agent by Holzbauer and Vogt(2) and Maxwell *et al.*(3) suggests that this agent might be acting to mask a rapid onset of reserpine action. We have tested this hypothesis by determining the effect of adrenergic blockade and amine oxidase inhibition on the onset of reserpine hypotension. The following is a report of our findings.

Methods. Twenty-five dogs anesthetized with 30 mg/kg sodium pentobarbital intraperitoneally and a continuous intravenous infusion of 0.1 mg/kg/minute of sodium pentobarbital were used. Femoral arterial pressures were recorded with the Anderson glass capsule manometer(4). All drugs were administered intravenously. Phentolamine HCl was administered over a 15-30 minute period to minimize its hypotensive effect. Observations on hypotension produced by reserpine were limited to the first half hour after reserpine administration. Choline p-tolyl ether bromide, an amine oxidase inhibitor first reported by Brown and Hey(5) was employed in these experiments.

Results. Reserpine phosphate on blood pressure. In 6 dogs 0.5 mg/kg intravenous reserpine phosphate produced no significant

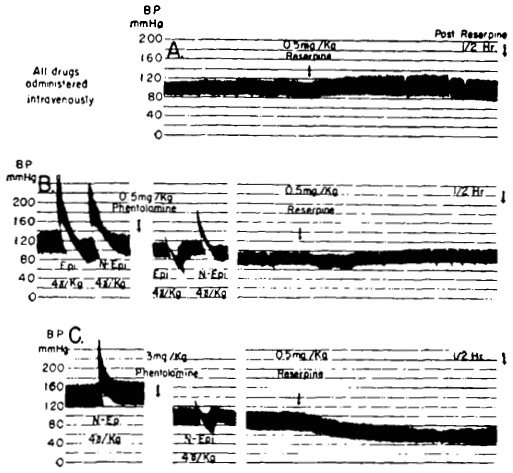

FIG. 1. Effect of adrenergic blockade on blood pressure response to reserpine phosphate.

change in blood pressure. Mean pressures varied from +5 to −10 mm Hg (−4 mm Hg average) over a half-hour period (Fig. 1-a).

Phentolamine (0.5 mg/kg) plus reserpine phosphate on blood pressure. Five-tenths mg/kg phentolamine produced a reversal of epinephrine pressor spikes and only a moderate reduction in nor-epinephrine pressor spikes in 4 dogs (Fig. 1-b). Subsequent administration of 0.5 mg/kg of reserpine phosphate resulted in insignificant variations in blood pressure ranging from −5 to +10 mm Hg (+2 mm Hg avg) over a half-hour period (Fig. 1-b).

Phentolamine (3 mg/kg) plus reserpine phosphate on blood pressure. Three mg/kg of phentolamine produced a very marked reduction of pressor response to nor-epinephrine in 7 dogs (Fig. 1-c). Subsequent administration of 0.5 mg/kg of reserpine phosphate produced changes in blood pressure ranging from −15 to −40 mm Hg (−30 mm Hg avg) during the first half-hour (Fig. 1-c). These reserpine-induced decreases in pressure could be demonstrated after phentolamine pretreatment which had lowered arterial pressures to levels ranging from 50 to 100 mm Hg.

Amine oxidase inhibitor plus reserpine phosphate. Ten mg/kg choline p-tolyl ether bromide were administered to 8 dogs. When the transient pressor spikes produced by this compound subsided, 1 mg/kg reserpine phosphate was injected. Reserpine phosphate administration resulted in pressor responses in 7 dogs which ranged from +10 to +40 mm Hg (avg +20 mm Hg) and lasted throughout a half-hour period (Fig. 2-a). In the 8th dog there was a blood pressure decline of 30 mm Hg after reserpine administration.

The effect of 10 mg/kg of choline p-tolyl ether upon the pressor responses to serotonin, epinephrine and nor-epinephrine was determined (Fig. 2-b). Responses to epinephrine and nor-epinephrine were potentiated by choline p-tolyl ether. The response to serotonin was prolonged but not dramatically enhanced.

Discussion. It is concluded from this work that the reduction in blood pressure produced by reserpine after phentolamine pretreatment is not a reflection of the epinephrine-reversal phenomenon. Concomitantly it is concluded that the vasoactive sympathomimetic humoral agent released by reserpine that is of greatest importance in sustaining blood pressure is not epinephrine but is most likely nor-epinephrine; and that this released substance masks an immediate moderate hypotensive effect of reserpine.

Pressor responses produced by the amine oxidase inhibitor plus reserpine further support the hypothesis of a rapid release of a sympathetic humoral factor by reserpine. The more dramatic potentiation of nor-epinephrine and epinephrine as compared with serotonin would suggest that serotonin plays only a minor role in the pressor response. Chessin *et al.*(6) have reported that iproniazid pretreatment will also cause reserpine to produce pressor responses.

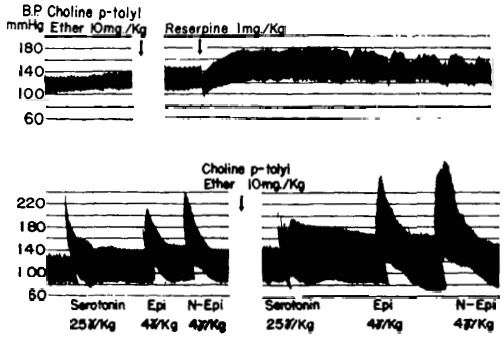

FIG. 2. Effect of amine oxidase inhibitor on blood pressure response to reserpine phosphate and pressor agents.

Summary. In proper doses administration of reserpine phosphate subsequent to adrenergic blockade with phentolamine will produce a more rapid decline in blood pressure than is commonly obtained by administration of reserpine alone. After pretreatment with amine oxidase inhibitor, choline p-tolyl ether, reserpine will produce pressor responses. These data are interpreted as supporting the hypothesis that reserpine releases sympathomimetic humoral agents which mask the early onset of the cardiovascular actions commonly attributed to reserpine.

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Effect of Increased Diphosphopyridine Nucleotide Levels on Rate of Ethanol Metabolism in the Mouse. (23282)

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The rate-limiting reaction in total oxidation of ethanol to CO_2 is the first step in the sequence of oxidation of ethanol to acetaldehyde(1). Three separate entities, ethyl alcohol, diphosphopyridine nucleotide,* and the enzyme alcohol dehydrogenase, participate in this reaction. It is generally agreed that the rate curve for disappearance of ethanol from blood follows a straight line rather than an exponential curve, except at low concentrations of blood alcohol(2). The enzyme, therefore is soon saturated with its ethanol substrate, and the availability of the alcohol does not appear to be a physiologically significant rate-limiting factor in its oxidation. This study was initiated in an attempt to determine whether the DPN concentration or amount of alcohol dehydrogenase present in liver may be the controlling factor in the disappearance of ethanol from the body.

Kaplan and coworkers(3) have induced DPN levels 10 times that of normal in the mouse liver by injection of nicotinamide 8-12 hours previously. Mice preinjected in this manner have been used in this work to study possible effects of the heightened DPN level on rate of ethanol oxidation. Both *in vivo* and *in vitro* studies have been performed.

Methods. In vivo experiments. Blood alcohol concentration was determined by the method of Newman and Newman(4). Adult mice of the C57 BL strain maintained on Purina Laboratory Chow were used. Six hours before administration of alcohol, the mice were injected intraperitoneally with 500 mg/kg nicotinamide in a solution containing 25 mg/ml. This time interval was chosen so that during the latter part of the 5 hours after alcohol administration, the DPN would be at optimum level in the liver as reported by Kaplan *et al.*(3). The ethyl alcohol was injected in 20% aqueous solution w/v in a single intraperitoneal injection at 4 g/kg. Alcohol injections were made to both mice preinjected with nicotinamide and to their untreated controls. At hourly intervals for 5 hours after alcohol injection, nicotinamide treated animals and controls were anaesthetized with chloroform and blood withdrawn from the heart which resulted in their death.

In vitro experiments. Slices. Webster Swiss mice were injected with 500 mg/kg nico-

* Diphosphopyridine nucleotide will be abbreviated to DPN