

SOME REMAINING PROBLEMS OF ALDOSTERONISM
FROM PERSONAL CASE

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I. PREFACE

Simpson and Tait (1952)¹⁾ extracted aldosterone from an excised adrenal and determined on its chemical formula. Not long after then Conn (1955)^{2,3)} reported the first case of primary aldosteronism. It has been eleven years since he established the concept of hyperaldosteronism⁴⁾ In the meantime many cases of primary aldosteronism^{5~13)} and pathology of hyperaldosteronism^{14~23)} have been brought to light pathologically to a great extent.

Recently renin-angiotensin system^{24~50)} has been studied. And it has been made clear that renin-angiotensin, a hypertensive substance, that is secreted from the kidney, will induce the secretion of aldosterone in the case of renal hypertension. Speaking of hypertension, the relation between the renal hypertension and aldosterone has especially attracted so much attention.

Not only nephrosis, cirrhosis of the liver, and the edema following cardiac failure that in the first place was thought to be the primary factor of secondary aldosteronism^{51,55)}, but also potassium-losing renal diseases^{56~69)} and certain hypertension (in renal hypertension and malignant

hypertension) are of this category. Thus at present it is thought to be important to differentiate secondary aldosteronism from primary aldosteronism cases of hypertension that have analogy with Conn's syndrome.

Wrong (1957)⁶⁸⁾ diagnosed the case of a 52-year-old man as primary aldosteronism for his hypertension, hypokalemic alkalosis, and increase of aldosterone in his urine before operation, after which, quite contrary to his expectation, he could find no histological abnormality in either adrenal. Hyperaldosteronism was not of an adrenal origin. He reported his successful treatment of a case of secondary aldosteronism with the ischemic kidney. Since his report we have heard of no more than thirty cases^{70~89)} of hyperaldosteronism of the renal origin in medical literatures up to date.

We, having concluded our diagnosis of this case as secondary aldosteronism brought about by the renal tuberculosis, present the clinical findings from this examination and the inquiry into the literature concerning this disease.

II. PERSONAL CASE

Patient (T. Y.) was a 38-year-old man. Family history revealed nothing of impor-

tance. Past history showed that he was undergone an operation because of bilateral tuberculous epididymitis at the age of 31. Present illness revealed that during the past two years, he has complained of fatigue, polydipsia and headaches. Physical examination demonstrated that he was moderately well nourished man without edema. Blood pressure ranged from 160/100 mmHg and the fundoscopy showed KW I, but the otherwise was non-contributory.

Laboratory Findings :

1) Blood :

Red blood cells : 594×10^4 , white blood cells : 8200, segmented neutrophils 49%, band neutrophils 4%, monocytes 6%, eosinophils 3%, lymphocytes 38%, Hb : 15.0 g/dl, Ht : 41%. Plasma volume (RISA) 56.9 mg/kg, bleeding time: 3', coagulation time: 8', clot retraction: 43%, prothrombin time: 100%, fibrinogen: 400 mg/dl, fibrinolysis : normal.

2) Blood chemistry

Urea: 17 mg/dl, NPN: 33.8 mg/dl, creatinine : 2.1 mg/dl, sp. gravity 1.027, total protein 6.4 g/dl, A/G : 1.67, Cl 102.8 mEq/L, Na 139 mEq/L, K 3.8 mEq/L, Ca 4.9 mg/dl, Mg 2.25 mEq/L, cholesterol (total) 179.5 mg/dl, cholesterol ester 70.5%, Weltman reaction 0.3%, thymol turbidity test 2.3, Meulengracht index 5.8, bilirubin (total) 0.8, alkaline phosphatase 8.9 King-King unit, acid phosphatase 4.3 Kind-King unit, GOT 21.5, GPT 17, LDH 225.

It is noted that potassium shows a little lower value than the normal limit, while Na, Cl and Mg stay within the normal.

3) Serum protein fraction

Al : 30.0%, G1 : α_1 -5.2%, α_2 -16.1%, β 14.3%, γ 34.4%.

4) Serologic tests

ASLO : 100 units, VDRL and complement fixation, nonreactive.

5) Acid-base balance

pH 7.5, Ht 35%, Pco₂ 34mmHg, Buffer Base 48 mEq/l, CO₂ cont. 42 vol %, O₂ cont. 19.1 vol %. The blood gas percentage and the acid-base balance both stand within the normal limits.

6) Urinalysis

volume ; 950-2400 ml/day, specific gravity ; 1.008-1.020, pH : 5.6. albumin (\pm). sugar (-), urobilinogen normal, sediment : red blood cells (-), white blood cells (-), casts (-). Na : 117 mEq/day, K : 15.75 mEq/day. Urine culture : negative. Na, K percentages both stand lower than the normal limits.

7) Saliva⁸⁹⁾

	I	II	III
Cl (mEq/L)	44.1	38.3	44.9
Na (mEq/L)	66.5	76.5	76.5
K (mEq/L)	8.0	5.0	4.9
Ca (mEq/dl)	6.3	7.0	7.45

The saliva reveals K and Na rather low, and Ca just normal and Cl rather high in terms of percentage.

8) Function tests of the endocrines

BMR : +7 %, Thorn test : 67 %, regitine test : negative, urinary 17 KS, 10.4 mg/day, 17 OHCS 7.2 mg/day.

The hypophyseal depressant test (by ACTH, Metopirone⁹⁰⁾) showed the following results (Fig. 1 & 2).

Urinary catecholamine⁹¹⁾ (by laboratory of medicine faculty of Tokyo University. : Director, Prof. Yoshitoshi) A-3.4 μ g/day, NA-17.1 μ g/day, VMA-0.36 mg/day.

Urinary aldosterone⁹²⁾ (Nippon University : Director, Prof. Oshima) 20.7 μ g/day.

Response of potassium administration⁹³⁾

By means of administration of Spirono-

		<i>Before</i> Potassium Administration	<i>After</i> Potassium Administration
Urine	Na (mEq/day)	315	304.1
	K (mEq/day)	16.8	42.8
Blood	Na (mEq/L)	141	129
	K (mEq/L)	3.3	4.9

lactone⁹³⁾ (Aldactone A) serum potassium rose to 4.4 mEq/L.

9) Fundoscopy : KW I

Orthostatic hypertension negative, ECG : no abnormal findings.

EEG : borderline, EMG : normal.

Angiotensin II infusion test showed⁹⁴⁻⁹⁸⁾ 15.7 milimicro gram per kilogram per minute and the rise in BP (diastole) was 20 mmHg.

10) Renal function tests

PSP test : 15' 10%, 70' 60%. Dilution and concentration test : 945 cc at 4 hr. specific gravity 1.010-1.020, creatinine clearance : 76.6 cc/min. Howard⁹⁹⁾ test, Renogram indicated no difference between the left and the right kidney.

11) Urological examinations

Cystoscopy : no pathologic findings. Indigocarmine test : R 3'10'', L 2'55''-3'05'' IP (Fig. 3), PRP and nephrotomography (Fig. 5) found dark shadows suggesting tumor around the right adrenal border of the right renal upside margin, but the segmental aortography (Fig. 4) revealed no calcium plaque in the renovascular branches.

The above clinical findings and other tests, especially the increase of aldosterone as well as hypokalemia, hypertension, nocturia, results of roentgenological examinations all compelled us to diagnose this case as primary aldosteronism.

III. OPERATION

We attempted adrenalectomy on this patient by thoraco-lumber approach under the general hypothermal anaesthetization. We found that the right adrenal was adhered retroperitoneally (behind the liver). Its basic margin touched V. cava inferior, and V. renalis. Moreover no isolated adenomas were discovered grossly.

And as the upper pole of the right kidney was firmly adhered to the renal surface of adrenal, having a remarkably hard lobulated form, we were compelled to perform total adrenalectomy and nephrectomy.

IV. PREOPERATIVE MANAGEMENT AND ANESTHETIZATION¹⁰¹⁻¹⁰⁸⁾

In order to raise the patient's serum potassium level before the contemplated operation, Aldoctone A 300 mg, was administered for nine days and KCl (24 tablets a day) for six days, to the patient, which resulted in 5.3 mEq/L of potassium level.

Method of Anaesthesia : G. O. P. Hypothermia with blanket cooling semiclosed method.

Gas machine : Octavian- No. 1, with the vaporizer (pentec) outside the circle.

Premedication : Neblizer, Alevaire 5 ml (twice), Ional sodium 50 mg (3 times), Opystane 35 mg×2A (intramuscular injection) Atropin. sulf. 0.5 mg (intramuscular injection).

Process : The effect of the premedication was considerable, for the patient showed no particular excitement at the time of entering the operation room, with blood pressure at 152-104, pulse at 83/min., respiration at 20/min. Induction was slowly

carried out with penthrane 0.5-1.0-1.5%. N₂O 3L/min., O₂ 3L/min. on the patient under our close watch. The patient was intubated after one hour and thirty minutes. In the meantime the respiration was quite spontaneous with the pulse constant at 80/min., while the blood pressure was abated only a little. The maintenance of the condition was kept with the constant supplies of penthrane 1%, N₂O 3L/min. throughout the operation. At the end of the operation the supplies of penthrane and N₂O were cut off to keep up O₂ at 5L/min.

Cooling was started after intubation and was kept up until operation was begun, while the body temperature went down from 36°C to 33°C after one hour, when the operation was carried out. The patient was quite at ease with blood pressure at 110-80 mmHg, pulse at 65/min. and the assisted respiration.

Rewarming was done for about one hour and forty minutes and the rectal temperature was raised from 32.2°C up to 34°C, after which it returned to be 35.8°C through natural rewarming at 8 p. m. The after drop during the sustained anaesthetization was 0.8°C, and the record low at the end of operation was 32.2°C.

Operation: Cooling was discontinued at the body discontinued at the body temperature of 33.0°C, when the operation was started. Operation took two hours and thirty minutes. Adrenalectomy was carried out two hours after operation started. The patient kept a stable condition with blood pressure at 115-85 mmHg, pulse at 65-75, with assisted or spontaneous respiration.

Recovery: After operation the patient was supplied with O₂ 5L/min. and assisted respiration. We found, while observing the patient's condition, that blood pressure

dropped to 95-80 one hour after operation. With the aid of carnigen 1/2 ampoule, blood pressure stood at 120-80, and pulse at 70. At 7:35 the patient regained his perfect consciousness with blood pressure 135-95 mmHg, respiration at 30/min. and pulse at 80/min. and was extubated. Remarks during anaesthesia and operation: Blood loss 425g, blood transfusion, fresh blood 400 ml, stored blood 200 ml, 5% glucose 650 ml, Dextran 500 ml, VB, 100 mg, VC 100 mg, Tiocetan 2 ampoules, Bislase 1 ampoule. Alinamin F 50, 40 ml.

a) Comparison between the Preoperative and Postoperative Results of Tests

It was observed, as the result of the operation, that there were lowering of blood pressure, disappearance of headache and

	Preoperation	Postoperation
BP	160/100mmHg	130/60mmHg
Blood chemistry		
NPN	43.8 mg/dl	37.6 mg/dl
Na	139 mEq/L	142 mEq/L
K	3.8mEq/L	4.5 mEq/L
Cl	102.8 mEq/L	96.2mEq/L
Ca	8.6 mg/dl	9.7 mg/dl
Mg	2.25mEq/L	2.40mEq/L
pH	7.5	7.48
Urinalysis		
Volume	1600 ml	1100 ml
sp. G.	1.014	1.022
pH	5.6	5.2
Na	117 mEq/day	396 mEq/day
K	15.75mEq/day	26.6 mEq/day
Renal function		
PSP test 15'	10%	25%
70'	60%	60%
Creatinine clearance	76.58cc/min.	80.41cc/min.
Function test of the endocrine		
Urinary aldosterone	20.7 µg/day	8.6 µg/day
Urinary 17KS	10.4 mg/day	7.7 mg/day
Urinary 17OHCS	7.2 mg/day	13.6 mg/day

fatigue, diminution of the urine volume, elevation of specific gravity of urine, increases of serum potassium and magnesium, and decrease of urinary aldosterone.

b) Pathology (Fig. 6, 7, 8, 9, 10, 11)

Nephrosclerosis probably following tuberculosis and adenoid hyperplasia of right adrenal gland.

The removed kidney weighed 90 gm. and on its surface irregularly scattered deep depressed areas were recognized. In the stem of the renal artery there was no sclerotic change. Histologically in almost all glomeruli were found the fibrous thickening of mesangium, hyalinization, narrowing of the capillary lumina and fibrous thickening of Bowman's capsules, even some of which were entirely hyalinized. In the interstice the increase of the fiber was seen diffusely. The depressed parts were cicatrized, resulting in dilapidation of the parenchyma with prominent atrophy of the cortex. In most parts of the medium-sized and small arteries the sclerotic changes such as some irregular fibrous thickening and increase of the elastic fiber of the intima narrowed the vascular lumina. Some parts of the arteries showed complete obstruction. And occasionally those vessels with such a thickening of the intima seemed to be accompanied by the lesion of the media. Furthermore, in some depressed scarred areas were seen the productive tuberculous foci with partial calcification. This might be what Hans Wildbolz¹⁰⁹⁾ calls a "fibro-indurative form". In the interstice and the pelvis marked lymphocytic infiltration was noted.

As pointed above, the findings in the kidney were quite complicated. However

as for sclerotic changes and cicatrization in glomeruli and interstice, they were understood to be ischemic changes caused by arterial narrowing or obstruction. Vascular changes, with the lesions seen both in the intima and in the media, were thought to be vascular fibrosis resulted from vasculitis. Namely the kidney shows evidence of ischemic changes and productive tuberculosis. The former, we understood, caused high blood pressure. The adrenal weighed 10 gm. and the width of the whole cortex was almost normal, but in the zona glomerulosa and the outer parts of zona fasciculata adenoid hyperplasia of clear cell was recognized. And outside the fibrous capsule three miliary adenomas were formed, which were composed of the clear cells, too.

V. COMMENT

1) Definition of Secodary Aldosteronism

Conn (1956)⁴⁾ gave the name of aldosteronism to the syndrome characterized by the symptoms such as hypertension, paralysis, polyuria, tetany, hypokalemia and hypersecretion of aldosterone. He distinguished two different categories out of this syndrome. and named them primary and secondary aldosteronisms.

Primary aldosteronism is the syndrome characterized by the hypersecretion of aldosterone that is caused by adrenal cortical tumor (adenoma or hyperplasia). The symptom will be improved by removal of adrenal tumor and hyperplasia. Secondary aldosteronism is caused by hypersecretory disorder of the adrenal cortex through some irritation that comes from somewhere other than the adrenal. It usually lacks the aldosterone-secreting tumor. In some of the reported cases of

secondary aldosteronism could be recognized either nodular hyperplasia or the normal gland histologically.

Some of the causes of secondary aldosteronism include potassium losing kidney diseases that occur along with an edematous condition through nephrosis, cirrhosis of

the liver, and heart failure, certain hypertension (malignant hypertension and renovascular hypertension), and villous adenoma of the rectum⁵⁴⁾

Following is the table of hyperaldosteronism by Laragh (1964)¹¹⁰⁾ :

Primary hyperaldosteronism (adrenal in origin)	Conn's Syndrome due to adrenal adenoma
Secondary hyperaldosteronism (extra-adrenal in origin) no tumor	A. Oedematous states
	1. Cirrhosis 2. Nephrosis 3. Heart failure
	B. Hypertensive states
	1. Malignant hypertension 2. Malignant or severe hypertension due to unilateral renal disease
	C. Alkalotic (normotensive) states potassium wastage Alkalosis retarded growth * Bartter syndrome

Bartter et al. (1962)^{52-a, b, c)} differentiated their syndrome—found in three Negro cases— from Conn's syndrome. The syndrome, like the case of primary aldosteronism, had hypersecretion of aldosterone and other symptoms of hypokalaemic alkalosis, tetany, inability of the adequate urine concentration with increased concentration of angiotensin in the blood, the manifestation of hypertrophy of juxtaglomerular apparatus, and hyperplasia of the adrenal.

As for the cause of this, Bartter et al., observing the fact that the blood pressure had a low reaction to angiotensin II, held that this syndrome was caused by a hypersecretion of aldosterone by means of Renin-Angiotensin system, following hyperplasia of juxtaglomerular apparatus through the congenital low sensitivity to angiotensin.

A case of hyperplasia of adrenal cortex without the symptom of adenoma was first reported in a 17-year-old boy who had a malignant hypertension by Buchem et al

(1956)¹¹¹⁾ More cases of the same sort have reported since then¹¹²⁻¹¹⁸⁾

Conn (1961)⁵⁾ named the case of hyperaldosteronism in a youth either without the tumor or with the bilateral adrenal hyperplasia in the adrenal cortex as "primary aldosteronism without adenoma" then later in 1964⁹⁾ he gave the term of congenital aldosteronism to the case, for he held that the cause of this was due to an abnormal function of the renal juxtaglomerular apparatus, and put it in the category of secondary aldosteronism.

We cannot overlook the fact that Conn had his view about this case changing after his first report.

2) Diagnosis of Primary Aldosteronism :

Conn (1964)⁹⁾ pointed out that the four main symptoms of primary aldosteronism were degeneracy of muscular power, polyuria (specially nocturnal polyuria), headache, and thirst, and as for other minor symptoms, he pointed out that there were abnormal sensation, visual distur-

bance, intermittent paralysis, tetany, and fatigue. Onsets of parasthesias, intermittent paralysis, and tetany do not occur in the case of males as often as in the case of females. Hypertension is general in all cases, most of which are of benign nature, and in about half of which mild retinopathy is manifest.

As for the frequency of primary aldosteronism according to sex, it occurs rather frequently in females (male: female 1:26), while according to age groups, 72% of the whole cases are occupied by the groups between their thirties through fifties. Solitary adenoma is 91% and multiple adenoma is 9%. Adenomas of less than 6 gm. 68%, those with the diameter of less than 3 cm 73% and more common left than right side 73 : 37 (almost 6 : 3).

As the result of the renal function test of 113 cases with primary aldosteronism we see the decreased concentrating ability (80%), albuminuria (85%), no response to pitressin (80%), while more than 60%

Clinical Findings of Primary Aldosteronism (Tumor) by J. W. Conn et al., (1964)

-
- I. Renal
 *1. Polydipsia
 *2. Polyuria
 *3. Nocturia
- II. Muscular
 *1. Weakness, usually episodic
 2. Flaccid paralysis, occasional
 3. Occasional tetany
 4. Manifest or latent paraesthesias
- III. Hypertensive
 *1. B.P. elevation—mild to very severe (270/160)
 *2. Headache—major symptom
 3. Retinopathy—minimal in relation to B.P. elevation
 4. Cardiomegaly—minimal in relation to B.P. elevation
- IV. Important Negatives
 1. Peripheral oedema—absent or minimal
 2. Grade IV retinopathy—absent
-

*—most common

showed normal glomerulotubular function. Biochemical findings of the urine and the blood include hypernatremia, hypochloremia, alkalosis caused by metabolic disturbance, alkaline urine, increased aldosterone and increased potassium in the urine, saliva and sweat, and normal dosage of 17KS and 17OHCS in the urine. Fifty-four % of the cases show abnormality in glucose tolerance test.

Conn made the following table as to the clinical symptoms of aldosteronism and biochemical functional alterations.

Biochemical and Functional Alterations of Primary Aldosteronism (Tumor) by J. W. Conn et al., (1964)

-
- I. Blood
 *1. Hypokalemia
 2. Hypernatremia
 3. Hypochloremia
 4. Hypomagnesemia
 *5. Alkalosis
- II. Urine
 *1. Increased Aldosterone excretion and or secretion
 *2. Normal 17-KS and 17-OHCS
 3. Decreased concentrating ability
 (a) Water restriction
 (b) Pitressin resistance
 4. Decreased ability to acidify
 (a) Neutral or alkaline urine
 (b) Decreased H⁺ and increased NH₄⁺
 5. Decreased renal conservation of K
 (a) High UK/PK at low PK values
- III. Na, K and body fluids
 *1. Increased body exchangeable Na } high
 *2. Decreased body exchangeable K } Na/K
 3. Low sweat Na concentration
 4. Low Na/K of saliva
 5. Increase plasma volume
 (a) Decreased haematocrit
- IV. ECG—Changes compatible with hypokalemia
-
- *—most common

3) Differential Diagnosis of Primary Aldosteronism and Secondary Aldosteronism⁽¹¹⁹⁻¹³⁶⁾.

Differential diagnosis has been discussed

Some Clinical Implications of Aldosteronism

	Primary	Secondary
Relationship of hypertension	(benign) mild	(malignant) not invariably severe
Retinopathy	Grade IV absent	papilloedema (75%)
Albumiuria	little	much
Peripheral oedema	none	present (lacking rarely)
Urinary Aldosterone	increased	increased
Serum electrolytes	hypokalaemia	hypokalaemia
potassium level	hypernatraemia	usually normal, occasionally low
sodium level	increased	decreased
Total blood volume	abnormal	normal
Circulatory reflexes	response to 4m μ g > min.>	response to <6.5m μ g < min.
Angiotensin infusion test	low (renin) level	high (renin) level
Plasma renin activity	no difference	involved on the affected side
Divided renal function	normal	unilateral constriction of the renal artery
Renal aortography	adrenal tumor present	adrenal tumor none
PRP, Nephrotomography	curable	ineffectual
Adrenalectomy		

by the scholars from biochemical, functional and roentgenographical views. The following is a table that shows the outline of differential diagnosis of aldosteronism discussed by them.

Until recently it has been held that primary aldosteronism always signifies hypokalemia. However Conn et al. recently (1965)¹³²⁾ reported a case of hypertension with increased aldosterone and low plasma renin activity despite of the normal value of conserve serum potassium, and named it "Normokalemic Primary Aldosteronism". He continued to explain that the hypertension of this case can be improved by removing the adrenal in which the small adenoma develops¹³⁵⁾.

Moreover Conn et al. (1966)¹³⁶⁾ added six more cases of normokalemic primary aldosteronism. He¹³¹⁾ suggested that the cases diagnosed as essential hypertension may conceal a good many small aldosterone-producing adrenal adenomas and that the most effective method of this diagnosis is to see hypersecretion of aldosterone in the urine and the suppression of plasma renin activity. He¹³¹⁾ again suggested that primary al-

dosteronism characteristically inhibits the function of renin-angiotensin.

4) Histological Examination of Adrenal Cortex and Observed Hyperaldosteronism. 173~146)

Hyperplasia of adrenal cortex can be observed commonly at autopsy in the adult males that while alive did not show any clinical incretional disturbances, and its frequency is remarkably high in the males of 60 or older. Russi et al. (1945)¹⁴⁰⁾ reported adrenal cortical adenoma in 1.45% of 9,000 autopsies and recognized two different sizes of adenoma, big and small. The big kind—Cushing's syndrome or adrogenital syndrome mainly—is incretionally active, and the small kind, 10 mm in diameter, is inactive incretionally, and this latter small adenoma can hardly be differentiated from aldosterone-producing adenoma.

Wilens and Plair (1962)¹⁴¹⁾ at New York Veterans Administration Hospital observed 1,000 autopsies from 1958 through 1961, and out of 993 they found 114 cases of bilateral cortical hyperplasia (11.5%), 35.1% of which were found to be of hyperten-

Table 1.

	Age	Sex	B.P.	Funduscopy	Albuminuria	Urinary Aldosterone		Pathological findings			Course	Clinical observation
						Pre. op.	Post op.	Renal artery	Kidney	Adrenal		
Wrong (1957) ⁷⁰⁾	54	M	Hypertension	K-W III		Raised			r. Renal ischemia, glomerular crowding, tubular atrophy. Hypertensive changes in l. Kidney.	Adrenal 5.2g, no tumor	Nephrectomy (r.) subtotal adrenalectomy. After operation symptoms had lapsed, BP returned to normal.	Thirst, polyuria, loss of weight, weakness, hypokalemic alkalosis.
Margolin et al. (1957) ⁷¹⁾	38	M	240/140	Papilloedema	over 1g/L	1.5 cat units per 10 ml. of plasma		Aortograms demonstrated an abnormal r. renal artery.	IP: Both poor concentration. RP: (r) Kidney slight distortion of the r. lower calyx r. Kidney 127g. (Infarction)		After Nephrectomy all the signs was improved.	Severe right flank pain, vomiting, fever, severe headaches and increasing irritability confusion, thirst, polyuria.
Dollery et al. (1959) ⁷²⁾	56	M	270/120	Papilloedema	22g/day	8.4 µg/day		The arteries of the kidneys were shrunken. Internal elastic lamina reduplicated, intimal fibrous endarteritis.	IP: r. Kidney poor concentration nephrogram; r. Kidney reduced clearance r. kidney 115g, l. kidney ×8×3.5 glomeruli normal tubules were mostly shrunken and separated by fibrous tissue.		r. Nephrectomy. Post-operative course: BP 190/90. Retinitis recovered. Serum potassium concentration normal.	Thirst, polyuria, severe headache, hypokalemia. Magnesium 1.7m Eq/L. bicarbonate 33m M/L.
	54	M	260/80	Papilloedema				Main left kidney artery with lumen reduced to a slit by fibrous tissue. Arteriosclerosis of the main renal artery with incomplete infarction.	IP: l. Kidney contracted	No evidence of tumor in the left adrenal.	Nephrectomy (l) Post operation, Retina recovered. BP normal. Serum potassium normal.	Headaches, thirst, nocturia, polyuria, loss of weight. Potassium 2.0mEq/L, chloride 79mEq/L, bicarbonate 31mEq/L, Urine of low specific gravity. ECG: Left ventricular hypertrophy 'U' waves.

Laidlaw et al. (1960) ⁷³⁾	55	M	190/140/ 170/90	Papilledema	(-)	19 μg/day	l. renal artery occluded with a thrombus	r. kidney 285g. l. kidney 125g. r. kidney was potassium depletion nephropathy. l. kidney was atrophy, infarction of the l. kidney.	r. adrenal 11g. l. adrenal 10g. A small cortical adenoma, nodular hyperplasia.	Bilateral adrenalectomy. Dead eight hours after operation.	Hypokalemic alkalosis, polyuria, alkaline urine of low specific gravity. Lower abdominal pain, blurring of vision.
	33	M	180/120	Papilledema	(-)	6.8 μg/day	Translumbar aortography: aneurysm of r. renal artery.	Nephrogram: r. kidney showed marked contraction of r. kidney. r. kidney: large infarct in the lower pole. Ischaemic atrophy of tubules and glomeruli.		Post nephrectomy (r) BP: 116/70 Papilledema regression.	Lower abdominal pain, headache, fatigue, nausea, thirst, nocturia, polyuria. Divided renal function suggested: ischaemic lesion of r. kidney.
Dérot et al. (1961) ⁷⁴⁾	46	M	200/90, 210/140	K-W I	10g/dl	70 μg/day	IIP and retrograde pyelogram with left contracted kidney.	r. kidney: nephrosclerosis, nephropathy complex. (pyelonephritis with thrombosis of l. renal artery)		l. nephrectomy Hypertension cured. Plasma electrolytes normal.	Headaches, asthenia, loss of weight, nocturia, positive Trousseau sign.
Fukuchi et al. (1961) ⁷⁵⁾	39	M	Hypertension			12.0-43.7 μg/day		Pyelogram: r. kidney hypoplasia. Figure of essential hypertension.	No adrenal tumor but hyperplasia.	Probe laparotomy. Hypertension cured. Anxiety disappeared.	Haematuria, anxiety, insomnia.
Wrong (1961) ⁷⁶⁾	26	F	230/90	KW IV		Not measured	Aortic aneurysm involving both renal arteries		Adrenals infarcted as result of surgery, but no tumour.	Excision of aneurysm and replacement by graft. Died after aortic resection.	Nocturia, plasma potassium 3.3m Eq/L, plasma total CO ₂ 31.2m M/L.

Hänze (1962) ⁷⁹⁾	16	M	230/150	Retinitis angio- spastica		110-173 $\mu\text{g}/\text{day}$	Tumor (pheochromocytoma) compressing renal artery and vein.	Kidney : potassium depletion and nephropathy.	Extraadrenal pheochromocytoma.	1. probe laparotomy. Post operation, clinical signs improved.	Polyuria, polydipsia, hypostheuria, tetany, hypokalemic alkalosis, hypochloremia.
Poutasse (1963) ⁸⁰⁾	34	F	190/110	Retinopathy III	(-)	66.9 $\mu\text{g}/\text{day}$	Aortogram : structure of r. renal artery segmental mural fibrosis.	IP : small r. kidney.	Plastic surgery (stenotic area of r. renal artery resected and artery anastomosed) After operation clinical signs improved.	Headaches, fatigue, muscular weakness, palpitation. Hypokalaemic alkalosis, ECG: "U", waves.	
Sambhi et. al. (1963) ⁸²⁾	44	F	200/110			17 $\mu\text{g}/\text{day}$ (secretion rate)	Aortogram : structure of r. renal artery. Lumen of r. renal artery reduced to 2 or 3 mm at its origin at the aorta.	Pyelogram : small r. kidney.	Aorto-renal graft postoperative BP returned to normal.	Duration of hypertension 5yr. with marked progression over past 2yr.	
	41	F	180/120			114 $\mu\text{g}/\text{day}$ (secretion rate)	Aortogram : l. kidney smaller than r. kidney, l. renal artery revealed a zone of stenosis.	Pyelogram : no definite abnormality. l. kidney revealed an old infarction.	Left splenorenal anastomosis. Postoperative BP returned to normal.	Duration of hypertension 10yr.	
	49	M	260/140			245 $\mu\text{g}/\text{day}$ (secretion rate)	Aortogram : complete obstruction of l. renal artery.	Pyelogram : small l. kidney. l. renal capsula was adherent over an irregular depressed in the lower pole : cortex in this area was dark red and finely granular.	1. nephrectomy. Post operative BP improved.	Duration of hypertension 2yr, hypokalemia.	
Schwab et al. (1963) ⁸³⁾	55	M	240/135	Retinitis angio- spastica	1.5-1.2 g/l.	120 7.5 $\mu\text{g}/\text{day}$	Aortogram : structure of l. renal artery. l. renal artery showed occlusion of atheromatous organized thrombosis.	Pyelogram : small l. kidney. 9 x 6 x 5 cm, atrophy of tubuli, sclerosis of glomeruli, interstitial fibrosis, & fibrosis of Bowman's capsul.	1. nephrectomy. After operation clinical signs corrected.	Headache, dysbasia, polyuria, polydipsia, tetany, thirst, hypokalemia.	

Nara et al. (1963) ⁸⁰	12	F	160/100 180/120	KW II	(+)	7.4-9.6 µg/day	PRP tomography : small l. kidney.	Autopsy : nodular hyperplasia of l. adrenal.	Headache, nocturia, paralysis of limbs, hypokalemic alkalosis. Howard test normal, RPF : impairment in ability to concentrate urine. Spironolactone test positive.
Goldberg et al. (1963) ⁸⁰	62	F	230/120	KW II	75/100 mg	40 µg/day	Aortogram : stenosis of r. renal artery at its origin. r. renal artery occluded the lumen.	IP : nonvisualization of l. kidney. RP : small l. kidney. l. kidney : 40gr, diffuse, severe arteriolar nephrosclerosis increased the granularity of the J. G. cells. r. kidney : moderate arteriolar nephrosclerosis.	1. Nephrectomy and patch-graft under hypothermia, all clinical signs disappeared after operation. Headaches, dizziness, polydipsia, polyuria, nocturia, weakness, thirst, hypokalemia.
Blagg et al. (1964) ⁸⁰	49	F	190/140	Retinopathy IV	(+)	Not measured	Aortogram: l. renal artery narrowed. r. renal artery showed degenerative arterial disease.	IP : poor concentration and small r. kidney.	Fatigue, anorexia, weakness of the legs, loss of weight and hypokalemia. Howard test showed no significant difference. ECG : left ventricular hypertrophy.
Smithwick et al. (1964) ⁸⁰	52	F	170/110	Reinitis with hemorrhages and exudate		Not measured	Aortogram : obstruction of r. renal artery, r. renal artery was obstructed by an arteriosclerotic plaque.	IP, Renogram : r. kidney no function, r. kidney : 64g, chronic pyelonephritis, ischemic tubular atrophy.	Rapidly progressive hypertensive cardiovascular disease, indigestion, constipation, nervousness, weakness, headaches, hypokalemia.
	51	M	220/160			55 µg/day	Renal biopsy: Arteriosclerosis grade III. Tubules normal.	r. adrenal 11gm. l. adrenal 7.0gm. Both nodular hyperplasia.	Extensive hypertensive cardiovascular disease (prolonged QT). Rising blood urea nitrogen. Hypokalemia.

Schröder et al. (1965) ⁹⁸⁾	54	M	190/110	Small hemorrhage and Gunn's phenomenon.	1.8-14.5 g/L	30-100 µg/day	4-5 µg/day	Aortogram : Stenosis of l. renal artery, thrombosis of l. renal artery.	IP : small l. kidney, l. kidney 85g, atrophy of l. kidney.			l. nephrectomy. After operation all clinical signs disappeared. hypokalemic ECG.	Headaches, fatigue, loss of weight, polyuria, dysbasia, hypokalemia, divided renal function tests showed difference, hypokalemic ECG.
	63	M	230/130	Papilledema	2.0-10.0 g/L	42 µg/day	10 µg/day	Aortogram: r renal artery completely occluded. Arteriosclerosis of renal artery.	IP : small r. kidney atrophy of tubulus, glomeruli normal.			r. nephrectomy. BP, plasma elec-trolytes returned to normal.	Headaches, fatigue, loss of weight, polyuria, diz-ziness, hypokalemic ECG.
Suzuki, Sasaki (1966)	38	M	160/100	KW I	(±)	20.7 µg/day	8.6 g/day	Aortograms no abnormal findings.	r. renal tubercu-losis (fibro-indurative form)	r. Adrenal hyperplasia.	r. nephrectomy, total r. Adrena-lectomy After operation BP re-turned to normal.	Fatigue, polydipsia, headache.	

sives. As for the 886 cases that lacked adrenal cortical hyperplasia, frequency of hypertension was 20.9%. They pointed out that when adrenal cortical hyperplasia is complicated by hypertension, aortical sclerosis will make a remarkable change.

Again Schamma (1958)¹⁴⁶⁾ and Scherwin (1964)¹⁴³⁾ studied on the single, big, but well-encapsulated adenoma of adrenal cortex. It was found that the frequency of aldosterone secreting tumor in the normotensive group of 220 cases was 1.8%, but that in the hypertensive group of the same 220 cases was 20.5%, which was very high. That indicated a definite relation between hypertension and Aldosterone-secreting tumor.

According to Symington¹⁴⁵⁾, the pathological characteristic of Conn's syndrome is, to observe grossly, a well-encapsulated canary-yellow tumor of small size ; to term it histologically, it is broad plastic zona glomerulosa, which is like glomerulosa and fasciculata cells.

Sasano (1965)¹⁴²⁾, pathologist, referring to hyperplasia concomitant with essential hypertension, pointed out that the most common adrenal change is a diffuse or nodular hyperplasia centering around the adult type zona glomerulosa on the peripheral cortex, and that when some of the nodes develop in adenomas, they can hardly be told from those of primary aldosteronism. He went on to say that the nodular hyperplasia might possibly be veered into the adenoma.

5) Renal Ichemia and Secondary Aldosteronism

Aldosterone, not like other cortical hormones, is not wholly controlled by ACTH. It has recently been made clear that what controls the secretion of aldosterone is renin-angiotensin system. That is, wall of

glomerular afferentia works as a stretch receptor, whose relaxation will induce renin from juxtaglomerular cells, and whose strain will inhibit the secretion.

Renin will act on a substrate in blood plasma that belongs to α -globulin demarcation, giving rise to Angiotensin I which is decapeptide, which in turn will be transformed into Angiotensin II through the converting enzyme in blood plasma. It is said that Angiotensin II, being octapeptide, will perform boosting to vascular tension on one hand, and will stimulate secretion of aldosterone when it acts on the adrenal on the other hand.

Renal ischemia, through the agent of renin, will be the cause of hypertension. But renin is a strong stimulant as to aldosterone secretion. So here comes up a clear chain relation such as renal ischemia \rightarrow increased renin secretion \rightarrow hyperaldosteronism. Thus secondary aldosteronism by renal ischemia became a well defined clinical entity. So far 30 cases have been reported. You can see the outline of the cases in Table 1.

Fitz et al. (1963)¹⁴⁷⁾ reported some rare cases of primary aldosteronism that involves renal artery stenosis. In the case reports that we gathered from the literatures we acknowledged four cases of complication of adrenal cortical hyperplasia with renal artery stenosis.

Wrong (1964)¹⁴⁹⁾ on this point says, "Either a patient with long-standing primary aldosteronism might develop renal ischemia because of the damaging effect of hypertension on the renal vascular, or renal artery stenosis might lead to the formation of an adrenal adenoma through the effect of long continued stimulation by the renin-angiotensin mechanism. At pre-

sent it is not possible to choose between these alternatives" But he admits the theory of adrenal adenoma formation by renovascular stenosis speculatively.

6) Trends of Hyperaldosteronism and Hypertension

When Carey L. C. and Ellison E. H. (1961)¹⁵⁰⁾ reported "primary aldosteronism and hypertension related to it" at the 68th Annual Meeting of the Western Surgical Association in December, 1960. Williams. R. (Columbus, Ohio) made two questions, saying, "First, how commonly is this disease a cause of hypertension, that is, in relation to other known causes? Second, since about 20% of the reported cases show recurrence of hypertension after surgery, I wonder why the authors feel that this is most likely due to failure to remove all tumor or hyperplastic adrenal tissue, rather than to renal arteriolar damage"

Here is Carey's answer to the second question, which interests us here in particular.

"In answer to Dr. Williams' second question, the hypertension of this disease recurs in about 20% of the cases. Other authors have suggested that the recurrence is due to severe renal damage. We have been unable to correlate either the severity or the duration of the patients' hypertension to the likelihood that he will have recurrence.

We feel that perhaps the recurrence is not due to renal damage, because the patients have most often an initial drop in blood pressure and then a return to hypertensive levels. It seems a very good possibility that a small adenoma is overlooked initially in these patients".

Reading Laragh (1964)¹¹⁰⁾ that was mentioned before, the theory of Bartter

syndrome (1962)^{52-a, b, c)} in secondary aldosteronism or the definition of aldosteronism and especially that of congenital aldosteronism as for hypertension by Conn (1961)⁵¹⁾, we understand that we cannot accept these matters easily without some necessary proofs.

VI. SUMMARY

As for our personal case, we placed it tentatively in the category of secondary aldosteronism, but we could acknowledge only four cases of cortical hyperplasia (of which our case is the fourth) in all 30 cases that we could gather from the literatures. We rather hesitate as to whether we should place it in the primary kind in a broad sense or in the secondary proper. Not only that, judging from all such complexity as the view of Wrong (1964)¹⁴⁹ that was mentioned a while ago, Sasano's pathological view (1965)¹⁴²⁾, Conn's view (1965)^{131), 132)} that 20% of essential hypertension cases have primary adrenal tumors, and Nesbit's proof (1966)¹⁵¹⁾ of cortical hyperplasia on the excised adrenal from the hypertensive patient, we have come to see a trend recently that the matter of aldosteronism is beginning to play its delicate role not only in the problem of classification of the primary and the secondary of aldosteronisms but also in the diagnosis of essential hypertension.

VII. CONCLUSION

We diagnosed the case of a 38-year-old man before operation, whose main complaints were fatigue, headache, polydipsia, hyposthenuria, and hypertension, as primary aldosteronism originating from the right adrenal, as examined with PRP combined nephrotomography, judging from his value of serum potassium at the low in the

normal limit, the increased aldosterone in the urine, no arteriolar narrowings on both sides as proved by renovasculography.

We attempted adrenalectomy on the patient through thoraco-lumbar approach under the hypothermic anaesthesia method, but with the intensive adhesion around the upper pole of the right kidney and the renal surface we were compelled to perform the total adrenalectomy and nephrectomy. We found that the case was histologically nephrosclerosis caused by fibrotic indurative typed renal tuberculosis concomitant with adrenal cortical hyperplasia. Moreover, we have added some review of the literatures concerning secondary aldosteronism caused by renal ischaemia, and referred to remaining problems of aldosteronism and hypertension up to date.

Before we conclude our report, we desire to express our deep appreciation of the assistance rendered us by Assistant Professor Hokano (Department of Pathology) and Professor Miyake (Department of Anaesthesiology). We also desire to express our thanks to the cooperations of Dr. Yamada (Director : Prof. YOSHITOSHI for the measurements of catecholamine, and Dr. Oda (Director : Prof. OSHIMA) for the measurements of aldosterone excretion.

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自家症例による Aldosterone 症の 2, 3 の問題

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症例は両側副腎丸結核の既往歴があり、2年前から多飲、疲労感、頭痛、高血圧 160~100 mmHg を主訴とした 38 才の男子である。血液化学所見としては、K 3.8 mEq/L, Na 139 mEq/L, Mg 2.25 mEq/L で尿中 17KS, 17OHCS, catecholamine は正常範囲であったが尿中 aldosterone 量は 20.7 μ g/day, RISA による Plasma volume は 56.9 ml/kg, Metopirone, Spironolactone test は陽性、腎機能は軽度の障害があり、眼底所見は KWI, Angiotensin infusion test は 15.7 milimicrogram per Kg per minute で血圧 (diastole) 20 mmHg 上昇をみた。Aortography では腎動脈に狭窄がなく、PRP, Tomography の併用により右側副腎腫瘍による“Primary aldosteronism”と診断した。

低体温麻酔の下に Thoraco-abdominal incision で Adrenalectomy を試みたが、右副腎と右腎との癒着が強く、止むなく右副腎摘出と右腎摘出を施行した。術後 1 カ月には臨床症状の改善をみた。

組織学的には腎結核一線維硬化型と副腎の線様過形成が認められた。

なお、Renal ischemia に基づく Secondary aldosteronism について Secondary Aldosteronism の定義、鑑別診断、高血圧と副腎皮質との関連性 Renal ischaemia による Secondary aldosteronism の報告例のまとめ、および Hyperaldosteronism と高血圧症についての問題点について文献的考察を加えた。

本論文内容は第 295 回日本泌尿器科学会東京地方会で報告した。

▨ : following ACTHZ 40 units
▤ : following 3g of Metopirone

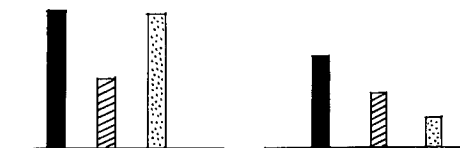


Fig. 1. Fluctuations in 17KS.

Fig. 2. Fluctuations in 17 OHCS.

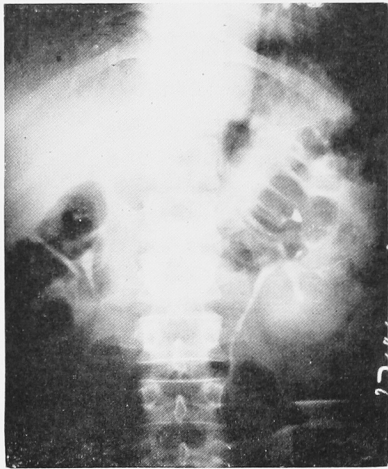


Fig. 3. Excretory urogram.

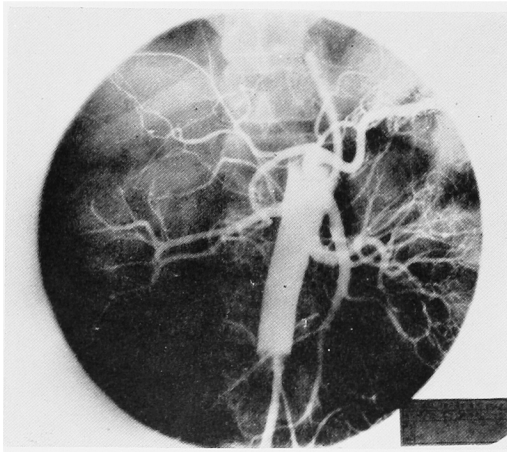


Fig. 4. Segmental aortogram.

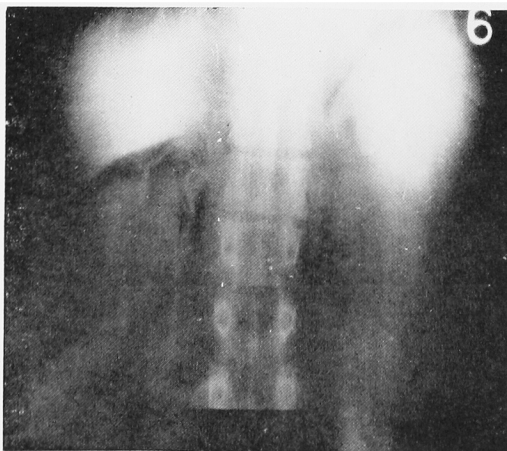


Fig. 5. Simultaneous retroperitoneal pneumogram and tomogram.

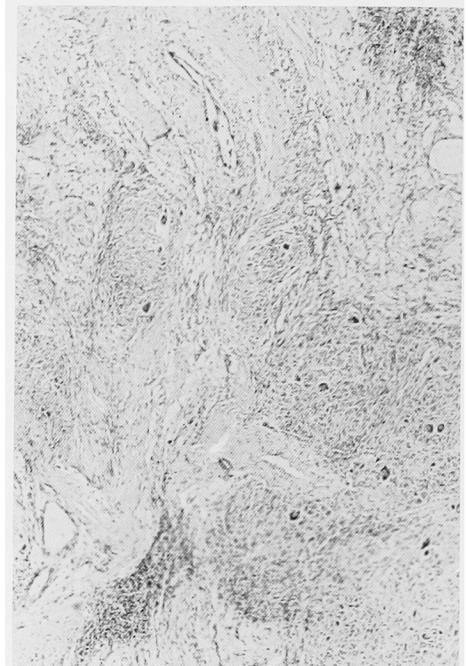


Fig. 6. The artery wall shows marked thickening and almost obliterate its lumen. And find a conglomerate tubercle in contact with its wall. $\times 4$.

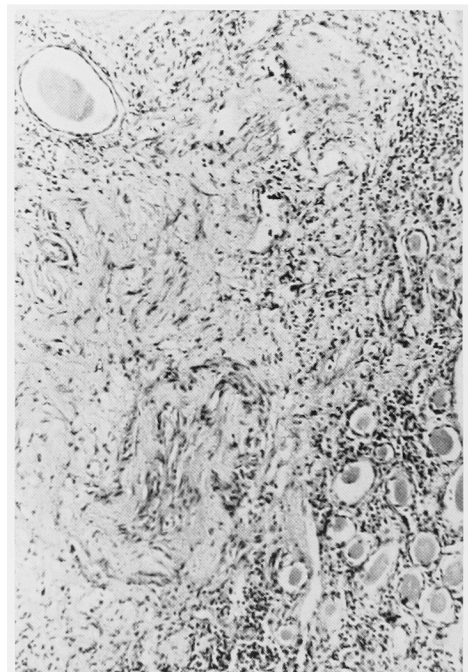


Fig. 7. The interlobular arteriole showing the thickening with almost complete obliteration of the lumen and marked fibrosis at the periarterial area. While others show many dilated tubules filled with colloid casts and abundant lymphocytes permeate in the interstitial tissue. $\times 10$.

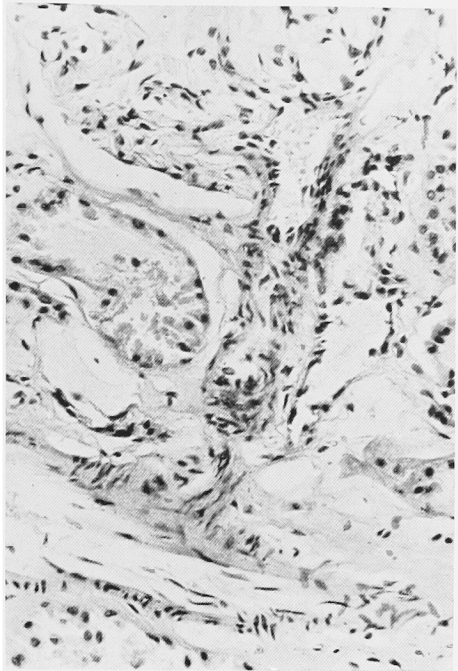


Fig. 8. The arterioles reveal its thickening. $\times 20$.

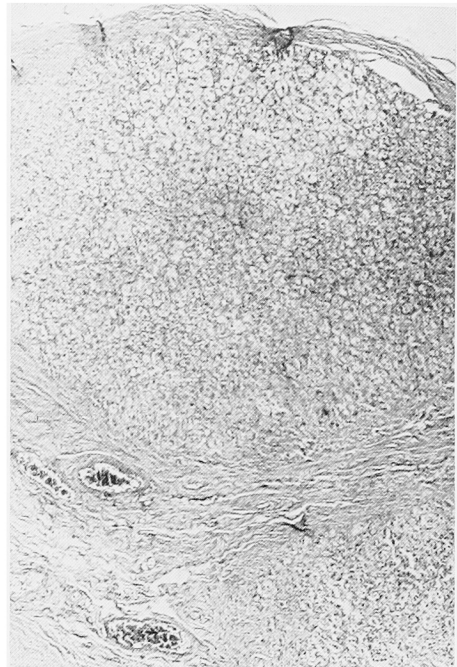


Fig. 10. Adenomatous nodule of the adrenal cortex. $\times 20$.

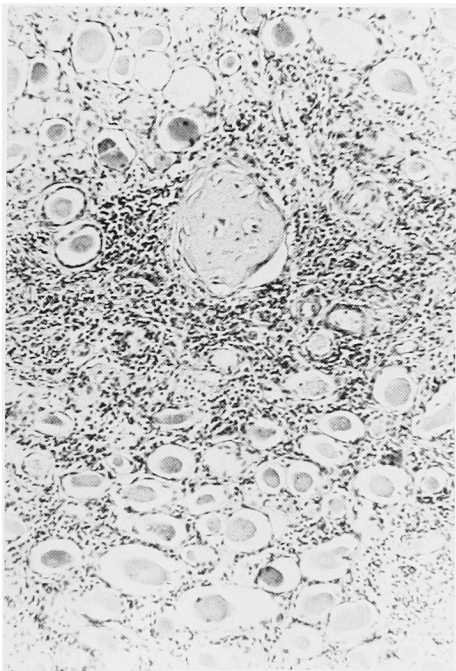


Fig. 9. Photomicrograph showing hyalinized glomerulus, resemblance to as in Fig. 7. $\times 20$.

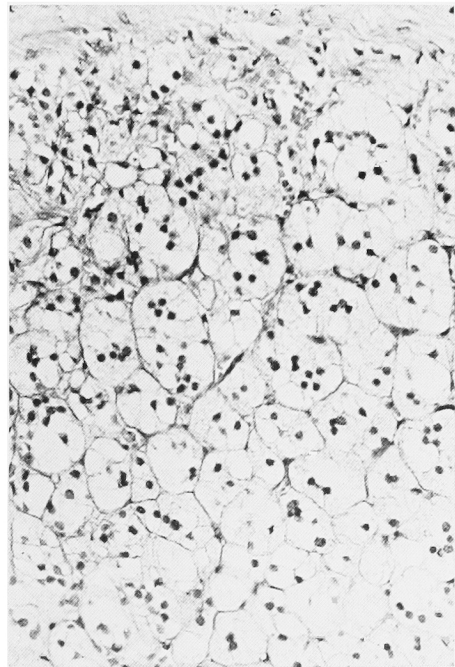


Fig. 11. The cortex shows the hypertrophy at the outer zone of zone fasciculata. $\times 20$.