Hypothalamic Hyper- and Hypotension Induced by the Destruction of the Tubero-mamillary Region in the Rat

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Various destruction in the tubero-mamillary region in hypothalamus induced hypertension and hypotension, on which etiological hormonal and neural factors were investigated pathologically, chemically and electrophysiologically, and the chronic effects of the lesions on blood pressure were compared with the acute effects of hypothalamic stimulation and destruction. The results provided the evidences that these hyper- and hypotensions were both classified into two main categories; adrenogenic and nonadrenogenic (perhaps neurogenic and partly thyroidogenic), and hypothalamic contribution to blood pressure regulation through nervous and endocrine systems was discussed in relation to the detailed localization of hypothalamic lesions.

THE MOST challenging problem to be solved in the research field on hypertension is the pathogenesis of the idiopathic disease, essential hypertension, in which the participation of the various components of neuro-endocrine homeostasis has been revealed up to the present. The primary etiological importance, however, has not yet been successfully ascribed to any of these factors in spite of the enormous amount of elaborate studies on the patient with essential hypertension.

On the other hand, recent progress in the experimental studies on the Spontaneously Hypertensive Rat (Okamoto and Aoki), which seems to be the most suitable model for human essential hypertension in various kinds of experimental hypertension, has revealed that multiple neural and humoral factors consisting of sympathetic, adrenomedullary, hypothalamic, adeno-hypophyseal-adrenocortical and thyroidal systems, are involved in the pathological process of the development of spontaneous hypertension.

These two facts obtained in the studies on both essential and spontaneous hypertensions suggest that the disturbances of neuro-endocrine homeostasis, on which proper functioning of the cardiovascular system is dependent, is of etiological importance for the development of these hypertensions of unknown etiology. Since neuro-endocrine homeostatic functions are integrated by hypothalamus, relationships between the hypothalamic dysfunction caused by the lesions placed in hypothalamus and the chronic changes in blood pressure have been extensively investigated in rats, and sustained hyper- and hypotension were obtained by hypothalamic destruction (hypothalamic hyper- and hypotension) as reported previously. Among these hyper- and hypotensive rats, the etiological factors involved in the hypertension induced by extensive medial anteromedian hypothalamic destruction was revealed to be obvious adrenocortical hyperfunction with complementary imbalance of electrolyte metabolism.

In the present studies humoral and neural factors involved in hyper- and hypotension

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induced by the destruction of the tuberomamillary region of the hypothalamus were investigated in relation to the sites of the lesions in chronic experiments, and in addition, acute experiments were performed to elucidate the stimulative effect of these sites of the hypothalamus and to compare the acute effect of the lesions with the chronic one.

**Materials**

About 320 male Wistar rats weighing from 200 to 320g were used in this study, after the blood pressure was repeatedly checked by the modified tail-water plethysmographic method for a period of over 4 weeks to exclude rats with spontaneous hypertension. Among them, 160 rats which survived longer than 2 weeks after hypothalamic destruction, 6 sham-operated rats which received electrolytic lesions in the parietal part of cerebral cortex, 5 renal hypertensive rats which were produced by ligation of the bilateral posterior branches of the main renal arteries, 5 neurogenic (cerebral) hypertensive rats which were produced by constriction of bilateral internal carotid arteries with a balloon of the tissue around the carotid sinus area, 5 bilaterally adrenalectomized rats which were maintained on tap water, and 14 nontreated controls served for a long-term observation of blood pressure, heart rate, body temperature and urinary output, for plasma corticosterone assay and histological studies on endocrine organs, and partially for the experiments as follows. For evaluation of thyroid function release ratio was examined in 49 rats (43 hypothalamus-lesioned rats and 6 sham-operated rats). Catecholamine contents of the left adrenal gland was measured in 21 rats (11 hypothalamus-lesioned rats and 10 controls). Neurochemical and histometrical studies on adrenal medulla were performed on 16 rats (12 hypothalamus-lesioned rats and 4 controls). Neurogram of splanchnic discharge was recorded electrophysiologically in 12 hypothalamus-lesioned rats, 5 controls and 3 hypotensive rats induced by acetylcholine (2γ/kg, i.v.) and sodium pentobarbital (60–90mg/kg, i.v.) administration. The effect of the total destruction of spinal cord (pithing) on blood pressure was observed in 9 hypothalamus-lesioned rats, 5 adrenalectomized rats, 7 hexamethonium-treated hypotensive rats which had been previously supplied with drinking water containing 500mg/dl hexamethonium, and 10 controls.

In addition to these experiments on hypothalamus-lesioned rats, acute effects of electrical stimulation and electrolytic destruction of hypothalamus were investigated in 41 rats, among which 21 rats survived longer than 2 weeks after hypothalamic stimulation and destruction. These survivors served for the comparison of the acute effect of hypothalamic stimulation and destruction with the chronic effect of the lesions placed in the hypothalamus. The conditions of housing and feeding of all these rats were the same as already reported in the preceding papers. Some rats which showed aphagia after hypothalamic destruction were fed on condensed milk through a stomach tube for 1 or 2 weeks until normal appetite recovered.

**Methods**

Electrolytic destruction of hypothalamus Under sodium pentobarbital anesthesia (30mg/kg, i.p.), the lesions were placed with a stereotaxic apparatus (model Tokyo-University-Nenen) using a mongol stainless steel electrode, 0.4mm in diameter, insulated to 0.3mm from a round tip, from which anodal and cathodal DC currents of 10 volts were allowed to flow for 12 seconds alternatively for two times. The bilateral paired lesions were within 2 mm apart from the midline, ranged from 3.4 to 5.4 mm rostral and from 1.0 to 3.5mm superior to the interaural zero point in De Grooth's stereotaxic coordinates. ECG were recorded immediately prior to and after the destruction using needle electrodes placed under the skin of the right and left forelegs and the right hindleg.

Long-term observation of blood pressure, heart rate, body temperature, urinary output and pupillary size: After the animals recovered sufficiently one week following operation, blood pressure was measured by plethysmographic method once a week until sacrifice from 5 to 20 weeks after hypothalamic destruction. During a period, from 4 to 10 weeks after operation, heart rate was recorded by ECG, rectal temperature was measured by an electronic thermometer (Natsume Co.) and daily urinary output measurements were made on the rats kept in metabolic cages. Pupillary diameters were checked by a microcalibrator under constant lightening.

Histological studies: After 5 to 20 weeks of observation, the animals were sacrificed by decapitation and their organs were dissected clean, weighed on a torsion balance or on a lever balance, and pituitary, kidney and pancreas were fixed in Zenker's solution and the others in 10 per cent formal. The endocrine organs and kidneys were histologically examined with hematoxylin and eosin (HE) stain. Pituitary and thyroid were also stained with periodic acid Schiff (PAS) stain, adrenals with sudan III. The brain including the hypothalamus was embedded in celluloidine, cut serially at 30μ and stained with galloycyanin-chrome alum and the localization of the lesions was examined histologically with reference to De Grooth's atlas and König's atlas and Kriegl's atlas.

renal medulla: The right adrenals were sliced sagit-
tally at the midplane of the medulla, and fixed in
cold (0-4°C) 0.1 M phosphate-buffered 6 per cent
 glutaraldehyde (pH 7.3) for a period of more than 2
 hours and cut on the thermo-electro freezing micro-
tome (Komatsu Electron Inc.) at 15 μ. The sections
 were dipped into cold veronal acetate-buffered 1 per
cent osmium tetroxide (pH 7.3) for a period of 90
 minutes for the demonstration of noradrenaline stor-
ing cells23. The dimensions of noradrenaline-storing
 cells thus stained were measured planimetrically
 under 300 magnification with the aid of a micro-
 projector (Leitz Typ. X3c Xenon) to obtain the di-
mensional ratio of noradrenaline-storing cell islets
to the whole adrenal medulla24.

Catecholamine contents of adrenal medulla: The
 left adrenals were dissected free of extraneous adipose
 tissue, weighed, minced and extracted with 10
 per cent trichloroacetic acid for 30 minutes. After
 filtration, noradrenaline and adrenaline were fluo-
 rometrically estimated with a Farrand spectrofluor-
ometer according to the detailed procedures by
 Euler and Lishajko25.

Plasma corticosterone assay: All rats were isolated
 individually prior to sacrifice and decapitated for
 blood collection without anesthesia at 8 a.m. with
 great caution to avoid putting them under stress.
 Corticosterone levels in the plasma were determined
 by the fluorometric procedure of Zenker and Bern-
 stein25.

Determination of the rate of thyroidal 131I release:
 Hypothalamus-lesioned rats and sham-operated rats
 received 5 μC of carrier free 131I intraperitoneally 1
 to 2 months after operation. The radioactivity of
 the thyroid region was measured 60 hours after 131I
 injection and 4 more times at 48 hour intervals dur-
ing the following 8 days. The rats were lightly an-
esthetized with ether inhalation25 and strapped on
 their backs to a board with the neck slightly elevated
 on a pillow. The thyroid region was placed just
 under a window (2.2 cm in diameter) of a lead shield,
 5 cm from a scintillation detector (Scinti. Probe,
 Shimadzu, Type B-201B) and counted for 1 minute
 with a 2-channel scaler (Shimadzu EC 10A) con-
nected with the scintillation detector through
 spectrometers (Shimadzu ES 7). The exact position-
ing of the thyroid was made with the aid of a rate
 meter and in addition, geometrical errors due to
 small differences in the position of the thyroid were
 avoided by taking the average of 3 counts preceded
 by replacement of the neck. Body background (B)
 was counted over the epigastric region and the total
 count over the thyroid (T) was corrected by one half
 of the body background as well as the absolute back-
ground (A), that is, corrected thyroidal activity =
 (T-A) - (B-A)/2. The validity of this formula indi-
cated by Wolff27 was confirmed experimentally in

our preliminary studies. These values were corrected
with physical decay and the biological half-life of
thyroidal 131I of each rat was calculated from the
slope of release curve which was obtained by the
method of least squares. During the experiment
the rats were kept under standardized conditions as
usual, i.e., in an environmental temperature of
24± 2°C, with humidity of 50 to 60 per cent, and
fed with Oriental's stock chow diet (NMF, Oriental
Yeast Co.).

Total destruction of spinal cord (pithing): Under
light ether anesthesia, rats were fixed on their backs,
intravenously infused with the minimum anesthetic
dose of α-chloralose (40 mg/kg) and canulated into
left femoral artery with thin polyethylene tube (1.0
mm in diameter) which was connected to a small
volume mercury manometer for recording blood
pressure kymographically. Through tracheal canula
inserted after tracheotomy, rats were maintained by
artificial respiration with air after intravenous
administration of flaxedil (0.1 ml). A 1.9 mm thin steel
rod was promptly inserted with minimum hemorrhage
through left orbita down to the end of spinal
cord to accomplish the destruction of whole spinal
cord, which was confirmed at autopsy after pithing.

Recording of splanchnic activity: Splanchnic dis-
charge was recorded in the rats lightly anesthetized
with α-chloralose (40 mg/kg, i.v.). Splanchnic nerve
was approached through incision at the back, dis-
sected and desheathed carefully, sectioned peripheral-
ly at the entry of coeliac ganglion and hooked up
with a small stainless steel bipolar electrode with an
extra rod for supporting the cut end of the nerve.
Potentials of the nerve were fed to and displayed on
a dual beam cathode ray oscilloscope (Nihon Koh-
den, VC-6) directly and simultaneously through the
additional filter circuits composed of bandpass filter
and clipping circuit which cut out non-neural compo-
ners of higher frequency and slower wave and of
lower amplitude below noise level. The activities
were then transformed into pulses of the same am-
plitude through a pulse generator and into tachogram
to detect the perpetual change in frequency and dis-
played on an ink-writing oscillograph. The pulses
were counted with a dekatron counter (Hitachi 100
scaler) connected to the pulse generator. Direct blood
pressure was recorded kymographically through fe-
moral artery during the recording. The details of
operative procedures and of apparatus as well as the
validity of this technique to record discharge of a
whole nerve in rats were reported and discussed in
the preceding article4.

Electrical stimulation of the hypothalamus: After
light α-chloralose anesthesia (40 mg/kg, i.v.) and
arterial canulation as described already, rats were
placed in the stereotaxic apparatus. The same elec-
trode as was used for destruction, was introduced

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unilaterally into the hypothalamus for stimulation so that the stimulated sites might be destroyed under the same conditions as in the previous experiments of hypothalamic destruction. An electronic stimulator (Nihon Kohden, MSE-3) connected with an isolating units (Nihon Kohden, MSE-JM) was used to deliver 2 volts square wave pulses, 1 msec. wide, at a rate of 100 pulses/sec, in trains lasting for 10 seconds, after these parameters were confirmed to be optimum for eliciting cardiovascular responses from the hypothalamus in rats under the conditions of this experiment. Four stimulations in average were applied and one unilateral lesion was placed later in each rat to avoid the complexity caused by the bilateral lesions which could not be located in the exact symmetrical position of each other. In some cases the contralateral side of the hypothalamus initially stimulated was stimulated and destroyed again 2 or more weeks later, after the effect of the first lesion was observed. In total, 155 points were stimulated and 41 lesions were placed in the posterior hypothalamic region which ranged within 2 mm apart from the midline, from 3.4 to 5.4 mm rostral and 1 to 3.5 mm superior to the interaural zero point in De Groot's stereotaxic coordinates. These hypothalamus-lesioned rats served for chronic observations and were examined histologically and with plasma corticosterone assay after sacrifice as mentioned before. The site of stimulation was also determined from the site of a lesion checked histologically in serial sections.

RESULTS

1) Chronic observation of changes in blood pressure following tubero-mamillary hypothalamic destruction. (Table I)

Out of 210 trials of placing lesions in the tubero-mamillary region of the hypothalamus 50 rats died of coma, aphagia or infectious diseases within 2 weeks postoperatively, and 160 rats survived long enough for chronic observation. Among these survivors 13 rats (8.1\%) and 38 rats (23.8\%) developed hypertension and hypotension, respectively, both of which were evidently higher or lower than 99 per cent confidence range of blood pressure (M ± 3SD, 97–145 mmHg) in age-matched control rats. The average blood pressure in these groups was as a matter of course significantly higher or lower than their own average preoperative blood pressure and the average of blood pressure in age-matched control or sham-operated rats. Forty-eight rats (30.0\%) maintained blood pressure within normal range and the other 21 rats (13.1\%) and 40 rats (25.0\%) showed borderline blood pressure between normotension and hypertension or hypotension, respectively.

As to the developmental course of hypertension and hypotension, 8 out of 13 hypertensive rats developed hypertension rapidly following operation to exceed the upper limit of normal range (145 mmHg) within 2 weeks and maintained hypertension thereafter (group R), and the other 5 rats became hypertensive gradually (group G). On the contrary, in 38 hypotensive rats, 27 rats developed hypotension rapidly which became lower than the lowest limit of normotension (97 mmHg) within 2 weeks (group R), and 11 rats took longer than 2 weeks to become hypotensive (group G). Borderline hypertension as well as borderline hypotension was divided into temporary hypertension (12 rats) or hypotension (19 rats) which was out of the normotensive range for more than 2 weeks but was not maintained (group T), and mild hypertension (9 rats) or hypotension (21 rats) which fluctuated within and out of normotensive range (group M). The last blood pressure of the borderline hypotensive group was significantly lower than their own preoperative pressure and control or sham-operated rats, but the borderline hypertensive group, most cases of which were temporarily hypertensive, was within normotensive range at sacrifice.

As for the control experiments to hypothalamic destruction, such experimental hyper- and hypotensions of known etiology as neurogenic hypertension, renal infarction hypertension and post-adrenalectomy hypotension as well as cortical-lesioned sham-operated rats and nontreated controls were employed. There was no significant difference between cortical-lesioned rats and nontreated controls. These two control groups showed a very slightly higher blood pressure, probably due to aging effect, at sacrifice, than their own blood pressure measured at the age corresponding to the preoperative stage of hypothalamus-lesioned rats. However, none of these control rats nor the other control rats used in this experiment, 45 in total, which had been repeatedly checked for 4 weeks to be normotensive, developed hypertension or hypotension out of the normotensive range during a

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TABLE I

Relationship of Blood Pressure with Weights and Histological Examining Organs' Weights of

Macroscopic findings, especially endo-

renal tissue was significantly lower than that of renal hypertensive rats, because the former showed temporary hypertension, while the latter showed a significant increase in blood pressure following operation. Adrenalectomized rats showed significant blood pressure in comparison with controls but the last operatively lower blood pressure 2 or 3 months postoperatively than that of control. The normotensive level at sacrifice 2 or 3 months after operation.
Crine organ weights in relation to blood pressure in hypothalamus-lesioned rats. (Table 1)

The most outstanding macroscopical findings were that 5 of 13 hypertensive rats showed marked adrenal enlargement and that 20 out of 38 hypotensive rats showed remarkable adrenal atrophy. The other cases of hypertension (8 out of 13 rats) and of hypotension (18 out of 38 rats) were not accompanied with marked change in adrenal weight. Therefore, hypertension or hypotension following the destruction of tubero-mamillary region in the hypothalamus was divided into 2 subgroups in each, i.e., hypertension with adrenal hypertrophy (A) and hypertension without adrenal hypertrophy (N) or hypotension with adrenal atrophy (a) and hypotension without adrenal atrophy (n). Borderline hypertensive or hypotensive cases could also be divided into 2 subgroups in reference to adrenal weight, i.e., borderline hypertension with adrenal hypertrophy (A') and without adrenal hypertrophy (N'), or borderline hypotension with adrenal atrophy (a') and without adrenal atrophy (n'). Group-A showed not only adrenal enlargement but also significant increase in heart weight to body weight ratio in comparison with controls (p<0.01), but Group-N, in which the blood pressure was almost the same as in Group-A, showed neither increase in adrenal and heart weight nor any change in other endocrine organ weights. On the contrary, Group-a showed that it was accompanied with not only marked adrenal atrophy but also a decrease in heart weight, which was, however, not confirmed in heart weight to body weight ratio because of a significant decrease in body weight in this group. Group-a also showed a significant decrease in pituitary, testis and kidney weight (p<0.001). Thyroid weight was decreased but not significantly in comparison with that of sham-operated rats. In Group-n, heart was significantly decreased both in weight and in the weight to body weight ratio compared with controls (p<0.001, p<0.01). Pituitary weight was lighter than that of controls but significantly heavier than that of Group-a. Decrease in weight of kidney compared with that of controls was not noted in comparison with that of sham-operated rats.

Among the borderline groups Group-A' showed no change in organ weights except for increased adrenal weight and Group-a' showed a significant decrease in pituitary and testis weight as well as in adrenal weight (p<0.001). No significant changes were noted among Group-N, -n', normotensive hypothalamus-lesioned rats, sham-operated rats and controls.

As to the other experimental hypertension and hypotension, organ weights in neurogenic hypertensive rats were not significantly different from those or controls, but rats with renal infarction hypertension showed significantly heavier heart weight than controls or neurogenic hypertensive rats. It was not clear, however, whether this difference resulted from etiologically specific factors in renal hypertension or merely from the significantly higher blood pressure level in this group. As a matter of course, kidneys in renal hypertension were decreased in weight because of partial atrophy due to infarction. In adrenalectomized rats, heart and kidney weights were increased only in their ratio to body weight. It was due to apparent failure in gaining weight in this group.

3) Histological findings on endocrine organs in hypothalamus-lesioned rats. (Table 1, Fig. 1-10)

In the rats with lesions placed in the tubero-mamillary region of the hypothalamus, marked histological changes were observed in the following endocrine organs, but not in the kidneys and others.

Adrenals: In all cases of Groups-A and -A', fascicular zones were remarkably wide and composed of somewhat irregular cell columns consisting of hypertrophic clear cells with a mixture of dark cells. The border between fascicular and reticular zone was not distinct and the glomerular zone was thin in general (Fig. 1, A). Fine sudanophilic granules were noted in the fascicular zone (Fig. 2, A). These findings, suggestive of increased adrenocortical function, were also found in 5 rats out of 48 normotensive hypothalamus-lesioned rats and even in 5 out of 34 rats in Group-n', although they were not so remarkable as seen in Group-A. On the contrary, in Groups-a and -a', the fascicular zone showed marked atrophy with decrease in number of cortical clear cells, but the glomeru-
lar zone was maintained or rather hypertrophic with clear cells, so that the border of the fascicular and glomerular zone appeared clear cut (Fig. 1, a, 2, a). However, all cases of Groups-N,

Fig. 1. Adrenal cortices of hypothalamus-lesioned rats (HE, ×40).
A: Hypertension with adrenal hypertrophy (No. 32)
N: Hypertension without adrenal hypertrophy (No. 132)
C: Nontreated control (C0)
n: Hypotension without adrenal atrophy (No. 677)
a: Hypotension with adrenal atrophy (No. 614)

Marked hypertrophy of fascicular zone with thin glomerular zone and severe atrophy of fascicular zone with thick glomerular zone were noted in A, and a, respectively. No remarkable change in N and n.

Fig. 2. Adrenal cortices of hypertension and hypotension with adrenal alteration (Sudan III, ×40).
A: Hypertension with adrenal hypertrophy (No. 710)
C: Nontreated control (C0)
a: Hypotension with adrenal atrophy (No. 614)

Fine sudanophilic granules in hypertrophic fascicular zone were seen in A, while coarse granules were noted mainly in glomerular zone in a.

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-N', -n, 29 out of 34 cases in Group-n', and 43 out of 48 normotensive hypothalamic-lesioned rats showed no marked change in adrenal histology (Fig. 1, N, n).

**Thyroid:** Thyroids provided rather characteristic histological findings in 3 out of 8 in Group-N, and 2 out of 5 in Group-N'. The follicles were small in general and composed of high follicular epithelia and pale stained colloid. (Fig. 3, NT) Reabsorption lacunae were manifested and especially multiple in number in the colloid adjacent to high follicular epithelia which contained PAS-positive granules in the cytoplasm (Fig. 4). These histologically active findings of thyroid were not so marked but also noted in 4 out of 48 in normotensive hypothalamic-lesioned rats and in a few in the other groups. On the contrary, histologically inactive thyroid was observed in 11 out of 20 rats in Group-N, 6 out of 18 in Group-n, 1 out of 6 in Group-n', 3 out of 34 in Group-n' and 5 out of 48 normotensive hypothalamic-lesioned rats, but not found in hypertensive or borderline hypertensive groups. The follicles were enlarged and composed of flattened follicular epithelia and rather darker or very palely stained colloid (Fig. 3, nt). Neither reabsorption lacunae nor PAS-positive granules in follicular epithelia were observed (Fig. 6).

**Pituitary:** As to the hypotensive groups, decrease in number of basophils was noted in Groups-a and -a'. In some cases basophils were rarely seen in the sections examined (Fig. 9).

![Fig. 3. Lower magnification of thyroids of hypothalamic-lesioned rats (HE, x100)](image)

**NT:** Hypertension (without adrenal hyper trophy) with histologically active thyroids (No. 511)

**C:** Nontreated control (C)

**nt:** Hypotension (without adrenal atrophy) with histologically hypoactive thyroids (No. 2083, The biological half-life of thyroidal $^{131}$I = 45.2 days)

Follicles were very small in NT.

![Fig. 4. Higher magnification of the thyroid in NT (PAS, x400)].](image)

Follicular epithelia were high and contained fine PAS-positive granules in cytoplasm. Multiple reabsorption lacunae were noted.

![Fig. 5. Higher magnification of the thyroid in C (PAS, x400)].](image)

![Fig. 6. Higher magnification of the thyroid in nt (PAS, x400)].](image)

Follicular epithelia were flattened.

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A half of the cases in these groups showed centrally located minute fibrosis which was due to partial destruction of portal circulation by the lesions adjacent to infundibulum. However, as pituitary without any fibrosis also showed a marked decrease in the number of basophils, such a derase was not only from destruction of portal circulation, but also from the common lesions in hypothalamus in these groups. Eosinophils were either increased or decreased in number in a half of these cases and chromophobes were increased in general. On the contrary, in Groups-n and -n' of hypotensive rats basophils were maintained as in controls (Fig. 10, n). A few vesiculated or vacuolated basophils (less than 5 in a section except for 2 cases) were seen in a half of the cases in these groups. Only in a few cases, these changes of basophils were coincident with adrenal hypertrophy. No constant findings on eosinophils and chromophobes were observed.

As to the hypertensive groups, basophils were hypertrophic and vesiculated in Group-A (Fig. 7). Either vesication or hyalinization, though in a few, was observed in all cases of Group-A'. High incidence of pathological basophils appeared likely to correspond with adrenal hypertrophy in these groups. Groups-N and -N' showed no constant change in pituitary cytology (Fig. 10, N), but one third or half of the cases in this group showed vesication, vacuolation or even hyalinization, which were sometimes observed in the cases with histologically active thyroid.

No definite findings on posterior pituitary were observed in these groups except for the atrophic tendency not infrequently seen in Group-a.

**Testes:** Eighteen out of 20 rats in Group-a and 2 or 4 cases in Groups-n, -a', -n', and nor-

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**Fig. 7.** Swollen and vesiculated (V) basophils in pituitary in hypertension with adrenal hypertrophy (PAS, ×400, No. 32).

**Fig. 8.** Pituitary cytology in a nontreated control rat (PAS, ×400, C).

**Fig. 9.** Cytological changes in pituitary in hypotension with adrenal atrophy (PAS, ×400, No. 614).

Basophils were markedly decreased in number and the few remaining ones were atrophic (b).

**Fig. 10.** Pituitary in hypertension (N) and hypotension (n) without adrenal alteration (PAS, ×400, n; No. 677, N; No. 257).

No typical change in pituitary cytology.
motensive hypothalamus-lesioned rats showed that their condition was accompanied with testicular atrophy. Hypo-spermatogenesis and hyalinization or thickened basement membrane of seminiferous tubules were observed histologically in these cases. No testicular atrophy was seen in hypertensive groups.

4) Plasma corticosterone level in hypothalamus-lesioned rats. (Table I, Fig. 11)

Plasma corticosterone level in Group-A (51.5 ± 23.4 μg/dl) was evidently higher (p<0.001) than that in controls (17.2 ± 3.9 μg/dl), neurogenic or renal hypertensive groups (12.1 ± 5.3, 18.5 ± 3.2 μg/dl), respectively. Though Group-A showed a significant increase in plasma corticosterone level, Groups-N and -N' were exactly in the same level as controls. As to hypotensive groups, no difference in plasma corticosterone level was proved between Group-n (21.1 ± 10.8 μg/dl) and controls. However, Group-a showed a prominent decrease (9.9 ± 4.1 μg/dl) and was not different from adrenalectomized rats (7.5 ± 2.0 μg/dl). A significant decrease in plasma corticosterone level was noted in Group-a' (11.3 ± 3.3 μg/dl, p<0.02), but not noted in Group-n' (18.9 ± 5.3 μg/dl) compared with controls.

No significant difference was observed between nontreated controls and sham-operated rats, and adrenalectomized rats showed a significantly lower level than controls and neurogenic or renal hypertensive rats. Neurogenic hypertension, probably due to cerebral ischemia, showed a decreasing tendency in corticosterone level, while renal infarction hypertension showed an increasing one. Although no significant difference between either of these hypertensions and controls was proved, a significant difference (p<0.05) did exist between neurogenic and renal infarction hypertension.

In summary, plasma corticosterone level corresponded well to blood pressure level in Groups-A, -A', -a', -a and adrenalectomized rats, while there was no such correlation between plasma corticosterone level and blood pressure in Groups-N, -N', -n', -n and neurogenic or renal hypertension (Fig. 11).

5) Histochemical findings and catecholamine contents of adrenal medulla in hypothalamus-lesioned rats. (Table II, III, Fig. 12–16)

As the histological examination on adrenal medulla stained with HE could not give any definite findings in hypothalamus-lesioned rats,
adrenal medulla was examined histochemically with noradrenaline reaction using glutaraldehyde osmium tetroxide technique. Histochimically demonstrated noradrenaline storing cell islets were rather increased and the reaction was intense in Group-a (Fig. 14), but not increased in Group-n, except for one of 4 cases in comparison with controls (Fig. 15, 13). These islets were moderately increased in one case examined in Group-N (Fig. 12) and slightly increased or decreased in normotensive hypothalamic-lesioned rats.

Histometrically measured dimension of noradrenaline storing cell islets was shown in the ratio to the dimension of the whole medulla tissue (Table II). The ratio was almost significantly (p<0.05) increased in Group-a (16.3±5.0), and very slightly but not significantly increased in Group-n (12.8±3.4) in comparison with controls (9.8±2.2). The ratio of only one case examined in Group-N was increased out of the range of 95 per cent confidence in control rats, but the ratio in normotensive hypothalamus-lesioned rats was within the normal range.

In order to confirm these histochemical findings, catecholamine contents were measured chemically and proved to be changed as follows, especially in Groups-a and -n which showed positive findings histochemically (Table III, Fig. 16).

(1) Although the adrenal weight was almost the same as in controls, Group-n showed a significant increase (p<0.001) in noradrenaline content either per one adrenal (4.79±1.10 µg) or per unit weight (0.25±0.05 mg/g), but was not significantly changed in adrenaline content in comparison with controls (noradrenaline: 2.63±0.57 µg, 0.14±0.03 mg/g). The ratio of noradrenaline to the total of noradrenaline and adrenaline (0.20±0.01) was also

Fig. 12. Histochemically demonstrated noradrenaline storing cell islets in adrenal medulla in hypertension without adrenal hypertrophy (×40, No. 303).

Fig. 13. Histochemical findings of adrenal medulla in a nontreated control rat (×40, No. C8).

Fig. 14. Noradrenaline storing cell islets in adrenal medulla in hypotension with adrenal atrophy (×40, No. 614).

Marked increase in noradrenaline storing cell islets were noted.

Fig. 15. Noradrenaline storing cell islet in adrenal medulla in hypotension without adrenal atrophy (×40, No. 1108).
greater than controls (0.15±0.04, p≤0.05).

(2) In Group-a, which showed to be significantly (p<0.001) lighter in adrenal weight (9±1mg) than controls (19±2mg), noradrenaline content of one adrenal gland (4.88±0.95 µg) was significantly increased in comparison with controls. Noradrenaline content of unit weight was also increased, but could not be compared properly with controls because of marked cortical atrophy in this group. On the contrary, adrenaline content (6.54±0.57 µg) was significantly (p<0.05) smaller than control (15.78±3.92 µg). Therefore, the ratio of noradrenaline to the total of noradrenaline and adrenaline (0.42±0.06) was markedly greater than the control value (0.15±0.04).

(3) Between Groups-a and -n, not only a marked difference in adrenal weight but also in adrenaline content (Group-n; 19.29±3.48 > Group-a; 6.54±0.57 µg) and in the ratio of

<table>
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</tr>
<tr>
<td>Group-a</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension Group-N</td>
<td>1</td>
</tr>
<tr>
<td>Group-A'</td>
<td>1</td>
</tr>
<tr>
<td>Normotensive hypothalamus-lesioned rats</td>
<td>4</td>
</tr>
<tr>
<td>Nontreated controls</td>
<td>4</td>
</tr>
</tbody>
</table>

M ± S.D.

- Group-a, -n: Hypotension with and without adrenal atrophy (respectively)
- Groups:
  - Group-N: Hypertension with adrenal hypertrophy
  - Group-A': Borderline hypertension with adrenal hypertrophy
- Statistical difference:
  - = = = = P<0.001, 0.01, 0.02, 0.05 (respectively)
  - from controls
- Lesions and detailed data are shown in Table VI

Fig. 16. Catecholamine content of adrenal medulla in hypothalamus-lesioned rats.
noradrenaline to the total of noradrenaline and adrenaline (Group-n: $0.20 \pm 0.01 < $ Group-a: $0.42 \pm 0.06$) were confirmed.

(4) Normotensive hypothalamic-lesioned rats showed no significant difference in adrenal weight, in adrenaline content and in the ratio of noradrenaline to the total of noradrenaline and adrenaline as compared with controls.

6) **Thyroidal $^{131}$I release ratio and blood pressure in hypothalamic-lesioned rats.**

(Fig. 17)

Among hypothalamic-lesioned rats with hypertension or borderline hypertension, one in Group-A and 3 out of 6 rats in Group-N' showed shorter biological decay than the normal range (M±2S.D.) obtained from sham-operated rats. One in Group-N' was, however, exceptionally longer in half-life than the controls. Among the hypertensive groups half-life was longer 3 out of 4 in Group-a and the other one was maintained within the normal range. On the contrary, one out of 5 in Group-n and 3 out of 6 in Group-n' showed acceleration in $^{131}$I release. Although most of these n- and n'-

<table>
<thead>
<tr>
<th>Table III Catecholamine Contents of Adrenal Medulla in Hypothalamic-Lesioned Hypotensive Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Group-n</td>
</tr>
<tr>
<td>No. BP before sacrifice of rats (mm Hg)</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Normotensive hypothalamic-lesioned rats</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Control rats</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td><strong>No. of adrenal weight, mg/g</strong></td>
</tr>
<tr>
<td>4.79 ± 1.20</td>
</tr>
<tr>
<td>4.65 ± 1.95</td>
</tr>
<tr>
<td>2.57 ± 0.98</td>
</tr>
<tr>
<td>2.63 ± 0.97</td>
</tr>
<tr>
<td><strong>Noradrenaline (NA) mg/g</strong></td>
</tr>
<tr>
<td>4.29 ± 3.48</td>
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<tr>
<td>4.54 ± 0.97</td>
</tr>
<tr>
<td>12.25 ± 0.24</td>
</tr>
<tr>
<td>15.78 ± 3.92</td>
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<tr>
<td><strong>Adrenaline (A) mg/g</strong></td>
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<tr>
<td>1.00 ± 0.12</td>
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<td>0.70 ± 0.04</td>
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<td>0.64 ± 0.13</td>
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<td>0.82 ± 0.18</td>
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<tr>
<td><strong>NA mg/g</strong></td>
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<tr>
<td>0.20 ± 0.01</td>
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<tr>
<td>0.42 ± 0.06</td>
</tr>
<tr>
<td>0.17 ± 0.05</td>
</tr>
<tr>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td><strong>Animal number</strong></td>
</tr>
<tr>
<td>677±1108</td>
</tr>
<tr>
<td>422±1167</td>
</tr>
<tr>
<td>86±72</td>
</tr>
<tr>
<td>81±75</td>
</tr>
</tbody>
</table>

M ± S.D. Group-a, n: Hypotension with and without adrenal atrophy (respectively)
C1 - C2: Non-lesioned controls
S1 - S2: Sham-operated controls
Statistical difference from controls: $P < 0.001, 0.05$  $P < 0.05$  $P < 0.05$
between Group-a and Group-n: $P < 0.001, 0.01, 0.05$

* Lesions and detailed data are shown in Table IV.

![Fig. 17. Correlation between thyroidal function and blood pressure in hypothalamic-lesioned rats.](Japanese Circulation Journal Vol. 31, May 1967)
Groups were within the normal range despite hypotension, in only one case of Group-n, which showed moderate hypotension without adrenal atrophy (n' in Fig. 17), $^{131}$I release was especially prolonged enough to be correlated with the grade of hypotension. Among normotensive hypothalamus-lesioned rats 8 out of 10 were within the normal range. Although the biological half life of sham-operated controls in this study was rather long, it was not due to the cortical lesions in these rats because some non-treated controls also showed the same tendency. It was mainly because all rats were kept on the ordinary diet consisting of manitoba wheat and dried sardine before $^{131}$I injection. But this slight prolongation of $^{131}$I release did not make it difficult to compare the thyroidal function in the rats maintained under the same conditions.

In summary, since 9 cases with shorter thyroidal $^{131}$I decay consisted of 4 hypertensive or borderline hypertensive (A, N'), 1 normotensive, 3 borderline hypertensive (n') and 1 hypertensive case (n), it was concluded that accelerated release of thyroidal $^{131}$I was not always accompanied with blood pressure elevation in these hypothalamus-lesioned rats. On the other hand, as the cases with moderately prolonged decay showed mild hypertension and normotension, such a moderate prolongation was not inevitably related with hypotension when adrenal function or others were maintained. Even in such a marked delay of the release as seen in t in Fig. 17 failed to induce hypotension, when adrenal function was supposed to be hyperactive (abrenal weight; 54 mg, the weight to body weight ratio; 27.0). Only one case with a markedly delayed release (n') could be related with moderate hypotension, which might be induced by thyroidal hypofunction without adrenocortical deficit. In addition, this experiment showed that thyroidal weight did not correspond as well to thyroidal function detected by $^{131}$I release ratio in hypothalamus-lesioned rats, as adrenal weight to adrenal function (plasma corticosterone level).

7) Observation of body weight, heart rate, daily urinary output and pupillary size in hypothalamus-lesioned rats. (Table I, IV)

Body weight measured two months after operation was significantly ($p<0.001$) smaller in Groups-A, and -a (224 ± 31, 255 ± 43 g) than in non-treated controls (330 ± 63 g). Gain in body weight during the first 2 months after operation was also significantly smaller in these groups. No significant difference from the control values in body weight and its gain was noted in the other groups. Some rats showed marked hyperphagia after operation and prominent gain in body weight exceeding 150 g during the first 2 months after operation. These obese rats were found in 2 out of 15 rats in Group-n and in 3 out of 18 normotensive hypothalamus-lesioned rats. Therefore, no special correlation was observed between obesity and blood pressure level.

Body temperature in the rats with lesions placed in tuberomammillary region of the hypothalamus was not significantly changed from that of controls, except for Group-a, which had a little but significantly ($p<0.02$) lower body temperature (36.1 ± 0.5°C). Lowering of the body temperature in this group appeared to correspond rather well to deficiency of adrenocortical hormones than to the localization or the extent of lesions in the posterior hypothalamus, to which heat producing mechanism was supposedly ascribed.

Heart rate measured under anesthesia was rather variable and no correlation was proved between acute change in heart rate following hypothalamic destruction and chronic change of blood pressure. In the heart rate measured 1 month after operation, only Group-a showed a significant decrease in comparison with their preoperative heart rate and the heart rate of age-matched control rats, respectively ($p<0.001$, $p<0.01$).

Urinary output examined on rats fed with stock chow diet in a metabolic cage was variable day by day and daily urinary output exceeded 20 ml only infrequently in control rats. But the rats with lesions in the tubero-mamillary part showed such individually different values that a significant increase in the mean value was noted in Groups-a, -n, and even in normotensive hypothalamus-lesioned rats compared with controls. Some showed moderate diabetes insipidus (daily output over 20 ml) and a few showed a severe one (over 80 ml). There seemed to be no relationship between diabetes insipidus and adrenal function.
TABEL IV

GAIN IN BODY WEIGHT, BODY TEMPERATURE, HEART RATE AND URINARY VOLUME IN HYPOTHALAMUS-LESIONED RATS

<table>
<thead>
<tr>
<th>No. of</th>
<th>Gain in body weight</th>
<th>Body temperature</th>
<th>Heart rate</th>
<th>Urinary volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rats</td>
<td>(g)</td>
<td>before op.</td>
<td>postop. change</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Group-A</td>
<td>4</td>
<td>20 ± 57</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Group-N</td>
<td>7</td>
<td>93 ± 44</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Group-A</td>
<td>18</td>
<td>21 ± 36</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Group-N</td>
<td>15</td>
<td>71 ± 47</td>
<td>2</td>
</tr>
<tr>
<td>Nontensive hypothalamus-lesioned rats</td>
<td>18</td>
<td>66 ± 49</td>
<td>3</td>
<td>36.3 ± 0.5</td>
</tr>
<tr>
<td>Nontreated controls</td>
<td>16</td>
<td>77 ± 20</td>
<td>0</td>
<td>36.7 ± 0.5</td>
</tr>
</tbody>
</table>

M ± S.D. * : Increase in body weight during the first 2 months after operation. ** : Heart rate of age-matched controls. ( ) : Individual values Statistically significant difference: #, #, ##, #. same as indicated in Table I. Ob. : The number of rats with obesity( gain in body weight during 2 months; over 150 g) Di. : The number of rats with severe diabetes insipidus(urinary volume; over 80 ml/day)

sipidus and blood pressure.

Acute effect of the lesions on pupillary size was various, and anisocoria was often observed in the rats which received asymmetrical lesions. Midriasis was frequently accompanied with rather laterally placed lesions which included LH, PF, F, PM, etc. apart from the mid-line of the hypothalamus. (The abbreviations of hypothalamic structures were shown in the legend of Table VI). Changes in pupillary size often recovered to normal size within 1 month after operation, so that there was no significant difference in the values measured with a calibrator among the experimental groups and controls.

Appendix: Effect of salt load on blood pressure of hypothalamus-lesioned rats. (Fig. 18)

As daily urinary output was increased in some rats with the lesions placed in tubero-mammillary region, a considerably large amount of salt (7%
in diet) was loaded to counteract supposed saluresis, if any, accompanying diabetes insipidus. The blood pressure of sham-operated rats was not influenced by a high salt diet fed for one month. The mild hypertension of one case in Group-N' decreased to normal range in spite of the high salt diet. However, mild hypotension in one case in Group-n was gradually normalized and severe hypotension in one case in Group-a became mild and was brought almost the normotensive range 1 month after the beginning of this treatment. These hypotensions returned gradually again after interruption of salt loading and was maintained below the normotensive range.

8) Effect of pithing on blood pressure of hypothalamus-lesioned rats and other hypotensive rats. (Fig. 19, 20)

To evaluate the humoral component of blood pressure post-pith pressure was determined in hypothalamus-lesioned rats, especially in hypotensive Groups-a and -n which seemed to have different mechanisms. Post-pith pressure of Group-a (25 ± 2 mmHg) was significantly lower than that of controls (33 ± 4 mmHg, p < 0.02), of normotensive hypothalamus-lesioned rats (37 ± 2 mmHg, p < 0.01) and of Group-n (32 ± 3 mmHg, p < 0.05), but almost at the same level as that of adrenalectomized rats (23 ± 3 mmHg). On the other hand, post-pith pressure of Group-

---

Fig. 19. Effect of pithing on blood pressure in hypothalamus-lesioned rats and other hypotensive rats.

(1) Group-a: Hypotension with adrenal atrophy.
(2) Group-n: Hypotension without adrenal atrophy.
(3) Group-N: Hypertension without adrenal hypertrophy.
(4) Adrenalectomized rat.
(5) Hexamethonium-treated rat.
(6) Nontreated control.

P: Pithing. DBP: Direct blood pressure before pithing. PPP: Post-pith pressure.
The post-pith pressure in (1) and (4) was lower than the other, while that in (2) and (3) was within the normal range of controls.

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n which was significantly higher than that of Group-a, was almost the same as that of controls and not significantly different from that of normotensive hypothalamus-lesioned rats. Moreover, one case which received pithing in the early stage of moderate hypertension following hypothalamic destruction (Fig. 19 (3)) showed no difference in post-pith pressure (30 mmHg) from controls.

As control experiments, the blood pressure of hexamethonium-treated rats with purely neurogenic hypotension was maintained after pithing at a rather high level which was significantly higher than that of controls (p<0.001) or of adrenalectomized rats (p<0.001). There seemed to be a tendency that the longer these rats received hexamethonium previously, the higher the post-pith pressure. These data of control experiments showed that humoral component of blood pressure, which maintained post-pith pressure was not deficient but rather increased in purely neurogenic hypotension induced by hexamethonium and was evidently reduced in hypotension due to the deficiency of the cortical hormones in adrenalectomized rats.

9) Spontaneous discharge of splanchnic nerve in hypothalamus-lesioned rats and acutely induced hypotensive rats.

(Fig. 21, Table V)

Splanchnic discharge was neurophysiologically recorded in hypothalamus-lesioned hypotensive rats (Groups-a and -n) and compared with that of acute hypotension induced by acetylcholine or sodium pentobarbital. In Group n, 2 cases out of 4 showed a decrease in frequency and the other 2 rats maintained almost

<table>
<thead>
<tr>
<th>Pre-pith pressure</th>
<th>85 ± 3</th>
<th>85 ± 18</th>
<th>115 ± 9</th>
<th>84 ± 18</th>
<th>90 ± 14</th>
<th>131 ± 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-pith pressure</td>
<td>50</td>
<td>46</td>
<td>32</td>
<td>37</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M ± S.D.</td>
<td>40</td>
<td>27</td>
<td>32</td>
<td>37</td>
<td>23</td>
<td>33</td>
</tr>
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</tbody>
</table>

Fig. 20. Comparison of post-pith pressure among various kinds of hypotension.

*Japanese Circulation Journal Vol. 31, May 1967*
normal frequency of spontaneous discharge. On the contrary, one out of 4 rats in Group-α showed a marked increase in frequency and the other maintained the frequency within normal range. In 4 normotensive hypothalamus-lesioned rats, frequency was distributed widely within and around normal range. The mean of the maximum amplitude was greater in Group-α and normotensive hypothalamus-lesioned rats than in controls. Although a definite conclusion was beyond this experiment because of the shortage in the number of cases examined and because of the wide distribution of the control values, the mean value of the frequency of spontaneous discharge was somewhat reduced in Group-γ, but not different in Group-α from

![Fig. 21. Spontaneous splanchnic discharge in hypothalamus-lesioned hypotensive rats and acutely induced hypotensive rats.]

The upper and lower traces of each oscillogram show directly displayed and filtered discharge, respectively.

1. Group-α: Hypotension with adrenal atrophy (No. 687; BP: 84 mmHg, 1065 pulses per 30 sec.).
2. Normotensive hypothalamus-lesioned rat (No. 1120; BP: 115 mmHg, 666 pulses per 30 sec.).
3. Group-γ: Hypotension without adrenal atrophy (No. 688; BP: 88 mmHg, 260 pulses per 30 sec.).
4. Acetylcholine-hypotension (No. N-2, Acetylcholine (2γ/kg, i.v.) was administered after recording of (5); BP: 95 mmHg, 912 pulses per 30 sec.).
5. Normotensive control (No. N-2, BP: 130 mmHg, 588 pulses per 30 sec.).
6. Hypotension under deep anesthesia (No. N-2, Pentobarbital sodium (85 mg/kg, i.v.) was administered after the recovery of blood pressure following (4); BP: 90 mmHg, 123 pulses per 30 sec.)
7. Xylocain (2%), painted at the proximal portion of a splanchnic nerve after each series of recording, completely blocked these discharges.

### Table V. Spontaneous Splanchnic Discharge in Various Hypotensive Rats

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>No. of rats</th>
<th>Blood pressure (mm Hg)</th>
<th>Frequency of discharges (Pulses/30 sec.)</th>
<th>Maximum amplitude of discharges (mv)</th>
<th>Animal number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus-lesioned rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group-α</td>
<td>4</td>
<td>85 ± 2</td>
<td>93 ± 2</td>
<td>395 ± 174</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Group-γ</td>
<td>4</td>
<td>71 ± 2</td>
<td>84 ± 2</td>
<td>650 ± 313</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>Normotension</td>
<td>4</td>
<td>120 ± 7</td>
<td>121 ± 8</td>
<td>456 ± 299</td>
<td>28 ± 3</td>
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<tr>
<td>Acutely induced hypotension</td>
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<td></td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>3</td>
<td>---</td>
<td>92 ± 6</td>
<td>1010 ± 95</td>
<td>60 ± 15</td>
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<tr>
<td>Pentobarbital sodium</td>
<td>3</td>
<td>---</td>
<td>85 ± 9</td>
<td>220 ± 125</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>Nontreated controls</td>
<td>5</td>
<td>128 ± 7</td>
<td>132 ± 8</td>
<td>618 ± 160</td>
<td>23 ± 3</td>
</tr>
</tbody>
</table>

* N ± S.D.  
* Direct blood pressure during recording  
* Group-α, -γ: Hypotension with and without adrenal atrophy (respectively)  
(a): 2 γ/kg i.v.  
(p): 60-90 mg/kg i.v.  
Significant difference from controls = = = = P ≤ 0.001, 0.01, 0.05, 0.05  

Fig. 22. Localizations of hypothalamic lesions in some rats which developed hypertension or hypotension.

(a) Group-A: Hypertension with adrenal hypertrophy.
(b) Group-a: Hypotension with adrenal atrophy.
(c) Group-N: Hypertension without adrenal hypertrophy.
(d) Group-n: Hypotension without adrenal atrophy.
(e) Hypertension (510, 511, 67) or temporary hypertension (632) with thyroidal hyperactivity and hypotension (2082) with thyroidal hypoactivity.

Abbreviations and detailed hypothalamic structures involved in these lesions were indicated in Table VI. Basic diagrams were cited from Dr. Groot’s atlas. The distance anterior to interaural zero point is shown in the lower right corner of each diagram.

*Japanese Circulation Journal Vol. 31, May 1967*
the control (Table V).

In acute experiments, frequency and amplitude were greatly increased during the hypotension following acetylcholine administration (2γ/kg, i.v.) but were prominently suppressed during hypotension under deep pentobarbital anesthesia (60-90mg/kg, i.v.). The discharge in Group-a appeared to have a similar tendency to the former and that in Group-n had a similarity to the latter (Fig. 21).

10) Sites of effective hypothalamic lesions for producing chronic change in blood pressure. (Table VI, Fig. 22)

As to the effective lesions for producing hypertension with adrenal hypertrophy or hypotension with adrenal atrophy (Group-A, -a), the common sites of lesions in Group-a were ARt, ARp and closely adjacent areas to these nuclei in the premammillary region. When the destruction of ARt and ARp was not sufficient, borderline hypotension with slight adrenal atrophy (Group-a') was induced. On the contrary, lesions in Group-A were very closely located to ARt and ARp but never invaded them. The common sites of the lesions were P just above ARt and ARp, and PMD and Mm over and behind ARp were also involved. Therefore, these rather complicated lesions were considered as being a composition of tubero-mid-dorsal lesion including P and mamillo-medial-ventral lesions including Mm. In addition, it was noted that most of these cases showed intense gliosis and iron deposition in the adjacent area to ARt and ARp, which sometimes included markedly hypertrophic gigantic nerve cells with obvious nuleoli. When the lesions were approximately the same as these but invaded a part of ARt or ARp, or when the posterior part of the lesions was comparatively large, hypertension failed to occur or only temporary hypertension (Group-A') was observed.

For the production of hypertension and hypotension without adrenal alteration, centrally located rather small lesions seemed to be necessary for the former and postero-medially or postero-laterally located extensive lesions for the latter. The central lesions for the former were rather localized, contracted with gliosis and distributed in PVG and a part of PH, DM, PMD and SUM, i.e., in the postero-mid-dorsal portion of hypothalamus. The common site was PVG which connected with the central gray in the midbrain posteriorly. Centrally located very small lesions, one-sided lesions or rather extensive lesions including medial hypothalamus failed to develop hypertension or induced only borderline hypertension. Extensive lesions for hypotension without adrenal atrophy consisted of two types, i.e., medial and lateral lesions. The medial lesions included PMD, PMV, PH, PF, a medial part of LHm, MPL, ML, Mm, MM, MI, F and MT. The lateral lesions included LHT, LHm, PF, MPL, ML and F. The common sites included in both types were LHm, PF, F, MPL, and ML. Even one-sided lesions in these nuclei, when extensive enough, could induce hypotension (Case 1108). However, small lesions in these nuclei could not induce hypotension and the small lesions in these common sites of the medial and lateral lesions induced only borderline hypotension, so that extensiveness of the lesions was necessary. Therefore, extensive medial or lateral lesions including LHm, PF, F and so on in common were necessary for producing hypotension without adrenal atrophy. However extensive these lesions were, they never invaded ARt and ARp largely, which seemed to be indispensable for maintaining adrenal weight. Hypotension, whether it was induced by medial lesions or by lateral ones, appeared to be the same, judging from the data obtained up to the present, i.e., histological findings, corticosterone level, physiological observation of body temperature and daily urinary output, catecholamine contents, post-pith pressure and so on. Ultra-extensive lesions including medial and lateral hypothalamus in the tubero-mamillary part except for arcuate nucleus was not successful because of very high mortality rate after operation.

Some hypertensive cases (N), borderline one (N') and normotensive hypothalamus-lesioned rats showed active histology of thyroid or acceleration of $^{131}$I release from thyroid. The lesions common to these rats were located in the tubero-medial dorsal portion of the hypothalamus including P, DMd, DMv, PF and F. These lesions and the lesions in Groups-N and -A overlapped each other, but the former was
<table>
<thead>
<tr>
<th>Product Code</th>
<th>Description</th>
<th>Quantity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
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<td>A01</td>
<td>Baseball</td>
<td>100</td>
<td>$5.99</td>
</tr>
<tr>
<td>B02</td>
<td>Football</td>
<td>50</td>
<td>$4.99</td>
</tr>
<tr>
<td>C03</td>
<td>Soccer Ball</td>
<td>15</td>
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<td>20</td>
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<tr>
<td>F06</td>
<td>Rugby Ball</td>
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<tr>
<td>G07</td>
<td>Tennis Racket</td>
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<tr>
<td>I09</td>
<td>Squash</td>
<td>8</td>
<td>$4.99</td>
</tr>
</tbody>
</table>

Note: All prices are in USD.
somewhat anteriorly to the latter and included P above ARa. A rather high incidence of active thyroidal histology in Group-N appeared likely to result from this overlapping. On the contrary, localized lesions in ARa as shown in Case 2082 (Fig. 22, Table VI) was accompanied with marked prolongation of thyroidal 131I release (n in Fig. 17), but without adrenal atrophy and low plasma corticosterone level which was induced by the lesion in ARt and ARp. This case showed the possibility of mild hypotension without adrenal atrophy, probably of thyroidal origin, which was evidently different in the site of the lesion from the hypotension in Group-n.

Various lesions in the tubero-mamillary part of the hypothalamus which failed to develop hypertension or hypotension were not only unsuitable in size but also in shape for the development of hypertension or hypotension, because a part of one lesion often appeared to cancel the expected effect of the other part of the lesion. In the case with asymmetrical bilateral lesions, lesions in one side were not enough or sometimes seemed to counteract the effect of the contralateral lesions.

11) Stimulation of the tubero-mamillary region of hypothalamus and comparison of acute and chronic effect of hypothalamic destruction. (Fig. 23, 24, 25)

(I) Electrical stimulation of hypothalamus with a unipolar electrode.

Preliminary studies on the effect of electrical stimulation in the tubero-mamillary part of the hypothalamus with a unipolar electrode showed that such current parameter used in this experiment as 2 volt-square wave pulses, 1 msec. wide, 100 cycle per second, was very effective and elicited more intense pressor response than the current with lower frequency. As the stimulative effect under these conditions was completely abolished by the destruction with 10 volt DC given for 12 seconds × 4, with alternation of polarity, the range of stimulation was rather localized and the directly stimulated area was within 1 mm in diameter. As shown in Fig. 23 (a), pressor response during stimulation of P point was completely abolished after destruction of this point (P'), but the stimulative effect of M point which was 1.8 mm apart from P point was maintained after destruction of P point as well as before destruction.

(II) Direct pressor effect and prolonged effect of stimulation.

Eleven points out of 155 stimulated sites gave depressor effect, 12 points gave no response and the other greater part of the points stimulated gave greater or lesser pressor effects, which could be divided into 3 types as follows:

(a) Monophasic type (M-type) Pressor effect was observed only during stimulation (Fig. 23 (a)).

(b) Prolonged or biphasic type (B-type) Pressor effect continued for some time after interruption of stimulation, or with a little fall from the raised level, blood pressure increased biphasically again without further stimulation (Fig. 23 (b) A).

(c) Delayed type No response was observed during stimulation and pressor effect appeared after the end of stimulation (Fig. 23 (c)).

Since the pressor effect of M-type was observed only during stimulation, this pressor effect was evidently due to neural discharge which originated from the stimulated sites of the hypothalamus. As not only neural mechanism but also participation of humoral factors, especially that of catecholamine released from adrenal medulla was indicated in B-type, hypothalamus was stimulated after the ligation of bilateral adrenal vessel. As shown in Fig. 23 (b), the pressor response of B type was hardly changed before and after the ligation of adrenal vessels (A, B). Hypothalamic stimulation, after the ligation of adrenal vessels was removed, induced somewhat greater indirect effect (C). Therefore, catecholamine released from adrenal medulla seemed to participate partially in the indirect response and the indirect response might probably depend on pressor substance released from peripheral nerve endings, other possibilities not being eliminated. Pressor response of D-type lacked direct effect during stimulation and appeared with a latent time after stimulation. As the tip of the electrode was located in arcuate nucleus adjacent to infundibulum, release of neurohumor from posterior pituitary was supposed to be one of the probable mechanisms.
(III) Correlation between pressor effect and the stimulated sites of the hypothalamus.

The direct effect seen in the response of M- and B-type was observed by the stimulation of various points of the tubero-mamillary region in the hypothalamus as indicated in the right side of coronal sections of the hypothalamus in Fig. 24 (a). But intense responses greater than 10 mmHg were obtained from medial parts of DMd and DMy, VMm, P adjacent to them, PH, PMD, PF and LHm including MFB. Other than the hypothalamus, such intense response were induced only by stimulation of zona incerta (Z) or fields of Forel (H2) which

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Fig. 23. Various effects of hypothalamic stimulation on blood pressure.
(a) Monophasic type (The pressor response was elicited only during stimulation and was abolished after destruction).
(b) Prolonged type (Indirect pressor response was not abolished by the ligation of adrenal vessels).
(c) Delayed type (Pressor response appeared with some latency, and was also abolished by destruction).

T: The localizations of the tip of electrode.
connected with tegmental area of the midbrain, and Nucl. dorsomedialis thalami (MD) which had close interconnection with the posterior hypothalamus.

The sites of the hypothalamus where an indirect effect in B-type was obtained, were well coincident with the sites which induced intense direct effect when stimulated, as shown in the left side of coronal sections of the hypothalamus in Fig. 24 (a). Intense indirect effect greater than 30 mmHg was observed when the medial part of DMd and DMv, P adjacent to them, VMm, PF, PH, PMV and LH were stimulated. Besides the hypothalamus, Z and MD also gave strong response. The sites which showed a stronger indirect effect than the direct one and a longer response exceeding 2 minutes, were DMd, P adjacent to it, PF, LH, Z and MD. As these sites included fiber connections, it was quite possible that the fibers stimulated directly induced excitation of other parts of the brain, such as the vasomotor area of brain stem.

Delayed effect in D-type obtained by the stimulation of the tuberal part (AR) just above the infundibulum showed longer pressor response after stimulation. Especially in the case shown in Fig. 23 (c) effect was maintained for longer than 5 minutes.

(IV) Acute effect of hypothalamic destruction.

Depressor effect was observed everywhere in the tubero-mamillary region of the hypothalamus by DC current (10 volts × 12 sec. × 4) delivered for destruction, but most of these depressor effects recovered to the initial level promptly or gradually (Fig. 25 (a)). Prolonged depressor effect was observed by the destruction of the medial part of Lhm, PMV and P or the medial part of DM, which coincided well with the sites which gave intense pressor response.

![Diagram](image)

**Fig. 24.** Acute effect of hypothalamic stimulation and destruction on blood pressure.

(a) Direct and indirect effect of stimulation on blood pressure.

The right and left sides of each diagram show direct and indirect responses, respectively.

(b) Direct and prolonged effect of destruction on blood pressure.

The right and left sides of each diagrams show direct and prolonged effect of destruction, respectively.

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when stimulated (Fig. 24, (b), (a)). No pressor response was observed during destruction. In some cases, destruction was followed by prolonged pressor response (Fig. 25 (b)). In three cases, pressor response following extensive de-
struction or ventricular hemorrhage was accom-
panied with bradycardia probably due to intra-
cranial hypertension. In the other five cases
lesions were so closely located to the pressor
area such as the medial part of DM, medial part

![Graphs and data]

Fig. 25. Comparison of the acute effect of destruction with the chronic one.
Left kymograms and right diagrams show acute and chronic effects, respectively.

(a) No particular acute effect, but hypertension with adrenal hypertrophy was observed later.
(b) A rather long-lasting elevation of blood pressure was observed only in acute stage.
(c) A negligible decrease in blood pressure in acute experiment appeared to shift into hypoten-
sion without adrenal atrophy.
(d) Hypotension with adrenal atrophy developed without particular acute effect of destruction.
The numbers in each kymogram show the distance superior to interaural zero point. The detailed
site of the lesion in No. 1108 is shown in Table VI.

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of LHm, ML and MM that the stimulative effect of destruction on the adjacent pressor area might cause pressor effect in the acute stage following destruction (Fig. 24 (b)).

(V) Comparison of the acute effect of destruction with the chronic one.

Twenty six out of the 41 rats, which were observed on the acute effect of destruction, survived longer, long enough for chronic observation on blood pressure. Among 26 survivors, 1 hypertensive rat (Group-A), 1 temporary hypertensive rat (Group-N'), 4 hypertensive rats without adrenal atrophy (Group-n; 3 with bilateral lesion), 1 hypertensive rat with adrenal atrophy (Group-a), 8 borderline hypertrophy (Group-n'; 2 with bilateral lesions) and 11 normotensive rats were obtained. The sites of the lesions in these rats corresponded with the localization of the lesions in each group as describe previously. Acute and chronic effects were compared especially on a few typical cases with one-sided hypothalamic lesions, because in the cases with a unilateral lesion there was no complexity due to the asymmetry of bilateral lesions, and chronic effect could be attributed to the size and site of one lesion.

(a) No particular response in acute stage, but hypertension was observed in chronic stage in one case out of 26 rats (Fig. 25 (a)). Though acute effect of the lesions was nothing particular or a very little, if any, pressor response, blood pressure reached 150 mmHg one week after operation. Autopsy revealed adrenal hypertrophy (adrenal weight to body weight ratio: 31.2). The site of the unilateral lesion was PMD, PMV, MMm, a part of PH and P, which were adjacent to intact ARp.

(b) Blood pressure elevation in acute stage, but normotension in chronic stage was observed in two cases of 26 rats (Fig. 25 (b)). One case was accompanied with prolonged pressor effect, longer than 20min. and had rather small lesions in PMD, PH, MMm and MMI, most of which could give pressor effect when stimulated (adrenal weight to body weight ratio: 10.4, plasma corticosterone; 12.9 γ/dl).

(c) Hypotension without adrenal atrophy was obtained in 4 cases (Fig. 25 (c)). Even when rather large unilateral lesions were placed in PMD, PMV and a part of DM, VM and P, blood pressure was maintained without alteration or very slightly decreased in acute stage. Chronic observation showed gradually developed hypotension without endocrine deficit in these cases (Case 1108 in Fig. 25 (c); adrenal weight to body weight ratio: 12.7, plasma corticosterone; 18.0 γ/dl).

(d) Hypotension with adrenal atrophy (Fig. 25 (d)). After a localized small lesion was placed in ARt and ARp, blood pressure was hardly changed in acute stage, but marked hypotension was observed later in chronic experiment (adrenal weight to body weight ratio: 8.6).

These experiments showed that acute and chronic effect of the lesions did not always coincide with each other. It was a matter of course that hypertension or hypotension, supposed to be of humoral origin as in (a) and (d), was accompanied with neither pressor nor depressor effects in acute experiment but became manifest in the chronic stage. The fact that rather small lesions in the pressor area induced prolonged pressor effect as shown in (b) indicated the possible mechanism that stimulative effect of destruction on pressor area could induce rather long-lasting elevation in blood pressure. Moreover, it was noted-worthy that rather extensive lesions in the tubero-mamillary part of the hypothalamus, even when acute effect was not marked or a fall in blood pressure was negligible as shown in (c), induced hypotension gradually in the chronic stage.

DISCUSSION

Hypothalamic destruction is supposed to be accompanied, more or less, with disturbances of its highly integrated regulation of nervous and endocrine systems. Therefore, hypertension and hypotension, i.e., chronic alteration of blood pressure level following hypothalamic destruction, should be scrutinized from the viewpoint of dynamic balance of multiple neural and humoral factors. This experiment was concentrated on the investigation of the following endocrine and neural factors and provided some clues to elucidate the mechanism of these hypertensions and hypotensions.

Adrenocortical factor: Some cases of hypertension following hypothalamic destruction
were accompanied with marked adrenocortical hypertrophy and high plasma corticosterone level (Group-A), while a half of the cases with hypotension showed adrenocortical atrophy and low plasma corticosterone level (Group-a). According to SKELTON et al.\(^\text{29}\) corticosterone administration produced experimental hypertension in rats which resembled the cortison-hypertension induced even without elevated salt uptake, and plasma corticosterone level higher than 25\(\gamma/\text{dl}\) could develop hypertension with the help of salt load. NOSAKA\(^\text{14}\) in our department demonstrated successfully a close relationship between high plasma corticosterone level and developmental process of hypertension induced by extensive medial antero- median hypothalamic destruction in rats both with and without salt load. Hypertensive rats with adrenal hypertrophy in the present study showed high plasma corticosterone level exceeding 35\(\gamma/\text{dl}\). Moreover, the control experiment on renal and neurogenic hypertensive rats revealed that these rats showed neither such an adrenal hypertension nor so high a plasma corticosterone level as seen in hypertensive hypothalamic-lesioned rats with adrenal hypertrophy (Group-A). Therefore, it could be concluded that adrenocortical hypertrophy and adequately high plasma corticosterone level for inducing hypertension in hypothalamic-lesioned rats were not the secondary effect of hypertension but of primary etiological importance. On the other hand, in hypertensive hypothalamic-lesioned rats with adrenocortical atrophy (Group-a) a decreased plasma corticosterone level as low as that in adrenalectomized rats was evidently the main etiological factor for hypotension. These facts provided definite evidences to support the etiological importance of adrenal function in hypertension and hypotension following hypothalamic destruction. Consequently, these hypothalamic hypertension and hypotension\(^\text{18}\) with prominent adrenocortical hyperfunction and hypofunction were named as hypothalamic-adrenocortical hypertension, and hypothalamicadrenocortical hypotension, respectively, for the convenience of future studies. On the contrary, hypertension and hypotension without marked alteration in adrenal weight and plasma corticosterone level (Groups-N, -n) were called hypothalamic-nonadrenogenic hypertension and hypotension.

It is in general agreement today that ACTH secretion is controlled by a corticotrophin releasing factor (CRF) released from hypothalamus\(^\text{20}\). But anatomically distinct areas concerned with the release of CRF is not yet clear. Since DE GROOT and HARRIS\(^\text{20}\) first suggested that the ACTH controlling area was in the posterior tuberal region, the bulk of evidences obtained by various experimental procedures have been indicated the ACTH controlling mechanism in the tuberomamillary region\(^\text{31-36}\) or median eminence itself\(^\text{30-40}\) except for a few reports. Extensive medial anteromedian hypothalamic destruction sparing the tuberal and posterior part of arcuate nucleus induced hypersecretion of corticosterone\(^\text{44}\) and rather extensive lesions in posterior hypothalamus other than arcuate nucleus (ARt, ARp) as seen in Group-n, maintained adrenocortical function, while the lesions invading it caused adrenocortical hypofunction. These findings added an evidence that the main hypothalamic nucleus which was related positively to adrenocortical function was the arcuate nucleus, especially the tuberal or premamillary part of it. On the other hand, it is known that lesions placed in the posterior median eminence was often accompanied with central necrosis of pituitary\(^\text{41}\) and in this study also an infarction was more or less observed in half cases of Group-a, so that it seemed to be impossible to eliminate the possibility that adrenocortical hypofunction in Group-a was not due to the destruction of CRF releasing area but due to pituitary infarction accompanying hypothalamic lesions. However, as the other half cases without pituitary infarction also showed adrenocortical hypofunction in this study and even pituitary grafts, when they were connected with median eminence, could preserve the adrenal function\(^\text{42}\), the destruction of ARt and ARp was supposed to be more essential for adrenocortical hypofunction than the very small pituitary infarction which sometimes inevitably followed the destruction of these parts. Therefore, it can be concluded that the disturbance of ACTH releasing mechanism mainly located in the posterior half of arcuate nucleus induces hypothalamic ad-
renogenic hypotension. Decrease in number of basophils noted in this group might result from the insufficiency of the destroyed hypophyseotrophic area, only in which basophils of implanted pituitary grafts were maintained\textsuperscript{45,46}.

As to the mechanism of hypothalamic adrenogenic hypertension two possibilities are conceivable. One possibility is the destruction of corticoids feed-back receptors or the inhibitory area of ACTH secretion. Except for median eminence which is probably controlled by the negative feed-back mechanism of cortical hormones\textsuperscript{46,47} or ACTH\textsuperscript{48}, receptor sites have been postulated in anteromedial hypothalamus\textsuperscript{45,46}, mamillary body\textsuperscript{44}, anterior periventricular, ventromedial and preamillary nuclei\textsuperscript{49}. Moreover, it has been reported that the lesions in posterior hypothalamus elevated the resting level of corticosterone\textsuperscript{40}, and that stimulation of upper posterior hypothalamus or preoptic area\textsuperscript{26} was followed by a decrease in 17-OHCS secretion and further that midbrain was also involved in the inhibitory\textsuperscript{51} or feed-back mechanism\textsuperscript{52} of ACTH secretion. The common lesions in hypothalamic adrenogenic hypertension were P, PMD and MM, which coincided very well with the postulated feed-back receptor or inhibitor sites as mentioned above and might include the connection to the inhibitory or feed-back mechanism of midbrain. It is quite probable that lesions in these parts induce adrenocortical hyperfunction. However, in contrast to the extensive lesions which seemed to be necessary to destroy the feed-back receptor in hypertension induced by medial anteromedian hypothalamic destruction\textsuperscript{44}, the lesions in hypothalamic adrenogenic hypertension reported here were rather small and contracted by surrounding gliosis. Even if all the posteriorly located feed-back receptors were destroyed, rather diffusely located feed-back sites in medial anteromedian hypothalimus might inhibit adrenocortical function. Therefore, the other mechanism is also conceivable. The stimulative effect of the lesions in contact with such a supposed CRF releasing site as arcuate nucleus may induce adrenocortical hyperfunction, for it has been reported that an irritative focal lesion is produced by electrochemical metallic deposition from stainless steel electrodes\textsuperscript{55,54}. Further experiments are necessary to determine which is the main mechanism of hypothalamic adrenogenic hypertension, the destruction of feed-back receptor sites, the irritative effect of lesions on CRF producing sites, or both.

\textbf{Adrenal medullary factor:} Since COUPLAND\textsuperscript{56} indicated the close relationship between adrenal cortex and the amount of noradrenaline in the medulla, recent biochemical studies\textsuperscript{56} on enzymatic synthesis of adrenaline in adrenal medulla have shown that the activity of phenylethanolamine N-methyltransferase, the enzyme that catalyzes the N-methylation of noradrenaline to adrenaline, falls following hypophysectomy because this enzyme activity is stimulated by adrenocortical steroids. Consequently, adrenal adrenaline content as well as this enzyme activity fell with a little increase in noradrenaline after hypophysectomy and the half-life of disappearance of adrenaline ranged from 30 to 80 days\textsuperscript{57}. Therefore, a marked decrease in adrenaline, less than a half of the control, and an increase in noradrenaline, both of which were proved in adrenogenic hypotension after a long-term observation up to 140 days following hypothalamic destruction, did result secondarily from adrenocortical insufficiency. Moreover, as this relative increase of noradrenaline to adrenaline was first noticed histochemically in adrenogenic hypotension and was confirmed histometrically, this study clearly demonstrated the parallelism of histochemical findings on adrenal medulla with chemical assay of catecholamine.

On the other hand, in nonadrenogenic hypotension not only noradrenaline content but also adrenaline content, though slightly, was increased. Therefore, catecholamine assay as well as plasma corticosterone assay supported the view that nonadrenogenic hypotension was never due to partial deficiency of cortical hormones, in contrast to adrenogenic hypotension which showed a marked decrease in adrenaline contents. As for the hypothalamic control of adrenal medulla, MAGOUN et al.\textsuperscript{58} confirmed that hypothalamic stimulation resulted in a secretion of adrenal catecholamine. Later the localization of the hypothalamic nerve tracts or centers which were involved in the selective secretion of two catecholamines was investigated, but has
not been clarified as yet. Noradrenaline and adrenaline were liberated by the stimulation of anterior hypothalamus and posterior hypothalamus adjacent to mamillary bodies, respectively, according to Redgate and Gellhorn. As a selective discharge of adrenaline or noradrenaline in response to electrical stimulation of the posterior part of hypothalamus which was destroyed in nonadrenogenic hypotensive rats, had also been reported, such an increase in adrenaline and noradrenaline content as seen in nonadrenogenic hypotension might be due to the retention of these catecholamines which resulted from lacking of secretory stimuli from hypothalamic structures closely involved in the secretion of these catecholamines. Moreover, the electronmicroscopical finding that the number of catecholamine granules appeared to be increased in denervated adrenals following splanchectomy supported this view, i.e., the retention of catecholamine in adrenal glands deprived of proper neural stimuli. However, this retention of catecholamines, if any, does not inevitably mean that the secretory disturbance of catecholamines is the main etiology of hypotension in nonadrenogenic hypotension, because these rats showed high post-pith pressure as controls, indicating no humoral deficiency in this hypotension. The increased catecholamine content might be a sign of generalized decrease of sympathetic activity, while a possibility of compensatory adrenomedullary hyperfunction to counteract hypotension could not be completely eliminated.

Thyroidal factor: Typical histology of thyroid such as increased acinar cell height, decreased amount of colloid and narrowing of follicle diameters or the contrary findings to these, has been considered to have some relation with thyroidal function under well controlled experiments. Better correlation was confirmed between thyroidal I release ratio and thyroidal function. Judging from these two criteria, it was noted that the destruction of the tubero-mamillary region of hypothalamus was often associated with thyroidal hyperfunction as well as hypofunction.

As for the localization of the lesions causing thyroidal hypofunction, a greater part of the cases of hypothalamic adrenogenic hypotension induced by the lesions in the posterior half of arcuate nucleus showed not only adrenal but also mild thyroidal I release ratio. Moreover, it should be pointed out that one case with lesions in the anterior part of arcuate nucleus showed hypotension and a marked prolongation of I release ratio without adrenocortical atrophy. Although D'Angelo indicated that the hypothalamic area regulating TSH secretion existed diffusely in the anterior and tuberal part, most authors have agreed well on the view that it is located rather anteriorly in the anterior tuberal region of hypothalamus. Because the lesions invading the anterior part of arcuate nucleus caused thyroidal hypofunction without adrenocortical atrophy, and because Nosaka's extensive medial anteromedian hypothalamic destruction resulted in adrenocortical hyperfunction with histologically inactive thyroid, admitting that the portion of the hypothalamus involved in the regulation of TSH and ACTH is overlapping and diffuse, it appears likely that the anterior part of arcuate nucleus and the fiber connection in it or some hypothalamic nuclei anterior to it are mainly involved in TSH regulation, but not in ACTH regulation which is supposed to be more concentrated in the tuberal or premamillary part of arcuate nucleus.

On the other hand, the localization of intrahypothalamic feed-back receptor of thyroid hormones was postulated to be in anterior hypothalamus but has not been established yet. Other than these sites, classical studies by Cahane and Cahane reported a histological picture of decreased or increased activity of the thyroid following lesions placed anterior or posterior to the level of pituitary and they postulated two centers, one situated between the optic chiasma and pituitary stalk which excited TSH secretion, and the other situated in the tuberomamillary region which inhibited TSH secretion. Although the former center has been supported by many authors up to the present, the latter inhibitory center has not yet been confirmed. This study added an evidence that active histology of thyroid or acceleration of thyroidal I release was observed following the tuberomamillary lesions which included P,
DM, PF and F in common and PH, PMD and MM in some cases, and supported the assumption of TSH inhibitor in these areas. Intrahypothalamic microinjection studies by Euler et al.\textsuperscript{16} failed to demonstrate intrahypothalamic receptor sites of thyroxine, but revealed that the microinjection of adrenaline into the vicinity of the mammillary body inhibited thyroidal release of $^{131}\text{I}$. This fact indicated another possibility of an inhibitory area around mammillary body in place of their speculation of thyroidal inhibition due to ACTH secretion induced by adrenaline. Moreover, Szentagothai et al.\textsuperscript{19} postulated by histometrical studies that AR, DM and premammillary nucleus were involved in the regulation of TSH secretion, whether acceleratory or inhibitory. Some of these nuclei were well consistent with the nuclei in the lesions which induced thyroidal hyperfunction in the present experiment. Our recent histochemical studies\textsuperscript{8} on the hypothalamus following the interferences with endocrine functions also indicated that some of the nuclei in posterior hypothalamus were involved in probable sites of TSH inhibitor.

As these lesions were adjacent to ARa, which was supposed to have an active role in TSH secretion, thyroidal hyperfunction due to the stimulative effect of the lesions on ARa could not be eliminated. In addition to the hypothalamic control of thyroidal function, a possibility that thyroidal hyperfunction would accompany an overactivity, if any, of autonomic nervous system could not be denied, for the autonomic nerve might have some physiological role in the control of thyroidal function\textsuperscript{27}.

Investigation on the correlation between thyroidal function and blood pressure in hypothalamus-lesioned rats showed that thyroidal function did not play so definitive a role in blood pressure maintenance as adrenocortical function, because some hypotensive rats had rather active thyroid while normotensive or even hypertensive cases had hypovactive ones. However, as hyperactive thyroid was noted in 3 out of 8 nonadrenogenic hypertensive rats and marked prolongation of $^{123}\text{I}$ release ratio was seen in one case of nonadrenogenic hypotension, thyroidal function might contribute to blood pressure maintenance. This correlation between thyroidal function and blood pressure appeared to correspond well with the clinical observation on not constant but frequent coincidence of Grave's disease with hypertension, or of hypothyroidism with hypotension\textsuperscript{28}. In the field of experimental hypertension it was confirmed that thyroxine\textsuperscript{29} enhanced and thyroidectomy\textsuperscript{30} inhibited hypertension. Cooperative effect\textsuperscript{31,32} of thyroid hormones with catecholamine or with sympathetic nervous system might be also concerned with the change in blood pressure in hypothalamus-lesioned rats.

**Neural factor:** Since the pioneer work of Karplus and Kreidl\textsuperscript{33}, the bulk of experiments\textsuperscript{11} proved that electrical stimulation of both anterior and posterior hypothalamus gave rise to prominent hemodynamic responses, and a close relationship between hypothalamus and sympathetic discharge was confirmed\textsuperscript{34}. Especially the posterior or lateral hypothalamus\textsuperscript{35–39} has been stressed as the portion where pressor responses are obtained by stimulation, in marked contrast to the portion of anterior hypothalamus which brings out parasympathetic response\textsuperscript{36}, sympathetic inhibition\textsuperscript{37} or sympathetic vasodilation\textsuperscript{37}.

However, hypothalamic tonic innervation of vascular control has been denied by many workers\textsuperscript{30,34} since Dittmer's first experiment\textsuperscript{35} showed that blood pressure remained relatively unaffected following supra-bulbar transection. On the contrary, Gellhorn et al.\textsuperscript{38,39} reported that posterior hypothalamic lesions or the injection of anesthetics into posterior hypothalamus led to a temporary or prolonged fall in blood pressure in acute experiment, and provided only one evidence indicating tonic sympathetic discharge originating in posterior hypothalamus. To obtain unequivocal evidence for and against supra-bulbar tonic vasoconstriction is a most difficult experimental task as pointed out by Bard\textsuperscript{11}, because even light anesthesia\textsuperscript{38} depressed hypothalamic influence and a possibility of irritative effect from injury can not be eliminated in the acute experiment of brain-stem transection.

Therefore, it is quite possible that the effect of posterior hypothalamic destruction which has been observed in acute experiment may not be the same as the chronic effect, though a
simple interpretation of the effect is more difficult in chronic experiment. (1) The present study showed that a sort of posterior hypothalamic destruction induced chronic hypotension without adrenocortical hypofunction. These hypotensive rats had neither thyroidal deficit nor apparent alterations in other endocrine organs. (2) Pithing experiments evidently showed that the post-pith pressure, which was maintained mainly by humoral component of blood pressure after the total depletion of neural factors, was not different in these nonadrenergic hypotensive rats from the post-pith pressure of controls and higher than in adrenogenic hypotensive or adrenalectomized rats, the hypotension of which was obviously ascribed to adrenocortical deficit. This fact suggested that nonadrenergic hypotensive rats were not insufficient in humoral factors but deficit in nonhumoral factor, perhaps neural factor. (3) Moreover, spontaneous sympathetic discharges, which were mainly concerned with vasoconstriction, appeared somewhat decreased in nonadrenergic hypotensive rats and even if they were not different from normotensive controls, they seemed to be less in frequency than those of adrenogenic hypotension or non-neurogenically induced hypotension such as acetylcholine-hypotension, but the conclusion needed further experiments because of the shortage of the number of rats employed. (4) The localization of the lesions in these hypotensive rats was postero- medio l or postero-lateral hypothalamus which brought out prominent pressor response when stimulated. The lesions were extensive and included these pressor points, which coincided well with those indicated in many reports, i.e., LHA, MFB, PF, and a part of PVC, DM and PH. (5) It should be noted that these lesions destroyed not only nuclear mass but also very important connections of hypothalamic to lower brainstem such as MFB, and PVC containing periventricular fiber system and others. (6) Although even the multiple lesions of these vasopressor areas were not always followed by a fall in blood pressure in the acute experiment as confirmed also in this experiment, it was noted that the lesions which depressed blood pressure slightly or gave no effect in acute stage induced hypotension gradually with a lapse of time in chronic experiments. As humoral deficiency due to other factors than adrenal and thyroidal ones can not be eliminated completely in nonadrenergic hypotension, the conclusion is beyond this article. However, these six evidences as mentioned above and the author’s recent observations on the slight but prolonged fall in blood pressure following acute specific separation of posterior hypothalamus from mesencephalon in rats (unpublished data) suggested that hypotension might be developed neurogenically when hypothalamic influence to medullary vasomotor center is removed. It is now clear that medullary vasomotor center have a sort of automatism but can not accomplish all the adjustments which the cardiovascular system displays, and without the superstructure of hypothalamus this center might lose precised regulation and overshoot in degree or deteriorate, and derangement or deviation of vasoregulatory mechanism from the steady state, whether it is due to lack of stimulative influence to vasomotor center from hypothalamus or due to predominancy of inhibitory influence, might become gradually manifest in course of time. Therefore, it comes as no surprise that these phenomena and hypotension probably of neurogenic origin could be observed only under long-term observation in chronic experiments which had been treated rather lightly up to the present time as compared with an enormous amount of acute experiments on hypothalamic regulation of vascular system. It might be said that hypothalamic regulation of cardiovascular system is not tonic but semitonic or a tonic-modulatory one.

On the contrary, as to the etiological factors of nonadrenergic hypertension, (1) post-pith pressure, though only one case was pithed, was not different from that of controls, and indicated no increase in humoral component of blood pressure. (2) Hypothalamic lesions in this group were relatively small in size, rather irregular in shape and surrounded more or less by contractive gliosis as compared with the large defect of brain substance as seen in nonadrenergic hypotensive rats. (3) Moreover, the sites of the lesions were located in the mid-dorsal-portion of posterior hypothalamus which elicited pro-
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minent pressor responses but never the depressor ones when stimulated. (4) The hypertensive effect of the small lesions in these portions was not so regularly reproducible as the hypotensive effect of the extensive lesions including the same portions. From these four reasons, it seems to be reasonable to speculate that the hypertensive effect of the lesions might not be due to the destruction of the depressor region or the interruption of inhibitory influence, but might result from the stimulative effect of the small lesions as described already.

Body fluid and electrolytes: Electrical stimulation of the median eminence in the vicinity of infundibulum showed a delayed pressor response, which could be ascribed to the release of vasopressin (ADH) in reference to similar experiments reported up to the present. Therefore, a decrease in ADH secretion, if any, following the destruction of the stimulating part of ADH secretion in tuberomamillary hypothalamus, or following the partial destruction of supraoptic-hypophyseal tract might induce the diuresis which was frequently observed in hypothalamus-lesioned rats in this study. However, it is doubtful whether such a decrease in ADH secretion exert any appreciable effect in blood pressure homeostasis, because hypertension developed even in rats with severe diabetes insipidus and urinary volume of non-adrenogenic hypertensive rats was not greater than normotensive hypothalamus lesioned rats.

Although the number of cases treated with high salt diet (7% NaCl) was lacking, this preliminary experiment showed that high salt diet failed to maintain temporary nonadrenogenic hypertension and that salt metabolism might not be involved in it. But the salt loading elevated the blood pressure into normotensive and nearly normotensive range in nonadrenogenic and adrenogenic hypotension, respectively. On the other hand, the interruption of salt loading resulted in the return of hypotension. As the salt loading in this experiment was excessive in amount and long in duration, normalization of blood pressure in both types of hypotension might be the nonspecific effect of a large amount of the salt loaded. Especially in adrenogenic hypotension, it is probable that the high level of sodium compensated the imbalance of body fluid or the alteration of vascular wall due to the severe deficiency of ACTH and corticosterone, or reestablished the vascular reactivity and the peripheral nerve function which had been reduced because of corticosterone deficiency. Corst had reported the extreme loss of salt and the diuresis which resulted from the lesions placed in the posterior hypothalamus of rats. But, firstly, the period of intense salt wasting following hypothalamic destruction lasted only from two to four weeks in the rat. Secondly, the urinary output in nonadrenogenic hypertensive rats was less than that in normotensive hypothalamus-lesioned rats. From these two reasons, the hyponatremia caused by the salt wasting following posterior hypothalamic destruction might possibly be a cause of temporary hypotension or one of the cooperating factors to develop hypotension but could not be the main cause of nonadrenogenic hypotension which was not infrequently sustained 10 weeks or more after hypothalamic destruction.

Although the glomerular zone is nonadrenogenic hyper- and hypotension showed no histologically detectable change, it can not be completely eliminated that nonadrenogenic hypotension especially might be related with electrolyte imbalance due to the disturbance in aldosterone secretion, because the diencephalic regulation of aldosterone, though this mechanism may not be of primary importance, can not be discarded. Therefore, investigation on salt metabolism in the hypothalamus-lesioned rats is a pending problem, and it is quite possible that hyponatremia, if any, contribute to the development of hypotension in cooperation with the almost undetectable slight depression of sympathetic discharge.

Other factors: One more factor which should be taken into consideration in the present study is the hypertensive effect of somatotropic hormone (STH) and its deficiency as a probable cause of hypotension. However, no abnormality was observed in body length, body weight and organ weight in nonadrenogenic hypertensive group. In the nonadrenogenic hypertensive group kidney weight was somewhat decreased but not significantly different from that of sham-operated rats. As nonadreno-
genic hypotensive rats had no microsplanchnia and were not stunted, they gave no sign indicating the shortage of STH.

Heart weight to body weight ratio was increased or decreased in adrenogenic hyper- or hypotension, respectively, and in addition, both the weight and this weight to body weight ratio were decreased in nonadrenogenic hypotension as compared with controls. These findings were secondary effects of hypertension and hypotension, but confirmed the existence of hyper- and hypotension from the viewpoint of macroscopical pathology, because cardiac hypertrophy is a common observation in systemic hypertension both in man\textsuperscript{119} and in rats\textsuperscript{120,121} while heart weight is reduced in essential hypotension\textsuperscript{122} and in hypotension due to ADDISON's disease\textsuperscript{123} in man.

Morphologically, no vascular disease was found in adrenogenic or nonadrenogenic hypertensive rats in comparison with the rather high incidence of vascular lesions in hypertensive rats induced by extensive medial anteromedian hypothalamic destruction\textsuperscript{10}. It is partly because of the short duration and the mild or moderate grade of hypertension, and partly because of the etiological difference of hypertension, especially in nonadrenogenic cases.

Hypothalamic destruction and hyper- or hypotension: In comparison with the bulk of acute experiments on the effect of hypothalamic stimulation and destruction, chronic observations on the effect of hypothalamic destruction on blood pressure have been scarce in number.

In 1950, HEINBECKER and PFEIFFENBERGER\textsuperscript{124} reported hypertension with adrenal hypertrophy and with obesity following the denervation of the entire neural hypophysis in dogs. Although this hypertension appeared to be adrenogenic in origin and was accompanied with the overaction of eosinophils in pituitary, adrenogenic hypertension in the present study showed neither obesity nor such histological findings in pituitary. In 1956, GELLHORN, NAKAO and REDGATE\textsuperscript{125} observed a rather long-lasting fall in blood pressure after posterior hypothalamic destruction, and indicated the tonic function of posterior hypothalamus. This lowering of blood pressure was evidently of neurogenic origin, but their experiments were, to our regret, limited only to acute ones. In 1960, KELLER\textsuperscript{126} reported hypotension in dogs which received near total hypothalamectomy, prechiasmal ablation or posterior hypothalamectomy, and attributed it to a decrease in energy metabolism. However, concrete evidences to prove etiological factors or to eliminate other neural and endocrine factors seemed to be lacking. In 1965, OKAMOTO, NOSAKA and YAMORI\textsuperscript{127} reported hypertension and hypotension after hypothalamic destruction in rats and tried to analyze the relationship between the detailed localization of the lesions and blood pressure or the alterations in endocrine organs. NOSAKA\textsuperscript{128}, one of these authors, discovered the adrenocortical hyperfunction as the main etiological factor in the hypertension induced by extensive medial anteromedian hypothalamic destruction. Re-

Fig. 26. The speculated sites of hypothalamic lesions necessary for the development of hypertension and hypotension.
ently, Bernardis and Skelton[^126,127] reported that lesions in VM prevented adrenal regeneration hypertension and depressed or prevented the blood pressure rise due to aging, especially when the lesions were placed in young rats, through the interference with neuroendocrine regulation of ACTH and perhaps STH. Furthermore, the present study added some evidences that lesions in tubero-mamillary part of hypothalamus induced hyper- and hypotension through the regulatory disturbances in hypophyseo-adrenocortical system, perhaps in sympathetic vasomotor innervation, and partly in hypophyseo-thyroidal system. The localizations of the lesions which were mostly probable to develop adrenogenic hyper- or hypotension and nonadrenogenic hyper- or hypotension were summarized in Fig. 26.

Although a full understanding of all the mechanisms of these hyper- and hypotension was beyond this study, the results of these experiments provided the evidences that the tubero-mamillary region of hypothalamus participates in the maintenance of blood pressure through endocrine systems as well as through tonic-modulatory neural influence to vascular system and that hypothalamic dys-function, whether it is caused by the stimulative or the destructive effect of the lesions, induces hyperension or hypotension due to the deviation of neuroendocrine homeostasis through the abnormality of one or some factors which cannot be compensated successfully by the other factors.

**Summary**

Various electrolytic lesions in the tubero-mamillary region of hypothalamus in Wistar rats induced hyper- and hypotension, on which chronic observation and the analysis of endocrine and neural factors were made (I). In addition, the acute effects of electrical stimulation and destruction were studied (II), compared with the chronic effects of the lesions (III) and the following results were obtained.

(I) Among 160 survivors hypertension and hypotension were observed in 8.1 and 23.5 percent, respectively. The other were normotensive and borderline hyper- or hypotensive cases.

(a) Mid-postero-dorsal lesions adjacent to intact arcuate nucleus induced hypertension in 5 rats (Group-A), which showed marked increase in adrenal weight and plasma corticosterone level, and cardiac hypertrophy. Adreno-cortical function was evidently hyperactive as compared with neurogenic or renal infarction hypertension.

(b) Medial postero-dorsal lesions including periventricular grey or nucleus induced hypertension in 8 rats (Group-N), which showed neither increase in adrenal weight and plasma corticosterone level nor alteration in other endocrine organs except for 3 cases with histologically active thyroids. The post-pith pressure of one case in this group was not different from the controls.

(c) Medial postero-tuberal basal lesions destroying arcuate nucleus induced severe hypotension in 20 rats (Group-a), which showed a prominent decrease in pituitary weight, in the number of basophils, in adrenal weight and plasma corticosterone level, and in cardiac weight. The adrenaline content of adrenal medulla was decreased, while noradrenaline was increased. More than half of this group was noted to have thyroidal hypofunction or gonadal atrophy. The splanchnic discharge was not different from that of control. The post-pith pressure and the plasma corticosterone level were as low as those in adrenalectomized rats.

(d) Extensive postero-medial and postero-lateral lesions including the postero-medial part of lateral hypothalamic nucleus, fornix, perifornical nucleus, prelateral and lateral mamillary nucleus in common, induced hypertension in 18 rats (Group-n), which showed a decrease in cardiac weight but no alteration in adreno-cortical, thyroidal function and other endocrine organs except for a slight decrease in pituitary weight. Both noradrenaline and adrenaline were increased in adrenal medulla. The splanchnic discharge showed a slight tendency to decrease and the post-pith pressure was maintained as high as that of controls.

(e) (i) Plasma corticosterone level and blood pressure were well correlated with each other in Groups-A, -a and adrenalectomized rats, but not in Groups-N, -n, and the rats with neurogenic or renal infarction hypertension. No hypertension was noted when adrenocorti-
cal insufficiency existed.

(ii) Lesions including arcuate nucleus induced adrenocortical hypofunction, while its function was maintained in spite of rather extensive tubero-mammillary destructions, sparing the arcuate nucleus, or of a lesion in the anterior part of the arcuate nucleus. The minimum hypothalamic area indispensable for producing CRF to maintain normal adrenocortical function was the arcuate nucleus, especially its postero-median part.

(i) The correlation of blood pressure with thyroid function indicated by $^{131}$I release ratio was not so definitive as that with adrenocortical function. Thyroidal hyperfunction was not rarely seen in Group-N, while the hypofunction was frequently noted in Group-A. Severe thyroidal hypofunction coincided with hypotension except when adrenal hyperfunction coexisted.

(ii) Rather small lesions located in the anterior part of arcuate nucleus induced thyroidal hypofunction without adrenocortical atrophy. Medial tubero-dorsal lesions, including periventricular nucleus adjacent to the anterior part of arcuate nucleus, dorsomedial nucleus and some other nuclei around these, were often accompanied with shorter half-life of thyroidal $^{131}$I or histologically active thyroid.

(II) (a) The electrical stimulation of the medial portion of dorsomedial and ventromedial nucleus or periventricular nucleus adjacent to these, posterior hypothalamic, dorsal premamillary, perifornical nucleus and the posterior portion of lateral hypothalamic nucleus elicited a moderate or intense direct pressor response and an indirect one following it after stimulation.

(b) In acute experiments, the destruction of the tubero-mammillary region of hypothalamus was followed frequently by a temporary depressor effect or no alteration in blood pressure, but sometimes by a prolonged slight lowering of blood pressure or a prolonged pressor response.

(III) (a) The case, in which no specific acute effects of hypothalamic destruction on blood pressure were observed, developed hyper- or hypotension with adrenal hypertrophy or atrophy (Group-A or -a, respectively) under chronic observation, and the discrepancy between the acute and the chronic effects of the lesions was confirmed in these groups. Moreover, even a negligible or a very slight prolonged fall of blood pressure in acute experiment was noted to shift to hypotension in Group-n in the chronic stage.

(b) The extensive lesions in Group-n included the greater part of the pressor area which were confirmed by electrical stimulation, while the rather small lesions in Group-N were situated within the pressor area in the tubero-mammillary region of hypothalamus.

In conclusion, these results indicated that several sorts of lesions in the tubero-mammillary region of hypothalamus induced hypertension due to adrenocortical hyperfunction (Group-A; adrenogenic hypertension) through the destruction of the feed-back receptor sites of corticosterone or the destructive irritation of CRF producing sites or through both of these mechanisms as well as hypotension due to adrenocortical hypofunction (Group-a; adrenogenic hypotension) by means of the destruction of CRF producing sites in arcuate nucleus, and moreover, caused hyper- and hypotension without alteration in adrenocortical function (Groups-N, and -n; nonadrenogenic hyper- and hypotension), perhaps due to the neural origin through the stimulative effects of lesions on medullary vasomotor center (Group-N) or through the deprivation of hypothalamic tonic-modulatory influence to the vasomotor center (Group-n) and partly due to thyroidal hypofunction through the destruction of the hypothalamic area involved in the production or the transportation of TSH releasing factors.

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