expected to have a higher incidence of associated delayed graft function and poorer graft outcome. Furthermore, catecholamines can cause renal vasoconstriction and lead to acute tubular necrosis.

Without addressing these issues, we feel that a randomized trial to compare catecholamines to no catecholamines in potential kidney donors is not justifiable.

However, a prospective study examining the same factors as Schnuelle et al but with accurate documentation of catecholamine dose, duration, and time-averaged blood pressure would provide valuable information, and could be carried out in a relatively short period.

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Reply from the authors

Geddes et al raised criticisms regarding the methodology of our study. Firstly, as mentioned in our study, the beneficial effect of donor catecholamine use on acute rejection after transplantation was clearly confirmed by univariate analysis, which argues against a chance association due to statistical overfitting of the multivariate model.

Secondly, treated and non-treated donors did not differ with respect to blood pressure, serum creatinine, and urine production before removal of the kidneys. Taking into consideration that the data on vasopressor employment to the donor reflect multicenter experience in the Eurotransplant area does not support uniform confounding by indication. Geddes et al suspect that the results could be biased in favor of catecholamine use, if vasopressors were preferentially given to donors without hemodynamic compromise and vice versa withheld from hypotensive donors, thereby causing an adverse outcome, which is quite unusual in a clinical setting. Moreover, this view is unlikely to be true, since there was a significant association between donor noradrenaline use and delayed graft function in our study. This observation can be explained with physiological reasoning of catecholamine-induced renal vasoconstriction leading to acute tubular necrosis, as emphasized by Geddes et al. The lower incidence in biopsy-proven rejections after catecholamine use remains a new and unexpected observation.

We agree that further information on accurate catecholamine dosage, duration of treatment, etc., is warranted before a randomized trial is to be justified. However, lack of these data does not in principle jeopardize the methods and outcome of the current study.

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Renal handling of albumin in normal rat

To the Editor: The study by Eppel et al presents surprising new data on the glomerular filtration of albumin and subsequent tubular reabsorption of intact albumin back to the circulation in rat kidney [1]. From their Table 4, the concentration of albumin in the glomerular ultrafiltrate can be calculated to be 2.3 mg/mL. Previous reported values in rat and dog have varied between <0.001 and 0.05 mg/mL (reviewed in [2]). The value presented by Eppel et al is thus a factor 45 higher than the highest concentrations reported. Based on their experiments the authors suggest a high capacity cellular reabsorption mechanism in the *very early* part of the proximal tubule, providing an explanation why previous micropuncture studies did not find the high concentration of albumin suggested by this study. The authors furthermore suggest that the reabsorption is transcellular. However, immunohistochemistry for endogenous albumin in the initial part of rat proximal tubule (Fig. 1A), reveals no difference in the intracellular concentration of albumin as compared to later parts of segment 1 of the proximal tubule. Furthermore, there is no evidence to suggest a transtubular transport of intact albumin, neither at the light microscope level nor at the electron microscope level (Fig. 1B). Albumin is always localized either in apical endosomes or in lysosomes as shown by double labeling for albumin and cathepsin B. A possible explanation for the results presented by Eppel et al is that the injected, probably in part denatured albumin, binds to the basolateral membrane of the tubules followed by a subsequent slow release simulating a transtubular transport of intact albumin. This mode of

action was demonstrated by Ottosen et al in a series of elegant papers [3], also reviewed by Christensen and Nielsen [4], to explain the unexpected findings of Mack et al of a similar apparent transtubular transport of protein [5].

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Reply from the authors

We are glad to have the opportunity to respond to the issues raised by Drs. Christensen and Birn. There is now overwhelming evidence that the glomerular capillary wall (GCW) is far more permeable to albumin than originally thought, and that albumin concentrations measured by micropuncture measurements do not accurately represent the result of purely "extracellular" transport involving filtration. It has now been demonstrated that albumin does not undergo charge repulsion by the GCW or the glomerular basement membrane (GBM) [1–8], but is simply size selected [6, 8]. In systems where renal funciton has been compromised by poisons, but normal glomerular size selectivity (as measured by fractional clearance of transport probes) has been retained, it has been demonstrated by micropuncture measurements that the glomerular ultrafiltrate has an albumin concentration of 2.3 mg/mL [9] (as predicted in our study [10]) and that albumin is transported as a molecule with an effective hydrodynamic radius of ~36Å [6, 8, 11]. The quantitative measurements of the retrieval pathway made in our study [10] fit precisely with that glomerular

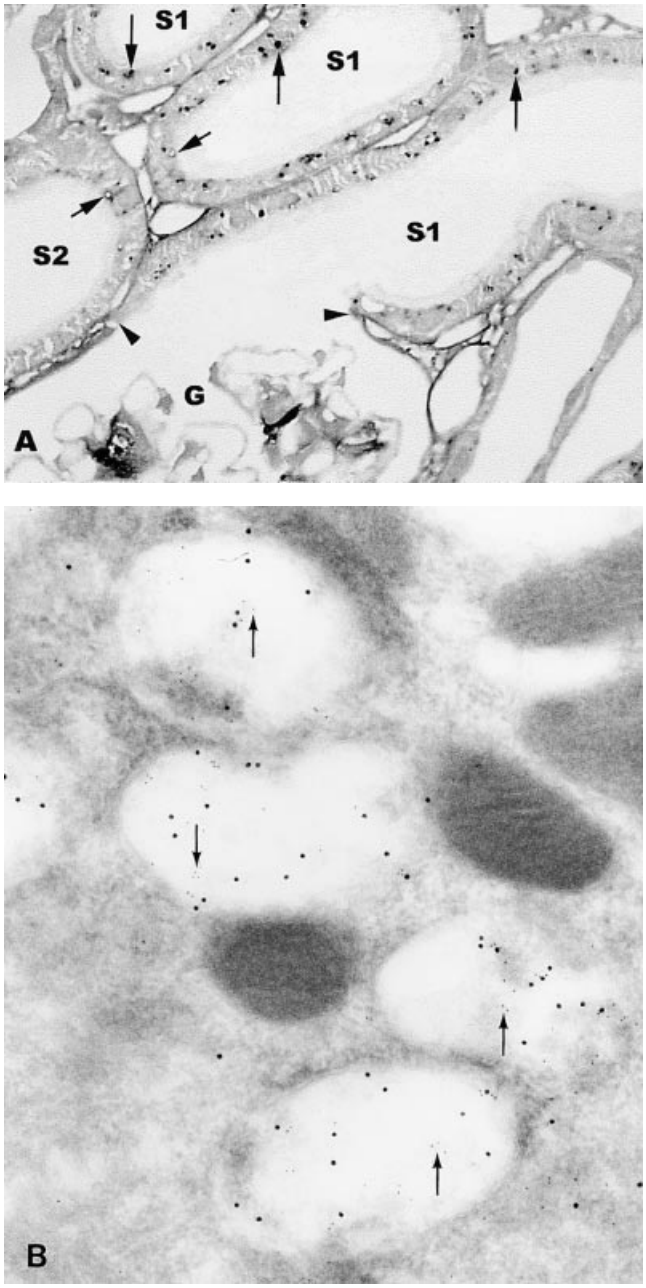

Fig. 1. (*A*) Immunohistochemical localization of endogenous albumin in proximal tubule. One micrometer cryosection of rat renal cortex was incubated with sheep anti-rat albumin and subsequently with peroxidase coupled rabbit antisheep immunoglobulin. Intense staining is observed in segment 1 of the proximal tubule (S1), but uptake is also seen in segment 2 (S2). Arrowheads indicate transition from Bowman's capsule of the glomerulus (G) to the proximal tubule. Small arrows point to apical endosomes containing albumin, large arrows demonstrate granular labeling for albumin with a location typical of lysosomes. There is no difference in labeling intensity between early and later parts of segment 1 (×700). (*B*) Electron microscope visualization of endogenous albumin in lysosomes of segment 1 proximal tubule of rat. The cryosection was incubated with sheep anti-rat albumin (15 nm gold particles) and rabbit anti-rat cathepsin B (5 nm gold particles) (arrows). At the electron microscope level labeling was seen exclusively in apical endosomes and in lysosomes. (×53,000).