Experimental Hypertension

Metabolism and the Genesis of Hypertension (II)

TADAYOSHI ABE

*The 1st Department of Internal Medicine, Kobe Medical College, Kobe
(Director: Prof. T. Tomomatsu)*

This report concerns with the experimental hypertension induced by the repeated injection of dinitrophenol and moniodoacetate to dog. The author succeeded to get the hypertension in 14 out of 17 cases. The venous return, renal clearance, urinary catecholamine, total 17-OHCS excretion and serum cholesterol were examined.

IN THE FIRST part of present study, a report was made on an experimental hypertension with successive injection of 2.4 dinitrophenol (DNP) and moniodoacetate (MIA) to the albino rats.

Subsequent studies have been undertaken to elucidate the mechanism in the causation of hypertension.

In the hypertension of albino rats reported previously induced by DNP and MIA, a mild albumiuria has been observed. It has been reasonably ascertained that the hypertension thus experimentally produced could hardly be from renal origin knowing lesser pathological findings, which brings a question of a possible morbid reason other than the renal factor.

Neuropathic factors have been emphatically proposed as the cause of hypertension, although hyperfunctions of the adrenal cortex and medulla have also been stressed as the endocrine sources which has already aroused an attention.

While, LOOMIS & LIPMAN¹⁾ had clarified that DNP specifically interferes with the oxidative phosphorylation of the tissue in vitro; at the same time metabolic stimulation in vivo has been reported^{2,3,4)}. In living organism, DNP markedly enhances carbohydrate metabolism^{5,6)}, raises body temperature, increases oxy-

gen consumption⁷⁾, and causes the drastic decrease of liver glycogen and hyperglycemia^{8,9)}. And, attempts are being made to explain these phenomena from the specific uncoupling action of DNP.

STONER et al.¹⁰⁾ and PARKER¹¹⁾ stated in their report that DNP and, similarly-acting substance, 2,3-Dinitro-orthcresol, although interferes the metabolism of phosphoric acid in vitro, if given in vivo, acts either mildly or becomes unstable. In this connection, FONNESU et al.⁸⁾ observing the effects of DNP on carbohydrate metabolism made clear that administration of DNP leads to a marked decrease of glycogen immediately thereafter, but its repeated injections would cause abnormal glycogen retention. According to YASUDA¹²⁾, the repeated administration of DNP could bring about abnormal glycogen increase, adrenal hyperplasia, with increased adrenal ascorbic acid along with enhanced carbohydrate metabolism, whereas no such changes would be observed in the adrenalectomized animals when DNP was given in single or repeated dosage. This coincides with the fact that when DNP is applied in vivo, it is well distributed in the adrenal tissues and is equivalent to in concentration of the serum level¹³⁾. The reactions as observed in the course of repeated injections of

(Received for Publication, May 20, 1966)

DNP seems to be associated with an important role played by adrenal function.

While MIA is known as the SH suppressing agent, its action is considered to be disturbed phosphorylation due to inhibition of phosphatase in a chemical process. Thus suppressed enzymes are said to be phosphoric acid glyceraldehyde dehydrogenase, alcohol dehydrogenase, and succinic acid dehydrogenase¹⁴⁾. Further, MIA is also described to the effect that its physiologic action disrupts the formation of actomyosin¹⁵⁾, inhibits the contractibility of muscle fibre¹⁶⁾, and beside, completely blocking the intramuscular sugar decomposition which induces the muscular contraction unaccompanied by the formation of lactic acid¹⁷⁾. And, VEZÁR^{18, 19)}, noting a similarity between the experimental intoxication symptoms produced by MIA and the hypofunction of the adrenal cortex, addition of riboflavin phosphoric acid, however, improves the general condition, made him assume the following deduction, that is MIA intoxication causes adrenocortical disturbance which in turn creates suppressed phosphorylation.

It has been well demonstrated that not only the administration of DNP and MIA would directly act on the various tissues, but it should be interpreted that the adrenals and thyroid glands serving an intermediate role. This raises an issue that whether or not presence of experimental hypertension would be an endocrine involvement. To investigate further, employing dogs, evaluations were made of blood pressure changes induced by the repeated injections of DNP and MIA, and measured for the changes of venous return of various organs, and examined for renal clearance, urinary catecholamine, total 17-OHCS excretion, serum cholesterol, PBI, and oxygen consumption.

METHOD

Seventeen normally healthy dogs each attached with a special dermocarotid artery bridge²⁰⁾, previously devised for indirect measurement of blood pressure, were divided into two group: one (6 males, 3 females) for DNP; the other (6 males, 2 females) for MIA, and daily consecutive intramuscular injection was carried out at the rate of 5 mg./kg. respectively. A period of injection lasted from 35 to 80

days for DNP group, and 45 to 60 days for MIA group.

Examination Method:

a) Blood pressure measurement:

Wrapping around the carotid artery bridge manchette of 3 cm. width and of 10 cm. length, the daily measurement was made by auscultation and palpation. The measuring of subject dog's blood pressure started first so as to get the animals accustomed to the manual operation for 2-3 weeks prior to the consecutive administration of DNP and MIA.

b) Renal clearance and venous return distribution rate:

DNP was given to 7 dogs and MIA to 6. Renal clearance and venous catheterization were tried on 3 dogs before the drug injection and prior to sacrificed. After anesthetizing with intravenous ouropan-soda and fixing the subject on an immobile table in dorsal position, Nelaton's catheter was inserted for the purpose of collecting urine. Then, as a means to increase urinary output, drip phleboclysis with about 20 cc./kg. of RINGER's solution was tried, and GFR, RPF, and FF were calculated by applying 0.5 cc./kg. of 10 per cent para-aminohippuric acid for renal plasma filtration (RPF), and 2.5 cc./kg., of 10 per cent thio-sulfate soda for glomerular filtration rate (GFR) with a single intravenous injection²¹⁾. In addition, as for the distribution of venous return, the flow rate, the perfusions of the superior caval the inferior caval vein,, the liver, the kidneys, and the vein of lower extremity were measured^{22, 23)}.

c) Serum cholesterol and serum protein-bound iodine (PBI):

Collecting the blood from the femoral vein prior to the initiation of injection and at the time of sacrificing, serum cholesterol was estimated by the method of ZACK-HENRY and PBI by the BAKER's ash-making method.

d) Urinary catecholamine and total 17-OHCS:

Keeping the dogs in the kennel with urine receptacle prior to the initiation of injection and sacrificing, 24-hour urine was collected, and measured of adrenalin and noradrenalin by THI method²⁴⁾, total 17-OHCS in the urine by a modified PORTER-SILBER-RADDY-SMITH-KUMAGAI method.

e) Oxygen consumption:

Subjected the dogs to with ouropan-soda anesthesia, oxygen consumption was measured by FUKUDA spirometer by inserting a tracheal cannula.

RESULTS

I) DNP Injected Group

i) Blood pressure:

The blood pressure of 9 subject dogs before the initiation of injection was 120-140 mmHg.

The variation of blood pressure after the

injection is shown in Fig. 1. The elevation of blood pressure was noted in general from the 7th day of the experiment. Blood pressure was most variable in the early period. However, no elevation was observed in 2 cases out of 9 (Fig. 2).

ii) Body weight:

As shown in Table I, the body weight decreased by 0.3–3.5 kg. due to DNP all but No. 6, but there was no change in general conditions.

iii) Urinary findings:

Throughout the period no urinary protein was detected. No change in urobilinogen nor urinary sugar was noted.

iv) Urinary catecholamine:

The urinary excretion of catecholamine before the injection is shown in Table I, according to which adrenalin was 0.86–5.2 γ /day averaging 3.3 γ /day, and noradrenalin, 4.6–8.2

γ /day averaging 5.7 γ /day, whereas the urinary excretion of catecholamine after the repeated injection of DNP was: adrenalin, 0.4–4.8 γ /day averaging 2.4 γ /day, and noradrenalin, 1.35–9.0 γ /day averaging 5.1 γ /day. This meant there was no significant change in catecholamine excretion. As to the cases in which hypertension developed as are shown in Fig. 3, adrenalin increased in 2 cases, decreased in 3 cases, and no change in 1 case; and noradrenalin increased in 2 cases and decreased in 4 cases.

v) Urinary total 17-OHCS:

The measurement of the urinary total 17-OHCS of 24 hours in 6 cases was made. The measured values, as shown in Table I, were 1.6–5.25 mg/day averaging 3.0 mg./day before injection and 0.9–4.7 mg./day averaging 4.3 mg./day after repeated injections. As to the elevation of blood pressure (see Fig. 3), in-

Fig. 1. Blood pressure change following long-term administration of DNP in dogs.

Fig. 2. Blood pressure change following long-term administration of DNP in dogs.

TABLE I EFFECT OF DNP ON OXYGEN CONSUMPTION, PBI, SERUM CHOLESTEROL AND URINARY EXCRETION OF CATECHOLAMINES AND 17-OHCS IN DOGS

Case No.	Duration of injection	Body Weight (kg)		Oxygen Consumption cc/min		P. B. I. γ /dl		Serum Cholesterol mg/dl		Catecholamines in urine γ /day				17OHCS in urine mg/day	
		Before	After	Before	After	Before	After	Before	After	Adrenaline Before	Adrenaline After	Noradrenaline Before	Noradrenaline After	Before	After
4	35	8.0	6.6	92	122.5	2.47	2.39	210	150	2.6	1.2	4.6	2.65	2.35	9.4
5	35	8.0	4.5	65	50	2.81	3.17	215	146.4	0.86	0.9	4.8	1.35	3.0	3.32
6	35	8.6	9.0	70	115	2.30	2.0	170	187.5	3.93	2.2	4.6	6.7	5.25	4.1
7	35	7.8	7.5	92	165	2.12	2.68	144	165	2.73	0.4	5.22	1.4	3.95	4.25
1	60	12	9.5	—	—	—	—	—	—	3.6	4.8	8.2	5.2	—	—
2	80	13	10	—	—	—	—	—	—	2.9	3.7	6.1	7.4	—	—
8	60	6.6	5.5	—	—	—	—	—	—	5.2	4.6	7.4	7.2	1.9	3.8
9	60	8.0	7.5	—	—	—	—	—	—	4.7	1.4	4.9	9.0	1.6	0.9
Mean		9.0	7.5	79.8	113.1	2.4	2.6	184.7	162.3	3.3	2.4	5.7	5.1	3.0	4.3

Fig. 3. Changes of urinary catecholamines and 17-OHCS excretion in dogs made hypertensive by administration of DNP. Mean

crease in 1 case, no change in 2 cases, and decrease in 1 case.

vi) Oxygen consumption:

A) Acute consumption test

Two healthy dogs were subjected to intravenous anesthetizing, consumed oxygen was measured followed by the intramuscular injection of DNP, 5 mg./kg., and when the consumed oxygen was measured again 30 minutes later, the values were 105–123 cc./min. averaging 114 cc./min. which showed a marked increase against the former value 65–70 cc./min. averaging 67.5 cc./min.

B) Chronic consumption test

As shown in Table I, the oxygen consumption values in 4 dogs were 65–92 cc./min. averaging 79.8 cc./min. before injection, and 50–165 cc./min. averaging 113.1 cc./min. in the 5–6th weeks after the initiation of injection which indicated a marked increase with an exception of 1 case. Incidentally, this measurement was made 24 hours after the last injection.

vii) Serum protein bound iodine (PBI):

PBI values in 4 dogs before injection were 2.12–2.81 γ /dl. averaging 2.42 γ /dl. and those in the 5th week after the initiation of injection were 2.0–3.17 γ /dl. averaging 2.56 γ /dl. which showed no significant change (Table I).

viii) Serum cholesterol (Table I):

Serum cholesterol values in 4 dogs before injection were 144–215 mg./dl. averaging 184.7 mg/dl., while those in the 5th week after the initiation of injection were 146–178 mg./dl. averaging 162.3 mg./dl. which meant no significant change.

ix) Systemic distribution rate of venous return:

As shown in Table II, the systemic distribution rates of venous return in 7 hypertensive dogs before injection were the superior vena cava flow (SCF), 29.2–36.6 per cent averaging 33.6 per cent: inferior vena cava flow (ICF), 63.4–70.8 per cent averaging 66.4 per cent: hepatic venous flow (HF), 18.3–39.0 per cent averaging

TABLE II HAEMODYNAMIC CHANGE AFTER ADMINISTRATION OF DNP IN DOGS

Dog No.	SCF %		ICF %		HF %		RF %		LLF & PF %		RPF cc/min		GFR cc/min		FF	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
4	33.5	36	66.1	64.5	18.3	12	9.2	11	39	41	174	196	33	36	0.19	0.18
5	29.2	44	70.8	56	23	33	13.9	4	33.9	19	184	162	46	34	0.25	0.21
6	35.1	27	64.9	72	23	13	10.9	20	31	40	163	152	26.4	32	0.16	0.21
7	36.6	45	63.4	55	24	22	19.4	6	20	27	158	144	41	36	0.26	0.25
1	33	23.9	67	76.1	33.8	29	15.4	8.7	17.8	38.4	170	142	38	30	0.22	0.20
2	32	27.3	68	72.7	35.5	27.6	15.5	12.8	18	32.3	162	146	43	34	0.26	0.22
3	36	28	64	72	39	44.8	15	13.5	14	13.7	184	152	40	35	0.22	0.19
Mean	33.6	33	66.4	66.9	28.1	25.9	14.2	10.9	24.8	30.2	170.7	156.3	38.2	33.9	0.22	0.21

Remarks: SCF; Superior caval flow, ICF; Inferior caval flow, RF; Renal flow
LLF & PF; Low limbs & pelvic visceral flow

28.1 per cent: renal venous flow (RF), 9.2–19.4 per cent averaging 14.3 per cent and low limbs & pelvic visceral flow (LLF & PF), 14–39 per cent averaging 24.8 per cent: those after the repeated injections were SCF, 23.9–45.0 per cent averaging 33.0 per cent: ICF, 55–76.1 per cent averaging 66.9 per cent: HF, 12.0–44.8 per cent averaging 25.9 per cent: RF, 4.0–20.0 per cent averaging 10.9 per cent: LLF & PF, 13.7–41.0 per cent averaging 30.2 per cent: thus, no change in SCF, but decrease in RF, and increase in LLF & PF were noted. (Fig. 4) x) Renal clearance (Table II) (Fig. 5):

The values of renal clearance in 7 hypertensive dogs (same dogs mentioned above) before injection were RPF, 158–184 cc./min. averaging 170.7 cc./min.; GFR, 26.4–46.0 cc./min. averaging 38.2 cc./min.; FF, 0.16–0.26 averaging 0.22, and those after the repeated injections were RPF, 142–196 cc./min. averaging 156.3 cc./min.; GFR, 26.4–46.0 cc./min.

averaging 33.9 cc./min.; and FF, 0.18–0.25 averaging 0.21. Thus, decrease was noted in

Fig. 4. Superior caval and renal flow after the administration of DNP and MIA in dogs.

Fig. 5. Change of renal clearance after the administration of DNP in dogs.

RPF and GFR.

xi) Histological findings:

Although in some instances an effusion in Bowman's capsules and urinary casts in the tubules were observed, the findings were generally negligible (Fig. 6), and no changes were noted in the heart, the arteries, and the adrenals.

II) MIA Injected Group

i) Blood pressure:

The blood pressure before the initiation of injection was 114–142 mmHg. As shown in Fig. 7, the pressure elevation was noted by the 10th day after injection in 7 out of 8 dogs. Although the pressure became markedly variable but it was elevated, however, only in one case no elevation had occurred. (Fig. 8)

ii) Body weight:

As shown in Table III, the pre-injection

body weight was 6.2–15 kg. averaging 10.9 kg. and that at the close of the experiment 5.0–13 kg. showing the decrease of 1–2 kg.

iii) Urinary findings:

Throughout the period of the present experiment, neither urinary protein nor urinary sugar was observed, and no change was noted in urobilinogen.

iv) Urinary catecholamine:

The urinary excretion of catecholamine before injection was, as shown in Table III: adrenalin, 1.1–2.7 γ /day averaging 2.1 γ /day and noradrenalin, 4.0–8.6 γ /day averaging 5.7 γ /day, whereas the values obtained in the 6th week after the initiation of injection were: adrenalin, 1.7–5.9 γ /day averaging 3.5 γ /day, and noradrenalin, 6.4–17.1 γ /day averaging 9.8 γ /day. When examined of each hypertensive dog, adrenalin increased in 2 cases, no

Fig. 6. Kidney of dog treated with DNP.

Fig. 7. Blood pressure change after long-term administration of MIA in dogs. Hypertension occurred in 7 cases.

change in 3 cases, and noradrenalin markedly increased in 2 cases and slightly increased in 3 cases (Fig. 9).

v) Urinary excretion of total 17-OHCS:

The excretion for 24 hours, as shown in Table III, was 2.4–4.2 mg./dl. averaging 3.5 mg./dl. and after the repeated injections the

excretion revealed 1.5–5.45 mg./dl. averaging 3.17 mg./dl. which was almost unchanged. When estimated of these hypertensive animals, as shown in Fig. 9, one dog showed an increase, while, the another had an decrease the remainders were unchanged.

vi) Oxygen consumption:

Fig. 8. Blood pressure change after long-term administration of MIA in dog. No hypertension occurred in this case.

TABLE III EFFECT OF MIA ON OXYGEN CONSUMPTION, PBI, SERUM CHOLESTEROL AND URINARY EXCRETION OF CATECHOLAMINES AND 17-OHCS IN DOGS

Case No.	Duration of injection	Body Weight (kg)		Oxygen Consumption cc/min		PBI γ /dl		Serum Cholesterol mg/dl		Catecholamines in urine γ /day				17-OHCS in urine mg/day	
		Before	After	Before	After	Before	After	Before	After	Adrenalin		Noradrenalin		Before	After
										Before	After	Before	After		
3	45	15	13	165	105	4.76	9.65	214	260	2.4	2.9	4.5	7.8	4.2	5.45
4	45	12	11	110	90	1.96	—	154	160	2.6	5.9	5.2	10.3	3.75	4.0
5	45	12.5	11.5	117	85	4.01	—	190	205	2.7	3.2	5.6	6.4	3.45	3.6
6	45	11.9	11	85	75	2.47	6.73	158	150	1.9	1.87	4.0	7.12	3.60	3.3
7	60	6.2	5.0	—	—	—	—	—	—	2.1	5.2	6.3	17.1	2.4	1.5
8	60	80	6.8	—	—	—	—	—	—	1.1	1.7	8.6	10.2	3.6	1.2
Mean	—	10.9	9.7	119.2	88.7	—	—	179	193.7	2.1	3.5	5.7	9.8	3.5	3.17

Fig. 9. Changes of urinary catecholamines and 17-OHCS excretion in dogs made hypertensive by administration of MIA.

A) Acute consumption test:

Anesthetizing one dog with Ouropoan-soda, the oxygen consumption was measured, and then giving MIA, 5 mg./kg. intramuscularly the consumption value was measured for the second time 30 minutes after the injection. Comparing these two values, 105 cc./min. and 115 cc./min. it was found that the latter was slightly greater, though it was less marked.

B) Chronic consumption test:

As shown in Table III, the consumption values before injection were 85–165 cc./min. averaging 119.2 cc./min., whereas those obtained prior to sacrificing were 75–105 cc./min. averaging 88.7 cc./min. which showed a decrease.

vii) Serum cholesterol:

As shown in Table III, the values before injection were 154–214 mg./dl. averaging 179 mg./dl., but those in the 6–7th weeks after the repeated injections were 150–260 mg./dl. averaging 193.7 mg./dl. which was not a significant change similarly as in cases of DNP injected

group.

viii) Systemic distribution rate of venous return:

The measured values are shown in Table IV which indicate that SCF, 30.8–48.0 per cent averaging 39.6 per cent, ICF, 52–69.2 per cent averaging 60.5 per cent, HF, 14.6–32.7 per cent averaging 22.1 per cent, RF, 12–28.1 per cent averaging 18.1 per cent, and LLF & PF, 13.4–27.4 per cent averaging 20.5 per cent. On the other hand, the values obtained in the 6–7th weeks after the repeated injections were SCF, 28–41 per cent averaging 34.3 per cent, ICF, 59–72 per cent averaging 65.7 per cent, HF, 26–42.4 per cent averaging 32.2 per cent, RF, 6–21.2 per cent averaging 12.4 per cent, and LLF & PR, 2.15–39.8 per cent averaging 30.7 per cent. Thus, a decrease was noted in SCF and RF. (Fig. 4)

ix) Renal clearance:

As shown in Table IV, the values before injection were RPF, 134–212.4 cc./min. averaging 171.6 cc./min., GFR, 28–53 cc./min.

TABLE IV HAEMODYNAMIC CHANGE AFTER ADMINISTRATION OF MIA IN DOGS

Dog No.	SCF %		ICF %		HF %		RF %		LLF & PF %		RPF cc/min		GFR cc/min		FF	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
3	48	41	52	59	14.6	26	13	6	24.4	27	140	137	42	33	0.3	0.24
4	45	39	55	61	21.5	30	12	9.5	21.5	21.5	212	161	53	35.4	0.25	0.22
5	44	38	56	62	22	26	14	8	20	28	136	170	28	42	0.2	0.25
6	32	31.4	68	68.6	32.7	28.6	20	8.4	16.5	31.6	195	178	43	35.5	0.22	0.20
1	30.8	28	69.2	72	20.6	40	21.4	21.2	27.4	39.8	212.4	186.4	38.6	32.0	0.18	0.17
2	37.5	28.6	62.5	71.4	21	42.4	28.1	21.2	13.8	36.4	134	158	40.6	31.4	0.3	0.19
Mean	39.6	34.3	60.5	65.7	22.1	32.2	18.1	12.4	20.5	30.7	171.6	165.1	40.9	34.9	0.24	0.21

Remarks: SCF; Superior caval flow, ICF; Inferior caval flow, RF; Renal flow
LLF & PF; Low limbs & pelvic visceral flow,

Fig. 10. Renal clearance after the administration of MIA in dogs.

averaging 40.9 cc./min., FF, 0.18–0.3 averaging 0.24, whereas those in the 5th week after the initiation of injection were RPF, 137–186.4 cc./min. averaging 165.1 cc./min., GFR, 31.4–42.0 cc./min. averaging 34.9 cc./min., and FF, 0.17–0.25 averaging 0.21. Thus, similarly as in cases of DNP group a decrease was noted in RPF and GFR (Fig. 10).

x) Histological finding:

There were no pathological findings concerning the heart, the artery, the kidneys, the adrenals, and the thyroid gland.

DISCUSSION

It has been possible to succeed in producing experimental hypertension by the actions of DNP and MIA in dogs. It is extremely variable as observed in the albino rats. And during the trial period it was found that no case of albumiuria was detected.

Since DNP and MIA apparently affect carbohydrate metabolism, the biochemical processes of the organs would be affected when administered, this is particularly true with both the vascular system and endocrinic organs.

For detecting the effect of the two compounds on the functions of the thyroid gland, oxygen consumption and PBI have been estimated. In DNP injected group, oxygen consumption distinctly increased in both acute and chronic tests, whereas serum protein bound iodine (PBI) showed no change in consecutive administration of DNP. While, in MIA injected group there was no significant changes in oxygen consumption; and in both groups they were entirely free from pathological changes. Therefore no findings for hyperthyroidism could be demonstrated.

It has been known that there exists a close correlation between hypertension and the adrenal cortex, as evidenced by Cushing's syndrome and primary aldosteronism, and further, experimentally by DOCA hypertension²⁵⁾ and pheochromocytoma. HOWARD²⁶⁾ and BOWERS²⁷⁾ have recognized the lowering of blood pressure upon adrenalectomy of the hypertensives; and CHWALLA²⁸⁾ and LOCKE²⁹⁾ observed the cortical hyperplasia in the histological findings of the adrenal cortex. It is hardly possible to study

experimental hypertension without going into the function of the adrenal cortex and the medulla, and that the relation between the actions of DNP and MIA and the adrenocortical functions could never be overlooked; the measuring of urinary total 17-OHCS and the excretion of catecholamine has been carried out in order to gain knowledge of the adrenocortical and medullary functions under DNP and MIA hypertensions.

Total 17-OHCS in the urine:

In the case of DNP hypertension group the average value had remained unchanged, but observing each case, there was an increase in one case, a decrease in the other, and no changes in two cases.

With MIA hypertension group one case tended to increase and a decrease was noted in another, though the average value remained fairly constant. This is to say that a significant increase was seen only in one case in both groups, and hardly any change to be noted in the remaining cases.

Catecholamine in the urine:

In the cases of DNP group, adrenalin and noradrenalin values found were either increasing, decreasing, or uncertain, however, the average value remained unchanged. In the cases of MIA group, the values of both adrenalin and noradrenalin increased, except in one case, noradrenalin value increased markedly.

Out of the measured values of urinary excretion of both total 17-OHCS and catecholamine, no results have been obtained that suggesting the adrenal gland participating in the hypertension produced by DNP or MIA. This has been ascertained further by the histologic investigation of the adrenal gland. Nevertheless, the increase was noted of the urinary excretion of total 17-OHCS in certain cases of DNP group and of the catecholamine in the urine of MIA group. It would seem possible, that the genesis of hypertension of this type might be explainable on the basis of the neurogenic factors.

In the measurement of the systemic distribution rates of venous return, the rates of renal vein had decreased in both groups. As to the superior caval flow rate is remained almost un-

changed in DNP group, whereas it decreased in MIA group. As to renal clearance RPF, GFR, and FF, in both DNP and MIA groups showed decrease. In view of these results, it is assumed that the changes in the renal clearance are attributable to hypertensive condition, and unrelated to renal damage as proved by the microscopic observation.

In the present study, however, no significant changes in the thyroid nor the adrenal function (cortex and medulla) could be observed so far as the present experimental results show, that is, hypertension produced by the consecutive injection of DNP and MIA, failed to affect the changes in the kidneys and cardiovascular system. It has been found that the causation of the hypertension produced by DNP and MIA could hardly be elucidated solely on the basis of renal-, endocrinic-, and neurogenic factors. It may be possible to interpret that the condition could still be regarded as an identical entity as that of essential hypertension.

SUMMARY

- 1) The consecutive administration of DNP and MIA to the dogs has resulted in inducing experimental hypertension.
- 2) Oxygen consumption has increased in DNP group, whereas it has decreased in MIA group. As to PBI, no significant change was noted in DNP group.
- 3) As to serum cholesterol, no significant change was observed in both DNP and MIA groups.
- 4) The urinary findings were essentially negative in both groups.
- 5) In the excretion of urinary catecholamine, no changes of adrenalin or noradrenalin was noted DNP group, but both of them were increased in MIA group.
- 6) The excretion of total 17-OHCS in the urine, failed to show any change in both DNP and MIA groups.
- 7) The measurement of the systemic distribution of venous return revealed that SCF and RF decreased in both groups.
- 8) Renal clearance has shown the decrease

of RPF and GFR in both groups.

9) Histological findings failed to show any distinct changes in both groups.

10) It has been reasonably shown that neither renal nor endocrinic factors are involved in the causation of hypertension due to DNP and MIA administration, from the foregoing results.

Acknowledgements

The author wishes to express his gratitude to Prof. Tatsuya Tomomatsu and Assistant Prof. Susumu Yorifuji for valuable suggestions in guiding this work; he is indebted for kind help to Dr. Michinari Morimoto, Yoshitaka Yamaguchi, Taisuke Masumoto, Hiroshi Taguchi, Moriyoshi Tanigaki, Hiroshi Matsuno and Tatsuhiko Motooka.

REFERENCE

- 1) Loomis, W. F. and Lipman, F., *J. Biol. Chem.* **173**: 807, 1948.
- 2) Peiss, C. N., and Field, J., *Arch. Biochem. Biophys.* **36**: 276, 1952.
- 3) Simon, E. W., *Biol. Rev.* **28**: 453, 1953.
- 4) Sproul, D. H., *Bioch.* **66**: 527, 1957.
- 5) Rongoni, E. and Ehrenfest, E., *J. Biol. Chem.* **115**: 749, 1936.
- 6) Pierce, F. T. and Field, J., *J. Biol. Chem.* **180**: 895, 1949.
- 7) Cameron, M. A. M., *Brit. J. Pharmacol.* **13**: 25, 1958.
- 8) Fennesu, A. and Severi, C., *Brit. J. Exp. Path.* **36**: 35, 1955.
- 9) Yasuda, T., *Folia. Pharmacol. Jap.* **54**: 1118, 1958.
- 10) Stoner, M. B., Threlfell, C. J. and Green, H. N., *Brit. J. Exper. Path.* **33**: 398, 1952.
- 11) Parker, V. H., *Biochem. J.* **57**: 381, 1954.
- 12) Yasuda, K., *Folia. Pharmacol. Jap.* **53**: 692, 1957.
- 13) Hukui, S., *Folia. Pharmacol. Jap.* **53**: 104, 1960.
- 14) Hiraide, J., SH no Shinpo. Igakushoin, Tokyo. p. 55-64, 1954.
- 15) Nagai, T., Terayama, Y., Maruyama, T. and Miyazaki, H., *Sapporo. Med. J.* **4**: 15, 1953.
- 16) Nishio, T., *Bull. Res. Inst. Diath. Med.* **4**: 297, 1954.
- 17) Lundsgaard, E., *Biochem. Z.* **217**: 162, 1930.
- 18) Verzar, F., *Biochem. Z.* **292**: 152, 1937.
- 19) Verzar, F., and Laszt, L., *A. Ges. Physiol.* **236**: 693, 1935.
- 20) Aoki, S., *Jap. Circul. J.* **26**: 455, 1962.
- 21) Asano, S., *Jap. Med. J.* **1908**: 116, 1960.
- 22) Tomomatu, T., Tanemoto, K., Ninomiya, H., Ino, T. and Inoue, Y., *Respiration and Circulation.* **6**: 613, 1958.
- 23) Ino, T., *Jap. Circul. J.* **24**: 1297, 1960.
- 24) Euler, U. S. von., *Acta Physiol Scandinav.* **33**: Suppl. 118, 57, 1955.
- 25) Green, M. D., *Ann. Int. Med.* **39**: 333, 1953.
- 26) Howard, G. and Hanly, *Lancet* **1856**: 199, 1955.
- 27) Bowers, R. F., *J. A. M. A.* **154**: 394, 1954.
- 28) Chwalla, R., *Endocrinology.* **29**: 129, 1952.
- 29) Locke, W., Talbot, N. B., Jones, H. S. and Worcester, J., *J. Clin. Invest.* **30**: 325, 1951.