STUDIES ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM: STUDIES ON HISTOLOGICAL CHANGES IN ADRENAL AND RENAL TISSUE; A FOLLOW-UP STUDY OF POSTOPERATIVE BLOOD PRESSURE IN PRIMARY AND IDIOPATHIC ALDOSTERONISM

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Adrenalectomy was performed on 20 cases diagnosed as primary aldosteronism on account of their complete conformity to Conn's new criteria and the results of clinical and biochemical examinations. Further, renal biopsy was performed on 15 of them. A single adrenocortical adenoma was found by gross observation in 12 out of the 20 cases (60%). Bilateral adrenocortical hyperplasia was found by pathohistological examination in 7 cases (35%) and in the remaining 1 case (5%) the adrenal cortex had almost normal appearance. Of the 12 macroscopical adenoma cases, by particular observation, 5 had an almost completely capsulated adenoma; abnormal findings of the renal tissue were not detected in these cases and the postoperative blood pressure recovered completely normal level. As to the other cases that had appeared as an adenoma to the naked eye, it was pathohistological, revealed that adenoma-like mass was continuous to the proper cortex to the adrenal and that hyperplasia was also present in the contralateral adrenal cortex, so these cases were regarded as adenomatous hyperplasia. The postoperative blood pressure was not restored to the normal level except in 3 of them, and sclerotic changes were markedly present in the afferent arteries of the kidney.

Of the hyperplasia cases, 4 were found to have micronodular hyperplasia with marked sclerotic changes in the interlobular artery of the kidney, and normal blood pressure was not recovered in these cases except one. The remaining 3 were cases of diffuse hyperplasia; in 2 of them the renal arteries were almost normal and blood pressure was restored to the normal level. Pathohistological findings of the adenoma, adenomatous hyperplasia, and hyperplasia suggest the possibility of transition from hyperplasia to adenoma.

It is conceivable that the changes in the renal tissue have a significant influence over the postoperative clinical improvement and normalization of blood pressure, and a part of differential diagnosis between primary aldosteronism and idiopathic aldosteronism.

Key Words: Aldosterone Renin Hypertension Primary Aldosteronism	Idiopathic Aldosteronism Adrenocortical Adenoma Adenomatous Hyperplasia Postoperative Blood Pressure
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MANY factors responsible for hypertension development and maintenance have not been entirely clear to us yet, though there have been a great many achievements on the factors of hypertension; e.g., hereditary diathesis and endocrinic, nervous, humoral, and vascular factors, etc. Since the first description of primary aldosteronism (P.A.) by Conn¹ was reported in 1955, this entity has drawn attention as a curable form of hypertensive diseases, followed by subsequent reports on its essential etiology and on numerous clinical cases in an effort to discover an approach to this clinical problem.

Davis *et al.*² and Laragh *et al.*³ proved that renin-angiotensin-system (R-A) is an aldosterone stimulating hormone, and that a feed-back mechanism was supposed to exist between R-A and aldosterone. According to the fact that aldosterone overproduction, recognized as the etiology of P.A., suppresses renin release from the kidney by the negative feed back of the R-A-aldosterone system, in 1964 Conn⁴ proposed the so-called renin test, which, as a result, enabled us to diagnose more easily many of atypical and asymptomatic case of P.A. which so far have been regarded as essential hypertension.

Among the cases diagnosed as P.A. on bases of their conformity to Conn's new criteria⁵ however, there are an increased number of idiopathic aldosteronins (I.A.)⁶⁻⁹ cases without any pathohistological evidence of adenoma. These cases present certain problems in relation to treatment of high blood pressure and other problems. Within the category of P.A. itself, there are included a considerable number of cases in which postoperative blood pressure never recovers the normal level. These facts indicate how complex it is to elucidate the mechanism of hypertension maintenance.

The following paper is a report on the comparative studies of the preoperative and postoperative clinical findings between P.A. and I.A. and on the microscopical observation of the difference in the adrenal and the kidney tissues between P.A. and I.A. from the view point of the function and structure.

MATERIALS AND METHODS

1. Materials

This report contains detailed studies of 20 hypertensive patients diagnosed as P.A. from the clinical and biochemical findings who underwent adrenalectomy from 1961 to 1970. (Seventeen of them were examined and operated upon in the

Nihon University Hospital, and the remaining 3 in another hospital.) Their ages ranged from 13 to 55. Seven patients were males, while 13 were females. The postoperative follow-up studies were continued from 1 to 11 years, and measurements of blood pressure, plasma renin activity and urinary aldosterone excretion and kidney function test were performed, with the patient hospitalized as a rule.

The standard procedures were as follows: The patients were not given any drugs for a week proceeding the measurements, and during this period they were on a constant diet of known electrolyte content (120 to 140 mEq of sodium daily). The time to measure blood pressure was 9 a.m. when the patients were at rest. The blood samples for the plasma renin activity determination were obtained both on a constant diet and after the patients had been on a special low-salt diet, in which sodium was kept as low as 30 to 40 mEq per day, for 4 days and had walked for two hours.

Urine samples for the aldosterone excretion measurement were obtained for 24 hours after at least one week on the constant diet and on the day before the post low sodium diet and up & about plasma renin activity determination. In female cases, their measurement was performed on urine in the follicular phase a week after the completion of the menses.

2. Methods

1. Plasma Renin Activity Determination

Five to 10 ml of 3.8% solution of ammonium salt of EDTA (pH 6.5) was put in a 100 ml polyethylene container, which was immersed in crushed ice. Peripheral venous blood was taken from the elbow vein through a polyethylene tube (internal diameter: 2 mm; length 50 cm) and dripped into the container. Twenty to 40 ml of blood was obtained. The blood was taken in supine posture when the patient was recumbent and in upright or sitting posture after he was up and about. Immediately after rapid refrigeration of the sample, serum was separated by centrifuge for 10 minutes at 3,000 r.p.m. at 0-5°C. The measurement method was almost the same of a new one by Boucher *et al.*^{10,11} (Fig.1). A special column for refrigeration was used for column chromatography. The rotary evaporator made by Shibata Co. Ltd. was used for evaporation and sublimation. The animals used for bioassay were male wistar rats, weighing approximately 200 g.

Pentobarbital sodium was injected into the

Fig.1. New procedure for measurement of human plasma renin activity.
(By R. Boucher et al.¹¹ 1966)

abdominal cavity at a close level of 5 mg per 100 g of body weight to achieve intraperitoneal anesthesia, and 0.5 mg of pentolinium tartrate and 0.05 mg of atropine sulfate for each 100 g of body weight were injected into the abdominal cavity as premedication.

After the animal was sufficiently anesthetized, a mid-line incision was made in the cervix, and then tracheotomy was performed. After a vinyl tube (internal diameter 1 mm; length 3 cm) was inserted, bilateral vagotomy was performed. A polyethylene cannula was inserted in the unilateral carotid. While recording the carotid blood pressure measured directly by U type mercury Sphygmomanometer on the kymograph, the sample was introduced from the cannula which had been inserted in the right femoral vein in the same way as in the carotid. Synthetic angiotensin II (Ciba) was used as a control.

The plasma renin activity was converted into nanograms of Angiotensin II per 100 ml of plasma.

Rats with inconstant basal blood pressure, and with blunt sensibility to and low recovery from angiotensin, were not used for the experiment. Tap water and M. F. produced by Oriental Yeast Co. Ltd. were used in order to feed the rats.

II. Urinary Aldosterone Excretion Measurement

Urine was collected in the dark and cold room during 24 hours. Five hundred milliliter out of the collected urine was used. The measurement method was Suzuki's¹² and Taniguchi's¹³ of our laboratory which utilizes thin layer chromatography and blue tetrazolium coloration because its convenience and handiness, instead of double isotope derivative dilution method (Fig.2).

III. Adrenal and Renal Tissues

When an adenoma was grossly found in the adrenal tissue, one of the adrenal glands containing the adenoma was totally extirpated. Exploratory partial resection was performed on the opposite adrenal gland. Immediately after the diameter of extirpated adenoma was measured

Fig.2. Procedure for measurement of urinary aldosterone excretion.
(By H. Suzuki¹² & A. Taniguchi¹³)

and photographed, it was fixed in 10% formalin solution. If no adenoma was found by careful gross examination and palpation at the time of the operation, both the adrenal glands were exposed, the left adrenal was totally extirpated and sliced immediately to confirm the macroscopical absence of an adenoma, and a half of the right adrenal gland was excised for exploratory purposes, which was studied histologically. Renal tissue was observed on 15 cases out of 20: an open biopsy was performed during the operation on 11 cases, and a needle biopsy 4 cases before the operation. Immediately after the biopsy, those tissue samples were fixed in 10% formalin solution and subjected to HE, PAS, EV Stains.

IV. Pathohistological Classification between Adenoma and Hyperplasia

When a single cortical adenoma with a cut surface of comparatively golden yellow appearance was carefully examined with the microscopical histology, it was in most cases incompletely encapsulated and a small part of it was directly attached to the proper cortical tissue. So the differentiation between adenoma and adenomatous hyperplasia was made to depend on the degree of capsulation around the adenoma, the conditions of the fibroid connective tissue existed in the adenoma tissue, the kind of cells composing the adenoma, and the degree of transition from the adenoma to the proper adrenal cortex.

When no adenoma was found in the adreno-

Fig.3. Adenoma group: Well capsulated, mature adenoma is shown above; completely uncapsulated adenomatous hyperplasia below and to the right; proper adrenal cortex below and to the left. (Case 17 C. H., H.E. x25)

TABLE I PATHOLOGICAL FINDINGS OF THE MICRONODULAR AND ADENOMATOUS HYPERPLASIA

	Subject				Constituent cells		Reaction of connective tissue
	Patient	age	sex				
Micronodular	5 S. S.	37	F	(B)	C		+
	6 C. K.	33	F	(R) (L)	C, E + T C, H		+
	7 H. N.	51	F	(B)	C, G + H		+
	8 N. K.	23	M	(R) (L)	G + H C + H		++
Adenomatous	9 R. M.	49	F		C, T + E		+
	10 M. T.	36	F		C, H		±
	11 F. T.	55	F		C, T + E		++
	12 J. K.	21	F		C, T + E		+
	13 T. S.	51	F		C, H		++
	14 T. S.	28	M		C, T + E		+
	15 H. M.	40	M		C, H		++

Constituent cells

C: clear cell type, E: compact cell type, G: zona glomerulosa cell type, H: hybrid cell type, T: transitional type (clear cell, compact cell)

Reaction of connective tissue

slight = ±: moderate = +: severe = ++

R = right adrenal L = left adrenal B = bilateral

Fig.4. Adenomatous group: An adenomatous lesion (above) is not encapsulated in this field and have a connection with proper adrenal cortex (below).
(Case 13 T. S., H.E. $\times 63$)

TABLE II PATHOHISTOLOGICAL FINDINGS OF ADENOMA

	Subject				Constituent cells of adenoma	Connective tissue	Changes of adjacent adrenal cortex
	Patient	age	sex				
Adenoma	16	T. S.	27	F	Almost clear cells	Capsule with lobular formation (almost)	Diffuse hyperplasia of zona glomerulosa
	17	C. H.	27	F	Almost clear cells Partially compact cells	Capsule (completely)	Adenomatous hyperplasia
	18	K. K.	33	F	Almost clear cells	Capsule with lobular formation (almost)	Micronodular hyper- plasia in zona glomerulosa
	19	M. T.	41	F	Almost clear cells	Capsule (almost)	Diffuse hyperplasia of zona glomerulosa
	20	M. K.	38	M	Almost clear cells Partially compact cells	Capsule (almost)	Micronodular hyper- plasia in zona glomerulosa

cortex and continuous or somewhat discontinuous hypertrophy of the zona glomerulosa was microscopically found, the case was diagnosed as diffuse hyperplasia. The hyperplasia which was microscopically localized and exclusive to the surrounding cells, and appear nodular without

heteromorphic cells was diagnosed as micronodular hyperplasia. The foregoing may be arranged into such classification as follows:

1) **Adenoma**

a) adenoma

Heteromorphism is seen in the cells. No tran-

sition is found between the adenoma lesion and the proper cortex. Almost all of its circumference is covered with a fibroid capsule (Fig.3, Table I).

b) adenomatous hyperplasia

It is apparently adenoma-like to the naked eye, and a certain extent of transitional site is found between the adenoma and the adjacent proper cortex. The majority of the constituent cells are clear almost similar to those in the adenoma (Fig.4, Table II).

2) Hyperplasia

c) micronodular hyperplasia

No remarkable change is found in the form of the adrenal with the naked eye except the circumscribed hyperplasia from the histological viewpoint. Its constituent cells are dilated and knotted pushing the surrounding cells aside. In many cases no capsule is formed around the nodule, though some incomplete capsule is found only in a few cases. No heteromorphism of cells is in the cells (Fig.5, Table I).

d) diffuse hyperplasia

It is a hypertrophy of even thickness of the zona glomerulosa of the adenocortex including somewhat discontinuous cases (Fig.6).

V. Measurement Methods of Renal Blood Vessels

Comparatively circular blood vessels were chosen for the measurement, transacted under a microscope with an ocular micrometer attached to the ocular lens, and measured for the major and minor axes across the tunica adventitia and those across the tunica intima. The actual procedure for the measurement is as follows: Suppose A by the major axis for the adventitia, A' that for the intima, B the minor axis for the adventitia and B' that for the intima. Then divide A' by A and multiply the quotient by 100. Divide B' by B and multiply by 100. Divide the sum of the two totals by 2 in order to get the average percentage of the inside diameter to the outside diameter. The formula is as follows:

$$\frac{(\frac{A'}{A} \times 100) + (\frac{B'}{B} \times 100)}{2} = \%$$

The vessels with a diameter of 10–80 μ were regarded as the afferent arterioles, while those with a diameter of more than 100 μ were regarded as the interlobular arteries. But the distinction between the two was not always possible, so for

convenience' sake, it was decided that the afferent arterioles were to have a diameter of 40–60 μ and the interlobular arteries a diameter of 140–160 μ . More than 10 vessels were chosen among them to be measured and averaged.

RESULTS

1. Clinical Features

Between 1960 and 1970, 20 patients who satisfied the clinical and biochemical criteria of P.A. underwent adrenalectomy. Twenty patients were macroscopically found to have a single adrenal cortical adenoma, 7 others bilateral adrenal hyperplasia, and the remaining one almost normal adrenal cortex.

The clinical features of the patients are listed in Table III. The mean age of these 20 patients was 33.7 years, consisted of 13 females and 7 males. The mean age of these 12 patients with **Adenoma** was 37.2 years and 9 females and 3 males were included. The mean age of those 8 patients with **Hyperplasia** was 28.3 years and 4 females and 4 males were involved. The mean duration of hypertension obtainable in most cases from the clinical history was 5.1 years (4.9 years for **Adenoma** group and 5.3 years for **Hyperplasia** group). Six patients had a positive family history of hypertension (3 cases of **Adenoma** group and 3 cases of **Hyperplasia** group).

The mean arterial blood pressure was 184.1/110.4 mmHg (194.2/114.3 for **Adenoma** group and 169/104.5 for **Hyperplasia** group).

The mean serum K content was 3.07 mEq/L, and 7 patients were normokalemic (2/12 of **Adenoma** group and 5/8 of **Hyperplasia** group). The mean aldosterone excretion was 28.65 μ g/24 hours (27.3 for **Adenoma** group and 30.5 for **Hyperplasia** group).

The mean plasma renin activity was 113.8 ng% at recumbency and 185.2 ng% when up and about plus low sodium intake (**Adenoma** group: recumbent 116.7 ng%, when up 168.5 ng%; **Hyperplasia** group, recumbent 110.1 ng%, 206.0 ng% when up). The **Adenoma** was located on the left side in 11 cases and on the right side in one case. Their sizes ranged from 0.4 $\times$ 0.5 $\times$ 0.3 cm to 2.1 $\times$ 1.8 $\times$ 0.8 cm.

It was impossible to distinguish **Adenoma** from **Hyperplasia** by those clinical features.

2. Pathohistological Findings of the Adrenals

In 12 out of 20 cases, there was a single adenoma grossly recognizable (0.4 $\times$ 0.5 $\times$ 0.3 cm–2.1 $\times$ 1.8 $\times$ 0.8 cm) which was carefully examin-

Fig.5. Micronodular group: A microscopic micronodular hyperplastic lesion is found across the zona glomerulosa and zona fasciculata. Its constituent cells are dilated and knotted pushing the surrounding cells aside. No capsule is found around the nodule. (Case 7 H.N., H.E. $\times 63$)

Fig.6. Diffuse hyperplasia group: A microscopic hyperplasia of zona glomerulosa, a homogeneous thickening of the zone and wedge-typed invasion into zona fasciculata in some places. (Case 4 H.A., H.E. $\times 160$)

TABLE III CLINICAL FEATURES OF PATIENTS WITH PRIMARY OR IDIOPATHIC ALDOSTERONISM

Subject		Blood pressure (Preop.)			Plasma		urinary		P. R. A.		Adrenal	
Patient	age	sex	family history	max/min	duration	Na	K	hypo K duration	recumb. up-right	side	size	
1	M.H.	24	M	+	166/96	2.5<	136	4.0	26.8	133	177	B
2	T.W.	13	F	+	160/110	0.5<	143	2.4	29.6	93	152	B
3	N.K.	28	M	-	160/106	10	142	3.7	41.0	75	290	B
4	H.A.	18	M	-	161/96	2	141	4.1	22.4	144	257	B
5	S.S.	37	F	-	175/104	17	140	3.6	28.9	118	280	B
6	C.K.	33	F	-	170/108	6	143	2.3	38.0	107	213	B
7	H.N.	51	F	-	210/126	1.5	135	3.2	32.0	<50	50	B
8	N.K.	23	M	-	150/90	3	142	4.0	25.1	161	229	B
9	R.M.	49	F	+	205/102	2<	143	2.4	33.0	115	203	L
10	M.T.	36	F	-	174/116	4<	141	2.6	27.7	73	182	L
11	F.T.	55	F	-	168/106	3	143	2.4	21.3	189	229	L
12	J.K.	21	F	-	219/128	3.5<	144	2.2	39.0	140	218	L
13	T.S.	51	F	-	200/120	13	143	3.0	—	180	209	L
14	T.S.	28	M	-	173/108	17	138	3.2	21.8	151	174	L
15	H.M.	40	M	-	195/123	4<	141	3.2	29.9	75	99	R
16	T.S.	27	F	-	181/114	2<	144	2.9	17.5	—	—	L
17	C.H.	27	F	+	190/110	2	142	3.5	24.2	80	151	L
18	K.K.	33	F	-	210/120	5<	144	2.0	36.3	114	170	L
19	M.T.	41	F	+	200/110	2<	134	3.7	20.0	<50	50	L
20	M.K.	38	M	+	215/115	2<	145	3.1	30.0	—	—	L

Normal values: urinary aldo. 5-16 µg/day. Up-right P.R.A. > 300 ng%

ed. According to the classification already mentioned in Methods, 5 cases out of 12 were with adenoma and 7 cases had an adenoma-like mass. Four out of 8 cases without an adenoma were cases of micronodular hyperplasia; the remaining 3 were cases of diffuse hyperplasia, and only one case showed almost normal cortical tissue. However in the latter, the *Golgi's* apparatus was very frequently observed in the cells of the zona glomerulosa through an electron microscope.

A completely encapsulated adenoma was found in only one among all the **Adenoma** cases, while in 11 of the 12 macroscopically **Adenoma** cases, a capsule covered most part of the adenoma and adenoma-like mass. When the capsule was carefully studied, it was attached, though only partly, to the cortical tissue.

Hyperplasia of varied degrees was noted in the zona glomerulosa adjacent to the adenoma and in the one of the contralateral adrenal cortex, which had been exploratorily obtained at the time of the operation, in 11 out of 12 cases.

3. Pathohistological Changes in the Renal Tissue

Pathological observations were made on renal tissue samples from 15 out of 20 cases, of which, 11 had been obtained by an open biopsy during the operation and 4 by a needle biopsy before the operation. In most cases the preoperative renal function was normal except some cases which sclerotic changes in the vessels were pronounced and the cortical function was somewhat depressed. In many of the cases with hypokalemia, medullary hypofunction was observed.

i) Diffuse Hyperplasia Group

It was found with this group that those cases which the postoperative blood pressure was never recovered had remarkable histopathological changes in the renal tissue, and that especially sclerotic changes were very severe in the afferent arterioles. In two cases (3 N.K, 4 H.A) with normal postoperative blood pressure, the renal tissue showed an almost normal pathohistological picture (Fig.7).

ii) Micronodular Hyperplasia Group

In this group more remarkable were the sclerotic changes from hyperplasia in the media of the vessels regarded as interlobular arteries rather than the histopathological changes in the afferent arteriolae (Fig.8).

In one case (5 S.S.) the postoperative plasma renin activity (postop. 6 M) rose to a high level.

iii) Adenomatous Hyperplasia Group

This group was characterized by the patho-

histological changes in the renal tissue of those cases in which postoperative blood pressure, especially that in the diastolic phase, was not normalized. That is the sclerotic changes of the afferent arterioles were more severe than in cases of micronodular hyperplasia. The interstitial tissue around the vessels were conspicuously deteriorated and the glomerulus, dominated by the severely sclerotic vessels, showed fibrotic and hyalinoid changes. The histological changes in the interstitial tissue were the severest among those groups (Fig.9).

iv) Adenoma Group

Pathohistological changes were hardly seen in either the renal vessels, and only a little hyalinoid changes in the glomeruli and cell infiltrations in the interstitial tissue were present (Fig.10).

Blood pressure had been recovered in all the cases in 6 months after the operation.

A comparative study was made on the relationship between the pathohistological changes in the renal vessels and the mean pre- and post-operative blood pressures (6 months post-operatively), Table IV. That is, dividing the renal vessels into two categories, those corresponding to the afferent arterioles and those corresponding to the interlobular arteries, the severity of the sclerotic changes in these vessels were related to the changes in the mean blood pressure as compared before and (6 months) after the operation (Fig.11).

In the diffuse hyperplasia group, the vascular changes were comparatively slight, and the improvement of blood pressure had been attained. In the micronodular group, there were many cases in which the changes in the interlobular artery were severe with no normalization of blood pressure. In the adenomatous hyperplasia group, there were many cases in which the sclerotic changes were severe in the afferent arterioles without normalization blood pressure. Postoperative recovery of blood pressure occurred only in the cases with a slight vascular changes. In the adenoma group, the pathohistological changes in the vessels were slight and all the cases became almost normotensive after the operation.

This had occurred regardless of the hypertension duration, the age of the patient, or the size of the adenoma.

4. Follow-up Study

Blood pressure was consecutively studied over about 1 to 10 years in the 15 cases from which

Fig.7. Renal biopsy in patient divided as diffuse hyperplasia group, renal vessel have a little thickness of media of small artery. Glomerulus and interstitial tissue shows no change. (Case 3, N, K., H.E. $\times 160$)

Fig.8. Renal biopsy in patient divided as micronodular hyperplasia group, the sclerotic changes from fibrosis in the media of small arteries were remarkable regarded as interlobular arteries rather than the changes in the afferent arterioles. (Case 5 S.S., P.A.S. $\times 160$)

TABLE IV RELATIONSHIPS AMONG RENAL HEMODYNAMICS, RENAL HISTOLOGICAL ALDOSTERONE EXCRETION RATE

		Subject		Renal function [Preop.]			Renal histol-		
							Blood vessel changes		Glomerular
		Patient	R.P.F.	G.F.R.	Fishberg's concentration test	Afferent arteriole	Inter- lobular artery	Thickness of base- ment membrane	
HYPERPLASIA	diffuse	2	T. W.	340	104	1016	+++	+	±
		3	N. K.	530	120	1030	+	+	—
		4	H. A.	526	126	1032	+	+	—
	micronodular	5	S. S.	390	84	1032	+	++	—
		6	C. K.	418	93	1011	++	++	±
		7	H. N.	340	60	1018	++	+++	±
	ADENOMA	adenomatous	9	R. M.	400	82	1022	+	±
12			J. K.	361	81	1021	+++	+	+
13			T. S.	400	77	1020	+++	++	+
14			T. S.	357	87	1023	+++	++	+
15			H. M.	575	104	1026	++	+	±
adenoma		16	T. S.	645	69	1020	+	+	+
		17	C. H.	530	81	1021	—	±	—
		19	M. T.	430	86	1020	+	—	—
		20	M. K.	313	89	1024	+	±	+
						cc/min	cc/min		

renal tissue had been obtained at the time of the operation. In all the cases the postoperative renal function was either unchanged or rather improved from the preoperative level. It is a pity that most of the cases were not under observation for a sufficient longtime, but it appears that if the operation should bring about a recovery from hypertension, it takes place a short time after the operation (Fig.12). In the hyperplasia group, when the changes in the vessels were slight there was an improvement or normalization of blood pressure, whereas in the adenoma cases with only

slight pathohistological vascular changes, complete recovery from hypertension was possible.

DISCUSSION

Since Conn¹ first reported on a case of primary aldosteronism in 1955, a considerable amount of researches have been reported in relation to the clinical features and pathohistology of this clinical entity. In this country, too, more than 200 cases have been reported, contributing to expansion of the range of curable hypertension.

FINDINGS AND POSTOPERATIVE BLOOD PRESSURE, P.R.A. AND URINARY

logical findings				Post operation 6 months			
changes	Interstitial tissue changes		Tubular changes	Clinical features			
Hyalini- zation	fibrosis	Cellar infiltra- tion	dilatation	B.P. max/min	serum K	urinary Aldo.	P.R.A. up-right
±	±	+	+	154/ 98	2.8	18.4	103
—	—	—	—	160/100	4.0	12.3	540
—	—	—	—	150/ 90	4.2	12.4	885
—	—	—	—	150/110	3.8	14.8	2500
±	+	+	+	152/100	3.0	21.0	201
±	+	+	—	180/100	4.1	12.4	800
++	+	++	+	120/ 80	4.3	8.4	731
+	++	++	+	166/114	4.8	6.9	577
+	+	+	+	164/104	4.2	15.0	450
++	++	++	+	140/104	4.5	5.4	432
±	+	+	+	150/100	4.0	14.6	556
±	±	±	+	118/ 80	4.3	5.2	—
—	±	±	±	124/ 78	4.2	9.6	864
±	±	±	±	134/ 74	4.0	7.0	530
+	+	+	+	120/ 80	4.1	8.8	—
				mmHg	mEq/L	μg/day	ng%

But recently the existence of idiopathic aldosteronism⁶⁻⁹ which is not accompanied by an adenoma though it completely satisfies Conn's⁵ new criteria of 1965, has been brought to attention. There has been some work concerned with the interrelationship between P.A. and I.A.¹⁴⁻¹⁷

On the other hand, recent follow-up studies conducted over a decade have confirmed that a significant percentage of P.A. cases which used to be regarded as a curable hypertension, do not recover the normal level of blood pressure after adrenalectomy, though varied in percentage from

worker to worker.^{14,15,18}

Among the minimum prerequisites to justify the diagnosis of P.A. and I.A.

(1) suppression of renin activity following low sodium and ambulation.

(2) over production of aldosterone and
(3) normal values for 17 OHCS, 17 KS.

The plasma renin activity (PRA) holds a significant position. The PRA suppression in aldosterone overproduction is achieved through water and electrolytes, presumably through the negative feedback mechanism of the R-A-aldosterone sys-

Fig.9. Adenomatous hyperplasia group: The pathological changes in the renal tissue were more remarkable, the sclerotic changes of the afferent arterioles were severer than the other groups. The glomerulus is hyalinized, and round cell infiltrations were increased in the interstitial tissue. (Case 14 T. S., H.E. $\times 160$)

Fig.10. Adenoma group: Pathological changes were hardly seen in the renal vessels, and only a little hyalinoid change and cell infiltrations were present. (Case 17 C. H., P.A.S. $\times 160$)

Fig.11. Grades on the changes in interlobular, afferent artery and lowering of blood pressure following operation in various adrenal changes. (postoperation 6 months)

Fig.12. Grades of the changes in renal vessel and lowering of blood pressure following in various adrenal changes. (until one-11 years postoperation)

tem. The relation between renin and aldosterone is affected not only in P.A., but in some other diseases. However the control mechanism of renin secretion should be first elucidated in order to discuss the pathogenesis from the changes in the R-A-aldosterone.

It has been well established that renin is secreted from J.G.C. of the kidney, but controversy has continued as to the mechanism for the secretion control—e.g., some suspect the presence of the baroreceptor mechanism,^{19,20} as represented by the stretch-theory, others suggest the action of the chemoreceptor system, as represented by the maculadensa theory,^{21–24} and still others insist on the participation of the renal sympathetic nerve system.^{25–29} Yet none of these theories can give a definite and clear-cut explanation for the mechanism of the renin secretion and its control.

It has been well accepted that abnormal increases of renin and aldosterone occur in the R-A-aldo. system affected by renovascular or malignant hypertension and *Bartter's* syndrome. Such an increase of PRA also noted in secondary aldosteronism—e.g., heart failure, nephrotic syndrome, cirrhosis of the liver, etc. On the contrary, abnormal decreases of PRA are observed chiefly in such diseases originating from the adrenal as represented by P.A. and I.A. Thus, the renin test is quite useful in differential diagnosis of hypertension diseases.

Among the clinical entities diagnosed as essential hypertension, what presents serious clinical problems is normokalemic P.A. (N.P.A.). In spite of the contradictions by *Kaplan et al.*³⁰ and *Laragh et al.*³¹ *Conn*³² demonstrated N.P.A. cases in 7.4% of 230 hypertensive patients screened out on the basis of P.A. with adrenocortical adenoma, with the P.R.A. suppression as the primary criterion.

In this country there have been only 5 cases of N.P.A. reported and as in case (18 K.K.)³³ in our series, the manifestations of N.P.A. might be regarded as the early stage of P.A. Yet N.P.A. is an established entity for which a method of screening should be developed through future efforts.

In relation to the renin suppression, hyporeninemia has drawn attention in recent years. *Creditor*³⁴ et al. performed the renin test on 30 cases of essential hypertension and *Weinberger et al.*³⁵ and *Fishman et al.*³⁶ reported on the cases of suppressed P.R.A. in which secretion of aldosterone was either normal or lowered. *Creditor*

suggests that hyporeninemia is brought about by over production of a substance with an aldosterone-like action, and a similar view was put forth by *Fishman*.

From the author's investigation, 26 cases (31%) of hyporeninemia with normal aldosterone secretion were demonstrated out of 84 cases of essential hypertension, and it was also noted that the incidence of hyporeninemia tends to rise as the age advances.

The pathogenesis of this hyporeninemia has not yet been clarified, though it can be assumed that it involves the participation of some unidentified mineralocorticoids other than aldosterone, excess intake of sodium, hereditary and environmental factor as well as enhanced aldosterone secretion in a certain group, etc.

While the P.R.A. suppression is said to be noted in 12 to 53% (mean 28%) of benign hypertensive cases,³⁷ *Liddle*³⁸ talked that in hypertensive patients with suppressed renin, blood pressure and P.R.A. were restored to normal by administration of spironolactone at a dose level of 400 mg/day for 6 consecutive weeks and there after satisfactorily maintained on 100 mg/day. This fact is quite interesting in that it gives due to elucidate the relationship between P.A. and I.A.

The disease which cannot be differentiated by the measurement of renin and aldosterone are a group of adrenopathies due to congenital enzyme defects. They are differentiable from the improvement brought about by dexamethasone administration. They are rare diseases, but the differentiation should be made always prior to the operation.

Among the syndromes satisfying *Conn's* new criteria, P.A. and I.A. are the most difficult ones to be diagnosed. Various tests have been contrived to differentiate the two—e.g., determinations of the submaxillary saliva potassium concentration,³⁹ severity of hypertension, amount of aldosterone secretion, serum potassium concentration, and degree of P.R.A. suppression,^{17,40} but none of them is regarded as a satisfactory method of differentiation.

A comparative study was attempted by the authors about the changes in P.R.A. and urinary aldosterone having resulted from administration of thiazide or spironolactone on each 2 of **Adenoma** and **Hyperplasia** cases, as classified according to the criteria stated in the [Method], while the patients were on a sodium deficient diet. It was found that urinary aldosterone was higher in

the **Adenoma** cases and the P.R.A. suppression appeared to have occurred more markedly than in the **Hyperplasia** cases, but the difference was not significant. It was revealed that, when the sodium restriction was continued on the **Adenoma** cases just as the serum potassium concentration was brought to normal by the spironolactone administration, there resulted a normal response of P.R.A. This fact suggests a possibility that too strict conditions for sodium restriction (sodium deficient diet + diuretics) at the time of the renin test may lead to overlook P.A. To avoid this and serve as the sound basis of diagnosis, the renin test should be conducted not once but repeatedly.

The mechanism for the aldosterone production in P.A. and I.A. is a controversial problem, as *Wolff et al.*⁴¹ suggested, but if practically little difference can be demonstrated by the present tests available, the differentiation between P.A. and I.A. is impossible for the present.

A great deal of works^{16,42-44} has been already reported as the pathohistological findings of the surgically extracted adrenal glands. From our detailed study on the **Adenoma** cases and **Hyperplasia** cases in the present series, a clear distinction between the two appeared not always possible. Of 12 cases that showed the macroscopic appearance of **Adenoma**, too, careful pathohistological observation revealed only one case (17 C.H.) in which the adenoma was completely separated from the proper cortex with a capsule of connective tissue and a venous sinus. In the other 11 cases the adenoma had various grades of continuity to the adrenocortex. No relation was demonstrated between the size of the adenoma and the degree of capsulation. Hyperplasia of zona glomerulosa was noted in the cortex excluding the adenoma in all the cases but one (9 R.M. case), and the samples exploratorily obtained from the contralateral adrenocortex at the time of adrenalectomy also showed hyperplasia, though varied in degree, in the zona glomerulosa in all the cases except one (19 M.T. case).

In the 7 cases without adenoma (35%) was noted the presence of the bilateral hyperplasia as had been cited in the [Method]. The presence of hyperplasia suggests that there had been a secretion stimulus from outside the adrenal. The co-existence of hyperplasia and adenoma may be interpreted as meaning there had occurred a gradual transition from one to the other, and the pattern inferred may be: micronodular hyperplasia → adenomatous hyperplasia → adenoma.

However, it is not clear in this series where the first stimulus which causes bilateral hyperplasia occurs from.

Although the proposition by *Newton et al.*⁴⁵ to classify P.A. between the true primary adenoma not suppressed by corticosteroid and the adenoma arising in a previously hyperplastic adrenal gland or glands is interesting in itself, such classification was not applicable to the present series.

The development of hyperplasia has been understood as essentially the result of a secondary stimulation^{6,8,46} but the responsible stimulant remains controversial. *Laragh et al.*¹⁵ reported a high incidence of previous pyelonephritis in hyperplasia cases and suspected the renin overproduction at some period as the cause of the hyperplasia. However, none of our cases had a history of pyelonephritis, but there were noted characteristic changes in the renal vessels, and the glomerulus, interstitial tissue, renal tubulus dominated by the severely sclerotic vessels.

The so-called malignant hypertension develops and grows aggravated through the vicious cycle of a combination of the refractory mechanism—renal disturbances → renin release → angiotensin → aldosterone overproduction—and the co-existent vasculitis, whereas in P.A., P.R.A. is usually low and the vascular impairment generally slight. From the study of the present series, it was found that the kidney function was fairly well preserved in all the cases and that there was a correlation between the changes in the renal tissue and the degree of postoperative improvement of the clinical conditions, particularly of blood pressure. That is, the postoperative blood pressure in the cases diagnosed as P.A. was dependent on the degree of renal vessel morbidity, and the more sclerotic the changes, the more difficult the improvement or normalization of blood pressure. The renal lesion showed little changes in the intima and sporadic changes in the glomerulus and interstitial tissue, and this fact suggested not preceding vasculitis or infection but rather arterial sclerosis.

In the **Adenoma** cases, vascular changes were remarkable in vessels with a diameter equivalent to the afferent arteries, and in the **Hyperplasia** cases, they were prominent in vessels the diameter of the interlobular arteries. From the postoperative examination, the kidney function was found either unchanged or improved as compared with the preoperative results. The high postoperative P.R.A. in those cases with unimproved

blood pressure and severe renal vessel changes indicates the participation of renin as one of the causes for the unimproved blood pressure. On the other hand, there are possibilities that the hyperplasia in the remaining adrenal may have a hand in preservation of hypertension and that microadenomas may have arisen again from the hyperplasia.

These problems will be also elucidated as the pathogenesis and interrelation of P.A. and I.A. are brought to light by future investigations.

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