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Primary Aldosteronism at Henry Ford Hospital in the 1980s

Max Wisgerhof, MD*

This report describes the experience with the diagnosis and treatment of primary aldosteronism at Henry Ford Hospital since 1980. Of the 28 patients who received the diagnosis, 13 had unilateral primary aldosteronism and 15 had idiopathic hyperaldosteronism. Individual cases are used to demonstrate clinical points. The clue to the presence of primary aldosteronism in a hypertensive patient is hypokalemia. The diagnosis is established by showing 1) high plasma aldosterone after intravenous saline or high urinary aldosterone after treatment with sodium chloride orally, and 2) low stimulated plasma renin activity. Treatment with potassium supplement should be given during the testing. Unilateral primary aldosteronism can be identified and localized by adrenal cortical scintigraphy using 131-iodine iodomethyl 19-norcholesterol (NP-59) during dexamethasone treatment to decrease cortisol synthesis. Unilateral adrenalectomy will cure the hypokalemia and relieve (60%) or improve (90%) the hypertension in unilateral primary aldosteronism. Idiopathic hyperaldosteronism is treated medically, with spironolactone or amiloride and calcium-channel blocking drugs. (Henry Ford Hosp Med J 1987;35:226-33)

Primary aldosteronism is the excessive secretion of the hormone aldosterone (1-3), from one or both adrenal glands, without a stimulus detected for the adrenal hyperfunction. The excess of the hormone leads to excesses of its effects: kaliuresis, sodium retention, and an increase in blood pressure. Primary aldosteronism is a new syndrome, relative to most other disorders of hormone excess, and is infrequent in occurrence. One form, the unilateral, adenomatous one (4), is curable. The bilateral, idiopathic hyperaldosteronism syndrome (5,6) has yet to be explained, and an aldosterone-stimulating hormone (7) has been suggested as its cause.

A total of 28 patients, the subjects of this report, have received the diagnosis of primary aldosteronism at Henry Ford Hospital since 1980. Thirteen patients had unilateral primary aldosteronism, and 15 patients had idiopathic hyperaldosteronism. Some of their characteristics are noted in Table 1. The proportion of males with idiopathic hyperaldosteronism is greater than those with unilateral aldosteronism. Individual cases will be used in this discussion to demonstrate clinical points about the diagnosis and treatment of primary aldosteronism at Henry Ford Hospital in the 1980s.

Diagnosis

Clues to the diagnosis

 Symptoms are particularly useful during the evaluation of a patient if they are reliable, specific clues to the presence of a disease. Patients with primary aldosteronism will not necessarily have symptoms which suggest the diagnosis:

Case 1—A 44-year-old woman presented with paroxysms of weakness, headache, chest pain, pallor, and hypertension. The spells began two years before presentation and were increasing in frequency and severity. The symptoms suggested pheochromocytoma, but her plasma concentrations of norepinephrine and epinephrine and urinary excretion of catecholamine metabolites were normal. Hypokalemia was noted, and evaluation disclosed the findings of primary aldosteronism due to a right adrenal aldosterone-producing adenoma (Fig 1). Adrenalectomy relieved the symptoms, cured the hypokalemia, and markedly improved the hypertension.

Case 2—A 55-year-old man presented with headaches of a few months duration, with blurred margins of the optic disks, a flame-shaped hemorrhage and a hard exudate in his retina, and a blood pressure of 204/104 mm Hg. Hypokalemia was present, and pursuit of an explanation for it led to the demonstration of the presence of bilateral, idiopathic hyperaldosteronism. Treatment with amiloride and nifedipine relieved the symptoms and controlled his blood pressure and serum potassium.

The clue to the presence of primary aldosteronism in a hypertensive patient is hypokalemia (8), rather than specific symptoms or signs. Hypokalemia can cause muscle symptoms which can be severe:

Case 3—A 32-year-old woman presented with acute pain and swelling in her left calf and progressive muscular weakness. She was anticoagulated for deep vein thrombophlebitis, but venography was negative. Subsequent evaluation confirmed the presence of hypokalemia and corrected the hypertension.

Surgical treatment is indicated for further cases, not uncommon, when the patient has no other explanation of the hypertension.

Establishing the diagnosis

The diagnosis is confirmed by clearly demonstrating the abnormal aldosteronism activity. This is done by procedures.

Case 4—A 44-year-old woman with hypertension and hypokalemia and vascular dilators of not more than 80 ng/dL. The hypertension returned when her blood pressure was measured.

The infusion of hypertonic salt solutions caused paroxysms of weakness, headache, chest pain, pallor, and hypertension. The spells began two years before presentation and were increasing in frequency and severity. The symptoms suggested pheochromocytoma, but her plasma concentrations of norepinephrine and epinephrine and urinary excretion of catecholamine metabolites were normal. Hypokalemia was noted, and evaluation disclosed the findings of primary aldosteronism due to a right adrenal aldosterone-producing adenoma (Fig 1). Adrenalectomy relieved the symptoms, cured the hypokalemia, and markedly improved the hypertension.

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**Table 1**  
Characteristics of the 28 Patients with Primary Aldosteronism at Henry Ford Hospital in the 1980s

<table>
<thead>
<tr>
<th>Patients</th>
<th>Unilateral Primary Aldosteronism (N = 13)</th>
<th>Idiopathic Hyperaldosteronism (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>31-62</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>27-75</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>127</td>
<td>109-173</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>110-160</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>3.1</td>
<td>2.8-3.8</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.8-3.8</td>
</tr>
<tr>
<td>Left adrenal affected</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Right adrenal affected</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Single adenoma*</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Multiple adenomas or nodules</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient has not been treated surgically.

Surgically-curable primary aldosteronism can be set aside from further diagnostic consideration in a hypertensive patient when the serum potassium is greater than 4.0 mEq/L, if the patient has not been treated with potassium or potassium-retaining drugs (9).

Establishing the diagnosis

The diagnosis of primary aldosteronism is established by clearly showing the presence of both inappropriately high aldosterone secretion and inappropriately low plasma renin activity. This data can be obtained from standard testing procedures:

**Case 4**—A 62-year-old woman presented with severe hypertension and hypokalemia. Compensated congestive heart failure and cerebral vascular disease were present. After the intravenous infusion of two liters of normal saline in four hours, her plasma aldosterone was 28 ng/dL. The removal of a left adrenal aldosterone-producing adenoma returned her serum potassium to normal and markedly improved her blood pressure.

The infusion of saline to detect aldosteronism (10) is less hazardous to the hypertensive patient than is giving the patient a large amount of sodium orally for three days because a severe hypertensive response to the sodium is more readily controlled during the close monitoring of the saline infusion. A severe hypertensive response is more likely if the patient does not have primary aldosteronism and has essential hypertension, particularly in the sodium-sensitive subset. A plasma aldosterone concentration of greater than 10 ng/dL after the saline infusion is diagnostic of aldosteronism. A normal concentration is less than 8 ng/dL. The protocol and results for this series of patients are shown in Table 2(A).

**Case 5**—A 54-year-old man had hypertension, unprovoked hypokalemia, and inappropriate kaliuresis. His plasma aldosterone concentration after two liters of intravenous saline was 4 ng/dL, a normal result. His serum potassium was 3.6 mEq/L. His urinary aldosterone was determined during the third 24 hours of treatment with sodium (3 g of sodium chloride three times daily with meals to prevent gastric irritation), and it was high, 37 μg/24 hr. An aldosterone-producing adrenal adenoma was removed, and his serum potassium and blood pressure returned to normal.

Measuring the excretion of aldosterone during the third 24 hours of treatment with 150 mEq of sodium orally per 24 hours is a standard test to detect aldosteronism (11). A normal result is less than 8 μg/24 hr. The protocol and results for this series of patients is shown in Table 2(B). Potassium depletion can impair aldosterone secretion in aldosteronism, and thus lower the urinary excretion and plasma concentration (12). Once unprovoked hypokalemia and inappropriate kaliuresis have been demonstrated, potassium supplement treatment should be given to achieve a normal serum potassium concentration, if possible, during assessment of aldosterone secretion.

**Case 6**—A 36-year-old woman presented with hypokalemia and hypertension. Her aldosterone excretion was 12 μg/24 hr during sodium treatment. Her plasma aldosterone concentration was 16 ng/dL after the saline infusion is diagnostic of aldosteronism. A normal concentration is less than 8 ng/dL. The protocol and results for this series of patients are shown in Table 2(A).
intravenous saline. Subsequently, a diagnosis of bilateral, idiopathic hyperaldosteronism was obtained.

Aldosteronism is usually less severe in idiopathic hyperaldosteronism than in aldosterone-producing adenoma, and the results from both saline infusion test and the assessment of aldosterone excretion may be useful in establishing the diagnosis of idiopathic hyperaldosteronism.

Low stimulated plasma renin activity is a requirement for the diagnosis of primary aldosteronism and can be demonstrated utilizing protocols which measure the response of plasma renin activity to acute sodium and plasma volume depletion by furosemide treatment, 40 mg orally at 6 PM, 12 AM, and 6 AM for three doses only (13), or three days of very restricted sodium intake (Table 2).

Table 2
Establishing the Diagnosis of Primary Aldosteronism

(A) Protocol used in this series to assess aldosterone secretion by measurement of plasma aldosterone after saline infusion:
1. Discontinue medications at least two weeks before testing. Use methyldopa or guanethidine to treat high blood pressure if necessary.
2. Treat with potassium chloride, 20 mEq three times daily.
3. Infuse two liters of normal saline intravenously during four hours.
4. Obtain a blood sample at the end of the saline infusion for measurement of aldosterone and potassium concentrations.

Results in patients in this series:

<table>
<thead>
<tr>
<th></th>
<th>Unilateral Primary Aldosteronism (N = 9)</th>
<th>Idiopathic Hyperaldosteronism (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone (ng/dL) after saline infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Range</td>
<td>4-82</td>
<td>5-21</td>
</tr>
</tbody>
</table>

(B) Protocol used in this series to assess aldosterone secretion by measurement of urinary excretion during sodium treatment:
1. Discontinue medications at least two weeks before testing. Use methyldopa or guanethidine to treat high blood pressure if necessary.
2. Treat with potassium chloride, 20 mEq three times daily.
3. Three days before collecting urine, begin sodium chloride treatment, 3 g of supplemental sodium chloride three times daily with meals. (This is 55 mEq sodium TID.)
4. On the third day of sodium treatment, collect urine for 24 hours for measurement of aldosterone, volume, creatinine, and sodium.

Results in patients in this series:

<table>
<thead>
<tr>
<th></th>
<th>Unilateral Primary Aldosteronism (N = 10)</th>
<th>Idiopathic Hyperaldosteronism (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary aldosterone (µg/24 hr) during sodium treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>Range</td>
<td>19.93</td>
<td>10-35</td>
</tr>
</tbody>
</table>

(C) Stimulated plasma renin activity:

<table>
<thead>
<tr>
<th></th>
<th>Unilateral Primary Aldosteronism (N = 13)</th>
<th>Idiopathic Hyperaldosteronism (N = 14*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng/mL/hr) after furosemide and upright posture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Range</td>
<td>not detectable-0.8</td>
<td>0.1-1.0</td>
</tr>
</tbody>
</table>

*One patient was not tested with this protocol.
renin activity in the individual patient with primary aldoste­
ronism is not a useful discriminate between the two conditions
[Table 2(C)].

Selecting Patients for Adrenalectomy

Measurements of blood pressure, potassium, aldosterone, and
renin activity determine the diagnosis of primary aldosteronism and can give a clue to the presence of unilateral primary aldosteronism. However, recommending adrenalectomy as treatment with the intent to cure the disorder requires demonstrat­
ing that unilateral adrenal disease is present and identifying which adrenal is abnormal.

Adrenal cortical scintigraphy during dexamethasone treatment (15) and computed adrenal tomography are the two imag­
ing techniques that have been helpful in identifying an aldoste­
erone-producing adenoma:

Case 7—A 31-year-old woman presented with severe hyperten­sion (240/130 mm Hg) and hypokalemia (2.0 mEq/L). During sodium ad­
ministration her aldosterone was very high in the urine (93 µg/24 hr) and plasma (82 ng/dL), and the plasma renin activity was not detectable after three doses of furosemide and upright posture testing. Computed adrenal tomography was performed to detect an aldosteronoma, and the adrenal glands appeared to be normal. Adrenal cortical scintigraphy was performed during dexamethasone treatment, and an early appear­
ing, unilateral image was seen in the area of the left adrenal gland (Fig 2). Left adrenalectomy removed a 2 cm cortical adenoma, which resulted in normal serum potassium and blood pressure.

Adrenal cortical scintigraphy with 131-iodine iodomethyl 19-
norcholesterol (NP-59) can be more sensitive and accurate than
computed adrenal tomography in identifying an aldosterone-
producing adenoma. The radiochemical NP-59 is taken up by
steroid-synthesizing tissue as is cholesterol as a precursor for
hormone synthesis. When dexamethasone treatment is given,
cortisol synthesis is markedly decreased, and an adrenal image
within five days after injection shows the site of the excessive
aldosterone production. The protocol for this test is shown in
Table 3. An aldosterone-producing adenoma leads to low al­
dosterone secretion in the other adrenal gland, and a unilateral
image would be due to the adenoma. The presence of idiopathic

| Table 3 |

<table>
<thead>
<tr>
<th>Localizing Unilateral Primary Aldosteronism by Adrenal Cortical Scintigraphy During Dexamethasone Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol to detect unilateral primary aldosteronism by adrenal cortical scintigraphy using the isotope NP-59:</td>
</tr>
<tr>
<td>1. Discontinue medications at least two weeks before testing. Use methyldopa or guanethidine to treat high blood pressure if necessary and use potassium treatment.</td>
</tr>
<tr>
<td>2. One week before injection of NP-59, begin treatment with dexamethasone, 1 mg orally four times daily, and continue it until an adequate scan result has been obtained.</td>
</tr>
<tr>
<td>3. Two days before injection of NP-59, begin treatment with iodine solution, three drops in water twice daily, and continue this for two weeks.</td>
</tr>
<tr>
<td>4. On the day of injection, before the injection obtain a blood sample for measurement of aldosterone and potassium.</td>
</tr>
<tr>
<td>5. Intravenous injection of the isotope NP-59.</td>
</tr>
<tr>
<td>6. Obtain the first adrenal scan three days after the injection.</td>
</tr>
<tr>
<td>7. Obtain scans on days four and five, as indicated, to obtain an adequate result.</td>
</tr>
<tr>
<td>Results in patients in this series:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Unilateral Image</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>*Adrenal venous sampling showed unilateral primary aldosteronism, and adrenalectomy confirmed the presence of an aldosterone-producing adenoma.</td>
</tr>
</tbody>
</table>
hyperaldosteronism, a bilateral adrenal disease not curable by surgery, can also be detected by scintigraphy:

**Case 8**—A 27-year-old woman presented with asymptomatic hypertension and hypokalemia. Her urinary aldosterone excretion was high (16 μg/24 hr) during sodium treatment, and the stimulated plasma renin activity was low (0.8 ng/mL/hr). Computed adrenal tomography showed the right adrenal gland to be normal, but the left adrenal could not be identified. Adrenal cortical scintigraphy during dexamethasone treatment showed bilateral adrenal images three days after injection of the isotope (Fig 3), and she was treated medically for idiopathic hyperaldosteronism.

The accuracy of scintigraphy for detecting an aldosteronoma has not been rigorously tested because patients with apparently bilateral adrenal disease have not undergone adrenal surgery after early attempts (mostly preceding availability of scintigraphy) at surgical treatment of bilateral disease failed to cure the disorder. A unilateral, early image, though, is strong evidence for unilateral primary aldosteronism which can be treated successfully by surgery. Adrenal scintigraphy is a test of adrenal function and thereby more useful than computed tomography which shows adrenal form without information about function. Nonfunctioning adrenal adenomas are present in high enough incidence for computed tomography results to be misleading. Table 3 shows the experience with scintigraphy in patients with primary aldosteronism at Henry Ford Hospital. Magnetic resonance imaging would be an extraordinarily useful technique if it could demonstrate adrenal enlargement and hyperfunction, without the necessity of contrast media or a radioisotope. Fig 4 shows a magnetic resonance image of an aldosterone-producing adenoma.

The direct demonstration of unilateral primary aldosteronism is more certain by adrenal vein sampling for plasma aldosterone measurements. This invasive procedure can be used when conflicting results are obtained from attempts to identify an aldosteronoma by other methods:

**Case 9**—A 40-year-old man presented with moderately severe hypertension (210/104 mm Hg) and hypokalemia (2.9 mEq/L). Primary aldosteronism was demonstrated by high aldosterone during sodium treatment (plasma: 44 ng/dL; urine: 34 μg/24 hr) and low renin activity (0.1 ng/mL/hr) after furosemide and upright posture testing. Computed adrenal tomography suggested an enlargement of the right adrenal, but adrenal cortical scintigraphy did not show an early image in the area of either adrenal gland, and his plasma aldosterone increased during upright posture in the morning (as the plasma cortisol decreased). These findings were not congruent for a right adrenal aldosteronoma, so adrenal vein sampling for aldosterone was performed during ACTH infusion. The ratio of aldosterone to cortisol in the right adrenal vein, 0.7 in the left adrenal vein, was reversed. The right adrenal vein contained aldosterone, the left adrenal vein contained cortisol only.

The use of adrenal veins for catheter insertion for the aldosterone measurement is not demonstrated. This should be from the pentetic acid or cholecystokinin for the conclusions in the case. The author's conclusions are based on the assumption that the pentetic acid was injected into the left adrenal vein from a single adrenal vein. The left adrenal vein is the more common vein.

**Case 10**—A 42-year-old man presented with no hypertension, high intake of sodium, and hypokalemia. Computed tomography showed an adrenal mass in the right adrenal vein. Adrenal vein sampling showed an aldosteronoma in the right adrenal vein. The patient was treated with spironolactone.

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The usefulness of the measurement of aldosterone in the adrenal veins is dependent upon the accurate placement of the catheter in the veins and upon a method of detecting and adjusting for the effect of endogenous ACTH on the secretion of aldosterone by both the diseased and normal tissue. The measurement of cortisol in the adrenal vein samples will aid in demonstrating the location of the catheter. (Adrenal venography should be minimized because of its risk of adrenal hemorrhage from the pressure of the contrast media injection.) Comparing the cortisol concentrations in the two veins can detect differences in ACTH stimulation to the two adrenals at the two times of sampling. (Simultaneous, bilateral catheterization and sampling are too hazardous.) An additional method of compensating for differing effects of stress on the aldosterone measurements is to infuse ACTH during the procedure (8). This will blunt the effect of endogenous ACTH. The ratio of aldosterone to cortisol in the samples from the adrenal veins and inferior vena cava caudal to the adrenal veins during the infusion of ACTH will more accurately identify unilateral aldosteronism than the measurement of aldosterone only without infusion. The ratio is higher in the vein of the affected adrenal, and in the other adrenal vein it is similar to or lower than that in the inferior vena cava. The ACTH infusion is 0.25 mg given intravenously during the one to two hours of the procedure. The infusion should begin about one hour before sampling to provide near constant, high-degree stimulation of aldosterone secretion.

Another testing procedure can give a strong clue to the presence of an aldosterone-producing adenoma, although it cannot identify which adrenal contains the adenoma. This test is the measurement of the response of plasma aldosterone to upright posture in the morning (16):

**Case 3**—Adrenal scintigraphy was performed during this woman's evaluation, but she had discontinued the dexamethasone treatment, thereby invalidating the results. The response of her plasma aldosterone to upright posture in the morning was utilized to obtain sufficient rationale for repeating the scintigraphy. After absolutely recumbent posture overnight her plasma aldosterone was 58 ng/dL; after four hours of upright posture, walking or standing with sitting 15 minutes of each hour, from 8 AM until 12 PM, her plasma aldosterone was 25 ng/dL. Concomitant cortisol measurements were 17 and 11 µg/dL, respectively. This was sufficient evidence for the presence of an aldosterone-producing adenoma to proceed with the second scintigraphy, which showed an early, unilateral image. Adrenalectomy removed an aldosteronoma and cured her hypokalemia.

**Case 10**—A 40-year-old man presented with hypokalemia and hypertension. His urinary aldosterone excretion was 34 µg/24 hr during a high intake of sodium, and his renin activity was 1.0 ng/mL/hr after stimulation. Adrenal scintigraphy did not detect images. He underwent posture response testing, and his plasma aldosterone increased from 16 to 44 ng/dL, as his cortisol decreased from 13 to 7.8 µg/dL during the upright posture in the morning. These findings were sufficient to conclude that he did not have surgically treatable aldosteronism, and he was treated medically.

The experience with this assessment of the plasma aldosterone response to upright posture in the morning in patients with primary aldosteronism at Henry Ford Hospital is depicted in Table 4.

The presence of an aldosterone-producing adenoma is not an absolute indication to remove it. This disorder is not known to transform into a malignant lesion or to have a certainly progressive natural history. The hypertension and hypokalemia will remain active problems in need of treatment, and treatment with spironolactone has been used in place of adrenalectomy. Adrenalectomy will cure the hypokalemia, but its effect on the hypertension is not 100% curative; 60% of patients will be cured, and 90% will have importantly improved high blood pressure. To predict which patients are likely to be cured of the hypertension as well as the hypokalemia, their response to high-dose spironolactone can be determined (17):

**Case 9**—This patient underwent successful surgical treatment for an aldosterone-producing adenoma. This was predicted by the response of his blood pressure to treatment with spironolactone, 400 mg daily in divided doses for three weeks. During this period his blood pressure decreased from 160/110 to 130/70 mmHg, and his serum potassium increased to 4.9 mEq/L. The return of his blood pressure to normal levels during high-dose spironolactone treatment predicted its return to normal levels by adrenalectomy.

**Case 11**—A 34-year-old man was found to have primary aldosteronism with urinary aldosterone excretion of 19 µg/24 hr during sodium treatment and a plasma renin activity of 0.8 ng/mL/hr after furosemide and upright posture testing. He had hypertension and hypokalemia. His blood pressure was 154/102 mm Hg before treatment with spironolactone and was 154/108 mm Hg after 400 mg of spironolactone daily for three weeks. Removal of an aldosteronoma cured the hypokalemia but not the hypertension.

**Treatment by Adrenalectomy**

When the diagnosis of primary aldosteronism has been established, and it has been localized to one adrenal gland, adrenalectomy is an appropriate recommendation, particularly if spironolactone treatment testing predicts that this treatment will cure the hypertension as well as the hypokalemia. To minimize the risks of anesthesia and surgery, the hypokalemia and hypertension should be corrected preoperatively:
Case 4—This older patient with hypertensive heart disease and cerebral vascular disease was at high-risk for surgery. Spironolactone treatment corrected her hypokalemia and hypertension preoperatively, and adrenalectomy was accomplished without complication.

Spironolactone blocks the effect of aldosterone on the distal renal tubules and also affects adrenal synthesis of aldosterone. The effects of spironolactone on the response of adenoma tissue to stimuli in vitro were studied among this group of patients, and spironolactone was found to influence the response of aldosteronomas to angiotensin II and ACTH (18).

Calcium-channel blocking drugs have been used to treat primary aldosteronism, because calcium flux has a role in the stimulation of aldosterone synthesis. This treatment can be utilized with that of a potassium-retaining drug:

Case 7—To prepare this patient for adrenalectomy, nifedipine, 40 mg daily, and spironolactone, 100 mg daily, were prescribed. After one month of this treatment, her blood pressure had decreased from severely elevated levels to 140/90 mm Hg. Her potassium was normal then, also.

The reported experience of treating patients who have an aldosterone-producing adenoma with calcium-channel blocking drugs alone, however, suggests that this treatment might not be reliable (19,20).

Adrenalectomy treatment for an aldosteronoma offers a likely cure of the hypertension and hypokalemia and is the usual treatment recommendation. The results of this treatment in this series of patients is shown in Table 5. It is not known how long the blood pressure must be monitored to conclude that the hypertension has been cured.

Hypoaldosteronism after removal of an aldosterone-producing adenoma can result in hypokalemia:

Case 11—This patient was 34 years old when he presented with hypokalemia and refractory hypertension (174/118 mm Hg). Unprovoked hypokalemia was present (2.7 mEq/L); his urinary aldosterone was 19 μg/24 hr, and stimulated plasma renin activity was 0.8 ng/ml/hr. Adrenal cortical scintigraphy showed a unilateral, right-sided image, and he underwent removal of a right-sided, aldosterone-producing adenoma. One week later his urinary aldosterone was 3 μg/24 hr and his serum potassium was 5.0 mEq/L; four months later his serum potassium was 4.5 mEq/L. His blood pressure was lower (150/98 mm Hg) and readily returned to normal with treatment.

An unexpected result of treatment of primary aldosteronism in this series was the appearance of a urinary stone:

Case 11—Two weeks after removal of an aldosterone-producing adenoma, this patient passed a calcium oxalate, urinary stone. Evaluation to detect the cause of the stone was negative.

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Case 12—A 43-year-old man with moderately severe hypertension and primary aldosteronism (urinary aldosterone 58 μg/24 hr during sodium treatment) was treated with spironolactone, 200 mg daily, and in two weeks he passed a urinary stone.

The association between the urinary stone and treatment of aldosteronism might have been coincidental, but aldosterone does enhance hydrogen ion excretion, and the development of hypoadosteronism, from surgery or from pharmacologic blockade, might have altered the physicochemical state of the urine to facilitate stone formation in these two patients.

Medical Treatment of Primary Aldosteronism

One of the subsets of primary aldosteronism (21) is glucocorticoid-remediable hyperaldosteronism, a familial form of bilateral primary aldosteronism which is suppressed by treatment with about 1 mg of dexamethasone daily (22). The excessive aldosterone secretion, hypokalemia, and hypertension remit during this treatment. The aldosterone excess remits within a few days, but the hypertension remits only after about four to six weeks of treatment:

Case 8—This patient had a family history of hypokalemia and hypertension, but the family members, her father and a brother, were not available for evaluation. The patient was shown to have bilateral primary aldosteronism by adrenal cortical scintigraphy, which utilizes dexamethasone treatment to suppress cortisol synthesis. After seven days of this dexamethasone treatment her urinary aldosterone was 9 μg/24 hr during a sodium intake of greater than 250 mEq daily, an indication of a persistently excessive secretion of aldosterone not suppressible by glucocorticoid treatment.

An attempt at glucocorticoid suppression has a risk of exacerbating the hypertension in primary aldosteronism, if glucocorticoid-remediable aldosteronism is not present in the patient. The seven- to 12-day period of dexamethasone treatment as part of scintigraphy has been safe, and it might be a suitable test for the familial disorder by detecting suppression of aldosterone secretion even though the hypertension might not have responded. The blood pressure should be monitored during the evaluation of patients with or thought to have primary aldosteronism.

The medical therapy of primary aldosteronism, not ameliorated by dexamethasone treatment, is that of spironolactone, amiloride, and, recently, calcium-channel blocking drugs. Spironolactone is predictably effective in correcting the hypokalemia and is useful in lowering the blood pressure. Amiloride is a potassium-retaining drug that does not antagonize aldosterone or inhibit its synthesis, but it can correct hypokalemia. An antihypertensive drug is needed with amiloride treatment and in some patients treated with spironolactone. The vasodilators nifedipine and verapamil have been used successfully for this purpose. It is not certain that they will be useful alone, but that prospect yet may exist in idiopathic hyperaldosteronism.

The goals of therapy in primary aldosteronism are a normal serum potassium concentration and a normal blood pressure, without adverse effects of therapy. The long-term risks of unsuccessfully treated primary aldosteronism have not been defined, but they would include those of uncontrolled hypertension. The
adverse effects of spironolactone primarily are those of its effect as an antiandrogen with potential for gynecomastia and impotence in men and menstrual irregularities in women.

A more specific therapy of the bilateral form of primary aldosteronism might be possible if its cause were known, but it is an idiopathic disorder. Because the pathology is usually a bilateral adrenal hyperplasia, it has been suggested that it is a secondary aldosteronism, resulting from a stimulus, such as ACTH in Cushings disease. A search for an aldosterone-stimulating factor has not yet clearly identified such a substance (23, 24). A deficiency of a physiologic inhibitor, such as serotonin (25) or dopamine (26), has been postulated as a cause of idiopathic hyperaldosteronism, but this does not appear to be the explanation either (27). The role of atrial natriuretic factor, which might be a physiologic inhibitor of aldosterone secretion (28), has yet to be determined in the pathogenesis of idiopathic hyperaldosteronism.

Idiopathic hyperaldosteronism is a rare disorder, comprising about one-half of the patients who have primary aldosteronism, itself a rare syndrome. Beyond the importance to the person with this unusual endocrine cause of hypertension it is similar to it low-renin essential hypertension, a relatively common idiopathic type of essential hypertension in which aldosterone secretion is not consistently high, but in which there appears an inappropriate degree of aldosterone secretion (29). To the extent that the pathophysiology of idiopathic hyperaldosteronism is similar to that of low-renin essential hypertension, the search for the cause of idiopathic hyperaldosteronism is important.

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References