INFLAMMATORY ARTHROPATHIES, OR INFLAMMATORY RHEUMATIC DISEASES

- Chronic inflammatory arthropathies
  - Rheumatoid arthritis
  - Spondyloarthropathies
  - Other multi-system rheumatic diseases: Systemic lupus erythematosus, Scleroderma, Vasculitis, and others
- Chronic joint infections

INFLAMMATORY ARTHROPATHIES

- Acute
  - Septic arthritis. Infection of joints with pyogenic bacteria
  - Crystal-induced arthropathies
    - Gout
    - Pseudogout
  - Joint hemorrhage, or apoplexy
    - Secondary to trauma; hereditary or acquired coagulopathy
  - Acute flare of a chronic arthropathy

Diagnosis of arthropathies

- History – Pain, swelling, dysfunction
  - Distribution
    - Monoarthritis, polyarthritis, symmetry
  - Duration and severity
    - Acute or chronic
- Physical examination
  - Swelling, tenderness, limitation of motion, deformities
  - Severity of abnormalities

Diagnosis of arthropathies

- Radiographic imaging
- Joint aspiration
  - Inflammatory arthropathies are usually associated with increases in joint fluid, or effusions.
  - Analysis of joint (synovial) fluid may reveal increased numbers of inflammatory cells, bacteria, crystals, hemorrhage

ORGANISMS IN SEPTIC ARTHRITIS

	Adults (%)	Children (%)
Gram Positive Cocci	35	27
S. aureus	10	16
S. pyogenes, S. pneumoniae, S. viridans Group		
Gram Negative Cocci		
N. gonorrhoeae and *meningitidis*	50	8
H. influenzae	< 1	40
Gram Negative Bacilli		
E. coli, Salmonella and *Pseudomonas species*	5	9
Mycobacteria and Fungi	< 1	< 1

Figure by MIT OCW.

Damage due to septic arthritis of the wrist on the right side of the picture.

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Gout

- A crystal-induced arthritis
- The pathogenesis of the disease is due to the supersaturation of the extracellular fluids with respect to monosodium urate
- These crystals induce acute inflammation following their ingestion by neutrophils
- Chronic inflammation also leads to tissue destruction around deposits on sodium urate crystals (tophi)

Gout: Clinical course

- Acute attacks
  - Acute monoarthritis, sometimes oligoarticular, subsiding after 1-2 weeks if untreated, or sooner if treated
  - Recurrent acute attacks with intervals of weeks to months, if no prophylactic treatment
  - Eventually, more frequent attacks becoming continuous with tissue destruction

At physiologic pH, uric acid is in the monoanion form. Monosodium urate precipitates when the total urate concentration exceeds 6.5 mg/100ml

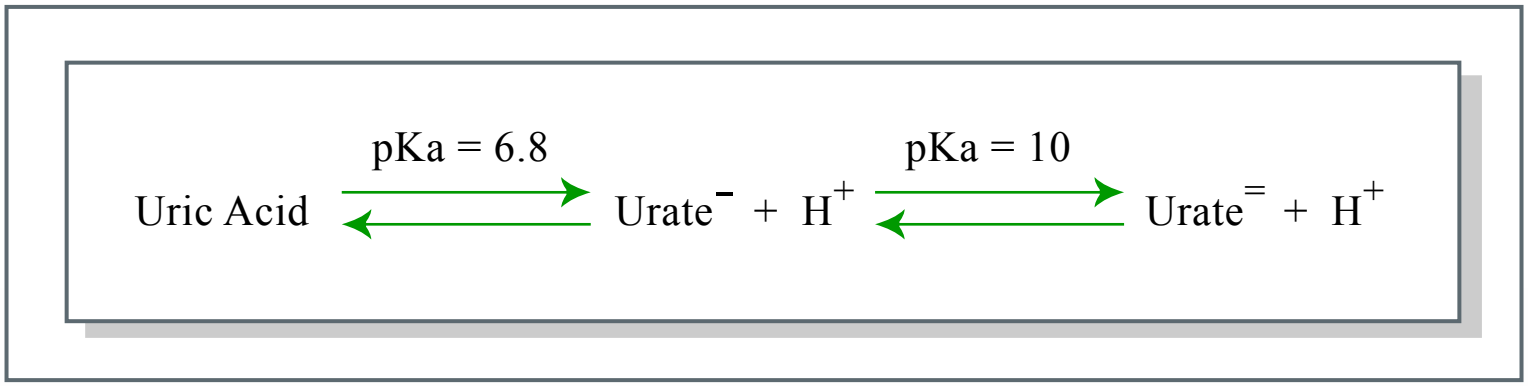


Figure by MIT OCW.

PREVALENCE OF GOUTY ARTHRITIS BY HIGHEST SERUM URATE VALUE[#]

Men			
Serum Sodium Urate Level (mg/100 ml)	**Total No. Examined**	**Gouty Arthritis Developed in**	
		No.	%
< 6	1281	11	0.9
6-6.9	970	27	2.8
7-7.9	162	28	17.3
8-8.9	40	11	27.5
> 9	10	9	90.0
Total	**2463**	**86**	**3.5**

[#]Framingham heart study.

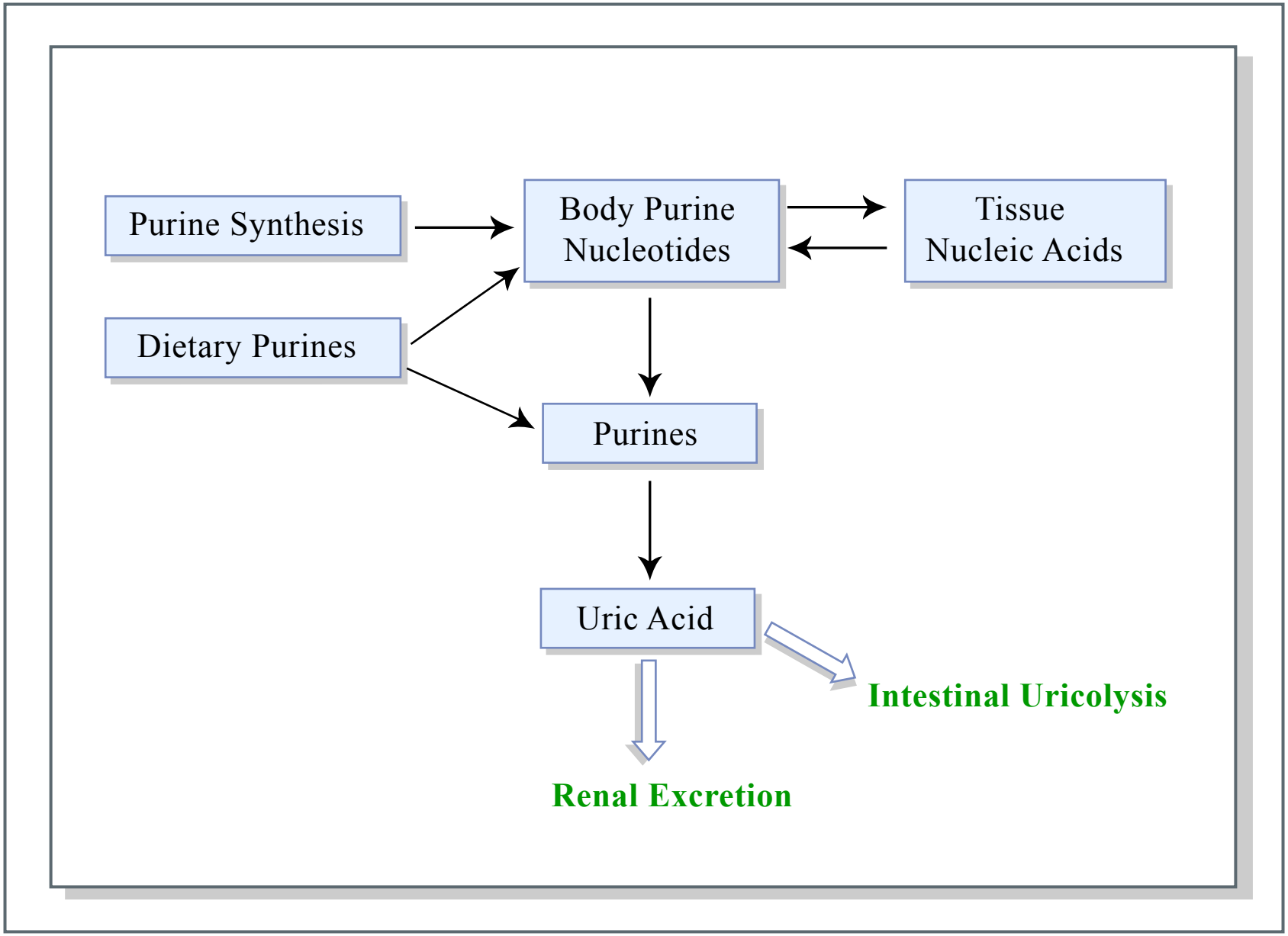


Figure by MIT OCW.

Hyperuricemia usually occurs because of relatively inefficient renal excretion

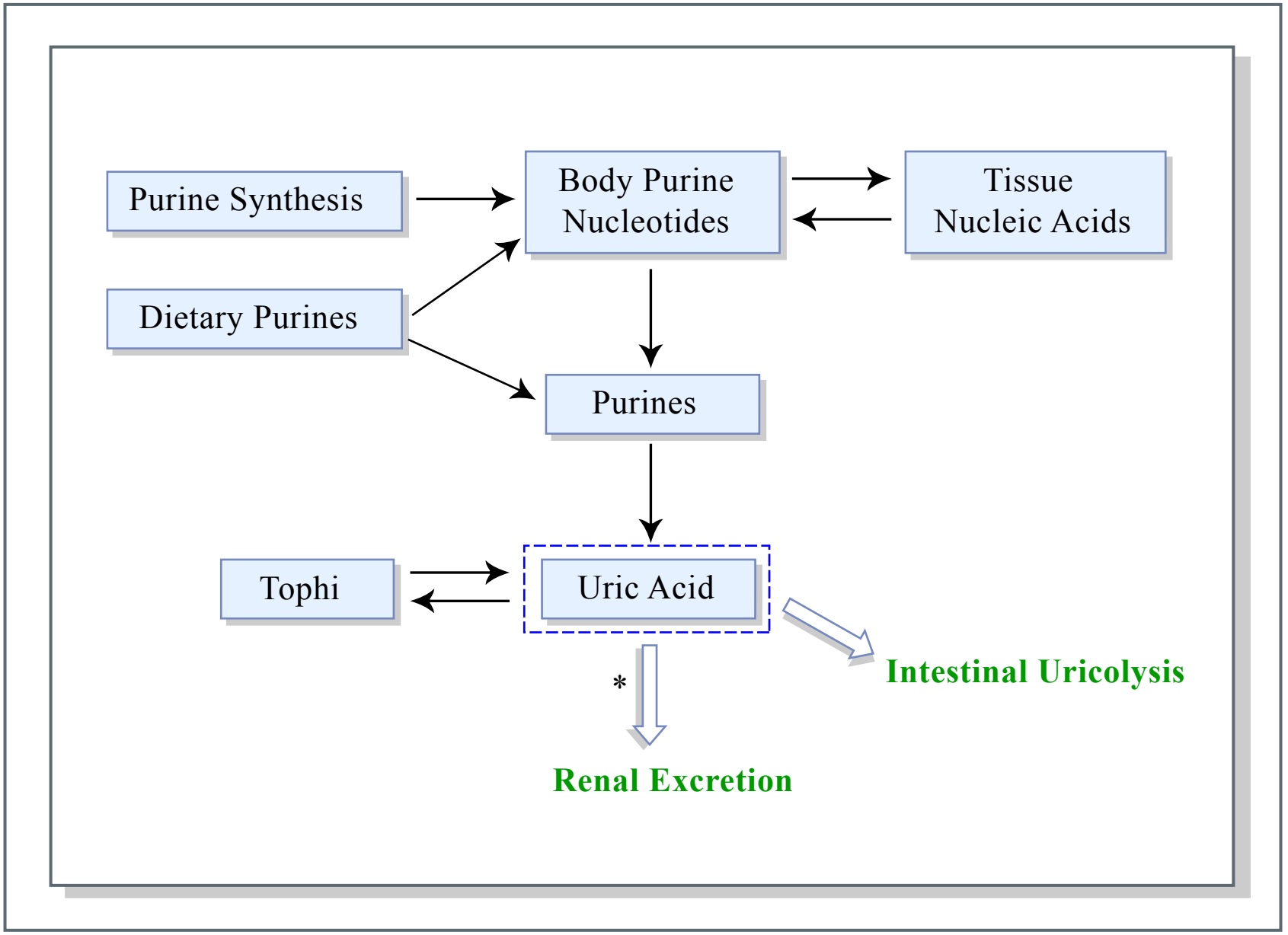
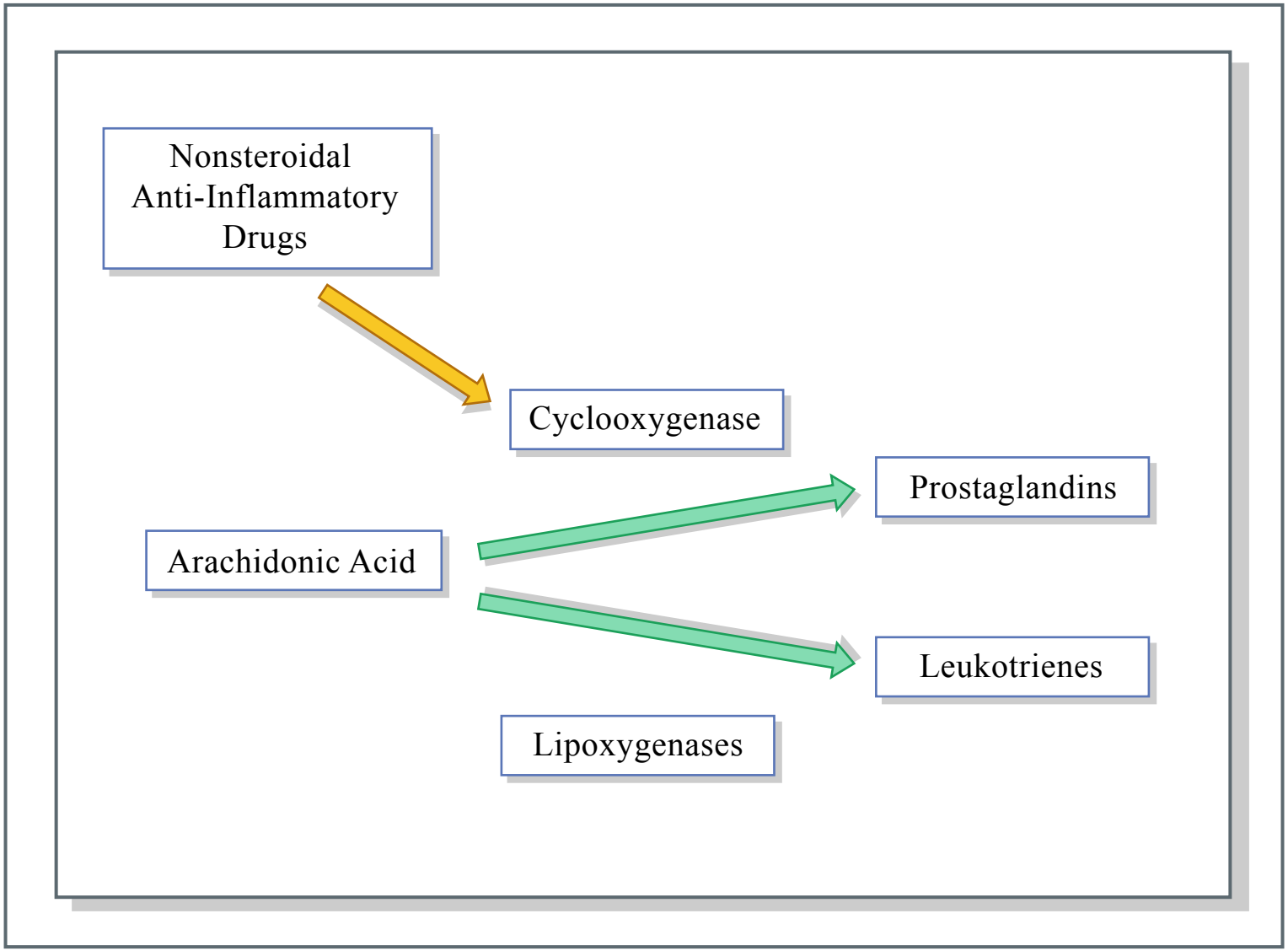


Figure by MIT OCW.

Treatment of acute gouty arthritis

- Nonsteroidal anti-inflammatory drugs
  - Cyclooxygenase inhibitors
- Colchicine
  - Inhibits microtubule function, and the phagocytosis of crystals
- Glucocorticoids
  - Multiple anti-inflammatory effects



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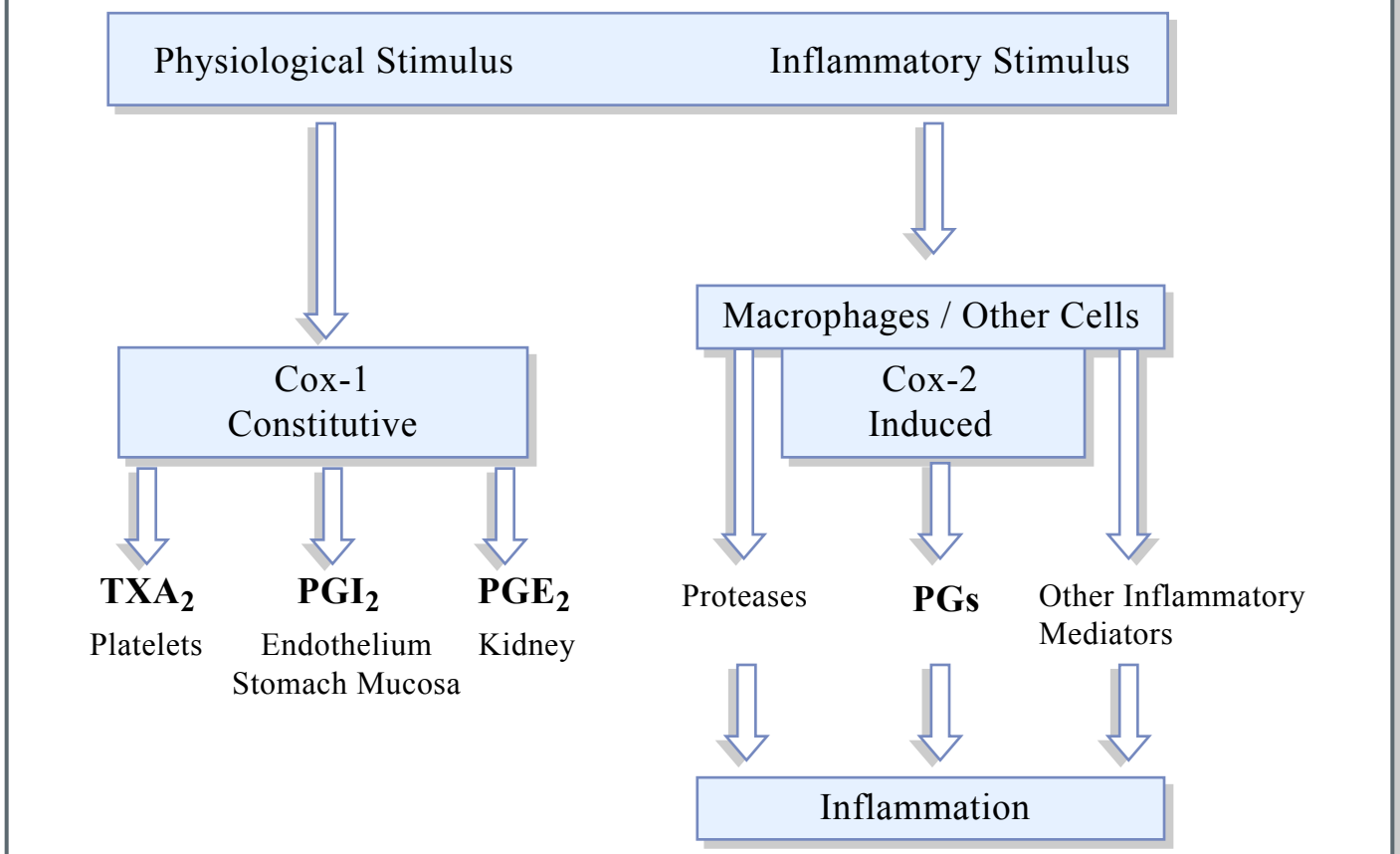
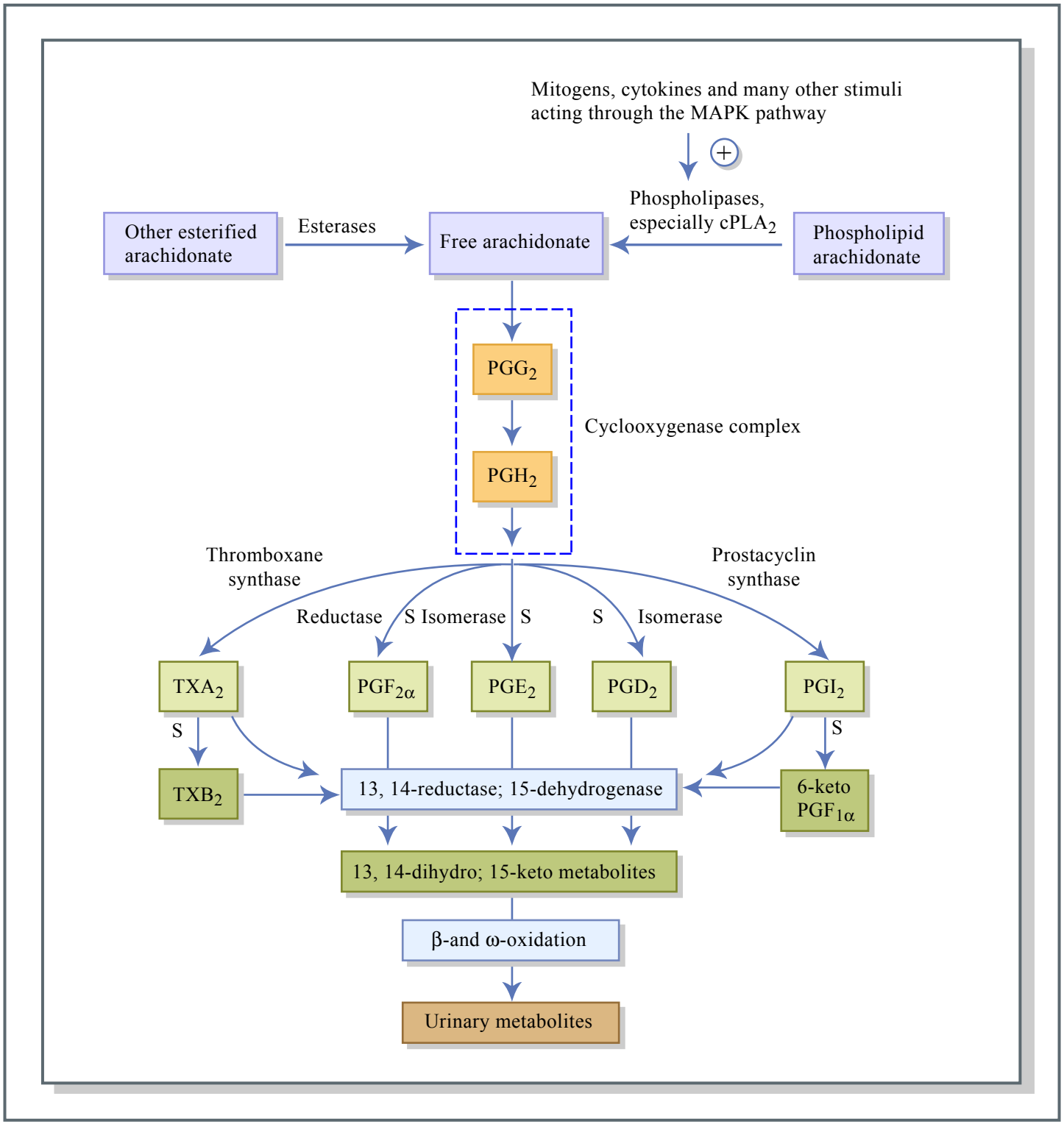


Relationship Between Pathways Leading to Generation of Prostaglandins by COX-1 or COX-2

Figure by MIT OCW.



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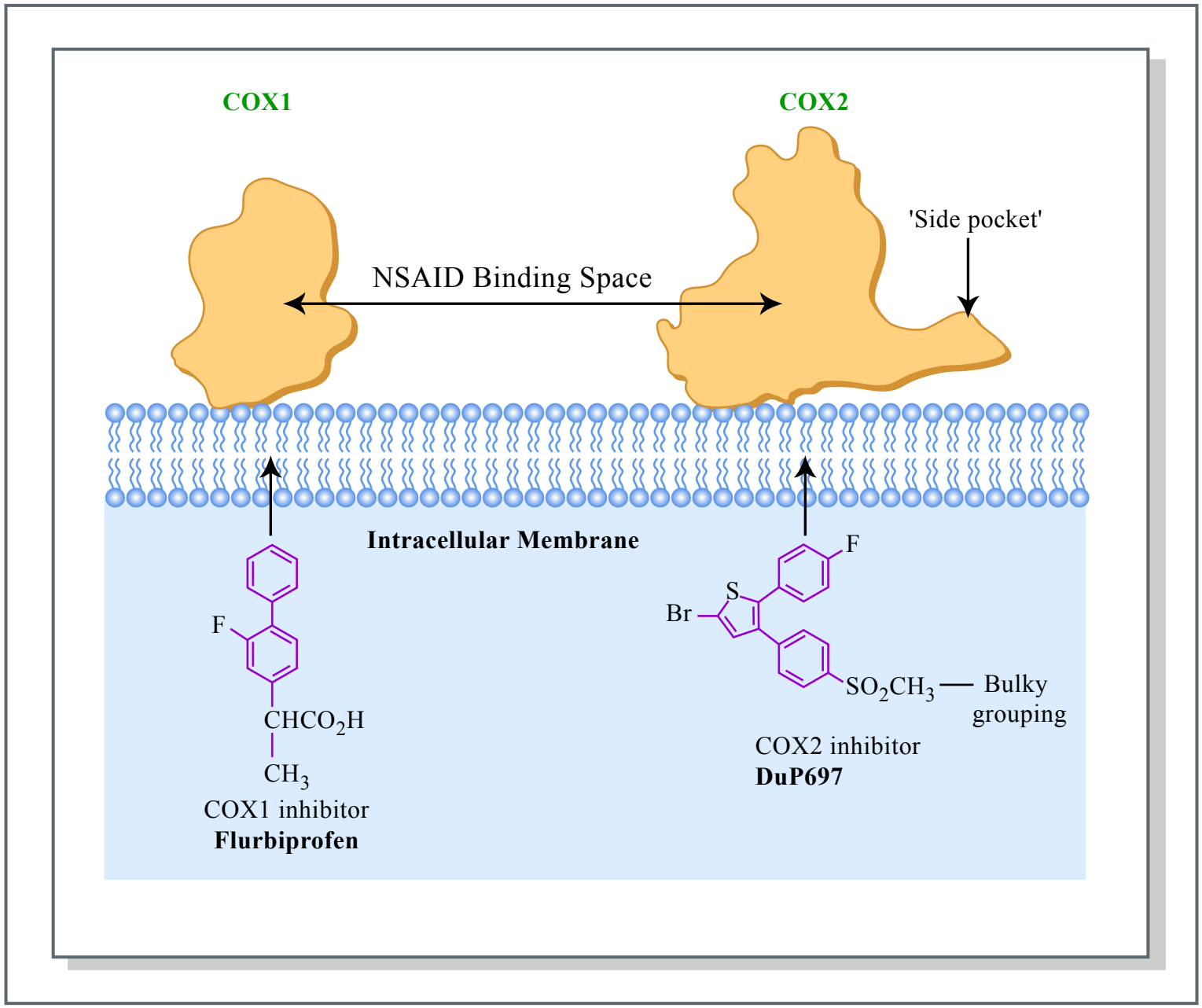


Figure by MIT OCW.

Nonsteroidal anti-inflammatory drugs

- Non selective
  - Ibuprofen
  - Naproxen
  - Indomethacin
  - Diclofenac
  - Nabumetone
  - Etidolac
- Selective for Cox-2
  - Coxibs
    - Celecoxib
    - Rofecoxib
    - Valdecoxib

    - Rofecoxib and Valdecoxib have been withdrawn from the market because of cardiovascular toxicity

Complications of selective Cox 2 inhibitors

- As predicted, selective Cox 2 inhibitors are less ulcerogenic that the non-selective drugs
- However, there may be vascular toxicity of the selective inhibitors

Vascular complications of selective Cox 2 inhibitors

- Blood platelets only have Cox 1, and their major eicosanoid product is thromboxane A2, a potent vasoconstrictor, and platelet aggregator
- Vascular tissues contain Cox 2, and a major eicosanoid product is prostacyclin, a vasodilator and an inhibitor of platelet aggregation

Vascular complications of selective Cox 2 inhibitors

- Clinical trials comparing selective Cox 2 inhibitors (coxibs) to non-selective inhibitors or placebo have shown that coxibs are associated with a small but statistically significant increased incidence of myocardial infarction and strokes

Prophylactic treatment of gout

- Aim is to reduce the levels of urate below the solubility of Na urate
  - Probenecid. Enhances the excretion of uric acid by the kidney
    - May also increase the likelihood of uric acid renal stones
    - Requires good renal function
  - Allopurinol. A xanthine oxidase inhibitor
    - Replaces some uric acid with xanthine and hypoxanthine, both more soluble than uric acid

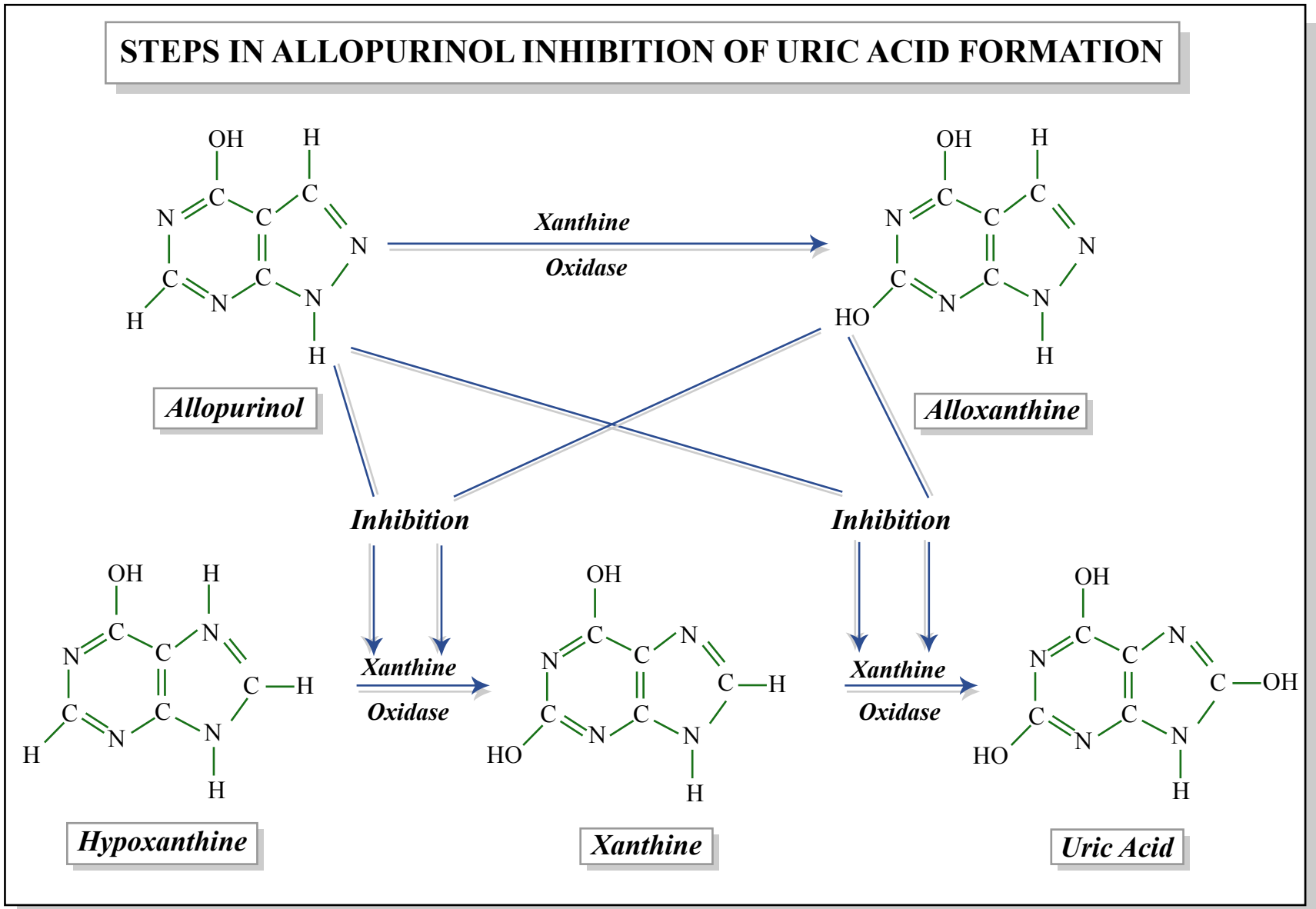


Figure by MIT OCW.

Pseudogout

- Acute arthritis caused by the deposition of calcium pyrophosphate dihydrate
- May be associated with osteoarthritis
- Treatment of acute attacks with nonsteroidal anti-inflammatory drugs or glucocorticoids
- No prophylactic therapy available

Pseudogout

- Diagnosis
  - Chondrocalcinosis on radiographs
  - Calcium pyrophosphate dihydrate crystals demonstrable on ultraviolet light microscopy
  - CPPD crystals differentiated from monosodium urate by:
    - Rhomboid shape
    - Positive sign of birefringence

SPONDYLOARTHROPATHIES

Ankylosing Spondylitis

Psoriatic Arthritis

Reiter's Syndrome

Reactive Arthritis

Enteropathic Arthritis

- **Regional Enteritis**
- **Ulcerative Colitis**

Juvenile Ankylosing Spondylitis

HLA-B27: DISEASE ASSOCIATIONS

DISEASE	ASSOCIATIONS
Ankylosing Spondylitis	>90%
Reiter's Syndrome	80%
Reactive Arthritis	85%
Inflammatory Bowel Disease	50%
Psoriatic Arthritis	
• With Spondylitis	50%
• With Peripheral Arthritis	15%
Whipple's Disease	30%

Figure by MIT OCW.

Prevalance of HLA B27 is highly variable among population groups

Canada; Haida Indians	50%
USA; Navajo	36%
Scandinavia; Caucasians	16%
USA; Whites	8%
Japan	<1%
China	2-9%
Africa; Blacks	0

Association of HLA B27 with ankylosing spondylitis

- The strongest association of any human disease with over 90% pos.
- Between 10-20% of persons with HLAB 27 have ankylosing spondylitis
- Less than 1% of persons without HLA B27 have ankyosing spondylitis
- HLA B27 pos monozygotic twins have 75% concordance for AS, and dizygotic twins only 25%, indicating that other genes are important as well.

The HLA B27 gene comprises over 20 alleles

- HLA B2705 is the most common and confers susceptibility to AS
- The alleles differ in a small number of amino acids, often in the peptide binding site formed by the α $\alpha\nu\delta$ β chains

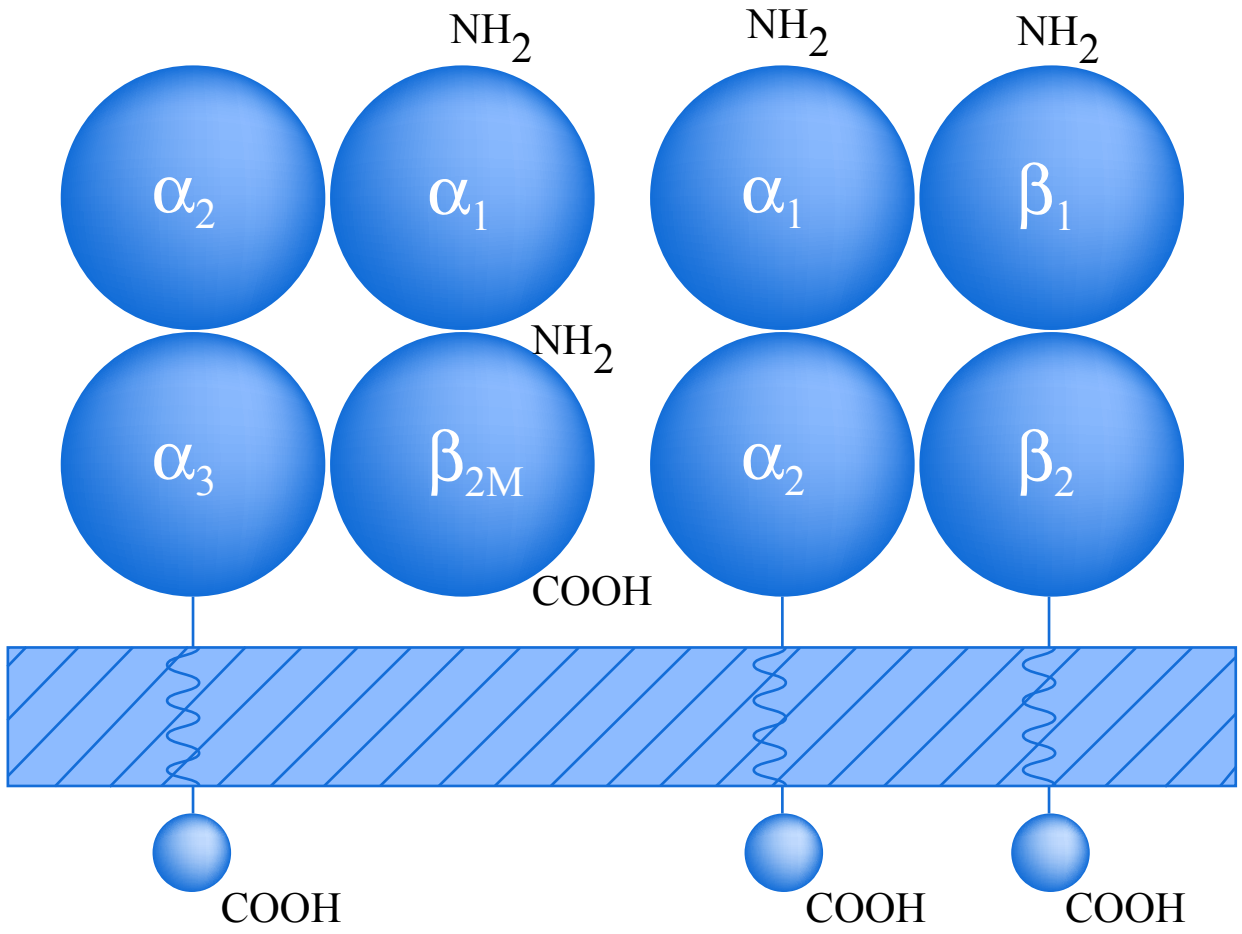
Not all B 27 alleles confer susceptibility to AS; no AS in these populations

- HLA B27 Allele

- West Africa
  - Gambia 6%
  - Mali
- Sardinia

- B 2703

- B2709



Domain structure of class I and class II MHC molecules.

Figure by MIT OCW.

Sacroiliitis in ankylosing spondylitis The SI joint margins are irregular due to inflammatory erosions

Figure removed due to copyright reasons.

Ankylosing spondylitis. The thoracic vertebrae show "squaring" (left), and there is ossification of the anterior spinal ligament in the lumbar spine (right)

Figure removed due to copyright reasons.

Ankylosing spondylitis. There is ossification of the lateral ligaments on this AP view of the lumbar spine. The calcific density, representing the ossification, is seen around the intervertebral discs.

Figure removed due to copyright reasons.

Ankylosing spondylitis: Gross path specimen of lumbar spine demonstrating ossification of the anterior spinal ligament

Figure removed due to copyright reasons.

Psoriatic arthritis

- A chronic, inflammatory arthropathy with pathology and many clinical features that are similar to rheumatoid arthritis.
- A spondyloarthropathy associated with psoriasis
- Treatment is similar to that of rheumatoid arthritis

Psoriatic arthritis: Note inflammatory changes in the DIP joints, left index “sausage finger”, onychodystrophy, and psoriasis of the skin.

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The role of infections in inflammatory arthritis

- 1. Septic arthritis: Usually implies pyogenic organisms infecting the joint. Chronic infections such as M. tuberculosis, fungi may also occur

- 2. Organisms with low grades of virulence, such as viral arthritis, B. burgdorferi

- 3. Organisms which may induce autoimmune reactions as occur in Reactive Arthritis. Rheumatic Fever is also an example of this mechanism

REVISED JONES CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC FEVER*

Major : Arthritis, Carditis, Chorea Erythema Marginatum, Nodules

Minor : Prior ARF or RHD, Arthralgias, Fever > 38°C, ESR > 120, + CRP, Leukocytosis, Prolonged PR Interval

Plus : Evidence of Recent Strep Infection:

Elevated ASO Titer, Antistreptococcal Antibodies, Group A Strep on Throat Culture Recent Scarlet Fever

**Diagnosis with 2 major or 1 major + 2 minor criteria and evidence of recent strep infection*

Figure by MIT OCW.

Rheumatic fever

- An autoimmune disease caused by immune reactions to components of the group A beta-hemolytic streptococcus
- Treatment of strep pharyngitis with antibiotics prevents subsequent rheumatic fever

Reactive Arthritis

- A chronic inflammatory disease affecting joints and other organs
- Formerly called Reiter's syndrome, it is now called Reactive Arthritis. This name is based on the occurrence of the disease following infections, usually enteric or genitourinary.

REITER'S SYNDROME

Seronegative Asymmetric Arthritis Following:

- **Urethritis or Cervicitis**
- **Infectious Diarrhea**

Often Associated With:

- **Inflammatory Eye Disease**
- **Balanitis, Oral Ulceration or Keratodermia**
- **Enthesopathy**
- **Sacroiliitis**

Skin disease in reactive arthritis: Keratodermia blennorragica

Figure removed due to copyright reasons.

Reactive Arthritis: enthesopathy
Note swelling at the achilles attachment (enthesis) on the left

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Transgenic human HLA B27 in rats

- HLA B27 and beta 2 microglobulin were transferred into Lewis rats
- The rats developed features similar to reactive arthritis in humans
- Conclusion: HLA B27 is a susceptibility factor

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MAJOR CLINICAL FEATURES OF LYME DISEASE

Stage 1: Early

Erythema Migrans

Flu-Like Syndrome

Malaise, Fever, Myalgia, Arthralgia, Headache, Stiff Neck

Figure by MIT OCW.

MAJOR CLINICAL FEATURES OF LYME DISEASE (Cont.)

Stage 2: Early Disseminated

- **Multiple or Recurrent Erythema Migrans**
- **Borrelia Lymphocytoma**
- **Migratory Arthralgia/Arthritis**
- **Meningoencephalitis**
- **Peripheral Neuropathy (Bell's Palsy)**
- **Carditis (Conduction Defects)**

Figure by MIT OCW.

MAJOR CLINICAL FEATURES OF LYME DISEASE (Cont.)

Stage 3: Late

Acrodermatitis Chronica Atrophicans

Intermittent/Chronic Oligoarthritis

Chronic Meningoencephalitis or Encephalitis

Sensorimotor Neuropathies

Figure by MIT OCW.

Inflammatory Rheumatic Diseases
Conclusions

- Acute and chronic inflammatory diseases involve the diarthrodial joints, the spine and other organ systems
- The etiology is known for gout and joint infections, but remains unknown for rheumatoid arthritis and spondyloarthropathies
- The facts that subtle infections (Lyme disease), and that rheumatic syndromes may follow known infections, suggests that infections could trigger other rheumatic syndromes whose etiologies are currently unknown.
- Associations of some rheumatic diseases with certain HLA antigens suggests that autoimmune mechanisms are operating