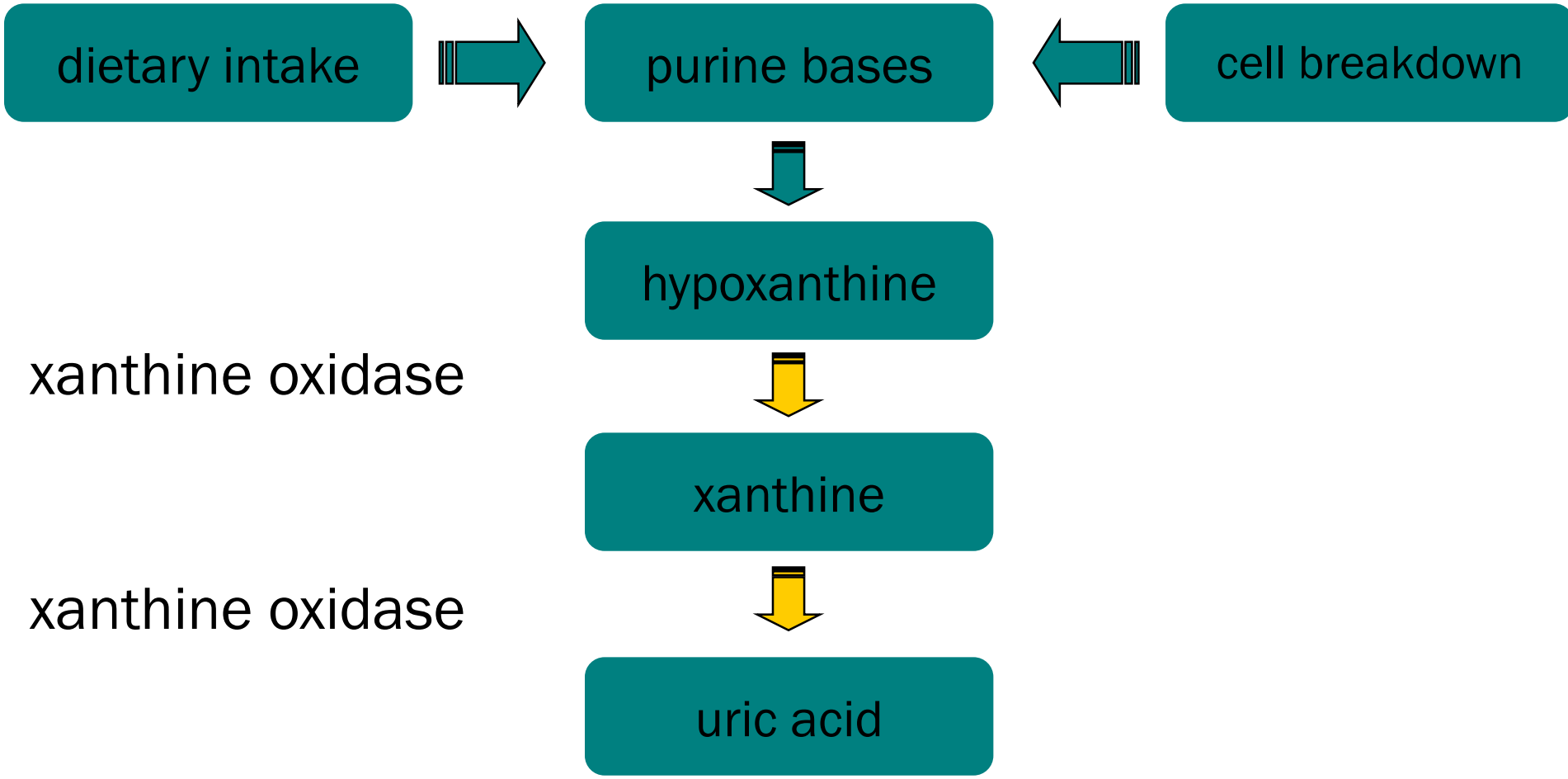
Uric acid and gout

Uric acid

- Metabolic end-product of the purine bases of DNA
- **Elimination:** renal excretion

- The reference ranges of UA
  - **> 416** umol/l (men)
  - **> 360** umol/l (women)

Uric acid metabolism



Hyperuricemia (HU) pathophysiology

- decreased excretion UA (underexcretors)

  renal hyperuricemia

- increased production (overproducers)

  metabolic hyperuricemia

- combination of these two mechanisms

- **Underexcretion**
  - most causes of HU
  - *altered uric acid excretion*
    - decreased glomerular filtration, decreased tubular secretion, enhanced tubular reabsorption
    - E.g.: renal insufficiency, patients with acidosis, diuretic therapy , diabetes insipidus

- **Overproduction**
  - a minority of patients presenting with HU
    - **exogenous** (diet rich in purines)
    - **endogenous** (increased purine nucleotide breakdown)
    - **enzymatic defects**
      - complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) - Lesch-Nyhan syndrome
      - partial deficiency of HGPRT (Kelley-Seegmiller syndrome)
      - increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity.
    - **Accelerated purine degradation**
      - cell proliferation and turnover (blast crisis of leukemias)
      - cell death (rhabdomyolysis, cytotoxic therapy)

Classification of HU

- **Primary HU** (90%)
- **Secondary HU** (10%) – symptom of an another disease, drug therapy,...

Gout

History

- Patient can by **symptomatic** or **asymptomatic**
- Identifying causative etiologies, comorbid conditions
- **Symptoms**
  - Acute gouty arthritis
  - Nephrolithiasis
  - Tophi
  - …

Physical examination

- Asymptomatic, no specific physical finding
- Symptomatic:
  - **acute gouty arthritis**
  - **chronic gouty arthritis** + **tophi** (in the helix or antihelix of the ear, along the ulnar surface of the forearm, in the olecranon bursa, or in other tissues)
  - **uric acid nephrolithiasis -** abdominal or flank tenderness and pain, and/or nausea and vomiting, hematuria

Clinical – 4 Phases

- Asymptomatic hyperuricemia
- Acute gouty arthritis
- Intercurrent period (6-24 m.)
- (Acute gouty arthritis)
- Chronic gout

Acute gouty arthritis

- A metabolic disease characterized by hyperuricemia and acute attacks of arthritis
- **History – triggers** – surgery, infecions, trauma, diet mistake
- **Presentation**
  - Severe pain, very tender to touch !
  - The redness (sometimes shiny, sometimes dull)
  - Warm
  - Sudden onset, usually early in the morning
- **Location**
  - **First MTP joint** (podagra - 50%), **other foot joint**, **ankle** or **knee** in 30% of first time cases

Acute gouty arthritis – Dg.

- **Medical history**
- **Physical examination**
- **Clinical presentation** – local symptoms + general symptoms
- **Laboratory:**
  - CRP, FW, WBC elevated
  - CAVE: Uric acid may be normal 20 to 40% of the time at the time of the attack
- **Synovial fluid analysis** - intracellular monosodium urate crystals in synovial fluid
- **x-ray**

Treatment

- ***Asymptomatic Hyperuricemia –*** initiating therapy is not recommended
- ***Acute Intermittent Gout -*** initiated within 24 hours of onset
  - NSAIDs, colchicine, corticosteroids (intra-articular injection or systemic)
- ***Chronic Tophaceous Gout***
  - Reduced urate production (xanthine-oxidase inhibitor) - **Allopurinol**, **Febuxostat**
  - Enhanced urinary excretion of uric acid (uricosuric agent) - **Probenecid**
- ***Other Treatment Considerations***
  - Avoid **high-risk medications** lead to hyperuricemia, (diuretics, cyclosporine, and tacrolimus...)
  - **Diet** - avoid excessive consumption of alcohol (especially beer),

Porphyrias

General informations I

- **Porphyrins** - precursors of heme
- **Heme**
  - Synthesised in a **multistep process**
  - **Defects of enzymes** needed at various steps - **accumulation** and **increased excretion of porphyrins and their precursors** - clinical syndromes known as **porphyrias**

General informations II

- **Inherited** - **acquired** (rarely)
- Often **AD inheritance**, some AR inheritance (CEP)
- Usually onset in **adulthood**
- Common manifestation only **after exposure** (fasting, menses, drugs, sunlight)

Classifications

- **Clinically classified** into:
  - those predominantly **involving the skin**
  - those manifesting as **disorders of the liver/nervous system** (neurovisceral)
  - combination involving **all three entities**

- **Classification-site of enzyme defect** (location of accumulation):
  - Hepatic
  - Erytropoetic
  - Erythrohepatic

Presentations

- **acute presentations** (acute intermittent, variegate, hereditary coproporphyria)
- **chronic, relatively stable presentation** (congenital, erythropoietic)

Derangements in porphyrin metabolism:

Disease state	Genetics	Tissue	Organ pathology
Acute intermittent porphyria	**dominant**	**Liver**	**Nervous system**
Hereditary coproporphyria	dominant	Liver	Nervous system, skin
Variegate porphyria	dominant	Liver	Nervous system, skin
Porphyria cutanea tarda	**dominant**	**Liver**	**Skin, induced by liver dis.**
Erythropoietic protoporphyria	dominant	Marrow	Gall stones, liver dis., skin
Congenital erythropoietic porphyria	recessive	Marrow	Skin, RES
Lead poisoning		All tissues	Nervous system, blood, others

History

- **Abdominal pain (**lasts hours to days)
  - the most common presenting symptom (90%) of an acute porphyria
  - colicky, located in the left lower abdomen but also nonlocalised
  - nausea and vomiting, obstipation
- **Muscle weakness and neurologic deficits**
  - Focal neurologic deficits such as tetraparesis
  - Limb pain, headache
  - A motor, axon-predominant neuropathy
  - Rarely seizures
- **Psychiatric symptoms**

Physical Examination

- **Abdominal pain**
  - Usually in acute porphyrias
  - Peritoneal sign - typically absent
  - Jaundice may or may not be present
- **Motor and sensory deficits and peripheral neuropathy** (neurology examination)
- **Skin rash , blistering lesions on sun-exposed skin**

Laboratory

- **Plasma:** ↑Fe, ↑cholesterol, ↓K, ↓Mg
- **Hypovolemia**
- **The urine**
  - ALA (↑↑), PBG (↑↑), porphyrines (↑)
  - Color - red to brown in natural light (red-wine urine - **patients with porphyria cutanea tarda**

Acute intermittent porphyria

- AD
- 20-40 years, > 2:1
- **Acute crisis** – triggers include drugs, hunger, stress, menstruation, hormones, …
- **Presentation:**
  - **Intensive abdomen pain** without peritoneal signs
  - **Acute peripheral neuropathy, encephalophathy** (with seizures)
  - **Psychiatric symptoms** – agitation, psychosis
- Between crisis – asymptomatic
- **Dg** – porphyrins, porphobilinogen, ALA in urine

Therapy

- **GOAL** - decrease heme synthesis and reduce the production of porphyrin precursors
- **Hematin** i.v. – in severe attacks
- **High doses of glucose** - in mild attacks
- **Symptomatic therapy:**
  - **Pain control** – narcotics (buprenorfin)
  - **Control tachycardia, prevent arrhythmia, treatment of hypertensive crisis** (beta-blockers, clonidine, or other recommended antihypertensives)
  - **Nausea and vomiting -** olanzapine, lorazepam, prochlorperazine
  - **Seizures** - gabapentin
    - CAVE - most classic antiseizure medicines can lead to acute porphyria attacks.

Porphyria cutanea tarda

- **AD**; **the most common porphyria**
- **Presentation:**
  - typical skin manifestations - skin fragility, erosions, vesicles, bullae, and milia in sun-exposed areas of the skin
  - No neurological symptoms
- **Risk factors** – alcohol, estrogens, hemochromatosis gene (HFE) mutations and the hepatitis C virus (HCV) **Therapy:**
  - **Avoidance of sunlight**
  - **Phlebotomy**
  - Chlorochine (depletion of porphyrines from liver) - rarely used now - adverse hepatic effects