Evaluation of Hematuria

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DISCLOSURE STATEMENTS

Nothing to disclose

Red Urine-Not Always Blood

- Blood
- Myoglobin
- Metabolites: Porphyrin, bile salts, melanin, methemoglobin, homogenistic acid, urates, tyrosinosis
- Due to food: Beets, blackberries, food coloring
- Due to drugs: Nitrofurantoin, chloroquine, deferoxamine, iron sorbitol, phenolphthalein

Bryant, J. Emergency Med, 2007

Definition:
Microscopic Blood in the Urine-When is it Abnormal?

- Everyone excretes RBCs in their urine
- Normals excrete 66,000 RBCs (0-425,000)/12 hours
- Patients with glomerular disease excrete 40-120 million RBCs/12 hours
- Abnormal Hematuria: >500,000 RBCs/12 hours which is equivalent to 2 or more RBCs/HPF (caveats: recent heavy exercise, menses, sexual activity, instrumentation)

Definition

- Macroscopic
- Microscopic
- Asymptomatic: Not associated with pain (dysuria, loin pain, renal colic), renal dysfunction, hypertension, proteinuria, or macroscopic hematuria.

- *A*symptomatic *M*icroscopic *H*ematuria (AMH) is common and presents the most significant diagnostic and therapeutic challenges

Micro-Hematuria: Scope of the Problem

Using >3 RBC/hpf on 3 occasions over 2-3 weeks:

- Prevalence

  Children: 2-6%

  Adults: 4%

  Men: 2-5%

  Women 5-11%

  39% may have single episode

  Potential kidney donors: 12%

Detection of Hematuria-The Dip Stick

- Dipstick relies on oxidation of an organic peroxide on the test strip by the peroxidase-like activity of hemoglobin
- False Positives: Myoglobinuria, hemoglobinuria, povidone-iodine, H_2O_2, bacterial peroxidases, semen, Ph>9
- False Negatives: Presence of ascorbic acid (supplements), formaldehyde (preservative), low pH
- Test Performance

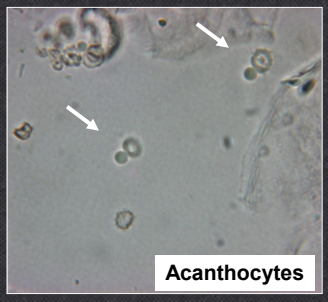
  Sensitivity-93-100%

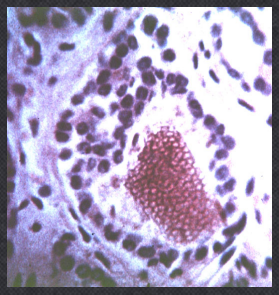
  Specificity-60-80%

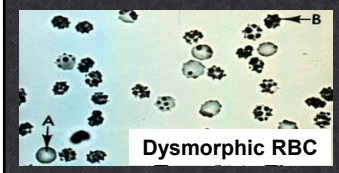
  Negative predictive value ~98%

Schroder, BMJ, 1994; Huussen J, Neth J Med, 2004

Use Urine Microscopy to Confirm RBCs Glomerular Hematuria







Acanthocytes:

- 98% specific, 52% sensitive if >5% of RBCs in a urine sample; sensitivity >80% if found in 3 consecutive urine samples
- Not inducible by changes in pH, osmolality
- Urine RBCs can be dysmorphic but not indicate glomerular bleeding, such as these (B) commonly found crenated RBCs, caused by osmotic shifts in RBC water

Hematuria in Adults

Diagnosis	Microscopic (n>2000)	Macroscopic (n>1200)
Cancer	0.5-5%	23%
Nephrolithiasis	5%	5-11%
Infection	1.7-4%	33%
BPH	3-13%	13%
Intrinsic Renal	2-11%	
No Diagnosis	43-57%	8-21%

Sutton, JAMA, 263:2475, 1990; Boman, Scand J Urol Neph, 2001; Murakami, J Urol, 144:49, 1990, Sultana, Br J Urol, 78:691,1999

Approach to Hematuria
Identify Origin of the Blood

Glomerular Hematuria

Micro- or Macroscopic

Abnormal Morphology
Proteinuria, active sediment

May be familial
- Check first degree relatives
- Look for hearing loss

Non-Glomerular Hematuria

Micro- or Macroscopic

Normal morphology

Isolated finding

To biopsy….or not to biopsy?

What nephrologists think about during the evaluation of microscopic hematuria

Case #1-Isolated Microscopic Hematuria

A 22 year old Asian male was found to have hematuria during a routine school evaluation. The patient was otherwise healthy, had no complaints, no significant PMH and physical exam was unremarkable including a normal blood pressure on no medications. No FH of kidney disease. SCr was 0.8 mg/dl. Urinalysis showed no protein but did show acanthocytes. 24-hour urine contained 115 mg protein. Would you do a kidney biopsy?

a. No, because the patient does not have abnormal proteinuria and kidney function is normal

b. Yes, because the UA indicates glomerular bleeding

c. Yes, because the patient appears to have a systemic process and the kidney may be involved

Case #2-Isolated Microscopic Hematuria

A 69 year old white female developed muscle aches one year ago, was diagnosed with polymyalgia rheumatica. She was treated with prednisone, felt better, but upon taper symptoms became much worse. She then developed left foot drop. A tentative diagnosis of mononeuritis multiplex was made. SCr was 0.7 mg/dl. Urinalysis showed no protein but did show acanthocytes. 24-hour urine contained 178 mg protein. Would you do a kidney biopsy?

a. No, because the patient does not have proteinuria and kidney function is normal
b. Yes, because the UA indicates glomerular bleeding
c. Yes, because the patient appears to have a systemic process and the kidney may be involved

Case #1 - Answer

- No biopsy was done. Patient was followed and after several years hematuria resolved, kidney function remained normal. Presumptive diagnosis of IgAN

Case #2 - Answer

- ANCA was 1:80
- Sural nerve biopsy was non-diagnostic
- A kidney biopsy was performed and showed pauci-immune crescentic GN

Renal Biopsy for Hematuria?

- Yes

Proteinuria Present (≥ 500 mg/day)

Abnormal Renal Function (Cr≥1.3)

Possible Systemic Process

Potential Kidney Donor

- No

No Proteinuria

Normal (stable) Renal Function

No Systemic Process

RATIONALE FOR NOT DOING A BIOPSY: The glomerular diseases that are most likely to cause isolated hematuria have no proven treatments, and in the *absence of proteinuria* carry an excellent renal prognosis

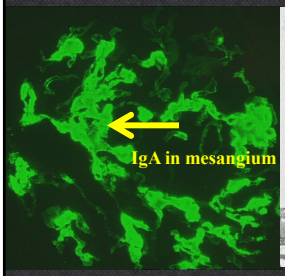
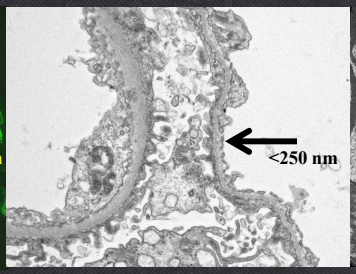
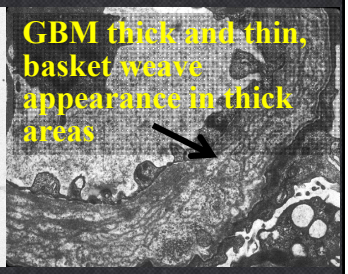
Pathologic Diagnosis of Hematuria

Microscopic Hematuria in 165 patients with no other renal or systemic findings:

Pathologic Diagnosis	% of Patients
None	53 (but 13%-no EM)
IgAN	30
Thin GBM	4
Mesangial Proliferation	7
FSGS	3
HTN, Membranous, Int Nephritis	3

Topham et al, Q.J. Med., 7:329:1994

Pathology of Common Causes of Isolated Microscopic Glomerular Hematuria

IgAN	Thin GBM	Alport's
		
Average age of onset 20-30, male preponderance, prevalence higher in Asia than US, UK, Canada, rare in people of African descent. Most common form of GN in Japan, China, Singapore, Taiwan.	TBM/Familial benign hematuria is due to an autosomal dominant defect in the alpha 3 or 4 chains of collagen type IV, with heterozygous expression. Isolated thin GBM disease may develop proteinuria and renal insufficiency	ALPORT'S: X-linked is most common. Defect in the alpha 5 chain of type IV collagen. Affected males, female carriers. Many males will develop proteinuria and renal insufficiency within first 2 decades

Natural History of Isolated Hematuria

Biopsy	IgAN	Thin GBM	Normal*
# of patients	12	13	20
Mean Age	30	35	30
Macroscopic Hematuria	6	1	1
Cr Clearance	109	115	113
11 Year Follow-up			
Hematuria	10	13	7**
Cr Clearance	**100**	**110**	**113**

*Mean Duration Hematuria 4 years; **5 of the 7 patients developed stones over the 11 year follow-up, suggesting they may have had crystaluria to start.

Niewuhof et al., KI, 49:222, 1996

Natural History of Isolated Hematuria

100 patients with AMH followed for an average of 32 months

	Bx	F/up
SBP	105+/- 13	113+/-11
DB	67+/- 7	68+/- 8
UPRC	0.09+/-0.07	0.12+/-0.14
Mean GFR	99+/-22	101+/-24
Scr	0.78+/-0.15	0.77+/-0.17
Adverse renal events (ARE)		
CKD	**0**	**2(2%)**
Proteinuria	**0**	**6(6%)**
Hypertension	**0**	**5(5%)**

Total of 10 pts ARE

4 proteinuria (FSGS, IgAN, minor GN, MPGN)

4 HTN (TBM, FSGS, 2 IgAN)

1 prot, HTN, CKD (IgAN)

1 prot, CKD (IgAN)

Kim et al, KJIM, 2009

Isolated Hematuria and ESRD-Adults

107,192 Japanese were screened with a single urine dipstick:

	18-29	>80
Men	0.9%	8.5%
Women	7.3%	15.3

10 years later the odds ratio for developing ESRD was calculated:

Men vs. Women	1.4
Hematuria vs. no hematuria	2.3
Proteinuria vs. no proteinuria	15

Iseki et al, Kidney Int, 1996

Effect of Proteinuria on the Differential Diagnosis of Hematuria

Microscopic Hematuria in 135 patients:

Proteinuria <0.3 g/d	Proteinuria up to 2.4 g/d
Thin GBM 43%	IgAN 46%
IgAN 20%	FSGS 13%
Normal 37%	Membranous, MPGN, AIN
	Acute prolif, Alport's

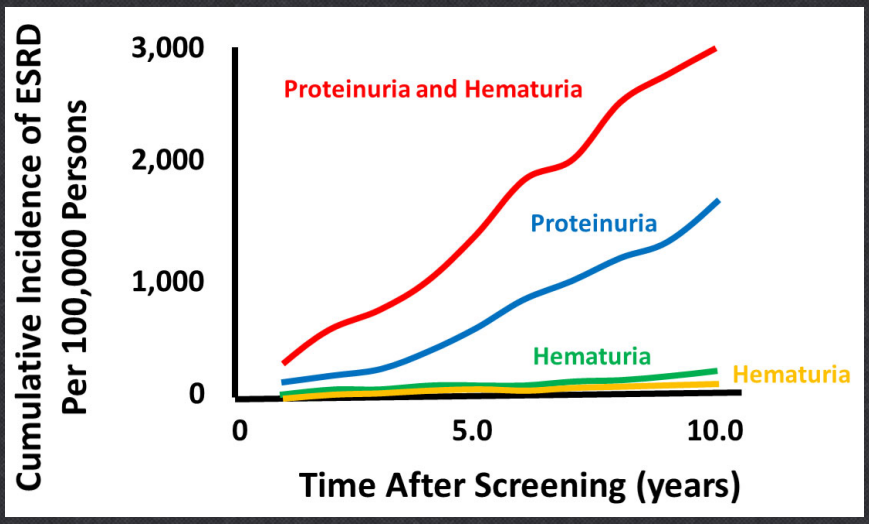
Proteinuria Changes Everything

In IgAN:

Proteinuria (g/d)	ESRD over 7-10yrs
0.3-0.99	10%
1-1.99	25-35%
2-2.99	40%
>3	60%

Hall et al, Clin Nephrol 2004

Natural History of Hematuria with Proteinuria



Iseki et al, Kidney Int, 1996

Kidney Biopsy For Microscopic Hematuria

Proteinuria Present (≥ 500 mg/day)

Abnormal Renal Function

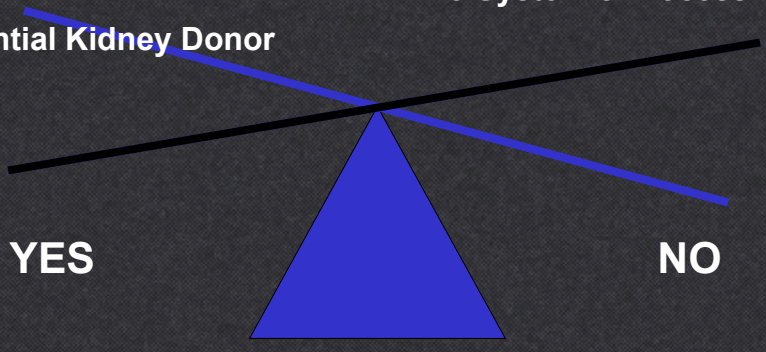
Possible Systemic Process

Potential Kidney Donor

No Proteinuria

Normal (stable) Renal function

No Systemic Process



Case #3-Systemic Disease and Macroscopic Hematuria

A patient with a past history of SLE (no nephritis) and clotting due to anti-phospholipid syndrome was taken off AZA 3 months ago. She called to say she saw blood in her urine. SCr was 0.7mg/dl, P/C ratio was 0.9, and INR was 3.5 on her usual dose of warfarin. What is the next step?

a. Stop the anticoagulation because she is bleeding due to a high INR
b. Restart immunosuppression with AZA, and add high dose prednisone 1mg/kg/d
c. Do a kidney biopsy
d. Perform a urinalysis
e. Do cystoscopy

WARFARIN RELATED NEPHROPATHY

AKI appears shortly after INR acutely increases to >3.0.

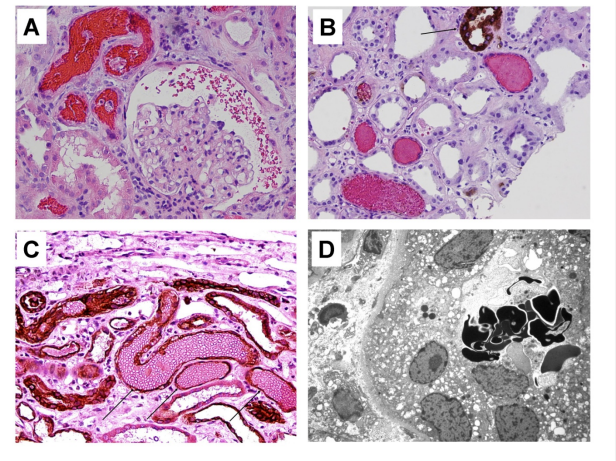
- WRN is common: Seen in 33% (CKD) and 16% (no-CKD) of warfarin-treated patients whose INR acutely rises to >3.0
- Patients with WRN have increased mortality (one-year mortality rate 31.0% versus 18.9% in no-WRN patients).
- WRN accelerates the progression of CKD
- WRN should be suspected on biopsy of patients on warfarin if the RBC casts are disproportionate to the degree of underlying glomerular injury
- WRN may be part of a broader Anticoagulant-Related Nephropathy-ARN, so switching anticoagulants is questionable

WRN is Common

- 103 CKD patients on warfarin therapy with serial measures of INR and serum creatinine
- Of these, 49 patients experienced at least one INR>3.0 and had Scr measured before and after the INR.3.0
- 18 of these patients (37%) had an unexplained increase in Scr>0.3 mg/dl associated with INR>3.0

Brodsky; Nephrology Clinical practice 2010

Biopsy Findings in WRN



- RBC in Bowman's space
- Glomeruli normal in appearance
- Dense RBC casts causing tubular obstruction
- RBC casts do not contain Tamm-Horsfall protein

Case #3-Answer

Kidney Biopsy Showed IgAN

No Histologic Evidence of LN or WRN

Case #4-Macroscopic Non-Glomerular Hematuria

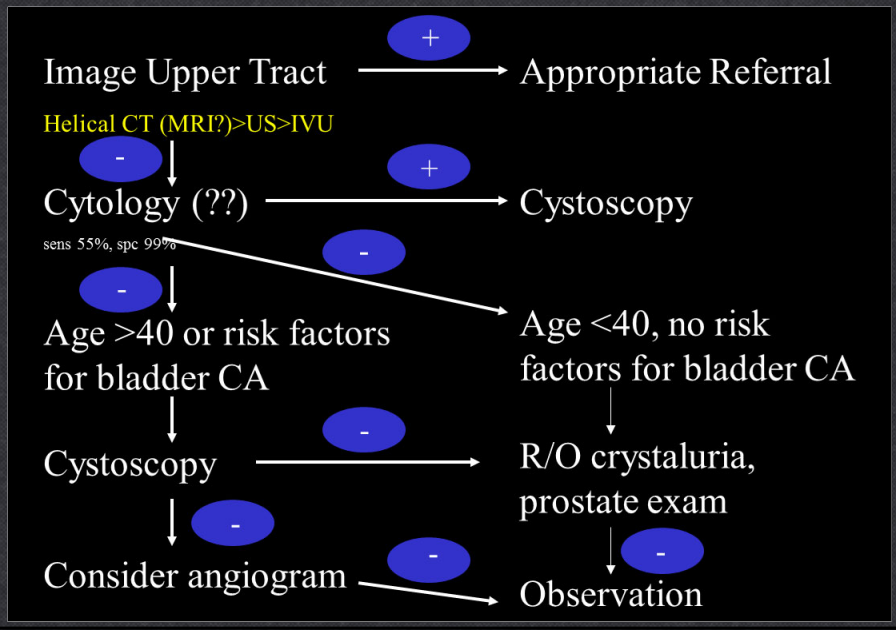
A 58 year old African American male complained of red urine and was found to have new hematuria. He had a SCr of 1.5 mg/dL and about a 500 mg/d urine protein excretion. These levels have been stable for years, and were attributed to long-standing, poorly-controlled hypertension. Blood pressure was now controlled. He was a former smoker, quit 5 years ago. He developed a DVT 2 months ago, and was on warfarin with an INR of 2.5. Urinalysis showed no bacteria, WBC, or casts, but he did have many eumorphic RBCs that were of uniform size. Renal ultrasound showed echogenic, 9cm kidneys. What next?

a. **Perform a kidney biopsy for suspected GN**
b. **Strain urine for kidney stones**
c. **Send urine cytology**
d. **Do cystoscopy**

Differential Diagnosis of Non-Glomerular Hematuria

- GU Cancer
- Nephrolithiasis (also hypercalcuria, hyperuricosuria)
- BPH
- Cysts
- Infection
- Anatomic Lesions (a-v fistula/malformation; hemangioma; angiomyolipoma; renal varicies)
- Hematologic (coagulopathy; platelet dysfunction; hemoglobinopathy)
- Ischemia/infarct; emboli; exercise; malignant HTN

Approach to Patients with Asymptomatic Non-Glomerular Hematuria



Performance Characteristics of Urine Cytology as a Screening Test for Bladder Cancer

	Sensitivity	Specificity	PPV	Prevalence
Micro Hematuria	0.45	0.86	0.11	4%
Gross Hematuria	0.55	0.99	0.43	18%

Chou and Dana, Ann. Int. Med, 2010

Urine Cytology: Cost Effective?

The American Urologic Society recommends urine cytology only in patients with risk factors for significant disease because:

- Sensitivity is poor
- Cystoscopy is so good at detecting TCC that urine cytology provides unique information in very few cases:
- In a series of 660 patients with TCC urine cytology was the only positive test in 4 (.06%). Therefore, the cost of cytology is high when cost is examined on the basis of unique diagnoses.

cytology $8369 cystoscopy $3235

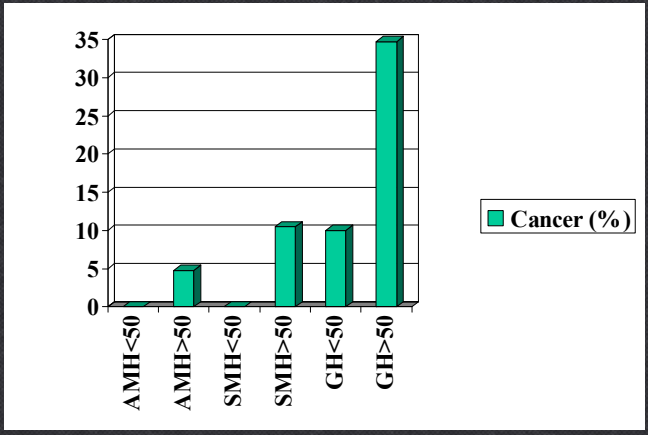
total cost = (cost of test)(#of tests)/(#of unique diagnoses)

Hofland and Mariani, J. Urol., 2004

Risk Factors for Urothelial Cancers

- Age (>50)
- Male sex
- Smoking
- Episodes of macroscopic hematuria
- Analgesic abuse (Phenacetin)
- Irritative voiding symptoms, previous GU history
- Exposure to aromatic amines/benzenes
- Exposure to cyclophosphamide
- Pelvic irradiation
- Exposure to aristolochic acid (herbal weight-loss)
- Parasitic infection (*Schistosoma haematobium*)

Hematuria in Adults-Cancer as a Function of Age, Symptoms, and Type of Hematuria



Age 50+ and gross hematuria are worrisome combination

Sultana et al, Br. J. Urol., 78:691, 1996

Case #4-Answer

- This patient had cystoscopy that revealed a transitional cell carcinoma of the bladder
- It was felt that anticoagulation unmasked the cancer
- The proteinuria and elevated SCr along with smaller, echogenic kidneys on US were felt to be consistent with hypertensive nephrosclerosis
- The TCC was successfully removed

Bonus Case

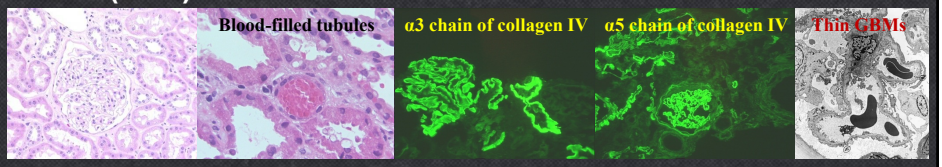
A 40 year old white woman presented with flank pain and red urine. She had similar episodes twice before. She did not recall if she had other symptoms with these, specifically colds or other acute illnesses, but this time she had a sore throat that began about 3 days ago. She has not seen a physician regularly. Someone on her father's side of the family required dialysis. Her father died of a stroke at age 45. Blood pressure was 145/95. Exam showed a red throat, clear lungs, unremarkable heart, and obesity, with a tender left flank. Urine dipstick showed large blood, 1+ protein, and no leukocytes. Urine sediment had too many RBCs to count, and they appeared to be eumorphic. SCr was 1.3 mg/dL. Which is correct?

a. You should quantify proteinuria and set up a kidney biopsy to rule out GN
b. You should send urine studies for calcium, oxalate, citrate, and sodium
c. You should get a detailed neurologic history
d. You should check complement component C3 and C4 levels
e. You should hospitalize, push fluids, and give narcotics for pain control

- The glomerular diseases most commonly associated with upper respiratory tract infections are IgAN and post-strep GN.
- IgAN occurs during the infection, usually soon after it is apparent
- Post-sterp occurs after the infection is resolved; the lag is usually several days to a couple of weeks
- There is not much proteinuria and this amount could be accounted for by the hematuria
- The RBCs do not appear to be dysmorphic
- Loin Pain Hematuria Syndrome is a diagnosis of exclusion
- Stones are possible, and a flat plate could be helpful, unless the stones were radio-lucent; also would not expect an increased SCr with stones under most circumstances
- But this patient appears to have either CKD or AKI, and a relevant family history ANSWER: C→ PCKD with cyst rupture

A Word About Loin-Pain Hematuria Syndrome

- Unexplained, disabling chronic flank pain and hematuria:
- Syndrome characterized by flank pain and micro- or macroscopic hematuria, often in Caucasian (93%) females (70%). No clear urologic etiology, although 50% have a history of nephrolithiasis, and most have abnormal urine risk factors for stones.
- Renal biopsy of these patients shows hemorrhage into multiple tubules. Glomeruli are normal on light and immunofluorescence, but EM often shows thin (51%) or thick (20%) GBMs.



Presumed Mechanism: Glomerular hematuria causes tubular obstruction, back-leak of glomerular filtrate, renal parenchymal swelling, with stretching of the renal capsule causing pain, plus an abnormal pain response. Correlation with stones remains obscure.

When No Diagnosis is Made

- If no diagnosis is made after initial evaluation, patients should be followed every six months
- It is not clear how often to repeat urologic studies.
- In one large study of 225 patients (Murakami et al, 1990) 91% of the serious (eg cancer, stones) lesions were found at the initial visit.
- An additional 9% (22 cases, 4 malignancies) were discovered over the next 1.5 years with extensive urologic testing every 6 months.