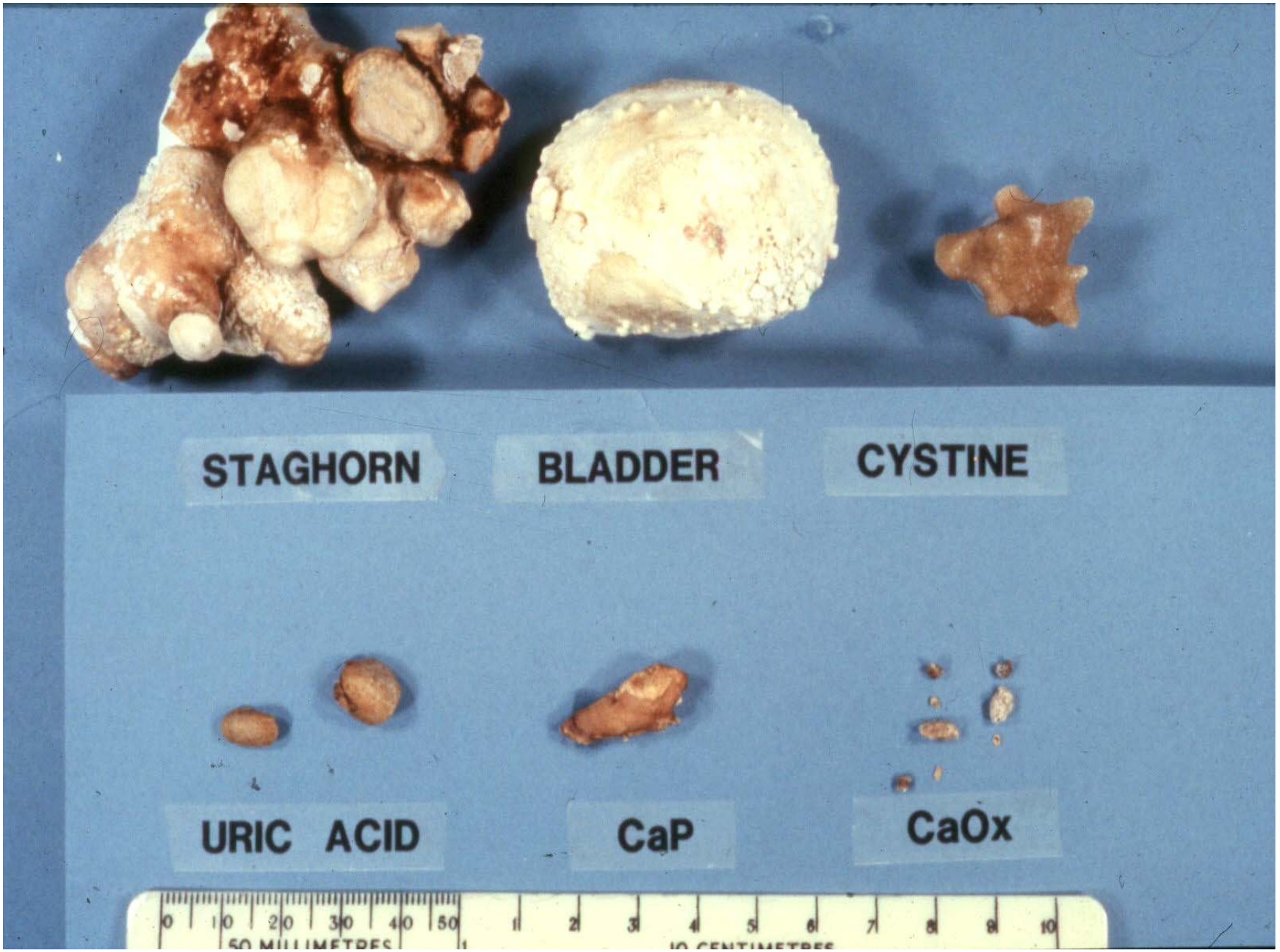
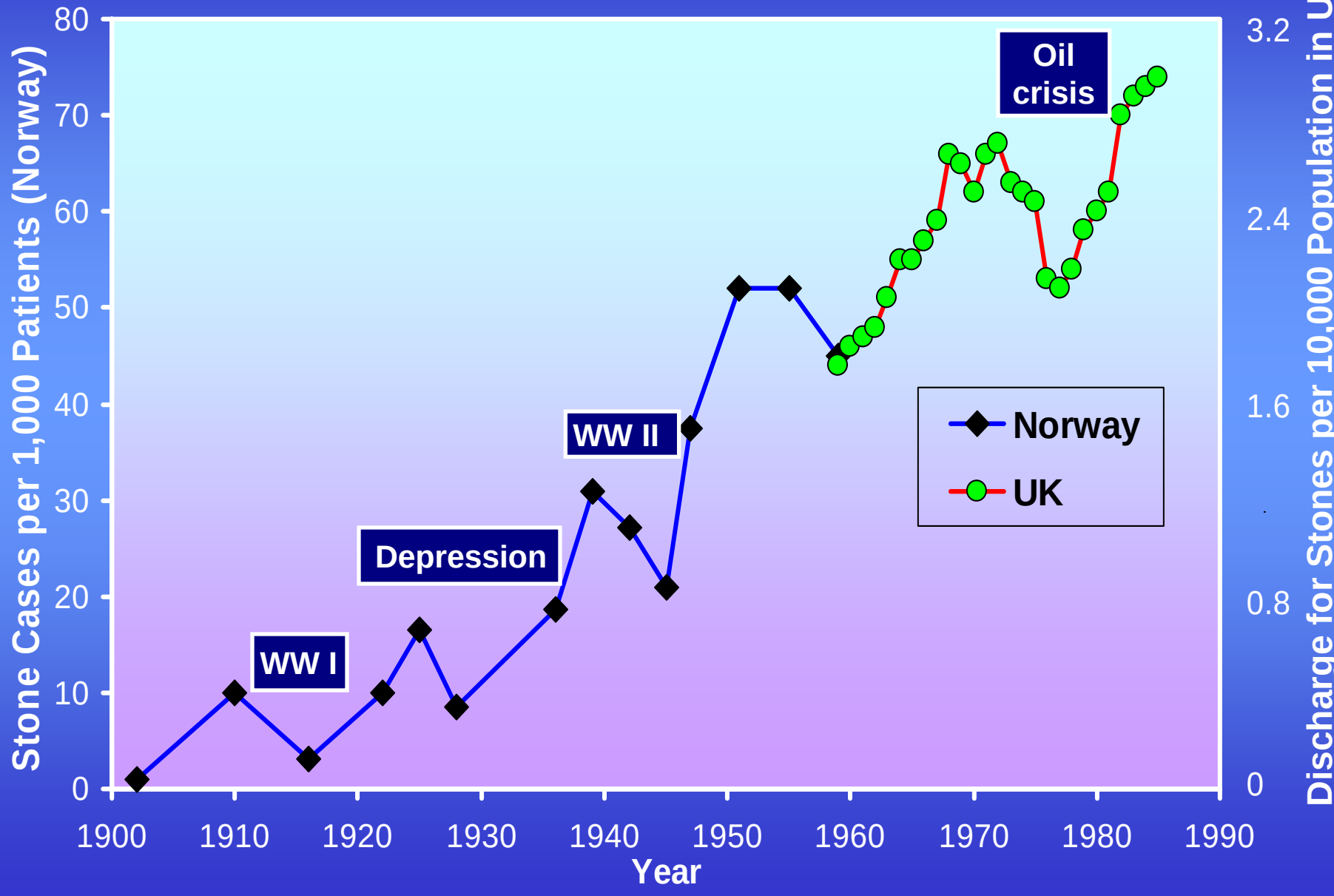
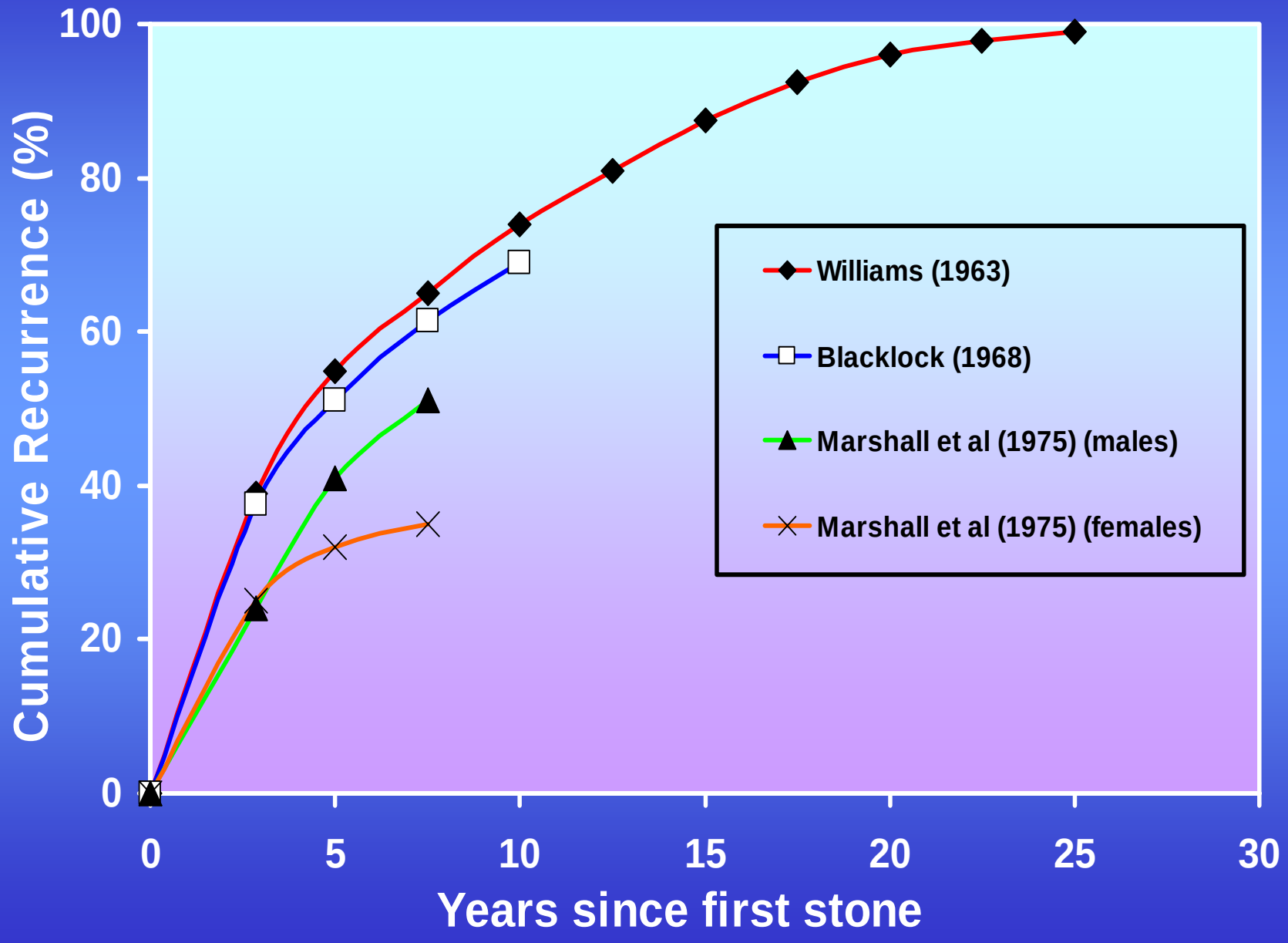
Prevention and Treatment of Urinary Stone Disease


STAGHORN
BLADDER
CYSTINE
URIC ACID
CaP
CaOx

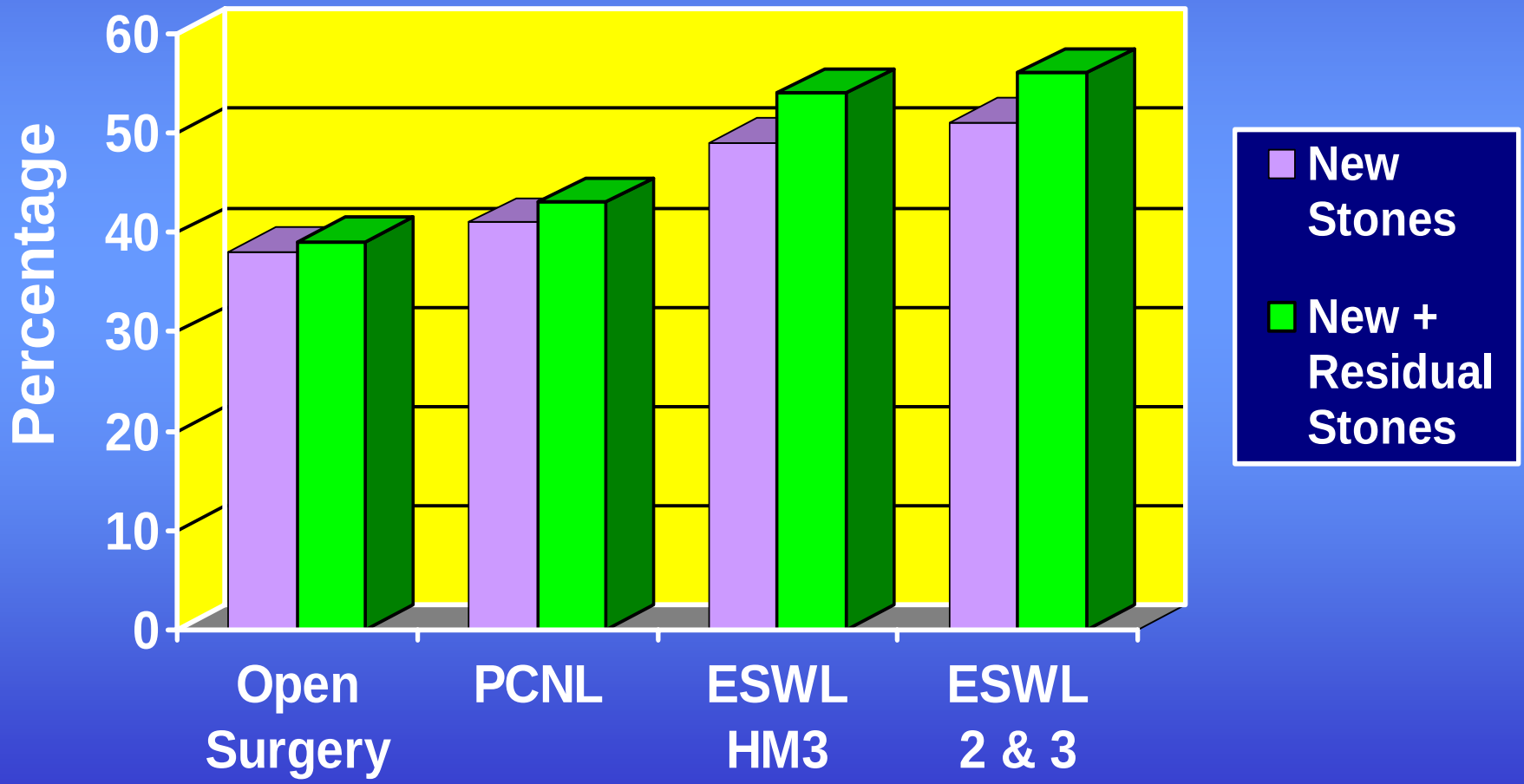
Occurrence of Urolithiasis during Last Century



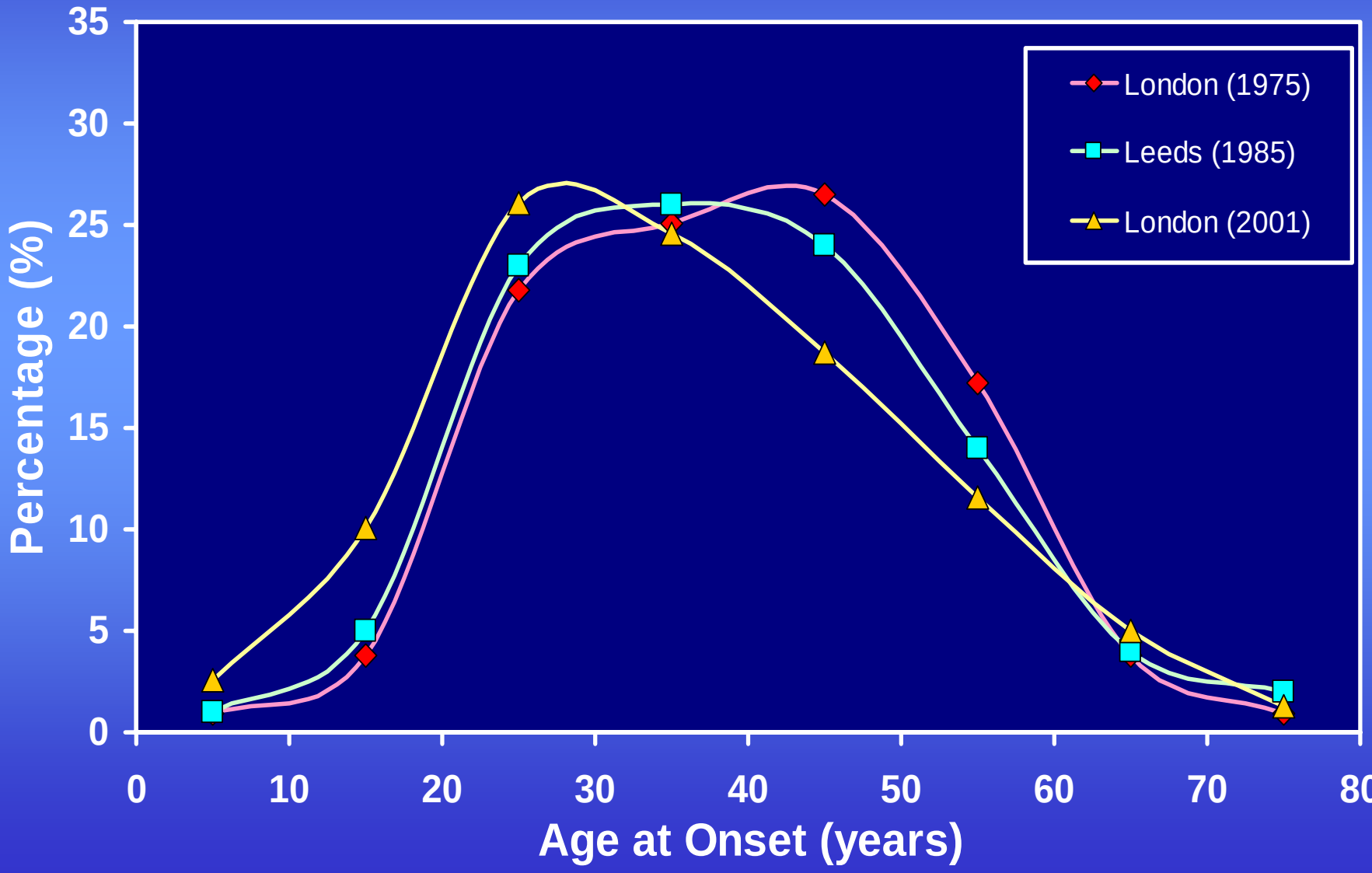
Cumulative Recurrence of Stone-Formation in UK



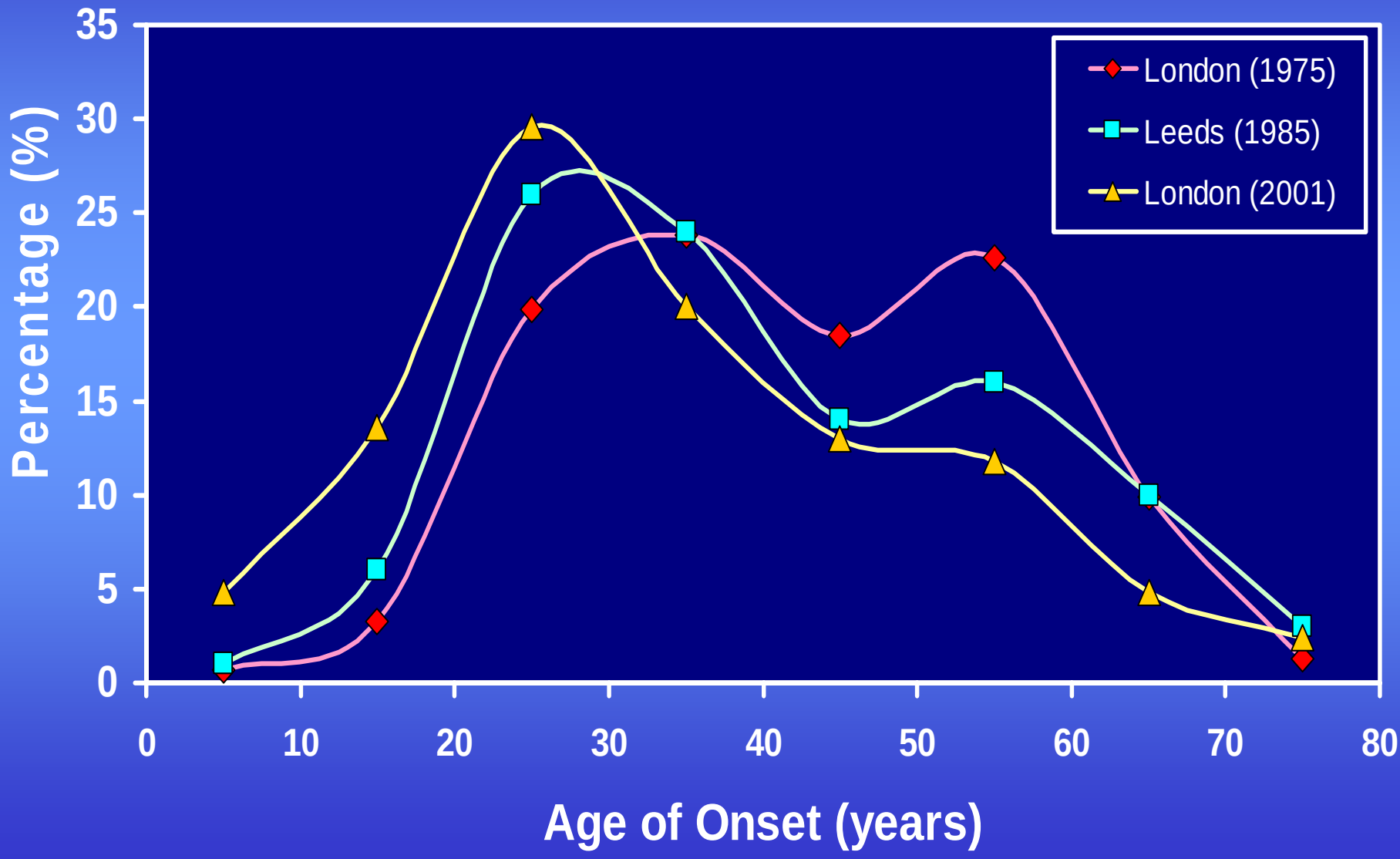
Stone Recurrence Rates 3 Years After Various Urological Procedures for Stone Management



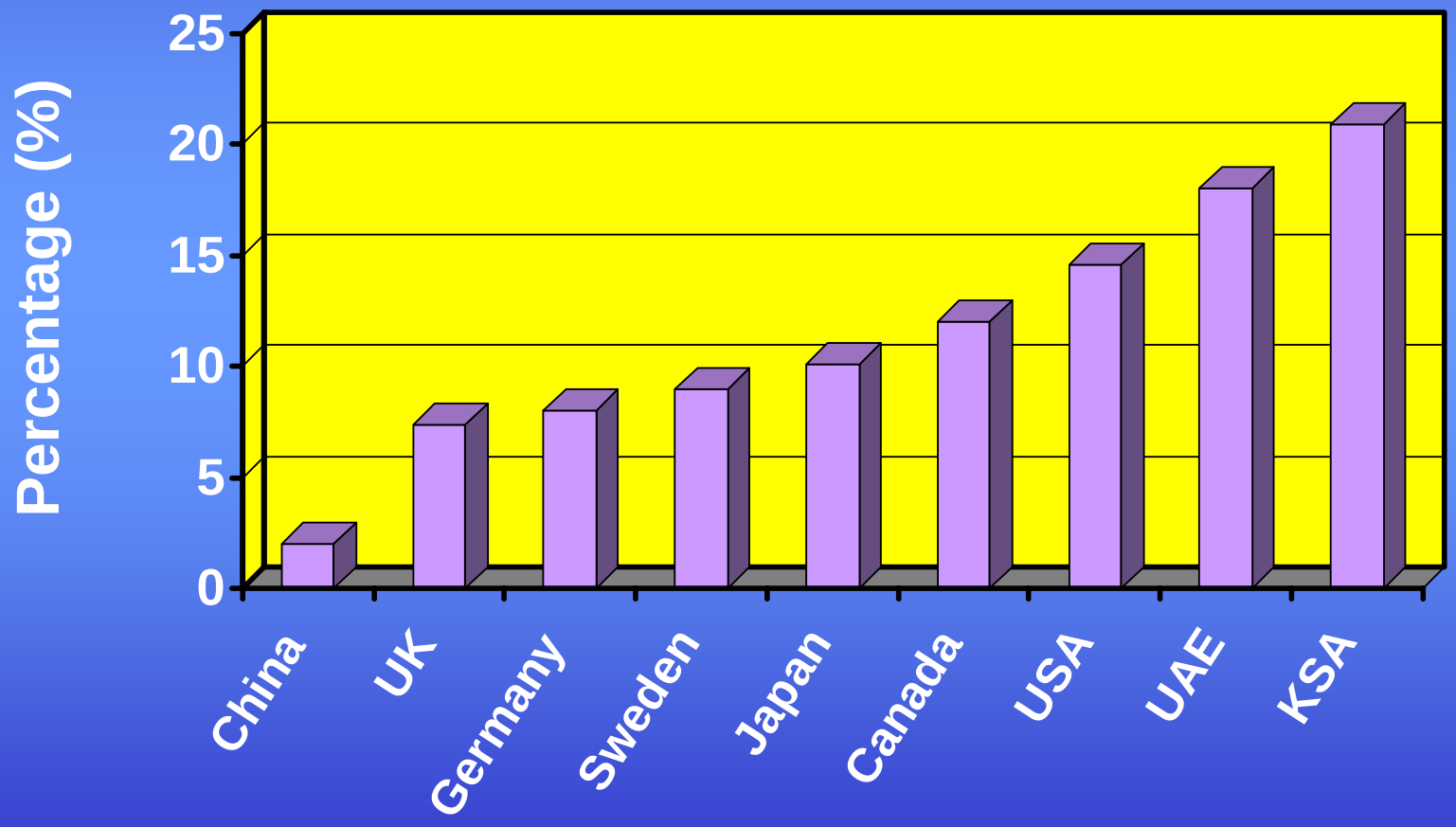
Age at Onset of Stones in Males



Age at Onset of Stones in Females



Life-Time Expectancy of Stone-Formation in Men Aged 60-70 in Various Countries



URINARY STONES

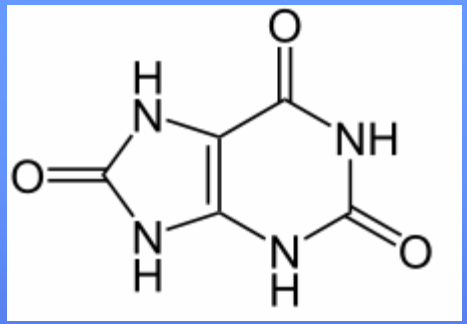
MINERAL (90%)

- Calcium oxalate
- Calcium phosphate
- Magnesium ammonium phosphate
- Uric acid/urates
- Cystine
- Xanthine
- 2,8-Dihydroxyadenine
- Silica
- Insoluble drugs (eg Indinavir, Triamterene etc)

WATER (7%)

ORGANIC MATRIX 3%)

- Mucoprotein
- Protein



Predominant Mineral	KSA (%)	USA (%)	UK (%)	KSA/UK* Ratio
Uric acid	14.6	10.1	4.5	5.1
CaOx	71.3	58.8	53.8	2.1
CaP	7.6	20.3	30.9	0.4
MAP	3.7	9.3	9.6	0.6
Rare	2.8	1.5	1.7	2.6

* Including overall Saudi/UK prevalence ratio in adults of 1.6:1

Mineral Solubilities in Water at 37ºC and pH 6

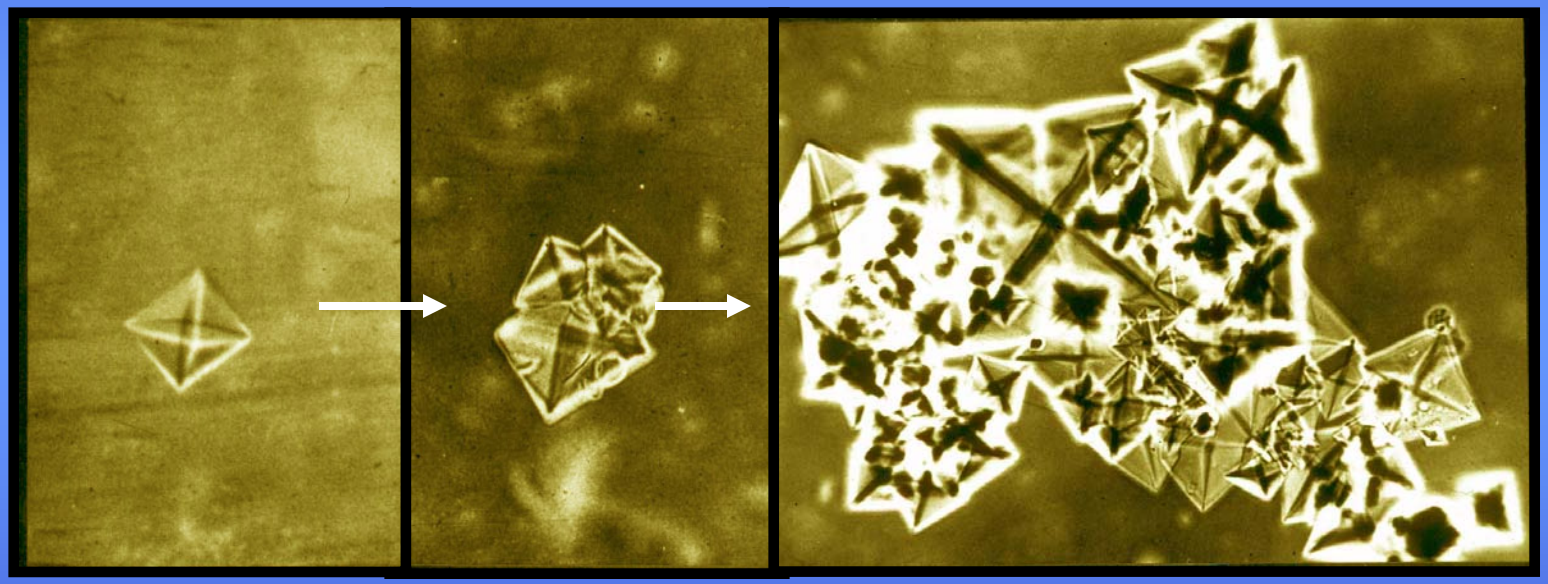
Mineral	Maximum Solubility (g/litre)
Calcium oxalate	0.0071
Calcium phosphate	0.08
Magnesium ammonium phosphate	0.36
Uric acid	0.08
Cystine	0.17
Calcium sulphate	2.1
Calcium citrate	2.2
Magnesium sulphate	293
Calcium chloride	560

Simplest Model of Urinary Stone-Formation

Free-Particle Model

1. Crystal nucleation
2. Crystal growth and agglomeration
3. Retention of critically-sized particle
4. Growth of trapped particle into stone

CaOx Crystals and Aggregates Growing in Urine



20μm 20μm 100μm

Calcium Oxalate Microstone

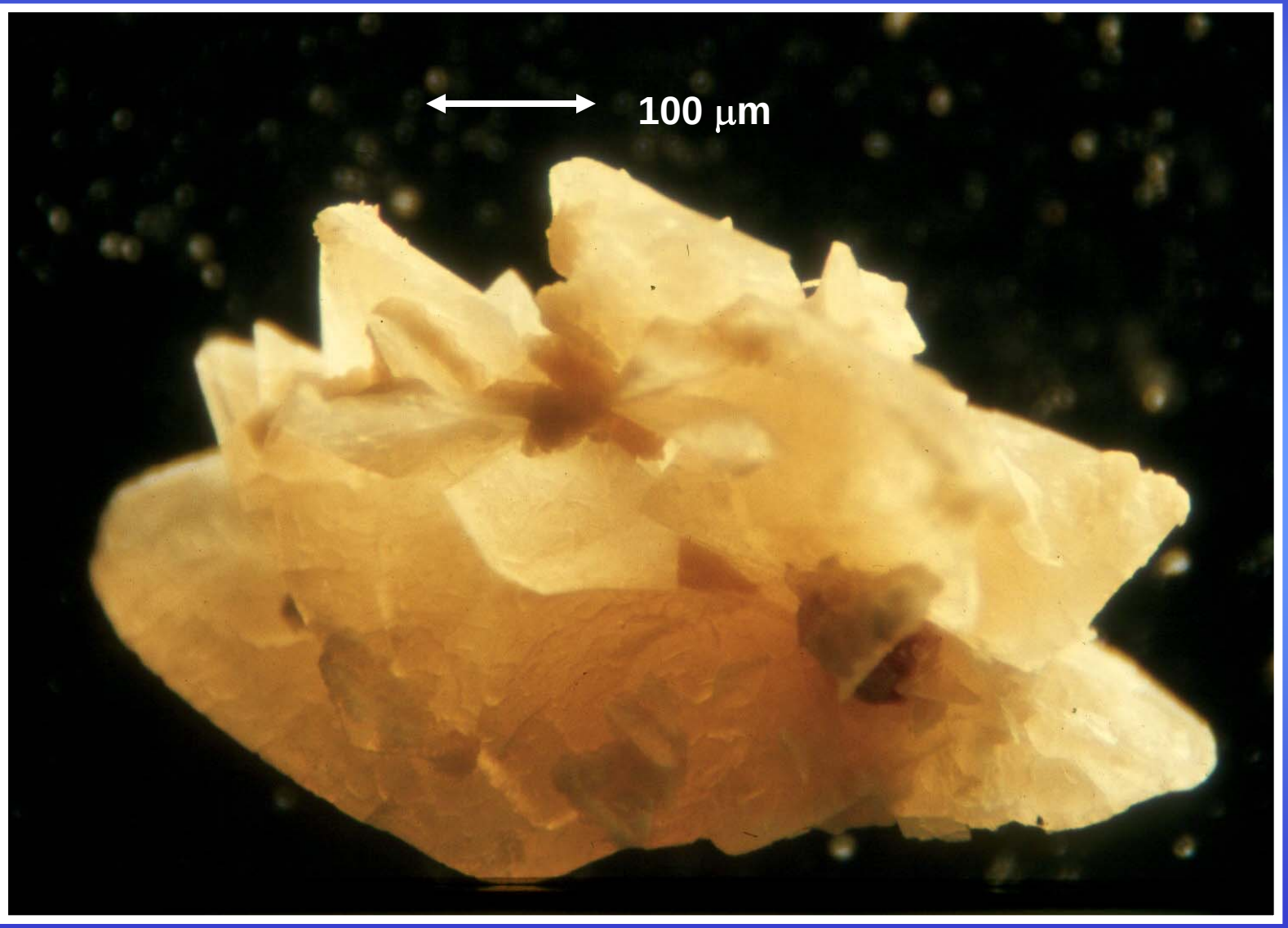
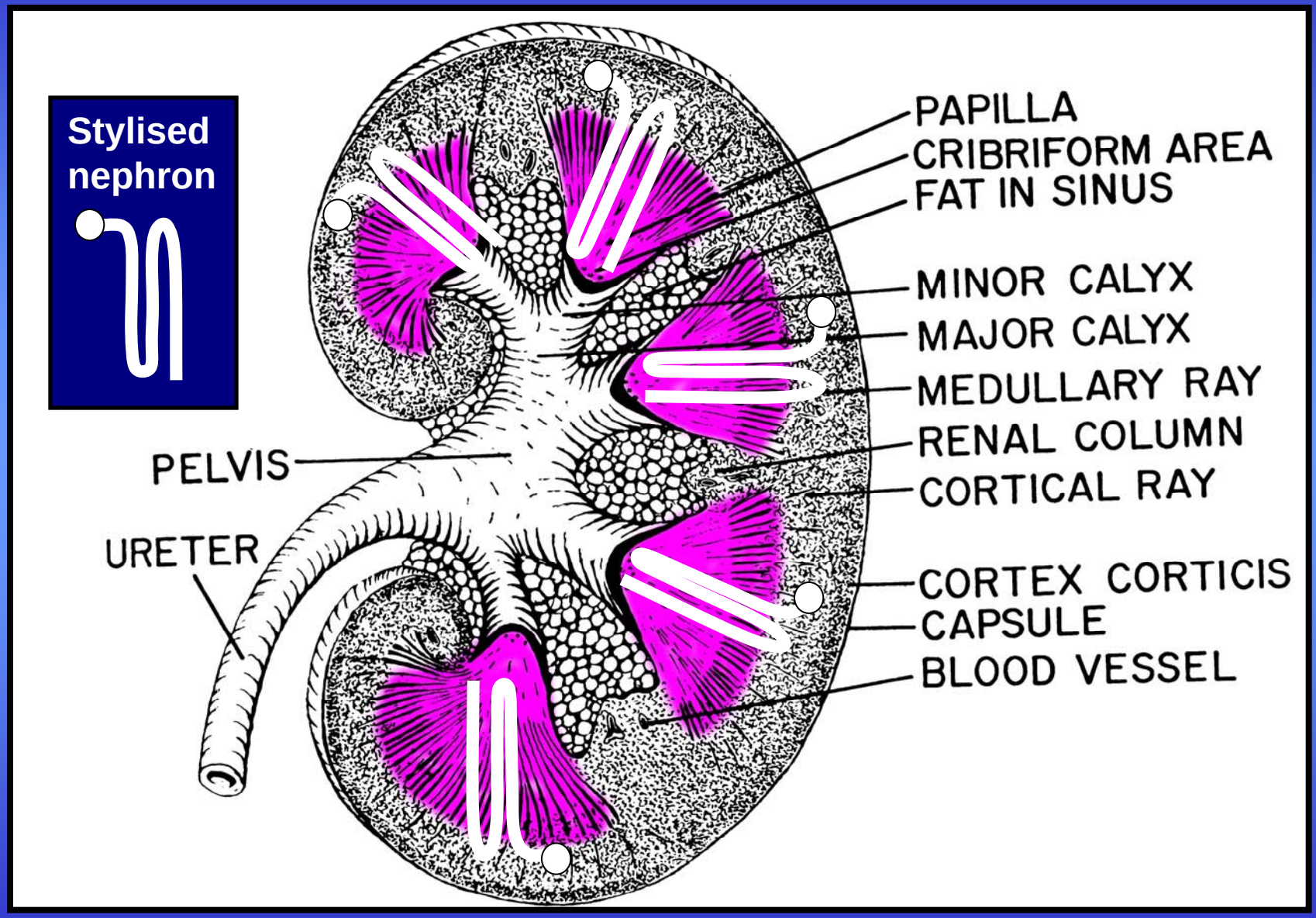
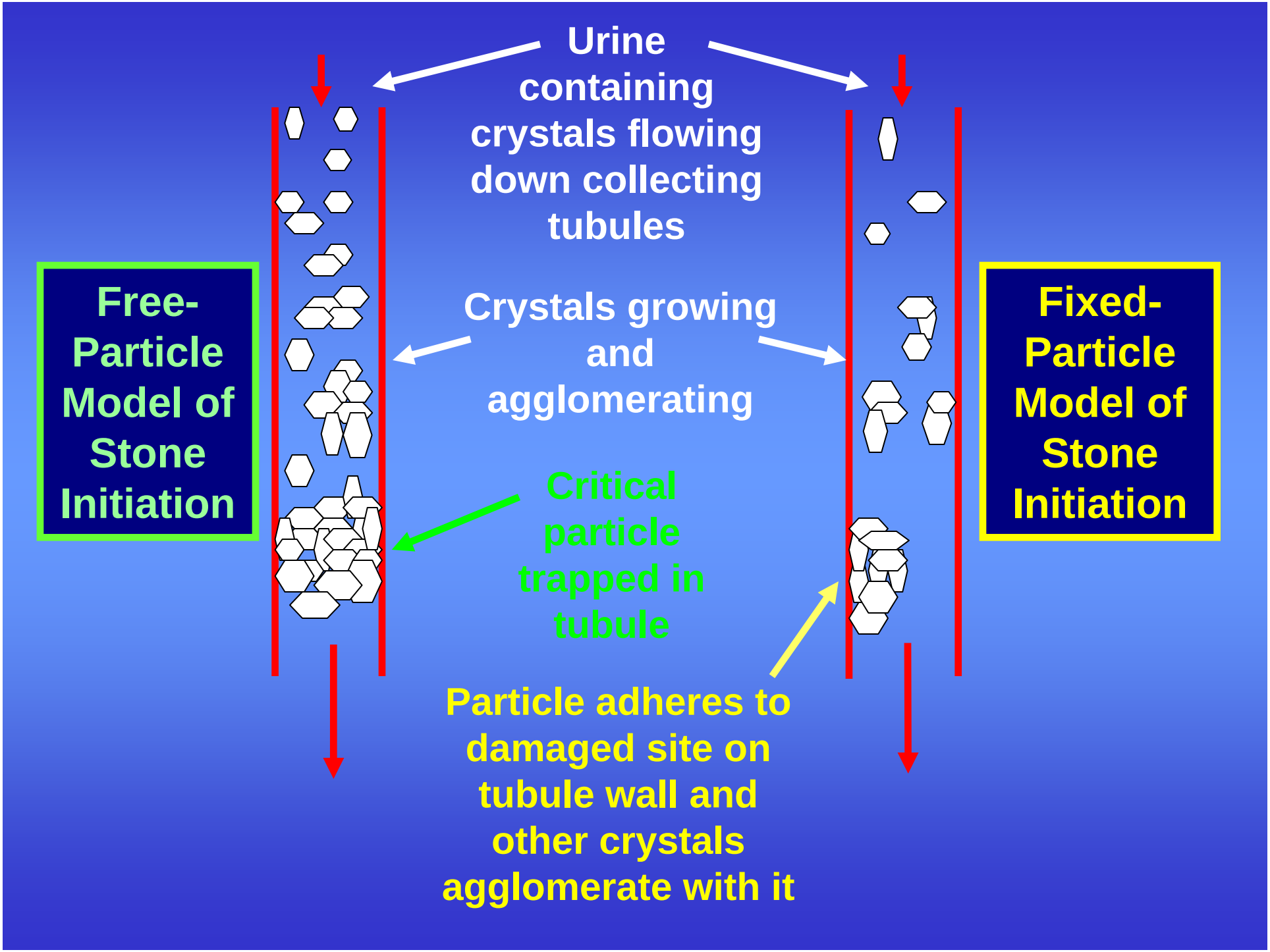
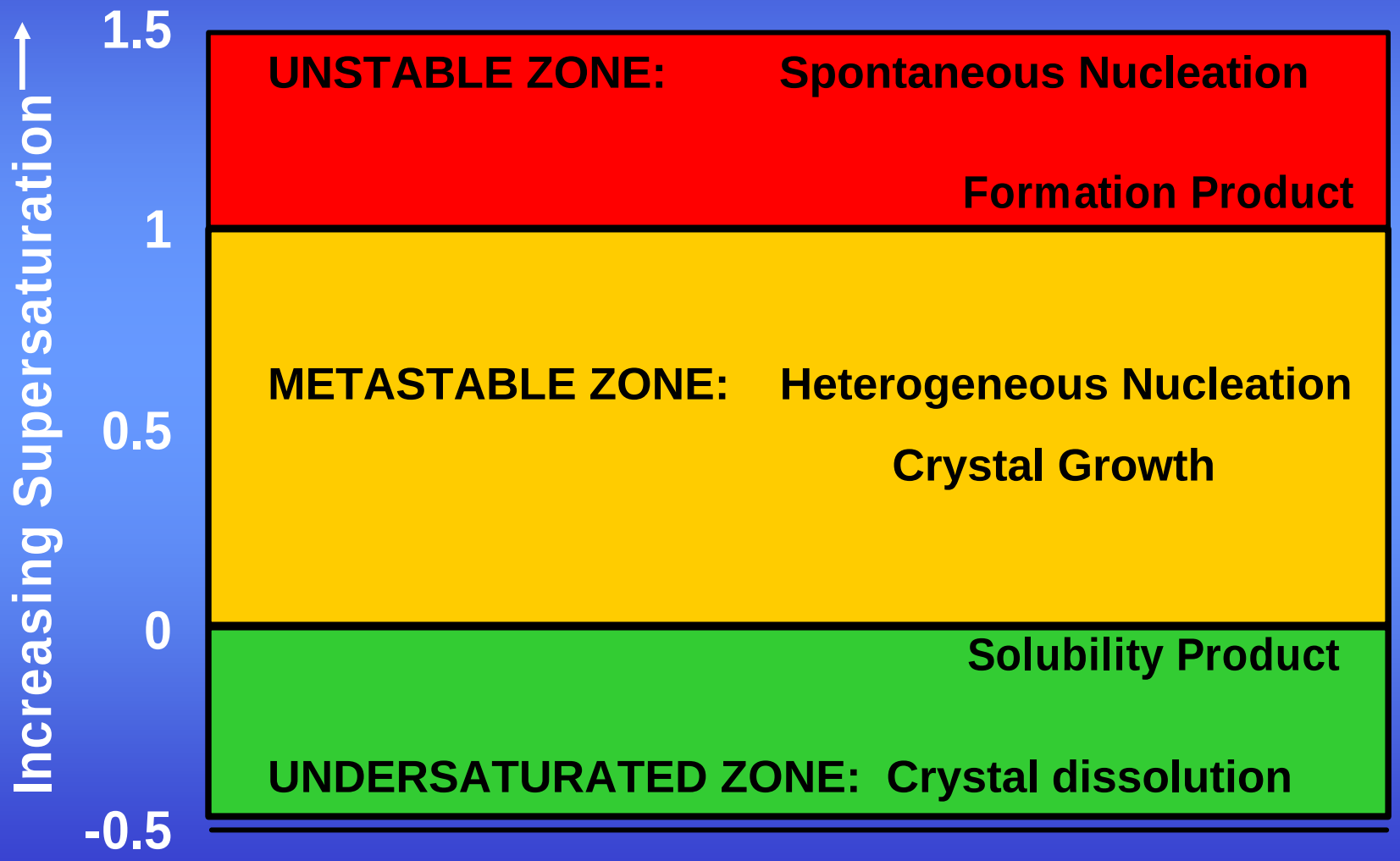


Diagram of Kidney

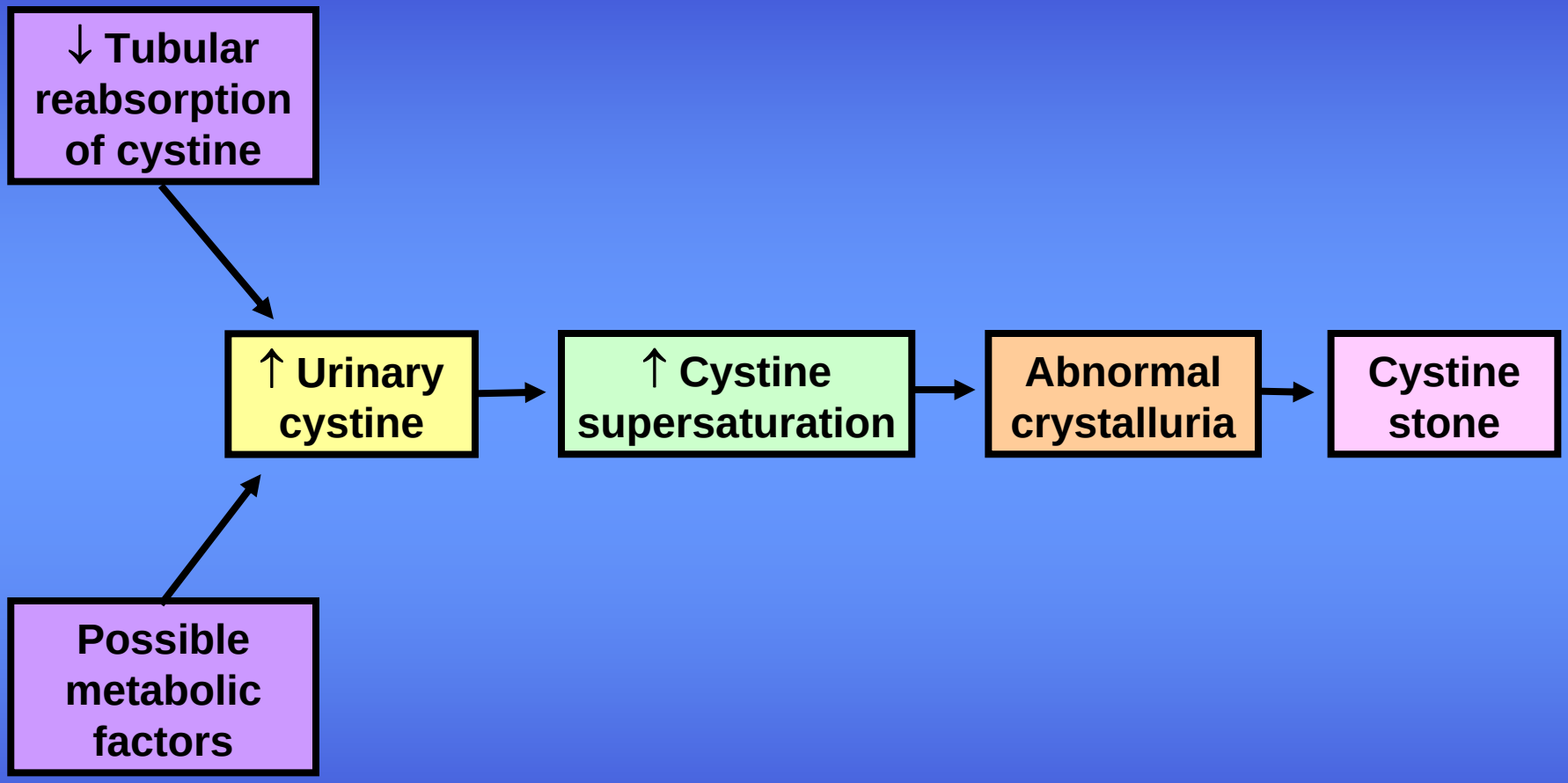



Urine containing crystals flowing down collecting tubules
Crystals growing and agglomerating
Critical particle trapped in tubule
Particle adheres to damaged site on tubule wall and other crystals agglomerate with it
Free-Particle Model of Stone Initiation
Fixed-Particle Model of Stone Initiation

Supersaturation of Urine



Risk Factor Model of Cystine Stone-Formation



Cystine Stone-Formation

Stone:	Cystine (+calcium phosphate)
Occurrence:	~1%
Age:	Child and adult
Gender:	Male and female

Abnormal	Normal
24-h Urine cystine ↑↑	Calcium metabolism
24-h Urine lysine ↑↑,	MSU
arginine ↑↑, ornithine ↑↑	

Risk Factors for Uric Acid Stone Disease

Pre-Urinary	Urinary
↓ Renal NH_3 production	↓ pH
Ileostomy	
Gout	↑ Uric acid
↑ Purine intake	
Glycogen storage disease	
Lesch-Nyhan syndrome	
Neoplastic disease	
↑ Percutaneous loss of fluid	↓ Volume
Diarrhoea	
Ileostomy	

Uric Acid Stone-Formation

Stone: Uric acid (+calcium oxalate)
Occurrence: ~5%
Age: 30 - 70
Gender: Male > female

Abnormal

Plasma uric acid ↑
24-h Urine uric acid ↑,
24-h Urine pH ↓
24-h Urine volume ↓

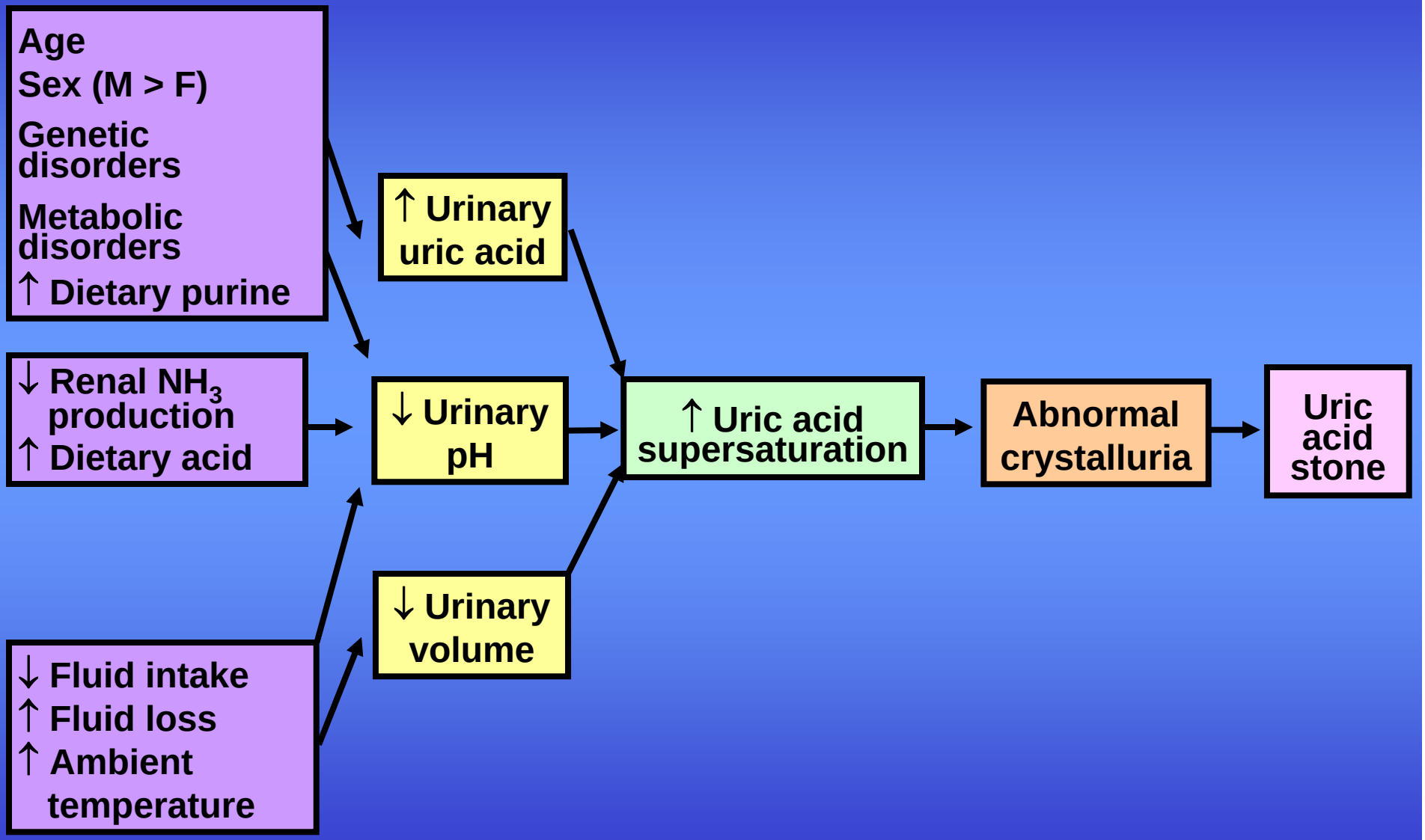
Normal

Calcium metabolism
MSU

Other Features

Ileostomy

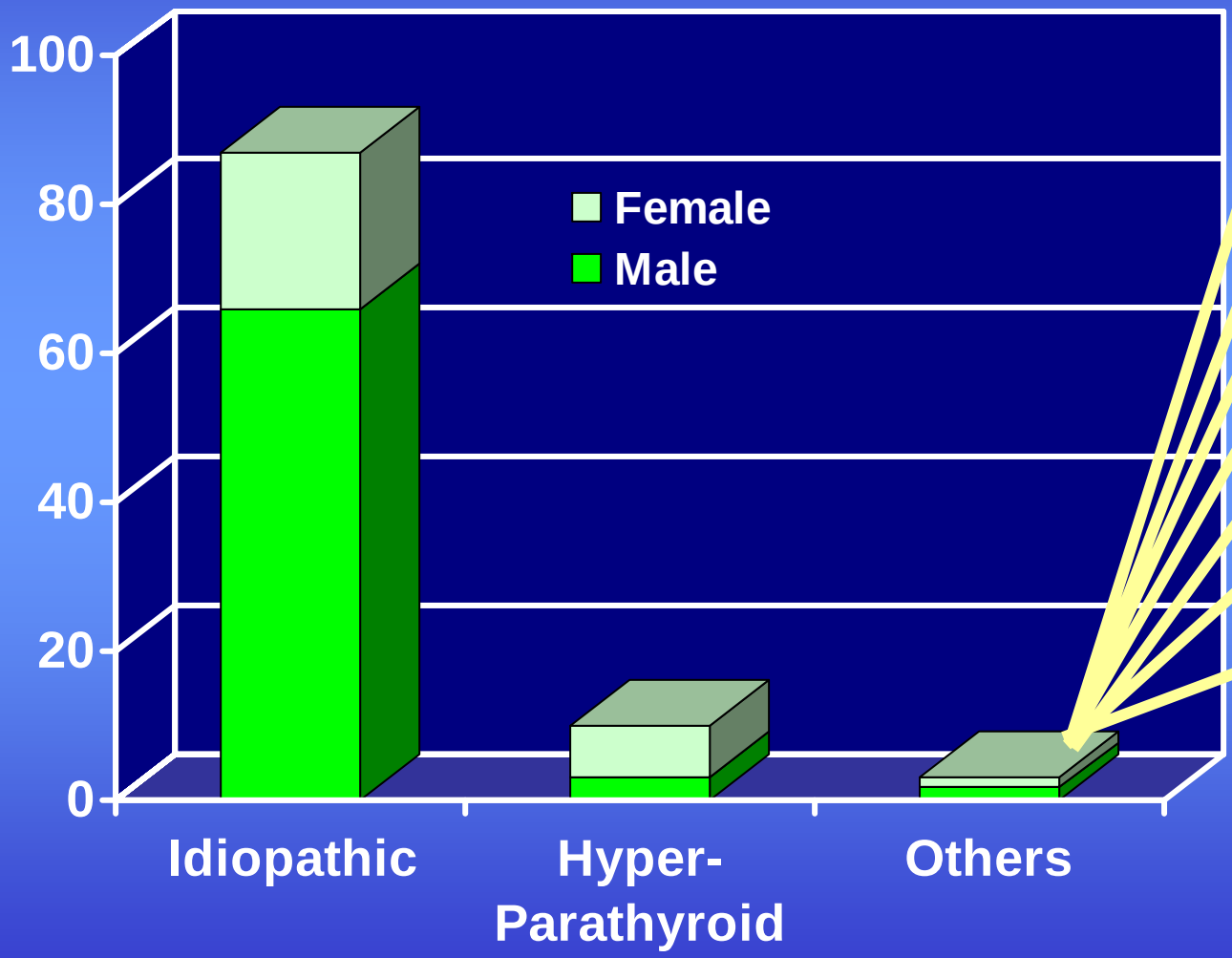
Risk Factor Model of Uric Acid Stone-Formation



Additional Features of Infected Stone-Formation

- There is a metabolic abnormality in > 50% of patients with infection stones
- Any anatomical abnormality may lead to infection
- Ammonia may cause damage to protective GAG layer
- Recurrence in 10% of patients after complete removal
- Recurrence in 85% of patients if fragments remain
- Antibiotics may suppress bacteriuria and afford symptomatic relief but rarely totally eliminate infection in the presence of calculi

Calcium Stone-Formation



- dRTA
- Hyperoxaluria
- MSK
- Steroids
- Hypervitaminosis D
- Immobilisation
- Milk-Alkali Syndrome

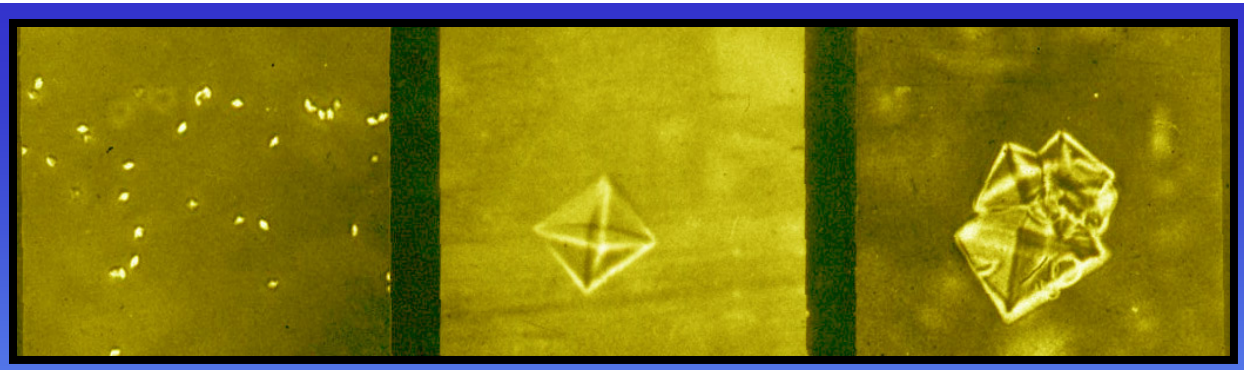
Inhibitors and Promoters of Crystallisation in Urine

INHIBITORS

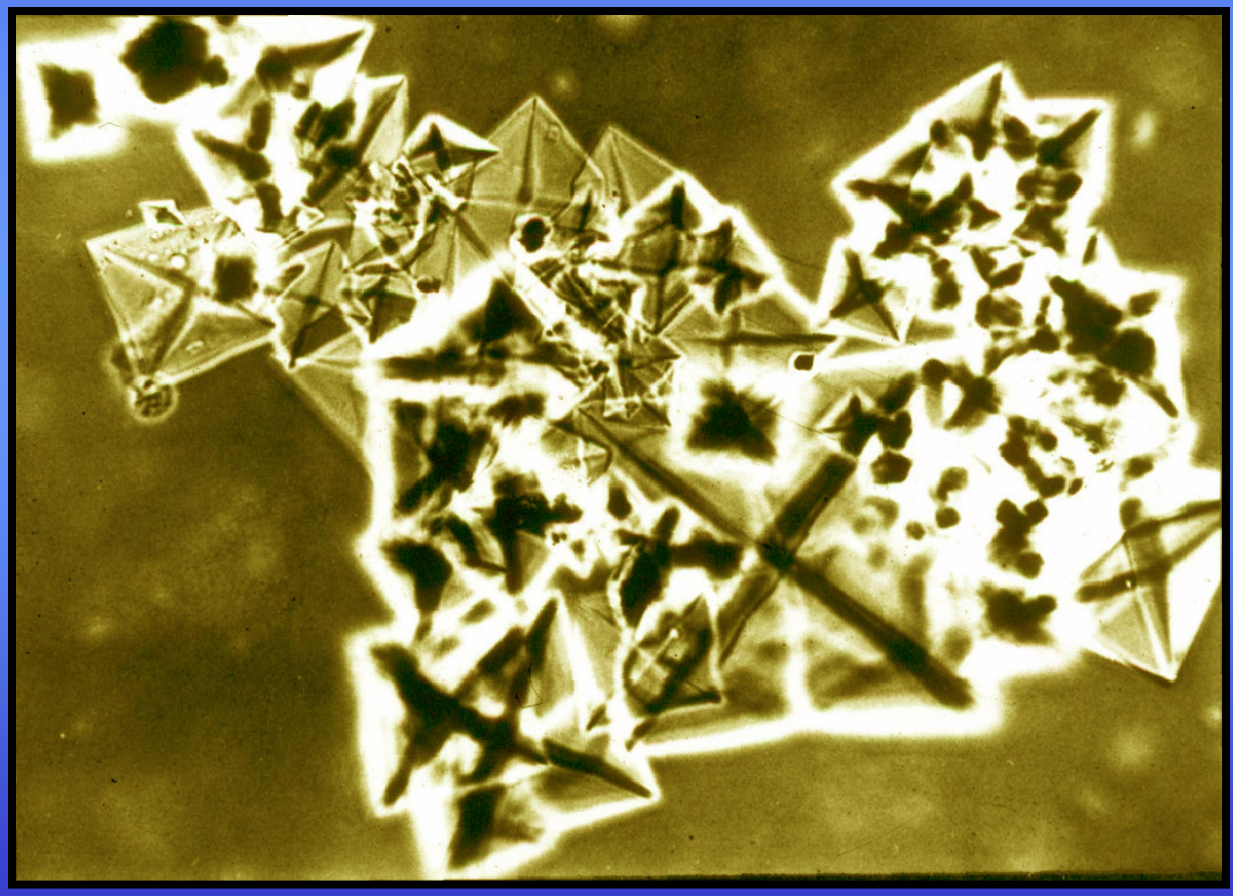
Citrate, Pyrophosphate, Magnesium, ADP, ATP, Phosphocitrate, Glycosaminoglycans, Tamm-Horsfall Mucoprotein, Uromodulin, (Osteopontin), α-1-Microglobulin, β-2-Microglobulin, Urinary Prothrombin Fragment 1, Inter-α-Inhibitor

PROMOTERS

Uromucoid (Polymerised THM), Matrix Substance A

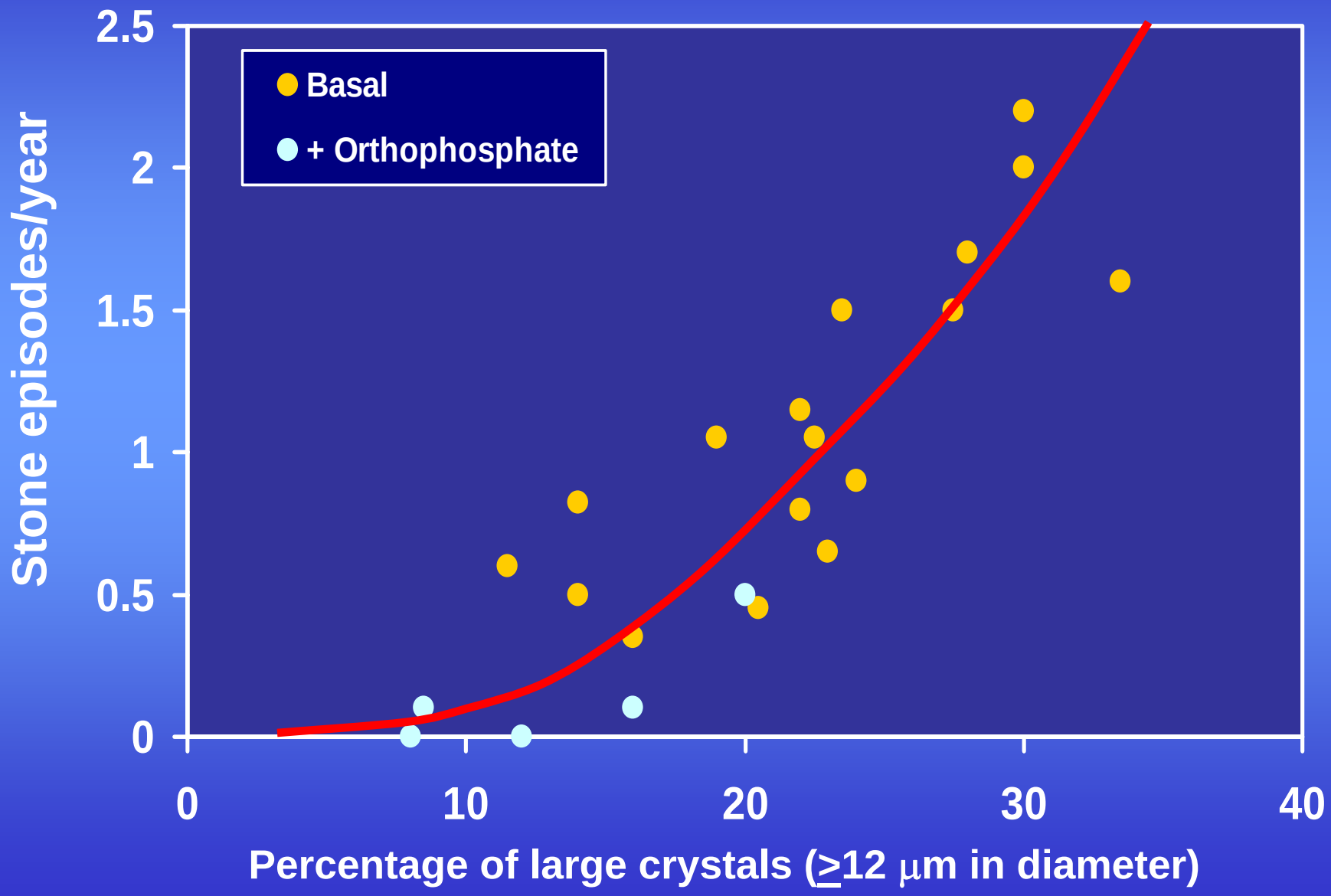


Normal Subjects RSF RSF

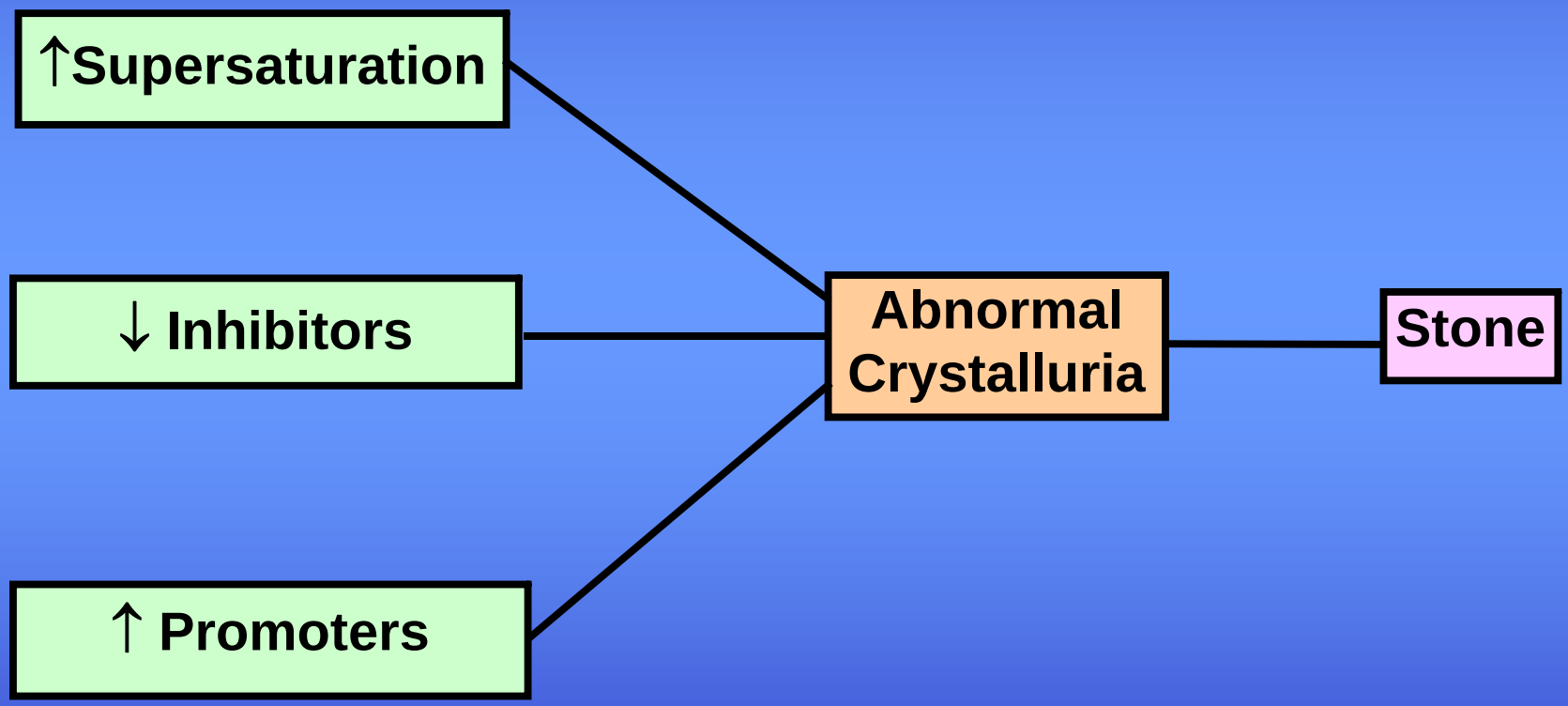


Recurrent CaOx Stone-Former (RSF)

Severity of Calcium Stone Disease and Crystalluria



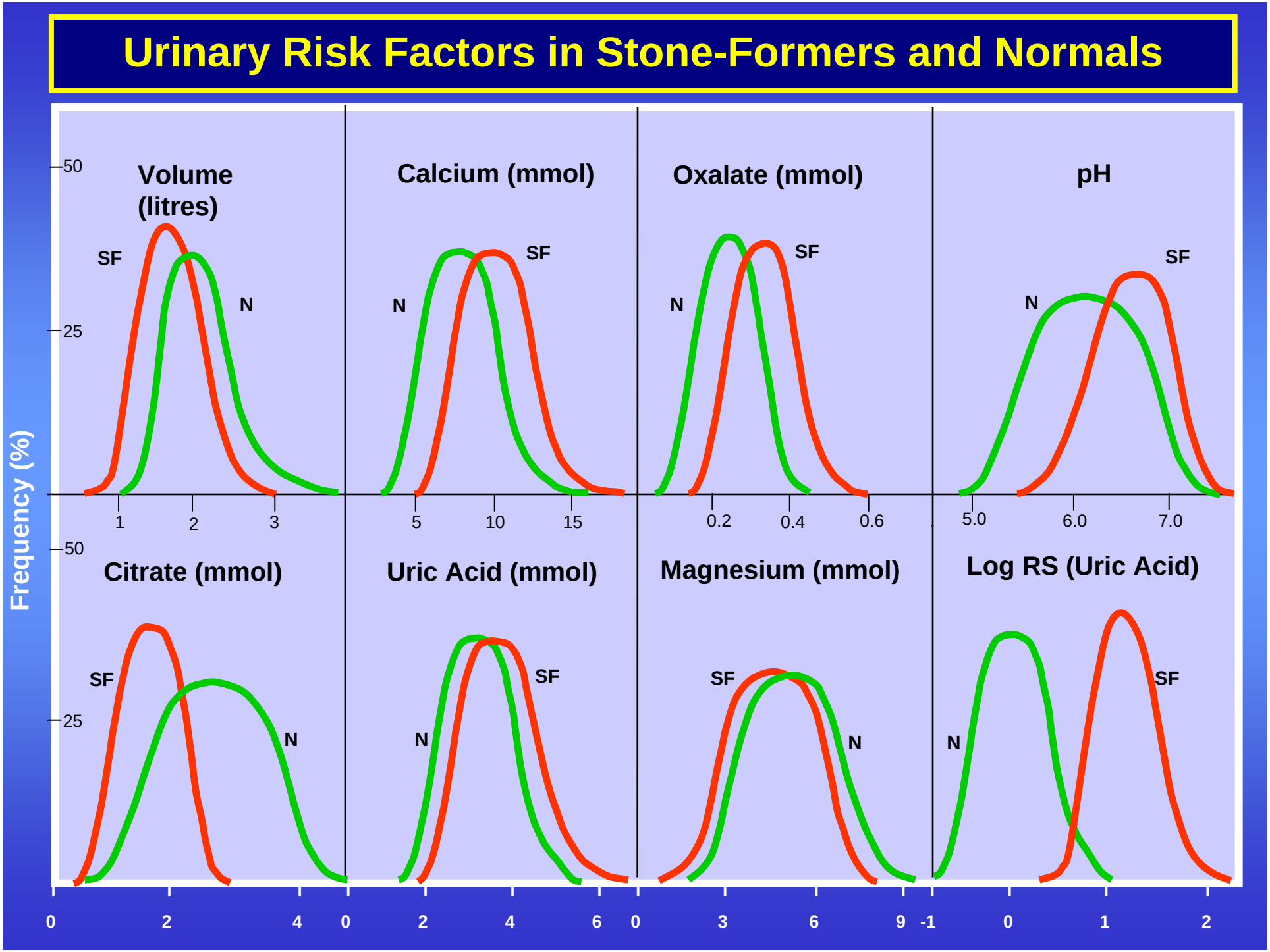
Risk Factor Model of Calcium Stone-Formation



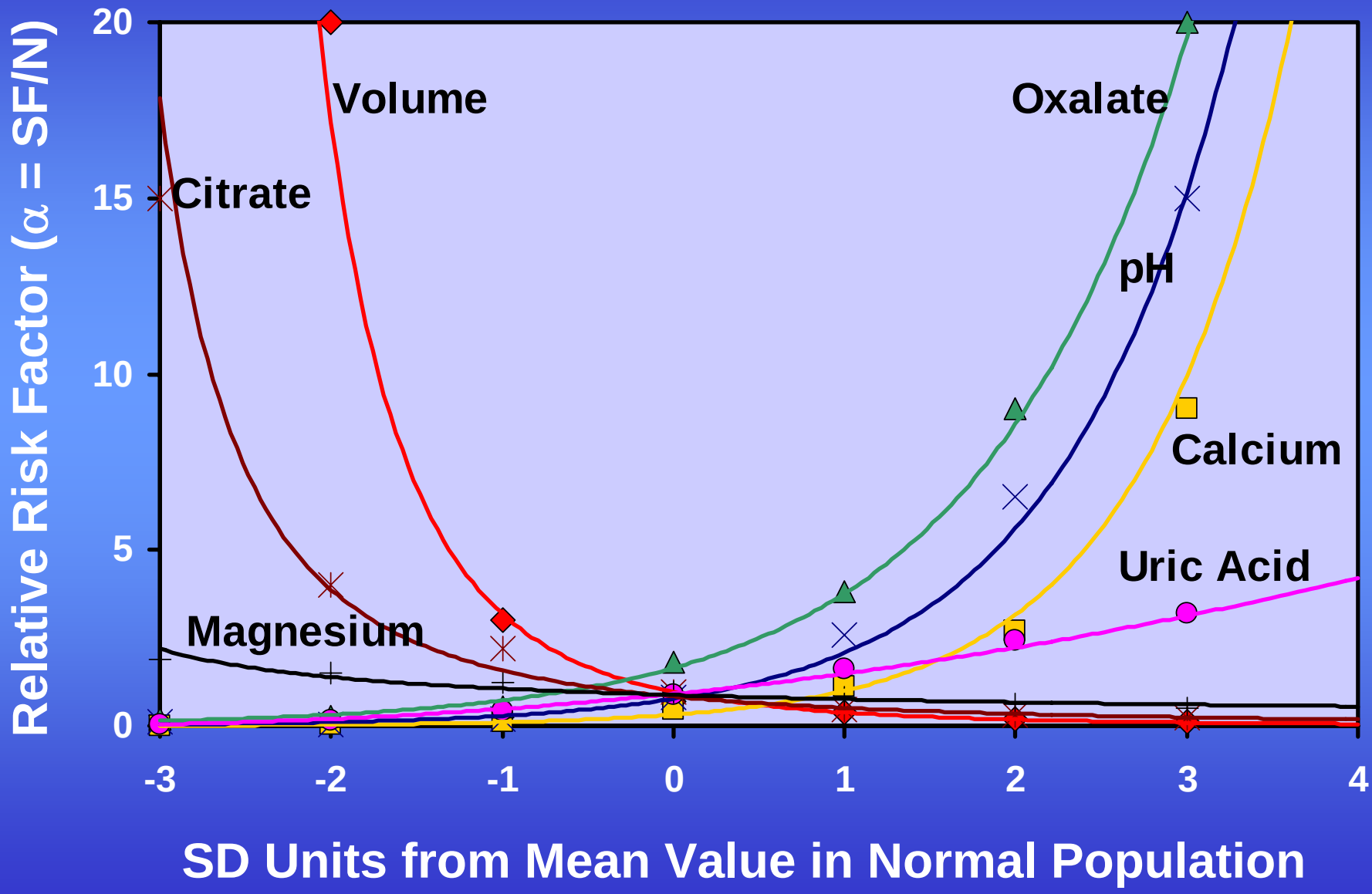
Urinary Risk Factors for Calcium Stone-Formation

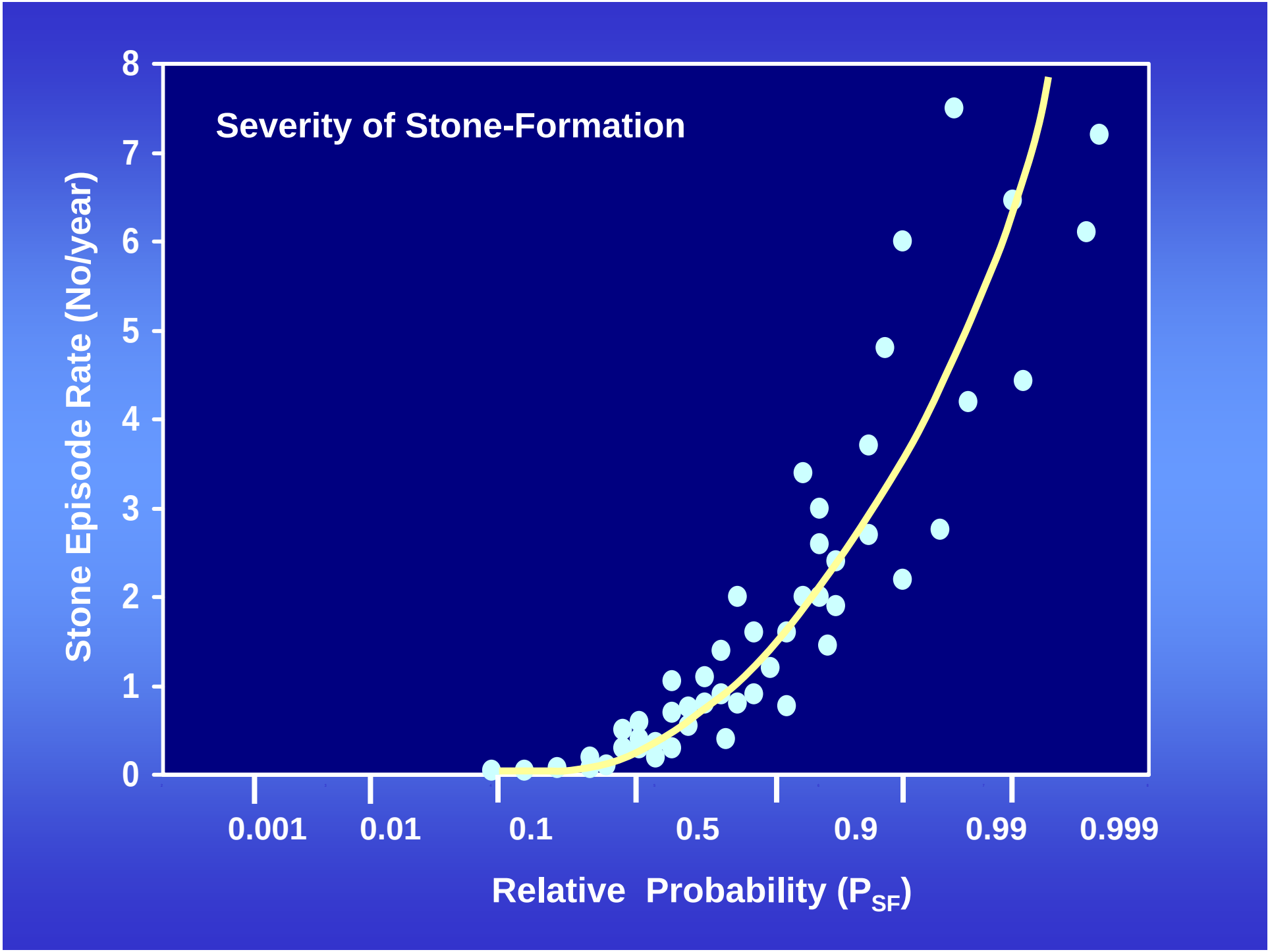
- Low urine volume
- Mild hyperoxaluria
- Increased urinary pH
- Hypercalciuria
- Hypocitraturia
- Hyperuricosuria
- Hypomagnesiuria

Urinary Risk Factors in Stone-Formers and Normals



Risk Curves for Urinary Risk Factors for Stone-Formation




Severity of Stone-Formation
Stone Episode Rate (No/year)
8
7
6
5
4
3
2
1
0
0.001
0.01
0.1
0.5
0.9
0.99
0.999
Relative Probability (P_{SF})

Example of Risk Accumulation in a "Normal-Looking" Urine from a CaOx/CaP Stone-Former Compared with that of a Normal

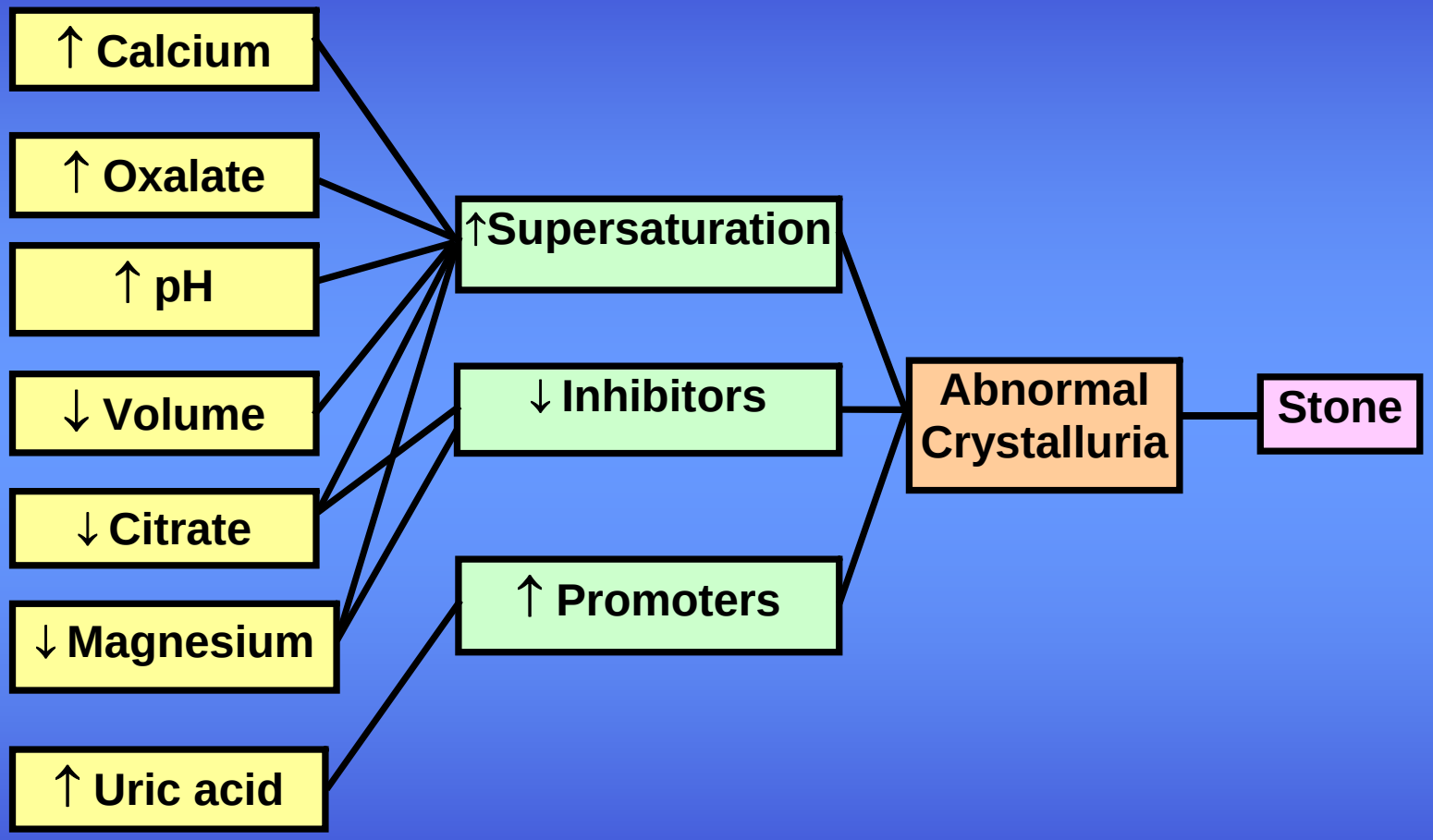
	Patient (AGW)	Normal (JHT)
Volume (litre/day)	1.50	1.65
pH	6.10	6.00
Calcium (mmol/day)	5.98	5.50
Magnesium (mmol/day)	3.62	4.50
Oxalate (mmol/day)	0.40	0.35
Uric acid (mmol/day)	3.66	3.20
Citrate (mmol/day)	2.11	2.50
P_{SF}(CaOx)	0.85****	0.35
P_{SF}(CaOx/CaP)	0.90*****	0.36
P_{SF}(CaP)	0.67**	0.42

Idiopathic Calcium Stone-Formation

Stone:	**Calcium oxalate and/or calcium phosphate or uric acid**
Occurrence:	**70%**
Age:	**15 - 75**
Gender:	**Male > female (3:1)**

Abnormal	**Normal**
24-h Urine volume ↓	**Plasma Ca, P_i, PTH**
24-h Urine pH ↑	**MSU**
24-h Urine calcium ↑	
24-h Urine oxalate ↑	
24-h Urine uric acid ↑	
24-h Urine citrate ↓	
24-h Urine magnesium ↓	

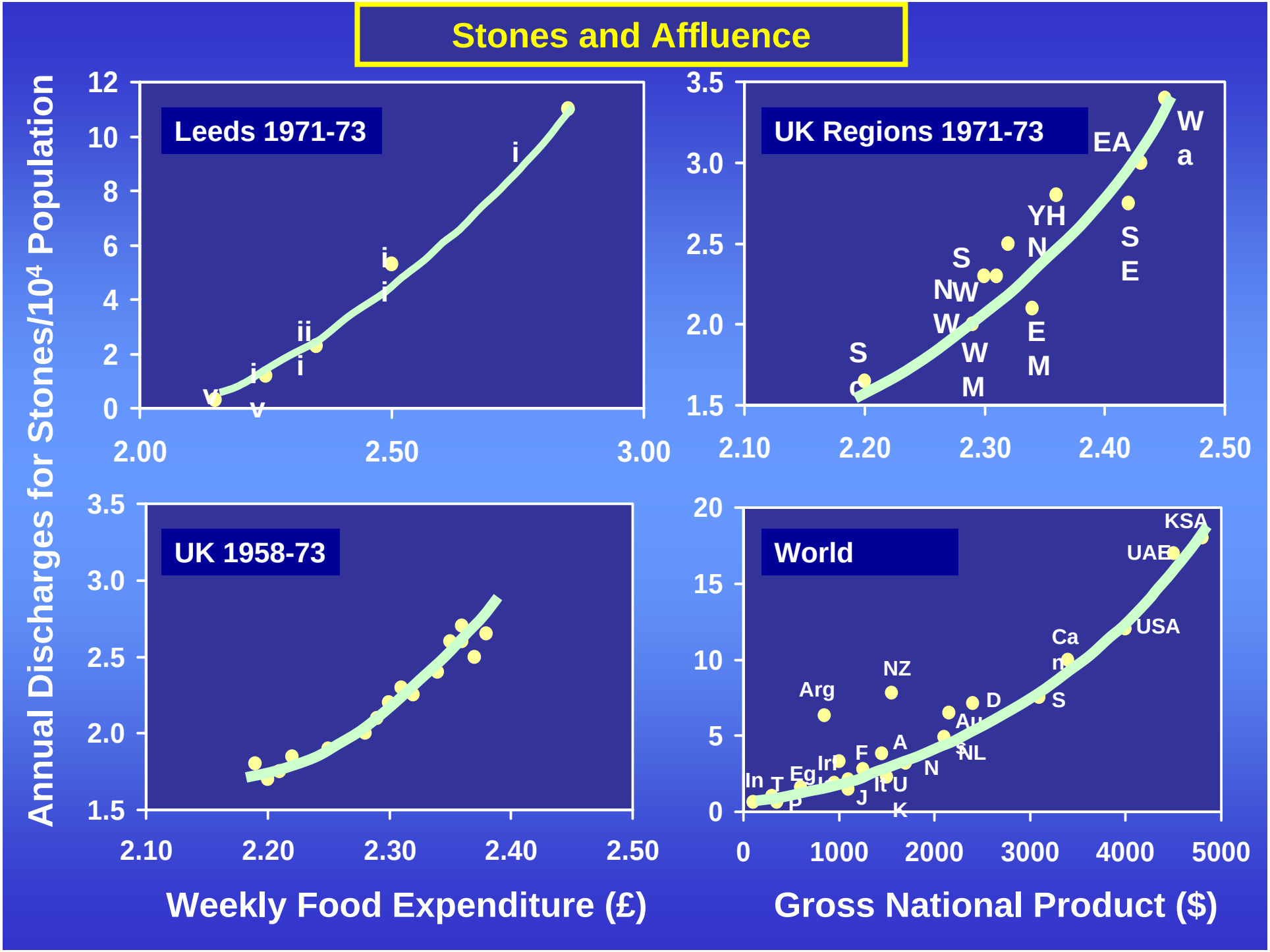
Risk Factor Model of Calcium Stone-Formation



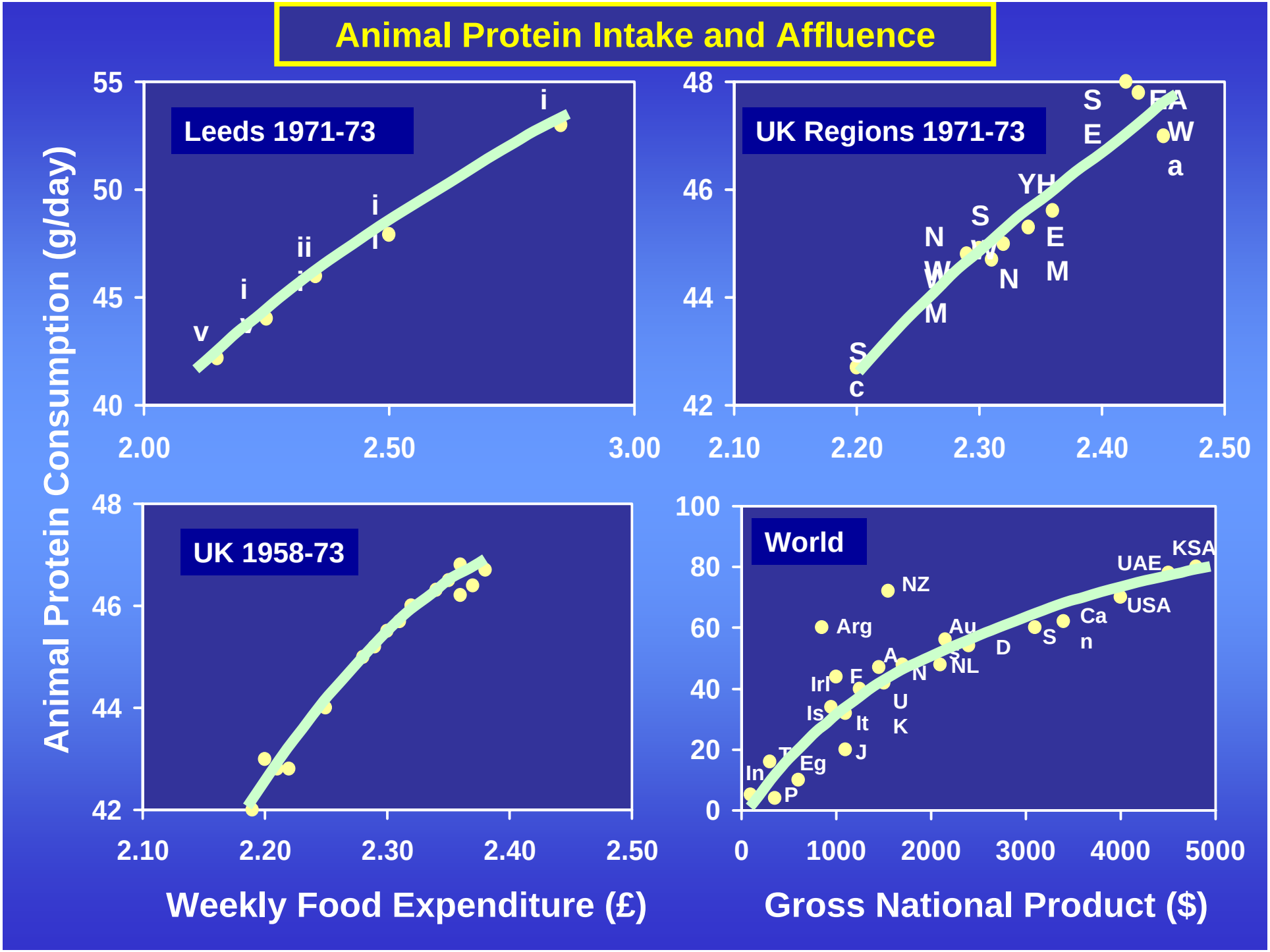
Epidemiological Risk Factors for Calcium Stone-Formation

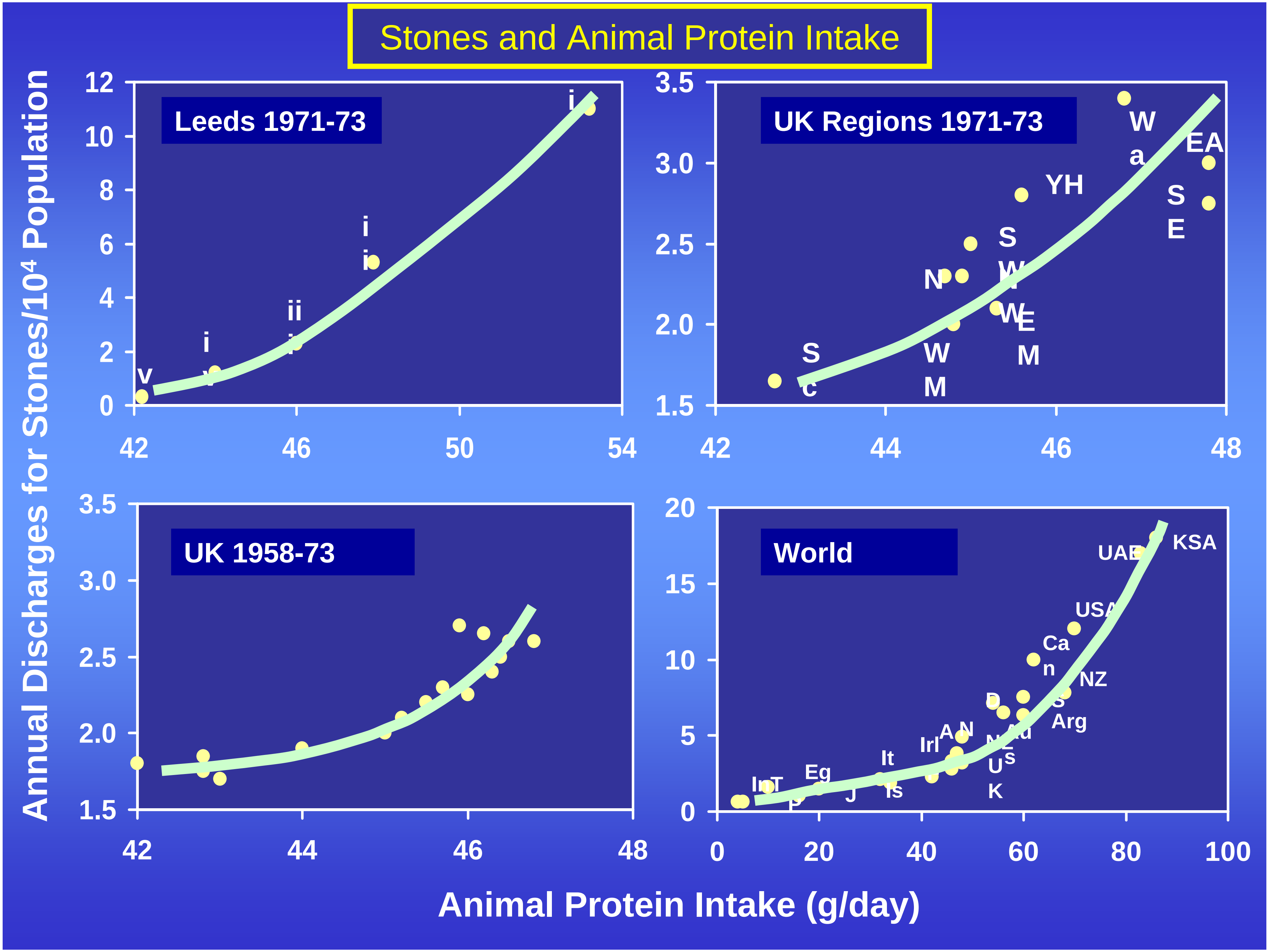
- Age
- Gender
- Season
- Climate
- Fluid Intake
- Stress
- Occupation
- Affluence
- Diet
- Metabolic disorders
- Genetic disorders

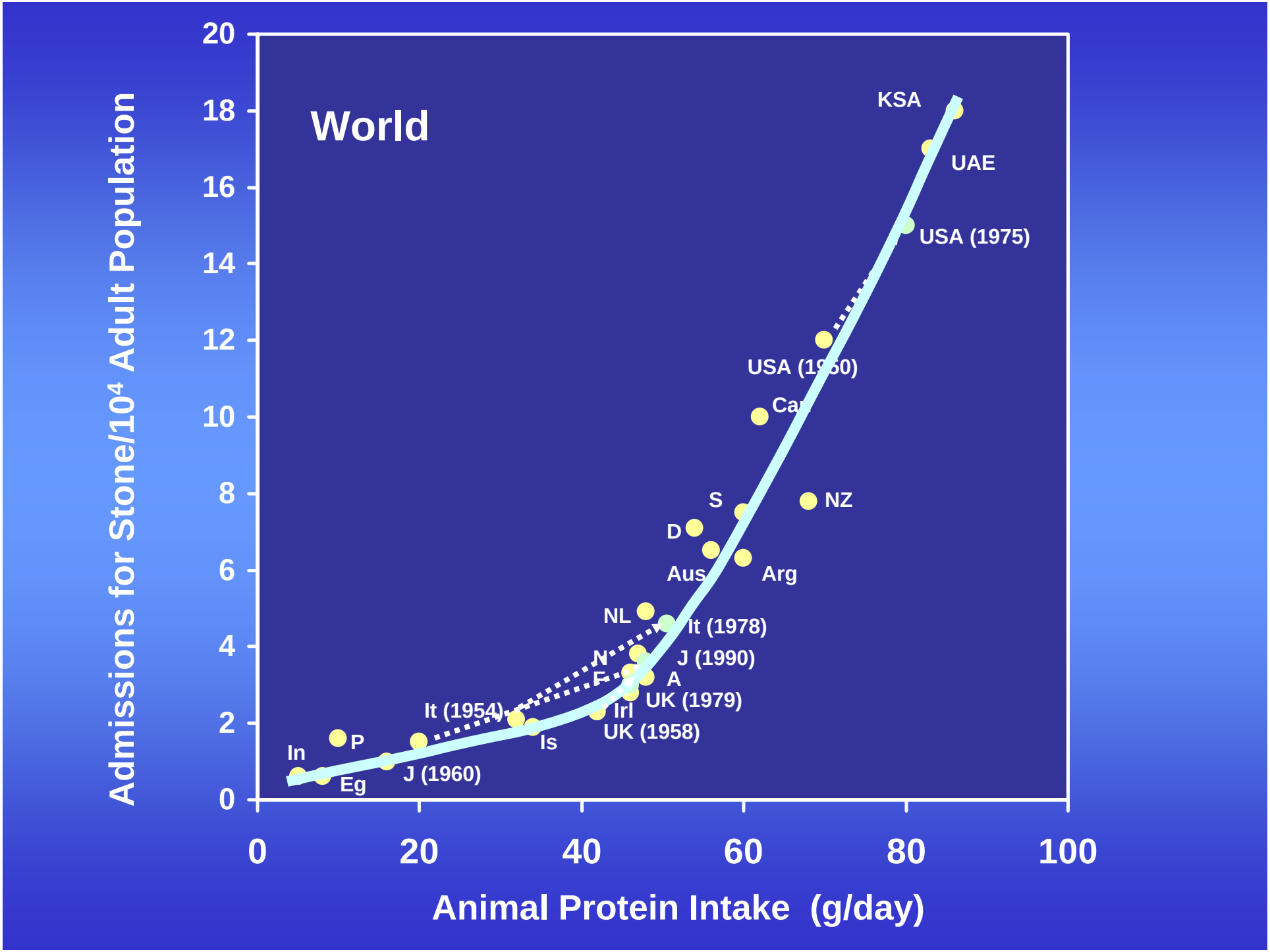
Stones and Affluence

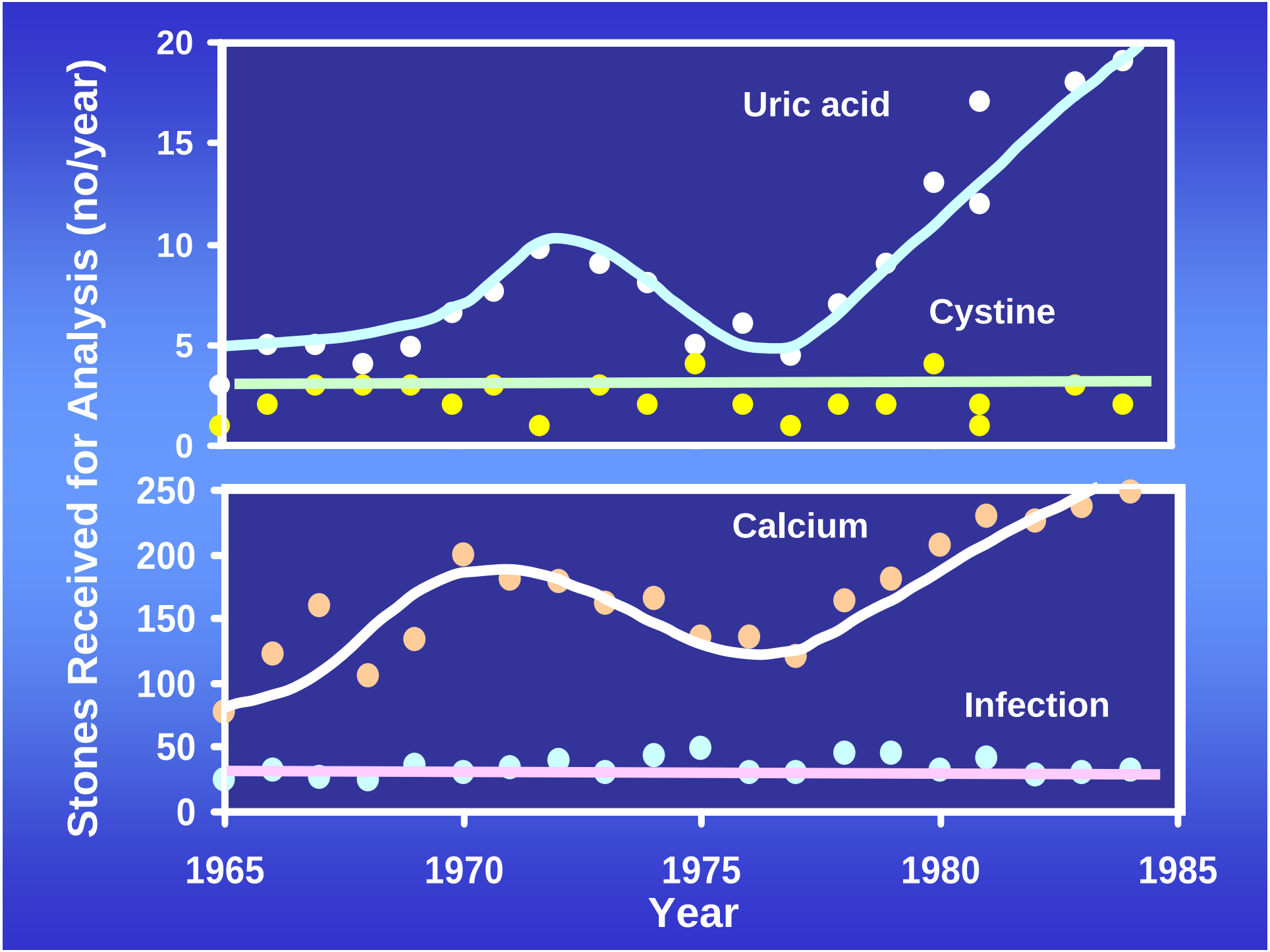


Animal Protein Intake and Affluence

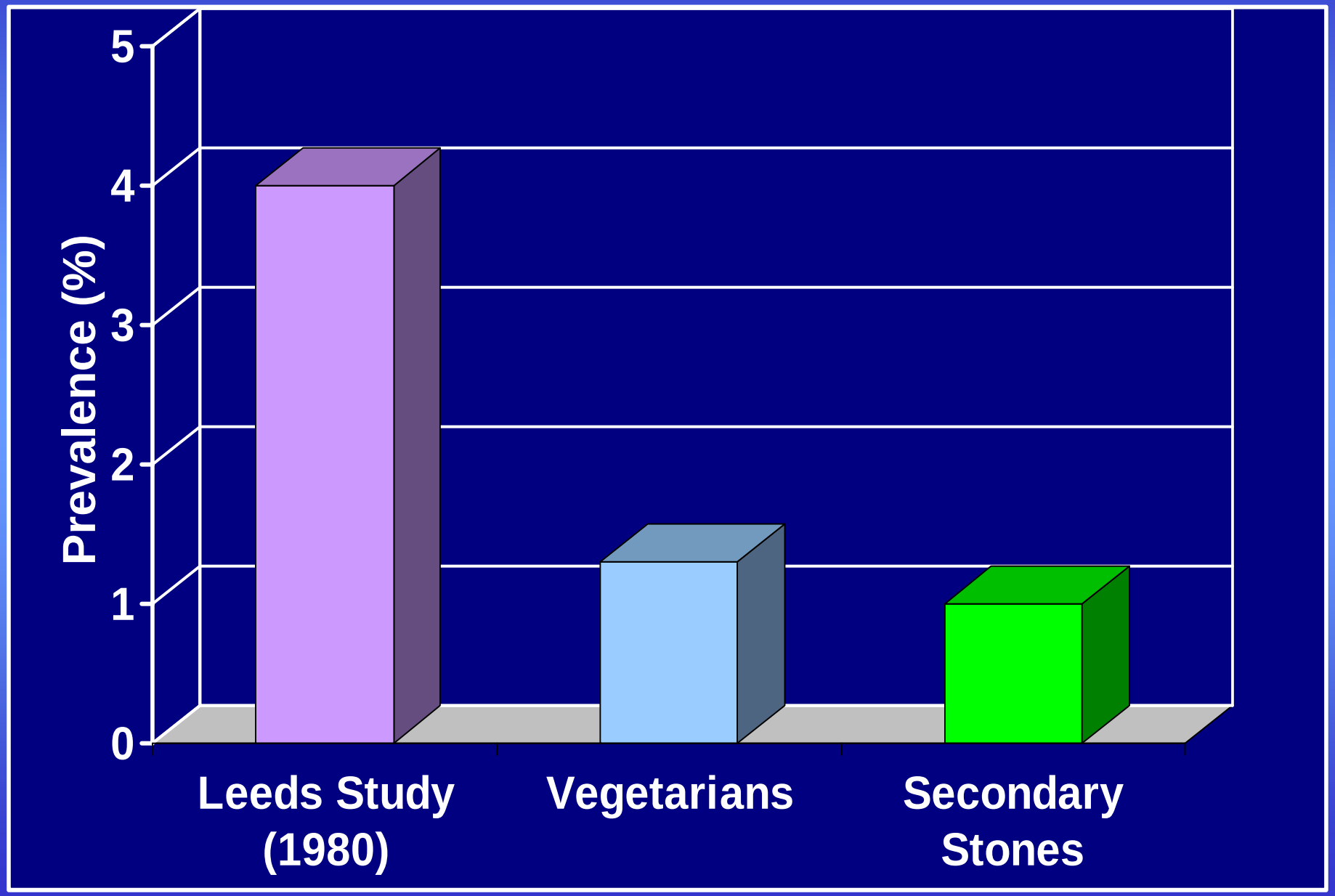



Stones and Animal Protein Intake
Leeds 1971-73
UK Regions 1971-73
UK 1958-73
World
Annual Discharges for Stones/10⁴ Population
Animal Protein Intake (g/day)
YH
EA
KSA
UAE
USA
NZ
Arg
It
Eg
Irl


World
Admissions for Stone/10⁴ Adult Population
Animal Protein Intake (g/day)
0
2
4
6
8
10
12
14
16
18
20
0
20
40
60
80
100
KSA
UAE
USA (1975)
USA (1960)
Ca
S
NZ
D
Aus
Arg
NL
It (1978)
J (1990)
A
UK (1979)
Irl
UK (1958)
Is
It (1954)
P
In
Eg
J (1960)

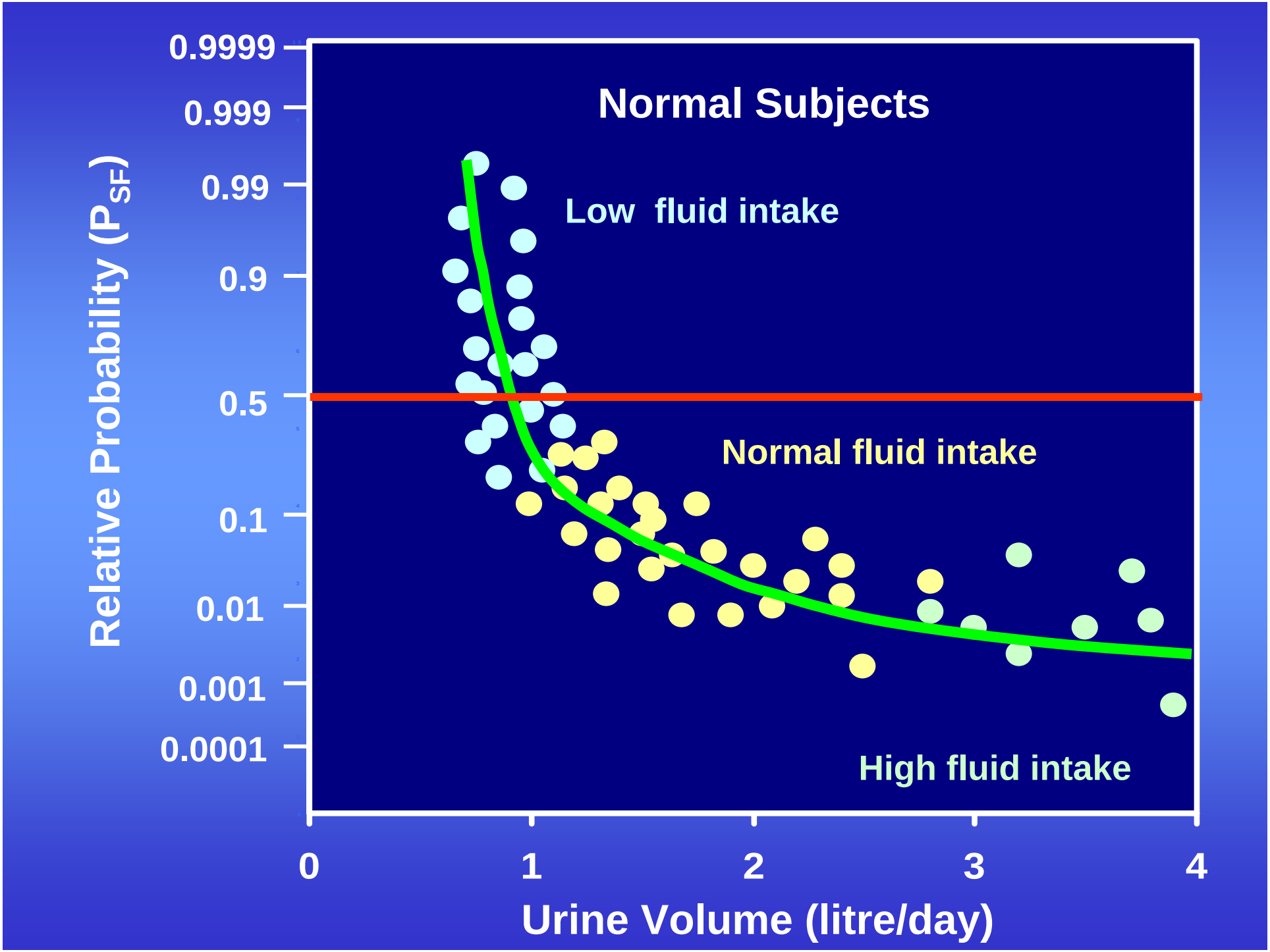

Stones Received for Analysis (no/year)
20
15
10
5
0
Uric acid
Cystine
250
200
150
100
50
0
Calcium
Infection
1965
1970
1975
1980
1985
Year

Prevalence of Urinary Stone Disease in Men



Other Dietary Factors Influencing Urinary Stone-Formation

↑ Calcium	-	↑ Urinary calcium
↓ Calcium	-	↑ Urinary oxalate
↑ Oxalate	-	↑ Urinary oxalate
↑ Sodium	-	↑ Urinary calcium
↑ Refined sugars	-	↑ Urinary calcium
↓ Fibre	-	↑ Urinary calcium
↑ Fibre	-	↓ Urinary volume
↓ Magnesium	-	↓ Urinary magnesium

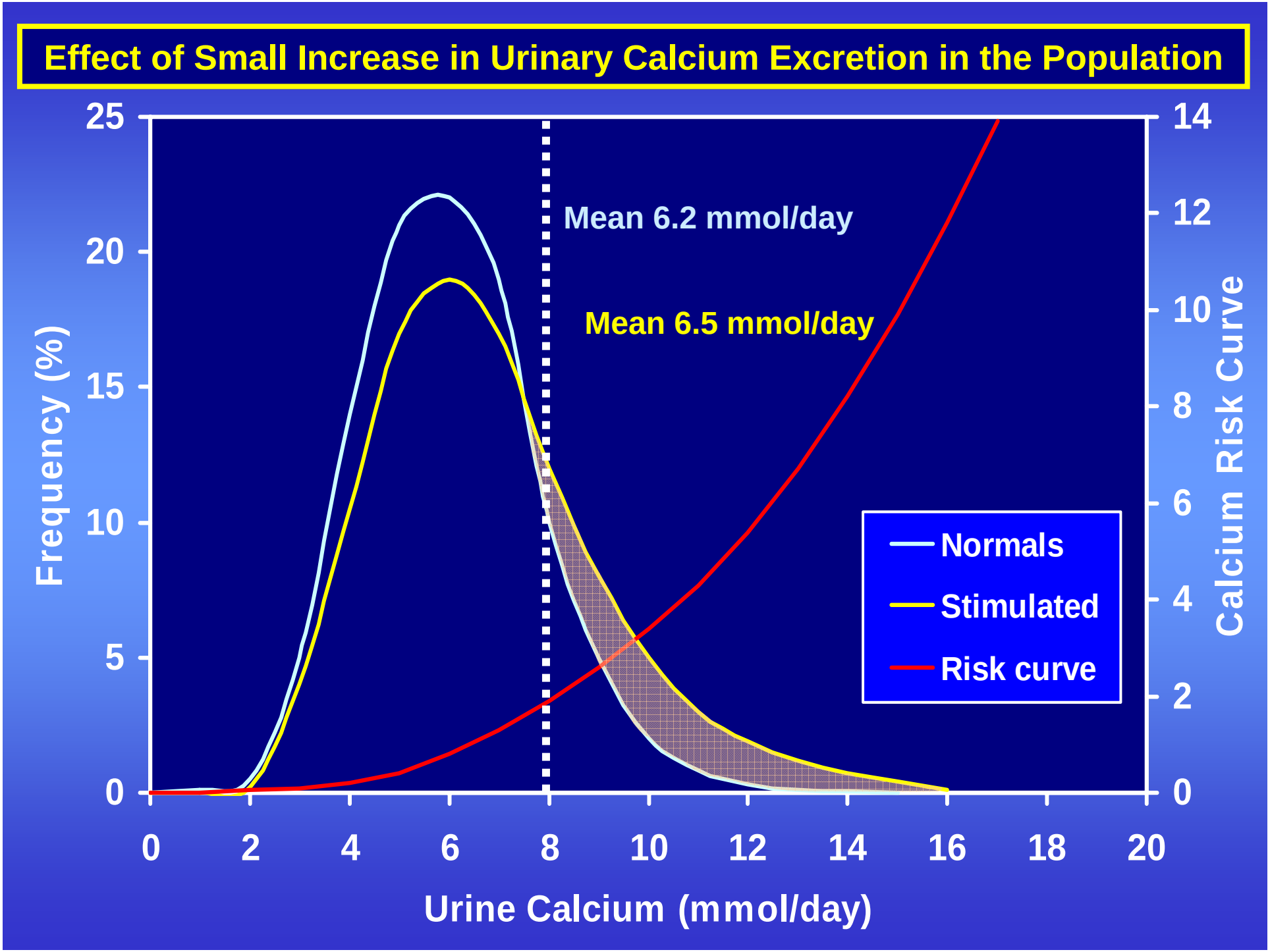

Normal Subjects
Low fluid intake
Normal fluid intake
High fluid intake
Relative Probability (P_{SF})
0.9999
0.999
0.99
0.9
0.5
0.1
0.01
0.001
0.0001
0
1
2
3
4
Urine Volume (litre/day)

Occupation, Low Urine Volume and Urolithiasis

Occupation	Percent of Male Stone-Formers	Urine Volume (litre/day)
Taxi-Drivers, Chauffeurs	5.6	1.42 ± 0.27
Chefs, Kitchen-Workers	6.3	1.31 ± 0.34

Dietary Risk Factors for Stones in Saudi Arabia

Dietary Constituent	UK	USA	KSA
Animal protein (g/day)	61	85	87
Calcium (mmol/day)	24.5	25.0	13.0
Oxalate (mmol/day)	1.4	-	3.8
Purine (mg/day)	150	257	265
Oxalate/Calcium	0.06	-	0.29


Effect of Small Increase in Urinary Calcium Excretion in the Population
Mean 6.2 mmol/day
Mean 6.5 mmol/day
Normals
Stimulated
Risk curve
Frequency (%)
Calcium Risk Curve
Urine Calcium (mmol/day)
0
5
10
15
20
25
0
2
4
6
8
10
12
14
0
2
4
6
8
10
12
14
16
18
20

Medical Management of Urolithiasis

Objectives:

- **To identify the particular risk factors for stone-formation in the patient concerned**
- **To reduce the supersaturation of urine with respect to the stone-forming mineral concerned in order to minimise the risk of forming abnormal crystals and aggregates in urine**
- **This may be achieved by means of dietary and/or medical treatment**

Medical Management of Non-Calcium-Containing Stones

Stone	Treatment
2,8-DHA	Very high fluids + allopurinol
Xanthine	Hereditary: High fluid intake + alkali (pH >7.4) Iatrogenic: Withdraw allopurinol
Cystine	Very high fluids + alkali (pH >7.5) or D-penicillamine or α-mercaptopropionylglycine
Uric acid	High fluids + alkali (pH >6.2) or reduce purine intake or allopurinol
Infected	Antibiotics + high fluids + oral acid (pH <6.2)
Iatrogenic	Discontinue drug concerned and replace with alternative treatment + high fluids

Medical Management of Calcium Stones

Patient Type	Treatment
Idiopathic	High fluids + relevant dietary advice or thiazides or phosphate or magnesium supplements or potassium citrate (K_3Cit)
Hyperparathyroid	Parathyroidectomy or high fluid + acids
1° Hyperoxaluric	High fluids + pyridoxine
2° Hyperoxaluric	High fluids + low Ox + high Ca or K_3Cit
Distal RTA	High fluids + thiazides or K_3Cit
MSK	Treat as for idiopathic
Corticosteroid	Discontinue steroids; treat as idiopathic
Milk-alkali syndrome	Discontinue alkali; reduce Ca + fluids
Vit D intoxication	Discontinue vitamin D supplements

Problems in the Medical Management of Patients with Urinary Stones

- It is impossible to treat stone patients satisfactorily without proper biochemical screening and this has been abandoned by many hospitals world-wide
- Most stone patients feel well most of the time apart from the occasions when they have renal colic
- It is difficult to motivate them to keep to their dietary or medical treatment over a long period and their biochemical risk of forming stones increases (the Anti-"Stone Clinic Effect")

The Anti-"Stone Clinic Effect"