RABIN MEDICAL CENTER
BEILINSON • HASHARON

Renal calculi formation and treatment : New insights

David A. Lifshitz, M.D.
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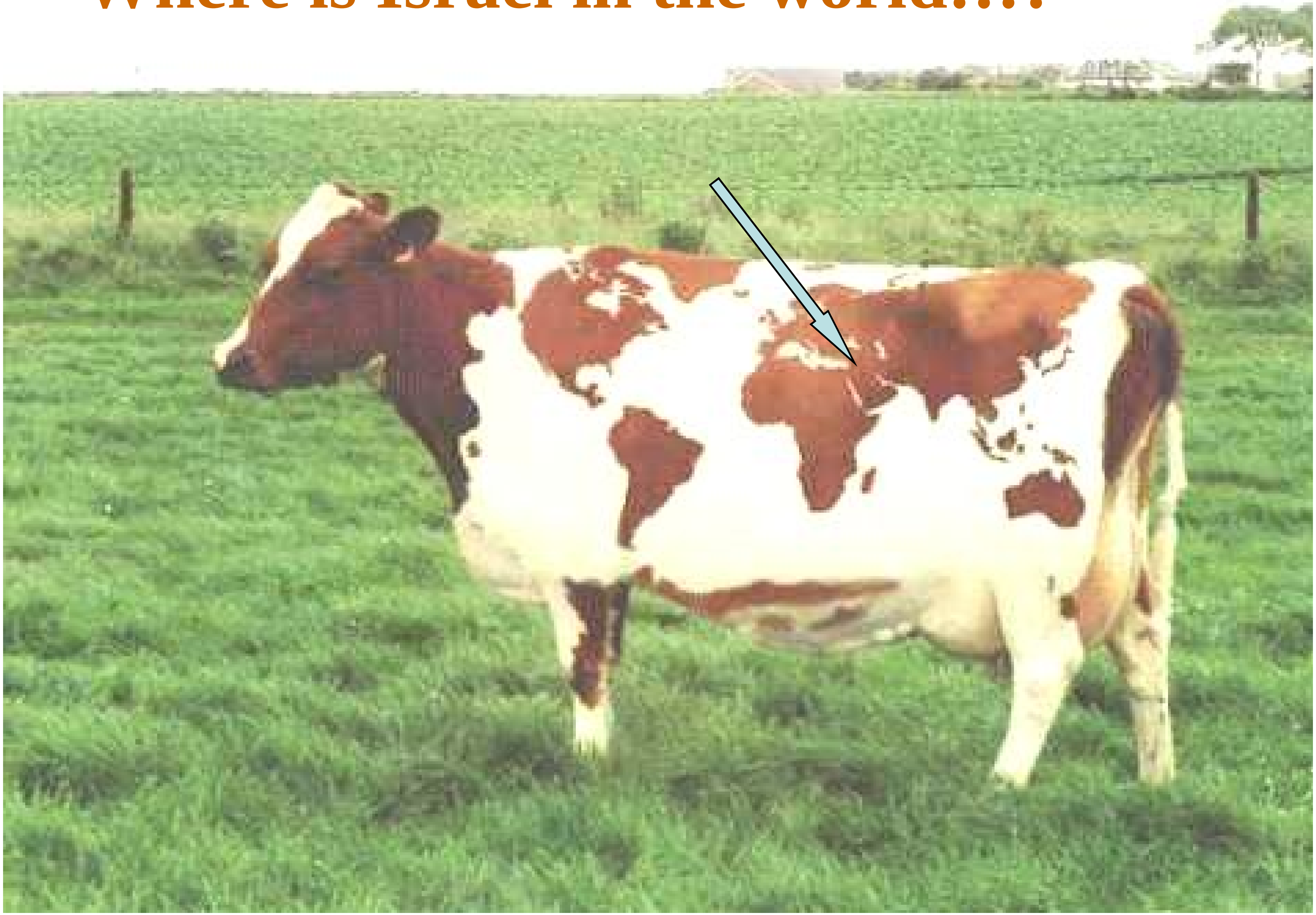
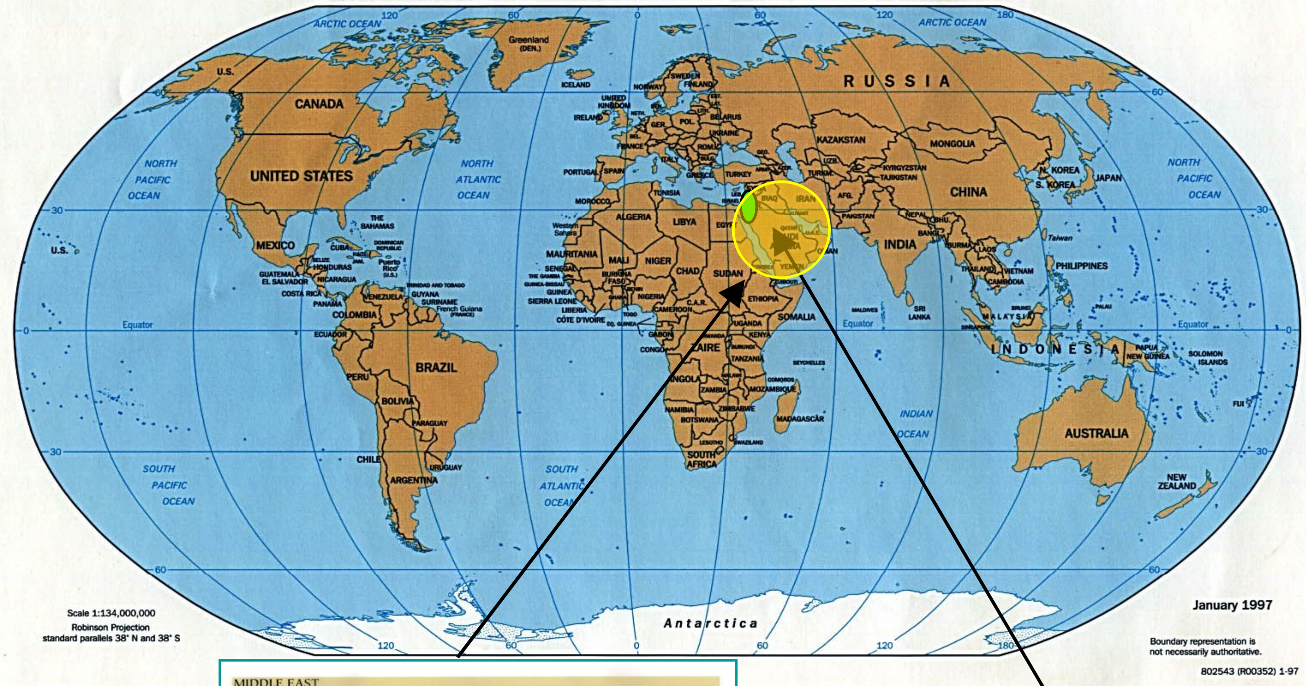
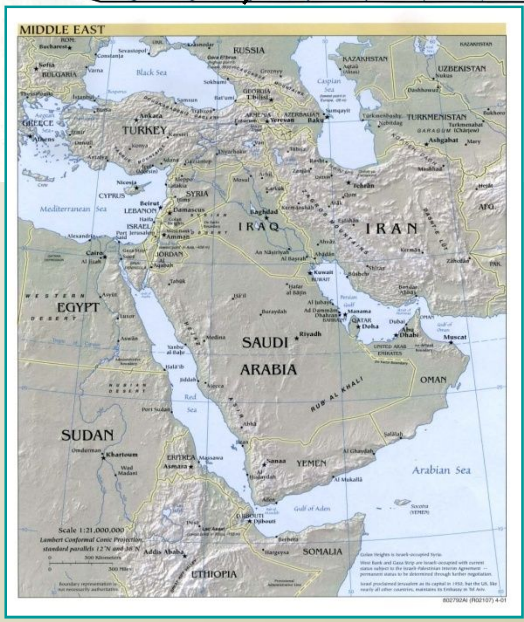
Where is Israel in the world…?



The World



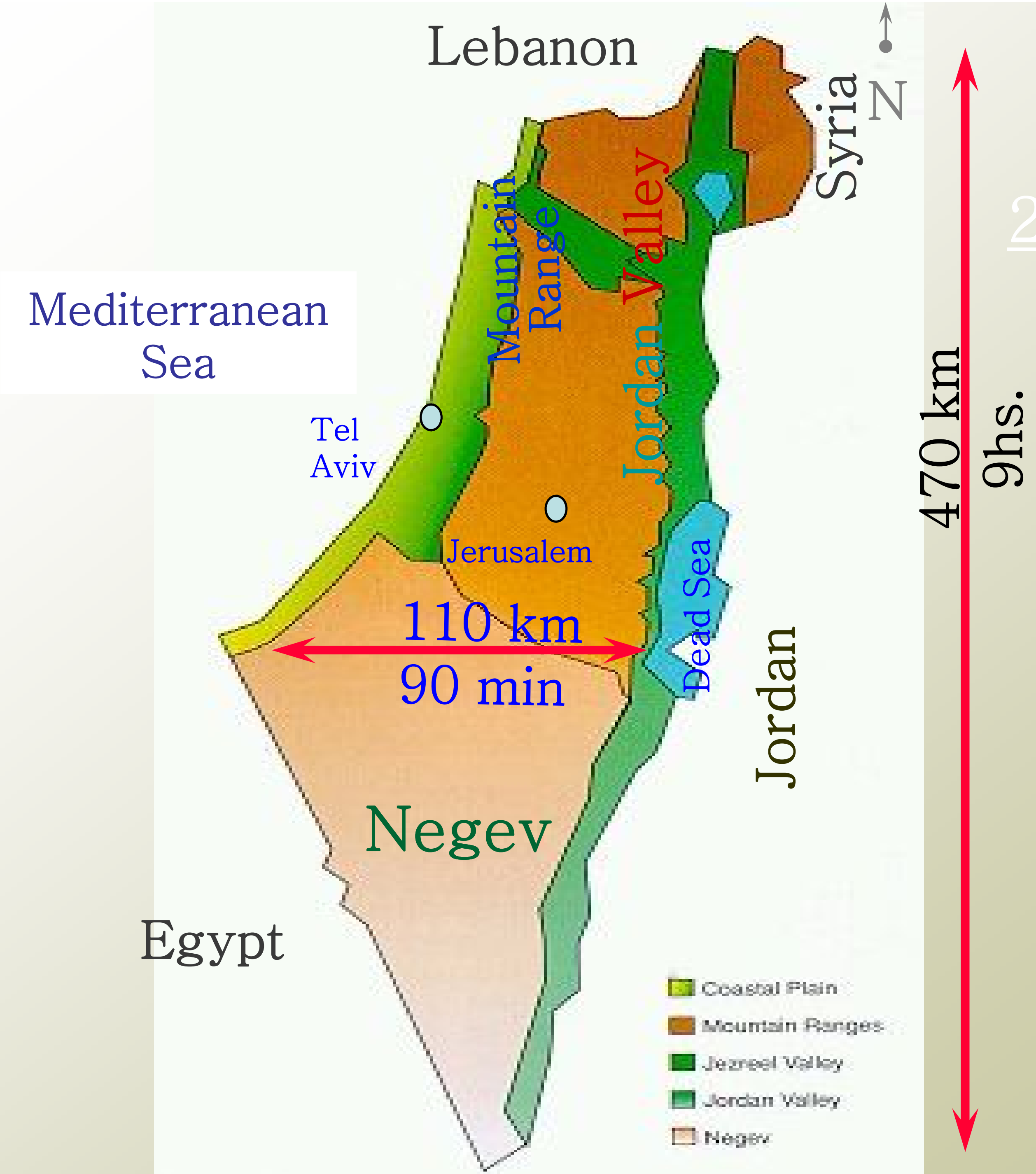
The Middle East



Israel

ISRAEL

21,000 Km^2



JERUSALEM

Health in Israel

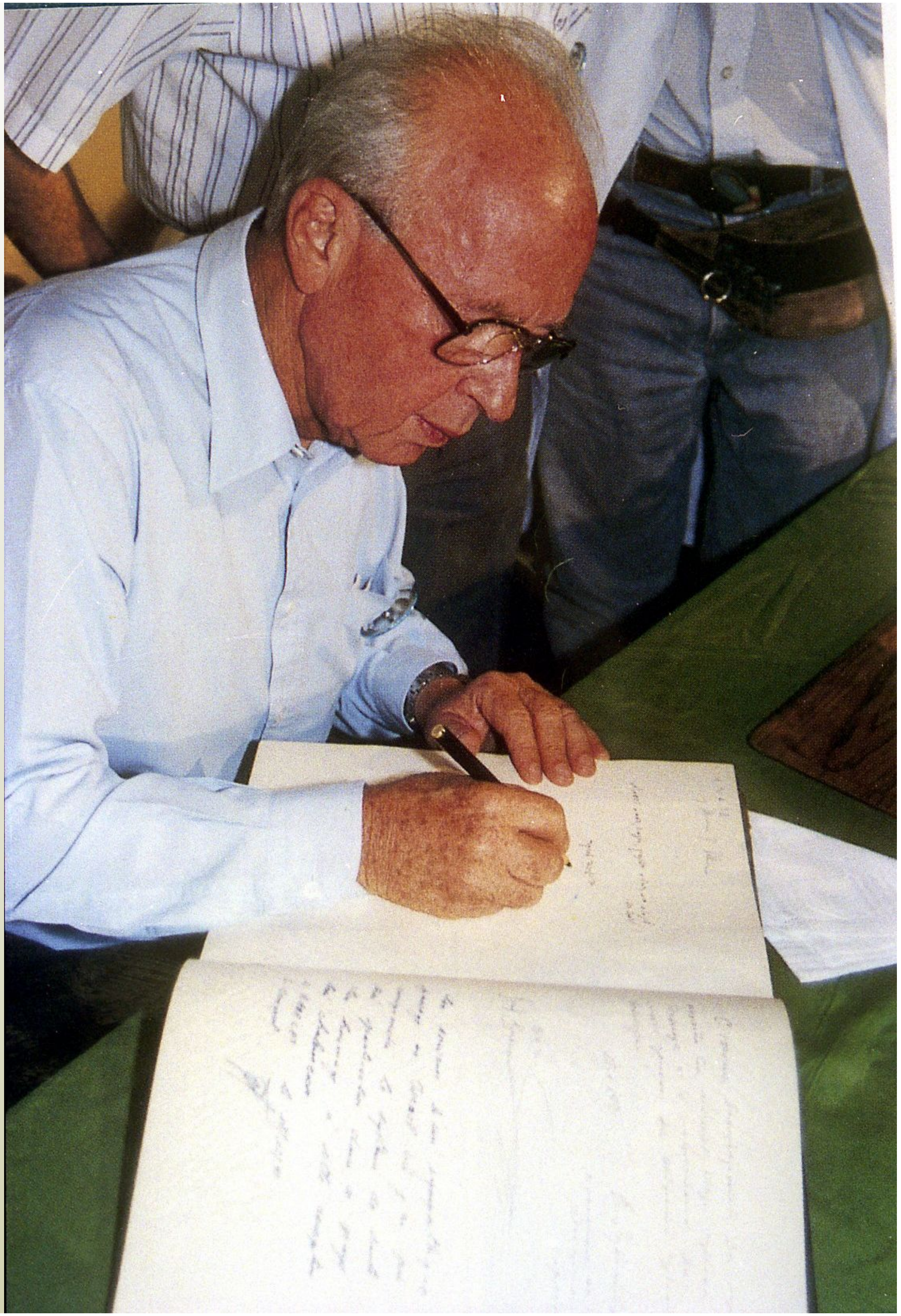
- **Health Ministry**
  - **Hospitals - 14**
  - **Insurers (Health funds / HMO) – 4**
- Clalit Health Services – biggest HMO
  - **Community health**
  - **Hospitals - 8**

Rabin Medical Center

Rabin Medical Center

Named in memory of Israel's late prime minister, Yitzhak Rabin.

The late P.M   Rabin



RMC: Facts and Figures

- In January 1996 Beilinson and Hasharon hospitals merged to form Rabin Medical Center. Together with Schneiders children's medical center it is the largest and leading medical complex in Israel,

- 1300 Beds
- 4,500 Staff Members
- 8,500 Births Annually
- 37 Operating Rooms
- 167,000 Emergency Visits
- 650,000 Outpatient Clinic Visits
- 34,000 Operations Annually
- 1,600 Cardiothoracic Operations Annually-The largest number in Israel
- The largest number of patients treated for cancer in Israel
- The largest number of organ transplants in Israel

RMC: Urology department

- Divided between three campuses:
  - Urouncology (All major surgery with a special emphasis on bladder substitution, RPLND & robotic surgery and LPN)
  - Pediatric urology
  - Endourology and laparosocpy
  - 13 staff members and 8 residents rotating between the campuses

  15 operating beds per week

  About 3000 cases per year

Renal calculi formation and treatment : New insights

- Stone composition epidemiology in Israel
- The impact of the metabolic syndrome on stone disease
- Uric acid stone dissolution: how can we be more efficient?
- New insight into the formation of CaOx stones
- RIRS (retrograde intrarenal surgery)- a new standard in the treatment of renal calculi

Urinary calculi in Israel: Epidemiologic distribution of stone composition

Shay Golan[1], Tamer Abdin[2], Ehud Gnessin[1], Nandakishore Shapur[2], Pinhas M. Livne[1], Dov Pode[2], David Lifshitz[1],

[1] Rabin medical center, Petach Tikva, IL, [2]Hadassah Hebrew University Hospital, Jerusalem, IL

Introduction

The epidemiological data regarding stone composition in Israel is based on anachronistic methods.

Unusually high percentage of uric acid component (~30%).

Purpose

To provide a contemporary description of stone composition distribution in Israel, based on modern analysis techniques.

Methods

In a bi-center study, using infrared spectroscopy and X-ray diffraction, stones from 538 patients were analyzed and demographic data was recorded.

Stone analysis techniques

- "**<u>Chemical analysis of renal calculi has been all but abandoned</u>**. Significant error may occur because qualitative and semi quantitative chemical analysis methods are not accurate (verrgauwe et al, 1994)"
- "X-ray diffraction and infrared spectroscopy are acceptable techniques for analyzing renal stones"

From Campbell's Urology, Eighth edition (2002), p:3272

Limitation of chemical analysis: No distinction for Ca-Phosp

Laboratory Report

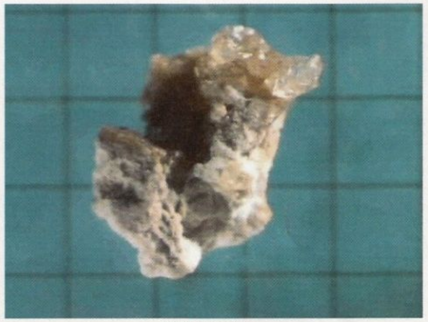
Interpretation

Results: 65% Calcium Phosphate (hydroxyapatite) Codeposited With
13% Calcium Oxalate Monohydrate (granular whewellite) Codeposited With
22% Calcium Oxalate Dihydrate (weddellite)

Physical Characteristics:
Size: 4.0mm x 5.0mm x 3.0mm **Weight:** 37.60mg **Number:** Numerous

Source: Left Ureter, Right Kidney **Method Obtained:** Not Stated

Exterior Image



Interior Image

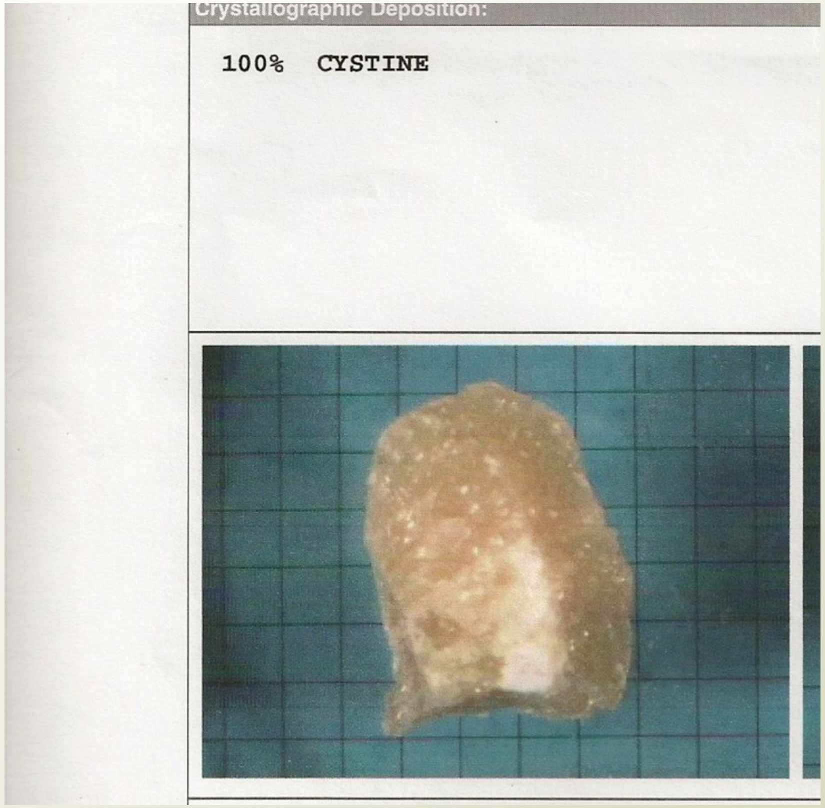
Comments

Electronically signed out by: James E. Lingeman, M.D., Laboratory Director Date: 02/

2004 :מדבקה

שם הבדיקה	תוצאה	טווח ויחידות	טווח גרפי	הערה
Ca OXALATE IN CALC	100	%		
CYSTINE IN CALCULI	0	%		
PHOSPHATES-CALCULI	4	%		
MAGNESIUM IN CALCULI	0	%		
URIC ACID IN CALCULI	3	%		
CALCIUM IN CALCULI	60	%		
AMMONIUM IN CALCULI	1	%		
OXALATE IN CALCULI	70	%		

Limitation of chemical analysis: May miss pure cystine



Crystallographic Deposition:

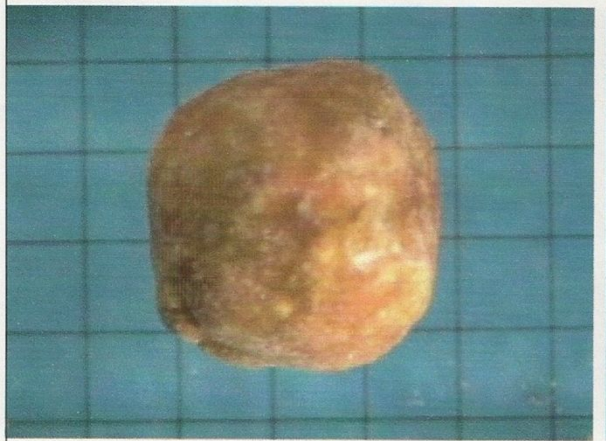
100% CYSTINE

שם הבדיקה	תוצאה	טווח ויחידות
CALCIUM IN CALCULI	10	%
OXALATE IN CALCULI	30	%
AMMONIUM IN CALCULI	0	%
PHOSPHATES-CALCULI	0	%
MAGNESIUM IN CALCULI	0	%
URIC ACID IN CALCULI	0	%
CYSTINE IN CALCULI	80	%
Ca OXALATE IN CALC	50	%

Limitation of chemical analysis: Underestimate the uric acid %

Crystallographic Deposition:

100% Uric Acid



שם הבדיקה	תוצאה	טווח ויחידות
Ca OXALATE IN CALC	100	%
CYSTINE IN CALCULI	0	%
PHOSPHATES-CALCULI	4	%
MAGNESIUM IN CALCULI	1	%
URIC ACID IN CALCULI	5	%
CALCIUM IN CALCULI	85	%
AMMONIUM IN CALCULI	0	%
OXALATE IN CALCULI	70	%

Table 1: Occurrence frequency of stone components according to homogeneity.

Stone component	Total Number (%)	Mixed (%)	Pure (%)
Calcium oxalate monohydrate	**399 (74.2)**	309 (57.4)	90 (16.7)
Calcium oxalate dihydrate	**183 (34)**	165 (30.6)	18 (3.3)
Calcium phosphate	**197 (36.6)**	188 (34.9)	9 (1.6)
Uric acid	**78 (14.5)**	30 (5.5)	48 (8.9)
Carbonite-apatite	**67 (12)**	64 (11.9)	3 (0.5)
Magnesium ammonium phosphate (Struvite)	**23 (4.1)**	22 (4)	1 (0.1)
Calcium hydrogen phosphate dihydrate (Brushite)	**13 (2.3)**	11 (2)	2 (0.3)
Cystine	**12 (2.2)**	0	12 (2.2)

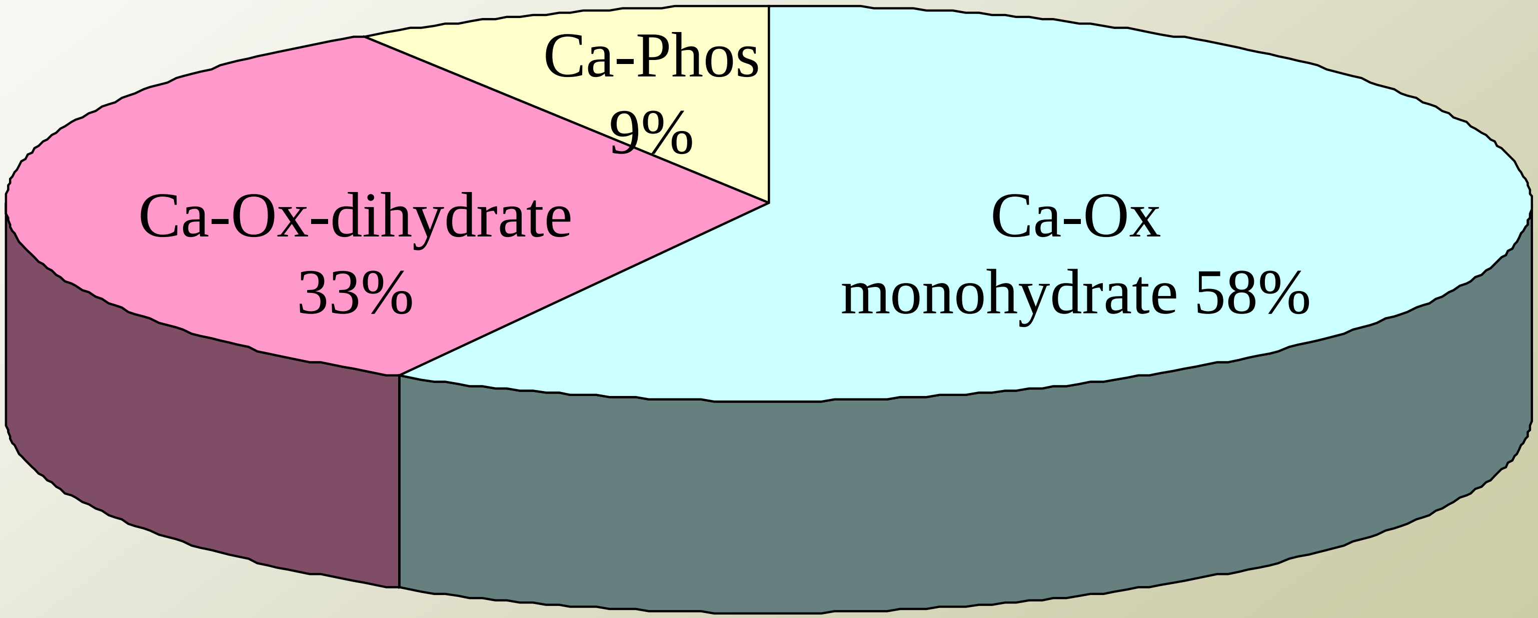
Table 1: Occurrence frequency of stone components according to gender and age.

Stone component	Total Number (%)	Male (%)	Female (%)	0-20 y (%) N=21 (4%)	20-40 y (%) N=142 (26%)	40-60 y (%) N=272 (51%)	>60 y (%) N=103 (19%)
Calcium oxalate monohydrate	**399 (74.2)**	77.3	65.0	47.6	71.1	78.7	71.8
Calcium oxalate dihydrate	**183 (34)**	38.2	21.9	47.6	48.6	28.3	26.2
Calcium phosphate	**197 (36.6)**	37.4	34.3	23.8	43.7	36.4	30.1
Uric acid	**78 (14.5)**	14.5	14.6	0.0	9.2	15.8	21.4
Carbonite-apatite	**67 (12)**	8.2	24.8	14.3	8.5	12.5	17.5
Magnesium ammonium phosphate	**23 (4.1)**	2.0	10.9	9.5	0.7	4.0	8.7
Calcium hydrogen phosphate dehydrate	**13 (2.3)**	3.0	0.7	4.8	1.4	2.2	3.9
Cystine	**12 (2.2)**	1.7	3.6	14.3	3.5	1.5	0.0

Conclusions

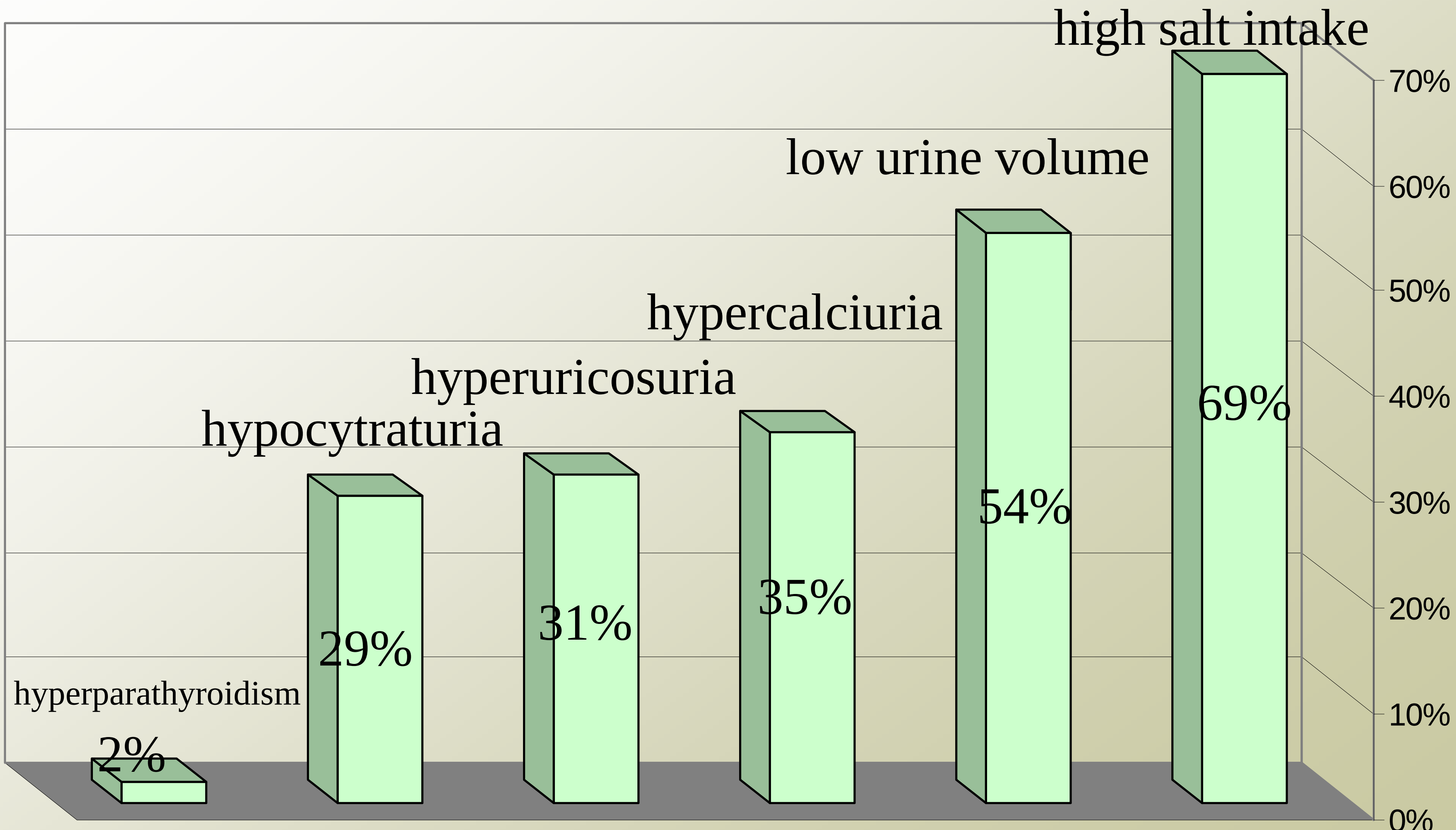
- **The most prevalent stone component in Israel is Calcium oxalate Monohydrate.**
- **The overall occurrence of uric acid is <u>14.5%</u> .**
- **The <u>occurrence of uric acid increases with age</u>, reaching 21% in people > 60 years old.**
- **A significant gender difference was noted in the distribution of CaOx stones and infection stones.**

The results of metabolic evaluation in CaOx stone formers in Israel



	The results of metabolic evaluation in CaOx stone formers in israel
Female/male	22/76
Average age	(17-73) 48
% Abnormality	92%
1	24%
2	37%
3+	31%

The results of metabolic evaluation



Stone disease in the 21 century

- The prevalence of stone disease went up in the US from 3% to 5% between the years 1970-2000 and still on the rise - diet related?
- The life time risk for a stone event is up to 10%
- Recurrence rate of 50% in 5-10 years, also true for a stone to become symptomatic
- The standard male/female ratio of 3:1 now is changing toward a smaller difference

The metabolic syndrome and renal diseases

- An NIH study has shown that patients with BMI >27 and stone history have lower GFR
- High BMI stone formers have more HTN
- INSULIN RESISTANCE diminishes amonia production in the kidney resulting in more acidic urine

The metabolic syndrome and stone disease

Diabetes Mellitus and the Risk of Urinary Tract Stones: A Population-Based Case-Control Study

John C. Lieske, MD, Lourdes S. Peña de la Vega, MD, Matthew T. Gettman, MD,
Jeffrey M. Slezak, BS, Eric J. Bergstralh, MS, L. Joseph Melton III, MD,
and Cynthia L. Leibson, PhD

• *Background:* Because nephrolithiasis has been associated with obesity, an important risk factor for type 2 diabetes mellitus (DM), we tested the hypothesis that DM prevalence is increased in individuals who develop renal stones. *Methods:* In an initial electronic analysis, prior diagnoses of DM, hypertension, and obesity were compared between all Olmsted County, MN, residents with a diagnosis code for nephrolithiasis between 1980 and 1999 and matched residents of similar age and sex (N = 3,561 case-control pairs). A random sample of 260 cases and corresponding controls was selected for detailed medical record review to confirm and characterize the stone event and obtain heights, weights, blood pressures, and glucose and cholesterol values. *Results:* In the electronic analysis, unadjusted odds ratios (ORs) for DM (OR, 1.29; 95% confidence interval [CI], 1.09 to 1.53), obesity (OR, 1.15; 95% CI, 1.02 to 1.31), and hypertension (OR, 1.19; 95% CI, 1.04 to 1.35) were increased significantly for nephrolithiasis cases versus controls; DM remained significant after adjustment for age, sex, calendar year, hypertension, and obesity (OR, 1.22; 95% CI, 1.03 to 1.46). Detailed record review of a subset showed significant increases for cases versus controls for body mass index (OR, 1.05; 95% CI, 1.01 to -1.09) and hypertension (OR, 1.71; 95% CI, 1.17 to 2.59). Odds for DM were increased, but not significantly, in the subsample (OR, 1.44; 95% CI, 0.76 to 2.72). Among cases with stone analyses, those with uric acid stones (n = 10) had a greater percentage of DM compared with those with all other stone types (n = 112; 40% versus 9%; *P* = 0.02). *Conclusion:* Findings from this population-based study suggest that DM, obesity, and hypertension are associated with nephrolithiasis, and DM may be a factor in the development of uric acid stones. *Am J Kidney Dis* 48:897-904.

The metabolic syndrome and stone disease

Body Size and 24-Hour Urine Composition

Eric N. Taylor, MD, and Gary C. Curhan, MD, ScD

• ***Background:*** Greater body mass index (BMI) is a risk factor for kidney stones. However, the relation between BMI and the urinary excretion of many lithogenic factors remains unclear. ***Methods:*** We studied urine pH, urine volume, and 24-hour urinary excretion of calcium, oxalate, citrate, uric acid, sodium, magnesium, potassium, phosphate, and creatinine in stone-forming and non–stone-forming participants in the Health Professionals Follow-Up Study (599 stone-forming and 404 non–stone-forming men), Nurses' Health Study (888 stone-forming and 398 non–stone-forming older women), and Nurses' Health Study II (689 stone-forming and 295 non–stone-forming younger women). Each cohort was divided into quintiles of BMI. Tests of linear trend were conducted by 1-way analysis of variance. Linear regression models were adjusted for age, history of stone disease, dietary intake, and urinary factors. ***Results:*** Participants with greater BMIs excreted more urinary oxalate (P for trend ≤ 0.04), uric acid ($P < 0.001$), sodium ($P < 0.001$), and phosphate ($P < 0.001$) than participants with lower BMIs. There was an inverse relation between BMI and urine pH ($P \leq 0.02$). Positive associations between BMI and urinary calcium excretion in men and stone-forming younger women ($P \leq 0.02$) did not persist after adjustment for urinary sodium and phosphate excretion. Because of differences in urinary volume and excretion of inhibitors such as citrate, we observed no relation between BMI and urinary supersaturation of calcium oxalate. Urinary supersaturation of uric acid increased with BMI ($P \leq 0.01$). ***Conclusion:*** Positive associations between BMI and urinary calcium excretion likely are due to differences in animal protein and sodium intake. The greater incidence of kidney stones in the obese may be due to an increase in uric acid nephrolithiasis. *Am J Kidney Dis* 48:905-915.

Take home message

- If you see a western obese, diabetic patient with renal calculi consider the option of uric acid stone and treat accordingly

The kinetics of uric acid stones dissolution

Bezalel Sivan[1], Yizhak Mastai[2], Ruth Fried[2], Pinhas. M. Livne[1], David A Lifshitz[1]
Rabin Medical Center – Departement of Urology [1], Bar Ilan University – Departement of Chemistry[2]

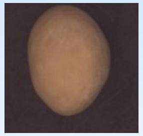
Background

Dissolution by oral medication is often the treatment of choice for patients diagnosed with non obstructing renal uric acid (UA) stones. Urine alkalization is the major goal . There is little data in recent years as to the optimal pH required for efficient chemolysis of UA stones.

Objective

To evaluate, in vitro using modern techniques, the dissolution kinetics of pure UA stones from patients and various parameters which may enhance chemolysis.

Methods



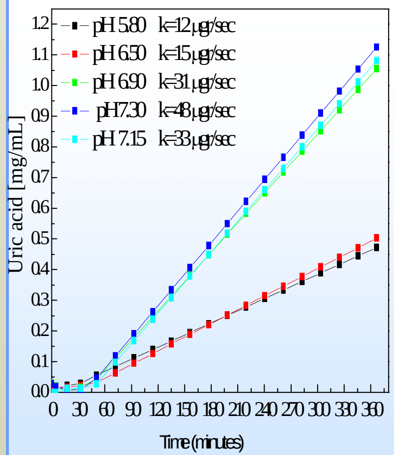
a. Whole UA stone?

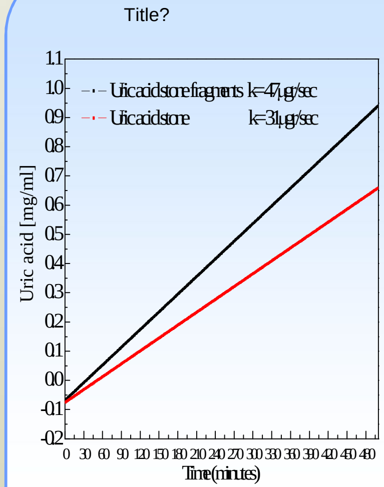
Fragmented stone?

- **Whole (Figure a) and fragmented stones (figure b) were obtained from patients who underwent percutaneous nephrolithotomy.**
- **The UA crystalline structure of the stones was verified with the use of X-ray diffraction (XRD).**
- **The kinetics of the solubility of UA stones was studied using Time Resolved UV-vis spectroscopy, which measures the changes of ultraviolet light absorbance due to soluble UA, at a wave length of 290nm. Measurements were performed at different increments of solution pH.**

Results

- **A significant difference in the rate of dissolution was found for higher pH values.**
- **Between a pH of 6.5 and 6.9 the rate of dissolution doubled**
- **Dissolution of fragmented stone was significantly more efficient.**
- **The rate of dissolution of fragments of UA stones is up to 52% faster than whole UA stones**

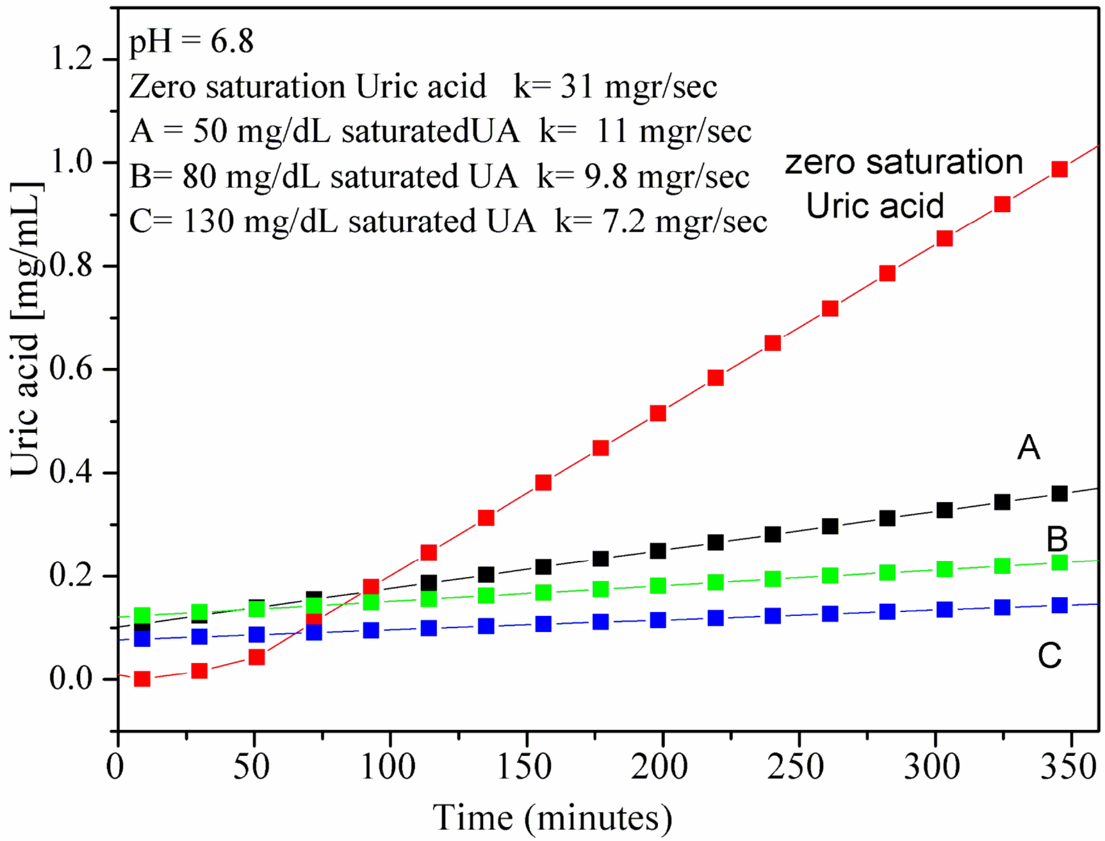




Conclusion

In vitro, there is a major difference in the efficacy of UA stone dissolution between the low and high range of the acceptable therapeutic goal. Further more, fragmented stones respond better than whole stones. The clinical implication of these findings may be that for a better response to oral chemolysis a combination of shock wave lithotripsy followed by alkalization of the urine close to pH 7 is needed.

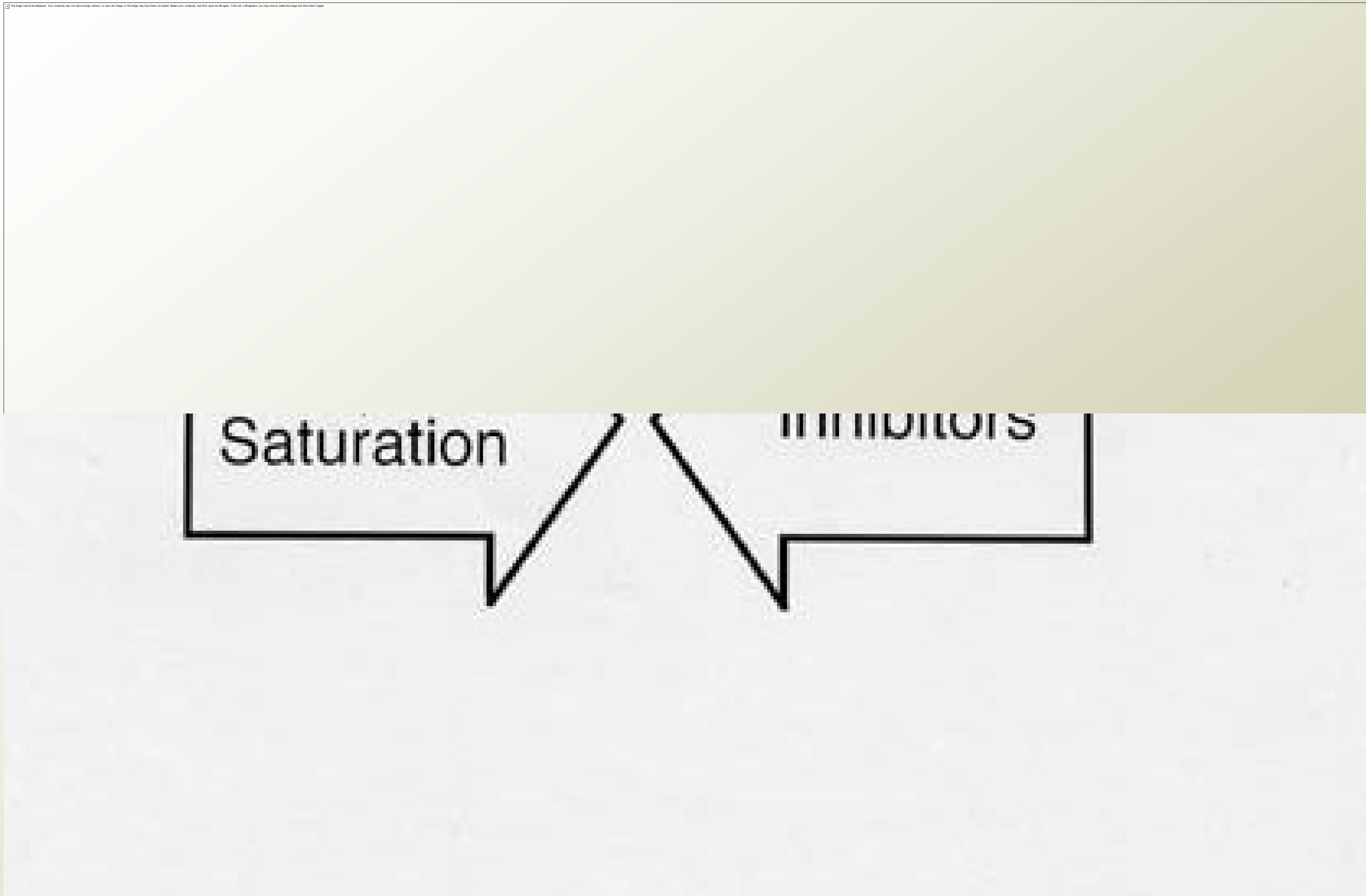
Do we need to reduce uric acid levels within the normal range to enhance dissolution?



Pathogenesis of CaOx stones

Metastable Zone: CaOx: SS<8 Brushite: SS<2.5 Uric Acid: SS<2	**Spontaneous nucleation does not occur** **Crystal growth can occur** **Inhibitors can impede or prevent crystallization**
Equilibrium Point: Solubility Product SS = 1	Crystals neither grow nor dissolve
Undersaturation Zone: SS < 1	Nuclei may dissolve (uric acid)

Pathogenesis of CaOx stones



Pathogenesis of CaOx calculi

- Urinary supersaturation vs. urine inhibitors
- Inhibitors: citrats, Mg, complex mucopolysaccharides.
- Promoters: stasis, nucleation, urinary pH
- Transit time from the kidney to the bladder is about 10 minutes, therefore, for a stone to be formed a fixed point (nidus) is required

0022-5347/05/1731-0117/0
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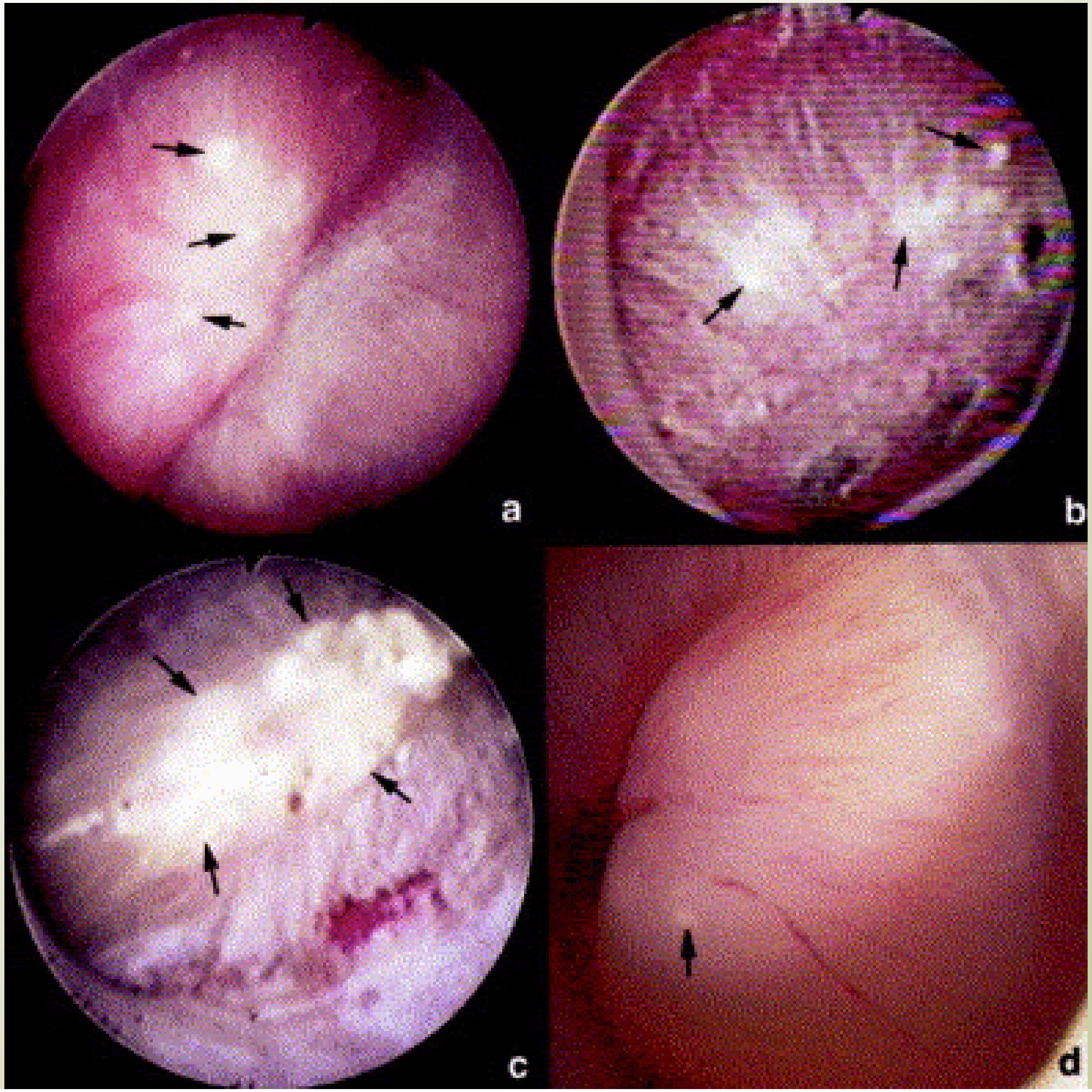
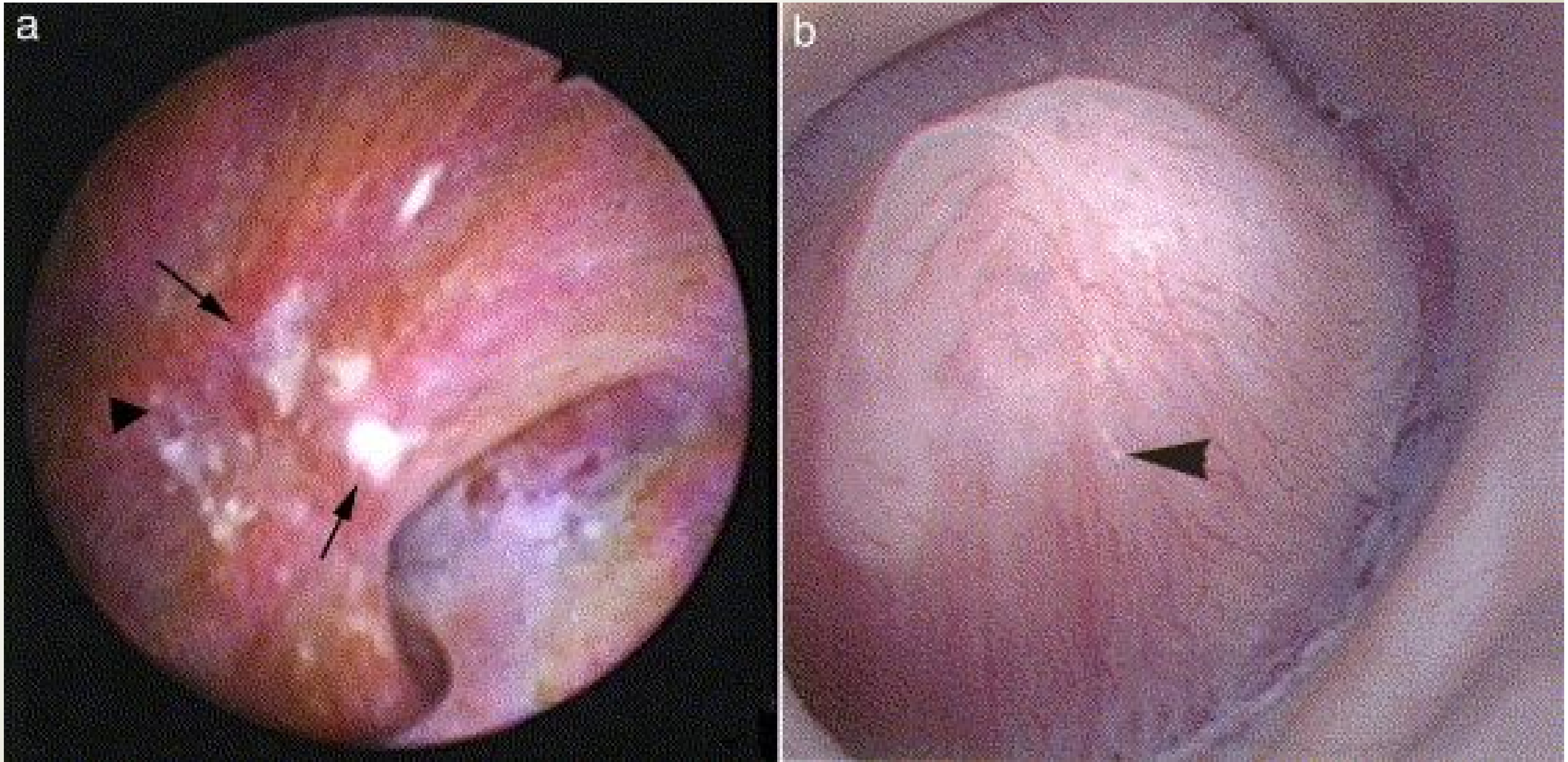
STONE FORMATION IS PROPORTIONAL TO PAPILLARY SURFACE COVERAGE BY RANDALL'S PLAQUE

SAMUEL C. KIM, FREDRIC L. COE, WILLIAM W. TINMOUTH, RAMSAY L. KUO,*
RYAN F. PATERSON, JOAN H. PARKS, LARRY C. MUNCH, ANDREW P. EVAN†
AND JAMES E. LINGEMAN‡,§



SF

Non SF



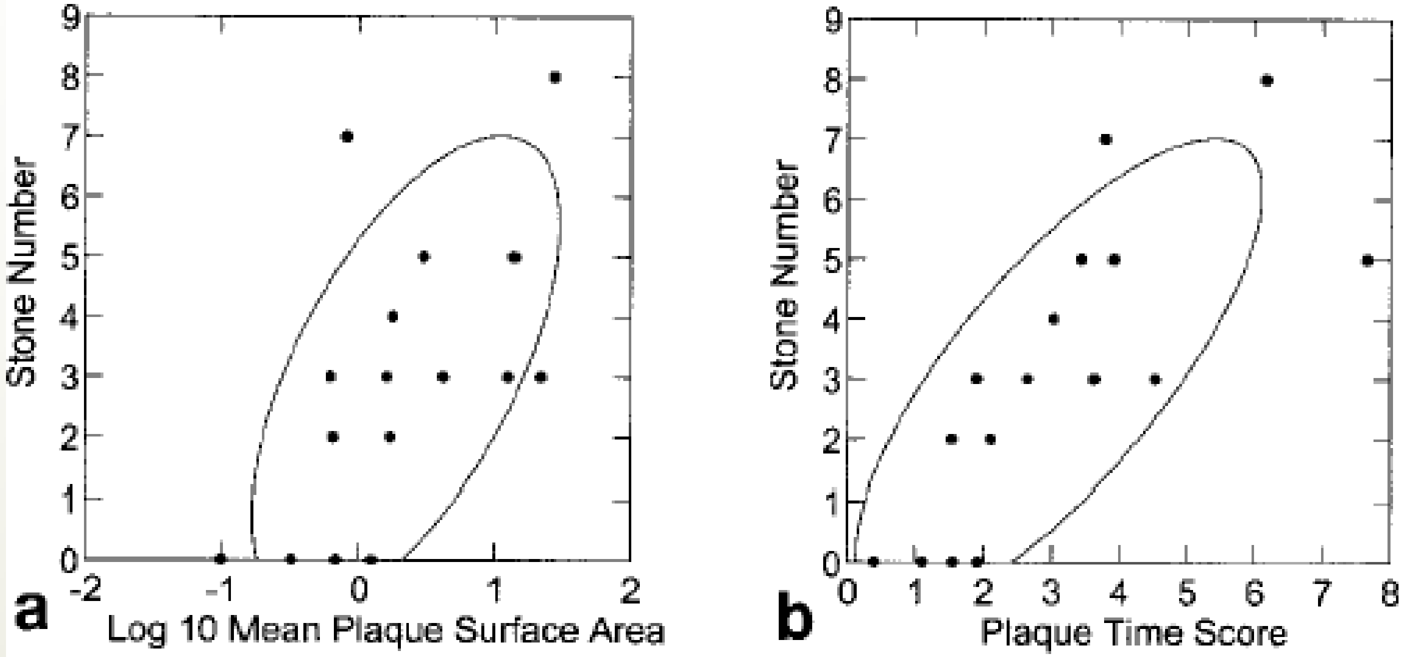


FIG. 1. *a*, number of stones vs log transformed mean plaque surface area. Nonparametric ellipse of containment includes 2 SD. *b*, number of stones vs multivariate regression equation from general linear model, including stone disease duration and plaque surface. Plaque time score × 1.788 + 1.386 × log 10 mean plaque surface area + 0.082 × time.

Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle

See the related Commentary beginning on page 6

Andrew P. Evan,[1] James E. Lingeman,[2] Fredric L. Coe,[3] Joan H. Parks,[3] Sharon B. Bledsoe,[1] Youzhi Shao,[4] Andre J. Sommer,[5] Ryan F. Paterson,[2] Ramsay L. Kuo,[2] and Marc Grynpas[6]

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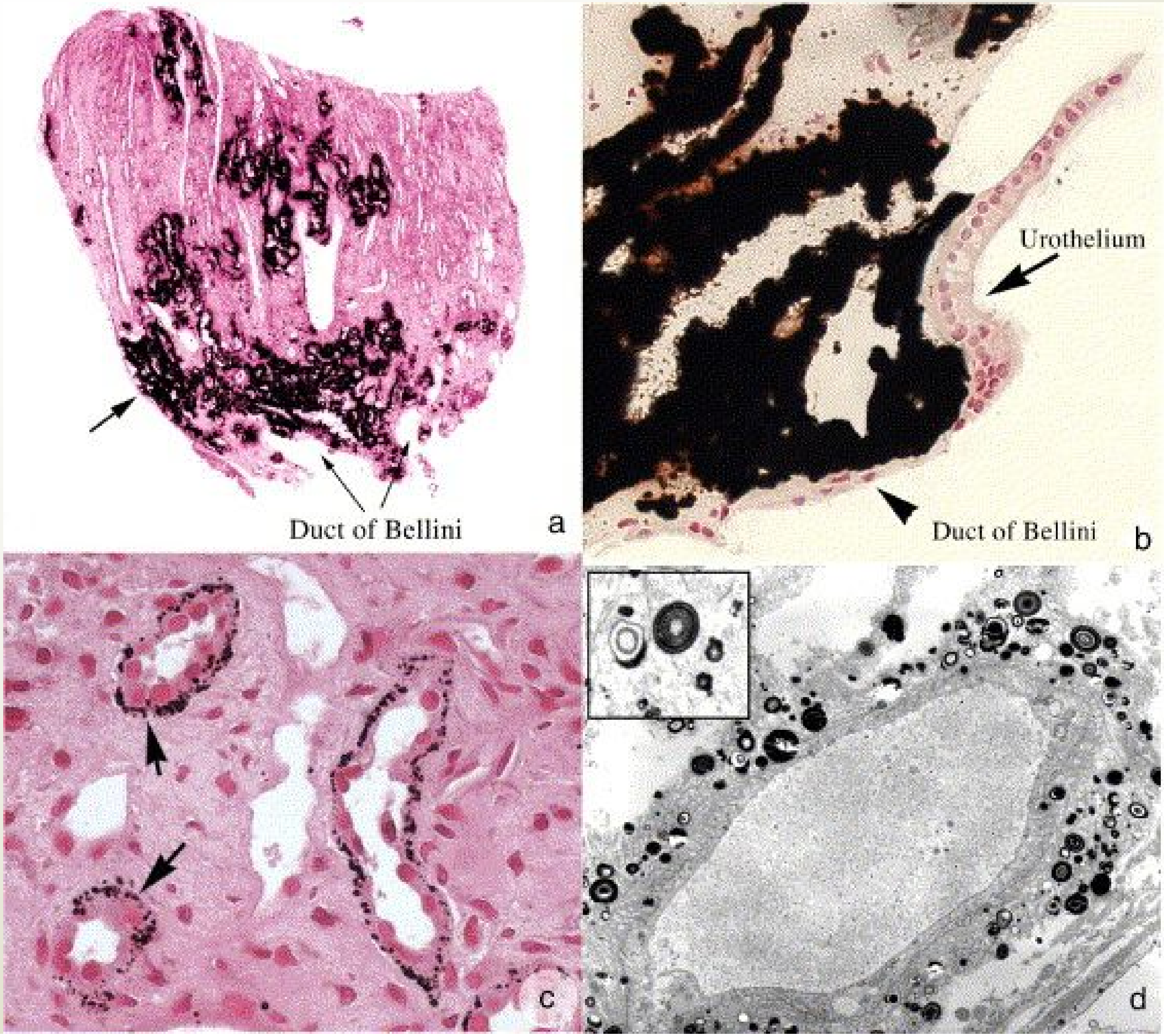
[2]Methodist Hospital Institute for Kidney Stone Disease, Indianapolis, Indiana, USA
[3]Nephrology Section, University of Chicago, Chicago, Illinois, USA
[4]Department of Histology, Jinzhou Medical College, Jinzhou, Liaoning, People's Republic of China
[5]Department of Chemistry and Biochemistry, Miami University, Oxford, Ohio
[6]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada

Our purpose here is to test the hypothesis that Randall's plaques, calcium phosphate deposits in kidneys of patients with calcium renal stones, arise in unique anatomical regions of the kidney, their formation conditioned by specific stone-forming pathophysiologies. To test this hypothesis, we performed intraoperative biopsies of plaques in kidneys of idiopathic-calcium-stone formers and patients with stones due to obesity-related bypass procedures and obtained papillary specimens from non–stone formers after nephrectomy. Plaque originates in the basement membranes of the thin loops of Henle and spreads from there through the interstitium to beneath the urothelium. Patients who have undergone bypass surgery do not produce such plaque but instead form intratubular hydroxyapatite crystals in collecting ducts. Non–stone formers also do not form plaque. Plaque is specific to certain kinds of stone-forming patients and is initiated specifically in thin-limb basement membranes by mechanisms that remain to be elucidated.

J. Clin. Invest. **111**:607–616 (2003). doi:10.1172/JCI200317038.


Duct of Bellini
a
Urothelium
Duct of Bellini
b
c
d

Pathogenesis: CaOx stones

- IH- Idiopathic hypercalciuria, normocalcemia
- Hyperclaciuric conditions (PTH, malignancy, hyperthyrodisim,sarcoidosis, immobiliziation, etc)
- Low urinary citrate
- Hyperoxaluria
- Hyperuricosuria

Pathogenesis: CaOx stones

- **<u>IH can be found in 30-60% of normocalcemic hyperclciuric patintes</u>**

Traditional classification of IH - relevant?

- : **(1) absorptive hypercalciuria, in which the primary abnormality was an increased intestinal absorption of calcium (vit D mediated)**
- **(2) renal hypercalciuria, characterized by a primary renal leak of calcium**
- **(3) resorptive hypercalciuria, characterized by increased bone demineralization**

- IH- is a spectrum of syndromes rather than different subgroups
- Effective treatment is the same in most patients (Thaizides + salt restriction)

RIRS (Retrograde Intrarenal Surgery)- a new standard in the treatment of renal stones

RIRS - Retrograde Intra Renal Surgery

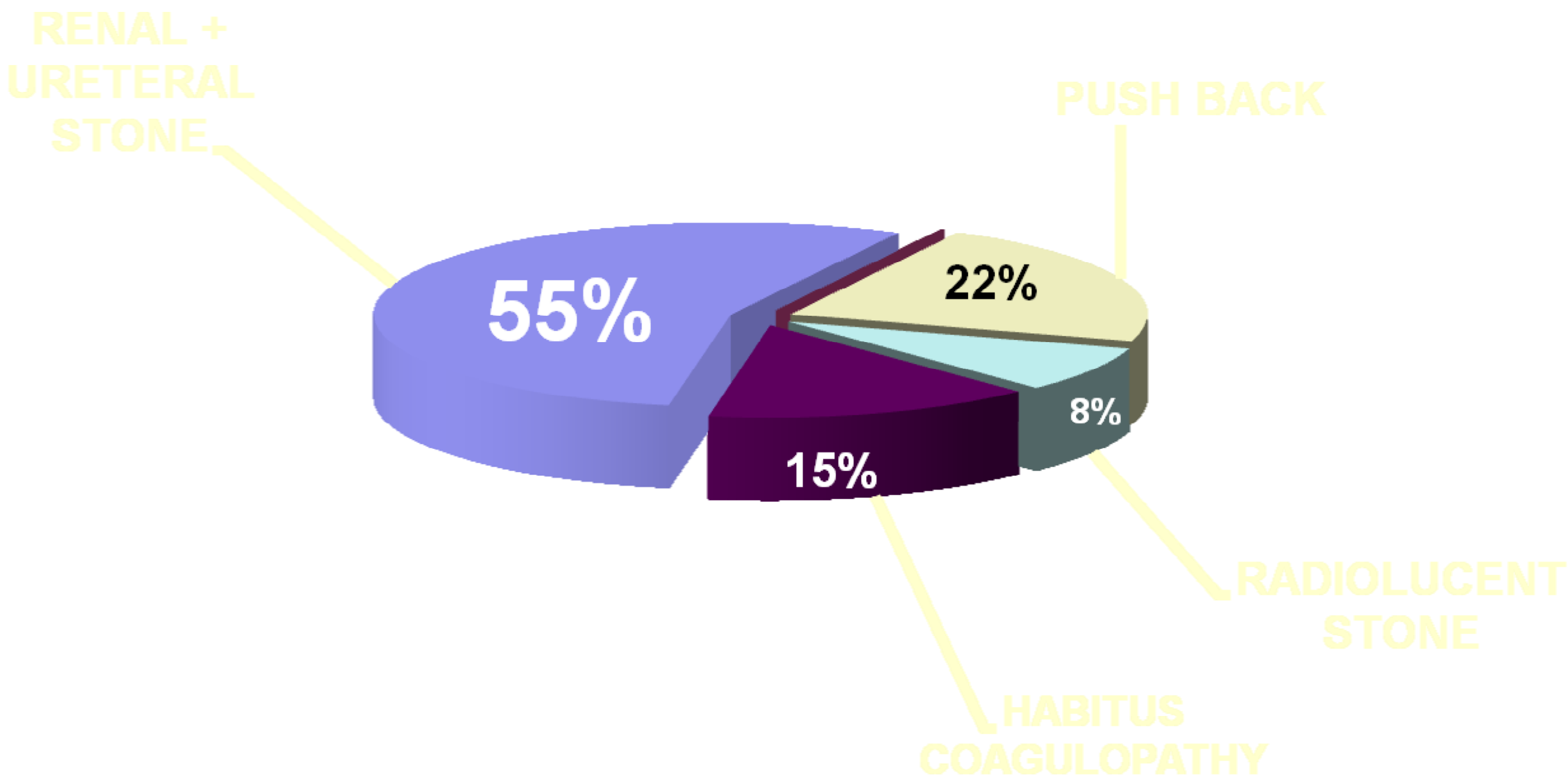
Indications:

- Radiolucent stones
- Ureteral and renal stones
- Failed SWL
- Cougulopathy
- Ureteral/renal stones indwelling D-J stent
- Special body habitus

RIRS the RMC experience

- Between 2001-2011: 2500 ureteroscopic procedures
- RIRS 430 (19%)

Indications for primary RIRS



Comparison of RIRS early and late groups

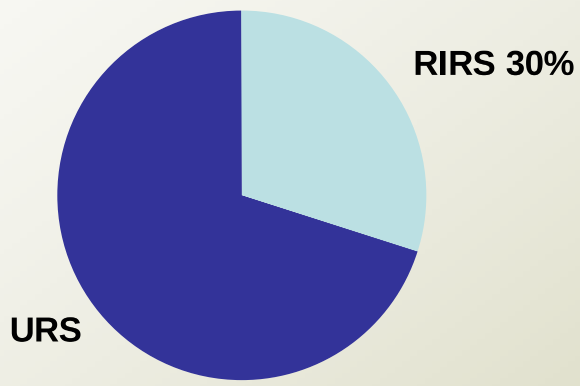
P	Late group	Early group	
	21 12	21 12	:Gender M F
P> 0.05	(4-17) 12	(4-15) 8.6	Mean stone size (mm)
P>0.05	51%	69%	Lower pole
P>0.05	(1-3) 1.3	(1-3) 1.4	mean stone number
P>0.05	33%	30%	Primary procedure

Comparison of RIRS early and late groups

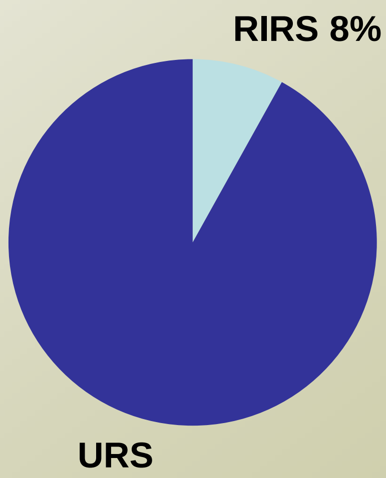
P Value	Late group	Early group	
NS	4	3	complications
NS	2	2	Median hospital stay
$P<0.05$	(28-93) 58	(48-187) 92	Surgery time (min)
NS	87	70	(%) Stone Free

Comparison of RIRS early and late groups

late group



early group



Comparison of RIRS early and late groups

Number of procedures per repair:

Early group – 19

Late group - 26

Price per repair about 130 Euro

Ureteroscopy

Renal Stones

- MP 1378 Lower pole renal stone management using flexible ureterorenoscopy with holmium laser (multi-centeric study).

  S. Alqahtani et al. Paris, France

  - A retrospective, multicenter study, N=199 pt.
  - Patients were divided according to stone size: group 1 (1-10mm), 2 (10-20mm), 3 (>20mm)
  - Stone free rate was 95%, 78% and 40% in group 1,2 and 3 respectively.
  - When allowing 2 sessions success rate improved in groups 2 and 3 to 86% and 82%, respectively.
  - Predictors for failure were infundibular length and width

- fURS offers excellent, single session, stone free rate for lower pole stones up to 1 cm in size. For larger stones good results can be achieved with two sessions.

Ureteroscopy

Renal Stones

- MP 926 The equivalency of treatment modalities for intermediate-sized renal calculi.
  J.D. Wiesenthal et al. St. Michael's Hospital, Canada
  - 137 patients treated for renal stones 100-300mm^2 (10-20mm)
  - SWL- 53 (39%), URS- 41 (30%), PCNL- 43 (31%)
  - Mean stone area was higher for PCNL ($p<0.001$)
  - Single treatment success was: 95.3%, 87.8% and 60.4% for PCNL, URS and SWL, respectively ($p<0.001$)
  - When allowing for 2 SWL treatments success rate improved to 79.2%, equalizing success rate between the groups.
  - Auxiliary treatments were more common after SWL- 42%!

- A patient with a renal stone 1-2 cm in size should be aware that PCNL followed by URS are significantly better options than SWL for a single session treatment

The results of RIRS for stones>15 mm

	RIRS מ"מ 15 >	RIRS מ"מ 15 <	
	10.6 (3-14)	19.6 (15-28)	Mean size (mm)
p<0.05	67	93	Surgery time (min)
N.S	1.1	1.4	Hospital stay (days)
p<0.05	5%	8%	Complications
N.S	78%	74%	Stone free rate
	77 %		

Take home message

RIRS should be considered and discussed with the patient as one of the first line options for treating renal stone

Pros and cons in comparison to SWL are now part of a routine dialog with the patient

RIRS should be performed in a proper set up with enough beck up equipment