Examinations of Renal Functions

Jan Živný

Department of Pathophysiology

jzivny@LF1.cuni.cz

Renal Functions

- **Excretion of water and water soluble substances**
- **Blood pressure** regulation
  - Renin-Angiotensin-Aldosteron
- **Erythropoiesis** regulation
  - Erytropoetin
- **Calcium** metabolism regulation
  - hydroxylation of 25-hydroxycholecalciferol to **kalcitriol** (1,25-dihydroxycholecalciferol)

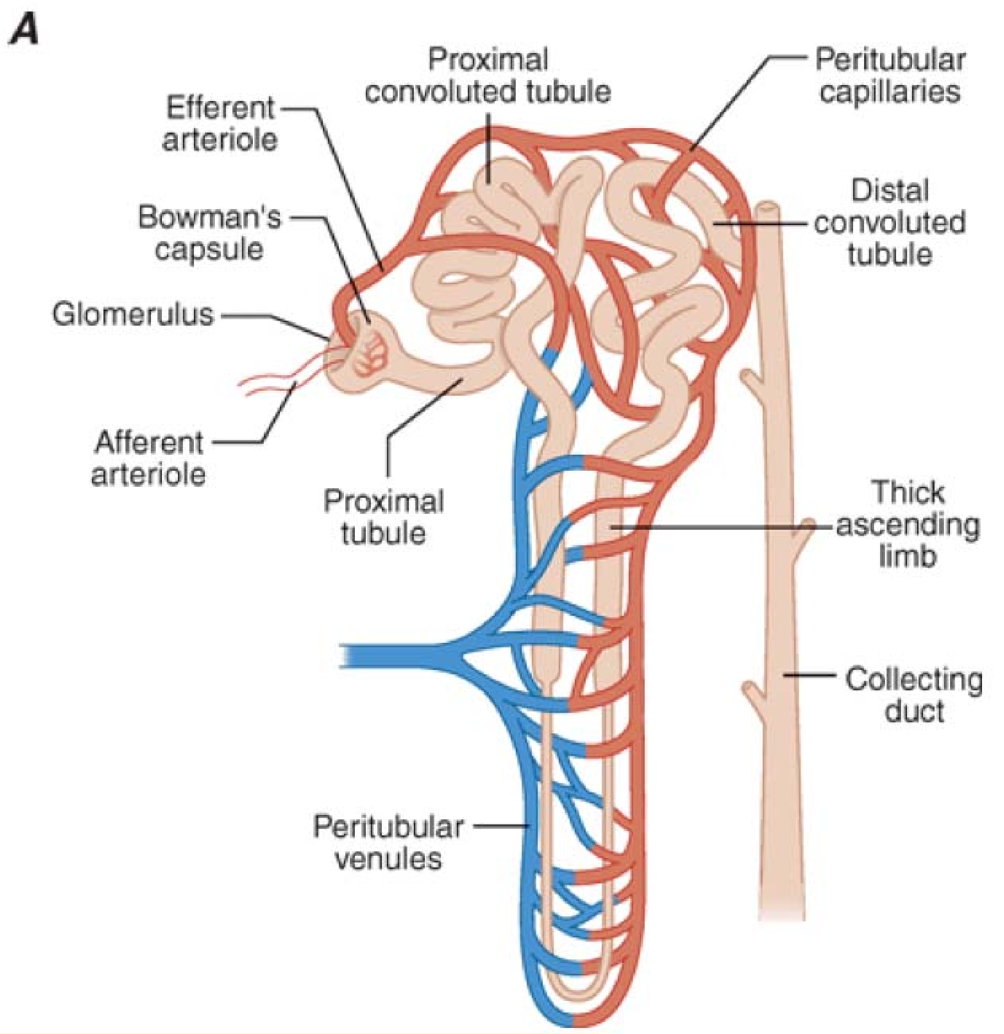
Managment of water and water soluble substances

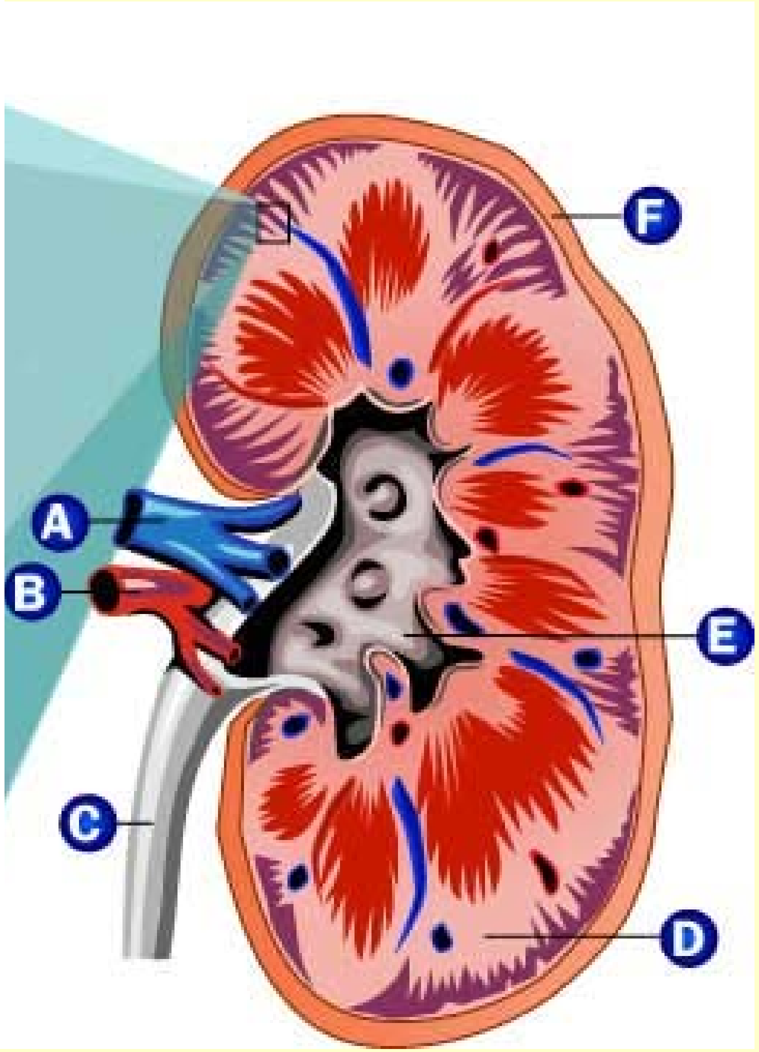
Glomerulr filtration

Tubulointerstitial functions

Nephron

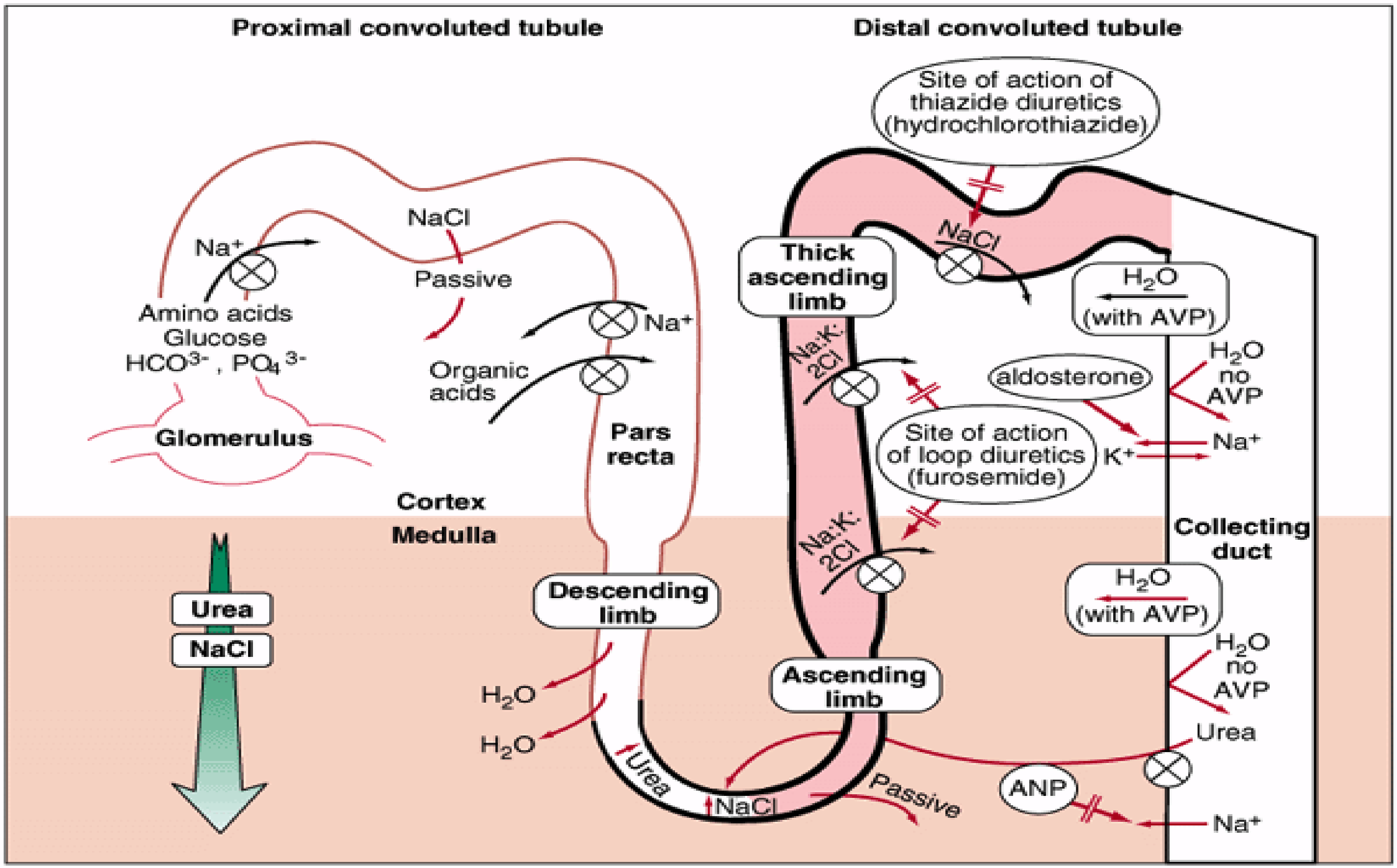
Kidney





Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Transport functions of the various anatomic segments of the nephron



General causes of renal damage

- Prerenal
  - Kidney perfusion defect
    - decrease in glomerular filtration
    - kidney ischemia – tubular necrosis
- Renal
  - Glomerular
    - increase in permeability
    - decrease in permeability
  - Tubulointerstitial
    - defect in concentration and acidification of urine

General causes of renal damage

- Prerenal
- Renal
- Postrenal
  - – Obstruction of urinary tract
    - Defect in urinary otput
    - Decrease in glomerular filtration
  - – Urinary tract infection

Examinations

- Urinary output
- Urinalysis (composition of urine)
- Composition of plasma
- Imaging methods and renal biopsy

Urinary output

Urinary output

- Quantitative changes
- Qualitative changes

Polyuria

> 2500 mL/day

- Increased water intake (compulsive water drinking)
- Osmotic diuresis (glycosuria - uncontrolled DM)
- Diabetes insipidus
  - decreased ADH release (hypothalamic or posterior pituitary disease)
  - decreased renal tubular response to ADH

Oliguria

adults: < 500 mL/day

young children: < 24 mL/kg body weight/day

- Renal failure
  - decreased renal perfusion (prerenal factors)
  - primary renal disease
  - ureteral or bladder outlet obstruction (postrenal factors)

Anuria

< 100 mL/day in adults

- Acute renal failure
- End stage of chronic progressive renal insufficiency
- Renal infarction or cortical necrosis (rare)
- Reversible urinary obstruction

- Prolonged anuria results in uremia

Nocturia

voiding during the night

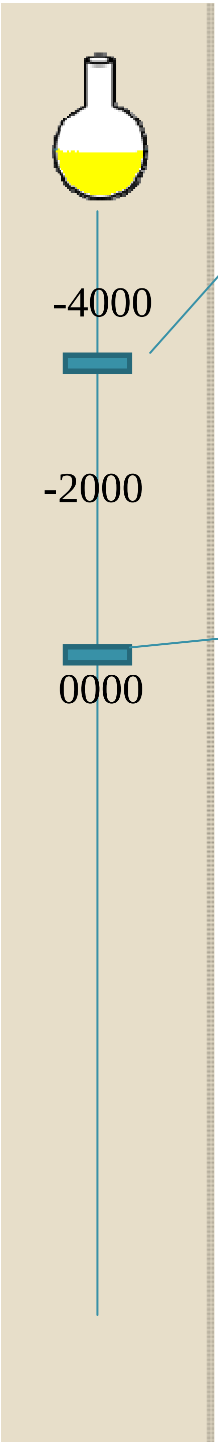
- Excessive fluid intake in the late evening
- Urine retention secondary to bladder neck obstruction (prostatism)
- Polyuria from a decrease in concentrating capacity
- Heart and liver failure

Dysuria
painful urination

- Usually due to bacterial infection
- Obstruction distal to the bladder
  - prostatic obstruction, urethral stricture, posterior urethral valves

Urinalysis

Slides on historical
perspective provided by
Anthony J. Bleyer, M.D., M.S.



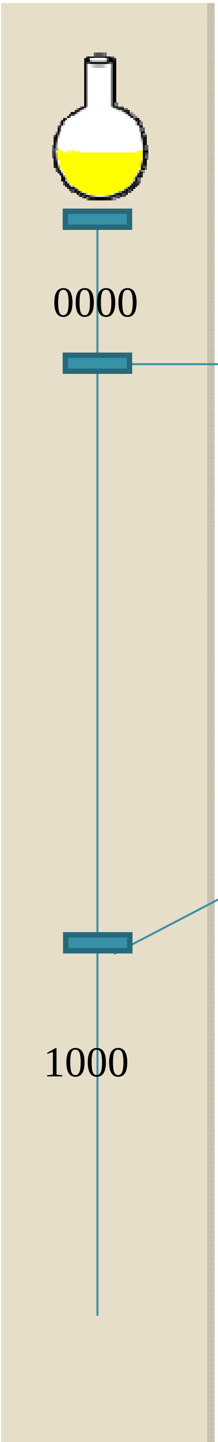
Sumerian and Babylonian Physicians

- Record insights about urine on clay tablets

Hippocrates ~ 400 BC

- "No other organ system or organ of the human body provides so much information by its excretion as does the urinary system."
- To understand is to prognosticate

Armstrong JA Kidney Int 2006



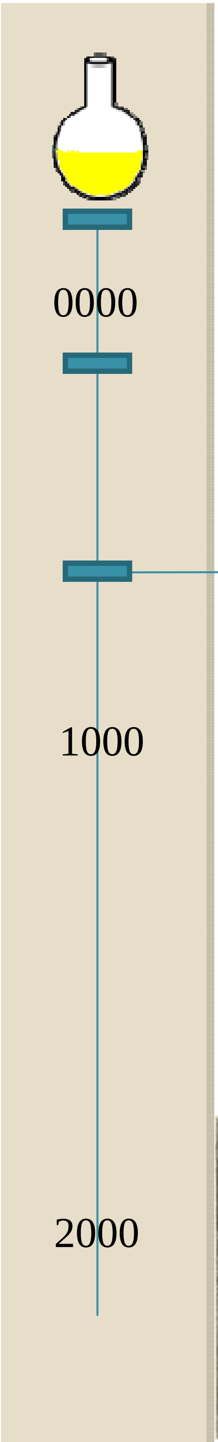
Galen ~ 200 A.D.

- Urine is a filtrate of blood
- Liquid ingested equals the urine expelled in a healthy person.

Theophilus Prostopatharios of Constantinople ~ 600 A.D.

- *De Urinis* –
  - Practical advice with precise theory
  - Description how urine is produced

Armstrong JA Kidney Int 2006



De Urinis ~ 600 A.D.

- Based on a chromatic spectrum using 10 colors subdivided into categories of thick and thin
- Standard examination technique
- Matula (examination jar)

Kouba E, et al.: Uroscopy. J Urology 2007

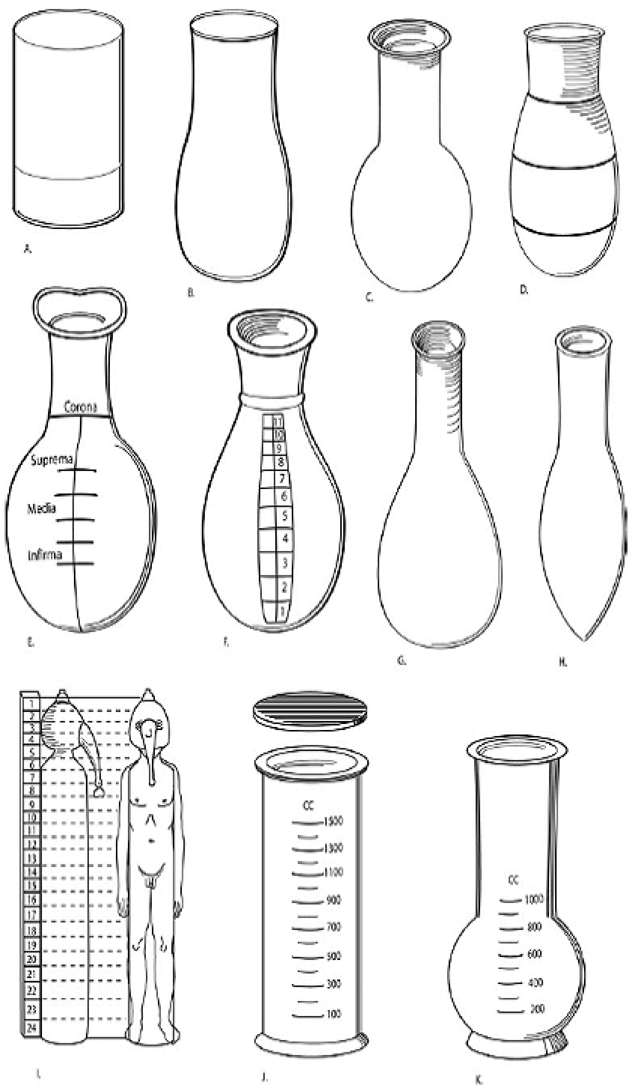


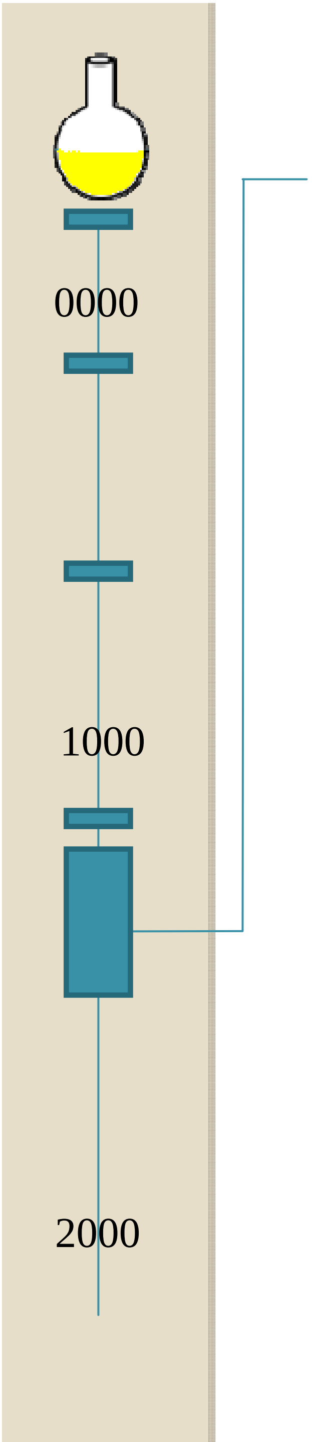
Figure 2. The vessels used to examine the urine, the matula, by uroscopists. Drawing based on figures reproduced in various manuscripts and published woodcuts from the 13th century (A) through 1895 (J, K).

Eknoyan G: AJKD 2007


XAT.COM

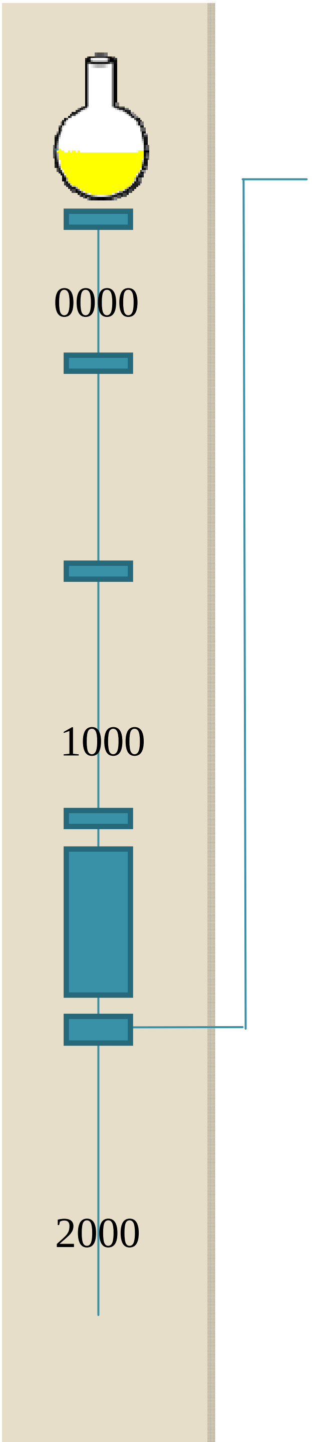
Chromogens

- Normal urine color
  - clear during water diuresis
  - deep yellow color when maximally concentrated due to chromogens (urobilin).
- Abnormal color
  - Food pigments (usually red urine)
  - Drugs (brown, black, blue, green, or red)
  - hematuria, hemoglobinuria, myoglobinuria
  - pyuria, precipitated phosphates in alkaline urine (Cloudy or milky urine)
  - precipitated urates in an acid urine (Brick dust urine)



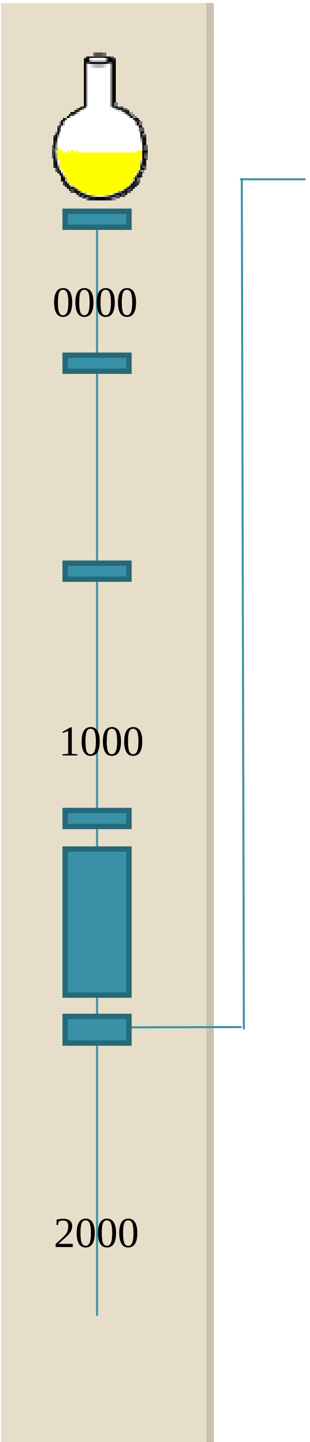
1300’s to 1600’s

- Dark ages for nephrology
- Pisseprophecy abounded



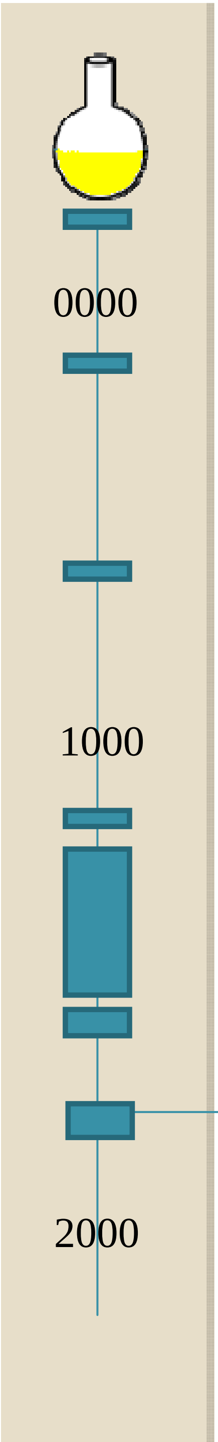
1600s – Science Evolves

- 1637 *Pisse Prophet* by Thomas Brian identifies pisseprophecy as quackery
- 1655 van Helmont measured specific gravity



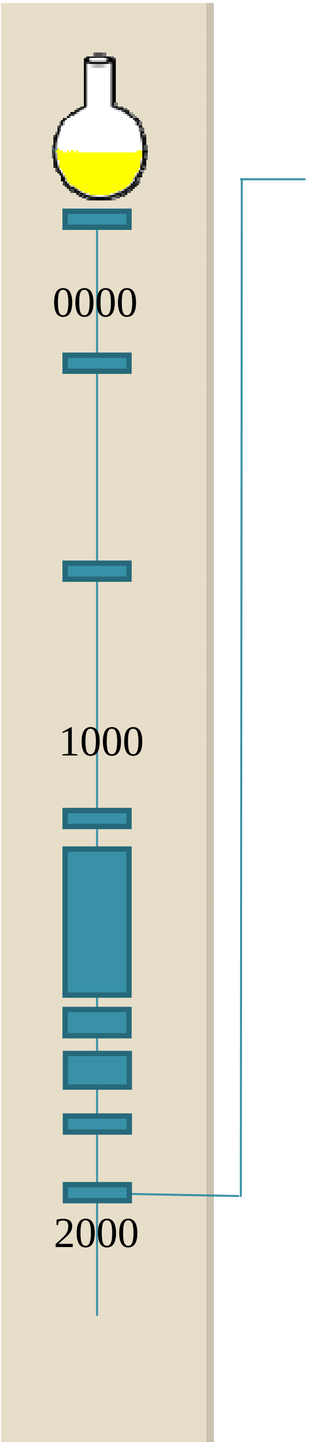
Thomas Willis (1621-1675)

- Described urine in diabetics as Quasi melle (as if imbued with honey)



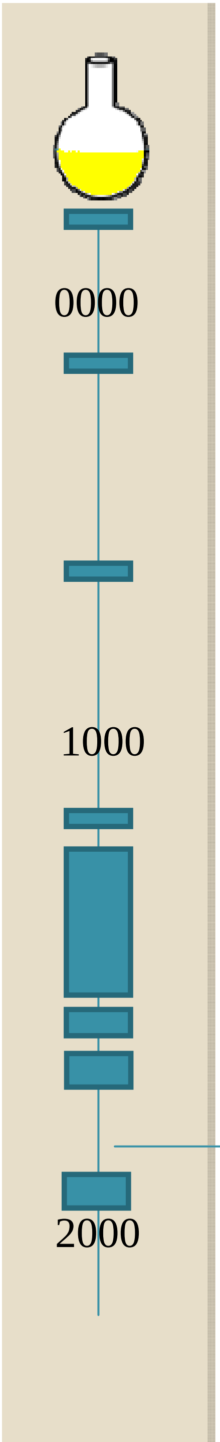
Age of Organic Chemistry

- Urea discovered and synthesized by Friedrich Wohler in 1828
  - Beginning of synthetic biochemistry and the decline of vitalism
- Other substances obtained from the urine:
  - Uric acid
  - Cystine



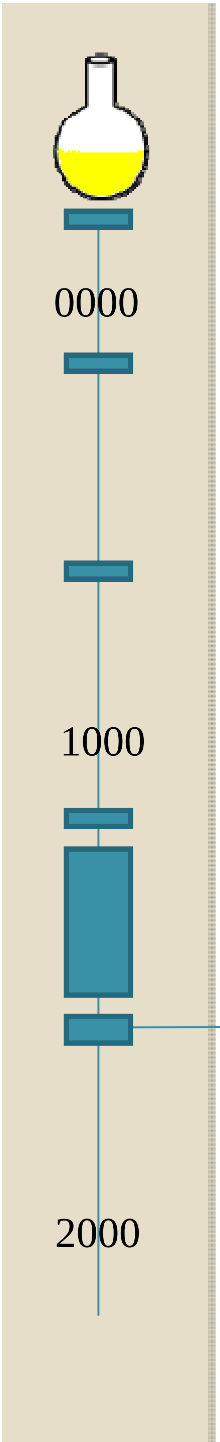
Age of Organic Chemistry

- 1910-1916
- Oscar and Rudolf Adler
- Blood test for glucose using benzidine
  - Used test for urine



Mortality of Diabetes Mellitus Early 1900's

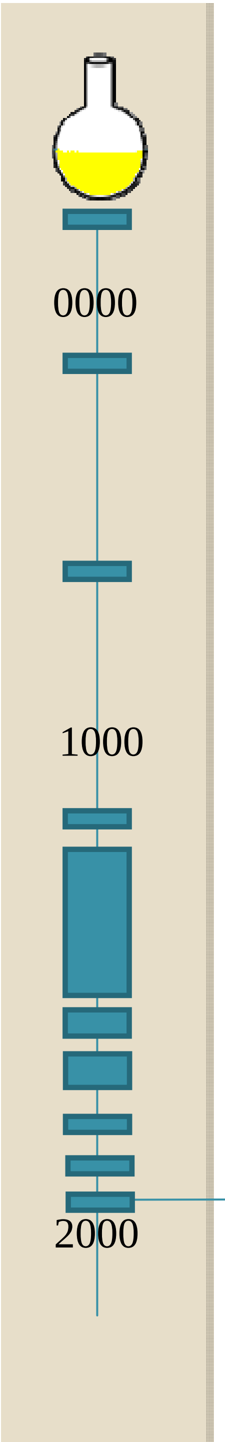
- 1890 Mortality in first year from diabetes mellitus: 67.5%
- 1900 Mortality in first year from diabetes mellitus: 47%
- 1910 Joslin: 14.8% (goal: glucose free urine) – method = starvation



The Urine Test Strip

- Simplify urinalysis by dry reagents
  - Robert Boyle litmus paper (1670)

Voswinkell P, Kidney Int 1994



Urine Dipstick

- Jewish chemists in Germany were working toward a test strip
- Work interrupted by Nazism

- 1956 – Lily and Ames launched dip and read test strips
  - Free promotional gift with diabetic medications

Urine dipstick is a group of chemical tests done at the bedside for glucose, protein, white blood cells, red cells, and specific gravity

Proteins in urine

- Dipsticks (bromphenol blue)
  - sensitive to 50 to 200 mg/L of albumin
  - less sensitive to globulins and mucoproteins
  - may be negative in the presence of Bence-Jones proteins
- Electrophoresis, immunoelectrophoresis, and radioimmunoassays

~ 1827 albuminuria (Bright)

Measurements of protein excretion

- 24-h measurement of total protein excretion
  - normal, < 150 mg/day)
- In a random sample of urine:
  - protein:creatinine ratio (normally < 0.2)

Causes of proteinuria:

- Altered glomerular capillary permeability
- “Over-flow” proteinuria: Elevated plasma concentration of particular proteins
- Decreased tubular resorption of filtered proteins

Bence-Jones Protein

- The first tumor biomarker in urine
  - ~ 1845

- Free immunoglobulin light chains in urine
  - Immunodetection
  - Multiple myeloma

Nitrituria
significant bacteriuria

- the dipstick test
  - conversion of nitrate (derived from dietary metabolites) to nitrite by the action of certain bacteria in the urine
- Positive test in 80% of cases of significant bacteriuria (bacteriuria ~10^5 bacteria/mL for ~ 4 h)
- Negative test does not exclude bacteriuria
- False positive – secondary contamination of sample with bacteria

WBC esterase
inflammation

- False-negative results may occur in the presence of
  - very concentrated urine
  - glycosuria
  - urobilinogen
  - Drugs (phenazopyridine, nitrofurantoin, rifampin, vitamin C)

Osmolality:

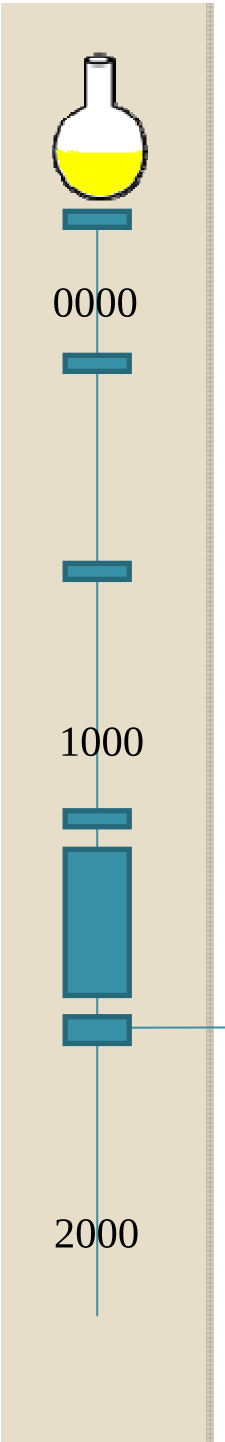
total concentration of solutes in the urine

- mOsm/kg of urine water
- Normal urine osmolality is 50 to 1200 mOsm/kg
- Depends on the circulating titer of ADH and the rate of urinary solute excretion

Plasma: 275-295 mOsm/kg

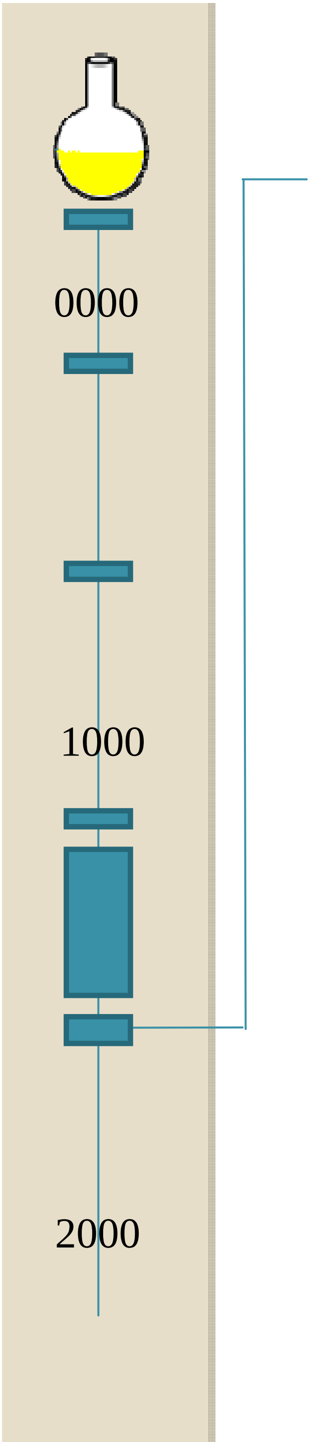
Urinary pH

- methyl red (red pH< 4.4 - 6.2 > yellow) and bromthymol blue (yellow < pH 6.0–7.6 > blue)
- Alkaline urine: infection of urease producing bacteria (*Proteus mirabilis, Klebsiella, Pseudomonas, Staphylococcus*)
- Distal type of renal tubular acidosis
  - suggested by a urine of more than pH 5.5 after an acid load



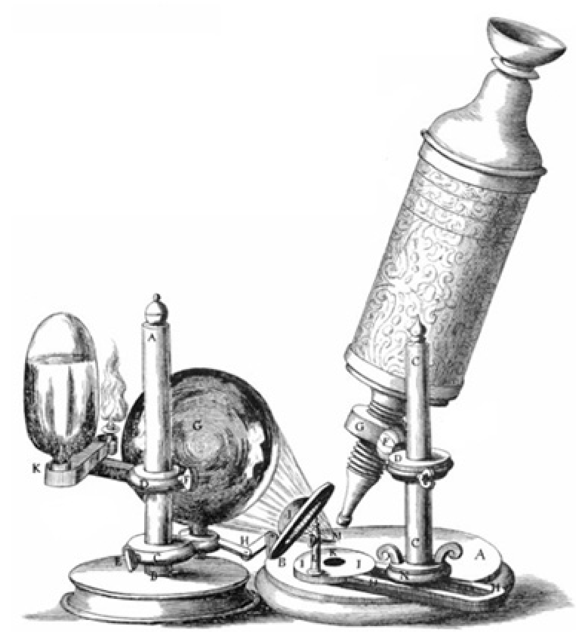
What about a microscope?

- Leeuwenhoek 1632-1723
  - Described crystals in the urine
- Robert Hooke (1635-1703)
  - Crystals appear to be a company of small bodies, partly transparent, and parto opacous, with some White, some Red, others of more brown and duskie colors.”

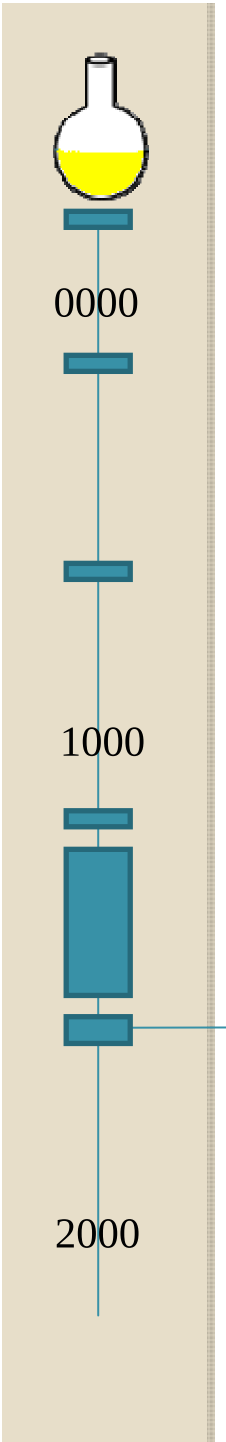


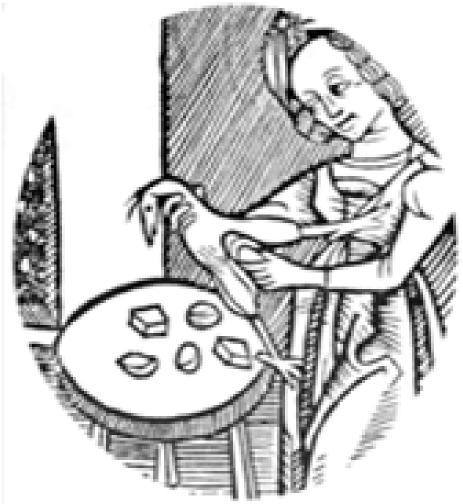
- First published picture of the urine

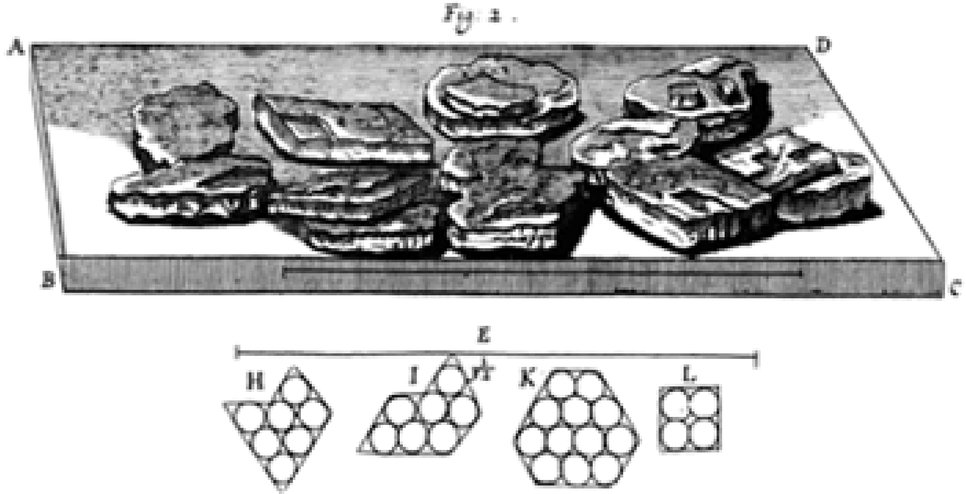
- Robert Hooke



Fogazzi GB, et al.
Kidney Int 2006







Robert Hooke: Micrographia 1665

Microscopic examination of sediment

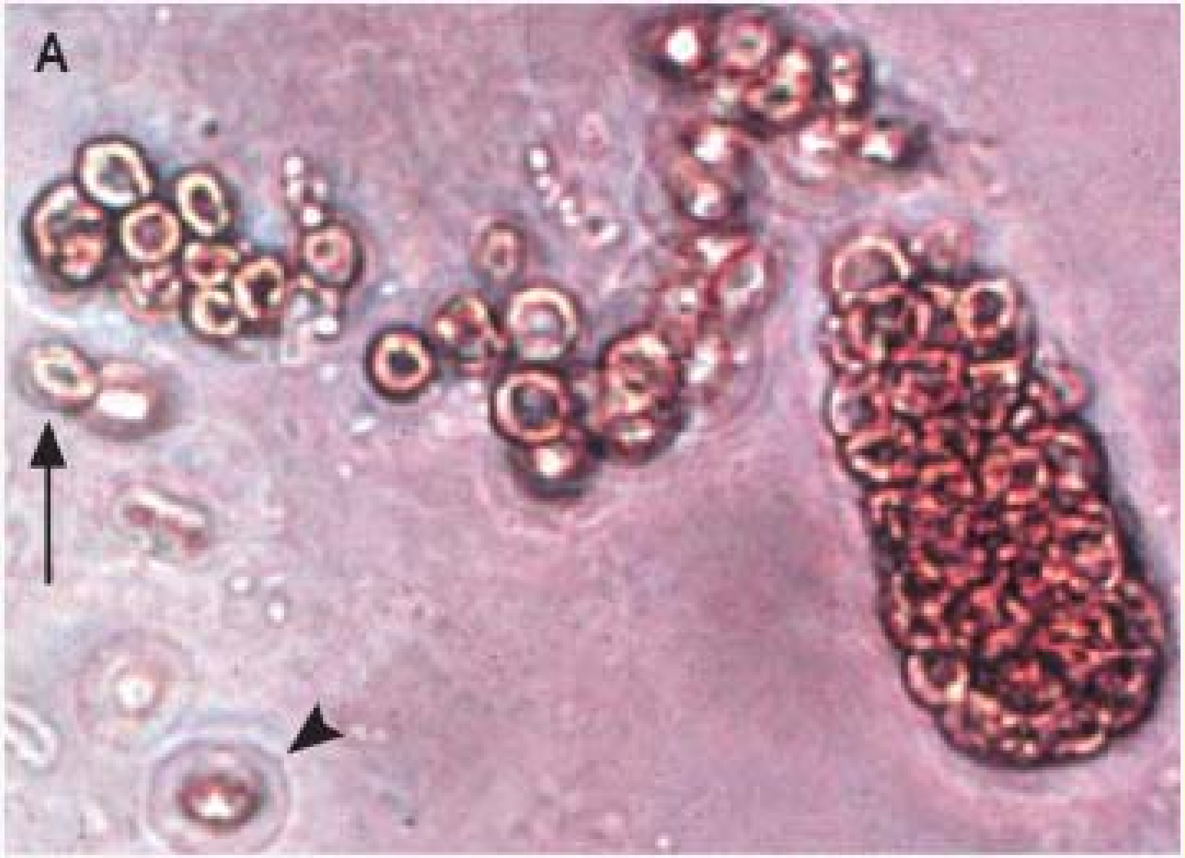
- Semi-quantitative estimation of specific cells and casts
- Quantitative analysis
  - Hamburger sediment – 3 hour urine collection
  - Addis sediment – 24 hour urine collection

Semi-quantitative estimation of specific cells and casts

- WBC numbers
- RBC: numbers and morphology
  - > 80% dysmorphic – glomerular origin of hematuria is suggested
- Epithelial cells
- Crystals of various salts (oxalate, phosphate, urate) or drugs (eg. sulfonamides)
- Casts
  - cylindric masses of mucoprotein in which cellular elements, protein, or fat droplets may be entrapped

- distinguishing of primary renal disease from diseases of the lower tract

Urinary sediment red-cell cast and red cells

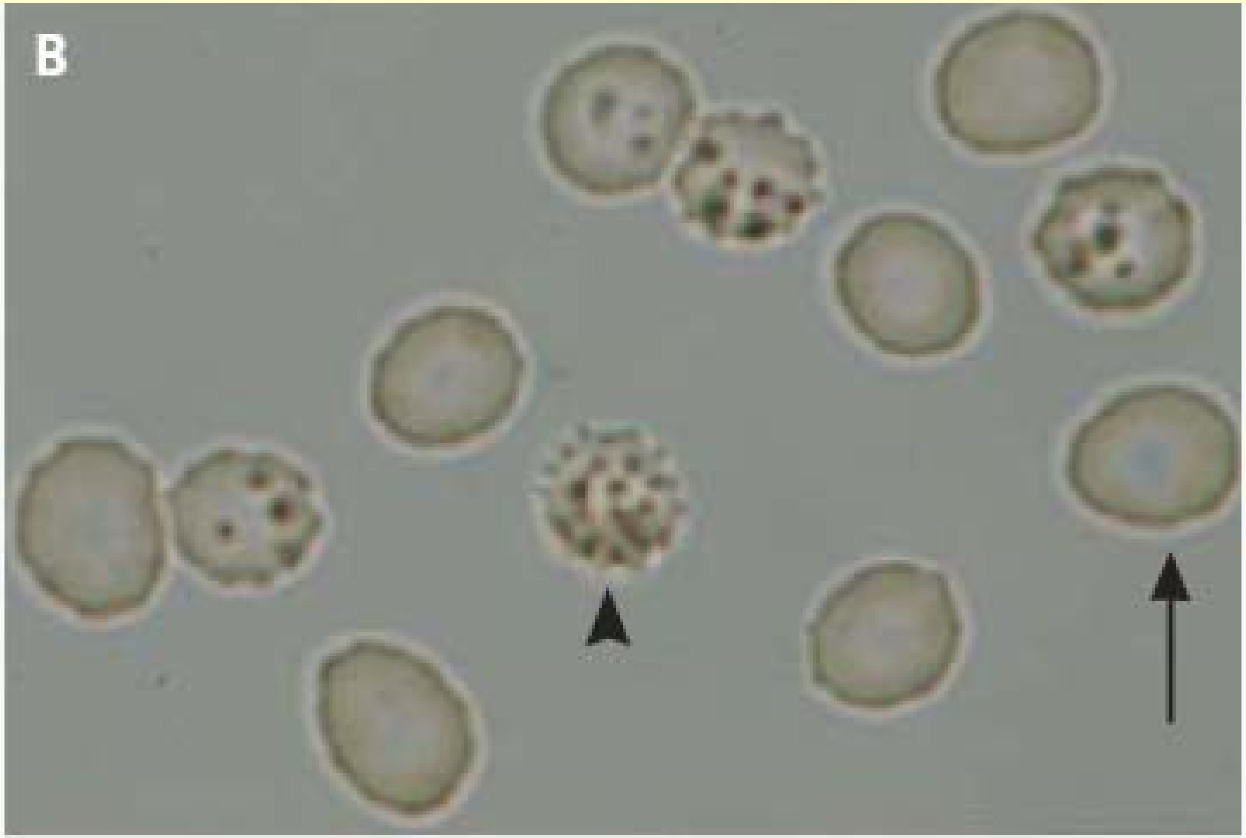


dysmorphic red cell (arrow) suggests a glomerular source

the uniform, biconcave disk shape of normal red cells (arrowhead) suggests nonglomerular

Red-cell casts indicate the presence of glomerular bleeding

Urinary sediment



- normal red cells (arrow)
- crenated red-cell forms with spicules (arrowhead).

Composition of plasma
and
Evaluation of glomerular filtration

Evaluation of glomerular filtration

Glomerular filtration rate (GFR) ~ 120 ml/min, i.e. 2 ml/s

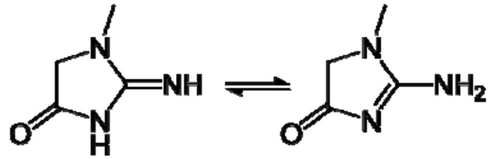
- **~ 170 L / day !!!**
- Constant at systemic blood pressure 80 - 180 mmHg (autoregulation)

Barrel of oil: ~159 liters
(42 US gallons)

GFR is estimated based on the plasma/serum and urine composition

- Creatinine
- Urea (BUN)
- Electrolytes (Sodium, potassium, chloride)

Serum creatinine



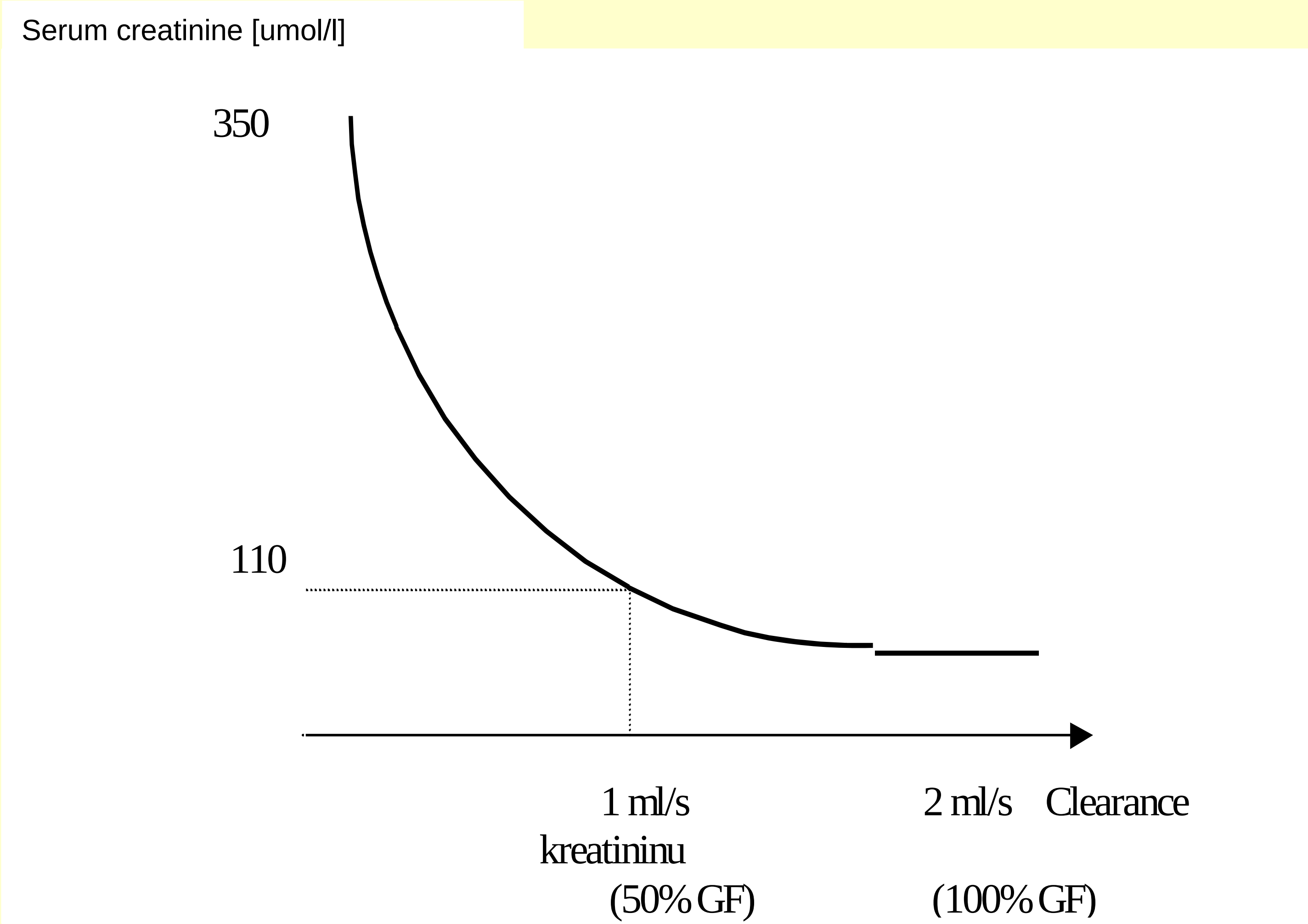
- Index of renal function
- Creatinine production and excretion are reasonably constant in the absence of muscle disease
- Varies inversely with the GFR
  - M < 110 µmol/L
  - F < 90 µmol/L

Measurement of GFR
Creatinine clearance

- 24 h urine collection
- $C_{cr} = U_{cr} \times V / P_{cr}$
- M: 140 to 200 L/day (70 ± 14 mL/min/m2)
- F: 120 to 180 L/day (60 ± 10 mL/min/m2)
- Decrease in creatinine clearance: after loss of 50 to 75% of the normal glomerular filtration capacity (surface)

Creatinine clearance

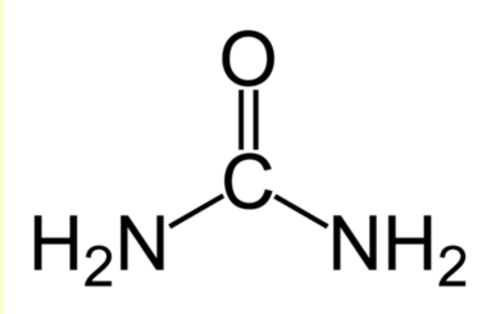
GFR; Glomerular filtration rate



Normal range M and F: 1.20–2.50 mL/s/1.73 m^2

Creatinine clearance

BUN (Urea)



- 1,7 – 8,3 mmol/l
- Urea is formed in the liver as the end product of protein metabolism
- Influenced by variations in urine flow rate and by the production and metabolism of urea

Decrease in glomerular filtration = Kidney failure

Acute

Chronic

Evaluation of tubular and tubulointerstitial functions

Tubular resorption

$$\text{Tubular resorption} = \frac{\text{GF in ml/s} - \text{volume of definitive urine in ml/s}}{\text{GF v ml/s}}$$

- Normal values:

  0,988 – 0,998 (98,8 – 99,8%)

Fraction excretion (FE)

- Ratio of glomerular filtrate excreted in definitive urine: total fraction excretion: 0,2 – 1,2%
- FE of given chemical:

$$\text{Fraction excretion} = \frac{U \times V}{GFR \times P \times f}$$

- **f = 1** if the concentration of given chemical is the same in GF as is in plasma
- **f** $<$ **1** chemical partially bound on plasma proteins e.g. Ca2+

- E.g.
  - FE of Na+ ~ 0,01 (1%) = 1% of filtrated sodiun is excreted

FE $>$ 1: tubular secretion is higher than resorption

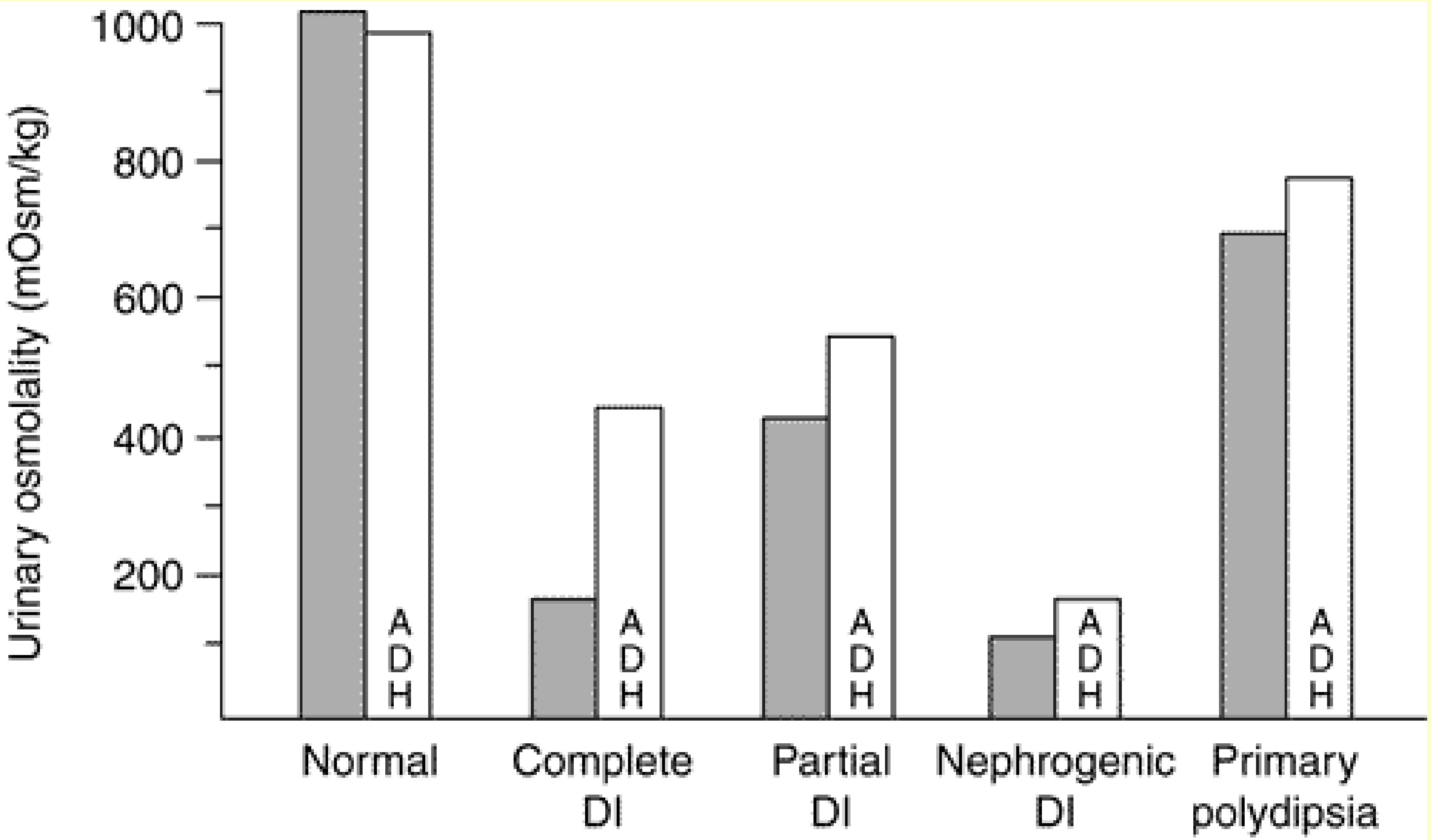
Tests of renal concentrating capacity

- Water deprivation for 12 to 14 h followed by the test of exogenous ADH response (5 U s.c. or 10 µg by nasal insufflation)
  - the urine osmolality is measured
  - Caution: In patients with renal failure

Tests of renal concentrating capacity

- Tubulointerstitial disease
  - toxic nephritis, pyelonephritis, infiltrate, fibrosis
- Diabetes insipidus
- Osmotic diuresis
- certain diuretics [furosemide, bumetanide, ethacrynic acid]
- K+ deficiency
- hypercalcemia

Tests of renal concentrating capacity



Maximum urinary osmolality after water deprivation (shaded bars)
Maximum urinary osmolality after vasopressin/ADH (open bars).

Urinalysis the Case

Anthony J. Bleyer, M.D., M.S.
Section on Nephrology
Wake Forest Medical School

The Present

- 45 year old African American male
- HIV +
- Presents with serum creatinine 8 mg/dl (707 umol/L)

- Referred to nephrology to start dialysis.

Urinalysis in HIV Nephropathy

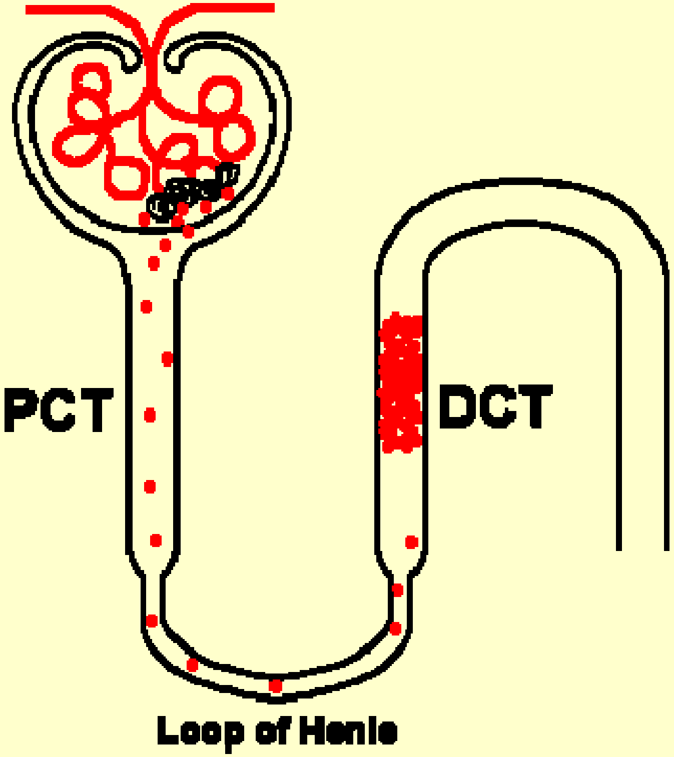
- Large amounts of protein
- Occasional protein casts
- No blood

Urinalysis in Patient

- 3+ blood
- Red cell casts

- Kidney biopsy
- Proliferative glomerulonephritis
- Pulse glucocorticoid therapy

Urinalysis in our patient: 3+ blood and red blood cell casts



Urinalysis in Patient

- Kidney biopsy
- Proliferative glomerulonephritis
- Pulse glucocorticoid therapy

Outcome

- Serum creatinine 100 umol/L
- 12 years later!
- Without urinalysis, patient would have died on dialysis.

End