sis had significant ovarian ascorbic acid depletion (OAAD) activity when injected into immature, pseudopregnant, female rats. Heating of the suspension increased the OAAD activity. The possibility of interference to the OAAD assay for LH by other OAAD-active substances is considered.

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Blood Pressure Response of Adrenal-Enucleated Rats to Restricted And Irregular Feeding Patterns and to Subsequent *ad Libitum* Realimentation.* (30470)

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Within recent years attention has been drawn to peculiar metabolic derangements caused by "stuff-and-starve" regimens as opposed to regular feeding ("nibbling")(2-8). The effect of starvation and subsequent realimentation on the dynamics of the cardiovascular system have also been studied(9-12). It was shown(9-11) that realimentation of previously starving pigs with glucose and starch resulted in hypertension, tachycardia, faltering pulse, extrasystoles and myocardial infarcts. Wilhelmj and McCarthy(11) found that realimentation of normal dogs with carbohydrate and high protein diets resulted in considerable increases of systolic and diastolic blood pressure and heart rate.

In the face of the evidence regarding blood pressure increases on realimentation in intact animals, it was conceivable that restricted and irregular feeding patterns and realimentation could augment blood pressure responses in rats with experimental hypertension. On the other hand, restricted feeding with attendant low sodium intake might suppress increases in blood pressure in a type of hypertension characterized by a large requirement for sodium, namely adrenal-regeneration hypertension. This requirement for sodium in adrenal-regeneration hypertension is particularly true for the first 2 weeks after adrenal enucleation(13,14).

The present note describes experiments on adrenal-enucleated rats to investigate whether restricted feeding patterns during the early post-operative time depressed blood pressure and whether such feeding regimens perma-

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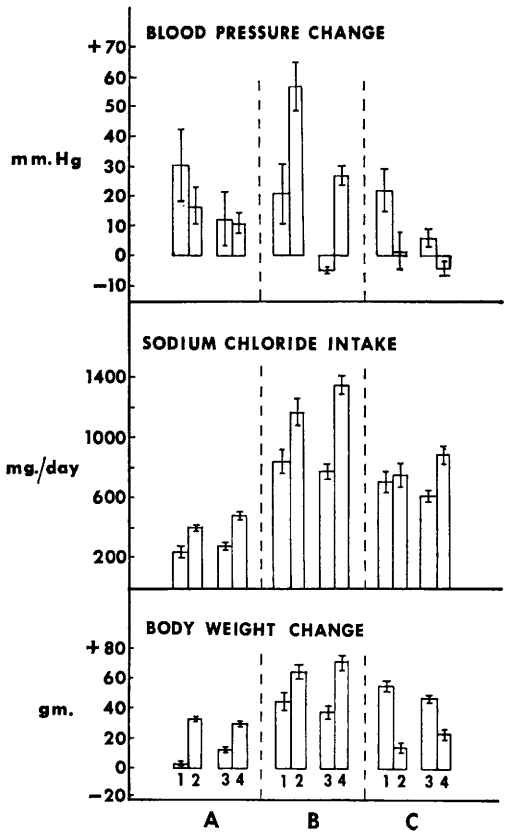

FIG. 1. Blood pressure changes, sodium chloride consumption and body weight changes of adrenal enucleated rats (Group 1—food-restricted, Group 2—fed *ad libitum*) and intact rats (Group 3—food restricted, Group 4, fed *ad libitum*) during 2 restricted feeding regimens (A and B) and a subsequent period of *ad libitum* realimentation (C). Mean values and Standard Error of Mean are given. The blood pressure and body weight changes reported are the differences between the blood pressure and body weight at beginning and at end of each experimental period.

nently suppressed the ability of the regenerating adrenal to cause the development of high blood pressure during subsequent *ad libitum* realimentation.

Eighty weanling female Charles River rats were divided into 4 groups of 20 rats each and treated in the following manner: Groups 1 and 2 were subjected to right-sided nephroadrenalectomy and left-sided adrenal enucleation (AE) on the 25th day of life(13). Groups 3 and 4 consisted of intact rats. All animals were fed a synthetic diet containing 4.2 Cal/g and 0.8% NaCl. Groups 1 and 3 were given food for restricted periods of time. Later they were realimented *ad libitum*. Groups 2 and 4 were fed *ad libitum* throughout the experiment. Duration of the experimental periods and of daily feeding is referred to in the Results section. All animals received 1% saline as drinking fluid *ad libitum* throughout the experiment.

Food and saline consumption were measured daily and the amount of sodium chloride consumed per experimental period was computed. Systolic blood pressure was determined on day 7 post-operatively and at the end of each experimental period by the microphonic manometer method of Friedman and Freed(14), with the rats under light ether anesthesia. Body weights were measured at the same time.

(A) *First experimental period—day 7 to day 14 post-operatively.* Fig. 1 shows the results of this and the following experimental periods. The food-restricted rats (Groups 1 and 3) were fed for one hour each day. The food-restricted AE rats (Group 1) showed a blood pressure increment similar to that of their *ad libitum*-fed AE controls (Group 2), despite a significantly lower sodium chloride intake and reduced body weight. The intact food-restricted rats (Group 3) showed a mean blood pressure rise almost identical with that of their intact *ad libitum*-fed controls (Group 4). Similarly, comparison of food-restricted AE and intact rats (Groups 1 and 3) as well as *ad libitum*-fed AE rats and their intact counterparts (Groups 2 and 4) showed no significantly different blood pressure increments.

(B) *Second experimental period—day 14 to day 35 post-operatively.* During this experimental period, the daily feeding time ranged from total starvation to feeding for 1, 2, 4, 8 and 24 hours in random fashion. The blood pressure increase in food-restricted AE rats (Group 1) was significantly less than that of the *ad libitum*-fed AE rats (Group 2, $p<0.02$). Further, a highly significant drop in blood pressure ($p<0.001$) occurred in the intact, food-restricted rats (Group 3) as compared with their *ad libitum*-fed controls (Group 4). The sodium chloride intake was significantly reduced in both groups on the restricted regimens (Group 1 *vs* Group 2,

$p<0.02$, Group 3 *vs* Group 4, $p<0.001$). The same obtained for body weight gains. It is noteworthy that both AE groups (1 and 2) showed significantly higher ($p<0.001$ and $p<0.001$, resp.) blood pressure increases than their respective intact counterparts (Groups 3 and 4). Despite the smaller blood pressure increment in Group 1 as compared with Group 2, the mean blood pressure of the former group was higher than that of its intact counterpart (Group 3).

(C) *Third experimental period—day 35 to day 45 post-operatively.* During this period the 2 groups (1 and 3) that had thus far been fed for restricted periods were realimented *ad libitum*. The mean blood presure increment of the formerly restricted AE rats (Group 1) was significantly greater ($p<0.05$) than that of the formerly (and presently) *ad libitum*-fed AE rats (Group 2). The blood pressure increment of the formerly food-restricted intact rats (Group 3) was significantly higher ($p<0.02$) than that of the corresponding intact controls (Group 4) as well, but the differential was much less than the differential between Groups 1 and 2. In contrast to the previous experimental period (B) the AE rats did not show significantly higher blood pressure increments than did their intact counterparts. There was no significant difference between the sodium chloride intake of Groups 1 and 2 or between Groups 3 and 4. The body weight increments were significantly greater in the formerly food-restricted rats (Groups 1 and 2, both $p<0.001$) when compared with their formerly (and presently) *ad libitum*-fed controls (Groups 2 and 4, resp.).

Metabolic effects of "stuff-and-starve" regimens *vs* "nibbling" have received considerable attention within recent years(2-8). That cardiovascular dynamics is affected by food restriction and the metabolic overloading attending realimentation has been shown by Brozek *et al*(15), who demonstrated in human volunteers that long-term food restriction resulted in decreases of both systolic and diastolic blood pressures. Realimentation normalized these parameters. Stapleton(16) has reported that the blood pressure of prisoners of war during realimentation not only returned to normal but overshot into frankly hypertensive levels. Observations in experimental animals have shown similar results (9-12).

The present findings are similar to the above reports on humans and intact animals, inasmuch as restricted feeding resulted in a depression of blood pressure in adrenal-enucleated as well as in intact rats. Skelton (12,13) has shown that adrenal-enucleated rats must be provided with large amounts of sodium chloride in order for adrenal-enucleation hypertension to develop, particularly during the first 2 weeks after adrenal enucleation. In the present study the food-restricted adrenal-enucleated rats had a lower sodium chloride intake than their *ad libitum*-fed adrenal-enucleated controls, and this reduced intake probably is one reason for the lower blood pressure rise seen in the second experimental period.

Inasmuch as adrenal regeneration and adrenal-regeneration hypertension require adequate amounts of ACTH(18) it may be pertinent that Handler and Bernheim's(18) findings that animals on low protein diets produce less ACTH. The ingestion of small amounts of food in the restricted groups of the present study undoubtedly amounted to a low protein diet.

It is noteworthy, however, that the adrenal-enucleated, food-restricted rats did show suggestive (first experimental period) and significant (second experimental period) blood pressure rises when these were compared to the blood pressure increases in the intact-food-restricted rats. That this occurred without correspondingly higher sodium intake suggests that the hypertensive potential of the regenerating gland has not been eliminated by the drastic restriction during these 2 experimental periods.

The fact that realimentation resulted in significant rises of blood pressure in formerly food-restrcted adrenal-enucleated as well as intact rats was not surprising in view of the findings of the Smiths(8-10), Wilhelmj and McCarthy(11), Brozek *et al* (15) and Stapleton(16) referred to previously. The fact that the formerly food-restricted adrenal-enucleated rats displayed a

greater increase in blood pressure than did their *ad libitum*-fed counterparts suggested again that the previous radical feeding regimens did not permanently suppress the hypertensive potential of the regenerating gland and if anything, accentuated its development. It may be pertinent to consider Selye's postulate that fasting renders the organism more sensitive to alarm stimuli(19). Undoubtedly, realimentation following restricted feeding represents an "alarm stimulus." It is noteworthy, particularly in the face of Skelton's original findings(12,13), that the increase of blood pressure in the formerly food-restricted AE rats in the present experiment was evident despite a sodium chloride intake similar to that of their *ad libitum*-fed counterparts as well as to that of the intact rats. In addition, the formerly restricted groups, both AE and intact, showed greater rises in body weight than did their *ad libitum*-fed controls.

The foregoing results confirmed the findings in humans and other experimental animals inasmuch as restricted feeding depressed blood pressure rises in both intact and AE rats. The experiment also showed that despite food restriction in the early post-operative periods, rats with regenerating adrenals showed greater blood pressure increments following realimentation than did their intact controls, although their sodium chloride intake was similar. Thus, despite early sodium restriction the regenerating adrenal maintains or increases its hypertensive potential which may be successfully challenged by *ad libitum* realimentation.

Summary. 1. Restricted food intake resulted in smaller increases of blood pressure in intact as well as in adrenal-enucleated (AE) rats when compared with corresponding controls but fed *ad libitum*. However, AE rats showed a greater increase in blood pressure when compared with intact rats, and this holds particularly for the food-restricted groups. 2. A 10-day realimentation regimen following periods of restricted feeding resulted in greater increases of blood pressure in formerly food-restricted AE rats than in corresponding intact animals. This increase in blood pressure occurred although the AE rats did not ingest more NaCl than the *ad libitum*-fed AE rats and intact controls. 3. It may be concluded that the regenerating adrenal does not lose its hypertensive potential despite food and thus NaCl restriction.

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