Update on the Medical Management of Urolithiasis

Or

Why do I form kidney stones and what can I do about it?

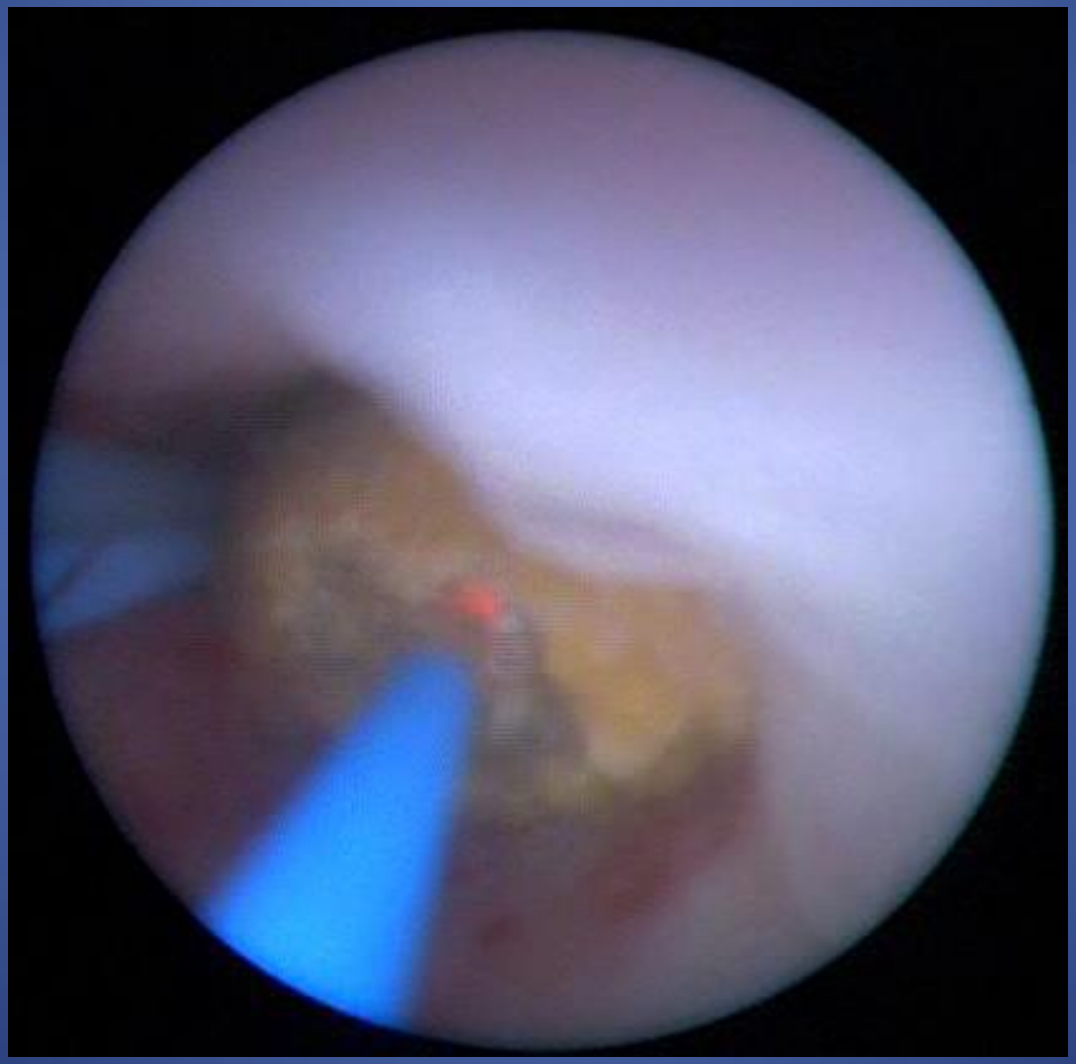
Scott J. Fabozzi, MD, FACS
Director, Kidney Stone Treatment and Prevention Program
Concord Hospital Center for Urologic Care

Objectives

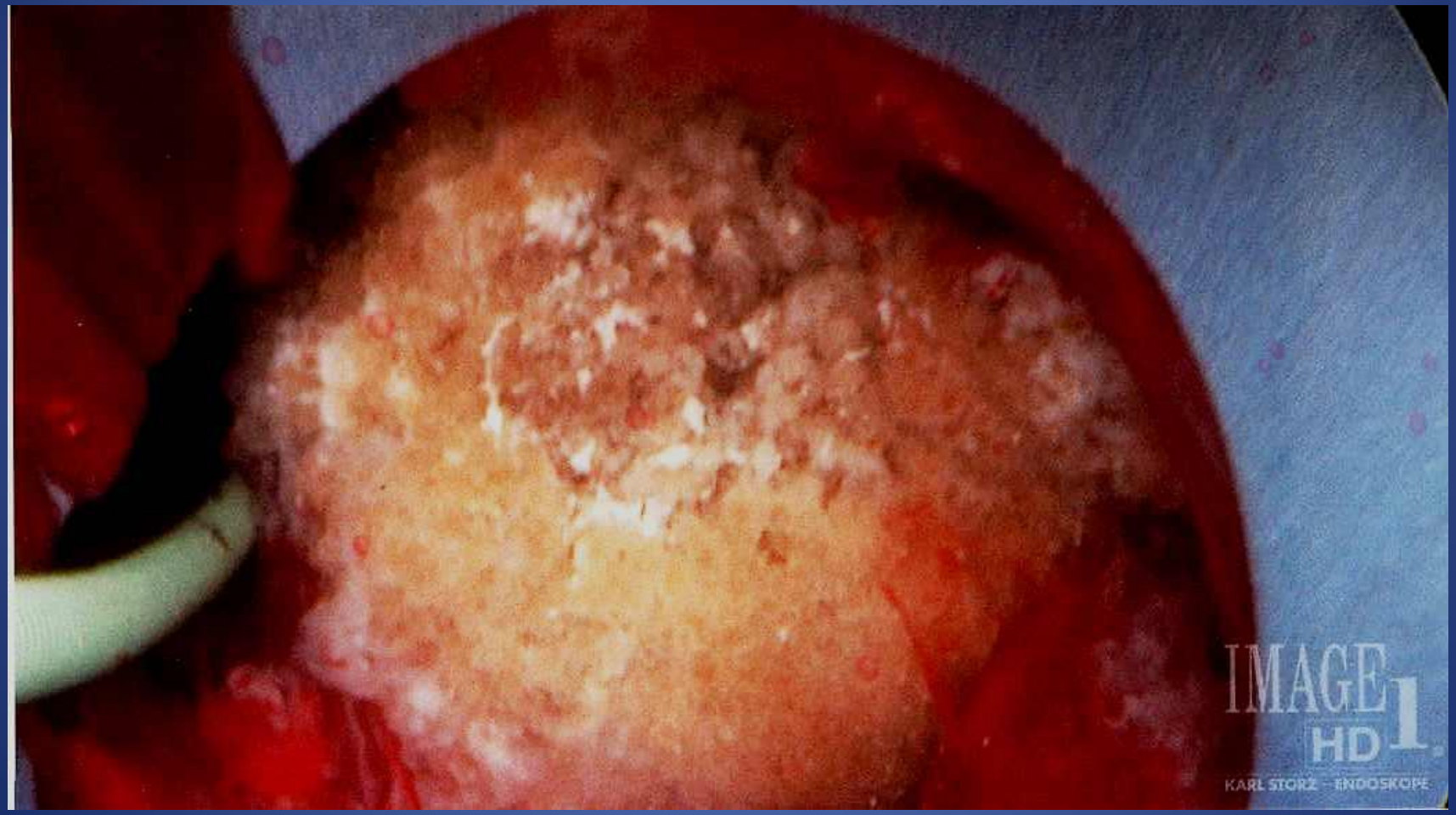
- Introduce new concepts regarding stone formation
- Provide an overview of the medical evaluation of the stone former
- Highlight important medical and surgical risk factors for stone formation
- Discuss the medical management of the stone former

ESWL

Laser lithotripsy



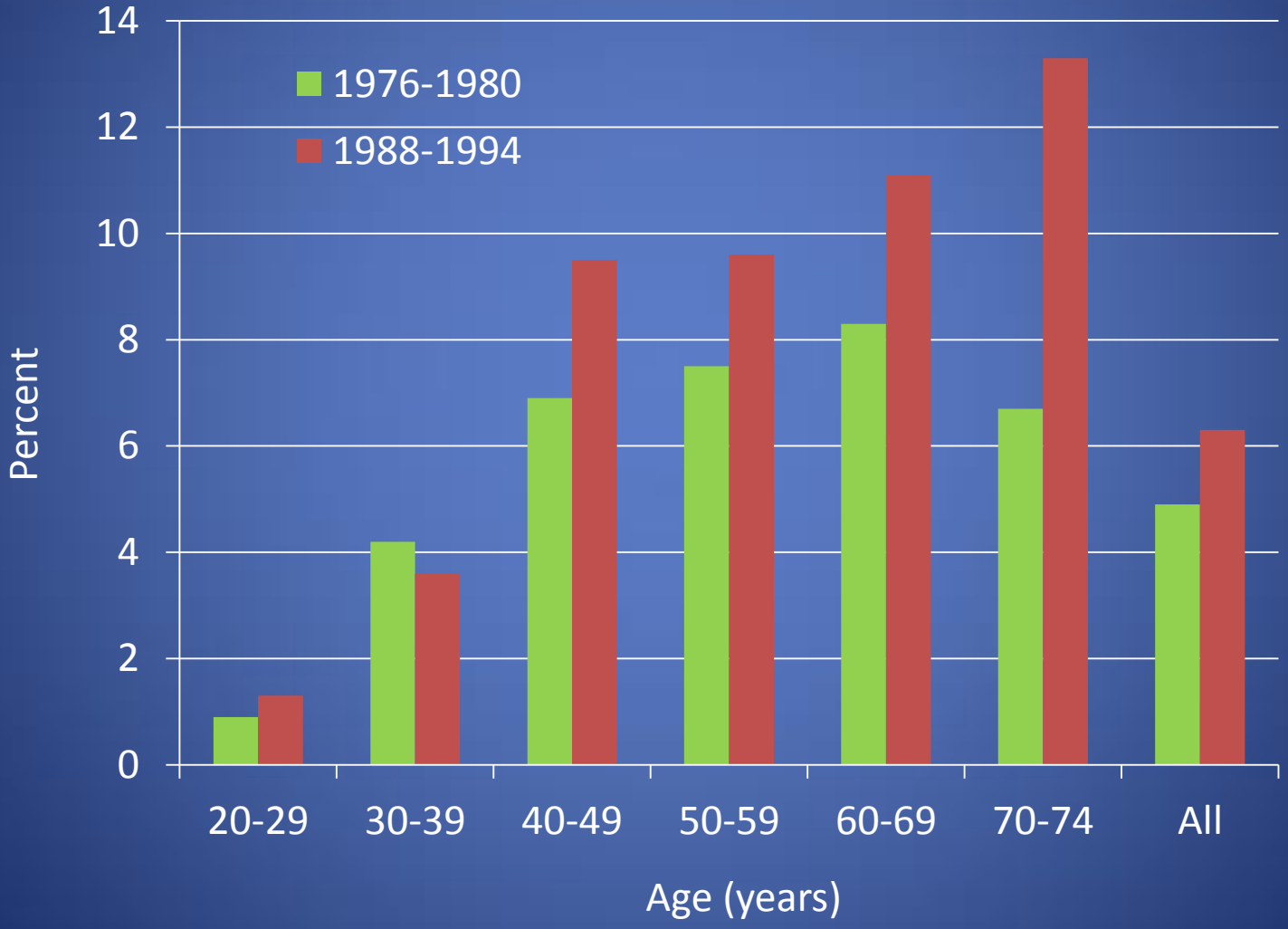
PCNL



Technologic Advances are Wonderful! BUT:

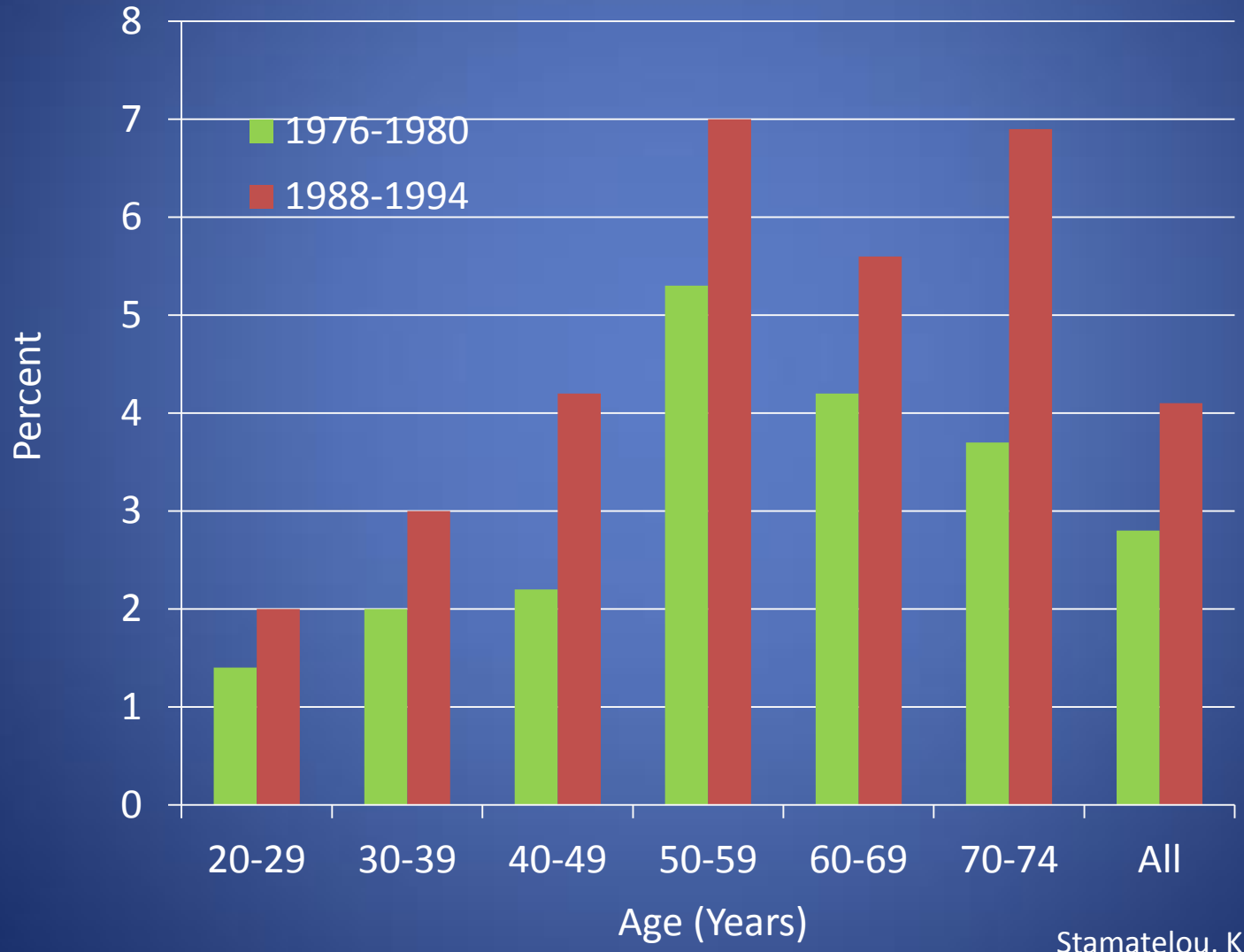
- Surgical treatments do not alter the course of the disease
- 10% prevalence in the US
- Recurrence after first stone:
  - Year 1 : 10-15%
  - Year 5 : 50-60%
  - Year 10: 70-80%
- $2.1 billion / year in 2000 (Pearle et al 2005)
- Fails to account for the lost wages, reduced work productivity

Prevalence of Kidney Stones by Age (Males)



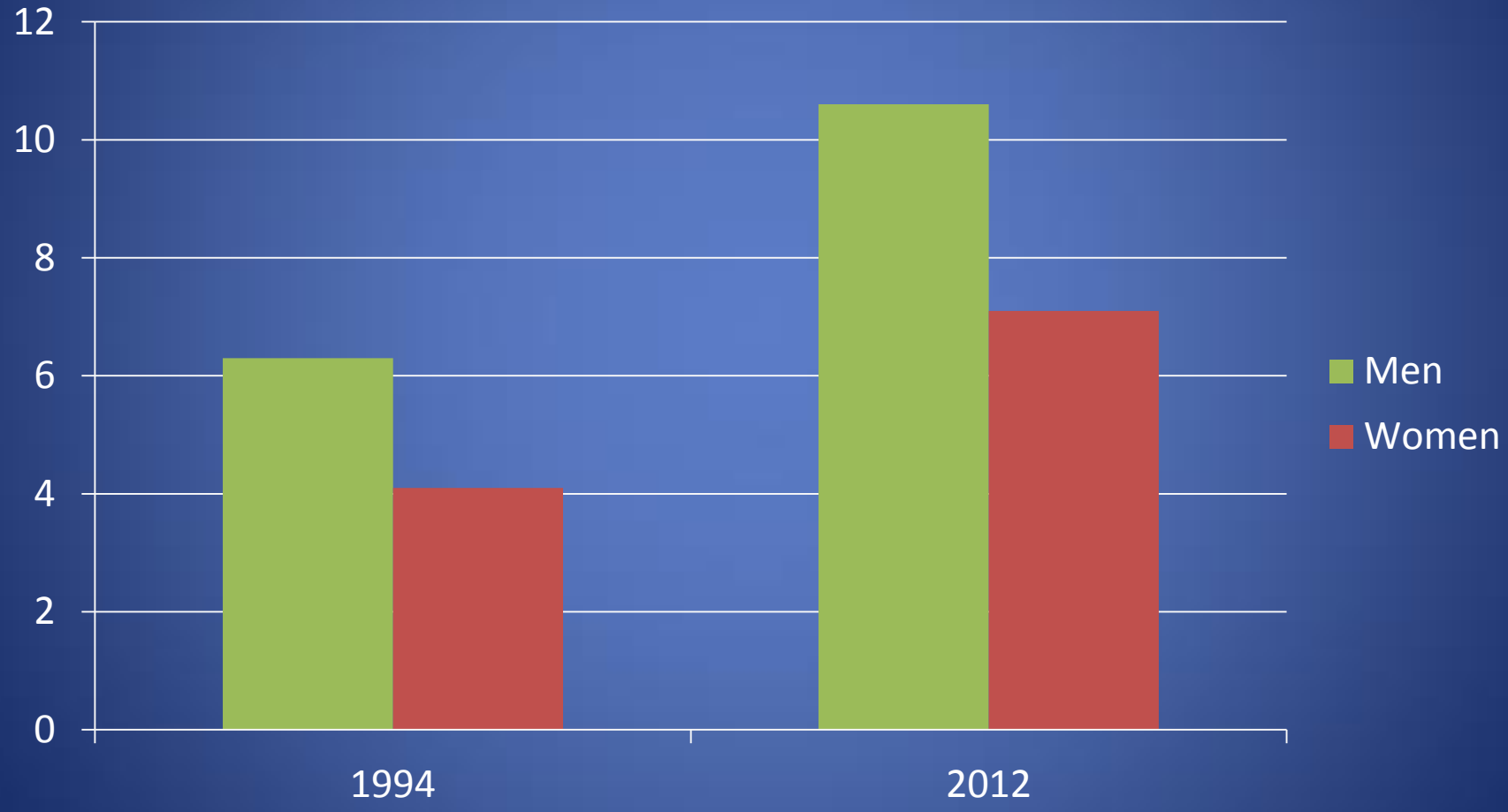
Stamatelou, Kidney Int, 2003

Prevalence of History of Kidney Stones By Age (Females)



Stamatelou, Kidney Int, 2003

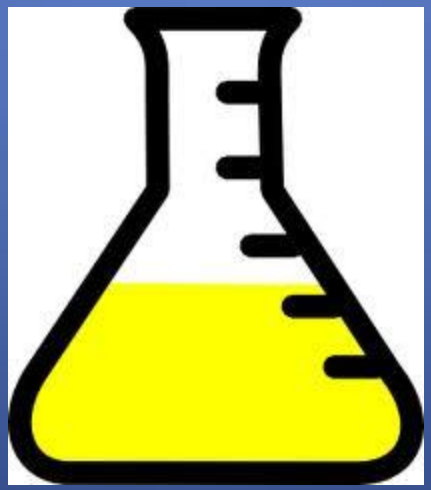
National Health and Nutrition Examination Survey



Scales Eur Urol 2012

Why do stones form ?
Free Crystal Particle Growth

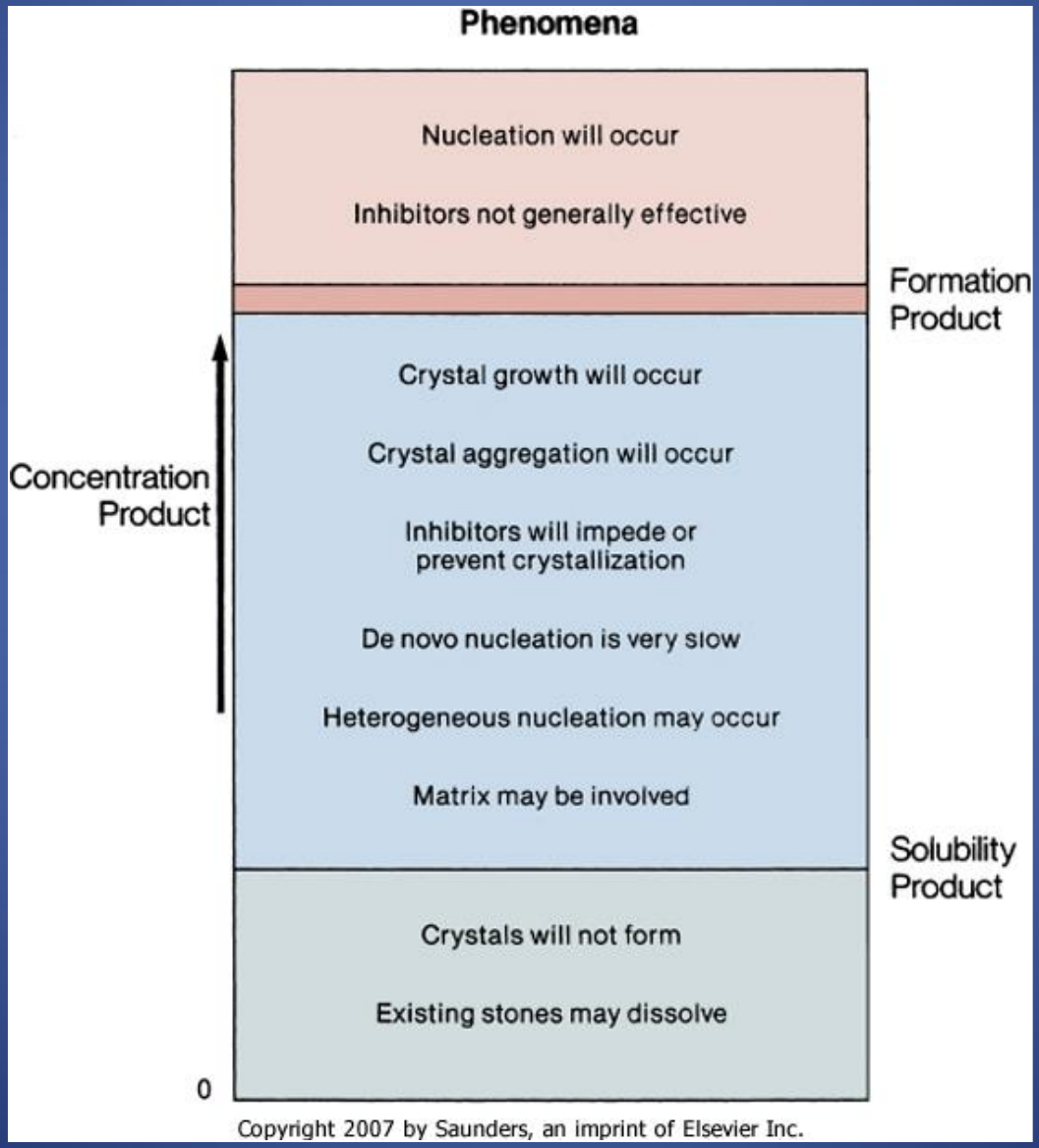
- Urine contains stone forming salts such as calcium and oxalate
- If these stay in solution, crystals do not form
- Crystals, which can become stones, form under certain circumstances



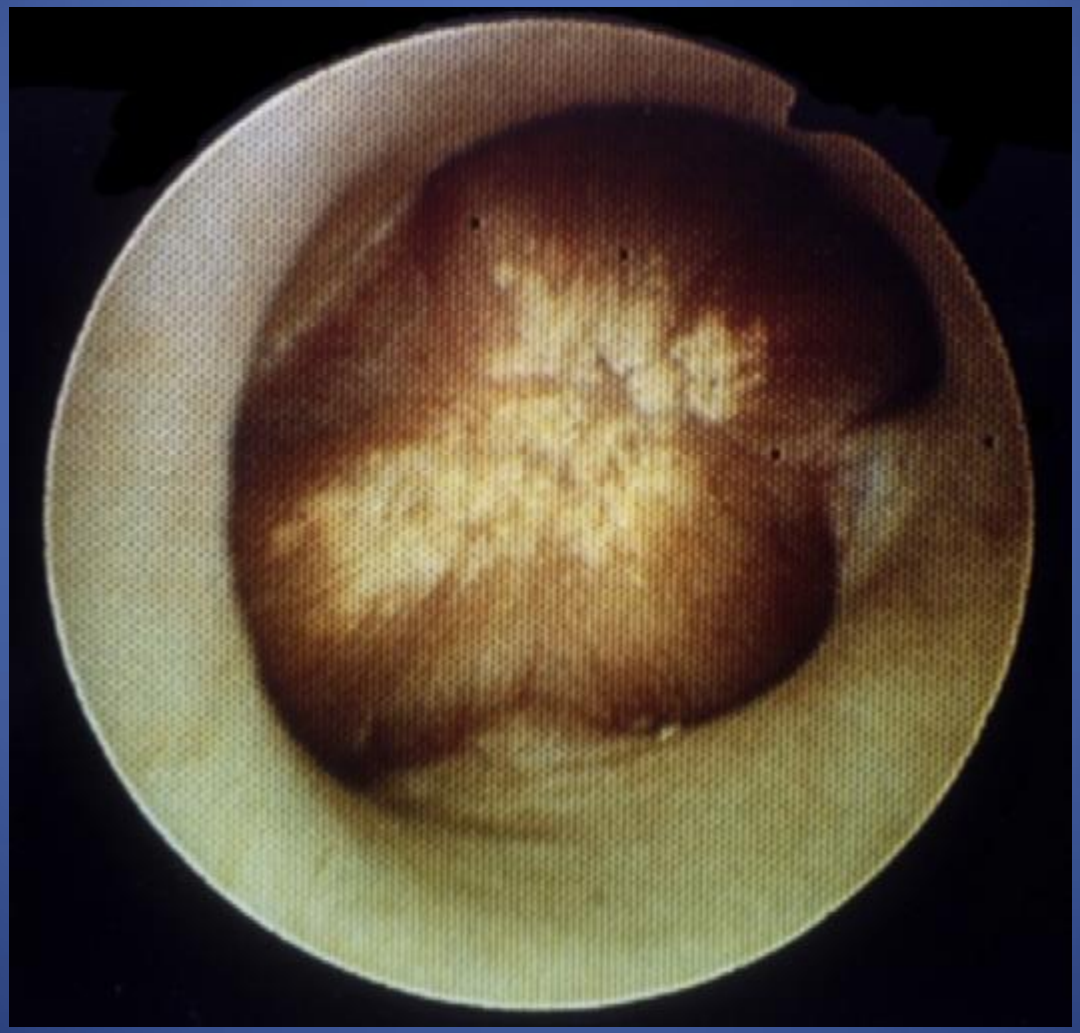
Factors That Promote Crystal Formation

- Concentration of stone forming salts
- pH
- Concentration of inhibitors

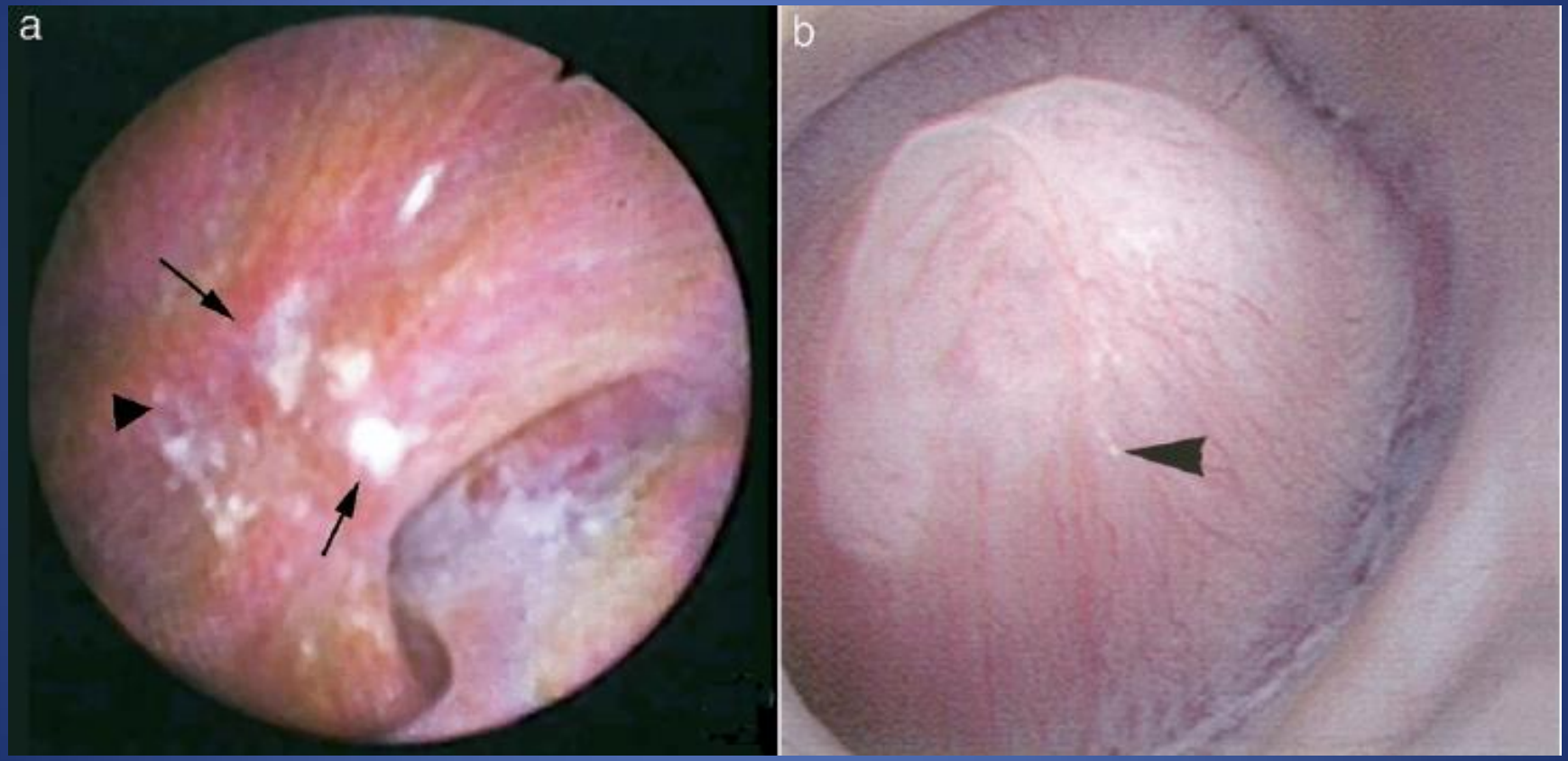
Pathophysiology: Supersaturation



Randall's Plaque



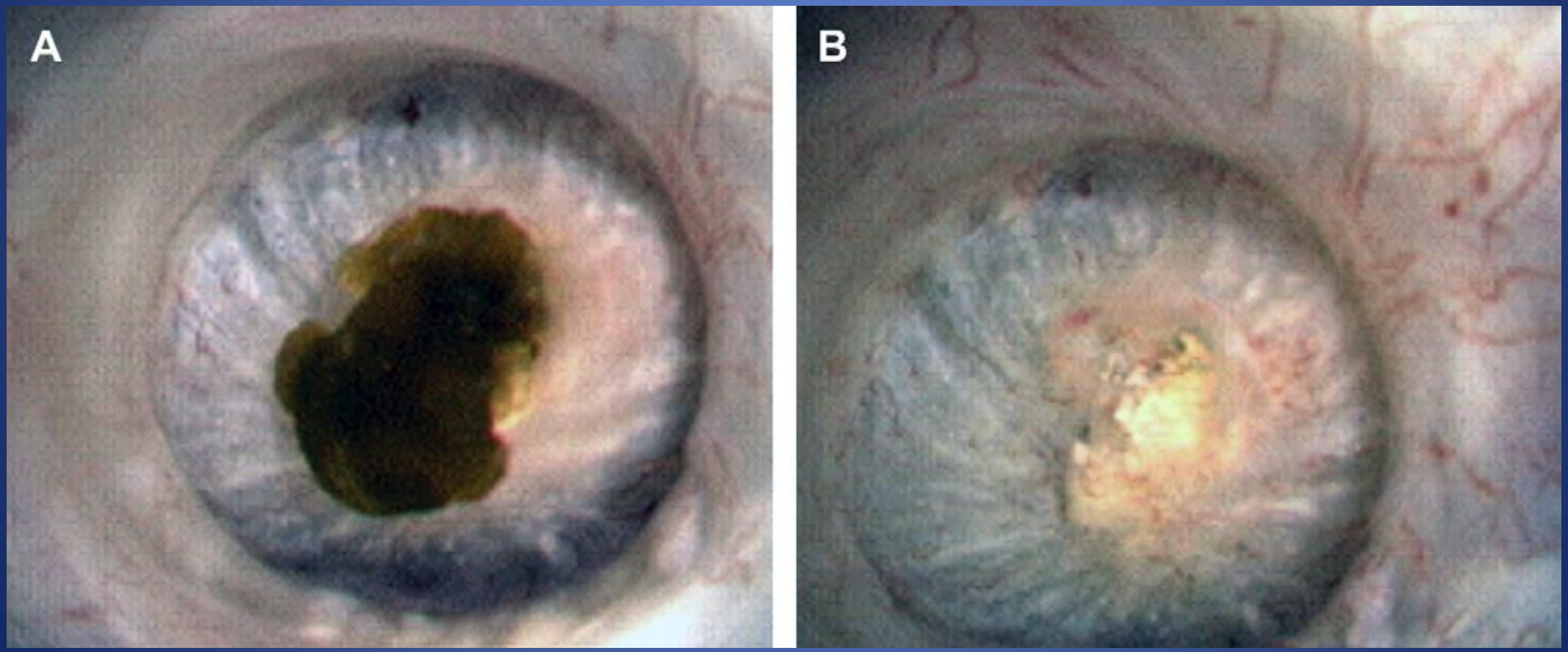
Randall's Plaque



Stone former

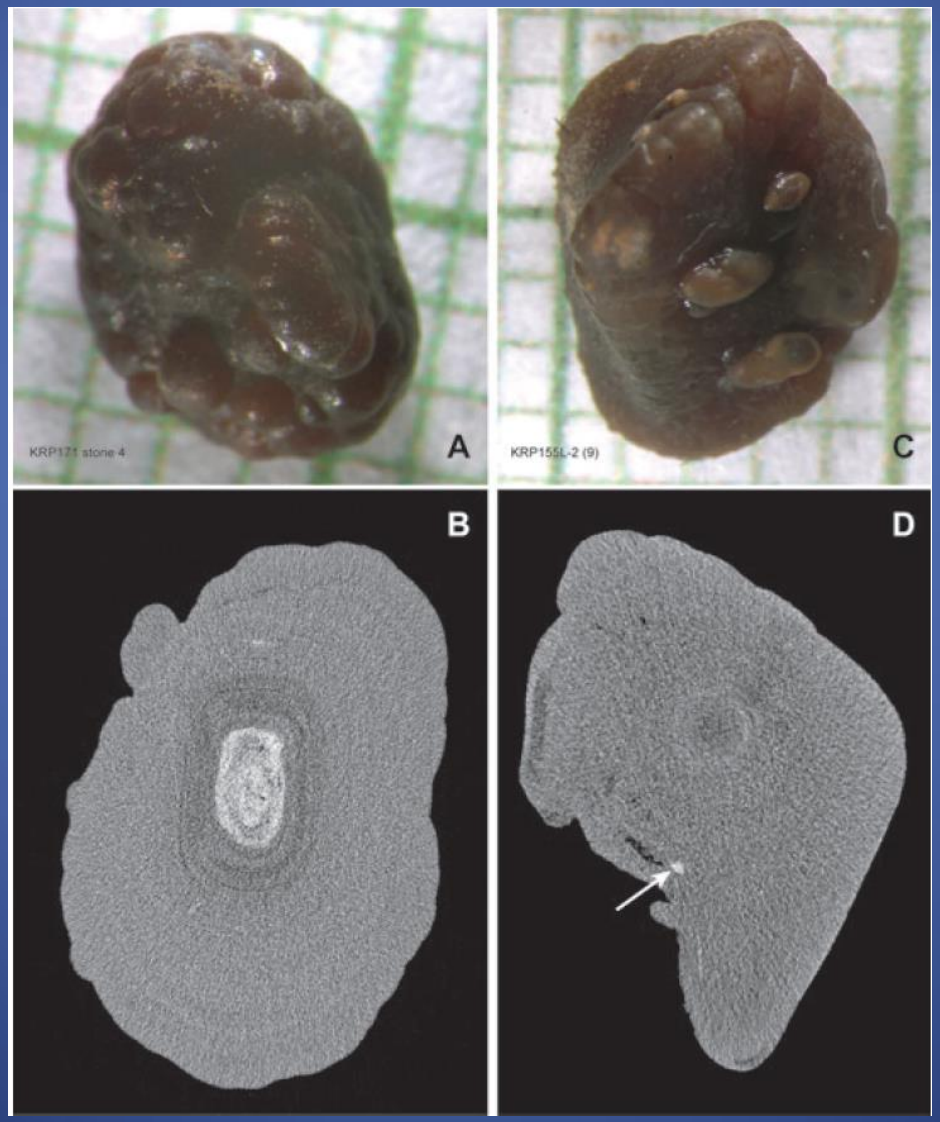
Normal

Randall's Plaque

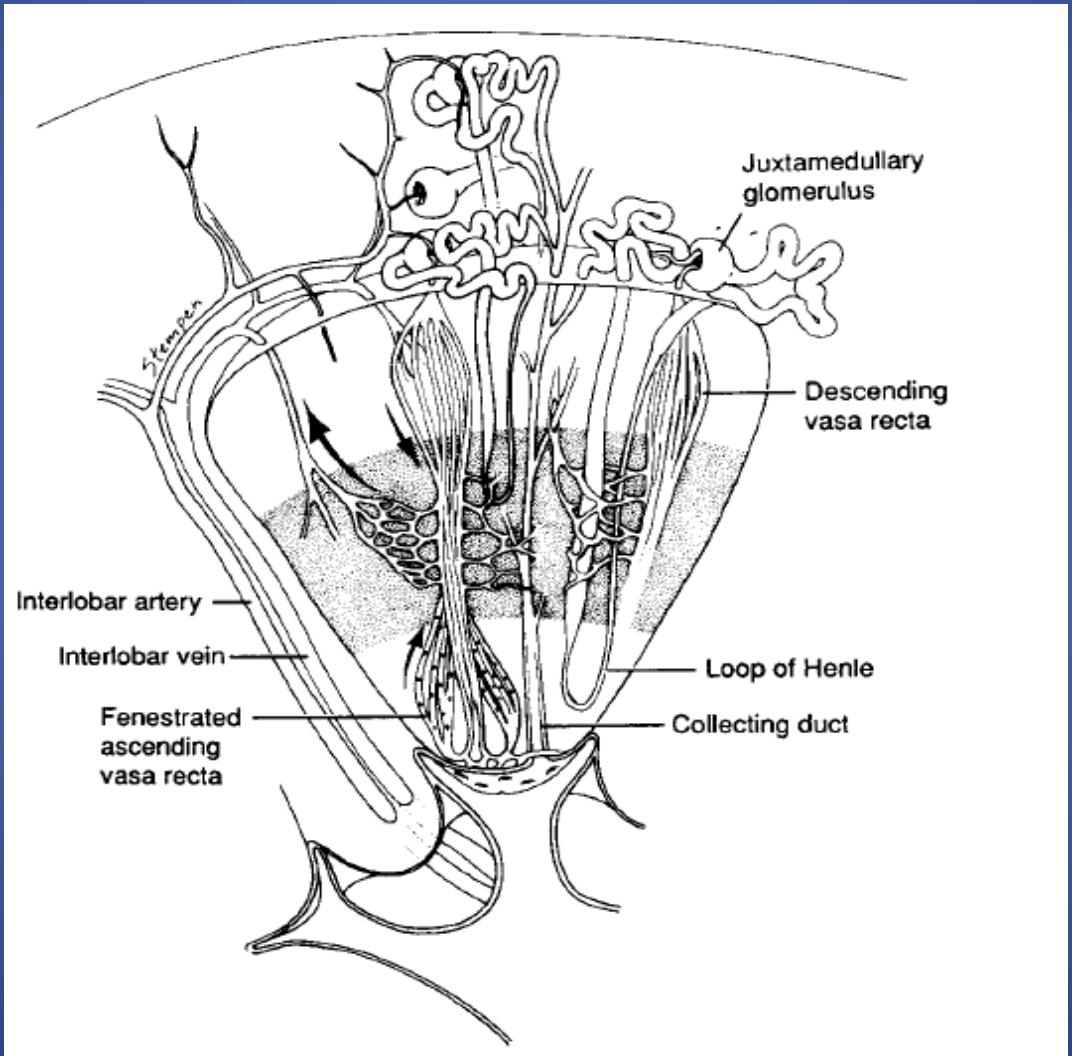


Attached Stone

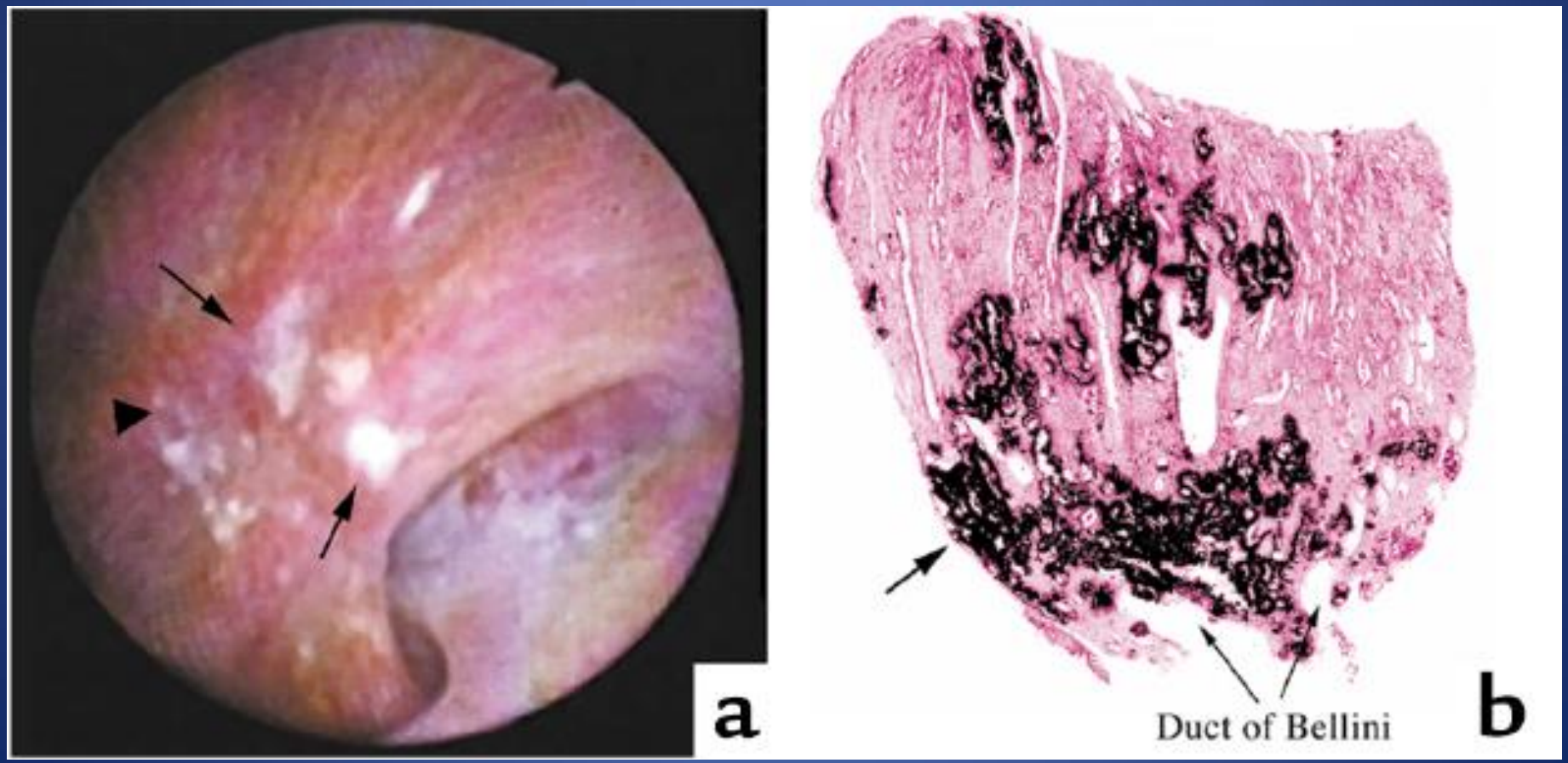
Unattached Stone



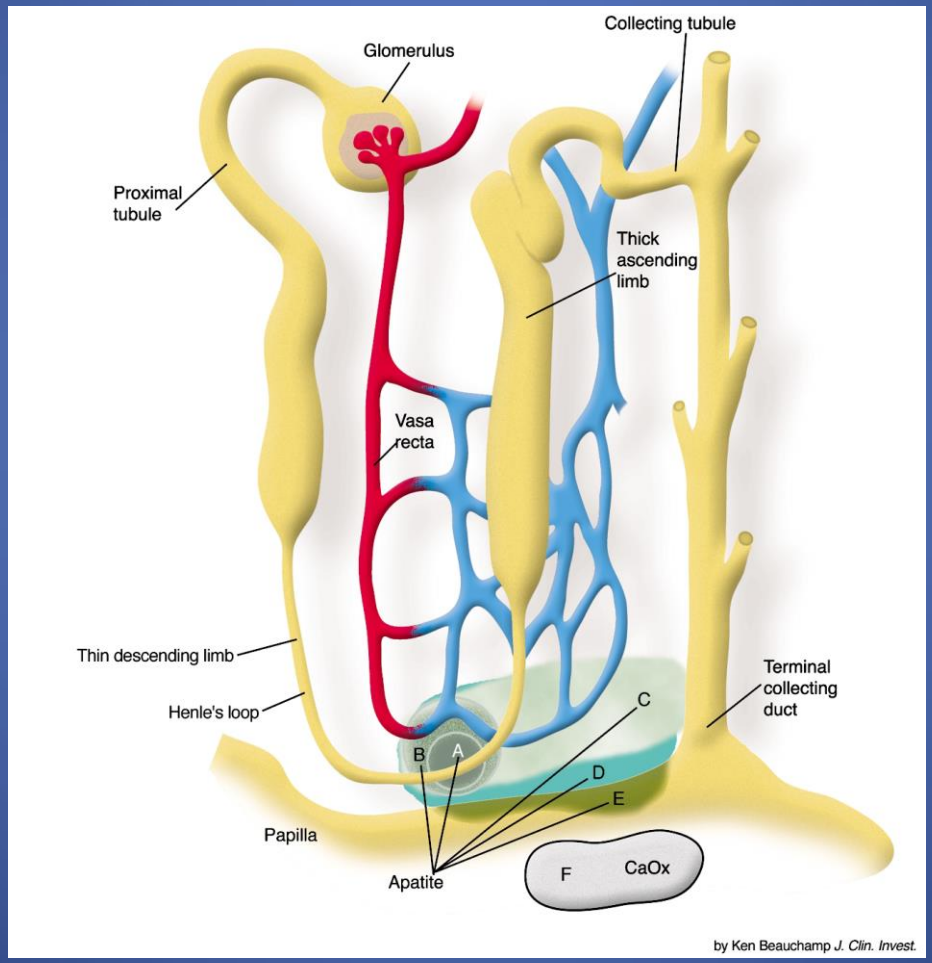
Renal Medulla



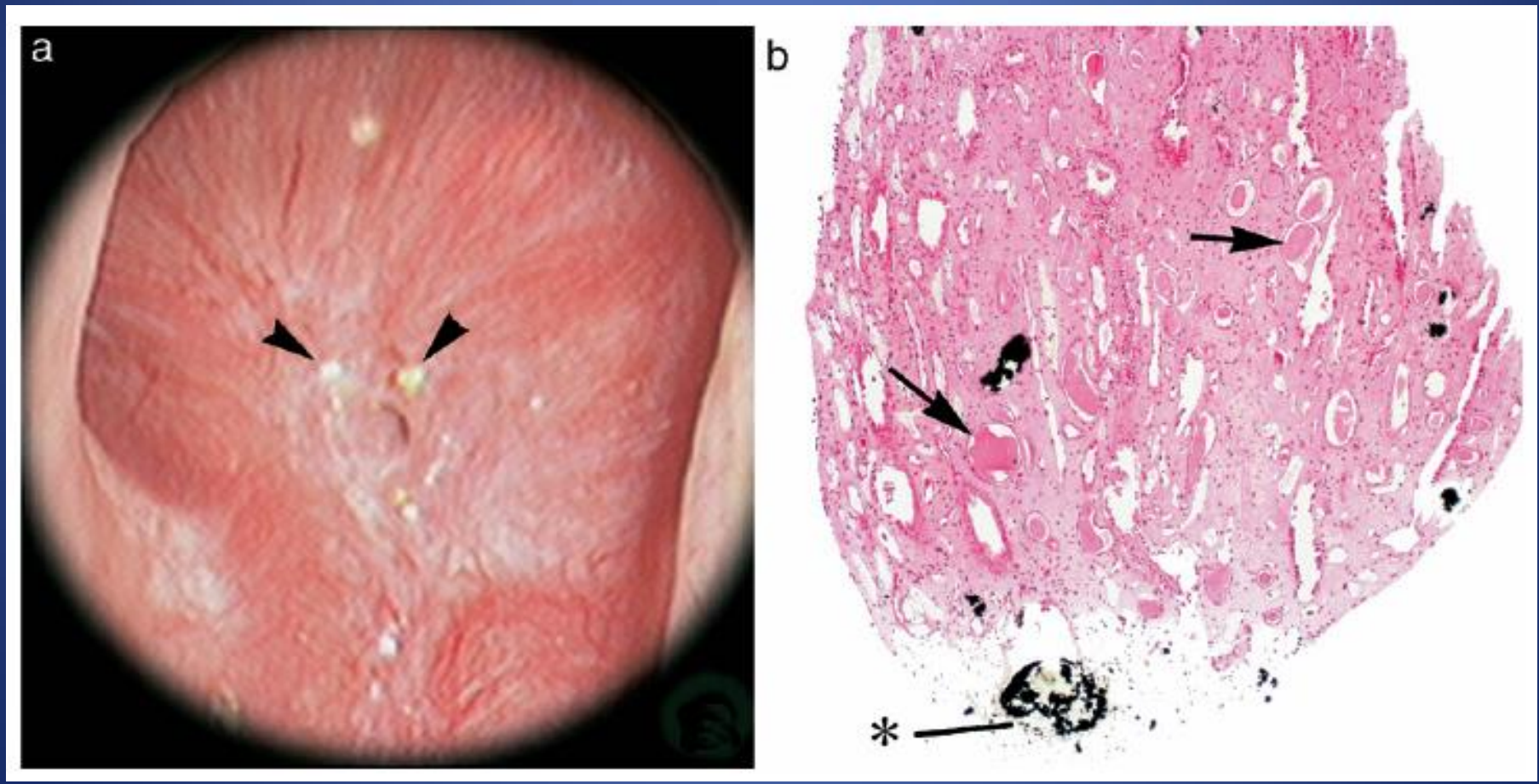
Calcium Oxalate Stone Former



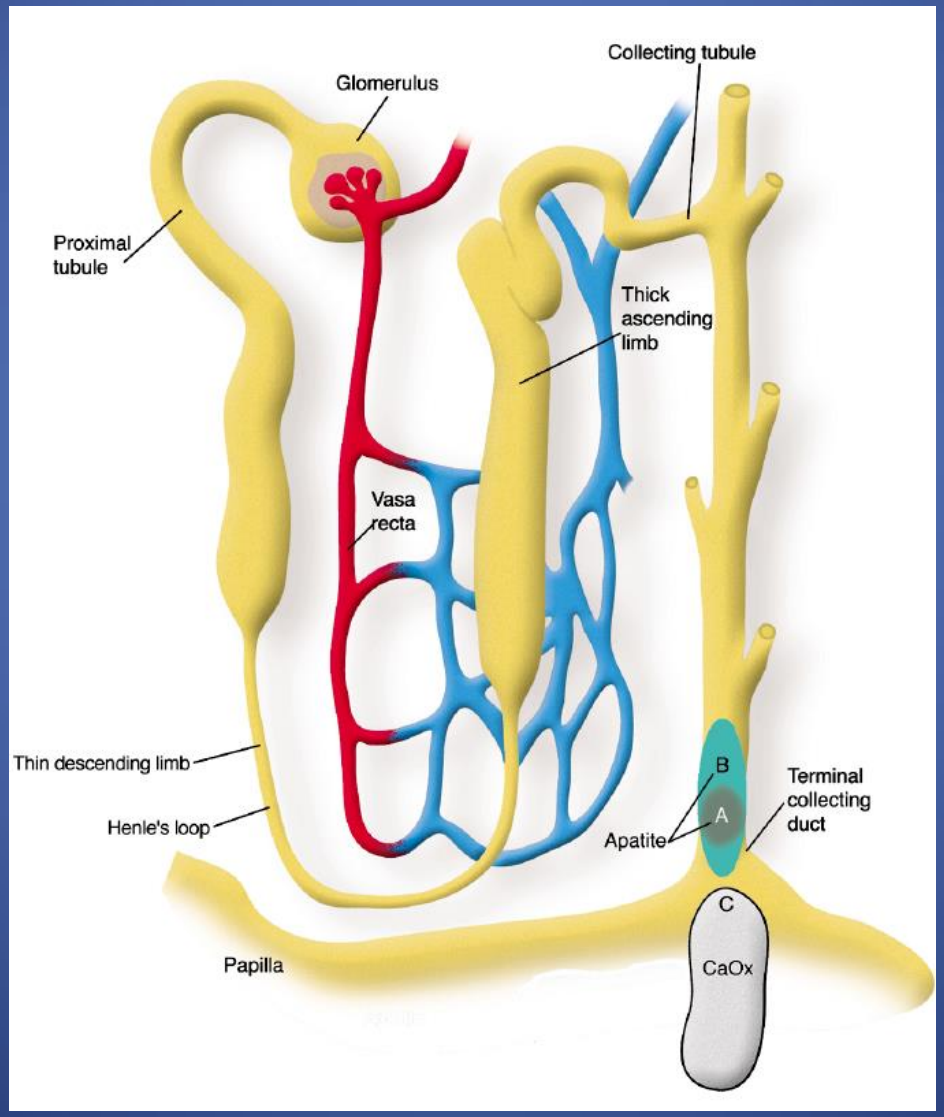
Calcium Oxalate Stone Former



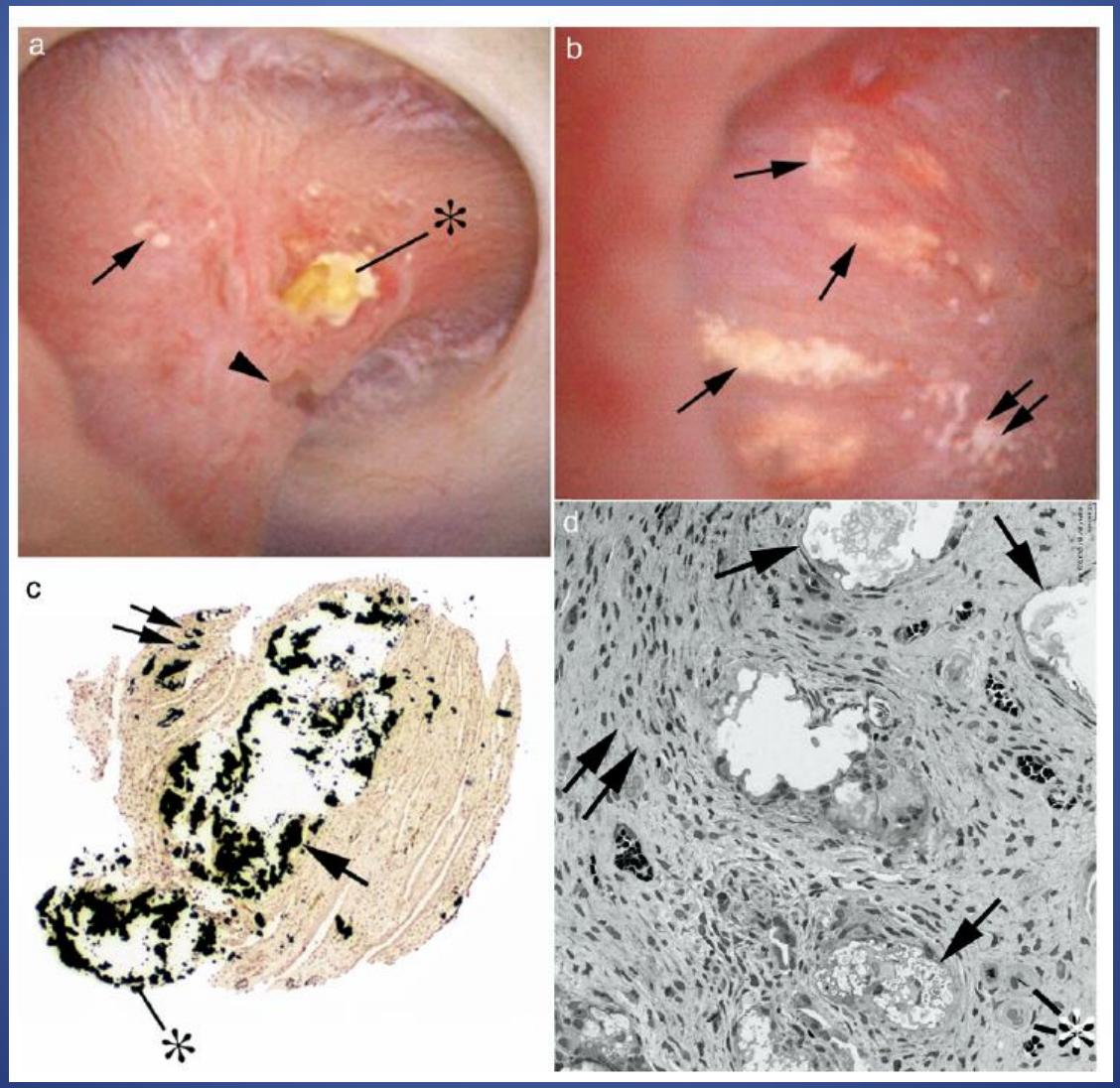
Intestinal Bypass Patient



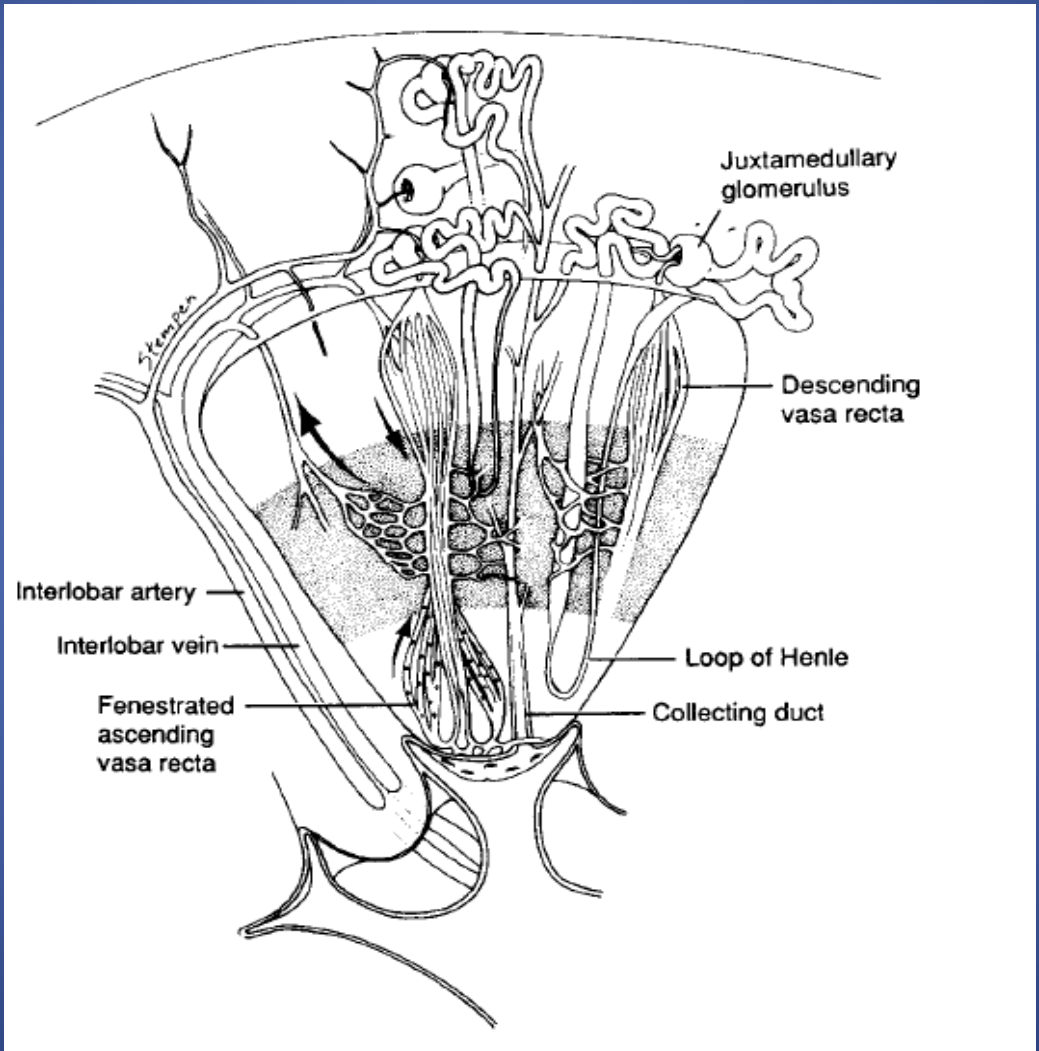
Intestinal Bypass Patient



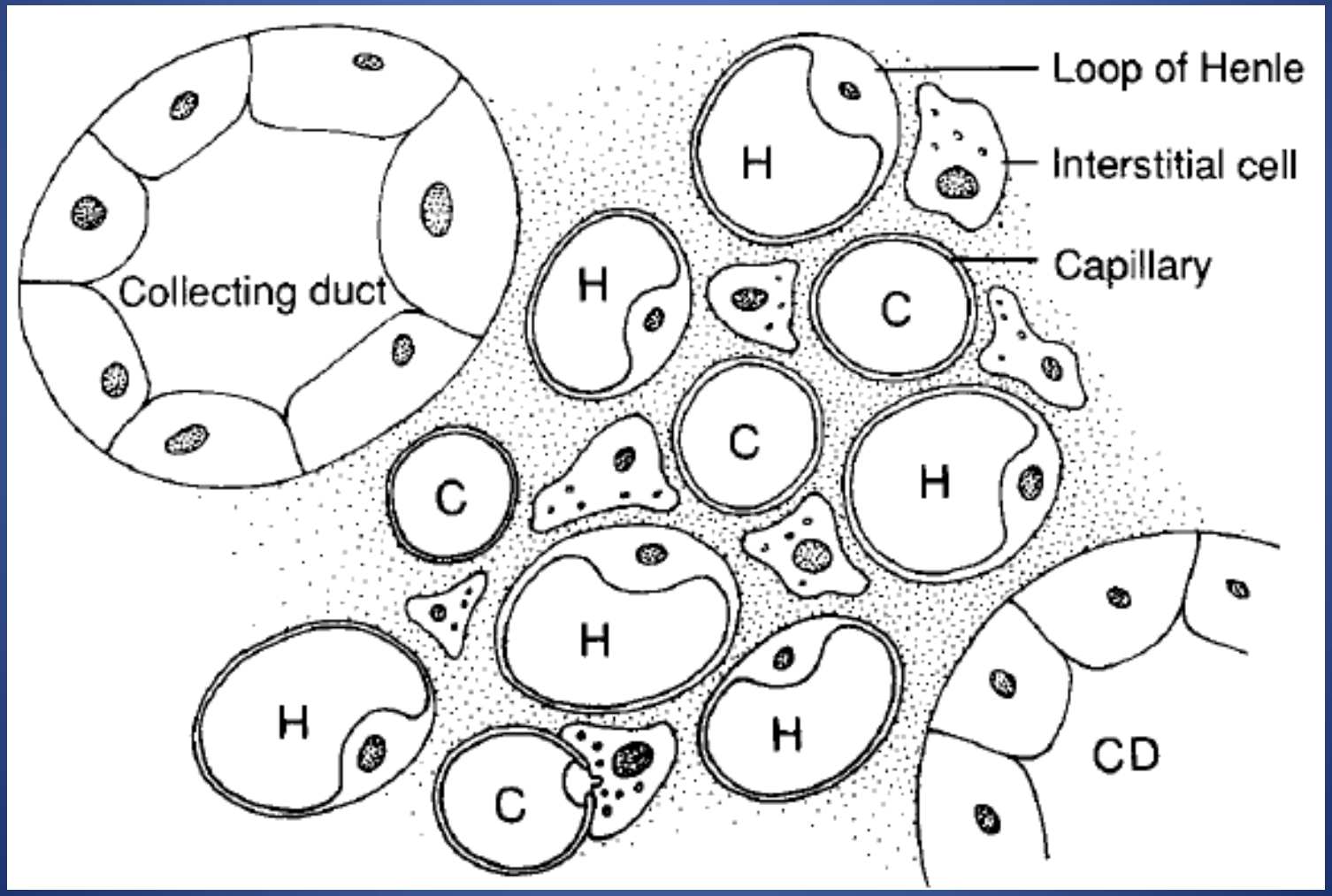
Brushite Stone Former



Renal Medulla



Vascular Etiology Theory



Evidence for Vascular Theory

- Epidemiologic
  - Association of atherosclerosis and hypertension with stones
- Clinical
  - Absence of stones with abnormal urinary studies and recurrent stones in spite of normal urinary studies
- Anatomical
  - Association of calcified vasculature with collecting tubules
- Physiological
  - Blood flow: laminar to turbulent and calcified vessels

Why do I form stones?

- Classic: Concentrations stone forming salts and inhibitors along with other factors such as urinary pH
- New: Complex pathophysiologic processes not fully understood in the renal medulla involving deposition of apatite at the tip of the papilla is the initial stone forming event
- New: Vascular pathology is the initial stone forming event

What can I do to prevent another attack?

- Improved diagnostic methods now uncover the underlying cause of stone disease in the vast majority of individuals
- Advances in selective therapy can reduce stone forming risk

Diagnostic Approach

- History and Physical
- Urine sediment
- Serum Chemistries
- Appropriate imaging
- 24 hour urine stone risk profile

History

- Prior stones and treatments
- Medical History: HTN, DM, Gout, others
- Prior GU surgery
- Prior GI surgery
- Bowel disease, fluid loss
- Stone-provoking medications
- Dietary factors

Medications

- Calcium and Vitamin D supplements
- Antacid and laxative use
- Lasix
- Vitamin C
- Topiramate

Minimal Diagnostic Tests

- Stone Analysis
- BMP
- Appropriate imaging
- Urinalysis
- 24 hour urine for Diagnostic Panel

Stone Composition

- Calcium containing: 75-80%
- Uric Acid: 10%
- Others: 10%
  - Struvite
  - Cystine
  - Sodium urate
  - Ammonium acid urate

24 Hour Urine

- Standardized, automated
- Volume recorded and aliquot sent to central lab
- Metabolic Factors (Ca, Ox, UA, citrate, pH)
- Environmental Factors (TV, Na, Sulfate, Phos, Mg)
- Physiochemical: Supersaturations

Values larger, bolder and more towards red indicate increasing risk for kidney stone formation.

Summary Stone Risk Factors

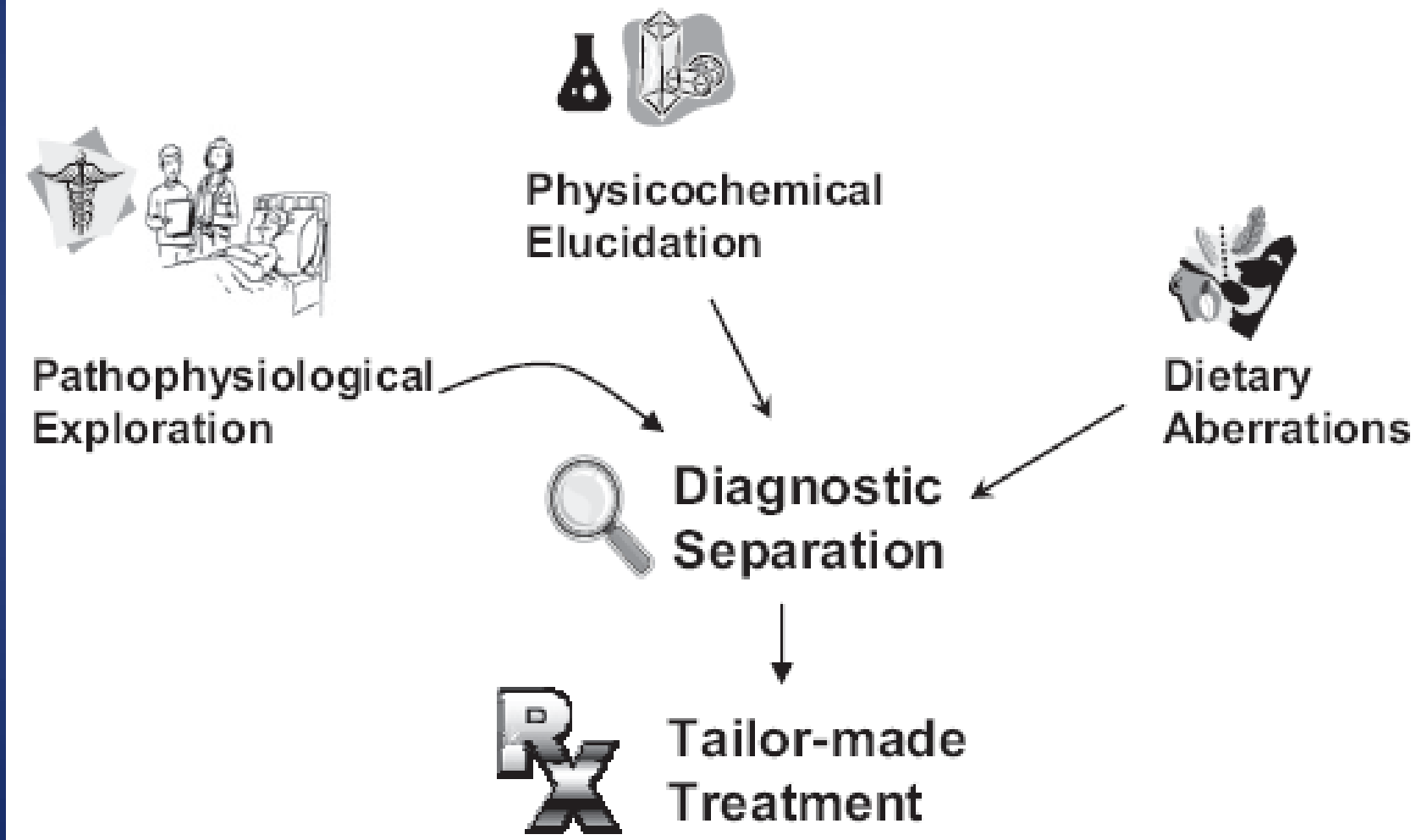
SAMPLE ID: **S470488** PATIENT COLLECTION DATE: **02/19/2009**

Interpretation Of Laboratory Results

Urine volume has fallen and is very low (was 2.11 and now is 1.25 l/d). Low urine volume in a stone former should always be corrected if possible. A good clinical goal is 2.5 liters daily. Recheck in 6 weeks and adjust fluid intake as needed. The low urine volume is permitting a combined increase of SS CaP and SSUA.

Calcium oxalate stone risk (SS CaOx) has risen and is high (was 4.27 and now is 9.85). In general, urine calcium, oxalate, citrate, and volume are the main factors responsible. The graphic display indicates which are most deviated from normal. Management suggestions are as noted above.

Diagnostic Approach



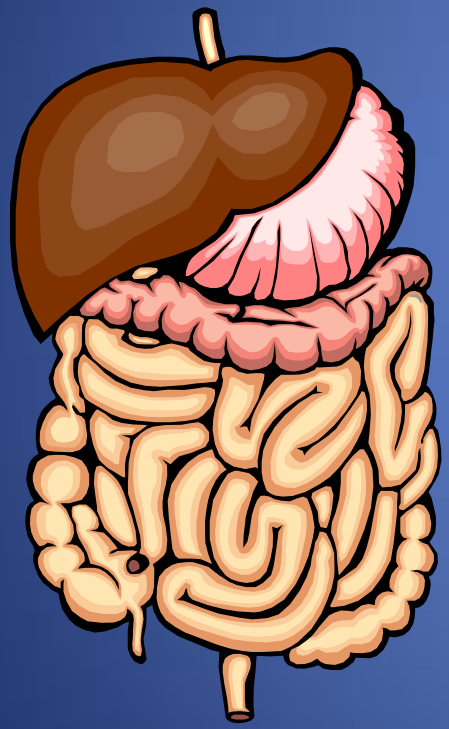
Calcium Stone Formation

- Hypercalciuria
- Hypocitraturia
- Hyperoxaluria
- Hyperuricosuria

Hypercalciuria

- Absorptive
- Renal
- Resorptive: Primary Hyperparathyroidism

Absorptive Hypercalciuria



Increased GI calcium absorption

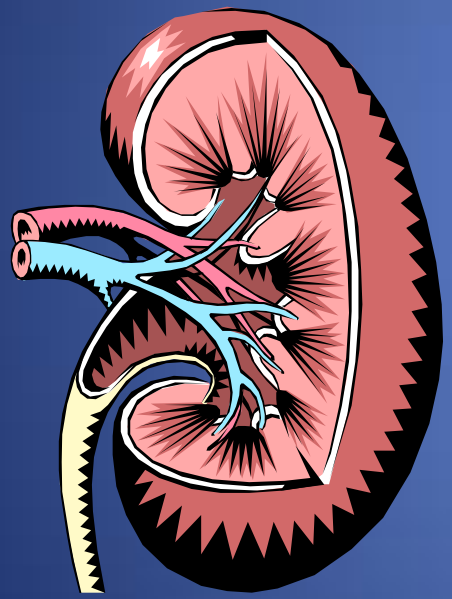
↓

Increased plasma Ca++

↓ ↓

Decreased PTH Increased urinary Ca++

Renal Hypercalciuria
“renal leak”



Increased urinary calcium → Decreased plasma Ca++

↓

Increased PTH

↙ Increased GI absorption

↓ Inc. Vit. D → Increased bone resorption

Resorptive Hypercalciuria

"Primary Hyperparathyroidism"

Increased PTH

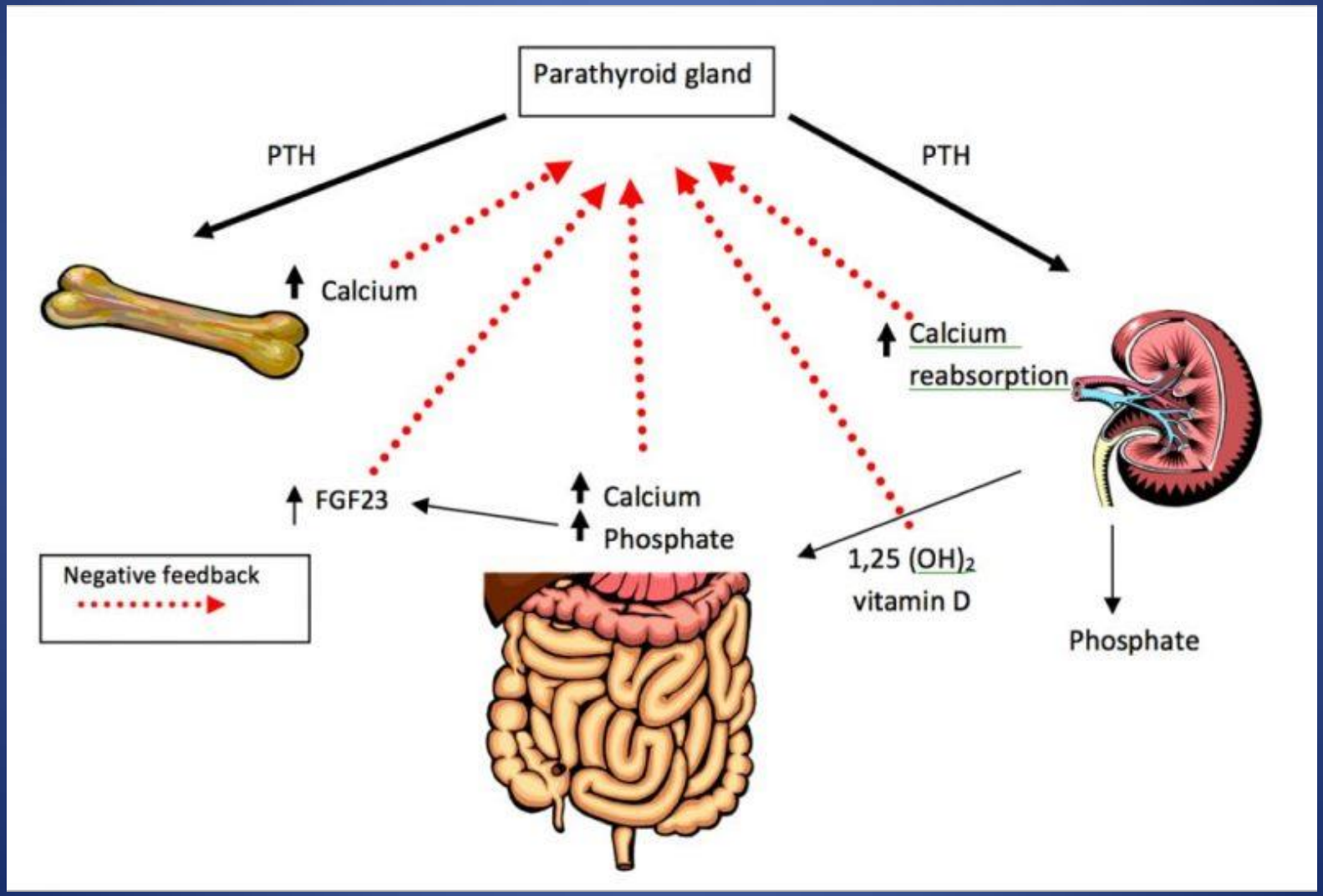
Increased bone resorption

Increased GI Ca++ absorption

Increased plasma Ca++

Increased urinary Ca++

Calcium Metabolism and Parathyroid Function



Bone Mineral Density and Hypercalciuria

Investigator	Measurement Method	Measurement Site	BMD Result
Lawoyin et al.,[22] 1979	SPA	Radius	↓ N
Fuss et al.,[23] 1983	SPA	Radius	↓
Pacifici et al.,[24] 1990	QCT	Spine	↓
Bataille et al.,[25] 1991	QCT	Spine	↓
Borghi et al.,[26] 1991	DPA	Spine	↓
Pietschmann et al.,[27] 1992	DEXA, SPA	Spine, radius	↓
Jaeger et al.,[28] 1994	DEXA	Spine, femur	↓
Weisinger et al.,[29] 1996	DEXA	Spine, femur	↓
Ghazali et al.,[30] 1997	QCT	Spine	↓
Giannini et al.,[31] 1998	DEXA	Spine, femur	↓
Misael da Silva et al.,[32] 2002	DEXA	Spine, femur	↓
Tasca et al.,[33] 2002	DEXA	Spine, femur	↓
Asplin et al.,[34] 2003	DEXA	Spine, femur	↓
Vezzoli et al.,[35] 2003	DEXA	Spine, femur	↓
Caudarella et al.,[36] 2003	DEXA, QUS	Radius, finger	↓

SPA = single photon absorptiometry; DEXA = dual energy x-ray absorptiometry; DPA = dual photon absorptiometry; QCT = quantitative computed tomography; QUS = quantitative ultrasonography; N = normal; ↓ = reduced.

Kidney Stones and Bone Health

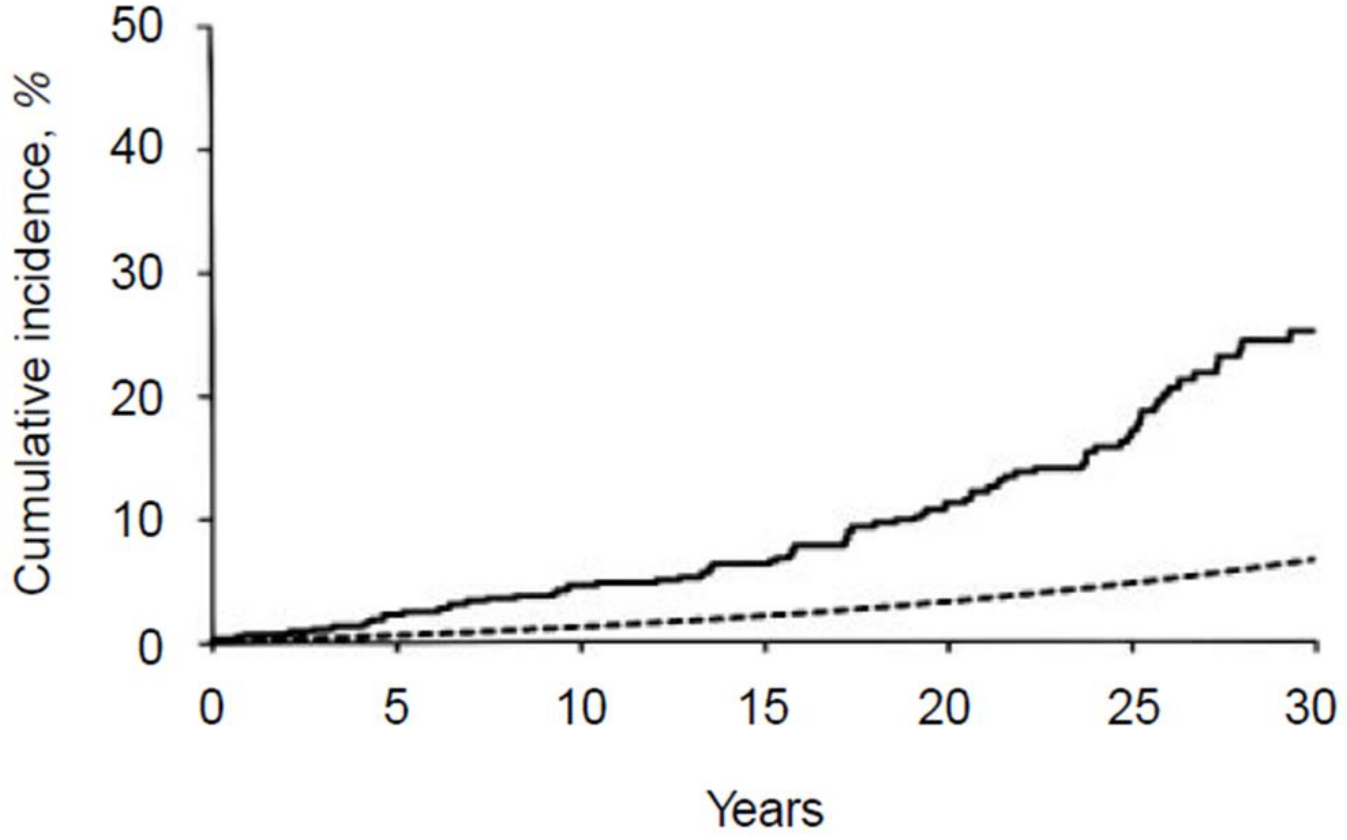


Fig. 3. Observed (solid line) and expected (dashed line) cumulative incidence of vertebral fractures among Rochester, Minnesota, residents following the initial episode of symptomatic urolithiasis, 1950 to 1974.

Melton, Kidney Int, 1993

Hypocitraturia

- Citrate is a well recognized inhibitor of stone formation
- Defined as <300 mg/day (arbitrary)
- 20-60% of calcium stone formers

Hypocitraturia

- Citrate is a well recognized inhibitor of stone formation
- Defined as <300 mg/day (arbitrary)
- 20-60% of calcium stone formers

Hypocitraturia

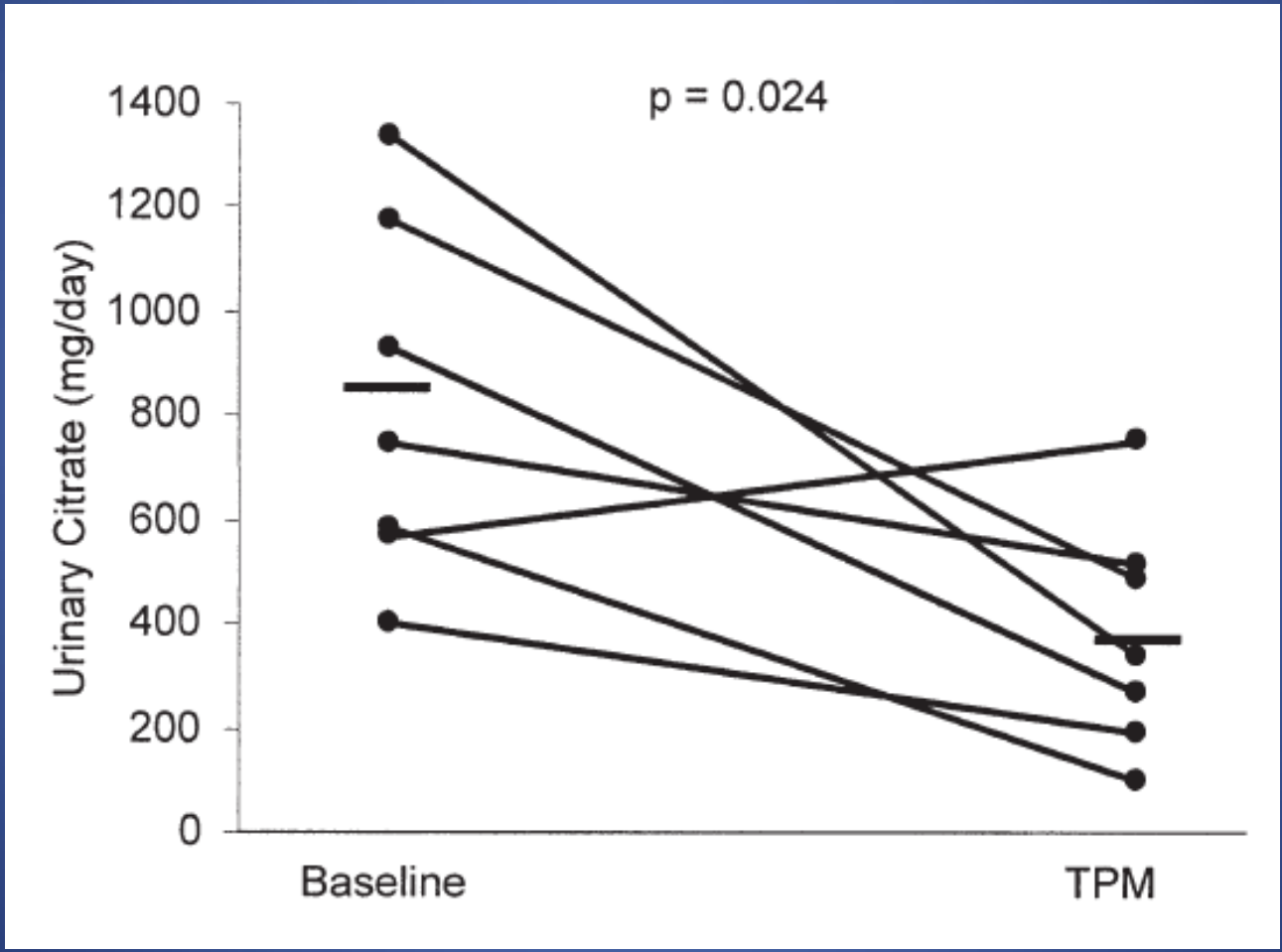
Pathogenesis

- Type I (Distal) RTA
- Chronic diarrheal states
- Excessive animal protein intake
- Thiazide induced hypokalemia
- Idiopathic
- Medication induced

Renal Tubular Acidosis:
Clues to Diagnosis

- Young female with early age of onset
- Nephrocalcinosis
- Urine pH > 6.5
- Profound hypocitraturia
- Hyperchloremic, hypokalemic acidosis
- Stone composition: Calcium phosphate

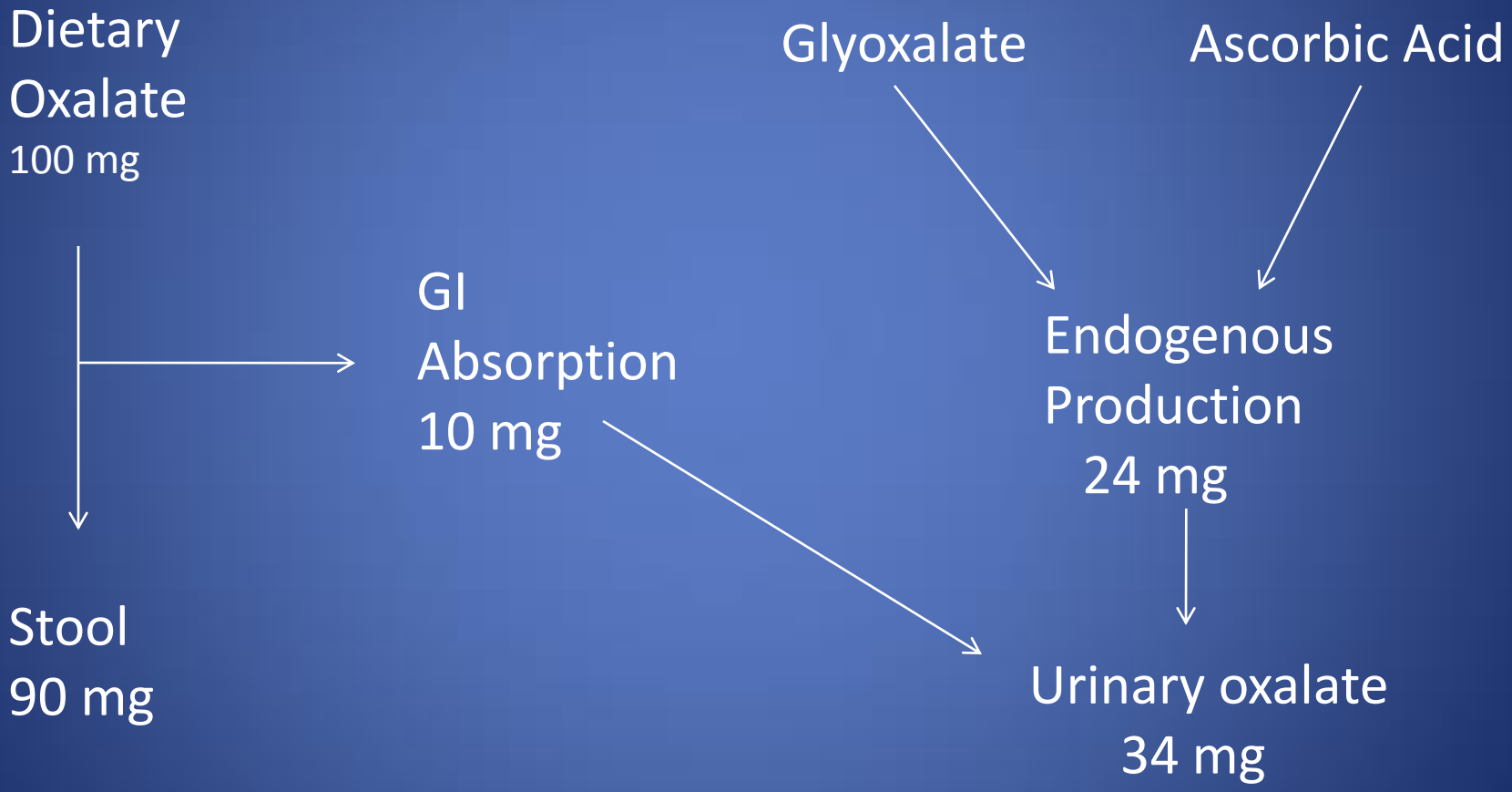
Topiramate and Hypocitraturia



Hyperoxaluria

- Idiopathic
  - Most common
- Enteric
  - Intestinal disease/resection
  - Bariatric surgery
- Primary
  - rare

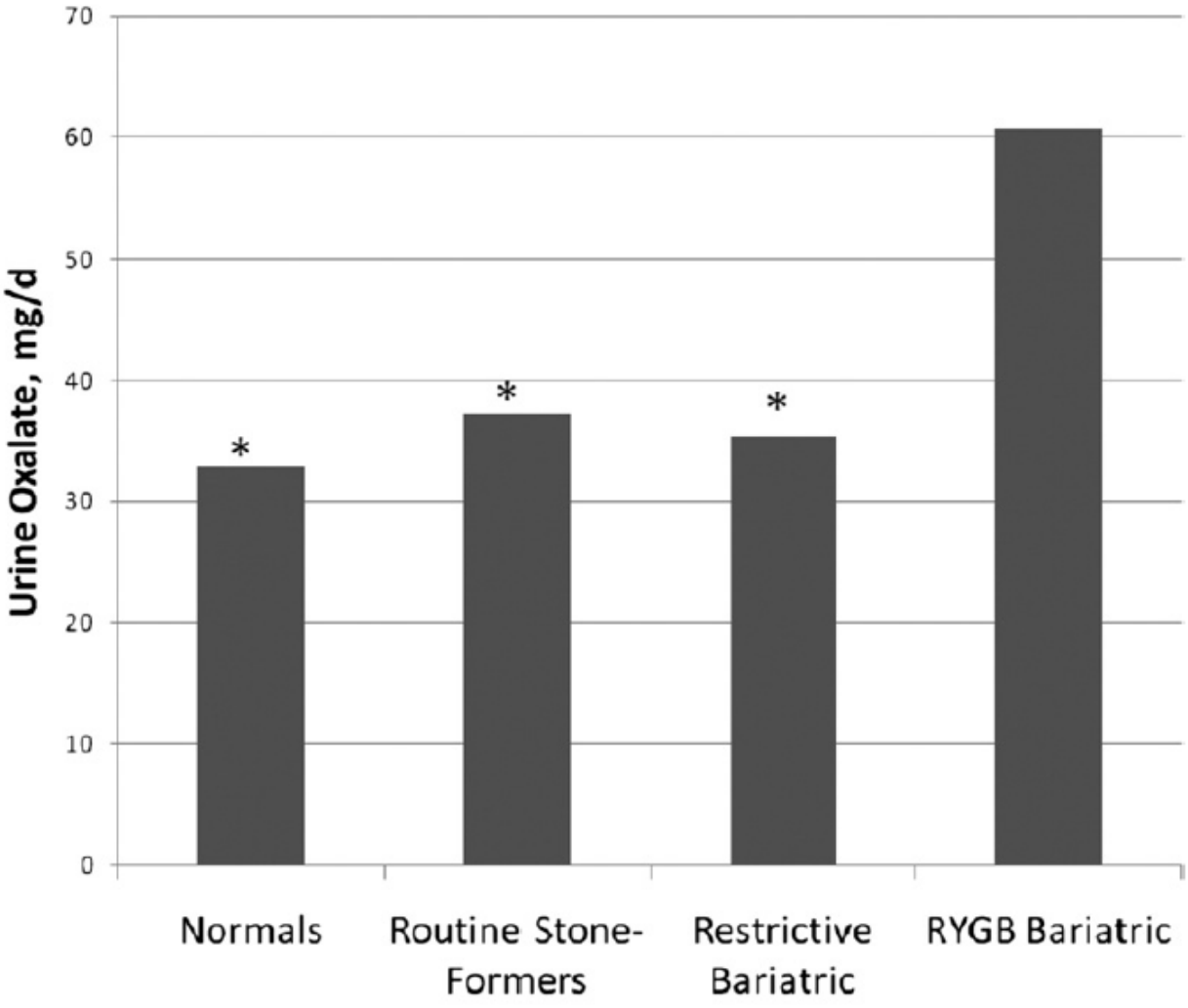
Oxalate Production



Enteric Hyperoxaluria

- Should be suspected in any patient with hyperoxaluria and a small bowel abnormality
- 5% of patients in specialized metabolic stone clinics
- Low urine volume
- Low calcium, magnesium, citrate excretion

Bariatric Surgery



* P<.0001 vs. RYGB Bariatric group

Bariatric Surgery and Stone Treatment

Table 2. *Summary of kidney stone procedures performed*

	No. (%)		p Value
	RYGB Group	Control Group	(chi-square test)
Shock wave lithotripsy	81 (1.75)	19 (0.41)	<0.0001
Ureteroscopy with or without lithotripsy	98 (2.11)	27 (0.58)	<0.0001
Percutaneous nephrolithotomy	6 (0.13)	3 (0.06)	0.5076*
Overall	153 (3.30)	43 (0.93)	<0.0001

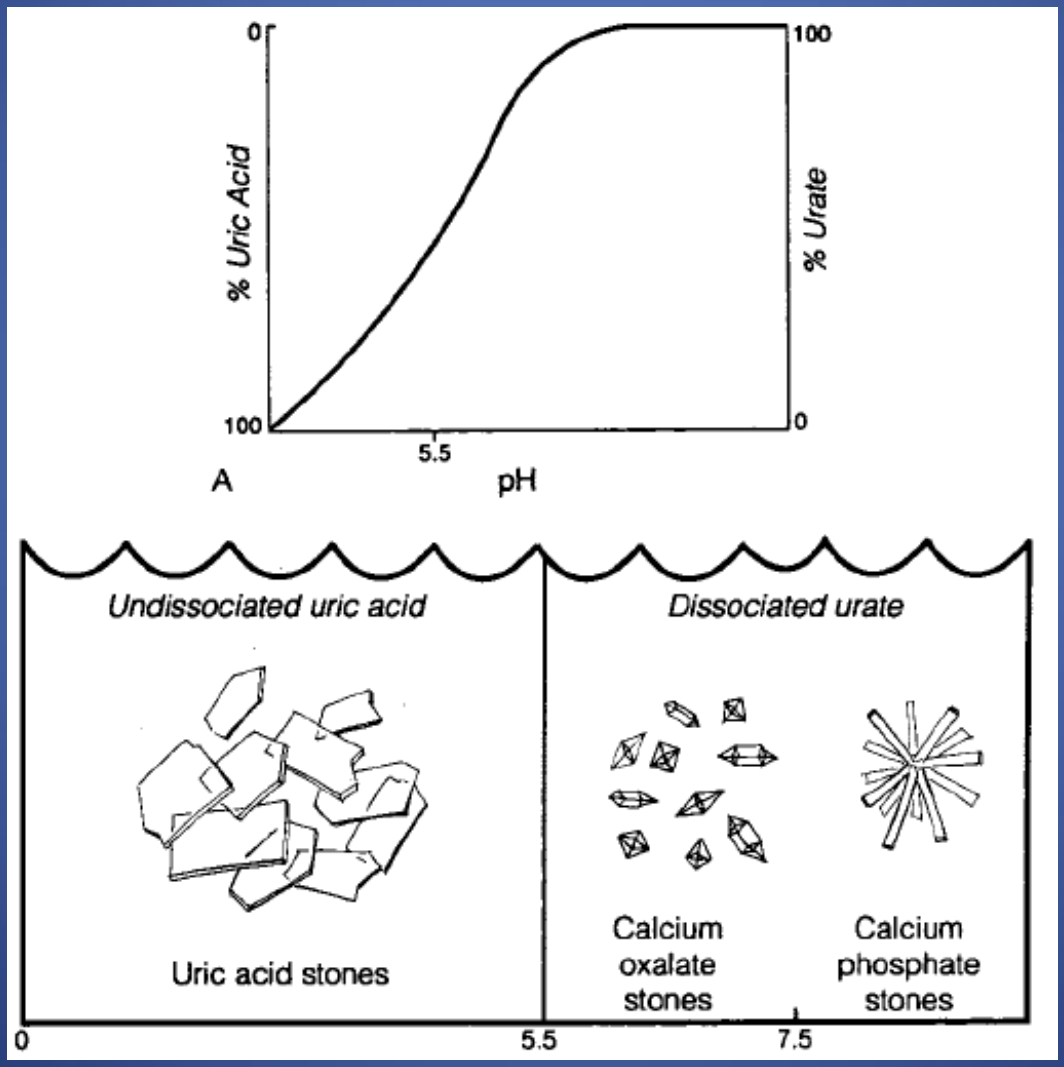
* Fisher's exact test.

Matlaga, J. Urol 2009

Hyperuricosuria

- Arbitrarily defined as uric acid excretion exceeding 600 mg/day
- Independent risk factor for calcium oxalate stone formation
- Excess dietary purine intake is the most common cause
- Others include gout, myeloproliferative disorders, multiple myeloma, hemolytic disorders

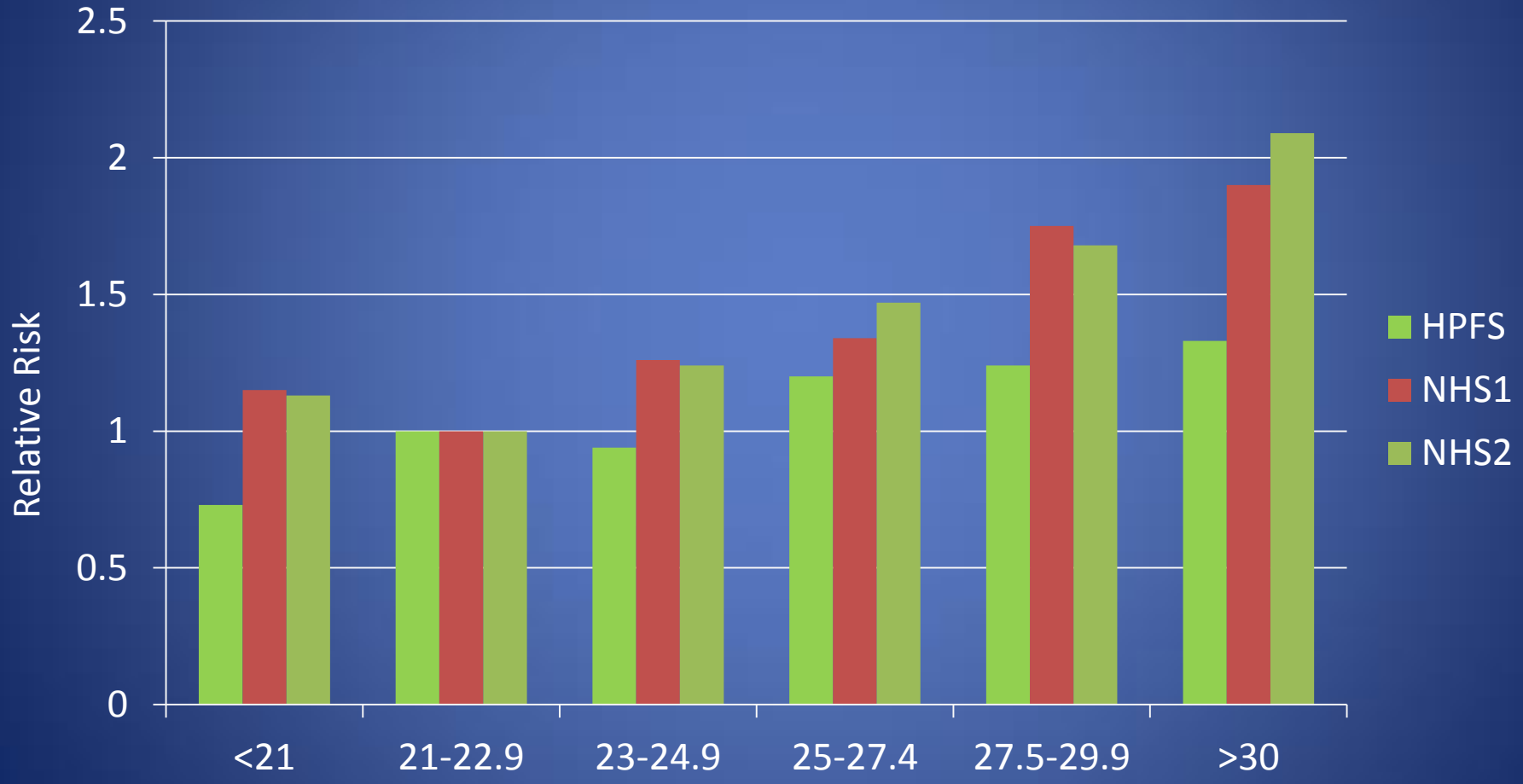
Hyperuricosuric CaOx Lithiasis: Pathogenesis



Obesity and Stones

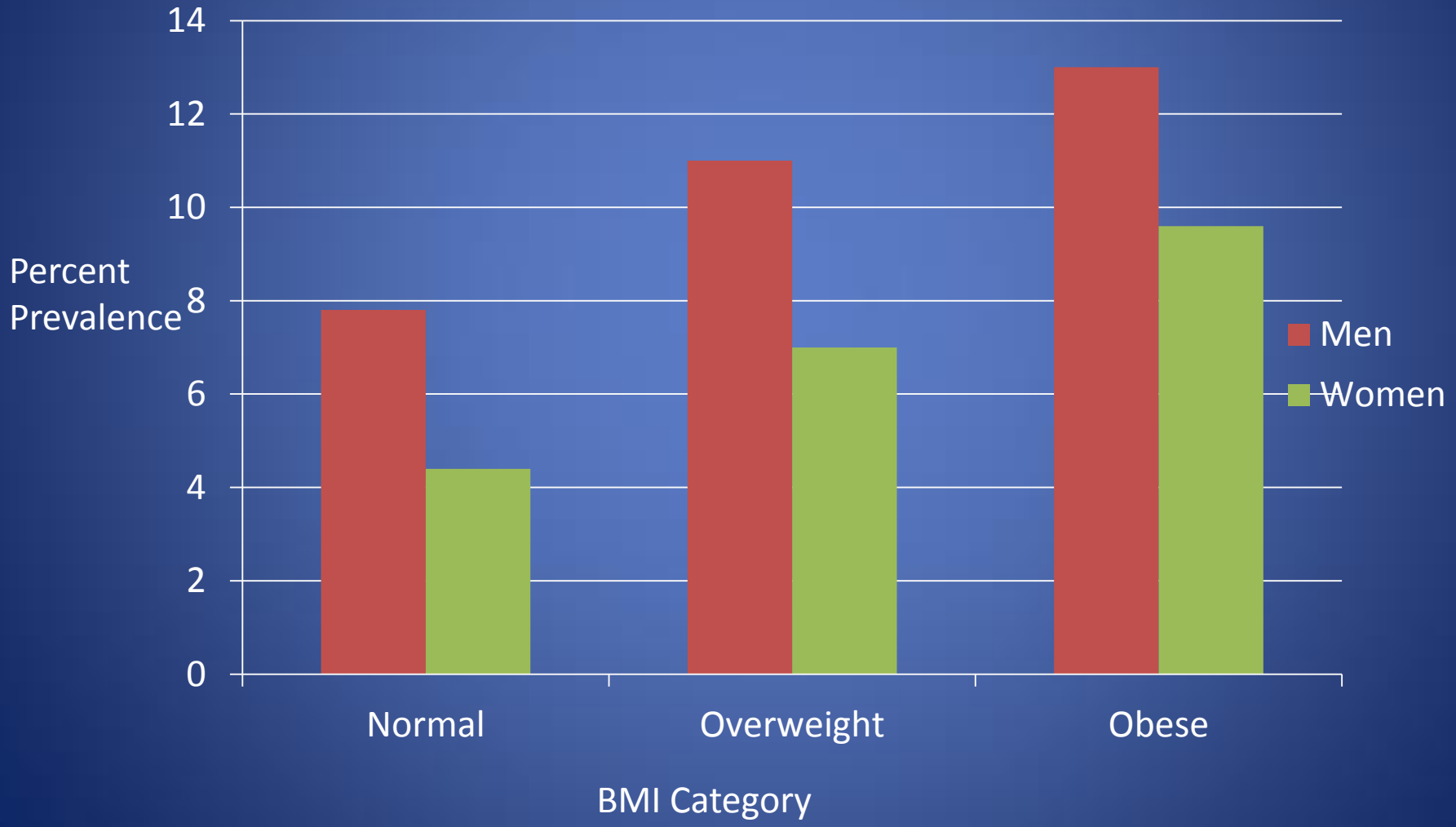
- Increasing incidence of stones has paralleled the increasing incidence of obesity
- Higher stone risk with increasing BMI
- Obesity closely associated with development of metabolic syndrome
- Higher risk of uric acid nephrolithiasis

Obesity Trends



Taylor , JAMA 2008

NHANES: Prevalence of Kidney Stones



Childhood Obesity

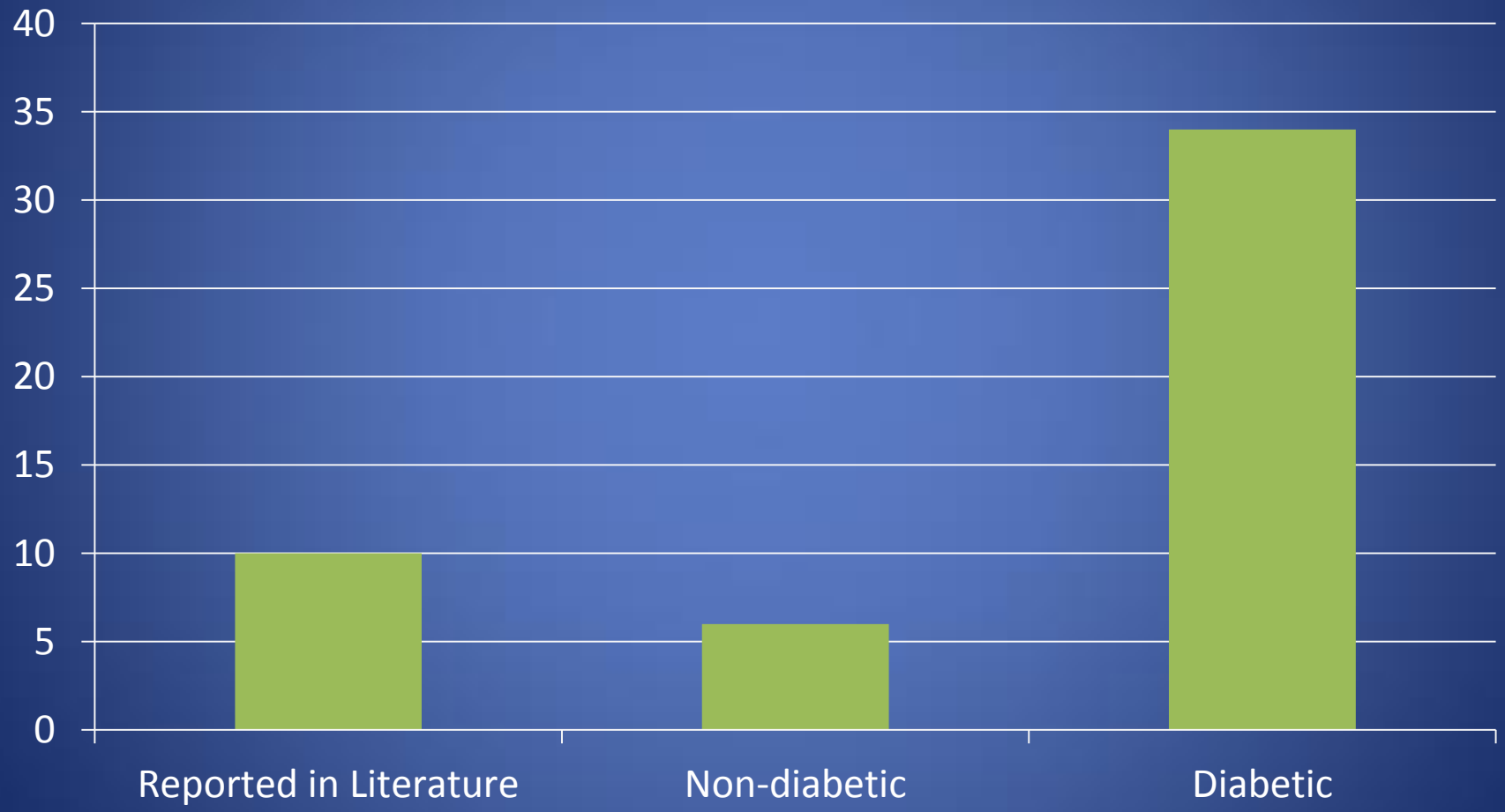
24 hour urine and Obesity

- Lower pH
- Lower citrate
- Higher oxalate
- Higher sodium and sulfate
- Higher uric acid

Diabetes and Stones

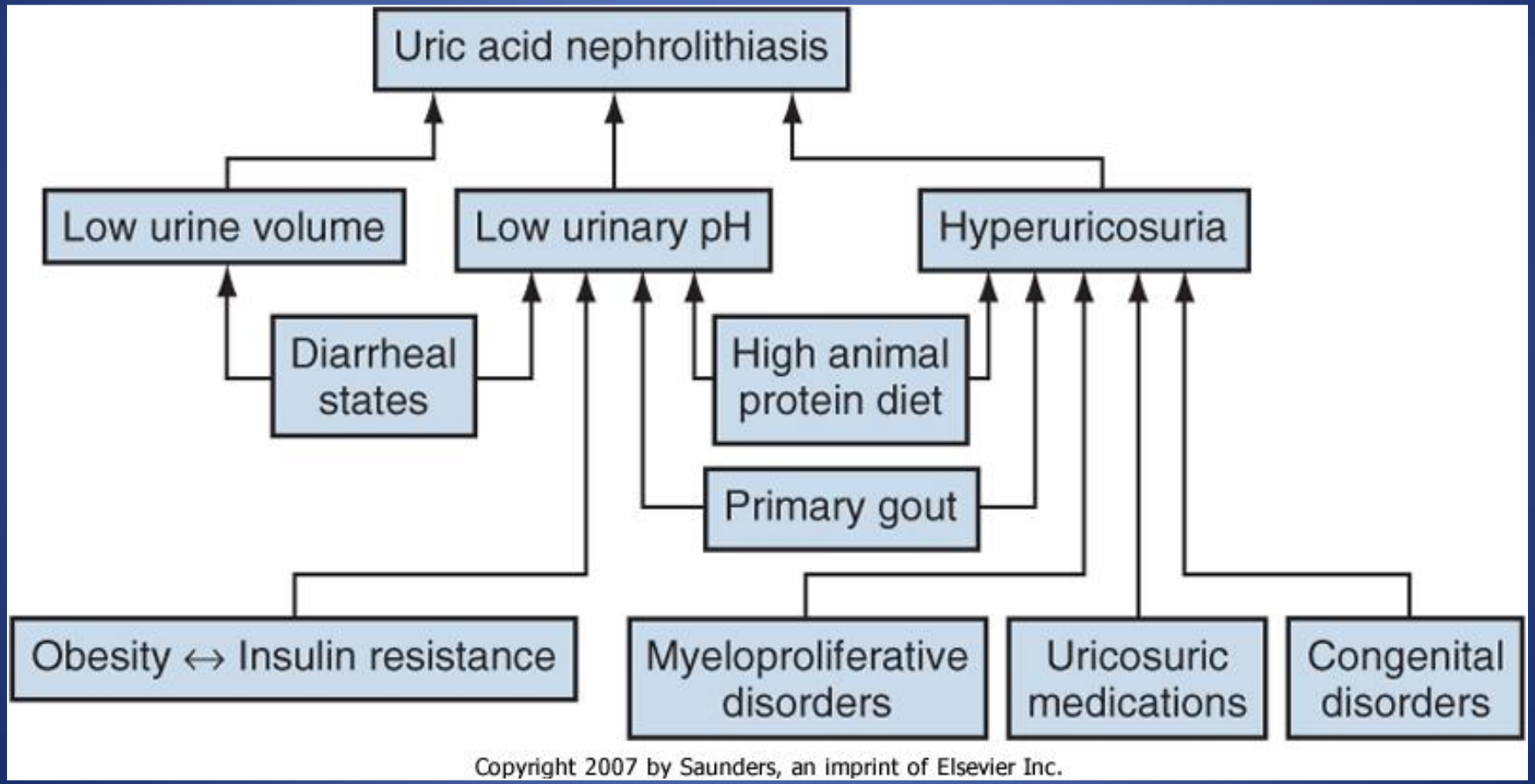
- DM (Type II) has been shown in population based studies to raise the risk of kidney stones
- Insulin resistance is the primary mechanism resulting in low urinary pH increasing uric acid stone risk
- Insulin resistance lowers urinary citrate thus increasing calcium stone risk

Prevalence of Uric Acid Lithiasis

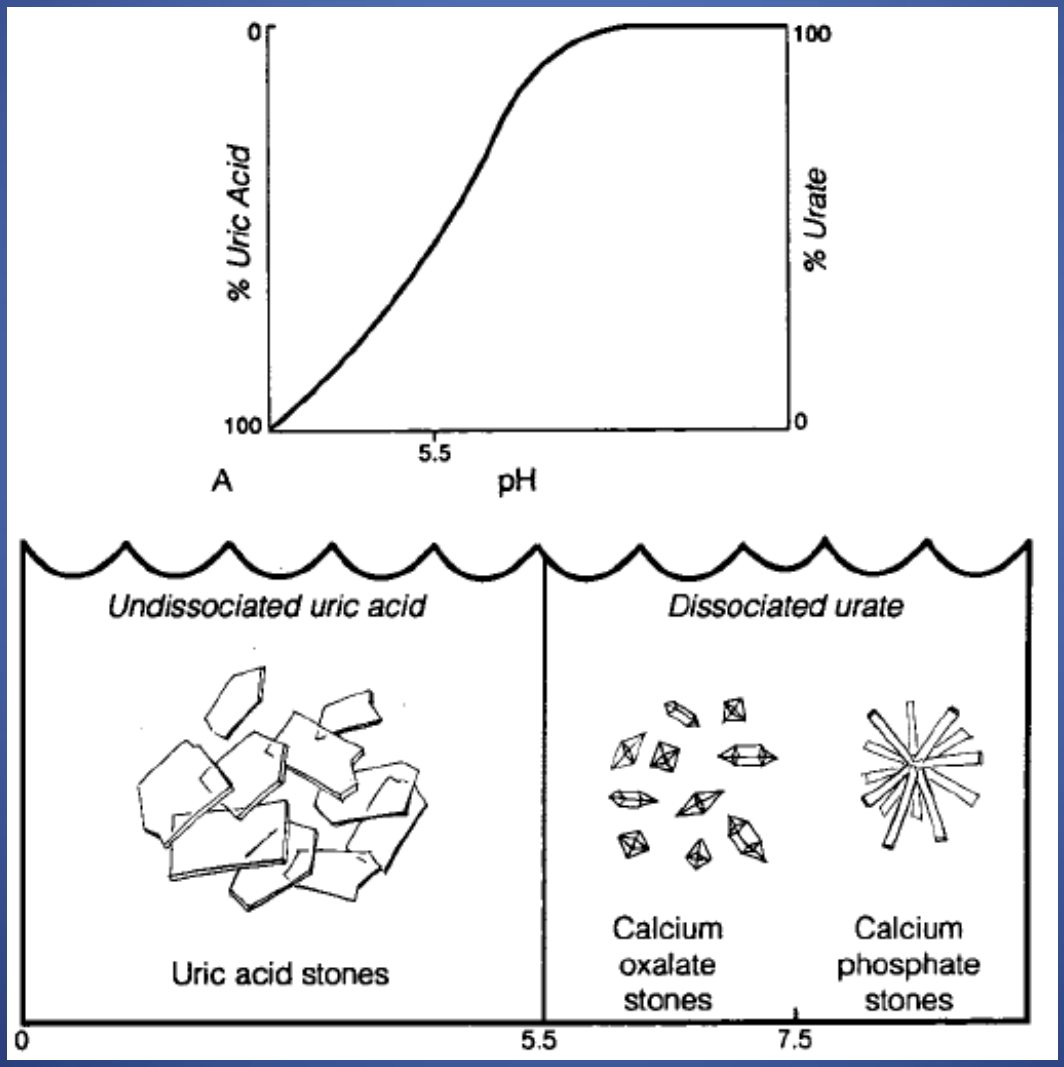


Pak et al, Urol 2003

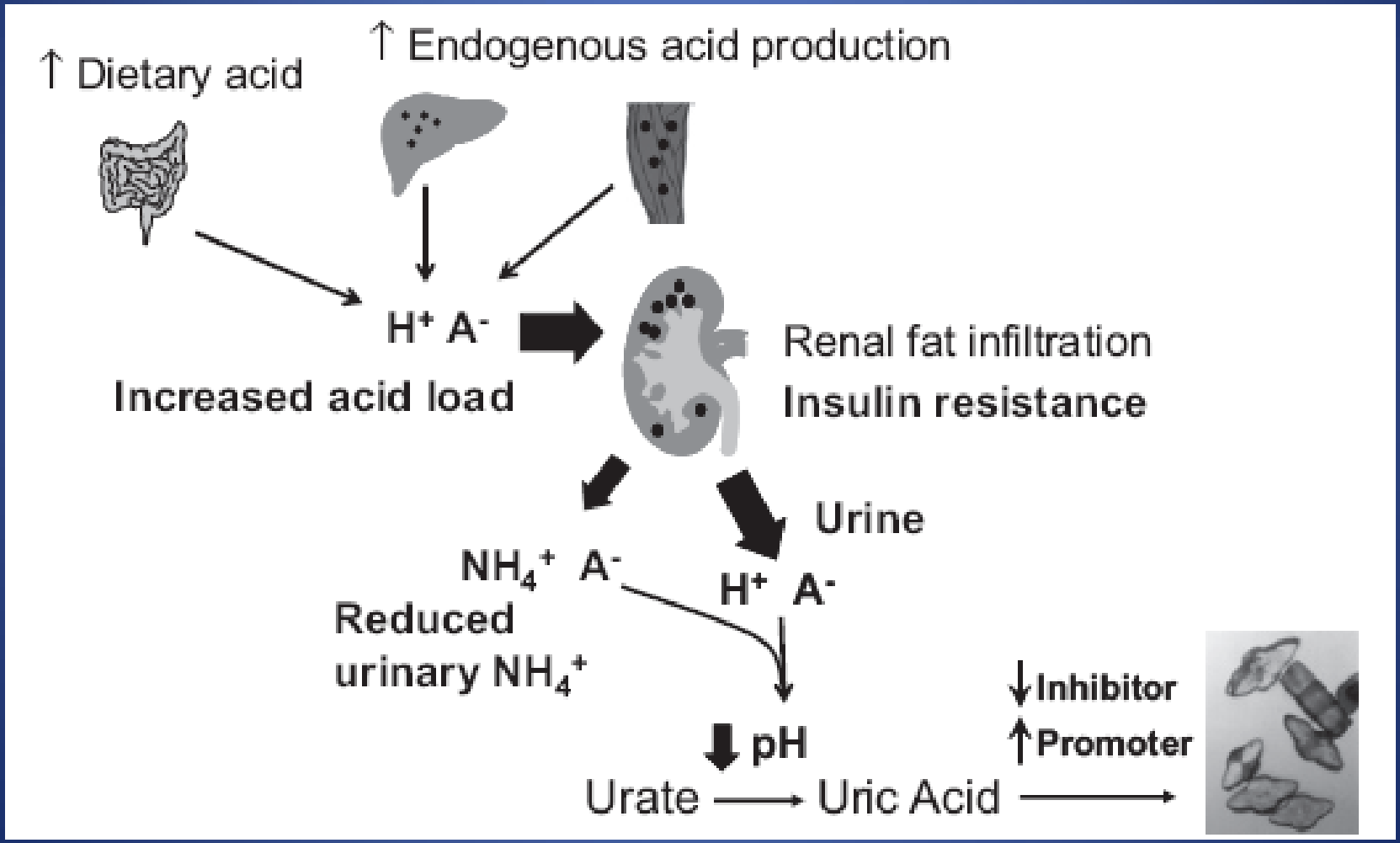
Pathogenesis of Uric Acid Lithiasis



Uric Acid Lithiasis: Pathogenesis



Uric Acid Lithiasis

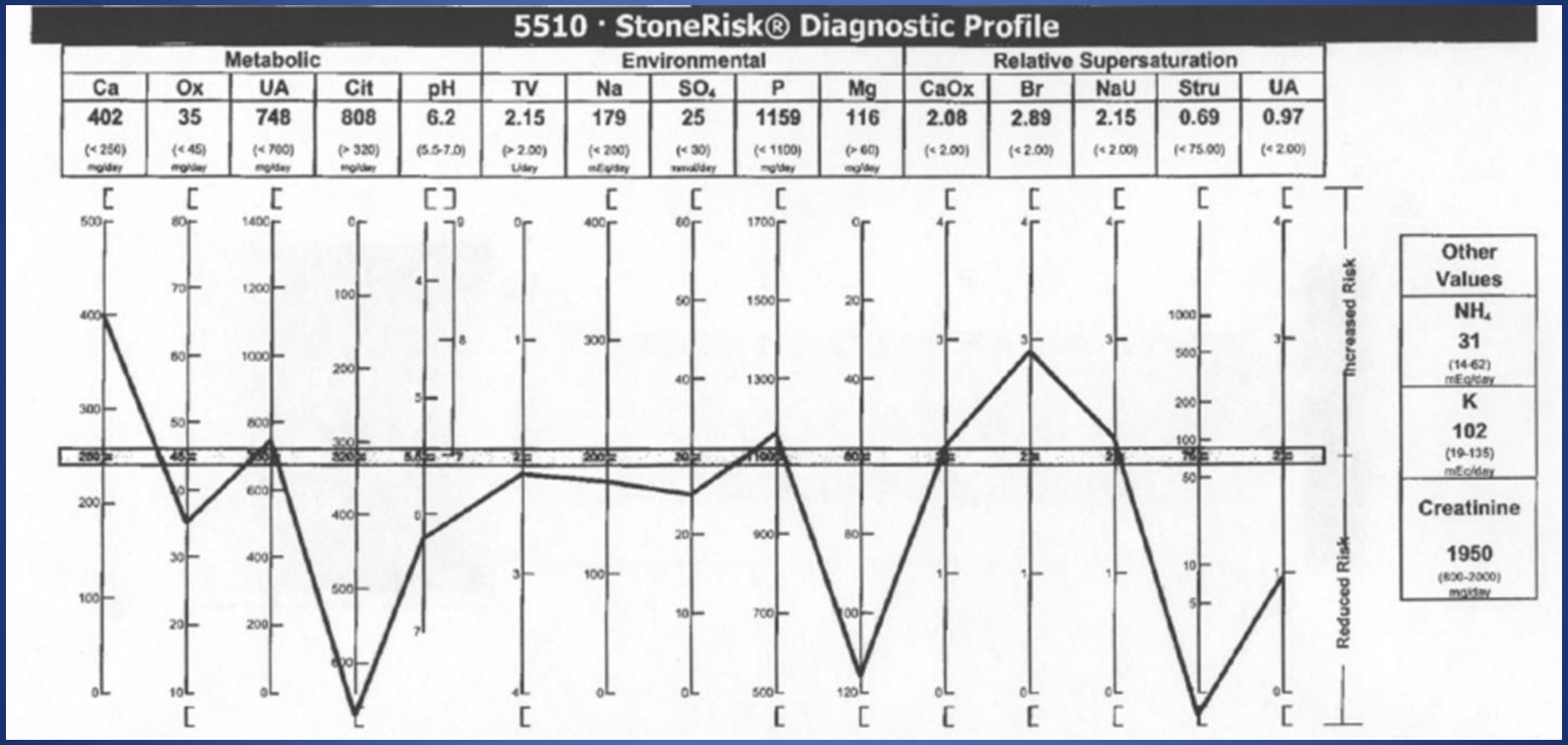


Treatment: Dietary Modification

- Borghi et al, Nutrition Rev. July 2006, 301-312
- High Fluid Intake: Ten 10 oz. glasses H_20/day or 2-2.5L urine/day
- Sodium Restriction: Keep salt intake to 2500 mg/day
- Oxalate restriction: oxalate rich foods and Vitamin C
- Adequate calcium rich foods
- Limit animal protein intake: 6 oz. servings
- Increase citrus fruit and juice intake

Medical Therapy: Rationale

- Many patients will have stone recurrence in spite of dietary modification
- Most stone formers have metabolic abnormalities that are not caused by, but are exacerbated by dietary indiscretions
- Many patients are poorly compliant with dietary modification


5510 · StoneRisk® Diagnostic Profile
Metabolic
Environmental
Relative Supersaturation
Ca 402 (< 250) mg/day
Ox 35 (< 45) mg/day
UA 748 (< 700) mg/day
Cit 808 (> 320) mg/day
pH 6.2 (5.5-7.0)
TV 2.15 (> 2.00) L/day
Na 179 (< 200) mEq/day
SO4 25 (< 30) mmol/day
P 1159 (< 1100) mg/day
Mg 116 (> 60) mg/day
CaOx 2.08 (< 2.00)
Br 2.89 (< 2.00)
NaU 2.15 (< 2.00)
Stru 0.69 (< 75.00)
UA 0.97 (< 2.00)
Increased Risk
Reduced Risk
Other Values
NH4 31 (14-62) mEq/day
K 102 (19-135) mEq/day
Creatinine 1950 (600-2000) mg/day

Thiazide Diuretics

- Patients with severe hypercalciuria (>275 mg/day)
- Patients with mild hypercalciuria and reduced bone mineral density
- Hypocalciuric action due to enhanced calcium reabsorption in the proximal renal tubule

Thiazides

- HCTZ 25-50 mg/BID
- Indapamide 1.25 – 2.5 mg/day
- Chlorthalidone 25 mg/day

  K-Cit 40-60 meq/day
- Moduretic (amiloride + HCTZ) ½ tab BID

Thiazides
Potential Hazards

- Hypokalemia: closely monitor and use potassium supplements
- Hypocitraturia: monitor and use KCit supplements
- Hyperuricosuria: purine restriction, possibly use allopurinol

Hypocitraturia: Potassium Citrate

- Corrects hypocitraturia in patients with calcium oxalate stones
- Provides potassium supplementation for patients on thiazides
- Corrects hypocitraturia in patients with RTA
- Maintains pH between 6.0-6.5 in patients with uric acid stones

Potassium Citrate

- Liquids/crystals
  - Polycitra-K
  - Citra-K
- Slow release pills
  - Urocit K

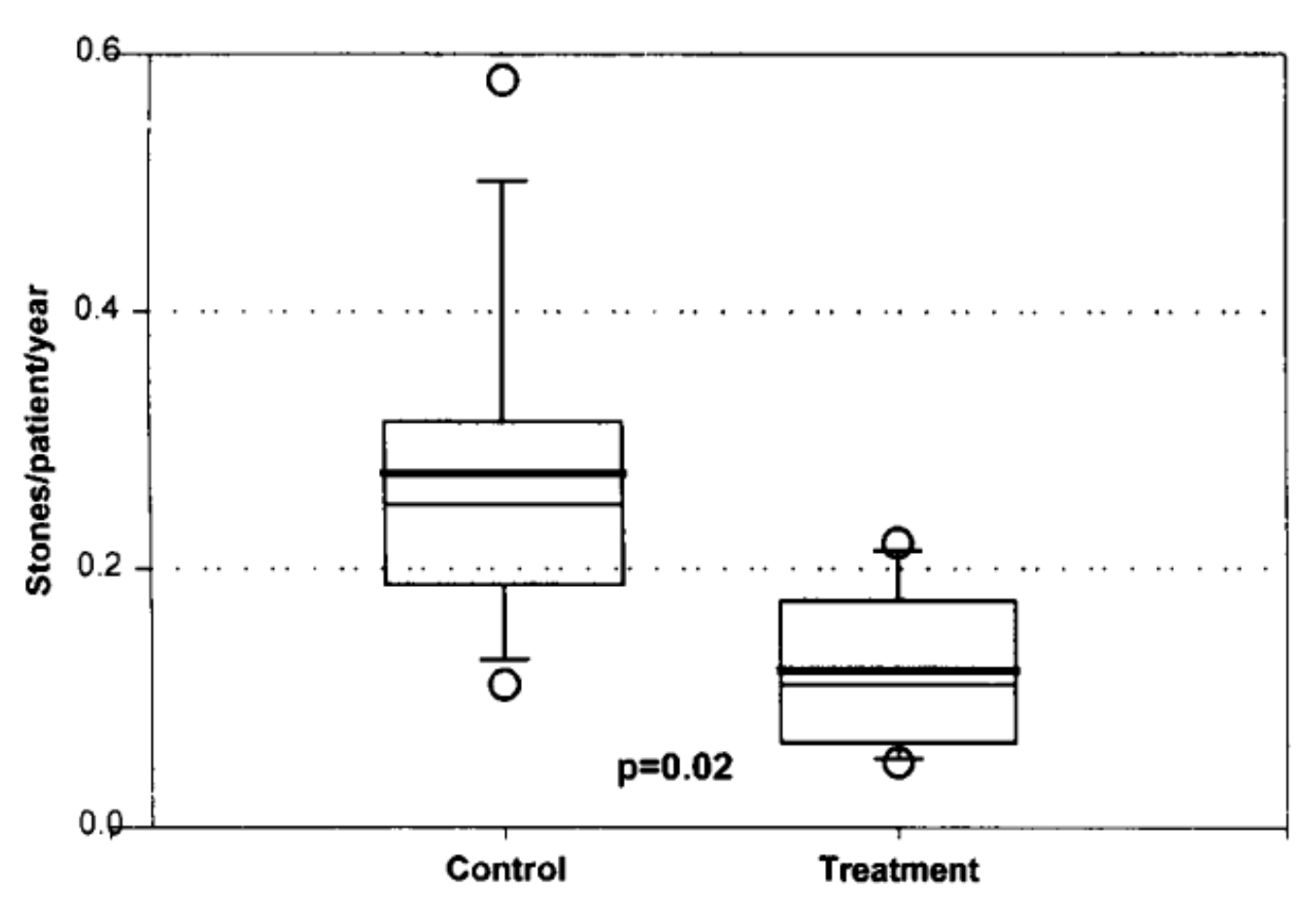
Potassium Citrate

	Liquid	Tablets
Minor GI complaints	+	++
Gastric erosions	0	0/+
Convenience	+	+++
Citraturic action	++	+++
Half-life	short	prolonged
Dose schedule	tid/qid	bid/tid

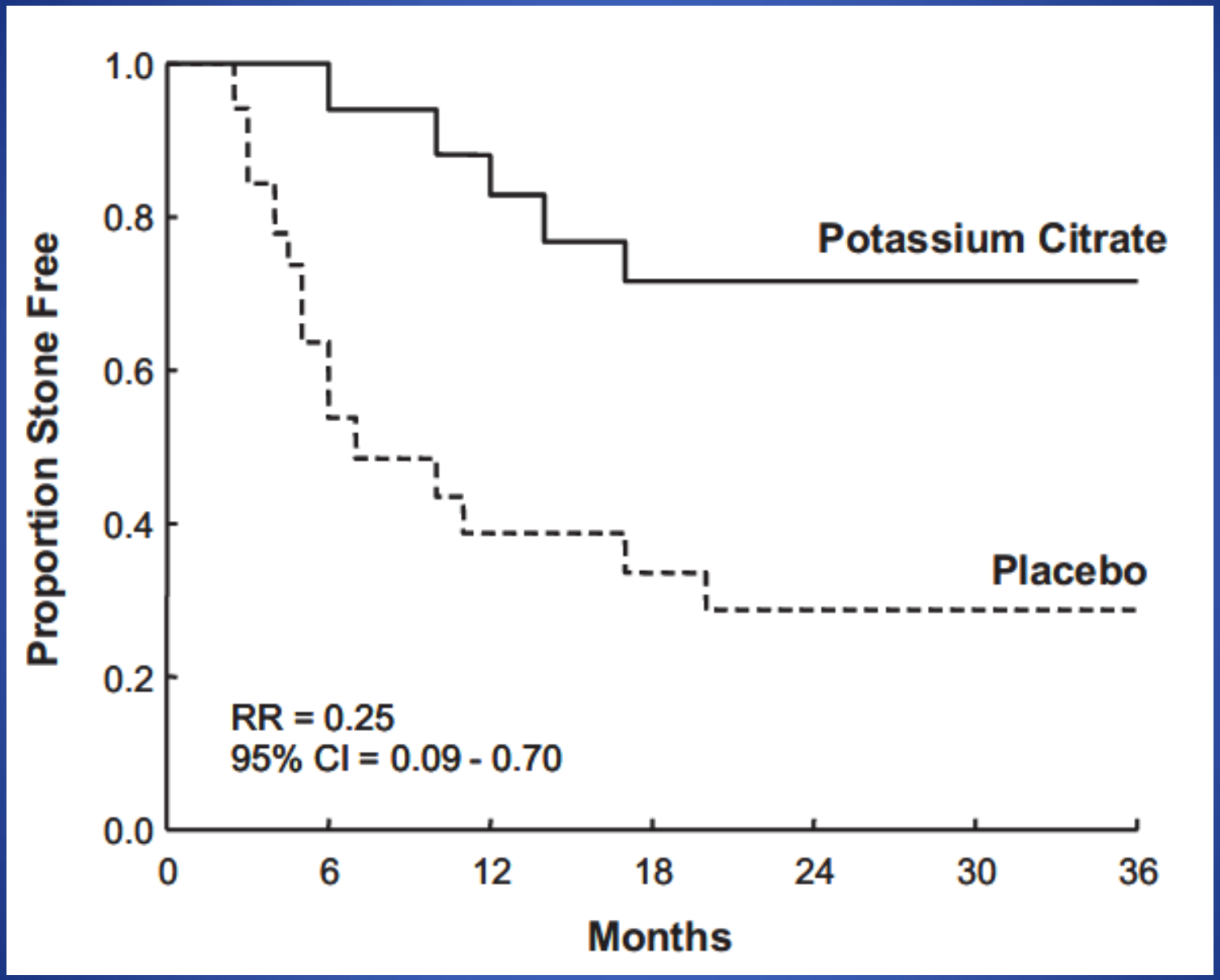
Allopurinol

- Used most appropriately in the recurrent calcium oxalate stone former with moderate to severe hyperuricosuria
- Failed dietary modification
- Dosed 200-300 mg/day
- Monitor liver enzymes
- Stephens-Johnson Syndrome: Report of skin rash or urticaria should prompt immediate cessation

Do Medications Work? Thiazides



Pearle J Endourol 1999



Barcelo, J Urol, 1993

Potassium Citrate Effectiveness Long-term

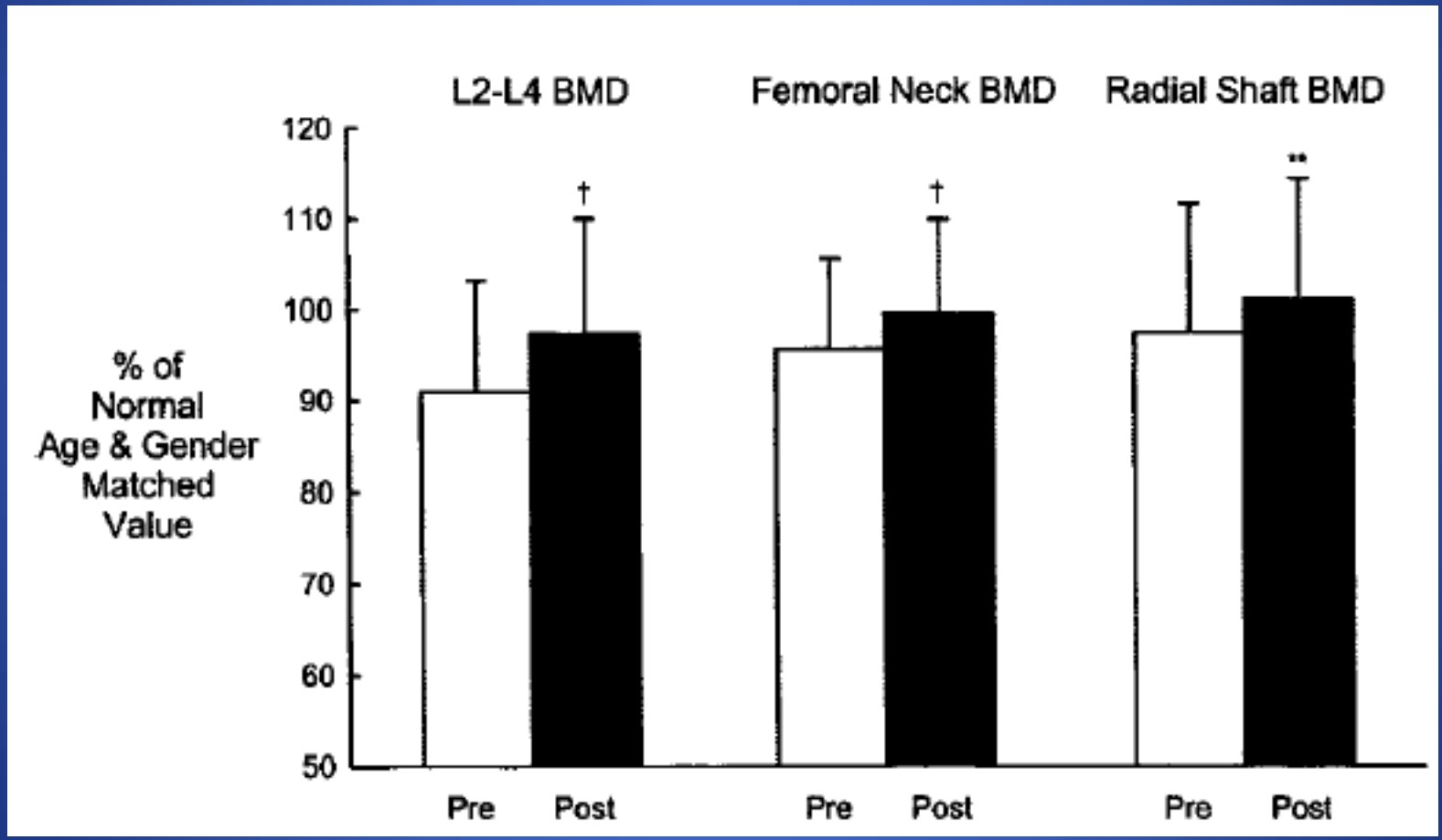
Table 5. *Stone formation in 134 patients only on KCit*

	Before KCit	After KCit
Stone formation rate change	1.22	0.19*
% Remission		72
% Decrease		94
% No change		2
% Increase		4

* Vs before KCit $p < 0.0001$.

Robinson J Urol, 2009

Medical and Dietary Treatment and Bone Health



Pak, J Urol, 2003

BMD and Potassium Citrate

	Mean L2–L4 Bone Mineral Density ± SD (p value)*	
	Gm./Cm.^{2}	% Change
Men:		
Baseline	0.981 ± 0.131	
Last	1.013 ± 0.133 (p <0.05)	3.3 ± 4.2 (p <0.01)
Women:		
Baseline	1.046 ± 0.070	
Last	1.072 ± 0.080 (p <0.05)	2.7 ± 1.7 (p <0.05)
Combined:		
Baseline	0.997 ± 0.121	
Last	1.027 ± 0.123 (p <0.01)	3.1 ± 3.7 (p <0.001)

* Significant difference from baseline to last measurement.

Pak, J Urol, 2002

Take Home Points

- Research into Randall's plaque formation is providing new insights into calcium stone formation
- A careful medical history and simple diagnostic evaluation will characterize most patient's stone forming risk

Take Home Points

- Obesity and metabolic syndrome are important risk factors for stone formation
- Type 2 DM is an important risk factor for stone formation
- Bariatric surgery is an important and increasing cause of stone formation
- Dietary modification can help lower stone forming risk

Take Home Points

- For many stone formers, genetic and medical risk factors will limit the effectiveness of diet changes alone
- For these patients, medical therapy is available and effective in reducing stone forming risk and in preventing complications of stones such as bone loss
- Kidney stone formation is often a reflection of a systemic medical/metabolic syndrome