Two syndromes associated with edema in the absence of renal, cardiac, hepatic, pulmonary, central nervous system, or vascular disease have been described in mature women: Streeten and Conn in 1951 reported edema of obscure origin in six women who demonstrated excessive daily weight gain, reversal of normal diurnal variation of water excretion, and inability to excrete a water load normally when erect, whereas diuresis occurred during recumbent posture. Aldosterone excretion was normal or only slightly increased. The altered water excretion in the erect position could be blocked by ethanol, by inflation of a cervical cuff to 15–30 mm Hg, and usually by sympathomimetic drugs. Erect posture after water loading in the recumbent position was associated with an increase in urine osmolality and decrease in free water clearance without alteration in glomerular filtration rate suggesting an inappropriate antidiuretic hormone effect. Clinical improvement or elimination of edema occurred during chronic administration of dextroamphetamine.

A second syndrome of "idiopathic" edema differing from the first by the presence of hyperaldosteronuria has been reported in a number of women. The hyperaldosteronuria in these patients appears to be secondary, however, rather than primary; hypertension and severe potassium deficiency were not usually observed. The edema was sometimes cyclic relative to menses and of variable severity. In one of these patients, a 39-year-old woman reported by Greenough and colleagues, the presenting symptom was postural hypotension. Investigations in that patient revealed a decreased glomerular filtration rate, an increased plasma volume, and a normal distribution and half-life of radioiodinated albumin. During tilt table studies an "arterial anemia" pattern of vascular response to erect posture was observed, i.e., a decrease in pulse pressure, increase in diastolic pressure, and an excessive increase in pulse rate. Administration of sympathomimetic drugs produced diuresis and suppression of aldosterone secretion to normal levels. These authors suggested that an abnormal venous pooling with deficient arterial filling during erect posture may be the basic defect in this syndrome.

Two additional women patients, perhaps representing the same or a similar syndrome, have been reported. One of these presented massive anasarca, hyperaldosteronuria, hypoalbuminemia with renal disease, and an adrenal adenoma. The other manifested paroxysmal episodes of shock postulated to be due to abnormal vascular permeability; aldosterone measurements were not done in this patient, however.

The present patient, an early adolescent, was first seen in this hospital at 14 years of age with a history of two years of edema of obscure origin. The present report is concerned with chemical and metabolic studies conducted on this patient over a 28-month period. She appears to be the first documented instance of early pubertal hyperaldosteronuria with associated "idiopathic" edema.

* The patient of Greenough and associates did present intermittent hypokalemia.
CASE REPORT

R. J. UAMC No. 19 32 06

In March, 1960, at the age of 11 9/12 years this red-headed white female adolescent experienced the gradual onset of swelling of both feet. The swelling was relatively mild initially and disappeared completely at night. Later the swelling was obvious in the morning but most severe in the evening; at no time did it completely disappear.

There were no clinical manifestations suggestive of cardiopulmonary, hepatic or renal disease, no symptoms of potassium deficiency, and no history of cellulitis or thrombophlebitis in her extremities. Twenty months after the onset of the pedal edema the patient was evaluated regarding a mild behavior disorder at which time swelling was relatively mild initially and obvious in the morning but most severe in the evening; at no time did it completely disappear. She was referred at that time to the University hospital for evaluation of her edema.

Family history and past history were non-contributory.

Physical examination revealed four plus pitting edema of her feet and ankles which extended to her mid-calf bilaterally. There was no evidence of phlebitis, cellulitis, or varicosities. Venous pressure was 60 mm of water. Height was 156 cm and weight 46 kg. Blood pressure was 110/68. Moderate breast development and moderate growth of pubic and axillary hair were present. Vaginal bleeding had not yet occurred; however, during the observation period approximately 27 months after the onset of her edema, her first menses was recorded.

Laboratory data included: hemoglobin 13.2 gm; WBC 5,700; normal differential count; urine pH 5.0; specific gravity 1.026; urinary reducing substances, qualitative protein, and microscopic examinations negative; 12-hour Addis count 2 million WBC and 246,000 RBC; 12-hour urinary protein (Esbach) negative; total serum protein 7.1 gm/100 ml; A/G ratio 5.0/2.1; serum protein electrophoresis normal; total serum cholesterol 170 mg/100 ml; blood urea nitrogen 16 mg/100 ml; serum sodium 147, potassium 4.6; CO2 combining power 26 and chloride 105 mEq/l; serologic test for syphilis negative; skin test for tuberculosis negative; skin test for histoplasmosis positive (15 cm erythema and 0.2 mm induration at 48 hours); ASO titer 100 Todd units; C reactive protein negative; thymol turbidity 3.0 units; cephalin flocculation at 24 and 48 hours negative; BSP retention 3%; twenty-four hour thyroid radiiodine uptake 26.1%, PBI 5.3 ug/100 ml and thyroxine degradation rate 42 mcg/day (determined from exogenous thyroxine 1m volume of distribution, plasma disappearance rate and PBI value). Chest x-ray and intravenous pyelogram interpreted as normal; bone age (by the standards of Cruelich and Pyle) 12-13 years. Radioiodine labeled diodrast activities measured simultaneously over the right and left kidneys during erect and recumbent posture were similar and revealed no evidence of unilateral renal disease.

METHODS

Salt intake was controlled using a basic 200 ug salt diet (approximately 4 mEq Na). Additional sodium intake was provided by daily provision of 52, 101, or 146 mEq sodium (as chloride) daily in addition to the basic diet. A five-day period of equilibration to a given sodium intake was routinely allowed unless indicated otherwise. Body weight was measured twice daily at 7:00 A.M. and 9:00 P.M. Urine was collected in two daily aliquots—7:00 A.M. to 9:00 P.M. and 9:00 P.M. to 7:00 A.M.

Urine osmolality was measured by freezing-point depression using a Fiske osmometer. Urine sodium and potassium content were measured using a Baird flame photometer and comparison with suitable standards. Urinary 17-hydroxysteroid excretion was measured as Porter Silber chromogen.11-13 Urinary 17-ketosteroid excretion was measured by the Zimmerman reaction using the method of Drekter and co-workers.14 The tetrahydro metabolite(s) of aldosterone was isolated by the method of Ulick and Lieberman15 as modified by Melby and colleagues.16 This fraction will be referred to hereafter as tetrahydroaldosterone. Blood and urine creatinine were measured by the Jaffe reaction as described by Peters and Van Slyke18 and PAH in blood and urine was measured by the method of Smith and associates.19

RESULTS

Daily Weight Gain

Streeter and Conn1 reported that daily weight gain in patients with idiopathic edema and inappropriate ADH secretion was excessive when compared to control subjects. In the present patient a mean day-
time weight gain of 2.4 lb* was recorded on the metabolic study ward on 105 mEq sodium daily; reduction of sodium intake to 3–5 mEq daily reduced the mean daytime weight increment to 1.7 lb. Daily weight gain at home averaged about 3 lb on an unrestricted diet. In five normal children of similar age and weight (85–105 lb) mean daytime weight increment at home on an unrestricted diet was 1.7 lb (range 1.4 to 1.9 lb).

**Salt and Water Excretion Studies**

Water loading test was normal; the patient was given an oral water load of 20 ml/kg after 4 hours of erect posture. Initial urine osmolality of 690 mOsm/kg decreased at peak diuresis (2 hours) to 100 mOsm/kg. Eighty-five per cent of the water load was excreted within 3 hours.

Results of a 13-day study of the effects of salt restriction and prolonged recumbent posture on body weight, urinary sodium and potassium excretion, and urine volume and osmolality are shown in Figure 1. Decreasing salt intake as well as 58-hour periods of recumbent posture resulted in sodium and water diuresis. With salt restriction (4.3 mEq sodium daily) sodium excretion promptly decreased over a 5-day period to approximately 1 mEq daily and diurnal weight variation was minimized. Potassium intake was estimated to be 119–135 mEq daily. The usual diurnal variation of urine volume and osmolality were observed throughout this period.

**Aldosterone Excretion and Secretion Studies**

Excretion of tetrahydroaldosterone (THA) related to recumbent and erect posture and variation in sodium intake is shown in Table I. THA excretion does not overlap with data from four normal female children of similar age and weight. The expected increase in aldosterone excretion with salt restriction and decrease with recumbent posture were observed.

THA excretion in daytime (14 hour) and overnight (10 hour) specimens was also determined on 105 mEq sodium intake. A mean of 136 μg (range 118–158) in four daytime specimens and 69 μg (range 64–85) in four corresponding overnight specimens were measured.

Acid hydrolyzable aldosterone and aldosterone secretion rate, by the double isotope derivative method of Kliman and Peterson,† were measured in the patient (R. J.) and in two control subjects. These data are shown in Table II. The excretion and secretion values on 105 mEq sodium daily (Table II) were not elevated as in Table I. The data in Tables I and II were obtained during different admissions approximately 3 months apart.

* All values present the mean of at least 10-day observation periods.

† Analyses done at Medinuclear Research Laboratories in Houston, Texas.
months apart; clinical manifestations were much milder during the time of the later determinations. Secretion rate was measured on an unrestricted diet and again on the fourth day of salt restriction in control subjects; measurements in patient R. J. were conducted on the fifth day of 105 and 56 mEq sodium intake and the sixth day of salt restriction.

**Response to Metopirone and Spirolactone**

A metopirone test was conducted by administration of 750 mg of the drug orally every 6 hours for 3 days. Twenty-four-hour urine specimens were collected for one day before, during, and for 3 days after drug administration for measurement of 17 hydroxy and 17 ketosteroid. Baseline 17 hydroxy and 17 ketosteroid values were 4.8 and 9.3 mg/24 hours respectively. A normal threefold increase in urinary Porter Silber reacting chromogen and twofold increase in 17 ketosteroid were observed by the second day of drug administration.

The response to spirolactone is shown in Figure 2. During this time the patient was on 105 mEq sodium daily. Six hundred mg of Aldactone was administered daily for a 9-day period. Weight loss, sodium diuresis, and temporary marked improvement in the edema occurred. Escape from the spirolactone effect was observed on the seventh day. A repeat study again demonstrated diuresis using 1,200 mg spirolactone daily but the escape phenomenon was not observed over a 10-day period of administration.

**Sodium Loading and Serum Potassium**

Because of the evident hyperaldosteronuria and the previously reported precipitation of hypokalemia by salt loading in patients with hyperaldosteronism, the effect of a 2-month period of 105 mEq
sodium and 100 mEq potassium intake daily on serum potassium concentration was conducted. Initial serum potassium concentration was 4.6 mEq/l; weekly determinations over this 2-month period varied between 4.4 and 4.6 mEq/l. During the entire 28-month observation period serum potassium concentration varied between 4.1 and 4.6 mEq/l. Thus, no tendency to hypokalemia, either spontaneous or secondary to salt loading, was noted.

### Renal Function Studies

Renal function studies during postural tilt table studies employing bilateral ureteral catheterization are shown in Table III. Urine volume, sodium excretion, PAH clearance, and creatinine clearance were similar bilaterally during recumbent posture. The data are thus recorded as combined values each representing the mean of at least two 10-minute observation periods. As will be noted PAH clearance decreased 68% and creatinine clearance 53% with assumption of erect posture. Sodium excretion rate decreased 75% without increased excretion of tetrahydroaldosterone.

Creatinine clearance was also measured day and night over a 3-day period. The mean daytime value (determined from three 14-hour specimens) was 71 ml/min (range 68–75) and mean overnight value (three 10-hour specimens) 65 ml/min (range 62–66). These values corrected to 1.73 square meters surface area were 89 and 80 ml/min respectively.

### Measurement of Plasma Volume and $^{113}$I Degradation Rate

Investigations of apparent volume of distribution of $^{113}$I albumin were determined by the usual isotope dilution technique 30 minutes after injection of radiiodinated albumin. Samples were assayed in a well-type scintillation counter. The initial plasma volume measurement was conducted at 8:00 A.M. at which time hemoglobin concentration was 13.0 gm/100 ml and hematocrit 43%. These studies were repeated at 6:00 P.M. after 10 hours of erect posture with suitable correction for radioactivity from the initial dose. Hematocrit at 6:00 P.M. was 33%. Plasma volumes were as follows:

- **8:00 A.M.** 2176 ml 5.0% body weight
- **6:00 P.M.** 3008 ml 6.8% body weight

During a separate hospital admission 2 months later, a study of the degradation rate of $^{113}$I albumin was conducted. Radioactivity in serum samples was counted as described. Serum albumin concentrations were measured in an autoanalyzer by the 2(4 hydroxy-benzeneazo) benzoic acid color reaction. Albumin specific activities were calculated in $\mu$C/gm albumin. These results are shown in Figure 3. As noted the half-life of the initial rapid phase of the degradation curve was 20.4 hours and was followed by an exponential decay curve with a half-life of about 11 days.

### Blood Pressure Response to Tilting

Figure 4 demonstrates the systolic and diastolic pressure, finger cuff pressure, and pulse response to tilting from 0 to 90° on a
idiopathic edema

Fig. 3. Disappearance rate of serum radiiodinated albumin. The initial rapid half-life presumably reflecting rate of distribution is followed by a more prolonged exponential curve probably indicating degradation.

Tilt table. The study was conducted fasting at 8:00 A.M. prior to assumption of erect posture. Tilting to 90° erect posture produced a normal increase in brachial diastolic pressure and transient increase in systolic pressure followed by a decrease in pulse pressure. Pulse rate increased excessively from 100 to 160 beats per minute and was maintained at this elevated level for a total 90-minute observation period. Similar responses were observed consistently in tilt table studies.

Response to Exogenous Angiotensin II and Norepinephrine Infusions

Infusions of angiotensin II (Hypertensin-Ciba) and norepinephrine (Levophed-Winthrop) were conducted during recumbent posture using a constant infusion pump (Model K679 manufactured by Engineering Specialists, Madera, Ohio) in control subjects and in Patient R. J. Infusions were continued at a given dose per kilogram body weight per minute until a constant

- These data were recorded by Dr. James Wilson using a Winston systolic follower for the finger pressure, a Baylor intermittent automatic blood pressure cuff for the brachial artery pressure, and a Fels cardiogilometer for heart rate.

blood pressure (measured at 5-minute intervals) was obtained (usually 20–30 minutes).

These data are shown in Figures 5 and 6. Figure 5 shows the systolic and diastolic BP response to angiotensin II recorded as the mean of two separate studies over a 1-week interval. The indicated normal range is constructed from the values in the three patients reported by Bartter and colleagues confirmed by an additional three normal early adolescent female volunteer subjects on our research ward. Both systolic and diastolic responses to angiotensin in Patient R. J. fall in the low normal range. The decrease in pulse rate, not shown in Figure 5, was minimal (less than 10%).

Figure 6 shows diastolic and systolic BP and pulse responses to norepinephrine infusions similarly conducted. Norepinephrine is recorded on the horizontal axis as μg norepinephrine base/kg/min. The shaded areas represent infusions conducted in five normal early pubertal adolescent subjects (2 male, 3 female). Three response tests in Patient R. J. are separately recorded. Response (a) was obtained during her second admission without therapy. Response (b) was obtained while on 12.5 mg

Fig. 4. Blood pressure and pulse responses to tilt table studies. For methods of measurement and recording the reader is referred to the text. With 90° erect tilting an increase in systolic and diastolic blood pressure occurred followed within 20 minutes by a decrease in pulse pressure and marked increase in pulse rate.
ephrine sulfate q.i.d. Therapy had been continued for a period of 3 weeks at the time of testing. Response (c) was obtained during her most recent admission when she had been without therapy for a 2-month period. These responses, particularly (a), are suggestively abnormal, e.g., the dose of norepinephrine necessary to produce a given increment in systolic and diastolic blood pressure was greater than in control subjects. In addition, significant progressive increase in pulse pressure and decrease in pulse rate with increasing infusion rates were observed in Patient R. J. as well as in control subjects. This increment in pulse pressure in Patient R. J. exceeded that in control subjects at high norepinephrine infusion rates (0.3 μg/kg/min).

**Catecholamine Excretion Studies**

Measurements of urinary catecholamine excretion during recumbent and erect posture* are shown in Table IV. Obvious increase in 4-hour norepinephrine excretion occurred in response to erect posture. This increase was not excessive in degree. In only one of the four studies did increase in 4-hour epinephrine excretion occur.

* Dr. Robert E. Greenberg of the Pediatric Department of Stanford University Medical School provided these analyses. Estimations were performed according to the method of Von Euler and Lishajko (Acta Physiol. Scand., 45:122, 1959).

**Response to Sympathomimetic Drug Therapy**

The reported improvement obtained using sympathomimetic drug therapy in the patient of Greenough et al.6 suggested possible benefit using such medication in the present patient. Mephentermine was chosen because of the availability of an oral dosage form. Figure 7 shows the acute effect of this therapy. A 2-day preliminary period of bed rest produced weight loss and fluid diuresis. Institution of mepentermine therapy (25 mg b.i.d.) 2 days after resumption of erect daytime posture produced a more profound (2 lb) weight loss and a more sustained diuresis. Chronic therapy with ephedrine sulfate (12.5 mg q.i.d.) or mepharine (25 mg b.i.d.) produced clinical

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*Fig. 5. Blood pressure response to infusion of angiotensin II. Increase in systolic or diastolic blood pressure (in mm Hg) is plotted against angiotensin infusion rate (in μg/kg/min). The stippled area represents the responses in 6 normal subjects (3 from the data of Bartter and associates5 and 3 from our study ward).*

*Fig. 6. Blood pressure and pulse responses to infusion of norepinephrine. Increase in blood pressure is plotted against norepinephrine infusion rate (as norepinephrine base—in μg/kg/min). The responses in the cross-hatched areas are those of 5 normal adolescent children. Responses a, b, and c are separate responses measured in the patient reported. See text for details.*
IDIOPATHIC EDEMA

Fig. 7. Body weight and fluid intake and output in response to oral administration of mephentermine. The body weight loss and fluid diuresis are evident.

improvement in edema; neither drug, however, eliminated the edema. Both drugs given chronically produced bothersome headache and dizziness.

COMMENT

The presently reported patient experienced the onset of edema of her feet and ankles at the age of approximately 12 years at a time when pubertal breast development was becoming manifest. No cardiac, hepatic, renal, CNS, or vascular disease was detected by the usual clinical diagnostic methods. Bilateral ureteral catheterization studies and I131 diodrast studies revealed no evidence of renal vascular anomaly or unilateral renal disease. Intermittent hyperaldosteronuria and excessive weight fluctuation were observed. Hospitalization on a constant diet without other therapy usually produced some improvement in her edema. Similar variability of the clinical manifestations and non-specific effect of hospitalization have been reported in adult patients with this syndrome.6

Spirolactone administration produced diuresis of approximately 5% body weight and improvement in edema suggesting that aldosterone played an etiologic role in the edema. Primary hyperaldosteronism is unlikely in the absence of hypokalemia and hypertension and in the face of the intermittent nature of the hyperaldosteronuria. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism, a syndrome recently reported by Bartter and his colleagues,22 would also seem unlikely; such patients manifest decreased blood pressure response to angiotensin II infusion as well as hypokalemia. The diastolic blood pressure response to angiotensin infusion in the present subject (as interpolated from Fig. 5) was similar in degree to that recently reported by Kaplan and Silah21 for normotensive adults (7.5 ± 1.5 mmHg/min for an increase in diastolic pressure of 20 mmHg).

The lack of decreased sensitivity to angiotensin in the presence of hyperaldosteronuria23 is probably explained by the intermittent nature of the aldosterone response in the present patient. The absence of hypokalemia, even after sodium loading might be similarly explained.

The decrease in PAH and creatinine clearances observed during the 90° tilt table studies (68 and 55% respectively, Table III) would appear excessive: Robinson and colleagues24 recently reported mean decreases of 39% (9.4–56.4%) in PAH clearance and 28% (0–66.5%) in inulin clearance* with acute assumption of erect posture (90°) in 23 adult patients. Such reduction in association with the measured increase in plasma volume of 38% during 10 hours of daytime erect posture would suggest an excessive pooling of plasma volume in the lower extremities while erect. This view, in agreement with that of Greenough and co-workers,6 is supported by the diuresis observed with recumbent posture (Fig. 1) and by the marked increase in pulse rate and decrease in pulse pressure (arterial anemia pattern)25 noted during the tilt table studies (Fig. 4).

The decreased “effectively circulating”
plasma volume produced by such pooling is presumably the stimulus for the increased aldosterone secretion. An increased aldosterone effect whether exogenous or endogenous, by itself will not usually produce edema; "escape" from excessive salt and water retention probably occurs in patients with normal renal function by increase in glomerular filtration (GFR) and consequent increase in sodium excretion. In the present patient the decrease in GFR observed with erect posture might be postulated as the contributing factor preventing such "escape," with the result that salt and water retention occur because of the decreased GFR and stimulation of aldosterone secretion. Thus, the plasma volume increases to compensate for that "sequestered" in the lower body. Recent evidence for a renal origin for aldosterone stimulating hormone would suggest that the decrease in renal blood flow observed with erect posture might have functional significance relative to the stimulation of aldosterone secretion. Redistribution of the "sequestered" extracellular and plasma volume to "effective" loci by recumbent posture or by administration of sympathomimetic drugs then leads to salt and water diuresis.

The reason for the abnormal sequestration of effective plasma volume during erect posture is not established. Ross and associates described a woman with anasarca, hyperaldosteronuria, and an adrenal adenoma; hypoalbuminemia was also prominent. The increased aldosterone secretion in that patient was attributed to an abnormal capillary leakage of protein. The extravascular exchangeable albumin appears to consist of two compartments with exchange half times of 3 to 5 hours and 24 to 30 hours respectively. The normal half time of exchange of plasma albumin with these combined extravascular compartments in the patient of Greenough et al. and in the present patient (20.4 hr, Fig. 3) would not support an abnormal vascular permeability to protein. The prompt mobilization of "sequestered" plasma volume during norepinephrine infusion, as demonstrated by the decrease in pulse rate and increase in pulse pressure (Fig. 6), and the marked increase in immediately exchangeable (30 min) plasma volume from 8:00 a.m. to 6:00 p.m. would favor a predominant intravascular rather than extravascular pooling in the present subject. In the absence of visible varicosities the pooling is presumed to be limited predominantly to the deep veins. Possible explanations for such intravascular blood volume pooling with erect posture include: (a) an inherent abnormality of vascular smooth muscle, (b) abnormal peripheral vascular adrenergic nervous innervation or responsiveness, and (c) a decreased or absent vascular response to circulating hormones, the most important of which is probably norepinephrine.

The increase in diastolic blood pressure (BP) with erect posture in the tilt table studies (Fig. 4) was maintained in large degree by the marked increase in pulse rate. Nonetheless, the diastolic blood pressure increment observed in these studies suggests qualitatively intact peripheral adrenergic stimulation and arteriolar responsiveness to erect posture. The early increase in diastolic pressure with erect tilting of normal subjects has been shown to precede by a short interval (a mean of 2 to 3 minutes) a 50 to 100% increase in circulating plasma norepinephrine levels. Subjects with "true" postural hypotension when tilted erect fail to show an increase in plasma norepinephrine and show a fall in diastolic pressure with an unchanging pulse rate. Thus, the pattern of vascular response to erect posture in the present subject is not similar to that in subjects with an absent norepinephrine response to erect posture. Moreover, an increase in norepinephrine excretion was measured during erect posture (Table IV).

The norepinephrine infusion studies during recumbent posture (Fig. 6) suggest a quantitatively decreased peripheral vascular responsiveness to this adrenergic agent. The infusion rates of norepinephrine in normal adults required to produce an increment in diastolic BP of 20 mm Hg (90.1
TABLE IV
CATECHOLAMINE EXCRETION STUDIES

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>R. J.*</th>
<th>recumbent</th>
<th>erect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (µg/4 hr)</td>
<td>1.91 (1.68–2.11)</td>
<td>3.21 (2.84–3.67)</td>
<td></td>
</tr>
<tr>
<td>Epinephrine (µg/4 hr)</td>
<td>0.64 (0.29–1.18)</td>
<td>0.82 (0.11–1.81)</td>
<td></td>
</tr>
</tbody>
</table>

* Values represent the mean and range observed in 4 separate 4-hour tests.

± 27.1 µg/kg/min)23 are similar to values in the control subjects in the present study. The response in R. J., similarly recorded, e.g., for a diastolic BP increment of 20 mm Hg, were approximately 160–400 µg/kg/min.

The abnormal intravascular blood volume pooling (probably in the deep veins) with erect posture was mobilized with sympathomimetic drugs as indicated by the decrease in pulse rate and increase in pulse pressure during norepinephrine infusion (Fig. 6) and the diuresis induced by oral mephentermine Fig. 7). Angiotensin II infusion had little effect on the “pooled” plasma volume (little decrease in pulse rate or increase in pulse pressure, Fig. 5) in agreement with the reported observations that this agent, in contrast to norepinephrine, appears to have little effect on venous tone.33, 34

These data suggest a basic defect in venous structure or vasomotor innervation as the etiology of this interesting syndrome in the present patient. The partial correction of the defect by administration of sympathomimetic drugs indicates, however, that the abnormal peripheral venous pool is, at least in some degree, responsive to sympathomimetic stimulation. Whether a quantitative deficiency of this response exists in this patient, however, cannot be decided on the basis of the present data.

All of the reported patients with this unusual syndrome of idiopathic edema and secondary hyperaldosteronuria have been women in their child-bearing years. The patient had an onset associated with obvious early pubertal breast development. Recent reports relating progesterone to increased aldosterone excretion in human subjects35 and estrogen to increased aldosterone secretion in rats36 would suggest that ovarian hormones may potentiate the compensatory aldosterone response to an existent borderline vascular abnormality and thus precipitate the clinical edema.

SUMMARY

A female adolescent with onset of the syndrome of “idiopathic edema and secondary hyperaldosteronuria” is reported. Investigations conducted over a 28-month period documented hyperaldosteronuria and an increased aldosterone response to salt restriction. The usual diurnal variation of salt and water excretion was observed. Recumbent posture, spironolactone or sympathomimetic drugs were observed to produce salt and water diuresis.

Recumbent renal function tests were normal; erect posture, however, produced a marked decrease in sodium excretion and in PAH and creatinine clearance. Immediately exchangeable plasma volume (30 min I131 albumin space) increased 38% between 8:00 A.M. and 6:00 P.M. during erect posture. An “arterial anemia” pattern of vascular response to erect posture was observed in tilt table studies; diastolic pressure increased normally but pulse rate increase was excessive. Blood pressure response to infusion of exogenous angiotensin II was normal; that to norepinephrine infusion seemed abnormal and was associated with a rather marked decrease in pulse rate and increase in pulse pressure suggesting mobilization of “sequestered” blood volume. Four-hour recumbent excretion of catecholamines and the 4-hour excretion response of norepinephrine to erect posture seemed
normal. Partial elimination of the edema occurred with chronic sympathomimetic drug therapy.

It is concluded that this unusual syndrome probably occurs secondary to a defect in peripheral venous structure or autonomic vasomotor innervation leading to excessive blood volume pooling in the lower body, excessive reduction in renal blood flow and glomerular filtration rate, and hyperaldosteronism. Consequent retention of salt and water with increase in lower body, excessive reduction in renal output. A case of massive peripheral edema as a consequence of conditions with hyperaldosteronism. The determination of urinary steroids. I. The preparation of pigment-free extracts and simplified procedure for estimation of total 17-ketosteroids. J Clin. Endocr., 12: 55, 1952.

REFERENCES


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IDIOPATHIC EDEMA AND HYPERALDOSTERONURIA: POSTURAL VENOUS PLASMA POOLING
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Pediatrics 1965;35;413

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