take prompt, corrective action before the agency initiates an enforcement action.[3]

The FDA is dedicated to improving the oversight of postmarketing requirements and commitments, updating the public regularly, and improving the clarity of our reporting. We think that it is reassuring that as of fiscal year 2015, a total of 88% of postmarketing requirements overall and 89% of FDAAA postmarketing requirements were progressing according to their original schedules.[4]

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Single-Nephron Glomerular Filtration Rate in Healthy Adults

TO THE EDITOR: Denic et al. (June 15 issue)[1] found a fairly constant single-nephron glomerular filtration rate (GFR) among kidney donors, even with declining numbers of nephrons in persons younger than 70 years of age. It is unclear whether there was a correlation between the number of nephrons and the single-nephron GFR in an analysis adjusted for demographic characteristics and other variables. It would be informative if the authors examined their data using such adjustments.

Low birth weight has been associated with chronic kidney disease in adolescents[2] and adults.[3,4] Low birth weight has been shown to be associated with a low number of nephrons, and it has been hypothesized, although not proved, that the lower number of nephrons that is seen in persons with a low birth weight causes a higher single-nephron GFR, thus increasing the risk of subsequent chronic kidney disease and hypertension.[5,6] If birth-weight data are available for the participants in this study, the correlation of birth-weight data with the single-nephron GFR and the number of nephrons might provide an opportunity to increase our understanding of the pathophysiological features of chronic kidney disease and hypertension in patients with a history of low birth weight.

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TO THE EDITOR: Denic et al. report estimates of the single-nephron GFR in humans. The resulting value of 80 nl per minute is somewhat higher than but generally consistent with measurements in animals which have been derived from direct sampling of glomerular ultrafiltrate.[1] Glomerular hyperfiltration occurs in models of diabetes and after the reduction of renal mass. The increased glomerular pressures and flows that drive

hyperfiltration play a role in the progression of kidney disease.

In the study conducted by Denic et al., an elevated single-nephron GFR was associated with risk factors for disease progression, including obesity, a family history of end-stage kidney disease, and more glomerulosclerosis, findings that suggest compensation in the remaining nephrons to maintain the total GFR. The authors suggest that enlarged glomeruli might be a beneficial adaptation; we suspect that it may not. Enlarged glomeruli are exposed to increased physical stress because of the greater glomerular-wall tension with greater capillary radius, as predicted by Laplace's law.[2] Bigger glomeruli may outstrip the capacity of podocytes to cover the enlarged surface. Such diminutions in podocyte density have been associated with adverse outcomes.[3] Finally, we wonder whether atubular glomeruli were discerned.[4]

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TO THE EDITOR: Denic et al. mention two limitations of their study — first, the actual single-nephron GFR of deep (juxtamedullary) glomeruli may be higher than the calculated single-nephron GFR that the authors report in their article; and second, the study population was predominantly white. We would like to connect both limitations in a common context. The juxtamedullary glomeruli in healthy blacks are substantially larger than in healthy whites, and in healthy whites superficial glomeruli are significantly larger than juxtamedullary glomeruli.[1]

Moreover, the predominantly white study cohort resided in Minnesota, where the sodium intake during the period of donor enrollment (2000 through 2011) was considerably higher than the recommended intake, as shown in the Minnesota Heart Survey.[2] The study cited by the authors shows that the single-nephron GFR depends not only on the location of the nephron in the cortex but also on the dietary sodium intake.[3] High sodium intake significantly increases the single-nephron GFR in superficial nephrons and concomitantly decreases it in juxtamedullary nephrons.[3] Such evidence is relevant to the calculation of the single-nephron GFR.

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THE AUTHORS REPLY: We agree with Agarwal that clarification of the relationship between the number of nephrons and the single-nephron GFR would be informative toward a better understanding of kidney biology. Indeed, the low number of nephrons that is associated with low birth weight[1] (data not available in our study) may be compensated for by an increase in the single-nephron GFR during early postnatal life. In our study involving 1388 living kidney donors, we found a negative correlation between the number of nephrons and the single-nephron GFR ($r=-0.75$ in an unadjusted analysis; $r=-0.78$ in an analysis adjusted with the use of partial correlations for age, sex, height, body-mass index, uric acid level, family history of end-stage renal

disease, and mild hypertension), but we believe that this finding is misleading. The problem is that the single-nephron GFR was calculated directly from the number of nephrons (specifically, the total GFR divided by the number of nephrons), and thus, the measurement error with the number of nephrons will alone result in a negative correlation between the single-nephron GFR and the number of nephrons. A sophisticated statistical simulation with ideally more measurement-error data than we had may help clarify the biologic correlation.

In general, we agree with Rosenberg and Hostetter that glomerular enlargement might be considered harmful. We have found that aging alone does not lead to glomerular hypertrophy, despite a considerable decline in the number of nephrons. However, certain risk factors for chronic kidney disease, such as obesity and family history of end-stage renal disease, are associated with glomerular enlargement and an elevated single-nephron GFR. Nonetheless, kidney donation itself leads to glomerular enlargement with increased single-nephron GFR in the remaining kidney but without evidence of glomerular hypertension,[2] and progressive chronic kidney disease rarely occurs after kidney donation. There may be a tipping point at which glomerular enlargement becomes maladaptive. Atubular glomeruli were not assessed in our study, because we analyzed only two consecutive 3-μm kidney-biopsy sections, which limited our ability to assess the entire glomerulus. Atubular glomeruli are often ischemic-appearing,[3] and ischemic-appearing glomeruli account for only 0.6% of the nonsclerosed glomeruli in this healthy population.[4]

As discussed by Zarogiannis et al., the single-nephron GFR may be higher in the deep (juxtamedullary) glomeruli than in the more superficial glomeruli in humans, as has been observed in studies in animals. Estimates of the single-nephron GFR cannot be calculated separately for deep and superficial nephrons in humans by the method we used. Since varying the dietary sodium intake in healthy humans does not change the total GFR,[5] it is also unlikely that the mean single-nephron GFR varies according to the level of sodium intake.

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Since publication of their article, the authors report no further potential conflict of interest.

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Glucocorticoid Sparing of Benralizumab in Asthma

TO THE EDITOR: Nair et al. (June 22 issue)[1] found in the ZONDA trial that the median blood eosinophil counts fell dramatically after treatment with benralizumab. In a previous trial, Bleecker et al.[2] found that blood eosinophil counts were reduced by benralizumab treatment. To avoid bias, what was done to prevent unmasking of the trial-group assignment to the investigators by means of the patients' eosinophil counts?

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