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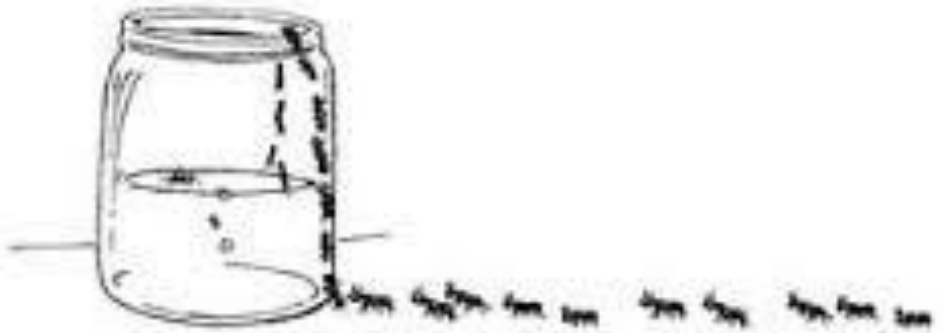
MLS Continuing Education Conference November 2014

PACE Session # 304 – 113 - 14

Urinary Casts: The Importance of Laboratory Identification

Urinalysis – The Beginning

- **The field of laboratory medicine started with the analysis of urine**
  - Records of urine study are found in cave drawings and Egyptian hieroglyphics
  - In the Middle Ages, urine examination was a major focus of physicians
    - Observations were basic, including:
      - Color
      - Clarity
      - Odor
      - Volume
      - Sweetness



Urinalysis - Progress

- **<u>17th century</u>**
  - Microscope was invented
- **This led to examination of urine sediment**
  - Methods were developed for the quantitation of urine sediment

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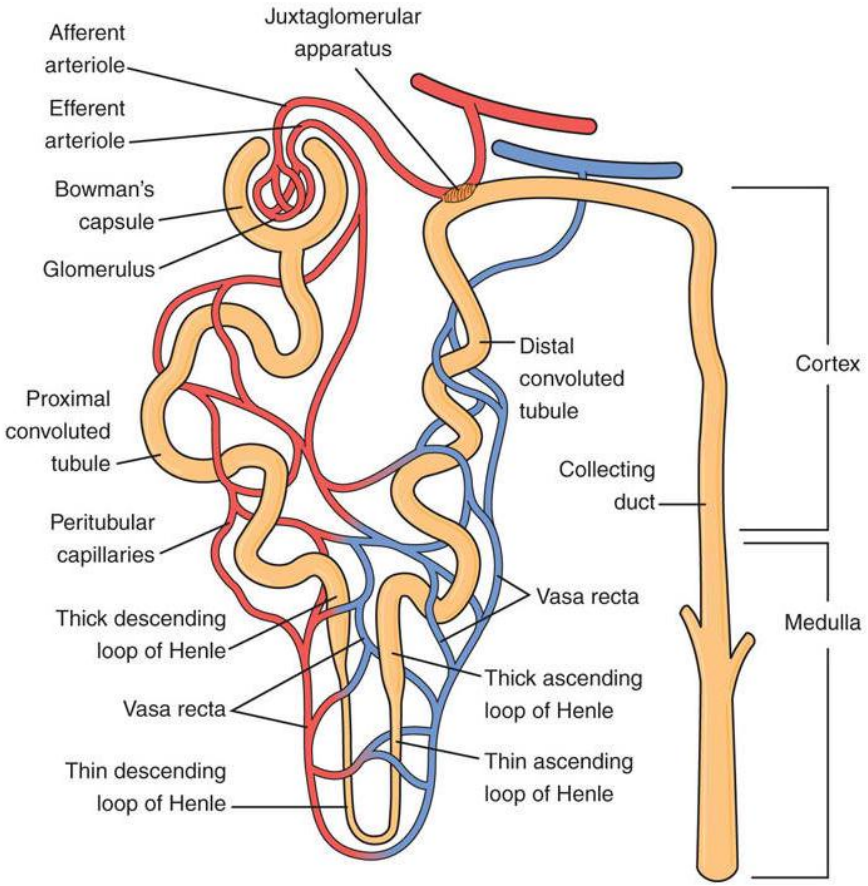
Sediment Constituents

- RBCs
- WBCs
- Epithelial cells (3 types)
- Oval fat bodies
- Bacteria
- Yeast
- Parasites
- Spermatozoa
- Mucus
- **Various casts**
- Various crystals

Urinary Casts

- Among the various constituents of urinary sediment, casts are unique in that:
  - They provide us with a microscopic view of the conditions within the nephrons
- Nephrons are functional units of the kidney
  - Each kidney contains between 1 and 1.5 million



Cast Composition

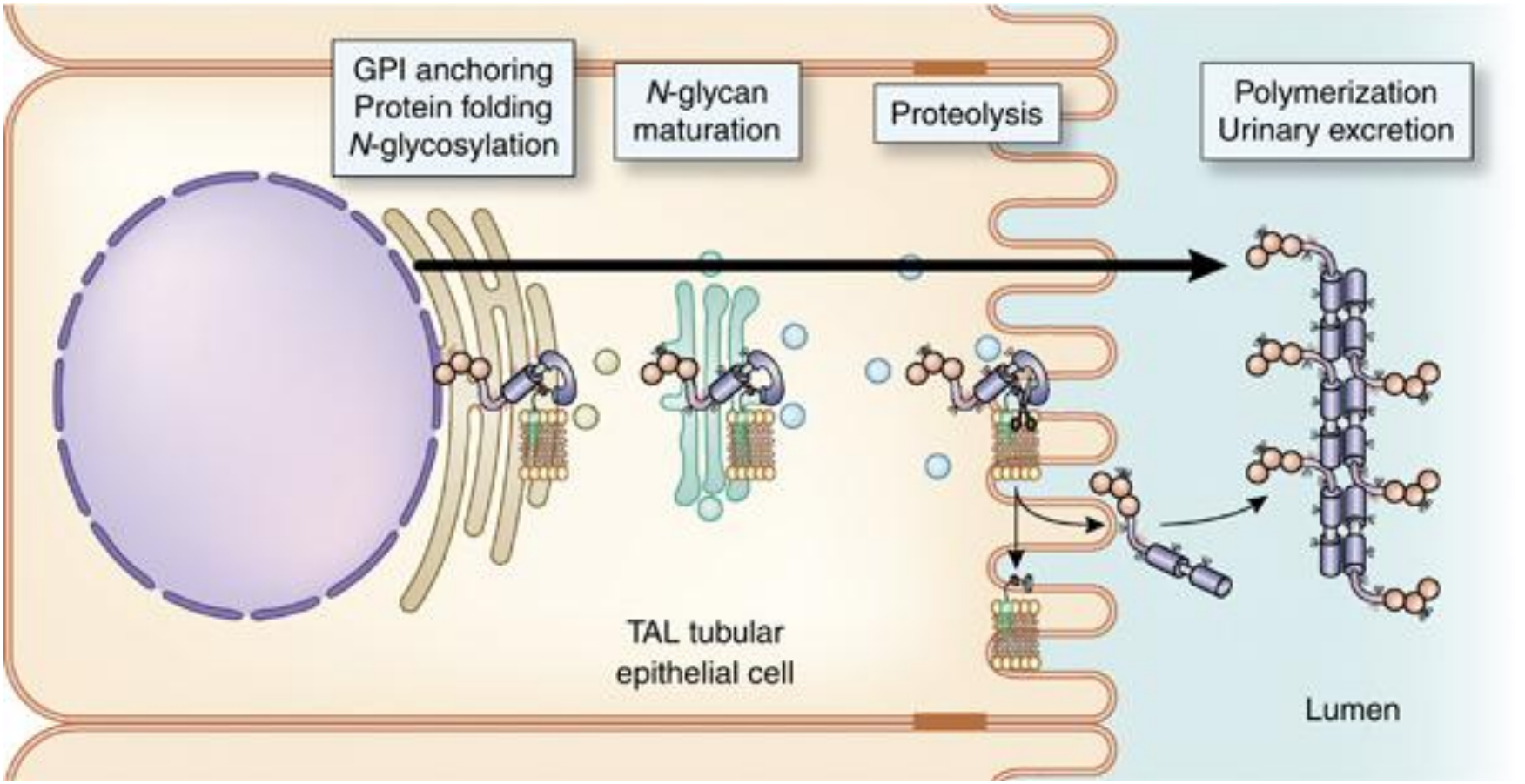
- All urinary casts are composed of the renal glycoprotein known as **Uromodulin**
  - More commonly known as ***Tamm-Horsfall protein***

- Uromodulin is produced exclusively in the kidney by the epithelial cells of the thick ascending loop of Henle
  - Also by the beginning segment of the distal convoluted tubule
  - Under normal conditions uromodulin is the most abundant protein found in urine

Uromodulin Characteristics

- **Characteristics**:
  - It is a mucoprotein
    - Approximately 70% protein & 30% carbohydrate
    - Secreted by RTE cells of the thick ascending loop and the distal convoluted tubule
    - Secreted into the filtrate as a soluble monomer
  - It has a high tendency to form polymers
    - There is a high gel-tendency
  - Tamm-Horsfall protein is not detected by the reagent strip protein reaction

Uromodulin Secretion



Uromodulin Function

- Biological function is still not fully understood

- What we do know:
  - Uromodulin is linked to water and electrolyte balance (polymeric form)
  - Soluble form helps to protect against urinary tract infection by fimbriated bacteria
  - Research has also suggested that uromodulin helps to prevent kidney stones by inhibiting the growth of the monohydrate form of calcium oxalate crystals

Factors Contributing to Cast Formation

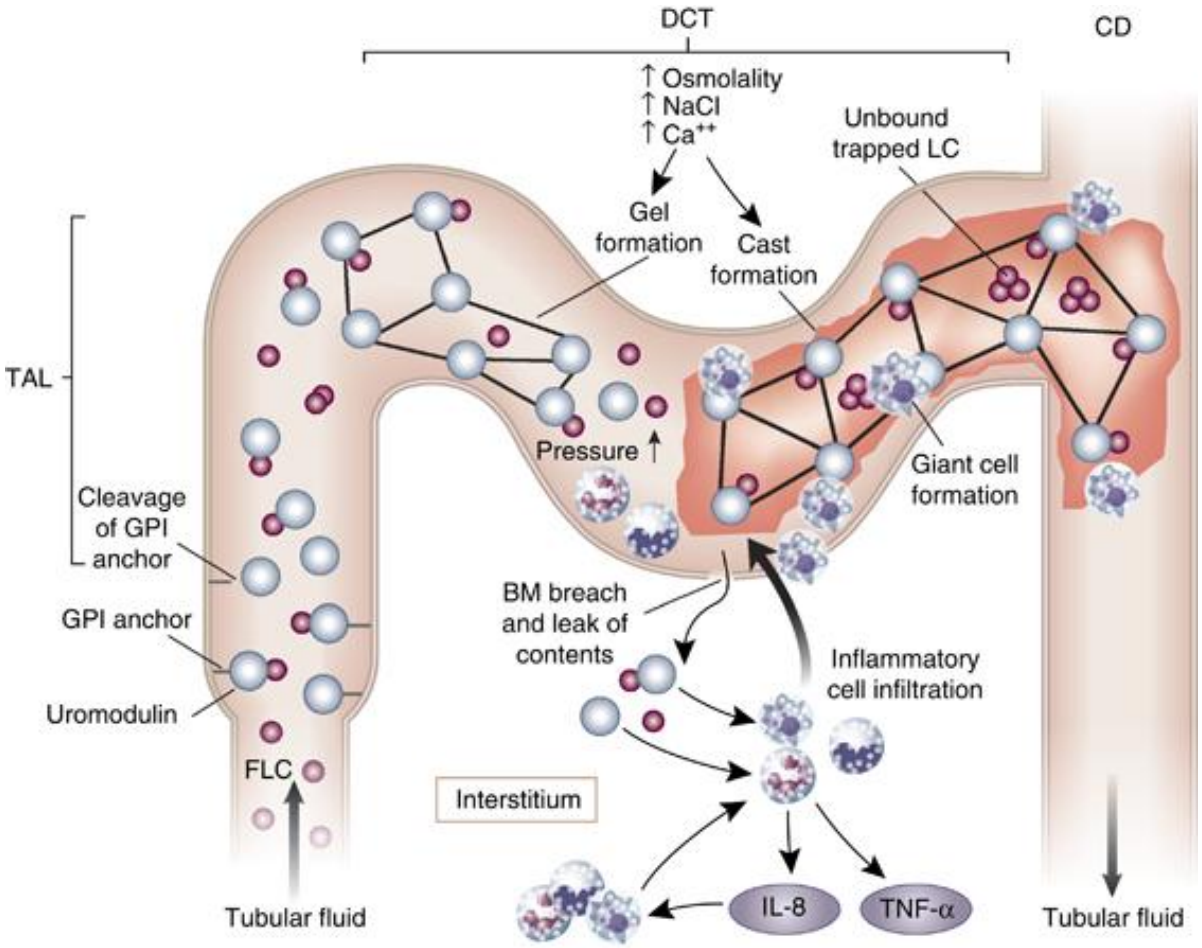
- Urinary casts are formed when there is an increase in uromodulin polymerization which increases gel-formation

- Factors which contribute to increased polymerization:
  - Urinary stasis which results in higher osmolality
  - Increasing concentrations of sodium and calcium
  - Decreasing pH
  - Increasing levels of uromodulin
    - Secretion increases with stress and physical exertion

Cast Formation

- **Step-by-step formation of a cast matrix as studied by electron microscopy**:
  - Uromodulin aggregates into individual protein fibrils which are attached to tubular epithelial cells
  - Protein fibrils interweave to form a loose network
    - At this point any constituents present in the filtrate may become enmeshed
  - Protein fibrils continue to interweave, resulting in a solid matrix
    - Blockage of the lumen decreases urine flow & increases pressure
  - Protein fibrils become detached from the epithelial cells
  - Cast is excreted

Cast Formation

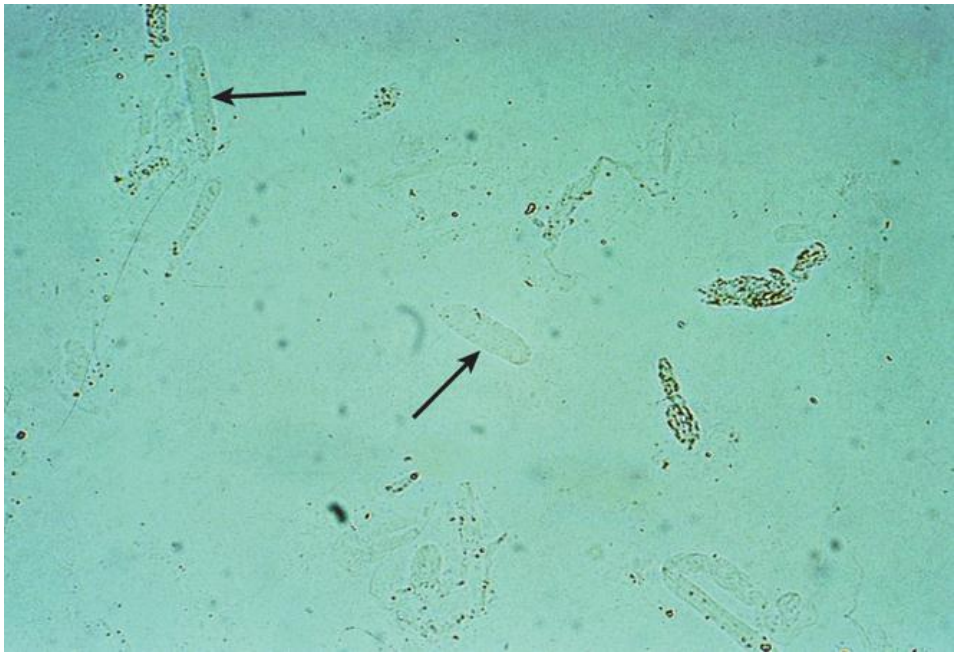


Specimen Concerns

- **For proper cast identification**:
  - Specimens should be as fresh as possible
    - Casts and cells disintegrate quickly especially in alkaline urine
  - Centrifuge at least 10 mL of urine
  - Scan for casts whenever the protein is positive
  - Scan for casts with 10x magnification
    - If using slide and coverslip, be sure to scan outer edges
    - Identify with 40x magnification

Hyaline Casts

- Most common & basic cast seen
- Almost pure uromodulin
- Colorless and difficult to see
- **Significance**:
  - Up to 2 casts/lpf is a normal finding
  - Large numbers may be seen in cases of dehydration or in times of physical or emotional stress



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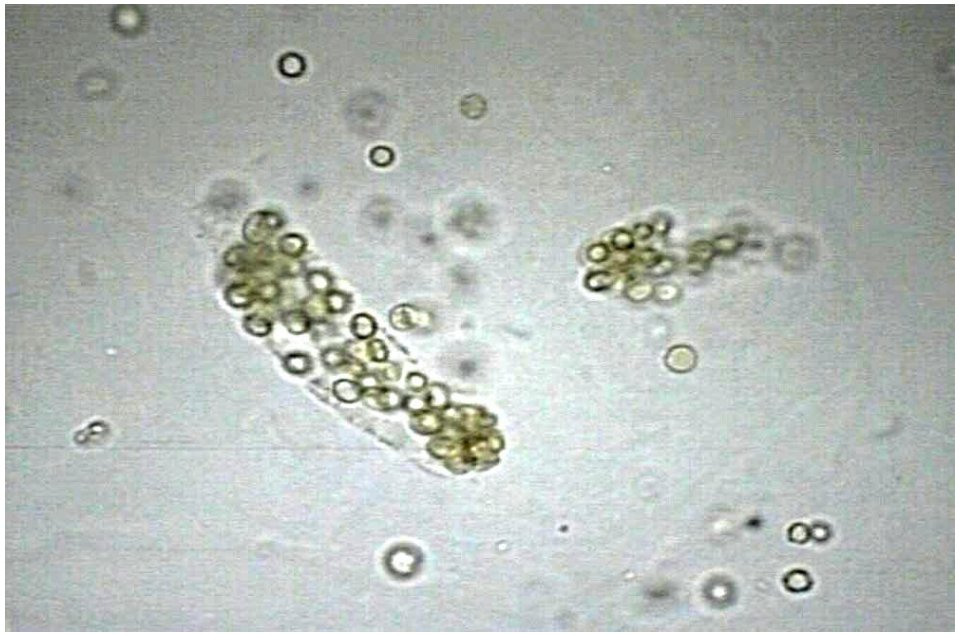
Hyaline Casts – Unstained & Stained

RBC Casts

- RBC casts indicate bleeding within the nephron
  - Primarily associated with **Glomerulonephritis**
  - Protein and free-standing RBCs should also be present
  - Ability to detect a visible matrix is important for ID



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RBC Casts – Stained & Unstained

Importance of Identification

- **Glomerulonephritis** accounts for 10%-15% of end stage renal failure cases in the USA
  - Begins with inflammation within the glomerulus mediated by autoimmune processes
  - Secondary impairment of renal function occurs over days to weeks

- Early diagnosis is **extremely** important
  - Even patients with mild renal impairment may quickly lose kidney function
  - Patients must be treated urgently

Types of Glomerulonephritis

- Post-infectious Glomerulonephritis
  - A form of acute glomerulonephritis seen after certain bacterial, viral, fungal, or parasitic infections
  - Becoming an increasingly seen complication of endocarditis after IV drug abuse
  - Post-streptococcal glomerulonephritis is the most common
    - Occurs within 12 weeks of initial infection with certain strains of *Streptococcus pyogenes*
    - Immune complexes composed of specific antibodies and bacterial M-protein are deposited on the basement membrane
    - **Anti-streptolysin O titer** is diagnostically useful

Types of Glomerulonephritis

- **IgA nephropathy**
  - Most common form of glomerulonephritis
  - Immune complexes containing IgA are deposited primarily on the mesangium of the glomerulus
  - Patients have increased levels of IgA
  - Disease is relatively silent for up to 20 years except for periodic episodes of hematuria
  - Gradually progresses to chronic glomerulonephritis and end stage renal disease

Types of Glomerulonephritis

- **Henoch-Schonlein Purpura**
  - Small vessel vasculitis
  - Primarily in children following respiratory infections
  - Usually begins with a rash of raised, red patches
  - Respiratory symptoms may include bloody sputum
  - Arthritis may be present
  - Abdominal pain with bloody stools
  - Renal involvement is most serious complication
    - Up to 50% of patients progress to a more severe form of glomerulonephritis and possibly renal failure

Types of Glomerulonephritis

- **Goodpasture Syndrome**
  - Appearance of a specific, cytotoxic autoantibody against the basement membranes of the alveoli and the glomeruli following a viral respiratory infection
    - Antiglomerular basement membrane antibody (anti-GBM)
  - Initial symptoms are respiratory including bloody sputum and difficulty breathing
  - Chronic glomerulonephritis and end stage renal disease are common
    - Disease progression can be rapid

Types of Glomerulonephritis

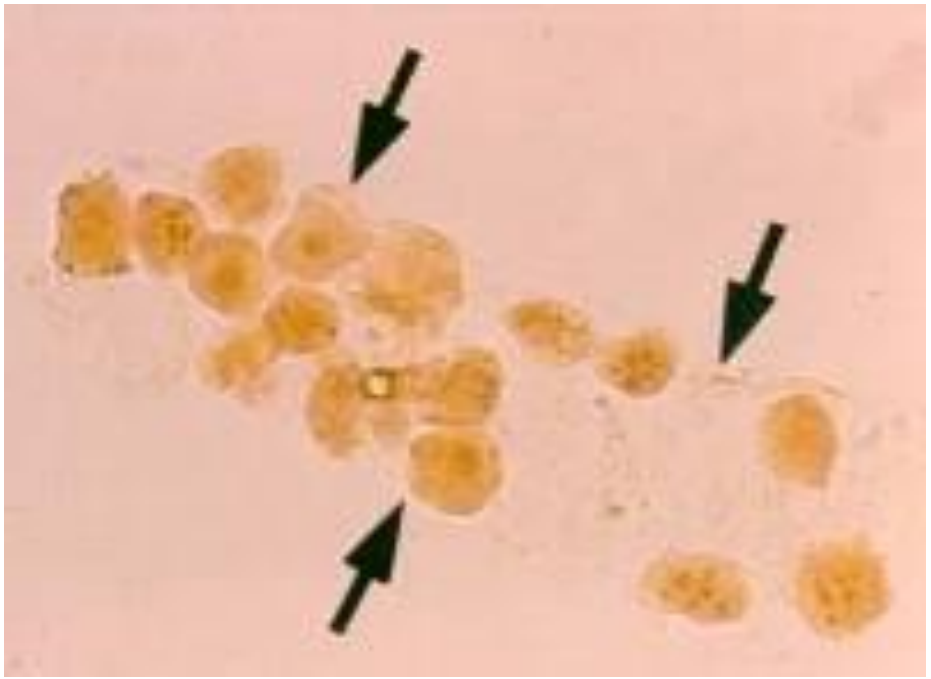
- **Wegener Granulomatosis**
  - Granuloma-producing, small vessel vasculitis
    - Primarily affecting lungs and kidneys
    - Pulmonary involvement is first presentation of disease
  - Key to diagnosis is the production of an autoantibody known as anti-neutrophilic cytoplasmic antibody (ANCA)
  - Commonly progresses to chronic glomerulonephritis and end stage renal disease

Types of Glomerulonephritis

- **Rapidly Progressive Glomerulonephritis**
  - Initiated by the depositing of immune complexes in the glomerulus
    - Usually a complication of a systemic immune disorder such as **systemic lupus erythematosus**
  - Also known as crescentic glomerulonephritis
  - Poor prognosis
    - Often ends in renal failure

Renal Tubular Epithelial Cell Casts

- Presence represents advanced destruction of the renal tubules
  - **Acute tubular necrosis**
- Potential causes:
  - Heavy metal toxicity
  - Chemical toxicity
  - Drug-induced toxicity
  - Viral infections
  - Transplant rejection
  - Interruption of renal blood flow



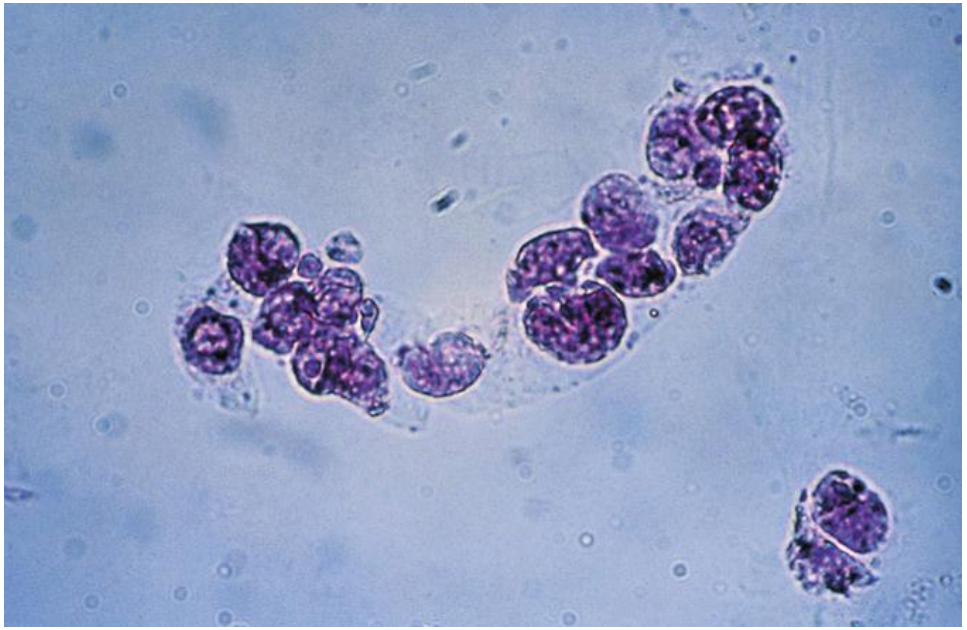
Acute Tubular Necrosis

- Nephrotoxic agents include:
  - Aminoglycoside antibiotics
  - Amphotericin B
  - Ethylene glycol
  - Heavy metal exposure
  - Mushroom poisoning
  - Hemoglobin & myoglobin

- May also see granular casts, waxy casts, & broad casts

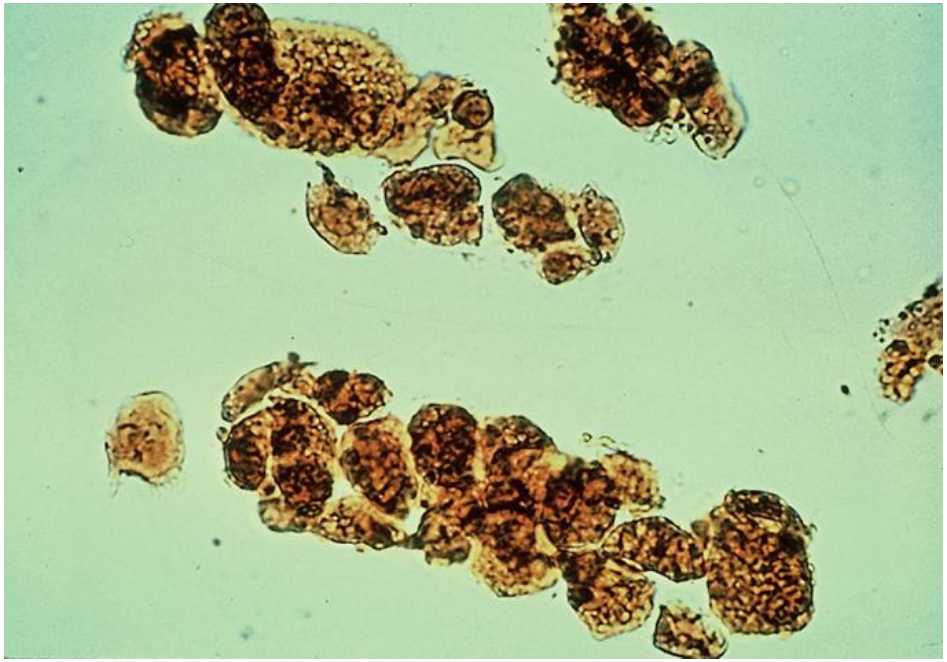
RTE Casts

- Staining can help in identifying RTE casts
- This RTE cast has been stained with Sternheimer-Malbin stain



RTE Casts

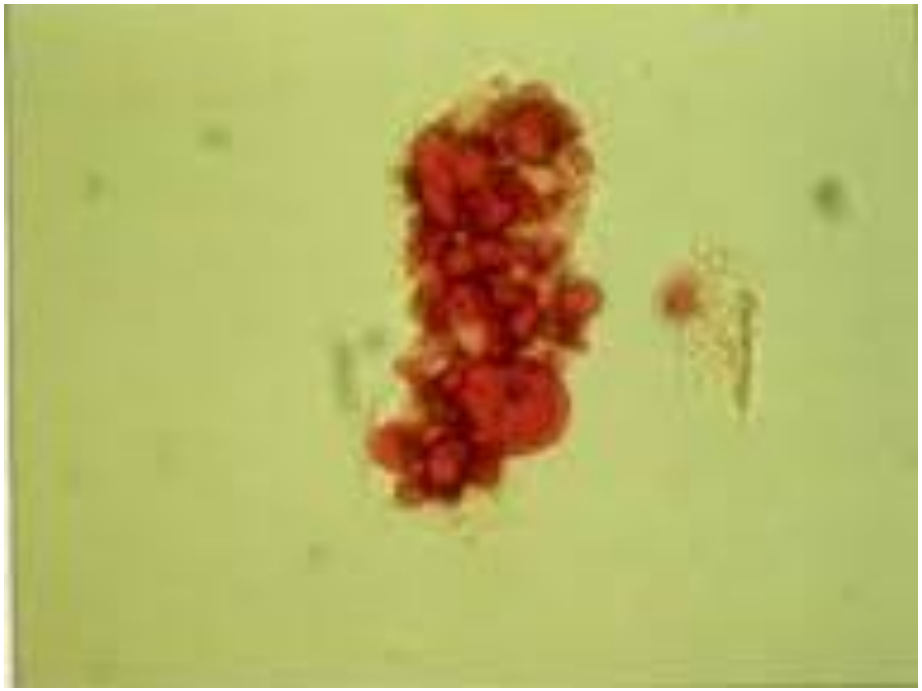
- This RTE cast came from a patient with active Hepatitis B
- The cells are stained due to the absorption of bilirubin from the filtrate

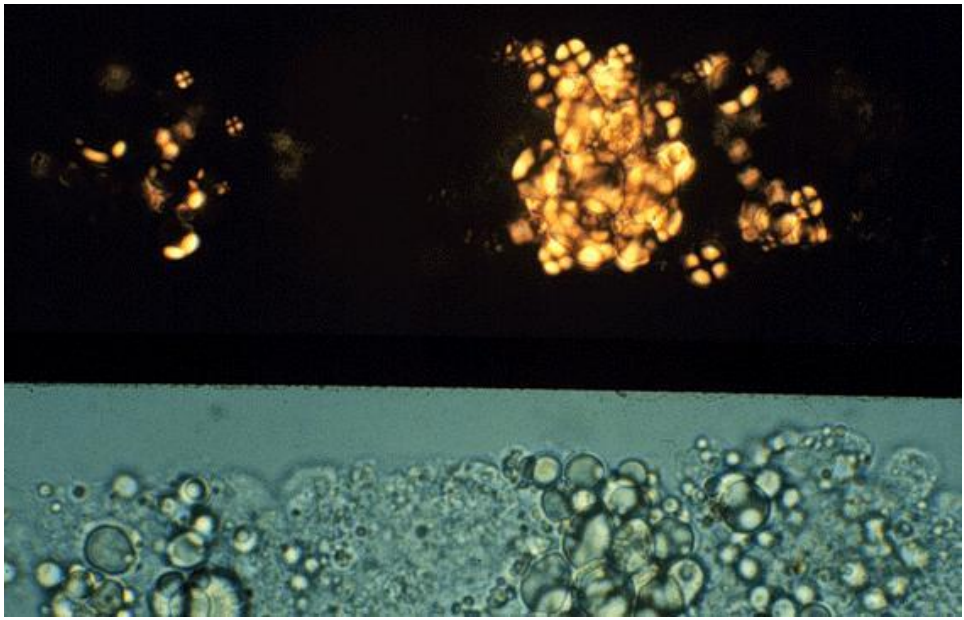


Fatty Casts

- Presence indicates lipiduria which is most often associated with **Nephrotic syndrome**
- Usually seen along with oval fat bodies and free fat droplets
- Identity may be confirmed with polarized light microscopy or staining with lipid stains such as Sudan III or Oil Red O

Fatty Casts - Stained & Polarized





The Nephrotic Syndrome

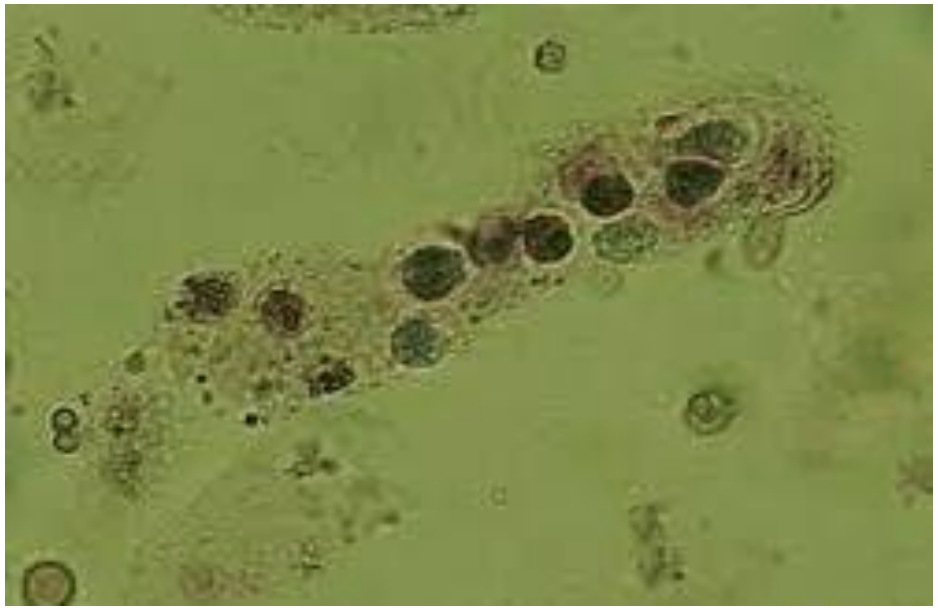
- Acute onset due to systemic shock or the progression of other glomerular disorders, such as glomerulonephritis
  - Glomerular membrane is damaged, resulting in a less tightly connected barrier
  - Net Result:
    - High molecular weight proteins and lipids are passed into the urine
    - Loss of albumin stimulates the hepatic production of lipids
    - Loss of protein leads to lower oncotic pressure which leads to edema
    - Depletion of immunoglobulins and coagulation factors places the patient at an increased risk of infection & coagulation disorders

The Nephrotic Syndrome

- Both glomerular and tubular damage may occur
- Condition may progress to chronic renal failure
- Additional sediment that may be found:
  - Oval fat bodies
  - Free fat droplets
  - RTE cells & casts
  - Waxy casts

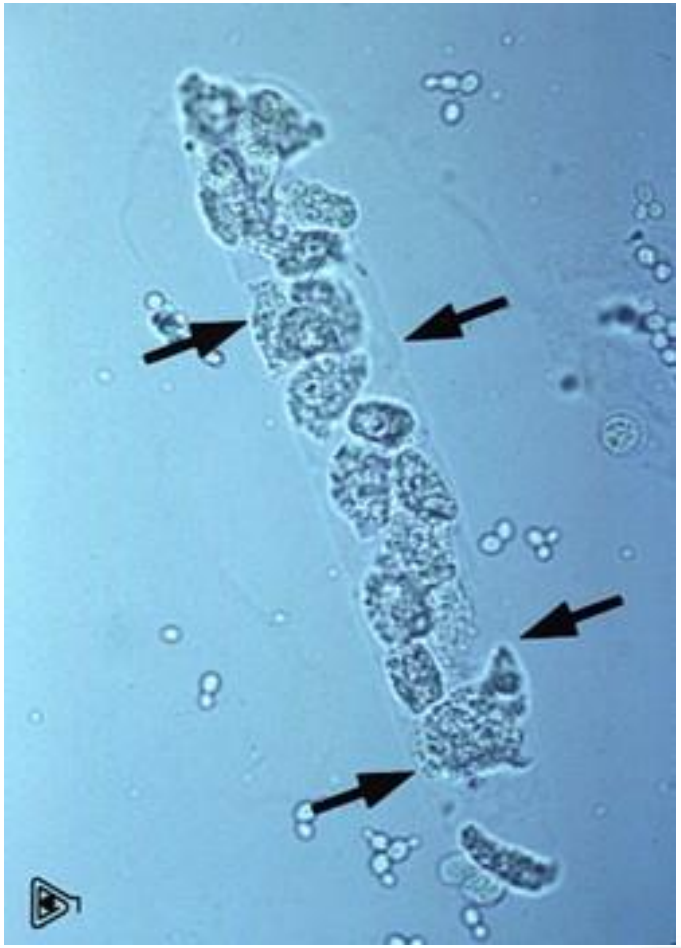
WBC Casts

- WBC casts with the presence of bacteria indicate **pyelonephritis**
  - May be acute or chronic
  - Results from the ascending movement of bacteria
  - Possible complications:
    - Renal abscess
    - Renal impairment
    - Septic shock



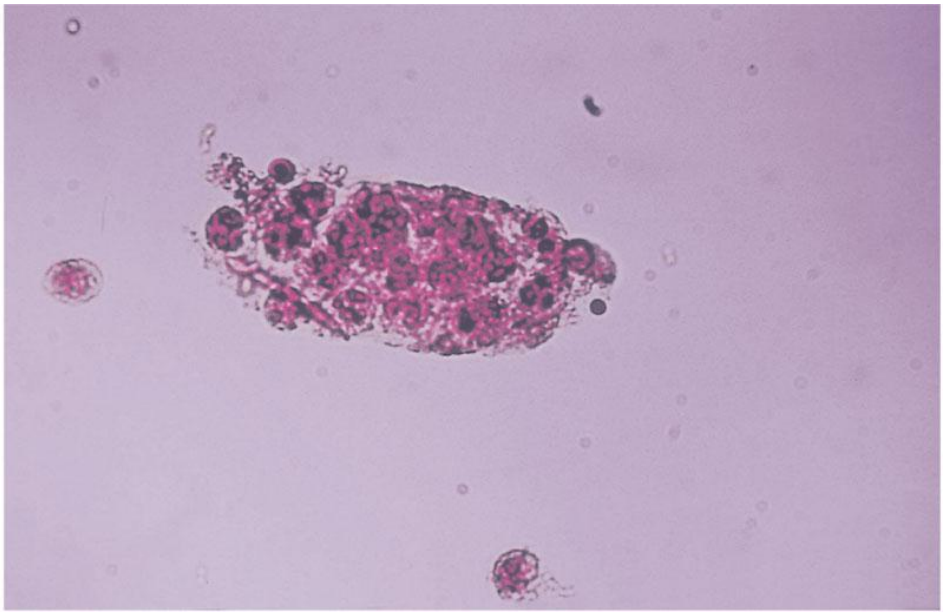
Chronic Pyelonephritis

- Chronic cases of pyelonephritis are usually due to structural defects which allow urinary reflux
  - Usually diagnosed in children
  - Leads to tubular damage and renal failure
- May also see waxy casts & broad casts



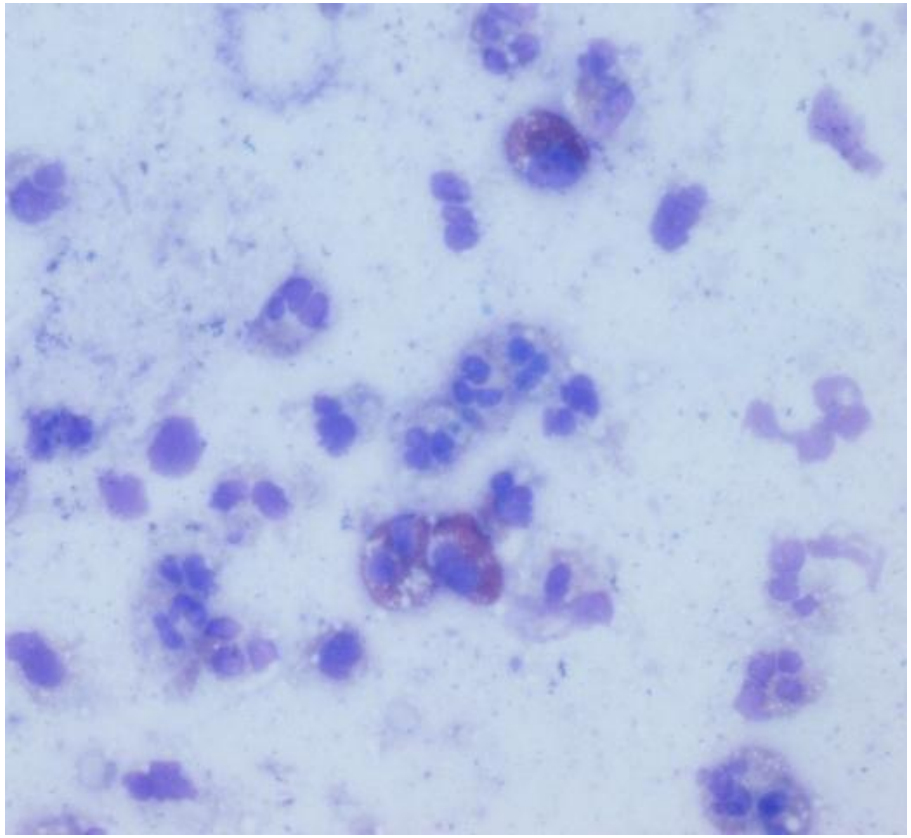
WBC Casts

- WBC casts without the presence of bacteria indicate **acute interstitial nephritis**
  - Primarily associated with an allergic reaction to a medication that occurs within the renal interstitium, leading to inflammation of renal interstitial tissues and renal tubules
    - penicillin, ampicillin, cephalosporins, NSAIDs, thiazide diuretics



Acute Interstitial Nephritis

- High percentage of eosinophils present
- Hansel stain may be used for identification of urinary eosinophils



Granular Casts

Fine Granular

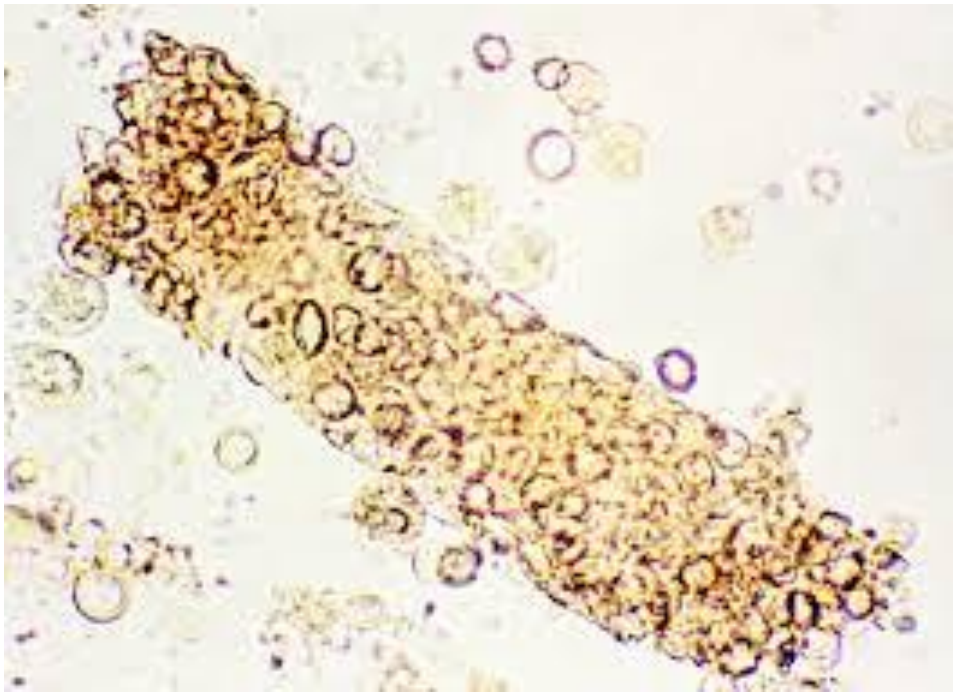
Coarse Granular

Granular Casts

- May occur as coarse or fine granular casts

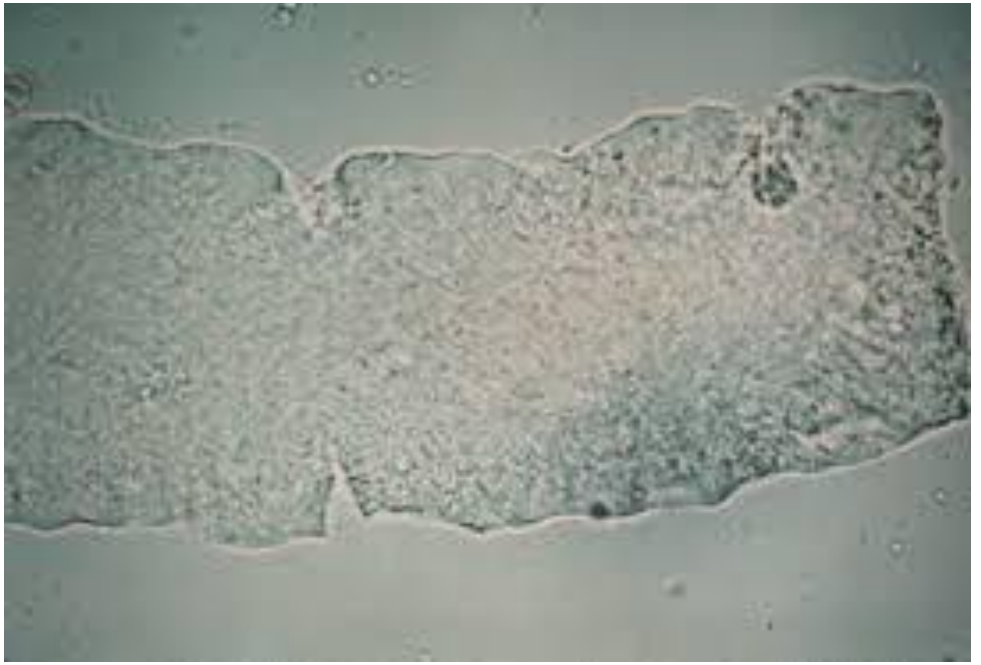
- **Origin of granules can be**:
  - RTE lysosomes (same significance as hyaline casts)
    - Excreted during normal metabolism
    - More are seen after exercise and activity
  - Disintegration of cellular casts
    - Pay extra attention to specimens with cells and granular casts

Degenerating RBC & WBC Casts



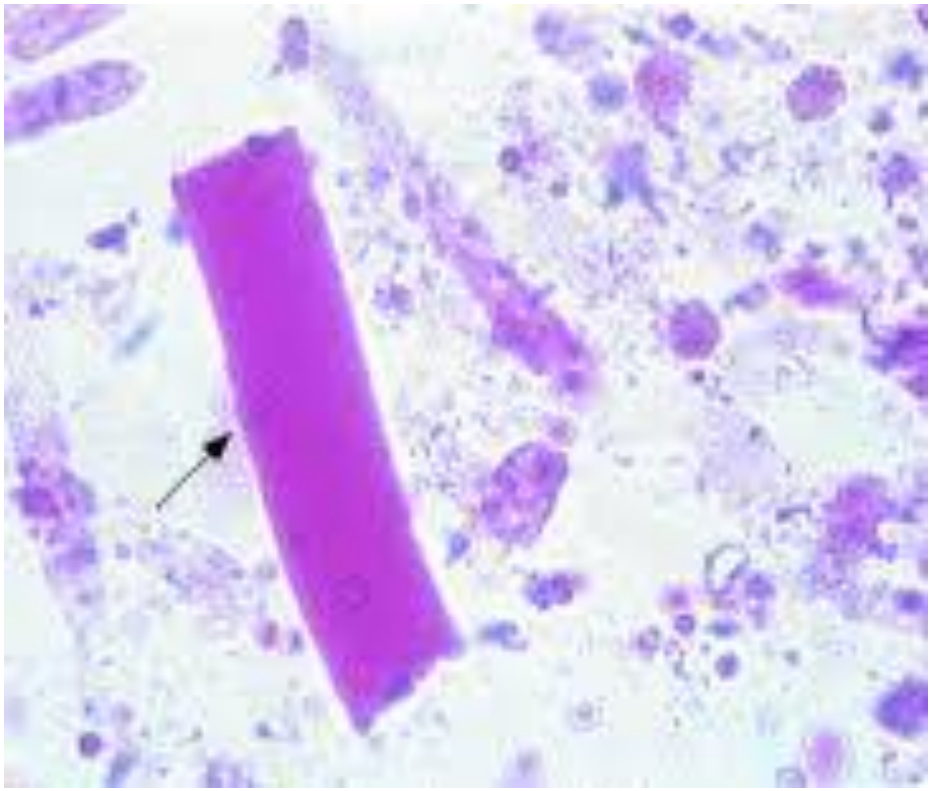
Waxy Casts

- Presence indicates extreme urine stasis
  - Seen in cases of renal failure
- Degenerated hyaline and granular casts



Waxy Casts

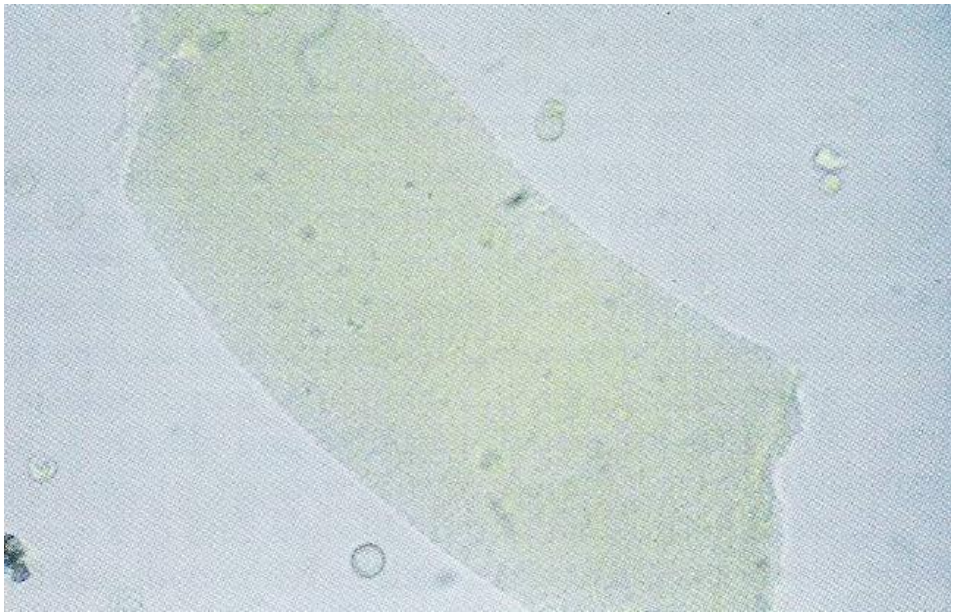
- Brittle appearance
- Highly refractile
- Often fragmented with jagged ends and notches
- Well visualized with stain



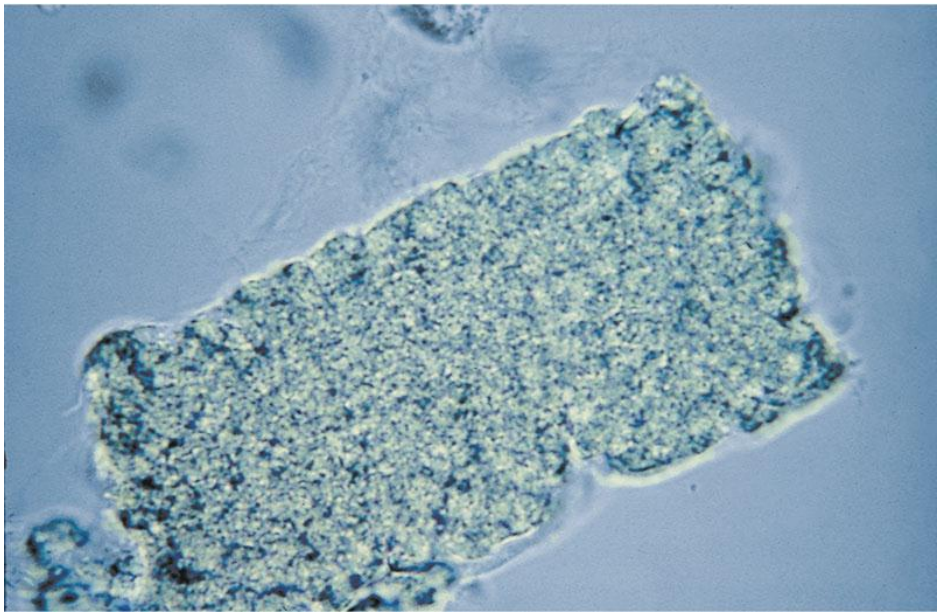
Broad Casts

- Also significant of extreme renal stasis
  - Also referred to as “renal failure casts”

- <u>Formed in</u>:
  - Collecting duct, or
  - Distal tubule that is widened due to destruction



Granular & Waxy Broad Casts



Renal Failure

- May be chronic or acute
- Chronic renal failure is seen as a progression of original renal diseases to end stage renal disease
- Casts that may be present:
  - Granular
  - Waxy
  - Broad

Acute Renal Failure

- Onset is sudden
- Usually reversible by correcting the cause
- Causes may be:
  - Prerenal – decreased blood flow
  - Renal – acute disease
  - Postrenal – obstruction

Acute Renal Failure

- Expected sediment related to cause:
  - RTE cells & casts = decreased blood flow
  - RBCs & casts = glomerular damage
  - WBCs & casts = infection/inflammation

Causes of Acute Renal Failure

- Prerenal
  - Decreased blood pressure/cardiac output
  - Hemorrhage
  - Burns
  - Surgery
  - Septicemia
- Renal
  - Acute glomerulonephritis
  - Acute tubular necrosis
  - Acute pyelonephritis
  - Acute interstitial nephritis
- Postrenal
  - Renal calculi
  - Tumors
  - Crystallization of ingested substances

What is the most likely condition?

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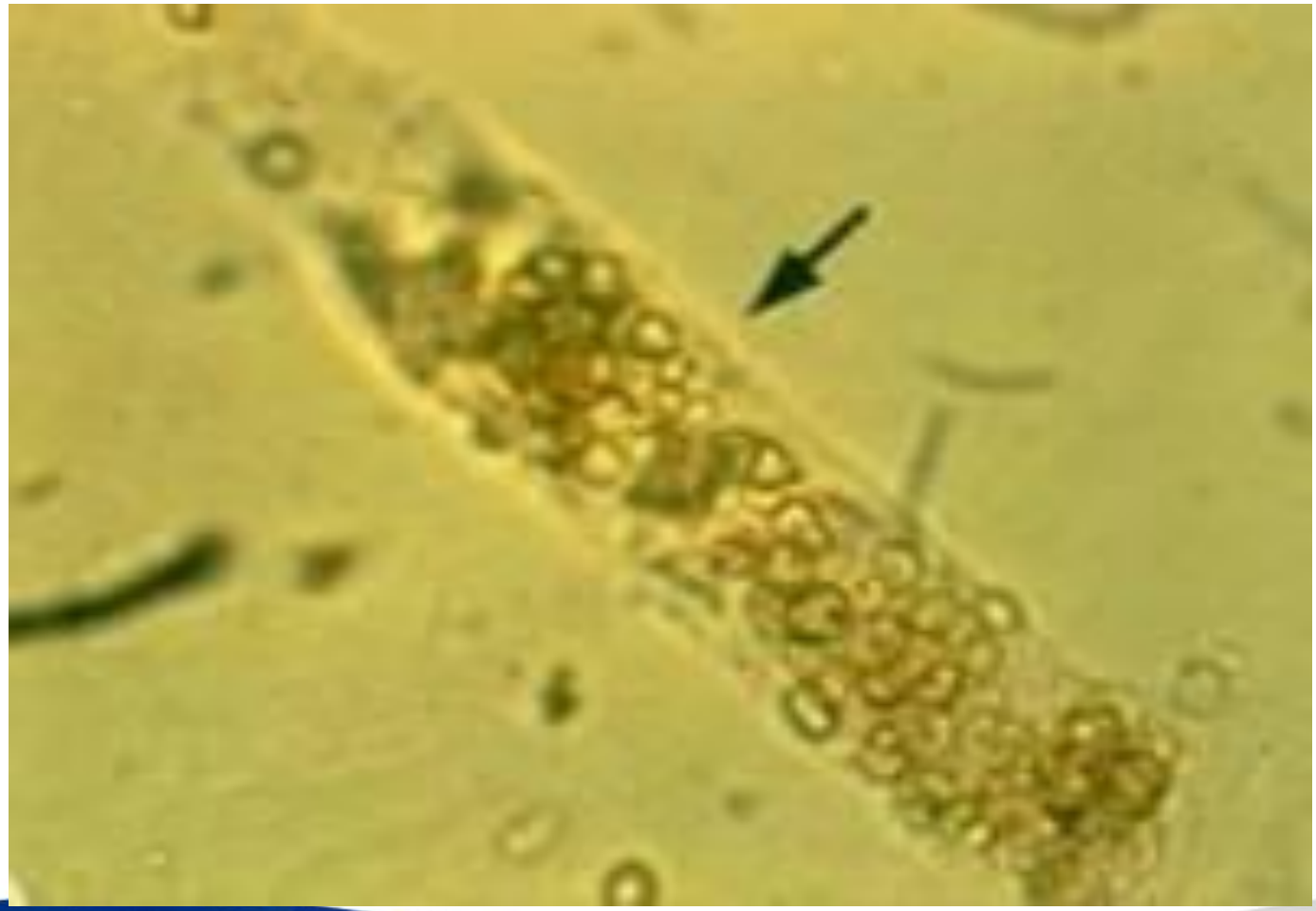

What is the most likely condition?

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Contact Information

Steven Edwards, MS(MLS)

Assistant Professor of Medical Lab Science

Lincoln Memorial University

6965 Cumberland Gap Pkwy

Harrogate, TN 37752

Office: 423-869-6232

Email: steven.edwards@LMUnet.edu