The Role of T Cells in the Pathogenesis of Hypertension Part I.

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Under the auspices of ISN, ERA-EDTA and ISP

IMMUNITY AND HIGH BLOOD PRESSURE (1976-1990)

Enhanced immune reactivity

Antibodies anti-renal tissue [1,2]
Antibodies to thymocytes in SHR [3]
HTN improved with 6MP [4, 1]
HTN improved with cyclophosphamide [4,5, 14]
Nude (athymic mice) and thymectomy prevent HTN [6,7,8]
T cell transfer from rats with renal infarction induce HTN [6]
Spleen cell transfer of rats with DOCA-salt hypertension induce HTN [11]
Reduction of blood pressure with anti-thymocytic serum [10]

Supressed immune reactivity

Thymic grafts from WKY rats improve hypertension in SHR [9]
Decreased DHT [12]
Reduced antibody formation in SHR [12]
Injections of IL2 ameliorate HTN [13]

[1] White FN, Grollman A.. *Nephron*. 1964;204:93–102; [2] Takeichi N, Ba D, Koga Y, Kobayashi H. *J Immunol*. 1983;130:501–505.; [3] Takeichi N, Ba D, Kobayashi H. *Cell Immunol*. 1981;60: 181–190. [4] Dzielak DJ. *Am J Physiol*. 1991;260:R459–R467. [5] Norman RA Jr, Dzielak DJ. *Proc Soc Exp Biol Med*. 1986;182:448–453.: [6] Okuda T, Grollman A.. *Tex Rep Biol Med*. 1967;25: 257–264. [7] Svendsen UG. *Acta Pathol Microbiol Scand A*. 1976;84:235–243. [8] Svendsen UG. *Acta Pathol Microbiol Scand A*. 1976;84:523–528. [9] Ba D, Takeichi N, Kodama T, Kobayashi H. *J Immunol*. 1982;128:1211–1216. [10] Bendich A, Belisle EH, Strausser HR.. *Biochem Biophys Res Commun*. 1981;99:600–607. [11] Olsen F. *Acta Pathol Microbiol Scand C*. 1980;88:1–5. [12] Takeichi N, Suzuki K, Okayasu T, Kobayashi H. *Clin Exp Immunol*. 1980; 40:120 –126. [13] Tuttle RS et al. Hypertension 1990; 15:89-94: [14] Bataillard A et al. Int J Immunopharmacol 1989; 11: 377-384

IMMUNITY and HYPERTENSION. Editorials/Reviews

Immune dysfuction interpreted as an adaptive response that would tend to reduce what would otherwise be life threatening increments in blood pressure

Bendich A, Belisle EH, Strausser HR. Immune system modulation and its effects on blood pressure of the spontaneously hypertensive male and female rat

Biochem Biophys Res Commun **1981**; 99: 600-607

..immune dysfunction is rarely mentioned in discussions on arterial hypertension

Dzielak DJ. Editorial: AIDS, lupus, rheumatoid arthritis-hypertension?

Hypertension **1990**; 15: 95-96.

...new data implicating T lymphocytes will eventually allow discovery of new therapeutic targets that may improve outcomes in cardiovascular and renal disease in humans.

Schiffrin EL. T lymphocytes: a role in hypertension?

Cur Opin Nephrology Hyperten **2010**, 19:181–186

Experimental conditions and animal strains in which hypertension has been found to be associated with renal interstitial inflammation.

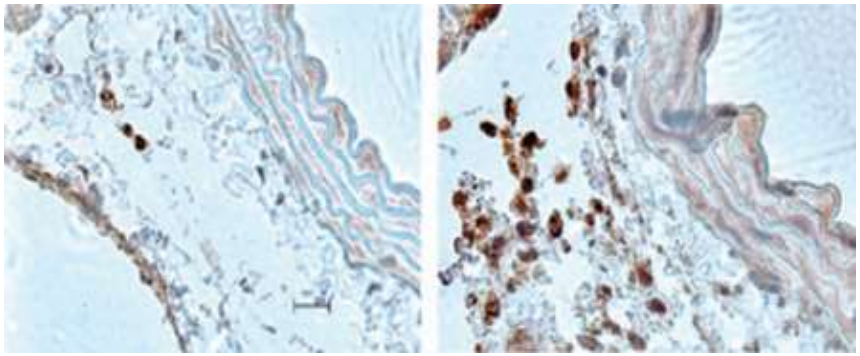
AORTA

AII-induced HBP

Sham

Ang II

CD3

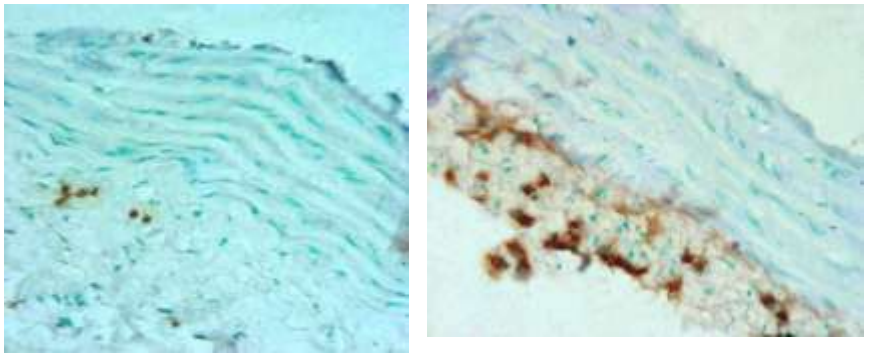


Guzik et al. JEM 204;2449-60, 2007

L-NAME-induced SSHTN

Control

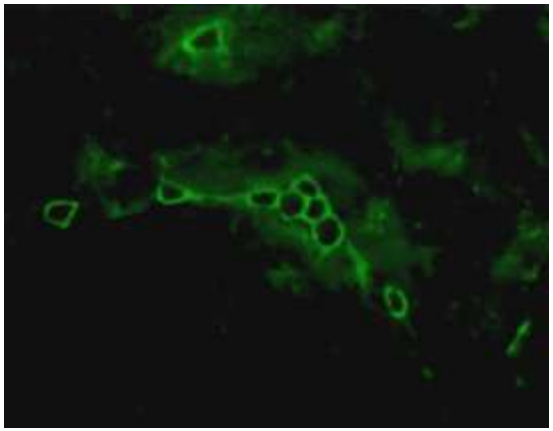
SSHTN



Quiroz et al. 2011

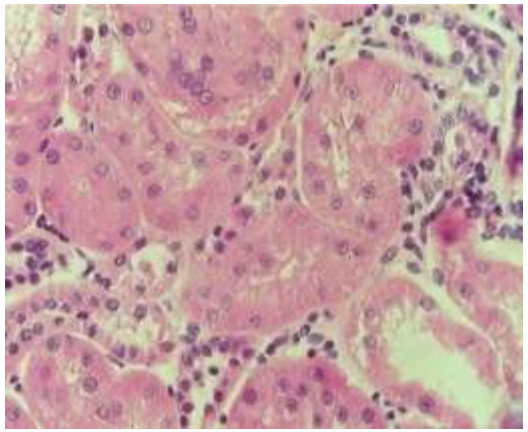
KIDNEY

SHR



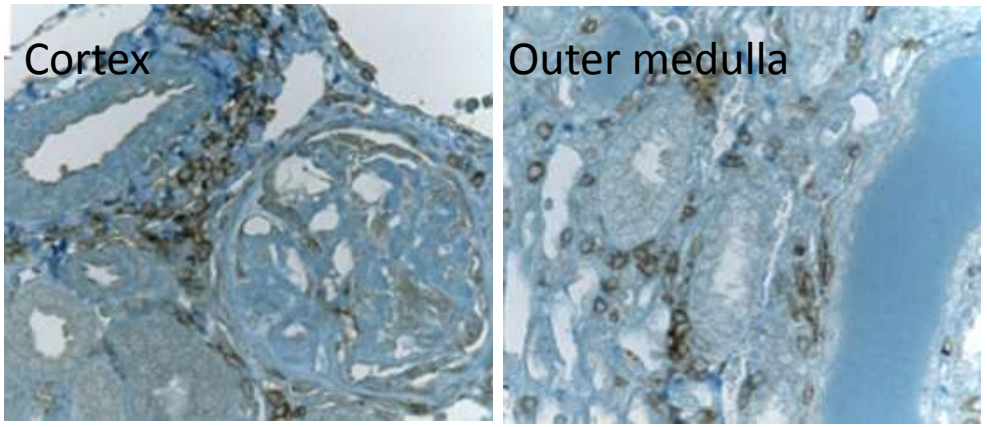
AJPhys 2002;282:F191-F201

L-NAME-induced SSHTN



AJPhys 2001,281:F38-F47

Dahl-Salt sensitive



De Miguel C et al. AJPhys 2010, 298; R1136-R1142enal

HUMANS

Interstitial lymphocyte infiltrations in kidney biopsies of hypertensive patients treated with sympatectomy

ÉTUDE HISTOLOGIQUE DE 55 BIOPSIES RÉNALES PRÉLEVÉES CHEZ DES MALADES HYPERTENDUS

Roger-J. GAREAU [1] et Georges-Etienne CARTIER [2],

Union Medical de Canada 1955; 84: 1134-42

7/55 patients had chronic interstitial nephritis

trouvaille histologique. Il est impossible de *déterminer*, par le seul examen des coupes histologiques, si la néphrite interstitielle influence l'évolution de la néphro-sclérose ou si elle provoque l'hypertension.

RENAL BIOPSIES IN HYPERTENSION

BY

R. H. HEPTINSTALL

British Heart Journal 1954; 16: 133

16/37 patients had lymphocyte infiltration & scars

Grade (Vasc. changes)	N cases/ N with L infiltrates (%)
0	1/0 (0)
I	12 /1 (8.3)
II	17/9 (52.9)
III	6/5 (83.3)
iV	1 /1 (100)
Total	16/37 (43.2)

HUMANS

Interstitial lymphocyte infiltrations in kidney biopsies of hypertensive patients treated with sympatectomy

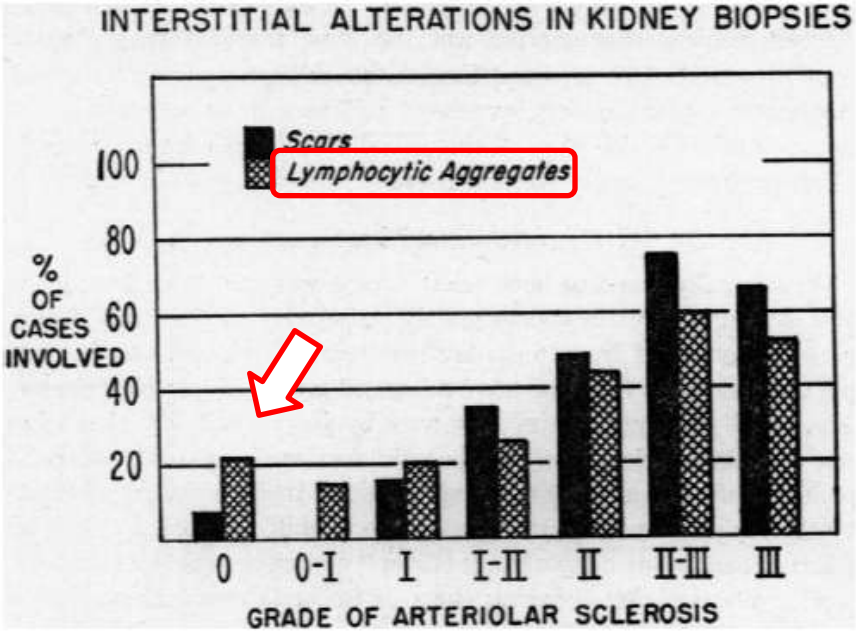
HISTOLOGIC STUDIES OF KIDNEY BIOPSY SPECIMENS FROM PATIENTS WITH HYPERTENSION*

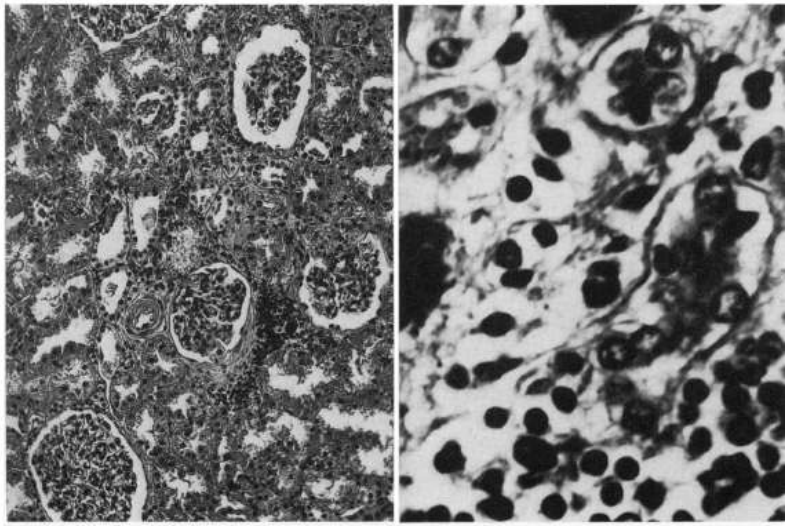
SHELDON C. SOMMERS, M.D.; ARNOLD S. RELMAN, M.D., and REGINALD H. SMITHWICK, M.D.

From the Departments of Pathology, Medicine and Surgery, Massachusetts Memorial Hospitals and Boston University School of Medicine, Boston, Mass.

Am J Pathol. 1958 August; 34(4): 685–715

Kidney biopsy specimens from 1,350 patients with hypertension who underwent sympathectomy were re-examined microscopically.





Interstitial Tissue

The normally inconspicuous renal stroma was infiltrated by collections of lymphocytes in approximately 20 per cent of the renal biopsy specimens obtained from "negative" and grade I groups, and in over half the specimens from the more advanced grades of vascular disease (Fig. 3). Unaccompanied as they were by plasma cells or other stigmas of inflammation, the lymphocytic foci were regarded as concomitants of renal atrophy and degeneration. In the kidney as well as in other organs, lymphocytes have been found collected at sites of basement membrane dissolution.[17] Oliver[18] and numerous other authors have emphasized the damaging effect of ischemia upon renal tubular basement membranes (Fig. 4).

Discussion

Less than 2 per cent of patients with hypertension were found at sympathectomy to have either insignificant or no arteriolar abnormalities in kidney biopsy specimens. Although two thirds of the cases revealed advanced renal arteriolar sclerosis, the presence of even a few individuals with apparently normal renal vessels is consistent with the view that hypertension precedes structural changes in the kidney vasculature.[7,8] The present material is probably not representative of patients in the initial stages of hypertensive disease, and there is reason to believe that the incidence of normal renal biopsy material would be higher in earlier or milder hypertension.

HUMANS

Tubulointerstitial inflammation in renal autopsy material of patients with hypertension with hypertension

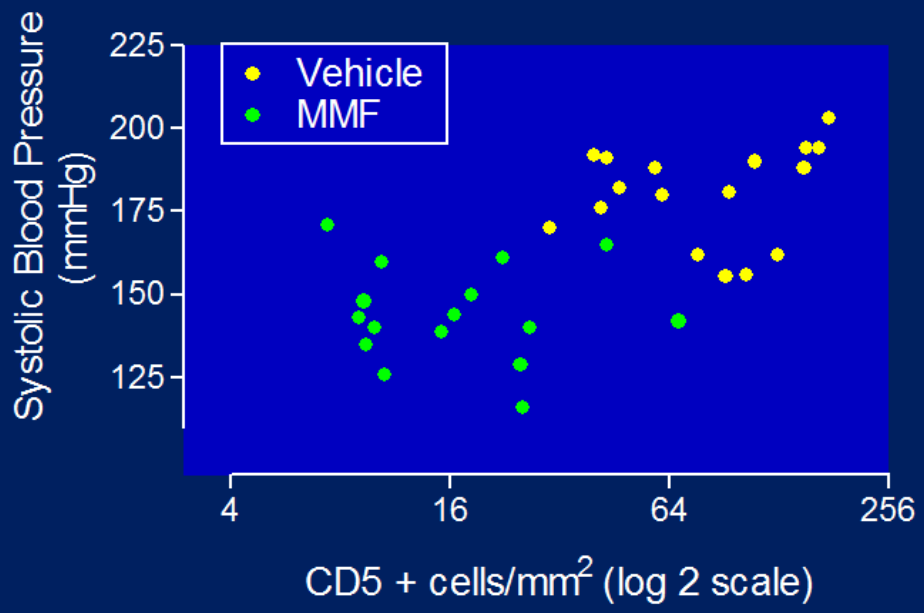
Clinicopathological Features of African Americans and Whites

Michael D. Hughson,Glenda C. Gobe, Wendy E. Hoy, R. Davis Manning Jr, Rebecca Douglas-Denton, and John F. Bertram,PhD5

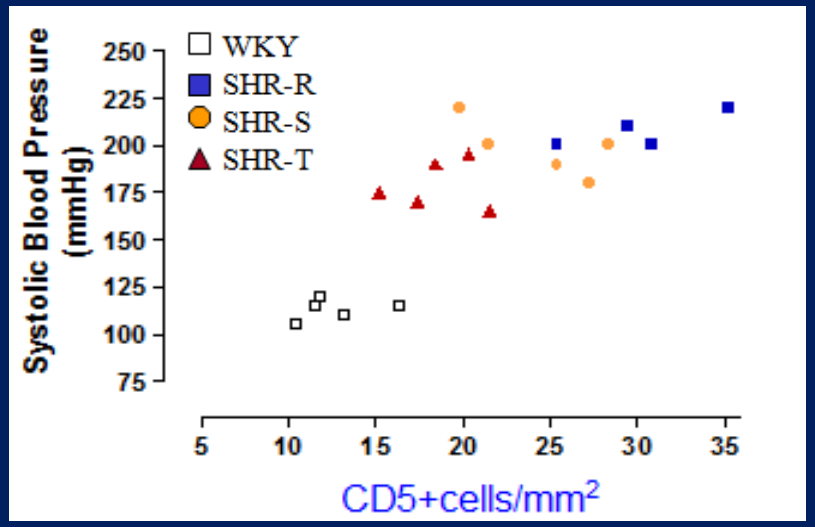
	N glom	CD68 +cells/mm2
African American Non-Hypertensive	951.807±268.7	3.9 (2.0-8.3)
African American Hypertensive	885.279±333.6	17.6 (9.9-31.5)***
White Non-Hypertensive	901.011±298.3	4.8 (2.3-12.9)
White Hypertensive	841.069±291.9	15.0 (7.6-26.8)***

American Journal of Kidney Diseases, Vol 52, No 1 (July), 2008: pp 18-28

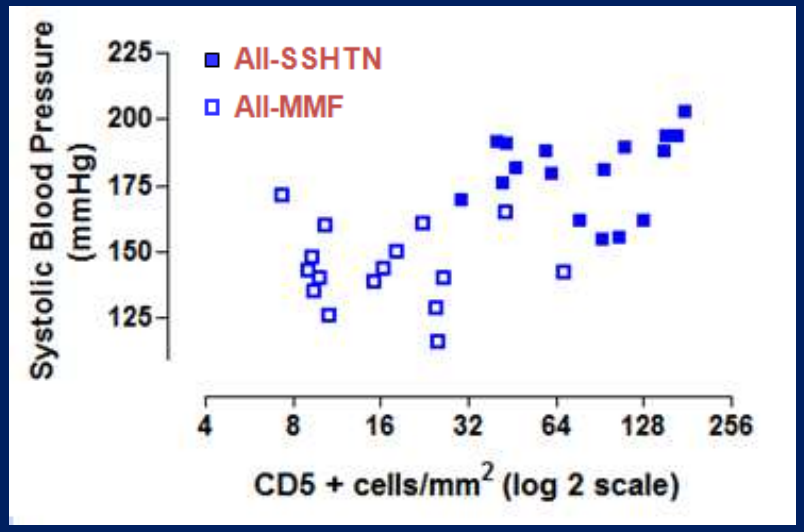
Intensity of renal lymphocyte infiltration is directly correlated with the severity of hypertension



Am J Physiol (*Renal*) 282:F191-F201, 2002



Hypertension 41:341-6, 2003



AJPhys Integ Comp Physiol 2001; 293, R251-R256

HUMANS

Correlation between intensity of TI inflammation and severity of hypertension

Associations of Glomerular Number and Birth Weight With Clinicopathological Features of African Americans and Whites. *Michael D. Hughson,Glenda C. Gobe, Wendy E. Hoy, R. Davis Manning Jr, Rebecca Douglas-Denton, and John F. Bertram,PhD5*

American Journal of Kidney Diseases, Vol 52, No 1 (July), 2008: pp 18-28

Table 6. Spearman Pairwise Correlations Between Age, Glomerular Number, Mean Arterial Blood Pressure, and Pathological Features of Arteriolonephrosclerosis

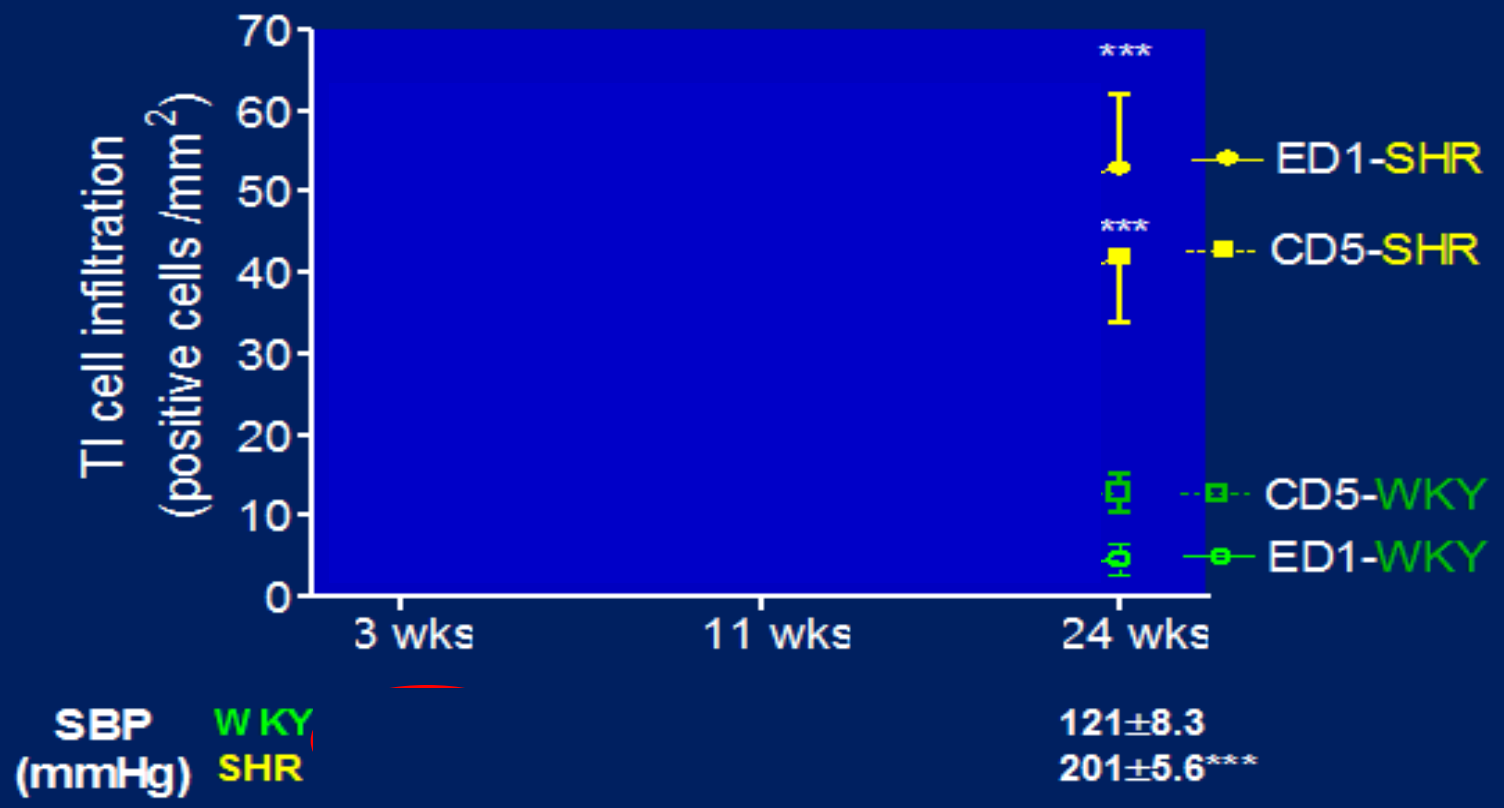
	N_{glom}	% GS	CF	It	Hyaline	CD68	MAP
Age	−0.149	**0.569**	**0.434**	**0.517**	**0.364**	**0.397**	**0.417**
	0.04	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
N_{glom}		**−0.245**	**−0.174**	−0.098	−0.025	−0.119	−0.007
		<0.001	**<0.02**	0.2	0.7	0.1	0.9
% GS			**0.662**	**0.566**	**0.455**	**0.522**	**0.436**
			<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**
CF				**0.525**	**0.422**	**0.520**	**0.446**
				<0.001	**<0.001**	**<0.001**	**<0.001**
It					**0.541**	**0.479**	**0.589**
					<0.001	**<0.001**	**<0.001**
Hyaline						**0.406**	**0.498**
						<0.001	**<0.001**
CD68							**0.582**
							<0.001

Note: Upper values are unadjusted correlation coefficients and lower values are probabilities. Significant relationships are in bold type. Cases of bacterial sepsis were omitted.

Abbreviations: N_{glom}, number of glomeruli; % GS, percent glomerulosclerosis; CF, cortical fibrosis; It, intimal thickening of interlobular arteries; Hyaline, arteriolar hyalinization; CD68, CD68 staining density; MAP, mean arterial blood pressure.

Renal lymphocyte infiltration precedes hypertension in the SHR

SHR

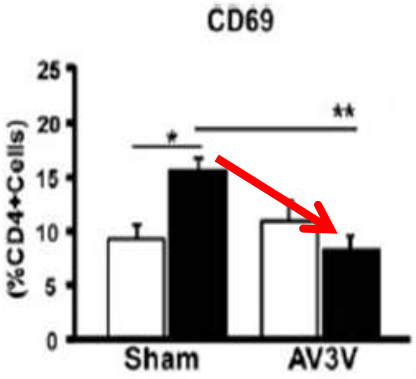


Am J Nephrol 24:587-605, 2004

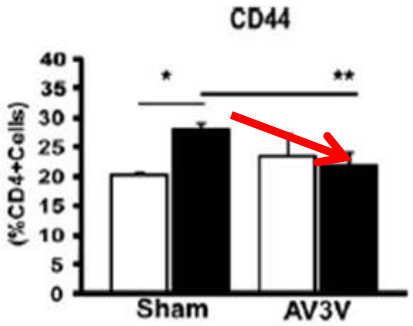
HYPERTENSION IS AMELIORATED BY SUPPRESION OF EARLY LYMPHOCYTE ACTIVATION AND HOMING

Anteroventral third cerebral ventricle lesions (**Marvar PJ et al. *Circ Res* 2010; 107: 263-70**)

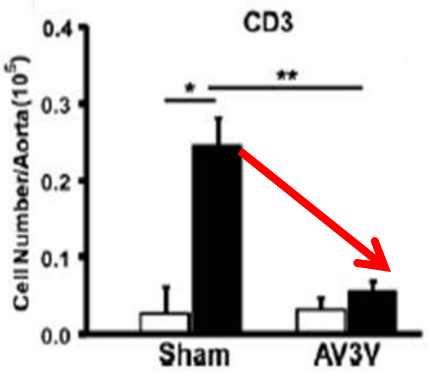
Early activation



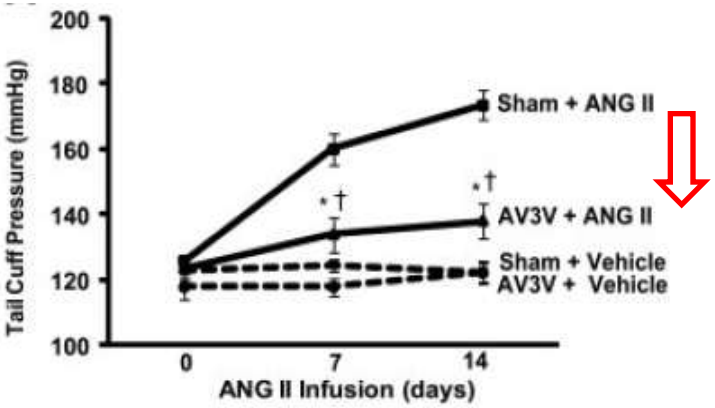
Tissue Homing



Aortic lymphocytes

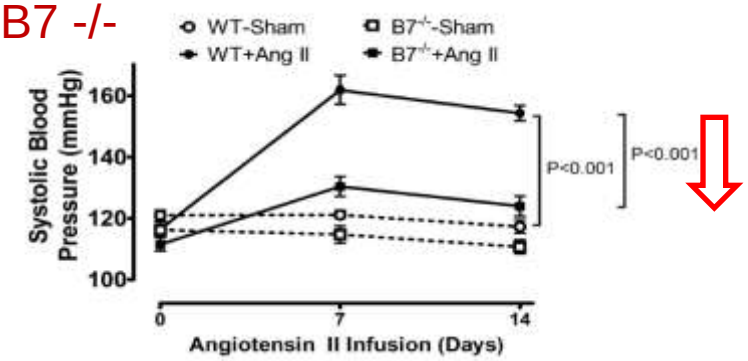


Blood Pressure

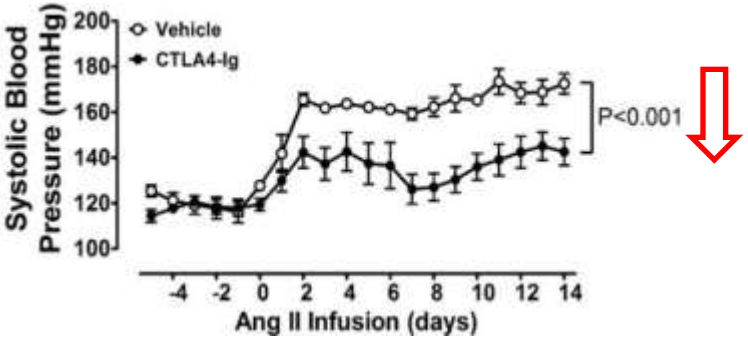


Suppression of the immune co-estimulatory axis (**Vinh A et al. *Circulation* 2010; 122: 2529-37**)

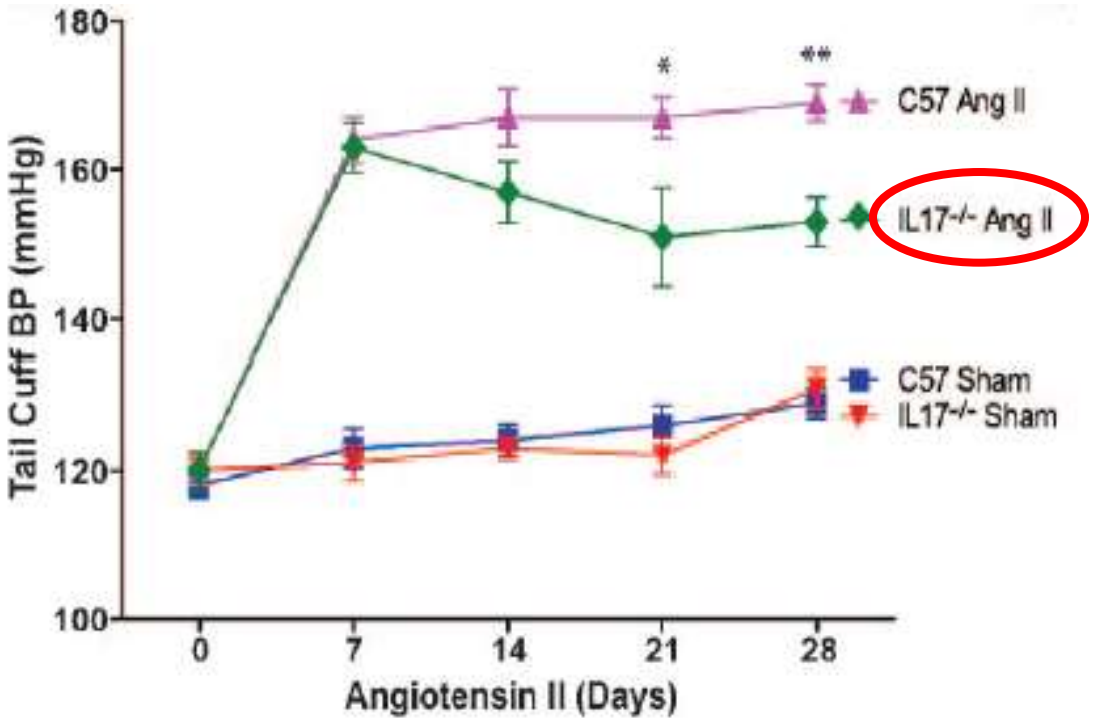
B7 -/-

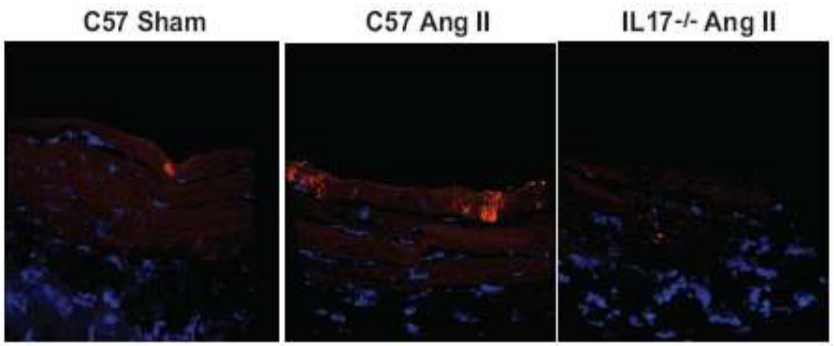


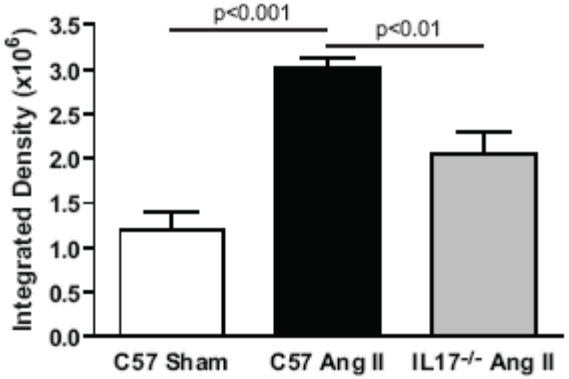
CTLA4-Ig



IL-17 promotes angiotensin II-induced hypertension







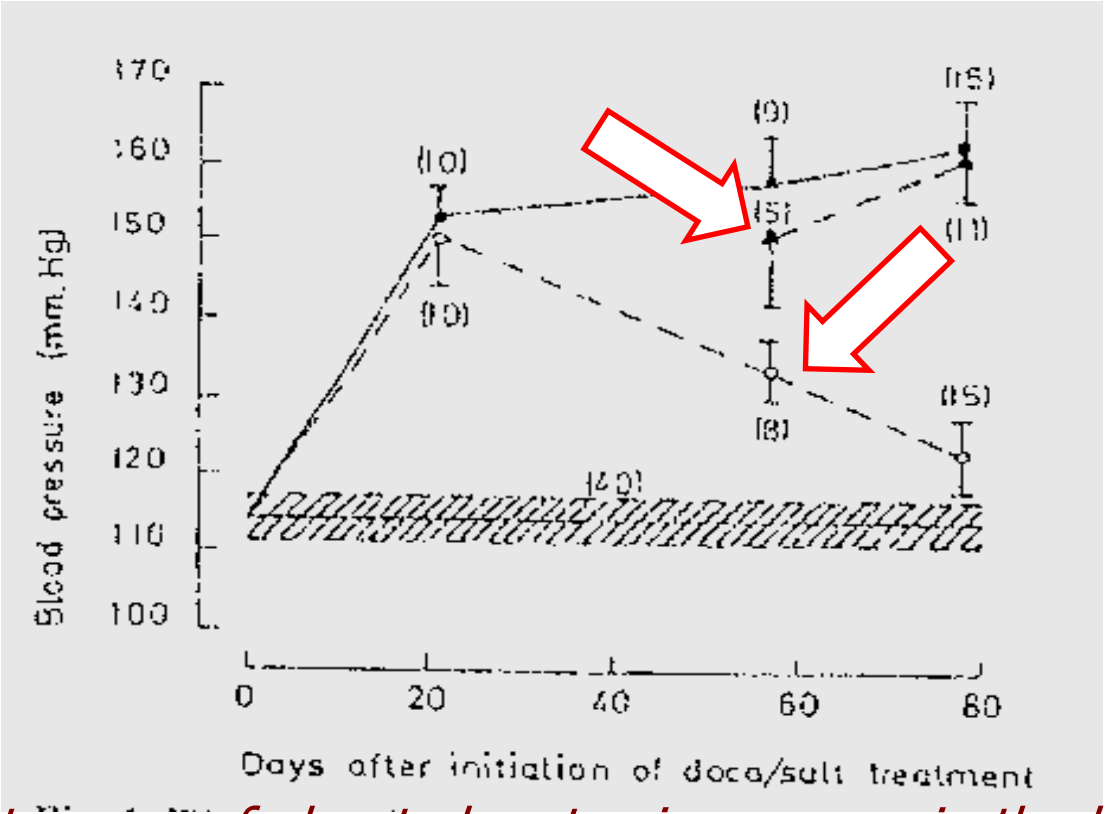
Madhur MS et al. Hypertension 2010; 55:500-7

IMMUNE SUPPRESSION AMELIORATES/PREVENT SSHTN

TREATMENT/CONDITION	EXPERIMENTAL MODEL	REFERENCE
Lymphocyte depletion		
Nude mice	DOCA-Salt hypertension	37
Neonatal thymectomy	Renal infarction (chronic phase)	38
	Lyon hypertensive rats	45
	Hypertensive NZB mice	46
Rag -/- mice	Angiotensin II-induced hypertension	47
Anti-lymphocyte serum	SHR	40
Cytokine depletion		
interleukin-6 knockout mice	Angiotensin II-induced hypertension	48
Inhibition of proinflammatory transcription factors		
Inhibition of NFkB	SHR	49
	dTGF rats	50
Immunosuppresive treatment		
Mycophenolate mofetil	SHR	51
	Dahl-Salt sensitive	52, 53
	AII infusion	42
	NOS inhibition	43
	chronic lead toxicity	55
	Overload proteinuria	44
	Cellophane wrapped kidney	55
	Prenatally programmed HTN	56
	Grade I hypertension (humans)	57
Cyclosporin A	dTGF rats	58
Cyclophosphamide	SHR	59
	Black New Zealand mice	46
	Renal infaction (Chronic phase)	39
Reduccion of oxidative stress(studies specifically looking for reduction in inflammation associated to lowering of BP)		
Antioxidant diets	SHR	60
	Mineralocortivoid hypertension	61
Melatonin	SHR	62

Hypertens Res. 2010;33:975-80

Thymus is necessary for salt–dependent hypertension

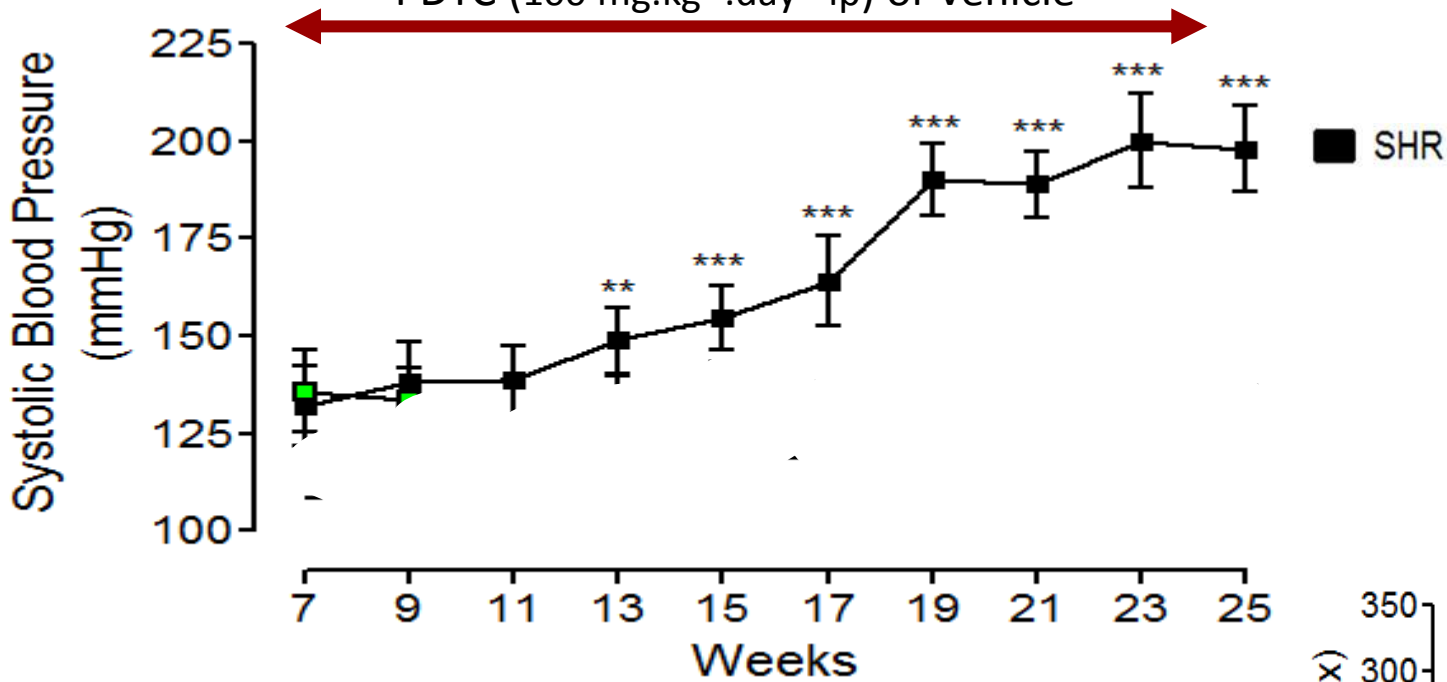


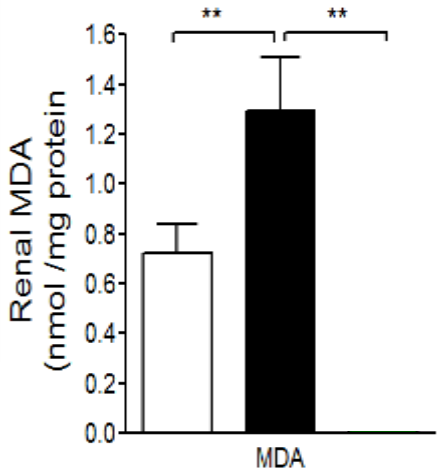
…"the maintenance of elevated systemic pressure in the late phase of the DOCA-salt hypertension might be causally related to thymus-dependent vascular lesions and due to progressive ischaemia resulting from multiple constrictions of small intrarenal vessels." Svendsen UG, Acta Path Microbiol Scan 84:523-528, 1976

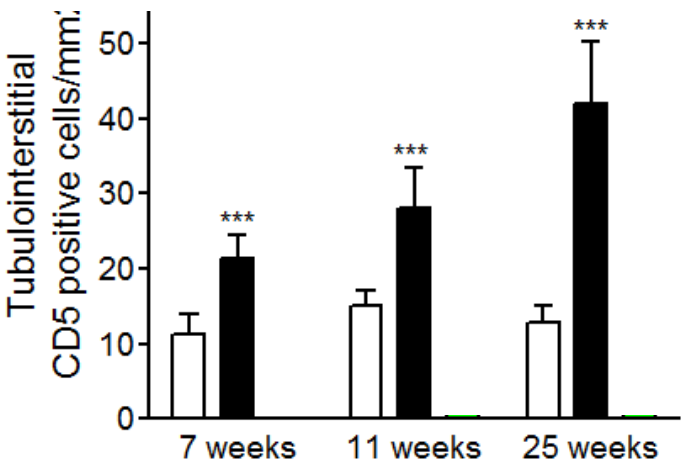
Inhibition of NFkB corrects HBP in SHR

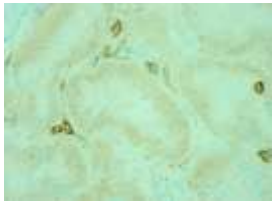
(J Pharm Exp Ther 2005, 315; 51-7)

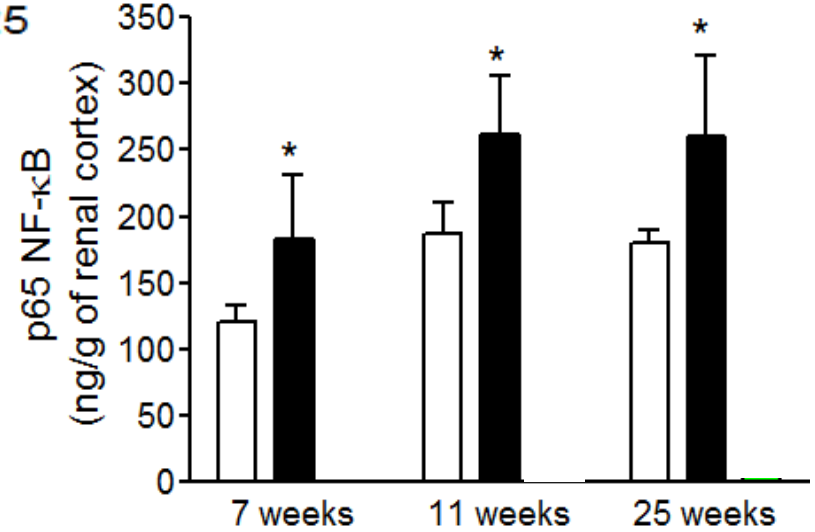
PDTC (100 mg.kg^{-1}.day^{-1} ip) or vehicle







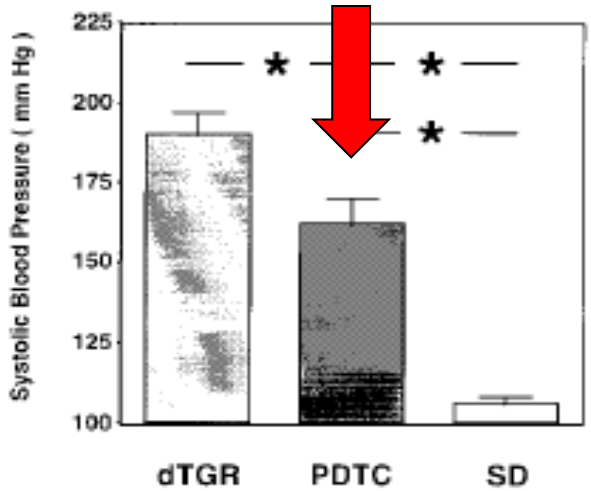


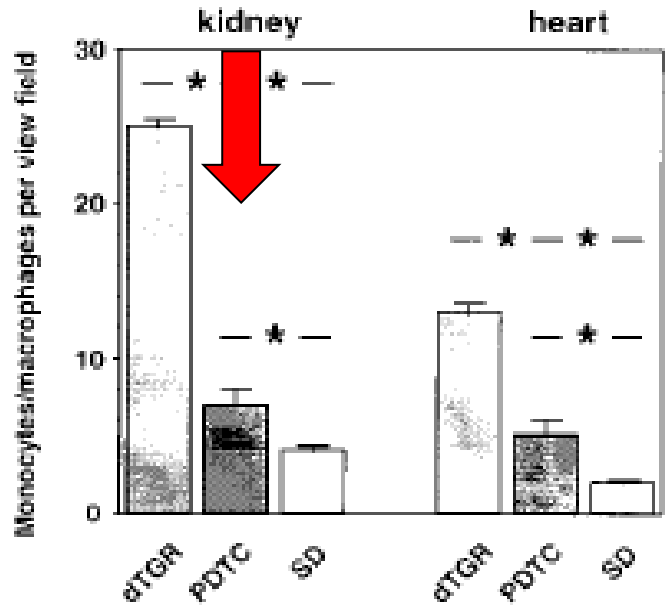


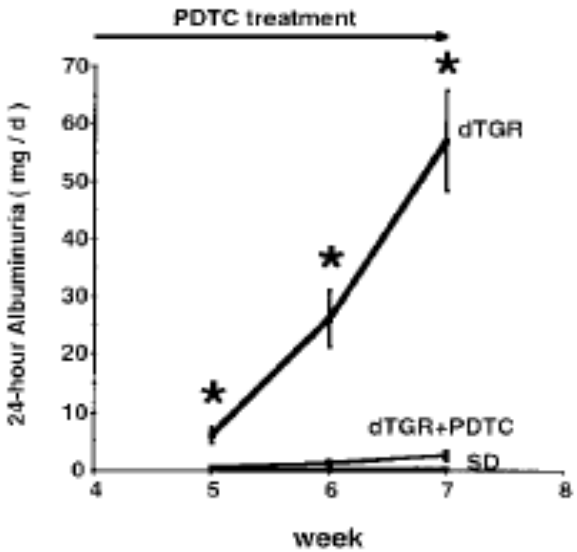
NF-κB Inhibition Ameliorates Angiotensin II–Induced Inflammatory Damage in Rats

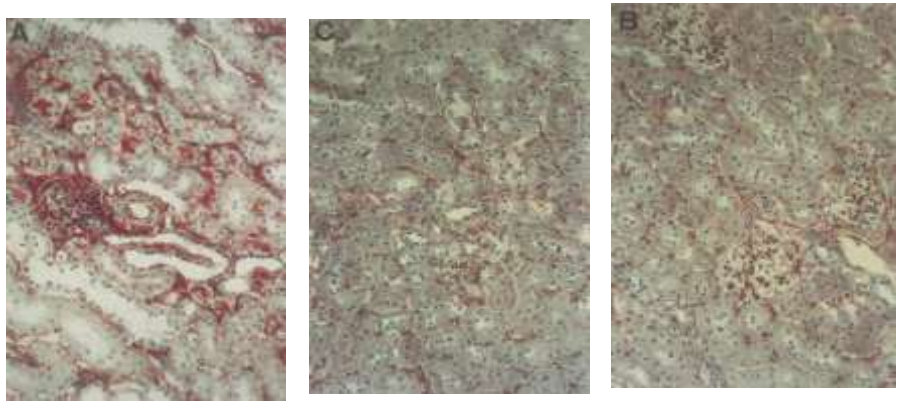
Dominik N. Muller, Ralf Dechend, Eero M.A. Mervaala, Joon-Keun Park, Folke Schmidt, Anette Fiebeler, Jürgen Theuer, Volker Breu, Detlev Ganten, Hermann Haller, Friedrich C. Luft

(*Hypertension*. 2000;35[part 2]:193-201.)



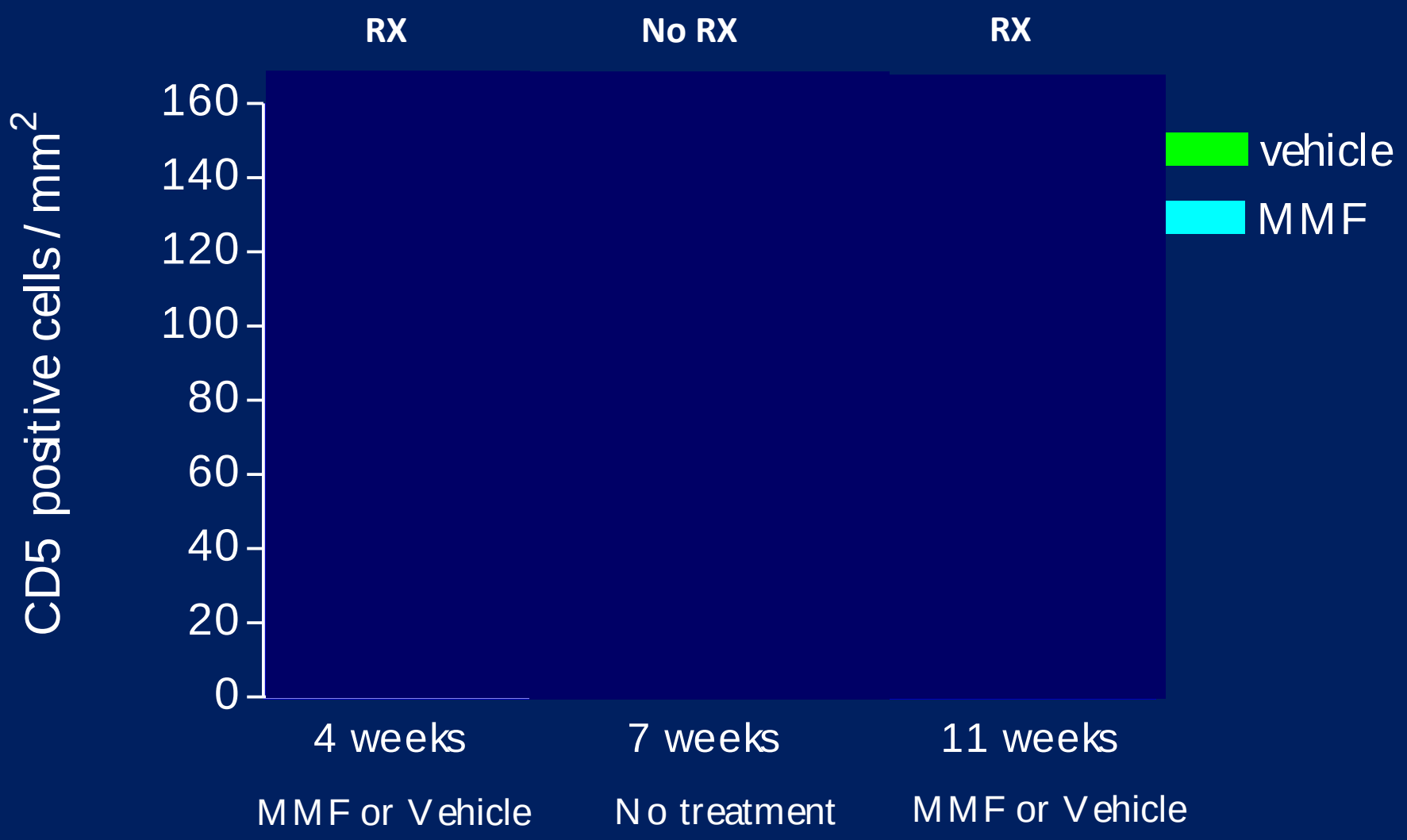






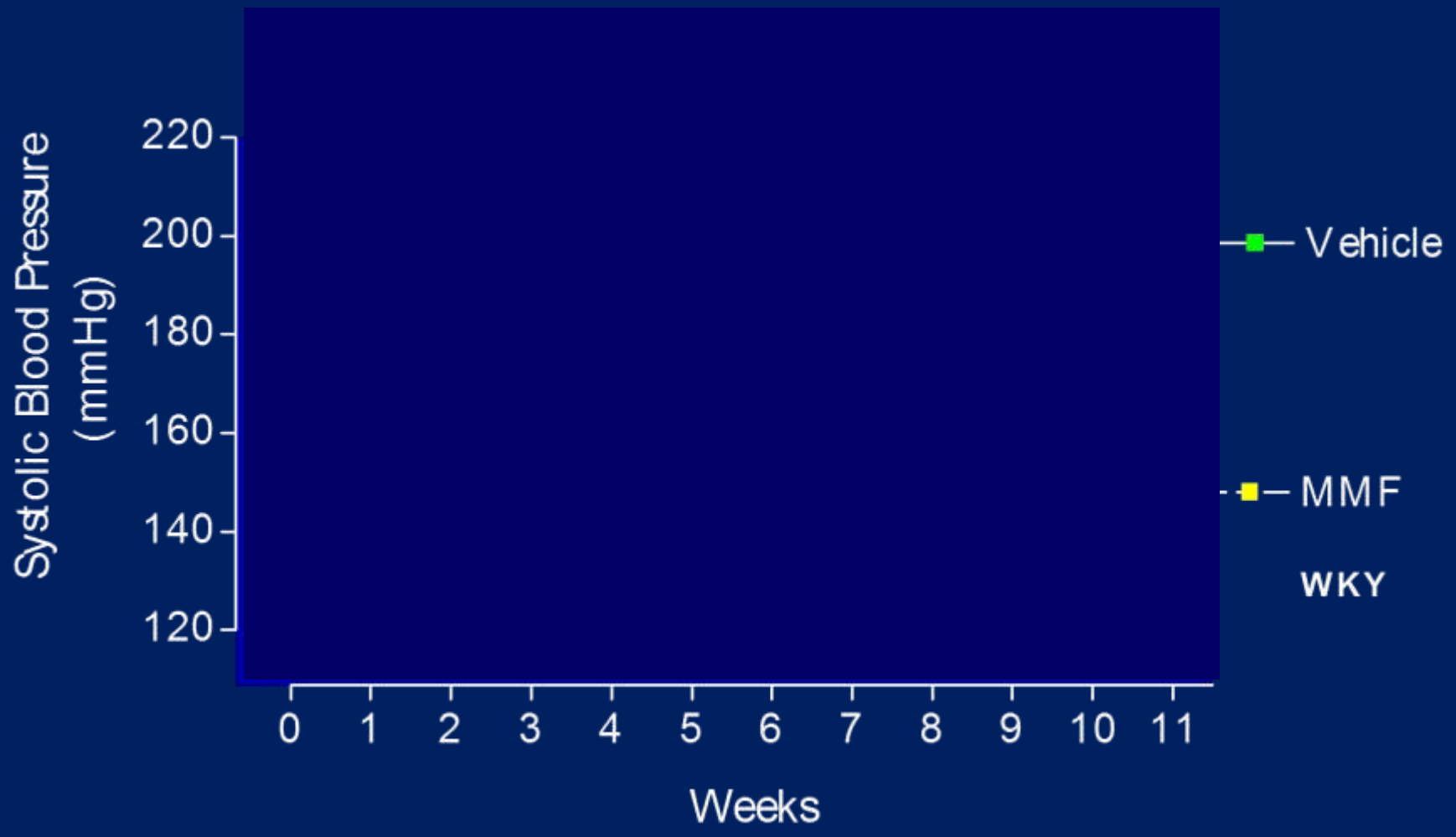
ICAM-1 Expression

MMF Rx improves hypertension in the SHR



Am J Physiol Renal 282:F191-F201, 2002

MMF Rx improves hypertension in the SHR (2)



*p<0.05, **0.01, ***p<0.001

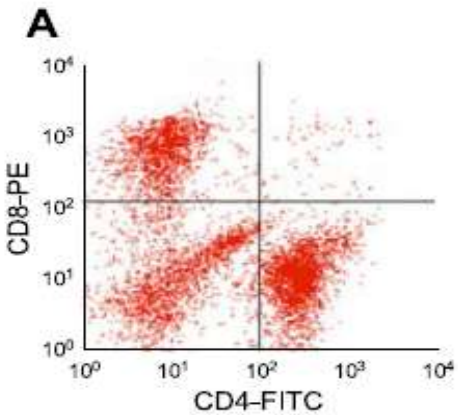
Am J Physiol Renal 282:F191-F201, 2002

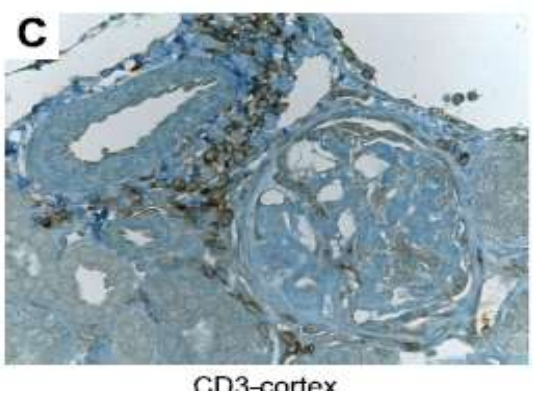
MMF Rx improves hypertension in the Dahl SS

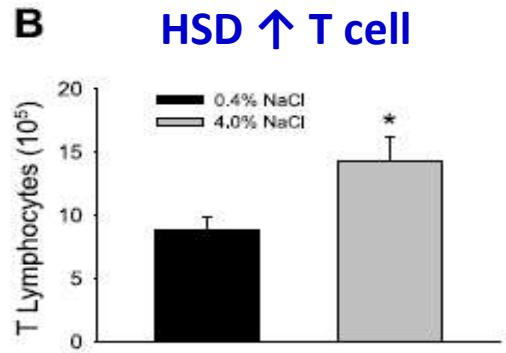
Am J Physiol Regul Integr Comp Physiol 298: R1136–R1142, 2010.
First published February 10, 2010; doi:10.1152/ajpregu.00298.2009.

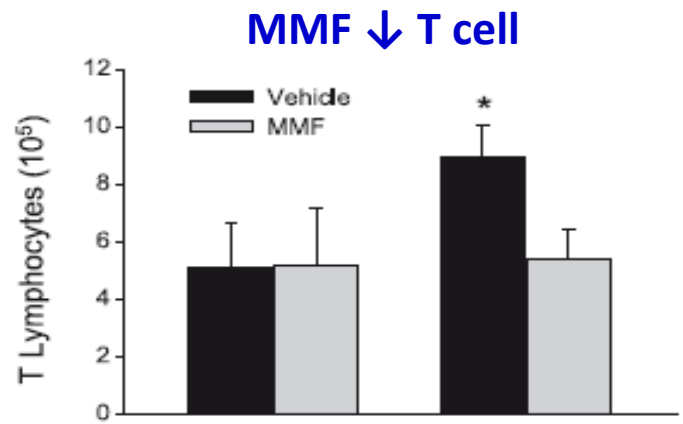
T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats

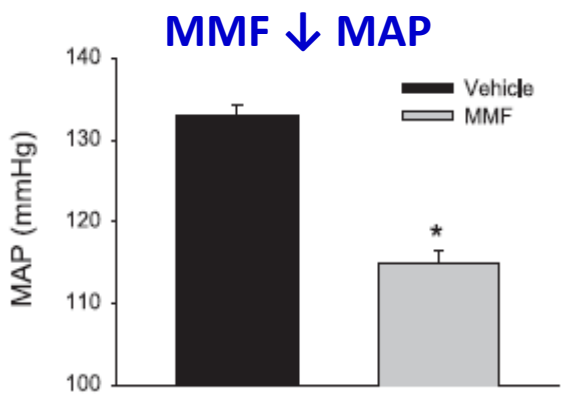
Carmen De Miguel, Satarupa Das, Hayley Lund, and David L. Mattson

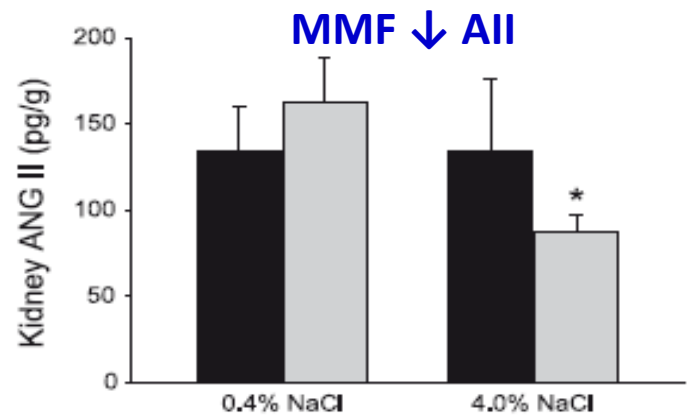




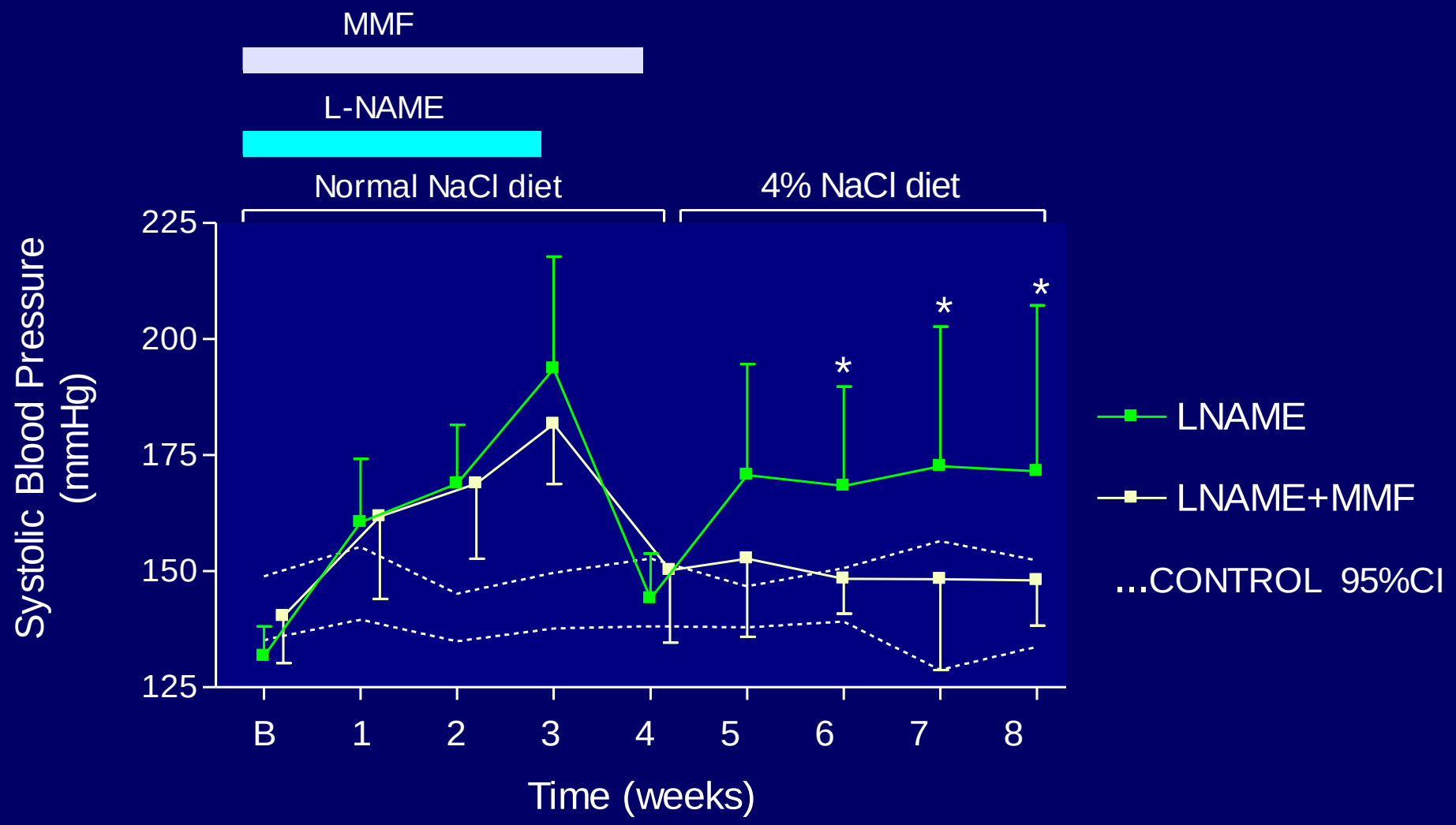








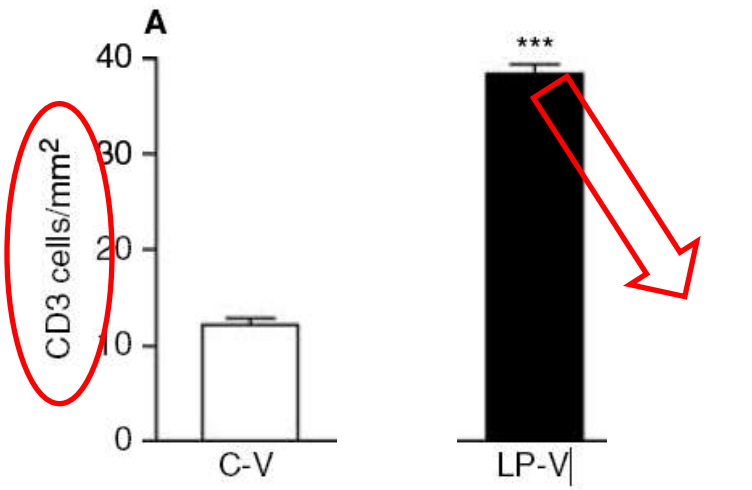
MMF prevents the development of LNAME-induced SSHBP

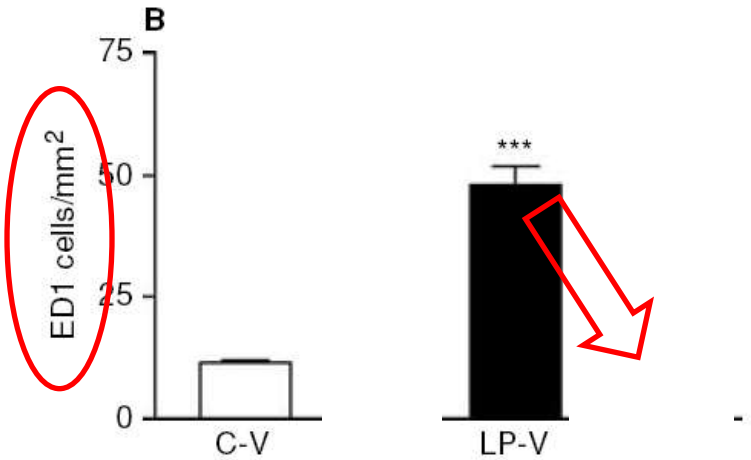


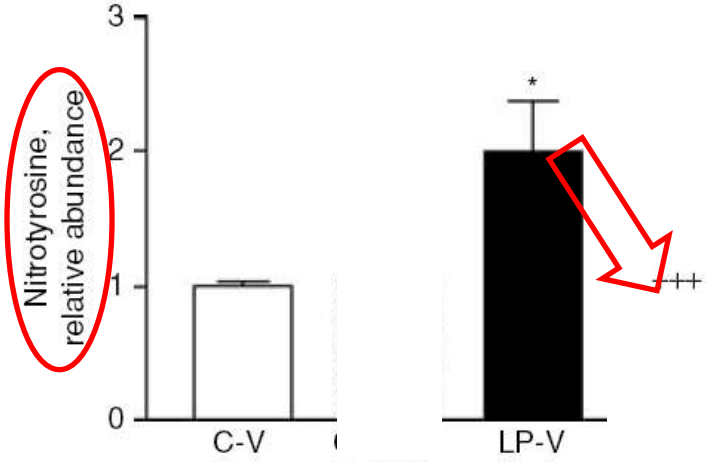
*p<0.01 vs control and p<0.05 vs MMF

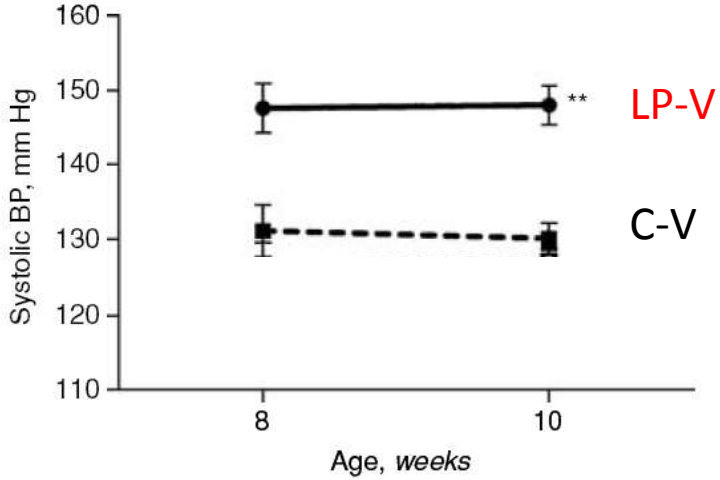
Am J Physiol Renal 2001; 281: F38-F47

MMF corrects prenatally programmed hypertension







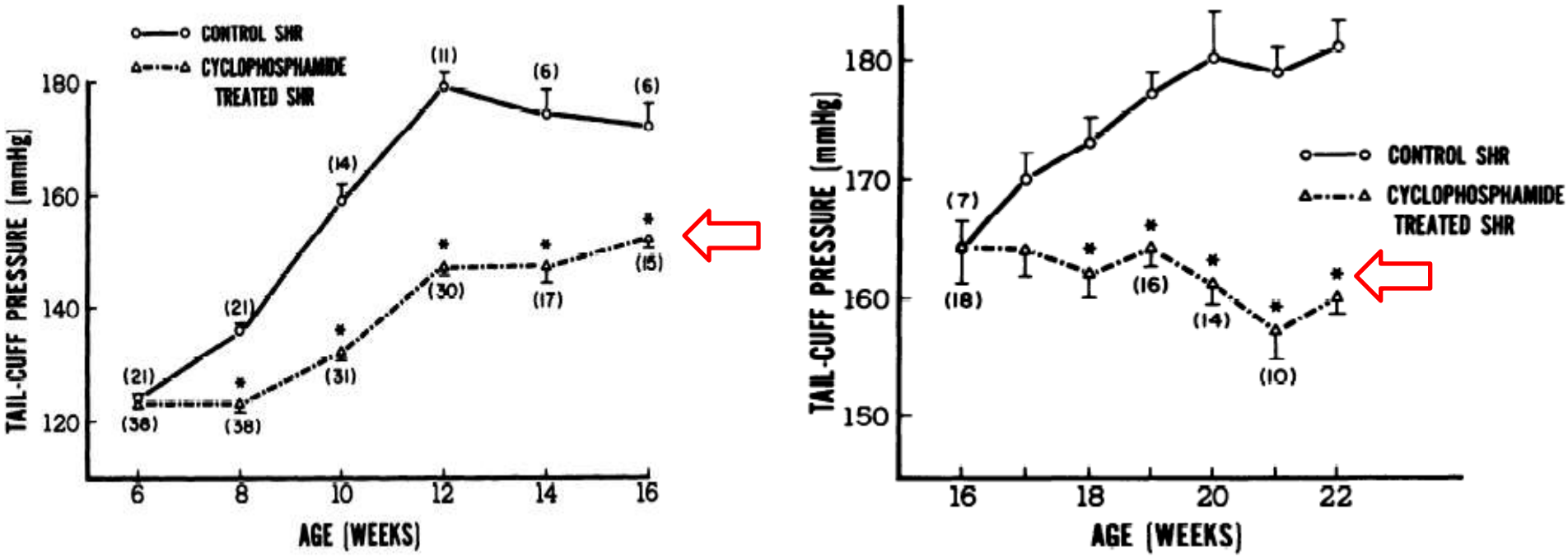


TYRUS STEWART, FLAVIA F. JUNG, JENNIFER MANNING, and V. MATTI VEHASKARI

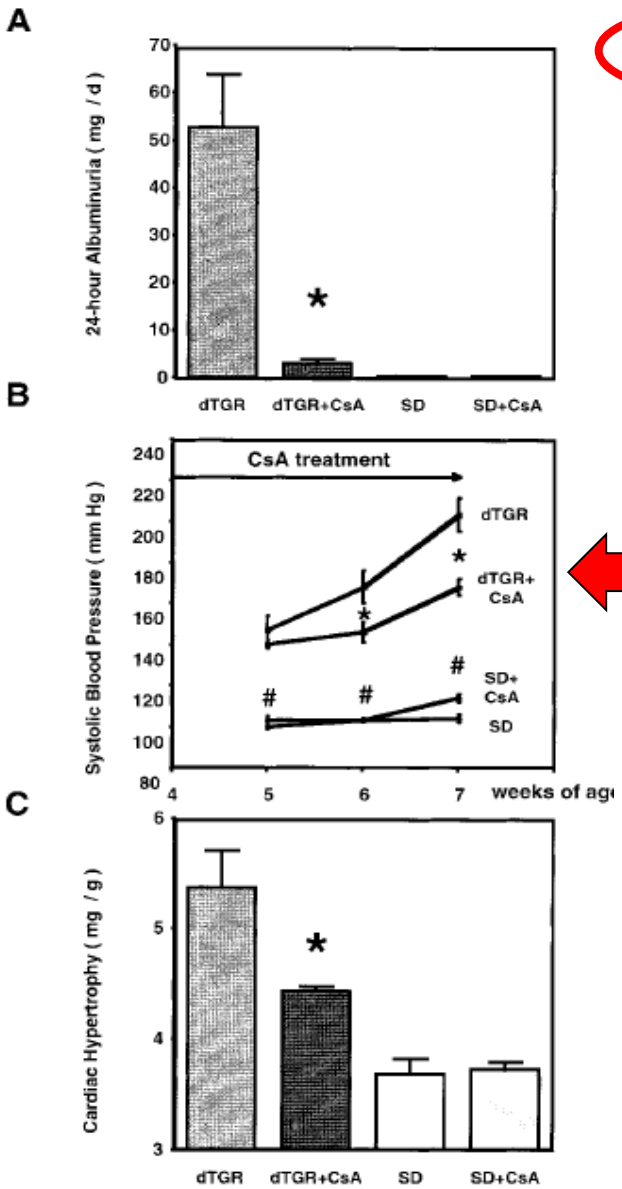
Kidney International, Vol. 68 (2005), pp. 2180–2188

CYCLOPHOSPHAMIDE AMELIORATES HYPERTENSION IN THE SHR

Khraibi AA, Norman RA Jr, Dzielak DJ. Chronic immunosuppression attenuates hypertension in Okamoto spontaneously hypertensive rats. *Am J Physiol* 1984; 247 (*Heart Circ Physiol* 16): H722-H726



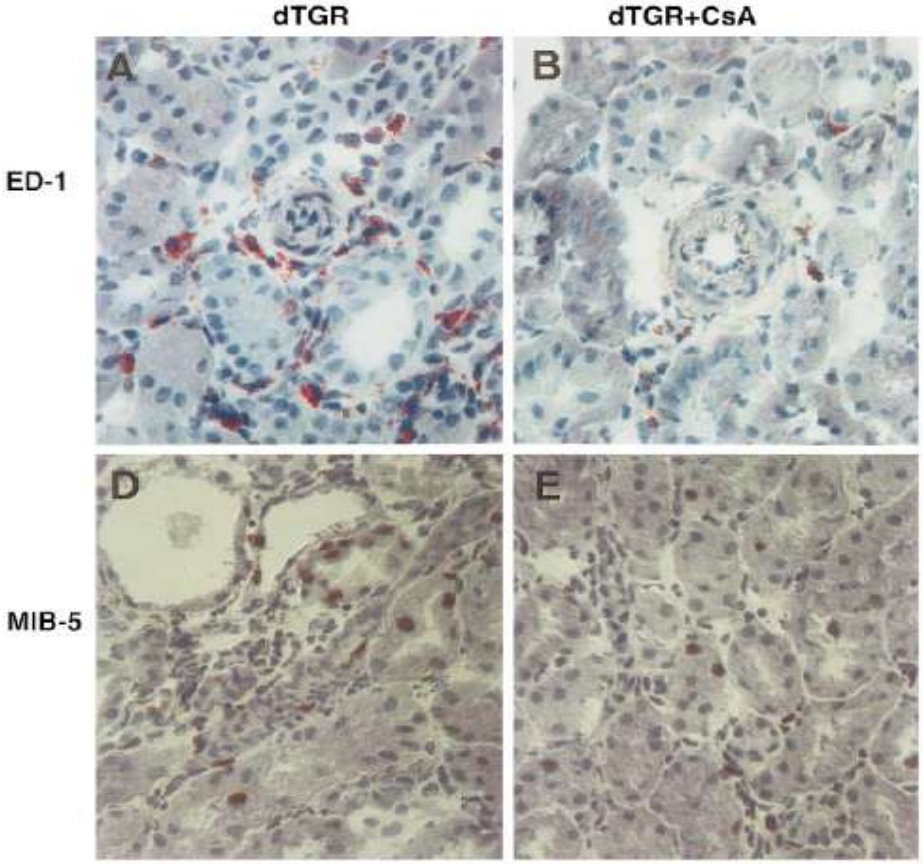
CYCLOSPORIN AMELIORATES HYPERTENSION IN THE SHR



Cyclosporin A Protects Against Angiotensin II–Induced End-Organ Damage in Double Transgenic Rats Harboring Human Renin and Angiotensinogen Genes

Eero Mervaala, Dominik N. Müller, Joon-Keun Park, Ralph Dechend, Folke Schmidt, Anette Fiebeler, Markus Bieringer, Volker Breu, Detlev Ganten, Hermann Haller and Friedrich C. Luft

Hypertension 2000;35;360-366

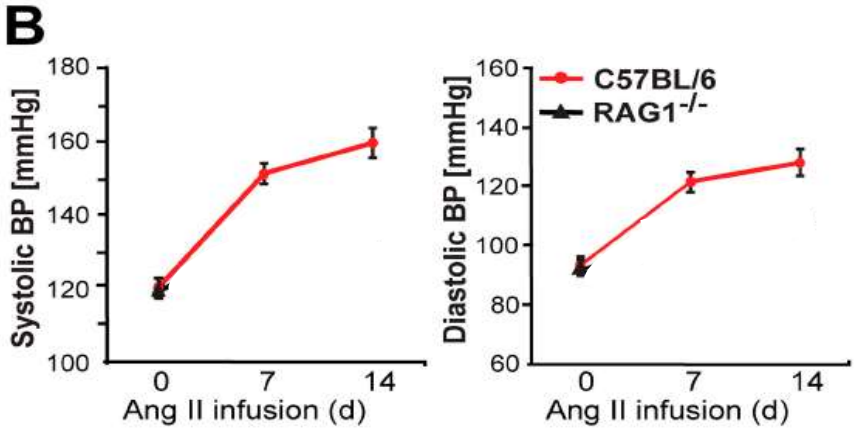


ABSENCE OF LYMPHOCYTES IS ASSOCIATED WITH RESISTANCE TO ANG II-INDUCED HYPERTENSION

Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction

Tomasz J. Guzik,[1,2] Nyssa E. Hoch,[1,2] Kathryn A. Brown,[1,2] Louise A. McCann,[1,2] Ayaz Rahman,[1,2] Sergey Dikalov,[1,2] Jorg Goronzy,[1,2] Cornelia Weyand,[1,2] and David G. Harrison[1,2,3]

JEM 204;2449-60, 2007



HUMANS

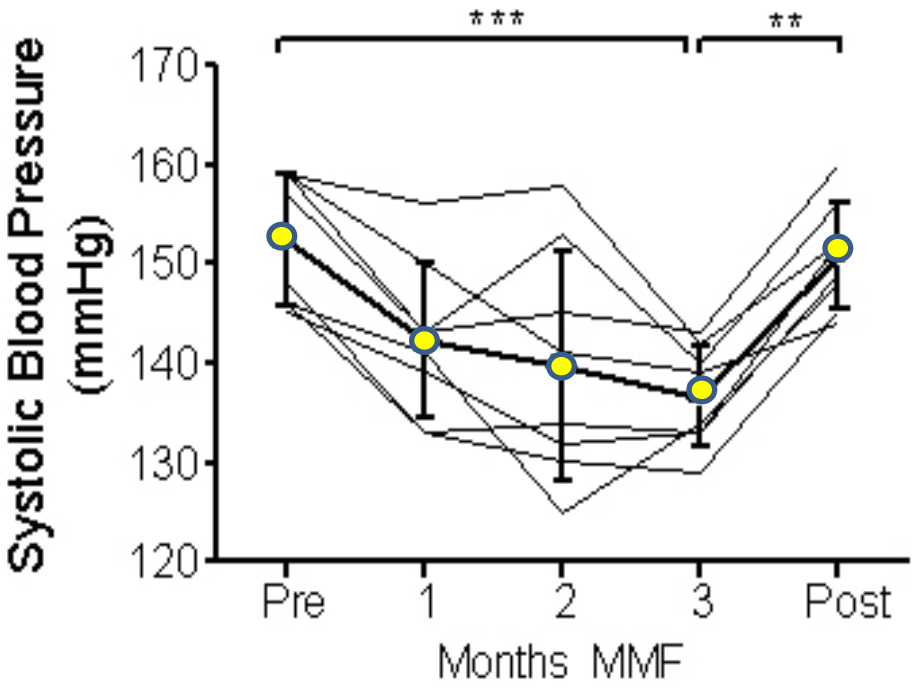
MMF improves essential hypertension

J Am Soc Nephrol 17: S218–S225, 2006.

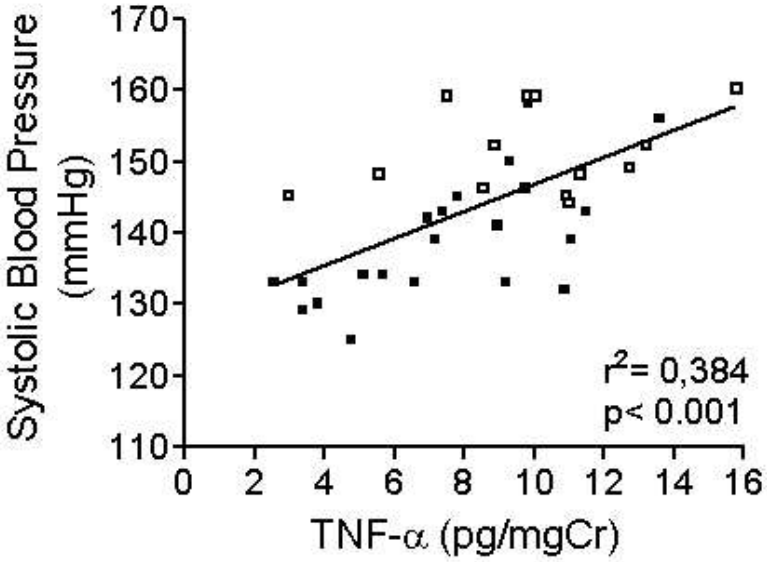
Mycophenolate Mofetil Treatment Improves Hypertension in Patients with Psoriasis and Rheumatoid Arthritis

Jose Herrera,* Atilio Ferrebuz,* Ernesto García MacGregor,† and Bernardo Rodriguez-Iturbe*

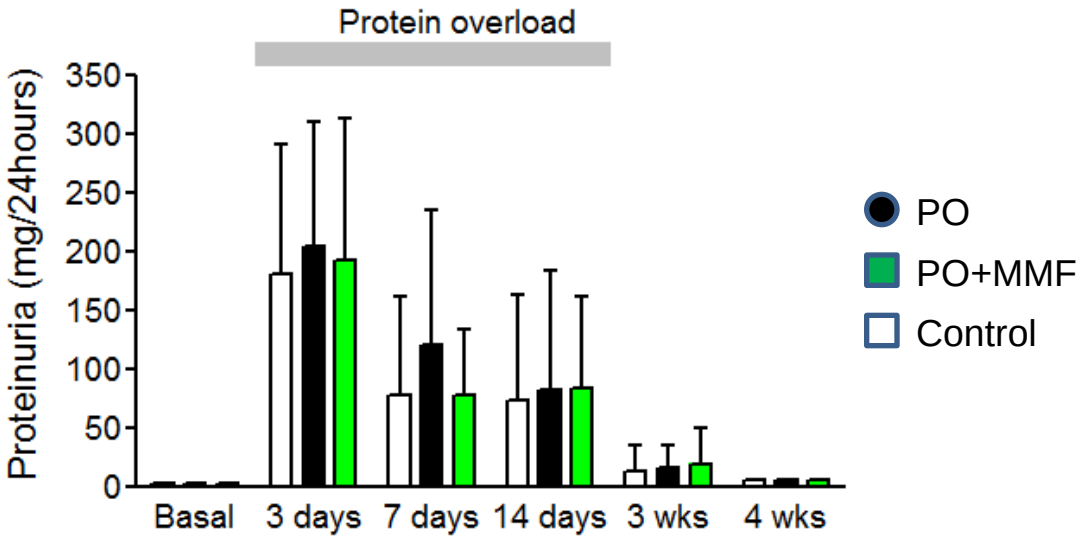
8 patients (6 females)
50-68 years
3 Psoriasis
5 Rheumatoid arthritis
3 month Rx MMF
All essential HBP grade 1
Normal renal function

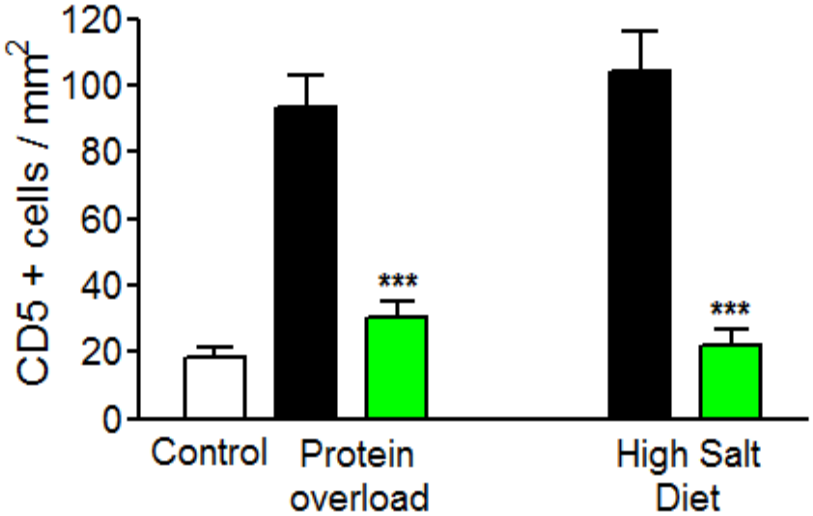


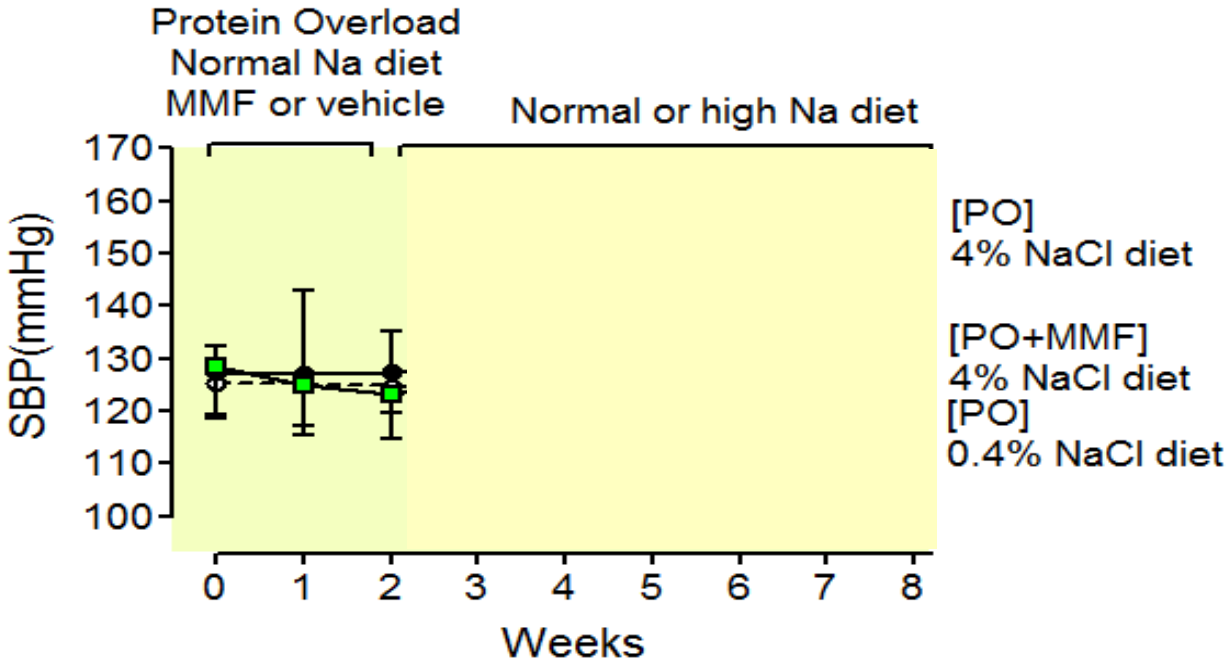
No change in medication
No change in Na intake
No change in protein intake

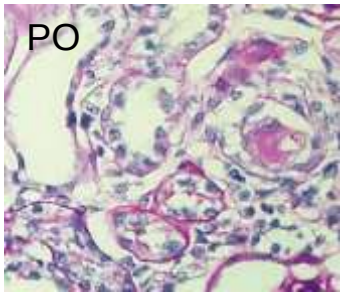


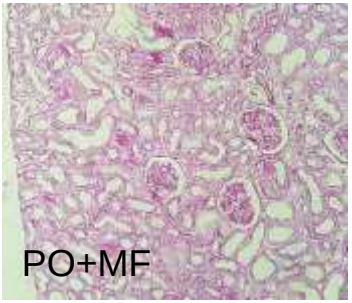
Overload proteinuria causes TI immune cell infiltration and SS Hypertension (AJPhys Renal 2002; 283:F1132-F1141)





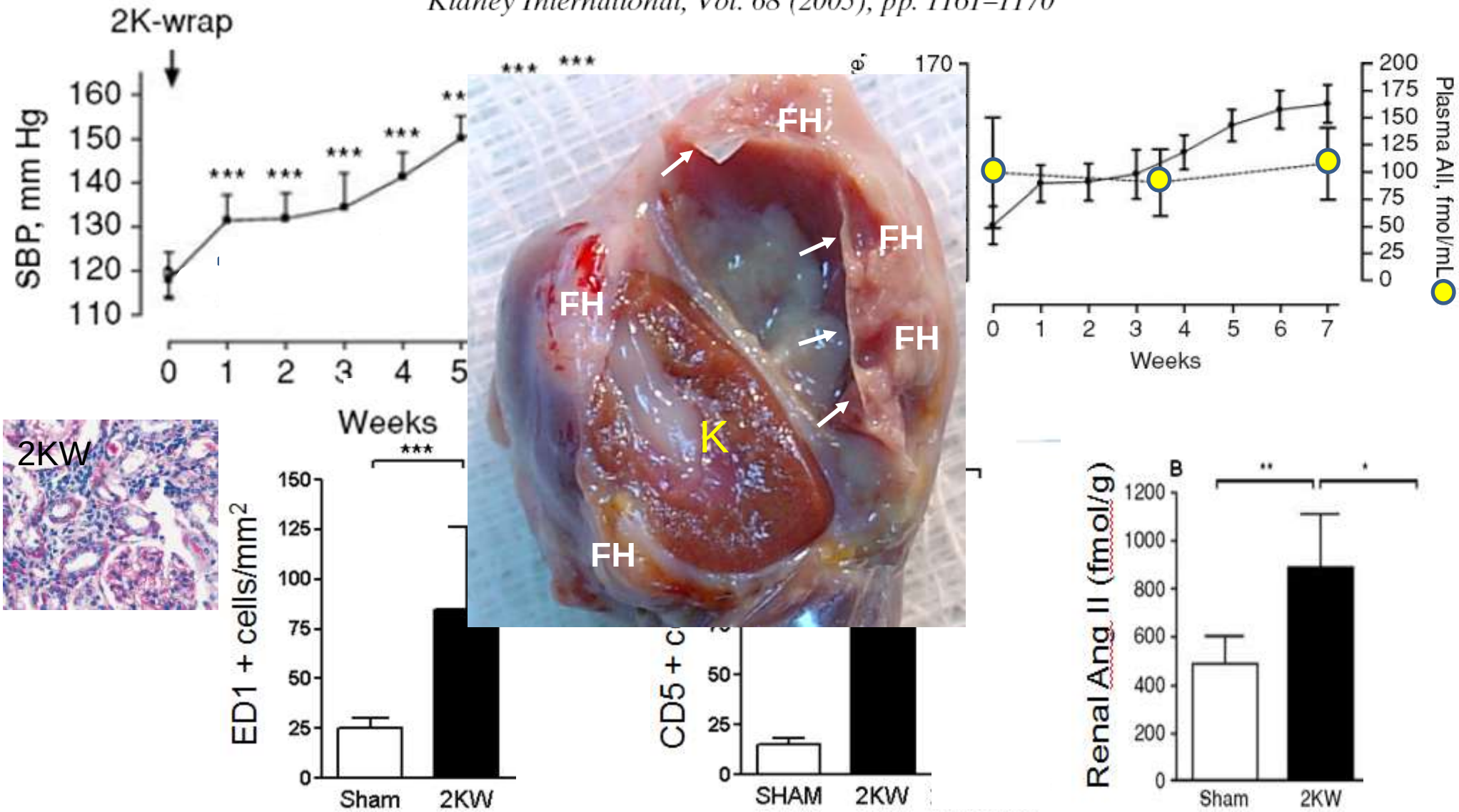






Hypertension in Page (cellophane-wrapped) kidney is due to interstitial nephritis

Kidney International, Vol. 68 (2005), pp. 1161–1170



HUMANS

Tubulointerstitial nefritis associated with hypertension (i)

Drug induced interstitial nephritis

Preddie DC, et al. *Clin J Am Soc Nephrol* 2006 ;1:718-22

Interstitial nephritis due to proton-pump inhibitors

Torpey N et al. *Nephrol Dial Transplant* 2004; 19:1441-46

HIV-associated interstitial nephritis

Parkhie SM et al. *Clin J Am Soc Nephrol* 2010; 5: 798-804

Aristolochic acid nephropathy

Yang L et al. *Nephrol Dial Transplant* 2011

Mortality Statistics > Acute tubulo-interstitial nephritis (mos recent) by country

Rank	Countries	Amount
# 1	Finland:	32.5483 deaths per 1 million peo
# 2	Iceland:	10.11 deaths per 1 million peo
# 3	Sweden:	8.44257 deaths per 1 million peo
# 4	Czech Republic:	7.81174 deaths per 1 million peo
# 5	Barbados:	7.1718 deaths per 1 million peo
# 6	Chile:	7.00832 deaths per 1 million peo
# 7	Slovenia:	5.96718 deaths per 1 million peo
# 8	Hungary:	5.89587 deaths per 1 million peo
# 9	Malta:	5.01839 deaths per 1 million peo
# 10	Croatia:	4.67082 deaths per 1 million peo

http://www.nationmaster.com/graph/mor_acu_tub_int_nep-mortality-acute-tubulo-interstitial-nephritis

Nephrol Dial Transplant (2004) 19: 840–843
DOI: 10.1093/ndt/gfh040

Nephrology
Dialysis
Transplantation

Analgesic nephropathy in Hungary: the HANS study

István Pintér[1,2], János Mátyus[3], Zoltán Czégány[4], Judit Harsányi[5], Marietta Homoki[6], Miklós Kassai[7], Éva Kiss[8], István Kiss[9], Erzsébet Ladányi[10], Lajos Lőcsey[11], Lajos Major[12], Mihály Misz[13], Lajos Nagy[14], Kálmán Polner[15], Jenő Rédl[16], István Solt[17], Béla Tichy[18], Marietta Török[19], Gábor Varga[20], Gyula Wagner[21], Imre Wórum[22], Béla Zsoldos[23], László Pótó[24], Katalin Dérczy[1], István Wittmann[1] and Judit Nagy[1]

Results. Our survey suggested analgesic nephropathy in 47 of 1400 patients (3.3%), 3-fold higher than the EDTA database estimate for Hungary. The analgesics most commonly abused were phenacetin-containing mixtures. The driving symptoms were mainly headache and joint pain. Cardiovascular complications were more common than in the rest of the dialysis population, independent of smoking and lipid values ($P < 0.01$).