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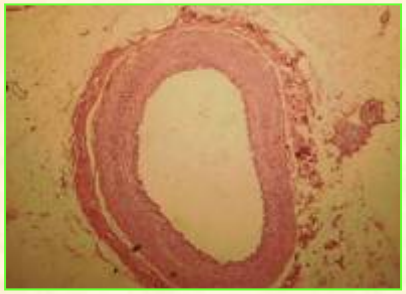
Disclosures

- Consulting and speaker fees from
  - Schering-Plough (Paris)
  - Hoffmann-La Roche (Toronto)
  - LFB (Paris)
- Educational subventions (research groups)
  - Hoffmann-La Roche (CanVasc)
  - Schering-Plough (FVSG)
  - Astra-Zeneca (FVSG)
- Advisory boards and programs
  - GSK (Toronto)
  - Hoffmann-La Roche (CanVasc)

Objectives

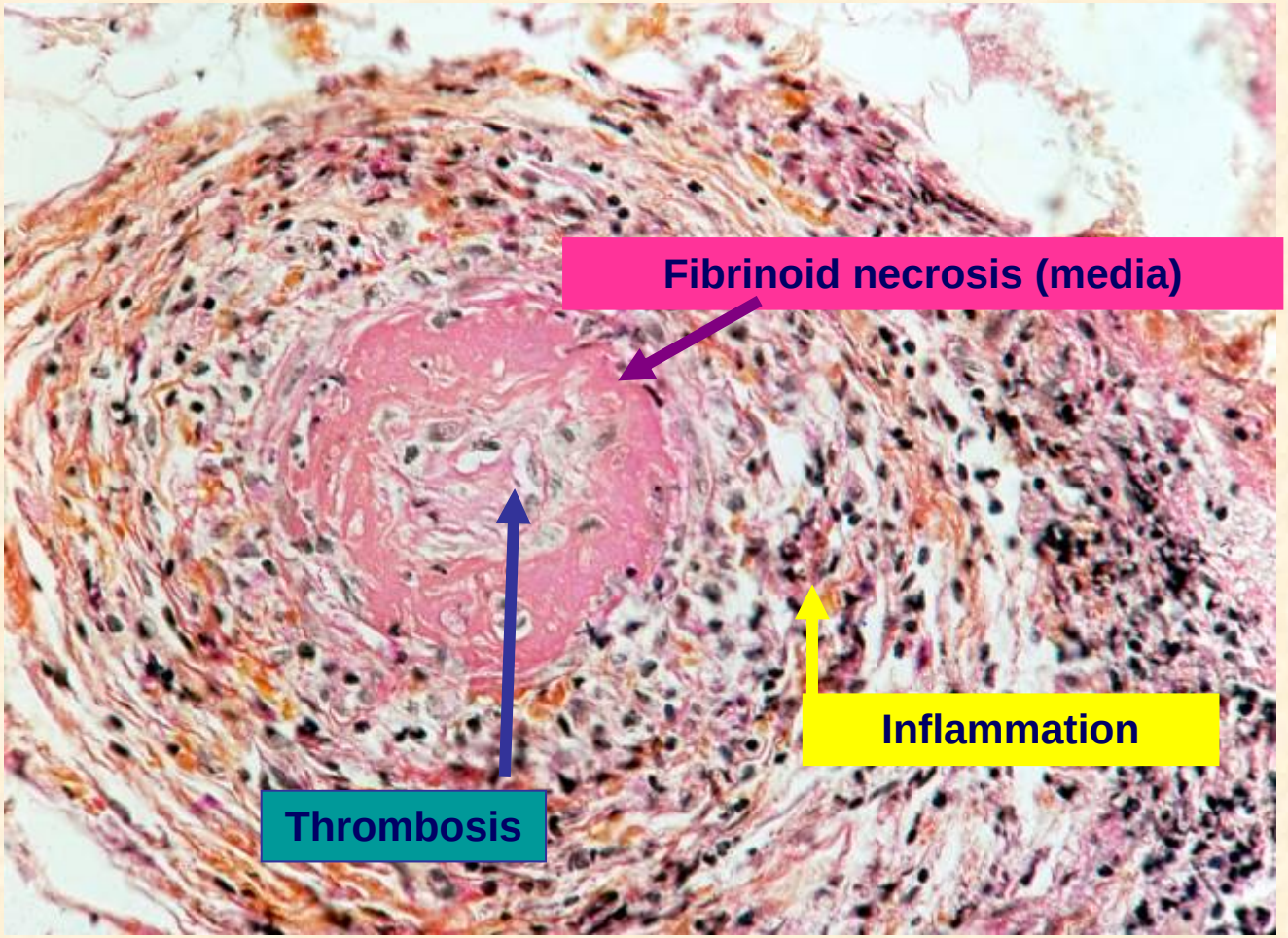
- What is vasculitis?
- How frequent is this condition?
- What are the typical manifestations?
- What are the severe manifestations?
- What is the treatment?
- What are the prognosis and outcomes?

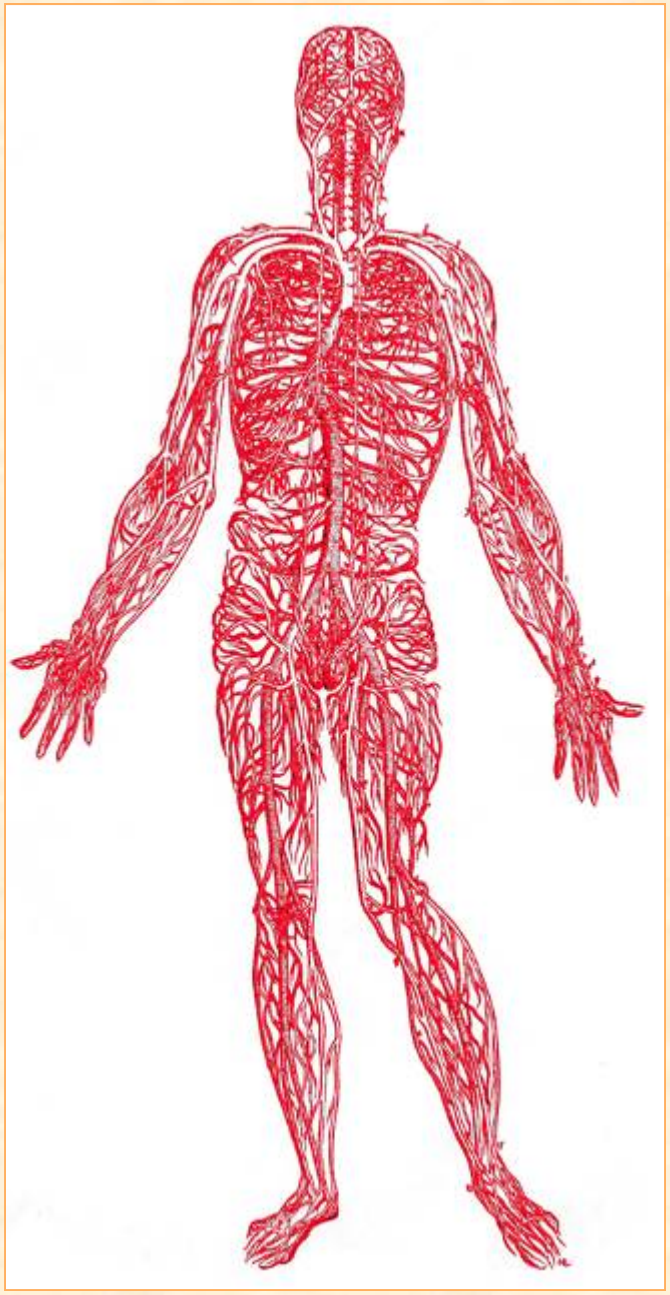
What is vasculitis?



Normal artery

Vasculitis





What is vasculitis?

96,500 – 160,000 km
60,000 – 99,500 miles

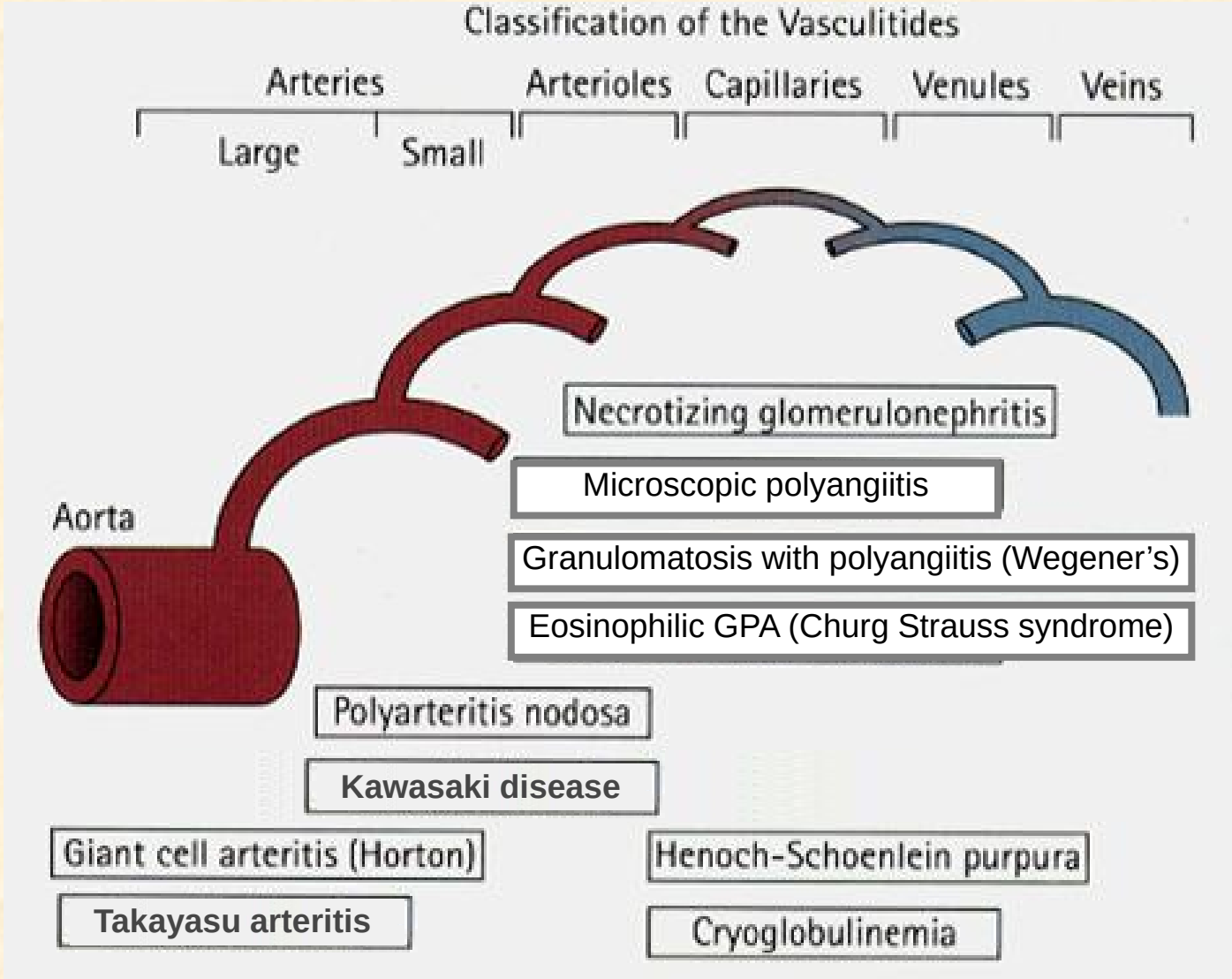
2,5 to 4 times the earth's perimeter

Almost ½ the distance between moon and earth

What is vasculitis?

- **Secondary systemic vasculitides**
  - **Drugs** (PTU…) **and toxic exposure** (cocaine, marijuana…)
  - **Infections**: HIV, HBV, HCV, CMV, VZV, HTLV1, EVB19…
  - **Cancers,** hematological neoplasm (lymphoma, leukemia)
  - **Auto-immune/systemic inflammatory diseases:** SLE 35-50%, RA 1-20%, Systemic scleroderma 5-10%, sarcoidosis, IBD

1994 Chapel hill Nomenclature



+ antiGBM

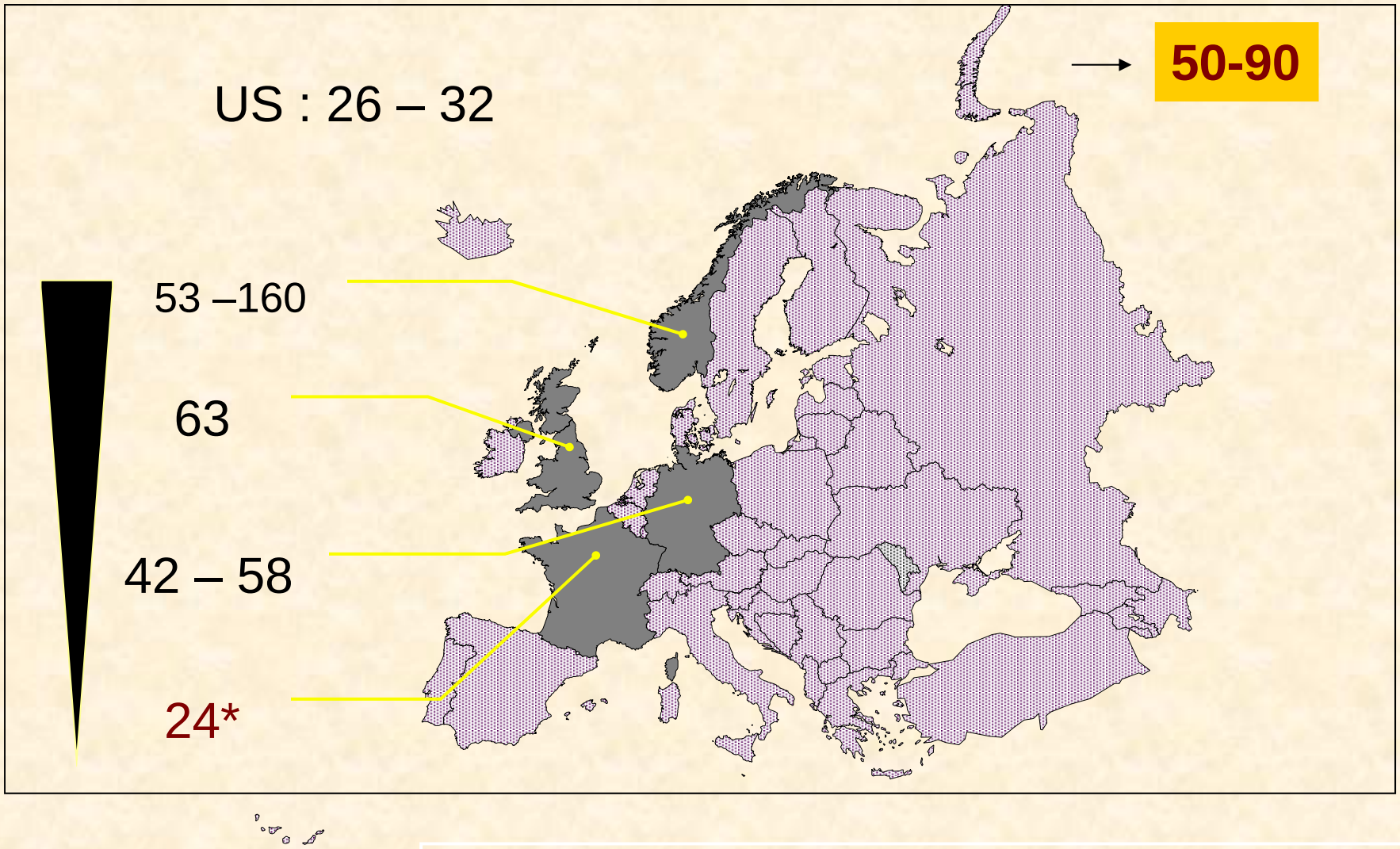
+ Behçet

Jennette et al. Arthritis Rheum 1994;37:187-92
Falk et al. Arthritis Rheum 2011 Apr;63(4):863-4

Vasculitis	Prevalence (per million)	Remarks	Annual Incidence (per million)	Remarks
GCA	1,400-16,000 (of population >50 y-o)	Crude estimates (no specific study)	100-300 (of population >50 y-o)	Down to 5 in Israel in late 1960s; Up to 370 in Norway in mid 1990s; 20 in subjetcs <60 and up to 520 in those >80 y-o in Minnesota
Takayasu	4-8	4.7 to 7 in the UK in early 2000s; Up to 40 in Japan (no epidemiological data for India, but probably at least the same)	1-2	Down to 0.4 in Germany; Up to 2.6 in Minnesota in late 1970s, and 3.3 in Kuwait
PAN	22-31 (in the late 1990s)	HBV-related PAN almost disappeared	0.9- 6.8	Up to 8 in the UK, 16 in Kuwait in the late 1990s, and 77 in Alaska in late 1980s (HBV endemy)
Kawasaki	-	Acute disease (in general, but damage)	100-500 (of children <5 y-o)	Down to 16 in Czech republic in late 1990s; Up to 2,180 in Japan; in US, 91 in Caucasian vs. 320 in Asian children in early 2000s
GPA	50-90	Down to 23 in Paris in 2000, 30 in NYC in 1990; Up to 160 in Sweden in 2007	5-10	Down to almost 0 in Japan, 2.9 in Spain; Up to 11 in Australia and Minnesota
MPA	25-50	Down to 25 In Paris in 2000; Up to 94 in Sweden in 2007	5-10	Down to 2.7 In Germany;Up to 15 in Japan, and 24 in Kuwait
CSS	10-15	Down to 7 in Germany in 1994; Up to 22 in Australia in 2004	1-2	Down to 0 in Japan; Up to 2.7 in the UK in late 1990s, and 4 in Minnesota in late 1970s
Behçet	10-500	Extremely wide ethnic variations (from 6 in the UK in late 1970s to 4,200 in Turkey in 2000); 100-300 in US , mainly in immigrants; 24 in European-descent vs. 175 in Asian-descent vs 350 in Norh-African- descent French population	-	No precise estimation (chronic disease and wide geographical differences); around 4 in Minnesota in mid 2000s
CNS-V	-	No data	2.4	Only 1 study, in Minnesota

40.000 **6.000**

Granulomatosis with PA



Prevalence/1,000,000 subjects *(≥ 15 yr)

PATHOPHYSIOLOGY

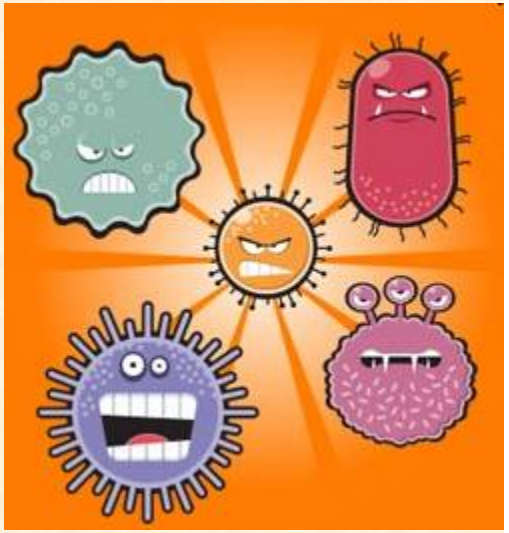
- **Genetic and epigenetic of ANCA-V**
  - **HLA**-DR1 & HLA-DQw7
  - HLA DR13/DR6 protective
  - **PiZ Allels (low alpha1-antitrypsin level)**
  - TNFa, ICAM-1, **membranous PR3**, C3nef allele gene polymorphisms
  - FcγRIIIb-NA1 Allel & atteinte rénale
  - 6p21.3 Locus
  - PTPN22 620W allel
  - CD226-Gly307Ser (DNAM-1) polymorphism
  - Transcriptome studies: up or down regulations
    - TLR2
    - RFc$_{\varepsilon}$- alpha
    - R-IL2-ß (p75)
    - TCF1

Role of external or environmental factors

PATHOPHYSIOLOGY

- **Exposition to :**
  - **silica** OR=3.23 (vasculitis ANCA+)
  - **cattle** OR=2.3 (vasculitis ANCA+)
  - hydrocarbons organics (vasculitis ANCA+)
  - asbestos 20.3% vs 6.9% (ANCA+)
  - smoking 11% vs 38% (vasculitis ANCA+)

PATHOPHYSIOLOGY



- **Infections**
  - HBV and PAN
  - HCV and cryoglobulin
  - Several studies, no proofs
  - Respiratory infections
    - No seasonal preference
    - No germ reproducibly found (BAL, lung biopsies)
  - *Staphylococcus aureus* and GPA

Clinical manifestations

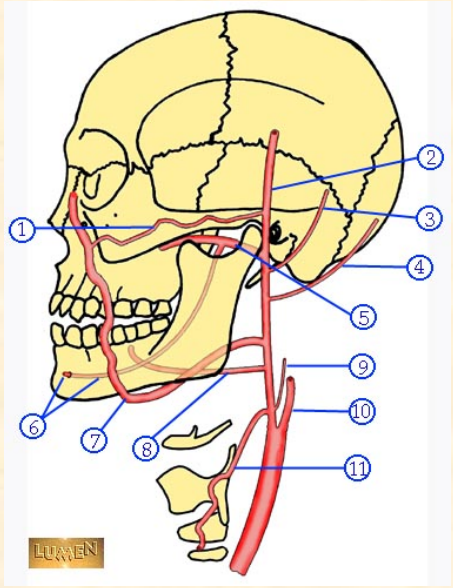

weight
loss


zzzzzzz

Inflammation

- Increased C-reactive protein
- Increased Sedimentation rate
- Increased WBC (neutrophils)

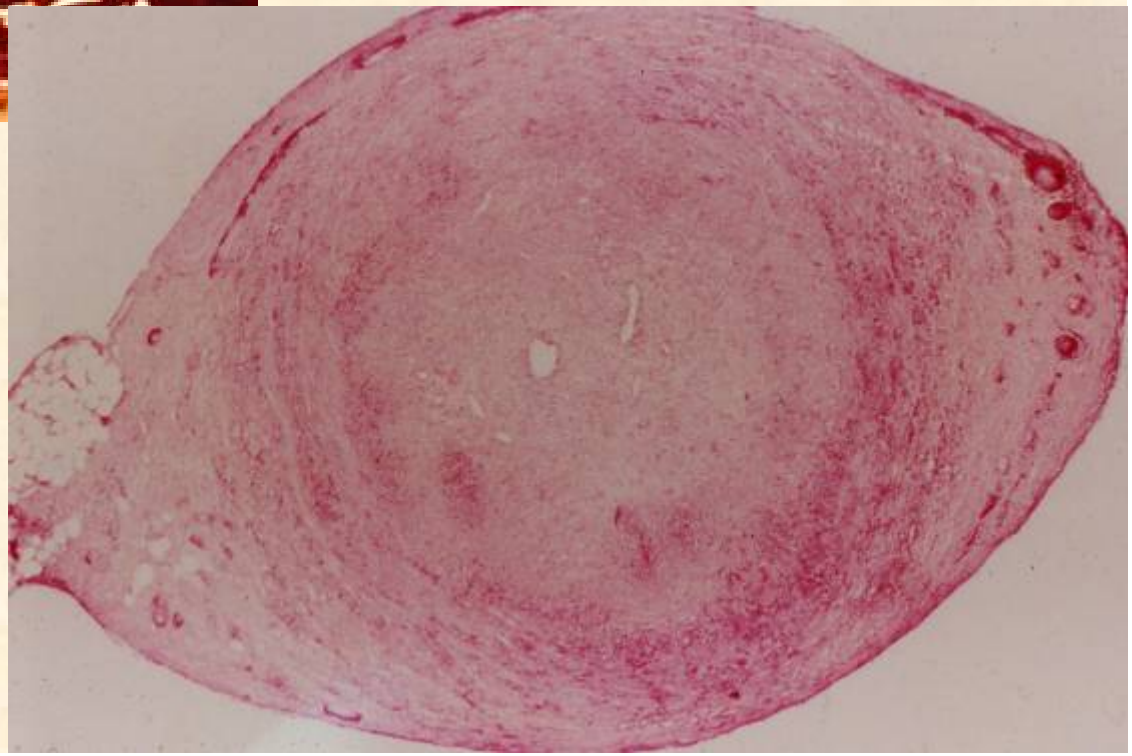
Giant cell / Temporal arteritis

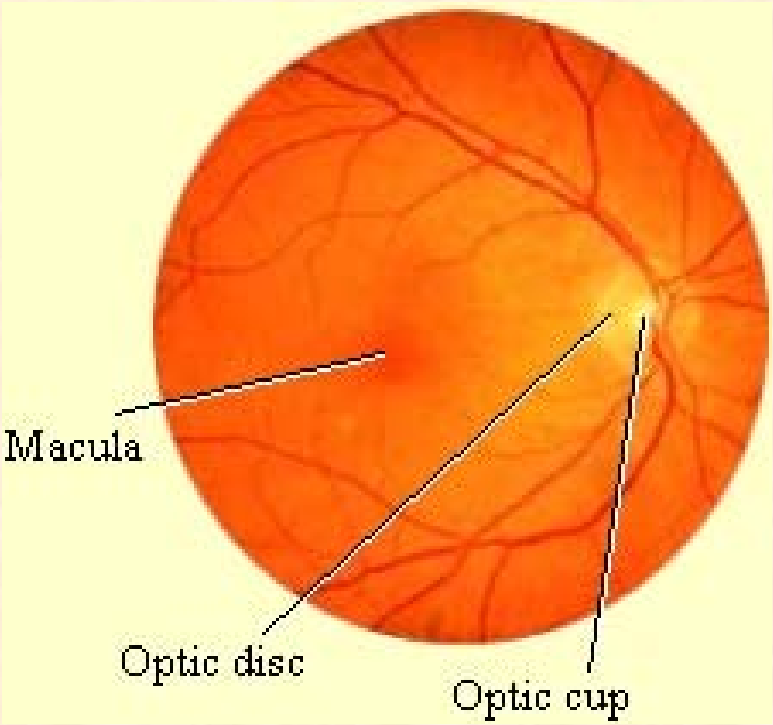


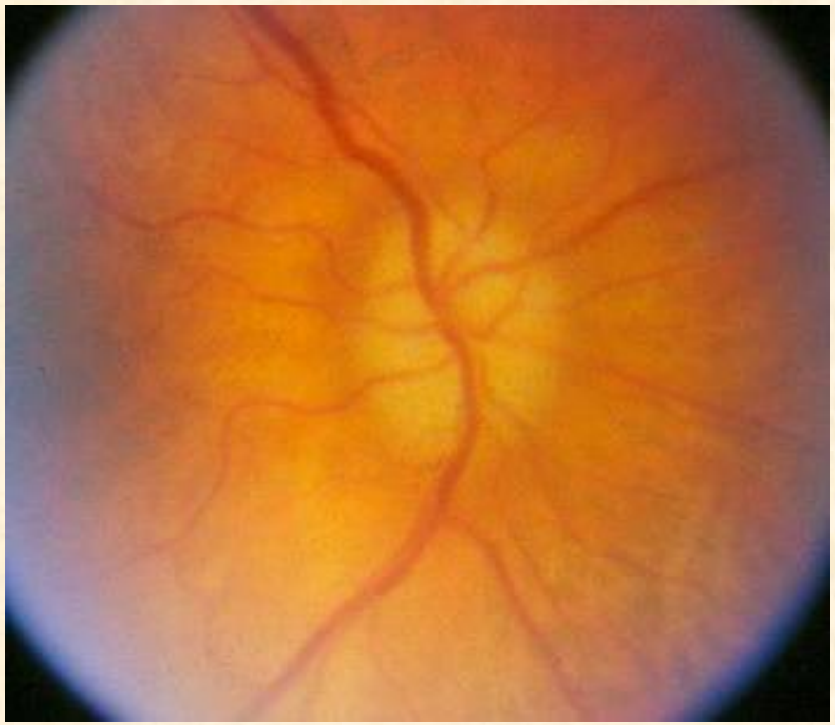
External carotid branches

Giant cell arteritis

Risk of occlusion +++



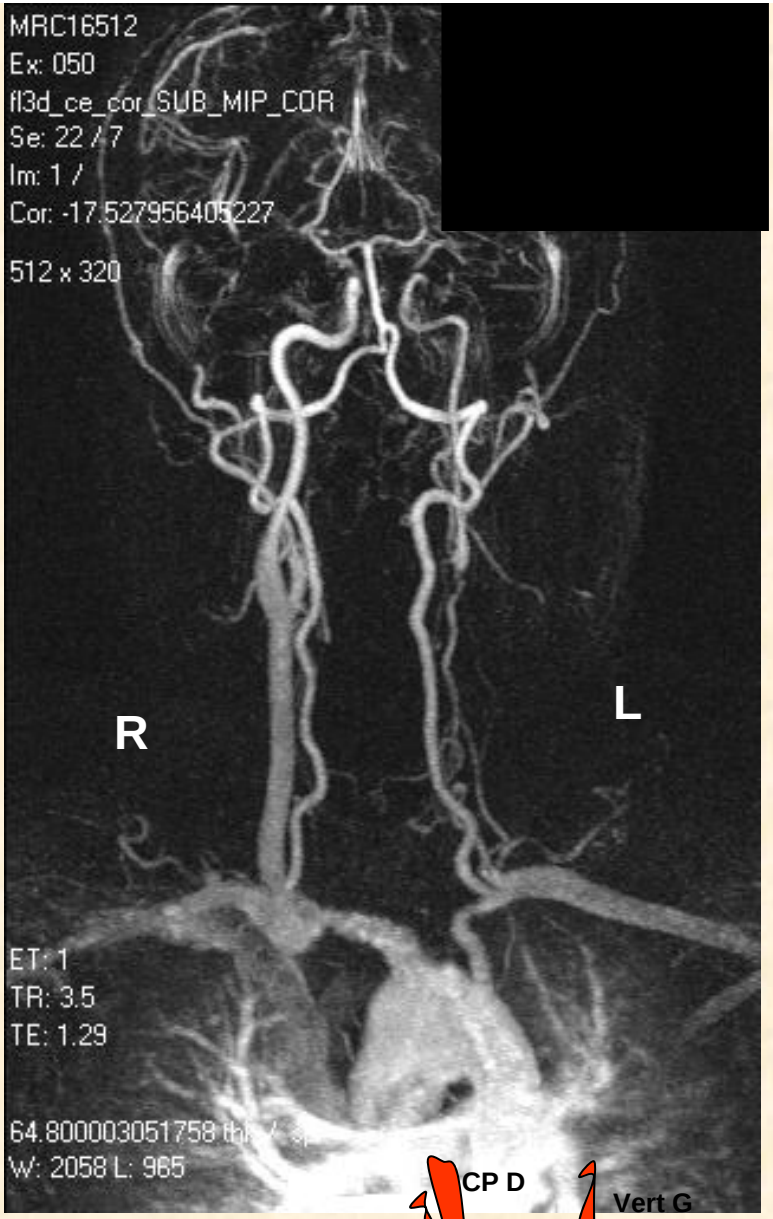

Macula
Optic disc
Optic cup



Stroke 4%

TAKAYASU's arteritis

- Pulseless women
- Women 15-25 years-old, Asians/Indians+
- Chronic disease
- Aorta and its first branches (arch++)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Ex: 050
fl3d_ce_cor_SUB_MIP_COR
Se: 22 / 7
Im: 1 /
Cor: -17.527956405227
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ET: 1
TR: 3.5
TE: 1.29
W: 2058 L: 965


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Scan T
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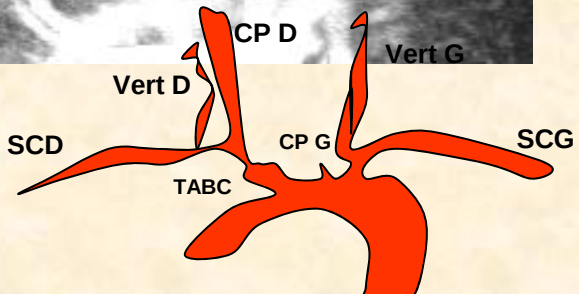
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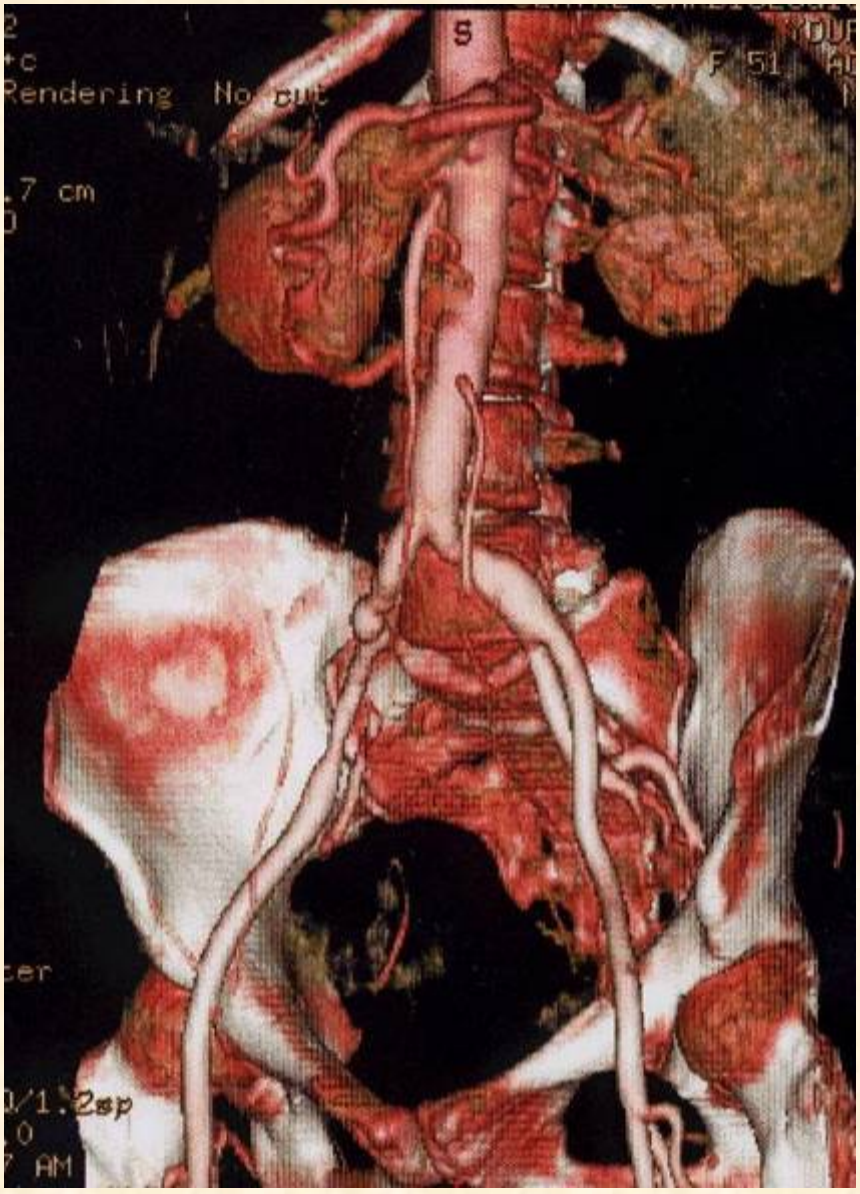
Vert D
SCD
CP G
SCG
TABC



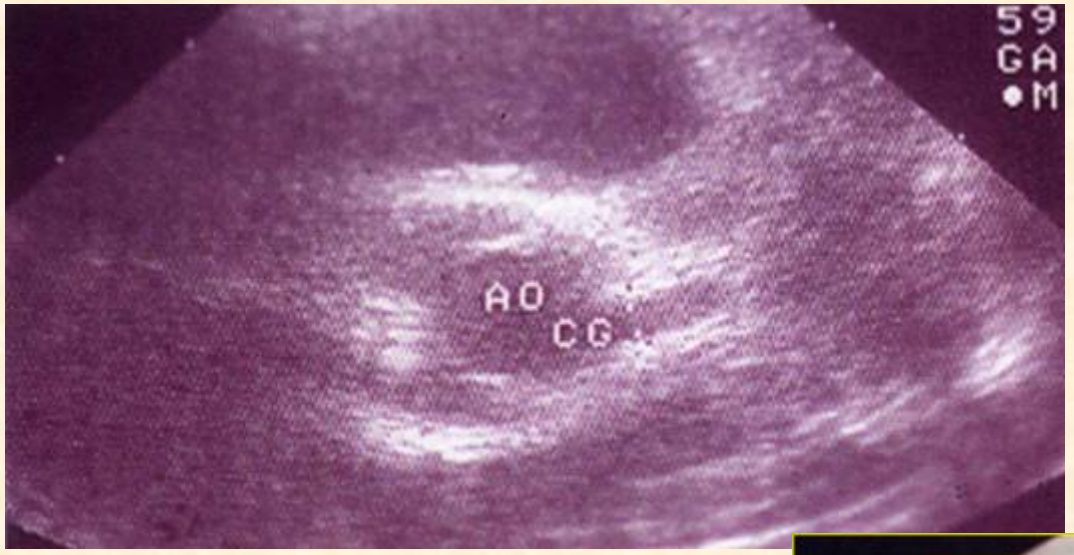
Renal artery stenosis
→ <u>High blood pressure</u>

Limb artery stenosis
→<u>Claudication</u>

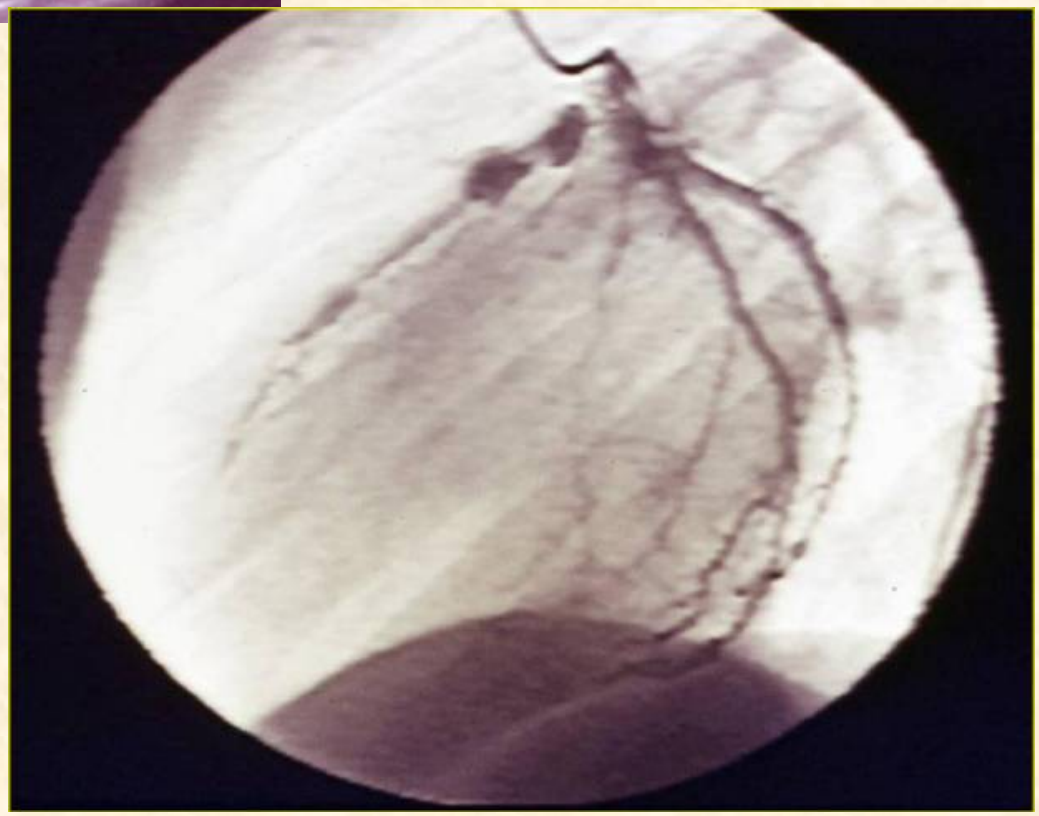
Cervical-cerebral arteries
→<u>Strokes</u>

KAWASAKI disease

- Lympho-cutaneo-mucous syndrome + fever
- Children 6-11 mo. Asia, 8-24 mo. US
- Epidemies → infectious link

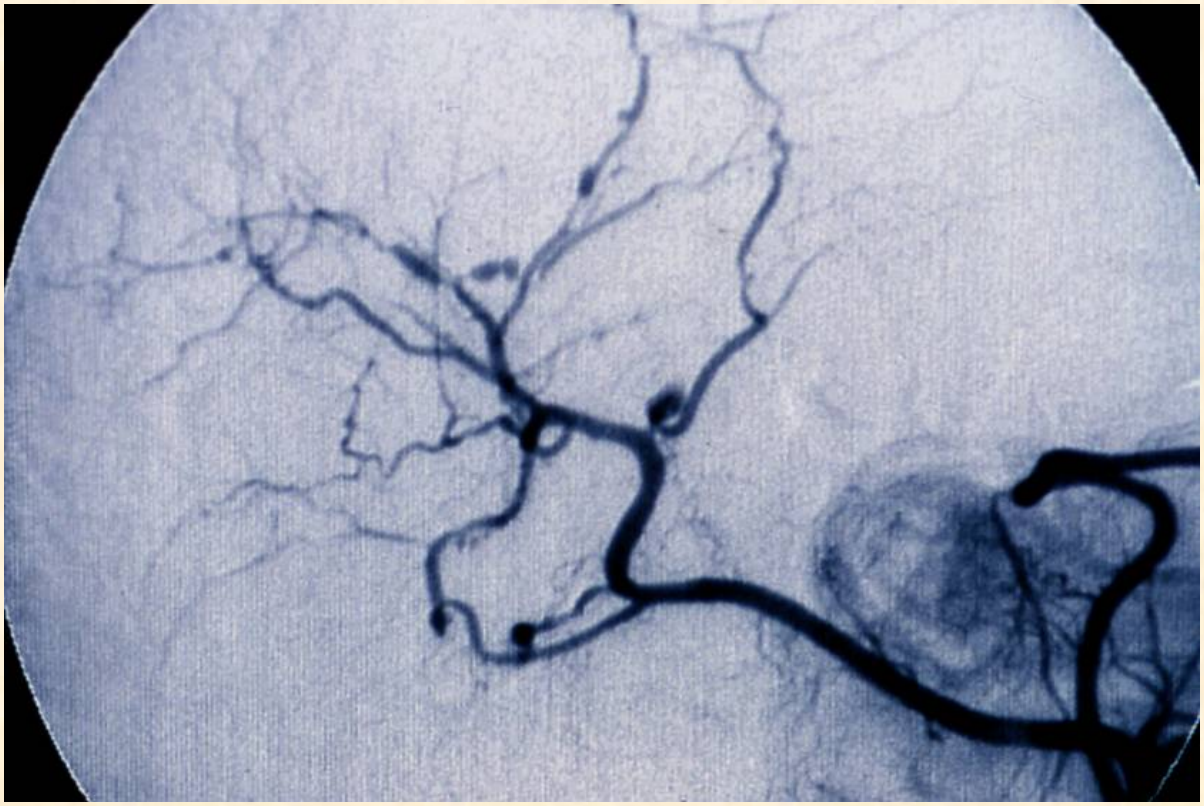


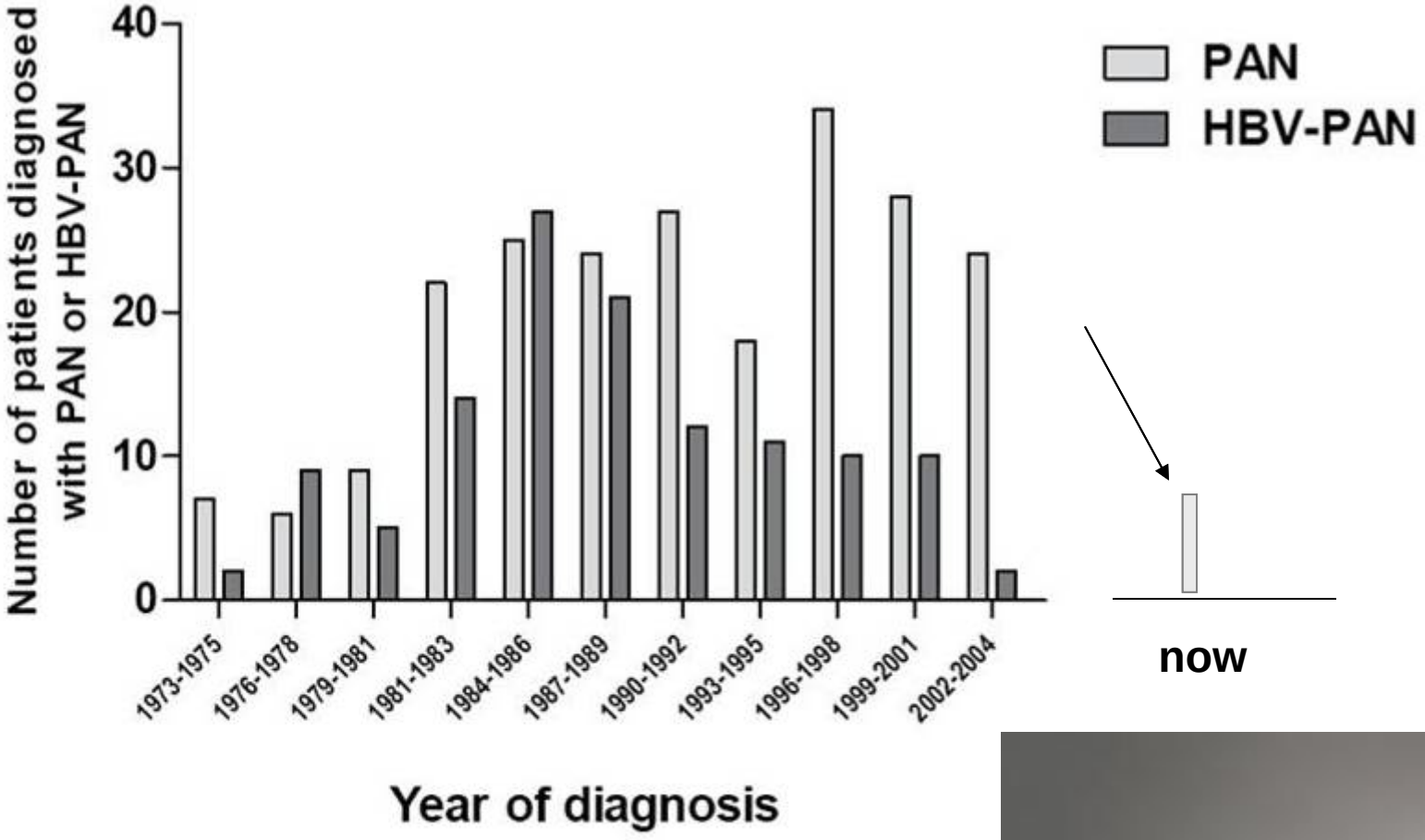
Coronary aneurisms
15-25% WITHOUT Rx



Polyarteritis nodosa

- Kussmaul 1866
- Necrotizing vasculitis → microaneurisms





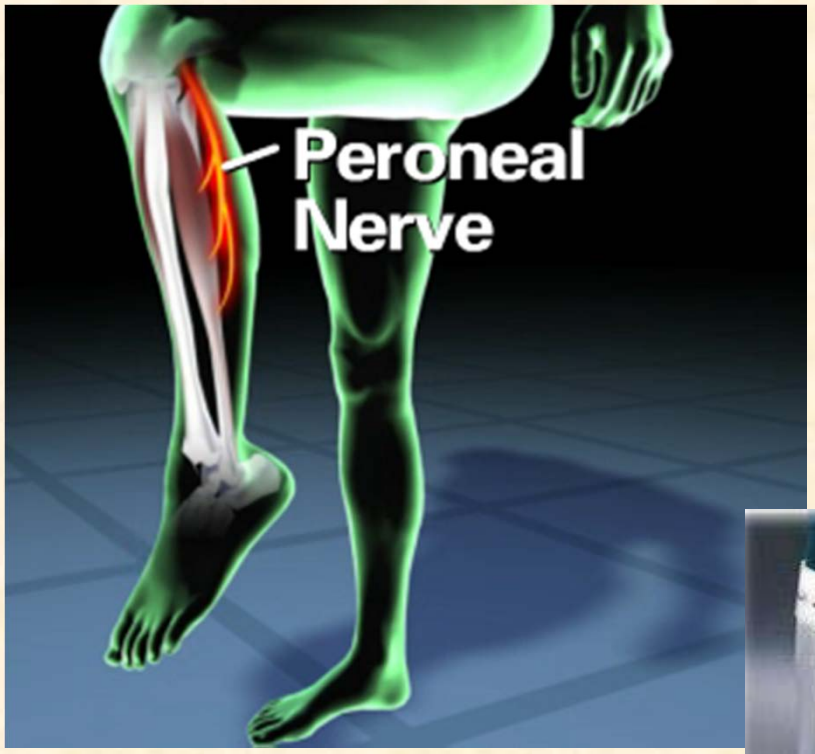
Pagnoux et al. *Arthritis Rheum* 2010;62(2):616-26

Small vessel vasculitis

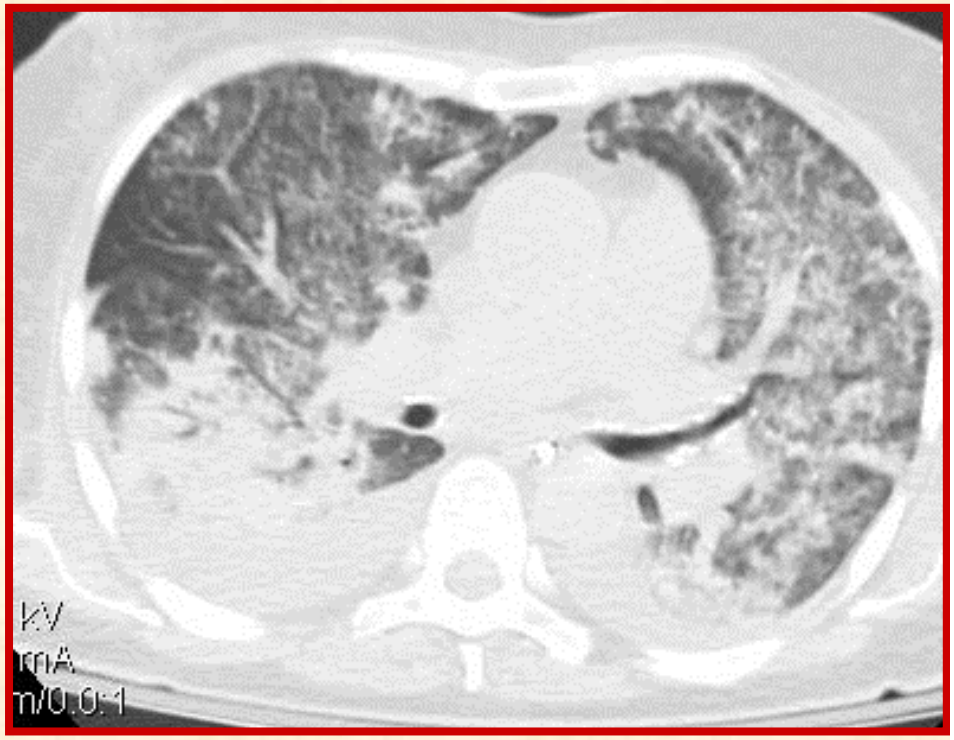
Skin manifestations
10-50% of the patients

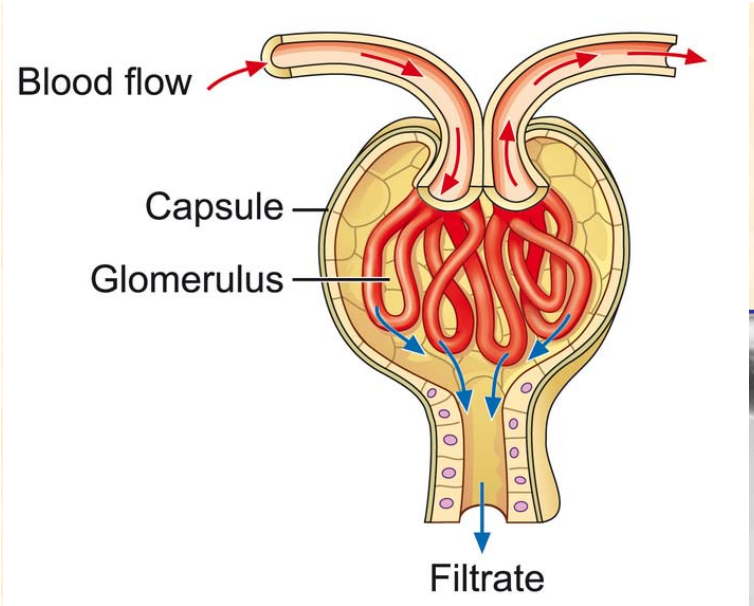
PNS involvement

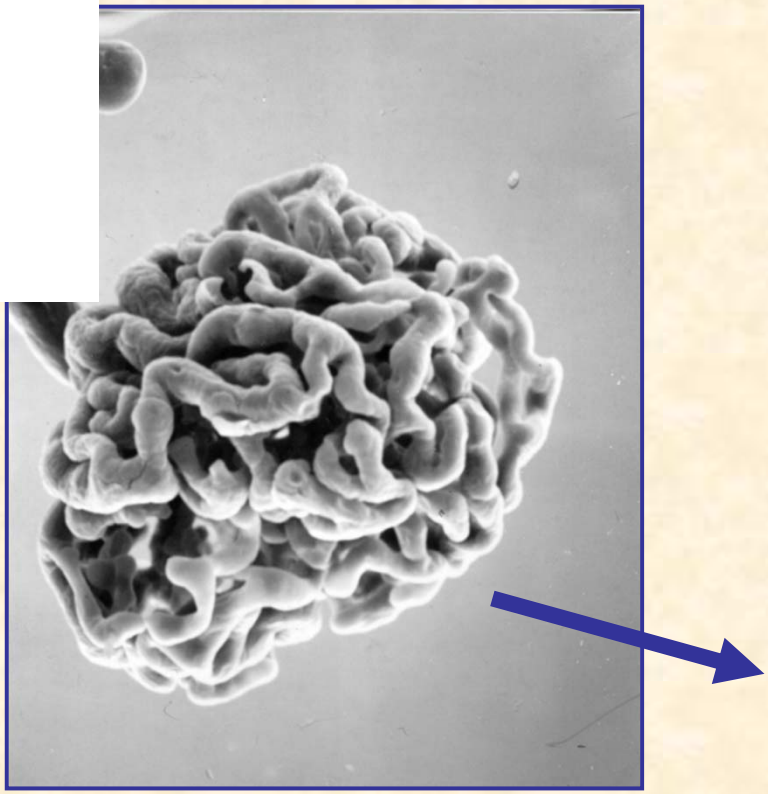
11-67% of the patients
→ MONONEURITIS MULTIPLEX



Alveolar hemorrhage



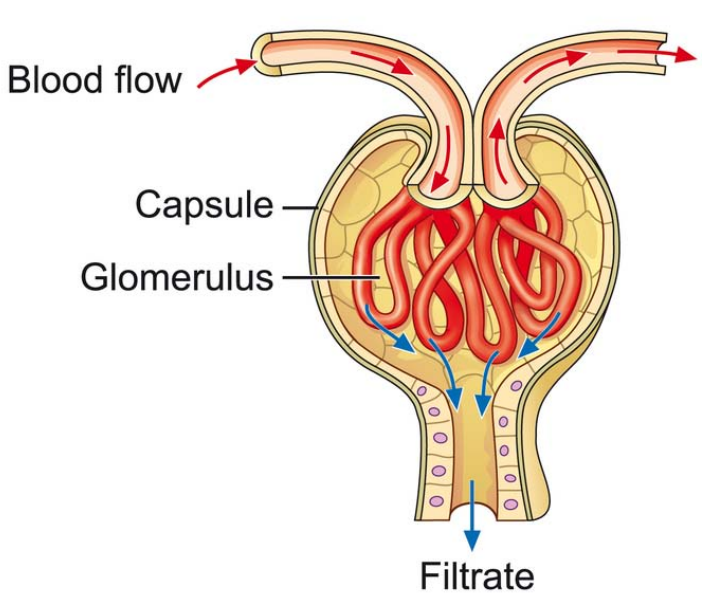


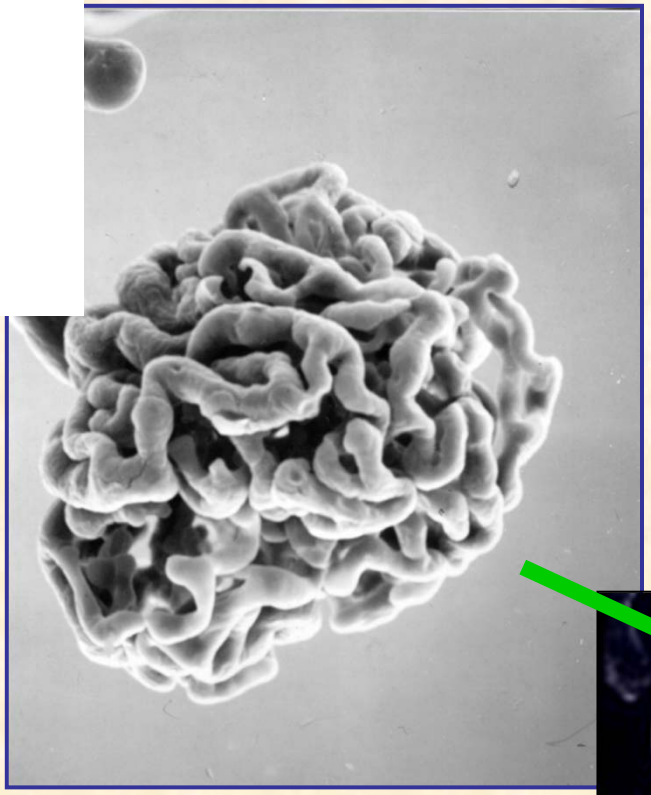


Kidney involvement

30-85% of the patients

MPA>GPA>>CSS

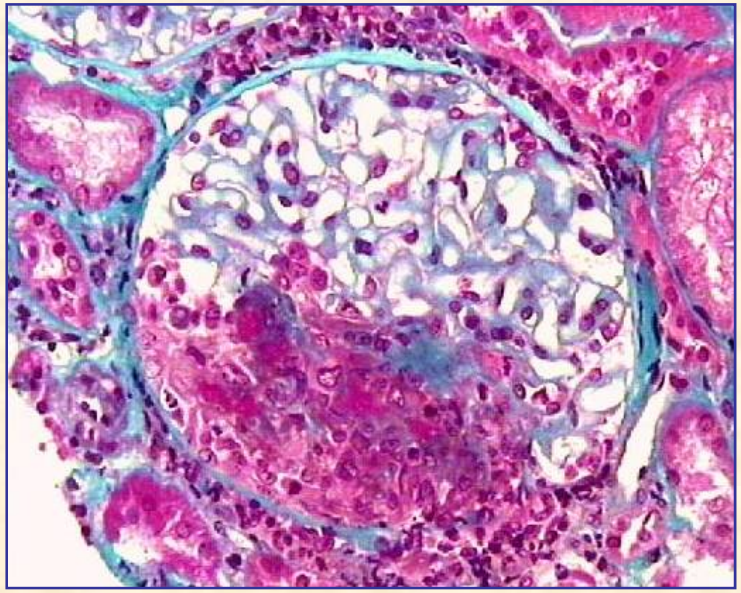




Kidney involvement

30-85% of the patients

MPA>GPA>>CSS



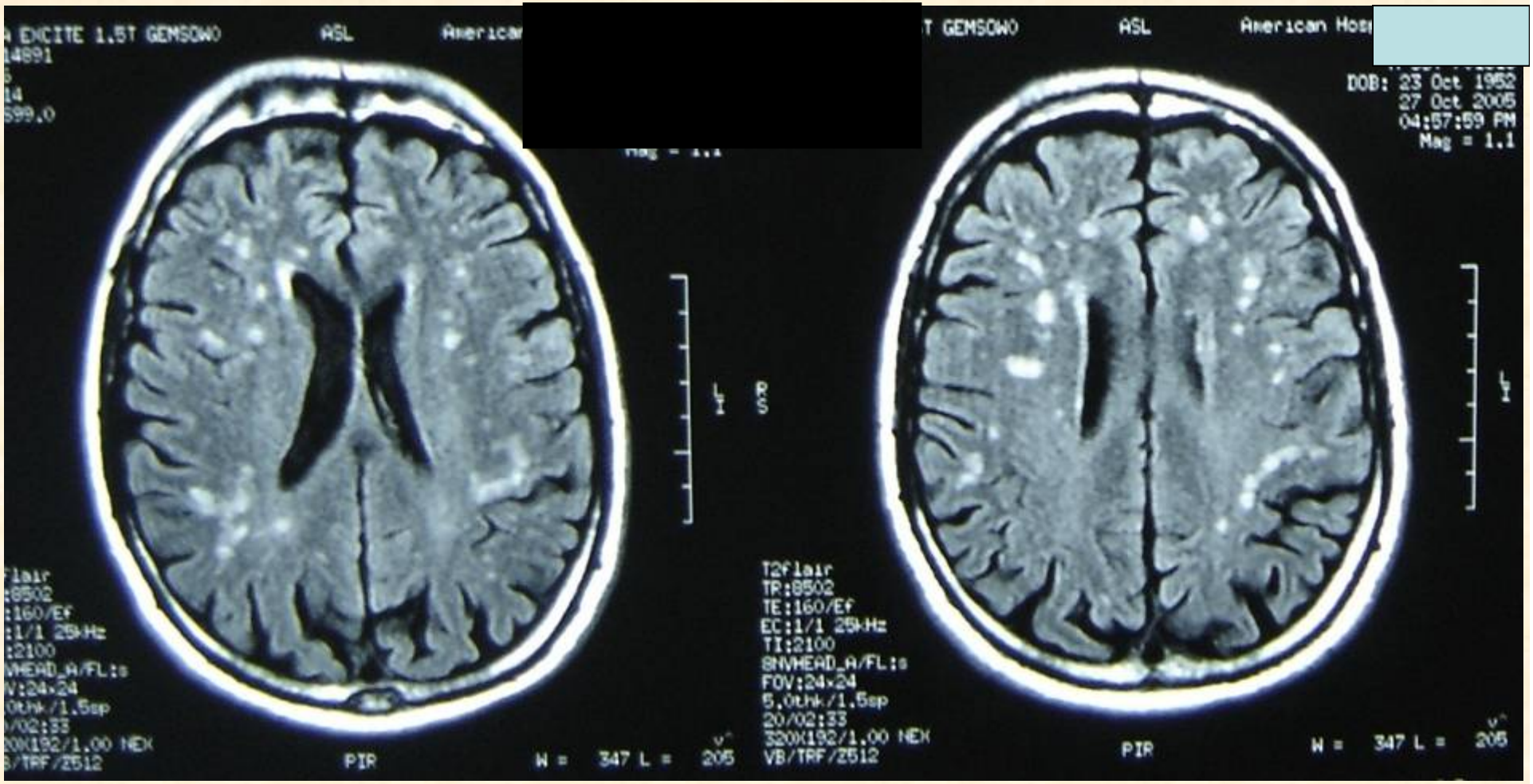
Necrotizing extracapillary GN

Rapidly progressive GN

Pauci-immune GN

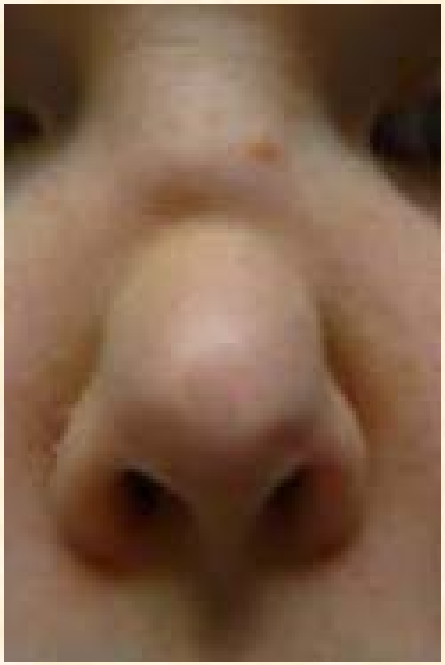
CNS involvement <10% of the patients

- Stroke
- Hypersignals

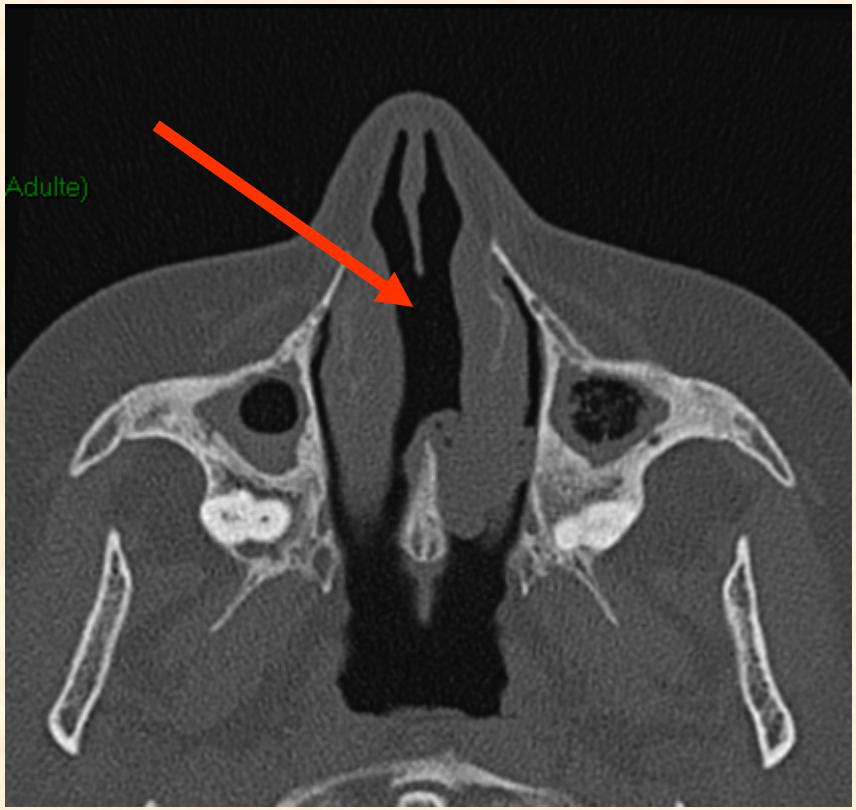


Serous otitis media
(bullaes)

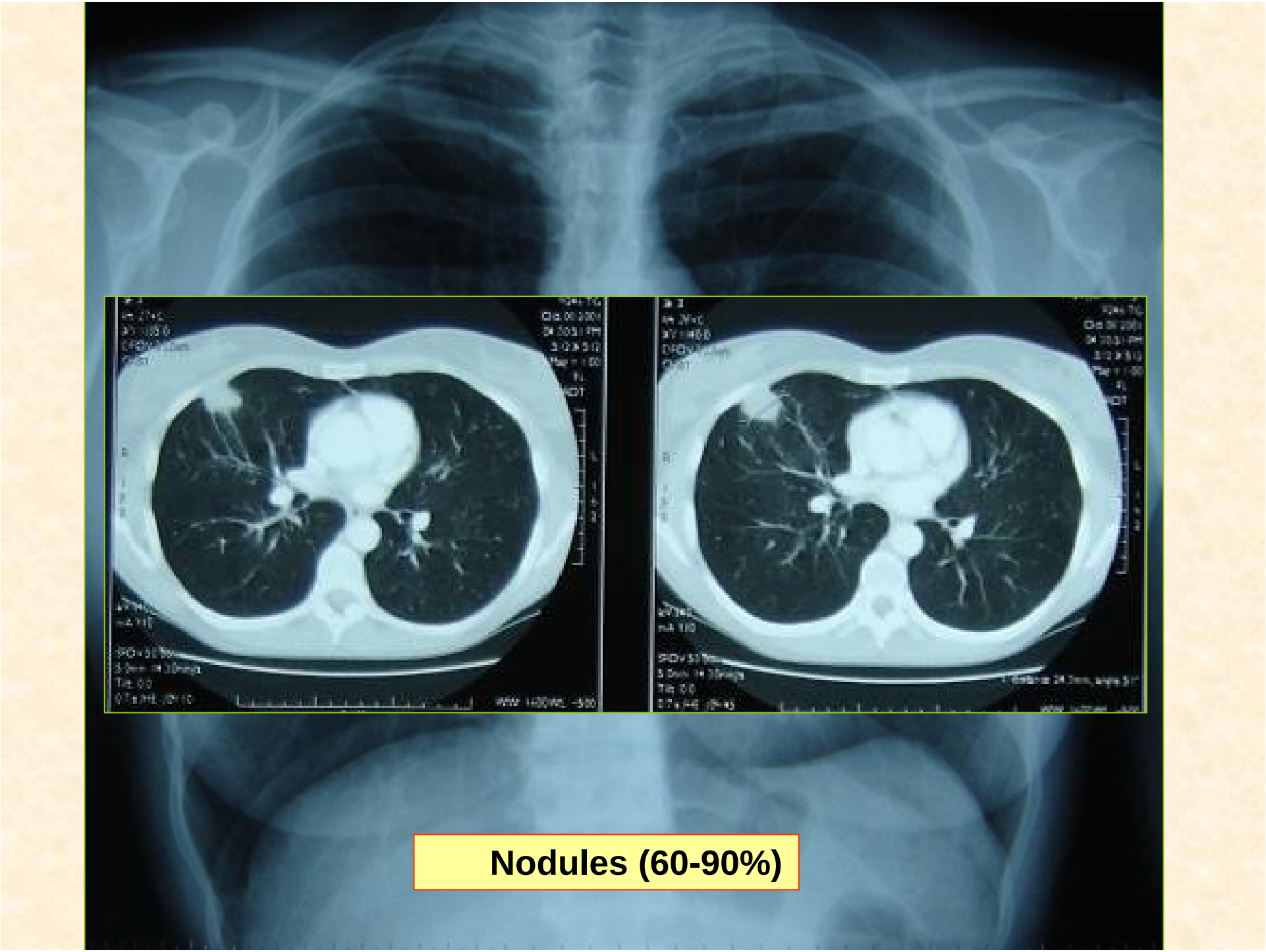
Granulomatosis with polyangiitis (Wegener)



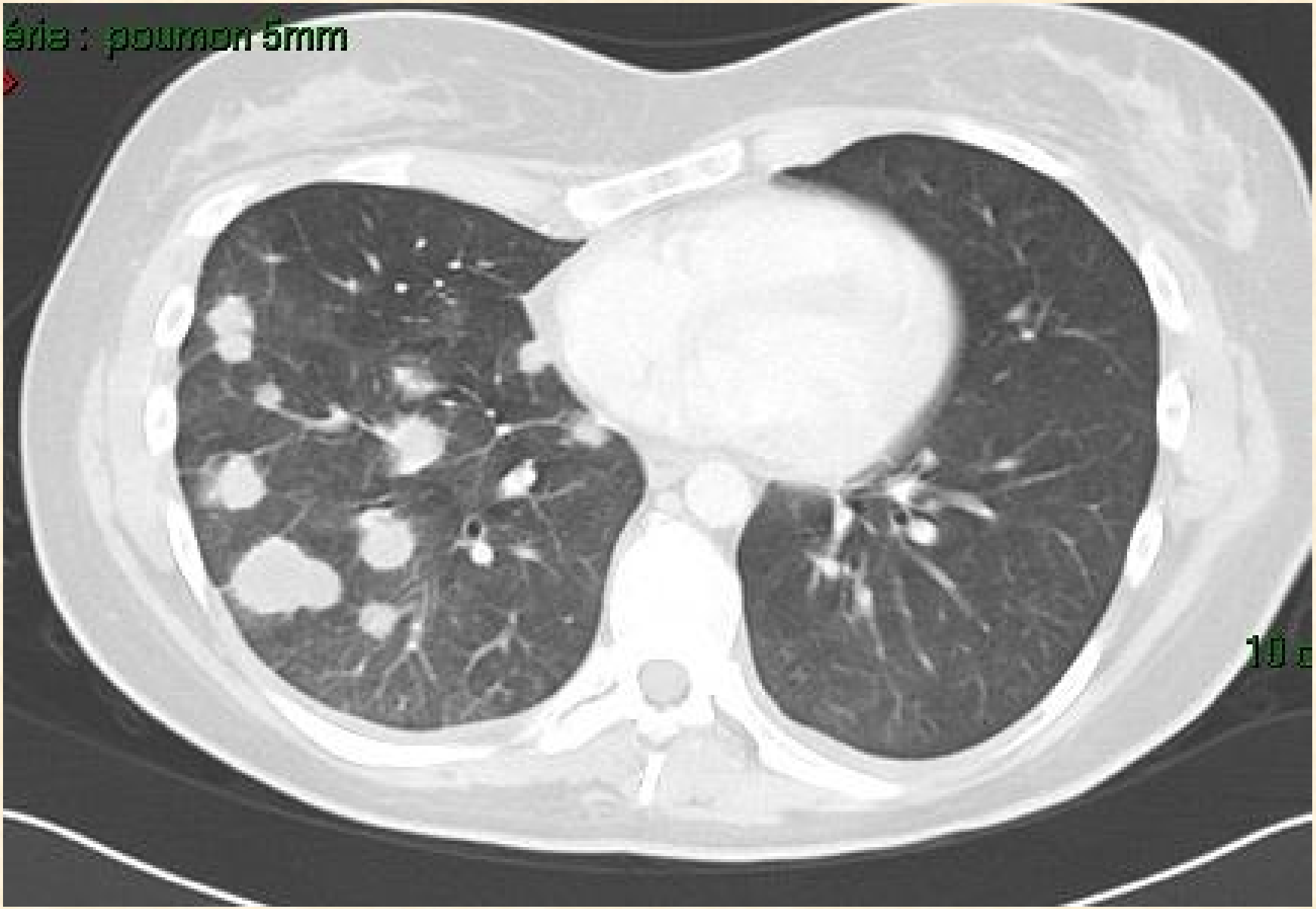
Rembrandt's portrait of Gerard de Lairesse with misformed nose. Oil on canvas, ca. 1665-67. Metropolitan Museum of Art.

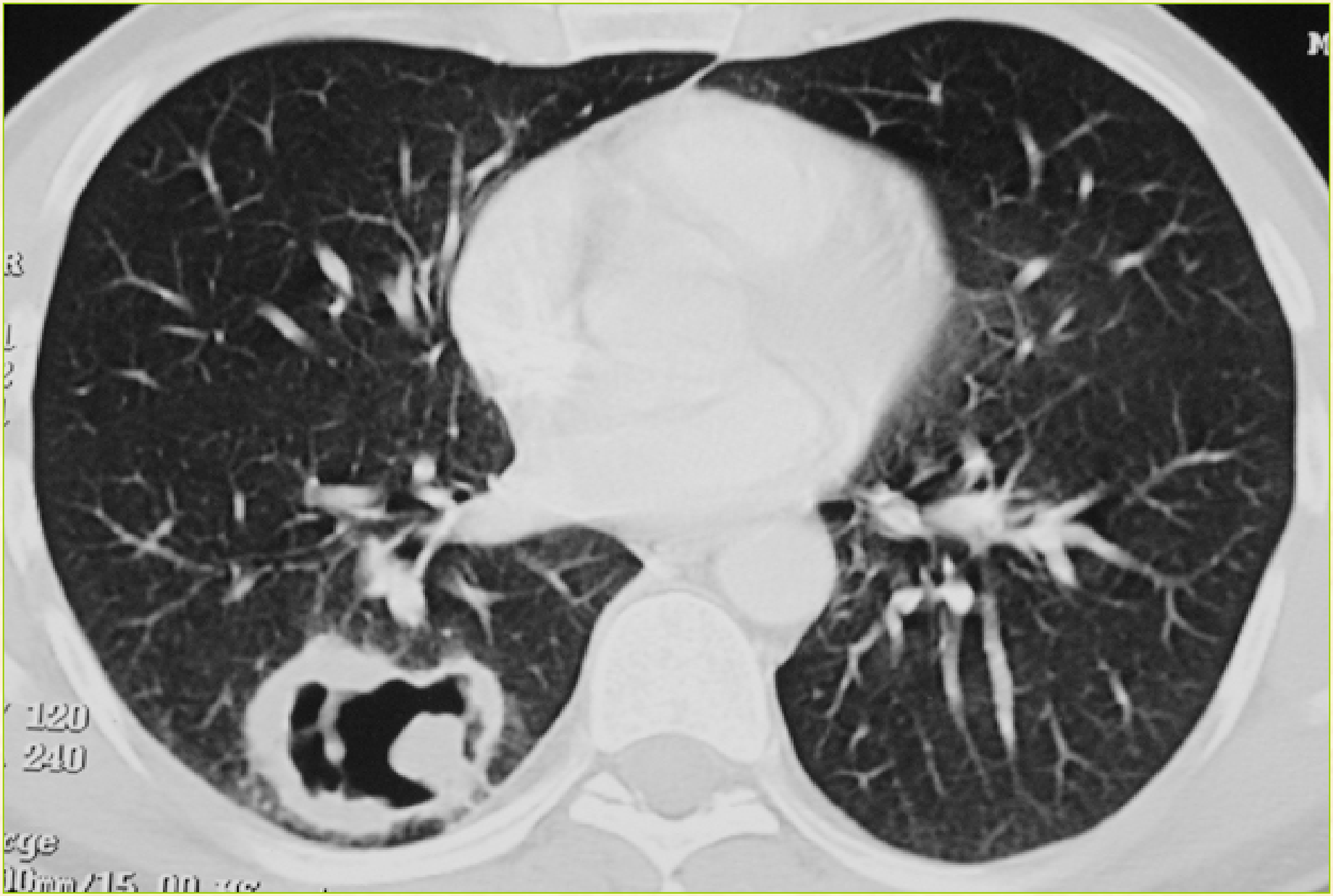


Septal perforation

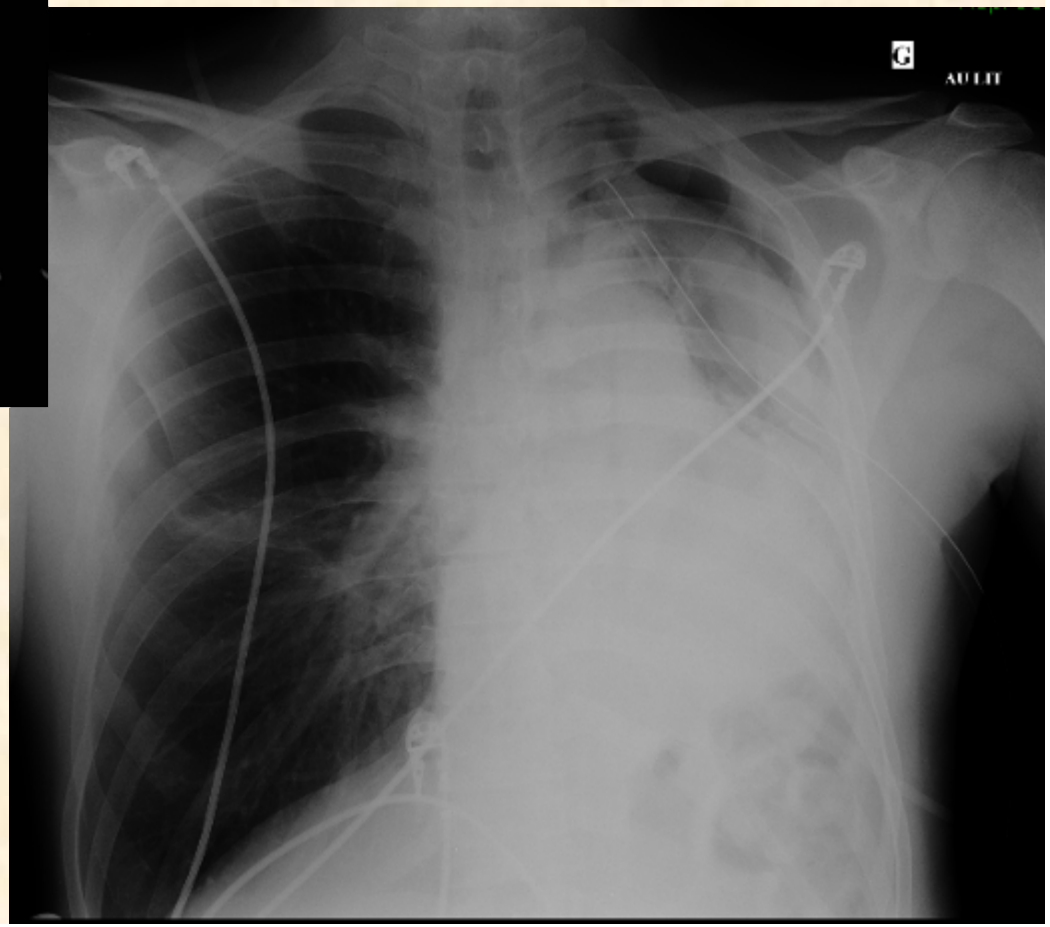


Nodules (60-90%)


érie : poumon 5mm


120
240


RADIOLOGIE COCHIN-A-
Sensation 16
VB10B
604 IMA 2
MPR 2
MPR 2
ALF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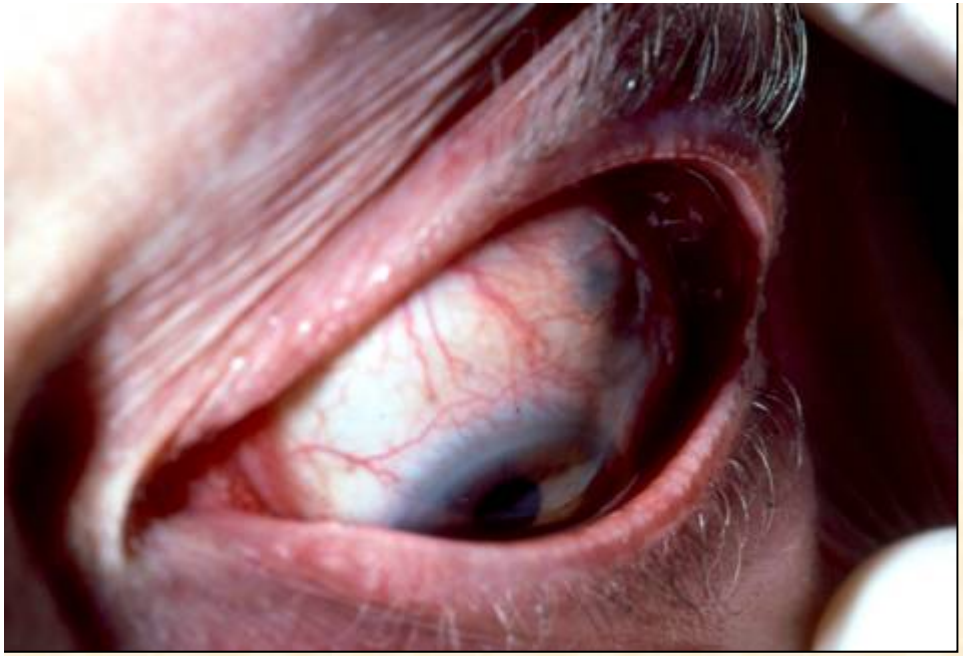
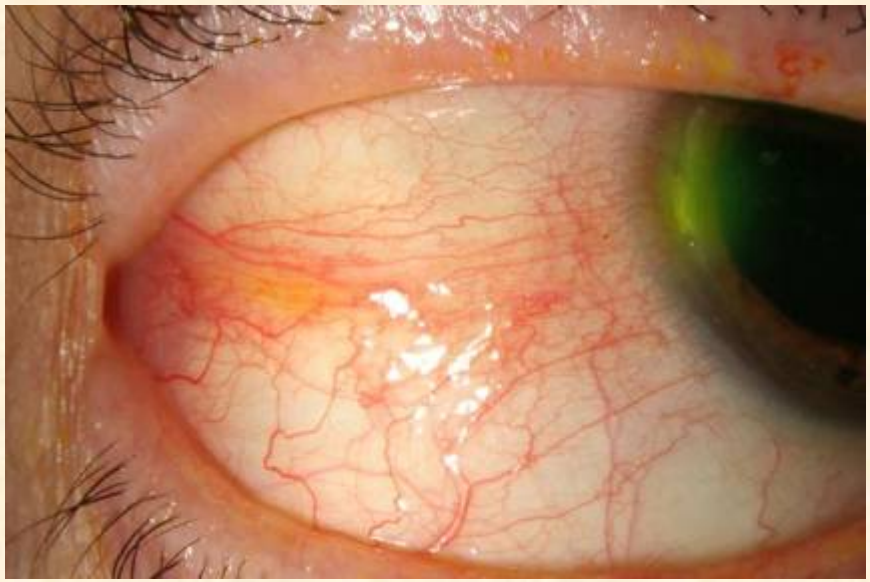
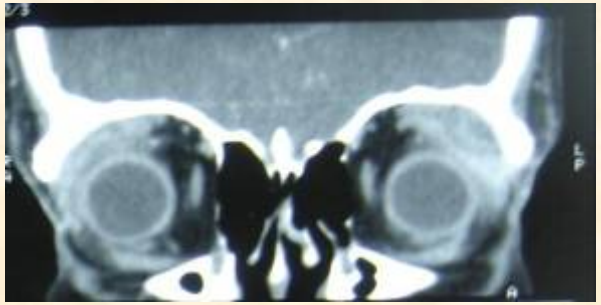
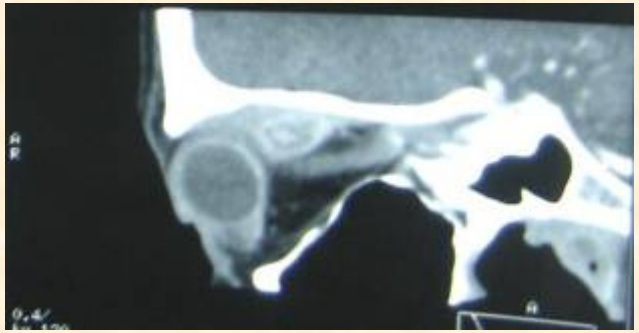


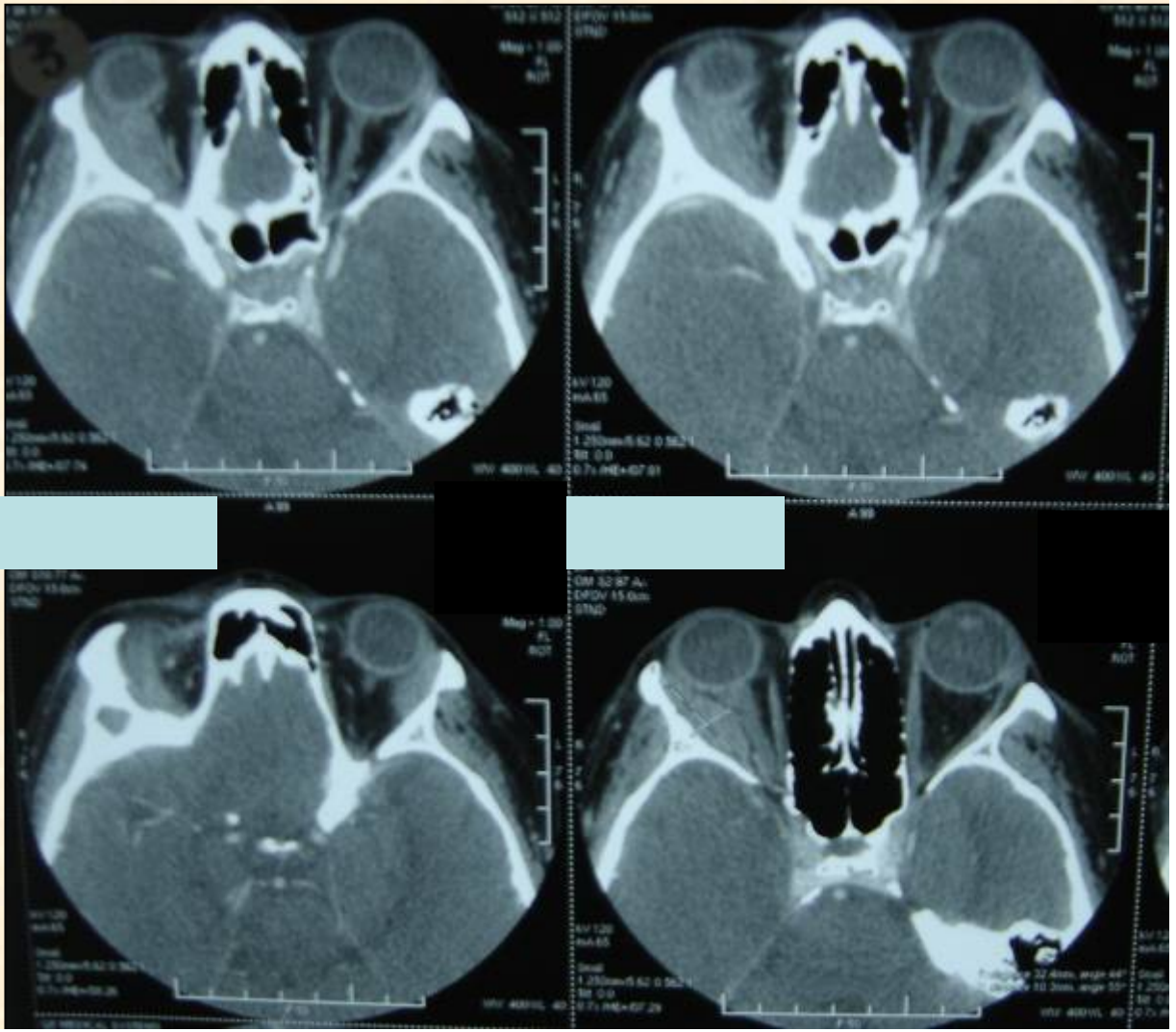


Eye

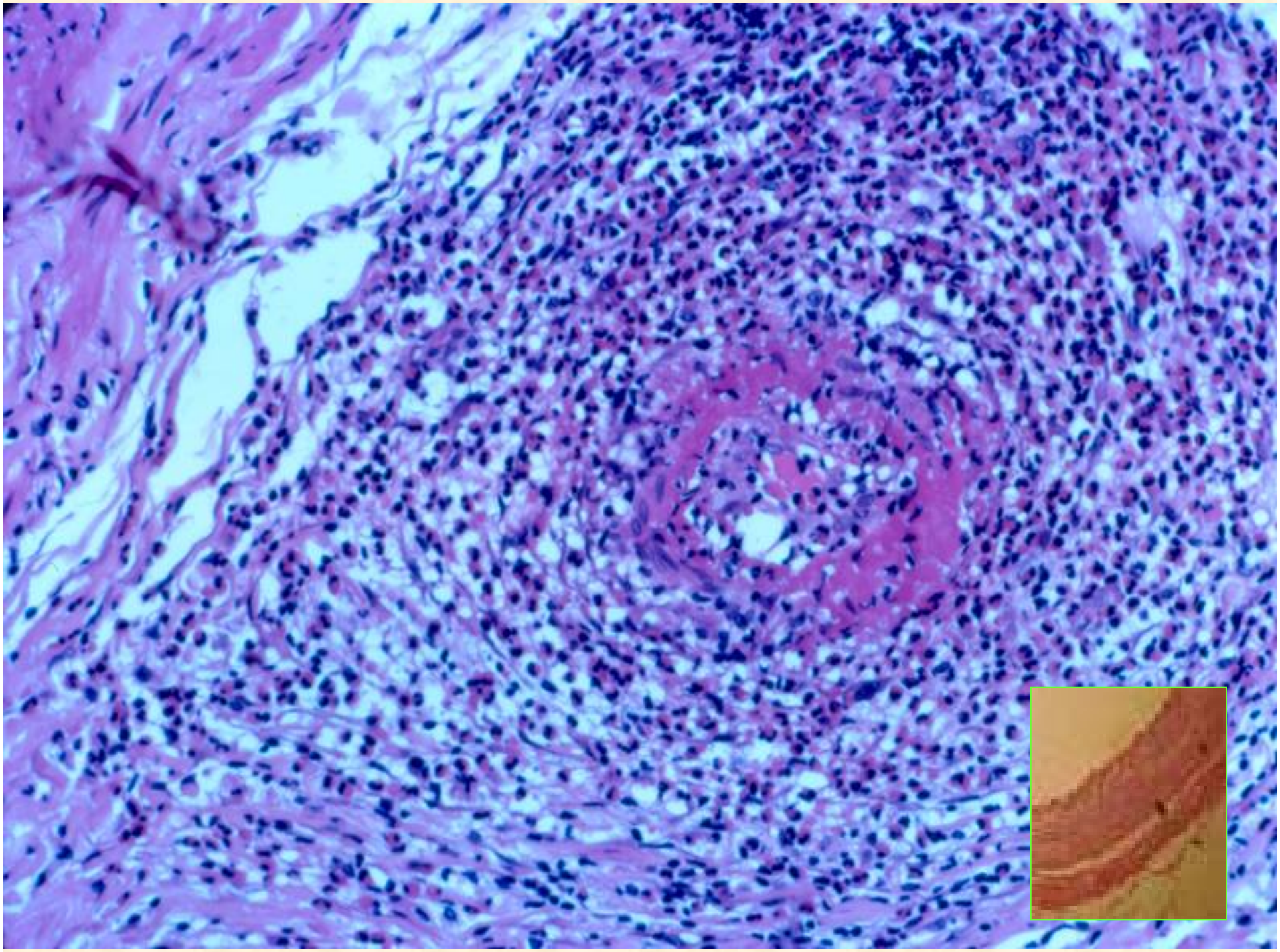
10-33% of the patients







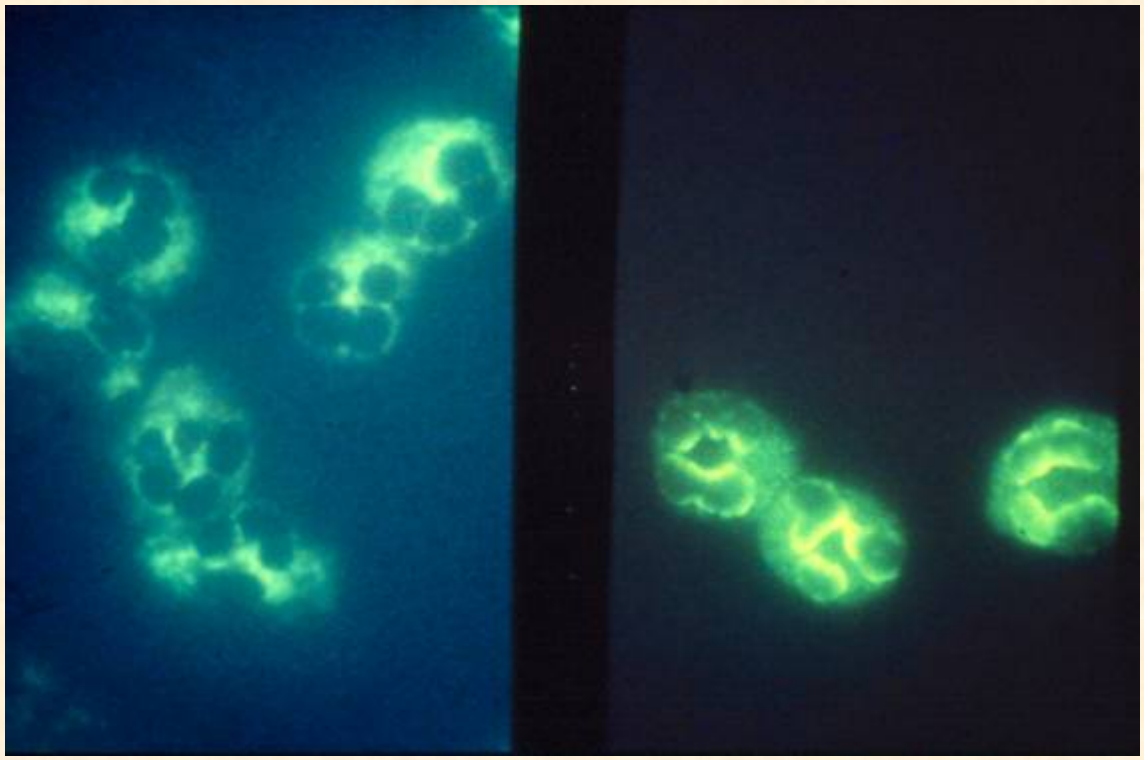
Biopsy



ANCA

C ANCA

GPA/Wegener



P ANCA

MPA

CSS/EGPA

C-ANCA : 90% PR3 proteinase 3

P-ANCA : MPO myeloperoxydase

cANCA antiPR3

ANCA

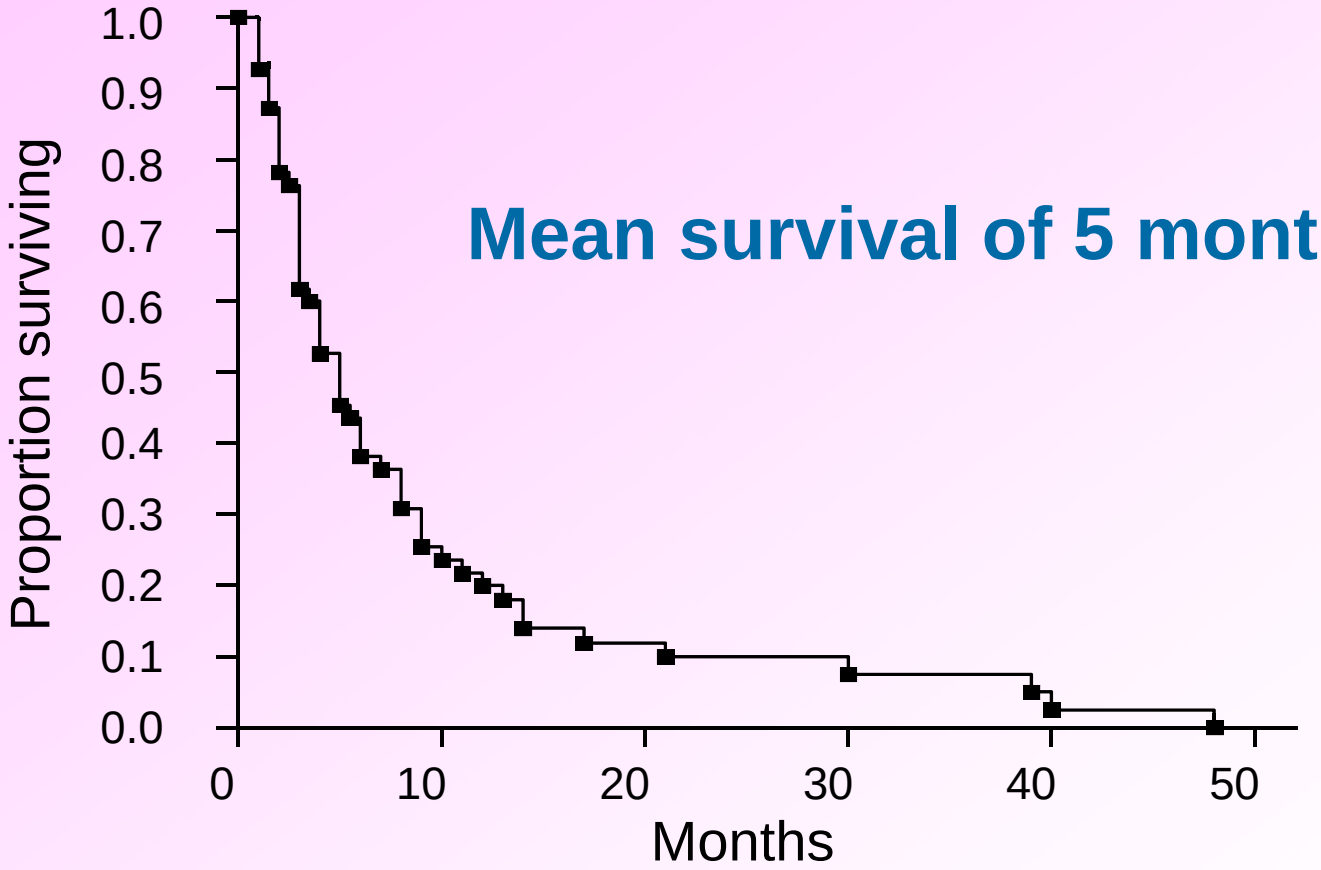
- Systemic GPA Wegener's = 90%
- Localized GPA Wegener's = 50%
- Microscopic polyangiitis >75%
- Churg-Strauss syndrome <40%

pANCA antiMPO

Treatment and outcomes

http://www.bangstyle.com/2011/10/diy-at-home-spa-treatments/

Without treatment, GPA is fatal



Mean survival of 5 months

56 patients diagnosed with GPA, untreated

Data from Walton EW, Br Med J. 1958;34:265-270 – Courtesy of Dr. Paul Brunetta.

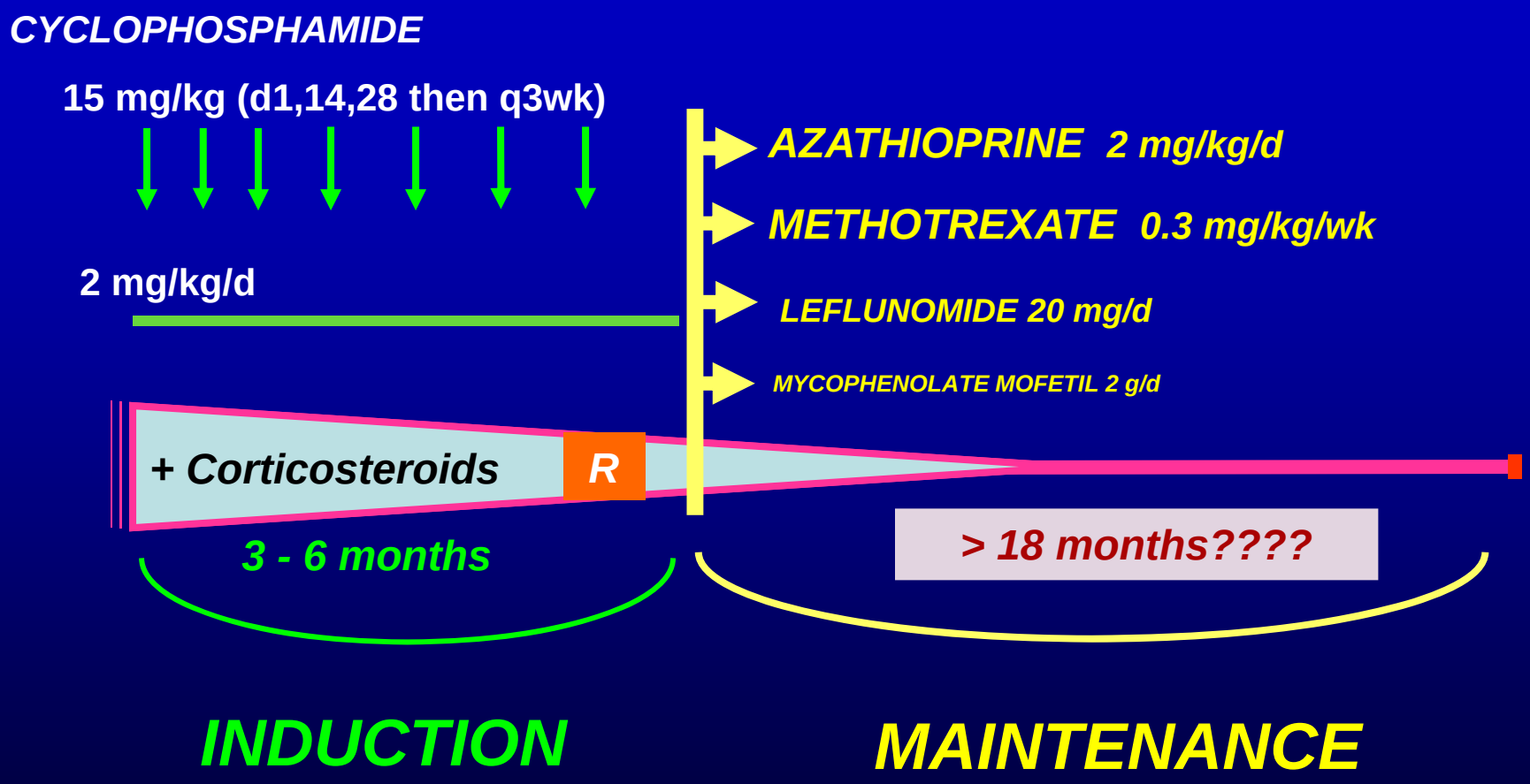
Corticosteroids

- 1948 : anti-inflammatory action of CS
  - Nobel price 1950: Kendall, Hench &Reichstein
- **<u>Cornerstone for almost all vasculitides</u>**
  - GCA, Takayasu
  - PAN
  - ANCA-associated vasculitis

(not Kawasaki?

limited use for virus-related vasculitides)

Treatment of severe GPA/MPA



+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

VASCULITIS ACTIVITY SCORE 2003

☐ Tick box **only** if abnormality represents active disease (use the Vasculitis Damage Index, VDI to score items of damage). If there are no abnormalities in a system, please tick the "None" box

○ If **all** the abnormalities recorded represent smouldering/low grade/grumbling disease, and there are no new/worse features, please remember to tick the box at the bottom right corner

	None	Active disease
1. General	☐	
Myalgia		○
Arthralgia or arthritis		○
Fever≥38.0 °C		○
Weight loss≥2 kg		○
2. Cutaneous	☐	
Infarct		○
Purpura		○
Ulcer		○
Gangrene		○
Other skin vasculitis		○
3. Mucous membranes/eyes	☐	
Mouth ulcers/granulomata		○
Genital ulcers		○
Adnexal inflammation		○
Significant proptosis		○
Red eye (Epi)scleritis		○
Red eye conjunctivitis/ blepharitis/keratitis		○
Blurred vision		○
Sudden visual loss		○
Uveitis		○
Retinal vasculitis/retinal vessel thrombosis/retinal exudates/ retinal haemorrhages		○
4. ENT	☐	
Bloody nasal discharge/nasal crusts/ulcers and/or granulomata		○
Paranasal sinus involvement		○
Subglottic stenosis		○
Conductive hearing loss		○
Sensorineural hearing loss		○
5. Chest	☐	
Wheeze		○
Nodules or cavities		○
Pleural effusion/pleurisy		○
Infiltrate		○
Endobronchial involvement		○
Massive haemoptysis/alveolar haemorrhage		○
Respiratory failure		○

	None	Active disease
6. Cardiovascular	☐	
Loss of pulses		○
Valvular heart disease		○
Pericarditis		○
Ischaemic cardiac pain		○
Cardiomyopathy		○
Congestive cardiac failure		○
7. Abdominal	☐	
Peritonitis		○
Bloody diarrhoea		○
Ischaemic abdominal pain		○
8. Renal	☐	
Hypertension		○
Proteinuria>1+		○
Haematuria≥10 rbc/hpf		○
Creatinine 125-249 µmol/l		○
Creatinine 250-499 µmol/l		○
Creatinine≥500 µmol/l		○
Rise in creatinine>30% or creatinine clearance fall>25%		○
9. Nervous system	☐	
Headache		○
Meningitis		○
Organic confusion		○
Seizures (not hypertensive)		○
Stroke		○
Cord lesion		○
Cranial nerve palsy		○
Sensory peripheral neuropathy		○
Motor mononeuritis multiplex		○
10. Other	☐	
		○
		○
		○
		○

Persistent disease only:

Tick here if **all** the above abnormalities are due to low grade grumbling disease and not due to new/worse disease ☐

BVAS 2003

Score 0 → 63

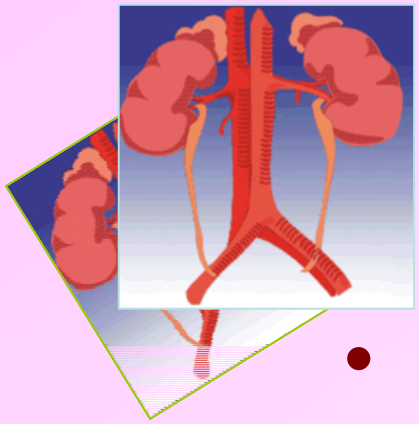
In practice 0 → 30

- 4 items

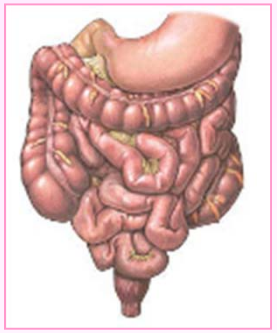
+ 4 items

+ merging of some items

The Five Factor Score

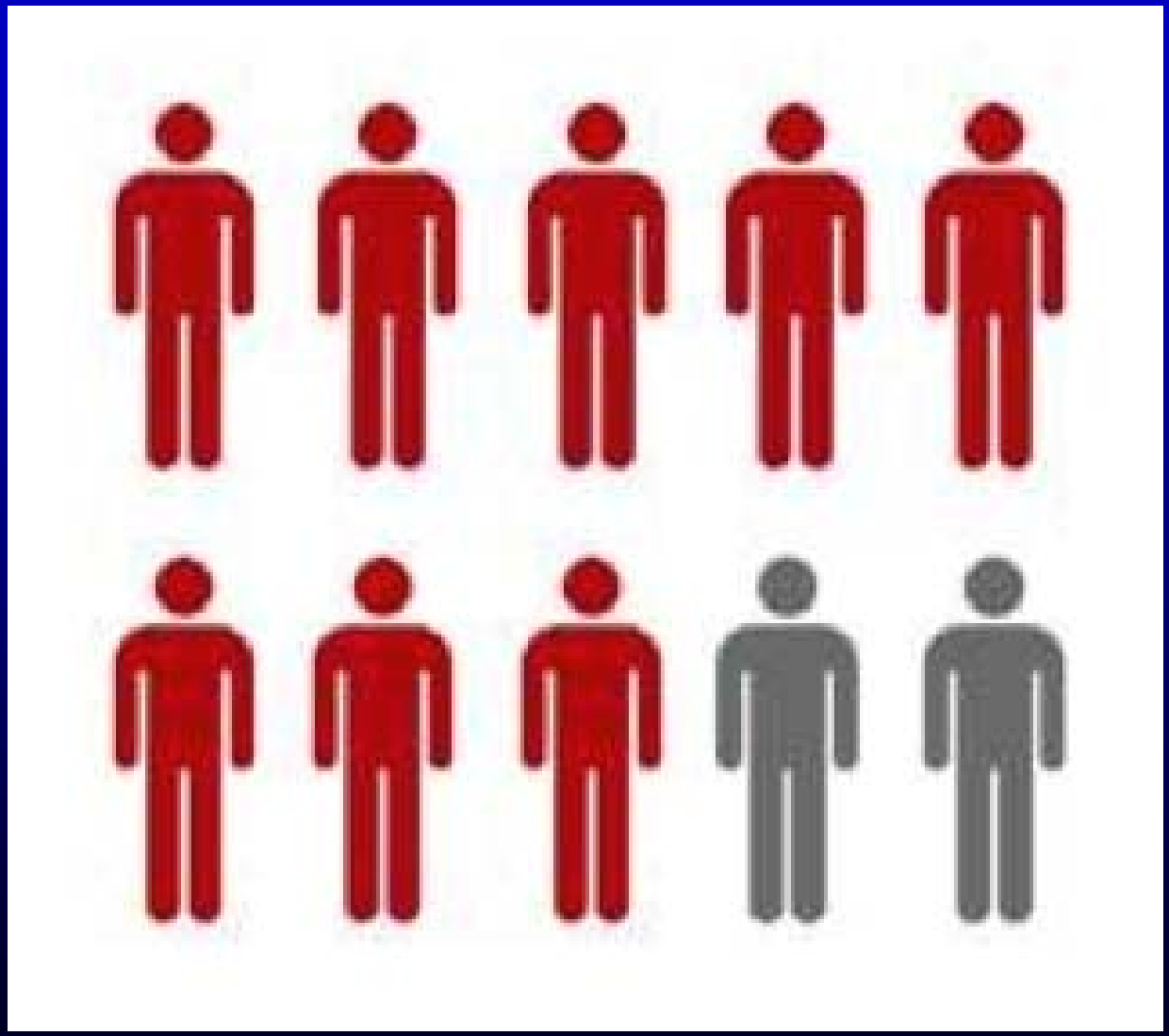


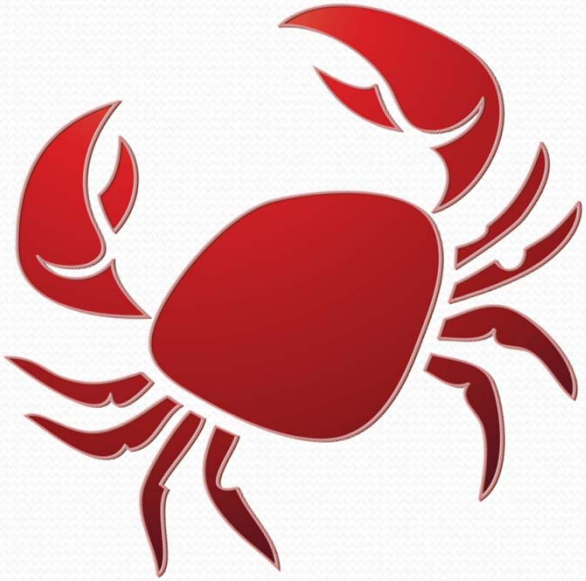
- **Proteinuria >1 g/day**
- **Creatinine level >140 µmol/l**
- **Specific GI involvement**
- **Specific cardiomyopathy**
- **Specific CNS involvement**



Guillevin et al. *Medicine* 1996;75:17-28

Remission 80-90% percent





Frequent relapses…

	Patients		Follow-up from Dg	Relapse rate	p
CYCAZAREM NEJM, 2003	WG, MPA	144	18 mo	AZA 15,5% vs. CYC 13,7%	NS
WGET NEJM, 2005	WG	180	27 mo	MTX 32,8% vs MTX/ETN 30,6%	NS
Langford Am J Med, 2003	WG	42	35 mo	52%	
WEGENT **Pagnoux, NEJM, 2009**	WG, MPA	126	37,3 mo	AZA 36,5% vs MTX 33,3%	NS
Sanders NEJM, 2003	WG, MPA	136	→ 5 yrs	AZA 42.3% vs. CYC 57.4%	NS

At 7 years, relapse rate 63.9% → 51.2% (445 patients)

Holle et al. Arthritis Rheum 2011 Jan;63(1):257-66

PEXIVAS

a RCT of plasma exchange and glucocorticoid dosing in ANCA associated vasculitis

3 Co-PIs: Mike Walsh (Canada), David Jayne (UK) and Peter Merkel (USA)

RAVE

(<350 µM)
(no severe AH)
ANCA+

1 à 3 MP pulse(s)

CS + **oral CYC** * 3 to 6 mo

+ placebo RTX

Rituximab + CS**

+ placebo CYC

AZA → M18

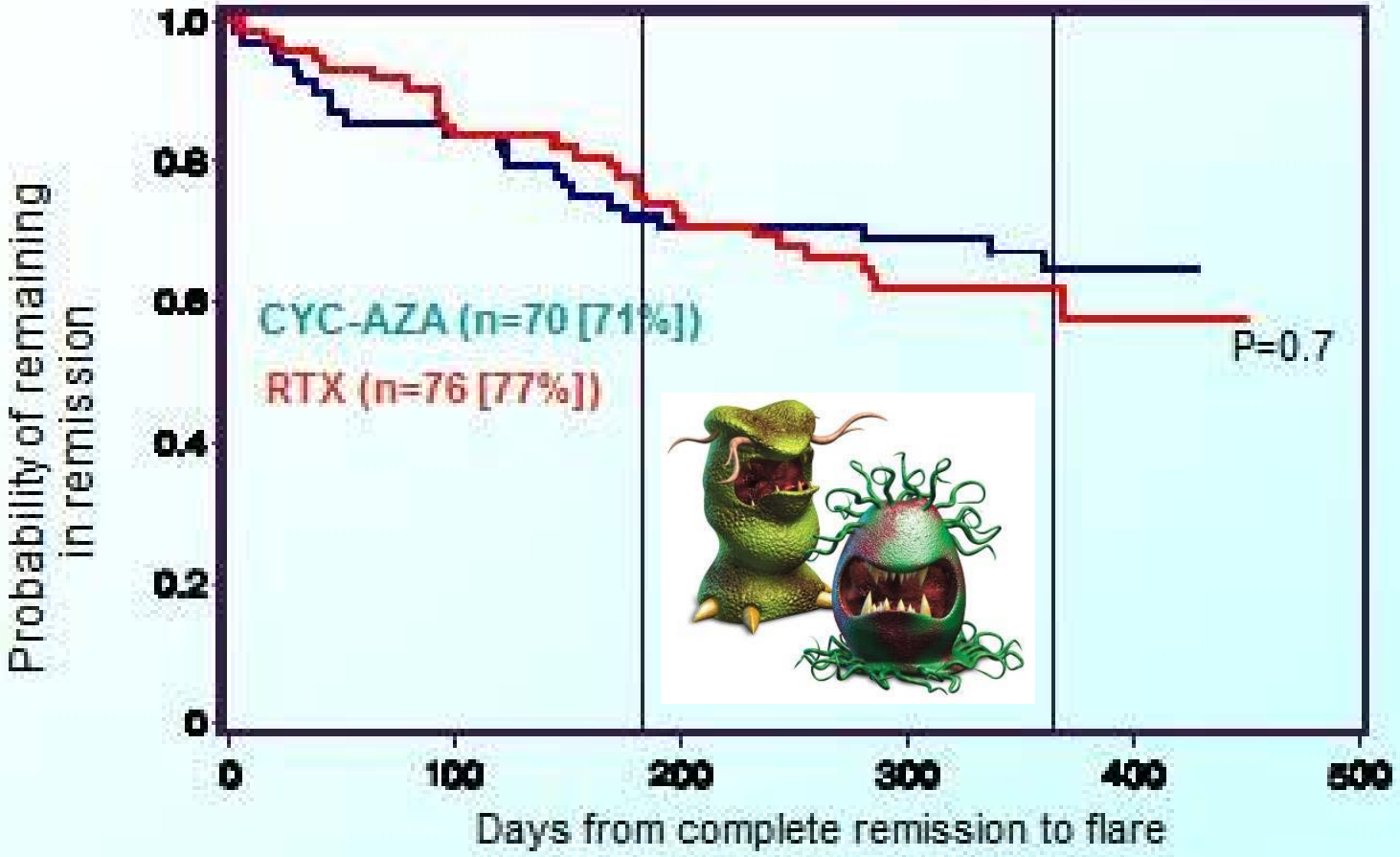
Placebo AZA

* oral CYC 2 mg/kg/d

** **RTX 375 mg/m2 x 4**

Duration of Complete Remission by Treatment Group

(n = 146 of 197; 74%)



No statistically significant difference in limited or severe flares by 18 months

Stone JH et al. EULAR, London, UK- May 2011 - Courtesy of Dr. Paul Brunetta

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:

a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
d) Cyclophosphamide is contraindicated; OR
e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
f) The patient wishes to preserve ovarian/testicular function for fertility.

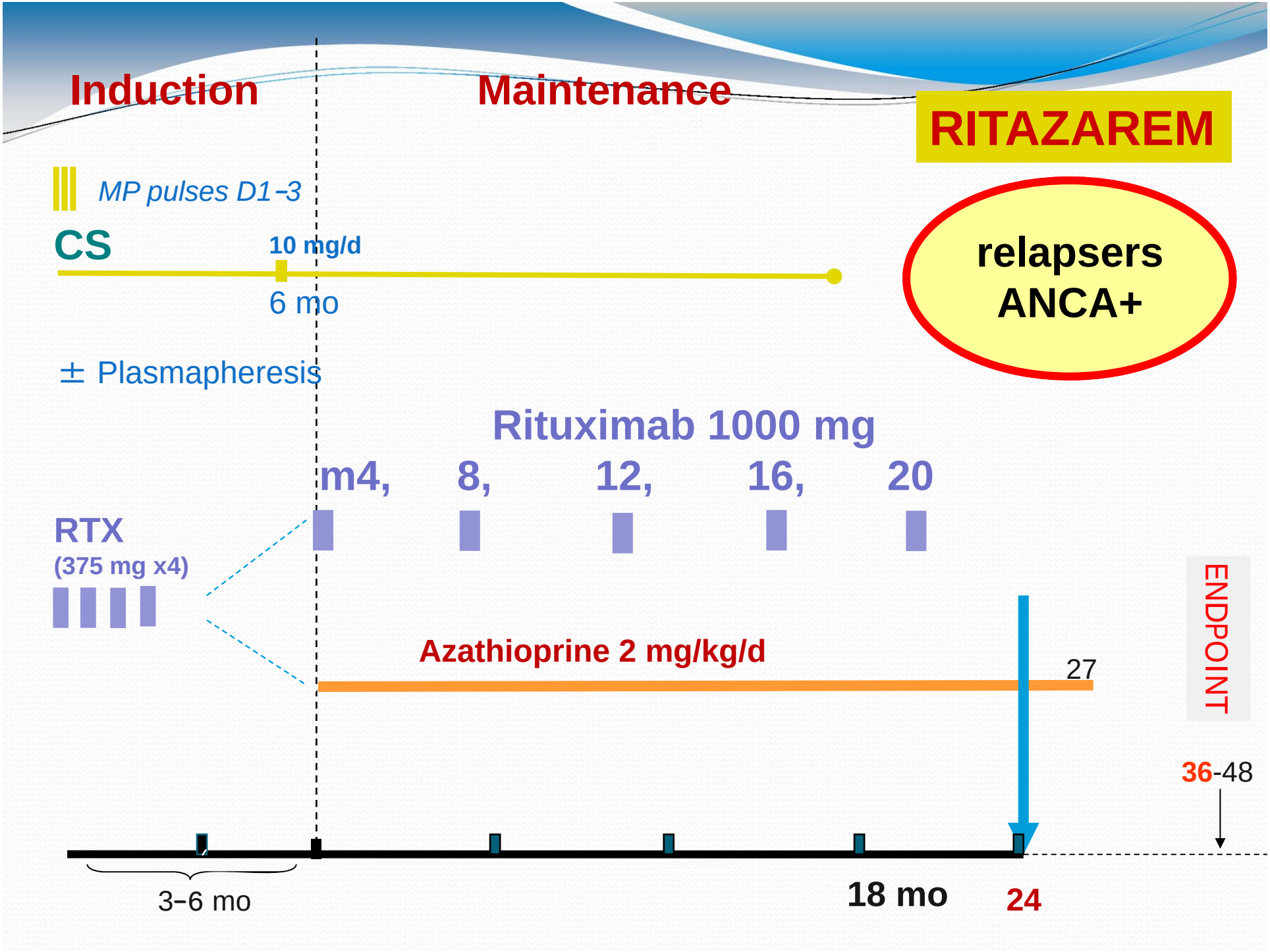
The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

Welcome Ritazarem!

+ induction for 1st relapsers
+ maintenance (for relapsers)


Induction
Maintenance
RITAZAREM
MP pulses D1–3
CS
10 mg/d
6 mo
relapsers
ANCA+
± Plasmapheresis
Rituximab 1000 mg
m4,
8,
12,
16,
20
RTX
(375 mg x4)
Azathioprine 2 mg/kg/d
27
ENDPOINT
36-48
3–6 mo
18 mo
24

Potential new strategies or agents

- Rituximab for maintenance in GPA/MPA
- Tocilizumab – GCA, Takayasu (GPA?)
- Mepolizumab – Churg-Strauss syndrome
- Belimumab – ANCA-vasculitis
- AntiC5-Receptor – ANCA-vasculitis

- AntiIL17, IL23…
- Syk inhibitors…
- Toll-like receptor modulators…


CANADIAN VASCULITIS NETWORK
CANVASC
2nd annual
CanVasc
meeting
Montréal or Toronto
November 22nd, 2012
Registration and information on
http://www.canvasc.ca