

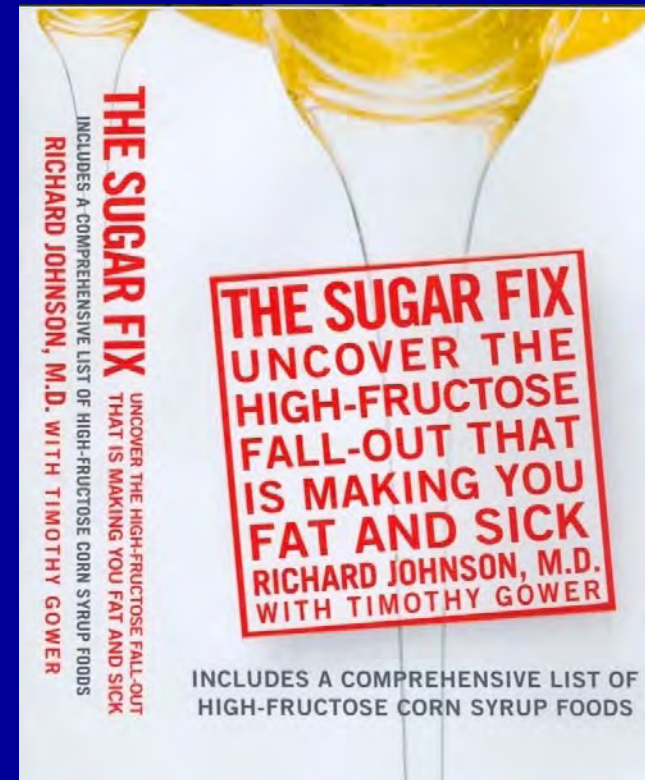
Role of Fructose in Metabolic Syndrome and Renal Disease

Richard J Johnson MD

Division of Nephrology, Hypertension and Transplantation
U of Colorado

Disclaimers:

*Dr Johnson is an inventor on several **patent applications** related to the lowering of uric acid or the inhibition of fructose metabolism as a means to prevent and treat obesity related diseases*



Obesity: An Ever Expanding Problem



Obesity: An Ever Expanding Problem

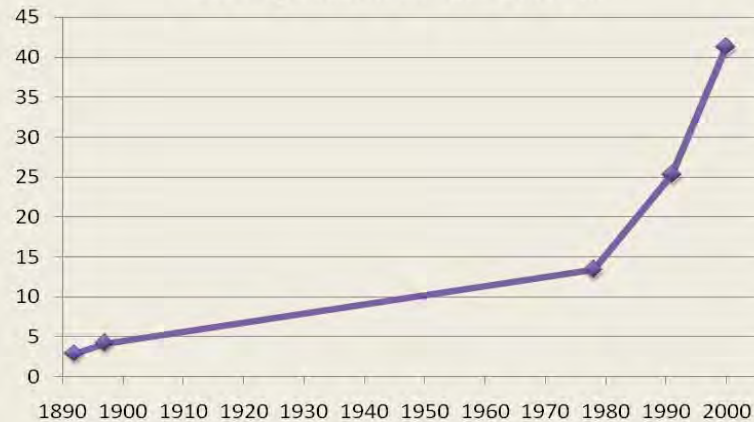


The Precursor to Diabetes: Metabolic Syndrome

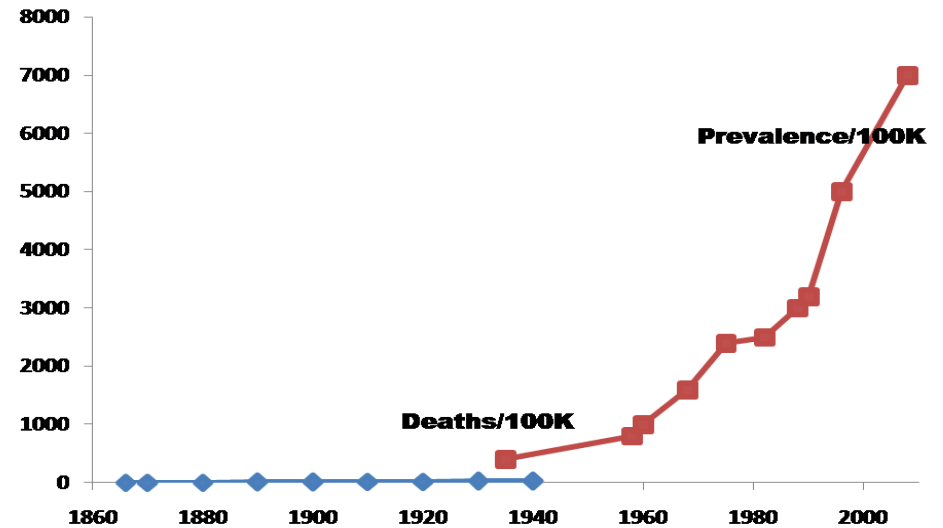
- **Truncal obesity**
- **Impaired fasting glucose (insulin resistance)**
- **Elevated triglycerides**
- **Low HDL cholesterol**
- **Elevated blood pressure**
- Other (Fatty Liver, elevated uric acid, microalbuminuria, elevated CRP, endothelial dysfunction, oxidative stress)

Incidence and Prevalence of Obesity and Diabetes in the U.S.

Obesity Rates in 60-Year-Old Men



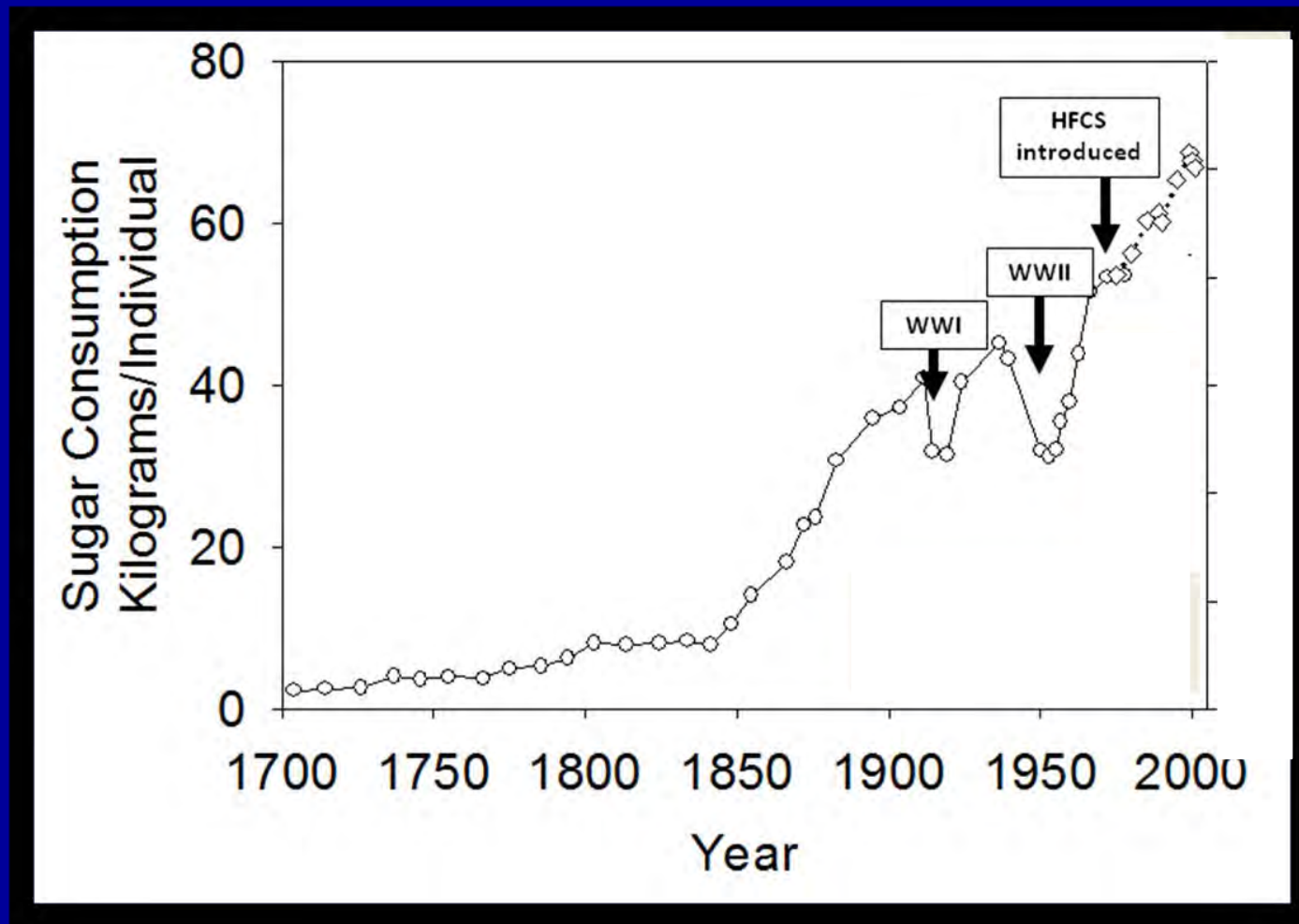
Diabetes / 100 thousand population



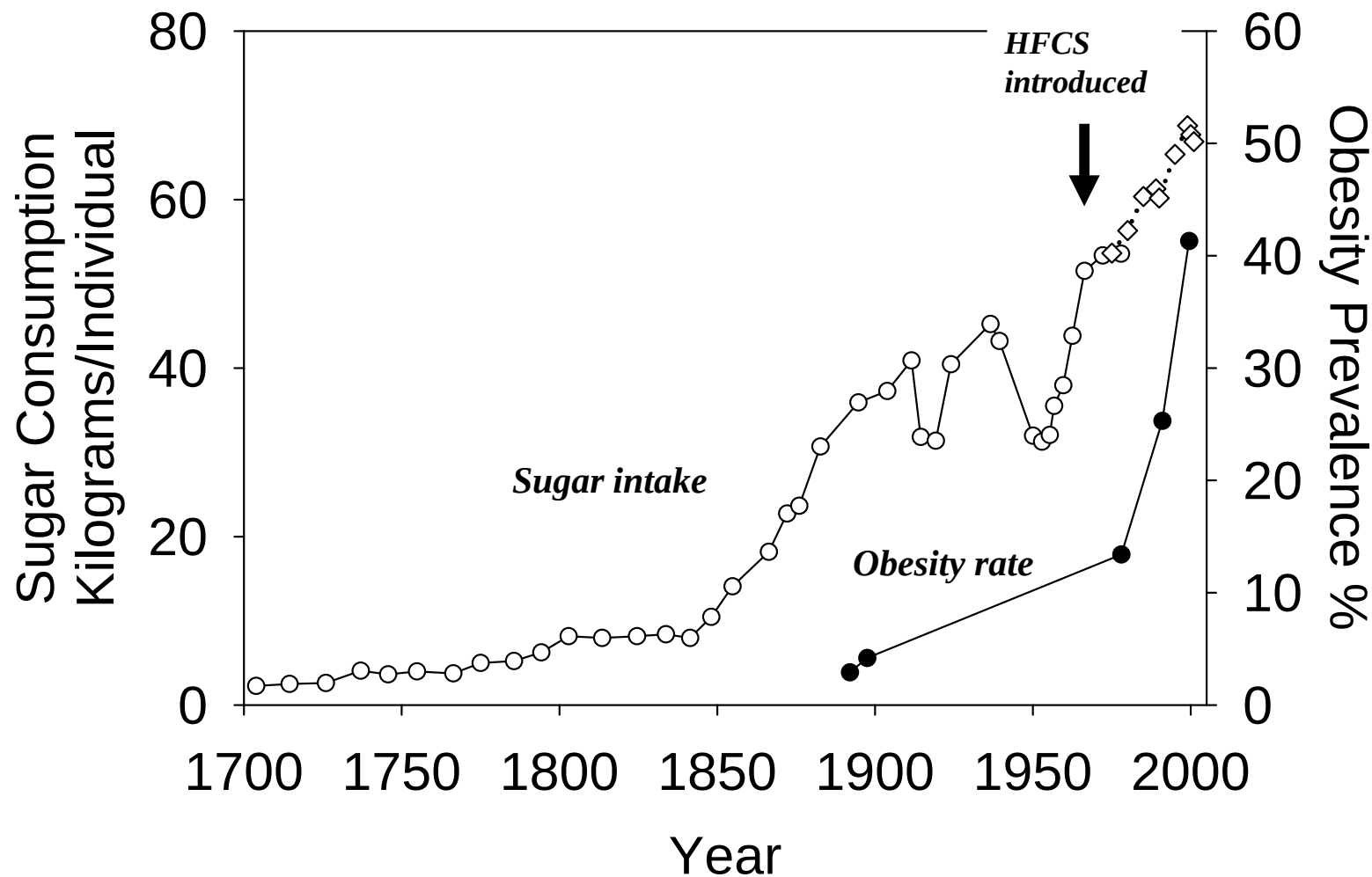
Sugar and Fructose

- **Sugar (sucrose)**: a disaccharide of glucose and fructose
- **High fructose corn syrup (HFCS)**: 55% fructose and 45% glucose as monosaccharides
- **Fructose** is also present in honey and fruit (especially fruit juices and dried fruits)

A Potential Role for Sugar in the Obesity Epidemic?



Sugar Intake Correlates with Obesity



Sugar intake per year

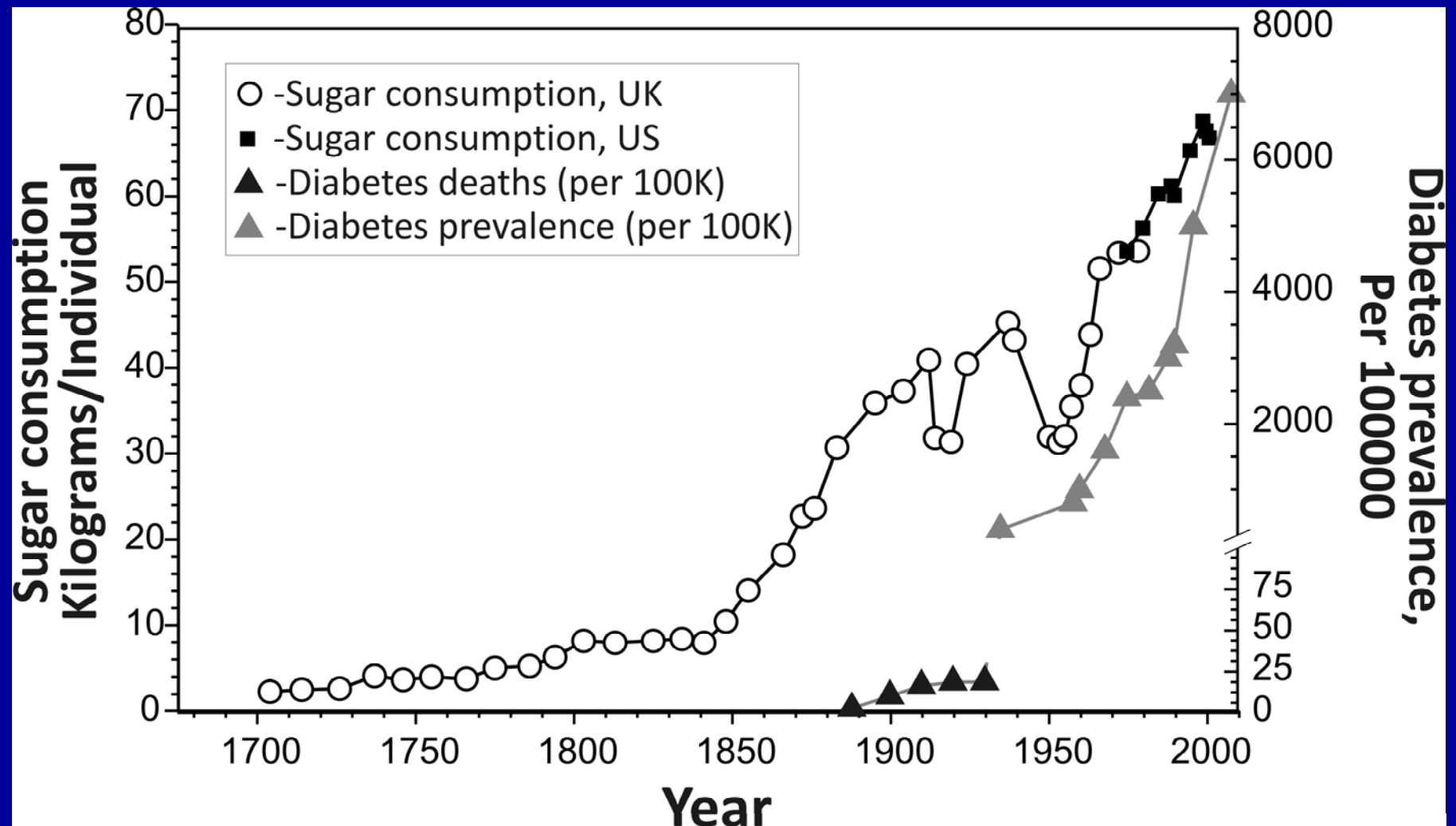
1700 4 lbs

1800 18 lbs

1900 90 lbs

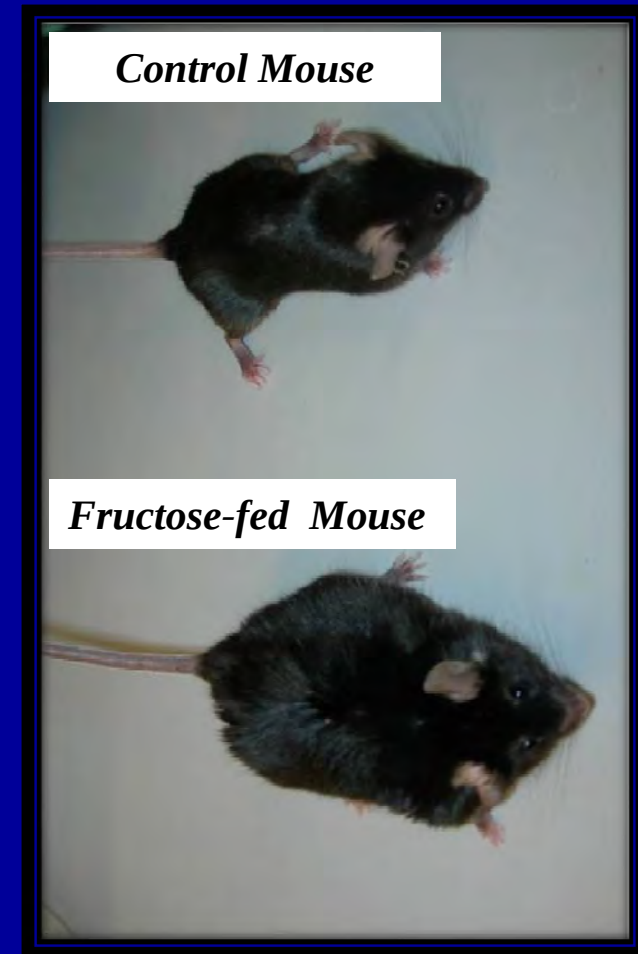
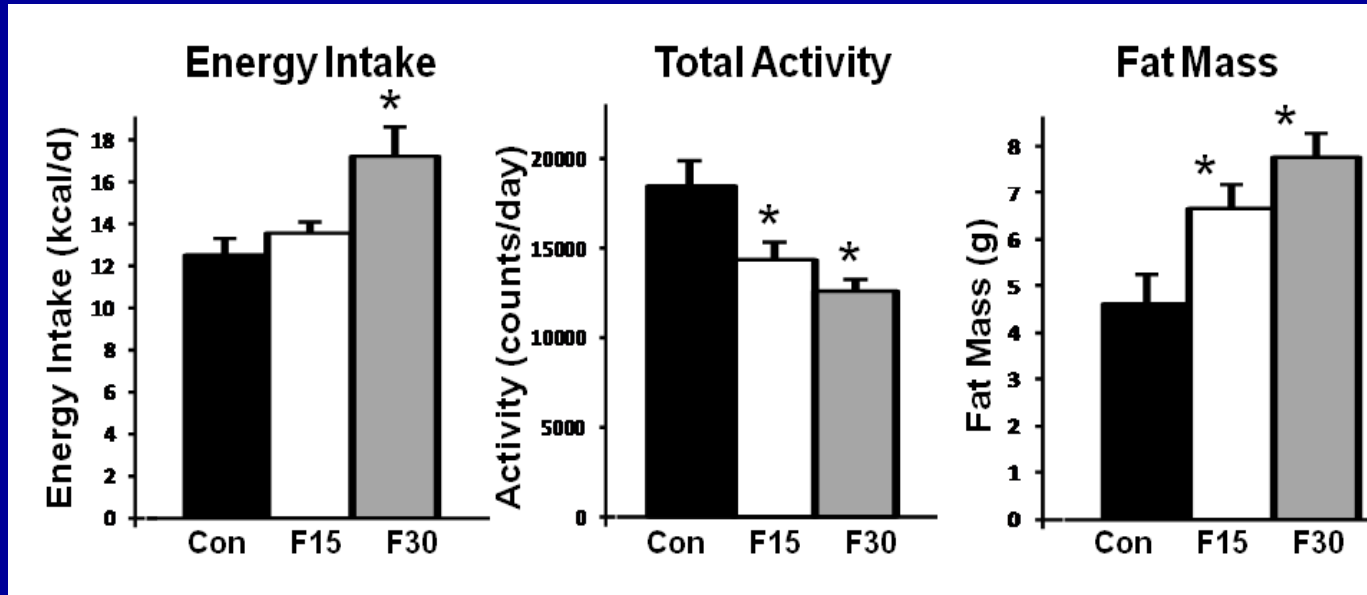
2000 155 lbs

Sugar Intake Correlates with Diabetes Rate



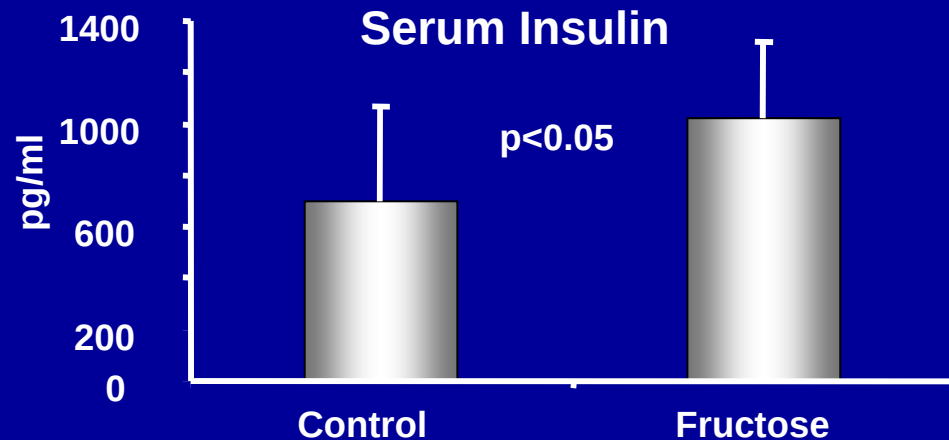
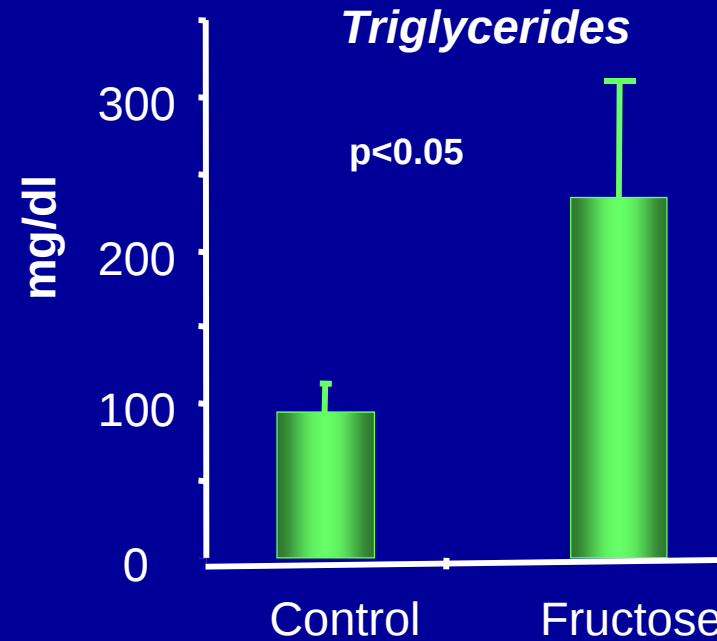
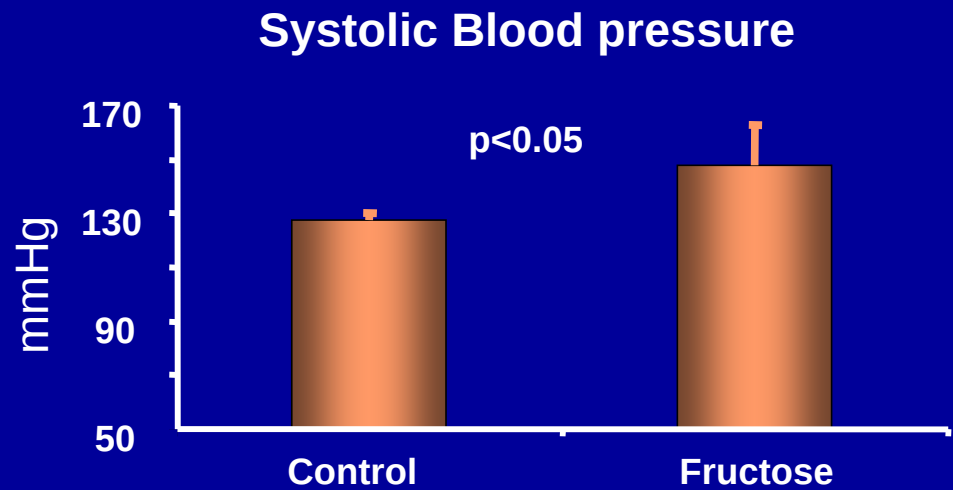
Role of Fructose in Obesity

*

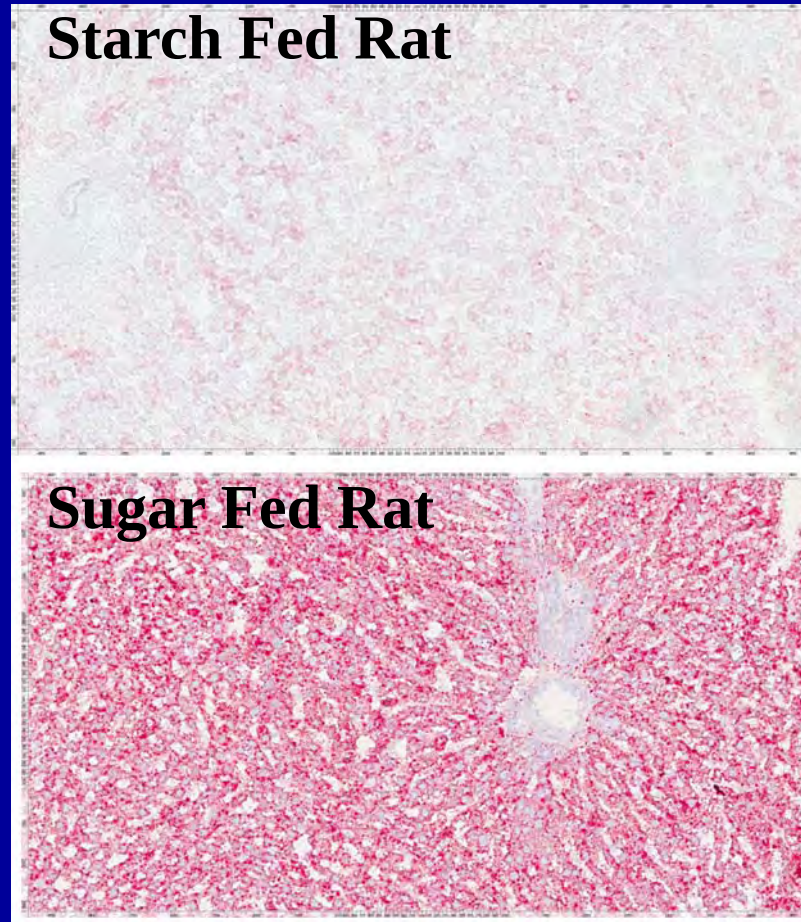


Ishimoto T, Jackman M, MacClean P, et al

Fructose Induces Metabolic Syndrome in Rats

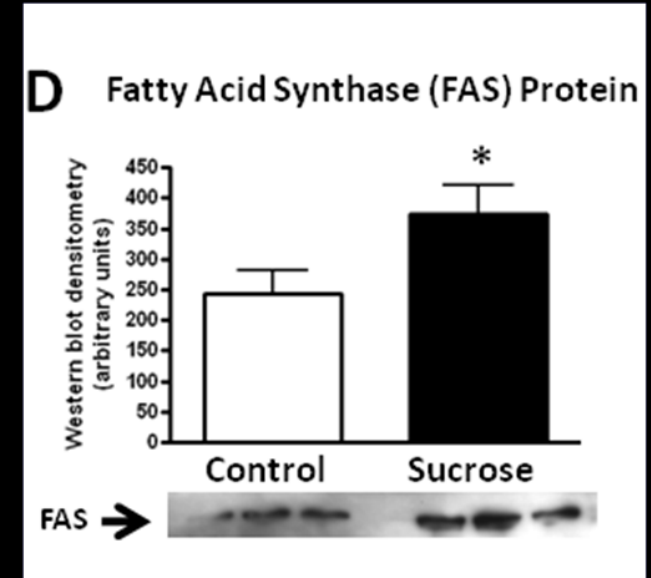


Fatty Liver Can be Induced by Sucrose Even with Caloric Restriction



Oil Red O Stain for Fat

↑ FAT SYNTHESIS

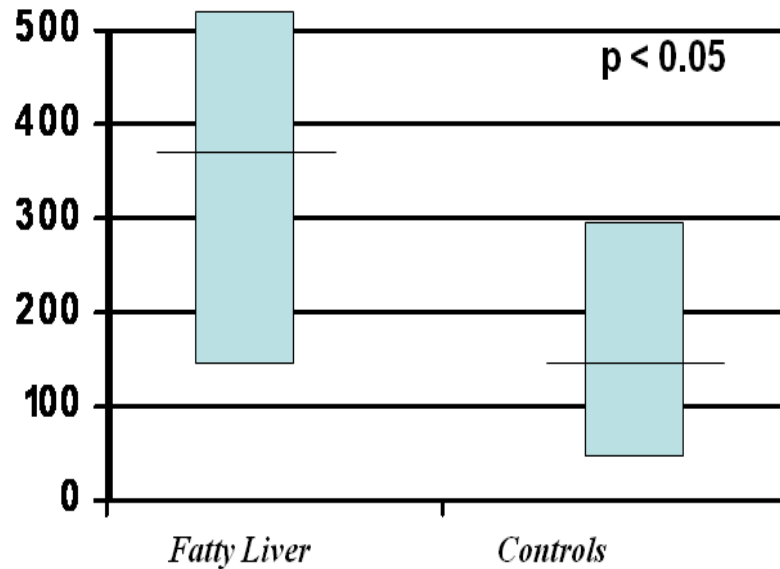


Sprague Dawley rats fed sucrose or starch diet for 4 months at 90% of normal intake

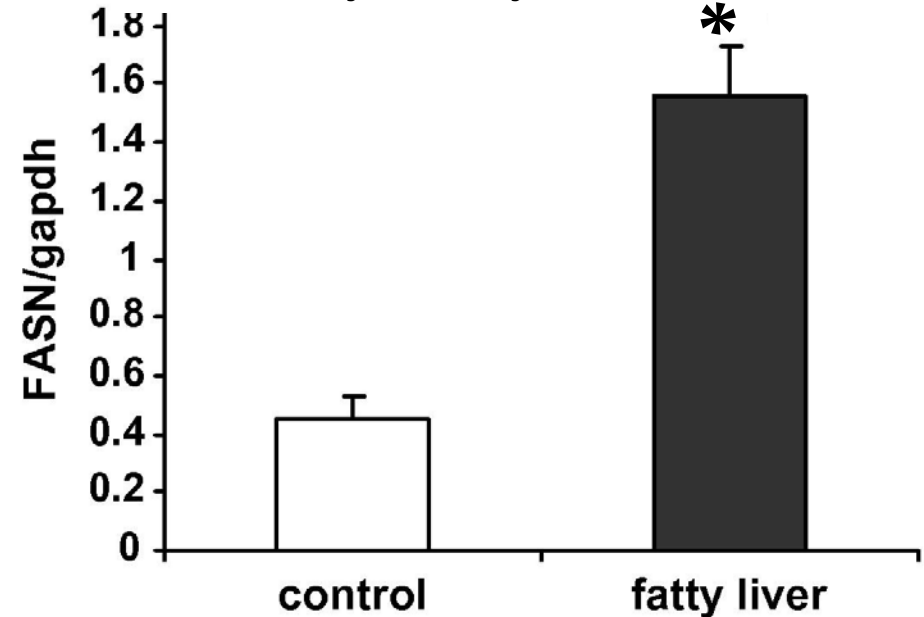
Roncal C and Lanaspa MA submitted

Fatty Liver Disease is Associated with Increased Soft drink Intake and Increased Fat Synthesis

Mean Caloric Intake Per Day from Soft Drinks

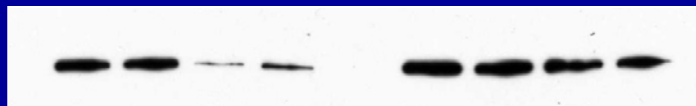


Fatty Acid Synthase



Control

Fatty Liver

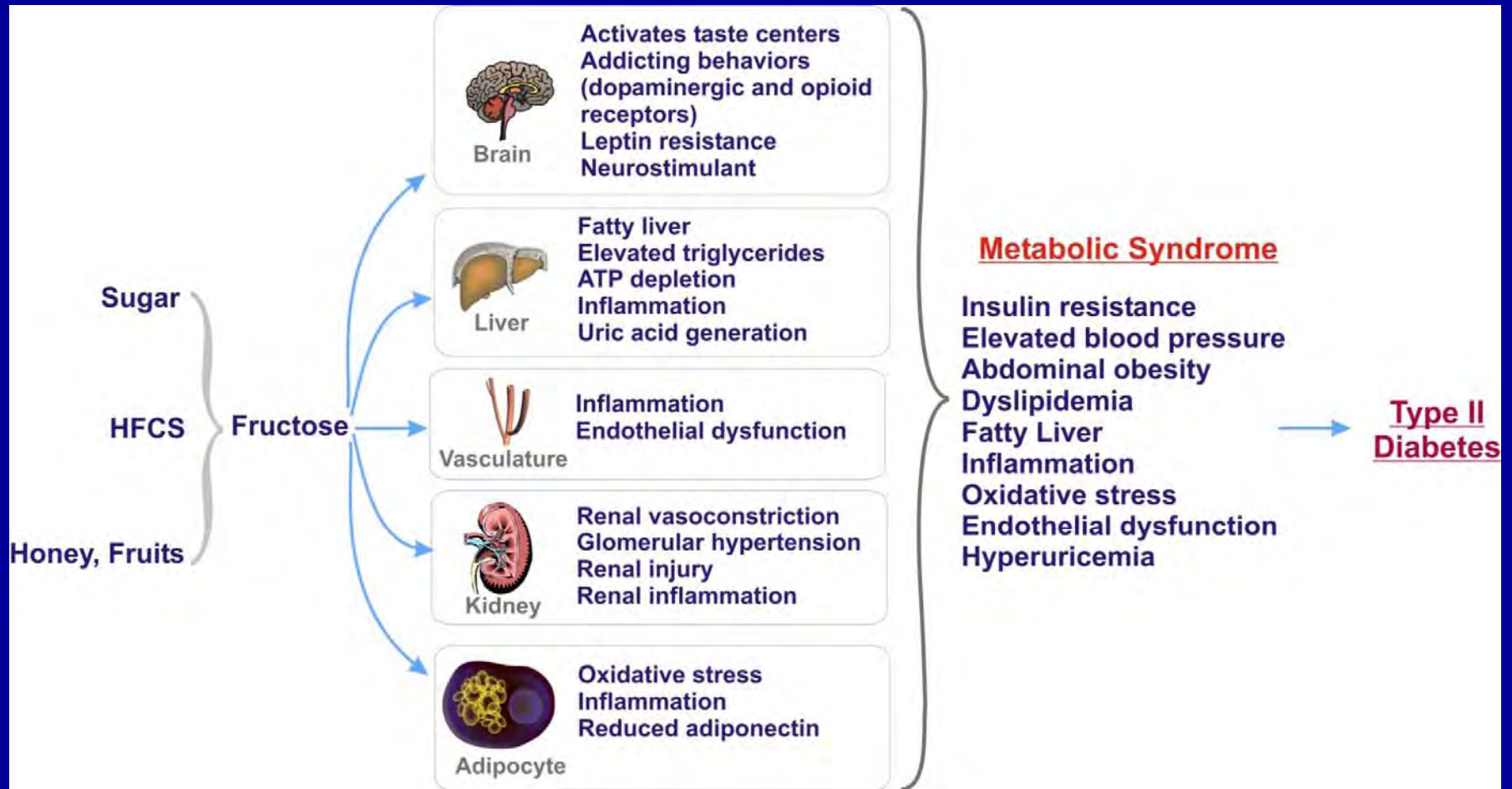


FAS

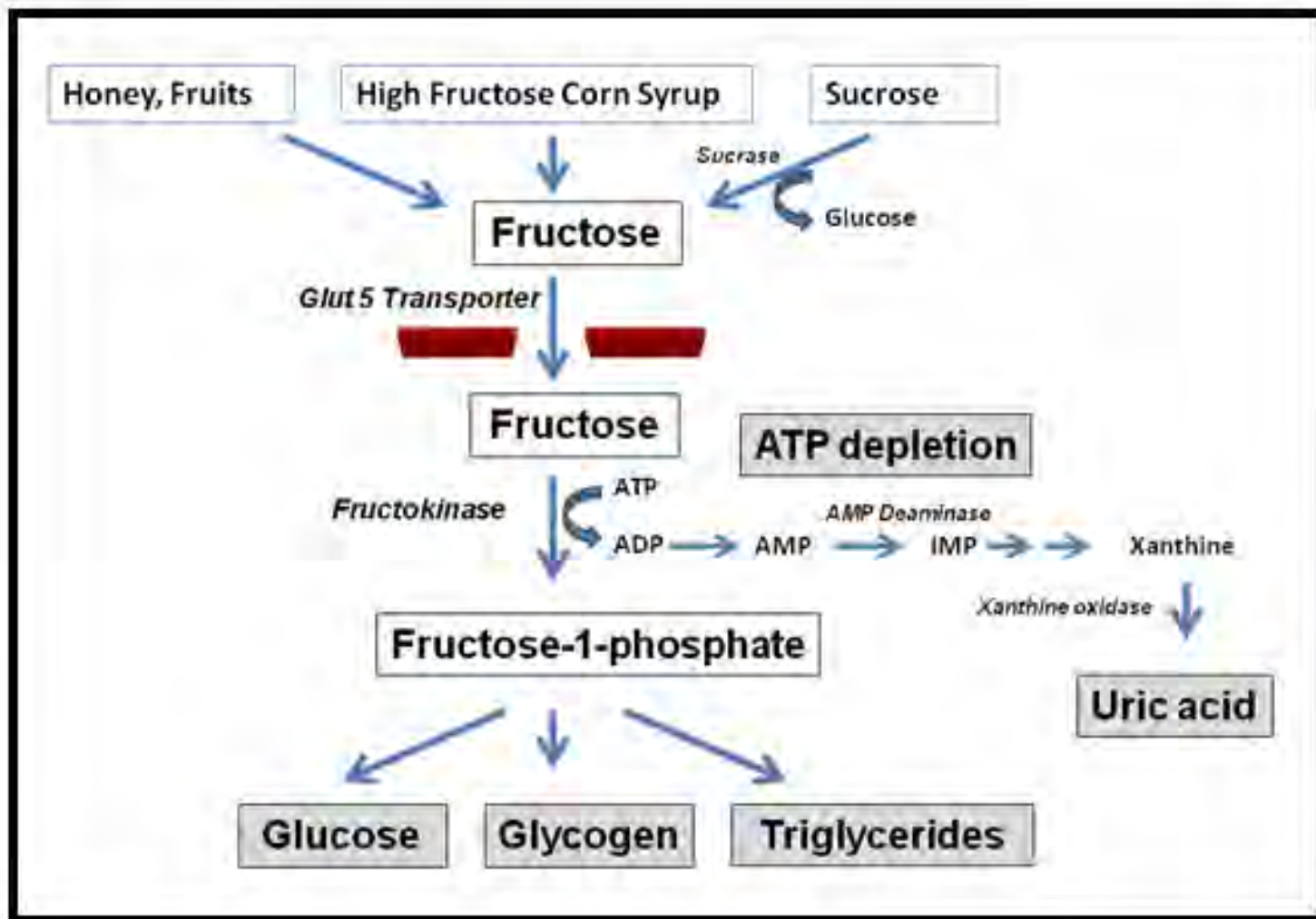
Effect of Fructose (200 g/d) for 2 weeks on Metabolic syndrome in Men: Menorca Study

	Baseline	Change	
<i>Metabolic Syndrome (NCEP-ATPIII)(%)</i>	19%		44%
<i>Triglycerides</i>	136 ± 15	55±20	P Value <0.001
<i>HDL Cholesterol</i>	46.5 ± 1.5	-2.5 ± 0.7	<0.001
<i>Insulin resistance (HOMA)</i>	1.7 ± 0.2	0.57 ± 0.16	<0.005
<i>Weight (kg)</i>	84.3 ± 2.3	0.6 ± 0.2	<0.003
<i>BMI (kg/m2)</i>	29.0 ± 0.6	0.2 ± 0.1	<0.003
<i>24 hr Systolic BP (mm Hg)</i>	126±2	7 ± 2	<0.001
<i>24 hr Diastolic BP (mm Hg)</i>	75 ± 2	5 ± 3	<0.001
<i>Uric acid (mg/dl)</i>	5.2 ± 0.2	1.1 ± 0.8	<0.001

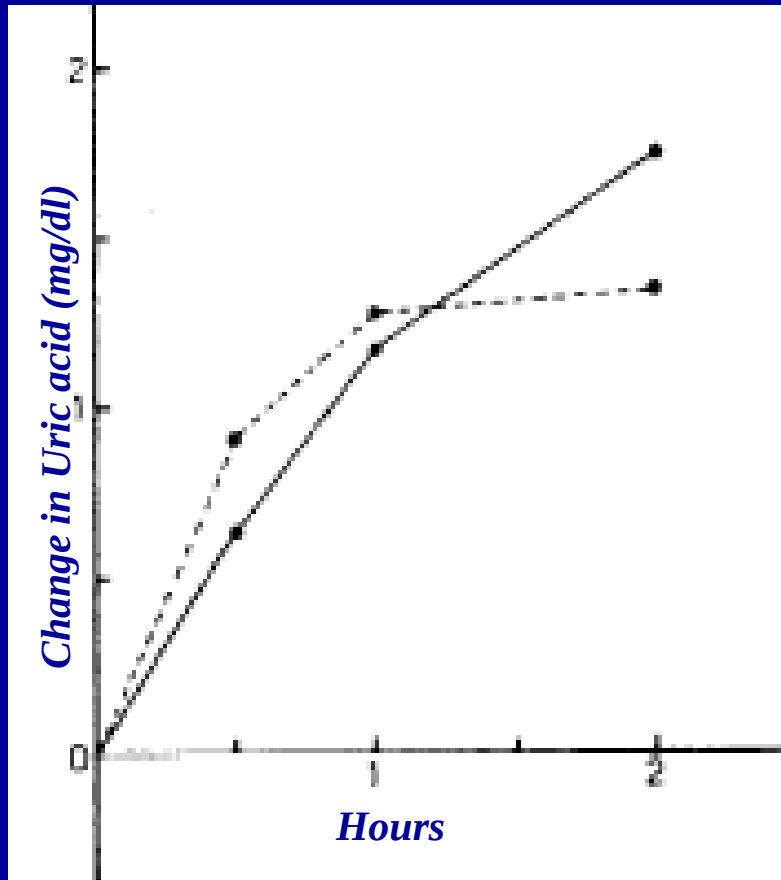
Fructose Induces Metabolic Syndrome in Animals



Fructose Metabolism

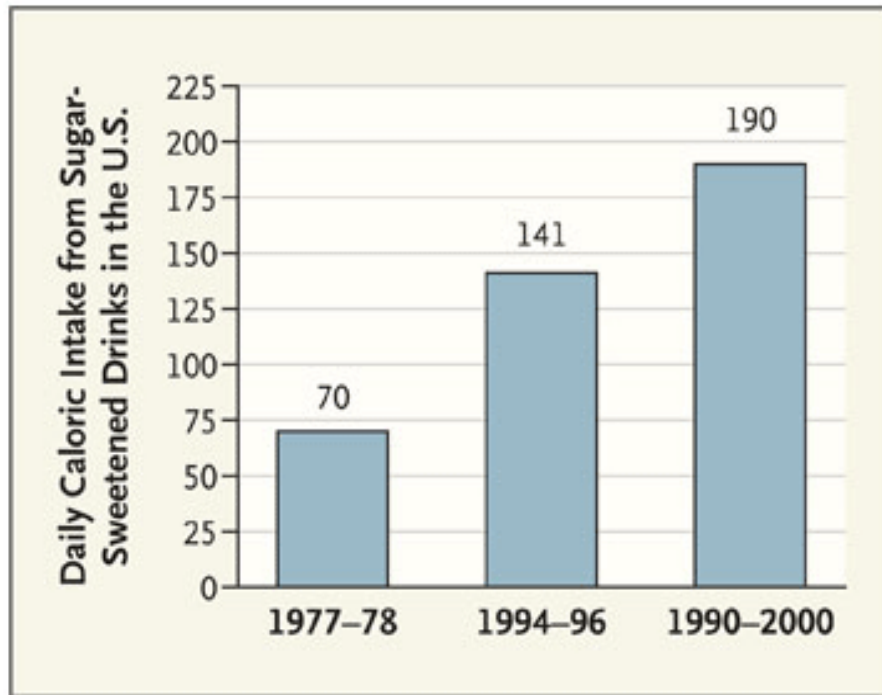


Fructose Acutely Increases Serum Uric Acid

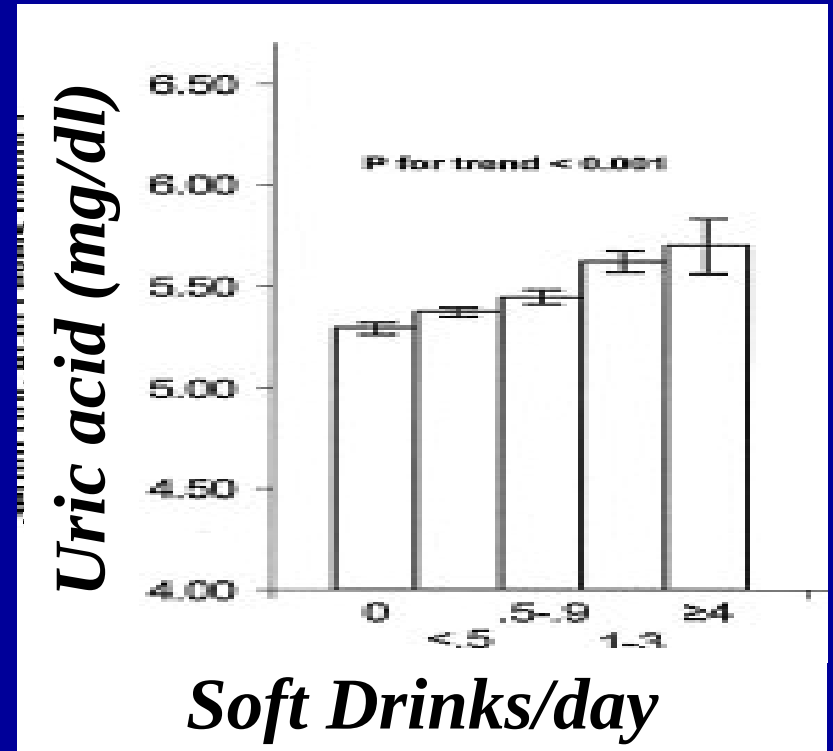


Fructose (1 g/kg body wt) increases serum uric acid within 30 minutes

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

Uric Acid Predicts Development of Hyperinsulinemia or Diabetes

Study (year)	Population	F/U	Independent	RR (C.I.)
ARIC	9,020 adults	11 YRS	Yes	1.3 (1.2-1.4)
Spokane	60 adults with MI	6 MOS	Yes	5.47 (1.6-17.7)
Rotterdam	4,536 adults	10 YRS	Yes	1.68 (1.22-1.30)
Framingham	5,209 adults	26 YRS	Men	2.3 (men) and 2.1 (women)
Osaka	2,310 adult men	6 YRS	Yes	1.78 (1.11-2.85)
Osaka	6,356 men	9 YRS	No	1.24 (0.9-1.7)
Mauritius	2,605 adults	5 YRS	Yes	1.37 (1.20-1.57)
Britain	7,735 men	12.8 YRS	Yes	1.5 (0.9-2.5)
Sweden	766 men	13.5 YRS	Yes	5.8 (2.2 - 16.0)
Kinmen	641 adults	7 YRS	Women	1.44 (1.13-2.25)
Finland	522 adults	4.1 YRS	Yes	1.87 (1.07-3.26)
Mauritius	4259 adults	5 YRS	Men	1.37 (1.11-1.68)
Nauru	266 adults	6 YRS	Women	Not given
Israel	10,000 men	5 YRS	Yes	1.35
China	2609 adults	9 YRS	Yes	1.4 (1.02-1.92)

Acute Effects of Uric acid

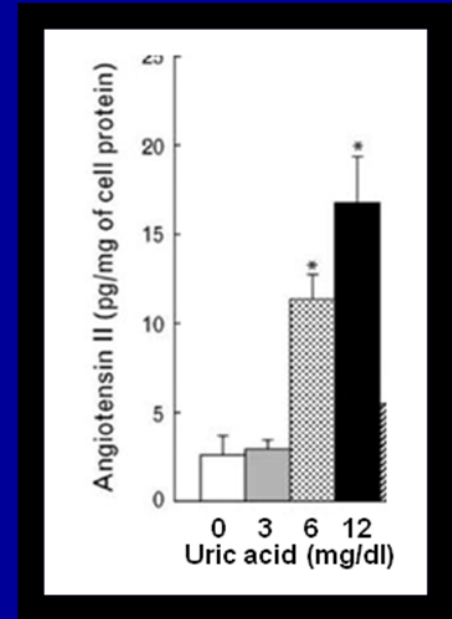
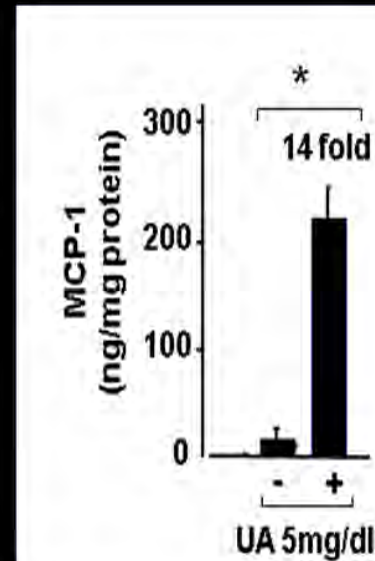
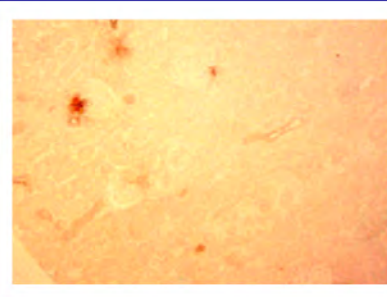
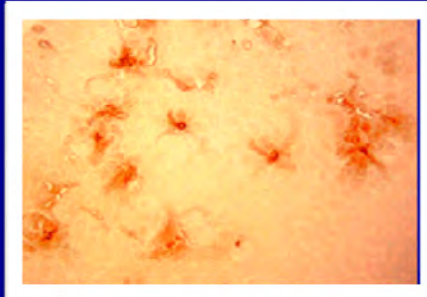
Uric Acid

Control

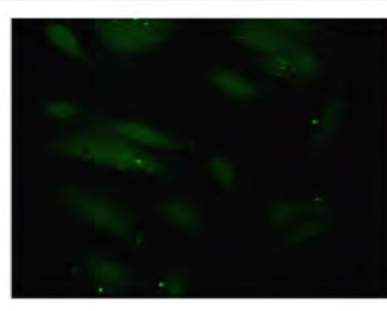
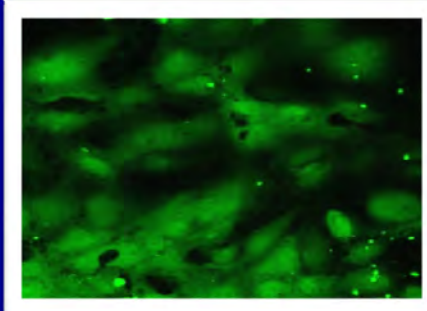
Inflammation
(MCP-1)

Angiotensin II

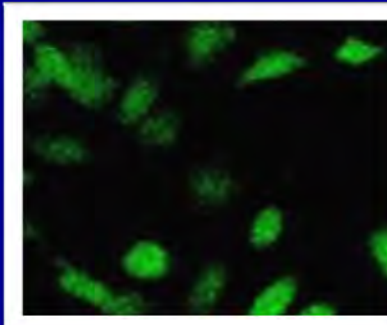
Renin



Oxidants

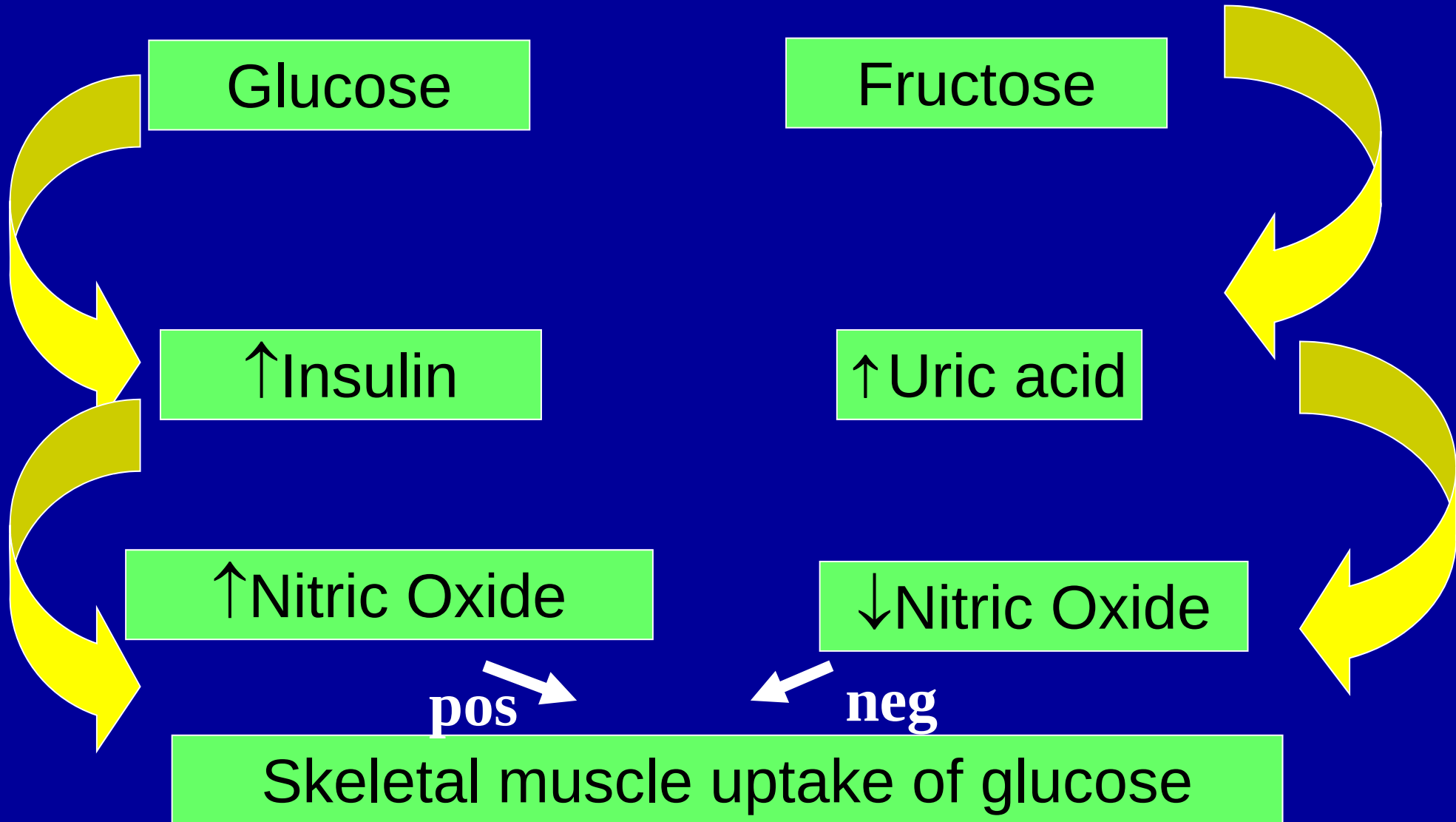


Nitric
Oxide



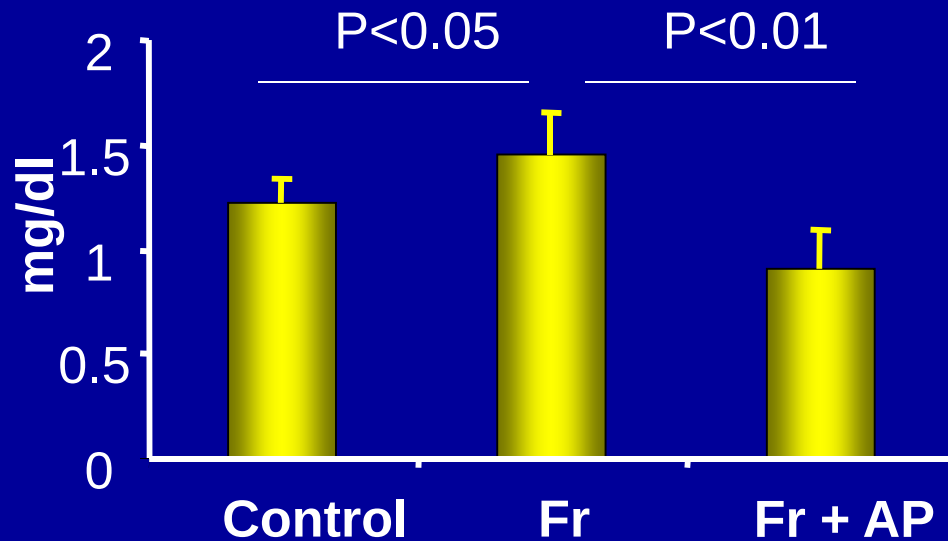
Hypertension 2003; 41: 1287-93 *Kidney Int* 2005; 267: 1739-42 *Am J Physiol* 2002;282: F991-7, *J Hypertens* 2010; 28: 1234-42

Fructose, Uric acid, and Insulin Resistance

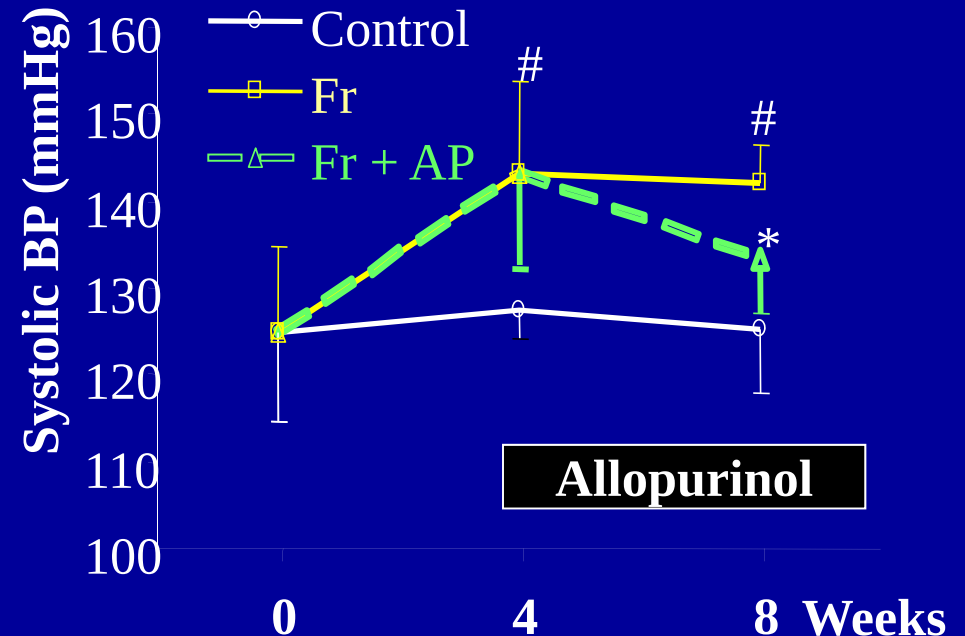


Fructose induced Hypertension is Uric acid Dependent

Serum Uric acid

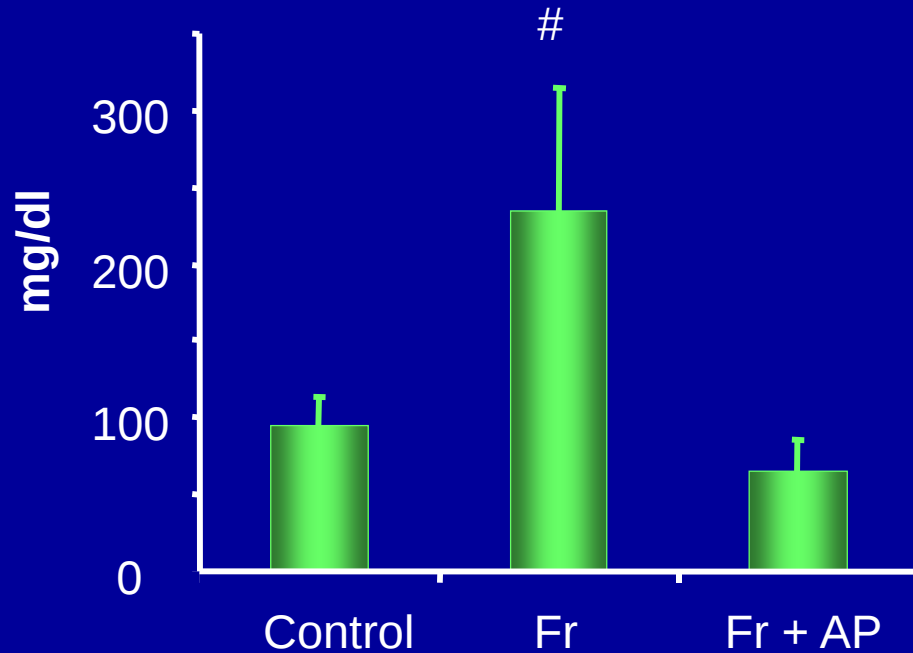


Blood Pressure

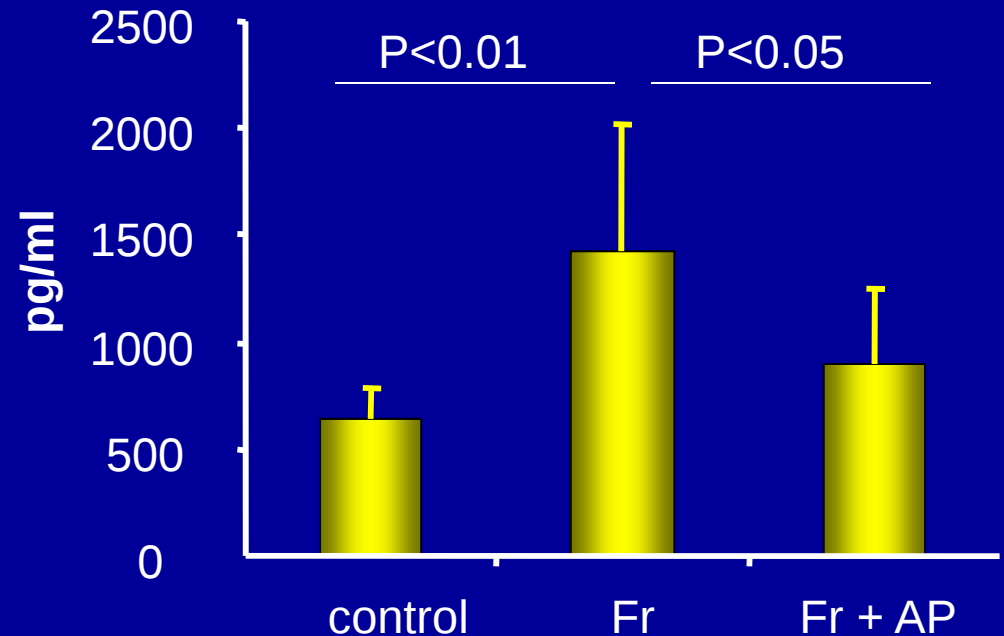


Allopurinol Improves Insulin Resistance and Dyslipidemia in Fructose-fed Rats

Triglyceride

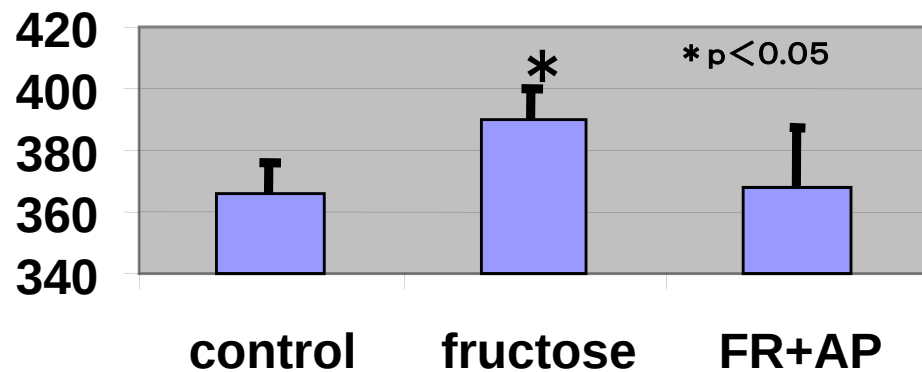


Fasting insulin

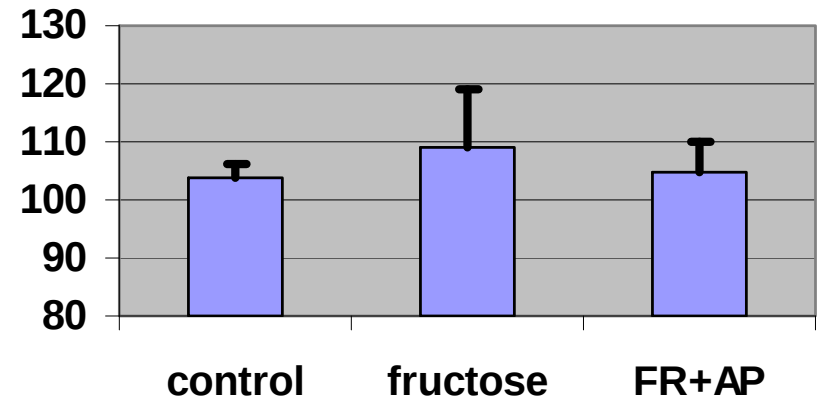


Allopurinol Prevents Obesity in Fructose-fed Rats

Body Weight (g)

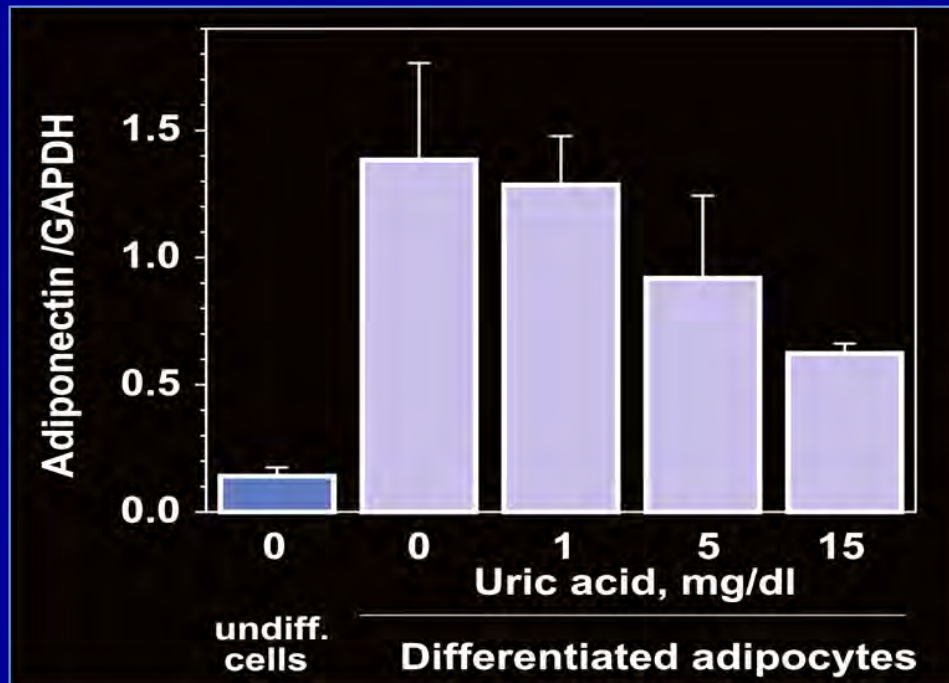


Calorie Intake (Kcal/d)

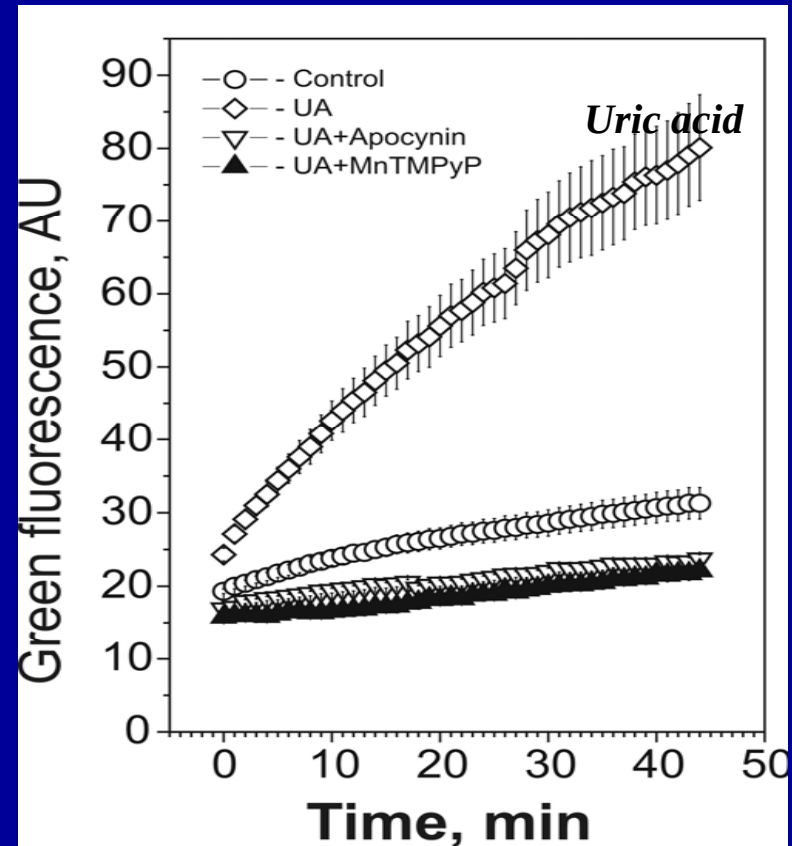


Uric acid Induces a Diabetic Phenotype in Adipocytes

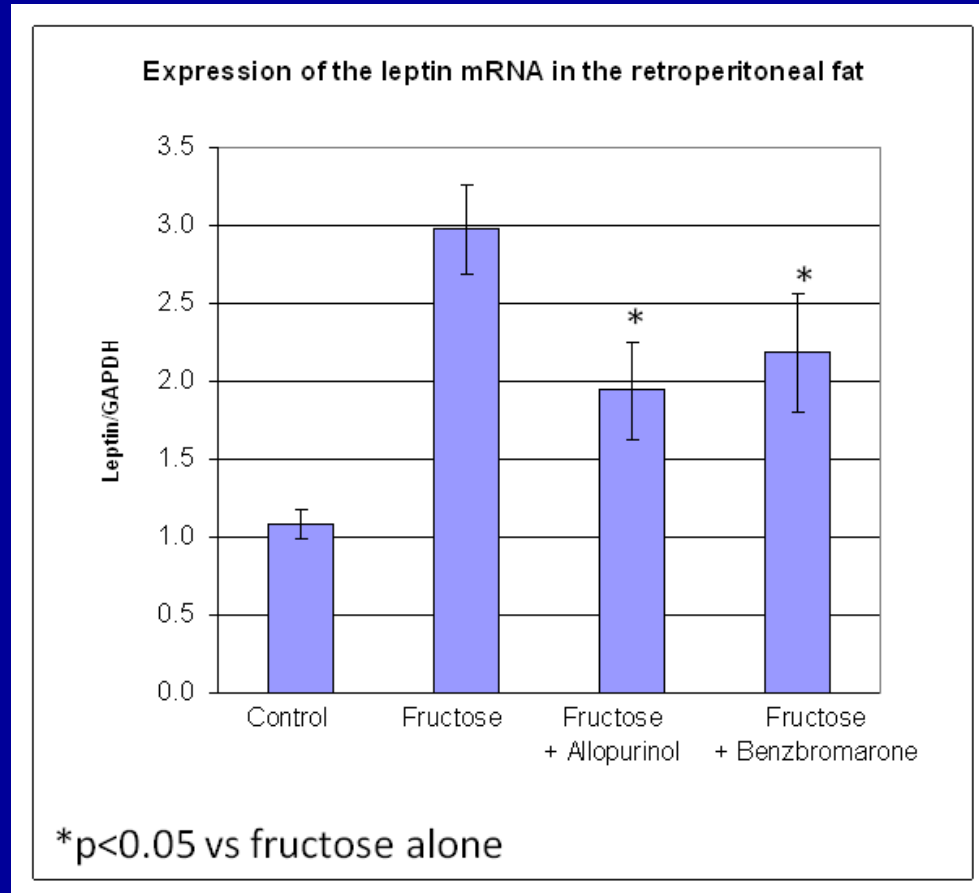
Adiponectin



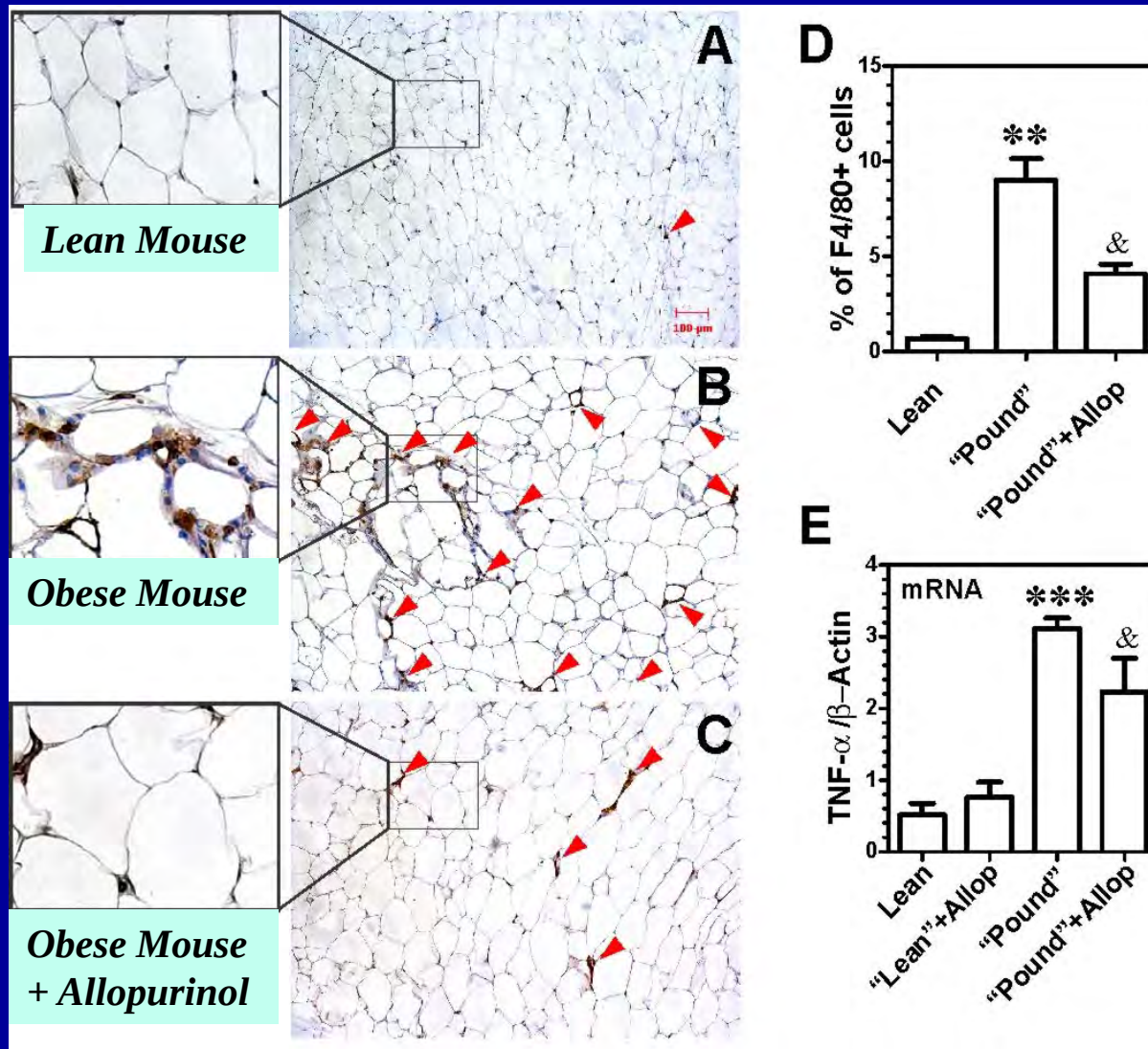
Oxidized Lipids



Allopurinol Reduces Leptin mRNA in Fat from Fructose Fed Rats

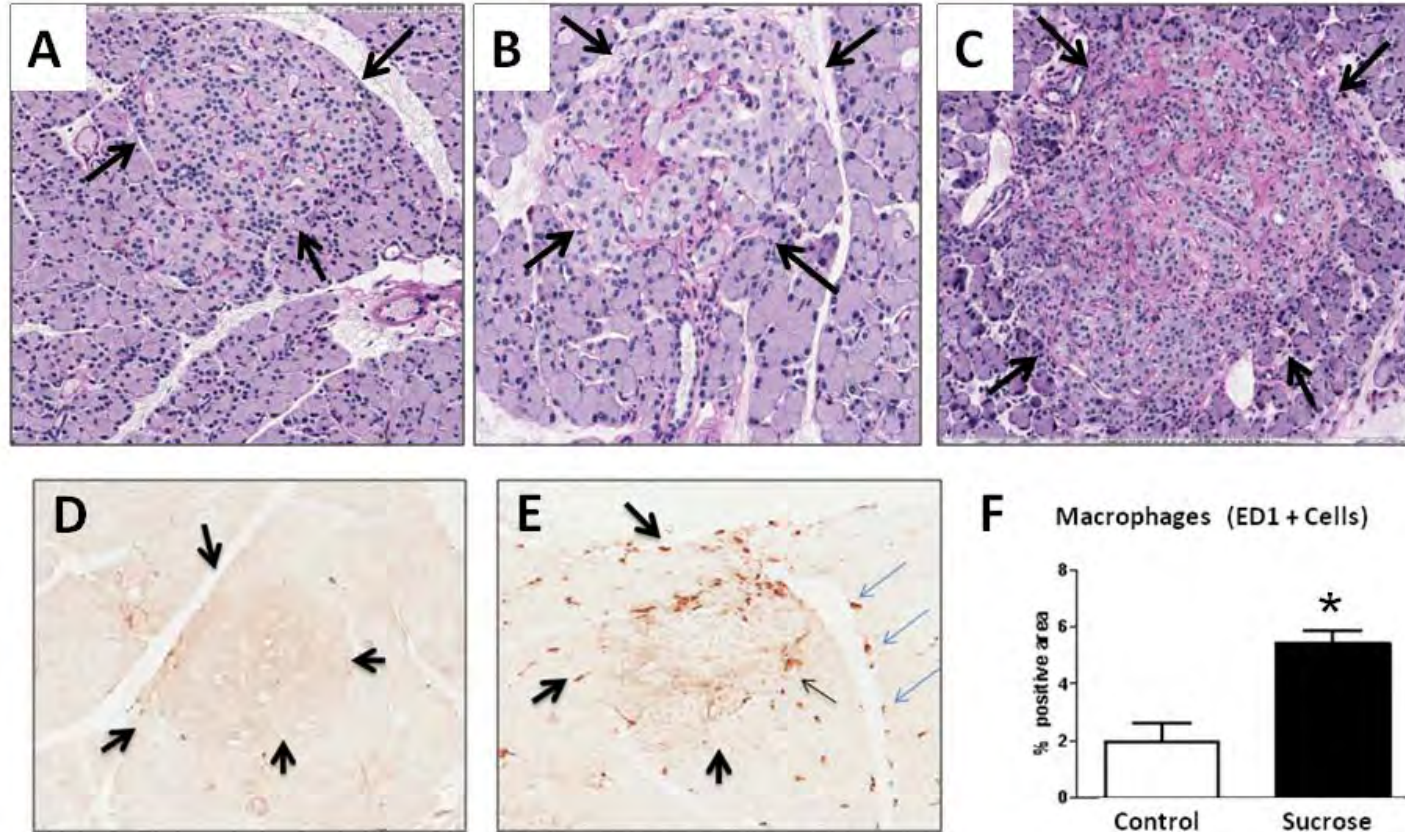


Allopurinol Reduces Fat Inflammation in Mice with Metabolic Syndrome

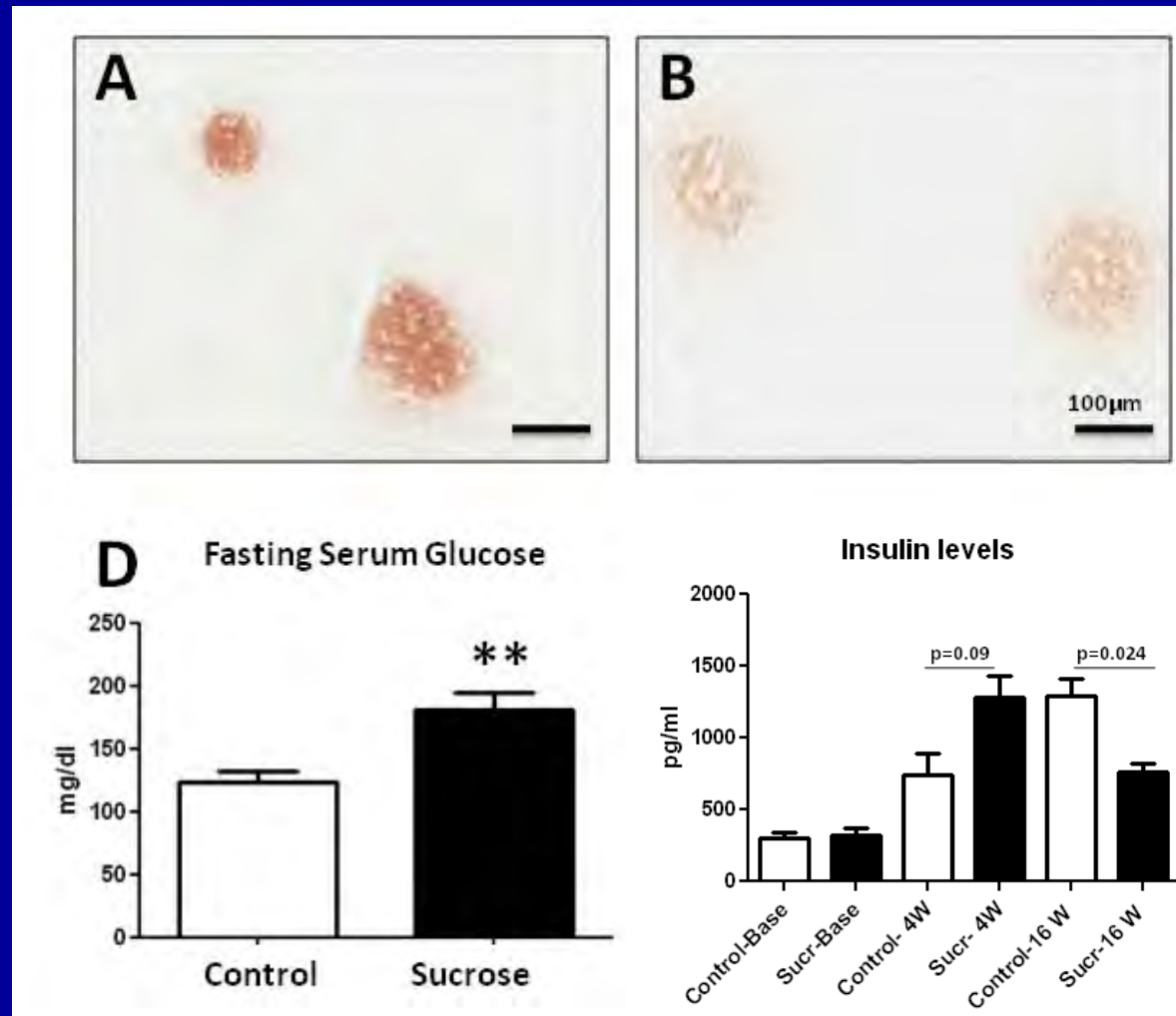


Sautin et al,
Diabetes 2011 in
press

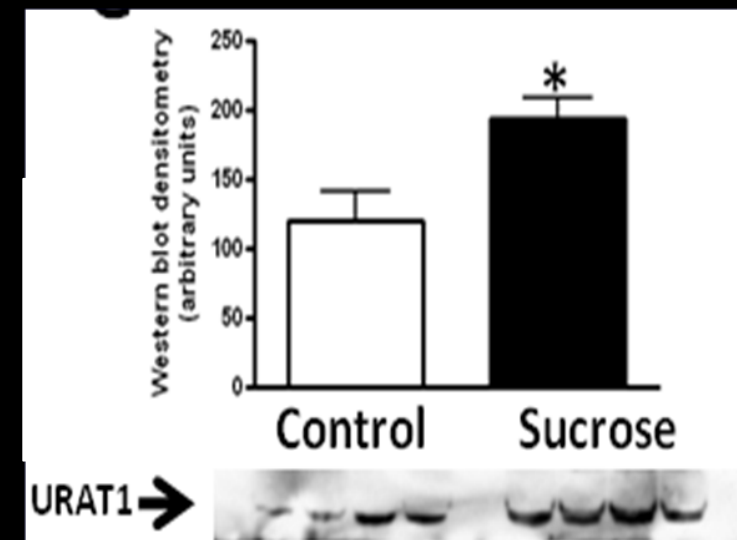
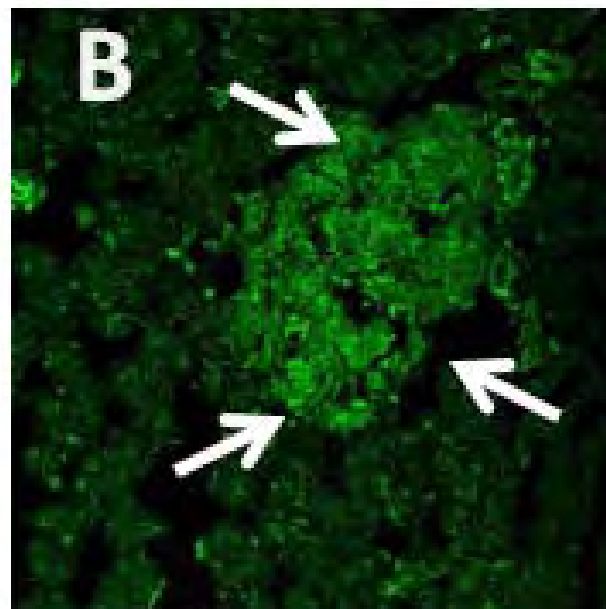
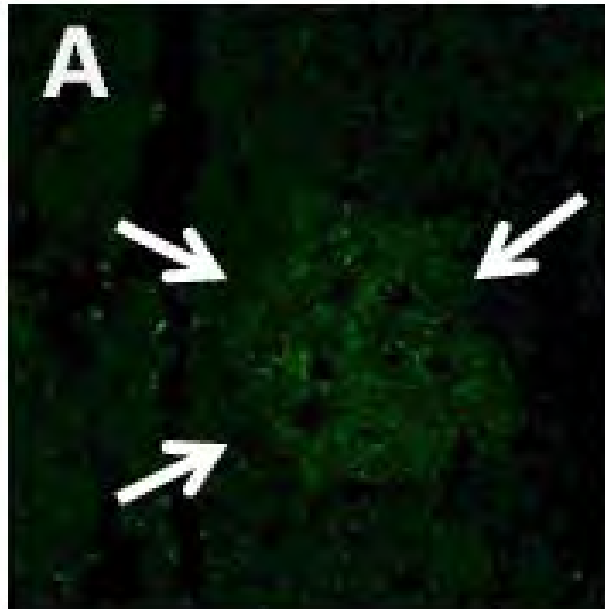
Sucrose Diet Induces Pancreatic Islet Injury



Type 2 Diabetes induced by Sucrose

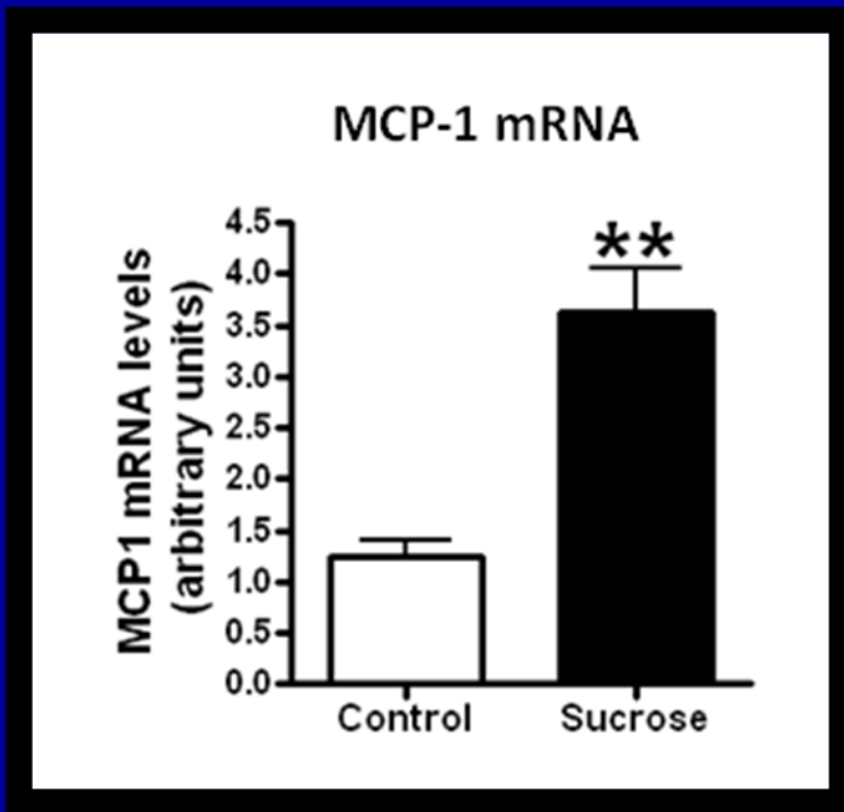


The Uric acid Transporter URAT-1 is Increased in the Islets

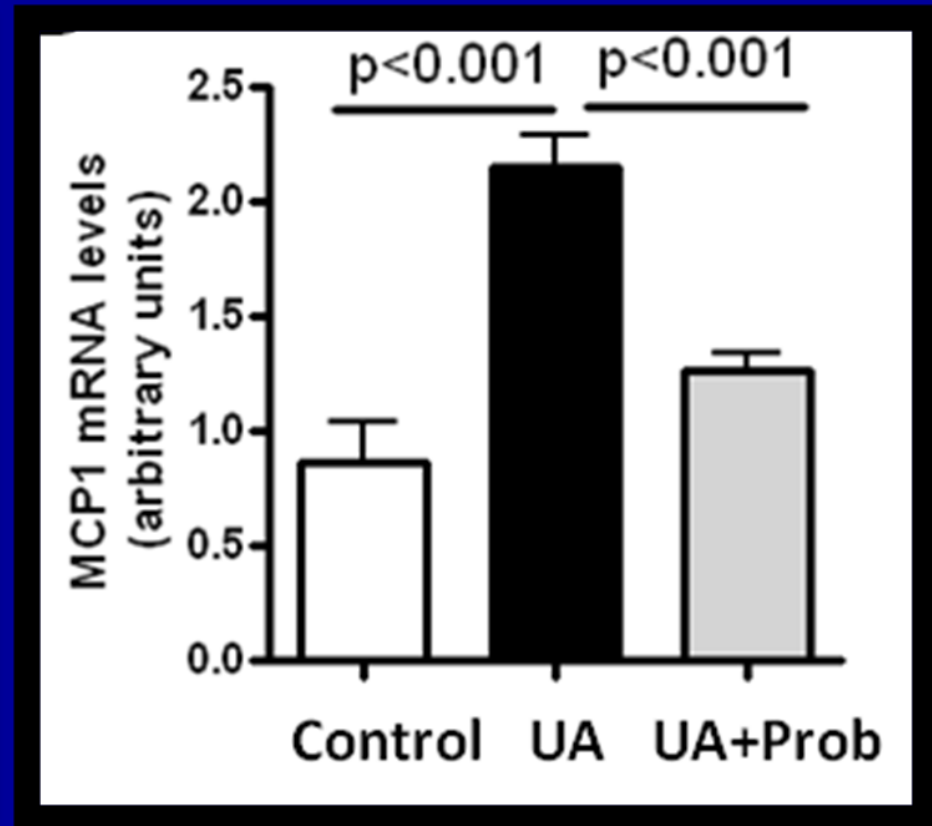


MCP-1 Induced in Pancreas of Sucrose Fed Fats

Whole Pancreas (PCR)



Rat Insulinoma Cells



The Evolution of Man



Proconsul, 18 MYA

Discovered by Mary
Leakey on Rusinga Island,
Lake Victoria, in 1948

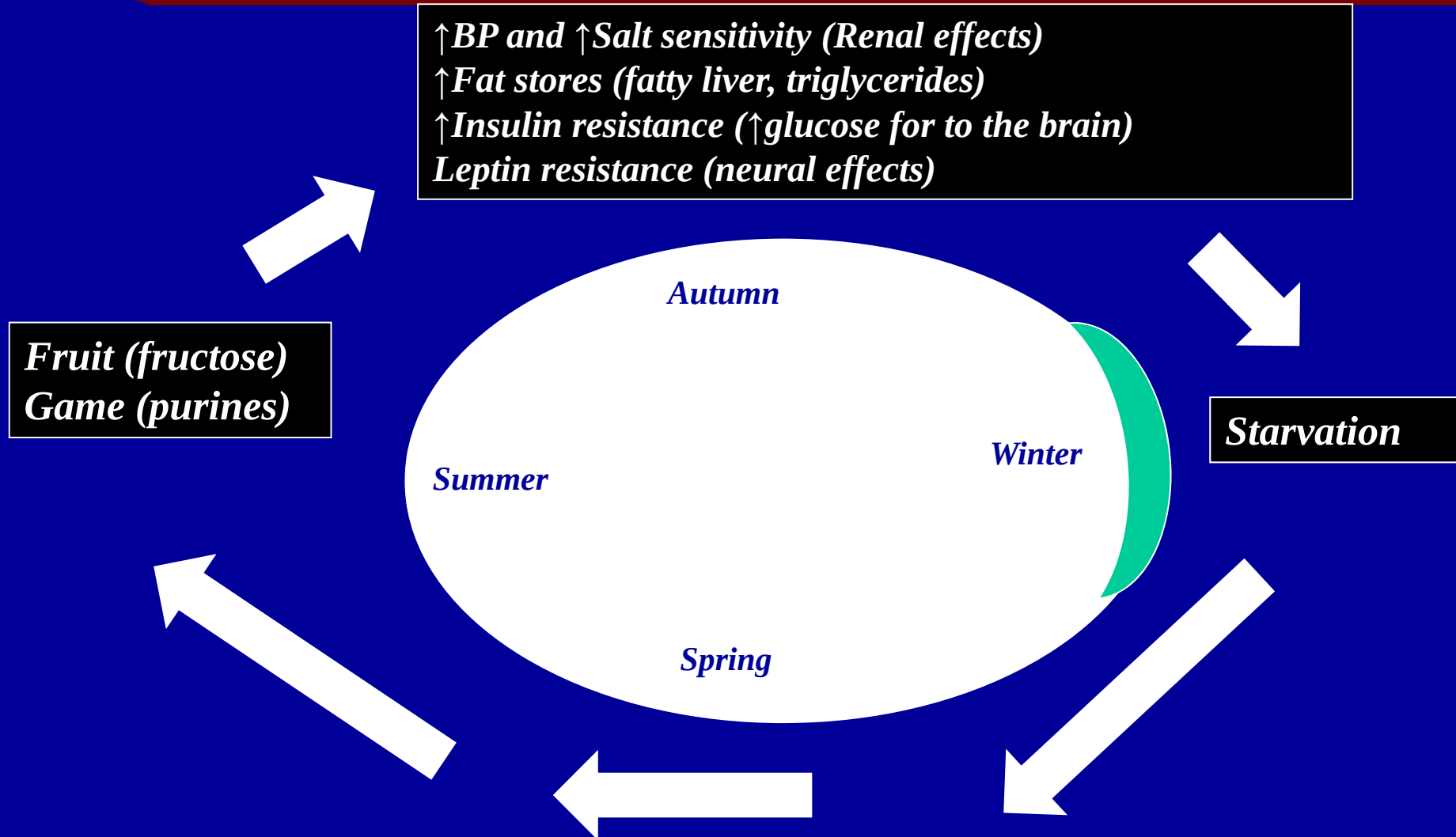
Early Miocene Apes were Fruit Eating



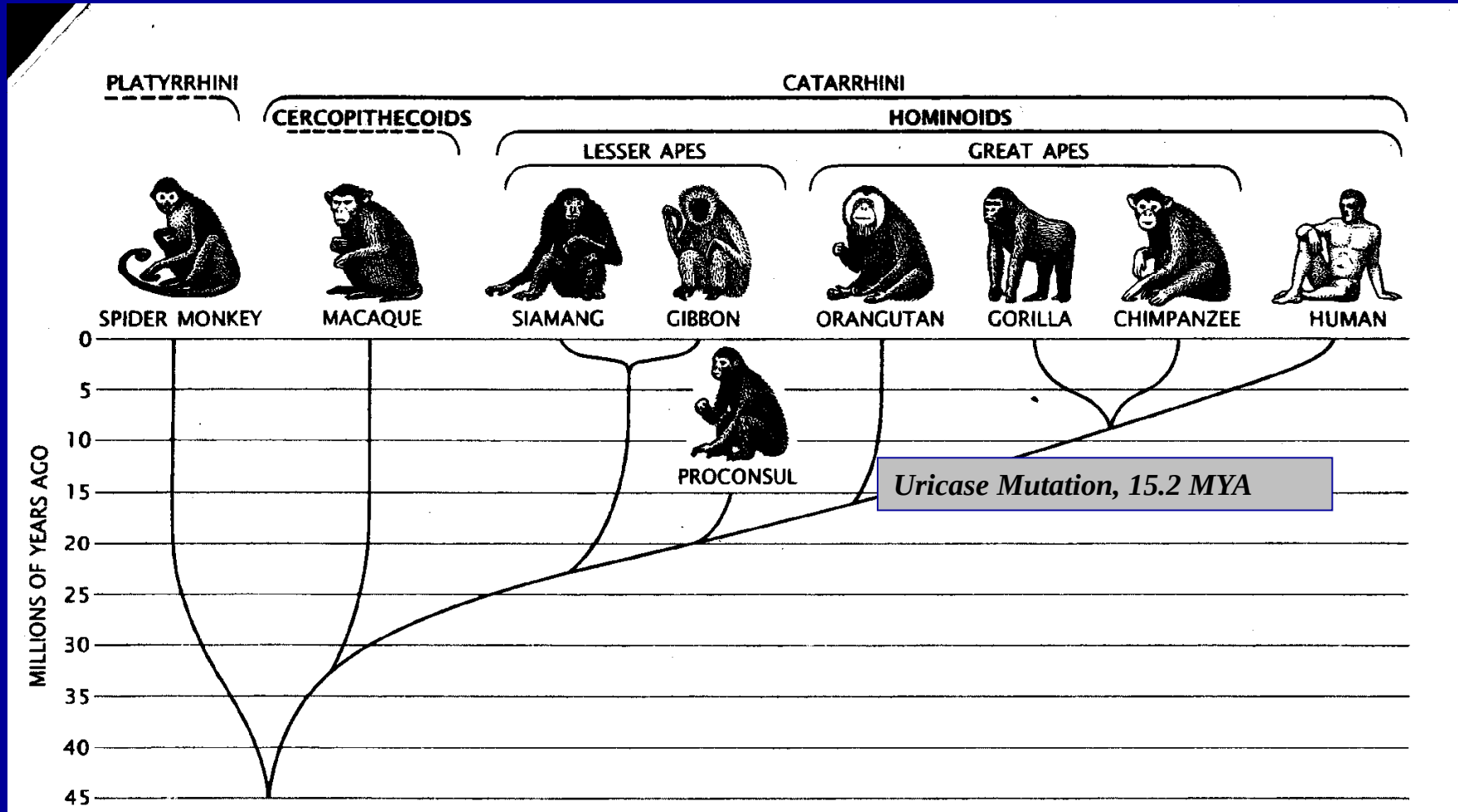
**Early Miocene
Apes were Fruit
Eating and Lived
in Lush Tropical
Rain Forests in
Africa**

(20-15 MYA)

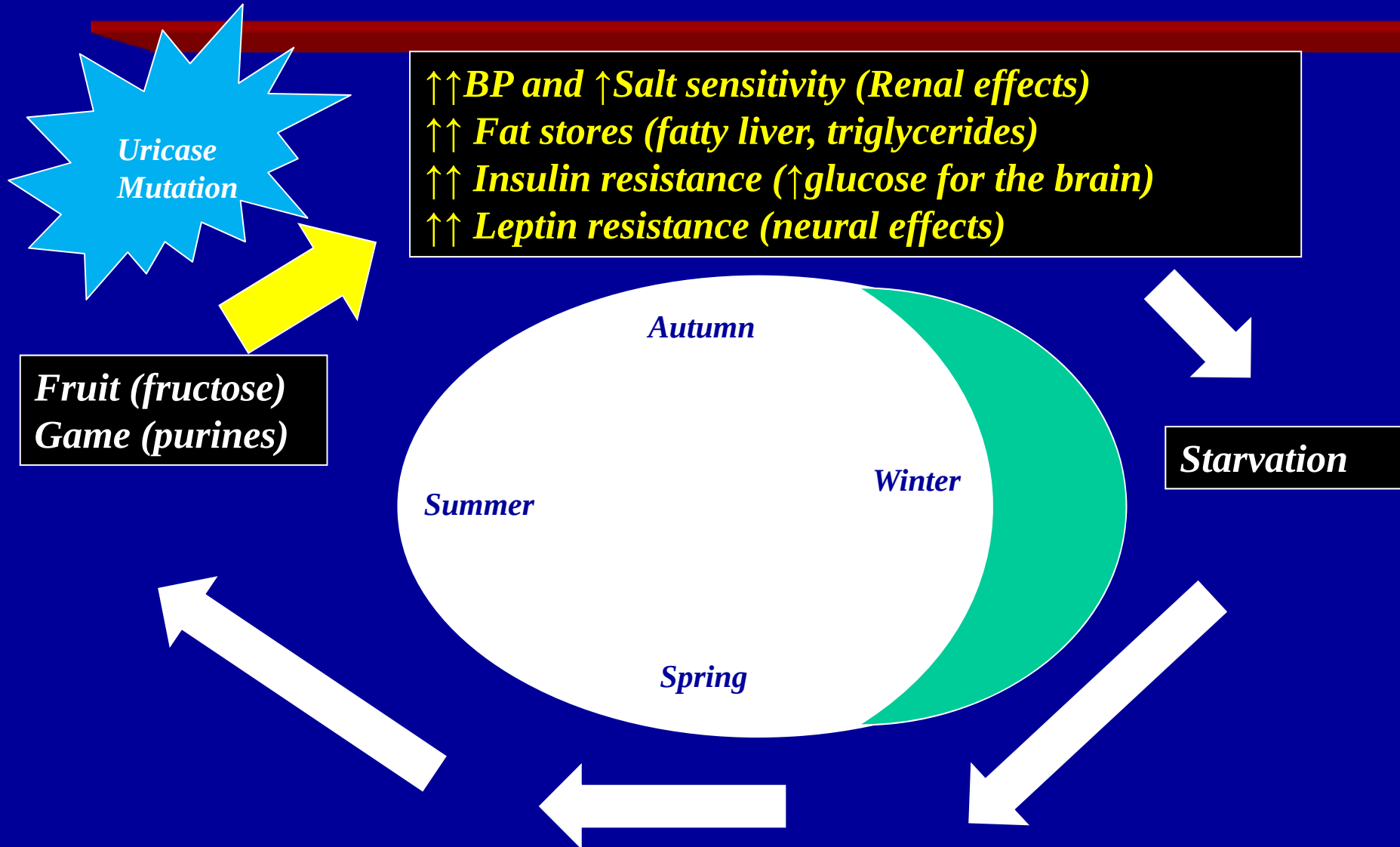
Fructose and Purines: Survival Factor(s)?



The Evolution of Man



Fructose: A Survival Factor

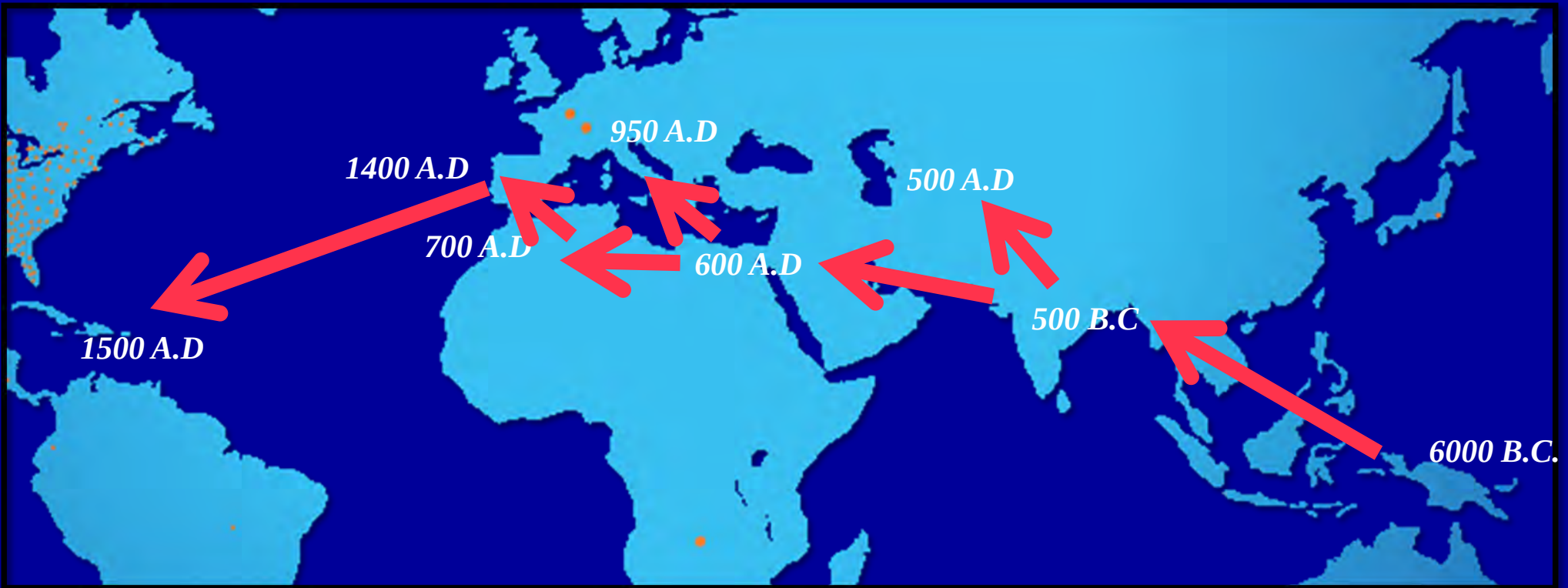


New Guinea, 8000 Years Ago



Saccharum officinarum:
The Noble Cane

The Spread of Sugar Cane



Sugar Plantations in Hispaniola



The Triangle Trade



Sugar: The Perfect Additive



1610-asia



1650-mexico



1615-africa



1550-barbados



Sugar Intake Linked to Diabetes



Haven Emerson (1874-1957)

New York Health Commissioner and
Director of Public Health at Columbia

Diabetes increased from 2.8 cases/100,000
in 1880 to 19 cases per 100,000 in 1920

Risk Factors

Wealthy

Over age 45

Sedentary

Men and postmenopausal women

Caucasian

Merchants in the Food Industry

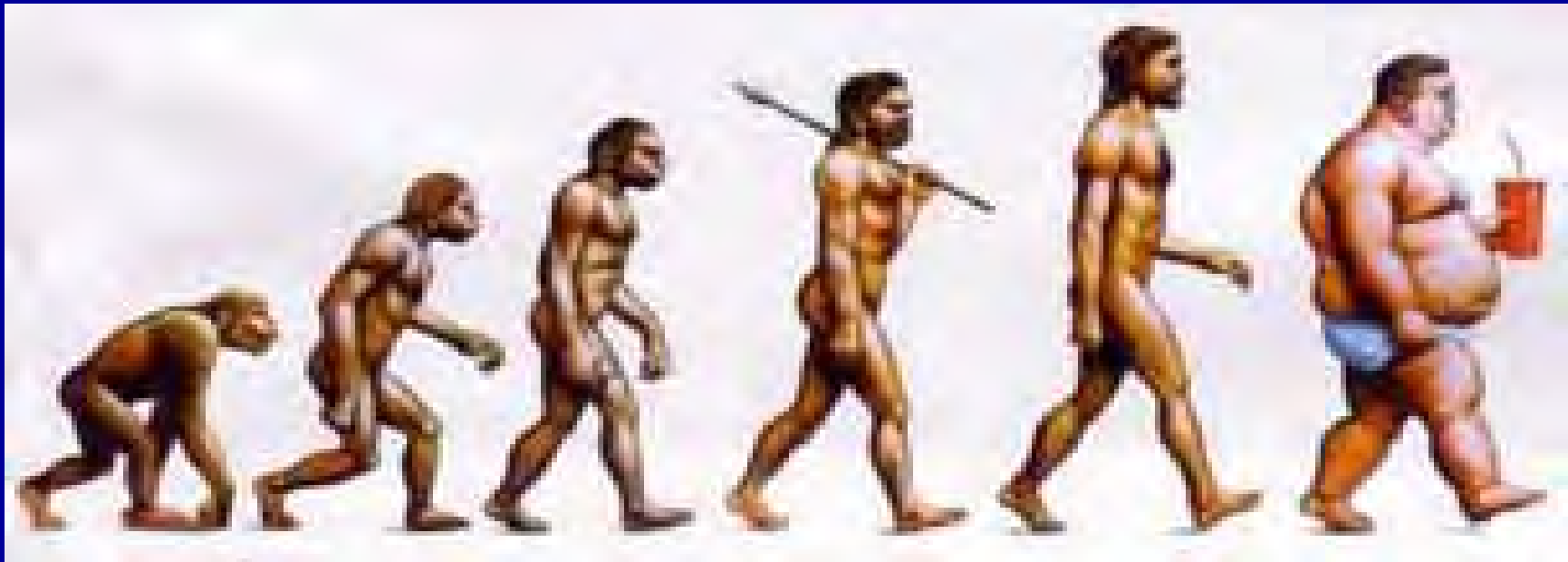
Sugar consumption

Arch Int Med 1924; 34:585-630

Could Fructose be the Driving Force for the Epidemic of Cardiovascular Disease?

- Fructose rich diets (15-25%) raises blood pressure, triglycerides, and induces insulin resistance and weight gain in humans (i.e, can cause the metabolic syndrome)
- Metabolic Syndrome has a major role in driving hypertension, diabetes, and chronic kidney disease

The Evolution of Man



The Economist, December 2003

Independent Collaborators

Gabriela Garcia



Dan Feig



Diana Jalal



Duk-Hee Kang



Miguel Lanaspá



Marilda Mazzali



Taka Nakagawa



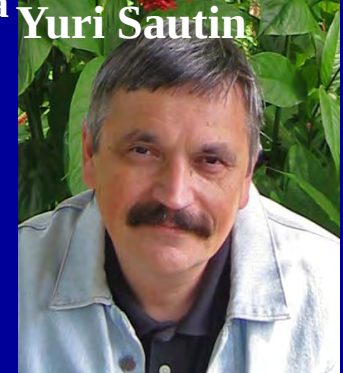
Chris Rivard



Gaby Sanchez-Lozada



Yuri Sautin



Pietro Cirillo

Mike Gersch

John Kanellis

George Henderson

Takuji Ishimoto

Wataru Kitagawa

Tomoki Kosugi

MyPhuong Le

Wei Mu

Xiaosen Ouyang

Karen Price

Sirirat Reungji

Carlos Roncal

Michiko Shimada

Mohamed Shafiu

Taka Nakayama

Katsuyuki Tanabe

Jeffrey Thomas

Susumu Watanabe

Sergei Zharikov