Treatment modalities

Prof Ally 2012

Analgesia

- Types of Pain

- Nociceptive /neuropathic

nociceptive

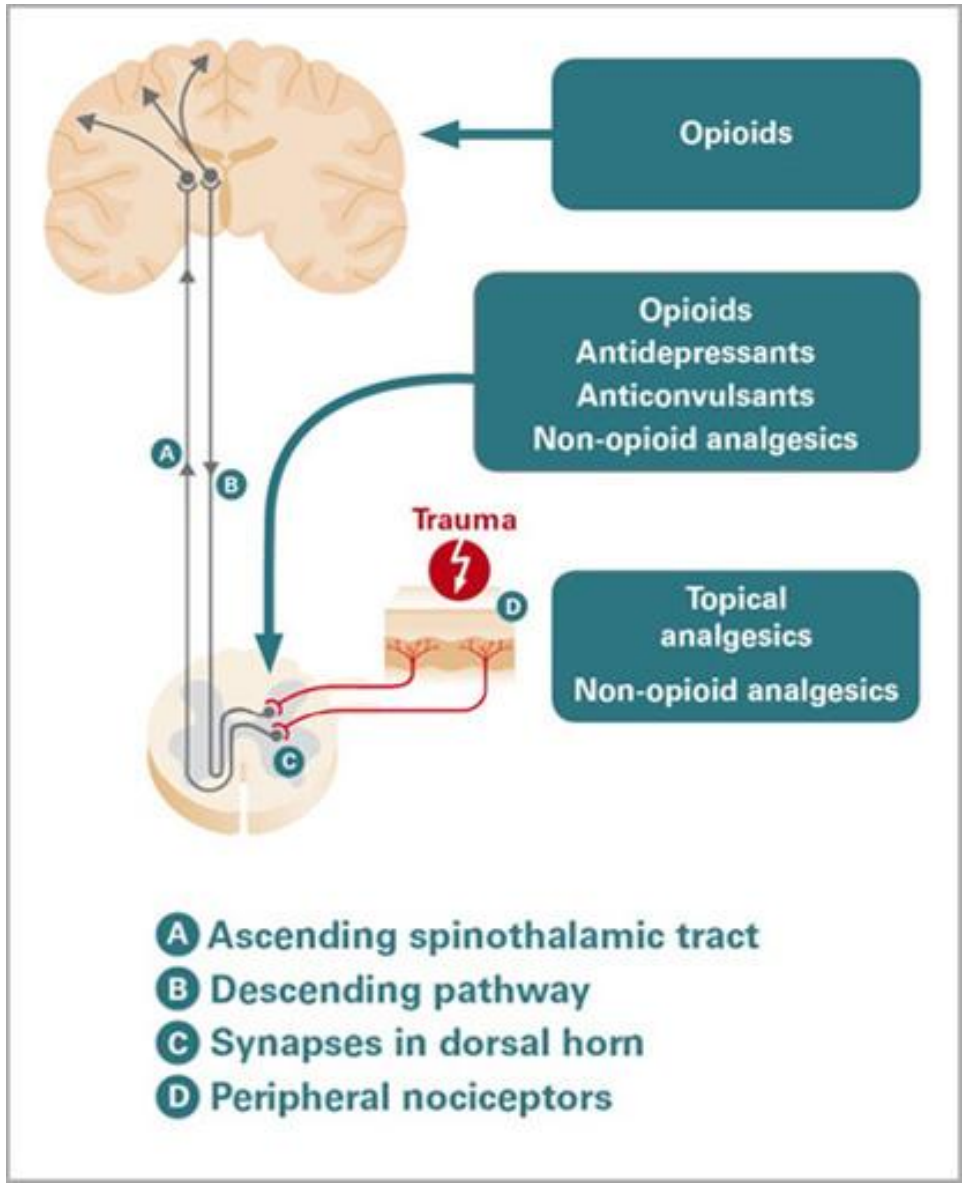
- Tissue damage -
- trauma, inflammation

Somatic (musculoskeletal):
- local pain
- referred pain

- Neuropathic pain: Damage to peripheral nerves –
- Stabbing, burning or shooting
- Often poor response

  to opioids

Tricyclics/anti-epileptics


Opioids
Opioids
Antidepressants
Anticonvulsants
Non-opioid analgesics
Trauma
Topical
analgesics
Non-opioid analgesics
A
B
C
D
A Ascending spinothalamic tract
B Descending pathway
C Synapses in dorsal horn
D Peripheral nociceptors

Paracetamol

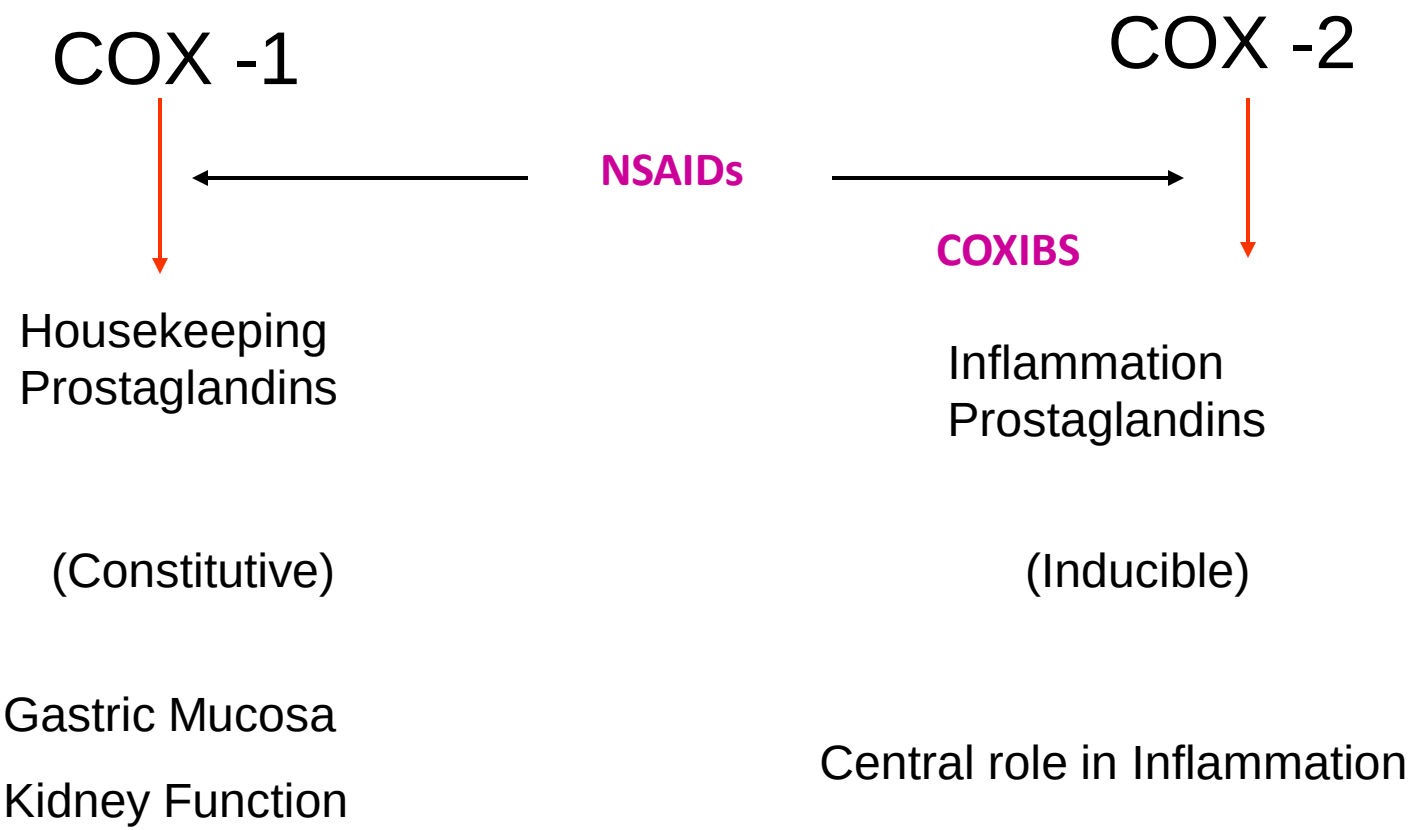
- Action: Inhibits cyclo-oxygenase centrally

- Rarely produces gastric irritation
- No inhibition of platelet function

- Can be given in combination .

- Up to 4 g per day if normal liver toxicity in high dose

The COXIB Solution: NSAID Mechanism
Arachidonic acid



What is the role corticosteroids

- Effective as ‘bridging’ therapy.
- Intra-articular injections are safe and effective.
- No role as oral monotherapy.
- Prednisone $\leq$ 10mg/d for joint disease.

Glucocorticoids

Disease-modifying effects of glucocorticoids in rheumatoid arthritis

- Significant reduction in radiographic progression when low-dose, glucocorticoids (conjunction with standard disease-modifying antirheumatic drugs such as methotrexate)

CORTICOSTEROID TOXICITIES

limit long-term use

duration of high-dose corticosteroids should not exceed 6–8 weeks

Adverse Effects of Glucocorticoid Therapy	
Metabolic	Central obesity, Glucose intolerance Hyperosmolar nonketotic coma
Endocrine	HPA-axis suppression Growth failure in children Menstrual irregularities
Musculoskeletal	Osteoporosis Aseptic necrosis of bone Myopathy
Cutaneous	Thin fragile skin , Purpura Striae Acne, Hirsutism Impaired wound healing
Ocular	Posterior subcapsular cataracts Glaucoma
Central nervous system	Psychiatric disorders Pseudotumor cerebri
Cardiovascular-renal	Sodium and water retention Hypokalemic alkalosis Hypertension
Gastrointestinal	Pancreatitis, Peptic ulcer Intestinal perforation
Impaired immune response	Bacterial, viral, fungal & parasitic

Using glucocorticoids differently

- Diurnal nature of symptoms and signs in RA -circadian variations

- Timing of glucocorticoid therapy - reduce the IL-6 surge in the night (natural cortisol levels are at their lowest).

- Timed-release formula that is taken at 10 p.m. and releases the active drug 4h later to mimic 2 a.m. dosing.

DMARDS

- Methotrexate
- Sulphasalazine
- Chloroquine
- Leflunamide
- biologicals

ANTIMALARIALS

Used

- hydroxychloroquine
- chloroquine

ANTIMALARIAL TOXICITIES

Gastrointestinal intolerance

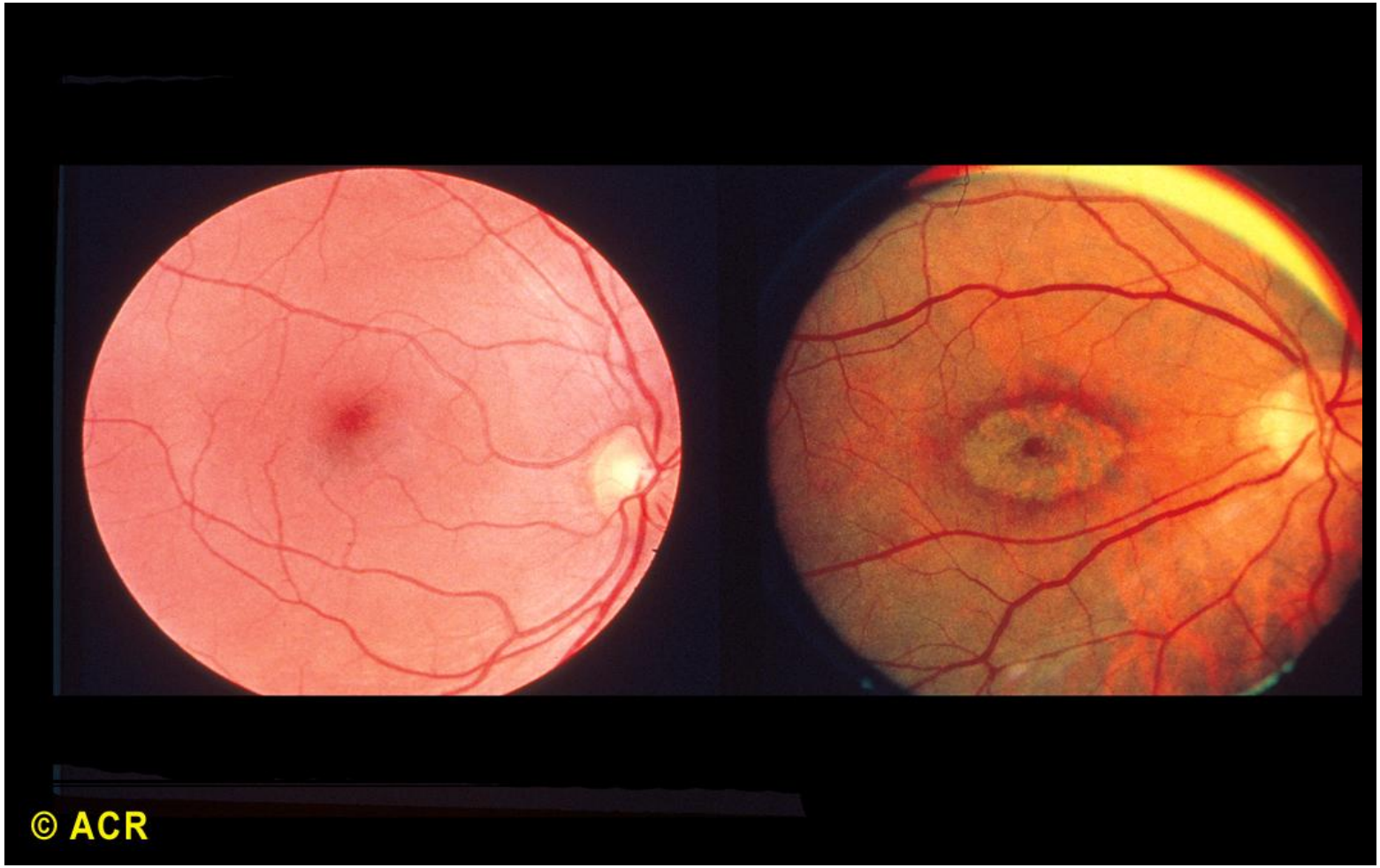
Cutaneous eruptions

Central nervous system toxicities

headaches, emotional changes, psychosis, ataxia, and seizures

discontinued in patients with suspected neuropsychiatric manifestations of lupus

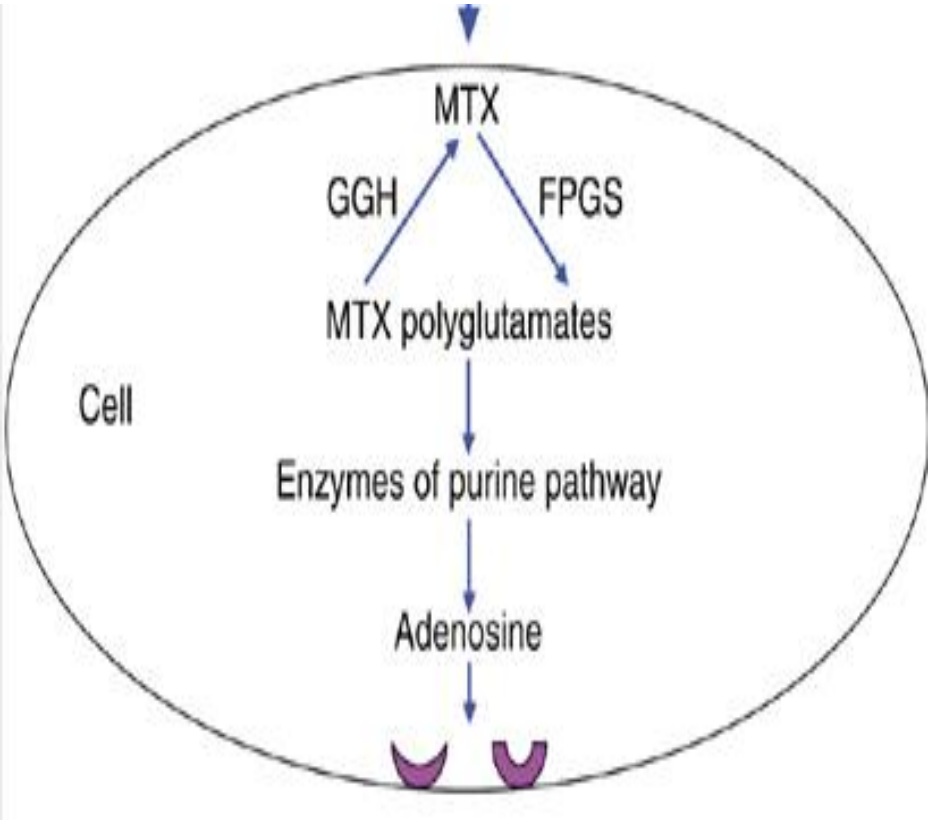
OCULAR TOXICITIES



methotrexate

- Inhibits dihydrofolate reductase (purine synthesis)

- induces adenosine release → anti-inflammatory effects.



MTX

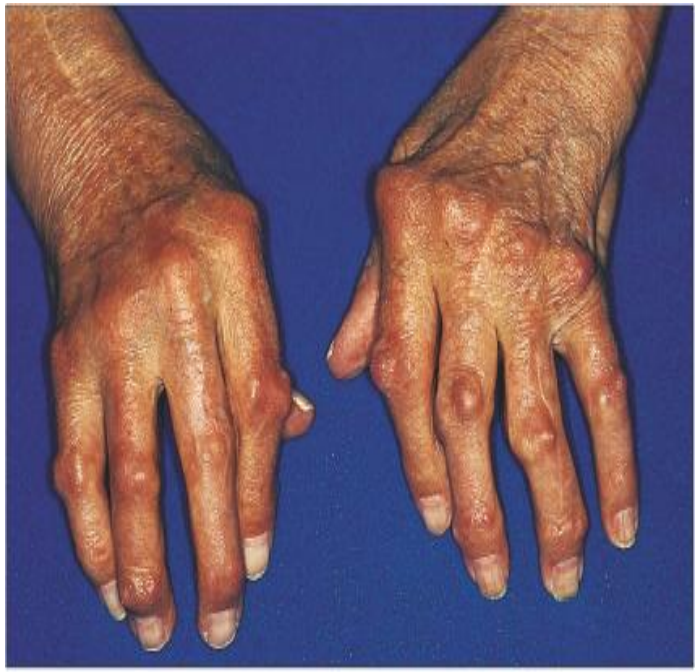
- Dosage escalation over 2-3 months up to 25 mg weekly(start 10-15mg)
- Approximately 4-6 weeks for response to start
- Doses should be administered in the evening to avoid nausea

MTX

- toxicity rather then lack of efficacy account for discontinuation
- administration of folic acid 5mg daily reduces side effects but does not diminish efficacy.
- doses ≥ 20mg may benefit form switching to subcutaneous route
- increased toxicity – renal dysfunction and in the elderly

Toxicity

- Nausea, diarrhoea, rashes, alopecia, mouth ulcers and stomatitis
- Marrow suppression
- Liver toxicity
- Pulmonary toxicity

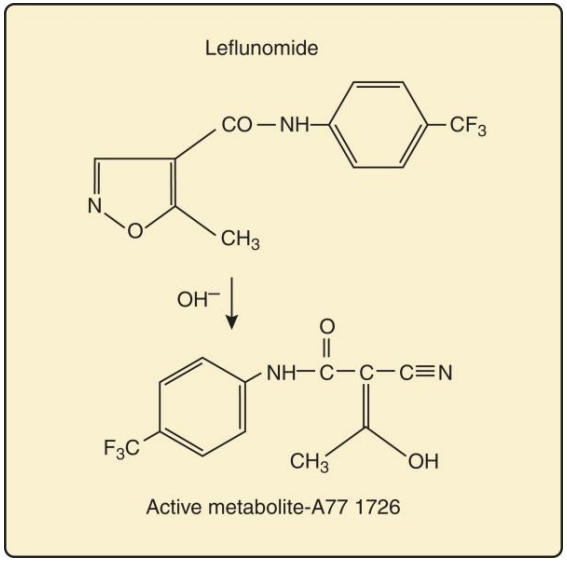


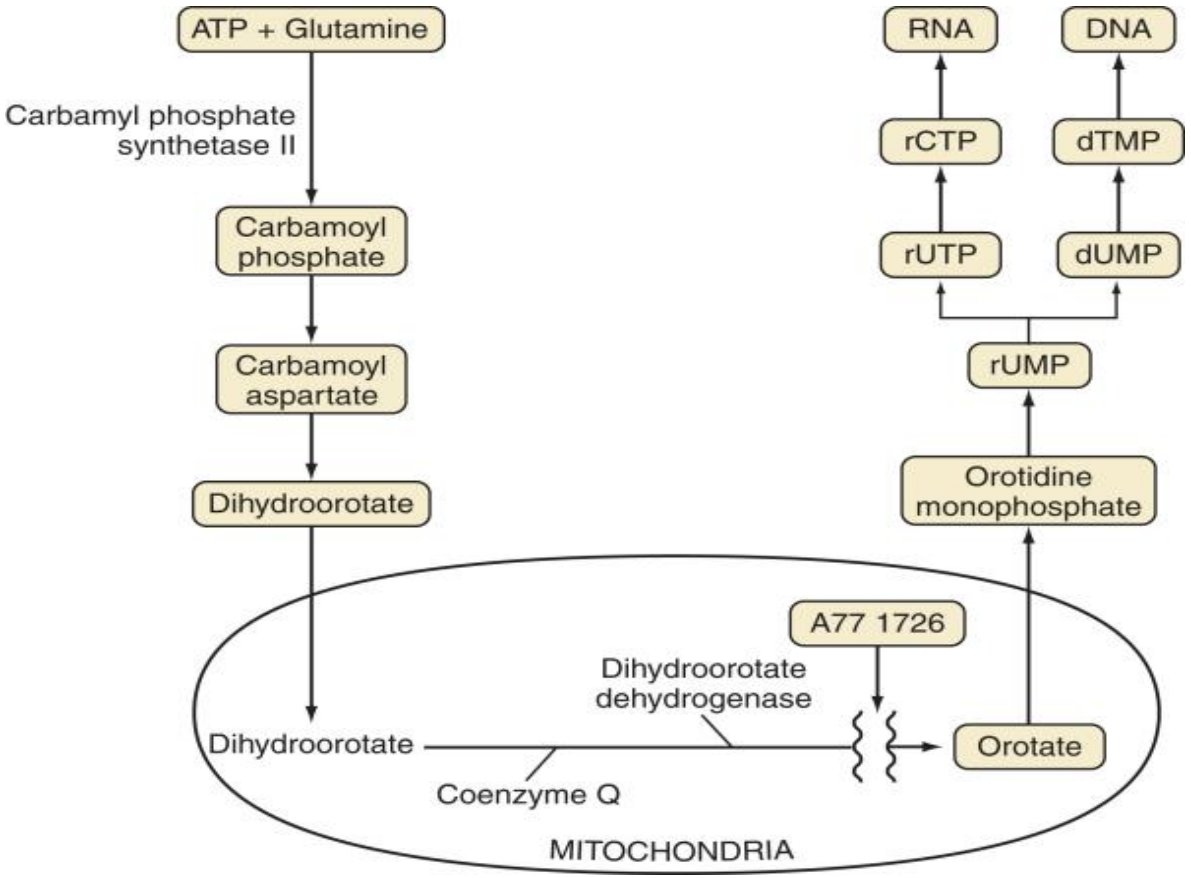
MTX

- Chest X-ray before start of therapy
- Routine monitoring - FBC and liver function assessments – AST, ALT.
- Blood tests must be done at baseline, then monthly for 3 months, and thereafter 4-12 weekly.

Leflunomide

- prodrug and is rapidly and completely converted to its active metabolite, malononitriloamide A77 1726

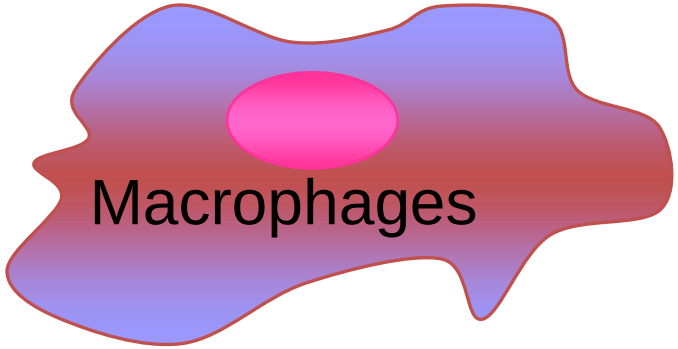



ATP + Glutamine
Carbamyl phosphate synthetase II
Carbamoyl phosphate
Carbamoyl aspartate
Dihydroorotate
RNA
DNA
rCTP
dTMP
rUTP
dUMP
rUMP
Orotidine monophosphate
A77 1726
Dihydroorotate dehydrogenase
Dihydroorotate
Orotate
Coenzyme Q
MITOCHONDRIA

Leflunomide

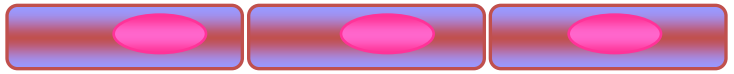
- a half-life of approximately 2 weeks
- enterohepatic recirculation
- may be present in the body months or years later
- cholestyramine
- 8 g three times daily, can reduce the apparent half-life of A77 1726 to 1 to 2 days

TNF: A Pivotal Cytokine in RA



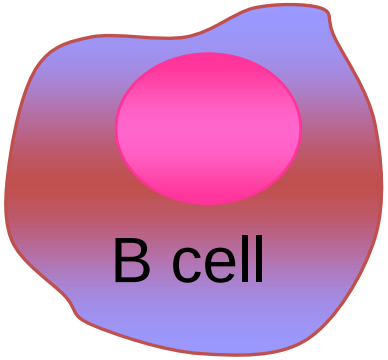
Increases proliferation and cytokine production

Endothelial Cells

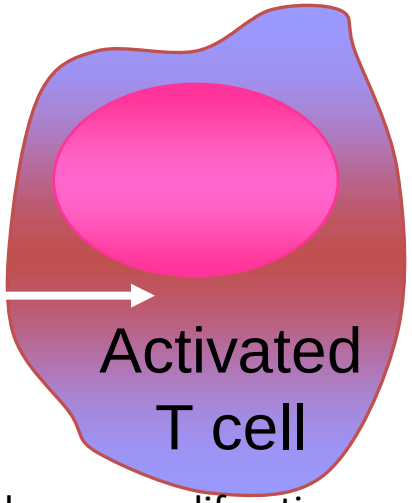


Expression of ICAM-1, VCAM-1, ELAM-1, IL-8

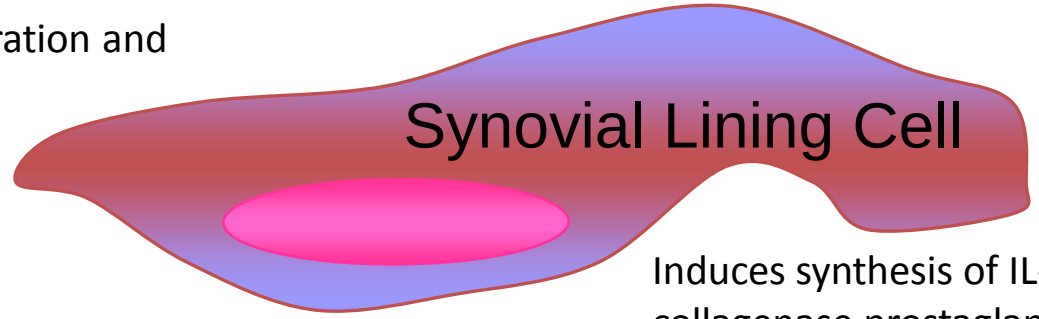
TNF



Increases proliferation and differentiation



Enhances proliferation, increases IL-2 receptor



Induces synthesis of IL-1, GM-CSF, Stromelysin, collagenase prostaglandins

From Harris Jr. ED: Rheumatoid Arthritis

Other immunosuppressive agents

Azathioprine

2-2,5mg/kg/day

widely used in the management of nonrenal lupus manifestations as a corticosteroid-sparing

CYCLOPHOSPHAMIDE (CF)

caution in patients with leukopenia

regular monitoring of WCC, HKT, PLT

WCC not below 2000 cells/mm3

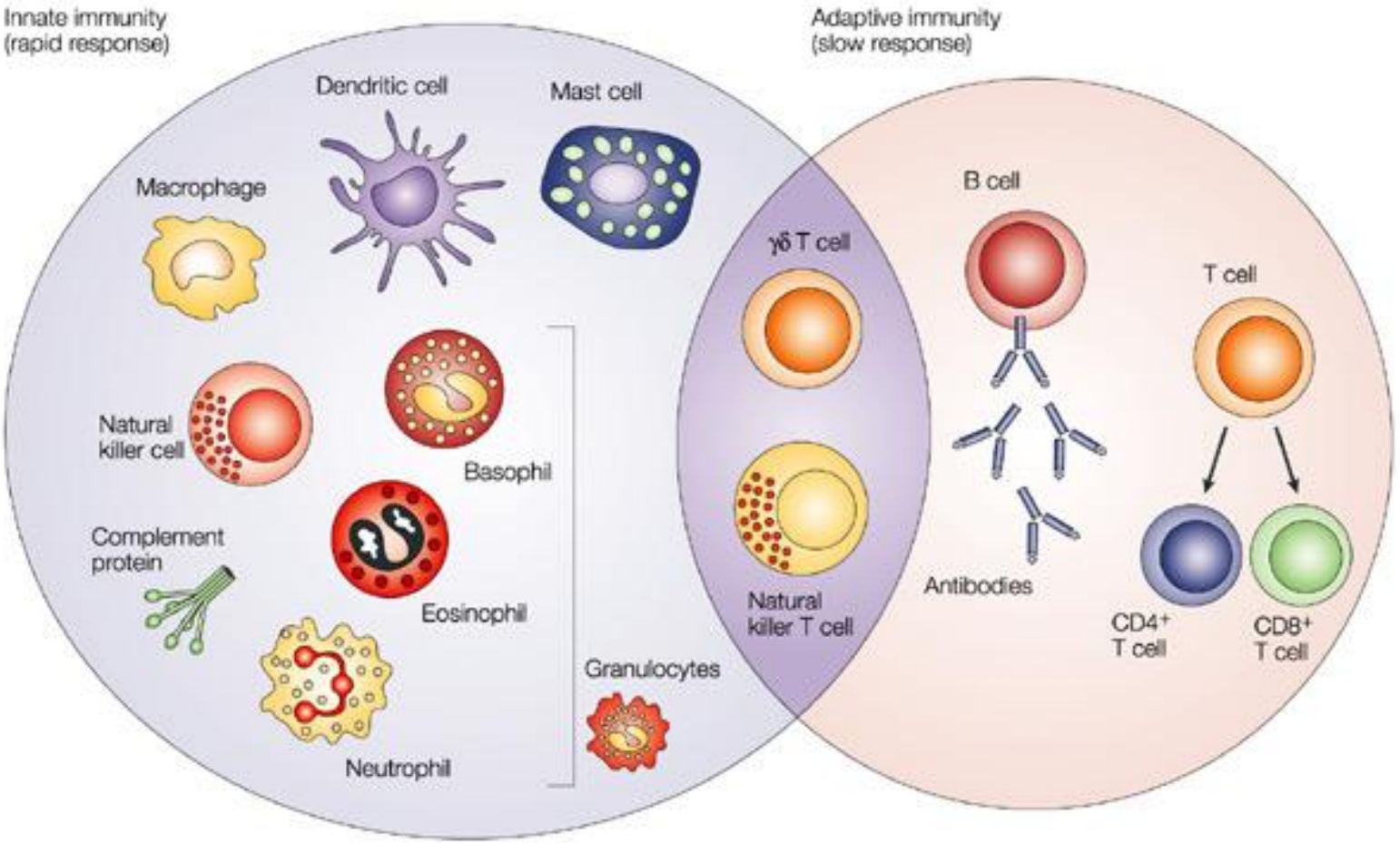
neutrophil count not below 1000 cells/mm

established teratogen

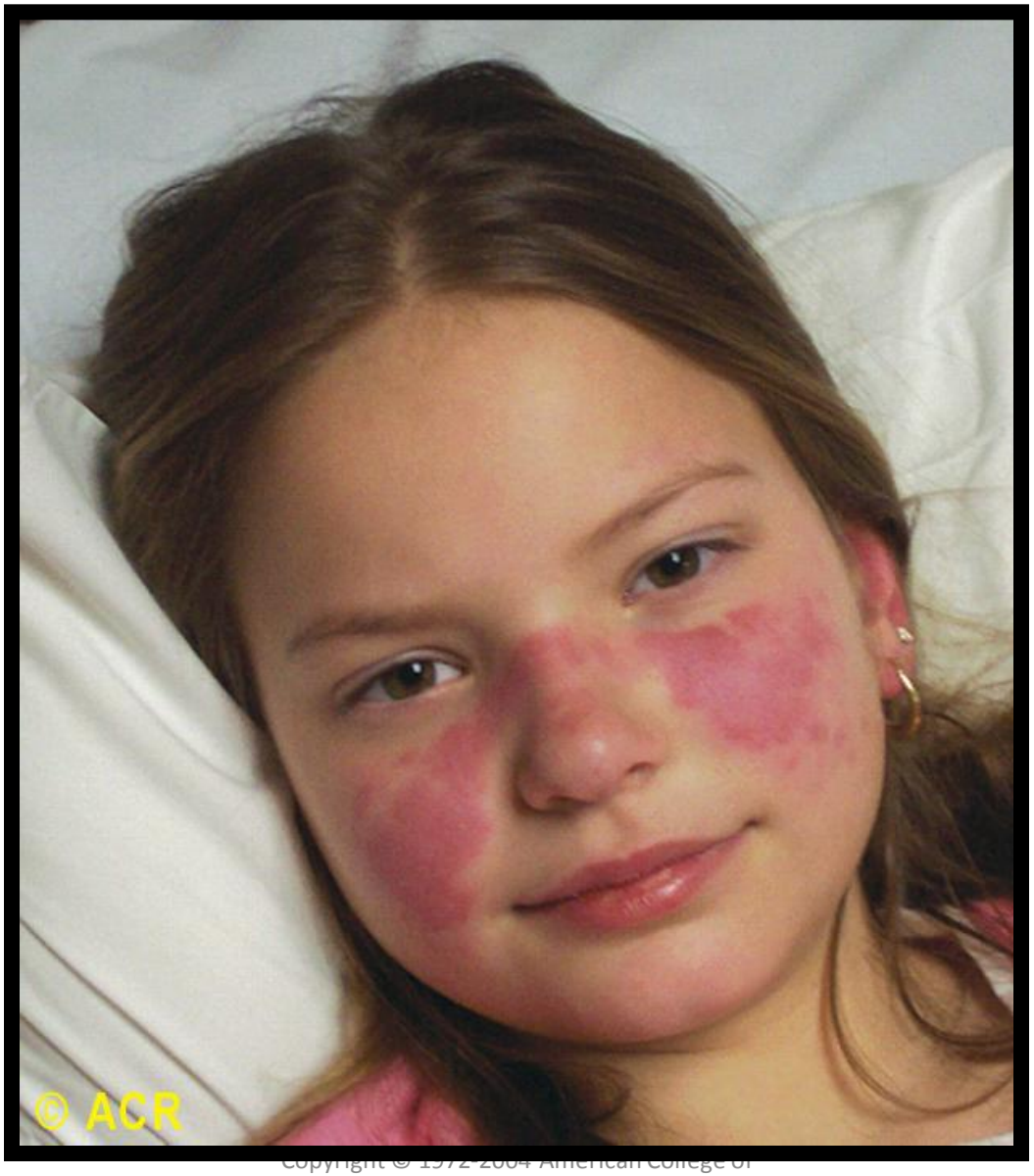
effective birth control

tests to exclude pregnancy before starting therapy

Immune response



Systemic lupus erythematosus: malar



Classification criteria for juvenile rheumatoid arthritis

- Age at onset <16 years
- Arthritis defined as articular swelling/effusion or the presence of two or more of the following signs:
  - **Limitation of range of movement**
  - **Joint tenderness on palpation**
  - **Pain on joint movement**
  - **Increased heat over joint**
- Duration of arthritis > 6 weeks
- Exclusion of other causes of arthritis

Juvenile rheumatoid arthritis subtypes, cont'd

- Onset type — Extraarticular manifestations
- Systemic — High spiking (quotidian) fever, severe anemia, rash,
- serositis, organomegaly leukocytosis, pharyngitis
-
- Polyarticular
  - **RF neg — Low-grade fever, mild anemia, malaise**
  -
  - **RF pos — Low-grade fever, mild anemia, malaise, nodules**
- Pauciarticular — Chronic iridocyclitis in 40%, increased incidence with +ANA
-
-

Systemic-onset juvenile rheumatoid arthritis: clinical features

- Spiking fevers
- Rash
- Lymphadenopathy
- Hepatosplenomegaly
- Pericarditis
- Pleuritis
- Arthritis

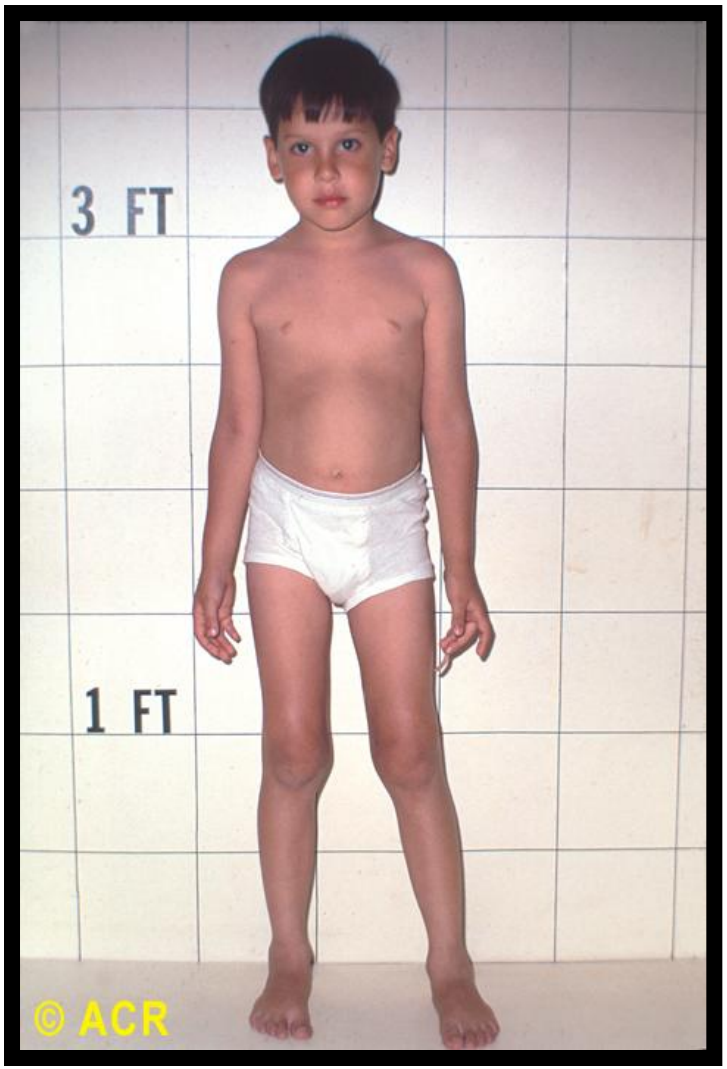
Childhood malignancy and bone pain

- Leukemia
- Lymphoma
- Neuroblastoma
- Histiocytosis
- Osteogenic sarcoma
- Ewing’s sarcoma

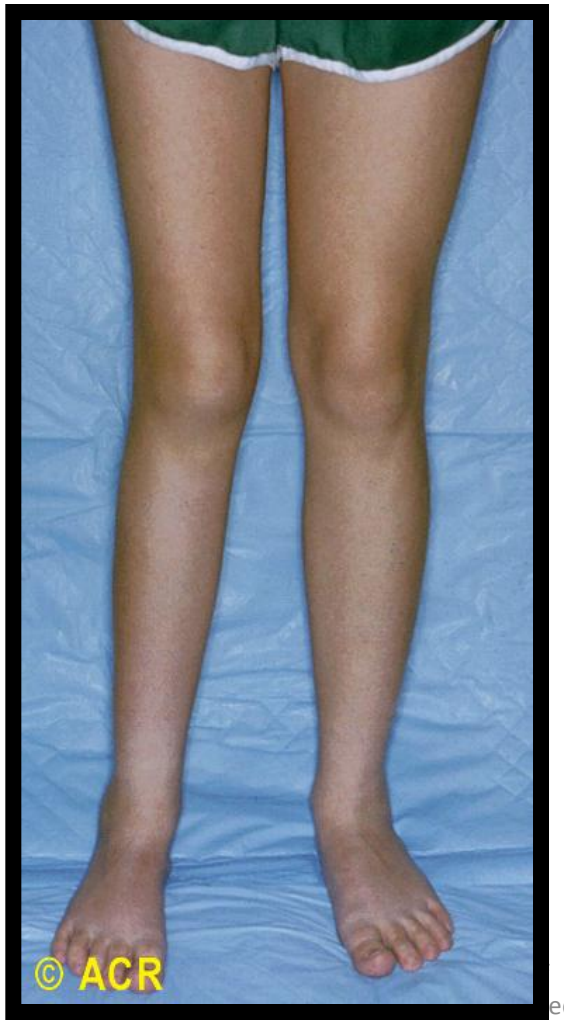
Clinical signs of malignancy

- Child appears miserable
- Low-grade fevers
- Night pain
- Pain out of proportion to physical findings
- Pain in both bones and joints
- Pallor, petechiae
- Hepatosplenomegaly
- Lymphadenopathy

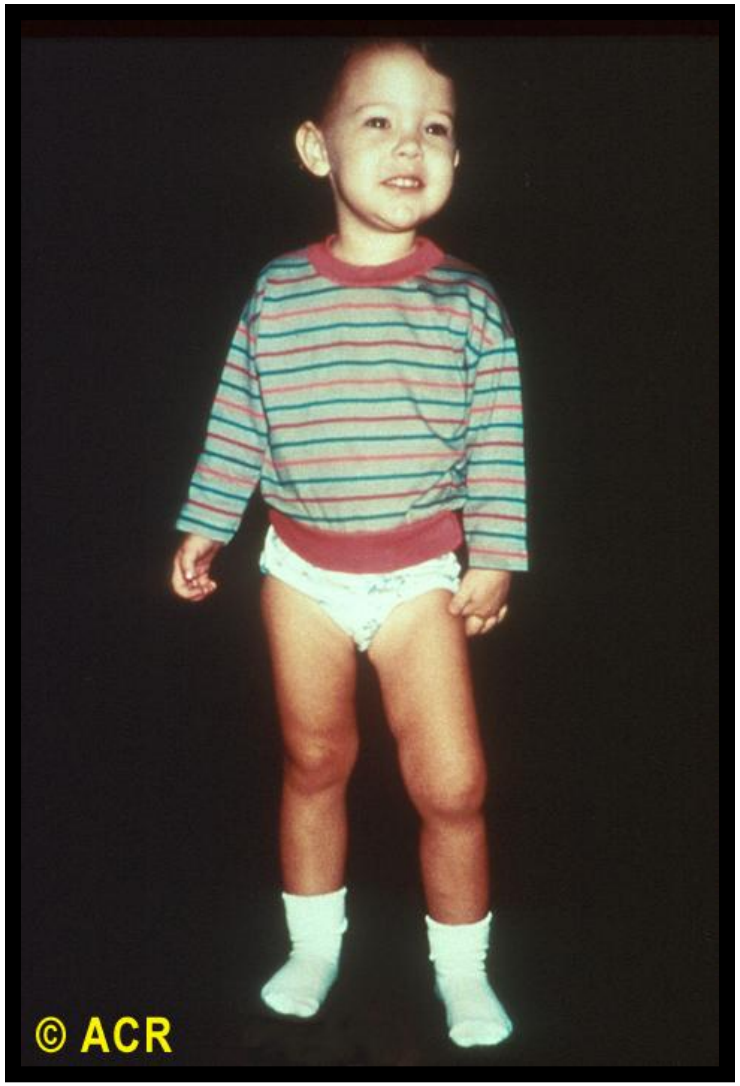
Juvenile rheumatoid arthritis: asymmetric growth



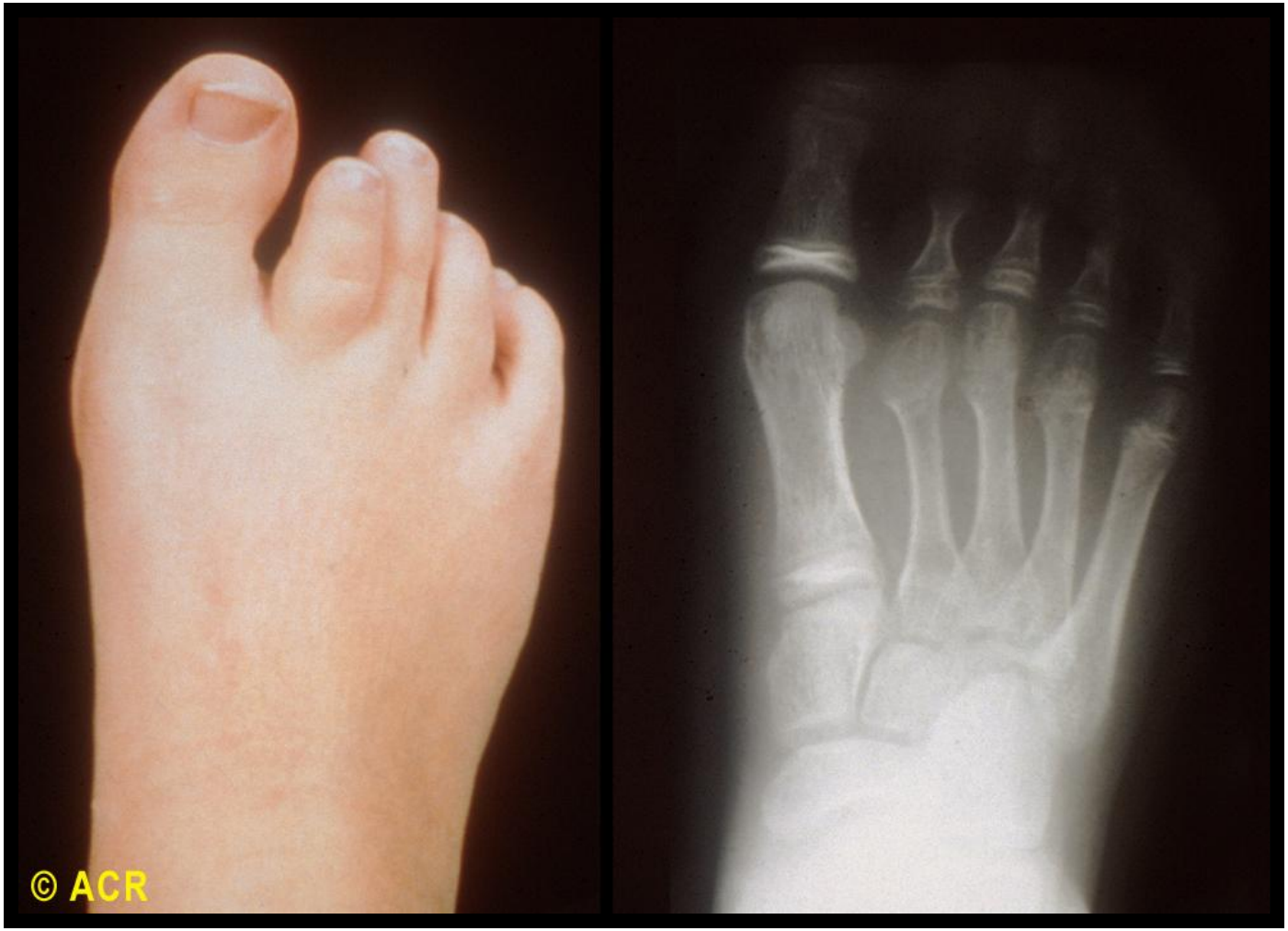
Juvenile rheumatoid arthritis: asymmetric growth, lower limbs



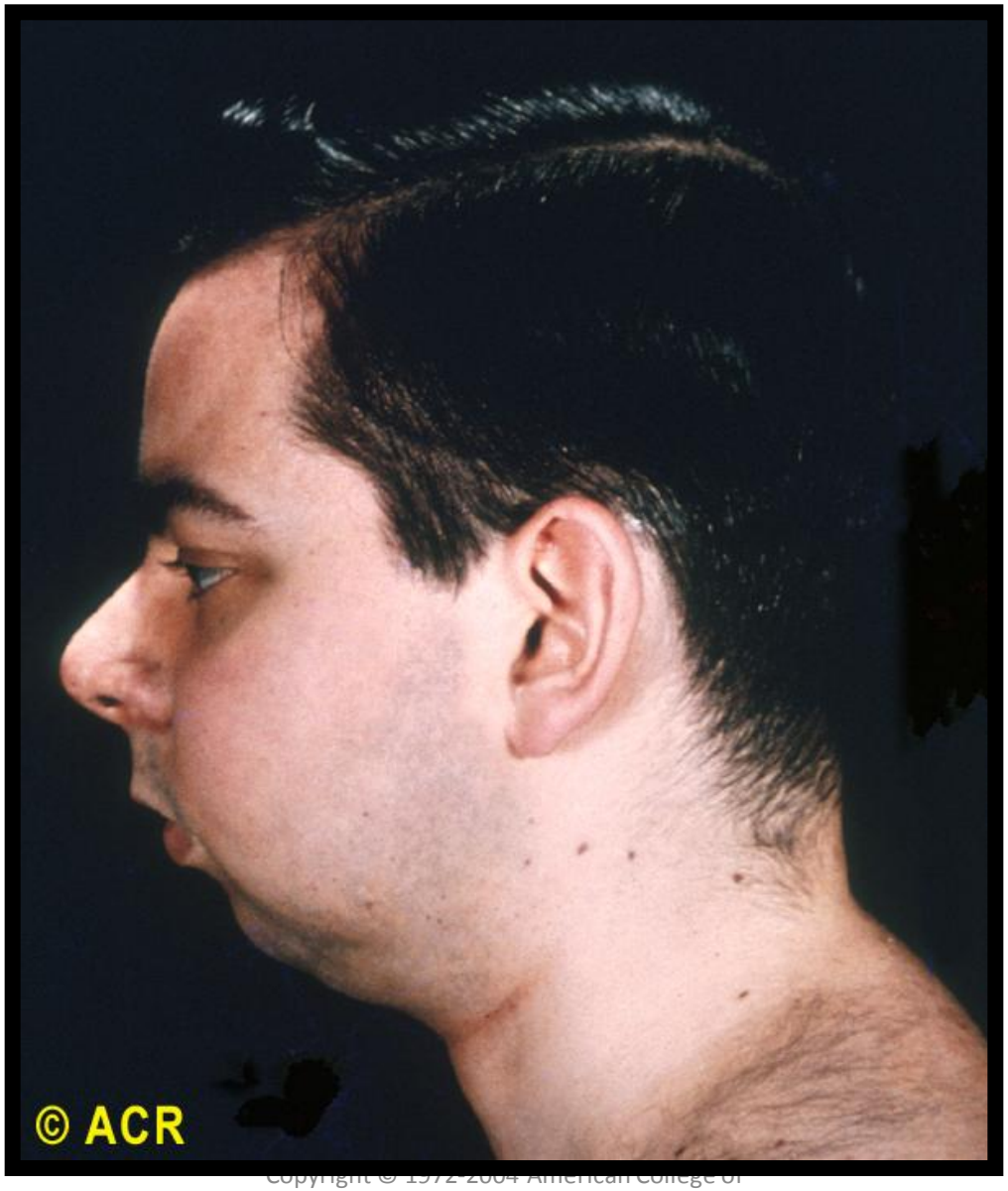
Juvenile rheumatoid arthritis: growth retardation



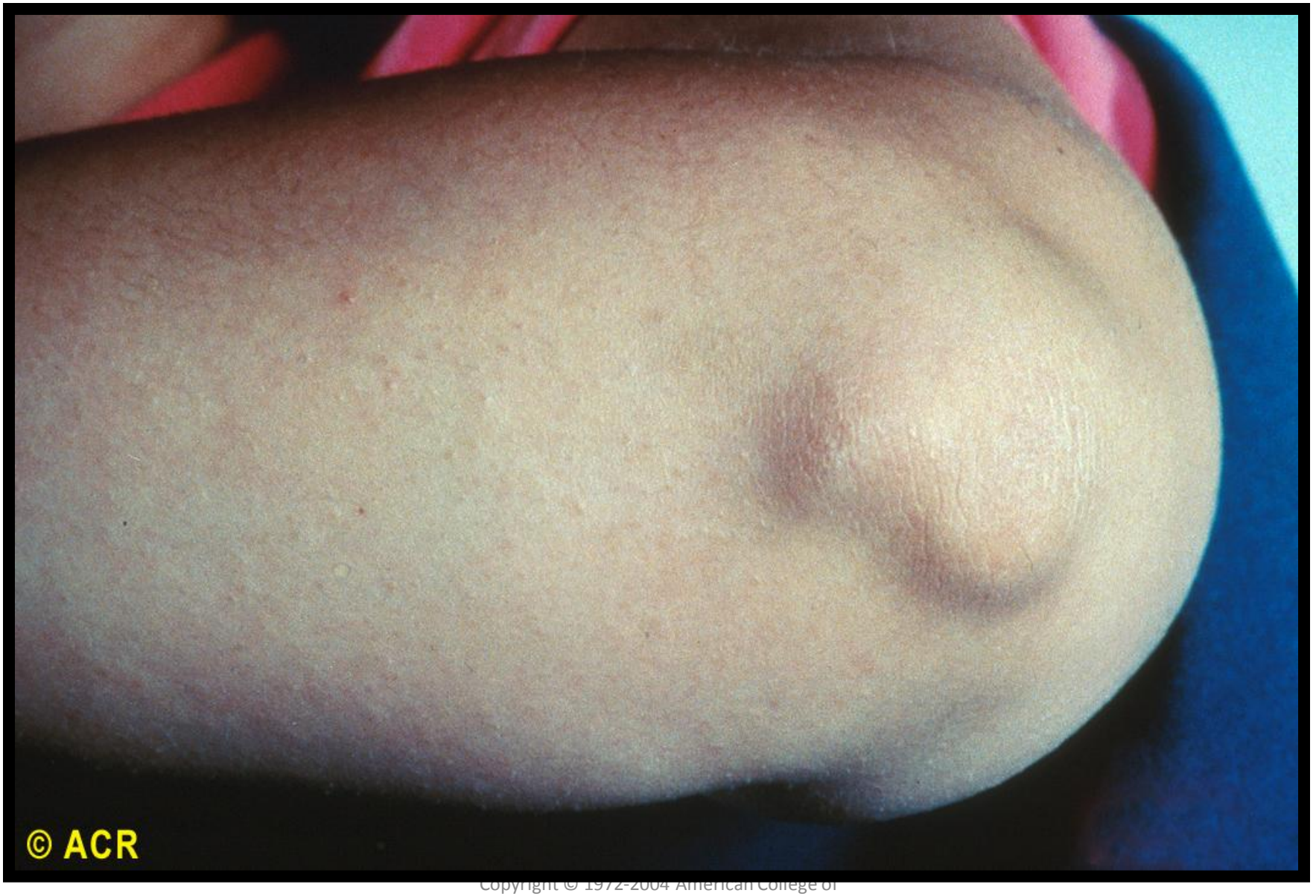
Juvenile rheumatoid arthritis: growth retardation, foot (clinical and radiograph)



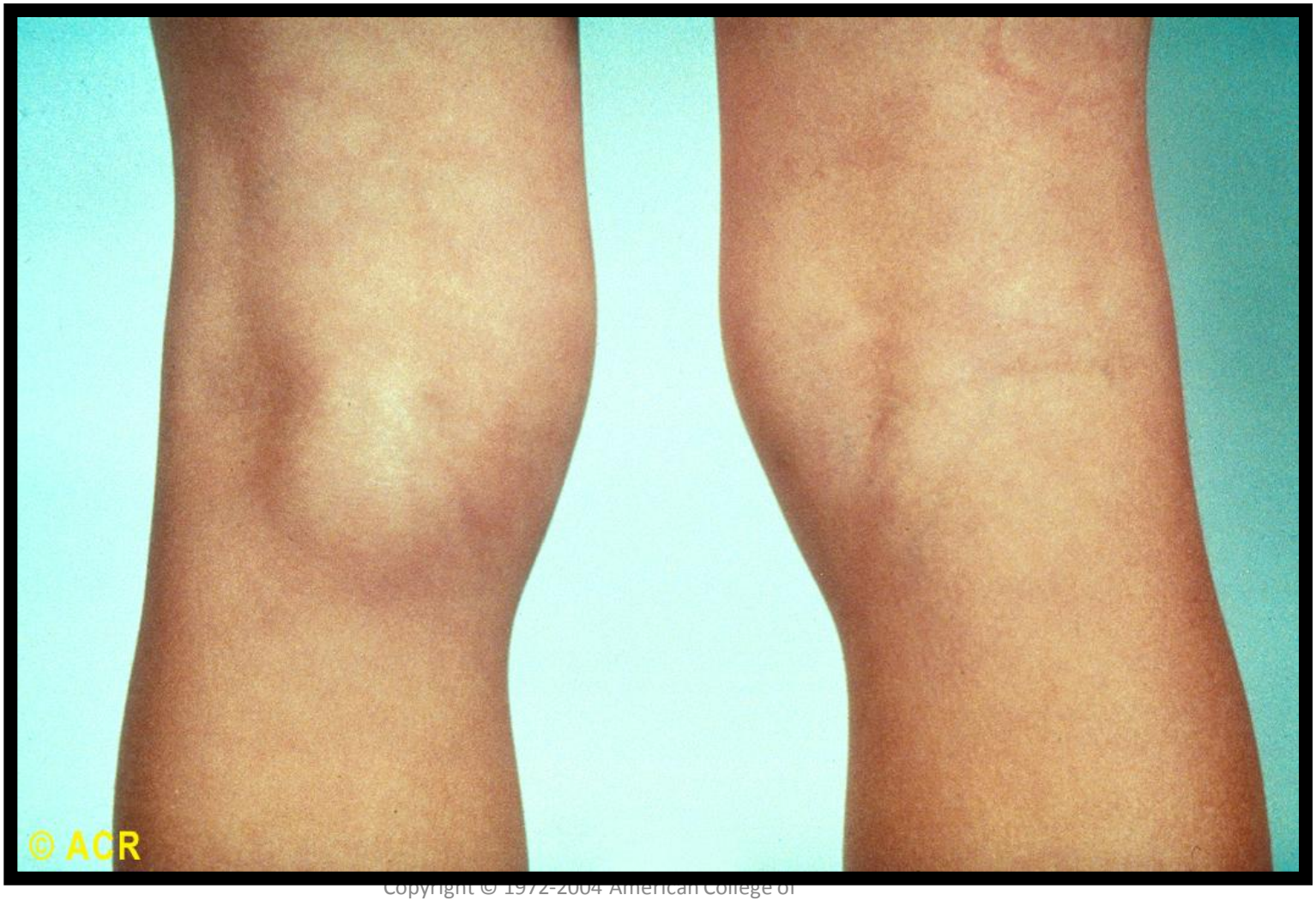
Juvenile rheumatoid arthritis:



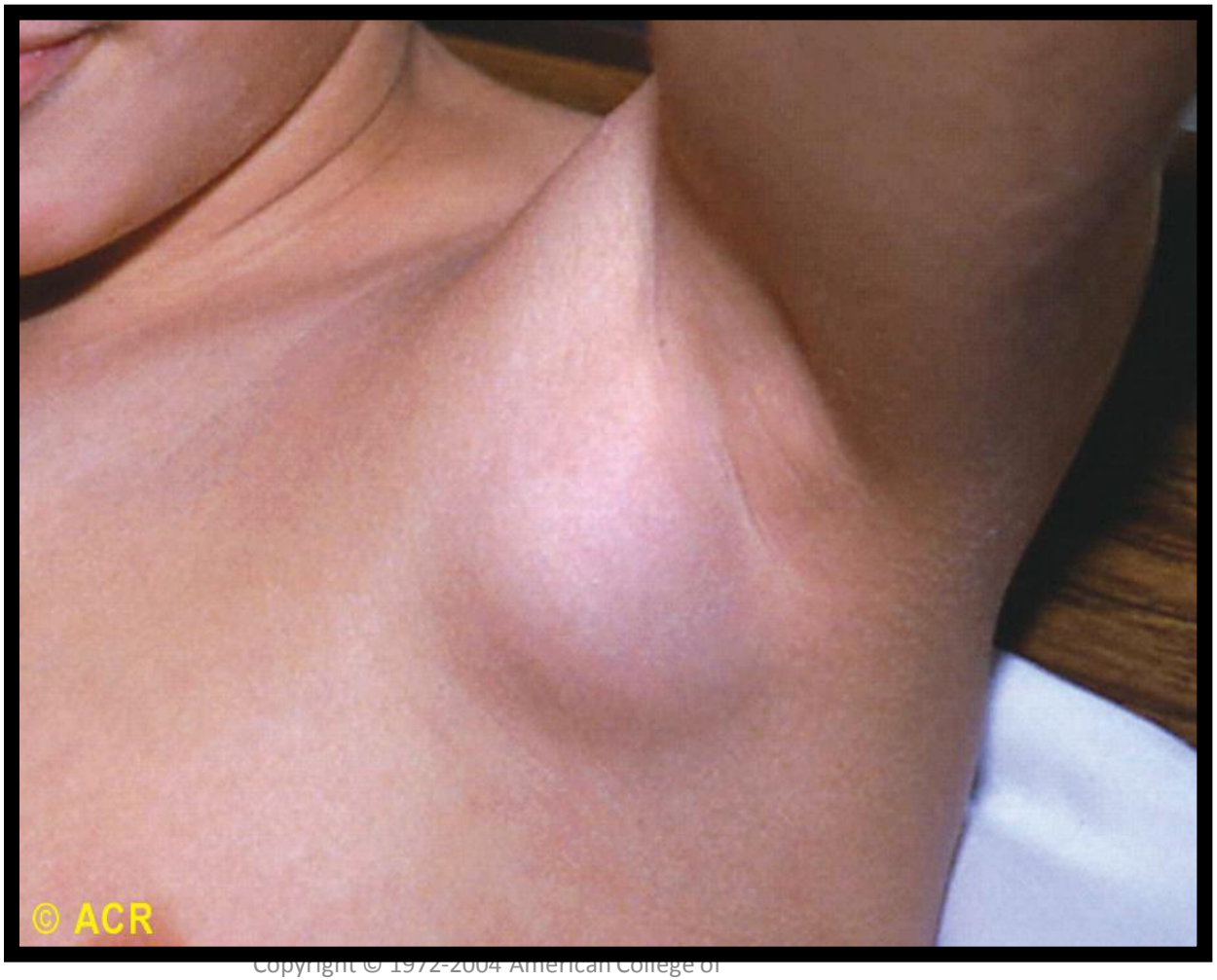
Juvenile rheumatoid arthritis: nodules,



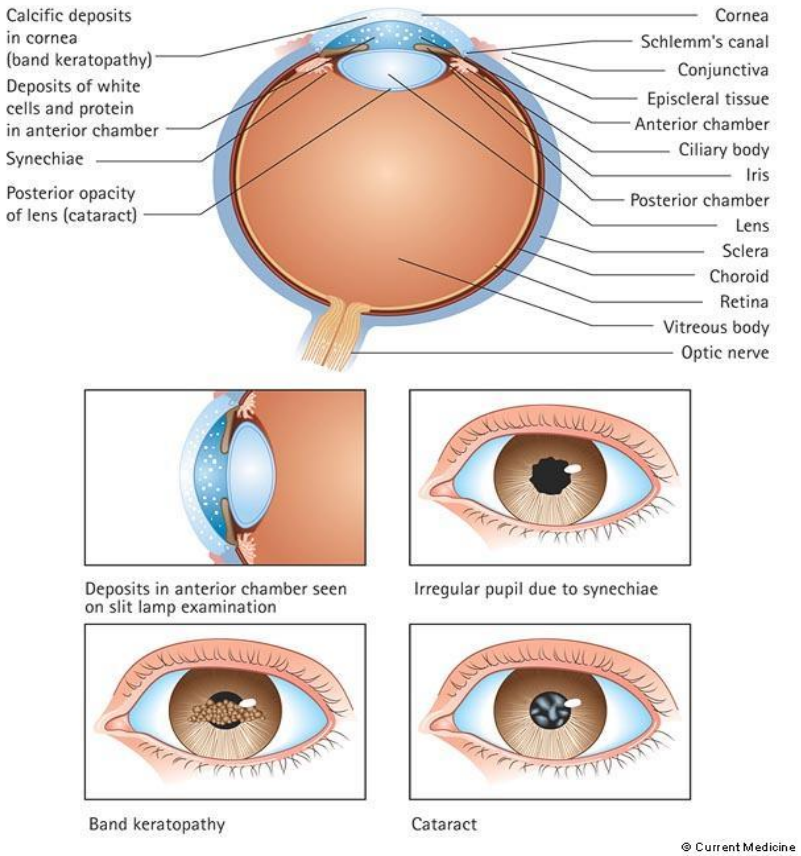
Popliteal cyst, asymptomatic: knee



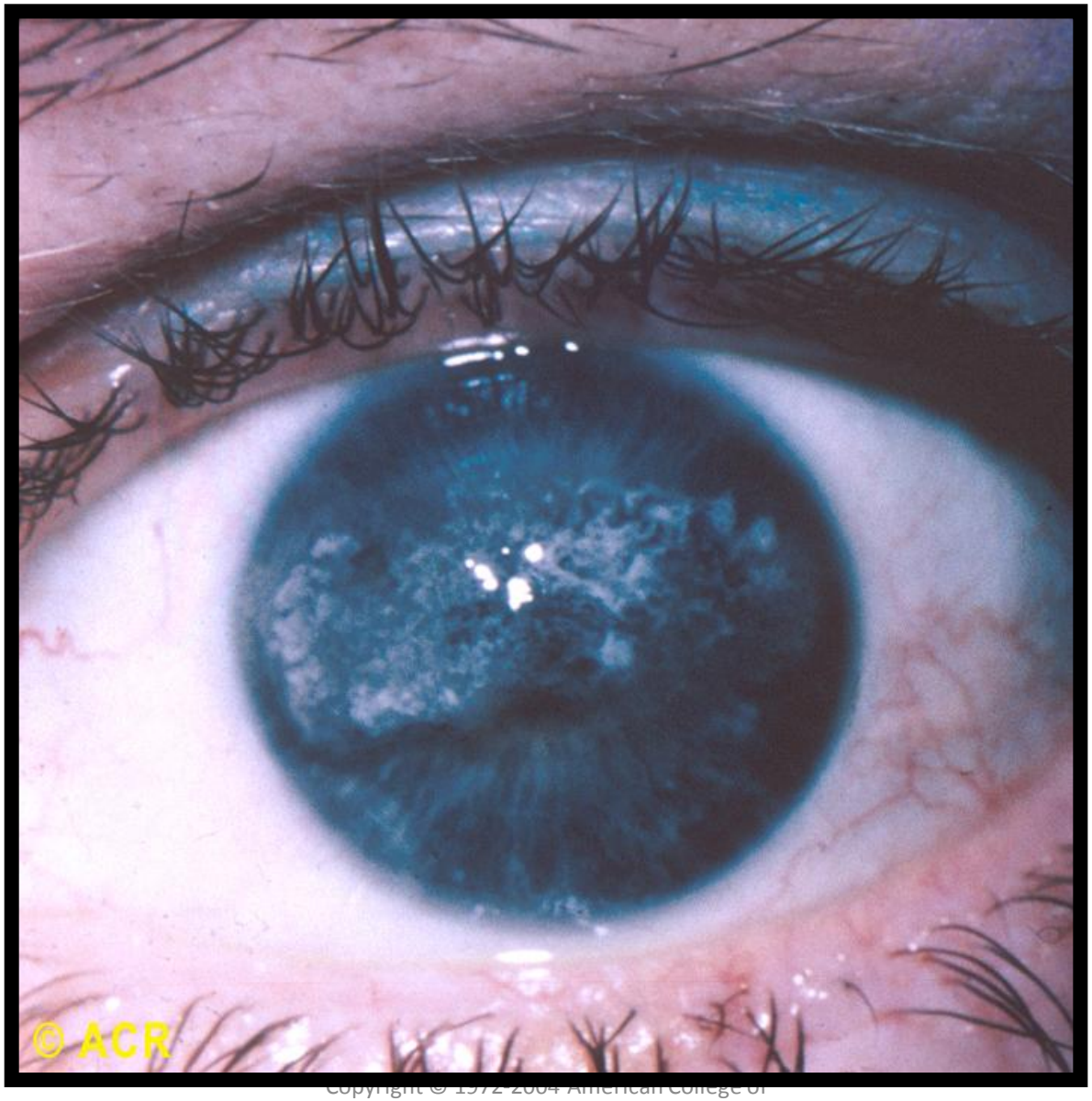
Systemic-onset juvenile rheumatoid arthritis: enlarged axillary lymph node



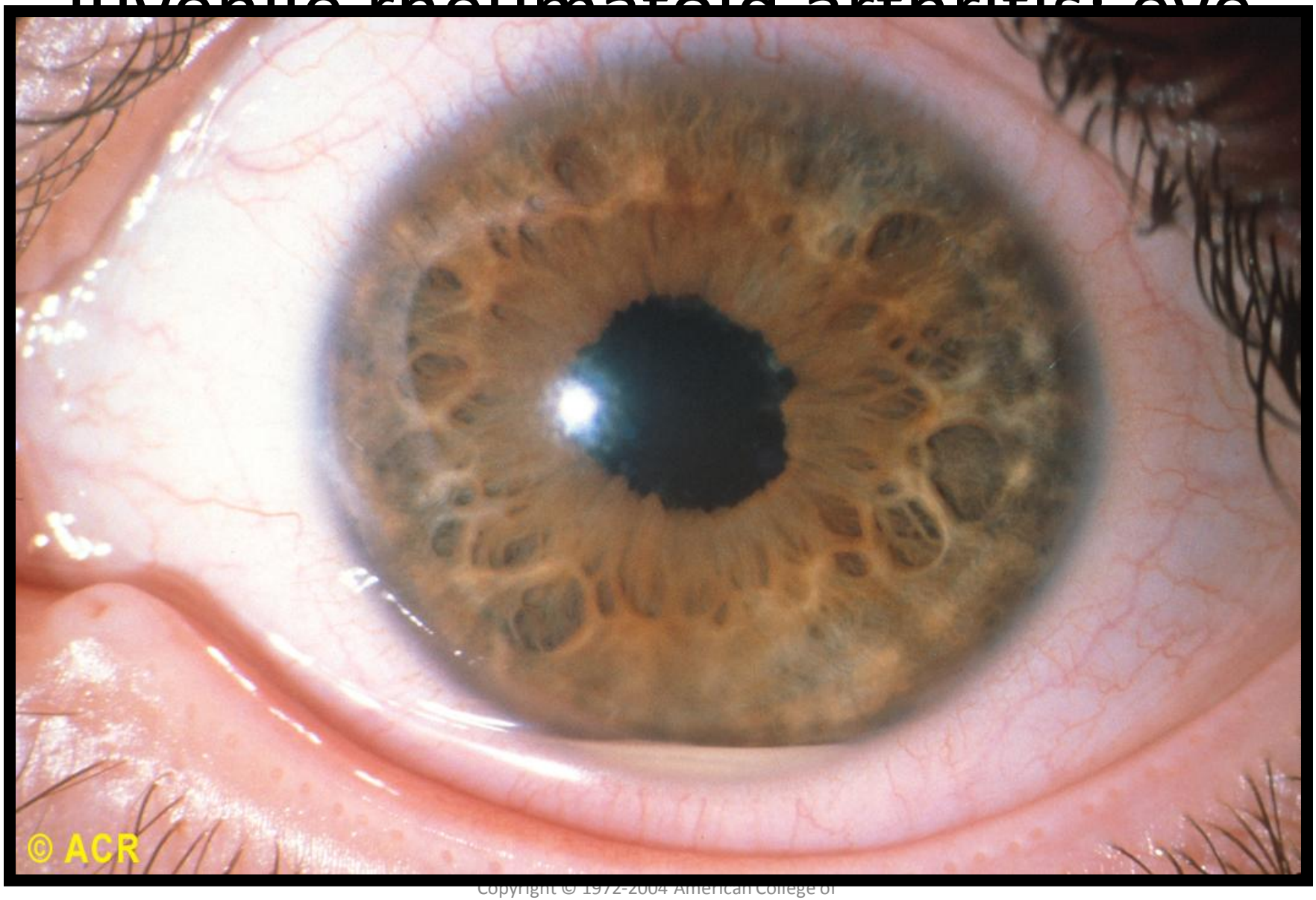
Ocular involvement in juvenile rheumatoid arthritis



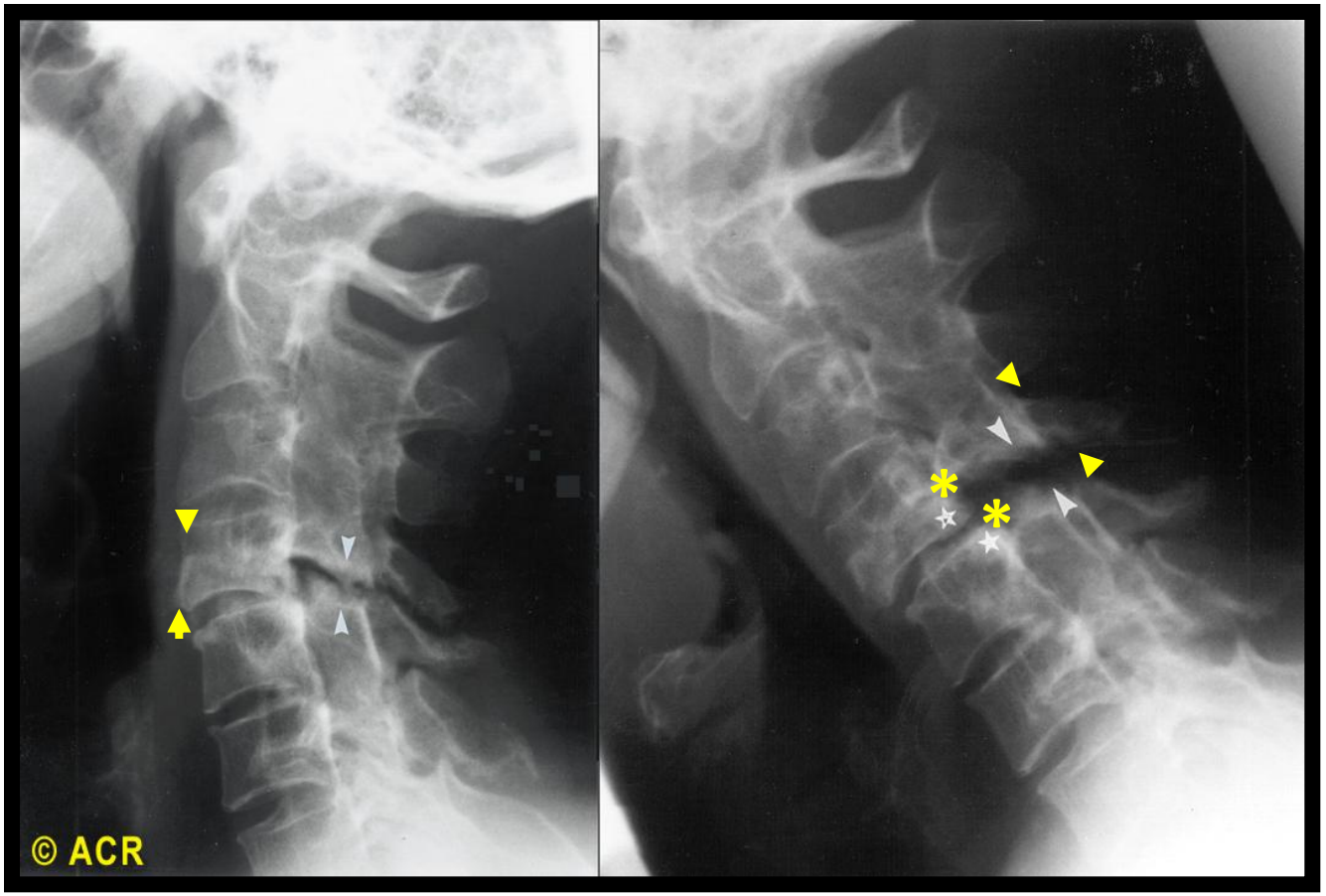
Juvenile rheumatoid arthritis: band



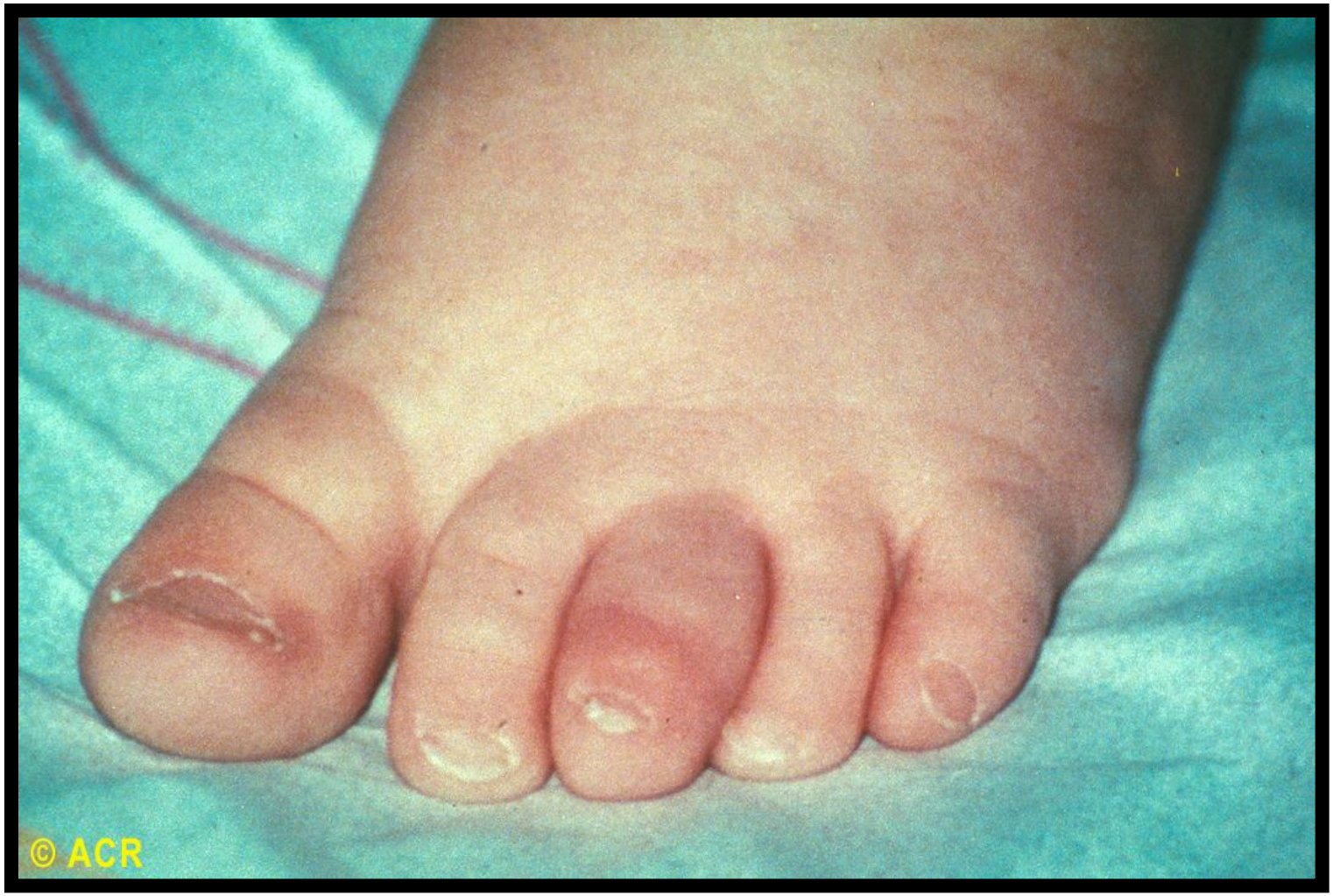
Juvenile rheumatoid arthritis: eye



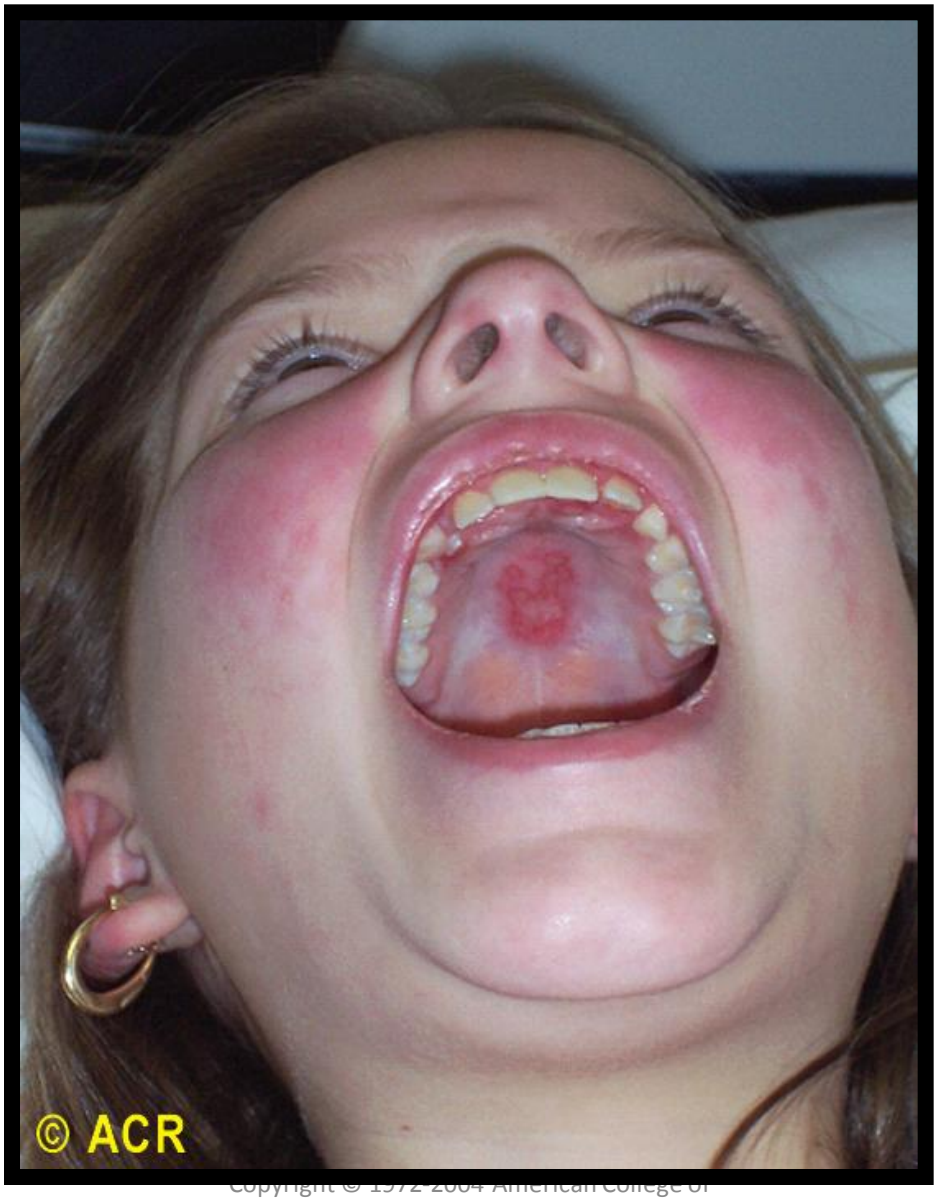
Juvenile rheumatoid arthritis: cervical spine (radiographs)



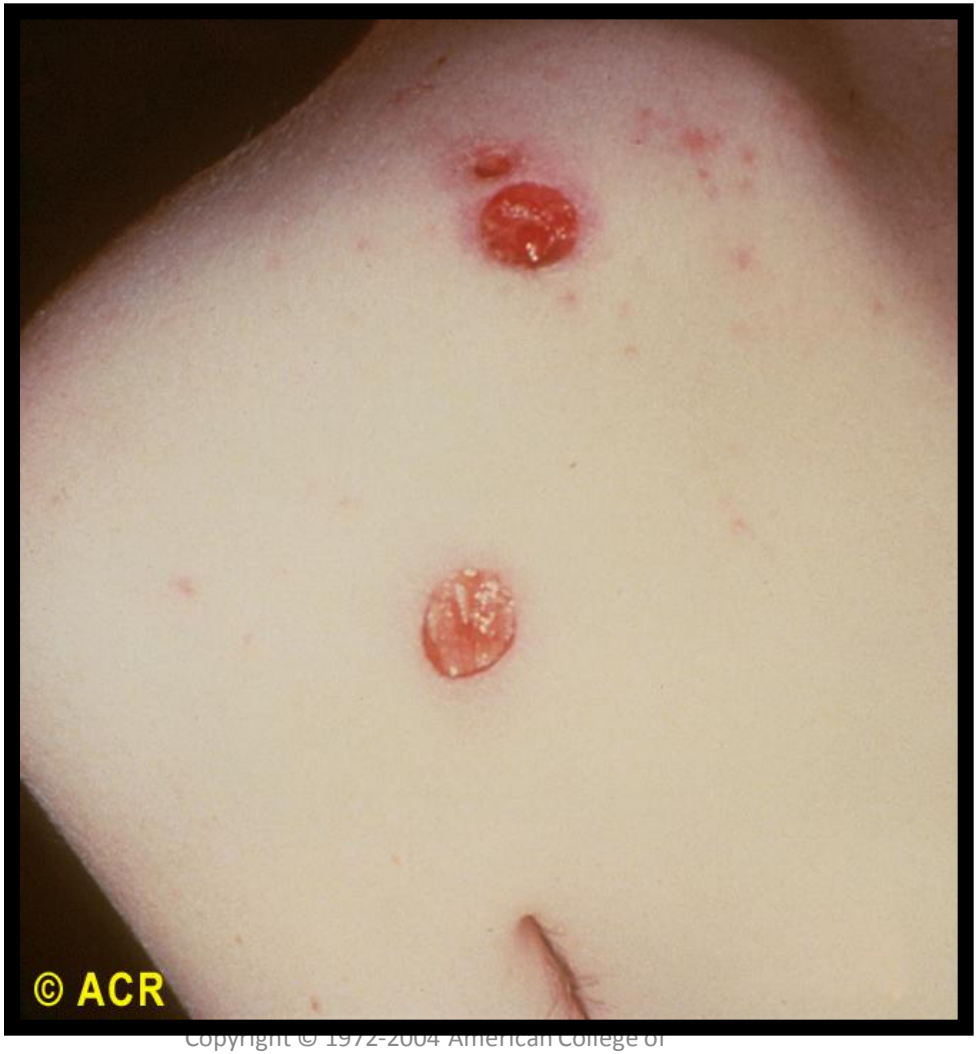
Psoriatic arthritis: dactylitis, toes



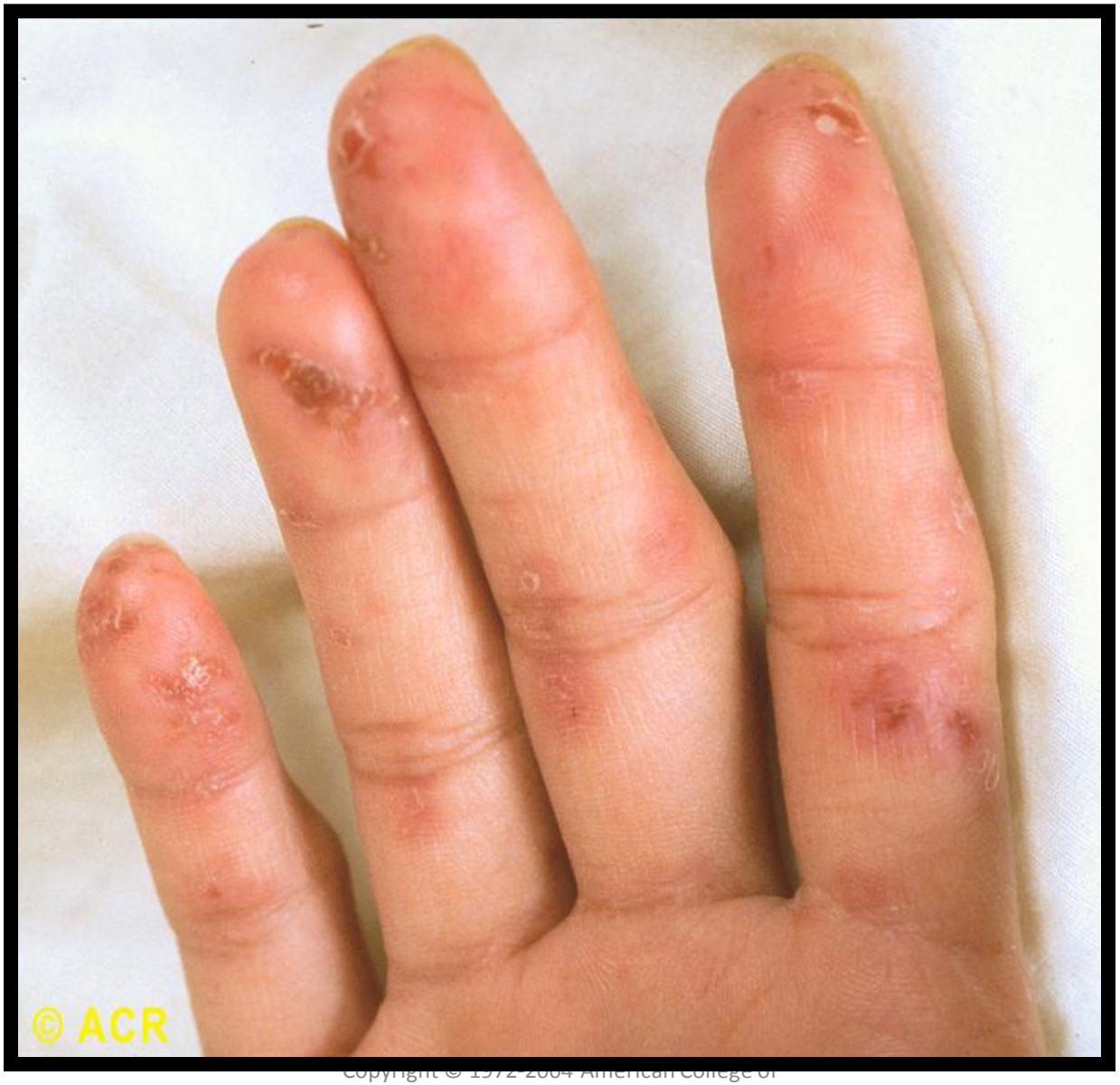
Systemic lupus erythematosus: oral



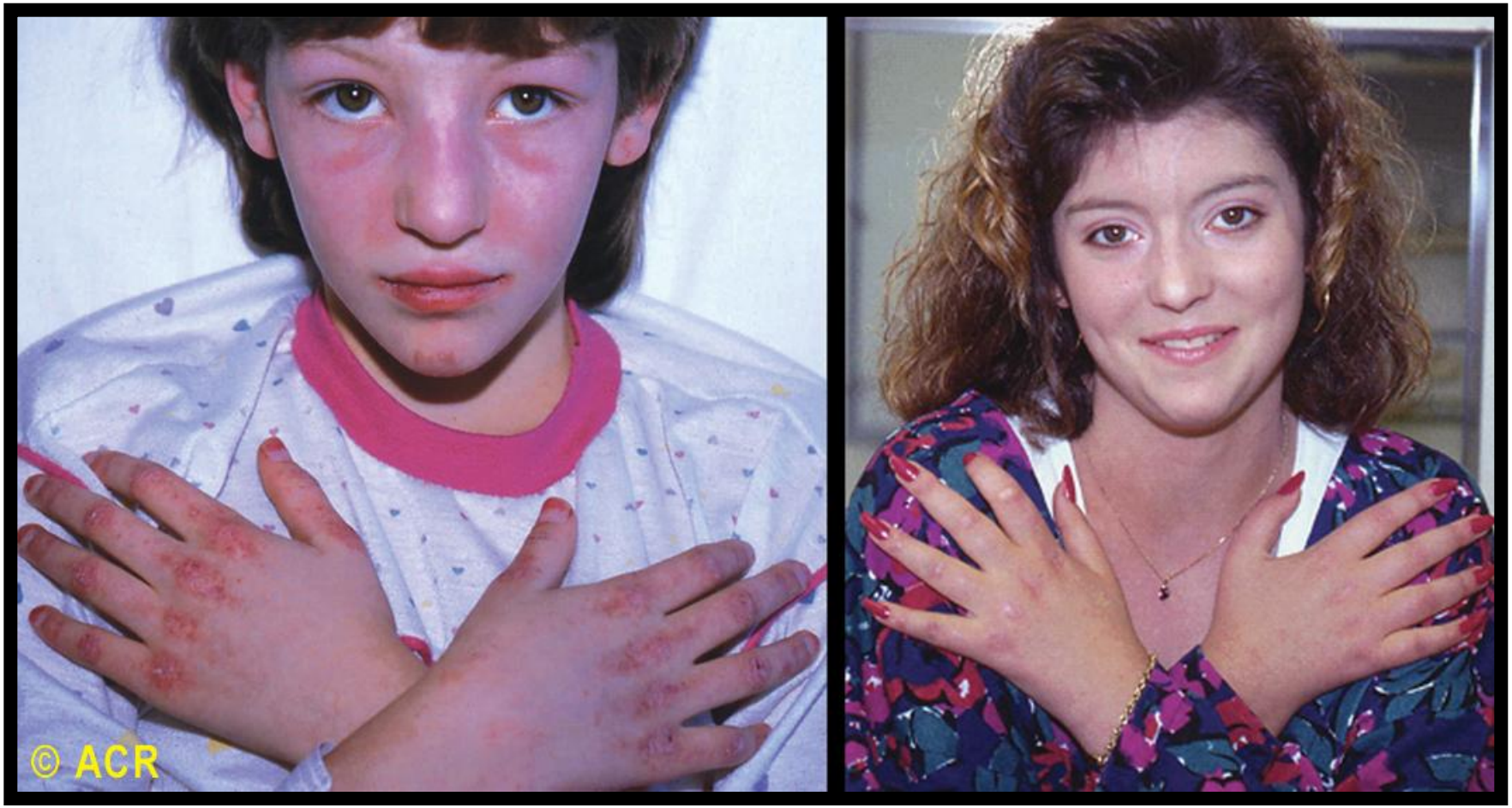
Systemic lupus erythematosus: vasculitic ulcers, shoulder



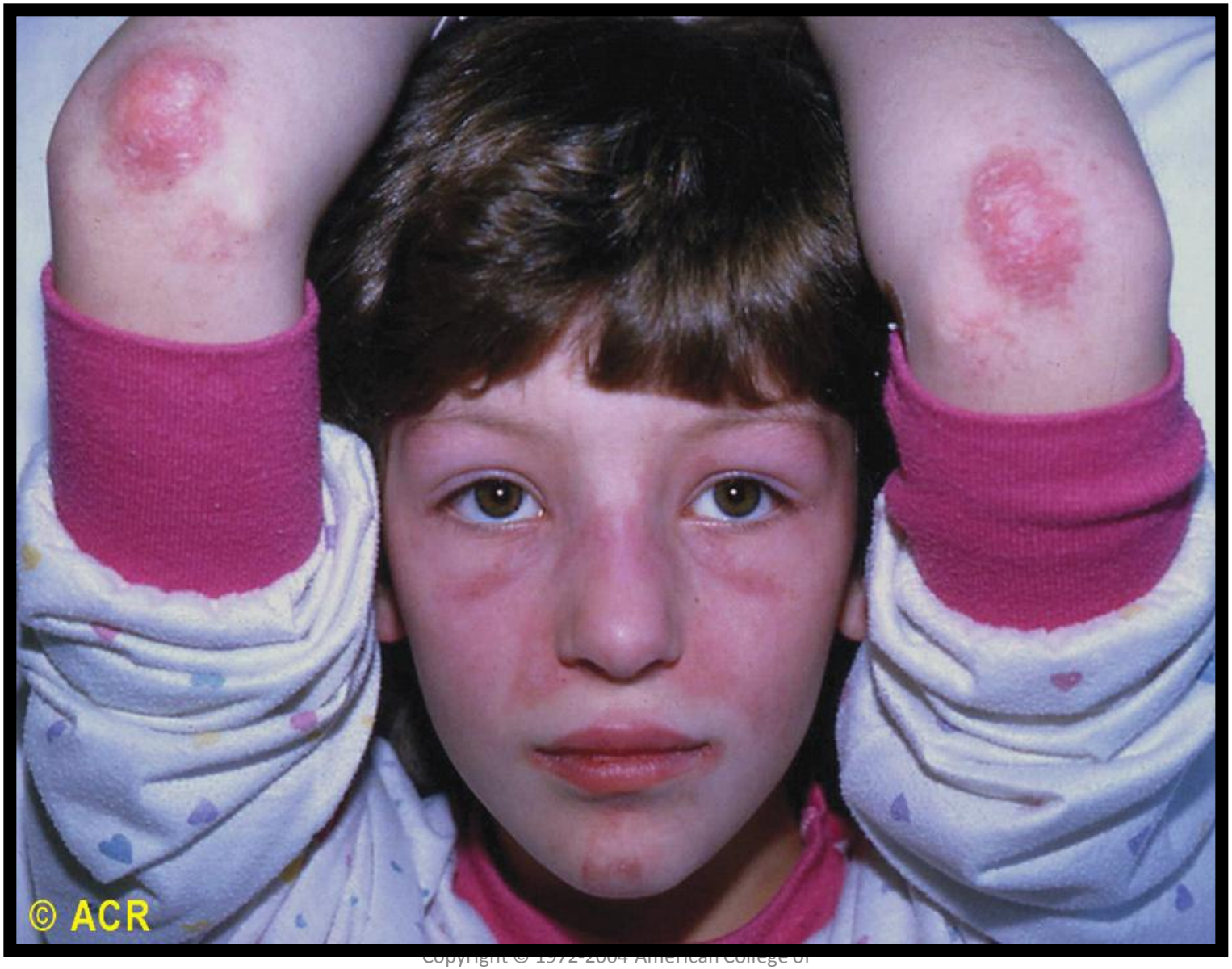
Systemic lupus erythematosus:



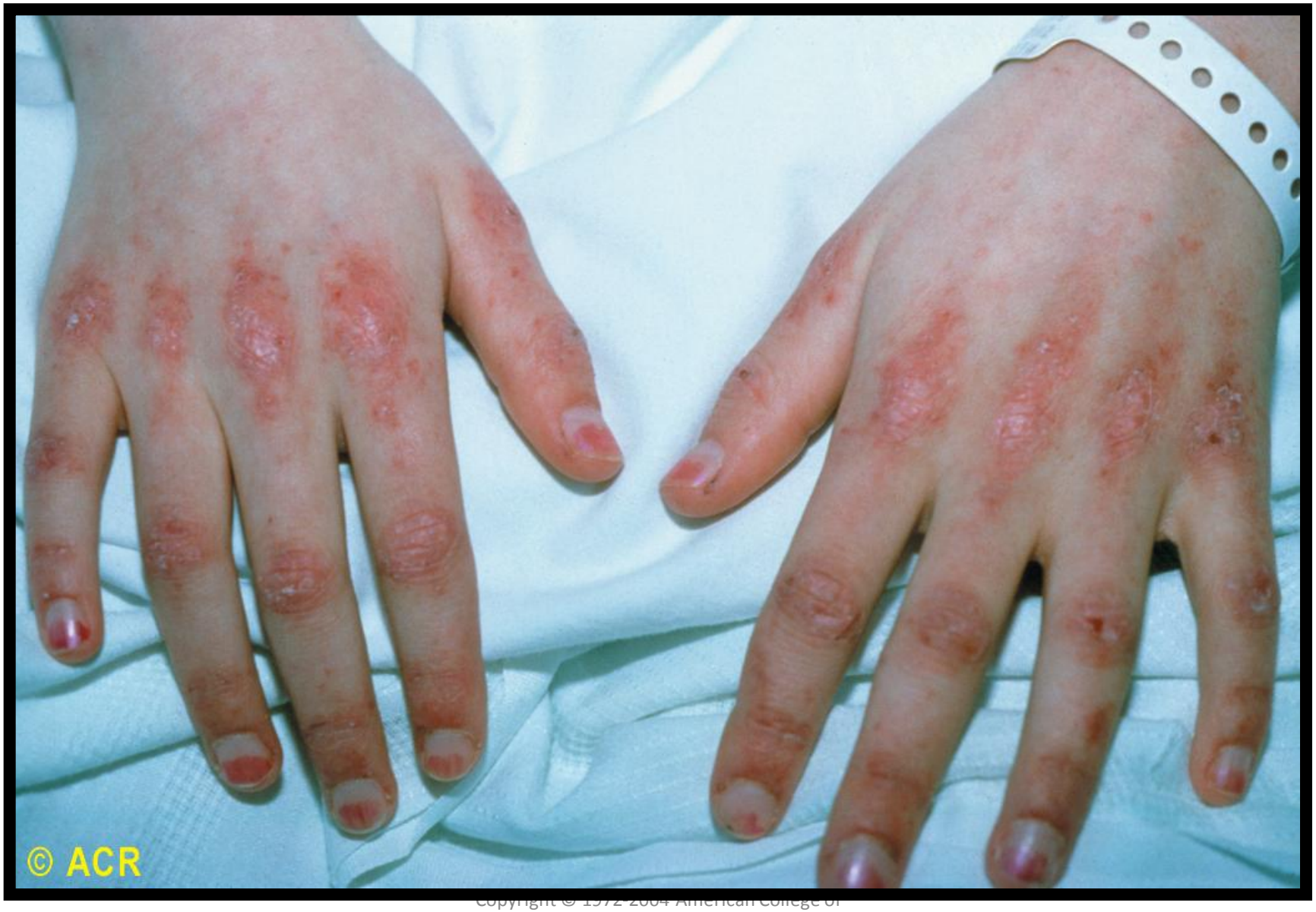
Dermatomyositis: rash, face and hands



Dermatomyositis: rash, face and



Dermatomyositis: Grotton's papules,



Dermatomyositis: calcinosis