Rheumatoid Arthritis

- prevalence ~ 1% with a F:M ratio ~ 3:1
- most common in the 4th & 5th decades
- moderate genetic predisposition ~ 30% monozygous twins
  ~ 5% dizygous twins
- multisystem disease of unknown aetiology
- characterised by a persistent inflammatory synovitis,
  a. usually symmetrical
  b. associated destruction of cartilage and bone
  c. characteristic joint deformities

Clinical Features

1. articular features
   - insidious onset with joint stiffness, pain and swelling - usually peripheral
   - swelling of proximal >> distal interphalangeal joints
     → 'swan neck' & 'button hole' deformities
   - may involve wrists, elbows, shoulders, knees, ankles and subtalar joints
   - cervical spine involvement is common
     i. atlanto-axial subluxation
        - anterior AAS ~ 80% and most common
          - transverse ligament destruction, worse in flexion
        - posterior AAS ~ 3-7%, due to odontoid peg destruction
          * extension may → anterior cord compression by atlas
        - vertical AAS ~ 10-20%, loss of lateral masses of C₁
          - odontoid may sublux through foramen magnum
          - potentially life-threatening cervicomedullary pressure
        - lateral/rotatory AAS
     ii. subaxial subluxation
        - less common ~ 10-20% of RA population
        - direct laryngoscopy generally well tolerated

2. systemic features
   - ~ 10% have onset with acute polyarthritis, malaise, fever & weight loss
   - Raynaud's phenomenon
   - lymphadenopathy - especially draining active joints
   - osteoporosis
   - muscle weakness and wasting
   - tenosynovitis, bursitis, popliteal cysts
   - subcutaneous nodules ~ 20% over the disease course
3. **cardiovascular**
   - asymptomatic pericarditis ± constrictive pericarditis
   - pericardial effusion ± tamponade
   - nodular | granulomatous complications - heart block
   - AMI, coronary insufficiency
   - cardiomyopathy
   - AI
   - diffuse necrotising vasculitis - nodular seropositive disease
   - mononeuritis multiplex due to involvement of vasa nervorum (cf. PN)

4. **pulmonary**
   - pleurisy ± pleural effusion ~ 25%
   - chronic interstitial fibrosis
   - obliterative bronchiolitis
   - pulmonary vasculitis
   - Caplan's syndrome, RA + 0.5 - 5.0 cm pulmonary nodules
   + pneumoconiosis (coal or other)

5. **neurological**
   - entrapment neuropathies - carpal tunnel
   - peripheral neuropathy - usually symmetrical & lower limbs
   - cervical cord compression - atlanto-axial or subaxial
   * common in long-standing RA
   > 4 mm odontoid-arch distance in flexion
   - nerve root compression, vertebrobasilar insufficiency, spinal artery occlusion

6. **haematological**
   - normochromic normocytic anaemia
   - low serum Fe++, low iron binding capacity, not responsive to oral iron
   - true iron deficiency 2° GIT haemorrhage from NSAID's
   - thrombocytosis with active disease
   - *Felty's syndrome* - splenomegaly, neutropenia & RA
   - seropositive, longstanding, but *inactive* disease
   ± anaemia, thrombocytopenia, lymphadenopathy
   ± weight loss, skin pigmentation & vasculitic changes

7. **ocular features**
   - episcleritis - benign but common in seropositive, usually painless
   - scleritis - inflammation of sclera & uveal tract, synechiae ± 2° glaucoma
   - scleralacia & scleralacia perforans
   - keratoconjunctivitis sicca ~ 10%
   - *Sjögren's syndrome* - keratoconjunctivitis sicca + xerostomia + CT disease
   - RA, SLE, PSS, polymyositis, myasthenia, etc.
   - multiple organ system Ab's

8. **amyloidosis**
   - ~ 25-50% of autopsies, making RA the *leading cause*
   - usually limited to *mild proteinuria*
   - rarely associated with nephrotic syndrome or renal failure
Ankylosing Spondylitis

- chronic inflammatory arthritis, affecting predominantly the SI joints and spine
- characterised by progressive stiffening and fusion of the axial skeleton
  1. typically young **males**, 2\textsuperscript{nd} & 3\textsuperscript{rd} decades
  2. M:F ratio ~ 9:1
  3. strong genetic disposition
     i. > 90% HLA-B27 positive
     ii. 1\textsuperscript{st} degree relatives show an increased incidence of,
        - psoriatic arthritis
        - inflammatory bowel disease
        - Reiter's syndrome
  4. **articular features**
     - usually insidious onset, with recurring lower back pain & stiffness
     - worse in mornings and following inactivity
     - usually **without** associated nerve root signs
     - chest pain due to involvement of the costovertebral joints
     - plantar fasciitis, Achilles tendonitis
     - severe spinal fusion & rigidity occurs only in a **minority**, and in most is not associated with marked deformity
     - rarely develop kyphosis of the thoracic and cervical spine
  5. **extra-articular features**
     - non-granulomatous anterior uveitis
     - aortic regurgitation
     - cardiac conduction defects
     - apical pulmonary fibrosis
     - amyloidosis
     - osteoporosis & myelopathy, associated with **atlanto-axial subluxation**

Systemic Onset Juvenile Chronic Arthritis Still's Disease

- occurs in 20% of children with juvenile chronic arthritis
  a. myalgias, arthralgias, weight loss, high fever
  b. eventually polyarthritis and growth retardation
  c. high ESR, anaemia of chronic disease, PMN leukocytosis
  d. lymphadenopathy, hepatosplenomegaly
  e. pleurisy, pericarditis, macular rash
  f. RF and ANF **negative**

**NB:** **remission** usually occurs within 6 months, 25% develop severe chronic polyarthritis
Systemic Lupus Erythematosus

**Def' n:** multisystem CT disorder of unknown aetiology, characterised by,
1. multiple **autoantibodies**
2. circulating **immune complexes**, and
3. widespread immunologically mediated tissue destruction

- incidence ~ 10-15:100,000, with 90% being **female**, usually of childbearing years
- overall survival > 10 years ~ 70%

### Antibodies

1. antinuclear ~ 95% - multiple nuclear & cytoplasmic Ag's
2. anti-DNA ~ 70%
3. antihistone ~ 70% - ↑% in drug induced SLE
4. antiphospholipid antibodies * 3 types
   i. lupus anticoagulant
      - results in ↑ APTT due to inhibition of "platelet phospholipid"
      - ↑ arterial & venous thrombosis ± thrombocytopaenia
      - ↑ spontaneous abortion
   ii. anticardiolipin
      - ↑ foetal death in SLE/pregnancy
   iii. false (+)ve VDRL
5. antiearythrocyte ~ 60% - small % develop haemolysis
6. antilymphocyte ~ 70% - leukopenia & ↓ T-cell function
7. antiplatelet - "ITP" like presentation
8. antineuronal ~ 60% - CNS lupus

### Aetiology

**NB:** multifactorial → genetic, envorinmental, and sex hormonal

1. **polyclonal B-cell** hyperactivity
2. disordered immunoregulation - ↓ T-cell supressor function
   - ↑ idiotype / anti-idiotype Ab production
3. delayed clearance of circulating immune complexes
4. ↑ HLA-DR2 & DR3
5. suspected, but not proven **viral activation**
6. **phospholipid** from enteric bacterial cell walls acts as polyclonal B-cell activator
Clinical Features

1. **systemic**
   - fatigue, malaise, fever
   - anorexia, nausea, weight loss

2. **cutaneous**
   - malar "butterfly" rash - exacerbated by UV light
   - discoid rash
   - photosensitivity
   - other rashes - diffuse maculopapular rash
   - urticarial, bullous
   - alopecia - regrows except in discoid lupus
   - vasculitic skin lesions - subcutaneous nodules
   - ulceration (usually on the legs)
   - palpable pupura
   - mucous membrane lesions - small painless ulcers

3. **musculoskeletal**
   - arthralgias & myalgias
   - seronegative polyarthritis
   - hand deformity & erosions - rare ± subcutaneous nodules
   - myopathy / myositis - inflammatory or 2° to therapy
   - ischaemic necrosis of bone - hip, knee & shoulder pain

4. **renal**
   - all have Ig-C₃ deposits in glomeruli
   - nephritis - persistent proteinuria > 500 mg/d
   - nephrotic syndrome
   - cylinduria, proteinuria and haematuria
   - most with mesangial or mild focal GN do not progress to CRF
   - in those with more active disease, CRF is a major cause of death
   - these tend not to respond to immunosupression & require dialysis & transplantation

5. **nervous system**
   - any section may be involved - spinal cord, peripheral nerves
   - cortex, meninges
   - headache, depression & anxiety
   - organic brain syndrome - phychosis
   - seizures (grand mal, petit mal, or focal)
   - hypothalamic dysfunction, SIADH, pseudotumour cerebri
   - focal infarction, extrapyramidal or cerebellar dysfunction
   - optic neuritis, cranial nerve palsies
   - transverse myelitis - paraplegia, quadriplegia
   - mononeuritis multiplex
6. **haematological**
   - anaemia of chronic disease ± haemolytic anaemia
   - leukopaenia, lymphopaenia
   - splenomegaly, lymphadenopathy
   - thrombocytopenia
   - **circulating anticoagulant** - phospholipid of prothrombin activator complex
     → ↑ APTT & 3 clinical sequelae,
     i. venous or arterial **thromboses**
     ii. **haemorrhagic** sequelae - especially if ↓ platelets or ↓ prothrombin
     - Ab's to factors VIII, IX
     iii. benign laboratory manifestation

7. **cardiopulmonary**
   - pericarditis ± effusion
     * present in virtually all patients
   - myocarditis
   - endocarditis - Libman-Sachs, usually silent but may have emboli
   - pleurisy ± effusions
   - lupus pneumonitis
   - interstitial fibrosis
   - pulmonary hypertension
   - ARDS, alveolitis, pulmonary haemorrhage

8. **gastrointestinal**
   - nonspecific - anorexia, N&V, mild pain, diarrhoea
   - vasculitis - bleeding, vascular thrombosis, or perforation
   - ascites
   - abnormal liver function

9. **ocular**
   - retinal vasculitis - cytoid bodies 2° infarction
   - conjunctivitis, episcleritis
   - sicca syndrome

10. **obstetric**
    - normal fertility
    - **recurrent abortion** ~ 30-50%
    - ↑↑ disease activity - 1st trimester & postpartum

### Drug-Induced Lupus

1. **procainamide** ~ 50-75% → ANA-Ab, 20% LE
2. **hydralazine** ~ 25-30% → ANA-Ab, 10% LE
3. others → methyldopa, chlorpromazine, d-penicillamine, OCP, isoniazid, ethosuximide, practolol
Progressive Systemic Sclerosis

**Essentials**

1. diffuse thickening of the skin, with telangectasia
2. areas of increased & de-pigmentation
3. Raynaud's phenomenon > 90%
4. dysphagia & hypomotility of the GIT
5. pulmonary fibrosis - ↓ DL_{CO}, ↓ C_L
6. glomerulonephritis
7. cardiac involvement - pericarditis, 1°→CHB, myocardial fibrosis
   - RVF 2° to pulmonary vascular disease

**Classification**

1. localised
   - morphea, or linear scleroderma
   - no visceral involvement & therefore benign
2. systemic
   i. limited ~ 80%
      - calcinosis cutis, Raynaud's phenomenon, oesophageal involvement, sclerodactaly, & telangectasia → **CREST syndrome**
      - skin changes limited to hands & face
      - lower risk of renal disease, but higher risk of pulmonary hypertension
      - better prognosis
   ii. diffuse ~ 20%
      - rapid progression visceral disease more common in this group
      - **hypertensive-uraemic** syndrome has a grave prognosis
      - death common within several years of onset

* cause is unknown, but the following have been implicated,

1. autoimmunity
2. fibroblast disregulation
3. occupational exposure
Connective Tissue Disease

- **Laboratory Findings**

  1. FBE - mild anaemia, ↑ ESR
     * rarely haemolysis, thrombocytopenia & microangiopathic changes
  2. serology
     i. ANF
     ii. **SCL-70** ~ 35% of diffuse disease
        ~ 20% of limited disease
     iii. anti-centromere ~ 1% of diffuse disease
        ~ 50% of limited disease

- **Treatment**

  1. symptomatic & supportive
     • Raynaud's - CEB's
     • oesophagitis - H₂-blockers, omeprazole
  2. ACE inhibitors for hypertensive crises
  3. penicillamine early for aggressive systemic disease
  4. prostacycline
  5. possibly - cyclophosphamide, methotrexate

  **NB:** steroids have little or no role, especially in the presence of renal disease
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\(^1\) principally cytoplasmic pattern in Wegener's
the perinuclear pattern is seen in patients with systemic vasculitis, or vasculitis limited to the kidney;
the sensitivity of the later is undetermined & tissue diagnosis is still required
VASCULITIS

Classification

1. necrotizing systemic vasculitis
   i. classical polyarteritis nodosa
      • small and medium sized vessels, especially at branch points
      • multiple organs involved, but lungs usually spared
   ii. allergic angitis and granulomatosis *Churg-Strauss disease
      • multiple organ granulomatous vasculitis, especially involving lung
      • peripheral blood eosinophilia & eosinophilic tissue infiltration
      • association with severe asthma
   iii. polyangiitis overlap syndrome

2. hypersensitivity vasculitis
   • common feature is small vessel involvement, predominantly affecting skin
   i. exogenous antigens proven or strongly suspected
      • Henoch-Schönlein purpura
      • serum sickness
      • drug induced vasculitis
      • infection induced vasculitis
   ii. endogenous antigens probably involved
      • neoplasia associated vasculitis
      • connective tissue diseases
      • congenital complement deficiencies
      • other underlying diseases

3. Wegener's granulomatosis
   • upper & lower respiratory tracts, plus glomerulonephritis
   • paranasal sinus involvement with pain and haemorrhage
   • mucosal ulceration, cartilage destruction (saddle nose)

4. giant cell arteritis
   i. temporal arteritis
   ii. Takayasu's arteritis

5. miscellaneous
   i. mucocutaneous lymph node syndrome - Kawasaki's disease
   ii. thromboangitis obliterans - Berger's disease
   iii. isolated cerebral vasculitis
**Investigation**

1. history & examination  
2. FBE, ESR, CRP  
3. biochem - renal function, LFT's  
4. urinalysis + sediment  
5. serology  
  i. RF  
  ii. HBV Ab & Ag  
  iii. autoantibodies  
  iv. C' levels  
  v. immune complexes  
6. ECG  
7. CXR  
8. angiography  
9. tissue biopsy

**Polyarteritis Nodosa**

**Essentials**

1. majority have involvement of,  
   i. kidneys  
   ii. muscles, joints  
   iii. nerves  
   iv. GIT  
2. skin and lung involvement is *unusual* but possible  
3. clinical manifestations referable to arteries involved, including,  
   • fever, anaemia, ↑ ESR  
   • haematuria, hypertension, abdominal pain  
   • livedo reticularis, mononeuritis multiplex  
4. diagnosis confirmed by *biopsy* or by *angiogram*  
5. 5 year survival  
   i. without treatment ~ 20%  
   ii. with steroids ~ 50%  
   iii. steroids & immunosuppressives ~ 80-90%
Clinical Features

- focal or segmental lesions of small to medium sized arteries
- acute necrotising inflammation of the arterial media with *fibrinoid necrosis* and inflammatory cell infiltrate, resulting in,
  1. aneurysmal dilatation
  2. haemorrhage
  3. thrombosis
  4. fibrosis

- arterial lesions in *all stages* of development may be observed
- essentially any organ in the body may be involved, however there is a predeliction for,
  1. kidney > 80%
  2. heart
     - hypertension > 50%
  3. liver, GIT & testis
  4. muscle
  5. vasa nervorum - multiple asymmetric neuropathies

- cause is unknown, however there is a strong association with *hepatitis B* ~ 30-50%
- immune complexes consisting of part of the HBV virion have been described in some patients
- more common in,
  1. young adults
  2. males:females ~ 3:1
  3. IV drug users
  4. other groups with increased seroprevalence of HBV

Investigation

1. FBE, ESR - anaemia, leukocytosis, ↑ ESR
   - eosinophilia more common if pulmonary involvement
2. urine - haematuria, proteinuria, cylinduria
3. serology
   i. RF, ANA, (+)VDRL, ↑ IgG *neither sensitive nor specific
   ii. HBsAg, HBeAg ~ 30-50%
   iii. p-ANCA ? sensitivity/specificity
      - perinuclear pattern against *myeloperoxidase* found in PAN, or in vasculitis limited to the kidney
4. biopsy | angiography ~ 70% sensitivity
   ~ 97% specificity *tissue diagnosis*
Polymyalgia Rheumatica & Giant Cell Arteritis

- The two disease processes show considerable overlap & frequently coexist
- However, each may occur separately

**Polymyalgia**

1. Middle-aged to elderly persons *rare before 50
2. Often abrupt onset with pain & stiffness of pelvis & shoulder girdle
3. Fever, malaise & weight loss
4. Anaemia & ↑↑ ESR
5. Course is generally limited to 1-2 years

**Giant Cell Arteritis**

1. The symptoms of polymyalgia almost always precede those of GCA
2. Importance of diagnosis of arteritis is due to risk of **blindness**
   → Obstruction of posterior ciliary & opthalmic arteries
3. Symptoms suggestive of arteritis include,
   i. Throbbing headache, scalp sensitivity
   ii. Jaw claudication
   iii. Visual symptoms
4. Non-classical presentation ~ 40%
   - Respiratory tract involvement, dry cough
   - Mononeuritis multiplex
   - Fever of unknown origin
Wegener's Granulomatosis

- rare disorder characterised by,
  1. vasculitis
  2. necrotising granulomatous lesions of upper & lower respiratory tract
  3. glomerulonephritis

**NB:** without treatment virtually always fatal within 1 years of diagnosis

### Clinical Findings

1. fever, weakness, malaise, weight loss
2. purulent sinusitis, rhinitis
3. septal ulceration, perforation
4. dry cough, chest pain, haemoptysis
5. polyarthritis
6. severe progressive renal disease
   - active sediment & deteriorating renal function
   - necrotising glomerulonephritis with multiple crescents

### Investigation

1. FBE - anaemia, occasionally microangiopathic
   - ↑↑ ESR, leukocytosis
2. biochem - renal function
3. urine - haematuria, proteinuria, casts
4. **c-ANCA** > 90% positive in active disease
   - p-ANCA also occurs but with lower frequency
5. CXR & sinus X Rays
6. biopsy *tissue diagnosis* is mandatory
   - other vasculitides may appear similar
Cryoglobulinaemia

1. palpable purpura - especially lower extremities
2. glomerulonephritis
3. peripheral neuropathy
4. occasional features - abdominal pain
   - elevated LFT’s
   - cardiac & pulmonary disease
5. positive serum test for cryoglobulins
6. majority have serological evidence of previous HCV infection

- **Subtypes**

1. type I - monoclonal protein without RF activity
   - associated with lymphoproliferative disease & hyperviscosity syndrome
2. type II - monoclonal protein with RF activity
3. type III - polyclonal protein with RF activity

**NB:** types II & III most commonly seen in patients with vasculitis

Henoch-Schönlein Purpura

1. small vessel vasculitis - predominantly seen in children
   - rarely, but also seen in adults
2. purpuric lesions - predominantly lower extremities
   - may be seen on upper limbs
3. localised areas of oedema, especially dorsal surface of hands
4. joint symptoms - majority of patients
   - knees & ankles predominate
5. abdominal pain ± GIT haemorrhage
6. haematuria - segmental GN with crescent formation
   - mesangial deposition of IgA, occasionally IgG
7. hypersensitivity to aspirin, food additives & drugs has been reported
8. majority of lab tests normal - ↑ ESR

**NB:** disease is usually self-limiting, lasting 1-6 weeks,
providing renal involvement is not severe
Marfan's Syndrome

**Def'n:** defined upon the basis of characteristic changes in three connective tissue systems,
1. skeleton
2. eyes
3. cardiovascular system

### Clinical Features

1. autosomal dominant - variable expression
   ~ 15-30% may be due to new mutations
   - the system abnormalities can be inherited independently in some families
2. **skeletal changes**
   i. tall with long limbs
   ii. long slender fingers & toes - *arachnodactyly*
   iii. overgrowth of the ribs - pes excavatum, pes carinatum, asymmetry
   iv. scoliosis / kyphosis
   v. hypermobility of joints - most are mild
   - rarely similar to Ehler's Danlos
   - very rarely stiff joint syndrome
3. **cardiovascular changes**
   i. mitral valve prolapse
   ii. aortic dilatation - from aortic root & progressive
   - dissection & rupture are common
   iii. high risk during pregnancy - up to 50% mortality in some series
4. **ocular**
   i. subluxation of the lens - *ectopia lentis*, usually upward
   ii. glaucoma - usually 2° lens dislocation or surgery
   iii. increased axial globe length - *myopia*
   - retinal detachment