with diabetes induced by streptozotocin after uninephrectomy prevented albuminuria for a long period.

We also verified whether MMF prevents development of anti-glomerular basement membrane (GBM) antibody-induced glomerulonephritis. Experimental nephritis in WKY/NCrj (MHC haplotype; $RT1^l$) rats was induced by an intraperitoneal injection of anti-GBM antibody (SR2). Then, the animals were given 20 mg/kg/day of oral MMF (treated group) or normal saline (control group) for 2 weeks. The results showed MMF significantly prevented urinary protein excretion (treated group vs. control group, 9.4 ± 4.3/creatinine vs. 21.7 ± 4.3/creatinine). However, daily administration of MMF significantly reduced the hematocrit level (24.0 ± 0.8% vs. 41.7 ± 1.5%) and suppressed body weight gain (13.4 ± 6.8% vs. 20.7 ± 7.0%). We paid much attention to MMF dosage for different rat strains. Few adverse effects occurred when we administered 20 mg/kg/day of MMF to Lewis rats (haplotype; $RT1^l$) in another experimental model. It was also reported that even when 80 mg/kg/day was orally administered to BN rats ($RT1^n$), no adverse effects occurred [3]. Because MMF is a critical dose drug and markedly affected by sensibility, there may be differences in doses among experimental animals, such as 10 mg/kg/day [2] and 80 mg/kg/day [3].

We congratulate Utimura et al [2] for their new approach to diabetic nephropathy, but wish to know if any adverse effects such as anemia and clinical symptoms occurred.

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Reply from the Authors

We wish to thank Dr. Takeda and his colleagues for their remarks. In the study in question, and in prior studies of the 5/6 renal ablation and the chronic nitric oxide inhibition models, we always administered mycophenolate mofetil (MMF) at 10 mg/kg/day. At this dose, diabetic rats ate normally, remained in good "clinical" condition, grew at the same rate as untreated controls, and developed no anemia (hematocrit = 42 ± 1% in diabetic treated vs. 44 ± 1% in untreated at 8 months of observation, $P > 0.1$). We avoided higher doses, which, in pilot studies, were systematically associated with anemia, stunted growth, and poor general condition. MMF has been associated with reversible anemia in transplant patients, suggesting that it may indeed depress the erythroid series [1]. We believe this is dose-dependent, and that MMF doses should be carefully titrated if this and other untoward effects are to be avoided. We are unaware of data on variable susceptibility among rat strains, although this is certainly possible.

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Myocardial function in Bartter's and Gitelman's syndromes

To the Editor: Bettinelli et al [1] recently reported the interesting observation of prolonged QT interval in the electrocardiogram in Gitelman's syndrome and concluded with the suggestion of increased risk for these patients of developing dangerous ventricular arrhytmias.

Although on a general basis this possibility cannot be ruled out, we believe that prolonged QT interval does not represent a peculiar finding of the disease commonly caused by hypokalemia and hypomagnesemia, per se. Moreover, the level of corrected prolonged QT interval that identifies, in association with syncope, a high-risk patient for development of ventricular arrhythmias is longer than 500 ms, which was found in only 1 out of 27 patients included in the study. Finally, to the best of our knowledge, there is no report of sudden death in patients with Bartter's or Gitelman's syndrome. In our cohort of Bartter's patients, whose genetic characterization later allowed the diagnosis of affected by Bartter's or Gitelman's syndrome, however, we reported specific abnormalities of cardiac function, independent of hypokalemia, characterized by the inability to adequately recruit

myocardial contractility [2], which could cause exercise-induced left ventricular dysfunction. Because myocardial recruitment is calcium-dependent [2], this abnormality is consistent with an anomalous intracellular signaling mediated by Gq protein, with the consequential abnormality of the intracellular calcium pathway we have reported [3, 4]. This defect contributes to anomalous vascular tone regulation [3, 4] and could be responsible for a generalized defect of vascular reactivity which also includes the myocardium. The presence in Bartter's or Gitelman's syndrome of an anomalous myocardial function reported by us [2], together with the observation of Bettinelli's group [1], may underscore the need to care for a possible anomaly of cardiac function in the clinical evaluation of Bartter's and Gitelman's patients that is generally underestimated.

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Reply from the Authors

Potassium (or magnesium) depletion alters cardiac excitability and prolongs the QT interval on standard electrocardiograms, which might impart an increased risk for development of arrhythmias, culminating in syncope or sudden death. Accordingly, we recently observed that the QT interval is often prolonged in Gitelman's syndrome, the most frequent and benign normotensive-hypokalemic tubulopathy. However, none of the patients had a history of unexplained loss of consciousness [1]. In addition, we reported the history of a 4-year-old boy with a normotensive-hypokalemic tubulopathy and a prolonged QT interval who suddenly died [2]. We were not able to classify the tubulopathy of the patient. In retrospect, we feel that his biochemical features strongly resembled those of a recently reported patient with a normotensive-hypokalemic tubulopathy caused by a gain-of-function mutation in the calcium-sensing receptor [3].

In their stimulating letter, Scognamiglio, Semplicini, and Calò [4] suggest that clinically relevant arrhythmias do not occur in patients with normotensive-hypokalemic tubulopathies. On the contrary, they suggest that chronic potassium and magnesium depletion might cause left ventricular dysfunction.

Recognizing that little is known about the occurrence of dangerous arrhythmias in patients with normotensive-hypokalemic tubulopathies, we recently sent a corresponding questionnaire to a group of pediatric nephrologists with clinical experience in the field of normotensive-hypokalemic tubulopathies. Furthermore, we are currently investigating ambulatory Holter monitoring, exercise testing, and echocardiography in our patients with Gitelman's syndrome.

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Ozonetherapy in a dialyzed patient with calcific uremic arteriolopathy

To the Editor: Some interesting papers on the therapy of calciphylaxis were published in 2002 [1, 2]. Here, we present the first report of successful treatment of calciphylaxis-induced ulcerations with ozonotherapy, a method not mentioned in these articles.

A 25-year-old female with Wegener's granulomatosis, hemodialyzed since 1994, manifested ulcers in her calves, thighs, and abdomen. Skin biopsy revealed calciphylaxis. Therapy, involving hemodialysis with noncalcium dialysate 5 to 6 days a week, antibiotics, and surgical debridement, failed. The patient did not tolerate hyperbaric oxygen therapy. The necrotic ulcerations enlarged and became superinfected. In 2001, we commenced treatment with ozonated autohemotherapy (O3-AHT), the modality used in our center in therapy for intermittent claudi-