Uric acid and its Role in Hypertension and Renal Disease

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Disclaimer: *Dr Johnson is an inventor on a patent with the University of Washington and Merck for allopurinol as a treatment of hypertension*

Gout, a Partner in Cardiovascular Disease

- Hypertension 50-60%
- Obesity 60-80%
- Metabolic Syndrome 70-80%
- Chronic Kidney Disease 50-100%
- Cardiovascular Disease

Is Hyperuricemia an Independent Risk Factor?

Independent

Atherogene
CASTEL
Chicago Heart Association Detection
Framingham 1988
Gothenburg
Heart Institute of Spokane
Hypertension Detection Followup Program
Honolulu Heart
MONICA
NHANES I
PIUMA
Rotterdam
SHEP
Syst-China
Worksite

Not Independent

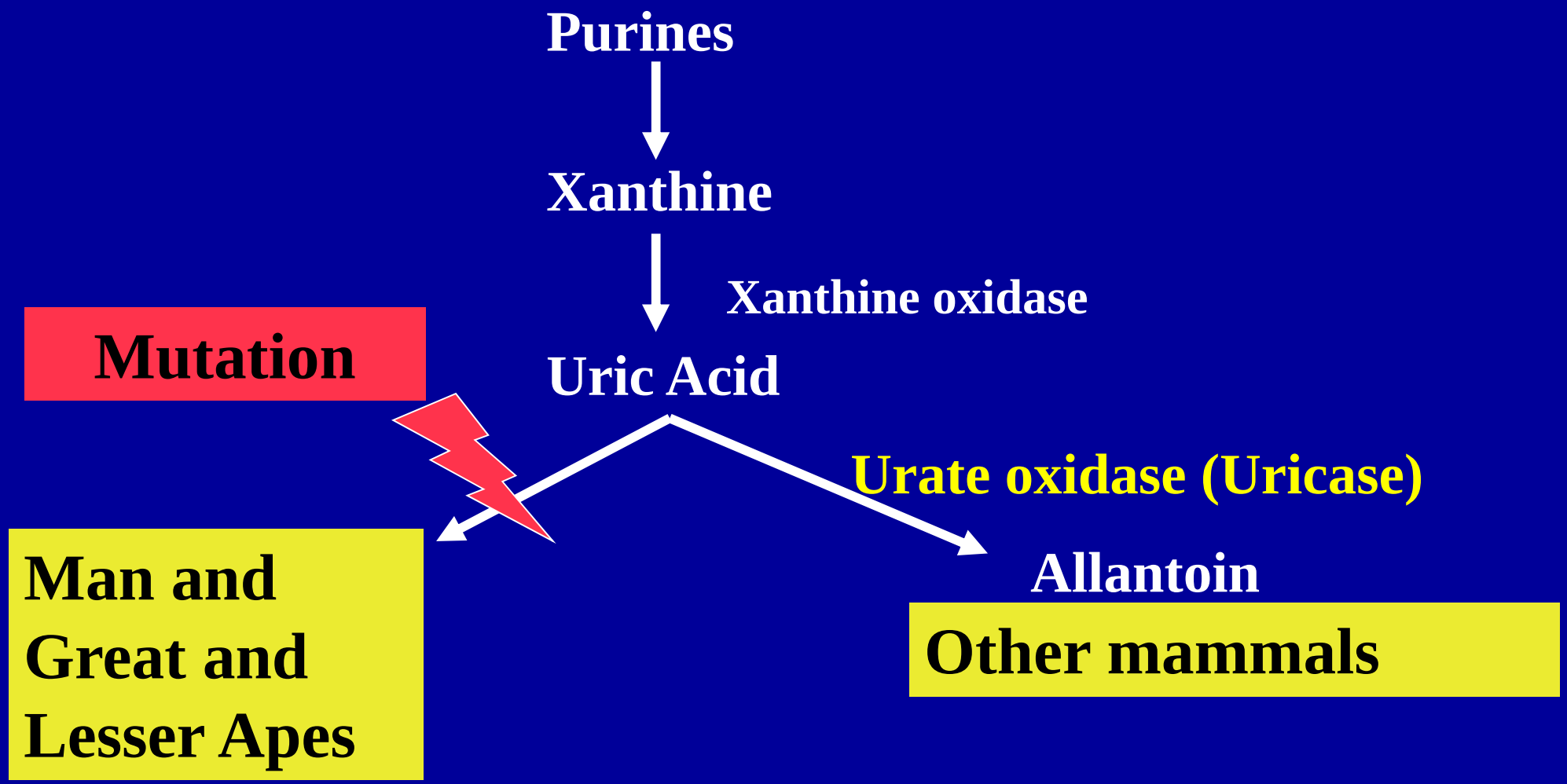
ARIC
British Regional Heart Study
Coronary Drug Project Report Group
European Working Party
Framingham 1999
Iceland
Social Institute of Finland
Syst-Eur

Meta-analyses for CHD Incidence

Uric acid is independent risk factor RR 1.09 (CI 1.03-1.16) (26 studies, 402,997 subjects) Arthritis Care Res 2010; 62:170-180

Uric acid is independent risk factor RR 1.13 (CI 1.07-1.30) (16 studies, 164,000 subjects) but was not significant in the 8 better performed studies (RR 1.02, CI 0.91-1.14) PLoS Medicine 2005;2:e76

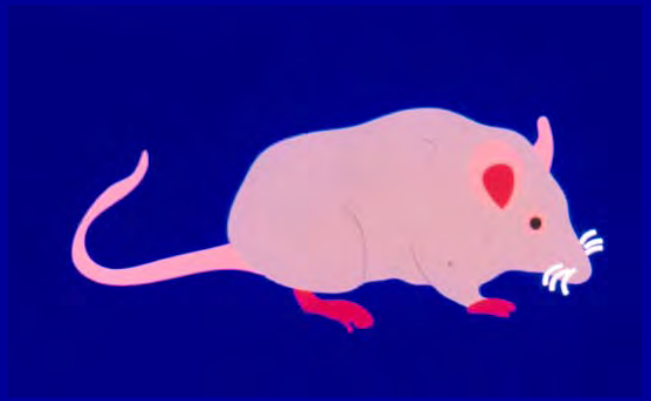
Uric Acid: A Product of Purine Metabolism



A Model of Mild Hyperuricemia

Uricase inhibitor

Oxonic acid (OA)



Normal Rat

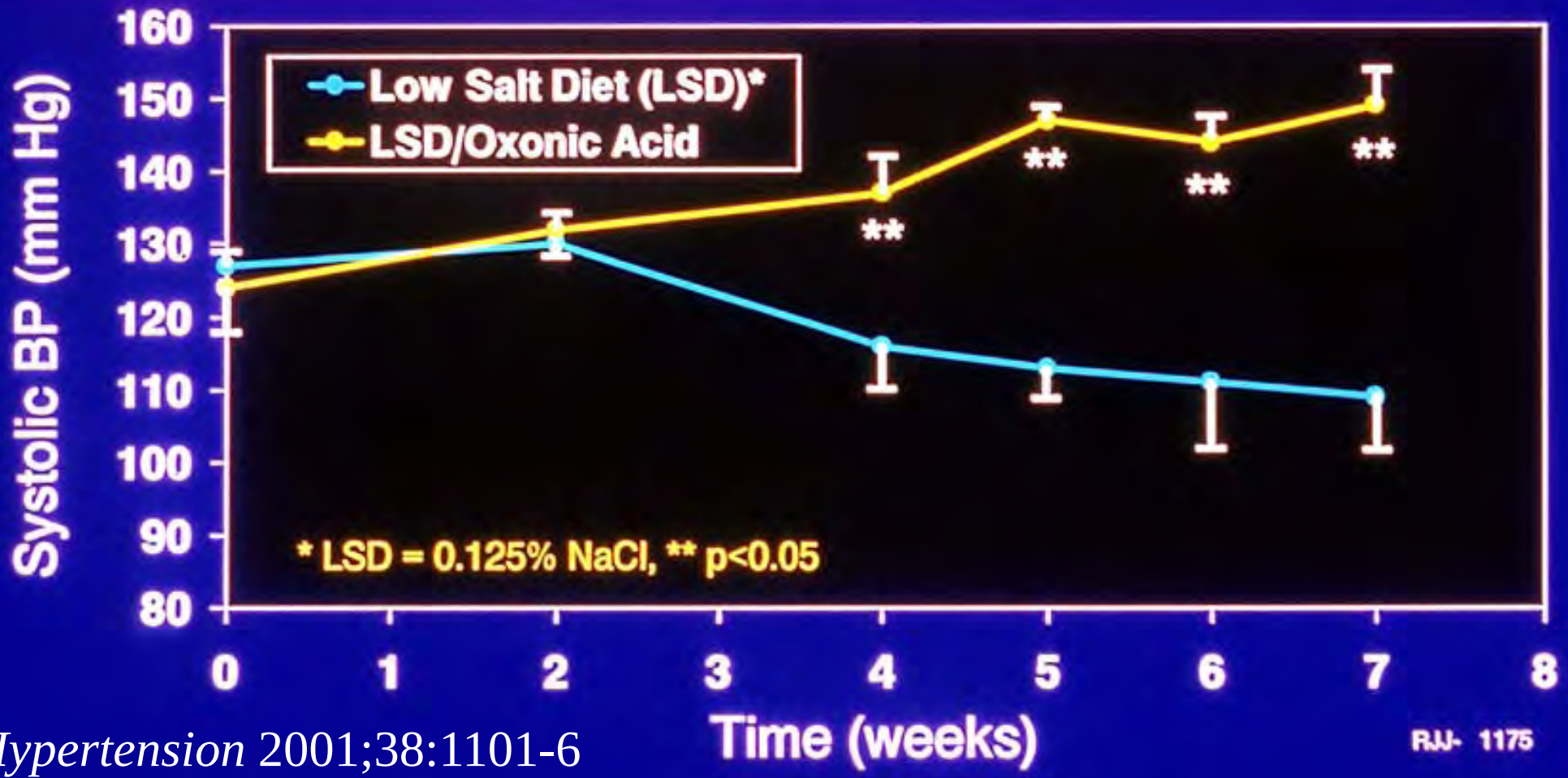
Uric Acid (0.5-1.4 mg/dl)

Hyperuricemic Rat

Uric Acid (1.7-3.0 mg/dl)

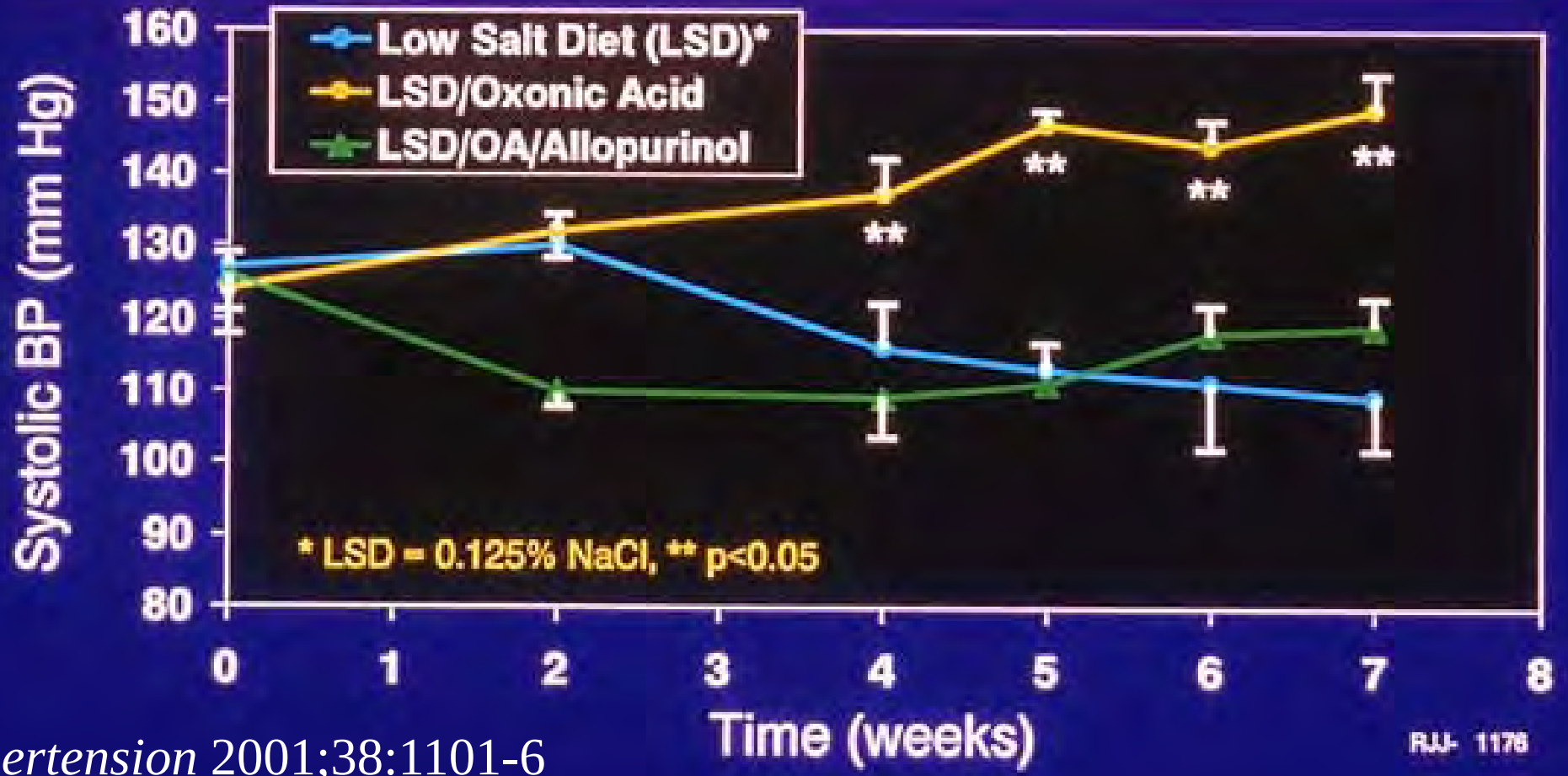
Hypertension 2001;38:1101-6

Chronic Hyperuricemia Increases Blood Pressure



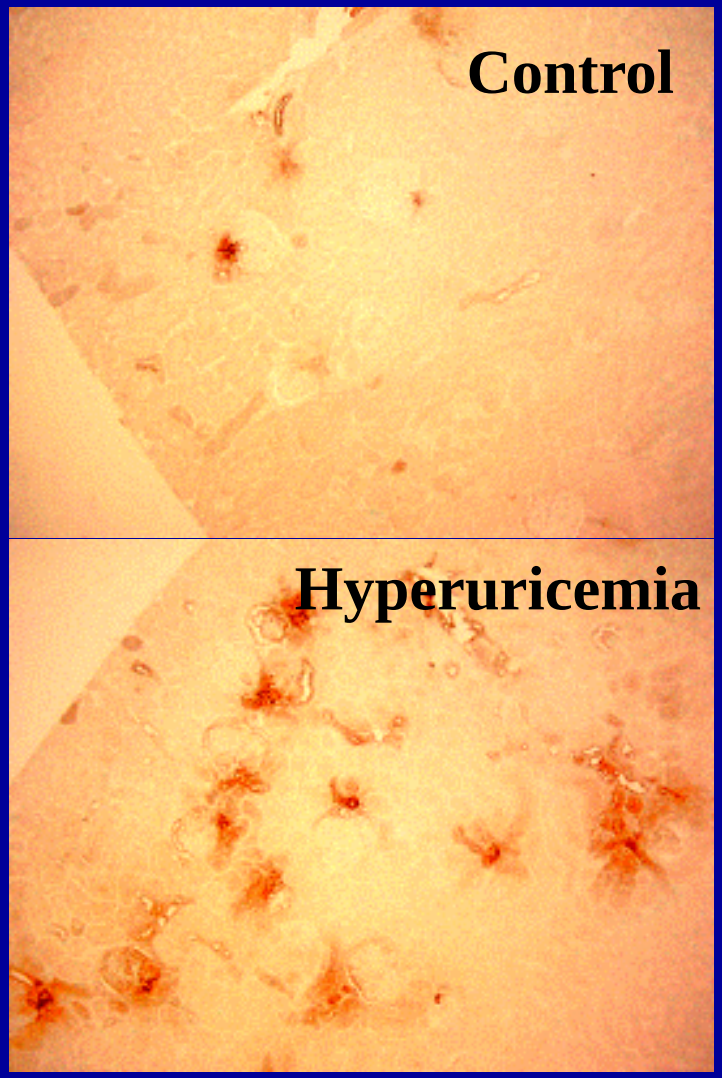
Hypertension 2001;38:1101-6

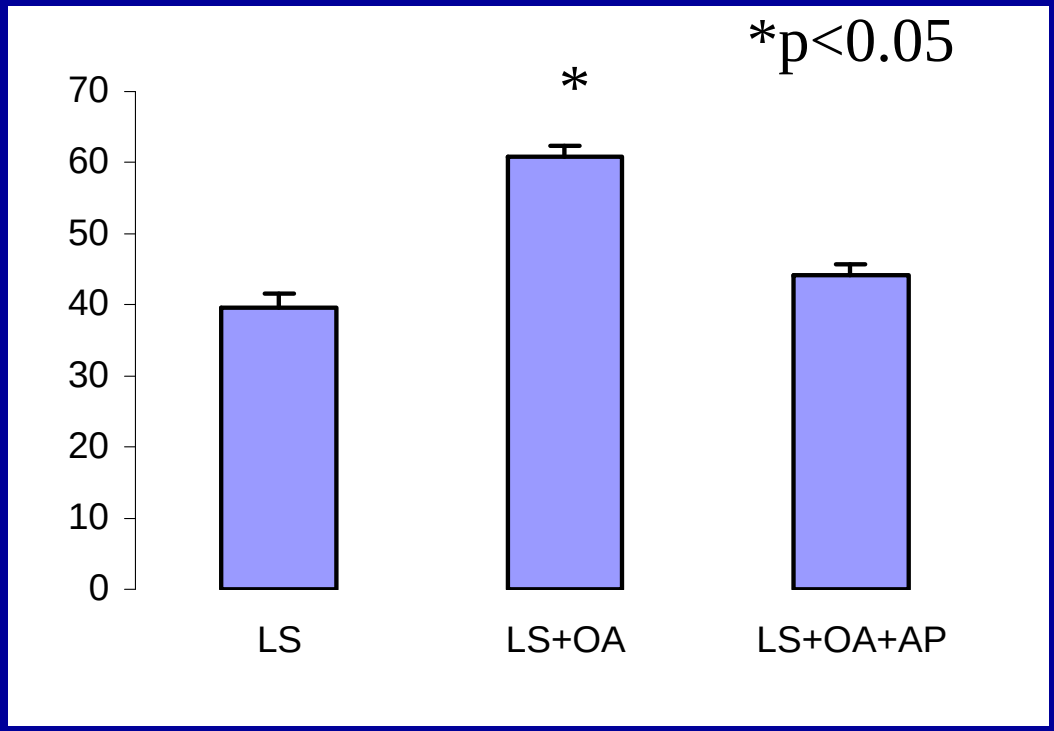
Allopurinol Prevents BP Increase in Hyperuricemic Rats



Hypertension 2001;38:1101-6

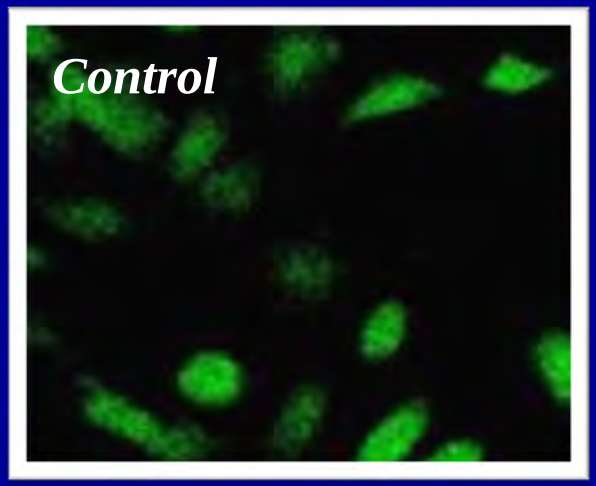
Hyperuricemia Increases Renin Expression

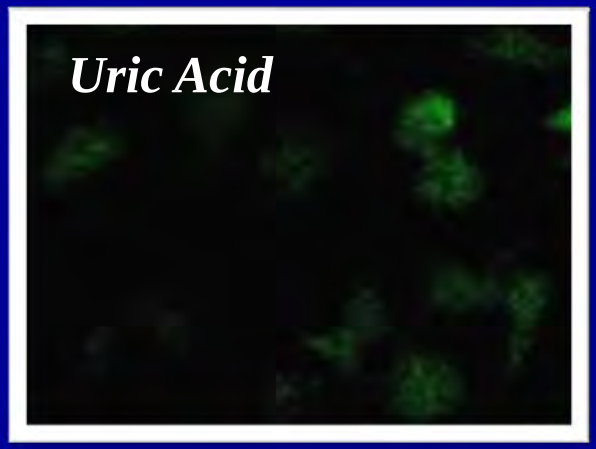


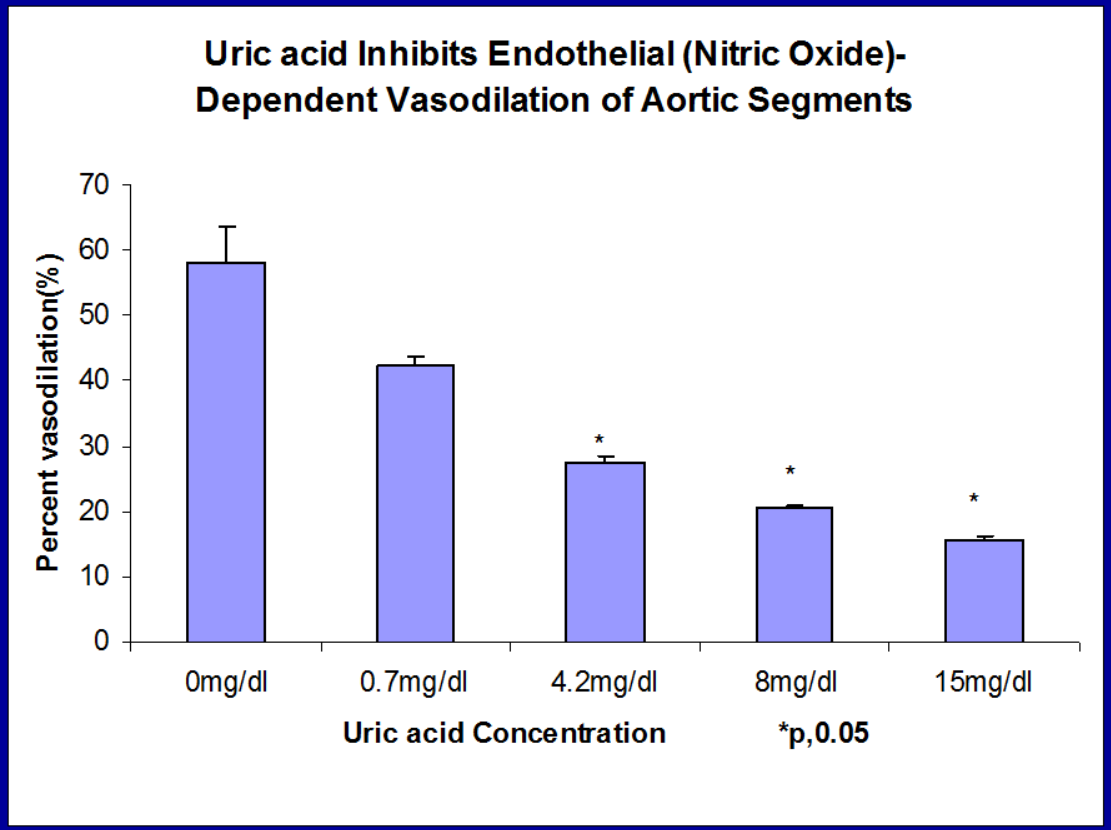


Mazzali et al Hypertension 38:1101-1106, 2001

Uric acid Lowers Endothelial NO Levels



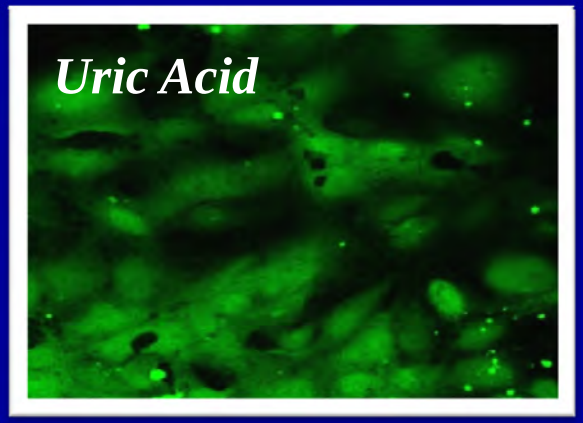


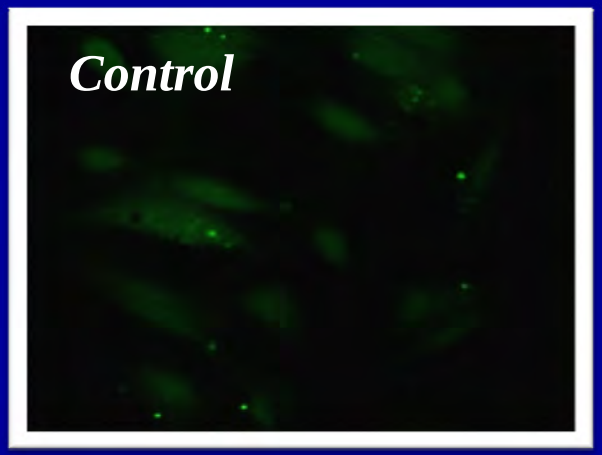


Nakagawa et al, Am J Physiol 2006; 290:F625-631

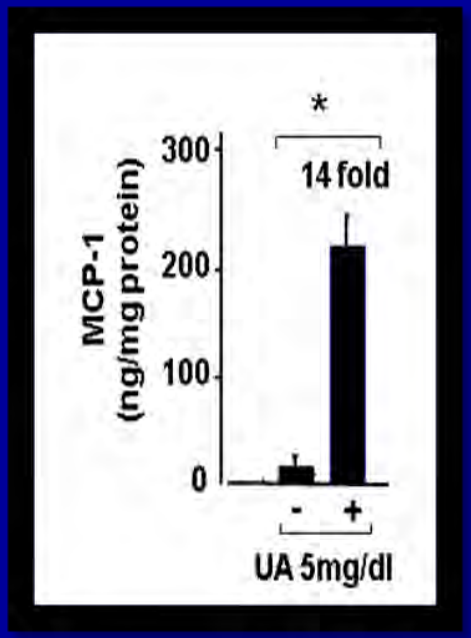
Acute Cellular Effects of Uric acid

Oxidants

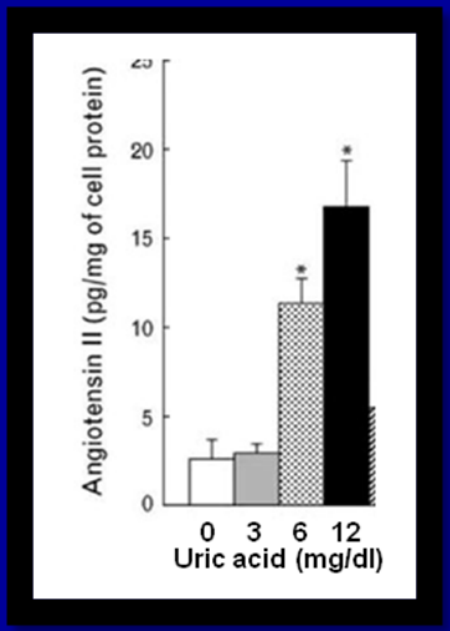




Inflammation (MCP-1)



Angiotensin II



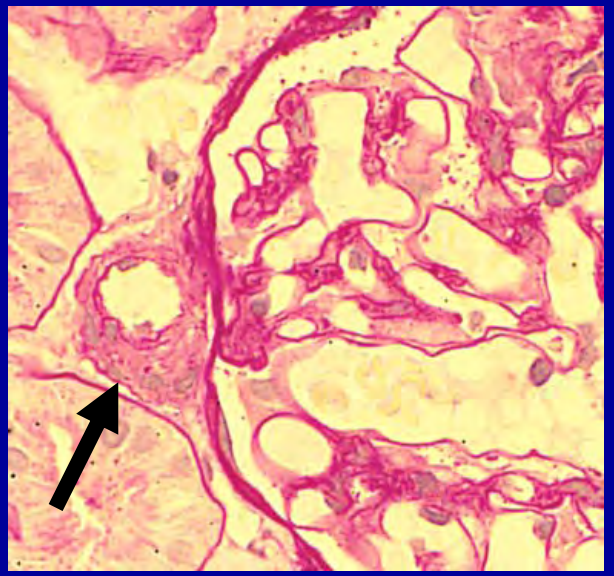
Hypertension 2003; 41: 1287-93 Kidney Int 2005; 267: 1739-42 Am J Physiol 2002;282: F991-7, J Hypertens 2010; 28: 1234-42

Hyperuricemia Induces Preglomerular Vascular Disease

Normal Rat

Hyperuricemic Rat

Essential Hypertension



Mazzali et al, AJP Renal Physiol 282:F991, 2002

Goldblatt's Hypothesis

*"[My view] is that the [renal] arterial and arterial sclerosis are primary, **but of unknown origin**, and that … the vascular disease… produces disturbances of intrarenal hemodynamics ….that determines hypertension"*

Goldblatt H. Physiol Reviews 27:120-165, 1947

Hypothesis

Could salt-sensitivity be the consequence of acquired renal injury?

NEJM 346:913, 2002

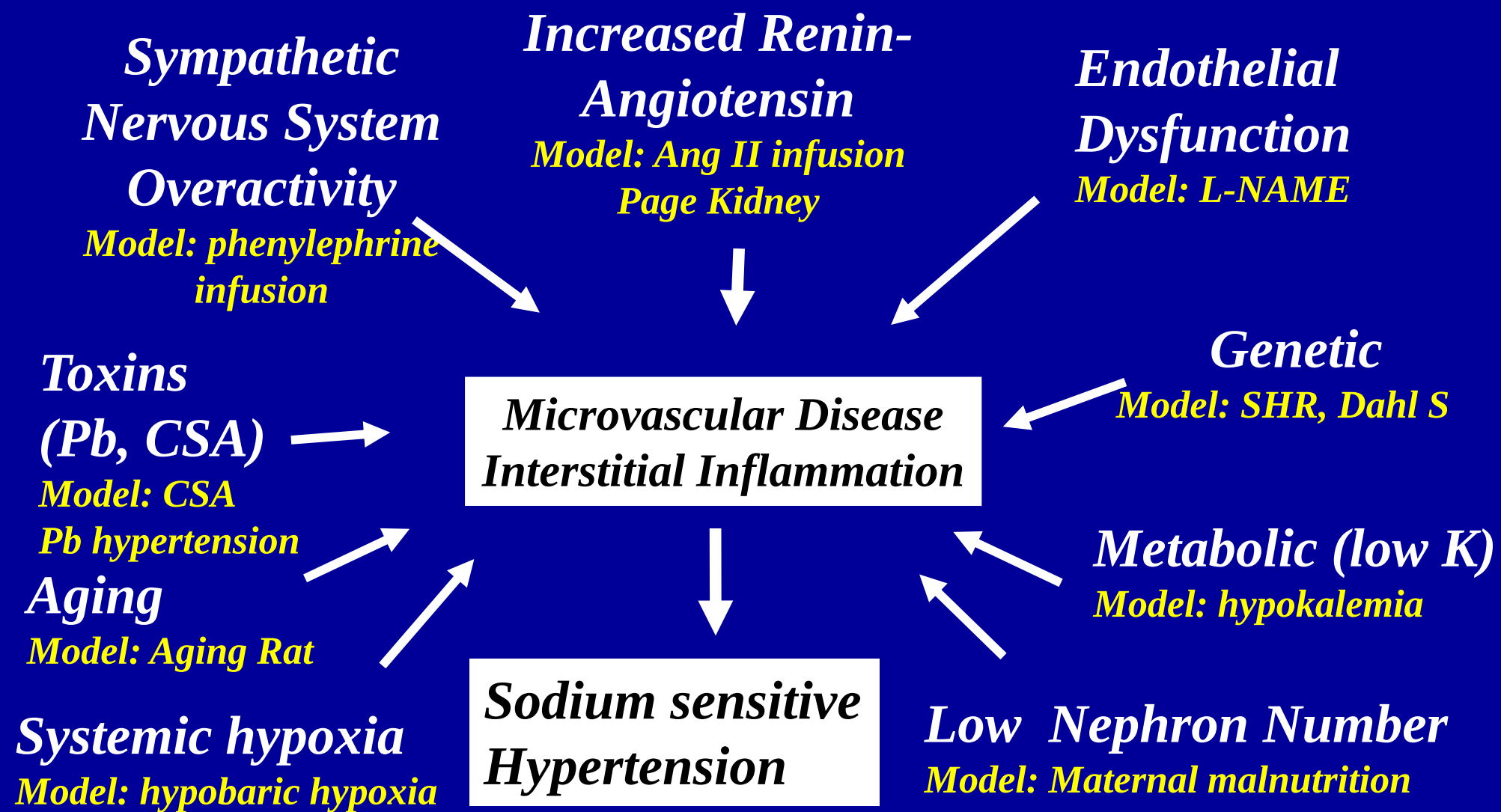
Mechanisms of Disease

SUBTLE ACQUIRED RENAL INJURY AS A MECHANISM OF SALT-SENSITIVE HYPERTENSION

RICHARD J. JOHNSON, M.D.,
JAIME HERRERA-ACOSTA, M.D.,
GEORGE F. SCHREINER, M.D., PH.D.,
AND BERNARDO RODRÍGUEZ-ITURBE, M.D.

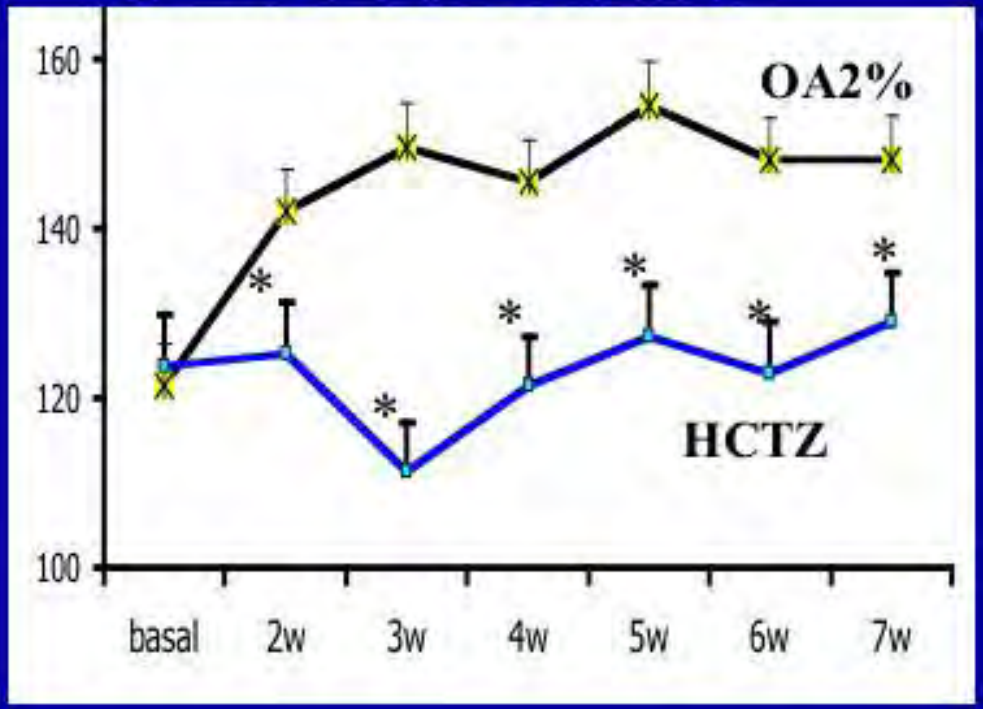
IN 1856 Ludwig Traube[1] proposed a role of the kidney in the pathogenesis of hypertension on the basis that hypertension and vascular disease were often associated with chronic Bright's disease.

Models of Salt-Sensitive Hypertension

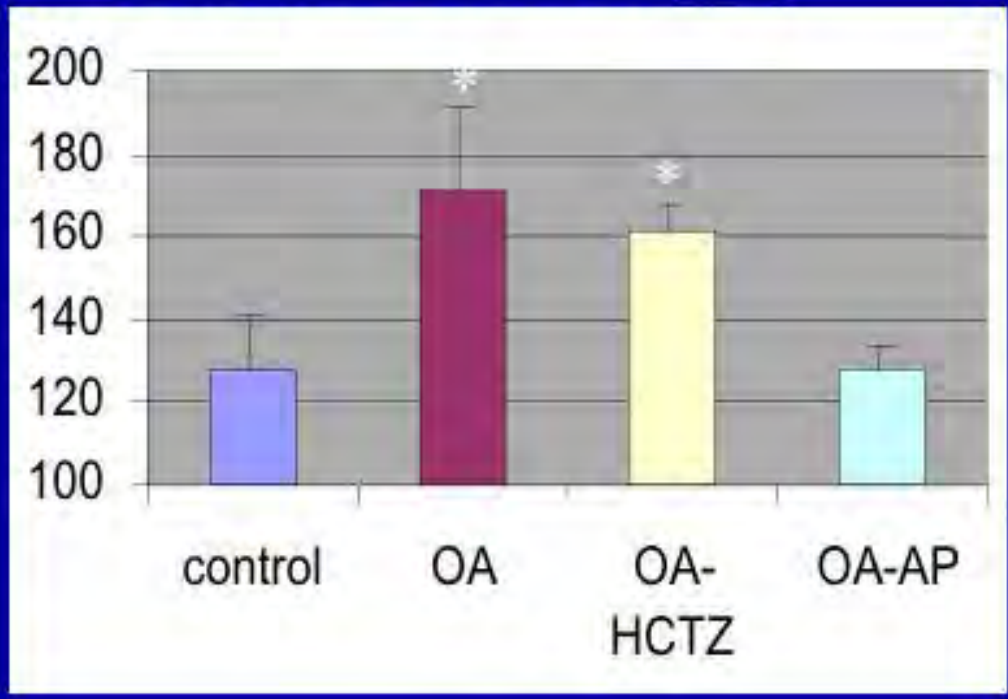


Does the Arteriolopathy Occur Independently of Blood Pressure?

Systolic Blood Pressure

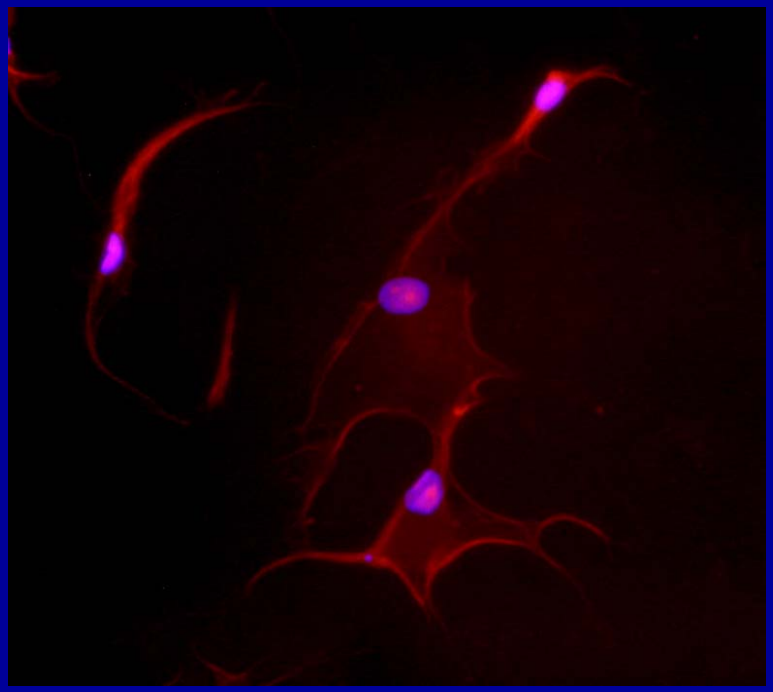


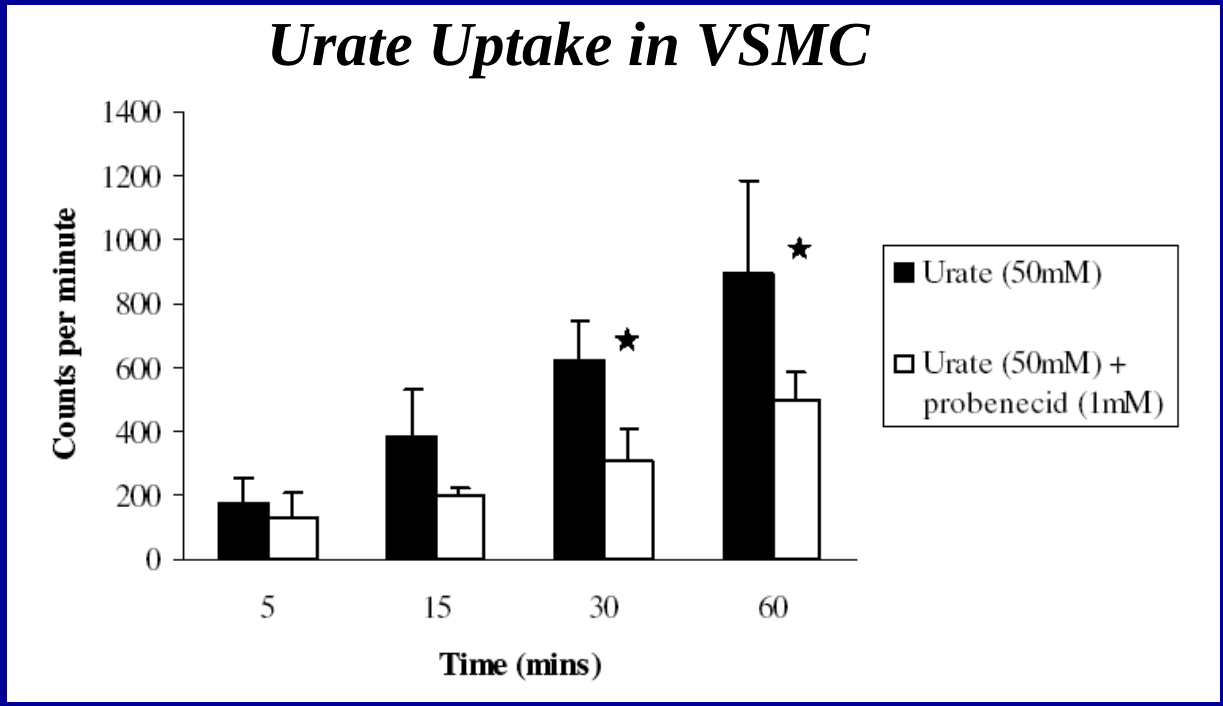
Arteriolar thickness (μm)



Mazzali M et al. Am J Physiol Renal Physiol 282:F991, 2002

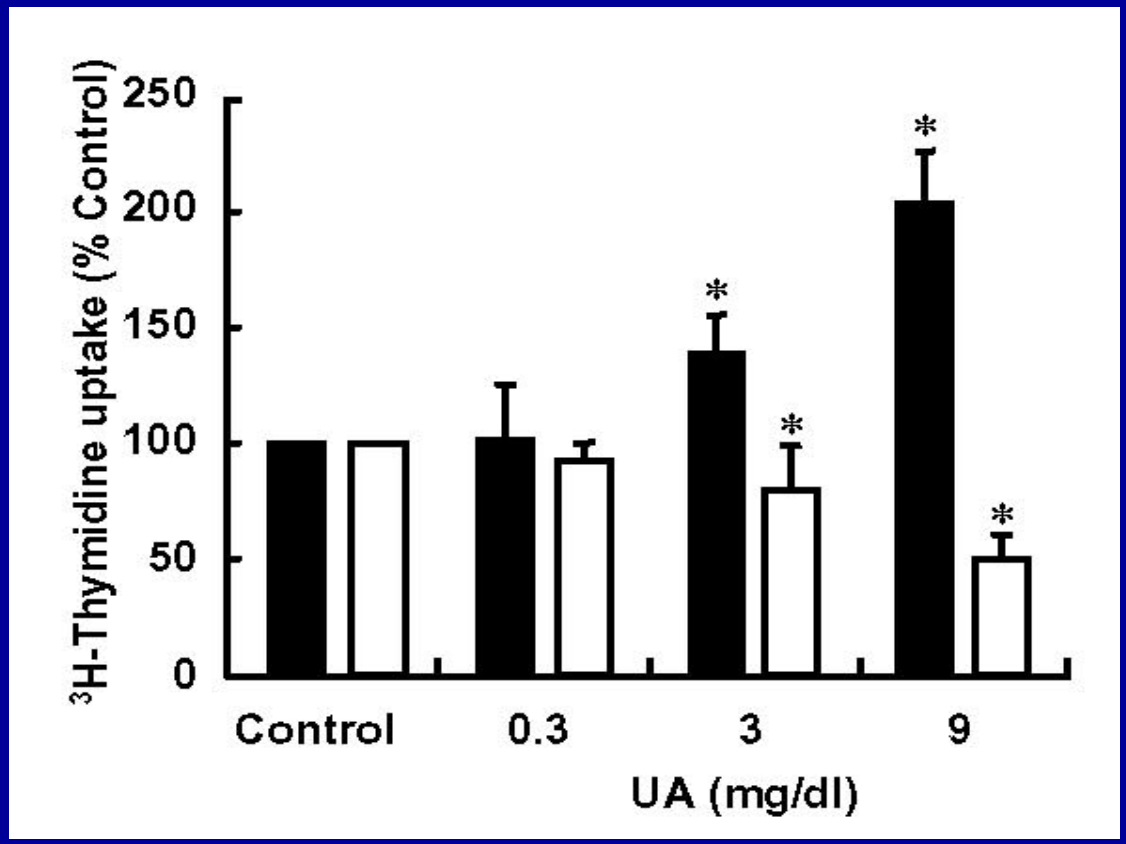
Human Vascular Smooth Muscle Cells Express the Urate Transporter, URAT-1





Price K, J Am Soc Nephrol, 2006

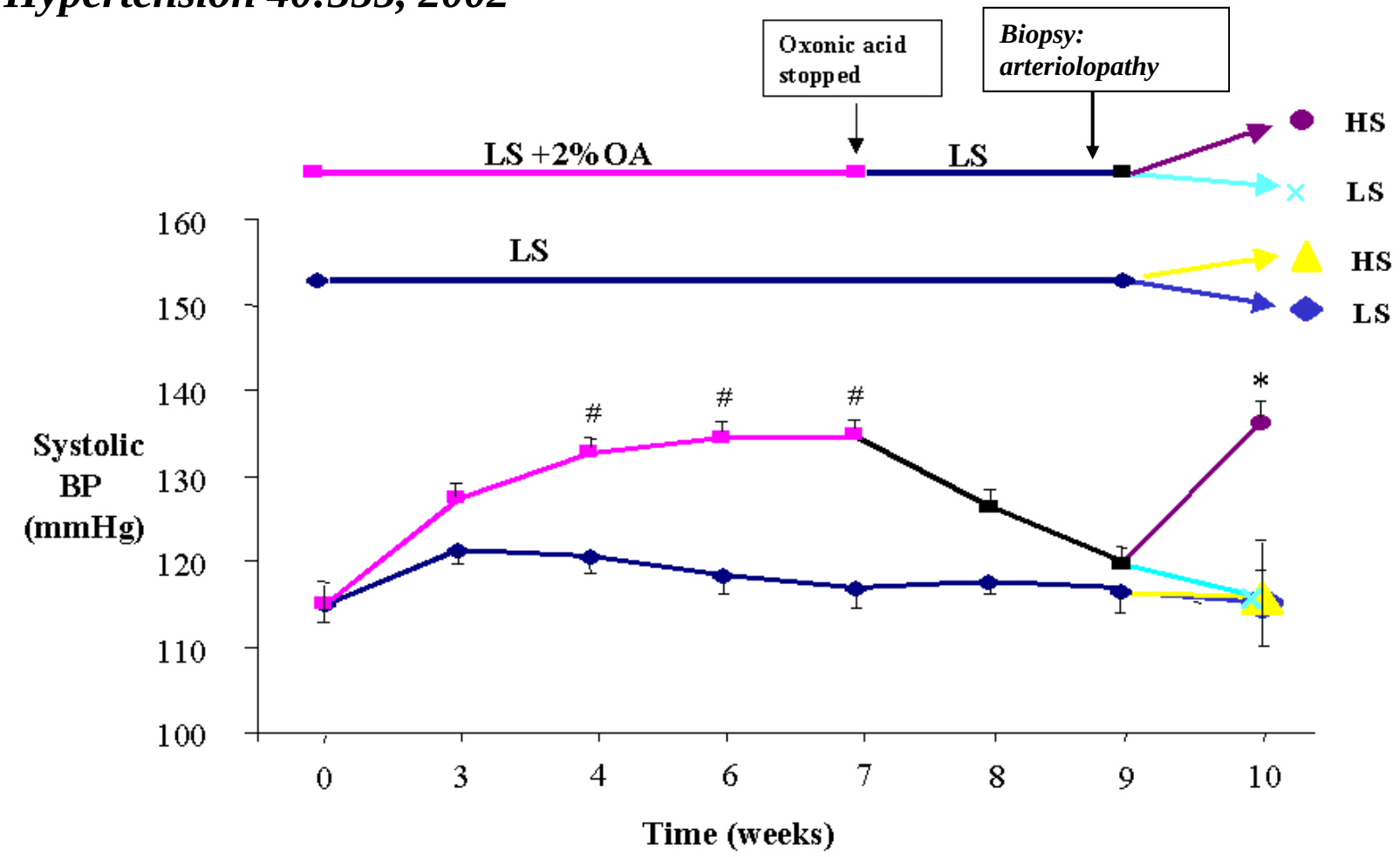
Uric acid Stimulates Human VSMC but inhibits Endothelial Cell Proliferation



Kang DH, et al JASN 2005; 16:35553-3562

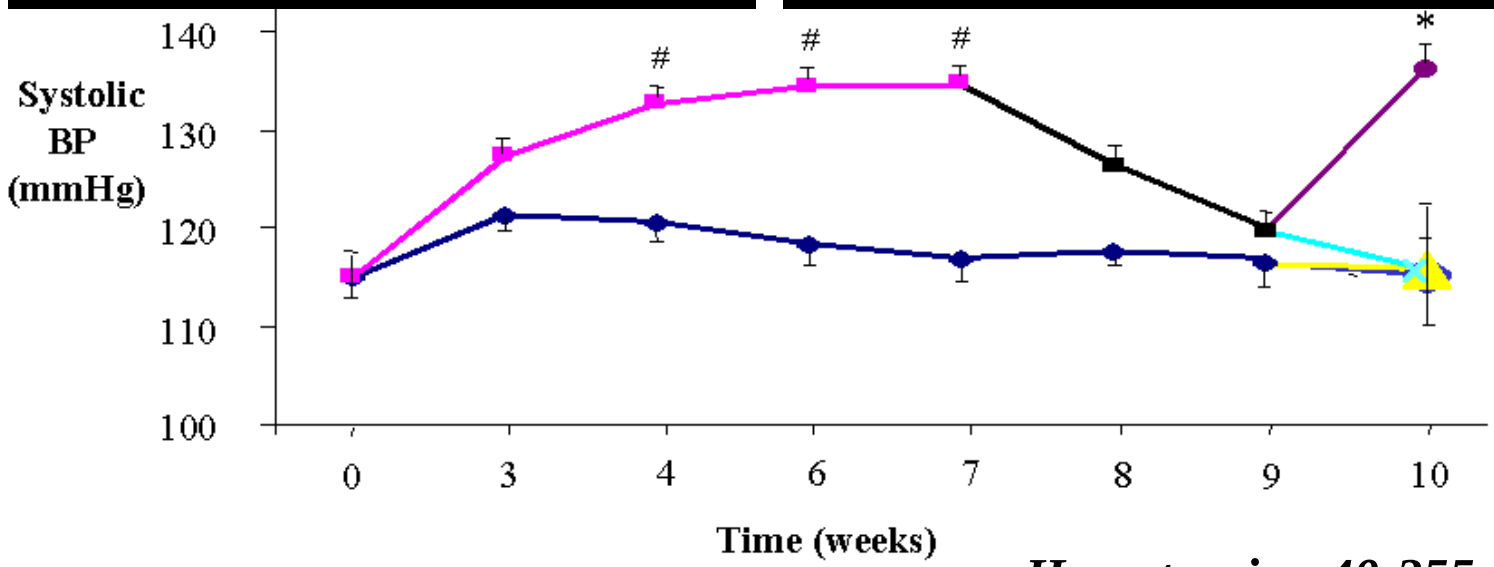
Hyperuricemia Induces Salt-sensitivity

Hypertension 40:355, 2002



Hyperuricemia Induces Salt-sensitivity

Uric acid dependent	Uric acid independent
Salt resistant	Salt sensitive
Renin and NO dependent	Volume dependent
No renal structural changes	Kidney: arteriolosclerosis and inflammation



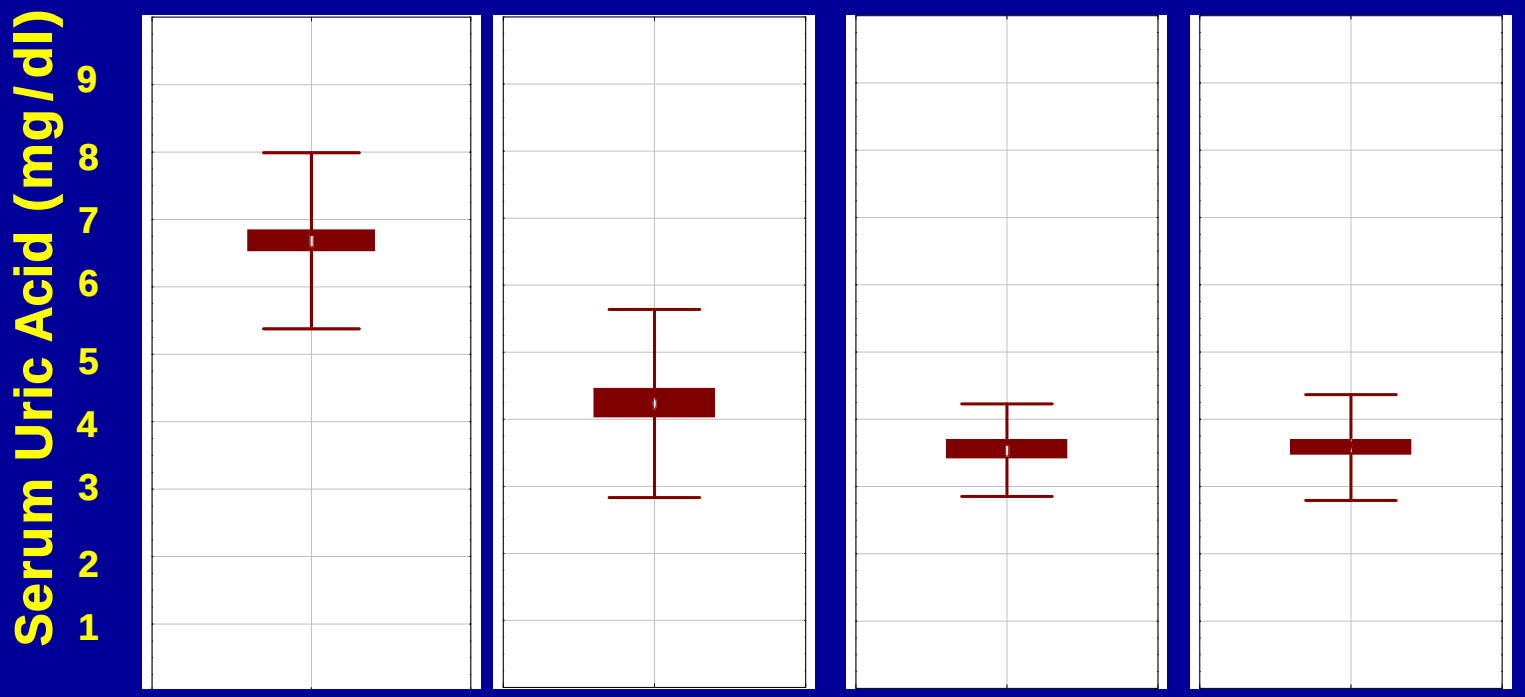
Hypertension 40:355, 2002

Is there Clinical Evidence for a Role of Uric acid in Hypertension?

Serum Uric Acid Predicts Hypertension

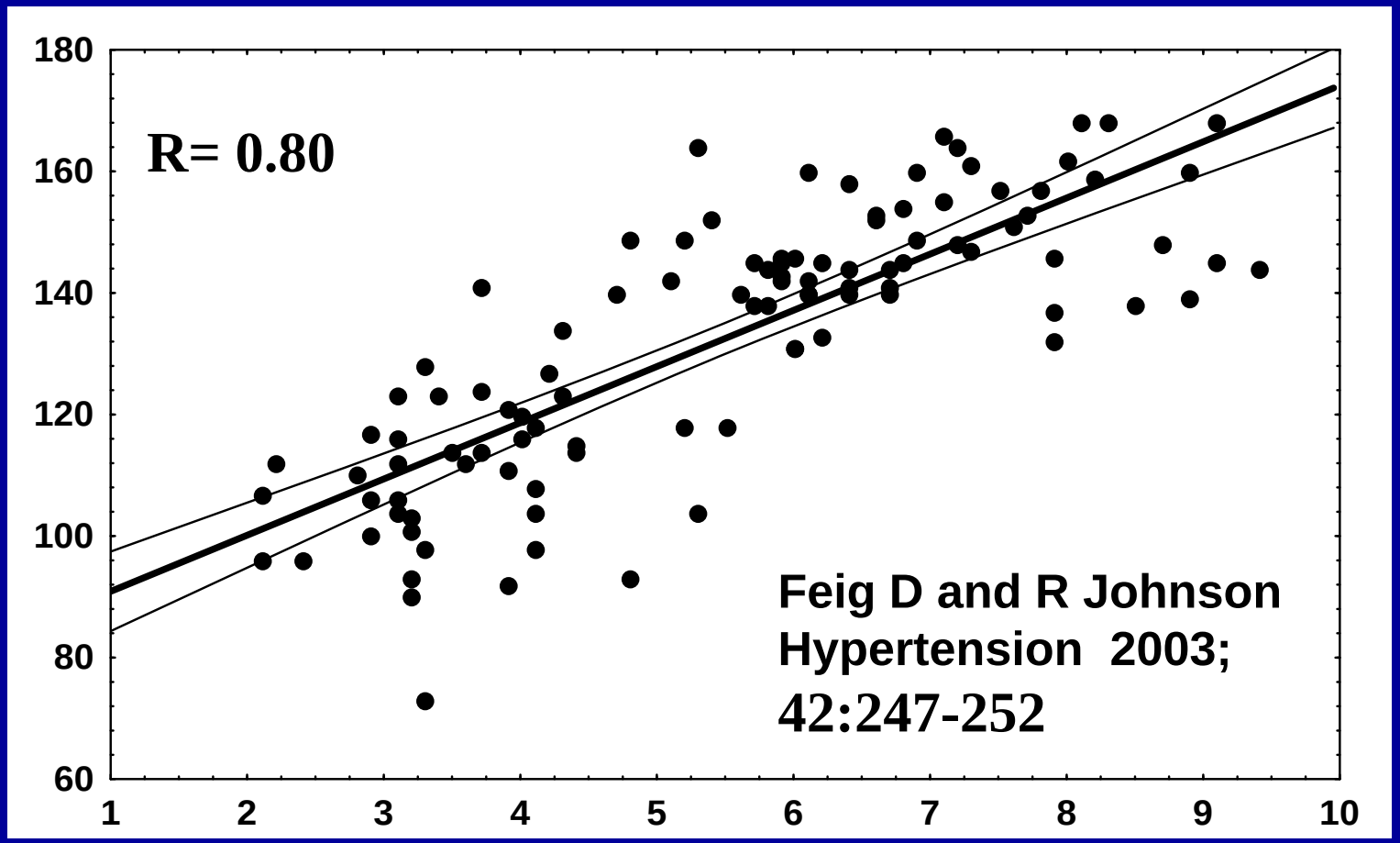
Study	Population	Relative Risk
Israeli Heart Study (Khan, 1972)	10,000 males	2- fold risk at 5 YRS
Kaiser Permanente (Selby, 1990)	2,062 subjects	2-fold risk at 6 YRS
Univ of Utah (Hunt, 1991)	1482 adults	2-fold risk at 7 YRS
Olivetti Heart Study (Jossa, 1994)	619 males	2-fold risk at 12 YRS
CARDIA study (Dyer, 1999)	5115 adults	2-fold risk at 10 YRS
Osaka Health Survey (Taniguchi, 2001)	6,356 males	2-fold risk at 10 YRS
Hawaii-Los Angeles-Hiroshima Study (Imazu, 2001)	140 males	3.5-fold risk at 15 YR
Osaka Factory Study (Masuo, 2003)	433 males	1.0 mg/dl UA predicts ↑27 mm Hg at 5 YR
Osaka Health Survey (Nakanishi,2003)	2310 males	1.6- fold risk at 6 YRS
Okinawa (Nagahama, 2004)	4489 adults	1.7-fold risk at 13YRS
Bogalusa Heart (Alper, 2005)	679 children	Increased risk at 11 YRS
Framingham (Sündstrom , 2005)	3329 adults	1.6-fold at 4 YRS
Normative Aging Study (Perlstein, 2006)	2062 males	1.5-fold at 21 YRS
MRFIT (Krishnan, 2007)	3073 men	1.8-fold at 6 YRS
ARIC (Mellen, 2006)	9,104 adults	1.5-fold at 9 YRS
Nurse Health Study(Forman, 2009)	1500 women	1.89 fold at 5 years
Health Professional Followup (Forman, 2007)	750 men	1.08-fold at 8 YRS* (Not significant)

Serum Uric Acid in Adolescents with Hypertension



Feig and Johnson, Hypertension 42:247-252, 2003

Relationship Between SBP and Serum Uric Acid in Adolescents



Systolic BP (mm Hg)

Uric Acid (mg/dl)

Effect of allopurinol vs placebo in newly diagnosed hypertension in adolescents

- **Randomized double-blinded placebo controlled cross-over design**
- **30 Children 11-17yr old, new diagnosis essential hypertension**
- **Uric acid >6mg/dl**
- **Pharmacologically naive**
- **Allopurinol 200mg bid vs. placebo**
- **Four week medication phases with 2 week washout between arms**

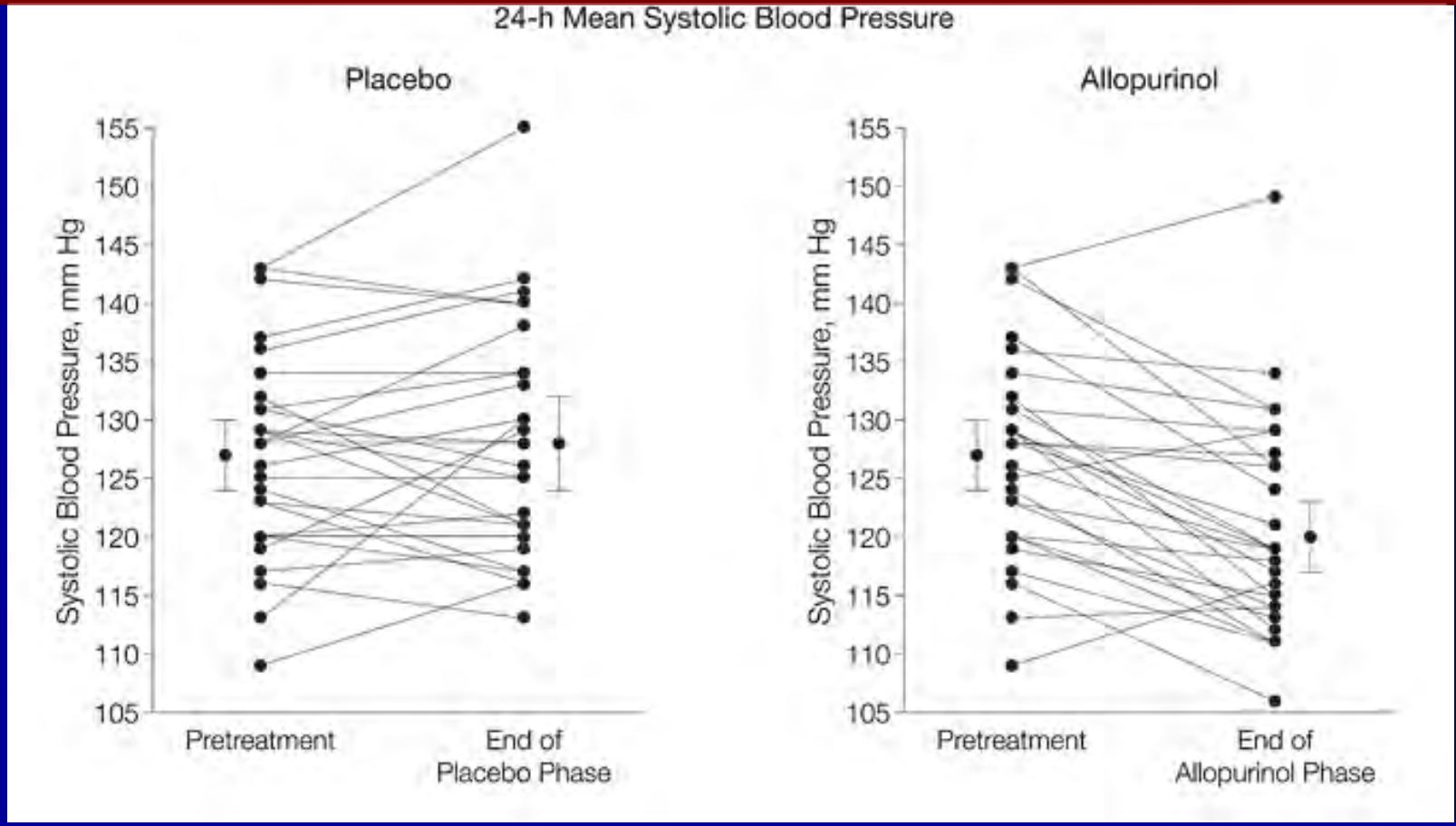
Feig et al, JAMA 2008; 300:924-32

Effect of allopurinol vs placebo in newly diagnosed hypertension in adolescents

Age	**15.1±2.1 yrs**
% Male	**60%**
Weight	**97±23 kg**
BMI	**33±6.5 kg/m^2**
Race	**White 46%** **Hispanic 23%** **African American 31%**
Uric Acid	**6.9±1.2mg/dL**

Feig et al, JAMA 2008 Aug 27;300(8):924-32

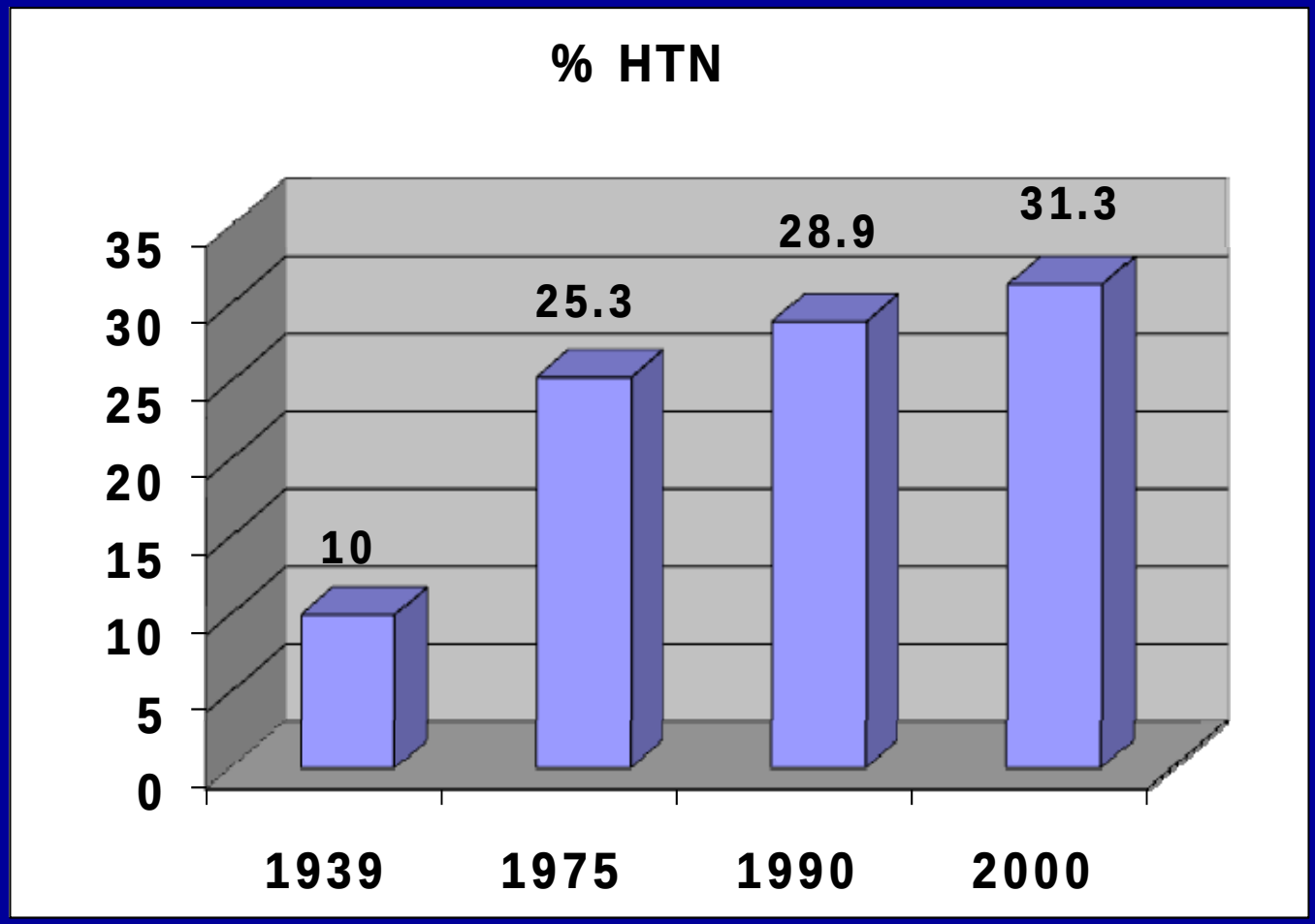
Lowering Uric Acid Reduces SBP in Adolescents with Hypertension



In Subjects whose Uric acid was reduced to < 5 mg/dl, 86% (19/22) became normotensive versus 3% (1/30) controls

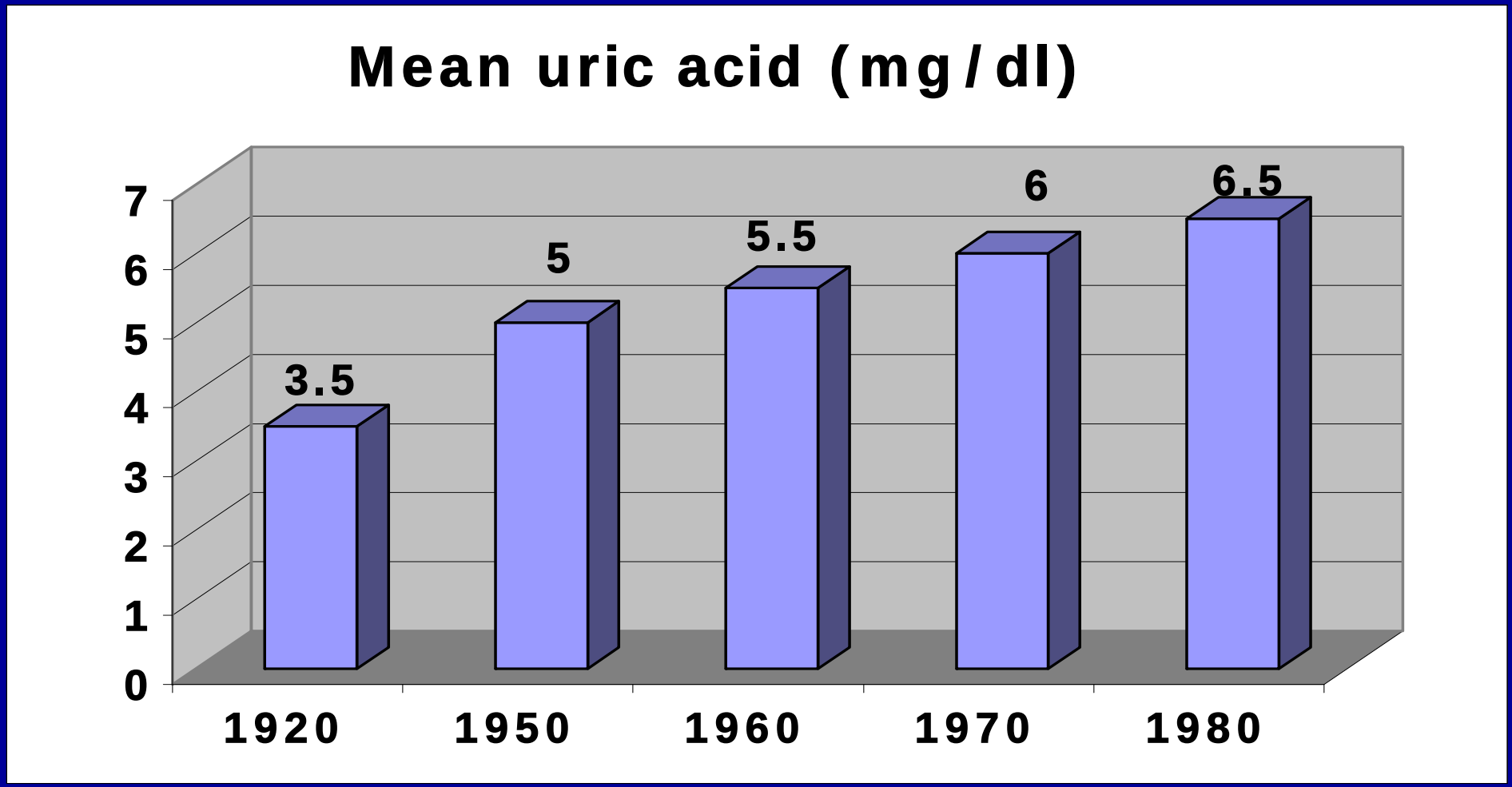
Could Uric acid have a role in the Epidemic of Hypertension?

Hypertension is Increasing



Johnson et al Am J Clin Nutr 86:899-906, 2007

The Gout Epidemic



Patterns of Food Intake in the USA

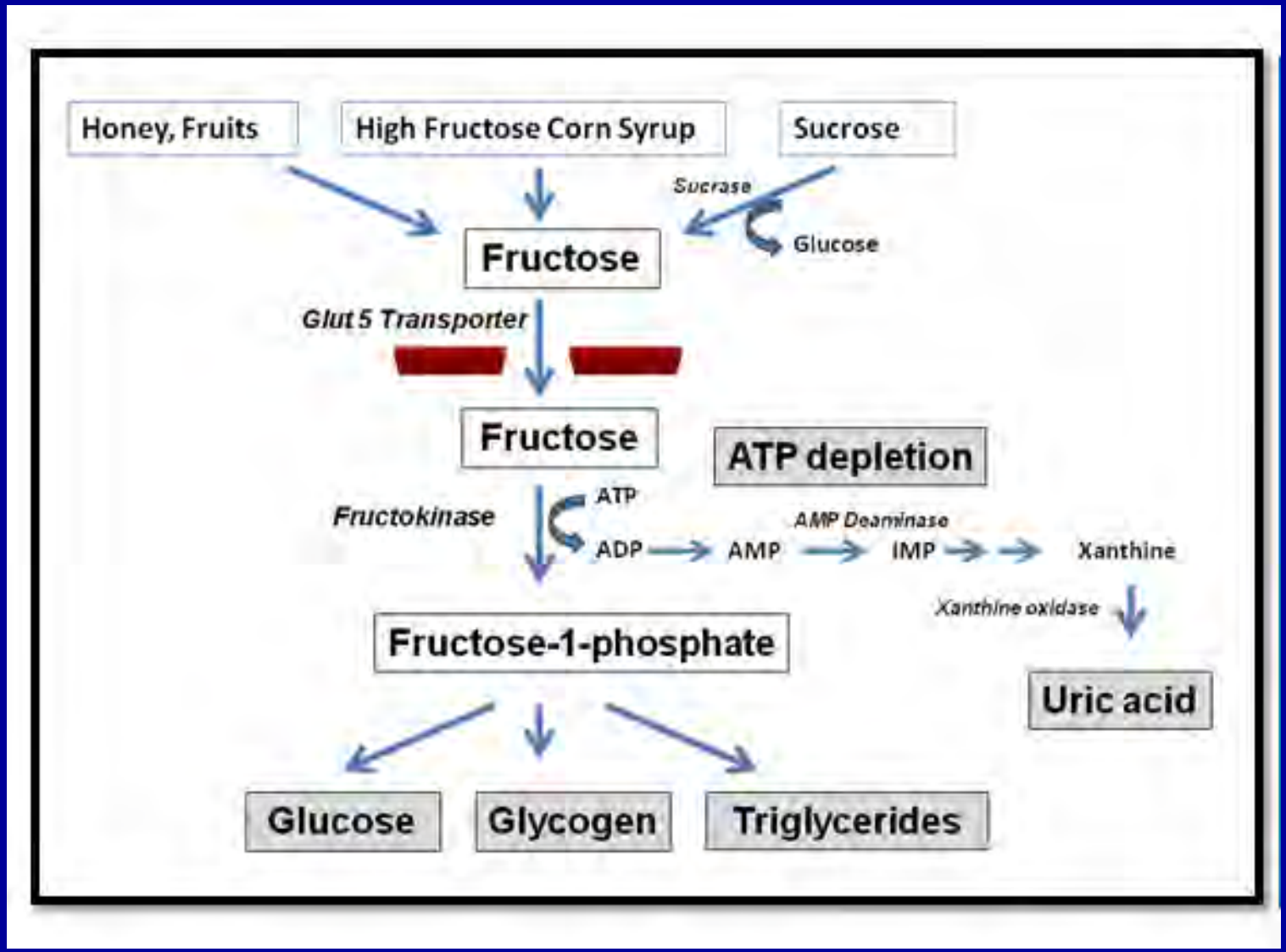
	1980	*1990*	*2000*
RED MEAT (lbs)	*126*	*112*	*114*
MILK (gallons)	*27.6*	*25.7*	*22.5*
SWEETENERS (lbs)	*123*	*132*	*149*
Sugar	*84*	*64*	*64*
High Fructose corn syrup	*19*	*50*	*63*
Fructose (total)	***52***	***57***	***64***

US Census Bureau, Statistical Abstract of the US, 2003, no 214

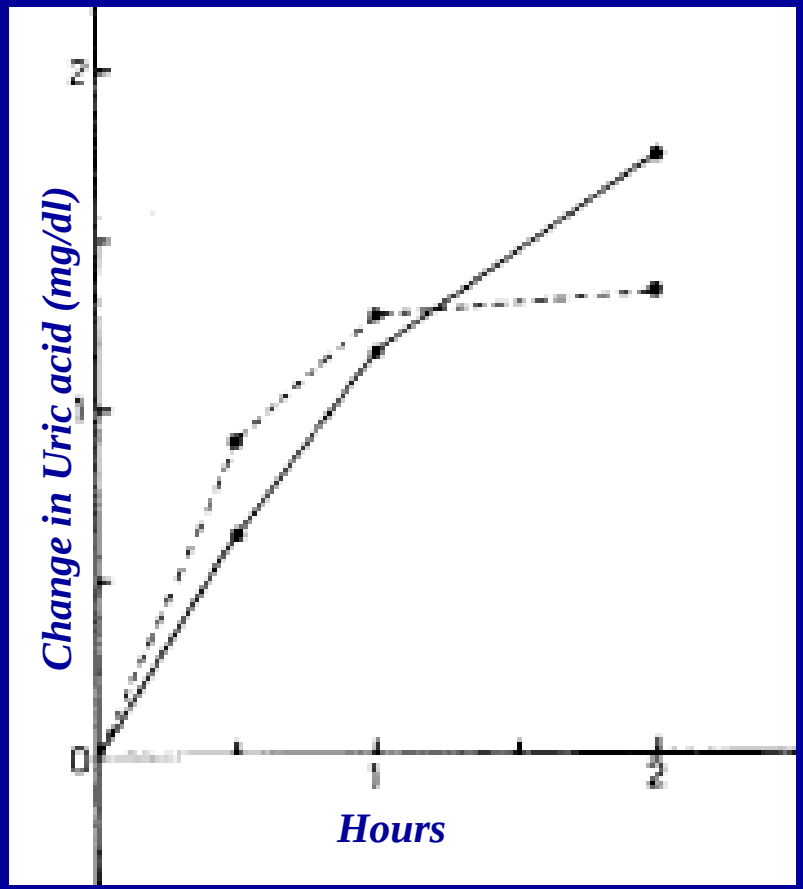
Sugar and Fructose

- **Sugar (sucrose)** consists of a disaccharide of glucose and fructose
- **High fructose corn syrup** (HFCS) is a mix of 55% fructose and 45% glucose
- Fructose and to a lesser extent, sucrose, are also present in honey and fruit (especially fruit juices and dried fruits)

Fructose Metabolism



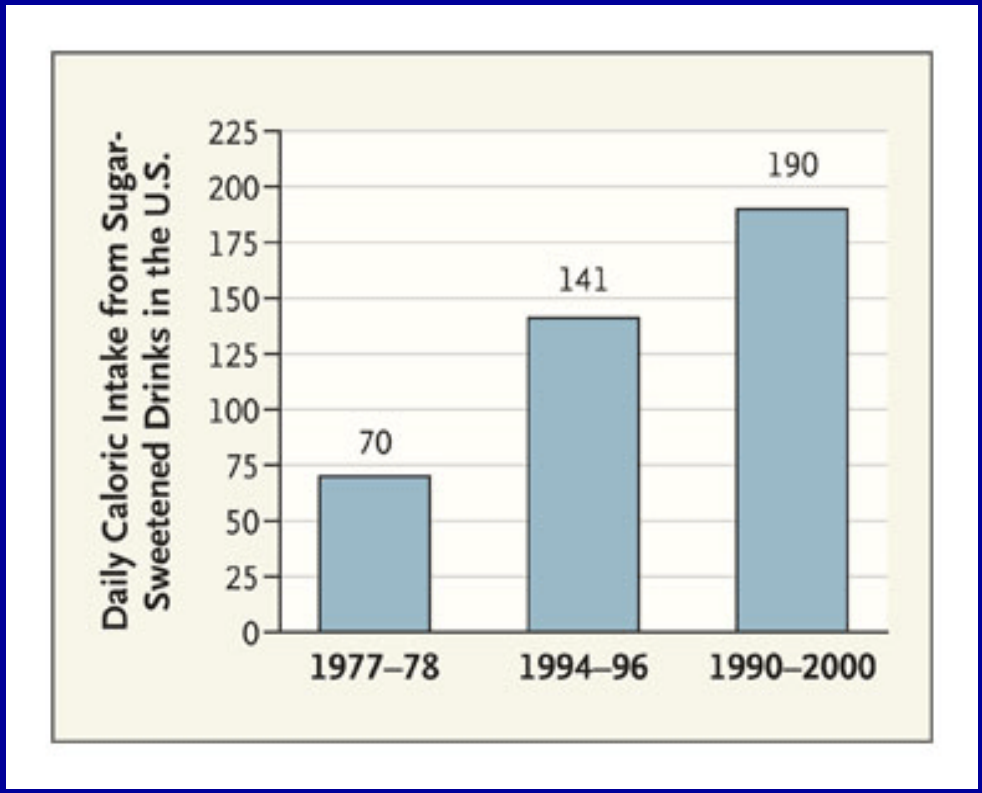
Fructose Acutely Increases Serum Uric Acid



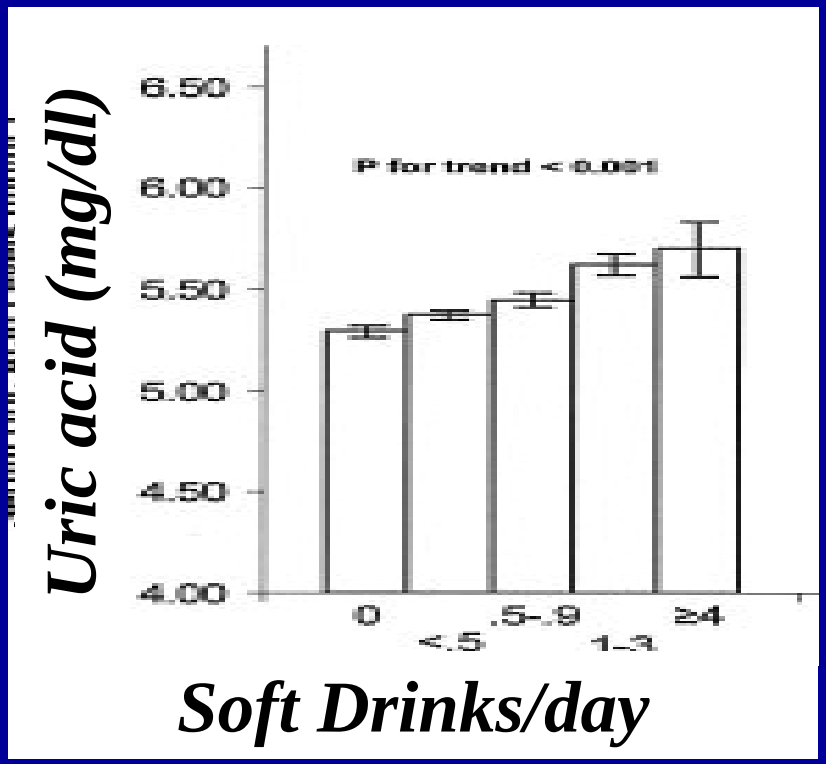
Fructose (1 g/kg body wt) increases serum uric acid within 30 minutes

Lancet 1970; 2:1310-1311

Soft Drink Consumption is Increasing



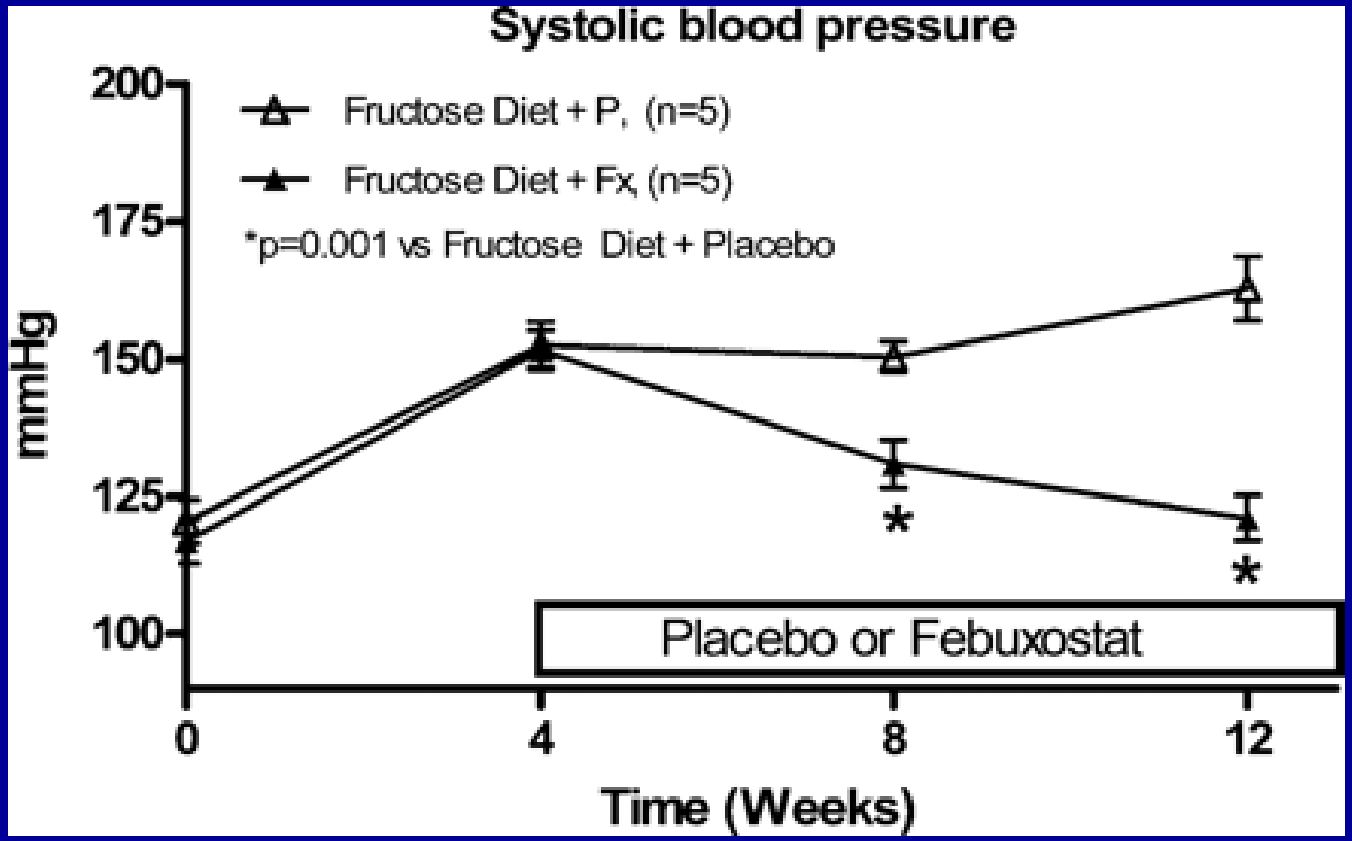
Nielsen and Popkin
Am J Prev Med 2004; 27:205-210



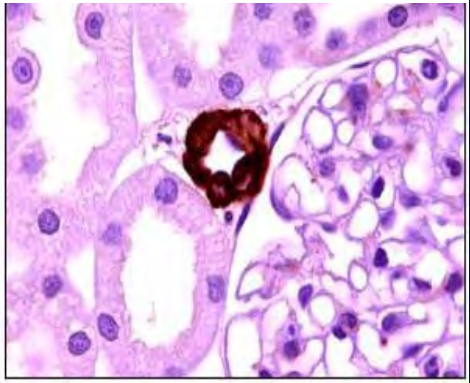
Third National Health and Nutrition Exam Survey
Choi et al Arth Rheum 2008; 59:109-16

Could Sugar be a True Risk Factor for Hypertension?

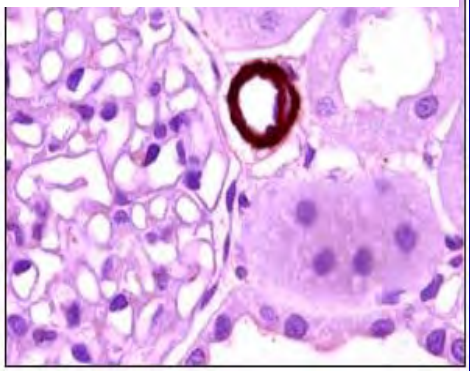
Fructose Induced Hypertension is Improved with Xanthine oxidase inhibitor (Febuxostat)



Fructose

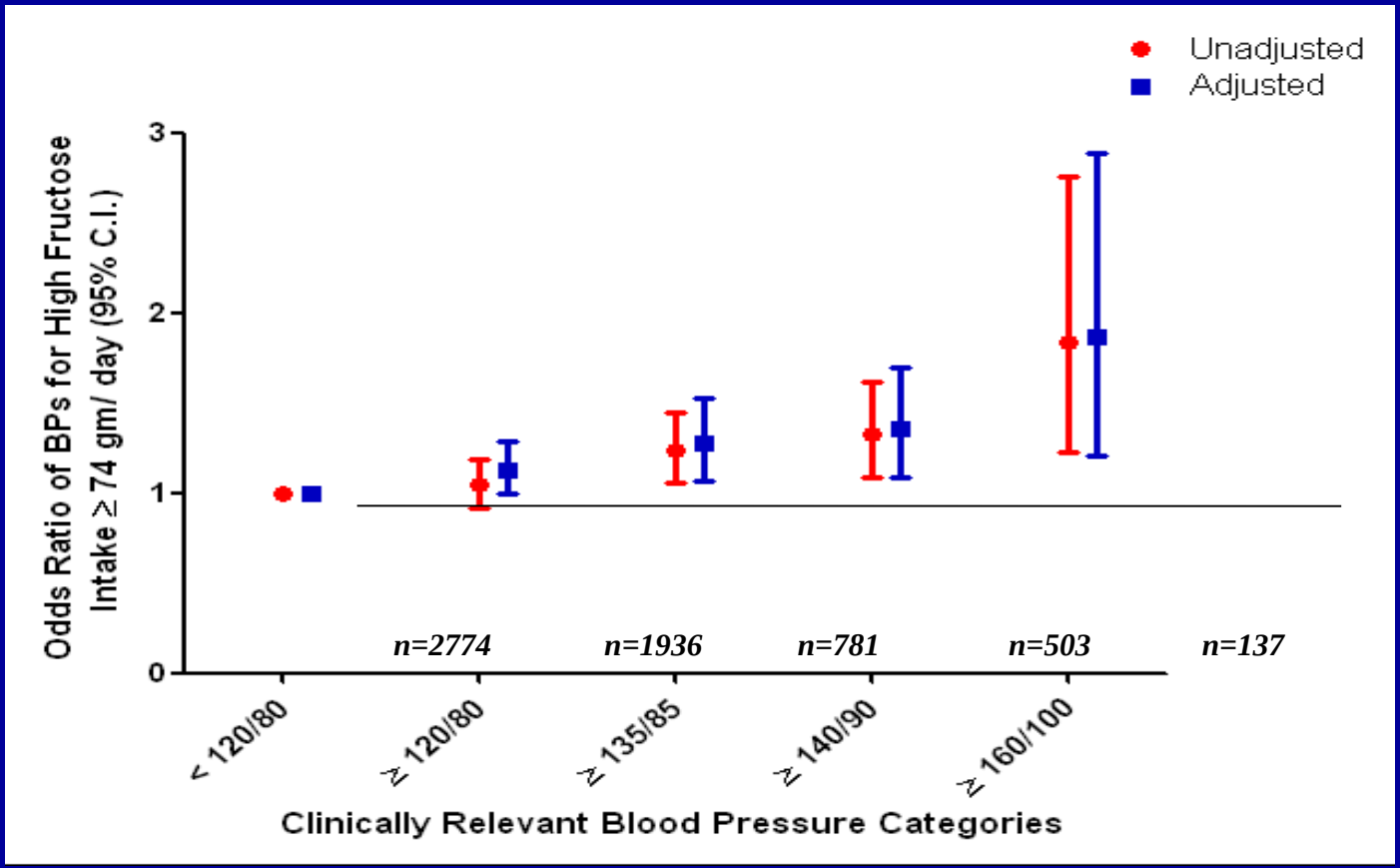


Fructose + Febuxostat



Sanchez-Lozada et al, Am J Physiol 2008; 294: F710-F718

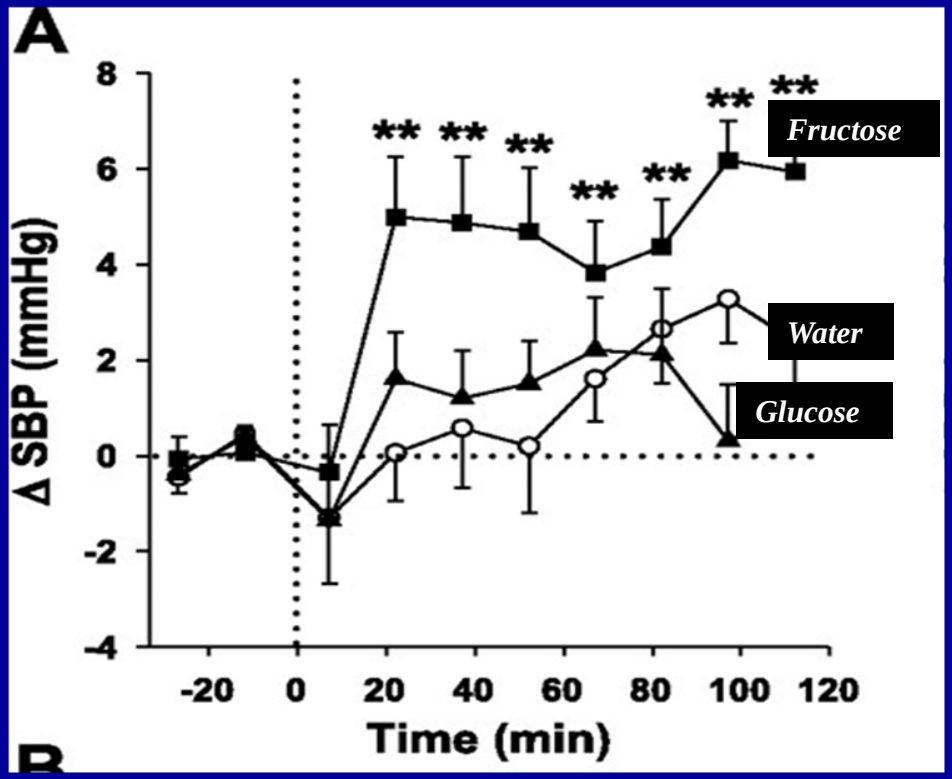
High Fructose Intake from Added Sugars is associated with Increased Risk of Elevated BP

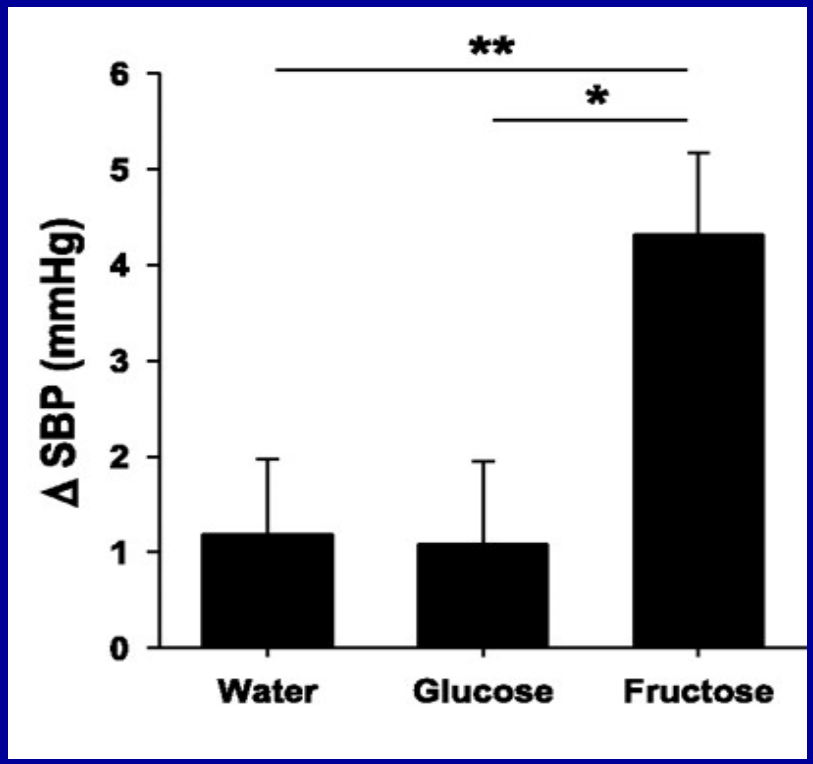


Risk for elevated BP in those with high (>74 g/d) vs low fructose (<74 g/d) intake in NHANES III

Jalal et al, J Am Soc Nephrol 2010; July issue

Fructose Raises Blood Pressure in Humans

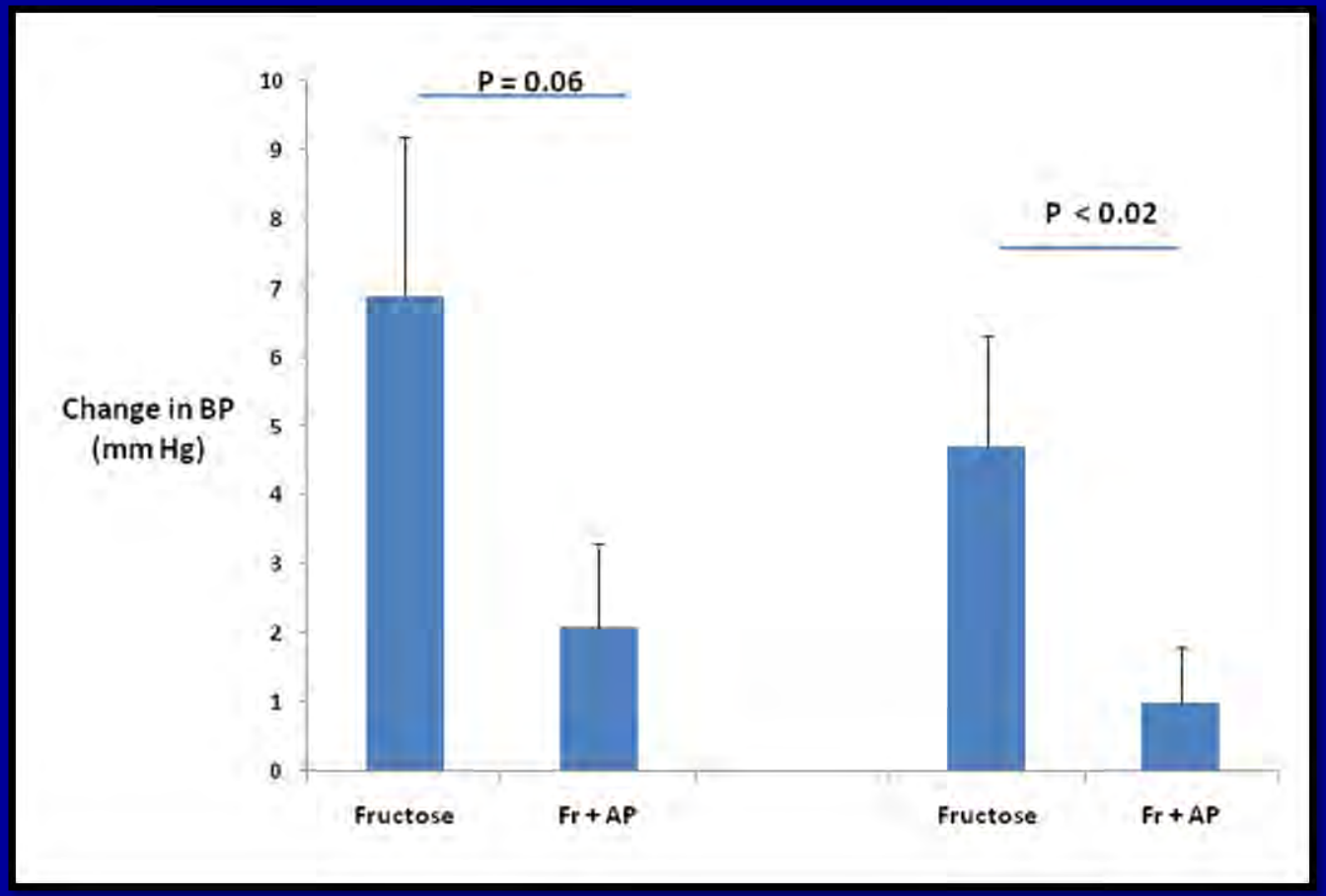




Males, 24 years old, given 60 g fructose or glucose

Brown, C. M. et al. Am J Physiol Regul Integr Comp Physiol 294: R730-R737 2008;

Fructose-induced Ambulatory BP Rise is blocked by Allopurinol



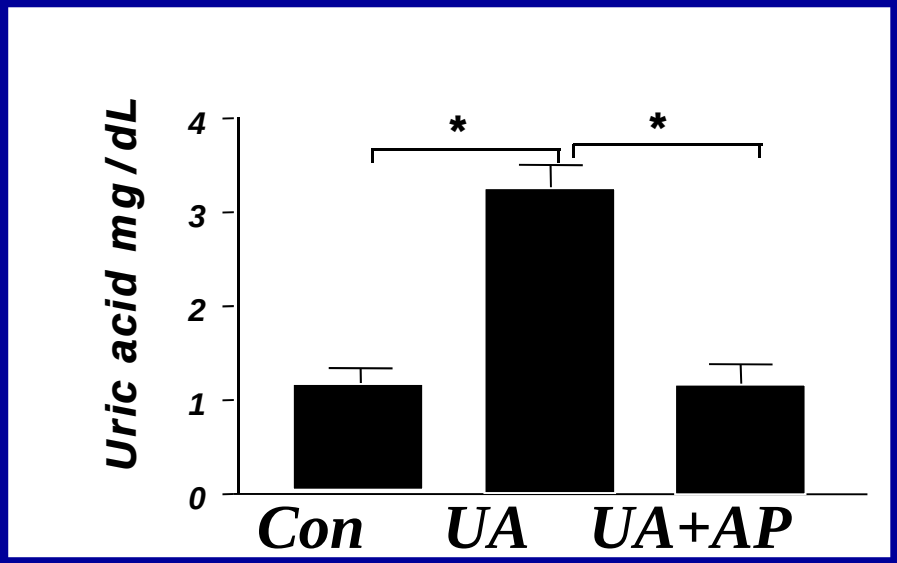
74 men randomized to fructose (200g/d) or fructose plus allopurinol for two weeks

Perez-Pozo et al Int J Obesity 2010; 34: 454-61

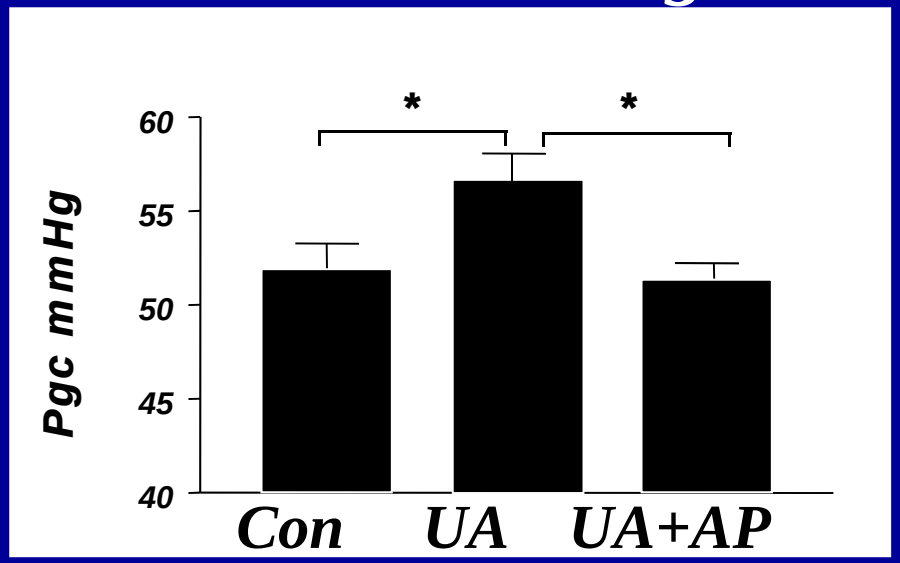
What is the Role of Uric acid in Renal Disease?

Hyperuricemia Causes Glomerular Hypertension in Rats

Uric Acid

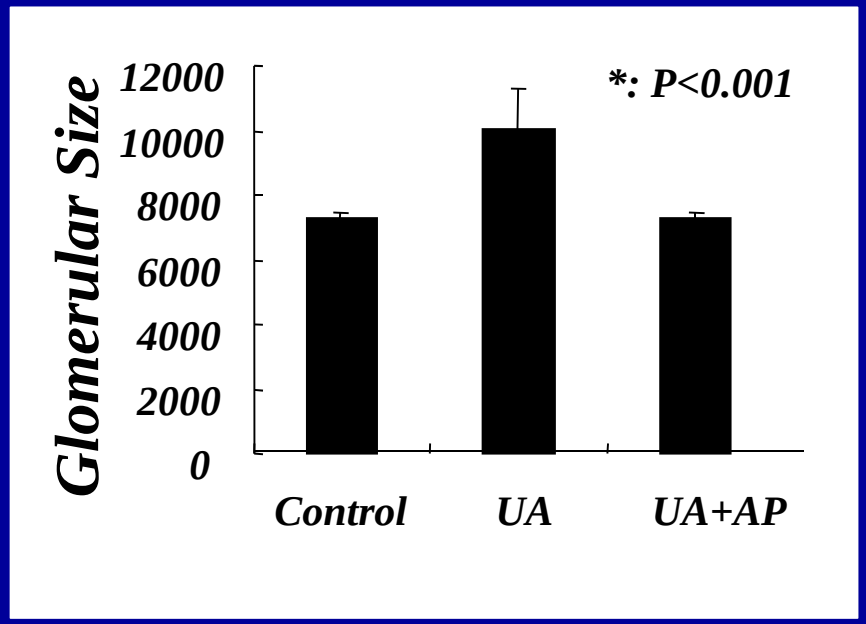


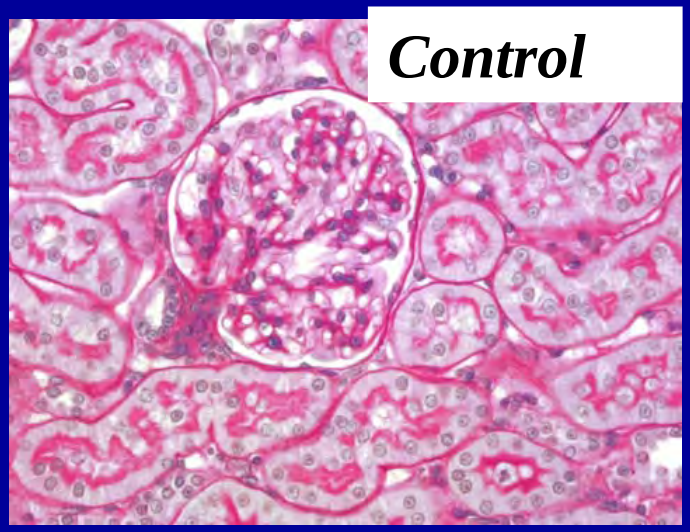
Glomerular Pgc

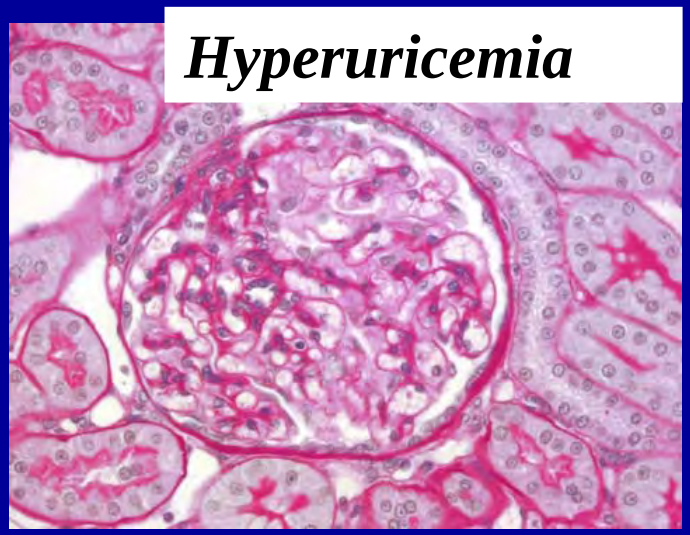


Sánchez-Lozada LG, et al. Am J Physiol Renal 2002; 283:F1105

Hyperuricemia Causes Glomerular Hypertrophy

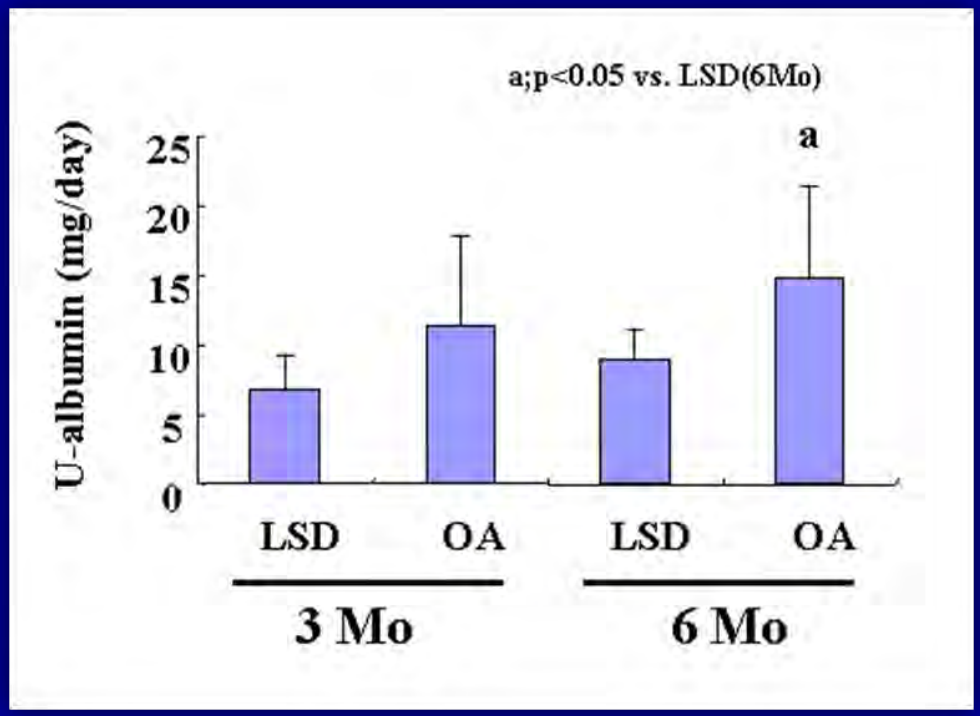


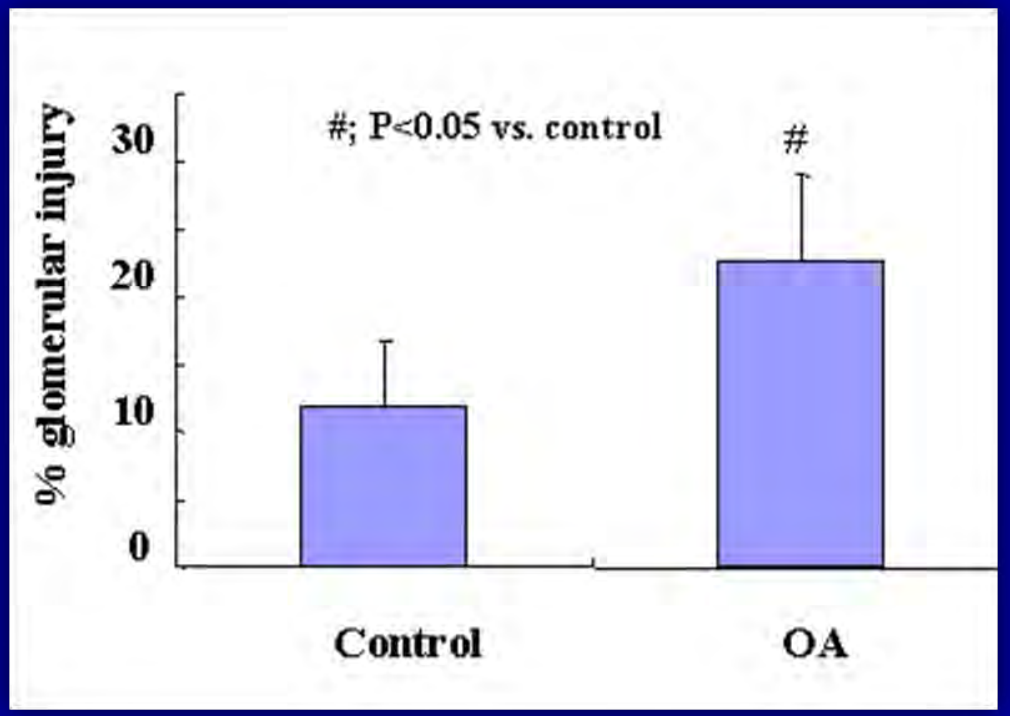


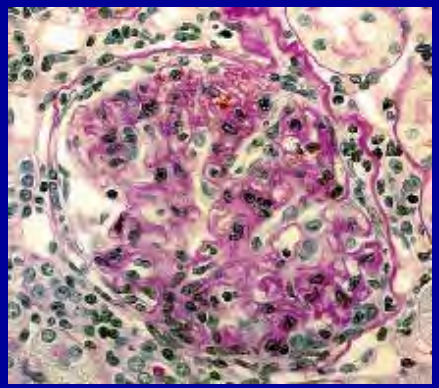


Nakagawa et al, Am J Neph 2003; 23:2-7

Hyperuricemia Causes Glomerulosclerosis

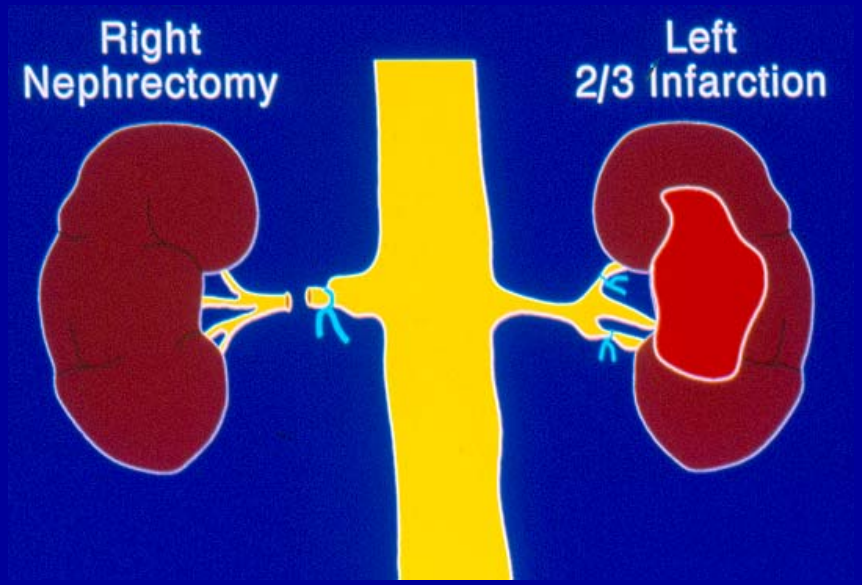






Nakagawa et al, Am J Neph 2003; 23:2-7

Role of Uric acid in Renal Progression

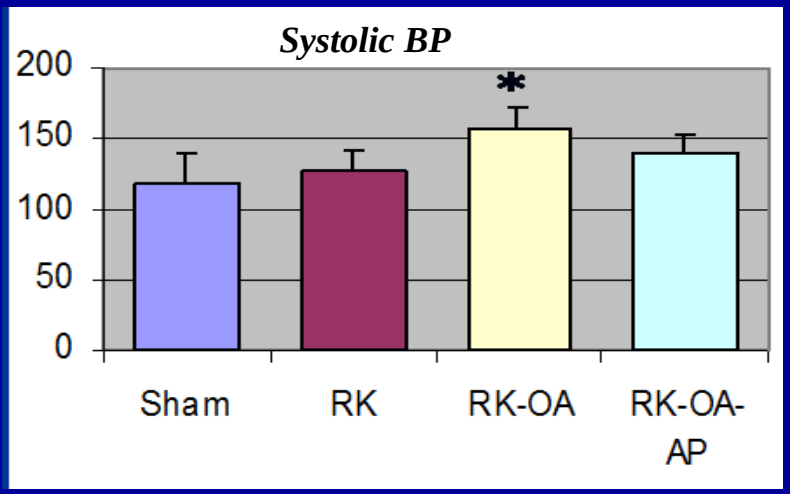


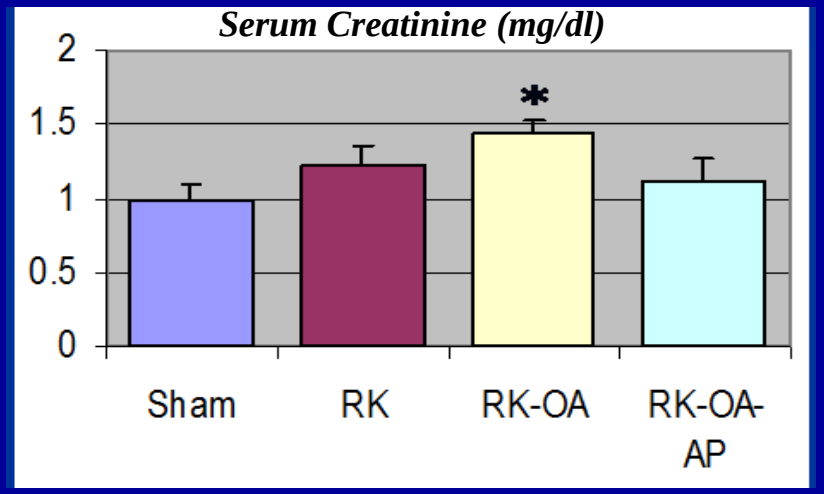
Groups:

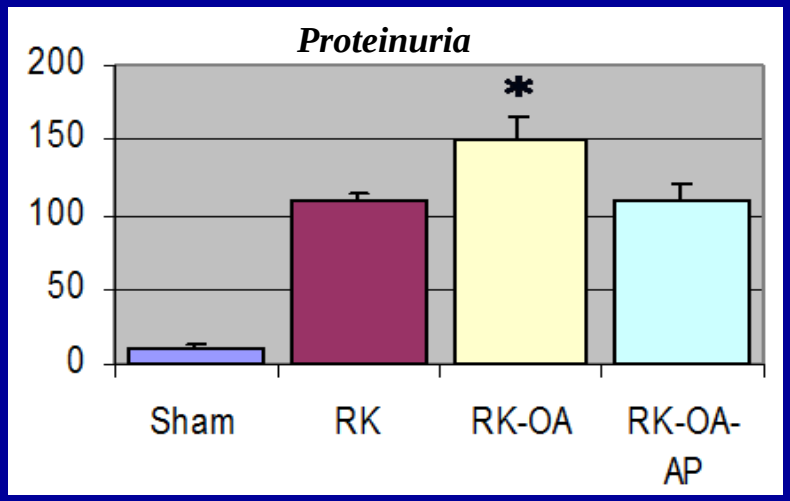
- ***Sham***
- ***Remnant Kidney (RK)***
- ***RK + Hyperuricemia (RK-OA)*** ***(induced by the uricase inhibitor, oxonic acid)***
- ***RK –OA and Allopurinol (RK-OA-AP)***

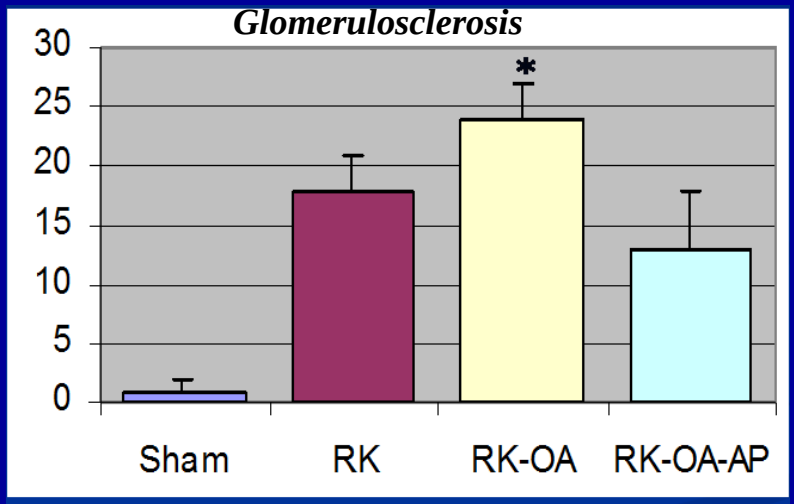
Kang et al, J Am Soc Nephrol 2002; 13:2888-97

Role of Uric acid in Renal Progression



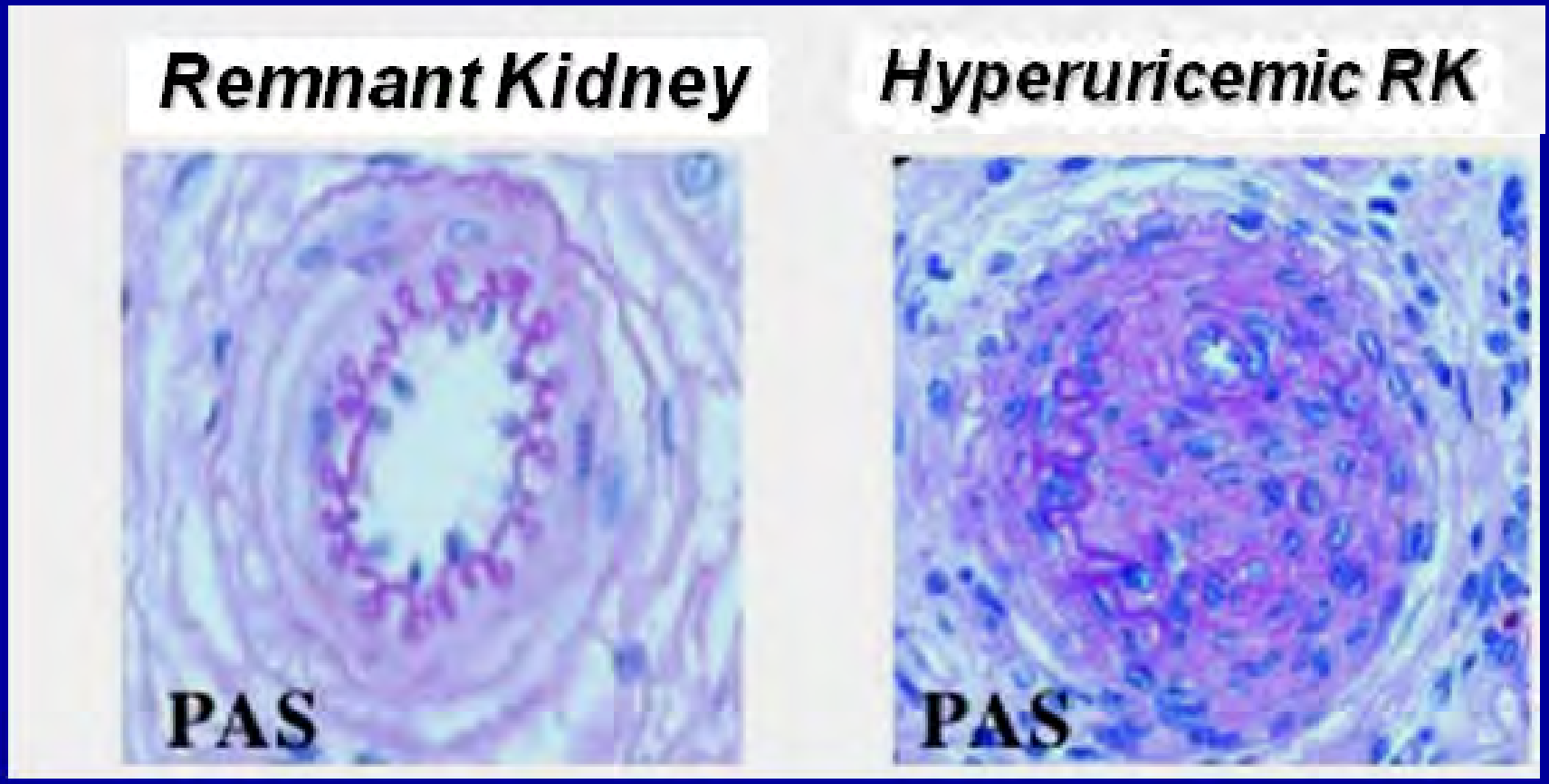






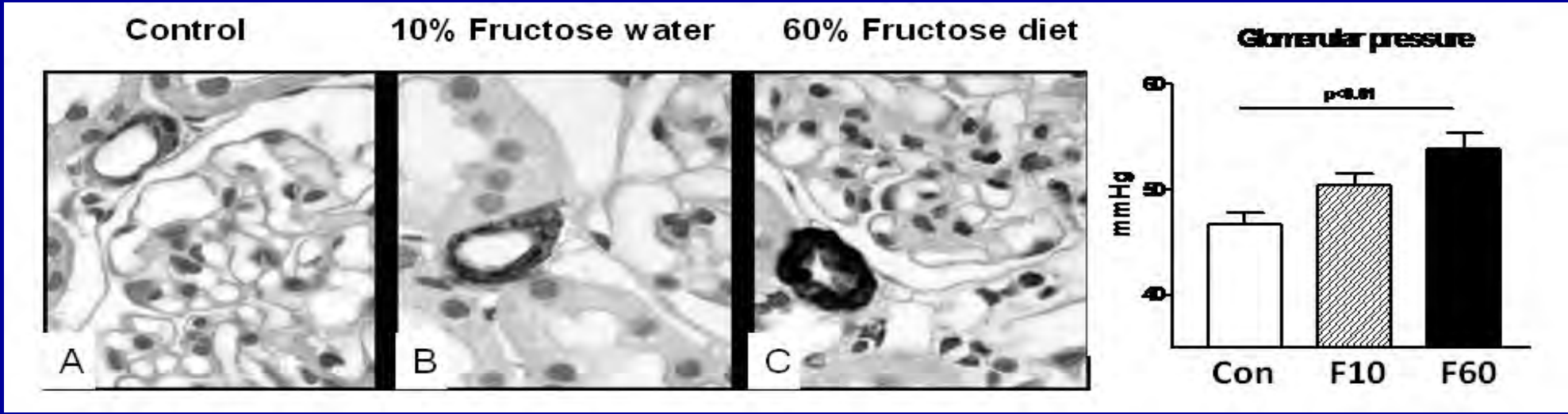
Kang et al, JASN 2002; 13:2888-97

Hyperuricemia Induces Vascular Disease in Rats with Kidney Disease



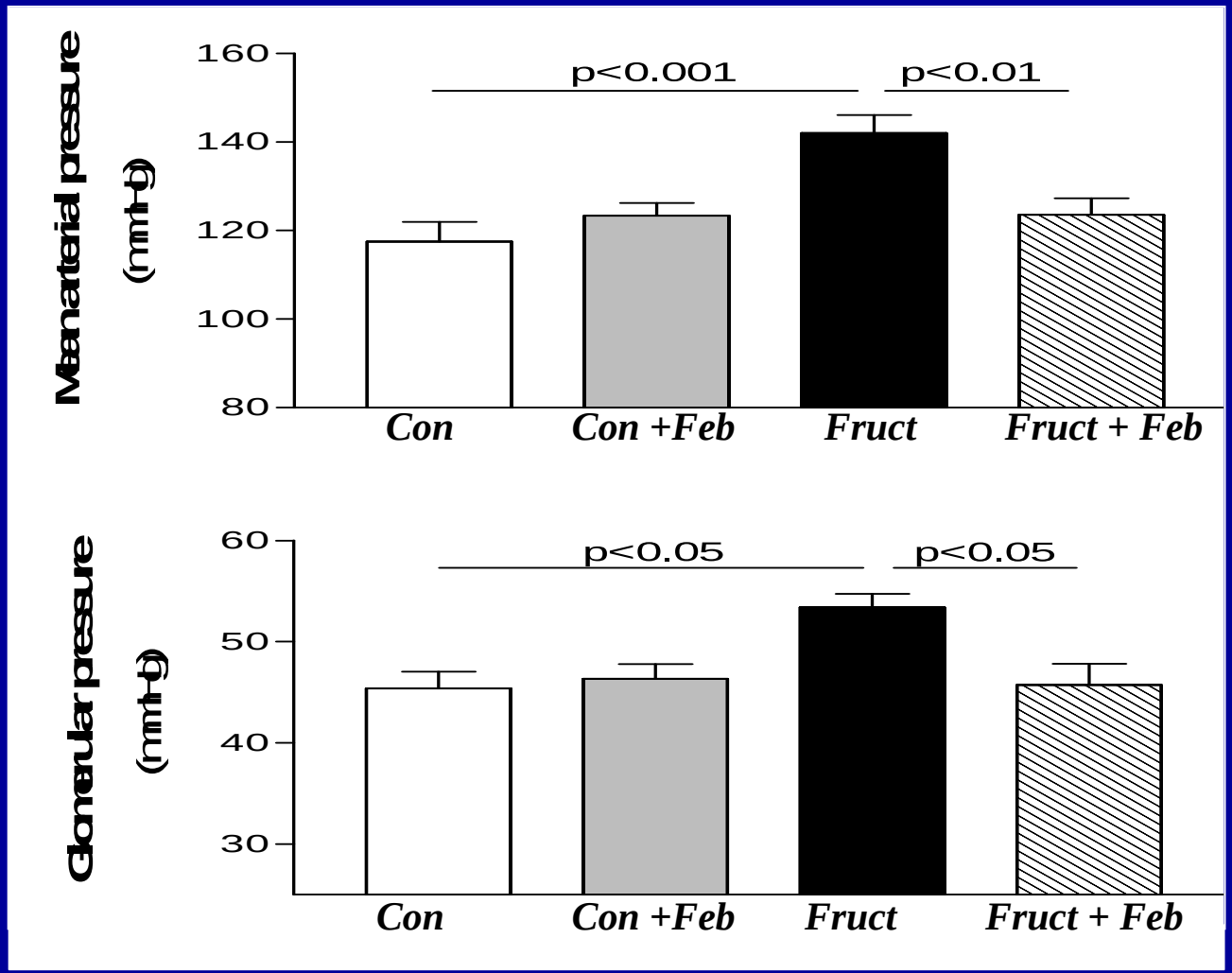
Kang et al, J Am Soc Nephrol 2002; 13:2888

Fructose Induced Renal Microvascular Disease and Glomerular Hypertension



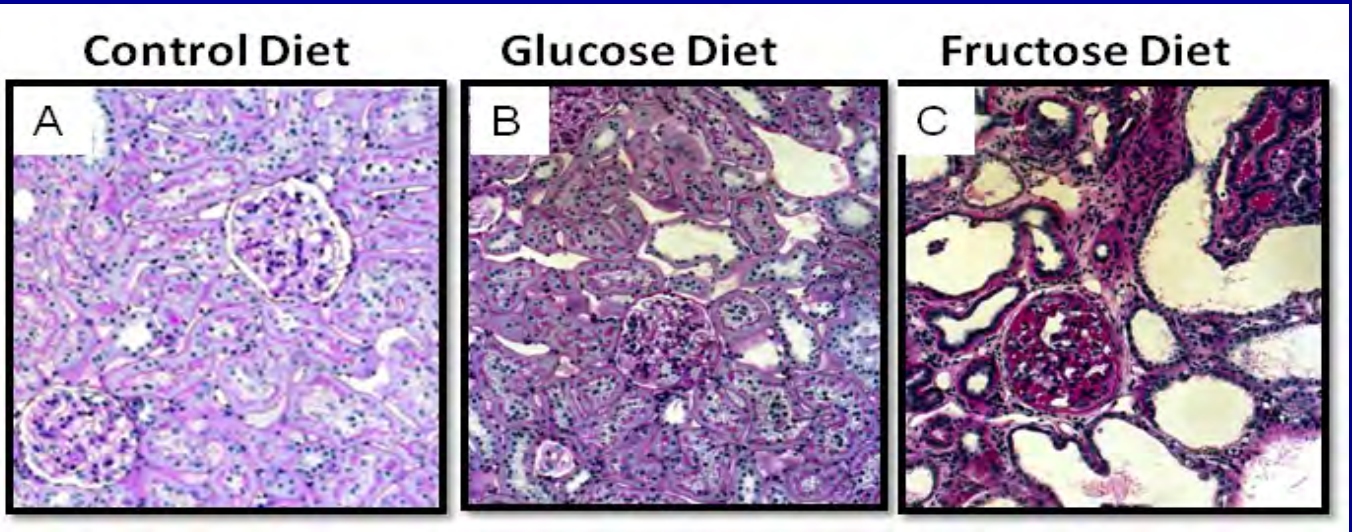
Sanchez-Lozada et al, Am J Physiol 2008; 294: F710-F718

Fructose-induced Hyperuricemia causes Systemic and Glomerular Hypertension



Sanchez-Loazada et al, Am J Physiol 2008; 294: F710-8

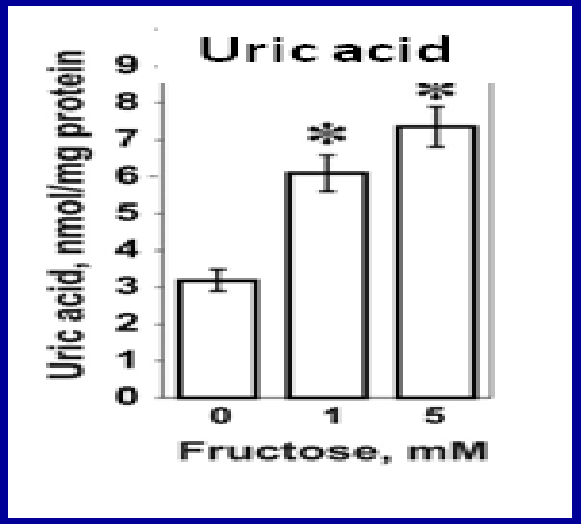
Fructose Accelerates Renal Disease in the Remnant Kidney

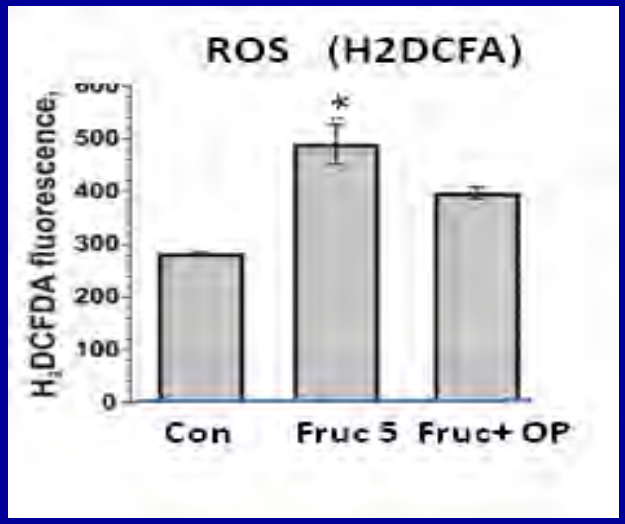


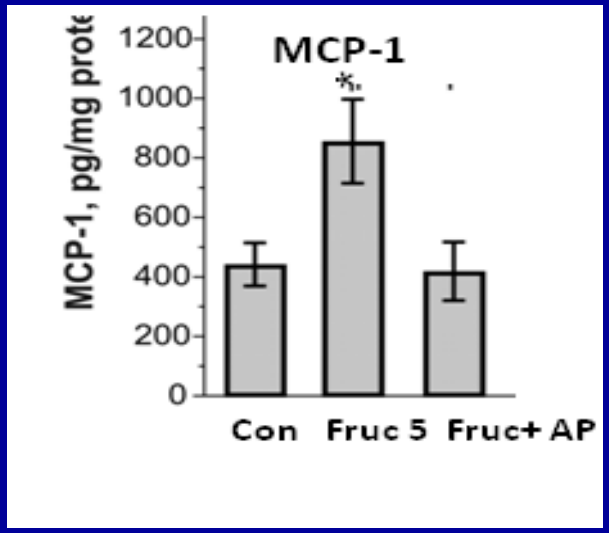
Diet	Proteinuria, mg/dl	$C_{creatinine}$, ml/min
Normal	33±5.7	1.23±0.04
Glucose	35±7.5	1.16±0.08
Fructose	73±15.4*	0.96±0.08*

Gersch et al Am J Physiol 2007; 293:F1256-61

Fructose Induces Inflammation in the Proximal Tubule

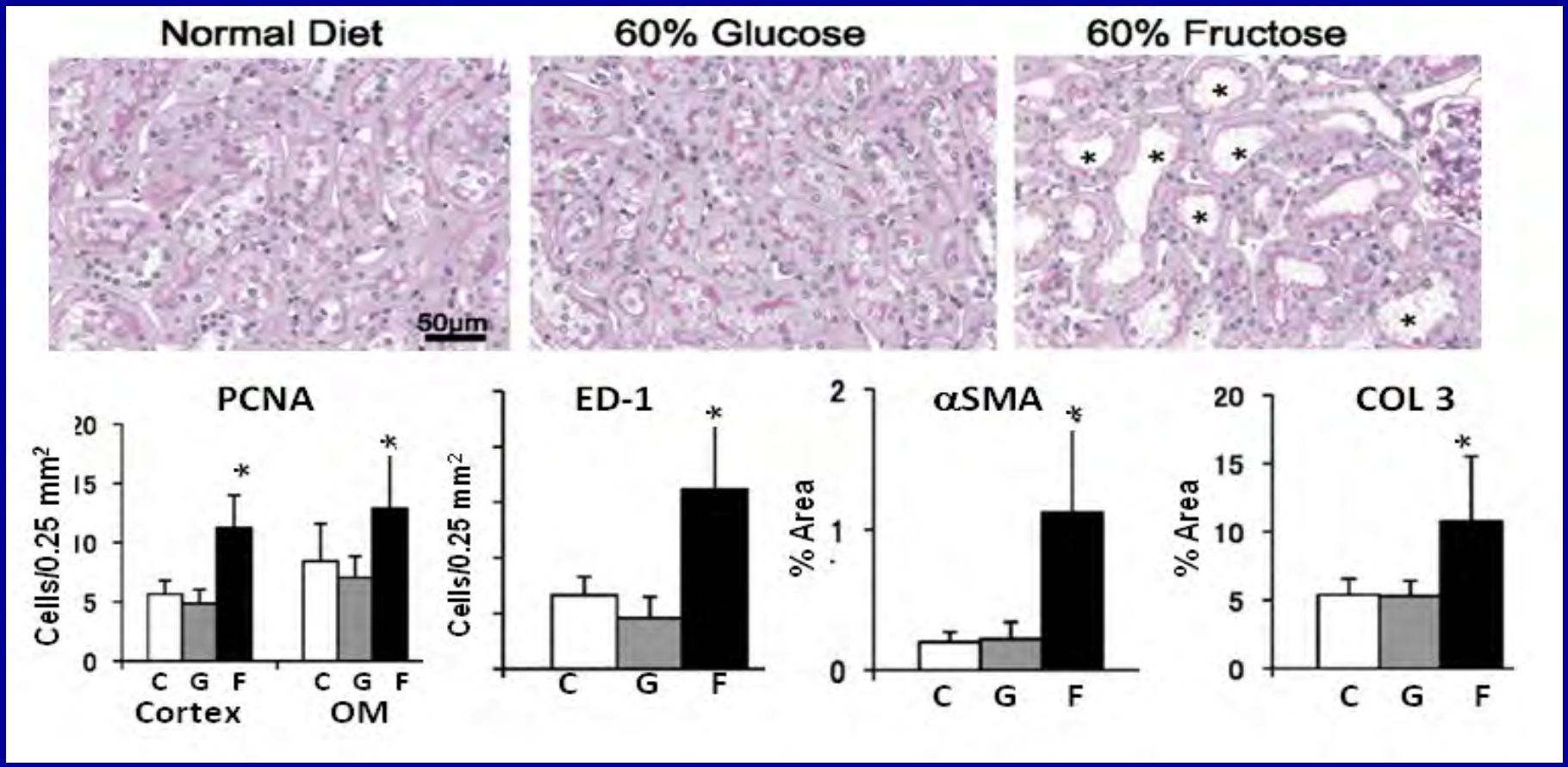






Cirillo et al , JASN 2007

Fructose causes Tubular injury in the Rat



Nakayama T. et al Am J Physiol Renal 2010; 298 : F712-20

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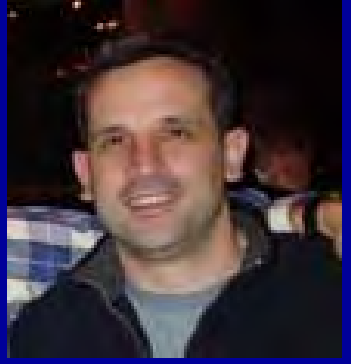

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