The Functional Homogeneity of the Nephron Population in Transplanted Cadaver Kidney in Man

TADEUSZ ORLOWSKI, LILIANA GRADOWSKA, JOANNA KLEPACKA and DANUTA ROWINSKA
I. Medical Department, Warsaw Medical School, Warszawa, Poland

Although cadaver kidney transplantation is nowadays a therapeutic method quite frequently used for the treatment of terminal renal failure, there is surprisingly scant information concerned with the function of such a transplanted organ. The degree to which this procedure alters the functional homogeneity of surviving nephrons is completely unknown. In the present studies, an evaluation has been made of the glomerulotubular balance for glucose of nephrons functioning after transplantation, using the glucose titration technique.

METHODS
Eight glucose titration studies were performed on 6 patients, selected from 20, who received cadaver kidney transplants between January 1966 and April 1969. Donors and recipients were matched in respect of major blood-group (ABO) only. Kidneys were perfused with modified saline solution. The time of warm ischaemia ranged from 7 to 29 min, the total ischaemia time from 36 to 120 min. Standard surgical technique was used. Bilateral nephrectomy was usually performed at the time of transplantation. In all patients studied urinary flow began immediately. Azathioprine, prednisolone, Actinomycin C, and in some cases, local irradiation of the graft during the first week postoperatively were used as an immunosuppressive regimen.

Glomerular filtration rate was measured with inulin, according to the resorcinol method of Roe et al. (1949). Glucose was estimated by glucose oxidase (Bergmeyer et al., 1963) or o-toluidine (Hyvarinen, 1962) methods. Glucose titration curves and frequency distribution curves were calculated by the methods of Smith et al. (1943). Individual curves were drawn by visual approximation. The amount of splay represented by the area between the theoretical curve of zero splay and the actual titration curve was expressed in arbitrary 'splay units' (s.u.). The normal splay, recalculated from Smith's (1951) data for healthy subjects did not exceed 215 s.u.
TABLE I. The values of $C_{\text{In}}$, $Tm_G$, $C_{\text{In}}/Tm_G$ ratio and splay units after cadaver kidney allotransplantation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>$C_{\text{In}}$ (ml/min)</th>
<th>$Tm_G$ (mg/min)</th>
<th>$C_{\text{In}}/Tm_G$</th>
<th>Splay (s.u.)</th>
<th>Day after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. B.</td>
<td>F</td>
<td>10.2</td>
<td>15</td>
<td>0.67</td>
<td>222</td>
<td>260</td>
</tr>
<tr>
<td>K. G.</td>
<td>M</td>
<td>37</td>
<td>119</td>
<td>0.31</td>
<td>719</td>
<td>268</td>
</tr>
<tr>
<td>B. R.</td>
<td>F</td>
<td>20.3</td>
<td>44</td>
<td>0.46</td>
<td>2200</td>
<td>337</td>
</tr>
<tr>
<td>E. B.</td>
<td>F</td>
<td>14.2</td>
<td>28</td>
<td>0.51</td>
<td>2224</td>
<td>344</td>
</tr>
<tr>
<td>Z. L.</td>
<td>M</td>
<td>27</td>
<td>65</td>
<td>0.42</td>
<td>3182</td>
<td>419</td>
</tr>
<tr>
<td>M. D.</td>
<td>M</td>
<td>29</td>
<td>83</td>
<td>0.35</td>
<td>601</td>
<td>595</td>
</tr>
<tr>
<td>K. J.</td>
<td>M</td>
<td>48.5</td>
<td>234</td>
<td>0.21</td>
<td>2087</td>
<td>661</td>
</tr>
<tr>
<td>K. J.</td>
<td>M</td>
<td>44.6</td>
<td>122</td>
<td>0.37</td>
<td>1484</td>
<td>751</td>
</tr>
</tbody>
</table>

$C_{\text{In}}$ = Inulin clearance; $Tm_G$ = maximal tubular transport of glucose

RESULTS

The maximal transport of glucose ($Tm_G$) ranged from 15 to 234 mg/min (Table I) and in 4 patients it was clearly depressed, sometimes more than $C_{\text{In}}$ (Figure 1).

![Figure 1. Maximal transport of glucose ($Tm_G$) after kidney transplantation, as related to inulin clearance ($C_{\text{In}}$). The sloping lines represent the mean (m) normal value (mixed sexes) of the ratio $C_{\text{In}}/Tm_G$ ± multiples of the standard deviation.](image-url)
In Figure 2 eight glucose titration curves are shown for the cadaver kidney, obtained in 6 patients studied. Some of them leave the theoretical line at a glucose filtered load/glucose maximal transport rate ($FL_G/Tm_G$) value of 0.10 and return to the line at a $FL_G/Tm_G$ value higher than 2.3, differing significantly from the normal curve, which diverges from the theoretical line at a $FL_G/Tm_G$ value of about 0.7 and returns to it at a $FL_G/Tm_G$ value of 1.5. This striking difference between curves obtained from healthy and transplanted cadaver kidneys, expressed in splay units, is highly significant (p<0.001). In all experiments the amount of splay was found to be very high, ranging from 260 to 3182 s.u. (Figure 3). No relationship of the magnitude of $C_{In}$ or the time elapsing from the transplantation to the amount of splay was observed.
Figure 3. The amounts of splay of the glucose titration curves obtained after kidney transplantation.

Figure 4. Frequency distribution curves for the glucose titration data from cadaver transplanted kidneys. \( \text{tm}/\text{Tm} \) indicates the rate of glucose reabsorption in saturated nephrons presented as a fraction of the \( \text{Tm} \) value for the whole kidney. \( r/R \) represents relative glomerular activity. The shaded area indicates the range of normal values.
The frequency distribution curves (Figure 4) illustrating the relative frequency of groups of nephrons with various levels of glomerulotubular balance for glucose were abnormal in all patients studied. In all cases this balance changed mainly towards glomerular preponderance. The percentage of nephrons with relatively low glomerular activity ($r/R$) was much lower (Figure 5).

**DISCUSSION**

The present studies show marked heterogeneity of the surviving nephron population of the cadaver transplanted kidney. The increase of splay was associated with appearance of groups of nephrons with change of glomerulotubular balance of glucose toward glomerular preponderance. The nature of this disturbance may be manifold.

Rieselbach et al (1964) found little increase in splay in patients with chronic renal diseases with glomerular filtration rate between 58 and 15 ml/min. A marked increase in the splay was consistently found in cases with filtration rate below 15 ml/min. Shankel et al (1967) on the basis of their experimental data concluded that 'when the total nephron population is critically reduced, splay evolves in the residual nephrons of the rat, whether disease is present or not'. From their studies it is clear that anatomic deformations of the parenchyma of the transplanted cadaver kidney is not the only possible explanation of the occurrence of splay in the glucose titration curve.
The frequency distribution curves obtained in 5 tests disclosed the existence of nephrons with low glomerular activity. An increased contribution to the elaboration of urine by juxtamedullary nephrons with low filtration pressure may be responsible for this defect.

The increased population of nephrons with high glomerular activity may result partly from spotty destruction of proximal tubules due to ischaemic rejection episodes, partly by alternation in the kinetics of glucose transport due to increased flow and volume of intra-tubular fluid in nephrons with compensatory hypertrophy of glomeruli.

The findings described above represent another example of the proximal tubular defects described in transplanted kidney by several authors (Massry et al, 1967; Orfowski et al, 1967; Better et al, 1969).

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