Hypertension and Histocompatibility Antigens

To the Editor:

The association of essential hypertension with human leukocyte antigen (HLA)-DR4 in the Brazilian Caucasian population is an exciting advance in the understanding of genetic mechanisms underlying hypertension.1

We wish to point out, however, a potential methodologic flaw in the analysis by Gerbase-DeLima et al.2 Blood pressures were not recorded in their control population. The presence of essential hypertensive subjects in the control population might minimize HLA frequency differences between cases and controls. If their controls were afflicted with essential hypertension to the same extent as the overall population, the lack of an association with HLA antigens other than DR4 might be explained. Although some of the control population in the Brazilian study consisted of "potential" organ donors, the authors failed to report to what extent individuals tissue typed for paternity testing or laboratory volunteers contributed to the cohort. Therefore, we feel that other HLA antigens may be associated with essential hypertension and might have been missed by the aforementioned analysis.

We have reported a similar analysis using a larger cohort of white Americans and African-Americans with hypertension-induced end-stage renal disease.2 In our analysis the control group consisted entirely of cadaveric kidney donors. Typically, individuals able to donate their kidneys are not affected by disease states that adversely affect renal function such as hypertension or diabetes mellitus. We found a strong association between HLA-DR3 in African-Americans and HLA-B35 in white Americans with renal microvascular damage from essential hypertension. The HLA-B35 association confirmed a report in white Europeans with malignant hypertension-induced nephropathy.3 In addition, HLA-A1 and B8 provided protection from hypertension-induced end-stage renal disease in white Americans in our study, and interracial analyses revealed that HLA-DR3 frequency was increased, beyond the expected racial differences, in blacks compared with whites.

We have also performed an association study between HLA antigens and type 1 diabetes mellitus-induced end-stage renal disease.4 The antigens most strongly associated with development of renal microvascular damage in diabetes were HLA-DR3 and DR4 in both whites and blacks. The possibility exists that a gene or genes linked to HLA-DR3 may predispose to renal microvascular damage from hypertension or diabetes mellitus. We agree with Gerbase-DeLima et al1 that the HLA-A, B, and DR molecules are not likely to be directly involved in essential hypertension and renal microvascular injury. Closely linked HLA-DQ alleles have been implicated as etiological factors in type 1 diabetes mellitus.3 It is possible that HLA-DQ or a nearby gene (or genes) in linkage disequilibrium with HLA-B or HLA-DR alleles are susceptibility genes for essential hypertension and microvascular injury. If so, the discordant results observed in different ethnic groups very likely are related to the varying linkage disequilibria that occur in these populations.

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References
5. Todd JA, Bell JJ, McDevitt HO: HLA-DQ8 gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 1987;329:599-604

The following is in response:

To the Editor:

We read with great interest the letter from Freedman et al regarding our article. One of their comments concerns the control population with which we compared the HLA antigenic frequencies observed in the hypertensive patients. We wish to clarify that potential kidney donors represented 50% and 25%, respectively, of the control individuals for HLA-AB and DR frequencies. Therefore, we agree that some present (or future) hypertensive individuals could be included among the control population. We do not believe, however, that this fact has precluded the finding of other HLA associations since there was no suggestion of increased frequency in the patients of any HLA antigen other than DR4. More generally, we could add that we are not aware of any important HLA–disease association that only emerged when the control population was thoroughly scrutinized to exclude any individual with the disease for which an HLA association was being searched.

Regarding the finding of Freedman et al3 of increased frequency of HLA-B35 in patients with end-stage renal disease due to hypertensive renal failure, we would like to take this opportunity to make some comments. Association with HLA-B35 was also reported by Forsberg and Löw2 in patients with malignant hypertension and terminal uremia, but this association was not found in other studies that did not involve terminal uremic patients (reviewed in Reference 3). Thus, HLA-B35 could represent a marker for severity of hypertension or for the development of severe hypertension in renal diseases rather than a marker for susceptibility to essential hypertension. It has been shown that HLA-B35 is associated with low intracellular levels of magnesium in humans and that in mice, the levels of both plasmatic and intracellular magnesium are influenced by the H2 complex, the equivalent of the HLA complex.1 The control of magnesium levels by genes within the H2 and the HLA com-

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plexes, and especially the association of HLA-B35 with both low magnesium levels and severe hypertension, is interesting since several studies suggest a causal relation between decreased concentrations of magnesium ion in blood or tissues and hypertension (reviewed in Reference 6).

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