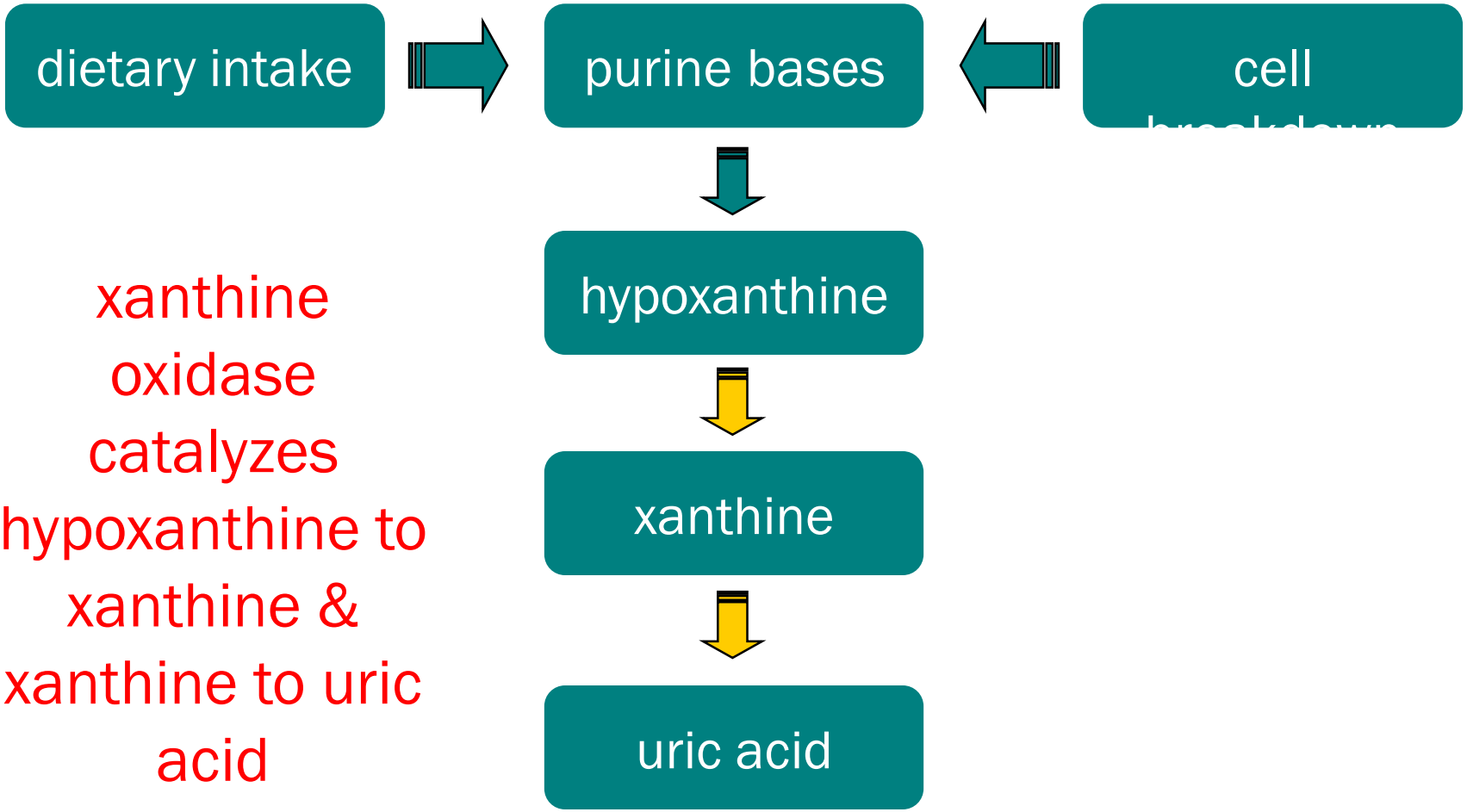
GOUT

- 55 y/o male
- 12 hours “pain in my big toe & ankle”
- went to bed last night feeling fine
- felt as if had broken toe this morning
- similar problems in right ankle & left wrist

Case presentation

- lab studies
  - serum uric acid = 11.5 mg/dl
  - 24-hour uric acid excretion = 300 mg
- left foot X-rays show bony erosion with overhanging edge, medial side of first metatarsal head

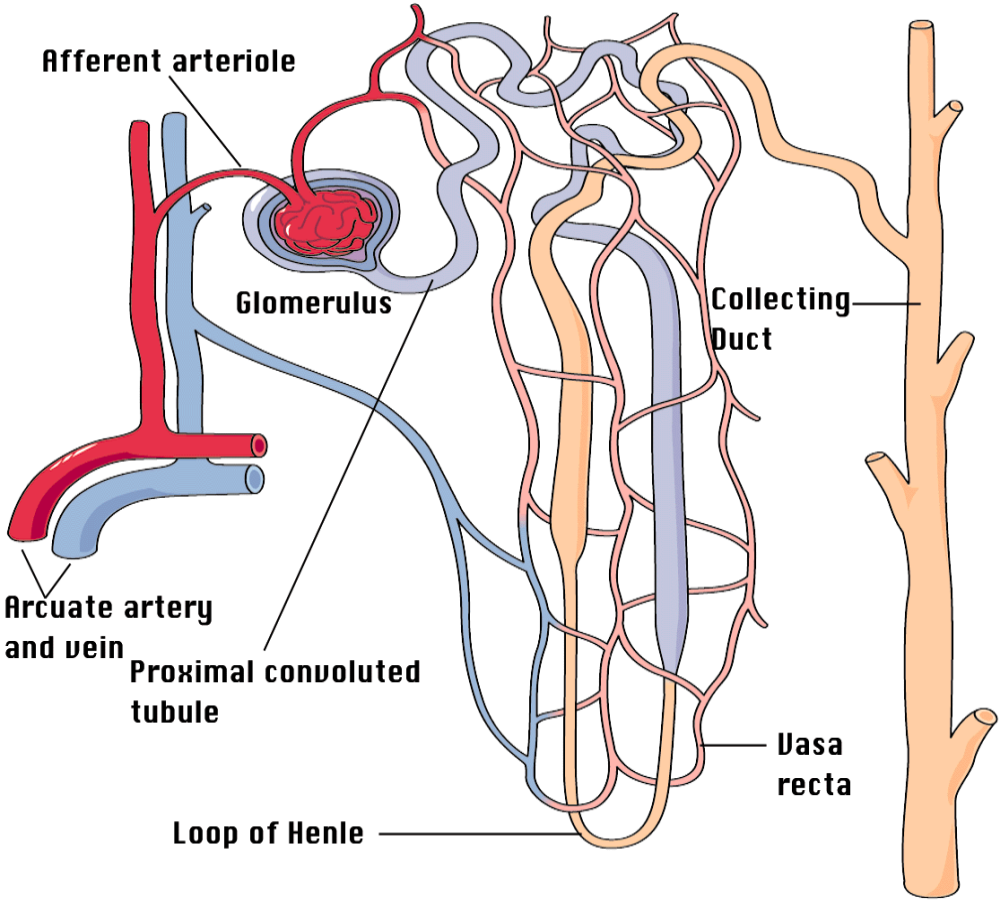
Uric acid metabolism



xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

Renal handling of uric acid

- glomerular filtration ⇩
- tubular reabsorption ⇧
- tubular excretion ⇩
- post-secretory reabsorption ⇧
- net excretion

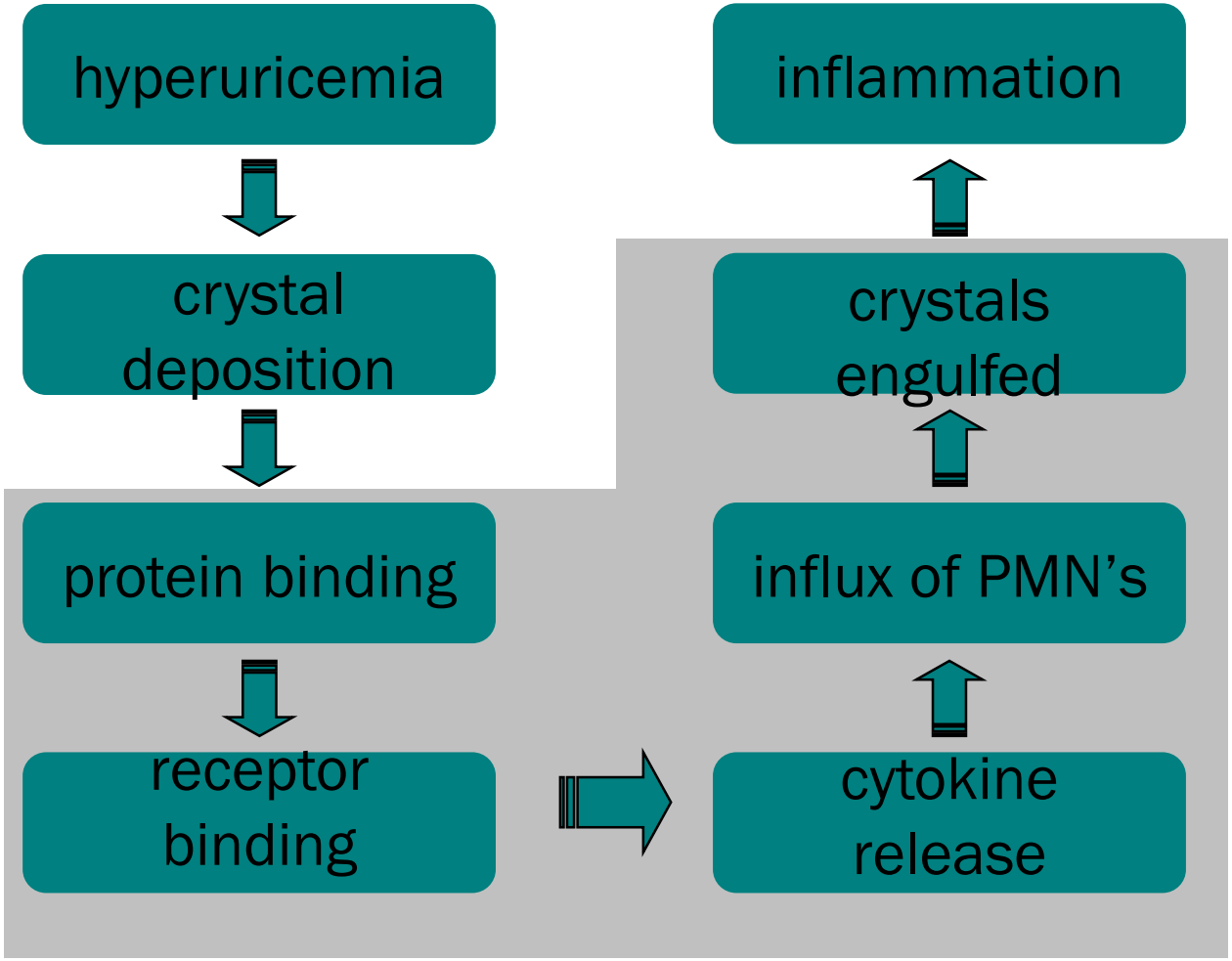


Classifying hyperuricemia

- serum uric acid level
- urine uric acid excretion (24-hour)

	overproduction	underexcretion
serum uric acid	high	high
urine uric acid	high	normal/low

Crystal-induced inflammation



PMN is critical component of crystal-induced inflammation

Drugs used to treat gout

Acute Arthritis Drugs

- colchicine
- steroids
- NSAID's

Urate Lowering Drugs

- allopurinol
- probenecid
- **Urate oxidase**

Urate Lowering Drugs

- prevents arthritis, tophi & stones by lowering total body pool of uric acid
- not indicated after first attack
- initiation of therapy can worsen or bring on acute gouty arthritis
- no role to play in managing acute gout

Colchicine - plant alkaloid

colchicum autumnale

(autumn crocus or meadow saffron)

Colchicine

- mechanism of action poorly understood???

inhibits microtubule depolymerization by binding to tubulin, one of the main constituents of microtubules

- reduces inflammatory response to deposited crystals
- diminishes PMN phagocytosis of crystals
- blocks cellular response to deposited crystals

Colchicine adverse effect

- Typical side effects of moderate doses may include gastrointestinal upset, diarrhea, and neutropenia.
- High doses can also damage bone marrow, lead to anemia, and cause hair loss. All of these side effects can result from inhibition of mitosis, which may include neuromuscular toxicity and rhabdomyolysis

adverse effects dose-related & more common when patient has renal or hepatic disease

Colchicine

- is an alternative for those unable to tolerate NSAIDs in gout.

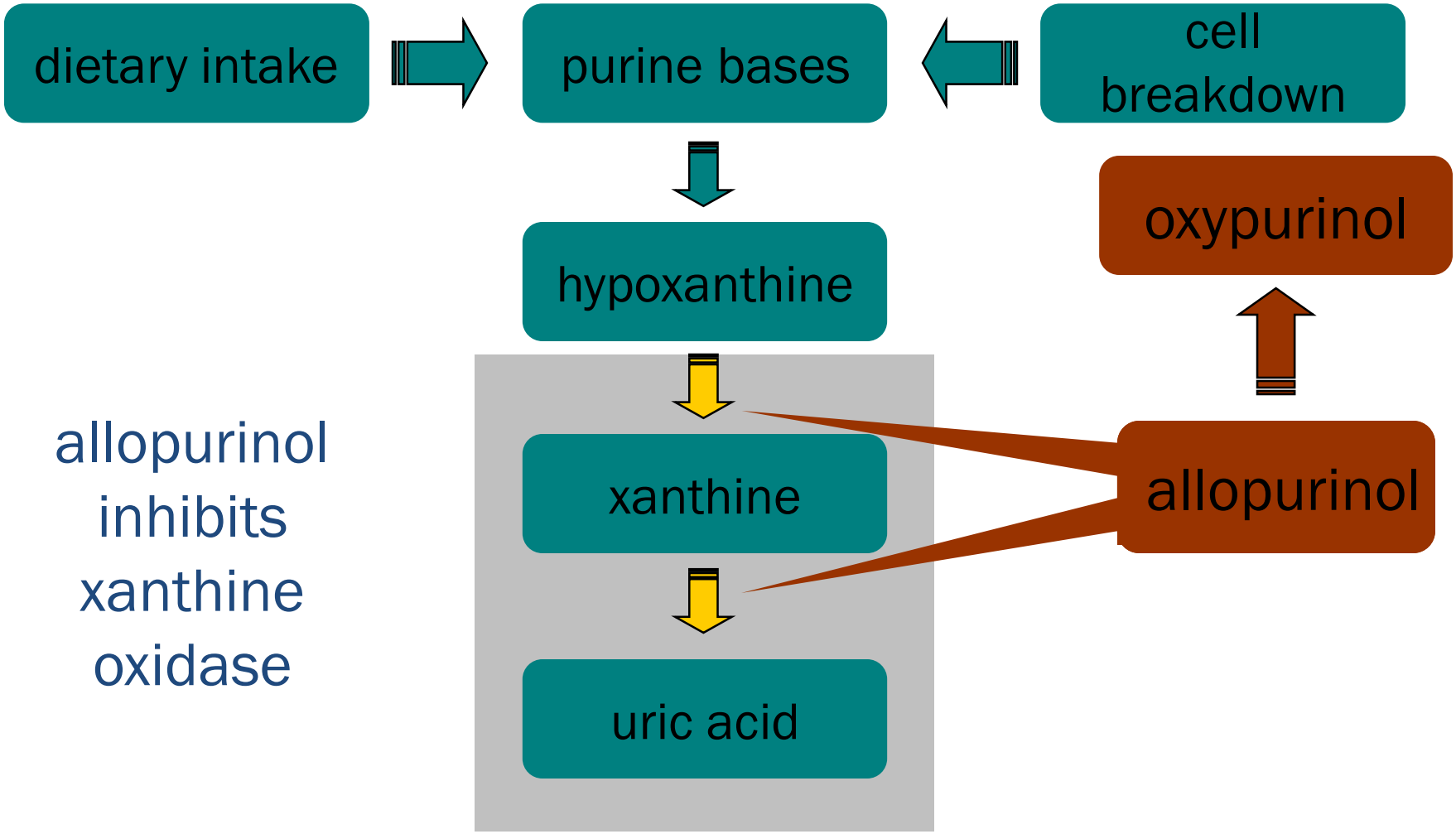
- more useful for daily prophylaxis (low dose)
  - prevents recurrent attacks
  - colchicine 0.6 mg qd - bid

- declining use in acute gout (high dose)

Allopurinol and Febuxostat

- Inhibitors of xanthine oxidase
- effectively blocks formation of uric acid

Uric acid metabolism



Allopurinol effects

Effect of Allopurinol on Total Serum Levels of Xanthine + Hypoxanthine

Normal	0.15 mg/dl
Allopurinol	0.35 mg/dl

saturation level of xanthine & hypoxanthine > 7 mg/dl

Allopurinol

- once daily dosing
- lowers serum uric acid levels
- lowers urine uric acid levels
- side effects rare,

diarrhea, nausea, abnormal liver tests

rash

Allopurinol and Febuxostat

- Are relatively contraindicated with concomitant use of theophylline and chemotherapeutic agents, namely azathioprine and 6-mercaptopurine, because it could increase blood plasma concentrations of these drugs, and therefore their toxicity.

Allopurinol – black box warning

THIS IS NOT AN INNOCUOUS DRUG. IT IS NOT RECOMMENDED FOR THE TREATMENT OF ASYMPTOMATIC HYPERURICEMIA

ALLOPURINOL SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS OF AN ALLERGIC REACTION

Urate oxidase

- uricase speeds resolution of tophi
- **Rasburicase** acute hyperuricemia in patients receiving chemotherapy.

- A PEGylated form of urate oxidase, **egloticase**, was FDA approved in 2010 for the treatment of chronic gout in adult patients refractory to "conventional therapy"

Uricosuric therapy probenecid

- blocks tubular reabsorption of uric acid
- enhances urine uric acid excretion
- increases urine uric acid level
- decreases serum uric acid level

probenecid

- moderately effective
- increases risk of nephrolithiasis
- not used in patients with renal disease
- frequent, but mild, side effects
- some drugs reduce efficacy (e.g., aspirin)

Renal handling of uric acid

- glomerular filtration ↓
- tubular reabsorption ↑
- tubular excretion ↓
- post-secretory reabsorption ↑
- excretion