
Stability of Blood Pressure Rank and Urinary Kallikrein Concentration in Childhood: An Eight-Year Follow-Up

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SUMMARY Previous studies in a population of 721 children aged 2–14 years demonstrated the familial aggregation of blood pressure in children, and a significant regression coefficient (b = 0.25) of follow-up on initial blood pressures over a four-year period. Urinary kallikrein concentration (UKal) also aggregated in families, was lower in black than in white children and was inversely related to blood pressure.

Further studies in the same cohort have been conducted. These variables were again measured in 484 children in 129 families seven to eight years after the initial blood pressure and three to four years after the original UKal measurements were made.

Familial aggregation again was found for blood pressure and urinary kallikrein. Blood pressure tracking was demonstrated by the finding that blood pressure scores at the third survey were related significantly to those at both previous surveys.

Kallikrein concentrations in casual urines at Survey 3 were related to those obtained at Survey 2 (r = 0.499), and were again significantly lower in black than in white children (log = 3.84 ± 0.8 vs 4.37 ± 0.7; P < 0.001). There were significant inverse relations between UKal/creatinine concentration and blood pressure in both white and black children.

Thus, familial aggregation of blood pressure, blood pressure rank and concentration of kallikrein in casual urine specimens are relatively stable in children over an eight-year period of observation. This study demonstrates in a free living population of normal children, a stable relation between blood pressure and an enzyme which is involved in the production of potent vasodilator peptides and is related to hypertension in adults.

STUDIES IN ADULTS have suggested that blood pressures are not only familialy aggregated, but that blood pressures obtained in early adulthood are predictive of pressures attained later in life; that is, that relative blood pressure rank tends to be stable in successive surveys.1, 2 In order to determine if these characteristics of adult blood pressures were also present in childhood, a study of blood pressures was begun in 1967 in families of children aged 2–14 years.3 This study reported that blood pressures were familialy aggregated in children with correlation coefficients similar to those found in adults. These findings were confirmed in several other populations.4–6 A second survey of the original cohort of children four years later showed that familial aggregation of blood pressure persisted and that there was a significant positive relation between the blood pressures obtained in the initial and follow-up surveys.7

Possible biochemical correlates of the blood pressure status of the children were sought. Several systems and biochemicals are related to the maintenance of systemic arterial pressure, including the renin-angiotensin-aldosterone axis, the central and sympathetic nervous systems and, perhaps, prostaglandins and kinins.8 Because measurement of the activity of these systems often requires blood samples and expensive methodology, we searched for a urine component that might be useful in the study of blood
pressure in children. Urinary kallikrein, a renal enzyme which attacks an alpha-globulin substrate to produce kallidin, a potent vasodilator kinin, was studied because urinary kallikrein excretion can be decreased significantly in untreated adults with essential hypertension.8,9

In the first follow-up survey of the children of the present test population, we demonstrated that urinary kallikrein concentration was aggregated in families, was markedly lower in black than in white children, and was inversely related to blood pressure.10 These conclusions were based on measurement of kallikrein concentrations in single voided urine specimens from 601 children. Because of the obvious limitations of basing these conclusions on a single casual urine specimen, we have reexamined these findings three to four years later in the same children. In addition, timed urine collections were obtained from a subsample of this population in order to relate data based on casual kallikrein determinations with those obtained with timed samples.

Materials and Methods

In the first survey in 1967–1968, blood pressures were taken in the homes of 721 children in 190 families. In the second survey in 1971–1972 we found 609 of these children, representing 163 families. The present study is a third survey of this population, and was completed in 1975. As before, families were visited in their homes and blood pressures were obtained. A total of 484 children in 129 families were examined. Of the 484 children, 365 had blood pressure recordings at all three surveys. Blood pressures of the mothers also were measured at the home visit.

Blood Pressure Determinations

As in the previous studies, blood pressures were measured using the Kass-Mollo-Christensen automated blood pressure recorder, which minimizes observer error.11 This device produces a permanent record of the blood pressure reading in the form of a papertape tracing. The details and the errors in measurement of the apparatus have been described.12,13 When four readings were made in 90 subjects simultaneously with the automated device and a random zero sphygmomanometer,14 the correlation coefficients for mean blood pressures obtained with the two devices were 0.98, 0.96 and 0.96 for systolic, and Korotkoff 4 and 5 (K4 and K5) diastolic pressures, respectively. Also, when 99 Korotkoff sound tracings were read and later re-read blindly by each of three observers, the probability was 99% that the actual mean difference in reading for systolic pressure would be between 1–3 mm Hg.15 Blood pressures were measured three times in succession after the subject had rested quietly in a chair for 5 minutes. The mean of the three readings was used in all calculations. Cuff sizes were used as recommended by the American Heart Association.16

As in previous studies, blood pressures were adjusted for age and sex with the use of the Z score or standard deviation unit (S.D.U.).2 The child's height and weight also were recorded. The use of Z scores in these children is justified, because blood pressures in each of these two-year age and sex groups are approximately normally distributed.

Urine Collections and Measurements

A casual, clean, voided specimen was obtained from each child and from their mothers. The urine was refrigerated immediately and stored at 4°C under toluene until analyzed for kallikrein, sodium, potassium and creatinine concentrations. All samples were numbered randomly and assayed before breaking the code. Urinary kallikrein was measured by the radiochemical esterolytic assay of Beaver et al.17 as modified by Margolius et al.,18 and values are expressed as α-N-tosylarginine methyl esterase units (E.U.) per ml. Urinary kallikrein concentrations in this population show a skewed distribution, but the logarithmic transformation is approximately normally distributed.19 Hence, the log urinary kallikrein concentration was used in all calculations. Sodium and potassium concentrations were measured by flame photometry and creatinine concentration was measured with a Programachem 1040.

Ten families were selected, on the basis of their availability for further study, from the highest or lowest blood pressure or kallikrein groups at the 1972 survey. None of these families happened to contain clinically hypertensive individuals (blood pressures greater than 140/90 mm Hg). These 10 families were visited in their homes, and timed urine collections were obtained to estimate hourly excretion rates of urinary kallikrein. Blood pressures also were measured at these visits.

Statistical methods included analysis of variance, contingency table analysis and simple and multiple regression analysis.

Results

Blood Pressure Data

Distribution

The distribution of blood pressures by age and sex for the population at the third survey is presented in figure 1. Three children were outside the age range shown and were not included in figure 1. As in the previous surveys, blood pressure rises with age for both sexes. In the third survey 295 (61%) of the children were black, 183 (38%) were white and six (1%) were classified as other race. There were no significant differences in blood pressures by race at any age at any of the three surveys of this population.

The pooled mean blood pressures over the three surveys by age and sex are presented in tables 1 and 2. These tables show the increase in blood pressure with age. Systolic blood pressure is slightly higher in adolescent boys than girls. As seen in table 3, the increase in systolic pressure during the eight-year inter-
val did not differ by initial age, although boys' pressures rose slightly more than girls'.

At each age group blood pressure is approximately normally distributed, as is the change in blood pressure from Survey I to Survey 3. For the entire cohort the median change in systolic blood pressure over the eight years was +5.3 mm Hg. Selected percentiles empirically derived from the frequency distribution of change in systolic blood pressure in mm Hg were: 2.5th percentile –19.3; 10th percentile –9.5; 50th percentile +5.3; 90th percentile +22.0; 97.5th percentile +30.0. Over 65% of the population showed an increase in systolic blood pressure during the period studied.

The children seen at all three surveys and those who were studied only at the first or second surveys were compared for initial blood pressure, sex, race, age at initial visit, and weight. There were no significant

| TABLE 1. Mean Systolic Blood Pressure by Age and Sex for All Children at All Surveys |
|-----------------|-----------------|-----------------|
| Age (years)     | Males           | Females         |
|                 | N (mm Hg)       | N (mm Hg)       |
|                 | sd              | sd              |
| 2               | 12              | 15              |
| 3               | 17              | 19              |
| 4               | 33              | 17              |
| 5               | 31              | 17              |
| 6               | 41              | 30              |
| 7               | 49              | 40              |
| 8               | 68              | 63              |
| 9               | 90              | 75              |
| 10              | 108            | 74              |
| 11              | 114            | 45              |
| 12              | 120            | 65              |
| 13              | 126            | 89              |
| 14              | 132            | 83              |
| 15              | 138            | 86              |
| 16              | 144            | 100             |
| 17              | 150            | 107             |
| 18              | 156            | 111             |
| 19              | 162            | 114             |
| 20              |                | 9                |
| Total           | 861            | 816             |

| TABLE 2. Mean Diastolic (K4) Blood Pressure by Age and Sex for All Children at All Surveys |
|-----------------|-----------------|-----------------|
| Age (years)     | Males           | Females         |
|                 | N (mm Hg)       | N (mm Hg)       |
|                 | sd              | sd              |
| 2               | 11              | 15              |
| 3               | 17              | 19              |
| 4               | 33              | 17              |
| 5               | 31              | 17              |
| 6               | 41              | 30              |
| 7               | 49              | 40              |
| 8               | 68              | 63              |
| 9               | 90              | 75              |
| 10              | 108            | 74              |
| 11              | 114            | 45              |
| 12              | 120            | 65              |
| 13              | 126            | 89              |
| 14              | 132            | 83              |
| 15              | 138            | 86              |
| 16              | 144            | 100             |
| 17              | 150            | 107             |
| 18              | 156            | 111             |
| 19              | 162            | 114             |
| 20              |                | 9                |
| Total           | 858            | 814             |
differences in initial systolic or diastolic blood pressures in the dropouts compared to those seen at all three surveys. The sex distribution at the initial visit was similar for the follow-up group and the dropouts. There was a slight shift in the racial composition of the population over time as has been reported previously. Of the 374 children seen at all visits, 38% were white, while 47% of the dropouts were white \((x^2 = 5.38, P = 0.02).\) The children who were not seen at all three surveys were slightly older initially than those who remained in the study (mean initial age = 9.05 ± 3.3 years vs 7.42 ± 2.8 years; \(P < 0.001).\) These changes over eight years probably reflect increased mobility of the older children and increased movement away from the Boston area. It is unlikely that these small differences affect the data and conclusions to be presented.

**Familial Aggregation**

As in the first two surveys, analysis of variance of blood pressure scores (table 4) demonstrates that for all three phases of blood pressure, the variance within families is significantly less than that among all children studied. Similar data were found when black and white children were analyzed separately. Also, intraclass correlation coefficients for siblings were similar to those reported in previous studies of this population [systolic \(+0.277 ± 0.05\) \((P < 0.001);\) K4 = 0.158 ± 0.05 \((P < 0.001);\) and K5 = 0.100 ± 0.05 \((P < 0.01)].\) The intraclass correlation is calculated between two random siblings from the same family. Higher levels of this correlation represent greater degrees of blood pressure aggregation among siblings.

A graphic representation of the familial aggregation of childhood blood pressures is shown in figures 2 and 3, based on the 175 families with two or more

### Table 3. Mean Increase in Systolic Blood Pressure Between Initial and Final Surveys Eight Years Apart

<table>
<thead>
<tr>
<th>Initial age (yrs.)</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean increase ± SD</td>
</tr>
<tr>
<td>2-3</td>
<td>19</td>
<td>4.2 ± 8.4</td>
</tr>
<tr>
<td>4-5</td>
<td>43</td>
<td>6.0 ± 11.1</td>
</tr>
<tr>
<td>6-7</td>
<td>35</td>
<td>7.3 ± 10.4</td>
</tr>
<tr>
<td>8-9</td>
<td>59</td>
<td>9.8 ± 13.7</td>
</tr>
<tr>
<td>10-11</td>
<td>31</td>
<td>8.6 ± 10.9</td>
</tr>
<tr>
<td>12-14</td>
<td>12</td>
<td>5.1 ± 21.8</td>
</tr>
</tbody>
</table>

### Table 4. Analysis of Variance of Blood Pressures at the Third Study

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic K4</th>
<th>Diastolic K5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>Mean Square</td>
<td>F</td>
</tr>
<tr>
<td>Among families</td>
<td>128</td>
<td>1.693</td>
<td>2.428</td>
</tr>
<tr>
<td>Within families</td>
<td>356</td>
<td>0.679</td>
<td>484</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>1.378</td>
<td>1.702</td>
</tr>
<tr>
<td>Within families</td>
<td>354</td>
<td>0.810</td>
<td>482</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>1.215</td>
<td>1.406</td>
</tr>
<tr>
<td>Within families</td>
<td>343</td>
<td>0.864</td>
<td>481</td>
</tr>
</tbody>
</table>

![Figure 2](http://circ.ahajournals.org/)

**Figure 2. Relation of mean systolic blood pressure scores in 175 random sib pairs (first survey). Each point represents the mean for the number of sib pairs shown in parentheses (see text).**
children studied at Survey 1. Two random siblings were selected from each family and were designated arbitrarily as Sib 1 and Sib 2. For both systolic and diastolic pressures the families were grouped by the blood pressure scores of Sib 1 in intervals of 0.25 S.D.U. For each group, the average score in S.D.U. for Sib 1 and Sib 2, respectively, are plotted in figure 2 for systolic and in figure 3 for diastolic pressures. The regression lines are computed from the regression of Sib 2 scores on Sib 1 scores for both systolic and diastolic pressures.

**Blood Pressure Rank Effects; Tracking Analyses**

The relation of the pressures obtained at the third survey to those of previous surveys was analyzed using three methods. First, simple regression coefficients were calculated for Survey 2 on Survey 1, Survey 3 on Survey 1 and Survey 3 on Survey 2 for the 365 children with readings at all three surveys (table 5). A goodness of fit test was performed to test the adequacy of the linear regression model for each pair of surveys. In each instance we accepted the null hypothesis of the goodness of fit of the linear model. For both systolic and diastolic pressures these coefficients ("tracking coefficients") increased significantly as the population aged and was restudied. This trend, seen in the children, has been confirmed recently using longitudinal data obtained from an entirely different population.20

Second, the relation between blood pressures obtained at any two surveys was analyzed using 3 × 3 contingency tables and the chi square test (tables 6 and 7). Table 6 shows that higher initial systolic pressures were associated with higher observed pressures at Survey 3 and that lower initial pressures were associated with lower observed pressures at Survey 3.

**Table 5. Relation of Blood Pressure Scores at Surveys in 1967, 1971 and 1975**

<table>
<thead>
<tr>
<th>Regression coefficients (n = 365)‡</th>
<th>Systolic (P)</th>
<th>Diastolic (K4) (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Survey 2 on Survey 1</td>
<td>0.264* (&lt;0.001)</td>
<td>0.125* (&lt;0.01)</td>
</tr>
<tr>
<td>2. Survey 3 on Survey 1</td>
<td>0.315† (&lt;0.001)</td>
<td>0.155 (0.03)</td>
</tr>
<tr>
<td>3. Survey 3 on Survey 2</td>
<td>0.463 (&lt;0.001)</td>
<td>0.356 (&lt;0.001)</td>
</tr>
</tbody>
</table>

*P (1, 3) < 0.01.
†P (2, 3) < 0.05.
‡For diastolic pressures, n = 364.

**Table 6. Relation of Initial (1967-68) to Survey 3 (1974-75) Systolic Blood Pressures**

<table>
<thead>
<tr>
<th>Initial scores</th>
<th>Survey 3 scores</th>
<th>≤ −1</th>
<th>−1 to +1</th>
<th>≥ +1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs*</td>
<td>Exp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1 to +1</td>
<td>16†</td>
<td>29</td>
<td>4</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Obs</td>
<td>(8.6)</td>
<td>(32.0)</td>
<td>(8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp</td>
<td>(49.2)</td>
<td>(168.2)</td>
<td>(44.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ +1</td>
<td>1</td>
<td>30</td>
<td>18</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>Obs</td>
<td>(10.2)</td>
<td>(37.8)</td>
<td>(10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>238</td>
<td>63</td>
<td>365</td>
<td></td>
</tr>
</tbody>
</table>

χ² = 24.13; P < 0.001.

*In standard deviation units (SDU). Higher pressures are represented by scores ≥ 1 SDU and lower pressures by scores ≤ −1 SDU. Intermediate pressures are listed as −1 to +1.
†Obs represents the observed frequency and Exp represents the expected frequency based on the assumption of independence of initial and Survey 3 scores.
than would be expected were there no relation between initial and follow-up blood pressures over the eight-year period of observation. The observed distribution differs significantly ($\chi^2 = 24.13, P < 0.001$) from the expected distribution. In table 7, the Survey 2 and Survey 3 pressures were compared using the contingency table method. In this table the relation of subsequent pressures to initial pressures is even stronger ($\chi^2 = 43.65, P < 0.001$). Similar data were obtained for diastolic (K4) pressures (Survey 1 vs Survey 3, $\chi^2 = 12.87; P < 0.025$ and for Survey 2 vs Survey 3, $\chi^2 = 12.73; P < 0.025$). These analyses are presented to display the data reflected by the tracking regressions in table 5.

Third, the capacity of blood pressures obtained at the first two surveys to predict blood pressures at the third survey was studied using multiple regression analyses (table 8). Both earlier surveys are significantly predictive of systolic pressures obtained at the third survey, although the effect of the second survey is greater than that of the initial survey. Similar data were obtained for K4 diastolic pressure (partial regression coefficients for Survey 1 = 0.132; $P = 0.023$; for Survey $2 = 0.255; P < 0.001$).

These three methods which analyze the same data all show that blood pressure tracking is demonstrated in childhood.

**Urinary Kallikrein Studies**

Because of the known variability of urine collections and because of the inverse relation of this enzyme and blood pressure, urinary kallikrein concentration was measured in 474 children, 385 of whom had been similarly studied three years previously, using a casual urine sample. The correlation coefficient of the urinary kallikrein concentrations obtained at these two studies was $r = 0.499$. Familial aggregation of urinary kallikrein concentration was demonstrated again in both races (table 9), and black children again had significantly lower urinary kallikrein concentrations than did white children (table 10).

Nine variables significantly affected urinary kallikrein at the third survey (table 11). These included urinary creatinine, urinary potassium, race, the mother's kallikrein/creatinine ratio, the presence of maternal hypertension under treatment, season, time of day, sex and the mother's systolic blood pressure. These variables accounted for 39% of the variability of urinary kallikrein concentration in these children. When mothers' variables were excluded, log urinary kallikrein concentration was inversely, and weakly, related to log urinary sodium concentration in the multiple regression equation ($b = -0.145, P = 0.04$).

At the extremes of the population, urinary kallikrein concentration adjusted for urinary creatinine concentration was inversely related to blood pressure (table 12). Mean systolic blood pressure in S.D.U. was significantly higher in those white families whose mean log kallikrein/creatinine was at the lowest 10% than in those white families in the highest 10% of distribution of log kallikrein/creatinine. Similarly, K4 diastolic blood pressure was significantly higher in those black families whose log kallikrein/creatinine was at the lowest 20% compared

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**Table 7.** Relation of Survey 2 (1971) to Survey 3 (1974-75) Systolic Blood Pressures*

<table>
<thead>
<tr>
<th>Survey 2 scores</th>
<th>Survey 3 scores</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ −1*</td>
<td>Obs*</td>
<td>18</td>
<td>33</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Exp</td>
<td>(8.9)</td>
<td>(33.3)</td>
<td>(8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1 to +1</td>
<td>Obs</td>
<td>44</td>
<td>176</td>
<td>41</td>
<td>261</td>
</tr>
<tr>
<td>Exp</td>
<td>(45.8)</td>
<td>(170.2)</td>
<td>(45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ +1</td>
<td>Obs</td>
<td>2</td>
<td>29</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>Exp</td>
<td>(9.3)</td>
<td>(34.6)</td>
<td>(9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>64</td>
<td>238</td>
<td>63</td>
<td>365</td>
</tr>
</tbody>
</table>

$\chi^2 = 43.65; P < 0.001$.

*In standard deviation units (SDU). Higher pressures are represented by scores ≥ 1 SDU and lower pressures by scores ≤ −1 SDU. Intermediate pressures are listed as −1 to +1.

Table 9. Analysis of Variance Log Urinary Kallikrein Concentration in 479 Children from 128 Families

<table>
<thead>
<tr>
<th></th>
<th>Mean square (variance)</th>
<th>Degrees of freedom (D.F.)</th>
<th>Ratio of mean squares</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among families</td>
<td>1.265</td>
<td>127</td>
<td>3.252</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Within families</td>
<td>0.389</td>
<td>361</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among families</td>
<td>0.986</td>
<td>73</td>
<td>2.566</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Within families</td>
<td>0.354</td>
<td>221</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among families</td>
<td>1.103</td>
<td>53</td>
<td>2.785</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Within families</td>
<td>0.396</td>
<td>126</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 8.** Predictive Value of First Two Surveys on Third Survey Score (Multiple Regression Coefficients)

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>b</th>
<th>se</th>
<th>t</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey 3 Systolic</td>
<td>Survey 1 Systolic</td>
<td>0.2067</td>
<td>0.048</td>
<td>4.35</td>
<td>&lt;0.001</td>
<td>365</td>
</tr>
<tr>
<td></td>
<td>score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Survey 2 Systolic</td>
<td>0.4085</td>
<td>0.047</td>
<td>8.62</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>−0.006</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
with those families in the highest 20% for this variable. Also, when selected for high or low diastolic blood pressure, white children with the 10% highest blood pressures had significantly lower log urinary kallikrein (4.15 ± 0.79 vs 4.636 ± 0.51; \( P < 0.05 \)) and urinary kallikrein/creatinine \((-0.548 ± 0.62 \text{ vs } -0.109 ± 0.62; P < 0.05\) than did white children with the 10% lowest diastolic blood pressures.

**Urinary Kallikrein Excretion Studies**

Timed urine collections were obtained from 36 children in 10 families. Participants were asked to void and note the time. When the nurse arrived in the home, a urine specimen was collected, time was noted, volume was measured and an aliquot was saved. Blood pressures were also taken at each visit. The hourly excretion rate for urinary kallikrein was estimated by multiplying kallikrein concentration per ml by total urine volume and dividing by the number of hours per collection. Excretion rates were significantly lower in 21 black children than in 15 white children (0.1099 ± 0.076 vs 0.2943 ± 0.179 E.U./hr; \( P < 0.001 \)).

Although the number of children studied with kallikrein excretion rates was too small to allow exclusion of the racial effect in the analysis, the 20% of children with the highest systolic blood pressures had lower urinary kallikrein excretion than the 20% with the lowest systolic blood pressure (0.193 ± 0.114 vs 0.411 ± 0.228 E.U./hr, 0.05 < \( P < 0.1 \)). At the 20% extremes, children with the lowest urinary kallikrein/hr had higher systolic blood pressure S.D.U.s than those with the highest urinary kallikrein/hr (0.287 ± 0.89 vs -0.439 ± 1.24, 0.05 < \( P < 0.1 \)).

**Discussion**

This eight-year study of blood pressures in children shows that significant familial clustering of blood pressures is present and reproducible.

The predictive significance of blood pressure in childhood depends on the consistency of the relation between blood pressure patterns in childhood and those in adulthood. The eight-year follow-up of children shows that familial clustering and reproducibility of blood pressure rank are consistent and significant features of blood pressure in childhood, much as in adults.1, 2

The present data also show a significant increase with aging of the population in the strength of the relation of initial to later blood pressures (table 5). Recent further analysis of this trend, using data obtained in longitudinal studies of blood pressure in adults, indicates that the tracking coefficients increase with age, reaching the adult level of about 0.6 by age 20.30 The factors that account for the increasing tracking correlation with age obviously require substantial study, and would seem to reflect some degree of environmental influence.

The role of the kallikrein-kinin system in the pathogenesis of any form of hypertension is unknown. The present observations indicate that urinary kallikrein concentrations in casual specimens are reproducible over a three-year period in a population of normal children. In addition, the observation of familial aggregation of urinary kallikrein concentration in childhood is repeatable. It is likely that these findings would be even stronger if variations in urinary volume and concentration had been controlled.

Two surveys in this population have shown that urinary kallikrein concentration is significantly lower

**Table 10. Urinary Kallikrein Concentration by Race**

<table>
<thead>
<tr>
<th>Race</th>
<th>N</th>
<th>Log E.U.*/ml ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black children</td>
<td>243</td>
<td>3.835 ± 0.75</td>
</tr>
<tr>
<td>White children</td>
<td>146</td>
<td>4.372 ± 0.74†</td>
</tr>
</tbody>
</table>

*E.U. = Esterase Units.
† \( P < 0.001 \).

**Table 11. Variables Significantly Affecting Urinary Kallikrein Concentration at Survey 3 (Multiple Regression Coefficients)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (log)</td>
<td>+0.328</td>
<td>0.043</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race*</td>
<td>+0.3103</td>
<td>0.081</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium (log)</td>
<td>+0.3523</td>
<td>0.061</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mother's kallikrein/creatinine (log)</td>
<td>+0.2095</td>
<td>0.048</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mother being treated for elevated BP</td>
<td>-0.2896</td>
<td>0.117</td>
<td>0.014</td>
</tr>
<tr>
<td>Summer†</td>
<td>+0.1503</td>
<td>0.065</td>
<td>0.022</td>
</tr>
<tr>
<td>Male‡</td>
<td>-0.1655</td>
<td>0.062</td>
<td>0.009</td>
</tr>
<tr>
<td>Time of day‡</td>
<td>+0.2020</td>
<td>0.071</td>
<td>0.005</td>
</tr>
<tr>
<td>Mother's systolic blood pressure</td>
<td>-0.0823</td>
<td>0.035</td>
<td>0.020</td>
</tr>
</tbody>
</table>

\( R^2 = 0.388 \).

*(1 = white/0 = black)
†(1 = yes/0 = no).
‡(1 = AM/0 = PM).
in black children than in white children. Nevertheless, no racial differences in blood pressures could be found at any ages studied. However, at the extremes of the population an inverse relation of urinary kallikrein concentration and blood pressure was clearly demonstrated in this as in the previous survey (table 12). In addition, a smaller group of children at the extremes of kallikrein concentrations or blood pressures at the previous survey were reexamined for kallikrein excretion rates. The black children again had lower urinary kallikrein than the white children. Also, there was a trend for these black children with low urinary kallikrein to have higher systolic blood pressures than those white children with higher urinary kallikrein.

It has been shown recently that black adults have significantly lower kallikrein excretion rates than white adults. In addition, kallikrein excretion is less responsive to the stimulus of sodium depletion in black hypertensive adults than in black or white normotensive or white hypertensive adults. Collectively, the studies of urinary kallikrein in black and white adults and children indicate a racial correlation to urinary kallikrein concentration.

Although urinary kallikrein excretion may reflect the level of activity of that enzyme within the kidney, it has not been determined if different levels of excretion of the enzyme are related in any way to specific aspects of kidney function or, of course, to the prevalence of hypertensive diseases in the white or black populations. However, blood pressures in populations of black adults are higher than in white adults, though no such difference has been demonstrated consistently for black vs white children. In this context, the observations presented here raise questions about possible genetic or other differences in urinary kallikrein excretion and the relation of this finding to the pathogenesis of essential hypertension.

It is not possible from these data to predict that children with low urinary kallikrein levels and/or high blood pressure for their age and sex groups will be at risk of developing hypertensive diseases in later life. However, these data do indicate that blood pressure tracking begins in childhood, that urinary kallikrein is, in general, inversely related to blood pressure in children, and that black children have lower urinary kallikrein levels than white children.

Acknowledgment
The authors are grateful to Olga Ulchak, R.N., for valuable assistance.

References
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Circulation. 1978;58:908-915
doi: 10.1161/01.CIR.58.5.908
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

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