

# Hypertension

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## *Editorial Comment*

# AIDS, Lupus, Rheumatoid Arthritis – Hypertension?

David J. Dzielak

**W**hat have these disease entities in common? There would be little argument among physicians and basic science investigators that an underlying defect in immunologic function is a major contributing factor in the etiology of acquired immunodeficiency syndrome, systemic lupus erythematosus, and rheumatoid arthritis. But immunologic dysfunction in hypertension is another matter. Physicians who treat hypertensive patients and researchers involved in the study of hypertension would quickly point to alterations in renal function, enhanced vascular smooth muscle reactivity, increased sympathetic tone or alterations in the renin-angiotensin system as major contributors to the development of hypertension. It would indeed be rare for immune function to be mentioned in discussions of this disease. Perhaps this should be reconsidered in light of the growing body of evidence that implicates altered immunologic function in the development of some forms of hypertension. The article by Tuttle and Boppana<sup>1</sup> that appears in this volume should certainly help to bring the involvement of immune mechanisms in the pathogenesis of spontaneous hypertension in rats into focus.

These investigators report that a single injection (5,000 units/kg) of human recombinant interleukin-2 (IL-2), given to young spontaneously hypertensive rats (SHR) before the development of hypertension, blocked the progressive elevation in arterial pressure as these animals grew to maturity. Furthermore, IL-2 administration to SHR with established hypertension lowered the elevated arterial pressure to control levels. This provocative finding, if verified by other laboratories, will certainly lend substance to the claim that immunologic dysfunction is a contributing factor in the development of hypertension in this model and might be implicated in human hypertension.

For the past several years, a number of research groups, including our own, have been involved in studies linking altered immune function with the development of spontaneous hypertension. Takeichi et al<sup>2</sup> suggested that the SHR was immunologically

dysfunctional. There are fewer immature thymic T cells in SHR than in Wistar-Kyoto control rats. The blastogenic response to T cell mitogens, delayed-type hypersensitivity reactions, allograft rejection, and antibody formation are all decreased. Bendich et al<sup>3</sup> demonstrated that treatment of SHR with antithymocyte serum effected a transient decrease in arterial pressure. Takeichi et al<sup>4</sup> later demonstrated the existence of a natural thymocytotoxic autoantibody in the SHR. This group<sup>5</sup> also reported that restoration of immune function by grafts of allogenic lymphoid tissue was associated with a decline in blood pressure. Subsequently, Takeichi et al<sup>6</sup> suggested that the depression of T cell function in the SHR was the result of a deficiency of thymic hormone secretion. The arterial pressure-lowering effect of IL-2 administration to SHR reported by Tuttle and Boppana<sup>1</sup> is in keeping with this hypothesis.

We initially examined the effect of immunosuppressive therapy on the development and maintenance of spontaneous hypertension.<sup>7</sup> Cyclophosphamide treatment arrested the progression of hypertension in adult SHR and attenuated the final level of hypertension in prehypertensive rats. In contrast to the results reported with IL-2 therapy, administration of cyclophosphamide failed to reduce established hypertension. Similar results were obtained in a later study<sup>8</sup> in which thymic tissue from normotensive Wistar rats was implanted in SHR with established hypertension. Thymus implants prevented the progression of hypertension but failed to lower the arterial pressure to that of Wistar control rats. Similarly, thymus implants into neonatal SHR attenuated the development of hypertension but failed to reduce arterial pressure to control levels. The thymic implants did not alter the absolute number of lymphocytes in the SHR. However, there was an increase in the blastogenic response of mononuclear cells to concanavalin A (Con A). The increased responsiveness to Con A is suggestive of an increase in activity of suppressor T lymphocytes in these rats.

The exact mechanisms by which treatment with the various immunomodulators alters immune function and lowers arterial pressure in the SHR remain to be determined. Thymic implants, IL-2 treatment, or administration of antithymocyte serum may exert an antihypertensive effect by correcting T lymphocyte

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abnormalities in the SHR. It is possible that enhanced T suppressor activity may decrease immune-mediated damage to either the vasculature or the kidney and prevent the progressive rise in arterial pressure seen in this model. This hypothesis is consistent with evidence in the SHR for abnormal glomerular membranes and polyarteritis.

Is there evidence implicating the immune system in other models of hypertension? Spontaneous hypertension in the New Zealand black mouse can be reversed by immunosuppressive therapy.<sup>9</sup> Neonatal thymectomy blocks the development of hypertension in the Lyon hypertensive rat.<sup>10</sup> Renal infarct hypertension may result from immune factors, as demonstrated by Grollman and colleagues.<sup>11</sup> We<sup>12</sup> were able to prevent the development of renal infarct hypertension by immunosuppressive therapy.

There is some evidence for immunologic defects in human essential hypertension. Certain hypertensive patients have elevated immunoglobulin levels, increased levels of autoantibody and delayed-type hypersensitivity reactions against their own vascular tissue.<sup>13</sup>

The results presented in the article by Tuttle and Boppana<sup>1</sup> and the existing body of evidence in the literature are compatible with the hypothesis that an immunologic dysfunction plays a role in the pathogenesis of spontaneous hypertension. The nature of the immunologic defect can only be speculative at this time. Further research is necessary to elucidate the mechanisms whereby immune system dysfunction contributes to the genesis of hypertension. This promises to be an exciting area for future investigation.

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