Urinary Aldosterone and Hypertension

By RANDALL H. TRAVIS, M.D., JOSEPHINE B. GARBST, PH.D., and ROGER JELLIFFE, M.D.

A POSSIBLE ETIOLOGIC ROLE of the adrenal cortex in the genesis of clinical hypertension has been recognized since Goldblatt's demonstration in 1937 that adrenalectomy prevents the expected development of hypertension following bilateral renal artery constriction. Recently, interest in this possibility has been intensified by reports that some hypertensive patients excrete and secrete increased amounts of aldosterone in the absence of any apparent known cause.

The following case report describes a hypertensive patient with increased urinary aldosterone attributable to renal sodium wasting, detectable only by severe sodium deprivation. Intensive antihypertensive therapy was associated with improved renal function and a fall in average urinary aldosterone.

Methods for Metabolic Studies

In collection of urine each voiding was immediately refrigerated. At the end of each collection period the total quantity excreted was frozen until analysis. Sodium and potassium contents of serum and urine were determined in duplicate with a Baird flame photometer with lithium internal standards. Serum chloride was determined by a modification of the method of Asper, Schales, and Schales. Serum and urine creatinine were determined by the method of Bonsnes and Taussky as modified by Brod and Sirota. "Creatinine clearances" were calculated in the usual way from the creatinine content of a 24-hour urine collection and the serum creatinine concentration of the morning of the same day.

The method used for measuring aldosterone was as follows: A 24-hour collection of urine was acidified to pH 1 and allowed to stand 24 hours at room temperature to hydrolyze aldosterone conjugate. The free aldosterone was extracted with chloroform, and the chloroform was evaporated to dryness after suitable washing. The dry steroid residue was chromatographed on paper in toluene saturated with propylene glycol. That part of the residue which migrated with cortisone was recovered and acetylated. The aldosterone diacetate was then freed from other steroid acetates by chromatography on paper in hexane saturated with propylene glycol. The aldosterone was quantitated by ultraviolet spectrophotometry. Normal values in this laboratory are: mean 9.1 ± 2.8 micrograms (standard deviation) per 24 hours.

Case Report

R. McK., V.A. no. 2029, a 44-year-old white male, rubber factory worker, was admitted to Crile Veterans Administration Hospital on August 18, 1958, with complaints of morning headache, asthenia, and intermittent tingling of the soles of the feet of 8 to 10 months' duration. He had been seen by a physician at intervals during 1957 for treatment of asthmatic bronchitis. Blood pressure was within normal limits at that time. The first significant hypertension was observed in June 1958, at which time a value of 158/98 mm. Hg was recorded.

Past medical history included a penile ulcer in 1939, treated with injections, and Plasmodium vivax malaria, incurred during World War II in the Pacific Theatre. Routine urine analyses in 1946 and in 1957 had shown no abnormalities.

Important findings on admission in August 1958 were blood pressure 230/120 mm. Hg, barely palpable spleen and liver, and ophthalmoscopic finding of bilateral scattered flame hemorrhages, "cotton wool" exudates, and arteriovenous nicking with mild right papilledema. Occasional wheezes and coarse rhonchi were heard at both lung bases. Cervical venous distention was not present. Cardiac borders were percussed within normal limits. Ankle edema was absent. Congestive failure was considered absent at this and at subsequent examinations. Lung findings, which were inconsistent, were attributable to asthmatic bronchitis. Slight hepatosplenomegaly was considered the result of malaria.

Laboratory findings were hematocrit value 49 per cent and white blood cells 10,500/ml. Of 11 random urine examinations made during this hospitalization, 10 showed a specific gravity of less than 1.010; one was reported as 1.012. Proteinuria...
ranged from 0 to 2 plus without significant cellular elements. Maximum specific gravity attained in the Fishberg concentration test (15 hours water deprivation) was 1.008 on two occasions. Urea clearance was 87 per cent of normal with blood urea nitrogen 7 mg./100 ml. Divided renal function tests showed bilateral appearance of indigo carmine in 3 minutes and bilaterally similar excretion of sodium, potassium, and chloride. Retrograde pyelography showed no significant abnormality. Chest x-ray showed a cardiac silhouette within normal limits and no significant lung pathology. The electrocardiogram suggested slight left ventricular hypertrophy. Phentolamine methanesulfonate, 5 mg. by rapid intravenous injection, caused no significant fall in blood pressure. Cephalin flocculation was reported negative, prothrombin time within normal limits, total serum protein 6.4, albumin 3.7, and globulin 2.7 Gm./100 ml. Bromsulfalein retention was 6 per cent in 45 minutes. During this hospitalization, the right gastrocnemius muscle and lymph node biopsies were negative. The L. E. test and the serologic test for syphilis were negative.

On the second hospital day, August 20, 1958, the patient had a generalized clonic-tonic convulsion. Skull films showed normal. Ventriculography performed 5 days later was within normal limits, and cerebrospinal fluid obtained at that time contained 23 mg./100 ml. of protein. Electroencephalography 2 days and 21 days after the seizure showed symmetrical, mild, diffuse abnormality.

The presence of headache, severe hypertension, and papilledema suggests that the convulsion was symptomatic of cerebral edema and hypertensive encephalopathy. No additional convulsions or episodes of encephalopathy have occurred.

On the day of the convulsion, August 20, chlorothiazide, 0.5 Gm. at 8-hour intervals, was begun. It was discontinued the second day following the convulsion, a total of 3.5 Gm. having been given. In the 5 days following the seizure, the patient ate but little, and fluid and electrolyte were given by intravenous infusion. The ward diet offered was estimated to contain 100 to 140 mEq. of sodium daily. In table 1 are shown serum electrolyte concentrations, known intravenous and oral electrolyte intake, and medication. (Dietary electrolyte is not known and not included.) In the first 3 to 4 days after the seizure there was a marked fall in serum sodium, potassium, and chloride and a rise in carbon dioxide combining power. The appearance of hyponatremia on August 23, despite an intake of at least 465 mEq. of sodium in the preceding 3 days, suggested a possible disorder of renal or endocrine electrolyte regulatory mechanisms.

Table 2 shows urinary aldosterone values obtained between September 11, 1958, and March 1, 1959. Also shown are chlorothiazide and dietary potassium supplements. During the entire period the patient was in the hospital with the exception of the intervals October 25 to December 8, 1958 and February 5 to 15, 1959. It can be seen that in six specimens examined, three aldosterone values were definitely elevated and one was borderline. No clear correlation with potassium intake or chlorothiazide administration is apparent.

During this hospitalization therapeutic trials of different combinations of chlorothiazide, reserpine, and mecamylamine hydrochloride were made without sustained reduction of blood pressure.

On March 19, 1959, the patient was transferred to the Metabolic Division of University Hospitals of Cleveland for study of sodium and potassium metabolism.

Complaints of headache and malaise persisted. Important physical findings were blood pressures of 225/110 and 270/160 mm. Hg in the left arm.

Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Na mEq./L</th>
<th>K mEq./L</th>
<th>Cl mEq./L</th>
<th>CO₂ mEq./L</th>
<th>Intake supplement (mEq)</th>
<th>Chlorothiazide</th>
</tr>
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<tbody>
<tr>
<td>Aug.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Na K Cl</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>19</td>
<td>3.6</td>
<td>90</td>
<td>28.5</td>
<td></td>
<td>310 310 0.5 Gm. t.i.d.</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>20</td>
<td>3.0</td>
<td>81</td>
<td>31</td>
<td></td>
<td>155 155 0.5 Gm. t.i.d.</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>21</td>
<td>2.4</td>
<td>79</td>
<td>27.2</td>
<td></td>
<td>54 54 0.5 Gm.</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>22</td>
<td>3.0</td>
<td>72</td>
<td>34</td>
<td></td>
<td></td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>24</td>
<td>3.1</td>
<td>77</td>
<td>36</td>
<td></td>
<td></td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>25</td>
<td>3.5</td>
<td>89</td>
<td>32</td>
<td></td>
<td>155 40 195</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>26</td>
<td>3.6</td>
<td>89</td>
<td>31.5</td>
<td></td>
<td>155 155</td>
<td>chlorothiazide</td>
</tr>
<tr>
<td>27</td>
<td>3.4</td>
<td>98</td>
<td>29.5</td>
<td></td>
<td>155 155</td>
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<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>chlorothiazide</td>
</tr>
</tbody>
</table>
and right thigh, respectively. Eyegrounds showed arterial narrowing and tortuosity and fluffy exudates in both eyes, with blurring of the right disk margin. The liver edge was barely palpable, smooth, and nontender.

Laboratory examinations revealed 3 plus proteinuria, 4.83 million erythrocytes per ml. of blood, hemoglobin 13.9 Gm./100 ml., reticulocytes 1.1 per cent of erythrocytes, and leukocytes 6,500/ml. A chest x-ray was within normal limits, and the electrocardiogram showed left ventricular hypertrophy.

On March 23, 1959, metabolic studies were begun with a daily intake of 13 mEq. of sodium and 200 mEq. of potassium. All medication had been discontinued on February 19 except codeine for headache. All food consumed by the patient was from analyzed single lots. Dishes were rinsed after each meal and rinsings were drunk. Figure 1 shows the results of these studies. With a sodium intake of 13 mEq. per day, urinary sodium consistently equaled or exceeded sodium intake. There was a progressive fall of serum sodium to 114 mEq. on the fourteenth day. At this time the patient was not clinically dehydrated but was apathetic and expressed salt craving. On the fifteenth day of study 300 mEq. of sodium were given intravenously as 5 per cent sodium chloride, and dietary sodium was increased to 200 mEq. by the addition of enteric-coated sodium chloride tablets to the otherwise unchanged diet. Marked sodium retention was observed on the first day only of increased sodium intake and thereafter the patient appeared to be in approximate sodium balance.

On the twenty-first and twenty-second days, severe headache was associated with negative sodium balance and reduced serum sodium concentration. Although the sodium deficit was apparently rapidly repaired, urinary aldosterone was still elevated 6 days later.

Renal potassium excretion was not remarkable at any time. (Kaliuresis induced by hypertonic saline infusion (study day 15) has been previously described in normal persons.22) The progressive fall in creatinine clearance with sodium deprivation has been described in normal persons and has been attributed to reduced plasma volume.18 Consistent changes in blood pressure were not observed at any time during these studies.

On May 20, 1959, the patient was returned to Crile Veterans Administration where he was equipped with, and trained in the use of a sphygmomanometer. Vigorous antihypertensive therapy was initiated. On June 3, 1959, he was discharged to the home of his sister with instructions to take 2.0 Gm. of sodium chloride daily with an ad lib. diet, reserpine 1.0 mg. daily, and mecamylamine hydrochloride as required to regulate blood press-

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**Figure 1**

Metabolic studies conducted March 23 to April 20, 1959, showing development of hyponatremia, reduced “creatinine clearance,” and increased urine aldosterone during 14 days of sodium intake restricted to 13 mEq. daily. After restitution of serum sodium by hypertonic saline infusion and increase of dietary sodium to 200 mEq. daily, 2 days of negative sodium balance resulted in a second fall of serum sodium.

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**Figure 2**

Photographs of right retina in September 1958 (left) and January 1960 (right) showing disappearance of exudates and papilledema and resorption of hemorrhages following reduction of blood pressure.
Table 2

Urine Aldosterone, September 11, 1958 to March 1, 1959

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine aldosterone ( \mu \text{g.}/24 \text{ hrs.} )</td>
<td>39</td>
<td>31</td>
<td>7</td>
<td>11</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Chlorothiazide ( \text{Gm./day} )</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Potassium supplement ( \text{mEq./day} )</td>
<td>50</td>
<td>0</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

sure. In this environment, he was able to maintain his systolic blood pressure at approximately 160 mm. Hg and experienced relief of headaches and an improved sense of well-being. After six months in the home of his sister, he moved to his father's home where he soon began to experience difficulty in controlling his blood pressure. On February 15, 1960, he was admitted to Crile Veterans Administration Hospital for re-evaluation. All medication was discontinued on admission.

During the first week following admission, blood pressure ranged from 230/120 to 180/100 mm. Hg. Remarkable improvement in the appearance of the eyegrounds had occurred. Figure 2 shows photographs of the right retina taken shortly after the first admission in August 1958 and the appearance of the same eye in February 1960. Papilledema, hemorrhages, and exudates had disappeared completely. Equivalent changes had occurred in the left eye. The only observed evidences of retinopathy were bilateral segmental arteriospasm and postpapilledema halo in the right eye. The remainder of the physical examination was unchanged.

Routine blood examinations were within normal limits. Urine analysis revealed a trace of albumin and occasional red and white cells in the centrifuged sediment. Serum sodium was 137 mEq./L, potassium 4.3 mEq./L, chloride 99 mEq./L, and carbon dioxide combining power 25 mEq./L. Urea clearance was 108 per cent of normal with blood urea nitrogen 12 mg./100 ml. The maximum specific gravity attained in the Fishberg concentration test (15 hours water deprivation) was 1.022 on one occasion and 1.020 on a second occasion. Of random urine specimens examined during this hospitalization, 41 per cent had specific gravities of 1.010 or less; 53 per cent had specific gravities greater than 1.010 and less than 1.016; and 6 per cent had specific gravities of 1.016 or greater, in contrast to the consistent hyposthenuria of the first admission.

Urine aldosterone values were 3.8, 7.1, and 6.5 \( \mu \text{g.} \) per 24 hours on March 7, 8, and 9 respectively, while the patient was taking the ward diet estimated to contain approximately 100 to 140 mEq. of sodium daily, without dietary electrolyte supplementation. These hormone values appear to be clearly different from those obtained on the first admission (table 2) on the same diet.

On March 22, 1960, the ward diet was changed to one having a calculated sodium content of 18 mEq. per day. This diet was continued for 28 days. During the first 12 days, daily urinary sodium excretion gradually decreased from an initial 122 mEq. to values generally less than 18 mEq., with occasional values as high as 23 mEq. and as low as 6 mEq. Serum sodium during the 28-day period ranged from 131 to 147 mEq./L, without regular pattern. On the twenty-eighth day the value was 137 mEq./L. Urinary potassium ranged from 41 to 91 mEq. daily, averaging 62 mEq.; serum potassium ranged from 3.8 to 5.0 mEq./L.

Although a rather long period was required to reduce urinary sodium excretion below intake, the patient was able to remain in sodium balance and to avoid hyponatremia for a prolonged period with a daily intake of only 18 mEq. This test of ability to maintain sodium balance with a low intake, while not precisely comparable to the study performed 1 year earlier, suggested an improved capacity for sodium retention.

Discussion

These data suggest the following sequence of events: In 1958, for unknown causes, the patient developed severe hypertensive disease with renal dysfunction characterized by loss of concentrating ability, proteinuria, and a tendency to renal loss of sodium. The tendency to sodium loss was compensated by increased aldosterone secretion, permitting maintenance of sodium balance with normal sodium intake. When sodium intake was reduced to 13 mEq. daily, however, a consistently negative sodium balance developed, leading eventually to hyponatremia (study days 1 through 14, fig. 1). This result occurred despite an apparent marked rise in...
aldosterone secretion and a reduction of glomerular filtration. Significant amounts of sodium persisted in the urine despite the presence of hyponatremia. When daily sodium was increased to 200 mEq., balance was restored, though only minimal sodium retention occurred. Thereafter, a brief period of negative sodium balance (study days 20, 21, and 22, fig. 1) resulted in a fall of serum sodium to near hyponatremic levels.

Following these metabolic studies, there occurred a remission of the disease process, possibly the result of therapy. This remission was manifested by improved appearance of the eye grounds (fig. 2) and improved renal function, shown by return of concentrating ability. Renal sodium conservation seemed improved as shown by the failure to develop hyponatremia during 28 days of low-sodium intake. Urinary aldosterone was well within normal limits when the diet contained an amount of sodium that previously had been associated with hyperaldosteronuria.

The hyponatremic syndrome described in this patient is clearly different from the hyponatremic syndrome attributed to "inappropriate secretion of antidiuretic hormone" by Schwartz, Bennett, Curelop, and Bartter, and is presumably of renal origin. The patients described by those authors did not lose weight as sodium loss continued, reflecting maintenance of extracellular volume. In our patient, sodium loss was accompanied by weight loss and decreased "creatinine clearance," reflecting reduction of extracellular volume.

In summary, it is postulated that this patient had the clinical syndrome of severe hypertension, associated with a renal sodium-losing tendency compensated by increased aldosterone secretion. Pharmacologic reduction of blood pressure was followed by improved renal function and amelioration of the tendency to sodium loss. A consequent reduction of aldosterone secretion was reflected in reduced urinary aldosterone.

The course of this patient suggests a possible explanation for the otherwise unexplained increase in aldosterone excretion observed in some hypertensive patients. It is unlikely that such findings reflect an idiopathic physiologically excess secretion of aldosterone as a sole etiologic agent in the genesis of hypertensive disease. The usual absence in hypertensive patients of the definite potassium deficiency, and alkalosis characteristic of Conn's syndrome suggests that increased aldosterone secretion in hypertension is secondary and compensatory.

The hypothesis is suggested that the increased aldosterone secretion occurring in some hypertensive patients is compensatory to a renal sodium-losing tendency. Validation of this hypothesis requires a demonstration that increased aldosterone secretion in hypertensive patients is usually associated with a renal sodium-losing tendency. Such evidence is neither available nor easily obtained, for if aldosterone compensation were effective, hyponatremia would not be produced except by very low sodium intakes over quite long periods of time, particularly if marked falls in glomerular filtration rate occurred.

The hypothesis is supported, however, by evidence that a renal sodium-losing tendency occurs with significant frequency in hypertensive patients.

Frank "sodium wasting nephritis" characterized by evidence of severe renal disease and hyponatremia with fairly high sodium intakes has been described in association with hypertension. A less obvious disorder was observed by Newborg and Kempner in a series of 159 patients with malignant hypertension treated with a rice-fruit diet (less than 7 mEq. of sodium daily). Of these patients, 20 per cent developed hyponatremia or hypochloremia of a degree sufficient to warrant modification of the diet. The authors comment that "inability to conserve electrolytes may, in some instances, be the chief manifestation of renal dysfunction and may occur in the absence of severe impairment of PSP excretion or of marked azotemia."

Several investigators have observed that, statistically, hypertensive patients excrete more sodium during and immediately following a standard infusion of hypertonic saline.
than do normotensive persons.\textsuperscript{18-23} This phenomenon is consistent with the postulate that the diseased kidneys of some hypertensive patients tend to excessive losses of sodium but such patients are prevented from developing a persistently negative sodium balance over a wide range of sodium intake by a compensating increase in aldosterone secretion. Since hypertensive saline infusion reduces aldosterone secretion,\textsuperscript{24} an aldosterone-compensated renal tendency to sodium-losing may become evident after such infusions.

The reported tendency of hypertensive persons voluntarily to ingest more sodium chloride\textsuperscript{25, 26} than normotensive persons is also consistent with a sodium-losing tendency.

\textbf{Conclusion and Summary}

A 44-year-old man with severe hypertension, hypertensive retinopathy, hypertensive encephalopathy, and loss of renal concentrating power was observed to have hyperaldosteronuria. Dietary sodium restriction revealed a renal sodium-losing tendency. Intensive therapy designed to reduce blood pressure was followed by improvement in eye-grounds, return of renal concentrating power, improved renal sodium-retaining power, and decreased urinary aldosterone excretion.

It is suggested that the hyperaldosteronuria of some hypertensive patients is a manifestation of an aldosterone-compensated renal sodium-losing tendency.

\textbf{References}


Now the properties of water have the result that more readily than other substances it exists simultaneously and in large quantities in the three phases of solid, liquid, and gas as ice, water, and aqueous vapor. This depends upon the high latent heats of fusion and vaporization, the high freezing point of water, and its vapor tension. Water enhances the complexity of the environment, and is one principal factor in the mobility of the environment as a whole. Further, it makes for stability; other things being equal, the greater the number of phases, the less the tendency to change. Among phases the disperse colloidal type is unique and of very great importance—almost the sole basis, indeed, of great physical complexity—and, as above shown, the peculiar properties of water highly favor the colloidal condition.

The solvent power of water much increases the number of components which may enter into a system of which it is a part; hence the large number of components of sea water, blood plasma, etc. The variety of compounds, both organic and inorganic, which contain carbon, hydrogen, or oxygen also causes enormous increase in the number of components of biological systems like protoplasm.

The specific heat of water, its latent heats of fusion and vaporization, and the high freezing point all contribute to the restriction of temperature range within the organism, in the waters, and over the whole surface of the earth. The vapor pressure of water has been shown to possess great and exceptional variability with change of temperature. This is the most important property of water meteorologically, and is the necessary condition for its ample circulation. The ratio between the gas pressure of carbonic acid and its concentration in water (absorption coefficient) has been shown to be the great factor in establishing the mobility of that substance.—LAWRENCE J. HENDERSON. The Fitness of the Environment. New York, The Macmillan Co., 1924, p. 258.
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Circulation. 1961;24:592-598
doi: 10.1161/01.CIR.24.3.592

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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