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 perisistent ***inflammatory synovitis***,

a. usually symmetrical

b. associated destruction of cartilage and bone

c. charcteristic 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 C_1
        - odontoid may sublux through foamen 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, thrombocytopaenia, 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
   - scleromalacia & scleromalacia 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***, 2nd & 3rd decades
2. M:F ratio ~ 9:1
3. strong genetic disposition
   i. > 90% HLA-B27 positive
   ii. 1st 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, Archilles tendonitis
   - severe spinal fusion & rigidity ocurs 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.	antierythrocyte	~ 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 & errosions — rare ± subcutaneous nodules
   - myopathy / myositis — inflammatory or 2° to therapy
   - ischaemic necrosis of bone — hip, knee & shoulder pain
4. ***renal***
   - ***all*** have Ig-C_3 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
   - thrombocytopaenia
   - ***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

- ***<u>Drug-Induced Lupus</u>***

1. ***procainamide*** ~ 50-75% → ANA-Ab, 20% LE
2. ***hydrallazine*** ~ 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 - $\downarrow DL_{CO}$, $\downarrow C_L$
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

- ***Laboratory Findings***

1. FBE - mild anaemia, ↑ ESR
   * rarely haemolysis, thrombocytopaenia & 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 - H_2-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

Antibodies to:	**ANA**	**RF**	**Sm**	**Ro | La**	**SCL-70**	**centro-mere**	**ANCA**
RA	30-60	70-85					
SLE	95-100	20	10-25	5-20			
Sjogren's	95	75					
Scleroderma • limited (CREST) • diffuse	 80-95 80-95	 25-33 25-33			 20 33	 50 1	
Polymyositis	80-95	33			10		
Wegener's	0-15	50					93-96[1]

[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 angiitis and granulomatosis *Churg-Strauss disease
     - multiple organ granulomatous vasculitis, especially involving ***lung***
     - peripheral blood eosinophilia & eosinophillic tissue infiltration
     - association with ***severe asthma***
   - iii. polyangiiitis 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 referrable 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 & imunosuppressives ~ 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 assymetric 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 seperately

- ***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*** & ***ophthalmic*** 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. polyarthralgia
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 XRays
6. biopsy — * ***tissue diagnosis*** is mandatory
    - other vasculitidies 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