Essential Hypertension: Defending the Contribution of a Congenital Nephron Deficit

To the Editor:

We read the recent review by Johnson et al in the March 2005 edition of Hypertension1 with great interest. The authors scrutinized the various hypotheses put forward to explain the mechanism responsible for the defect in sodium handling generally accepted to underlie the renal origins of hypertension. This was a timely and thorough review of the literature, but we write to defend one of the potential mechanisms we feel was undervalued: a congenital reduction in nephron number.

It has become apparent that the timing of partial renal ablation is critical in determining its long-term effects. As stated by Johnson et al, uninephrectomy in adult life (ie, once nephrogenesis is complete) does not necessarily lead to the development of hypertension. However, interruption of nephron formation during nephrogenesis, either surgically or pharmacologically in animal models or in the case of unilateral renal agenesis in humans, clearly does result in the onset of hypertension in later life.2 While nephron number, per se, may not program hypertension, a maladaptation to the nephron deficit limited to the period of nephrogenesis may play a critical role. The absence of increased frequency of hypertension in renal transplant donors does not mitigate against a role for congenital nephron insufficiency in promoting hypertension but instead may highlight a critical window in determining risk.

The absence of hypertension in the 1900s in populations exposed to suboptimal maternal nutrition is easily reconciled with respect to the theory of predictive adaptive response.3 Adaptations made by the fetus in response to adverse intrauterine conditions induce a phenotype better suited to a deprived postnatal environment, providing the fetus with a survival advantage once born into that environment. However, if born into a plentiful environment, the adaptations may actually pose a considerable disease risk. Disparity between the prenatal and postnatal environments may therefore be the critical factor. It is perhaps only in those born into a rich environment or in developing countries undergoing transition, such as India, that the repercussions of such a disparity will emerge.

Finally, the authors are right to treat the relevance of birth weight in determining disease risk with skepticism. Birth weight is nonspecific and insensitive as a marker of the intrauterine environment: nonspecific because it is the product of many genetic and environmental factors that may or may not be relevant to the developing cardiovascular system, and insensitive because it fails to reflect those intrauterine factors that may affect the cardiovascular system without affecting birth weight. Thus, it is not surprising that the relationship between birth weight and cardiovascular risk is sometimes weak and inconsistent. Experimental animal models are vital in identifying the true causal mechanisms and have shown prenatal undernutrition to consistently program nephron deficit and hypertension, independently of changes in birth weight.

Although we defend the contribution of a congenital nephron deficit in determining hypertension risk, we do not wish to detract from the conclusions drawn in the review. The various hypotheses put forward are all likely to contribute to the development of disease in some way, but the interactions between them make it difficult to assess their relative contribution.

Response

We thank Drs McMullen and Langley-Evans for their astute defense of the role of congenital low nephron hypothesis in the pathogenesis of essential hypertension. It was not our intention to negate the important contributory role for genetic or congenital mechanisms in the pathogenesis of hypertension. We also agree that the massive epidemic of hypertension in developing countries from a near absence in the early 1900s to a prevalence of >25% today could reflect an interaction with changing environmental (eg, dietary) factors. However, the near-complete absence of hypertension in developing countries before 1940 suggests that nephron number alone cannot account for hypertension. Furthermore, just as genetic factors are unlikely to account for >20% of essential hypertension,1 studies using low birth weight as a surrogate marker for low nephron number suggest that low nephron number also accounts for only 20% of overall cases of hypertension.2

So how does low nephron number translate into an increased risk for hypertension? One proposed explanation is that low nephron number reflects the presence of maternal and fetal endothelial dysfunction, possibly attributable to substances such as uric acid that can freely enter into the placenta.3 As the child grows up, he/she may be at risk for persistent endothelial dysfunction resulting from either hereditary or familial/environmental factors.3 Studies in experimental animals with reduced nephron numbers also develop preglomerular arteriolar disease, resulting in altered autoregulation.4 As discussed in our editorial,1 the evidence for a role of preglomerular arteriolar disease in the pathogenesis of hypertension remains strong. Indeed, it is interesting that preglomerular arteriolar disease was prominent in the kidney autopsies in Keller et al’s study, which also showed a reduced nephron number in subjects with essential hypertension.5 Thus, we conclude that congenital nephron number and genetic factors have important contributory roles in the pathogenesis of hypertension, but that other factors, such as environmental (dietary) factors, and acquired preglomerular renal microvascular disease and tubulointerstitial inflammation, are likely the major factors in the development of hypertension.

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