Genetic Influences on Renin, Aldosterone, and the Renal Excretion of Sodium and Potassium Following Volume Expansion and Contraction in Normal Man

Clarence E. Grim, M.D., Judy Z. Miller, Ph.D., Friedrich C. Luft, M.D., Joe C. Christian, Ph.D., M.D., and Myron H. Weinberger, M.D.

SUMMARY To investigate the influence of heredity on plasma renin activity (PRA), plasma aldosterone concentrations (PAC), blood pressure, and the renal excretion of sodium and potassium following volume expansion and contraction in normal man, we studied 37 pairs of monozygotic (MZ) and 18 pairs of dizygotic (DZ) twins. Volume expansion was achieved by the intravenous infusion of 2L normal saline; volume contraction was accomplished by a low-sodium diet and 120 mg oral furosemide. The presence of genetic variance was tested by calculating the within pair and among component estimates of genetic variance.

Outpatient 24-hour-urine collections suggested that MZ and DZ twins ingested diets similar in sodium and potassium content, and failed to reveal genetic influences on the dietary preferences for these electrolytes. The PRA values suggested heritable influences during both the volume expanded and contracted state with the added stimulus of upright posture. Heritable influences were observed on PAC and were most apparent in the basal state on the day of volume expansion. An influence of heredity on blood pressure was most apparent during volume contraction. Urinary sodium excretion (U\textsubscript{Na}V), urinary potassium excretion (U\textsubscript{K}V), fractional excretion of sodium (FE\textsubscript{Na}), and fractional excretion of potassium (FE\textsubscript{K}) revealed evidence of significant genetic variance under the condition of volume expansion. In that state, systolic blood pressure was directly correlated with PRA, PAC, and inversely with FE\textsubscript{Na}. The data suggest that the renal regulation of sodium and potassium excretion is in part influenced by heritable factors that may in turn contribute to the development of hypertension in some individuals. (Hypertension 1: 583–590, 1979)

Key Words • renin • aldosterone • sodium • potassium • genetics • heredity • natriuresis • kaliuresis

The role of heredity in the etiology of hypertension is well established in a variety of experimental animal models.1–4 In the Dahl salt-sensitive and salt-resistant strains of rats, the susceptibility to hypertension related to sodium intake is clearly a function of differences in genetic substrate.1, 2 In man, the relative contributions of heredity and environment to the development of hypertension are less clear.5, 6 Dietary sodium intake is recognized as a major environmental factor predisposing to the development of essential hypertension in man.9 Although the evidence relating dietary sodium intake to the development of hypertension is compelling, it is derived from indirect sources.10 Dahl has indicated that there is a strong correlation between dietary sodium intake and the prevalence of hypertension among, but not within, populations of different geographical areas and different races.10 In the United States there is a greater incidence of hypertension among blacks than whites.11 We have found that normotensive black Americans excreted an intravenous sodium load more slowly than normotensive whites.12, 13 In addition, normotensive blacks developed greater increases in blood pressure when exposed to extremely high sodium intake compared to normotensive whites.14 We postulated that the differences observed between our black and white subjects might best be explained by genetic influences on renal sodium excretion. In the present study, we ex-
amined possible genetic influences on the renal and hormonal responses to volume expansion and contraction in a twin model.

The data suggest that there are strong heritable influences on natriuretic responses following intravenous saline infusion, as well as on plasma renin activity and plasma aldosterone values. Such influences may serve to explain, at least in part, the heritable nature of hypertension and the differing susceptibilities to the development of essential hypertension within populations.

Methods

Normotensive twin pair volunteers with no immediate family history of hypertension were recruited from the existing twin panel in the Department of Medical Genetics, Indiana University, from the college registration records of Indiana University, and by advertisement. The protocol was approved by both the Indiana University Medical Center Human Use and Clinical Research Center committees. All participants were preselected for a previous history of a normal blood pressure and the absence of drug ingestion. Females were excluded if they had taken oral contraceptives in the preceding 3 months. Moreover, females were studied only during days 5 to 15 of their menstrual cycle to minimize variance due to cyclical hormonal changes. The subjects were enrolled after informed consent was obtained, and were admitted to the Indiana University Clinical Research Center for the duration of the protocol.

Zygosity was determined by extensive genotyping and dermatoglyphic analysis. The twins were routinely categorized according to blood group antigens ABO, Rh, MNS, Kell, Duffy, Kidd, P, and Secretor status. In addition, PGMI, haptoglobin and the enzymes acid phosphatase, amylase I, and amylase II were evaluated by previously described techniques. Fifty-five twin pairs participated in the study. Thirty-seven pairs were monozygotic (21 male, 16 female) and 18 pairs were dizygotic (13 male, five female). The twins ranged in age from 14 to 27 years and all were white. The responses of the twins were compared to those of 15 normal, white, non-twins with no family history of hypertension. These subjects ranged in age from 15 to 26 years, and were subjected to the same protocol.

The protocol has been described in detail in previous reports. Dietary sodium and potassium intake were unrestricted before admission. In the hospital, dietary sodium intake was 150 mEq/day and potassium, 70 mEq/day, unless otherwise indicated. Each subject was instructed to collect a 24-hour-urine specimen on the day before admission. On the day of admission, a careful history and physical examination were performed, supine and standing measurements of blood pressure were made, and baseline hemogram and serum chemistries were obtained. Blood pressure measurements made on this and subsequent days were obtained four times daily at 8:00 a.m., noon, 4:00 p.m., and 10:00 p.m., in the supine and upright positions by specially trained nurses using mercury manometers (Baum, Inc., New York, NY). The fifth Korotkoff component or point of sound disappearance was accepted as the diastolic pressure. Mean arterial blood pressure was calculated from the summation of one-third the pulse pressure and the diastolic pressure.

Sodium Loading Day

On this day, the suppressibility of the renin-angiotensin-aldosterone system and the natriuretic response were determined after saline infusion. At 6:00 a.m., the subject was awakened. Blood samples were obtained for measurement of sodium, potassium, creatinine, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) while the subject was recumbent. The subject then assumed an upright posture (standing or walking) until 8:00 a.m., at which time he or she was instructed to void completely. Blood samples for PRA and PAC were obtained in the upright position. The subject then assumed the recumbent position until noon while receiving a 4-hour intravenous infusion of 2 liters of isotonic (0.9%) saline (500 ml/hr) beginning at 8:00 a.m. At noon, a 4-hour urine collection for electrolytes and creatinine was terminated and blood was obtained for PRA and PAC, as well as sodium, potassium, and creatinine determinations. After completion of the infusion, the subject was permitted to move about and received a 150 mEq sodium, 70 mEq potassium diet. At 10:00 p.m., a 10-hour-urine collection was terminated. At 8:00 a.m. the following morning, a "sleep" urine collection was completed. The total sodium intake on this day was 458 mEq.

Sodium Depletion Day

On the morning following saline administration, while recumbent at 6:00 a.m. and again at 8:00 a.m., after 2 hours of upright posture, blood was obtained for electrolytes, creatinine, PRA, and PAC. The diet on this day was limited to 10 mEq sodium, 70 mEq potassium and 25 ml water/kg body weight. Furosemide (40 mg) was given orally at 10:00 a.m., 2:00 p.m., and 6:00 p.m. An awake urine collection was terminated at 10:00 p.m. and a "sleep" specimen completed at 8:00 a.m. the morning following sodium depletion. A supine blood sample was obtained at 6:00 a.m. In order to evaluate the response of PRA and PAC to the stimulus of upright posture following sodium and volume depletion, blood was again sampled at 8:00 a.m. after 2 hours of ambulation.

Laboratory Methods

Sodium, potassium, and creatinine concentrations in blood and urine were measured by an IL flame photometer and standard autoanalyzer techniques (Technicon, Tarrytown, NY). PRA and PA concentrations were measured by previously reported immunoassay techniques.
Data Analysis

Creatinine clearance was calculated from the formula $Ccr = (U_{Cr} \times V)/P_{Cr}$, where $Ccr$ is the creatinine clearance in ml/min, $U_{Cr}$ and $P_{Cr}$ the urine and plasma creatinine concentrations, and $V$ the urine volume per minute. The fractional excretion of sodium ($FE_{Na}$) and potassium ($FE_{K}$) were calculated by dividing the respective clearance of these ions by the clearance of creatine and multiplying the quotient by 100. The results are expressed in percent.

Data from monozygotic (MZ) and dizygotic (DZ) twins provide an opportunity to test for the existence of genetic variation in traits. Since MZ twins are genetically identical and DZ twins are related as full siblings, a given trait would be expected to exhibit smaller twin pair differences for MZ twins than DZ twins if genetic influences are present. On the other hand, if the trait is only influenced by environmental variability, the MZ and DZ twin-pair differences should be approximately equal.

The statistical methods involved in the analysis of MZ and DZ twin data have been recently reviewed by Christian et al. The equality of total variance was evaluated by the $F$ ratio: $(Within\ DZ/Within\ MZ)$. This method, which provides the most conservative estimate under conditions of unequal total variances in the two types of twins, has been previously described in detail elsewhere. These estimates are less influenced by environmental factors and are superior to other estimates under conditions of unequal total variances in the two types of twins. Heritability estimates do not account for dominance or interactions between genetic and environmental sources of variance. Estimates greater than one arise due to sampling variation in the relatively small sample size of the present study. In addition to the TWINAN program analyses, conventional statistical analysis, i.e., analysis of variance, and regression analysis were performed by means of a computerized statistical program.

Results

Table 1 displays the analysis of height, weight, and body surface area in the current sample of MZ and DZ male and female twins. The total variances for height were unequal ($F'$ probability < 0.001) in all twins, indicating that the more conservative among component $F$ test is more appropriate in this instance. Both the within pairs and among pairs component estimates were highly significant ($p < 0.001$) and the heritability estimate was 0.84. In the case of weight, the total variances for the two types of twins were not unequal, and therefore the within pairs estimate was accepted as evidence for the existence of genetic variance ($p < 0.05$). Surface area also demonstrated genetic variance. Since the total variances were not unequal ($p = 0.09$), the within pairs estimate was acceptable ($p < 0.01$); however, both estimates were significant ($p < 0.05$). There was no evidence for heterogeneity of genetic variance in the two sexes when analyzed separately for any of the variables studied. Therefore, we report subsequent data for both sexes analyzed together.

The 24-hour-urine collections used as estimates of dietary sodium and potassium intake revealed a sodium and potassium excretion of $164 \pm 12$ SEM mEq/24 hrs, and $66 \pm 4$ SEM mEq/24 hrs respectively, for MZ twins, and $150 \pm 11$ mEq/24 hrs, and $68 \pm 5$ mEq/24 hrs, respectively, for DZ twins. The values for MZ and DZ twins were not significantly different ($p > 0.05$). In addition, the analysis failed to reveal the presence of genetic variance for sodium and potassium intake by either the within pair or among component $F$ tests.

The results of the analysis on urinary sodium excretion ($U_{Na}V$), fractional excretion ($FE_{Na}$) and plasma sodium ($P_{Na}$) appear in table 2. A genetic influence on $U_{Na}V$ was identified during the night following saline and for the entire sodium loading day ($p < 0.05$). A genetic influence on $FE_{Na}$ was observed during the saline infusion ($p < 0.01$), during the night following saline ($p < 0.05$) and for the 24-hour period ($p < 0.05$). $P_{Na}$ showed evidence of genetic variance ($p < 0.01$) following the saline infusion. Urinary potassium excretion ($U_{K}V$), fractional excretion ($FE_{K}$) and plasma potassium ($P_{K}$) appear in table 3. Genetic in-
fluences were observed on $FE_K$ during saline ($p < 0.05$), $U_{K,V}$ and $FE_K$ during sleep ($p < 0.05$), and during the entire 24-hour period ($p < 0.05$). A genetic influence on $P_K$ was identified on the morning following the sodium loading day. Genetic influences were not demonstrable in either sodium or potassium analyses on the sodium depletion day.

The mean values of MZ and DZ twins for all variables in the present study were not significantly different ($p > 0.05$) with the single exception of the isolated difference is likely due to chance alone, the analysis of genetic variance at this particular determination should be interpreted with caution.

The analysis of PRA values is shown in table 4. The among component $F'$ test revealed significant genetic variance in the recumbent PRA values for all twins prior to ($p < 0.001$), and immediately after the saline infusion ($p < 0.05$). A substantial genetic influence ($p < 0.01$) was also observed on the recumbent 6:00 a.m. value following the sodium loading day. This influence persisted with the assumption of upright posture as shown by both the within pair ($p < 0.01$) and among component ($p < 0.05$) estimates. After volume depletion with furosemide, significant genetic variance was still observed with either supine ($p < 0.05$) or upright ($p < 0.01$) posture. The analysis of PA values also appears in table 4. Genetic variance was identified by either the within pair ($p < 0.01$) or among component ($p < 0.05$) tests at 6:00 a.m. before saline infusion, and by the within pair estimate after saline ($p < 0.05$). Thereafter, genetic variance was identified only inconsistently.

The analysis of blood pressure determinations, which is not depicted in the tables, failed to reveal genetic variance when the mean blood pressure measurements were pooled over each 24-hour period. Significant genetic variance was observed on the volume contraction day ($p < 0.05$) in upright systolic and diastolic pressure at 8:00 a.m. ($H^2 = 0.70$), upright diastolic blood pressure at noon ($H^2 > 1.0$), supine systolic ($H^2 = 0.85$) and diastolic ($H^2 > 1.0$) pressure at 10:00 p.m. and upright systolic pressure at 10:00 p.m. ($H^2 > 1.0$).

In the twins, mean systolic blood pressure was directly correlated with the sodium loading day 6:00 a.m. supine PRA ($r = 0.29, p < 0.01$), and PA ($r = 0.23, p < 0.02$) measurements. Systolic blood pressure was inversely correlated with the 24-hour $FE_{Na}$ ($r = -0.28, p < 0.01$). In addition, the 4-hour and 24-hour $FE_{Na}$ were inversely correlated with the 6:00 a.m. supine PRA values ($r = -0.27, p < 0.01; r = -0.21, p < 0.05$).

Data from the 15 non-twin normal subjects were analyzed and compared to those obtained from MZ and DZ twins. The PRA, PA, natriuretic and kaliuretic responses following sodium loading and depletion did not differ in the twins and non-twin normal subjects ($p > 0.05$). Both PRA and PA were correlated in twins and non-twins except immediately after saline infusion. The 6:00 a.m. supine correlations on the saline day were: MZ twins $r = 0.42, p < 0.001$; DZ twins $r = 0.61, p < 0.001$; and non-twins $r = 0.60, p < 0.03$. The slopes of the lines defining the regressions were not different. Consistent correlations between age, weight, height, and blood pressure were

### Table 1. Body Size Variables in 55 Pairs of Twins

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
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<th>Mean squares</th>
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</thead>
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<td></td>
<td>MZ</td>
<td>DZ</td>
<td>F' Probability*</td>
<td>MZ</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All twins</td>
<td>168.8</td>
<td>174.6</td>
<td>0.001</td>
<td>1.41</td>
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<td>Males</td>
<td>174.8</td>
<td>175.6</td>
<td>0.26</td>
<td>1.74</td>
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<td>Females</td>
<td>160.2</td>
<td>171.0</td>
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<td>0.94</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>All twins</td>
<td>63.4</td>
<td>66.0</td>
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<td>18.83</td>
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<td>Males</td>
<td>66.1</td>
<td>67.5</td>
<td>0.68</td>
<td>18.52</td>
</tr>
<tr>
<td>Females</td>
<td>59.2</td>
<td>59.5</td>
<td>0.08</td>
<td>19.31</td>
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<td>Body surface area</td>
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<td></td>
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<tr>
<td>All twins</td>
<td>1.72</td>
<td>1.79</td>
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<tr>
<td>Males</td>
<td>1.80</td>
<td>1.82</td>
<td>0.35</td>
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<tr>
<td>Females</td>
<td>1.61</td>
<td>1.69</td>
<td>0.07</td>
<td>0.003</td>
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</table>

*Refers to test of equality of total variance for the two types of twins.
†Significance determination refers to within pair F test.
‡Significance determination in this column refers to among component F' test.
§p < 0.001
||p < 0.01
**p < 0.05.
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TABLE 2. U_{Na} (mEq/Collection), FE_{Na} (Percent), P_{Na} (mEq/Liter) on the Day of Sodium Loading

<table>
<thead>
<tr>
<th>Collections</th>
<th>Mean</th>
<th>F' Probability*</th>
<th>Within pair†</th>
<th>Among pair‡</th>
<th>Mean squares</th>
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<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
<td>DZ</td>
<td></td>
</tr>
<tr>
<td>8 a.m.-Noon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U_{Na} (mEq/Collection)</td>
<td>52.2</td>
<td>55.8</td>
<td>0.37</td>
<td>189.51</td>
<td>189.89</td>
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<tr>
<td>FE_{Na}</td>
<td>1.58</td>
<td>1.41</td>
<td>0.001</td>
<td>0.47</td>
<td>0.12</td>
</tr>
<tr>
<td>P_{Na}</td>
<td>140.8</td>
<td>142.5</td>
<td>0.13</td>
<td>3.41</td>
<td>15.06§</td>
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<td>Noon-10 p.m.</td>
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<tr>
<td>U_{Na} (mEq/Collection)</td>
<td>228.6</td>
<td>259.7</td>
<td>0.47</td>
<td>1154.79</td>
<td>1833.44</td>
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<tr>
<td>FE_{Na}</td>
<td>1.85</td>
<td>2.04</td>
<td>0.18</td>
<td>0.14</td>
<td>0.16</td>
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<tr>
<td>U_{Na} (mEq/Collection)</td>
<td>68.7</td>
<td>61.3</td>
<td>0.75</td>
<td>294.98</td>
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<td>FE_{Na}</td>
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<td>0.17</td>
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<td>P_{Na}</td>
<td>140.0</td>
<td>142.2</td>
<td>0.001</td>
<td>4.64</td>
<td>4.00</td>
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<tr>
<td>U_{Na} (mEq/Collection)</td>
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<td>376.9</td>
<td>0.72</td>
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</tr>
<tr>
<td>FE_{Na}</td>
<td>1.59</td>
<td>1.64</td>
<td>0.05</td>
<td>0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Significance determination refers to within component F test.
†Significance determination refers to among component F* test.
‡Significance determination refers to within pair F test.
§Refers to sex of twins.

Discussion

Studies in the rat, including the transplantation experiments of Bianchi et al. and Dahl et al., as well as the studies of Tobian on the intrinsic natriuretic capacities of kidneys in salt sensitive and resistant rats, raised the possibility that the excretion of sodium may also be under the influences of heritable factors in man. Experiments by Rapp demonstrating genetic influences on the juxtaglomerular granularity and renin in rats and mice, in addition to the demonstration that 18-hydroxy-deoxy-cortico-sterone production in the Dahl rat is under genetic control, suggested that components of the renin-angiotensin-aldosterone system in man may be influenced by genetic variance as well. In the present study, we employed a twin model to address these questions.

The data from the MZ and DZ twin pairs frequently demonstrated inequality of total variance. The interpretation of twin data under circumstances of unequal total variance is admittedly controversial. Although Haseman and Elston have suggested that it may be inappropriate to test for the presence of genetic variability under such circumstances, Christian et al. have shown that when biases due to environmental differences in variance are removed, one may safely test for genetic variability. The among component estimate employed in the present study has less power than within pairs estimates, and consequently requires greater numbers of subjects.

In the present study, differences in the total variance of the two types of twins were attributed to differences in environmental sources of variability. Nance has suggested that it may be more appropriate to attribute the inequality to genetic differences. It is likely that such an assumption would result in a significant difference in the means of the two types of twins. A difference in means was found in only one instance (table 3) in our data. Recent studies have suggested that prenatal maternal environmental influences may be responsible for inequity in total variance of the two types of twins. Presently, the methods for testing for such differences require knowledge of the placentation of the MZ twins, information which was not available in our sample.

As expected the analysis revealed consistent genetic influences on height, weight and body surface area in both male and female twins. These readily quantified variables serve to illustrate the twin model.

No heritable influences were observed on the outpatient 24-hour-urinary sodium values. Although a single 24-hour-urine value is a relatively crude indicator of sodium intake, the data do not suggest a heritable salt appetite responsible for sodium intake. On the other hand, after volume expansion, a strong heritable influence was observed on FE_{Na} and FE_{K}. Genetic influence was also demonstrated on U_{Na} and U_{K, V}, but not during the saline infusion. The plasma sodium at the termination of the saline in-
fusion revealed the presence of genetic variance, which may explain the genetic influence on FE$_{NA}$ but not U$_{NA}$V during this period.

Plasma renin and aldosterone values showed a strong heritable component in the basal state. Following the sodium loading day, heritable influences were still observed on PRA with the added environmental stimulus of upright posture. Heritable influences on plasma renin and aldosterone values were less consistent in the recumbent state. However, the stimulus of upright posture following volume depletion apparently unmasked heritable influences on both PRA and PAC.

These data suggest, for the first time in man, the presence of strong heritable influences on the renal excretion of sodium, which are most readily identified in the volume expanded state. Such influences were also observed under both volume expanded and contracted conditions on PRA and PAC. The renin-angiotensin-aldosterone system is recognized as one of several feedback loops that influence renal sodium excretion. Guyton and co-workers have suggested that the kidney functions as the final common pathway of blood pressure regulation in both the normotensive and hypertensive state through its control of salt and water excretion. Factors that affect the kidney and its ability to excrete salt and water may be responsible for the development of hypertension, particularly in societies which ingest large quantities of dietary sodium. An inherited renal functional deficiency in handling an excessive extracellular fluid volume expansion would serve to explain the susceptibility of some individuals to the development of hypertension at states of high sodium intake, and the relative resistance of others. The evidence that differences in salt intake contribute to differences in blood pressure within human populations is inconclusive. Although Grim et al. found that several estimates of sodium intake were correlated with blood pressure in their normotensive population, correction for body size removed this effect. Conceivably, such correlations within populations are difficult to document because the range of sodium intake within such populations is relatively narrow and the genetic makeup of the individuals is quite heterogeneous. When comparing diverse populations across a wide range of sodium intake, a correlation between dietary sodium intake and the prevalence of hypertension is readily demonstrable.

No consistent heritable influences on mean arterial blood pressure were observed. Genetic variance was observed on systolic blood pressure in the volume contracted state. The failure to identify consistent genetic variance on blood pressure is not surprising since the twins represented a narrow age range, and since the study was restricted to normotensive subjects. Furthermore, minute-to-minute blood pressure regulation is greatly subject to environmental stimuli and is characterized by considerable variability even within the same individual. Pickering has emphasized the wide range of blood pressure observed in normal individuals during the course of their daily activities.

Although we attempted to standardize the environmental conditions as much as possible, it is likely that even four supine and upright blood pressure measurements throughout the day are insufficient to

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**Table 3.** U$_{N}$V (mEq/Collection), FE$_{K}$ (Percent), P$_{K}$ (mEq/Liter) on the Day of Sodium Loading

<table>
<thead>
<tr>
<th>Collections</th>
<th>Mean</th>
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<th>Within pair†</th>
<th>Among pair‡</th>
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<td>DZ</td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
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<tr>
<td>8 a.m.—Noon</td>
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<td></td>
<td>F' Probability*</td>
<td>Within pair†</td>
<td>Among pair‡</td>
</tr>
<tr>
<td>U$_{K}$V</td>
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<td>22.7</td>
<td>1.00</td>
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<tr>
<td>FE$_{K}$</td>
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<td>17.8</td>
<td>0.02</td>
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<td>24.15</td>
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<td>P$_{K}$</td>
<td>4.3</td>
<td>4.3</td>
<td>0.04</td>
<td>0.09</td>
<td>0.11</td>
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<td>49.7</td>
<td>0.68</td>
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<td>FE$_{K}$</td>
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<td>4.08§</td>
<td>0.09</td>
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<td>4.26</td>
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<tr>
<td>P$_{K}$</td>
<td>4.3</td>
<td>4.4</td>
<td>0.40</td>
<td>0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>24 hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U$_{K}$V</td>
<td>72.8</td>
<td>80.7</td>
<td>0.61</td>
<td>73.16</td>
<td>161.11§</td>
</tr>
<tr>
<td>FE$_{K}$</td>
<td>10.62</td>
<td>11.27</td>
<td>0.45</td>
<td>2.46</td>
<td>5.87§</td>
</tr>
</tbody>
</table>

*Refers to test of equality of total variance for the two types of twins.
†Significance determination refers to within pair F test.
‡Significance determination refers to among component F' test.
§p < 0.05.
|p < 0.01.
provide a completely accurate estimate of daily mean blood pressure. The heritable nature of essential hypertension has been well established in previous reports, including studies of twins and families of MZ twin pairs.

During volume expansion, systolic blood pressure was directly correlated with 6:00 a.m. supine PRA, PA, and inversely correlated with \( FE_{Na} \). In addition, \( FE_{Na} \) was inversely correlated with these same PRA and PA determinations. In a previous study of a large group of normal and hypertensive subjects investigated with the same protocol, we found that PRA was inversely correlated with \( FE_{Na} \). Were the factor responsible for the heritability of blood pressure completely unrelated to both the kidneys' ability to excrete sodium and the renin-angiotensin-aldosterone system, the feedback control of blood pressure on PRA should result in an inverse correlation between blood pressure, PRA and PAC, and a direct correlation between blood pressure and \( FE_{Na} \). Our study yielded opposite results in every instance, suggesting that the heritability of blood pressure is not independent of the renin-angiotensin-aldosterone system and the renal excretion of sodium. Since a primary elevation of PRA would be expected to increase blood pressure, PAC, and decrease \( FE_{Na} \), the present data are more consistent with a role for renin in the heritability of blood pressure. Further investigations will be necessary to resolve the issue.

Extrapolation of the present findings to patients with essential hypertension should be done with considerable caution since no hypertensive twins were included in our study, and since essential hypertension is likely to be a heterogeneous group of disorders. We did, however, compare the twins to a non-twin population of similarly aged normal subjects of the same race. Twins and non-twins responded similarly to sodium loading and depletion and had similar PRA-PAC relationships suggesting that the twins were not unique or different from non-twin normal subjects.

Unfortunately, the narrow age and body size range, as well as the relatively small number of subjects,
precluded detailed comparisons of relationships between body size, PRA, and blood pressure between twins and non-twins.

In summary, our study suggests that the inherited differences in the intrinsic renal functional capability for handling a sodium load previously demonstrated in the Dahl rat, may also be present in man. Such differences would at least partially explain the mechanism for the inherited tendency toward essential hypertension in man when subjected to the environmental influences of a high salt intake.

References

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Genetic influences on renin, aldosterone, and the renal excretion of sodium and potassium following volume expansion and contraction in normal man.

C E Grim, J Z Miller, F C Luft, J C Christian and M H Weinberger

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