

Wegener's Granulomatosis

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Definition

- Classic triad
 - Necrotizing granulomas of the upper and lower respiratory tracts
 - Systemic vasculitis
 - Focal glomerulonephritis
- Limited form
 - No renal involvement

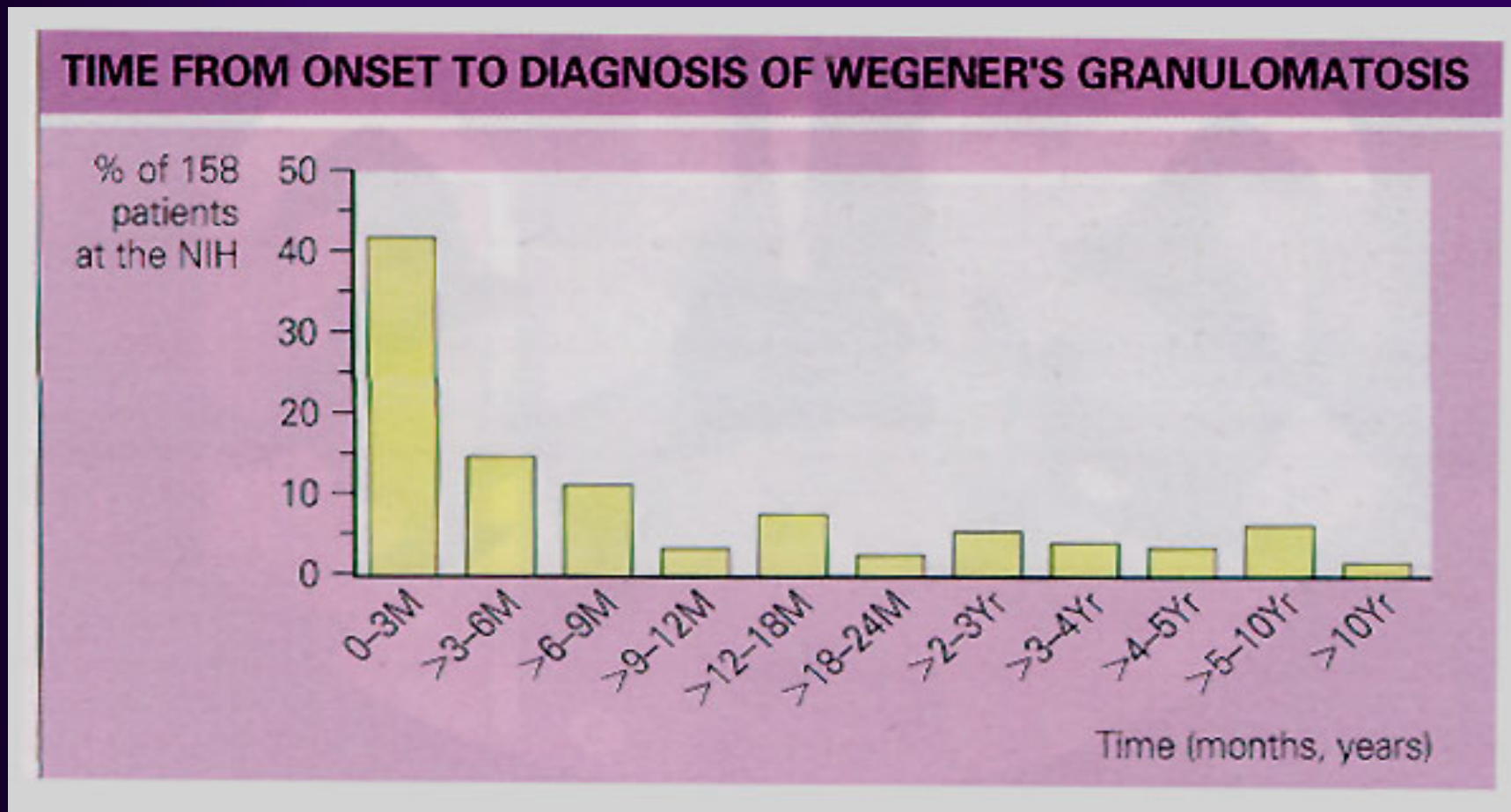
History

- First described in 1931 by Heinz Klinger
- Detailed description by Dr. Friedrich Wegener in 1936 and 1939
 - “Rhinogenic granulomatosis with special involvement of the arterial system and kidneys”
- Clinicopathologic description by Godman and Churg in the 1950s
- Treatment with glucocorticoids and cyclophosphamide described by Fauci and Wolff in 1973

Epidemiology

- M:F ratio = 1:1
- Mean age 41 years (range 9 to 78 years)
- Prevalence 3.0 per 100,000
- Caucasian predominance

Clinical Presentation



1990 Criteria for WG

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3. Urinary sediment	Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
4. Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

The presence of any 2 or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%

Malignancy in WG

FREQUENCY OF MALIGNANCY IN 158 PATIENTS WITH WEGENER'S GRANULOMATOSIS

	Observed (O)	Expected (E)	O/E	P value
Total	10	4.12	2.4	<0.01
Bladder	4	0.12	33.3	$<7.9 \times 10^{-6}$
Lymphoma	2	0.18	11.1	<0.01
Others	4	3.82	1.0	0.5

O/E data based upon NCI registry data for both sexes, ages 45–59, during 1982–86

Observed rate of malignancy in WG population = 791/100,000/year

Expected rate in US population = 335/100,000/year

Clinical Presentation

- Otorhinolaryngologic
- Pulmonary
- Renal
- Ocular
- Cutaneous
- Musculoskeletal
- Neurologic
- Gastrointestinal
- Genitourinary
- Cardiac

WEGENER'S GRANULOMATOSIS: TYPE AND FREQUENCY OF DISEASE MANIFESTATIONS



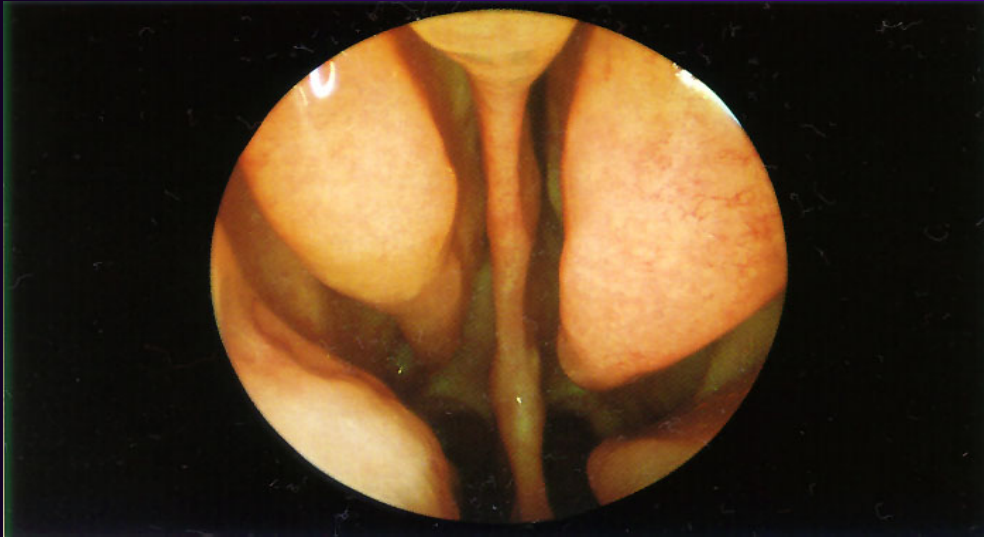
Rhinologic Manifestations

- Epistaxis
- Saddle nose deformity
- Sinusitis
- Septal perforation
- Nasal ulceration and crusting

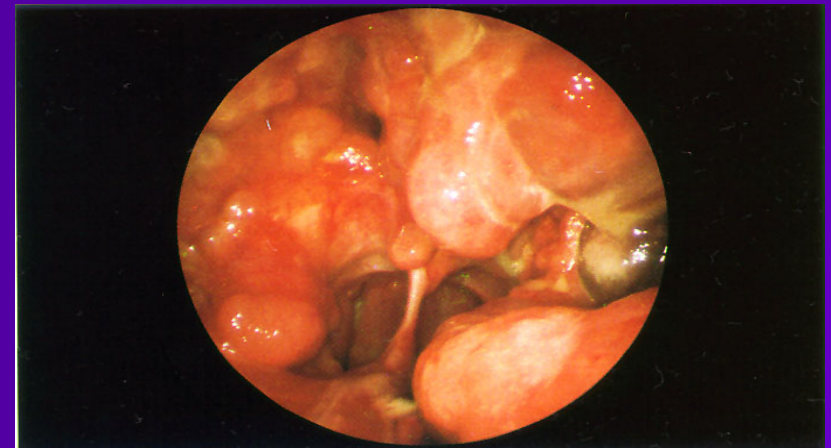
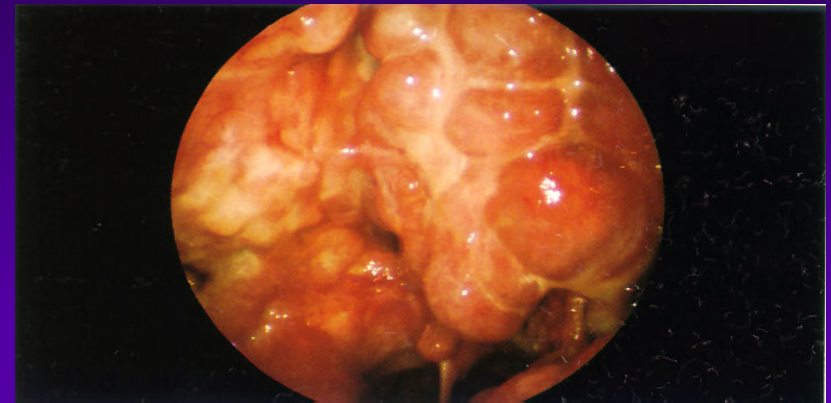


Rhinologic Manifestations

Septal perforation

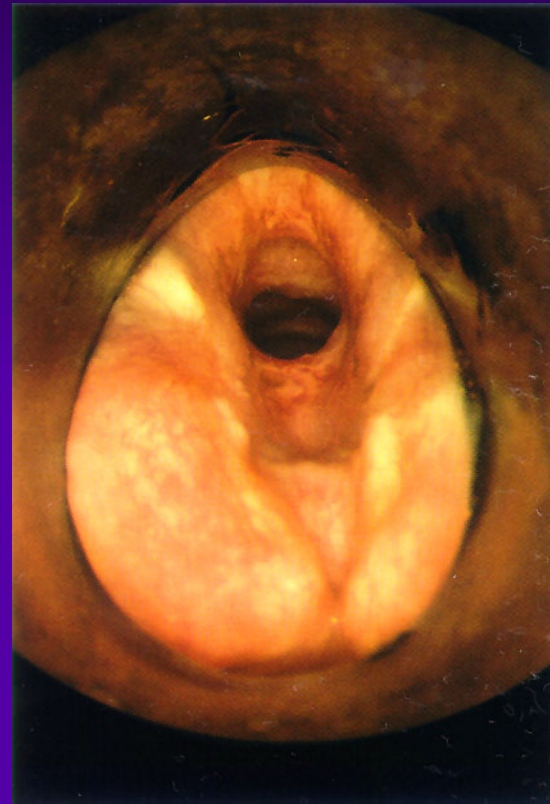
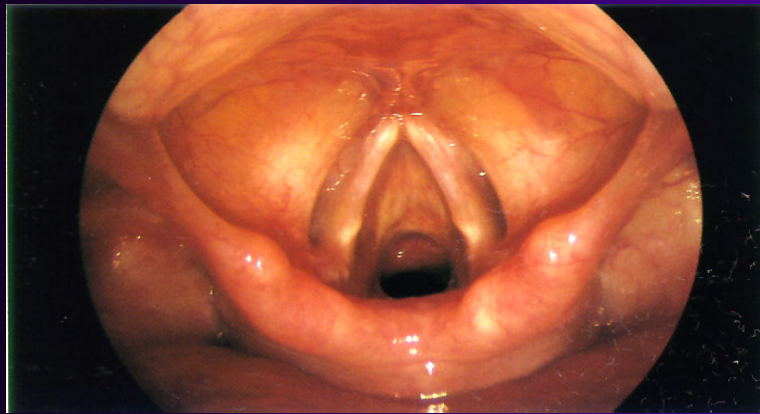


Nasal ulceration

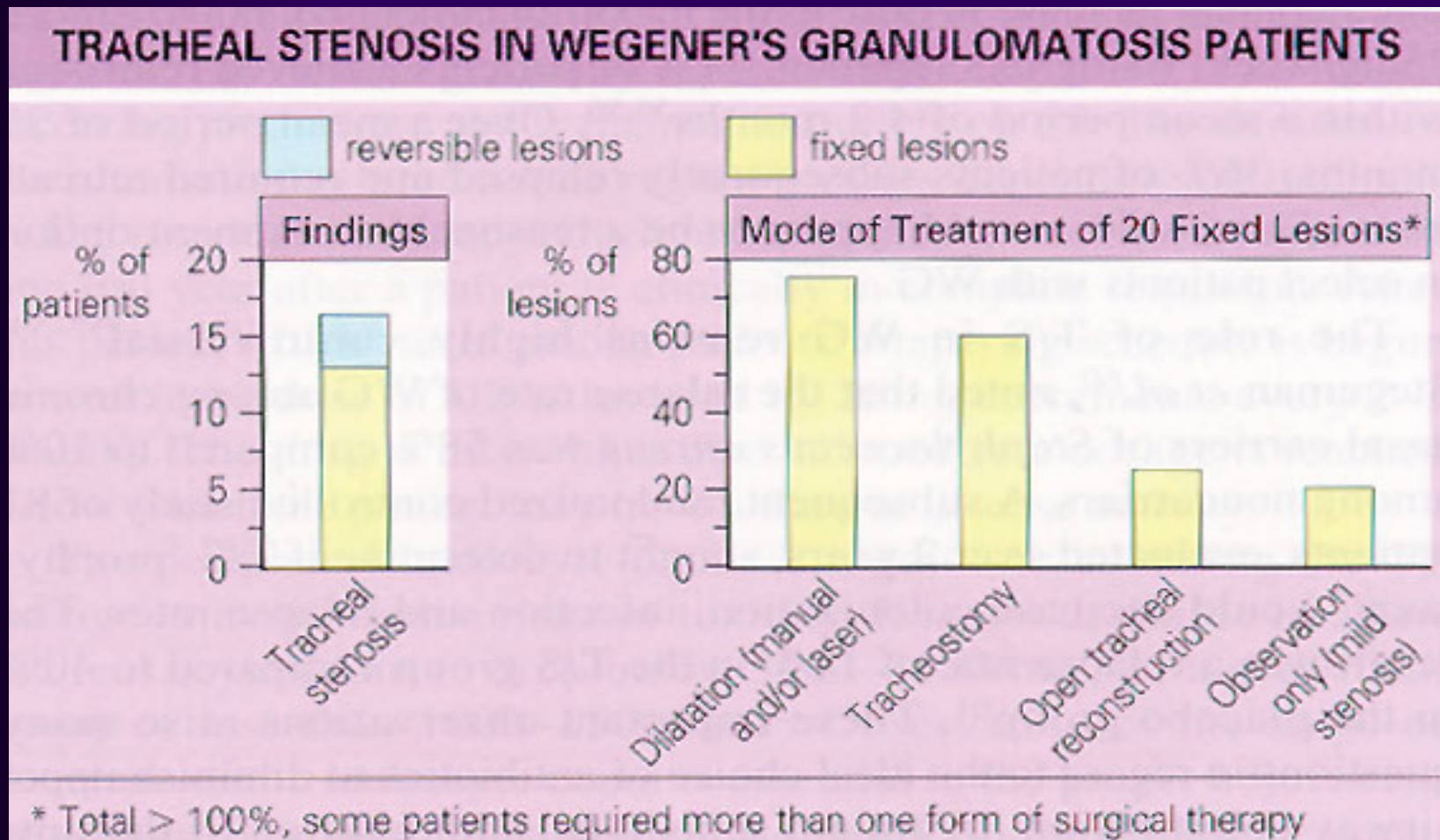


Laryngotracheal Manifestations

- Hoarseness
- Stridor
- Subglottic stenosis



Laryngotracheal Manifestations



Otologic Manifestations

- Otitis Media (Serous > Suppurative)
- Hearing Loss (Conductive > Sensorineural)
- Chondritis
- Otitis Externa
- Tympanic membrane granulomata

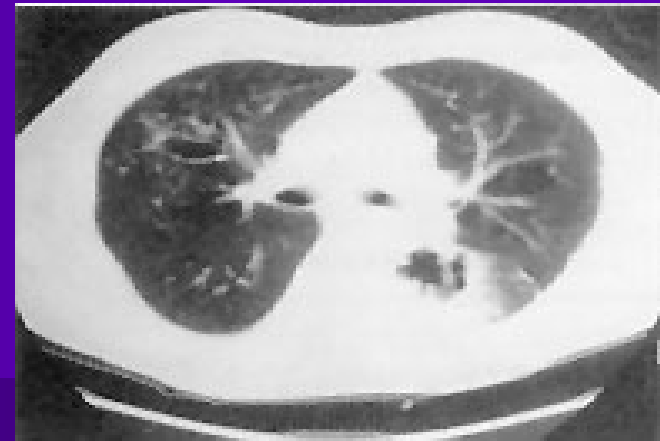
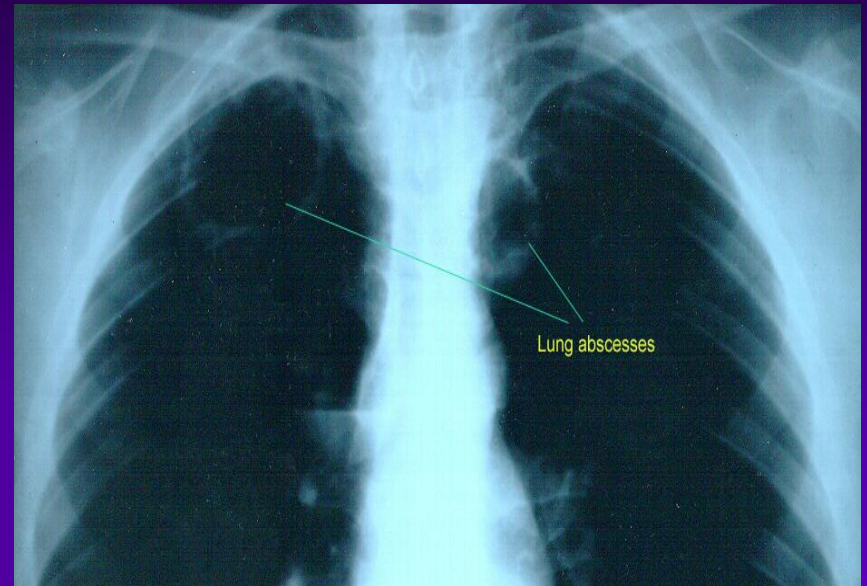
Oral Manifestations

- Painful oral ulcers - ulcerative stomatitis
- Hyperplastic gingivitis
- Painful enlargement of submandibular and/or parotid glands



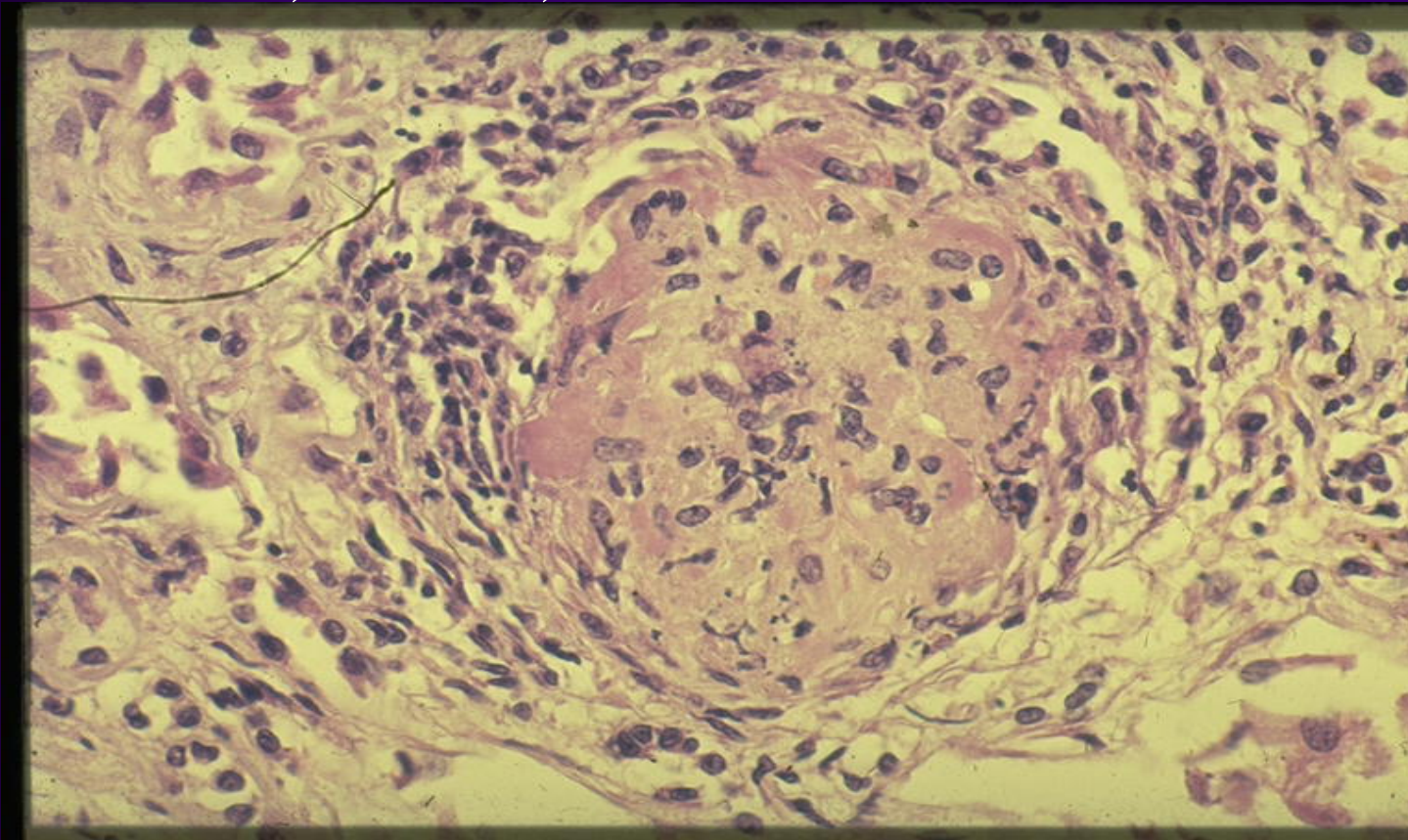
Pulmonary Manifestations

- Radiologic findings
 - Pulmonary infiltrates
 - Pulmonary nodules
- Pulmonary symptoms
 - Cough
 - Hemoptysis
 - Pleuritis



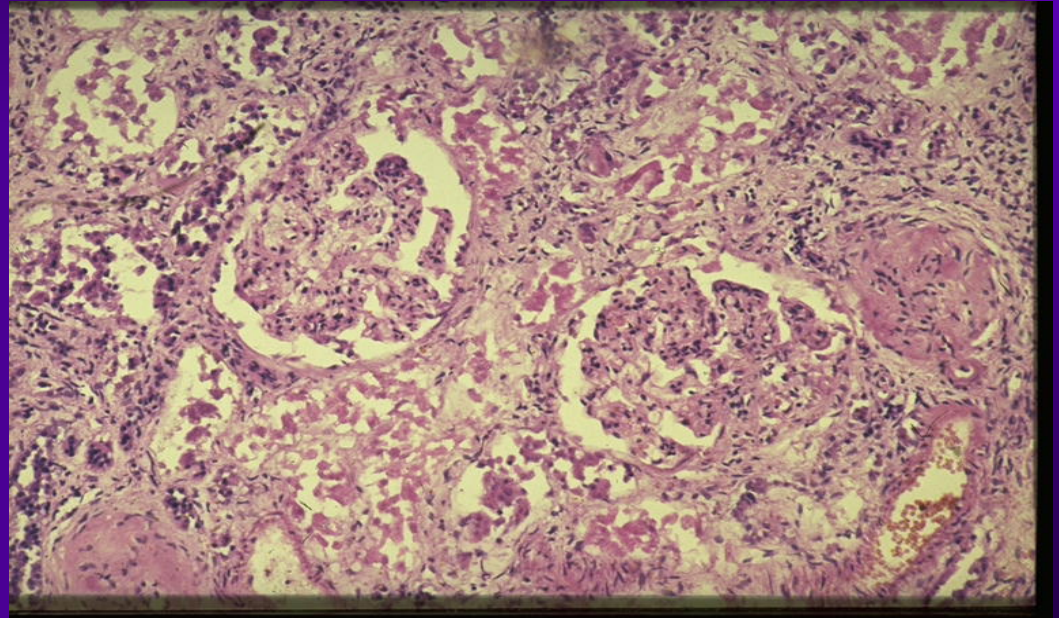
Pulmonary Manifestations

Vasculitis, Necrosis, Granulomas



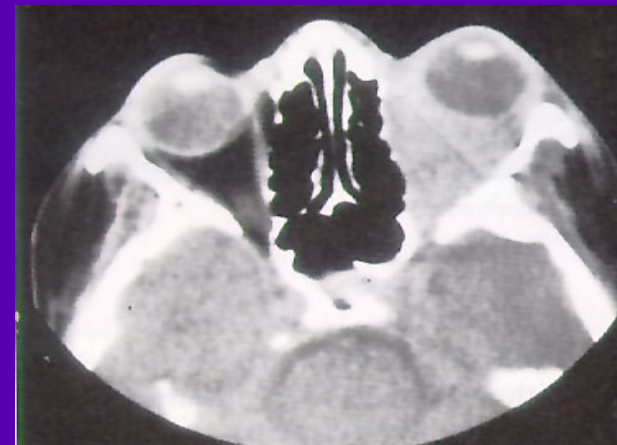
Renal Manifestations

- Defined by pathologic findings on kidney biopsy and/or the presence of an active urinary sediment and functional abnormalities



Ocular Manifestations

- Keratitis - corneal ulceration
- Scleritis - episcleritis
- Conjunctivitis
- Uveitis
- Proptosis, pseudotumor of the orbit
- Nasolacrimal duct obstruction
- Retinal artery thrombosis
- Retinal vein occlusion
- Optic neuritis



Cutaneous Manifestations

- Ulceration
- Palpable purpura
- Subcutaneous nodules
- Papules
- Vesicles
- Pyoderma gangrenosum
- Raynaud's phenomenon



Musculoskeletal Manifestations

- Arthralgia
- Myalgia
- Arthritis
 - Monoarticular
 - Migratory oligoarthritis
 - Symmetric or asymmetric polyarthritis of small and large joints
- Migratory pauciarticular disease

Neurologic Manifestations

- Peripheral neuropathy
 - Mononeuritis multiplex
 - Distal symmetrical
 - Unclassified
- Cranial neuropathy
- External ophthalmoplegia
- Cerebrovascular events
- Seizures
- Cerebritis
- Miscellaneous
 - meningitis, temporal arteritis, spastic paresis, diabetes insipidus, ataxia, Horner's syndrome, papilledema, diplopia, vertigo

Gastrointestinal Manifestations

- Abdominal pain
- Diarrhea
- Bleeding
- Bowel perforation
- Cholecystitis
- Ascites
- Nonhealing perianal ulcers
- Recurrent acute pancreatitis
- Pancreatic mass with extrahepatic obstruction

Genitourinary Manifestations

- Ureteral obstruction
- Hemorrhagic cystitis
- Granulomatous or necrotizing prostatitis
- Necrotizing urethritis
- Orchitis
- Epididymitis
- Penile necrosis

Cardiac Manifestations

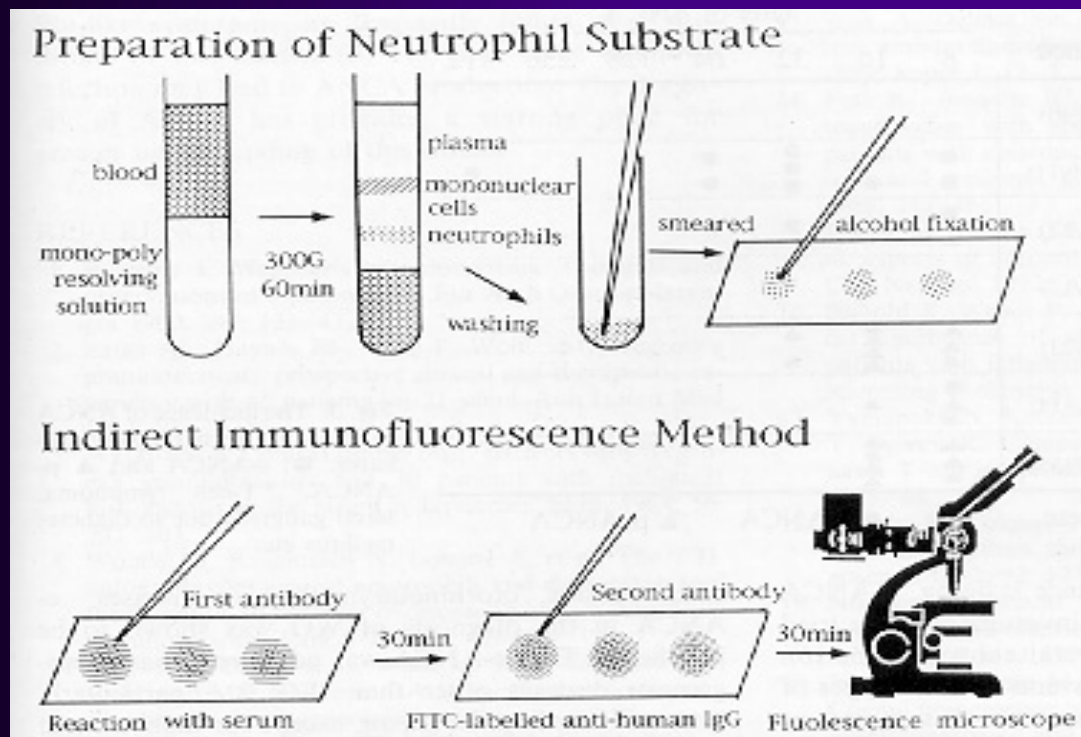
- Pericarditis
- Coronary vasculitis
- Myocarditis
- Cardiac arrhythmia

Antineutrophil Cytoplasmic Antibodies (ANCA)

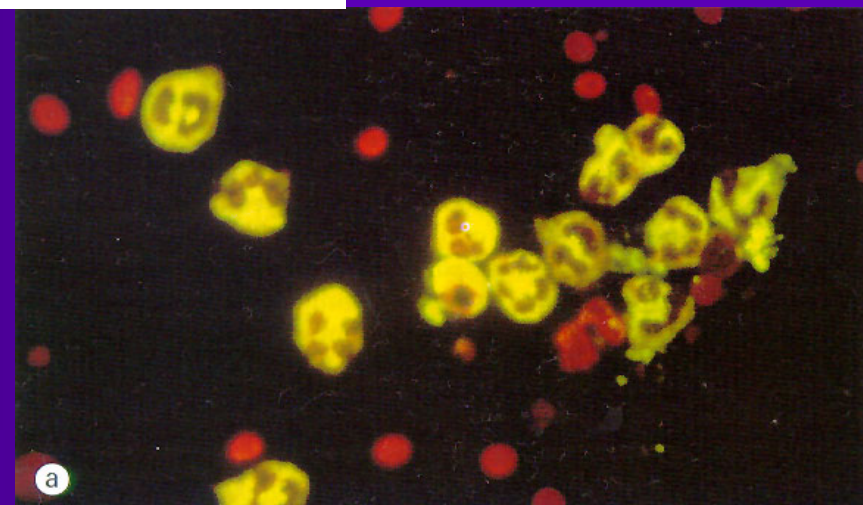
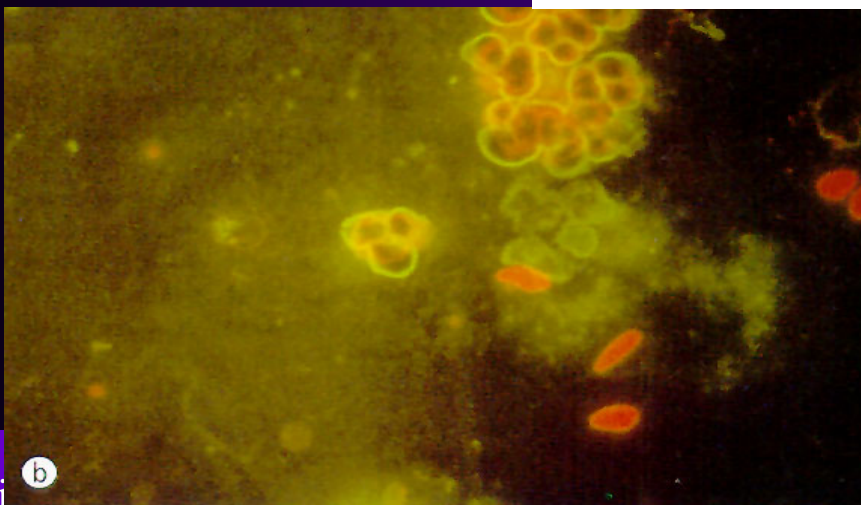
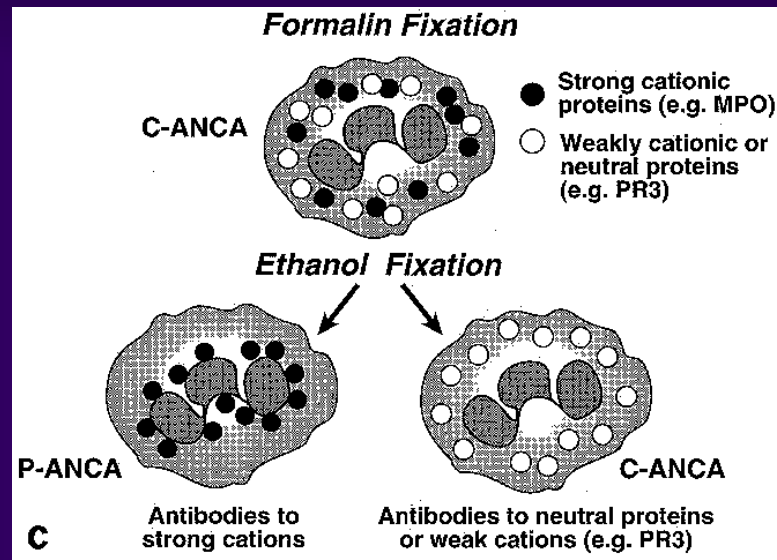
- Method of detection

 - Indirect immunofluorescence

 - ELISA



Indirect Immunofluorescence



Perinuclear ANCA (pANCA)

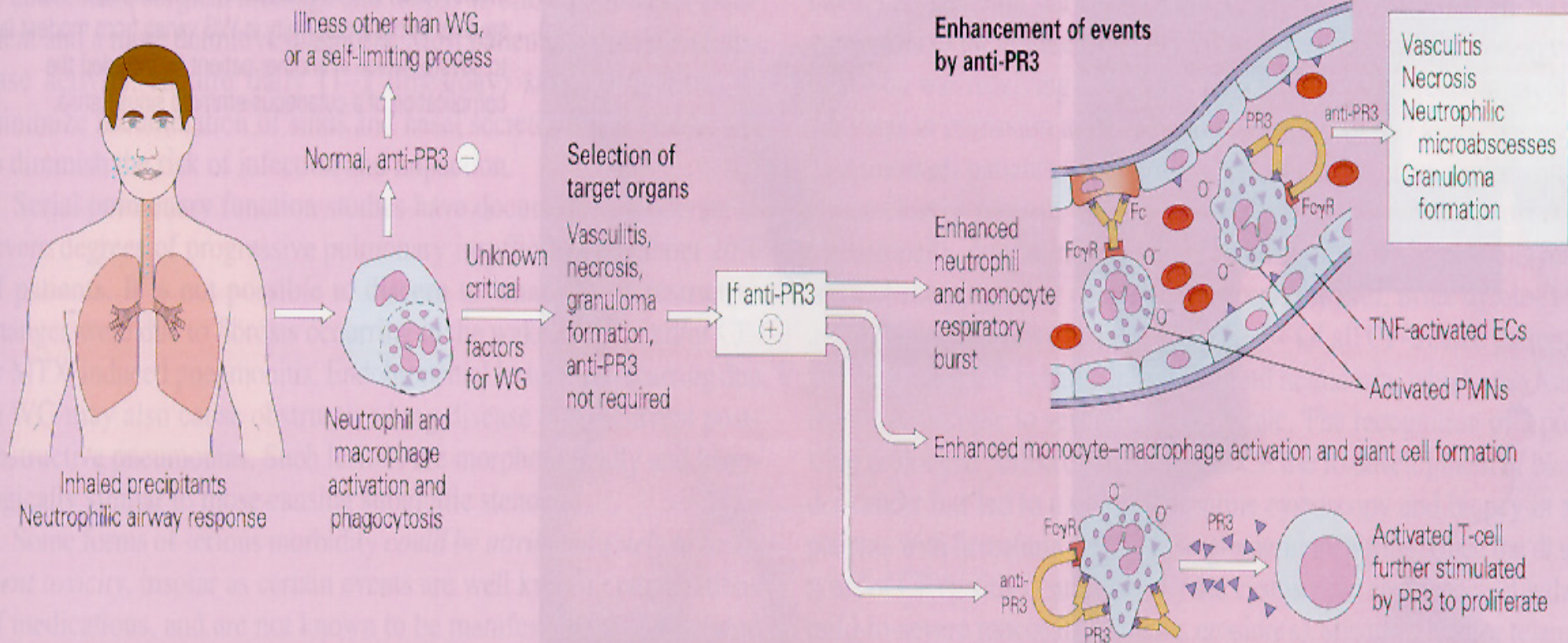
- An artifact of ethanol fixation, not seen in formalin fixation
- Caused by antibodies mainly against myeloperoxidase, but also against elastase, cathepsin G, azurocidin, lactoferrin, and lysozyme
- Associated with microscopic polyangiitis (40-80%), but can be seen in rheumatic diseases, inflammatory bowel disease, HIV, amoebiasis, or drug reactivity

Cytoplasmic ANCA (cANCA)

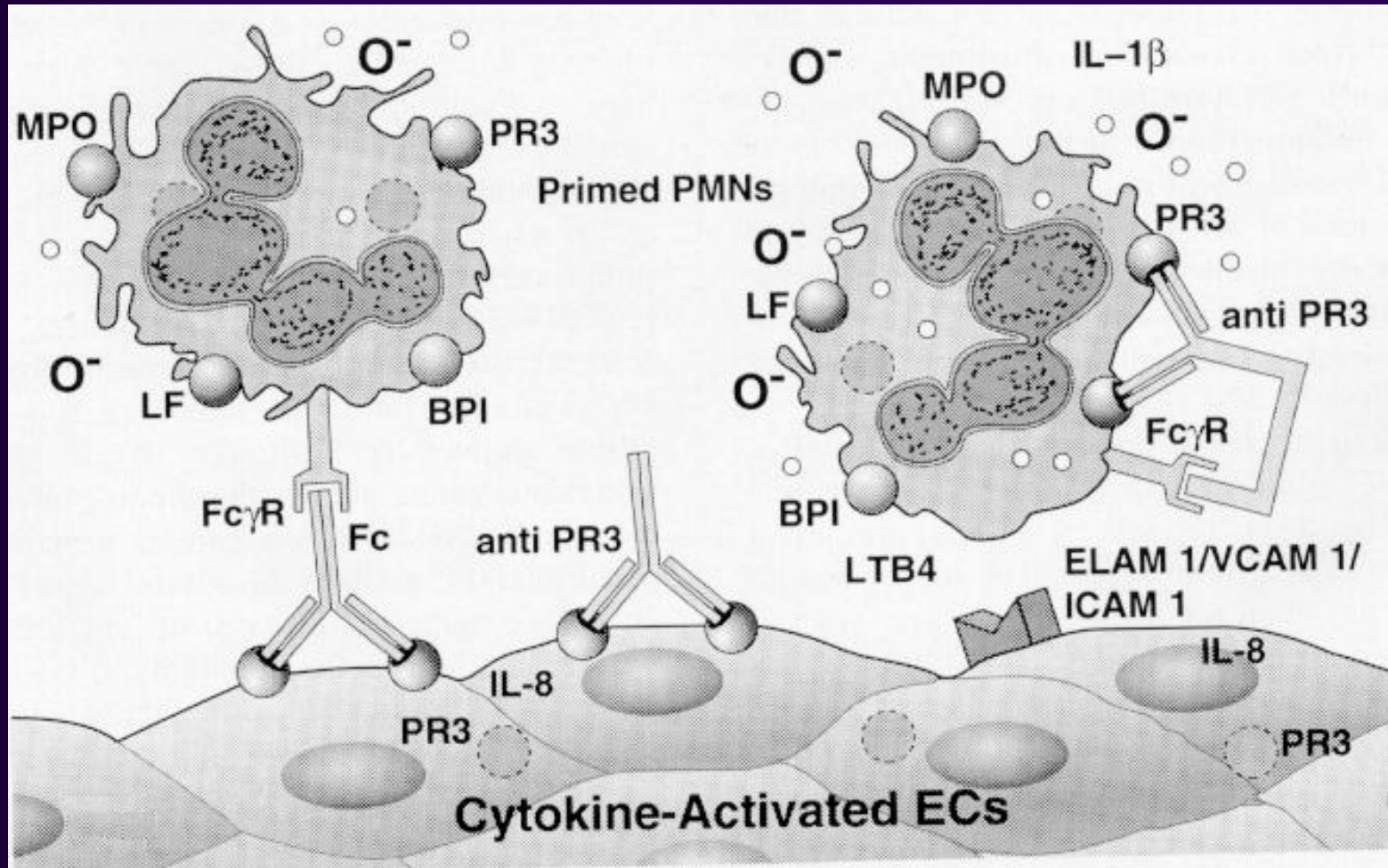
- Coarse granular, centrally accentuated, cytoplasmic fluorescence pattern seen in ethanol-fixed neutrophils
- Caused by antibodies against proteinase 3 (PR3)
 - 29 kDa serine protease in the azurophylic granules of neutrophils
- Best association with Wegener's granulomatosis
 - Sensitivity - 28 - 92% (dependent on extent, severity, activity of disease at time of sampling)
 - Specificity - 80 - 100%

Pathogenesis

PATHOGENESIS OF WEGENER'S GRANULOMATOSIS: HYPOTHESIS



Pathogenesis



Clinical Application of ANCA

- Extremely useful in patients with multiple clinical symptoms of Wegener's granulomatosis
 - post-test probability of ~98%
- Not useful in patients with only one symptom of Wegener's granulomatosis
 - post-test probability of 7 - 16%

Sequential ANCA testing

- Persistent high titers or rising titers of ANCA are often associated with relapse from remission of WG
- However, not predictive of time to relapse
- Not recommended for monitoring of disease progression

Treatment

- Methotrexate
 - 0.15 - 0.30 mg/kg/week
 - In combination with GC, 76% marked improvement and 69% complete remission
- Antimicrobial agents
 - Trimethoprim/sulfamethoxazole
- Surgical intervention
 - Inflammatory process should always be suppressed concurrent with, or prior to surgical intervention

Treatment

- Glucocorticoids (GC)
 - Initial high dose
 - prednisone at >1 mg/kg/day
 - Maintenance
 - prednisone at 1 mg/kg/every other day
- Cyclophosphamide (CY)
 - 2 mg/kg/day
- GC + CY resulted in a 91% marked improvement and 73% complete remission

Complications of Treatment

- Glucocorticoid induced
 - Cataract
 - Osteoporosis-related fractures
 - Aseptic necrosis
 - Diabetes mellitus
- Cyclophosphamide induced
 - Cystitis
 - Bladder cancer
 - Lymphoma
 - Myelodysplasia
 - Hair loss
 - Infertility
 - Severe infections
 - Pneumocystis carinii pneumonia

Conclusions

- Wegener's granulomatosis is a spectrum of disease with variability in clinical presentation, severity, and course of disease
- Monitoring of WG should be done from an organ-system approach
- Otolaryngologic manifestations are the most common at initial presentation of WG
- Treatment options have increased survival but have serious side effects