Hypertension May Be Transplanted with the Kidney in Humans: A Long-Term Historical Prospective Follow-Up of Recipients Grafted with Kidneys Coming from Donors With or Without Hypertension in Their Families

Ettore Guidi,2 Daniela Menghetti, Silvano Milani, Giuseppe Montagnino, Paola Palazzi, and Giuseppe Bianchi

ABSTRACT
In several genetic hypertensive rat strains, transplantation studies have established that the kidney carries at least a portion of the genetic message for hypertension. In man it has, of course, been more difficult to obtain clearcut results. This historical prospective observational study, double-blinded for knowledge of donors' and recipients' familialities for hypertension, concerns 85 transplanted patients, not treated with cyclosporine and with stable renal function, followed up for an average of 8 yr. Both the donors' and the recipients' families were carefully characterized for presence or absence of hypertension. After transplantation, in recipients without hypertension in their own families, a kidney coming from a "hypertensive" family determines less withdrawal and more introduction of antihypertensive therapy (AHT) than a kidney from a "normotensive" family (odds ratio for AHT introduction 5.0, confidence interval, 1.4 to 17.8; P = 0.017). In recipients with familial hypertension, the origin of the kidney does not influence the prevalence of hypertension after transplantation. More detailed analyses show that, in recipients without familial hypertension, the transplantation of a "hypertensive" kidney determines a tenfold larger increase in the requirement of antihypertensive therapy than the transplantation of a "normotensive" kidney, to obtain a similar blood pressure control (P = 0.003). This result is confirmed by the analysis of time-profile trends for antihypertensive therapy, adjusted for missing data, in the most clinically stable period (2nd to 10th yr after transplantation). The transmission of familial hypertension with the kidney is thus seen only in recipients coming from "normotensive" families, because familiality for hypertension blunts the effect of a "hypertensive" kidney.

Key Words: Genetics of hypertension, familiality for hypertension, kidney transplantation, kidney donors, post-transplantation hypertension

Kidney transplantation offers a straightforward approach to the still unsolved problem of whether the kidney is victim or culprit of hypertension. In at least five genetic rat models for human "essential" hypertension (1–9), the kidney carries at least a portion of the genetic message for blood pressure (BP) regulation, inasmuch as transplantation of a kidney from a genetically hypertensive rat causes hypertension in the recipient, whereas this does not happen when the kidney comes from a rat with a nongenetic form of hypertension (10). In some of these experiments, secondary functional changes caused by hypertension itself were excluded by controlling donor rats' BP with drugs or by transplanting kidneys of prehypertensive rats. A review on the renal abnormalities described in these animal models was recently published (11).

To reproduce these experiments in humans, 20 yr ago, soon after the inception of the kidney transplantation program in Milan, we began a historical prospective observational study searching for BP differences in recipients related to the presence or absence of donors' familial hypertension taken as an indicator of future development of "essential" hypertension in the recipients.
donor. Because donors are usually young and normotensive, this approach is the only feasible one in man.

In this article, we report our long-term study of the suitable recipients from the entire Milan transplantation program starting from its beginning in April 1969 and ending with the introduction of the cyclosporine immunosuppression protocol in July 1983. We excluded cyclosporine-treated recipients because of the well-known pressor effect of this drug. We reduced the possible biases of this historical prospective observational study by extensively recording recipients’ BP (1 yr before and after transplantation, for an average of 8 yr) and by using unequivocal and robust indicators of the BP status both before and after transplantation, such as the presence or absence of antihypertensive therapy (AHT) during an entire year. This study is double-blinded for what concerns patients’ and doctors’ knowledge of both donors’ and recipients’ familialities for hypertension.

In accordance with previous preliminary reports published by our group (12, 13), the results show that hypertension is transferred via a “hypertensive” donor’s kidney. However, this effect is seen only in recipients without familial hypertension, whereas recipients with familial hypertension seem to be protected from the effects of a “hypertensive” kidney.

**PATIENTS AND METHODS**

**Selection and Classification of Patients**

From the Milan kidney transplantation program, between April 1969 (beginning) and July 1, 1983 (beginning of routine cyclosporine therapy), we selected 85 patients who had received their kidney from 67 donors fulfilling the following six criteria:

1. The possibility of obtaining a direct measurement of BP of both of the donor’s and both of the recipient’s parents. Whenever possible, we also measured BP and collected medical histories for other family members invited to be present at the time of our visit to the family, which was scheduled at least 1 yr after transplantation. BP measurements were taken in the sitting position three times at 5-min intervals with a mercury sphygmomanometer (Baumanometer; W.A. Baum Co., Inc., Copague, NY). For obvious reasons, the identities of the recipient and of the donor were never disclosed to the donor’s family and to the recipient, respectively.

2. Having at least one of the recipient’s native kidneys in situ, to exclude the few bi nephrectomized patients.

3. A yearly serum creatinine mean level lower than 250 μmol/L (2.8 mg/dL), at least in the 1st yr of follow-up, excluding acute rejections. When the creatinine yearly mean level exceeded this value, the subsequent years of follow-up were discarded.

4. No graft artery stenosis suspected or proven on the basis of refractory hypertension, unexplained deterioration of renal function, or appearance of abdominal bruits (we did not perform routine arteriography in these patients for ethical reasons).

5. No *de novo* or recurring glomerulonephritis or transplant glomerulopathy on clinical and laboratory grounds (including graft biopsy).

6. Age greater than 13 yr.

Recipients were classified on the basis of the presence or absence of hypertension in the families of their donor as well as in their own. A family was defined as “normotensive” if both parents had a BP of less than 150/90 mm Hg (mean of three consecutive readings by two of us) without any AHT, whereas it was defined as “hypertensive” if one or both parents were receiving AHT or had a BP equal to or higher than 150/95 mm Hg. BP and clinical information obtained from other first- or second-degree relatives were always consistent with the classification of the family. On this basis, the following four groups were obtained:

- Kidney from a “normotensive” family to a recipient with “normotensive” family D−R− (n = 22)
- Kidney from a “hypertensive” family to a recipient with “normotensive” family D+R− (n = 23)
- Kidney from a “normotensive” family to a recipient with “hypertensive” family D−R+ (n = 18)
- Kidney from a “hypertensive” family to a recipient with “hypertensive” family D+R+ (n = 22)

**Collection of Pre- and Post-Transplantation Data**

Data from the recipients were collected from their clinical follow-up charts. The following pretransplantation variables were collected: familial hypertension (see above), sex, original nephropathy, BP after each hemodialysis treatment (mean of all the recorded measurements done in the last year before transplantation) and AHT (cumulative dosage in milligrams for each of the AHT drugs taken during this year), total duration of hemodialysis treatment (no patient underwent other dialytic procedures), age, height, body weight, and body surface area at the time of surgery.

After transplantation, we recorded the yearly mean levels for BP, plasma creatinine, steroid dosage (in prednisone equivalents) and its alternate day or daily administration, number of rejections, and AHT. Every recipient’s data reported on the clinical charts were recorded both during hospital admissions and during visits as outpatient. The recipients were seen at least six times a month during the first 4 months, at least two times a month during the next 8 months, at least once a month during the first 3 yr, and at least every other month afterward. The changes in BP, AHT, and plasma creatinine levels occurring during acute rejections were excluded from the analysis because of the probable presence of additional pathophysiologic mechanisms affecting BP. Supplemental doses of steroids administered during rejections were included in the records, on the assumption that they might have a long-term effect on BP. As already mentioned, when the yearly mean level of serum creatinine exceeded 250 μmol/L (2.8 mg/dL), we interrupted the collection of data.
In conclusion, data on 717 patient-years, with a mean follow-up period of 8 yr/patient (range, 1 to 20), were collected. The patients were followed-up in three Milanese Renal Units (Ospedale Maggiore Policlinico, Divisione di Nefrologia; Ospedale Maggiore Policlinico, Clinica Medica I; and Ospedale Niguarda Ca'Granda, Divisione di Nefrologia; referred to as A, B, and C, respectively, in Table 1) by three teams of nephrologists for a total of 12 physicians, who utilized similar strategies for hypertension management in transplanted patients.

AHT Analysis

All three renal units had a BP target for transplanted patients of 130 to 140/80 to 90, and AHT was suspended when diastolic BP fell below 85 mm Hg.

Four classes of drugs (diuretics, β-blockers, central α2-agonists, and vasodilators) made up 89% of the total prescriptions, and, inside these classes, four drugs (furosemide, propranolol, clonidine, and dihydralazine) represented respectively 57, 61, 73, and 91% of class prescriptions.

AHT was analyzed with two different approaches. First, we looked at the absence or presence of AHT during the entire last year of hemodialysis before transplantation and at the absence or presence of AHT during the entire last year of follow-up after transplantation. These data were then analyzed with nonparametric statistics.

Second, to standardize the potency of the various prescribed drugs, for each drug taken by the recipients, an AHT unit was defined as the minimum dosage of its pharmaceutical formulation available in Italy at the time of its prescription (Table 2). After calculation of the total yearly amount of AHT units taken by each patient, the analysis was carried out on the logarithm of (AHT units + 1) (log AHT units), on the usual assumption that the pharmacologic response is proportional to the logarithm of the dose.

The effect of transplantation on BP and AHT requirements

### TABLE 2. Drugs taken by the 85 selected recipients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>25</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>25</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>50</td>
</tr>
<tr>
<td>Amiloride</td>
<td>5</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25</td>
</tr>
<tr>
<td>Triamterene</td>
<td>25</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>80</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>100</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>200</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>40</td>
</tr>
<tr>
<td>Nadolol</td>
<td>80</td>
</tr>
<tr>
<td>Labelolol</td>
<td>100</td>
</tr>
<tr>
<td>Alpha-Methyl-Dopa</td>
<td>250</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.15</td>
</tr>
<tr>
<td>Reserpine</td>
<td>0.1</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>10</td>
</tr>
<tr>
<td>Prazosin</td>
<td>1</td>
</tr>
<tr>
<td>Dihydralazine</td>
<td>10</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>2.5</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>300</td>
</tr>
<tr>
<td>Verapamil</td>
<td>40</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20</td>
</tr>
<tr>
<td>Lacidipine</td>
<td>4</td>
</tr>
<tr>
<td>Captopril</td>
<td>25</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5</td>
</tr>
</tbody>
</table>

*The minimum dosage for each drug available in Italy at the time of prescription was defined as one "unit."

### TABLE 1. Pre- and post-transplantation (tx) data of the four groups of recipients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D-R-</th>
<th>D+R-</th>
<th>D-R+</th>
<th>D+R+</th>
<th>P Values, D+ vs. D-</th>
<th>All R</th>
<th>R-</th>
<th>R+</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>23</td>
<td>18</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female %</td>
<td>27</td>
<td>30</td>
<td>28</td>
<td>14</td>
<td>0.58 0.82 0.28</td>
<td>0.58</td>
<td>0.82</td>
<td>0.28</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 ± 10</td>
<td>35 ± 10</td>
<td>31 ± 10</td>
<td>30 ± 8</td>
<td>0.78 0.39 0.59</td>
<td>0.78</td>
<td>0.39</td>
<td>0.59</td>
</tr>
<tr>
<td>Glomerulonephritis %</td>
<td>77</td>
<td>74</td>
<td>78</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months of Hemodialysis</td>
<td>37 ± 21</td>
<td>22 ± 16</td>
<td>34 ± 25</td>
<td>38 ± 28</td>
<td>0.28 0.01 0.65</td>
<td>0.28</td>
<td>0.01</td>
<td>0.65</td>
</tr>
<tr>
<td>Pre-tx SBP (mm Hg)</td>
<td>128 ± 21</td>
<td>133 ± 20</td>
<td>129 ± 21</td>
<td>131 ± 25</td>
<td>0.49 0.49 0.78</td>
<td>0.49</td>
<td>0.49</td>
<td>0.78</td>
</tr>
<tr>
<td>Pre-tx DBP (mm Hg)</td>
<td>82 ± 16</td>
<td>82 ± 11</td>
<td>82 ± 12</td>
<td>84 ± 16</td>
<td>0.73 0.99 0.64</td>
<td>0.73</td>
<td>0.99</td>
<td>0.64</td>
</tr>
<tr>
<td>Pre-tx Log AHT Units</td>
<td>2.19 ± 0.34</td>
<td>0.88 ± 0.32</td>
<td>1.52 ± 0.38</td>
<td>1.36 ± 0.33</td>
<td>0.03 0.01 0.75</td>
<td>0.03</td>
<td>0.01</td>
<td>0.75</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>59.5 ± 8.8</td>
<td>62.9 ± 10.8</td>
<td>64.3 ± 11.3</td>
<td>66.6 ± 13.3</td>
<td>0.22 0.26 0.56</td>
<td>0.22</td>
<td>0.26</td>
<td>0.56</td>
</tr>
<tr>
<td>Renal Units (A/B/C %)</td>
<td>64/32/5</td>
<td>61/22/17</td>
<td>50/33/17</td>
<td>45/18/36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of Follow-Up</td>
<td>9 ± 5</td>
<td>8 ± 6</td>
<td>9 ± 5</td>
<td>8 ± 6</td>
<td>0.51 0.53 0.77</td>
<td>0.51</td>
<td>0.53</td>
<td>0.77</td>
</tr>
<tr>
<td>Serum Creatinine (mg/mL)</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>0.13 0.30 0.29</td>
<td>0.13</td>
<td>0.30</td>
<td>0.29</td>
</tr>
<tr>
<td>Prednisone (mg/yr)</td>
<td>5673 ± 2616</td>
<td>6390 ± 3044</td>
<td>6449 ± 3258</td>
<td>7106 ± 3195</td>
<td>0.28 0.40 0.53</td>
<td>0.28</td>
<td>0.40</td>
<td>0.53</td>
</tr>
<tr>
<td>Alternate Day %</td>
<td>57</td>
<td>39</td>
<td>47</td>
<td>53</td>
<td>0.46 0.15 0.64</td>
<td>0.46</td>
<td>0.15</td>
<td>0.64</td>
</tr>
<tr>
<td>Rejections/Yr</td>
<td>0.25 ± 0.65</td>
<td>0.23 ± 0.46</td>
<td>0.16 ± 0.26</td>
<td>0.22 ± 0.47</td>
<td>0.88 0.90 0.62</td>
<td>0.88</td>
<td>0.90</td>
<td>0.62</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>136 ± 11</td>
<td>135 ± 15</td>
<td>133 ± 14</td>
<td>138 ± 12</td>
<td>0.19 0.42 0.29</td>
<td>0.19</td>
<td>0.42</td>
<td>0.29</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>90 ± 8</td>
<td>89 ± 8</td>
<td>89 ± 8</td>
<td>90 ± 8</td>
<td>0.99 0.78 0.80</td>
<td>0.99</td>
<td>0.78</td>
<td>0.80</td>
</tr>
</tbody>
</table>

If not otherwise indicated, values are means ± SD. AHT, antihypertensive therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure.

See the Patients and Methods Section Collection of Pre- and Post-transplantation data, for definition of A, B, and C.
was evaluated by calculating for each recipient the Δ for systolic BP (SBP), diastolic BP (DBP), and log AHT units, subtracting the post-transplantation yearly means of these variables from the means of the last year before transplantation, taken as the baseline value.

**Statistical Methods**

For each recipient, we determined the three possible outcomes after transplantation, i.e., suspension of AHT, no change in AHT, or introduction of AHT. Differences in the occurrence of the above outcomes between D+ and D-, D+R- and D-R-, and D+R+ and D+R- were tested by Fisher’s Exact Test (14,15).

For each variable under study, the mean individual values per year were averaged over the entire length of follow-up (global means). Global means were fitted by an analysis of variance (ANOVA) model for one-way layout (16). The hypothesis of no difference between D+ and D- patients both without and with consideration of their own familial hypertension were tested. Least-significant differences (LSD), at 5% level, were also calculated, when appropriate, to test the hypothesis of no difference between the four groups.

To check the dependency of post-transplantation AHT increase from preexisting AHT, we determined the regression slope between Δ log AHT units and pretransplantation AHT units for all 85 recipients; the symmetry around this slope of the four recipients’ groups was subsequently tested by χ² calculation.

A more detailed analysis focused on the period from the 2nd to the 10th yr of follow-up. In this period, there was a sufficient number of patients for each group (from 81 at the 2nd yr to 36 at the 10th yr) and early or late events that might have affected BP did not occur. Time profiles for Δ log AHT units were fitted by an ANOVA model for split-plot design with repeated measures (16); the hypothesis of no difference in trend between groups was tested. Data were expressed as least-squares means (17), based on the model and thus adjusted for the confounding effect of missing data, which affect raw means.

Data management and analysis were carried out by using the SAS® statistical analysis system, Version 6.03 (18).

**RESULTS**

Table 3 reports the characteristics of the donors and their families for each group of recipients. One-way ANOVA was performed first without considering the recipients’ familiality (first P column) and then considering also the recipients’ familiality for hypertension (second and third P columns). Both SBP and DBP of “hypertensive” donors’ parents were higher, despite an approximate 30% prevalence of AHT. The 67 donors had only five children, all very young and normotensive. We interviewed and measured the BP of 43% of all donor siblings, and in no case were we left with doubts about the classification of the family. The donor siblings’ BP in “hypertensive” donor families was significantly higher, with presence of AHT in 17% of R- and 5% of R+ families.

The donors from a “hypertensive” family (and their parents, not shown in the table) were older than those with a “normotensive” one (P < 0.01 in every comparison), sex distribution was similar between the groups, and death of donors with hypertension in their family was more likely to have been caused by an intracerebral hemorrhage than by a trauma. The latter difference was statistically significant only when all recipients (R- and R+ together) and R+ recipients were considered (P = 0.03 and P = 0.05, respectively).

The familial data of the recipients are shown in Table 4. The parents of recipients with familial hypertension (R+) had, of course, both SBP and DBP values higher than those of recipients without familial hypertension (R-), despite a 40% prevalence of AHT (P < 0.01 in all of the possible comparisons). The hypertensive familiality of recipients was equally distributed between the recipient groups receiving a D- or a D+ kidney (last three columns of Table 4).

The nonparametric analysis of AHT introduction, maintenance, or withdrawal after transplantation is shown in Table 5. The recipients of “hypertensive” kidneys, D+, are less likely to have experienced withdrawal and more likely to have experienced introduction of AHT than recipients of a “normotensive” kidney, D- (P = 0.052). However, when the recipients were grouped according to their own familiality for hypertension, D+R- recipients never experienced

### TABLE 3. Anthropologic and familial data and cause of death of the donors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D-R-</th>
<th>D+R-</th>
<th>D-R+</th>
<th>D+R+</th>
<th>P Values, D+ vs. D-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor Parents' SBP</td>
<td>128 ± 12</td>
<td>161 ± 22</td>
<td>127 ± 12</td>
<td>158 ± 34</td>
<td>&lt;0.01  &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Donor Parents' DBP</td>
<td>82 ± 7</td>
<td>98 ± 12</td>
<td>80 ± 7</td>
<td>92 ± 17</td>
<td>&lt;0.01  &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Donor Parents' AHT (%)</td>
<td>0 ± 0</td>
<td>30 ± 0</td>
<td>0 ± 0</td>
<td>33 ± 0</td>
<td>0.01   &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Donor Siblings' SBP</td>
<td>116 ± 11</td>
<td>134 ± 21</td>
<td>109 ± 12</td>
<td>131 ± 25</td>
<td>&lt;0.01  &lt;0.01  0.01</td>
</tr>
<tr>
<td>Donor Siblings' DBP</td>
<td>72 ± 10</td>
<td>86 ± 10</td>
<td>68 ± 9</td>
<td>84 ± 11</td>
<td>&lt;0.01  &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Donor Siblings' AHT (%)</td>
<td>0 ± 0</td>
<td>17 ± 0</td>
<td>0 ± 0</td>
<td>5 ± 0</td>
<td>0.01   &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Donor's Age</td>
<td>20 ± 6</td>
<td>28 ± 12</td>
<td>19 ± 6</td>
<td>31 ± 11</td>
<td>&lt;0.01  &lt;0.01  &lt;0.01</td>
</tr>
<tr>
<td>Female (%)</td>
<td>23 ± 0</td>
<td>35 ± 0</td>
<td>33 ± 0</td>
<td>23 ± 0</td>
<td>0.89   0.38   0.47</td>
</tr>
<tr>
<td>Cerebral Hemorrhage (%)</td>
<td>21 ± 0</td>
<td>38 ± 0</td>
<td>13 ± 0</td>
<td>44 ± 0</td>
<td>0.03   0.30   0.05</td>
</tr>
</tbody>
</table>

*If not otherwise indicated, values are mean ± SD. D: donor; R: recipient; -, family without hypertension; +, family with hypertension.

*b Information on parents is complete.

*c Siblings' BP and prevalence of AHT was obtained in 86 of 200 subjects, i.e., 43% of the total.
TABLE 4. Familial data of the 85 recipients divided according to the presence or absence of hypertension in the family of their donor and their own familya

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D−R−</th>
<th>D+R−</th>
<th>D−R+</th>
<th>D+R+</th>
<th>P, R+ vs. R−</th>
<th>D+ vs. D−</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>23</td>
<td>18</td>
<td>22</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parents' SBP</td>
<td>138 ± 19</td>
<td>137 ± 14</td>
<td>169 ± 25</td>
<td>161 ± 30</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parents' DBP</td>
<td>80 ± 5</td>
<td>82 ± 6</td>
<td>100 ± 11</td>
<td>97 ± 16</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parents' AHT (%)</td>
<td>0</td>
<td>0</td>
<td>42</td>
<td>39</td>
<td>0.80</td>
<td>0.61</td>
</tr>
</tbody>
</table>

a If not otherwise indicated, values are mean ± SD. See Table 1 for abbreviations.

TABLE 5. Differences in the suspension and introduction of AHT in recipients after transplantation of a "normotensive" (D−) or "hypertensive" (D+) kidney according to Fisher's Exact test (14, 15)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Suspended</th>
<th>No change</th>
<th>Introduced</th>
<th>P</th>
<th>Odds Ratio for AHT Introduction – Y/n a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td>D−</td>
<td>40</td>
<td>6 (15) b</td>
<td>25 (63) b</td>
<td>9 (22) b</td>
<td>0.017</td>
<td>5.0 (1.4 to 17.8)</td>
</tr>
<tr>
<td>D+</td>
<td>45</td>
<td>2 (4)</td>
<td>23 (52)</td>
<td>20 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R−</td>
<td>22</td>
<td>3 (14)</td>
<td>13 (59)</td>
<td>6 (27)</td>
<td>0.79</td>
<td>1.5 (0.3 to 7.2)</td>
</tr>
<tr>
<td>R+</td>
<td>23</td>
<td>0 (0)</td>
<td>8 (35)</td>
<td>15 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D−</td>
<td>18</td>
<td>3 (17)</td>
<td>12 (66)</td>
<td>3 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+</td>
<td>22</td>
<td>2 (9)</td>
<td>15 (66)</td>
<td>5 (23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Values within parentheses are 95% confidence limits.
b Numbers in parentheses are percentages.

AHT withdrawal and experienced AHT introduction more often than D−R− recipients (P = 0.017), whereas this difference was absent if the recipient came from a "hypertensive" family (P = 0.79). The more frequent development of hypertension in D+ is thus almost entirely attributable to the D+R− group. This group displays less withdrawal and more introduction of AHT also when it is compared with the other three groups (P = 0.01, not shown in the table).

Table 1 shows the pretransplantation and posttransplantation data of the four recipient groups, analyzed by one-way ANOVA. As can be seen from the table, gender, age, type of kidney disease, SBP and DBP before transplantation, body weight at the time of surgery, renal unit, years of follow-up, serum creatinine level, prednisone dosage (both averaged over the entire follow-up) and schedule of administration, rejections, and BP after transplantation are not different when we divide the recipients according to the donor familiarity for hypertension, regardless of each recipient's familiarity. In contrast, the D+R− group experienced fewer months of hemodialysis than the other three, and D− patients needed significantly more AHT units to control their BP before transplantation than D+ patients (P = 0.03). This difference occurred because of the D−R− group (P = 0.01), whereas D−R+ recipients were not different from D+R+ patients (P = 0.75). This clustering of hypertensive patients in the D−R− group is not attributable to the recipients' familiarity for hypertension or to any of the variables that we measured.

BP and AHT changes after transplantation are instead shown in Figure 1: ΔSBP and ΔDBP are positive and not different in every comparison, indicating that kidney transplantation made BP control slightly more difficult in all groups. Notwithstanding the slight increase in BP, the control of hypertension was good in every group both before and after transplantation, because in no group did SBP and DBP exceed 140 and 90 mm Hg, respectively. However, the maintenance of these similar BP levels requires very different increases of AHT between the groups; D+ recipients need a mean increase of AHT approximately ten times greater than D− recipients (Δ log AHT units [mean ± SE] 1.21 ± 0.28 versus 0.22 ± 0.28, P = 0.015). This difference is magnified in the D+R− versus D−R− comparison (Δ log AHT units 1.81 ± 0.39 versus 0.10 ± 0.39, P = 0.003), and it is absent in the D+R+ versus D−R+ comparison (Δ log AHT units 0.57 ± 0.37 versus 0.36 ± 0.42, P = 0.71). Calculation of the LSD between the four groups confirms that D+R− group is the only one that differs from the other three. If we look at the cumulative yearly dosages of the four most prescribed drugs, i.e., furosemide, propranolol,
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We also performed a separate analysis on R− patients, excluding from the D−R− group the four recipients with the highest pretransplantation AHT units, to achieve a nonsignificantly different pretransplantation AHT, with respect to the other groups. The difference in Δ log AHT units between D−R− and D+R− groups remained highly significant (0.21 ± 0.47 versus 1.81 ± 0.39, P = 0.01).

To isolate a clinically stable period without acute rejections and clinical complications of the 1st yr and possibly without the late deterioration that every grafted kidney more or less suffers, we isolated the period of time between the 2nd and the 10th yr after transplantation and analyzed the time profile of Δ log AHT units, using an ANOVA model for split-plot design with repeated measures. These results are reported in Figure 2 and confirm that D+R− recipients require an increase of AHT greater than D−R− recipients (P = 0.04), whereas D+R+ recipients require the same increase of AHT as D−R− (P = 0.71) recipients; P value decreases because of the loss of patients during the follow-up (see the Statistical Methods section).

DISCUSSION

In this prospective historical study, we have analyzed the effect of the origin of the transplanted kidney, with respect to hypertension in the donors' families, on post-transplantation BP, evaluated as requirement for AHT. The results described here support two main conclusions.

The first is that a "hypertensive" kidney determines more requirement for AHT in recipients than a "normotensive" one, i.e., that the kidney is able to transmit a familial type of hypertension in man. The second is that this effect is restricted to recipients without familial background for hypertension.

To our knowledge, this is the only human study...
The first reported a long-term careful observation of kidney transplantation after transplantation, becoming normotensive studies supporting our findings must be mentioned. However, two other human studies supporting our findings must be mentioned. First, the donors from “hypertensive” families are older than the donors from “normotensive” ones, but their average age was below 30 yr. This difference could affect BP, even though renal function has always been described as constant in the 20- to 30-yr age span (30). Moreover, this age difference is present both in the R+ and in the R— groups, whereas an effect on hypertension was seen only in the latter recipients, indicating that the age of the donor and need for post-transplantation AHT are not related. Not surprisingly, the parents of the “hypertensive” donors were also older than those of the “normotensive” ones. Some younger parents of “normotensive” donors could thus have been misclassified because their hypertension had not yet developed. This occurrence, however, would have blurred and not enhanced the difference in the pressure effect of the donors’ kidneys. (2) The duration of hemodialysis before transplantation in D+R— patients is shorter than in the other three groups. Could one average additional year of dialysis have an influence on BP levels for 8 yr after transplantation? Although this possibility cannot be excluded, it seems highly unlikely. (3) Finally, the D—R— group had a higher requirement for AHT before transplantation than the D+R— one, but was not different from the other two groups, when compared by LSD calculation. This unbalanced baseline was certainly the result of chance, because no familial or clinical characteristic that we measured could account for it. Third, in our parametric analyses, we chose to use the Δ values for BP and AHT requirement (post-transplantation minus pretransplantation values) instead of the absolute values, on the assumption that the causes that made the patients hypertensive before are also at work after transplantation, given the chronic and self-perpetuating nature of hypertension. Although this assumption may be somewhat simplistic, and it could be argued that the D+R— group had the largest increase of AHT because it was the least hypertensive before transplantation, this trend was not present in D—R— and D+R+ recipients who were not different from D+R— ones for pretransplantation AHT, but experienced a much smaller increase of AHT after transplantation. Moreover, the results for the two R— groups balanced for pretransplantation AHT showed that this difference was not important for post-transplantation AHT requirement. Finally, one or more of the secondary types of hypertension observed in transplant patients could be a confounding factor. However, because sex, age, renal disease, body weight, length of follow-up,
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renal function, rejections, and prednisone schedule and dosage are not different in the four groups, it is unlikely that there are differences in secondary types of hypertension. Moreover, the parametric analyses were repeated on recipients in whom the serum creatinine level was less than 175 μmol/L (2.0 mg/dL), without substantial change of the results.

ACKNOWLEDGMENT

This study evolved over the course of approximately 20 years with the help of many people variously involved in the organization of the kidney transplantation program in Milan, Italy. The authors thank all donors and recipient family members and the nurses, social workers, technicians, and physicians who tracked the families and collected the data. Particular thanks are due Drs. G. Mecca and E. Gotti and all the nursing staff of the Divisione di Nefrologia, Ospedali Riuniti di Bergamo; Drs. M. Maritano and V. Gravame of the Centro Trasfusionale di Immunologia dei Trapianti, Ospedale Maggiore Policlinico, Milan; the physicians and nurses of the Cattedra di Chirurgia dei Trapianti, Ospedale Maggiore Policlinico, and of the Divisione Pizzamiglio II, Ospedale Niguarda Ca’Granda, Milan; the physicians and nurses of the Divisione di Nefrologia e Dialisi, Ospedale Maggiore Policlinico, Milan; Prof. F. Quarto di Fallo and Drs. G. Bucchiante, F. Vallino, and A. Vaznoli of the Servizio di Dialisi, Istituto di Clinica Medica I, Ospedale Maggiore Policlinico, Milan; Prof. L. Minetti and Drs. A. Durante, G. C., and E. Minetti of the Servizio di Dialisi, Istituto di Clinica Medica I, Ospedale Niguarda Ca’Granda, Milan; the physicians and nurses of the Dialysis Units of S. Donato Milanese, Bergamo, Albenga, Reggio Emilia, Como, Pietrasanta, Alessandria, Melegnano, La Spezia, Treviso, Lecco, Varese, Bergamo, Torino (Ospedale Mauriziano), Rivoli, Brescia, Pavia, Busto Arsizio, Desto, Bollate, Otranto, Casarano, Casale Monferrato, Massa Carrara, and Monza. In addition, the authors acknowledge Drs. G. Martott, V. Dallosta, C. Avanzi, T. Stellato, M. Cornacchiari, L. Brevi, M. Corti for help while visiting donors’ and recipients’ families; Dr. Giorgio Binelli of the Dipartimento di Genetica e di Biologia dei Microrganismi, Università degli Studi di Milano, for helpful discussions; and Nicola Borgese, Ph.D., CNR Center for Cytopharmacology, Milan, for helpful criticism and linguistic advice.

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