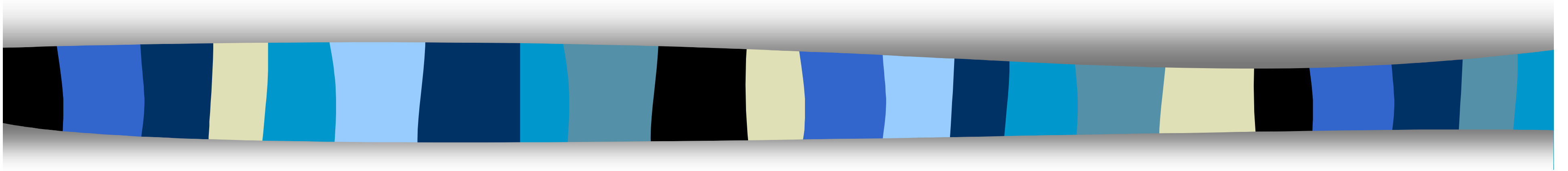
Connective Tissue Diseases



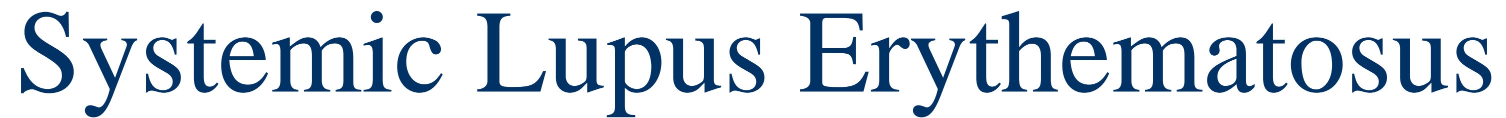
Edward D. Buckingham, MD

Byron J. Bailey, MD

- collagen vascular diseases, autoimmune diseases
- knowledge of immune system
- difficult to diagnose
  - nonspecific symptoms
  - tend to overlap
- common histiologic feature
  - inflammatory damage CT and blood vessels
  - fibrinoid material deposition

- lymphoid stem cell
- B-cell
- T-cell
- macrophage or monocyte
- NK cells

- abnormal interaction
- three theories
  - – sequestered antigen
  - – exogenous antigen
  - – altered antigen



- General
  - autoimmune multisystem disease
  - prevalence 1 in 2,000
  - 9 to 1; female to male (1 in 700)
  - peak age 15-25
  - immune complex deposition
  - photosensitive skin eruptions, serositis, pneumonitis, myocarditis, nephritis, CNS involvement

Systemic Lupus Erythematosus

- specific labs - native(Double stranded) DNA, SM antigen
- lupus like reaction(procainamide, hydralazine, ect)
- LE cells

SLE - Diagnostic Criteria

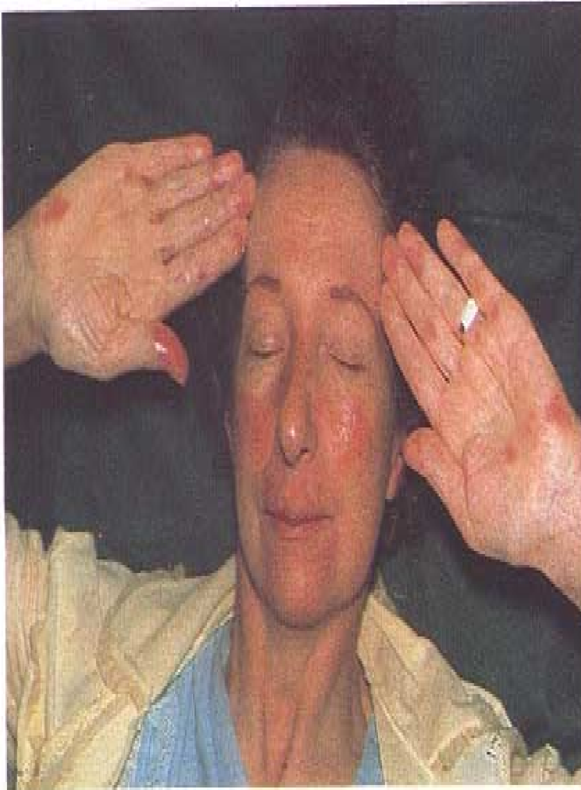
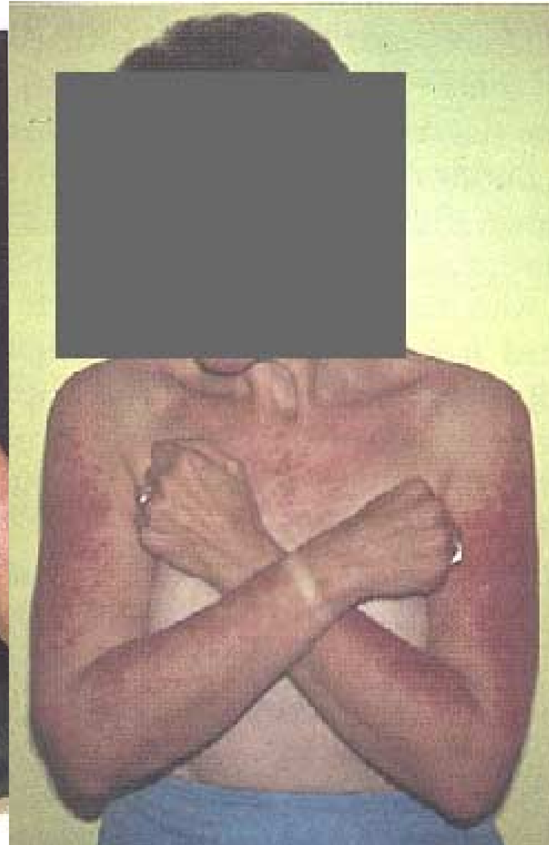
Diagnostic criteria[a]	Percent/incidence
Malar rash	64
Discoid rash	17
Photosensitivity	37
Oral ulcers	15
Arthritis	90
Proteinuria (0.5 g/dL) or cellular casts	20
Seizures or psychosis	19
Pleuritis or pericarditis	19
Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia	11–40
Antibody to DNA or Sm antigen, + LE prep, or false +RPR	15–60
Positive fluorescent antinuclear antibody[b]	95

[a]The diagnosis of SLE requires the presence of four of the 11 criteria (96% sensitivity, 96% specificity).

[b]Increased antibodies to double-stranded DNA are pathognomonic.

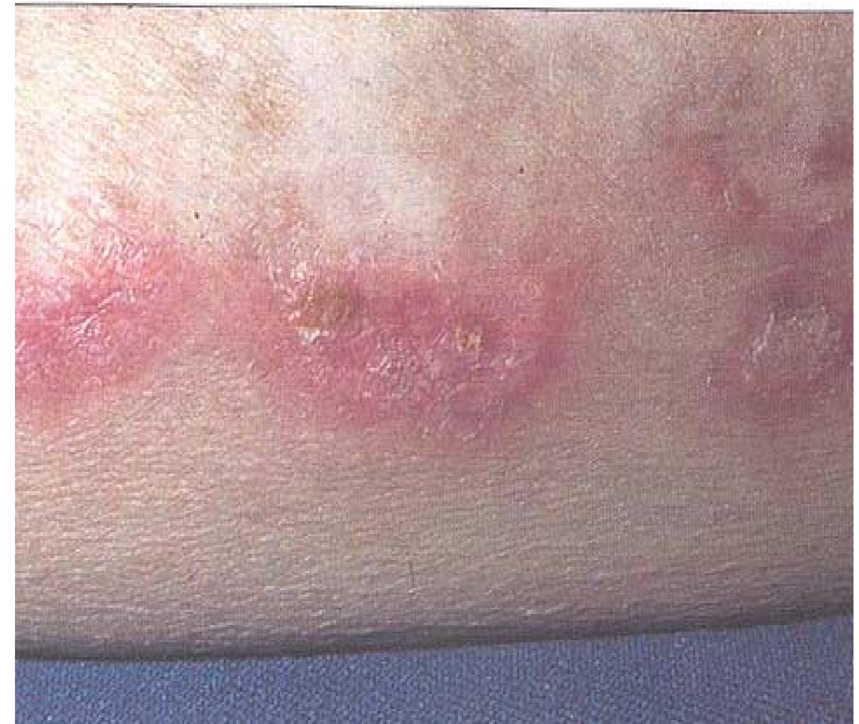
- Head and Neck Manifestations
  - Malar rash first sign in 50%
  - Erythematous maculopapular eruption after sun exposure
  - Oral ulceration

SLE

- Head and Neck Manifestations
  - 3-5% perforated nasal septum
  - larynx and trachea involvement rare
    - TVC thickening, paralysis, cricoarytenoid arthritis, subglottic stenosis
  - acute parotid enlargement 10%

- Head and Neck Manifestations
  - xerostomia occas
  - neuropathy 15%
  - discoid lupus



- Treatment
  - avoid sun exposure
  - NSAIDS
  - topical and systemic steroids
  - antimalarials
  - low-dose methotrexate
  - azothioprine, cyclophosphamide restricted
  - symptomatic treatment
    - saliva substitutes, Klack’s solution
  - postprandial rinses with H2O2 and H2O

Rheumatoid Arthritis

- General
  - synovial tissue involvement
    - symmetric peripheral joints (hands, feet, wrists)

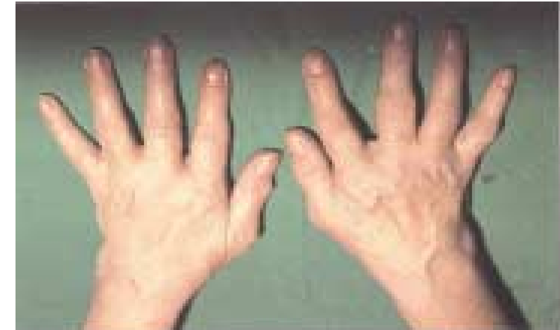


Fig. 3 Early RA. Synovial thickening of PIP joints and wrists. Deformity minimal.

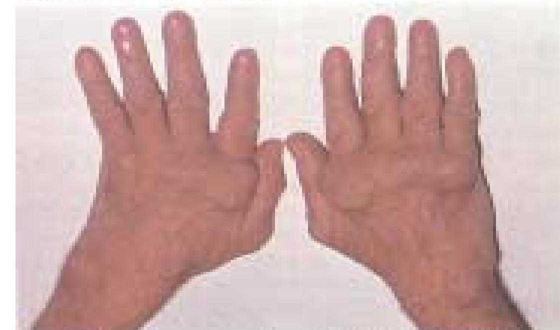
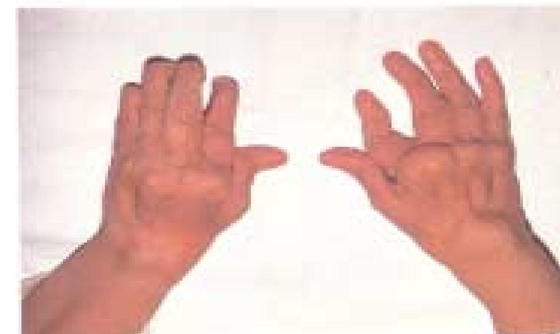


Fig. 4 RA at later stage. Considerable MCP joint thickening, subluxation and ulnar deviation.

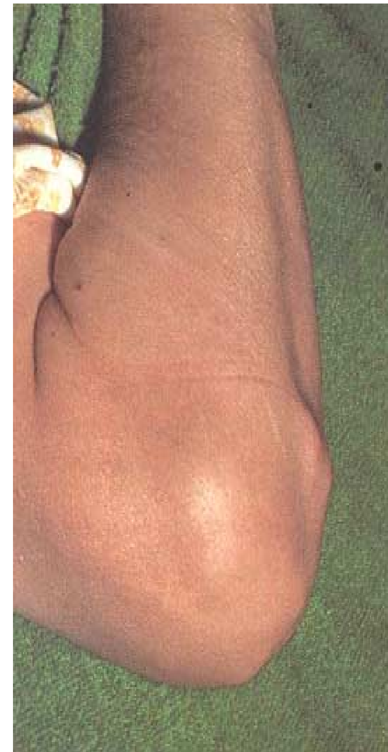
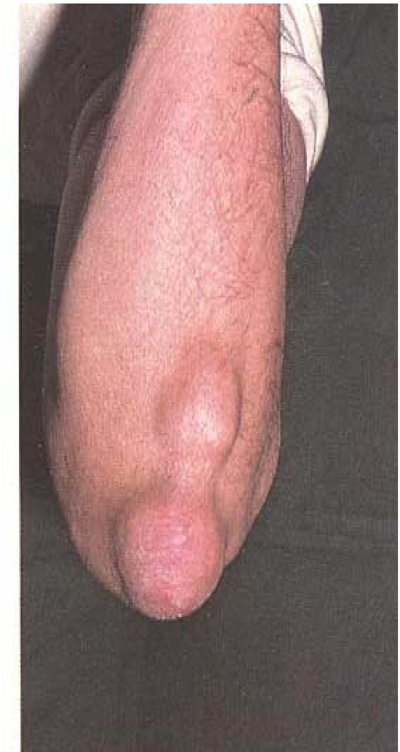


RA

- General
  - nonarticular muscular structures
    - tendon, ligament, fascia
  - systemic disease occas.
    - vasculitis, pulmonary fibrosis
  - pathogenosis
    - inflammatory cell infiltrates
    - synovial proliferation
  - HLA Dw4

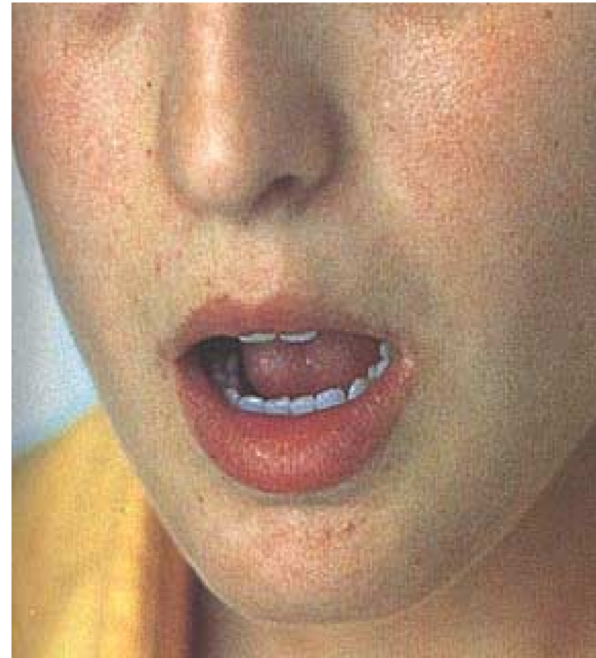
RA

- General
  - prevalence
    - 1% of population
    - 2-3 times F>M
    - 4th and 5th decade
  - signs and symptoms
    - morning stiffness lasting greater than 30 min
    - sub-Q rheumatoid nodules
    - synovial fluid inflammation 2K - 75K 50% PMN's

- General
  - diagnosis based on clinical grounds
  - labs
    - RF pos. in 12 months 90%
    - RA associated nuclear antigen (RANA)
    - anti-RA-33

- Head and Neck Manifestations
  - TM joint
    - 55% symptomatic
    - 70% incidence on X-ray
  - juvenile RA - micrognathia



- Head and Neck Manifestations
  - cricoarytenoid joint
    - most common cause of arthritis
    - 30% patients hoarse
    - 86% pathologic involvement
    - exertional dyspnea, ear pain, globus
  - hoarseness
    - rheumatoid nodules, recurrent nerve involvement
  - stridor
    - local/systemic steroids
    - poss. Tracheotomy

- Head and Neck Manifestations
  - CHL
    - ossicular chain involvement
    - flacid TM
  - SNHL
    - unexplained
    - assoc. with rheumatoid nodules
  - cervical spine
    - subluxation

RA

- Treatment
  - physical therapy, daily exercise, splinting, joint protection
  - salicylates, NSAIDS, gold salts, penicillamine, hydroxychloroquine, immunosuppressive agents
  - systemic steroids should be avoided
  - prognosis
    - 10-15 yrs of disease
      - 50% fully employed
      - 10% incapacitated
      - 10-20% remission

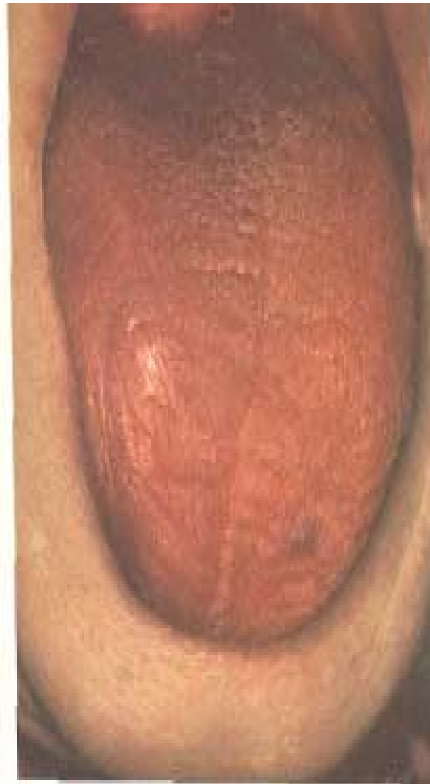
- General
  - immune mediated
  - destruction of exocrine glands
  - primary
    - sicca syndrome- isolated d/o lacrimal and salivary glands
  - secondary
    - sicca complex- assoc. with other CTD

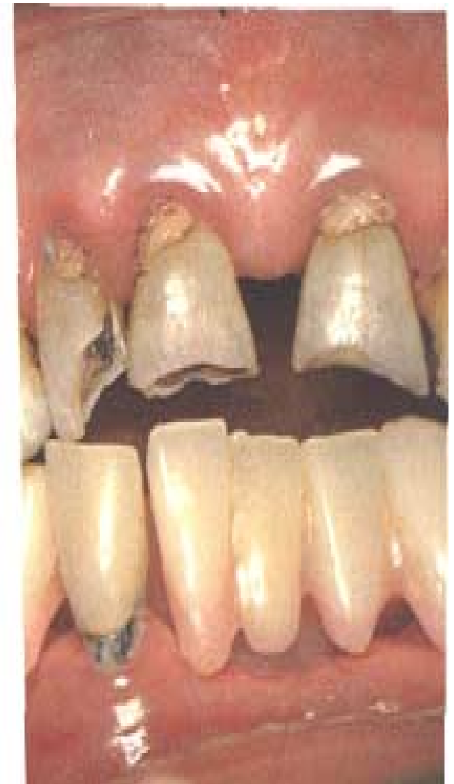
- General
  - prevalence
    - 1% population
    - 10-15% of RA patients
    - 9 to 1 F>M
    - onset 40-60 yrs
  - increased risk of lymphoma
    - pehaps 44 times risk

- General
  - clinical manifestations
    - xerophthalmia, keratoconjunctivitis
    - xerostomia
    - other areas
      - skin, vagina, genitalia, chronic bronchitis, GI tract, renal tubules
  - diagnosis
    - minor salivary gland biopsy
    - labs
      - RF and ANA
      - SS-A/Ro 60%
      - SS-B/La 30%

Sjogren's Syndrome

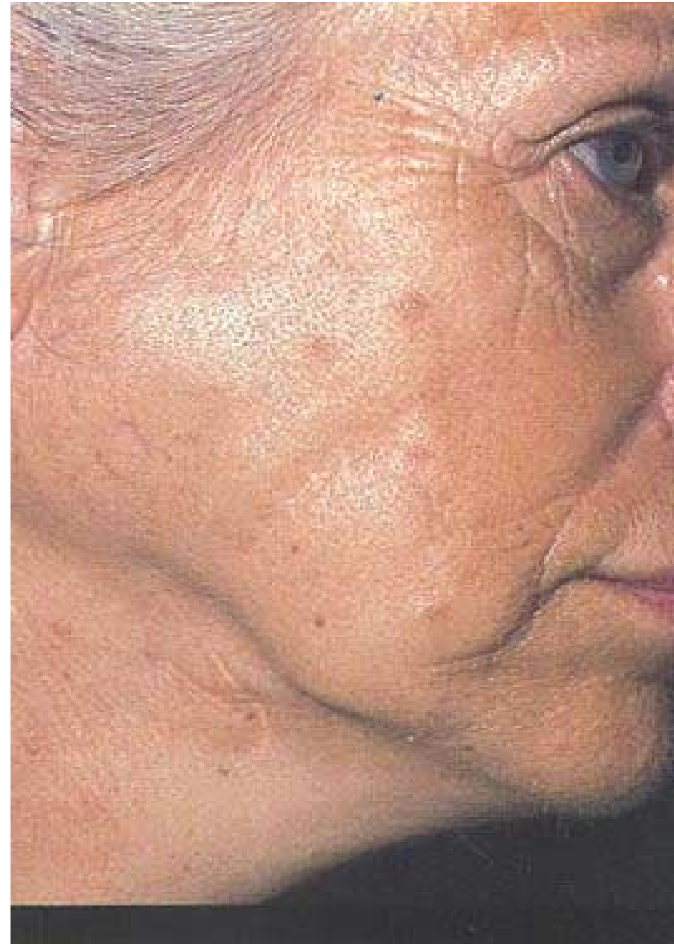
- Head and Neck Manifestations
  - 80% c/o xerostomia, most prominent symptom
  - difficulty chewing, dysphagia, taste changes, fissures of tongue and lips, increased dental caries, oral candidiasis





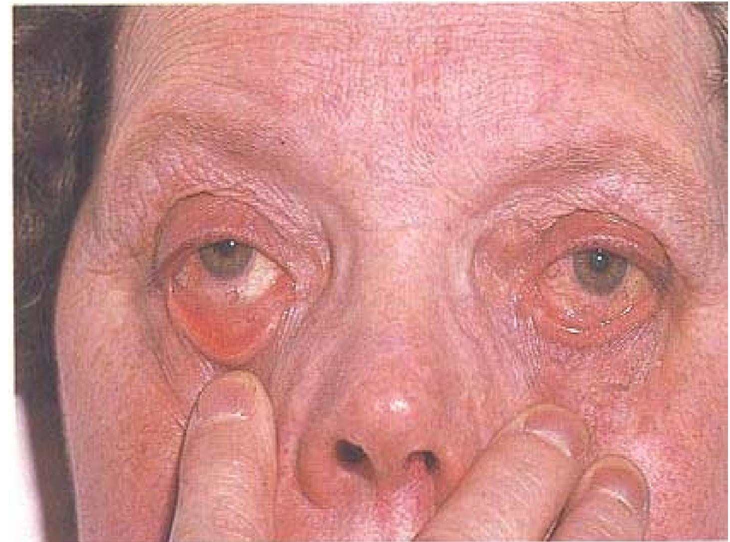
Sjogren's Syndrome

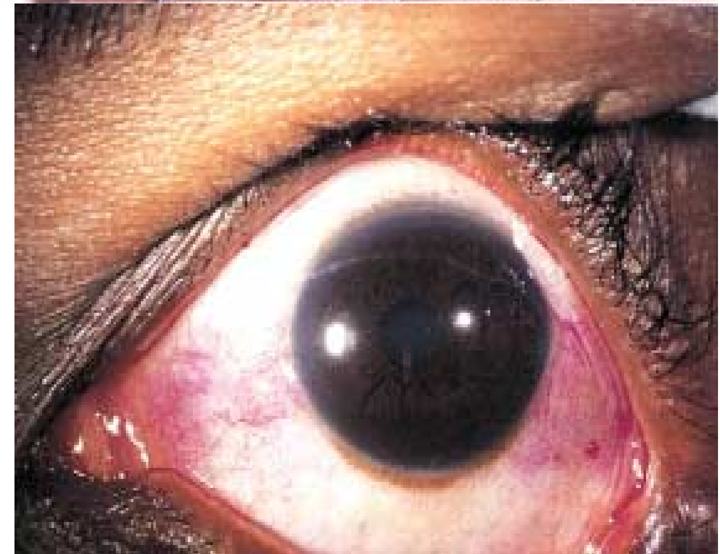
- Head and Neck Manifestations
  - salivary quantification- salivary scintigraphy
  - salivary gland enlargement



Sjogren's Syndrome

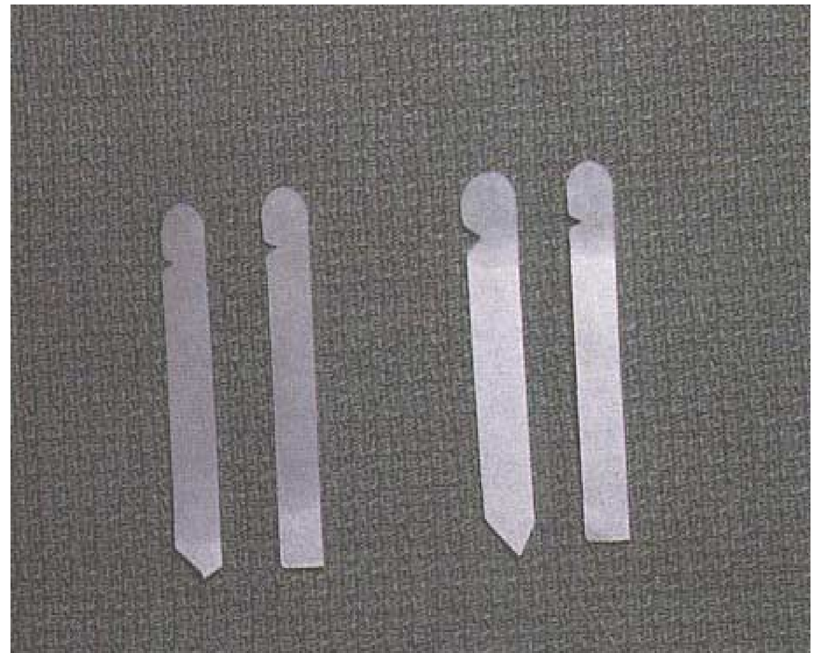
– eye complaints
  - dryness, burning, itching, foreign body sensation
– keratoconjunctivitis sicca
  - corneal abrasions - rose bengal staining





Sjogren's Syndrome

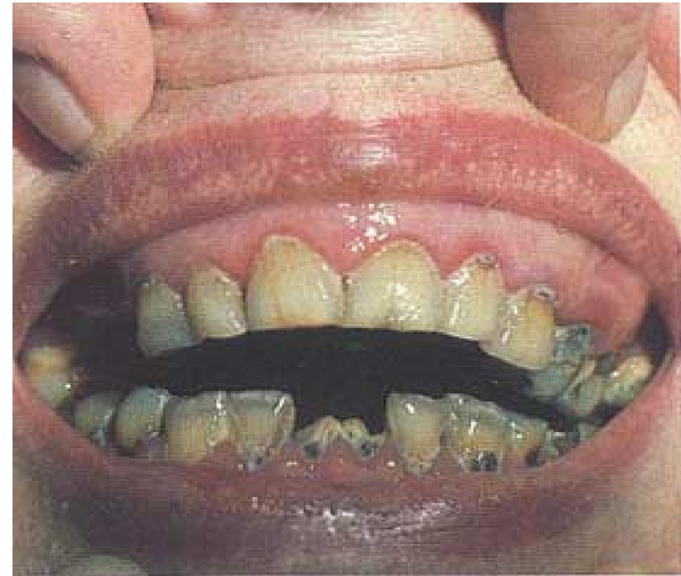
- Schirmer I
- Schirmer II
- nasal crusting, epistaxis, hyposmia
- diagnostic algorithm
  - history>Schirmer I>Schirmer II or rose bengal staining or other supportive evidence>minor salivary gland biopsy



- Treatment
  - symptomatic
    - oral fluid intake
    - saliva substitutes
    - artificial tears
  - avoid
    - decongestants
    - antihistamines
    - diuretics
    - anticholinergic

Sjogren's Syndrome

- Treatment
  - pilocarpine
  - clotrimazole/nystatin
  - close dental supervision
  - surveillance for malignancy



Scleroderma

- General
  - increased depostion collagen in interstitium of small arteries and connective tissue
  - sclerotic skin changes, often multisystem disease
  - prevalence
    - 4-12/million/year
    - 3-4 to 1 F>M
    - 30-50 yrs
    - prognosis
      - black worse white
      - men worse women

- General
  - presentation
    - Raynaud’s phenomenon
    - edema fingers and hands
    - skin thickening
  - visceral manifestations
    - GI tract, lung, hear, kidneys, thyroid
  - arthralgias and muscle weakness often

Scleroderma

- General
  - four categories
    - diffuse cutaneous
      - worse prognosis
    - limited cutaneous (CREST)
      - more benign, less renal
    - systemic sclerosis sine scleroderma
      - visceral manifestations without skin changes
    - systemic sclerosis in overlap
      - concomitant with SLE, polymyositis, RA

Scleroderma -CREST

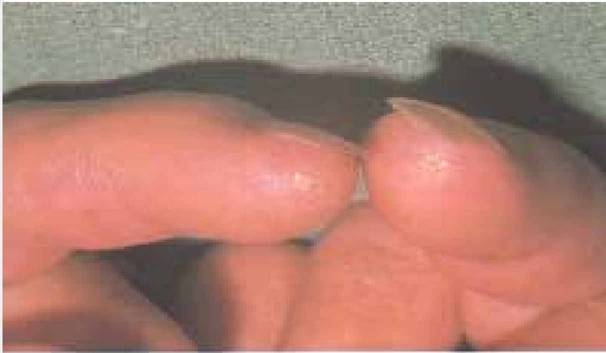
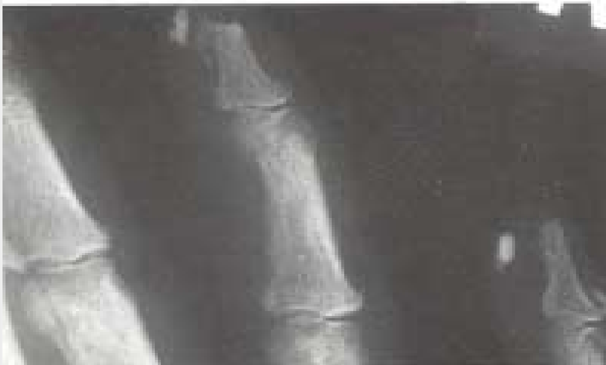
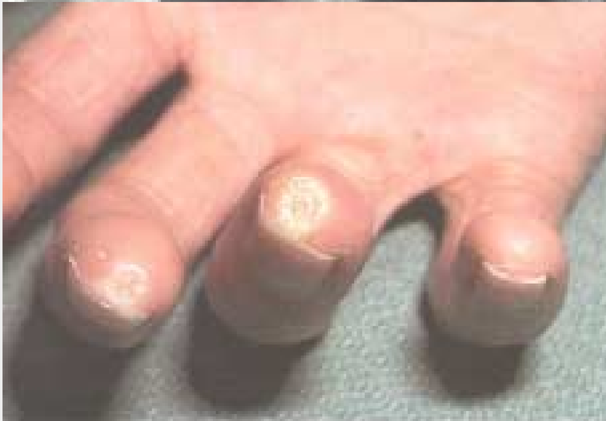
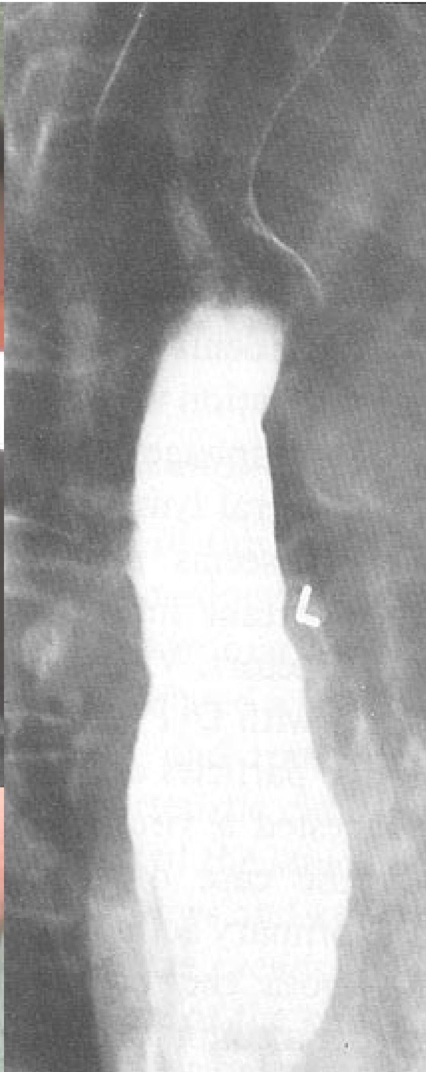
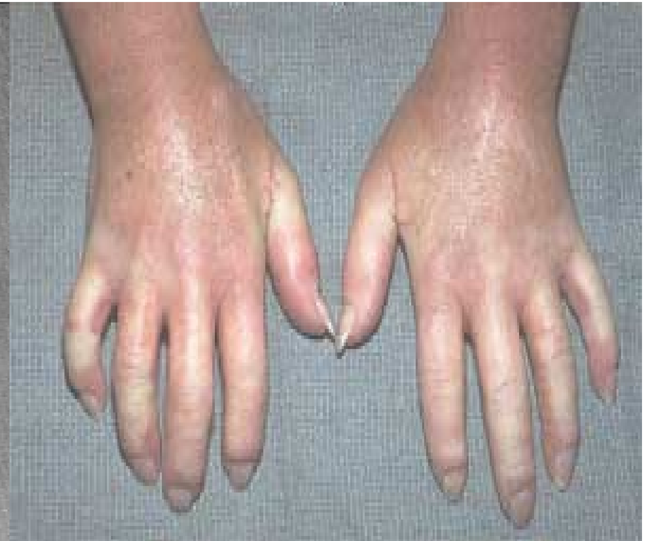


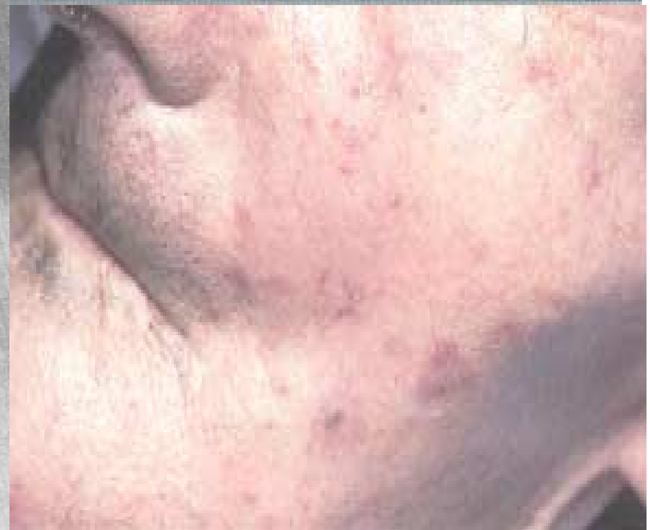
Fig. 74 Scleroderma. Calcinosis cutis.







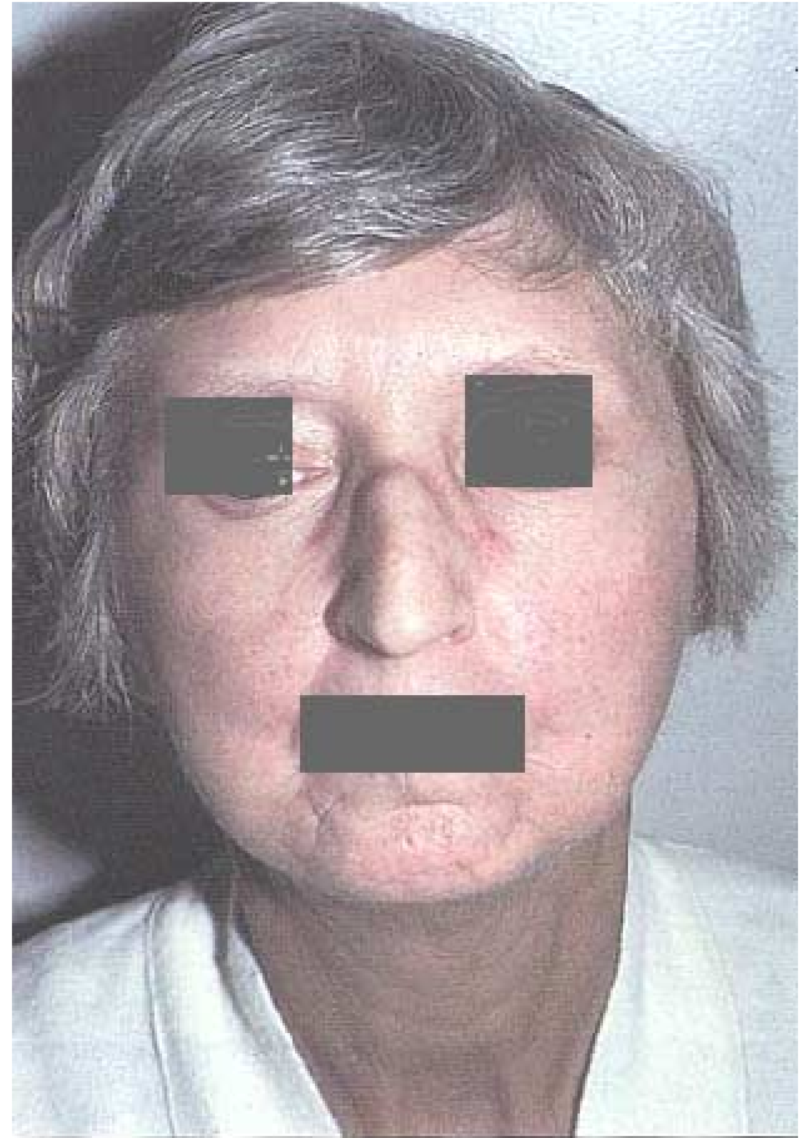




- General
  - labs
    - diffuse cutaneous- anti-ScL-70
    - limited cutaneous- anticentromere
    - ESR, anemia, ANA, hypergammaglobulinemia, RF, LE cells,
    - abnormal EKG 50% (low voltage, axis deviation, conduction defects)

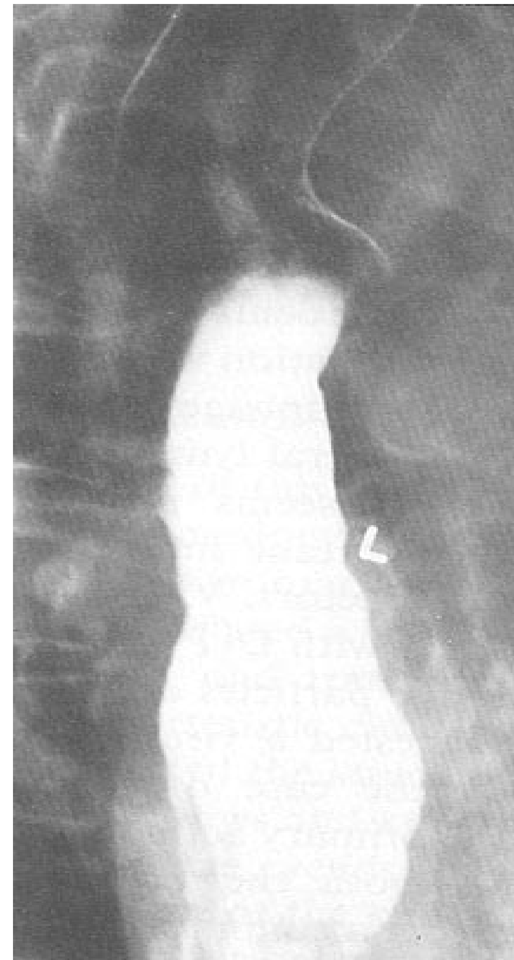
Scleroderma

- Head and Neck Manifestations
  - 80 % have, 30% present with
  - tight skin, thin lips, vertical perioral furrows
    - dermal and subcutaneous inflammatory process
    - edema preceeds epidermal atrophy, loss of appendages



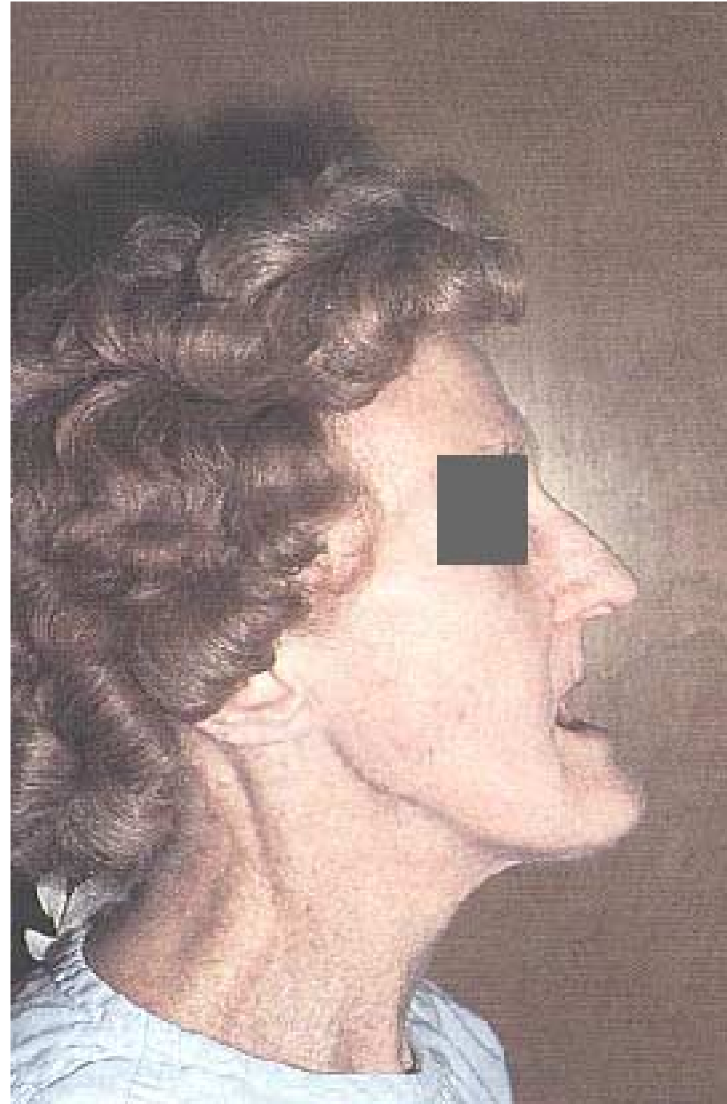
Scleroderma

- Head and Neck Manifestations
  - dysphagia
    - most common initial complaint
    - 80% distal 2/3 pathology on BS
    - decrease/absent paristalsis, dilation, hiatal hernia



Scleroderma

- Head and Neck Manifestations
  - decreased mouth opening
    - initial complaint 19%



- Head and Neck Manifestation
  - – gingivitis, periodontal thickening
  - – translucent zone around dental roots
    - considered pathognomonic by some
  - – 25% xerostomia, xerophthalmia
  - – laryngeal involvement, hoarseness 50%
  - – Raynaud’s of tongue infrequent
  - – trigeminal nerualgia, facial nerve palsy infrequent

Scleroderma

- Treatment
  - symptomatic
    - calcium channel blockers in Raynaud’s
    - H2 blockers for reflux
    - NSAIDS and steroids for arthralgias and myalgias
    - hand rehab
    - intra-arterial reserpine- decreases vasoconstriction>healing

- General
  - group of disorders
  - proximal muscle weakness
  - nonsuppurative inflammation skeletal muscle
  - prevalence
    - 5 cases/mil/year
    - 2 to 1 F>M
    - 40-60 yrs
    - pediatric variant 5-15-yrs

Myositis

- General
  - criteria
    - proximal muscle weakness
    - elevated serum CPK
    - myopathic changes on EMG
    - muscle biopsy inflammation
    - definitive with four, probable with three, possible with two
    - dermatomyositis skin rash with above

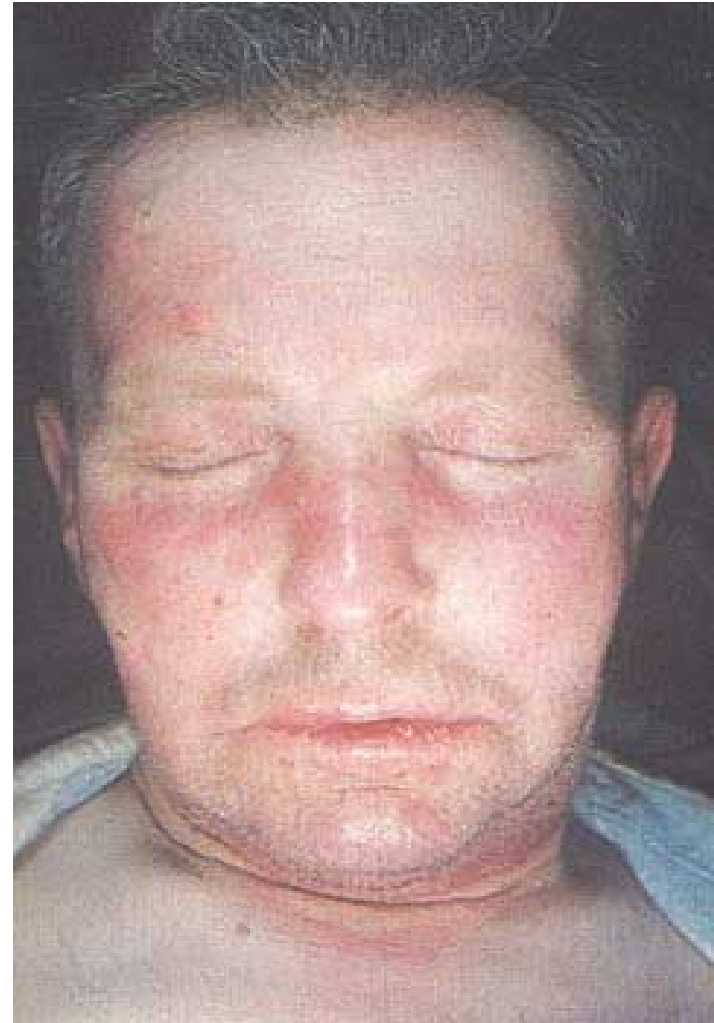
Myositis

- General
  - labs
    - anti-tRNA synthetases
  - up to 20% associated with malignancy
    - lung, ovary, breast, stomach
    - parotid, tonsil reported
    - dermatomyositis with nasopharyngeal carcinoma, endemic areas

- Head and Neck Manifestations
  - weakness neck muscles
  - difficulty phonation, deglutition, nasal regurgitation
  - dysphagia from upper esophagus
  - may result in aspiration pneumonia

Myositis

- Head and Neck Manifestations
  - skin lesions
    - predilection for eyelids, nose, and cheeks



- Treatment
  - steroids if symptomatic
  - methotrexate, immunosuppresives nonresponders
  - H2 blockers
  - metoclopromide

- General
  - recurring inflammation cartilaginous structures
  - eventual fibrosis
  - prevalence
    - F>M
    - 25-45
    - equal racial
  - can affect any cartilagenous structure
    - including heart valves and large arteries

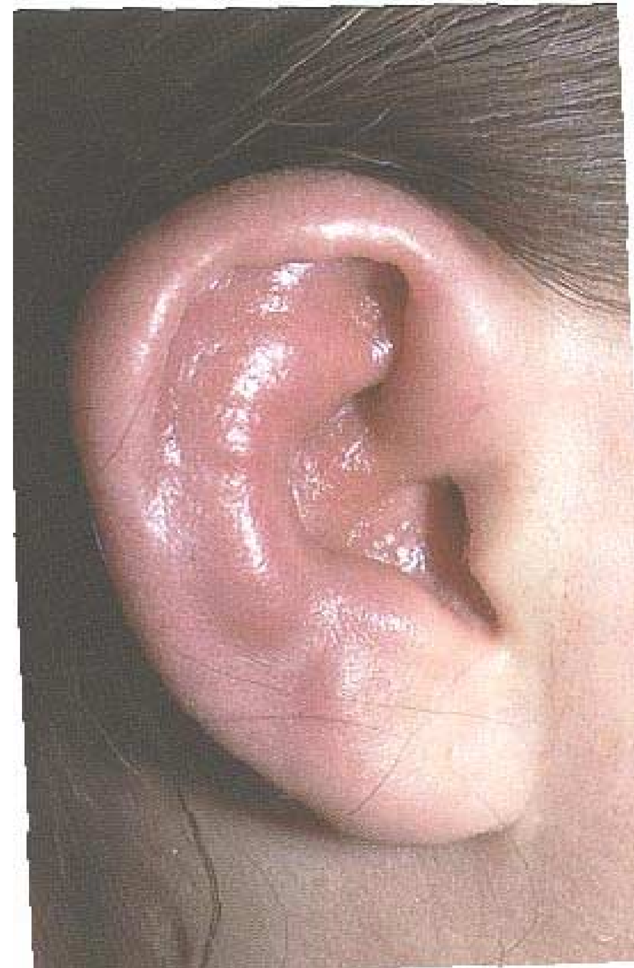
Polychondritis

- General
  - diagnostic criteria
    - recurrent chondritis auricles
    - nonerosive inflammatory polyarthritis
    - chondritis of nasal cartilages
    - inflammation of ocular structures
    - chondritis of laryngeal or tracheal cartilages,
    - cochlear (SNHL, tinnitus) vestibular (vertigo) damage

- General
  - labs
    - ESR, leukocytosis, anemia
  - histology
    - loss of basophilic staining of cartilage
    - perichondral inflammation
    - destruction fibrotic replacement

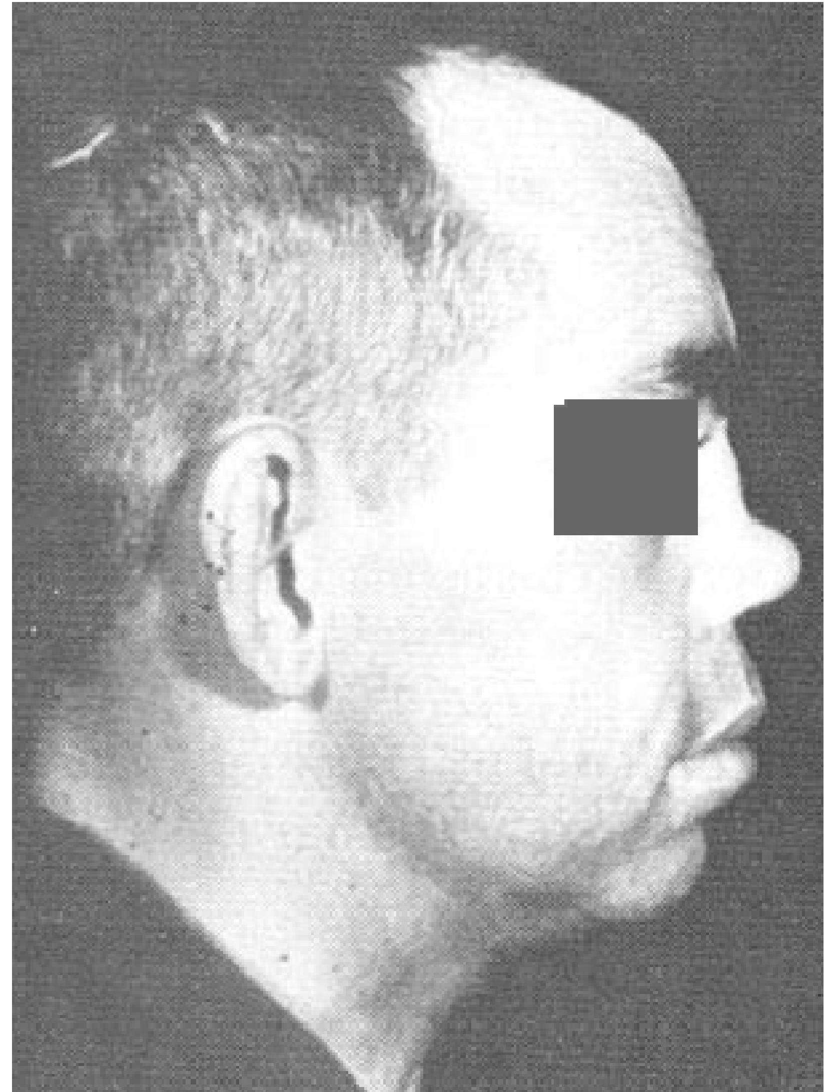
Polychondritis

- Head and Neck Manifestations
  - auricular chondritis, nonerosive arthritis most common
    - sudden onset erythema, pain,
    - spares EAC
    - feature presentation in 33%
    - present in 90%
    - occasional LAD
    - resolution 5-10 days with or without



Polychondritis

- serous otits, SNHL, 49% inner ear symptoms
- nasal chondritis
  - devolopes in 75%
  - not necessarily coincides with auricular



- laygeal involvement
  - nonproductive cough
  - hoarseness
  - stridor
  - 53% airway involvement

- Treatment
  - salicylates, ibuprofen-symptomatic relief
  - steroids for life threatening
  - dapson (anti-leprosy) reduces lysozymes

- General
  - 1972
  - coexisting features
    - SLE,scleroderma, polymyositis
  - high titers anti-U1 RNP
  - prevalence
    - unknown
    - 80% female
    - 30-60 years

- General
  - diagnostic criteria
    - elevated anti U1-RNP plus
    - three of either
      - hand edema
      - synovitis
      - myositis
      - Raynaud’s phenomenon
      - acrosclerosis

Mixed Connective Tissue Disease

- Head and Neck Manifestations
  - combination of features of other CTD
    - mucocutaneous rash, malar rash, discoid lupus, sclerodermatous changes, nasal septal perforation, esophageal dysfunction
- Treatment
  - steroid therapy for symptomatic relief
  - immunosuppressives for complications of vital organs

- inflammation and necrosis of blood vessels
- immunologic mechanism
- any blood vessel involved
- diverse symptoms and overlap
- difficult classification

TABLE 11. *Classification of Systemic Vasculitides*

1. Hypersensitivity vasculitis
   - Serum sickness
   - Henoch-Schönlein purpura
   - Cryoglobulinemia
   - Associated with hypocomplemententemia and urticaria
   - Associated with other autoimmune diseases
   - Associated with other diseases (infections, neoplasia, etc.)
2. Polyarteritis nodosa
   - Classic polyarteritis nodosa
   - Allergic angiitis and granulomatosis (Churg-Strauss)
   - Undefined systemic necrotizing vasculitis
3. Wegener's granulomatosis
4. Giant cell arteritis
   - Giant cell arteritis/temporal arteritis/polymyalgia rheumatica
   - Takayasu's arteritis
5. Miscellaneous
   - Mucocutaneous lymph node syndrome (Kawasaki's disease)
   - Behçet's disease
   - Cogan's syndrome
   - Thromboangiitis obliterans
   - Many other syndromes

- pathogenesis
  - unclear
  - deposition of antibody-antigen-complement in vessel walls
  - antigen deposition triggering lymphcytic reaction

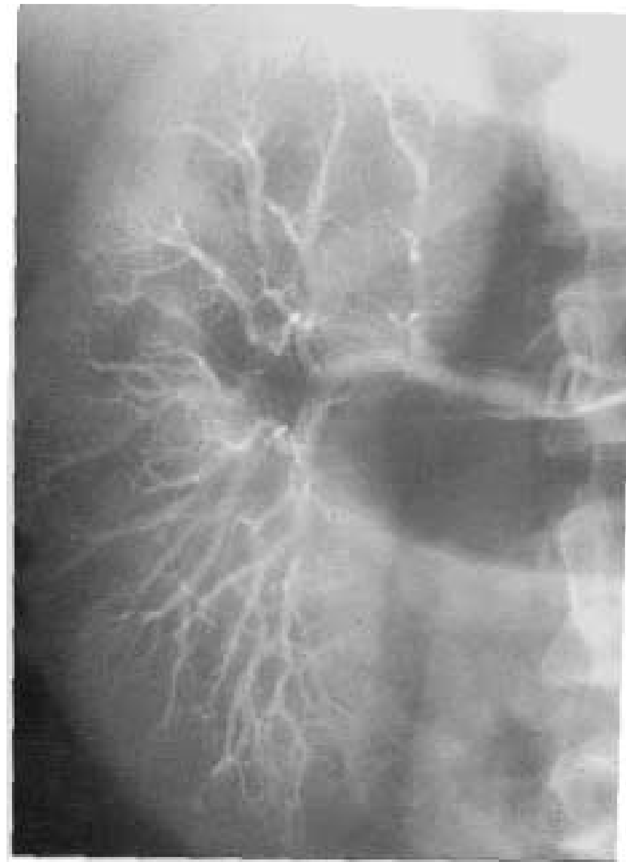
- clinically
  - multisystem disease
  - symptoms- obliterative narrowing end-organ ischemia
  - specific diagnosis rarely on clinical grounds
  - serologic testing yield diagnosis minority
  - biopsy often necessary

- General
  - collective term group of diseases
  - inflammation of small vessels
    - arterioles, capillaries, venules
  - circulating and deposited immune complexes
  - skin always involved
    - hemorrage or classic purpura
  - major organ system involvement less common

- Head and Neck Manifestations
  - petechiae, purpura of oral and nasal mucosa
  - angioedema
  - serous otitis media
- Treatment
  - usually self limited
    - especially when only skin involved
  - systemic involvement- more aggressive

Polyarteritis Nodosa

- General
  - prototype of vasculitides
  - prevalence
    - 2-3 to 1, M>F
    - 50-60 yrs
  - hepatitis B antigen in 30%
  - small and medium arteries, aneurysms



- General
  - tissues
    - GI tract, hepatobiliary system, kidney, pancreas, skeletal muscles
  - complaints
    - non-specific multisystem (malaise, weight loss, anorexia, fever)
  - signs
    - progressive arthritis, myopathy, neuropathy, hepatic and renal failure, GI bleeding

- Head and Neck Manifestations
  - few
  - ear
    - sudden bilateral SNHL infrequent
    - vestibular symptoms infrequent
  - rarely ulceration of nasal, buccal, soft palate mucosa, cranial nerve palsies
- Treatment
  - Steroids- benefit not long term

- AKA allergic angiitis and granulomatosis
- General
  - resembles PAN
  - triad of systemic vasculitis, asthma, peripheral and tissue eosinophilia
  - nasal symptoms prominent
  - unlike PAN-lungs always involved
  - malaise, night sweats, fever, weight loss, myalgias
  - peripheral eosinophilia up to 74%, ESR

- Head and Neck Manifestations
  - Nasal symptoms
    - nasal obstruction, rhinnorhea, nasal polyps, sinusitis
    - 25% severe nasal crusting recurrent in 24-48 hrs
    - occasional septal perforation
- subcutaneous nodules
  - path will show eosinophilia
- history of allergy

- Treatment
  - Steroids

- General
  - necrotizing granulomas of upper airway, lower airway, kidney
  - bilateral pneumonitis 95%
  - chonic sinusitis 90%
  - mucosal ulceration of nasopharynx 75%
  - renal disease 80%
  - hallmark pathologic lesion
    - necrotizing granulomatous vasculitis

Wegener's Granulomatosis

- antineutrophil cytoplasmic antibody (c-ANCA)
  - sensitivity 65-90%
  - high specificity
- need to confirm diagnosis
  - often 3-4 biopsies necessary
  - nasopharynx commonly involved good site
  - open pulmonary biopsy occasionally needed
  - untreated mortality of 90% at two years

Wegener's Granulomatosis

- Head and Neck Manifestations
  - nasal symptoms
    - crusting, epstaxis, rhinnorrhea, erosion of septal cartilage, saddle deformity, recurrent sinusitis
  - oral cavity
    - hyperplasia of gingiva, gingivitis

- upper airway
  - edema, ulceration of larynx (25%) significant subglottic stenosis (8.5%)
- otologic
  - serous otitis media (20-25%), CHL, suppurative otitis media, SNHL, pinna changes similar to polychondritis, facial nerve palsies

- Treatment
  - meticulous dental and nasal care
  - middle ear drainage
  - cyclophosphamide 2 mg/kg plus prednisone 1 mg/kg
    - remission 93%
  - azathioprine or methotrexate alternative to cyclophosphamide

Wegener's Granulomatosis

- Treatment
  - – isolated sinonasal disease
    - low dose steroids, saline irrigation, antibiotics as needed
  - – subglottic stenosis
    - may warrant tracheotomy

- General
  - temporal arteritis
    - form of giant cell
    - only extracranial vessels affected
  - focal grannulomatous inflammation
    - medium and small arteries
  - most common vasculitis
  - prevalence
    - increases with age
    - 850/100,000 age >80

- symptoms
  - headache(constant, boring)
    - most common initial complaint 47%
    - 90% eventually develop
- ESR usually > 50 mm/hr
- confirmation temporal artery biopsy
  - symptomatic side 5-7 cm
  - if negative biopsy contralateral side
  - false negative rate 5-40%

- Head and Neck Manifestations
  - temporal artery tender, erythematous 50%
  - scalp tender
  - jaw claudication 50%
  - lingual claudication 25%
  - vertigo and hearing loss reported
  - ascending pharyngeal artery
    - involvement > dysphagia

- Head and Neck Manifestations
  - cranial nerve deficits, VB insufficiency, psychosis > IC disease
  - blindness > 1/3 untreated patients
    - field deficits, amaurosis fugax

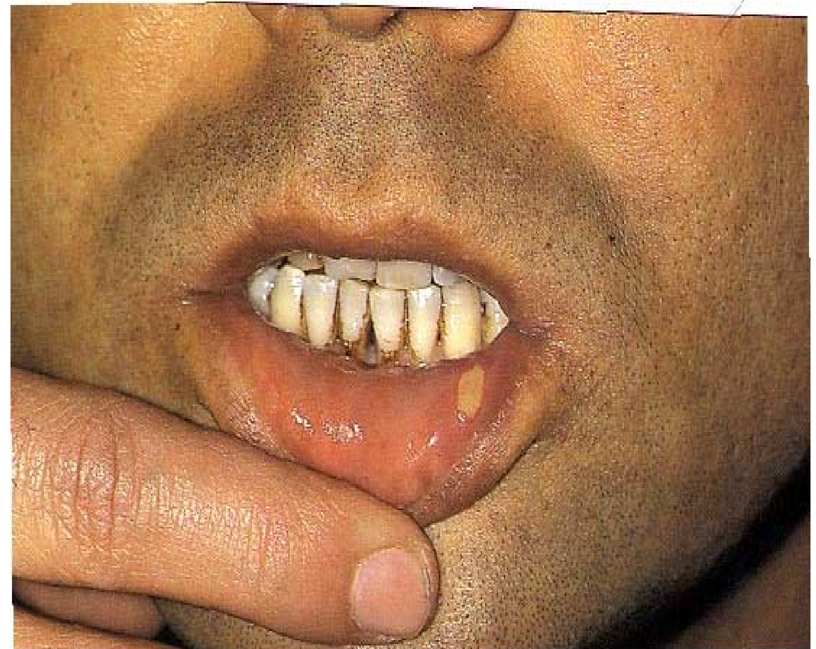
- Treatment
  - prednisone
  - normalization of ESR and symptoms
  - up to two years

- accompanying syndrome in 50% GC arteritis
- clinical syndrome
  - muscular pain
  - morning stiffness proximal muscles
  - increased ESR
  - no inflammatory joint or muscle disease
  - low grade fever, weight loss, malaise

- treatment
  - low dose prednisone if isolated
  - as with GC if associated

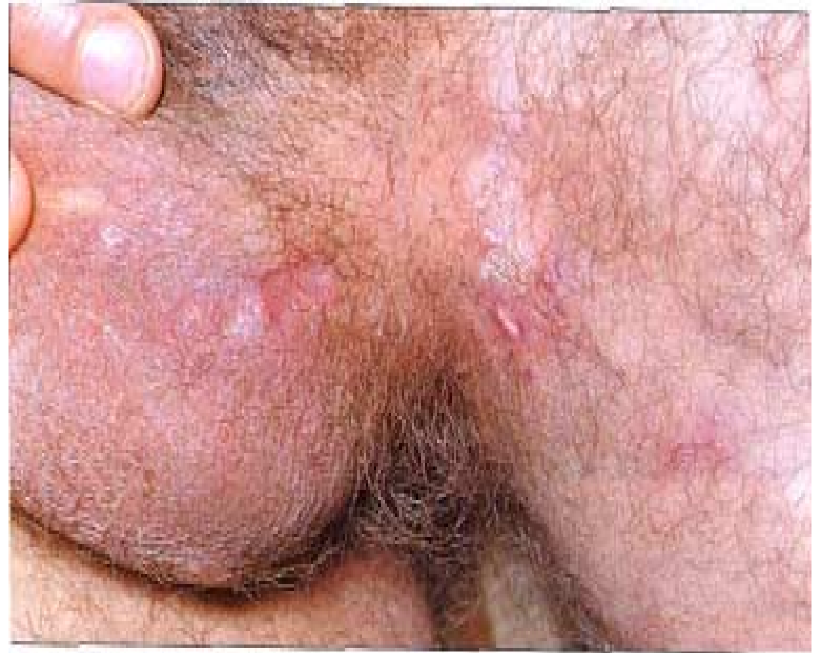
Behcet's Disease

- Vasculitis with triad
  - oral, genital ulcers, uveitis or iritis
  - oral
    - aphthous-like
    - painful, clusters on lips, gingiva, buccal, tongue
    - less often palate, oropharynx



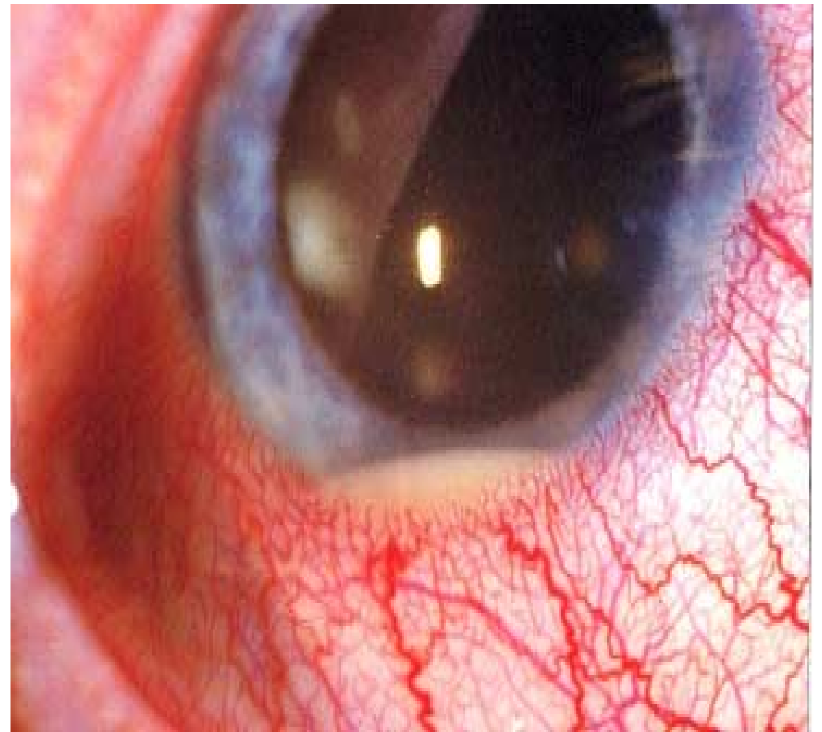
Behcet's Disease

- genital
  - similar in appearance



Behcet's Disease

- occular
  - uveitis, iritis
  - hypopyon
- healing in days to weeks some scarring
- symptoms simultaneously, months apart



- other findings
  - progressive SNHL, tinnitus, vertigo
  - nasal, laryngeal, tracheal mucosal ulceration
  - CNS involvement, bowel dysfunction, large vessel arteritis
- treatment
  - azothioprine, methotrexate possibly, not documented

- General
  - rare disease young adults
  - vestibuloauditory dysfunction, interstitial keratitis, nonreactive syphilis test
  - frequent post URI
  - vestibuloauditory
    - Menier's like -bilateral usually
      - fluctuating hearing loss
      - vertigo
      - tinnitus
      - aural pressure

- General
  - occular symptoms
    - photophobia
    - lacrimation
    - eye pain
  - may resolve and reappear month later
  - advanced- hearing loss progressive, weak or abscent calorics
  - ear symptoms may precede or follow eye

- Treatment
  - occular
    - topical steroids and atropine
  - vestibuloauditory
    - some evidence treated within 2 weeks of onset hearing loss may be avoided

- General
  - AKA mucocutaneous lymph node syndrome
  - pediatric age group
  - signs and symptoms
    - fever, red dry lips, erythema oral mucosa, polymorphous truncal rash, desquamation fingers and toes, cervical lymphadenopathy
    - oral cavity erythema and cervical lymphadenopathy presenting symptoms
    - cardiac abnormalities cause 1-2% mortality