Immunpathology I.

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The purpose of the immunsystem to

Maintain the integrity of human organism

Warrant the individulaity

Protect against infectious diseases

Protect against tumors

Clinical Course of Inflammation

HYPERACUTE (Peracute)

ACUTE

SUBACUTE

SUBCHRONIC

PRIMARY CHRONIC (e.g. PCP)

SECONDARY CHRONIC

LOCAL SIGNS OF INFLAMMATION ACCORDING TO CELSUS
„ cardinal symptomes ”

CALOR

RUBOR

TUMOR

DOLOR

FUNCTIO LAESA (added by Rudolf VON VIRCHOW)

GENERAL OR SYSTEMIC SIGNS OF INFLAMMATION

FEVER
TACHYCARIDA
LEUKOCYTPSIS
INFECTIOUS ANEMIA

MORPHOLOGY

ACUTE: NEUTROPHILS, EOSINOPHIL GRANULOCYTES

AFTER SOME TIME REPLACED BY „ ROUND CELLS ” : MONOCYTES, MACROPHAGES, LYMPHOCYTES

IN ALLERGIC OR VIRAL INFLAMMATIONS:
LYMPHOCYTES AND PLASMACELLS ALREADY IN THE ACUTE PHASE

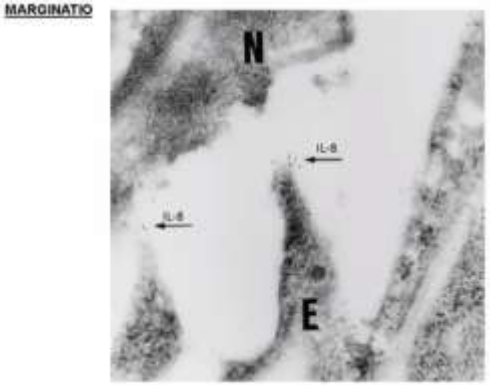
IN AUTOIMMUNE DISEASES AND IN IMMUNSUPPRESSED PATIENTS (TRANSPLANTATION, TUMOR PATIENTS) the inflammatroy cells of the chronic phase might appear in the the beginning of the course of inflammation

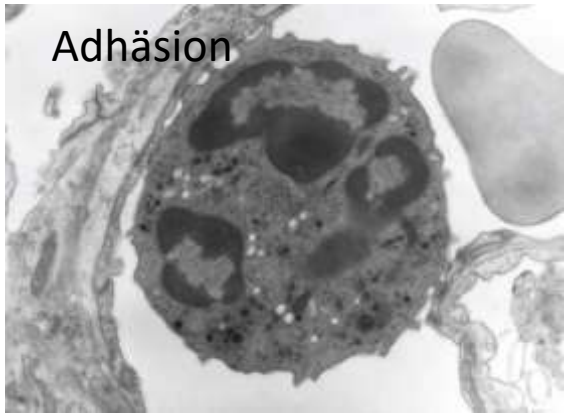
LOCAL OR SPREAD INFLAMMATORY RESPONSE
(HYALURONIDASE, KOLLAGENASE, STREPTOKINASE, FIBRINOLYSIN)

SEPTIC SPLEEN

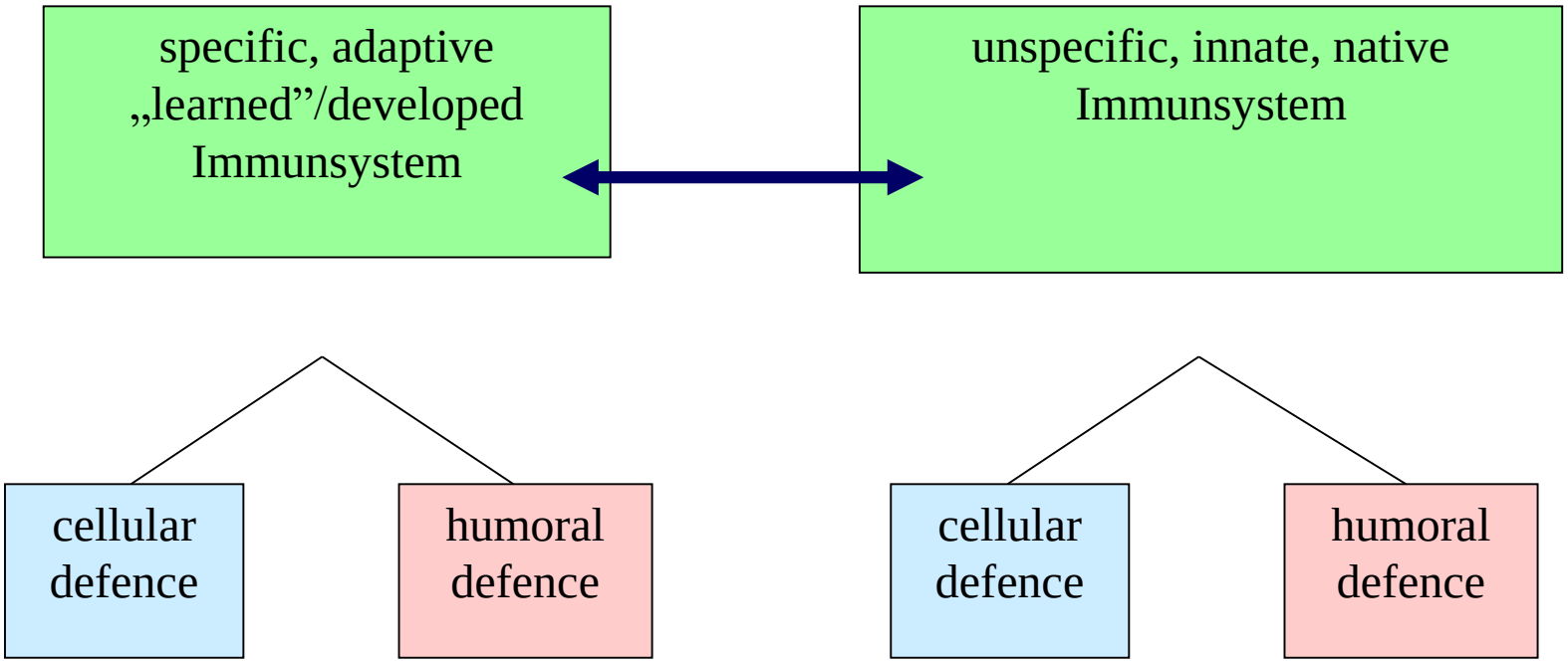
Neutrophil Granulozyten
(sekretieren Enzyme, töten Bakterien)
Eosinophil Gr.
(MBP, ECP) gegenParasytenm Würme
Makrophagen (organisieren das Entzündungsprozess: Zytokine, Aktivierung der Zellen, verbinden mitgeborene und gelernte Immunität)
Endtohel Zellen (Exsidation, Leukozyten Wanderung)
Fibroblasten (rgenerationÖ
Thrombozyten: (bFGF, TGFb, PDGF)
Lymphozyten

Migration der Leukozyten
- Marginatio
- Rollen
- Adhäsion
- Transmigration (Diapedese)
- Chemotaxis





Immunsystem to defend from noxa

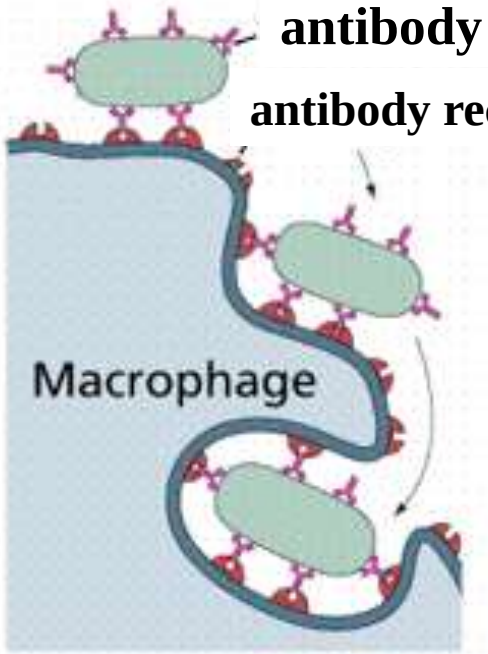


- Lymphocytes
- Antibodies
- Makrophages
- Granulocytes
- NK cells
- Mast cells
- Dendritic cells
- complement
- Lysozyme
- C-reaktive Protein

Cells of unspecific immune system

macrophages, dendritic cells, granulocytes,
mast cells, NK cells

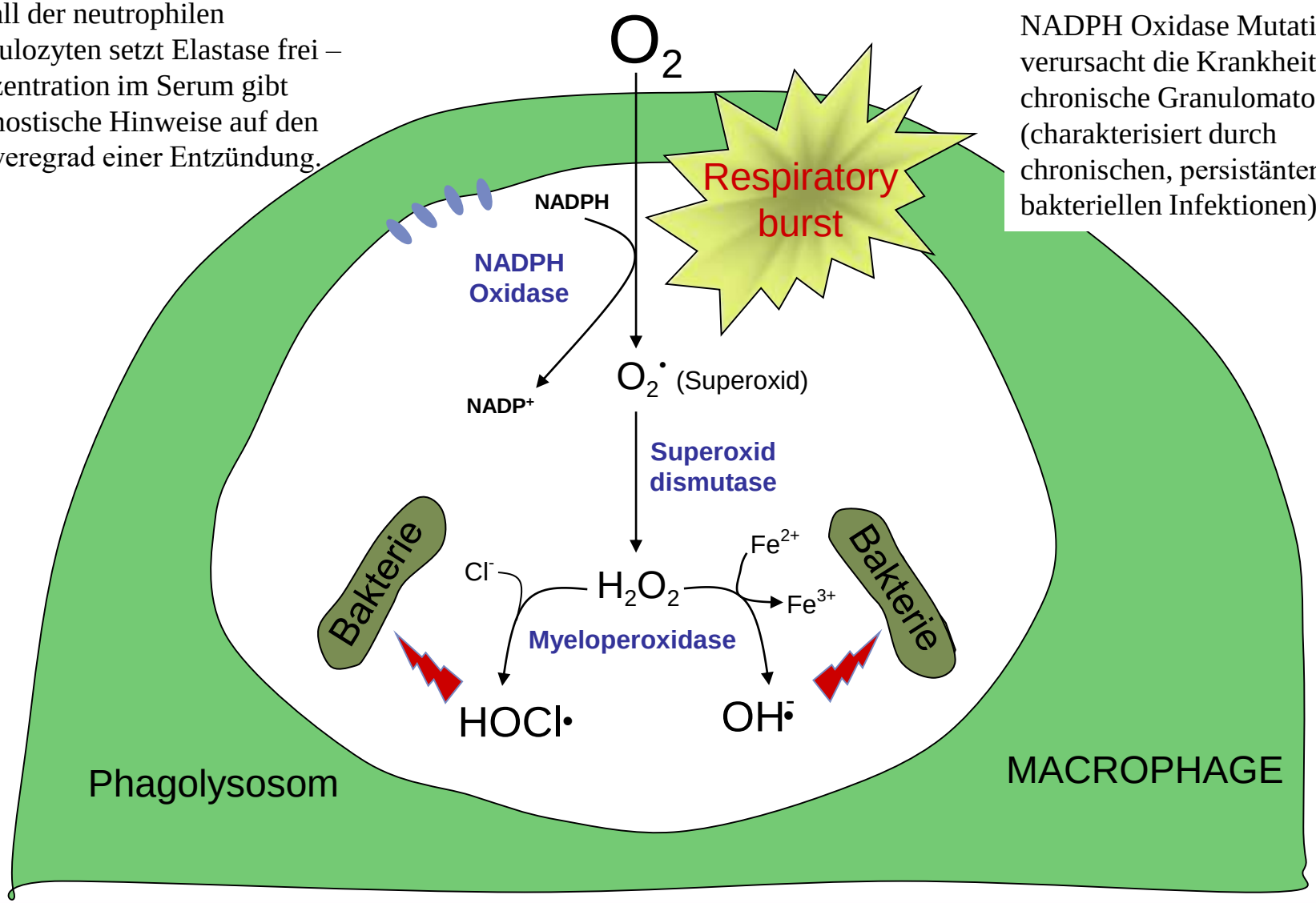
Phagocytosis
of a bacterium covered by IgG



Phagocytosis by macrophages and neutrophile leukocytes

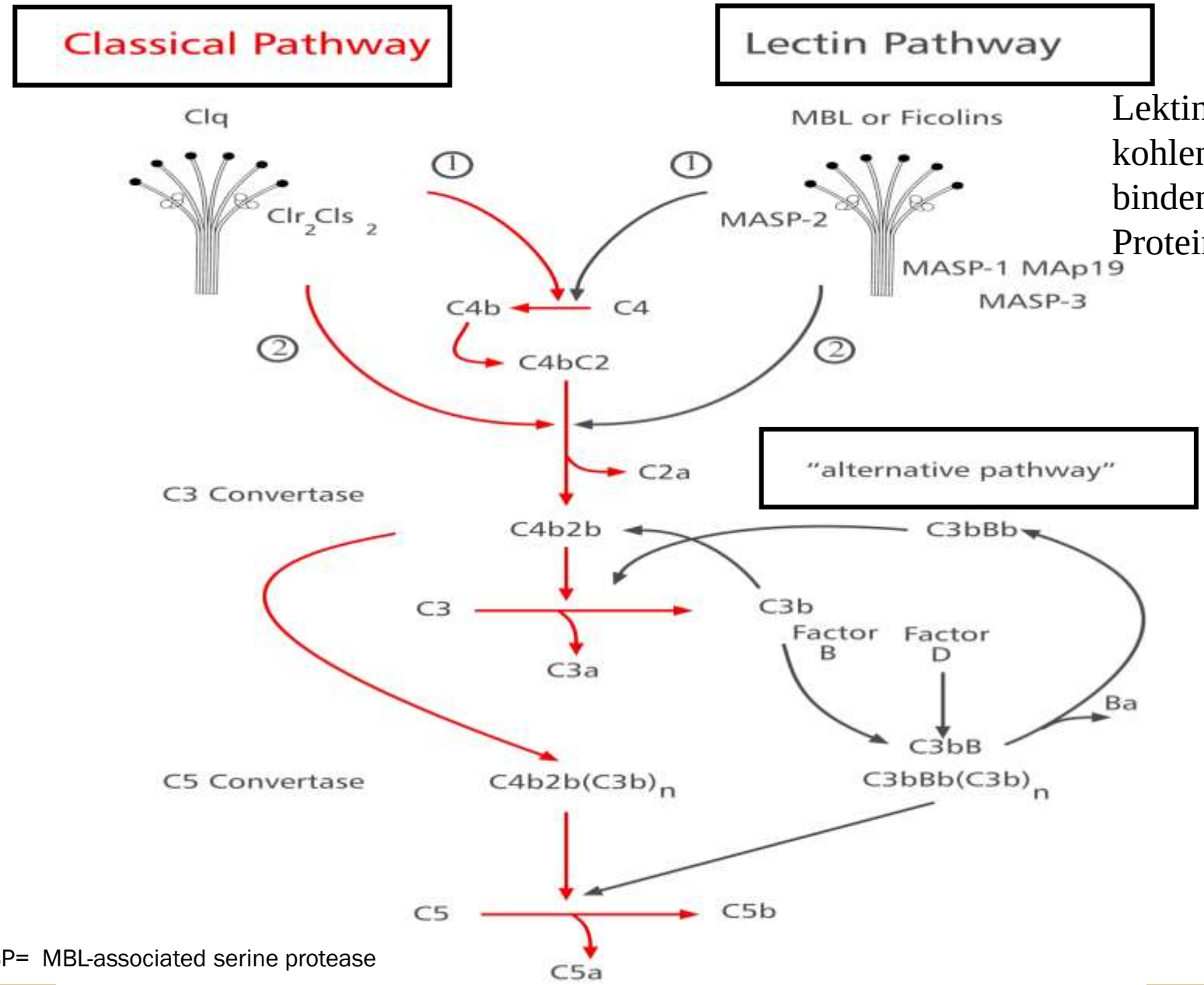
Zerfall der neutrophilen Granulozyten setzt Elastase frei – Konzentration im Serum gibt diagnostische Hinweise auf den Schweregrad einer Entzündung.

NADPH Oxidase Mutation – verursacht die Krankheit chronische Granulomatose (charakterisiert durch chronischen, persistänten bakteriellen Infektionen).



NK - natural killer cells

- Originally described as anti-tumorcell
- Important role in rejection of an implant, in elimination of virus infected cells as in certain bacterial and fungal infections
- Target cells: MHC class I-negative cells („immune evasion“)
- No activation by APC is necessary (activated by cytokines IL-12, IFNγ)
- Acts independently of antigens and und ~antibodies
  - It is also possible to act mediated by antibodies: → „Antibody-dependent cell-mediated cytotoxicity“ - ADCC
- Maturation is independent of thymus
- no memory

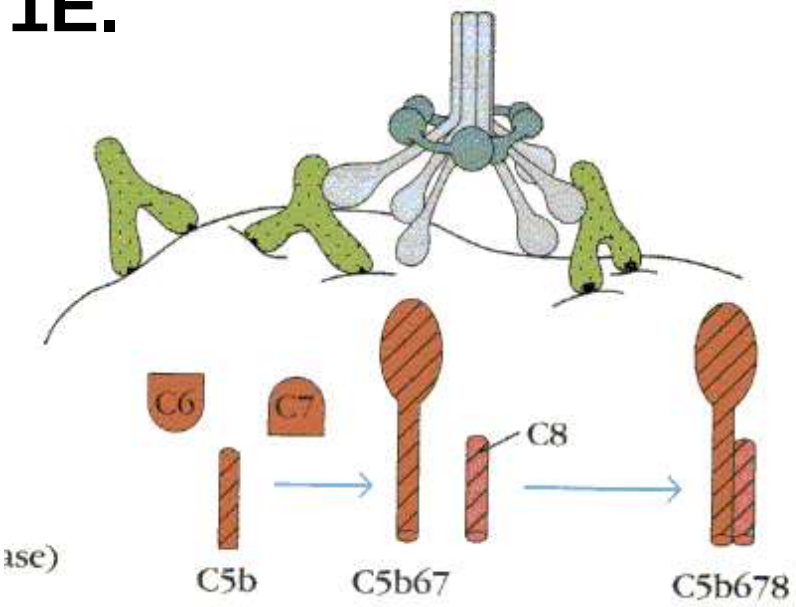


Lektine sind kohlenhydrat-bindende Proteine

MASP= MBL-associated serine protease

Complement activation: classic pathway

1E.



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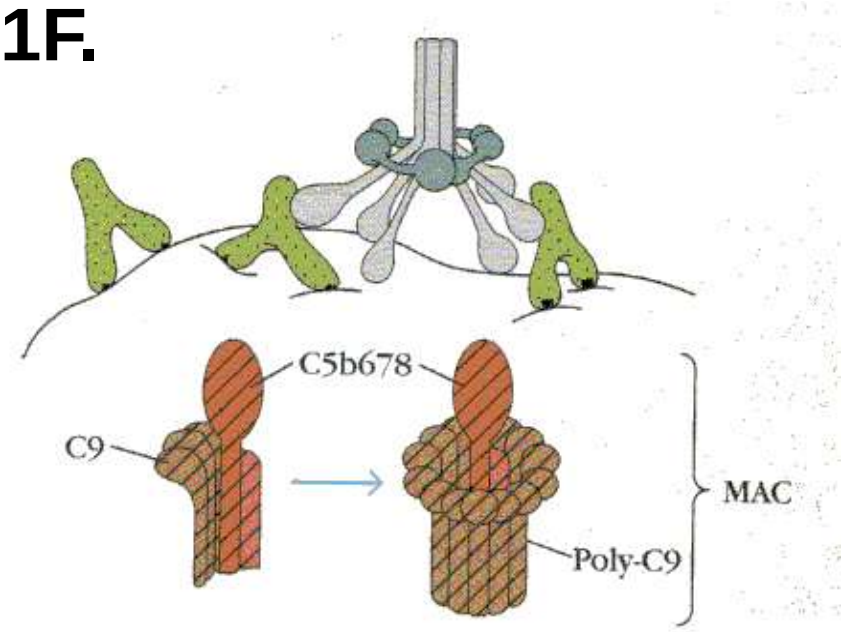
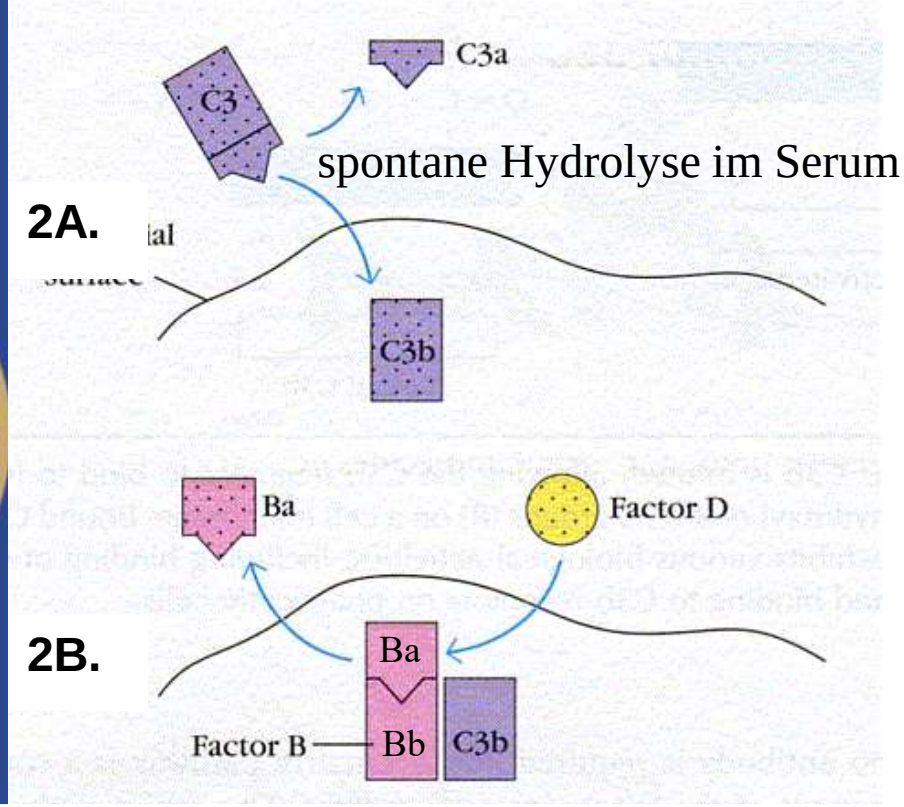
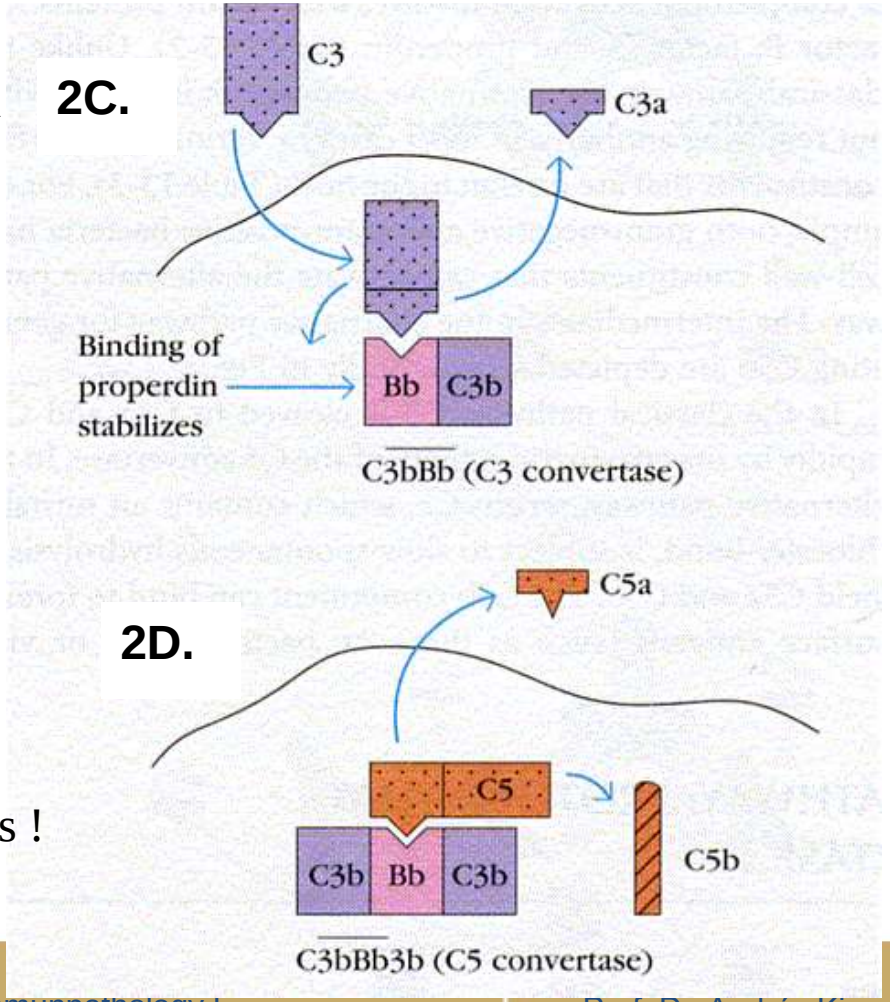


MAC-membrane-attack complex

Complement activation: alternativ way (antibody undependent)





Initiation by foreign bacterial surface molecules !
Sialin acid on eucaryotic cells inhibit C3b!!!

Quelle: Kuby Immunology, W.H. Freeman and Company

CELLULAR COMPONENTS

NEUTROPHIL GRANULOCYTES

EOSINOPHIL GRANULOCYTES: by PARASITES ,
by ALLERGY
(Asthma: bronchial mucosa)
NORMALLY: IN THE MUCOSA

BASOPHYL GRANULOYTES: Histamin, Heparin

TISSUE MAST CELLS (MACROPGHAGES): Heparin, Histamin

CELLULAR COMPONENTS

MODIFIED Macrophages: EPITHELOID CELLS, Synthesis of proteases, elastases and kollagenases

NUCELI: „footstep" form nuclei

Fusion of macrophages, eventuelly epitheloid cells results in:

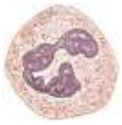
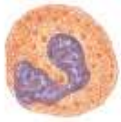
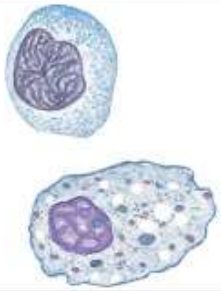
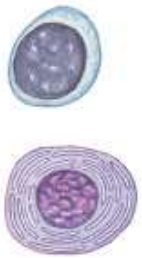
GIANT CELLS: mostly in granulomas
(nodule like growth made of granulation tissue)

Langhans GC: Tuberculosis, Sarkoidosis, Lepra, Syphilis, Toxoplasmosis, Morbus Boeck, Morbus Crohn

Foregin body type Giant Cell

Touton Giant Cell: Fatty necrosis

CELLS OF INFLAMMATION

	Basophils and Mast Cells	*Neutrophils*	*Eosinophils*	*Monocytes and Macrophages*	*Lymphocytes and Plasma Cells*	*Dendritic Cells*
						
% of WBCs in blood	*Rare*	*50–70%*	*1–3%*	*1–6%*	*20–35%*	*NA*
Subtypes and nicknames		Called "polys" or "segs" Immature forms called "bands" or "stabs"		Called the mononuclear phagocyte system	B lymphocytes, Plasma cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells Memory cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation in lymph nodes
Classifications		*Phagocytes*				
		Granulocytes				
			Cytotoxic cells		*Cytotoxic cells (some types)*	
				Antigen-presenting cells		

CYTOGENIC MEDIATORS

HISTAMIN in ALLERGIC (hypersensitivity) INFLAMMATION

SEROTONIN:

PROSTAGLANDINE:

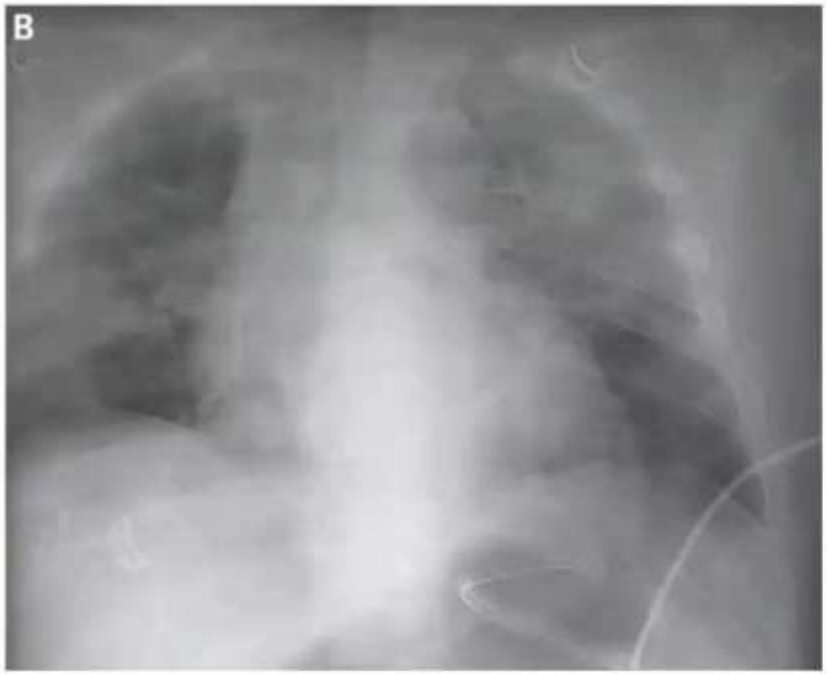
LYMPHOKINE:

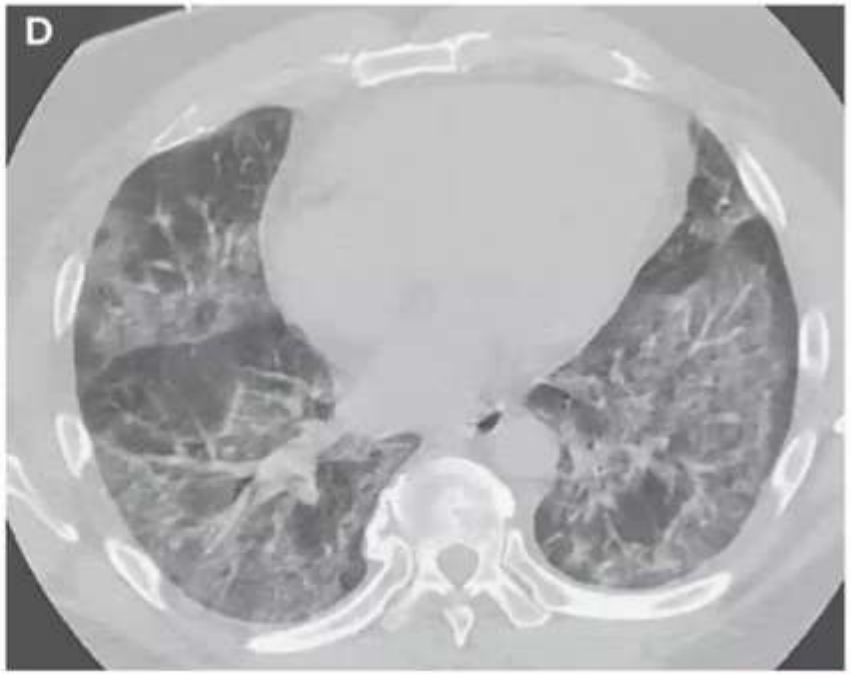
LEUKOTRIENE:

PLATELE ACTIVATIONS FAKTOR (PAF):

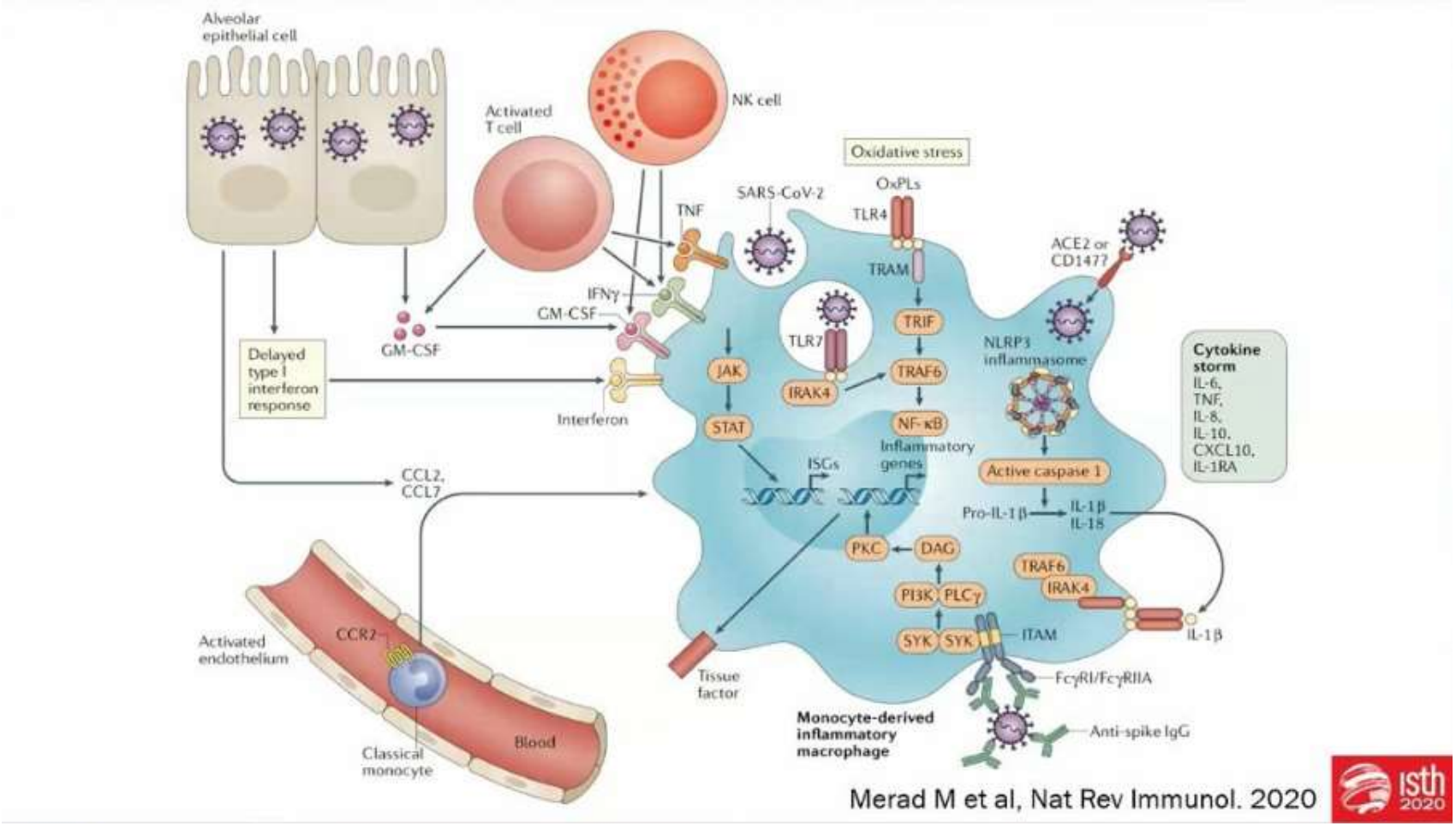
INTERFERON: α: from LEUKOCYTES,
β: from FIBROBLASTS
γ: from ACTIVATED T-LYMPHOCYTES

Severe COVID-19





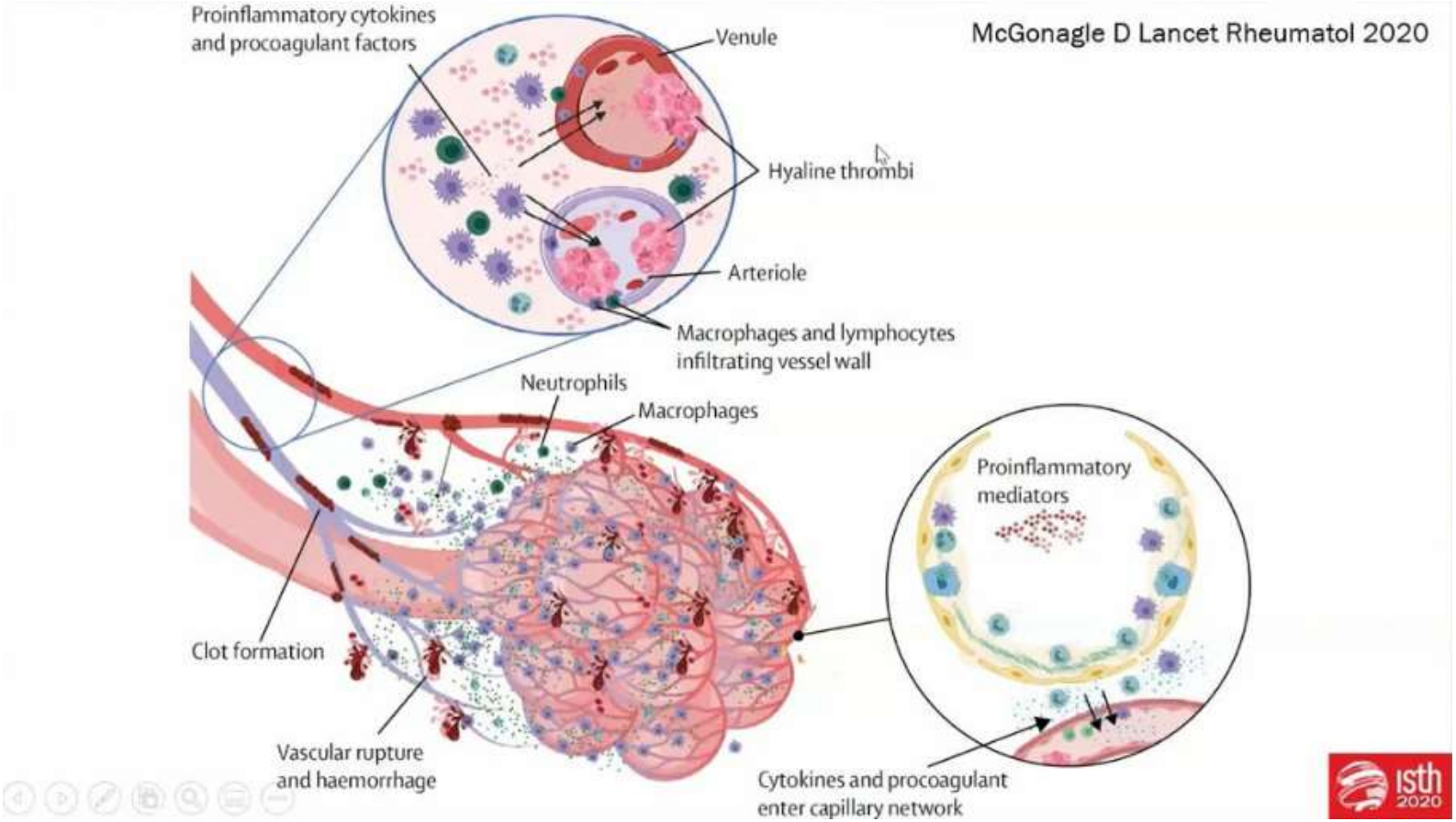
Bhatraju PK et al NEJM 2020


Alveolar epithelial cell
Activated T cell
NK cell
Oxidative stress
SARS-CoV-2
OxPLs
TLR4
TNF
TRAM
ACE2 or CD147
IFNγ
GM-CSF
GM-CSF
TLR7
TRIF
NLRP3 inflammasome
Cytokine storm
IL-6, TNF, IL-8, IL-10, CXCL10, IL-1RA
Delayed type I interferon response
JAK
IRAK4
TRAF6
Interferon
STAT
NF-κB
Inflammatory genes
ISGs
Active caspase 1
CCL2, CCL7
Pro-IL-1β
IL-1β
IL-18
PKC
DAG
TRAF6
IRAK4
PI3K
PLCγ
SYK
SYK
ITAM
IL-1β
CCR2
Activated endothelium
Tissue factor
FcγRI/FcγRIIA
Monocyte-derived inflammatory macrophage
Anti-spike IgG
Classical monocyte
Blood
Merad M et al, Nat Rev Immunol. 2020
ISTH 2020

Inflammation is caused by immune dysregulation in severe COVID-19

- Lymphocytopenia is characterised by low CD4+ with predominance of Th2 lymphocytes, low CD19+ lymphocytes, and low NK cells
- Monocytes display a reduced expression of both CD14 and HLA-DR
- An inverse correlation exists between HLA-DR molecules on CD14-monocytes and serum levels of IL-6

Giamarellos-Bourboulis E et al. Cell 2020
Lombardi A et al doi: https://doi.org/10.1101/2020.05.01.20087080


Proinflammatory cytokines and procoagulant factors
Venule
McGonagle D Lancet Rheumatol 2020
Hyaline thrombi
Arteriole
Macrophages and lymphocytes infiltrating vessel wall
Neutrophils
Macrophages
Proinflammatory mediators
Clot formation
Vascular rupture and haemorrhage
Cytokines and procoagulant enter capillary network
isth 2020

Unspecific immunity –

Resistence: epithelial barrier
to release bactericide materials
complement system – to opsonize
neutralisation of viruses
to release mediators
chemotaxis
to increase permeability of vessels
degranulation of mast cells
cytolysis
lysozyme – muramidase attacks walls of bacteria
c-reaktive protein – acute –phase-protein
Interferones
Granulocytes, macrophages – phagocytosis
reactions of inflammations
lower pH of different secreted fluids:
sweat
gastric juice
mucins

Specific Immunity: **targeted on a specific infectious agent**

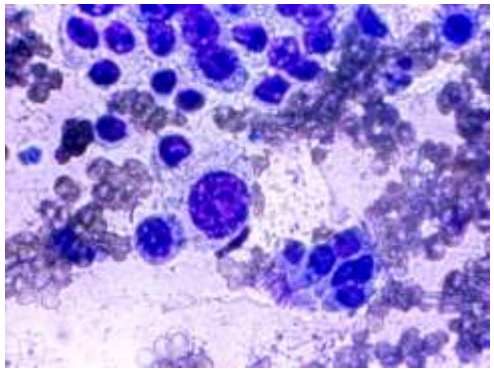
Llymphatic system

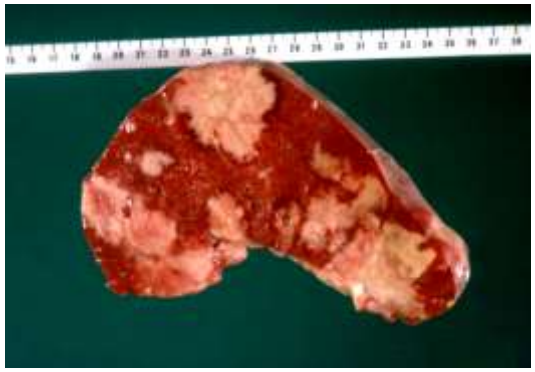
humoral Immunity – B-cells

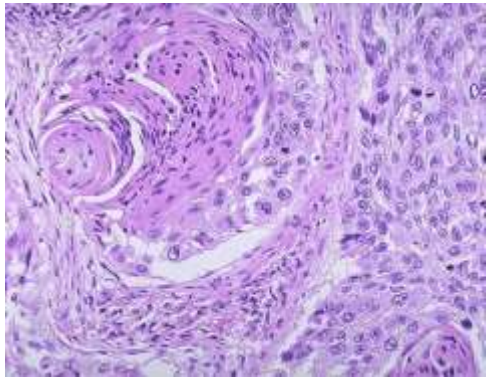
cellular immunity - T-cells

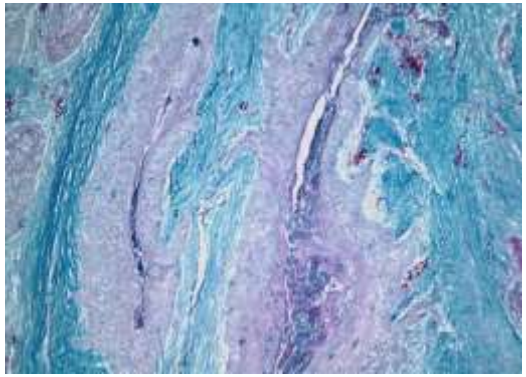
XX. Century Technologies

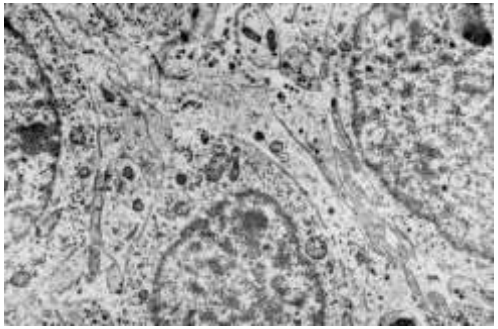
- Macroscopy (grossing)
- Zytology
- Histology
- Cytochemistry
- **Immunhisto/**
- **cytochemistry**
- Electronmicroskopy
- Molecular Biology
- Molecular genetics
- XXI. Century

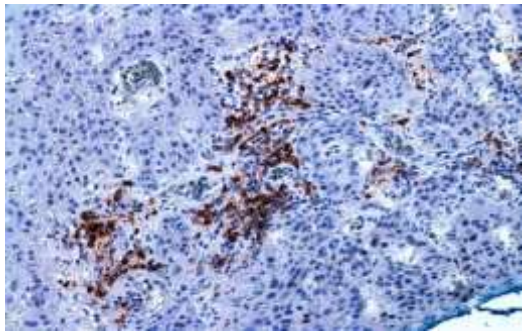






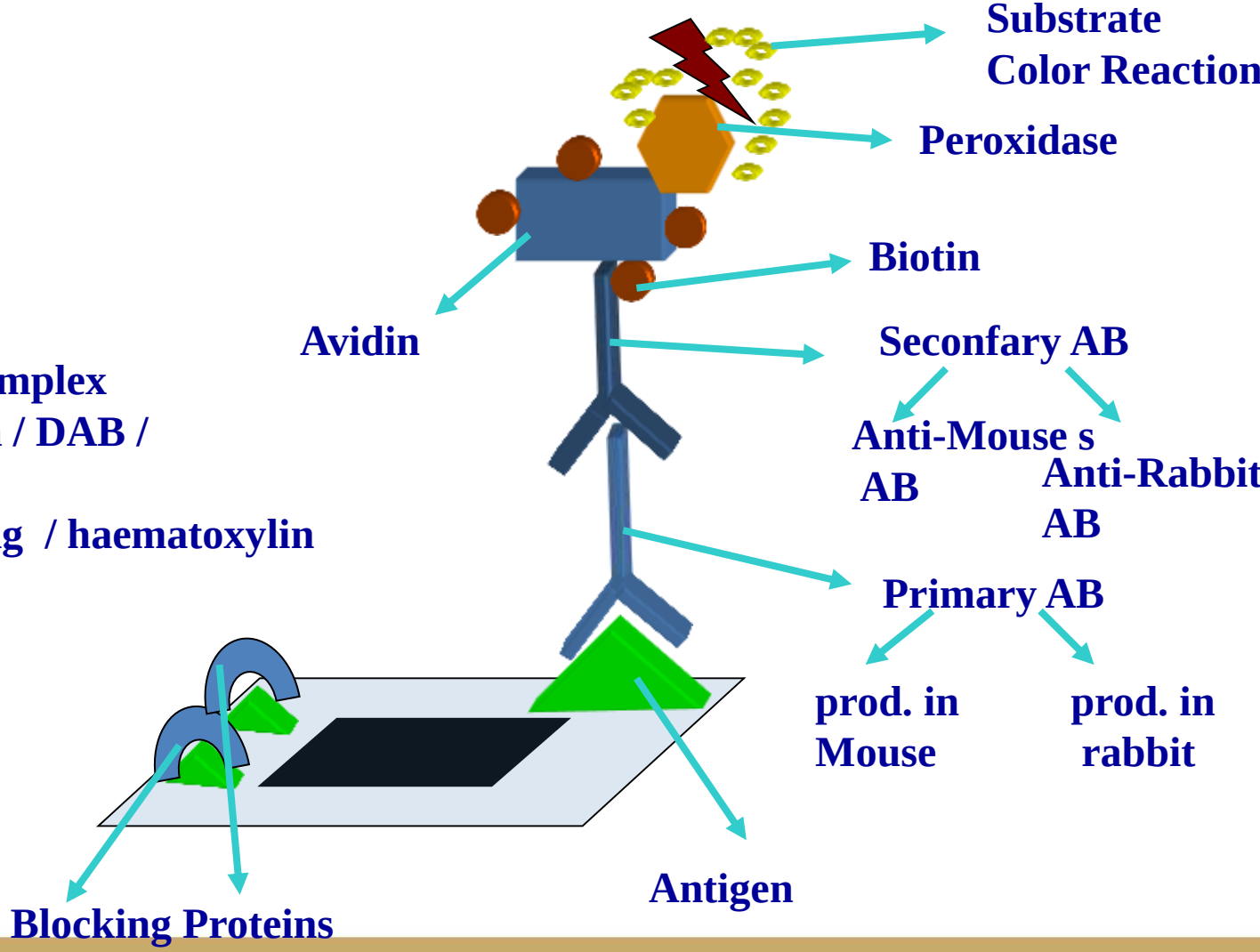






Immunhistochemistry

- Deparaffinization
- Antigen Retrieval / Microwave treatment (proteases, pressure cooker, etc,)
- Blocking Serum
- Primayr AB
- Secondary AB
- Avidin - Biotin - Complex
- Peroxidase Reaction / DAB /
- Backgorund staining / haematoxylin (Nuclei are blue)



The Nobel Prize in Physiology or Medicine 1984
Niels K. Jerne, Georges J.F. Köhler, César Milstein

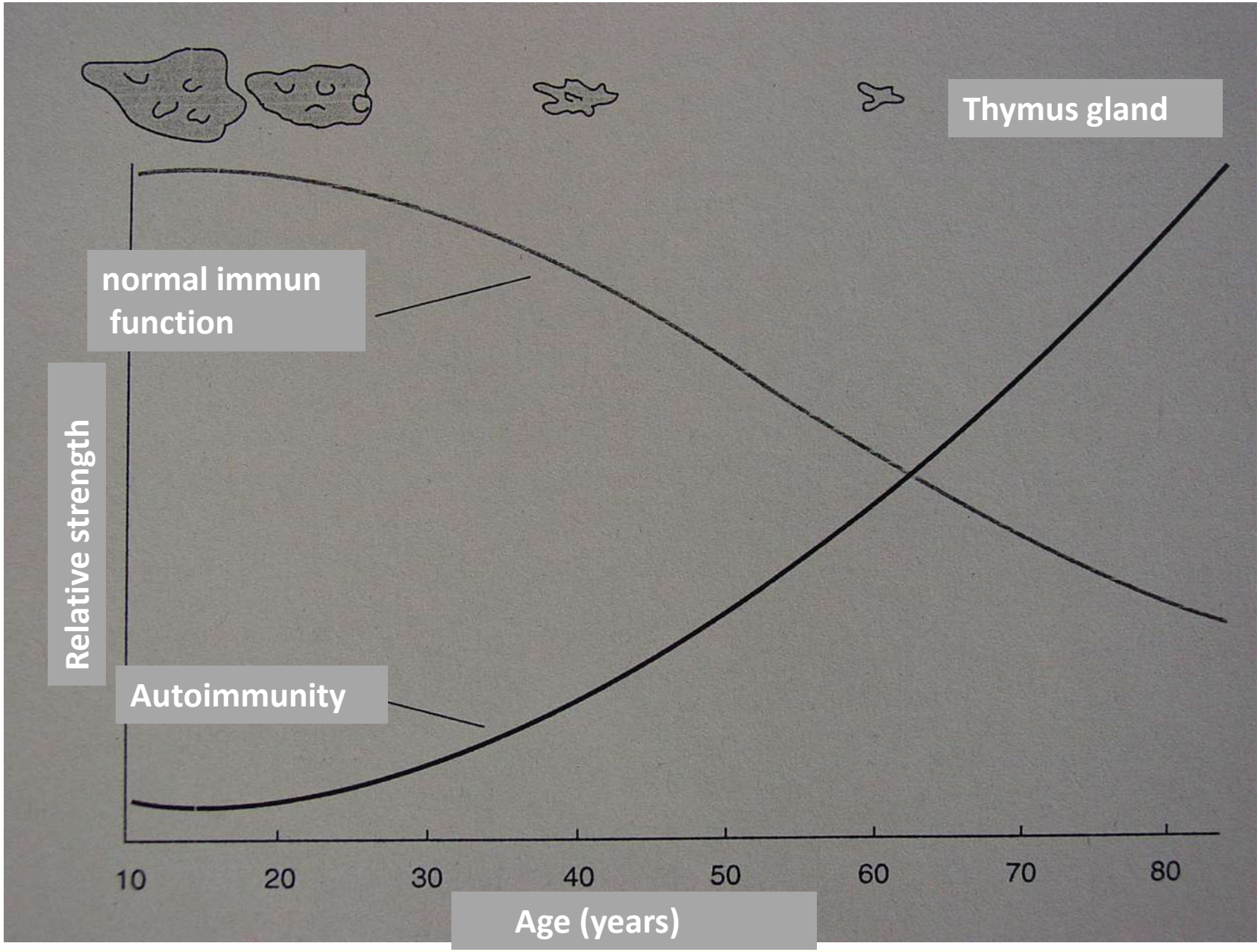
The Nobel Prize in Physiology or Medicine 1984

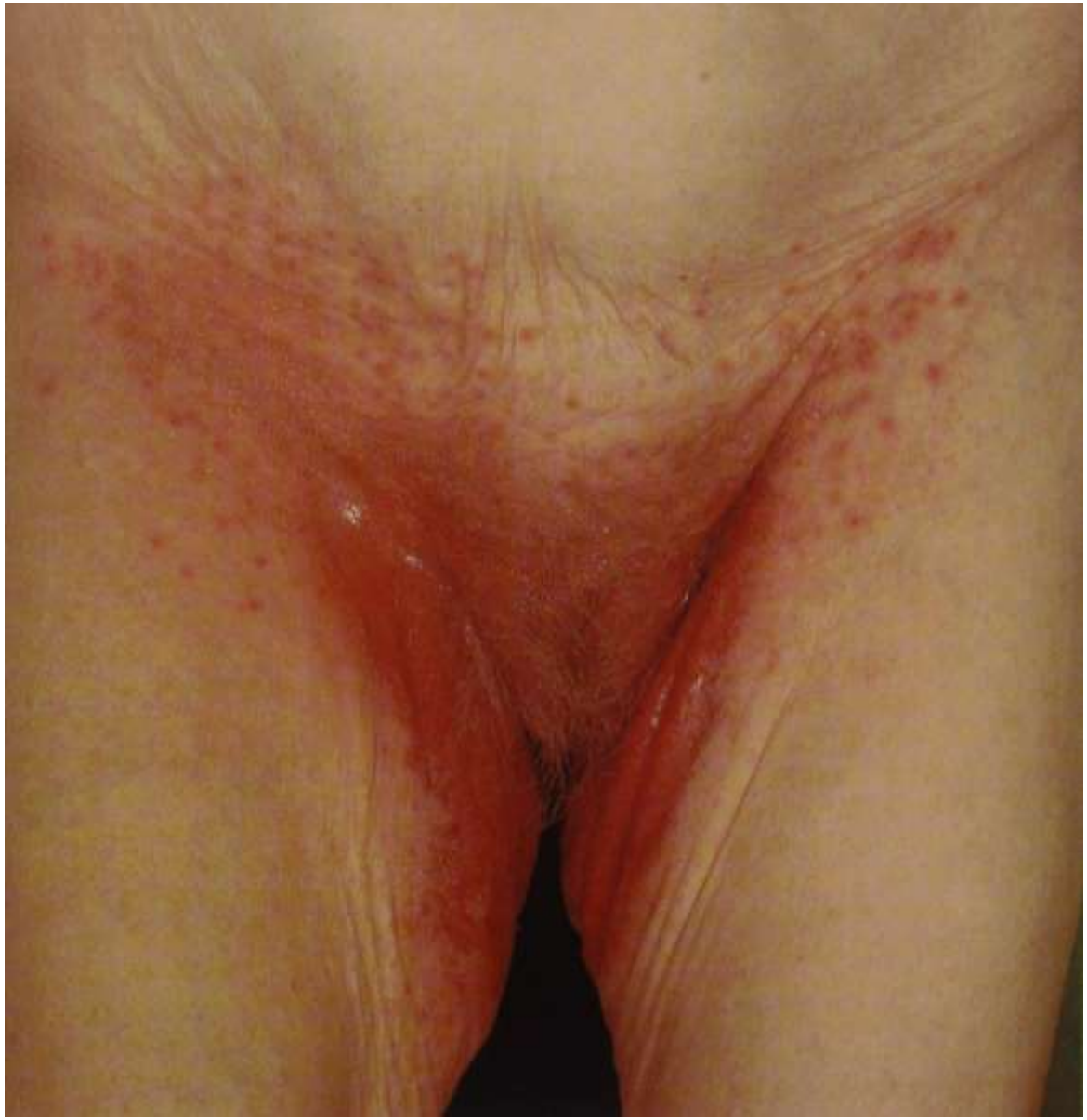

Niels K. Jerne


Georges J.F. Köhler


César Milstein

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein *"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"*.


Thymus gland
normal immun function
Relative strength
Autoimmunity
10
20
30
40
50
60
70
80
Age (years)



Candidiasis - Soormycose

Oral mucosa

In folds between finger big folds of the skin

glans penis

female genital region vagina

Mainly elderly and obese Women

Predisposition:

- diabetes
- wet surfaces
- Vitamin-B deficiency
- preganancy
- atrophy

Immuntolerance: suppressed or missing reactivity

For certain defined Antigens, while the reaction aginast other antigens is maintained.

in rmbryonal phase – by not matured immune system – antigens are as own structures accepted and this condition is maintained.

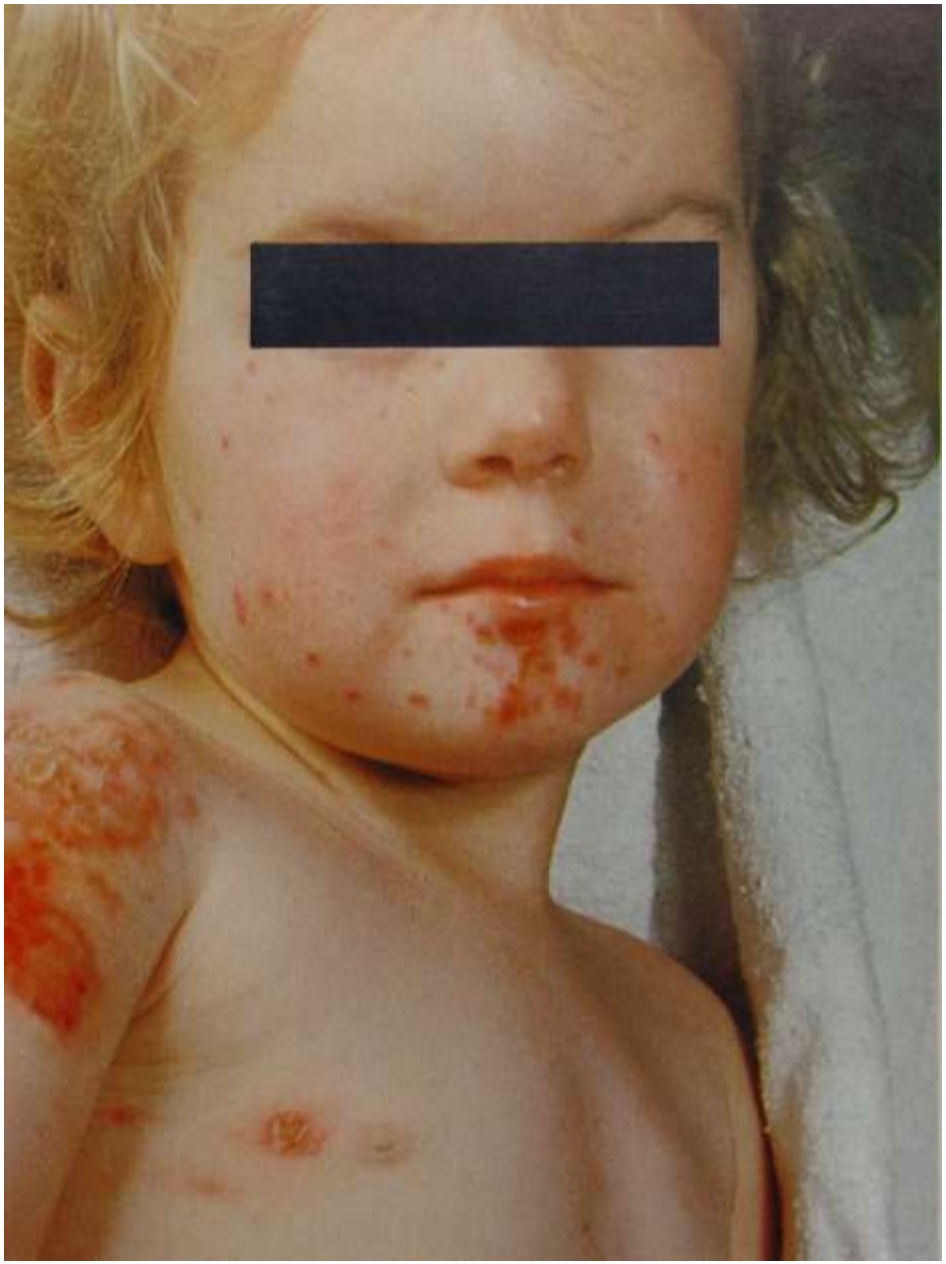
Differentiation between »self«)and „foreign”/ »not-self« might be lost later for certain „tolerogenes”, therefore, this can lead to autoaggressive diseases.

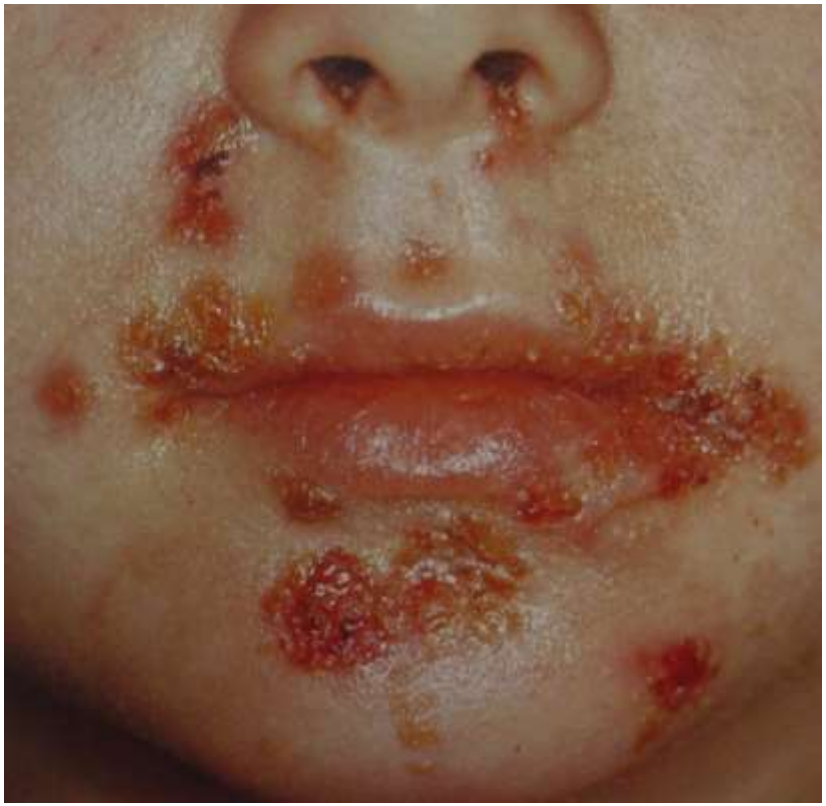
Angeborene: gegenüber körpereigene Antigene (Autoantigene)

Acquired: reciproke immuntolerance of twins
(vessel anastomoses in the placenta)

Immune defciency syndrome: deficient immune reaction

general insuffitienty of the organism to react with immune answer for an otherwise suffitient antigen stimulus
(the opposite of a specific tolerance)



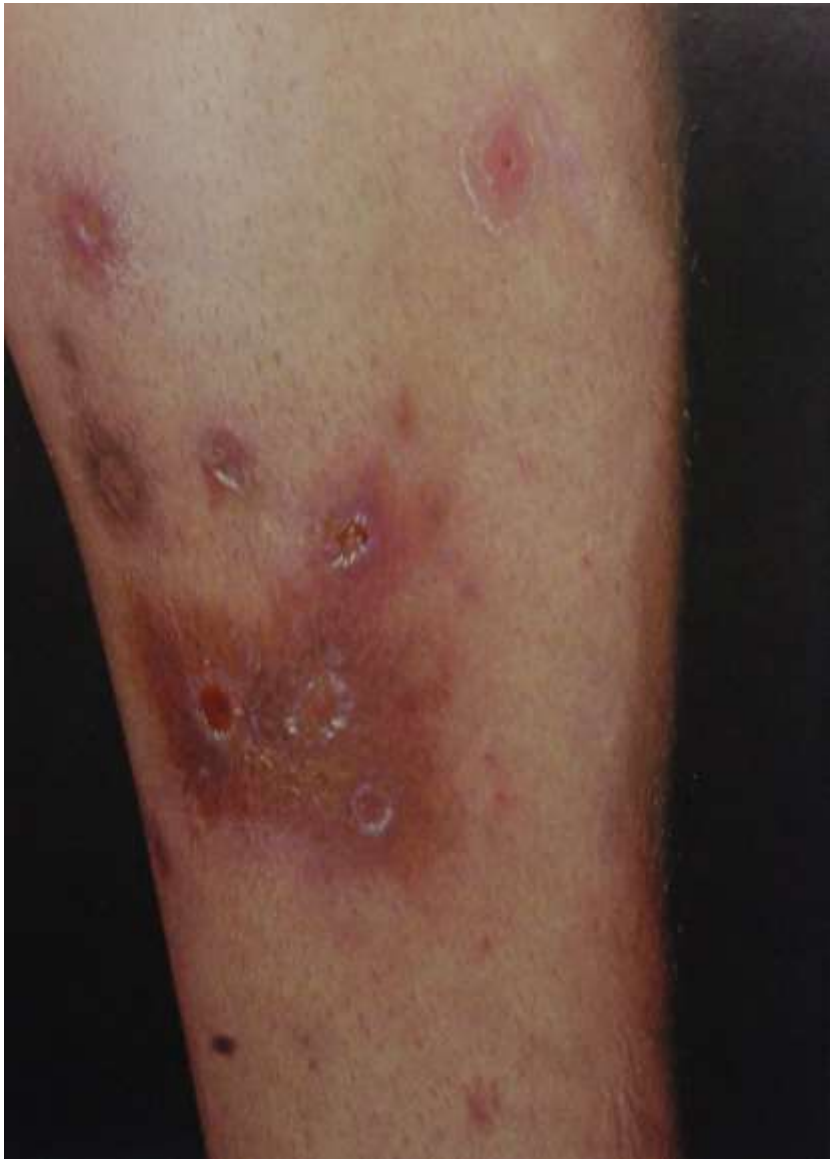


Impetigo contagiosa

Primary purrlent infection of the epidermis. Mostly by immundefitien children

Unclean/ non / higienic circumstances and cratches facilitate spreading

compl.: Impetigo-Nephritis



Ekthyma

Exulcerated Pyodermia

compl.: Lymphangitis
Lymphadenitis, Phlebitis

ß-hämolytih streptococci

Decreased defence of the skin

Local circulatory disturbance

Tumorimmunity

Tumors occur more frequently in patients with weak immun system/immundeficiency

Caueses: age, chemotherapy, irradiation, immundefects

Tumor cells develop mechanims to evade the immune system:

selection of antigen negative variants (subclones)

lost or reduced expression of histocompatibiliy antigens

$\Rightarrow$ tumorcells avoid cytotoxic T-cells

missing peptidantigen-co-stimulation

immunsuppression, for example secretion of TGF-ß by tumors

Apoptosis of cytotoxic T-cells through expression of FAS-Ligands:
e.g. melanoma, hepatocellular carcinoma

Immun defence reactions: lymphocytes, natural killer cells

macrophages

Oncologic Immuntherapy

Specific activated T-cells e.g. lymphokines activated Killer cells

gained from the blood of patients

stimulated in cell culture

giving back to the patient

Therapuetic application of blocking antibodies directed against epidermal growth factor receptor: EGFR
Receptor protein C-Kit (Thyrosin kinase function) CML, GIST
overexpressed ,e,bran associated receptores - Herceptin (Erbb2)

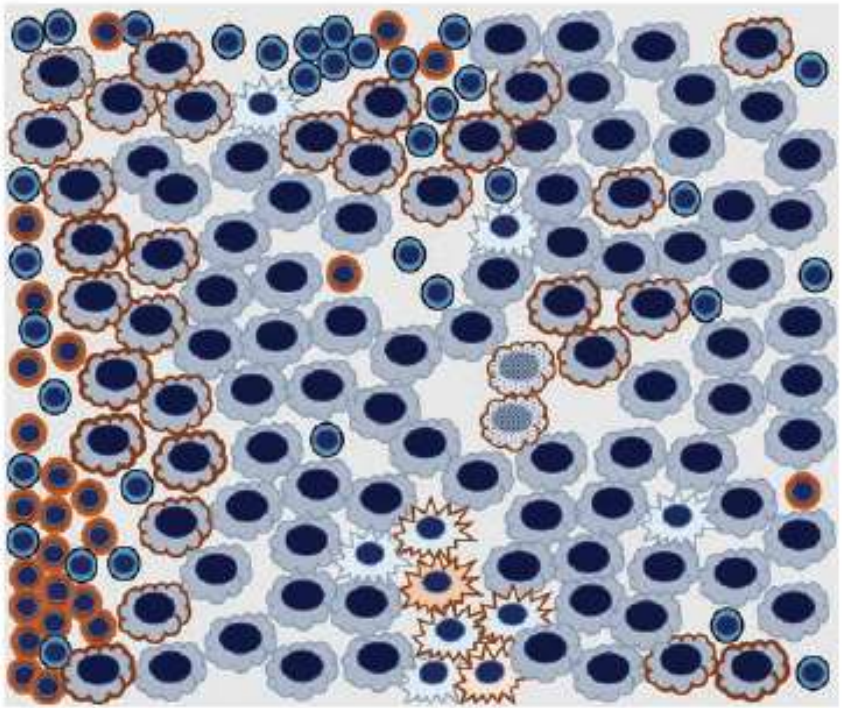
To raise antigeneicity by infaction with apathogenic viruses

Immunprofilaxis in specific cases: – e.g. HBV-Vaccine to prevent primary hepatocellular carcinoma

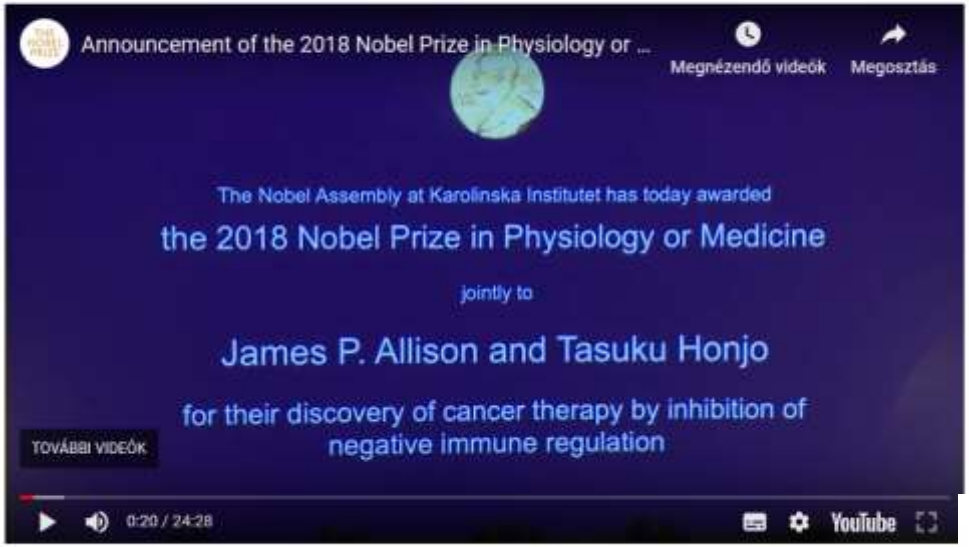
PD-L-1 and PD-1 Blockers

	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)	Atezolizumab (anti-PD-L1)	Durvalumab (anti-PD-L1)	Avelumab (anti-PD-L1)
NSCLC első vonal metasztatikus (monoterápiában)	ALK- és EGFR-negatív esetekben **Kísérő IVD: 22C3 ≥50% TPS**				
NSCLC első vonal metasztatikus nem laphám (kemoterápiával)	IHC nélkül alkalmazható ALK- és EGFR-negatív esetekben		IHC nélkül alkalmazható ALK- és EGFR-negatív esetekben		
NSCLC másodvonal	**Kísérő IVD: 22C3 ≥1% TPS**	IHC nélkül alkalmazható* Kiegészítő: 28-8 ≥1% TPS	IHC nélkül alkalmazható* Kiegészítő: SP142 ≥50% TC / ≥10% IC	**Kísérő IVD: SP263[3] ≥1% TC**	
SCLC (előrehaladott) első vonal (kemoterápiával)			IHC nélkül alkalmazható		
SCLC (előrehaladott) másodvonal		IHC nélkül alkalmazható			
Urotheliális első vonal (cisplatinkezelésre alkalmatlanoknál)	**Kísérő IVD: 22C3 ≥10 CPS**		**Kísérő IVD: SP142 ≥5% IC**		
Urotheliális másodvonal (korábban platinaalapú kezelésen átesett)	IHC nélkül alkalmazható	IHC nélkül alkalmazható* Kiegészítő: 28-8 ≥1% TPS	IHC nélkül alkalmazható	Kiegészítő: SP263 ≥25% TC vagy ≥1% ICP és ≥25% IC vagy ICP=1% és IC=100%	IHC nélkül alkalmazható
Fej-nyaki laphámrák első vonal	Kísérő: 22C3 ≥1 CPS	IHC nélkül alkalmazható Kiegészítő: 28-8 ≥1% TPS			
Fej-nyaki laphámrák másodvonal	**Kísérő IVD: 22C3 ≥50% TPS**	IHC nélkül alkalmazható			
Klasszikus Hodgkin-limfóma másodvonal	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
Melanóma	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
RCC első vonal (kombinációban)	IHC nélkül alkalmazható	IHC nélkül alkalmazható			IHC nélkül alkalmazható
RCC másodvonal		IHC nélkül alkalmazható			
Tripla-negatív emlőrák			**Kísérő IVD: SP142 ≥1% IC**		
Méhnyakrák	Kísérő: 22C3 ≥1% TPS				
Gyomorrák	Kísérő: 22C3 ≥1% TPS				
HCC	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
Merkel-sejtes karcinóma	IHC nélkül alkalmazható				IHC nélkül alkalmazható

	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)	Atezolizumab (anti-PD-L1)	Durvalumab (anti-PD-L1)	Avelumab (anti-PD-L1)
dMMR/MSI-H kolorektális karcinóma	IHC nélkül alkalmazható	IHC nélkül alkalmazható			
dMMR/MSI-H (bármely tumor)	IHC nélkül alkalmazható				



Prize announcement



Announcement of the 2018 Nobel Prize in Physiology or Medicine by Professor Thomas Perlmann, Secretary of the Nobel Committee for Physiology or Medicine, on 1 October 2018.

"We can cure cancer with it"

Klas Kärre, member of the Nobel Committee, on the life-changing possibilities of this year's Nobel Prize awarded discovery. Professor Kärre, member of the Nobel Committee for Physiology or Medicine, was interviewed by freelance journalist Lotta Fredholm following the announcement of the 2018 Nobel Prize in Physiology or Medicine.

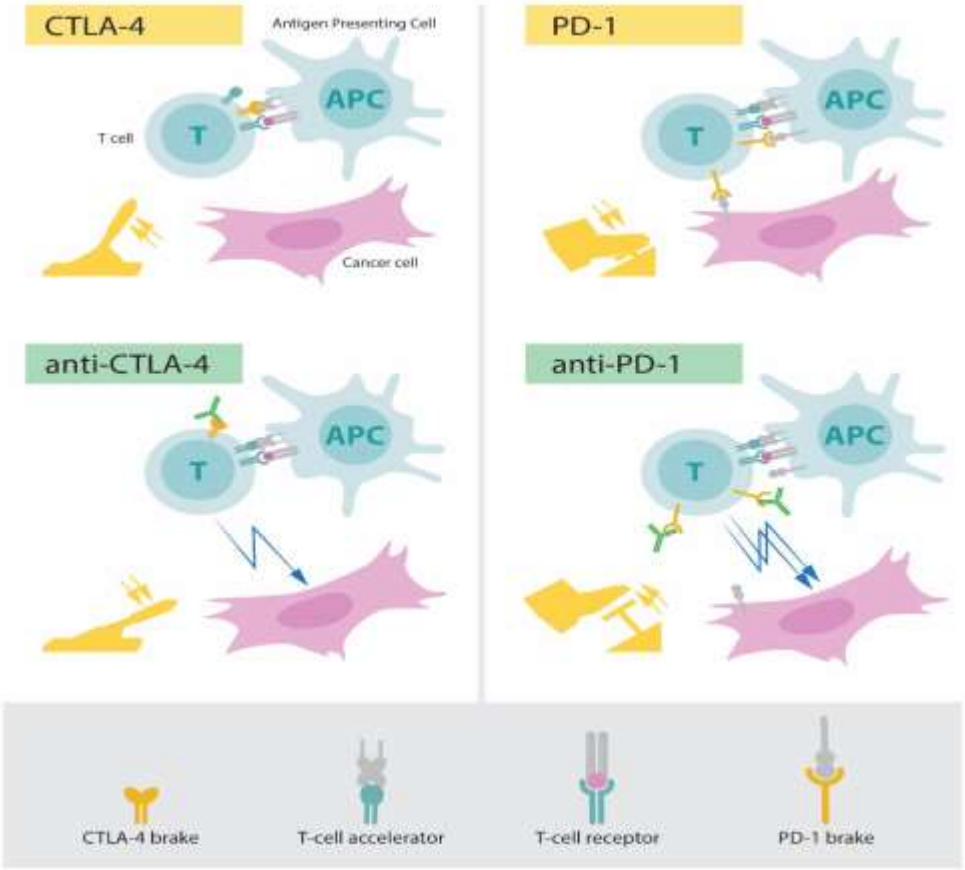
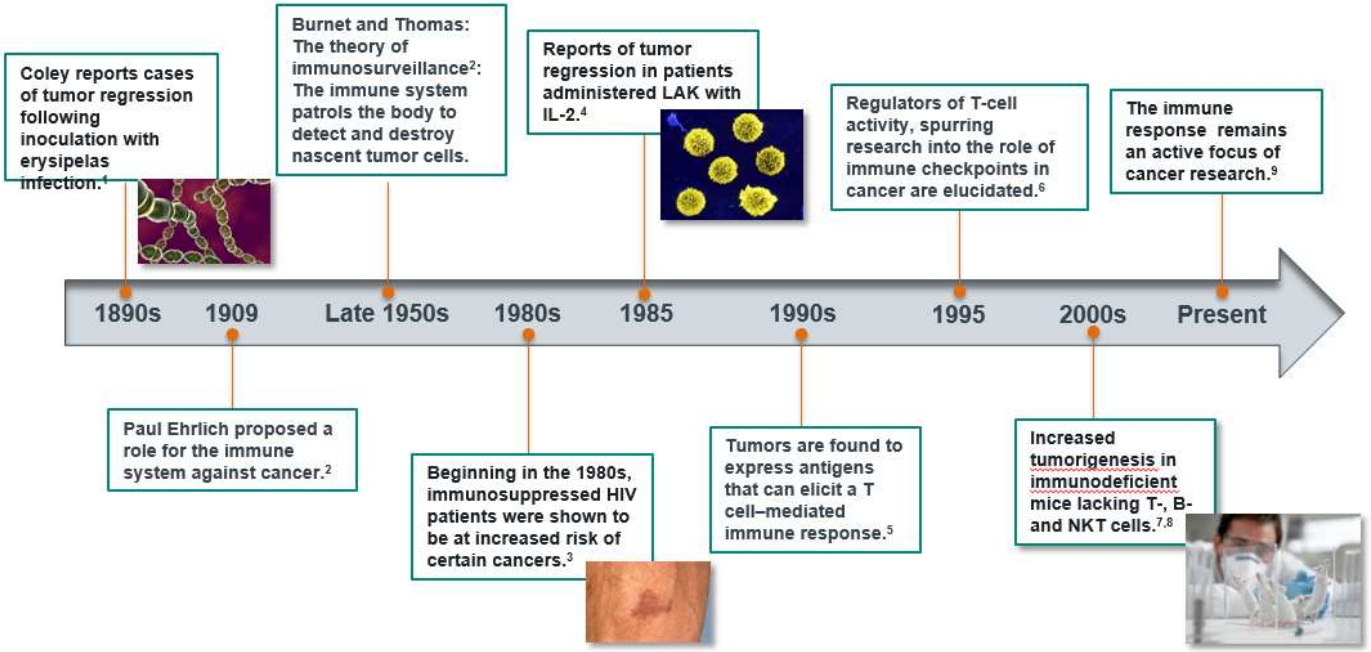


Figure: Upper left: *Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as "non-self". A protein functioning as a T-cell accelerator is also required for T cell activation. CTLA- 4 functions as a brake on T cells that inhibits the function of the accelerator.* ***Lower left:*** *Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells.* ***Upper right:*** *PD-1 is another T-cell brake that inhibits T-cell activation.* ***Lower right:*** *Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.*

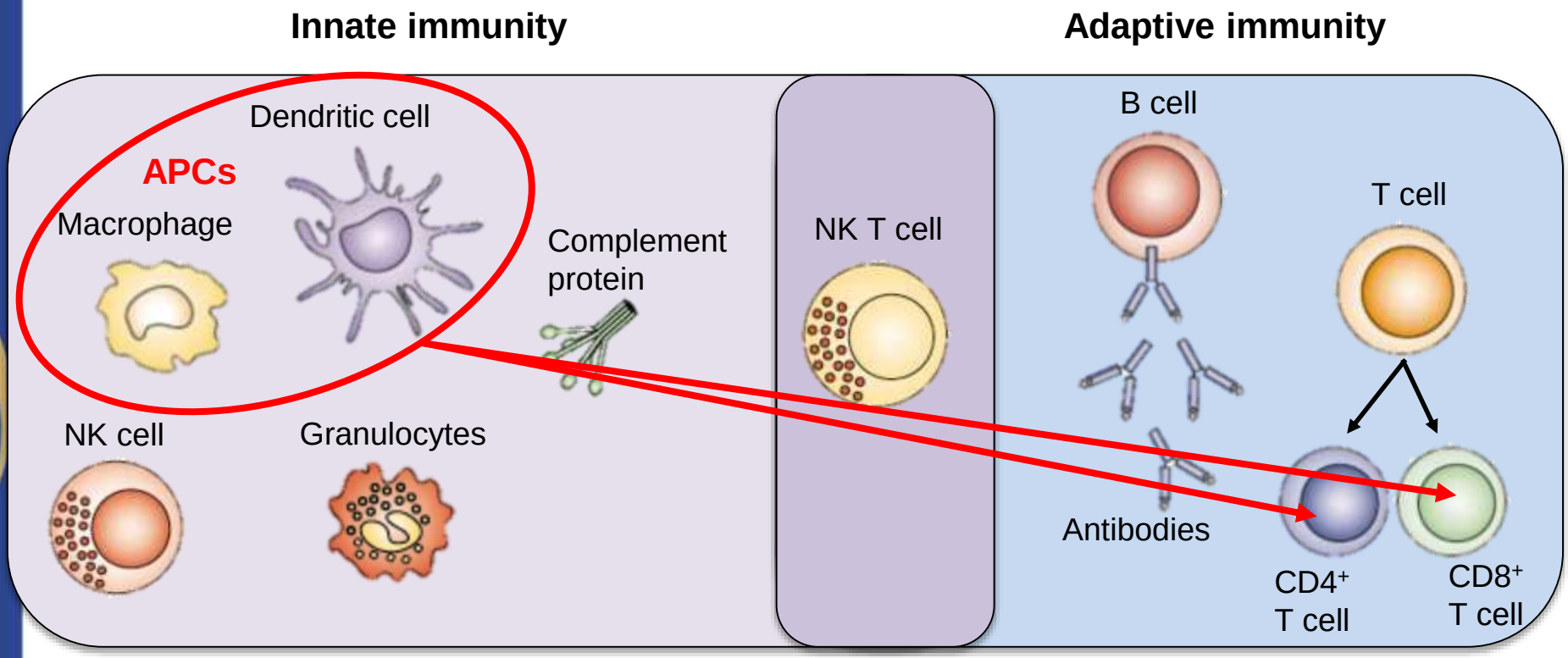
What Have We Learned About the Role of the Immune System in Oncology?



HIV = human immunodeficiency virus; LAK = lymphokine-activated killer; IL-2 = interleukin-2; NKT = natural killer T.

1. Coley WB. *Am J Med Sci.* 1893;105:487–511. **2.** Ichim CV. *J Transl Med.* 20058;3:8. **3.** Levine AM et al. *Curr Probl Cancer.* 1987;11:209–55. **4.** Rosenberg SA et al. *N Engl J Med.* 1985;313:1485–1492. **5.** van der Bruggen P et al. *Science.* 1991;254:1643–1647. **6.** Tivol EA. et al. *Immunity.* 1995;3:541–547. **7.** Vesely MD et al. *Annu Rev Immunol.* 2011;29:235–271. **8.** Shankaran V. et al. *Nature.* 2001;410:1107–1111. **9.** Drake CG *et al. Nat. Rev. Clin. Oncol.* 2014;11: 24–37.

The Immune System



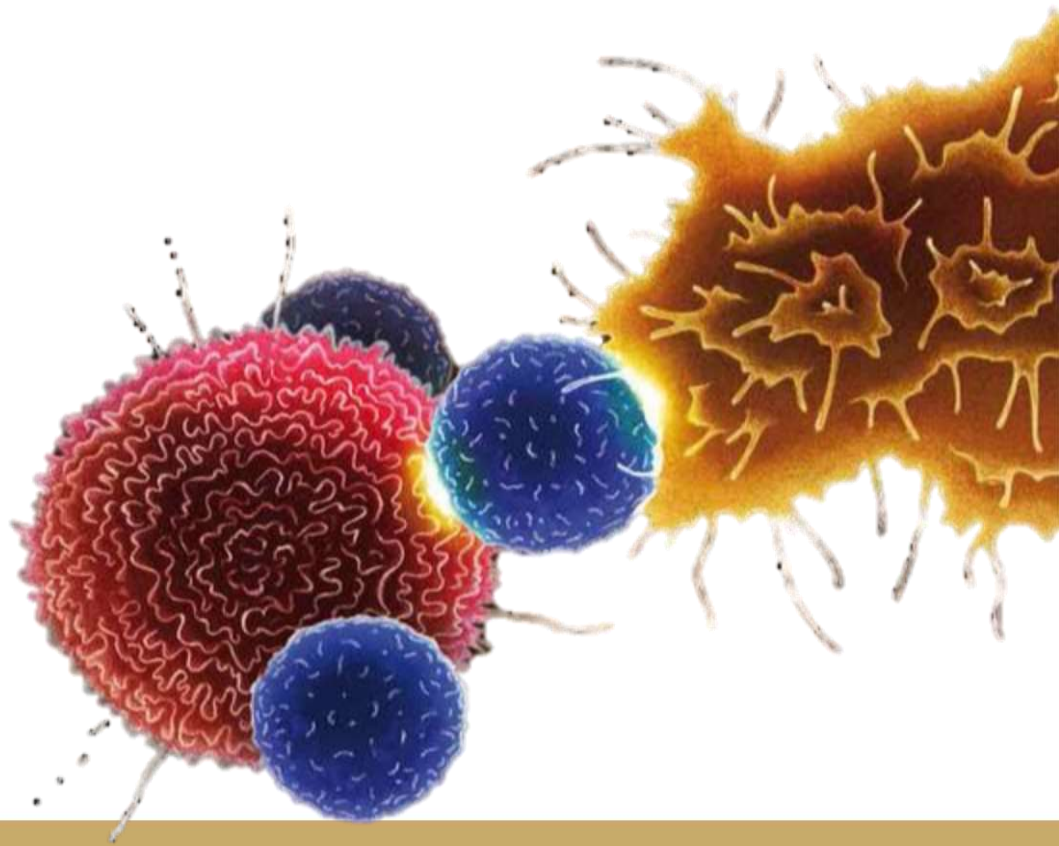
⇒ **fast response and low specificity**

- **Antibodies**
- **Cytokines**
- **Ag receptors (10^9 / individual)**

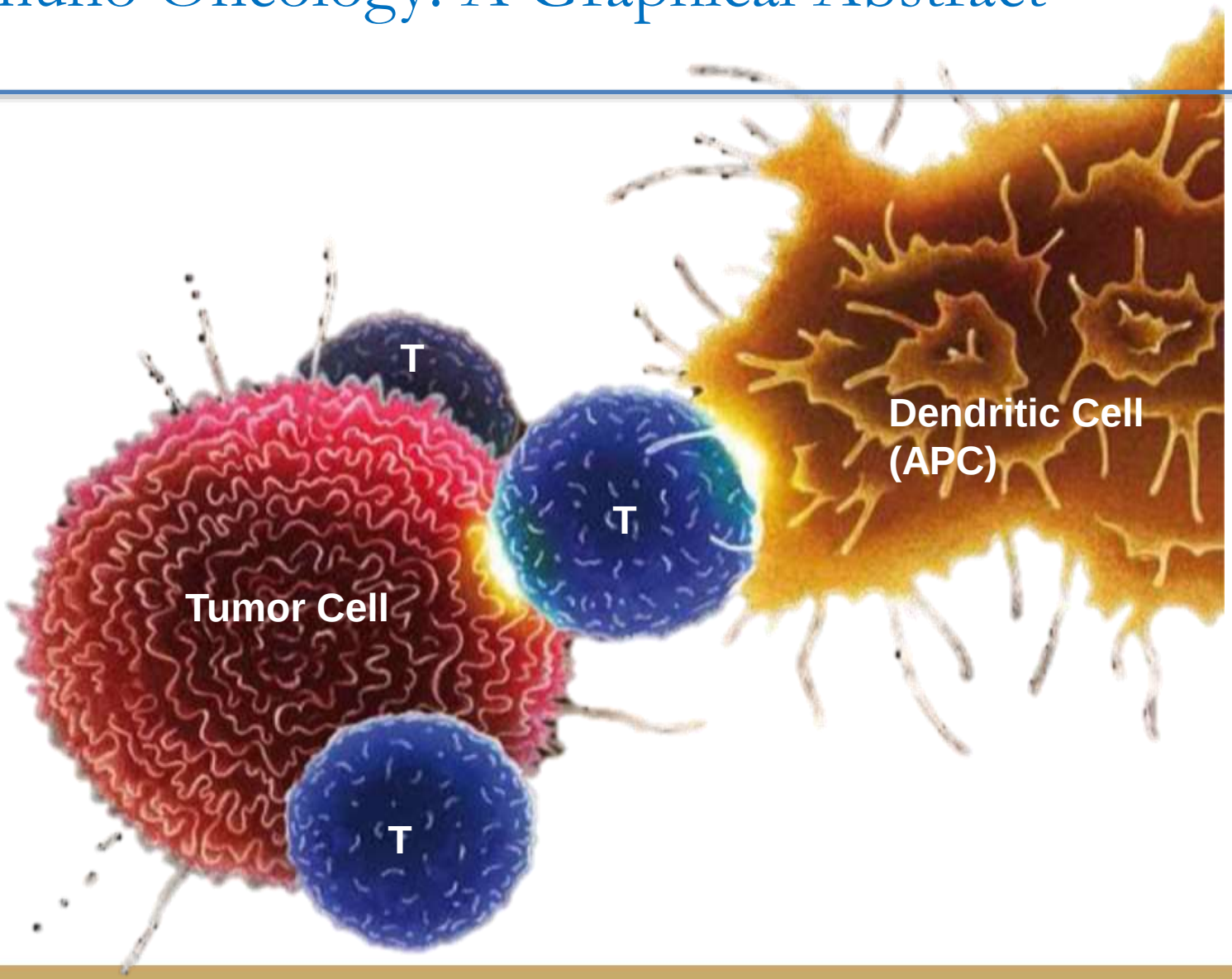
⇒ **specificity, diversity, and memory**

Dranoff, 2004

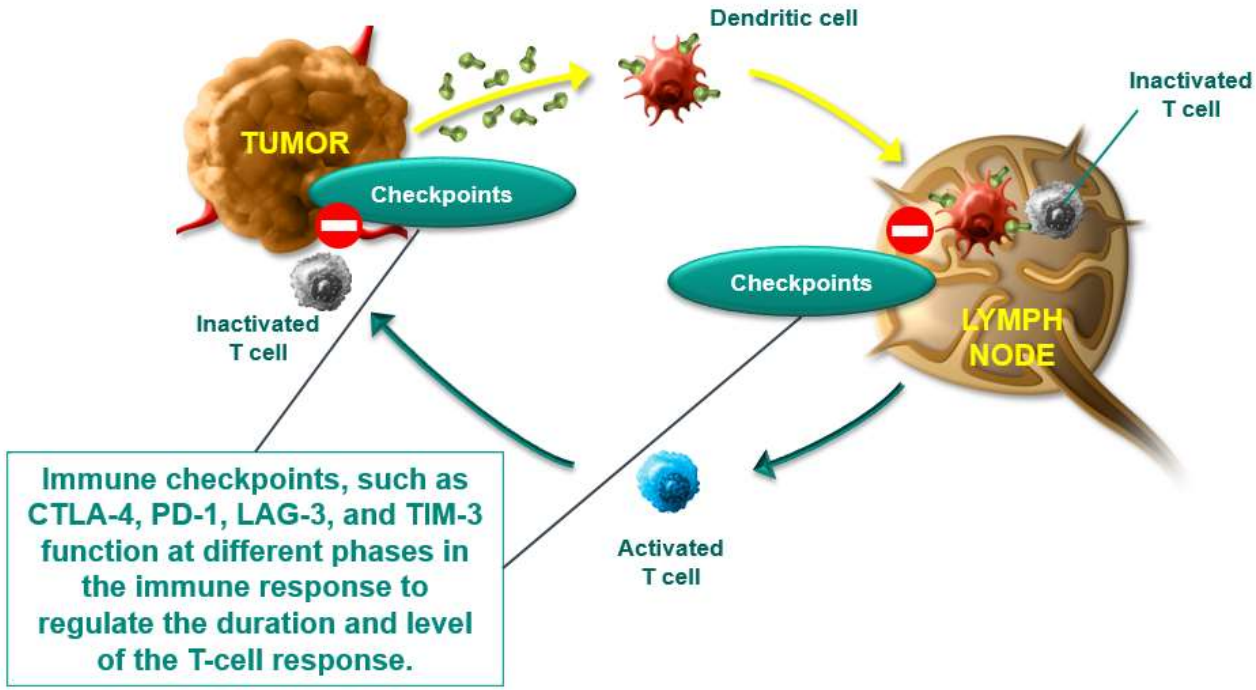
"Immune Checkpoint-Blockade In Cancer" Beginning of a New Era!



Immuno Oncology: A Graphical Abstract



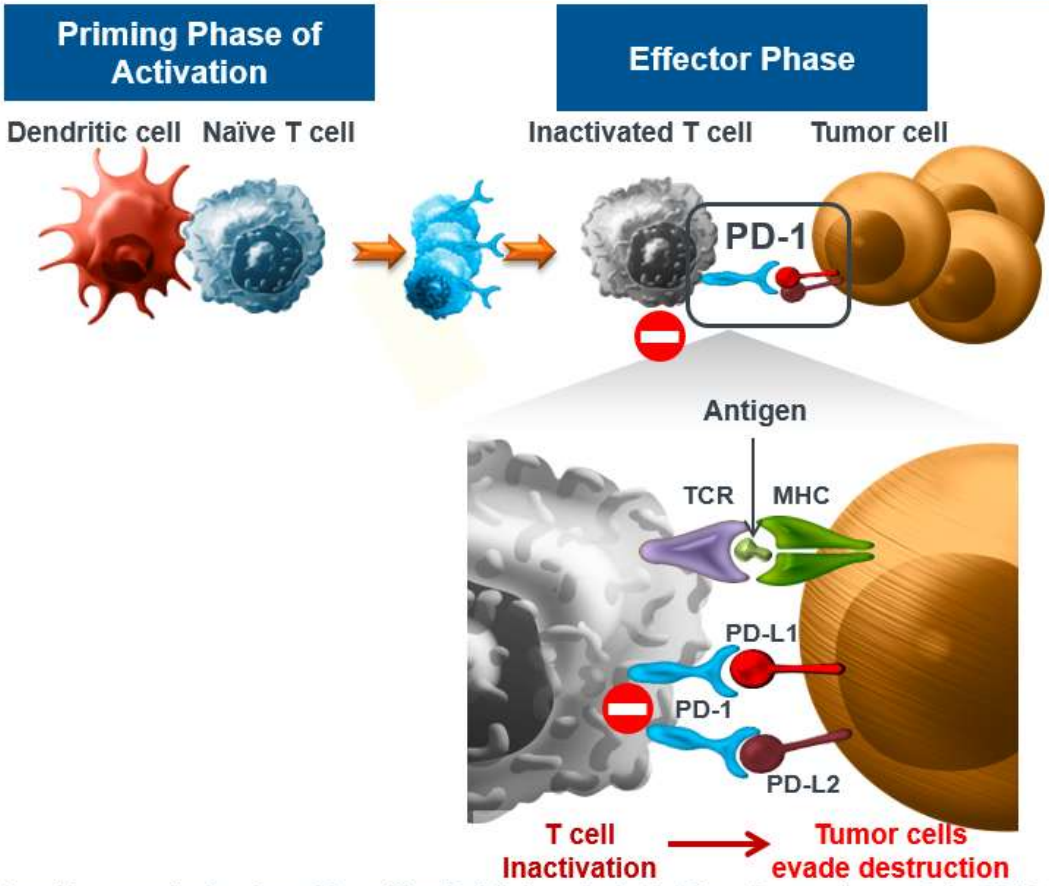
T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]



CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1; LAG-3 = lymphocyte activation gene 3; TIM-3 = T-cell immunoglobulin and mucin protein 3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

3. Exploiting the PD-1 Immune Checkpoint Pathway[1]



- PD-1 is upregulated on activated T cells during the effector phase of the immune response
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells to downregulate T-cell activity in the effector phase

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PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

The Founders of Modern Immunology and Immuno-Therapy

Robert Koch

Paul Ehrlich

William Coley

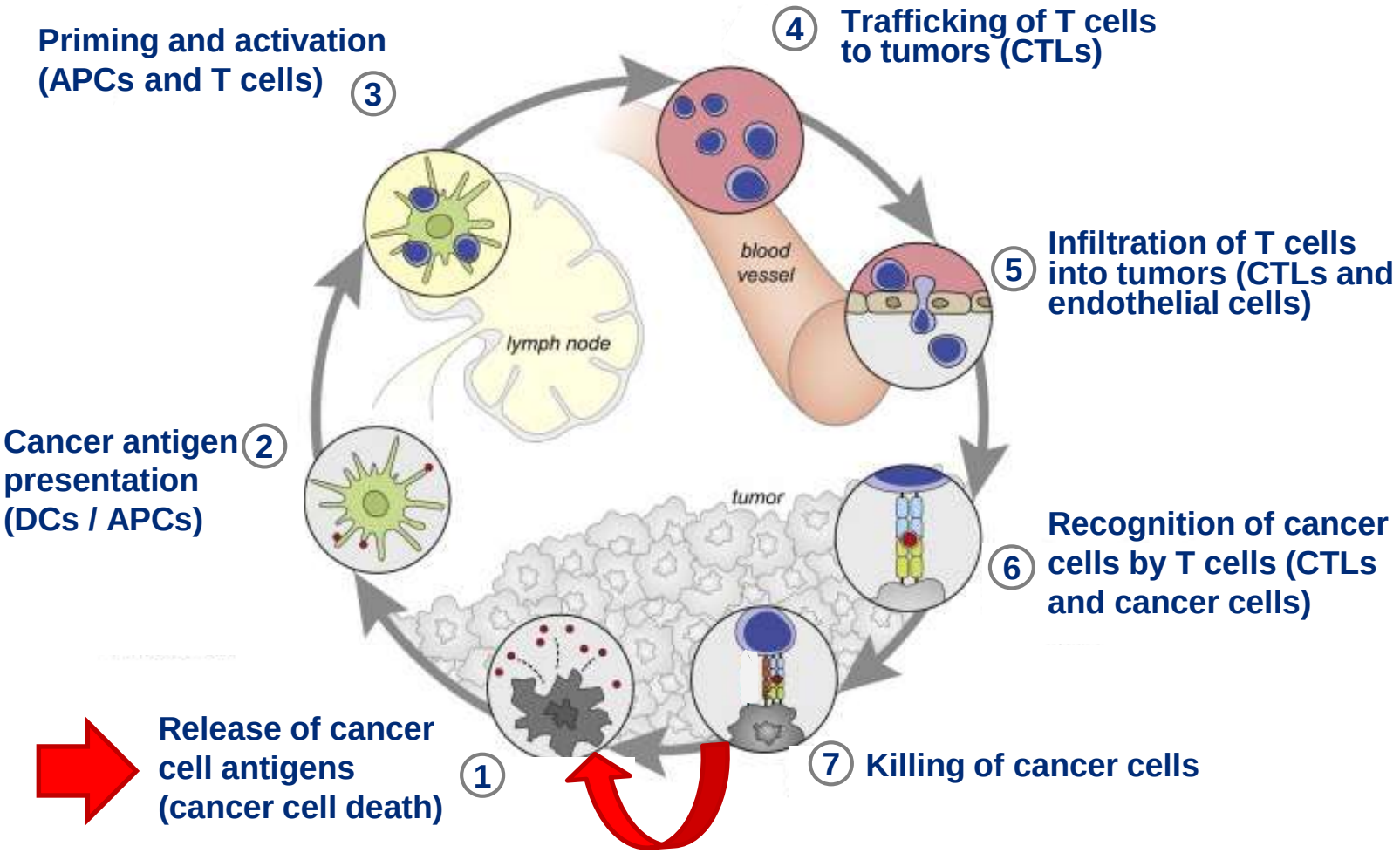
Emil v. Behring

Louis Pasteur

Rudolf Virchow

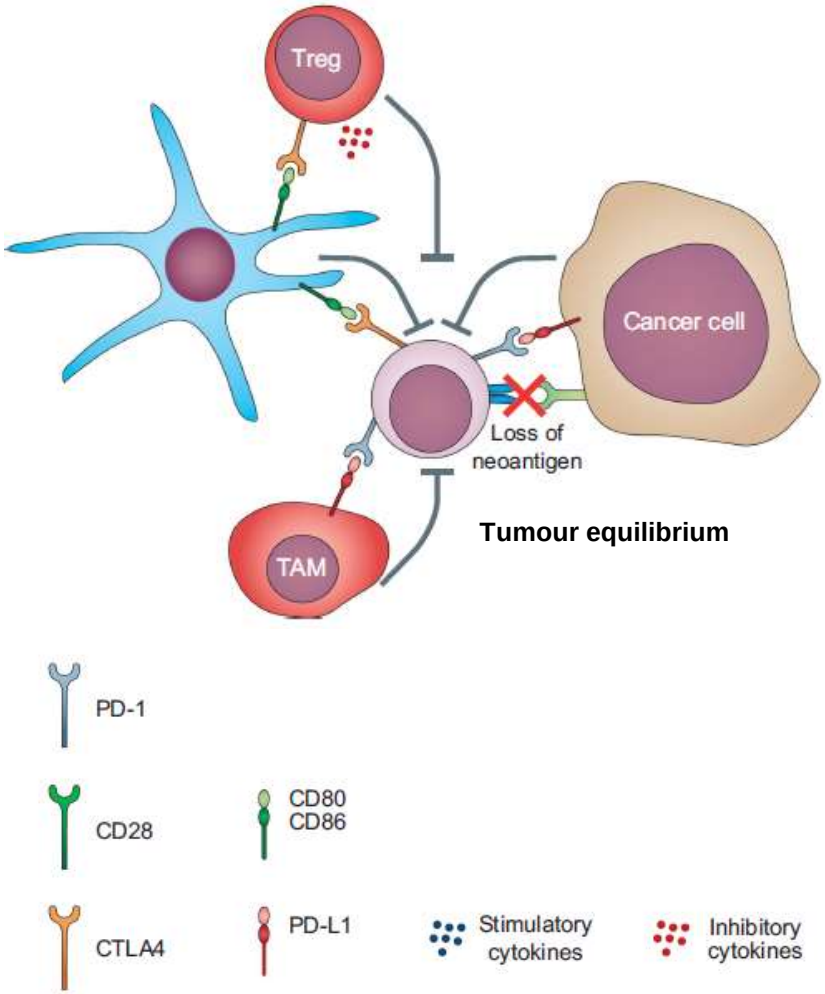
Ilja Iljitsch Metschnikow

The Cancer-Immunity Cycle
- Immunoediting: 1.) Elimination -



Chen and Mellman Immunity, 2013, 39:1-10

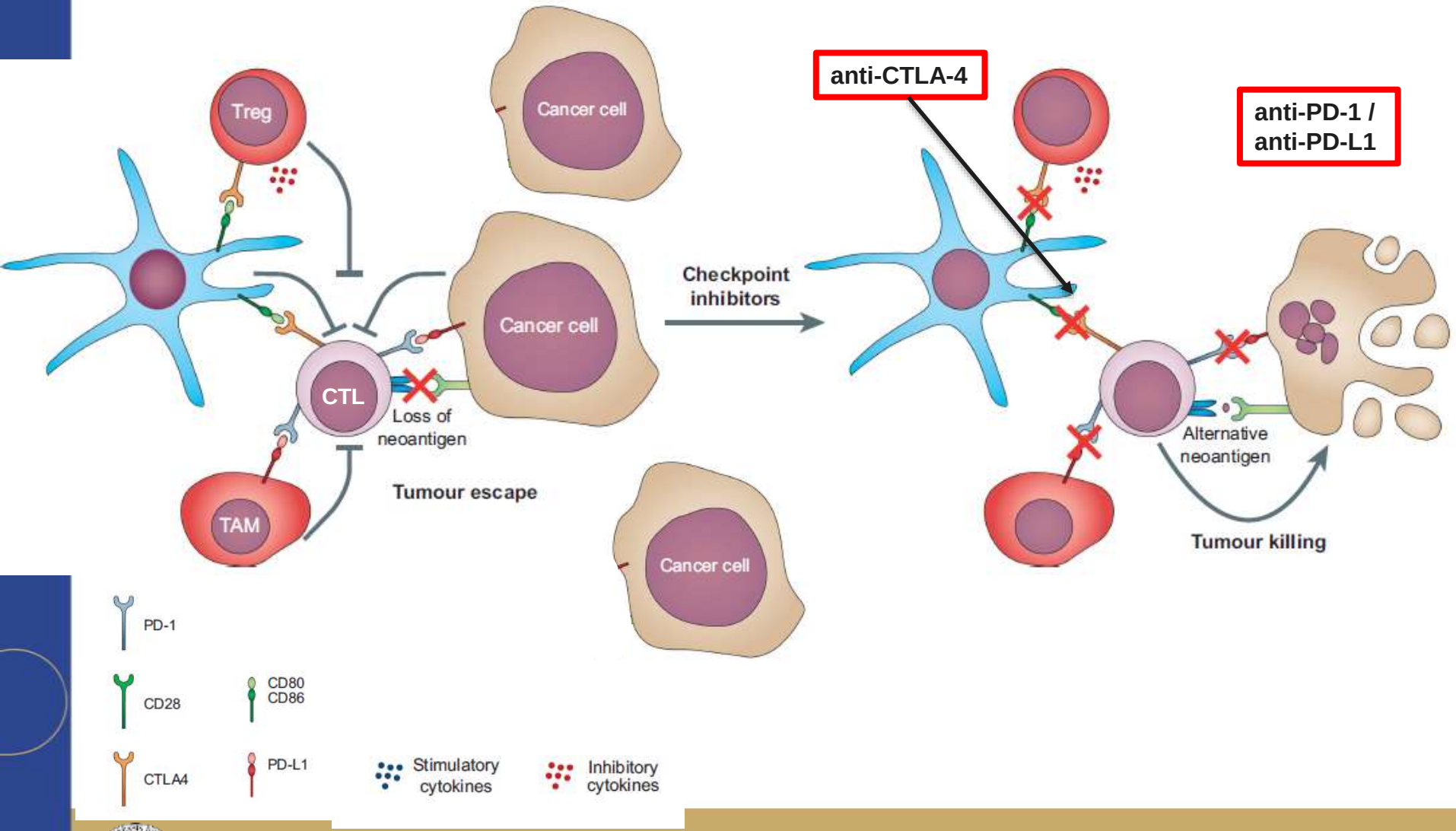
The Cancer-Immunity Cycle
- Immunoediting: 2.) Equilibrium -



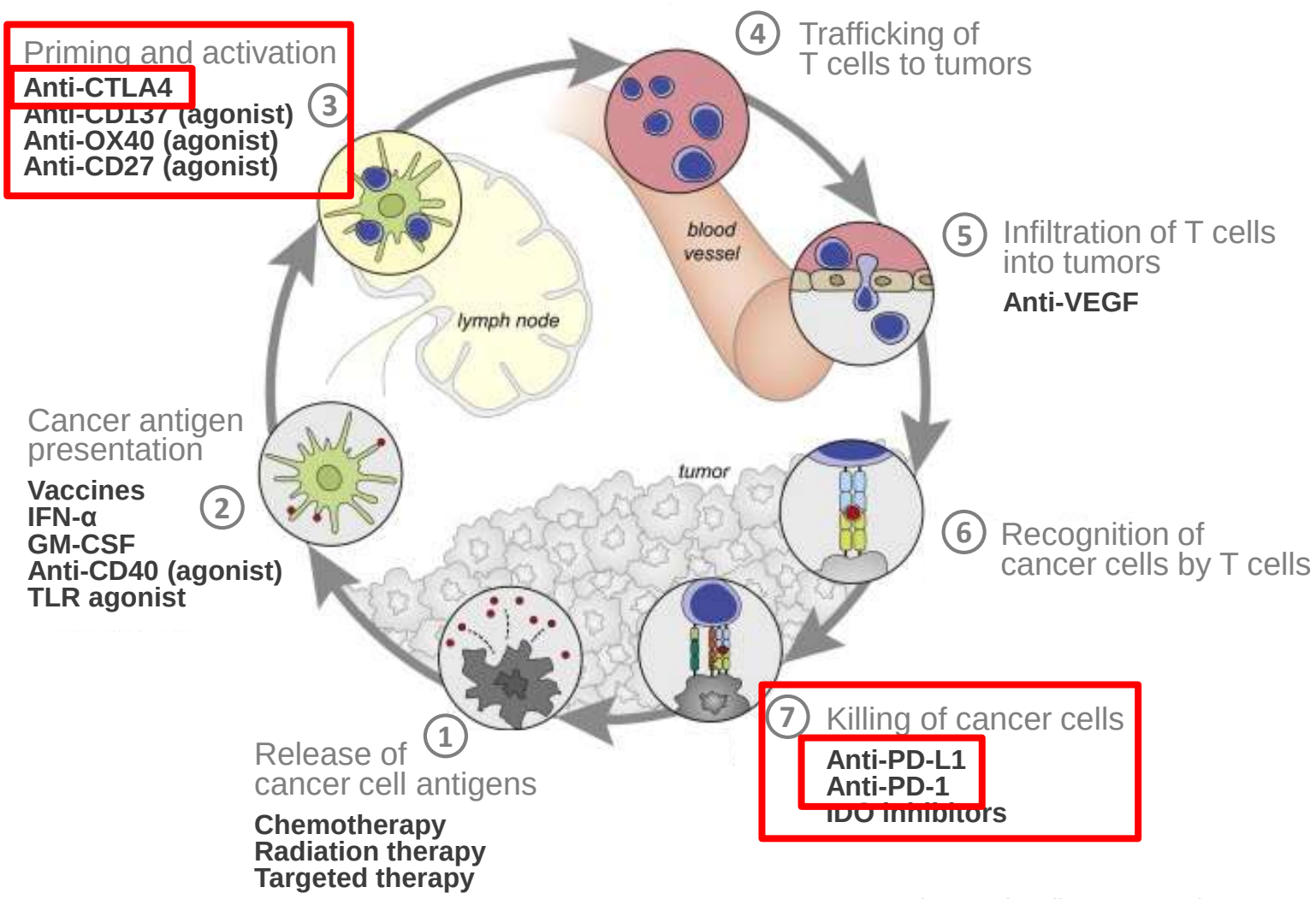
Tumour equilibrium

Phan et al., 2015

Immune Checkpoint Inhibitors

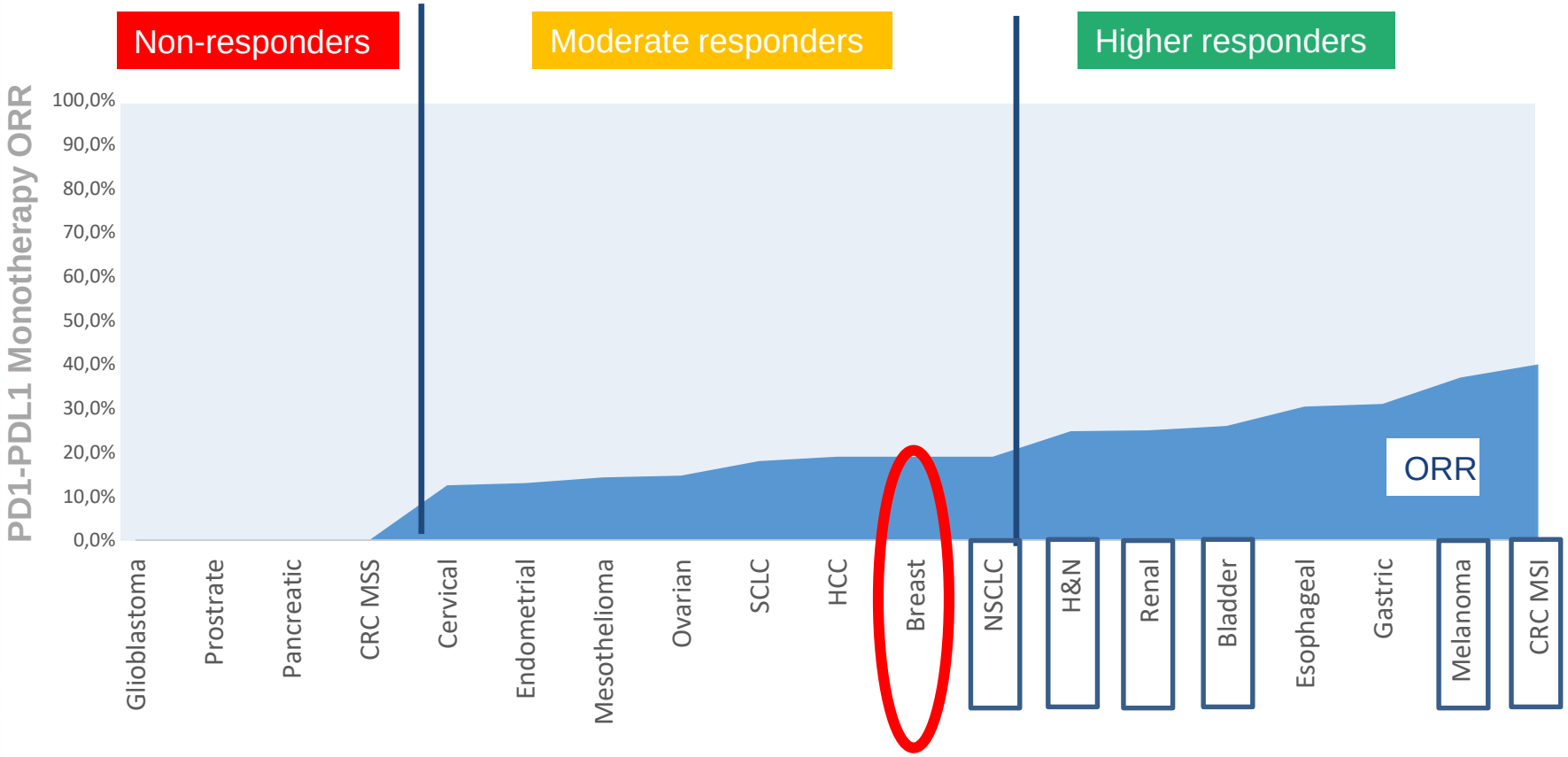


Immune Checkpoint Inhibitors

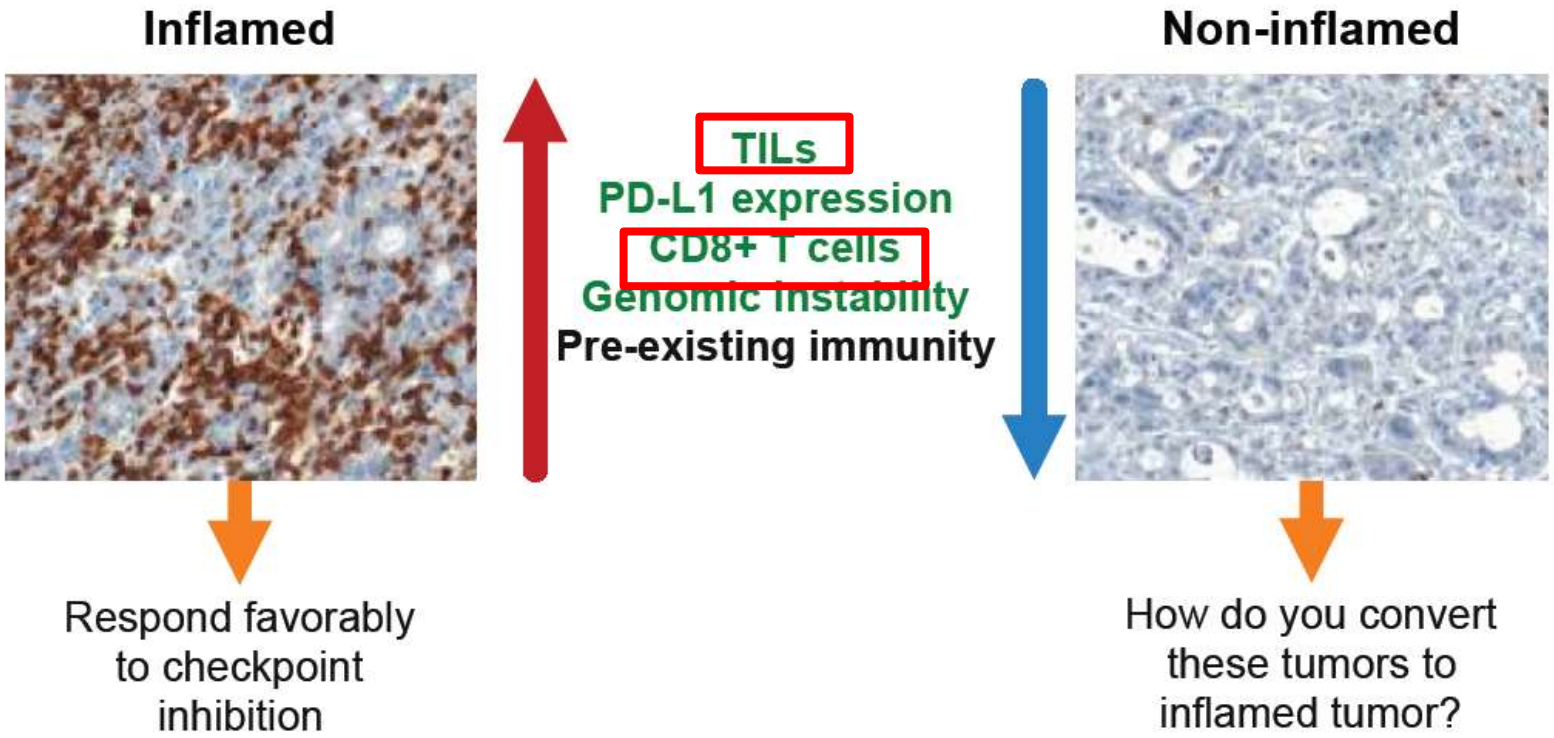


Chen and Mellman Immunity, 2013, 39:1-10

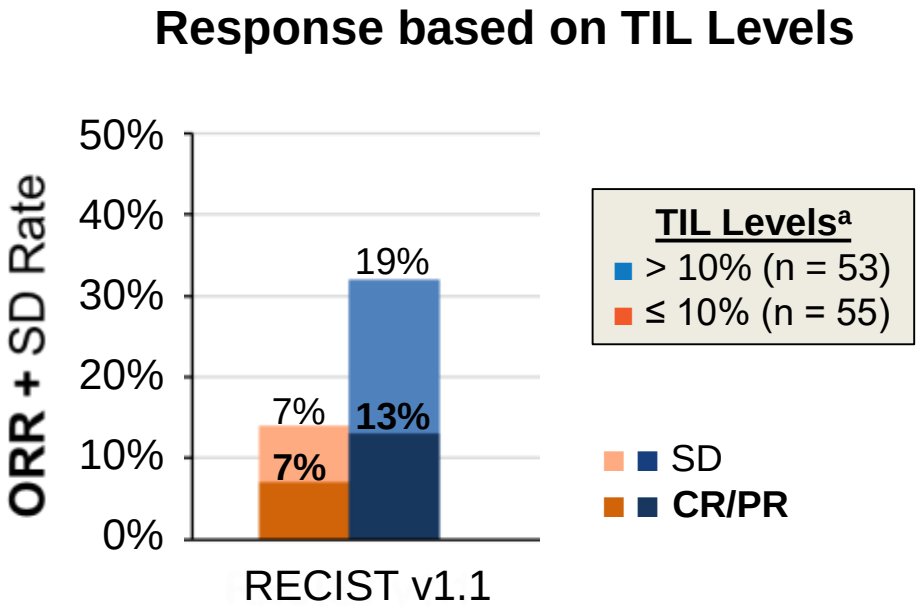
Three Categories of Response to Anti-PD-1/PD-L1



Immunogenic vs. Non-immunogenic Tumors

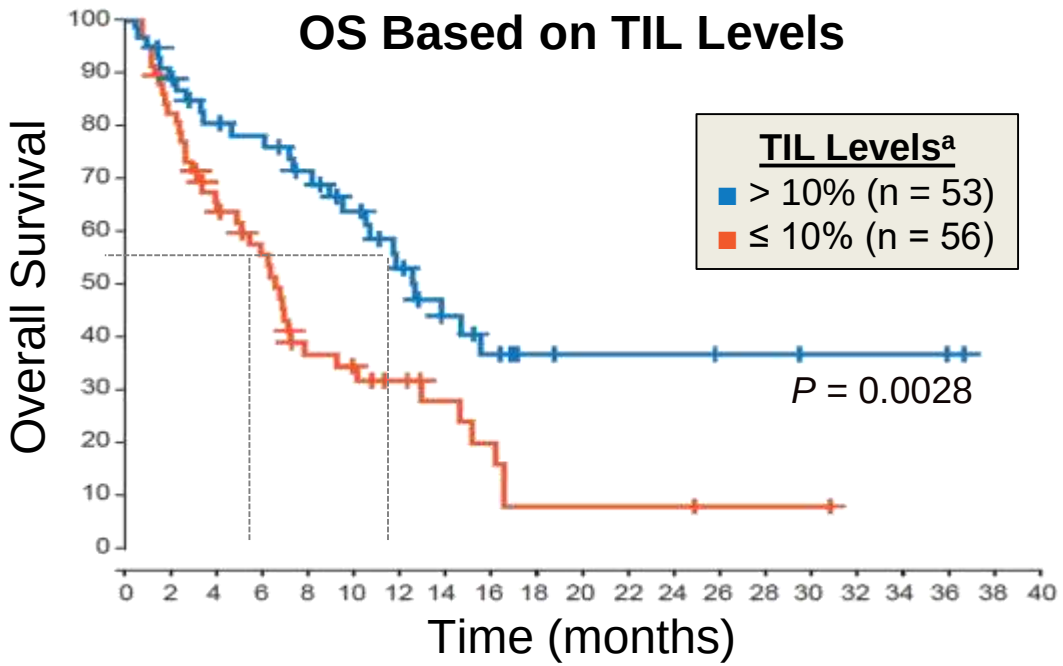


Biomarker Analysis: Tumor-Infiltrating Lymphocytes



Schmidt P. et al. AACR 2017 Phase Ia Atezolizumab in TNBC

Biomarker Analysis: Tumor-Infiltrating Lymphocytes

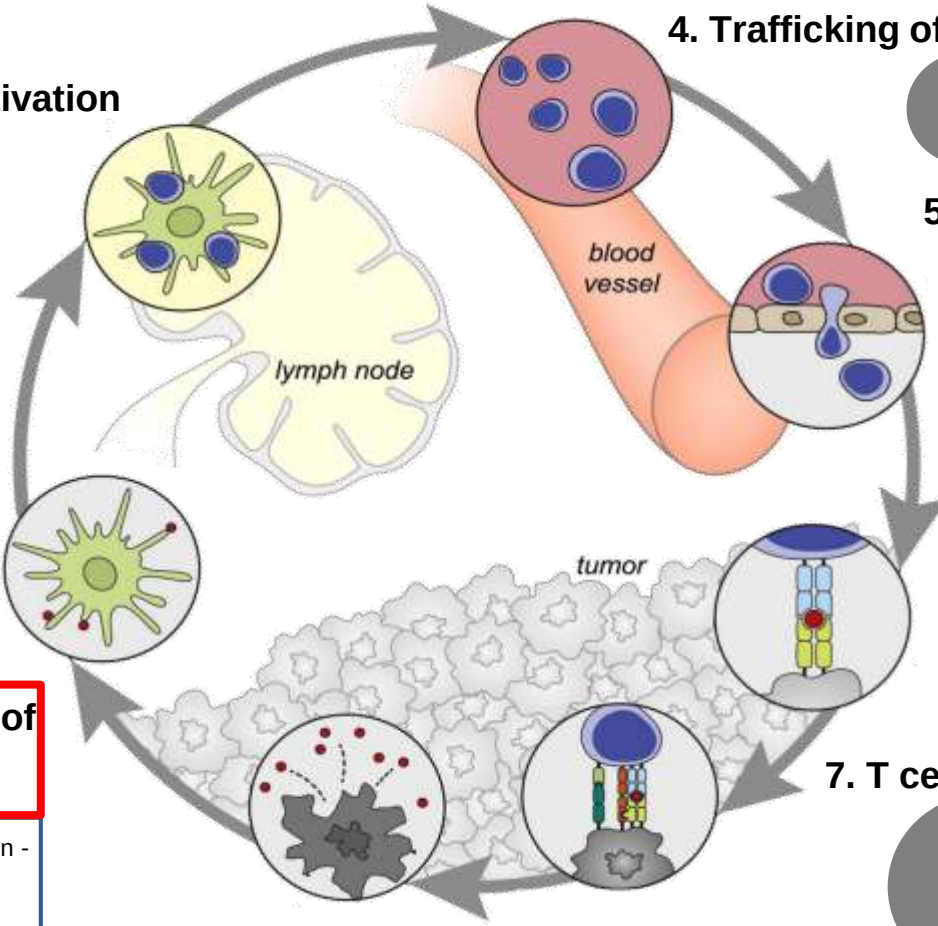


	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

- Higher ORR and longer OS were seen with higher baseline TIL (CD8) infiltration

Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

Future Directions in Immuno-Oncology



1. Release/Exposure of cancer antigens
Chemotherapy

2. Cancer antigen presentation

3. Priming and activation
16 7

4. Trafficking of T cells to tumors
14 1

5. Effector T cell Infiltration into tumors
11 12 2

6. T cell recognition of cancer cells
29 23 4

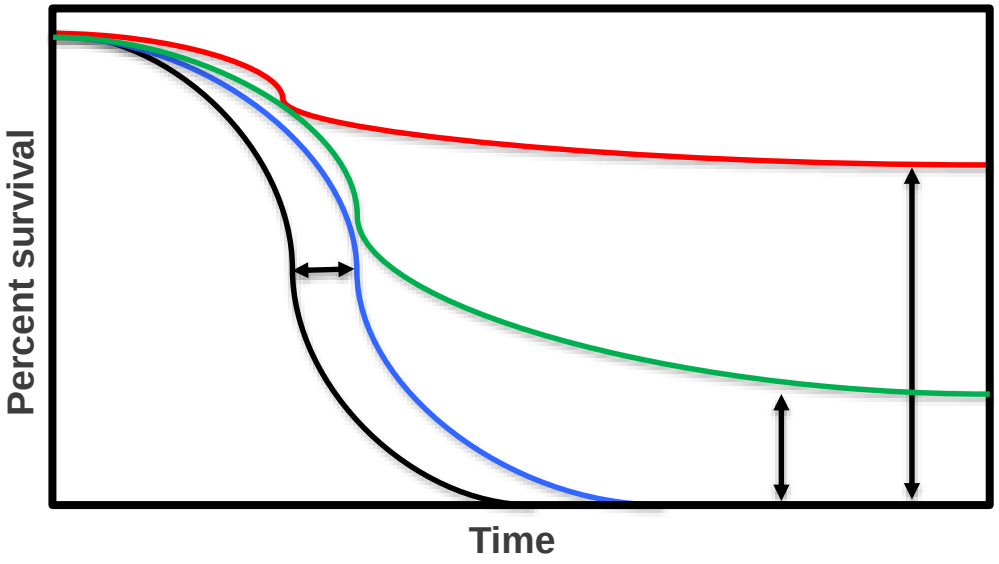
7. T cell killing of cancer cells
26 12

The bubble contains # of trials in -
- Phase I
- Phase II
- Phase III

Note - Trials may test more than 1 agent

Chen and Mellman Immunity, 2013, 39:1-10

Summary and Future Directions



Chemotherapy

Targeted therapy

Immune checkpoint therapy

⇒ **long lasting responses**
⇒ **applicable in various cancer types**

Combination therapy

⇒ **increase in response rate**
⇒ **increase in efficiency**

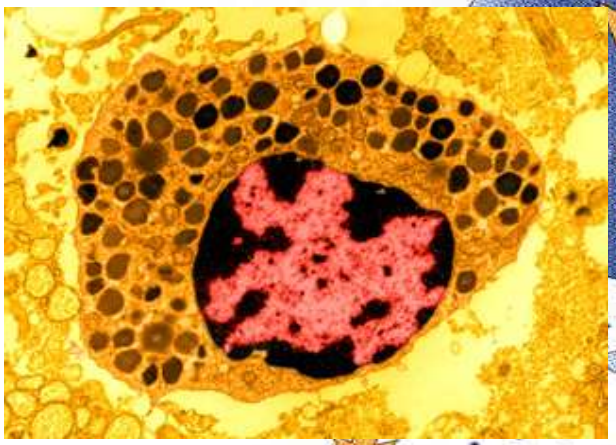
Typ I. Hypersensitivity Reaction

1. Antigen Exposition — IgE Production
2. Antigen Exposition — IgE Production / Binding (Mast cells, basophyle Leukocytes FcεR)

DEGRANULATION

LTB4	Histamin	Histamin
Chemotactic Faktors	PAF	LTD4
Zytokine	PGE2	PE
	LTD4E4	PAF
Chemotaxis/Exsudation	Vasodilatation	Spasmus of smooth muscles
Glattmuskulatur		
	increased permeability of the vessels	
Eosinophile		
Mckrophage	EDEMA	

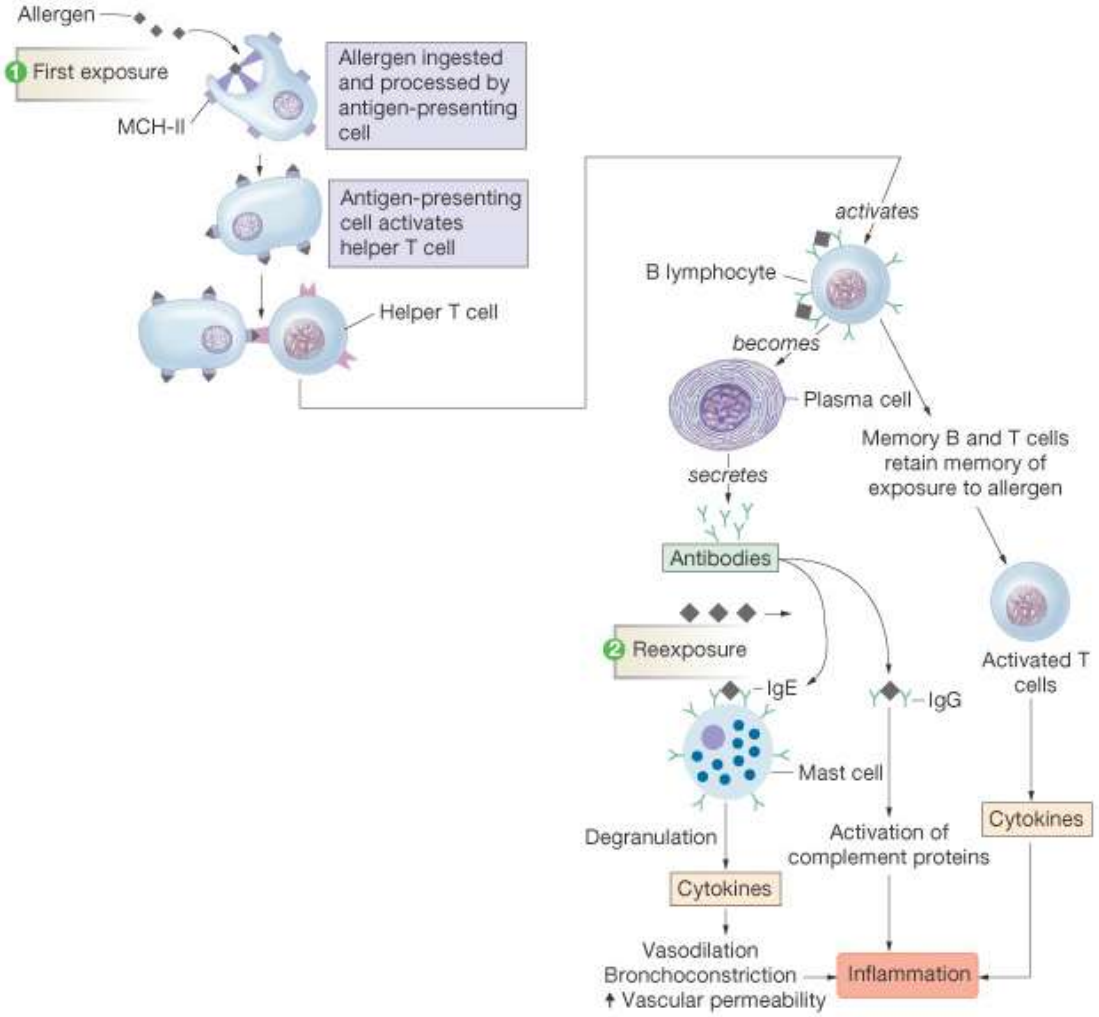
ACTIVATION OF MAST CELLS IN TYPE I HYPERSENSITIVITY *REACTION*



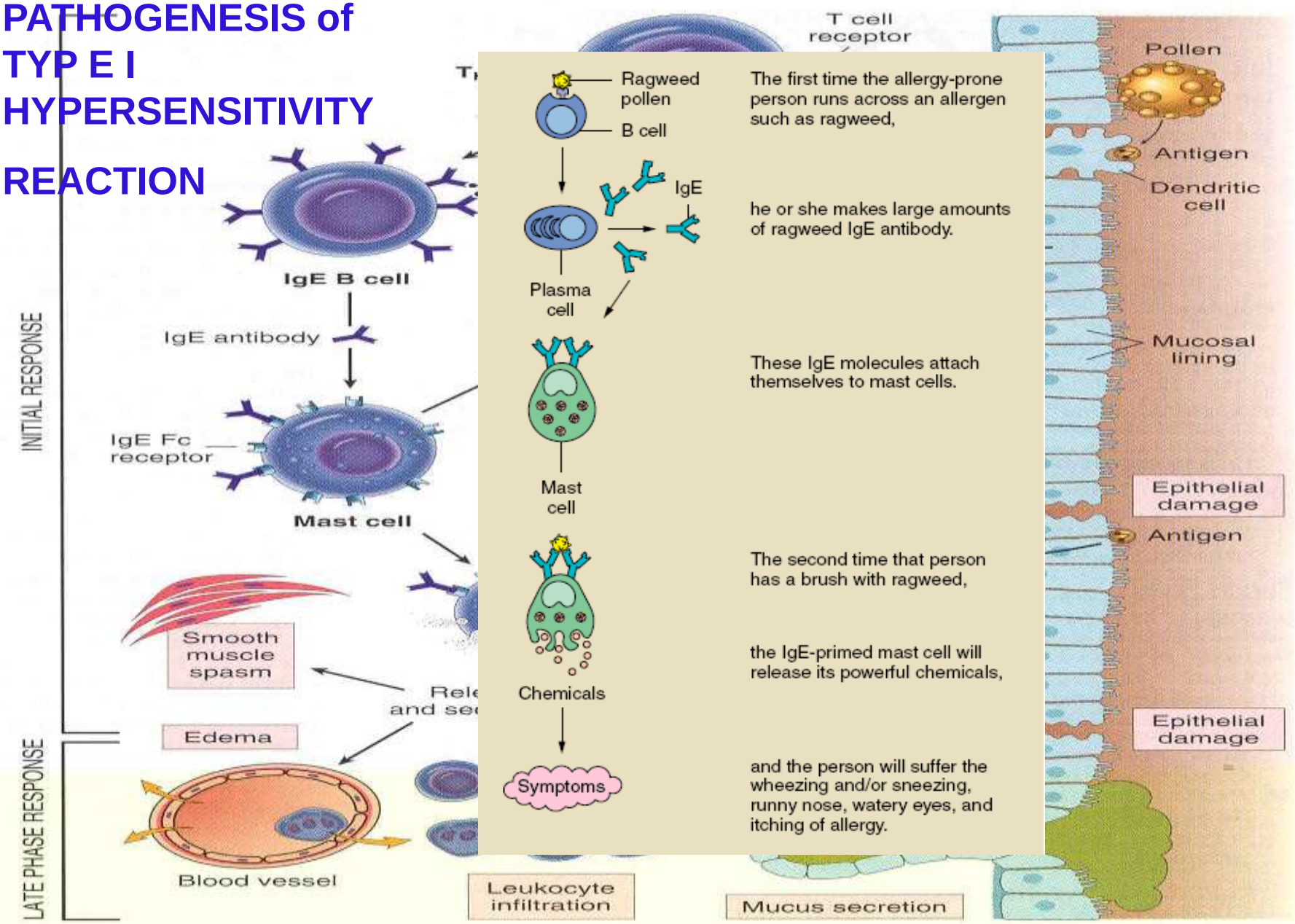
Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for activation of phospholipase A_2
Signals for cytokine gene activation
Nucleus
Membrane phospholipids
Granule contents
- Histamine
- Proteases
- Chemotactic factors (ECF, NCF)

Secreted cytokines
Arachidonic acid
PAF
Leukotrienes B_4, C_4, D_4
Prostaglandin D_2
Primary mediators
Secondary mediators

Allergic inflammation on non-pathogenic noxa

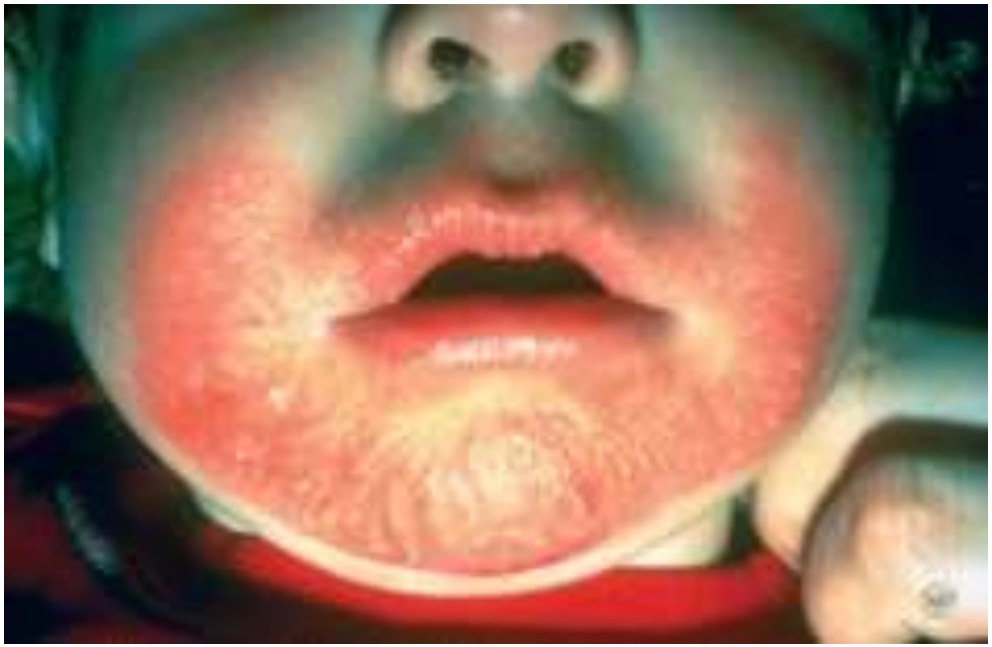


PATHOGENESIS of TYP E I HYPERSENSITIVITY REACTION

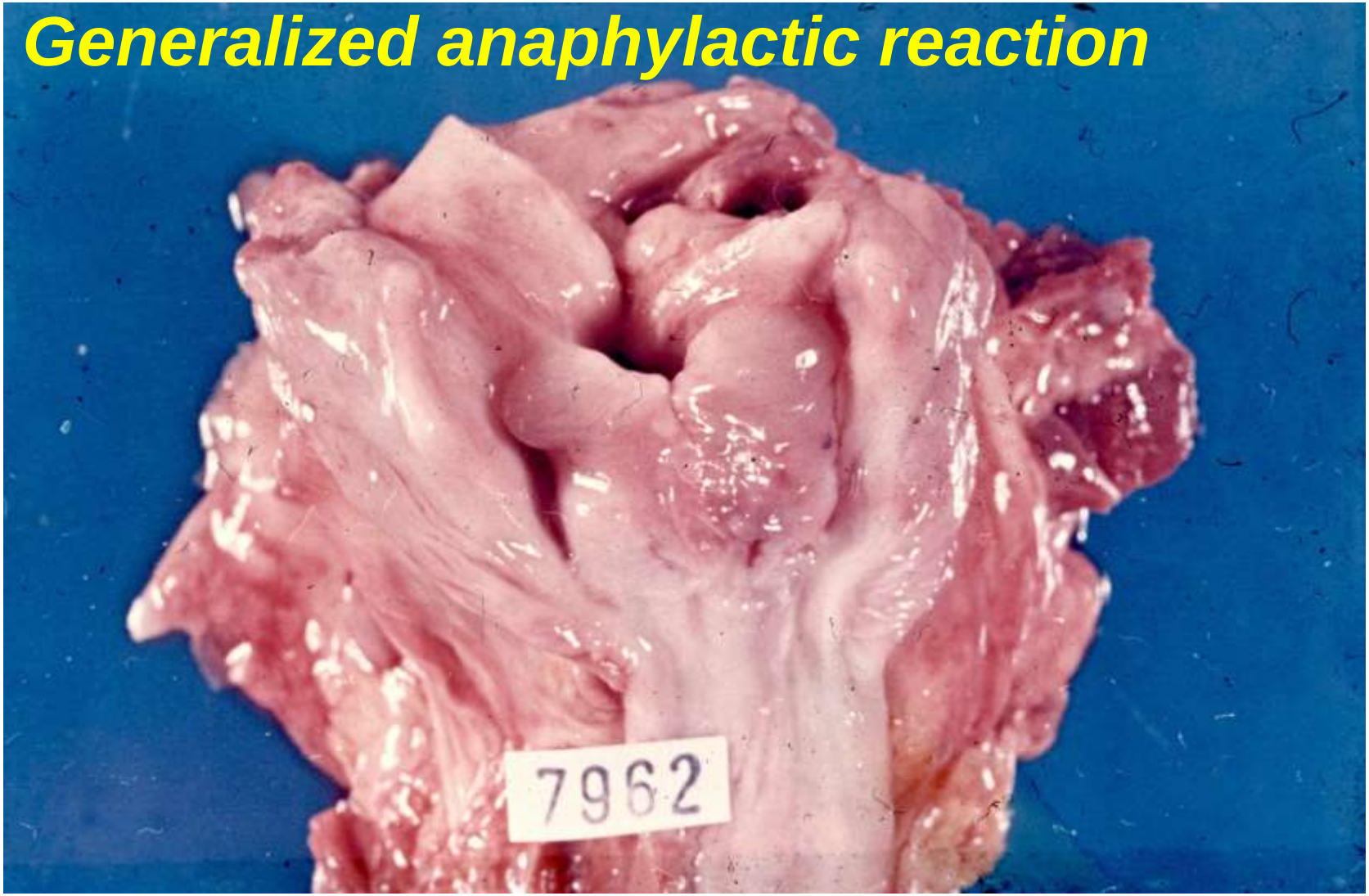


Allergy

- Local: Rhinitis, Asthma, Conjunctivitis
  - ➥SKIN: Urticaria, Ekcema, Angioneurotic
  - ➥Edema
- Systemic: Anaphylactic Shock
- (Adrenalin: Relaxation of smooth muscles, no vasospasmus)



Generalized anaphylactic reaction

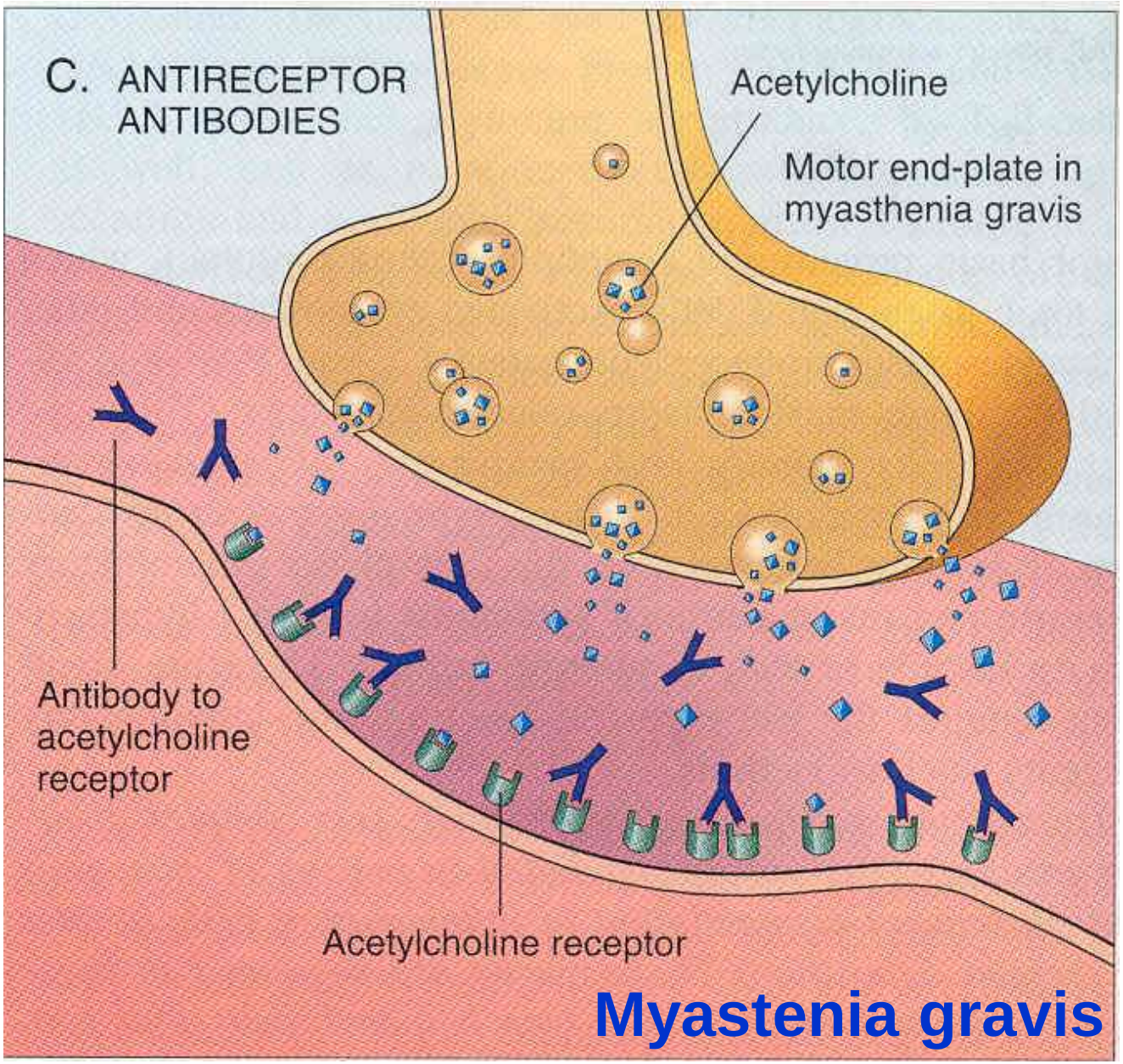


https://www.youtube.com/watch?v=j8wwNpkpEN0

Glottis edema

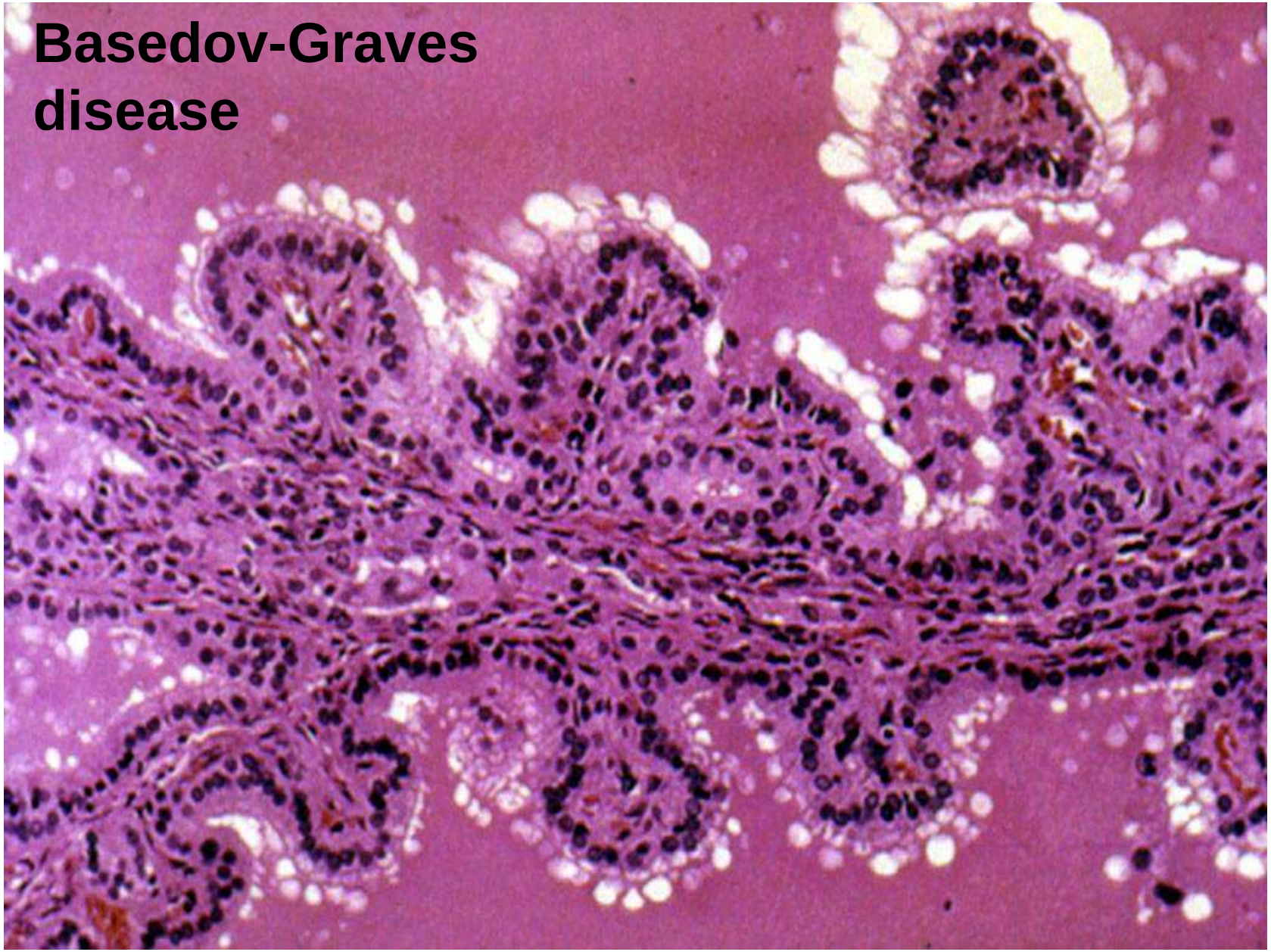
Typ II. Hypersensitivity Reaction

Complement-Dependent
Target cells: AB Binding
C5-9 C1423
Complement-dependent cell death Opsonisation/Phagocytosis
AB dependent cellular Zytotoxicity
Target cell AB Binding (Fc Exposition)
FcR+ Effector cell -contact (NK cell, makrophage)
Target cell death
Anti Receptor AB mediated
Anti-receptor-AB Production
Target cell AB Binding
Receptor-Inhibition Receptor-activation
(AchR, myasthenia gravis) (TSHR, Hyperthyreosis)

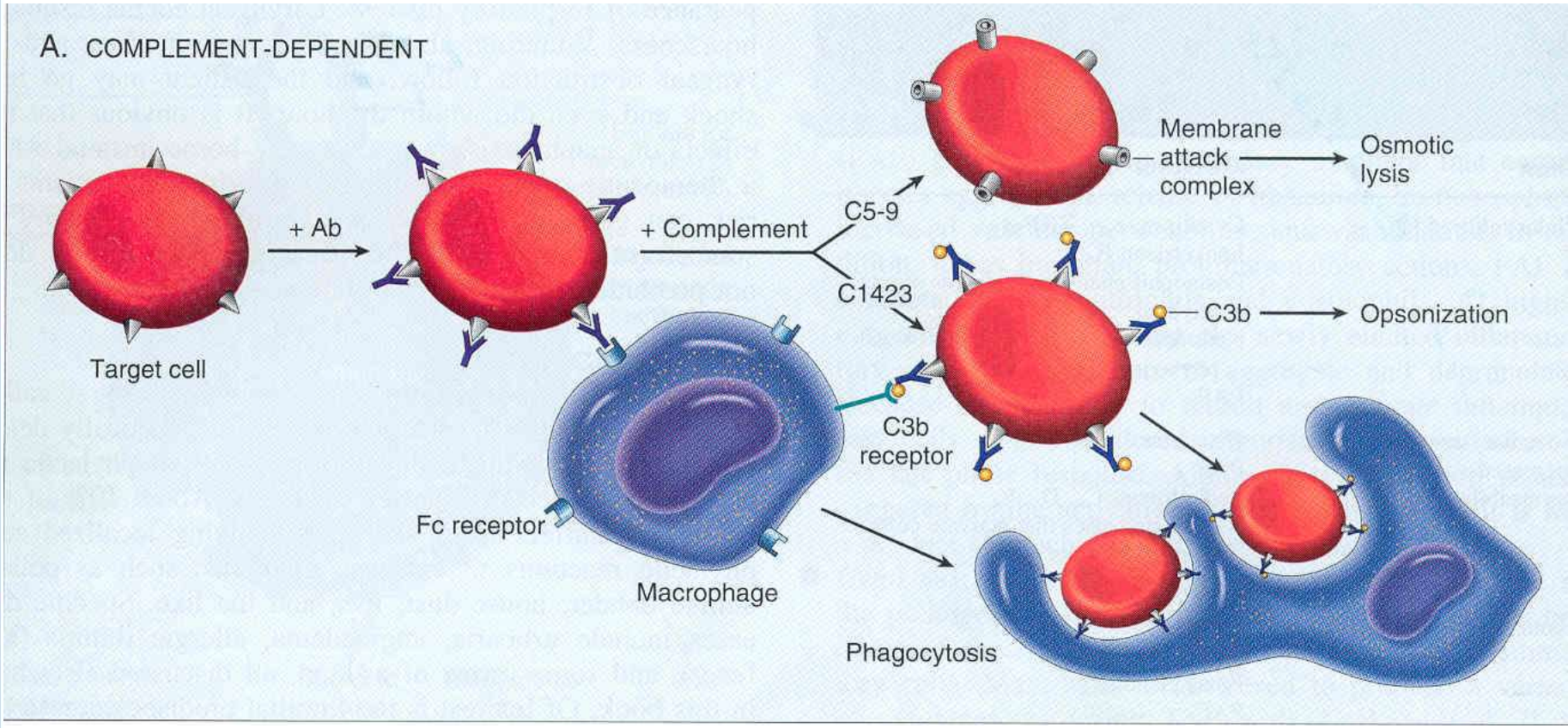


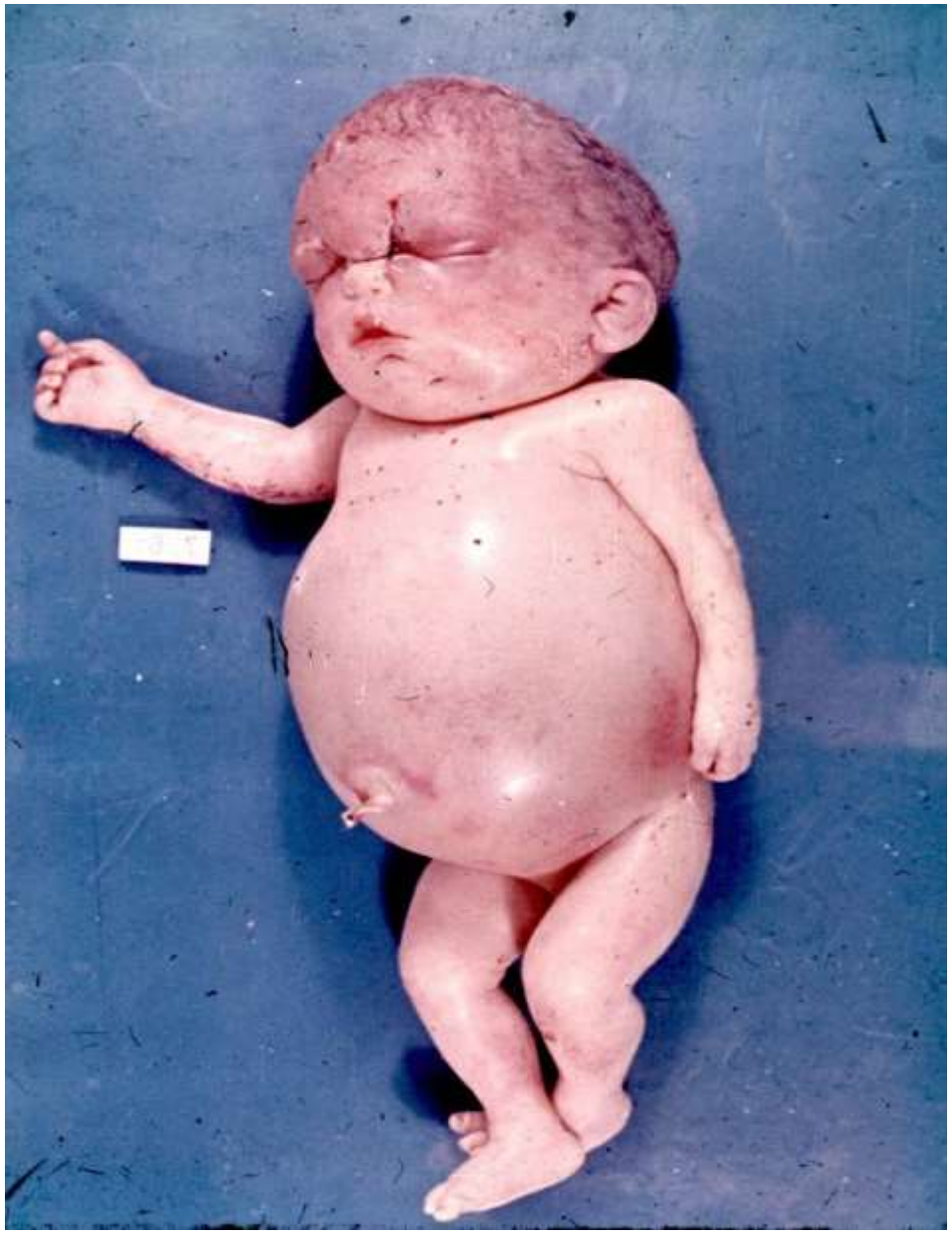
Myastenia gravis

Basedov-Graves disease



Typ II. Hypersensitivity Reaction *(cytotoxic)*

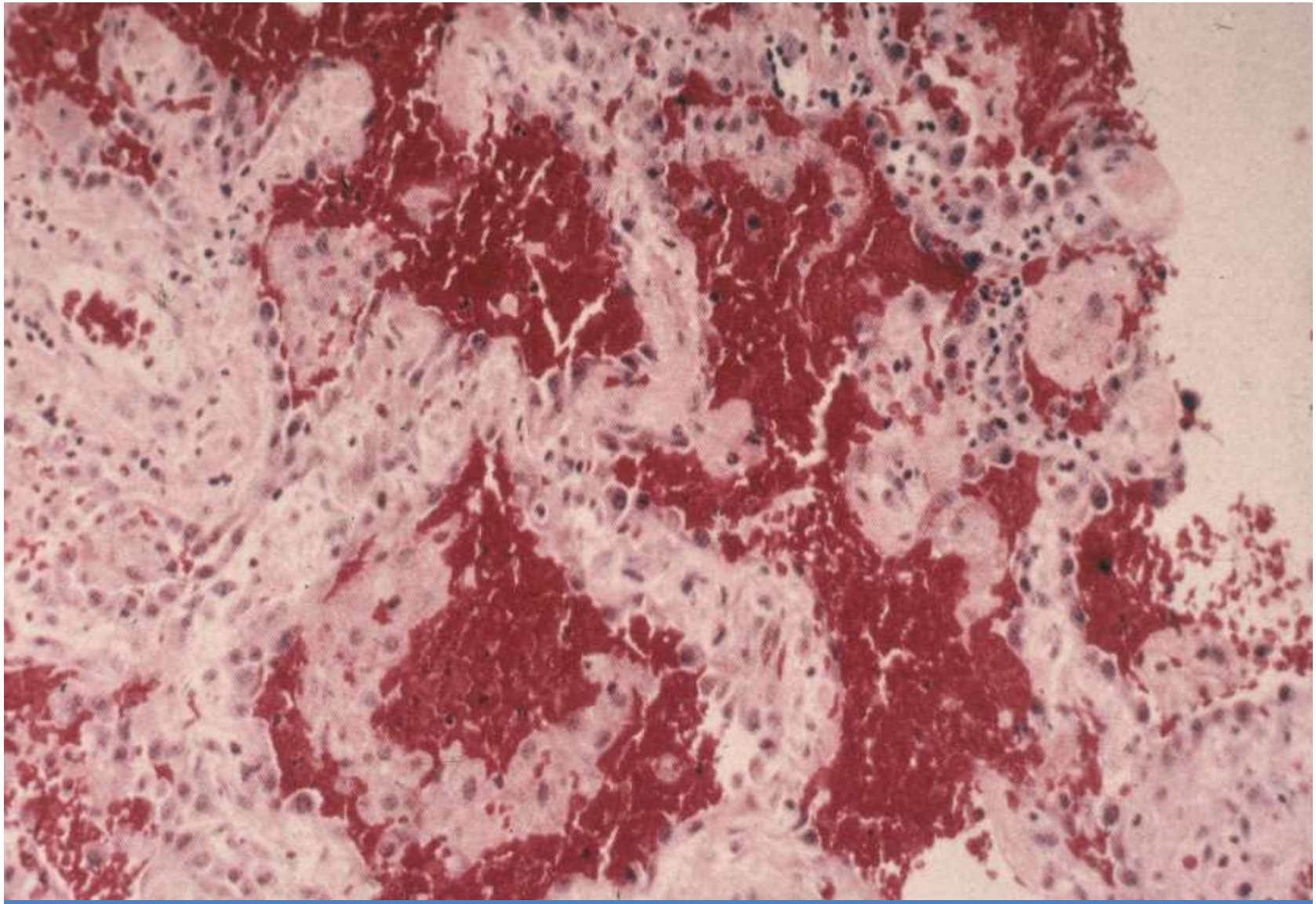




Hydrops foetus universalis

Rh Incompatibility

(Parvovirus B 19 Infection)



Bleeding in the lung, Goodpasture Syndrome

Typ III. Hypersensitivity Reaction

2. Antigen-Exposition — Antigen/AB Complex development (circulation)
Immuncomplex deposition
(kideny, liver, serous membranes, wall of the vessels)

Vasodilation — Neutrophilic Migration — Thrombocyte Aggregation

Degranulation — Microthrombus

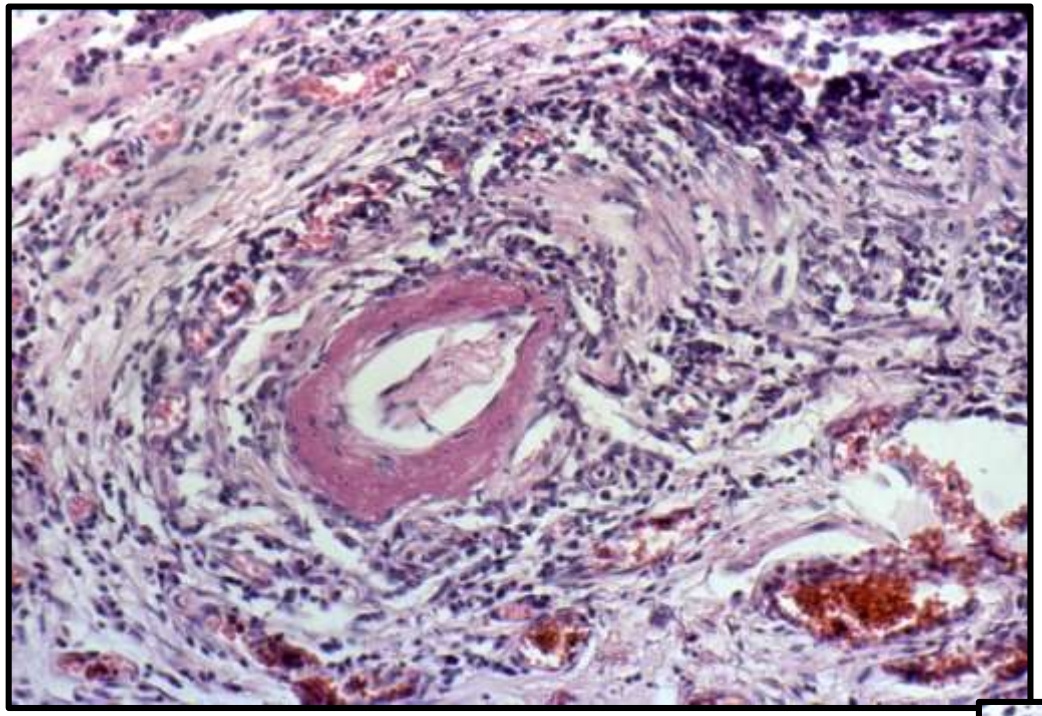
Edema — Ischemia

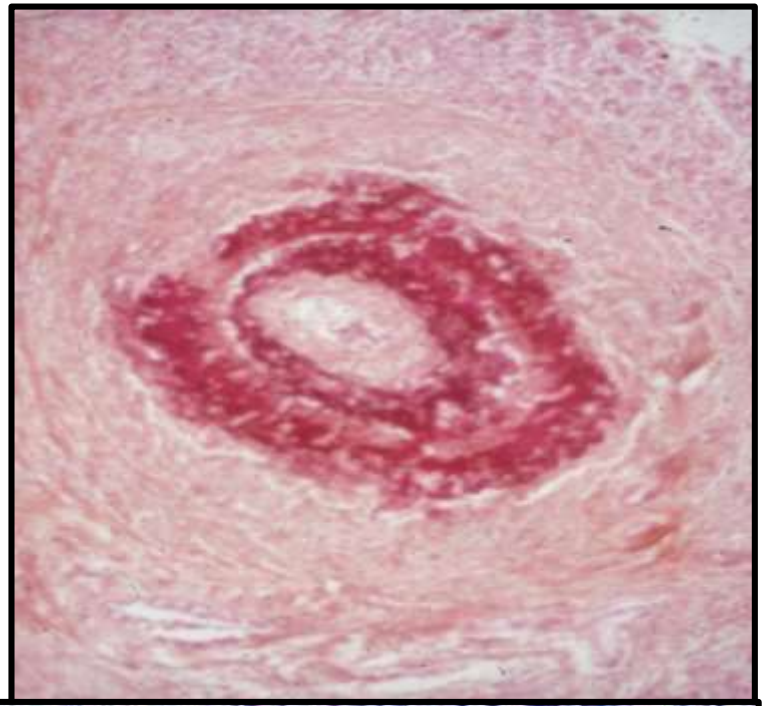
tissue necrosis

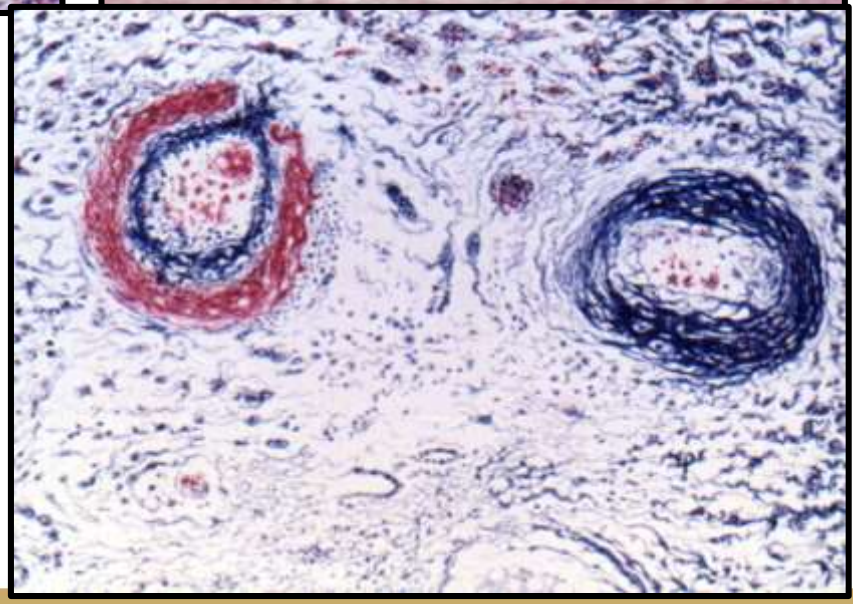
Patomechanism

- Acute:
- AG/AB Complex (Se), Deposition Inflammation.....C3b (Phagocytosis)C5b,6/7: Chemotaxis, (inflammation), C5-9 Membrane Attack Complex...Cell death

- Fibrinoide Necrosis of the wall fo the vessels, Vasculitis (new)





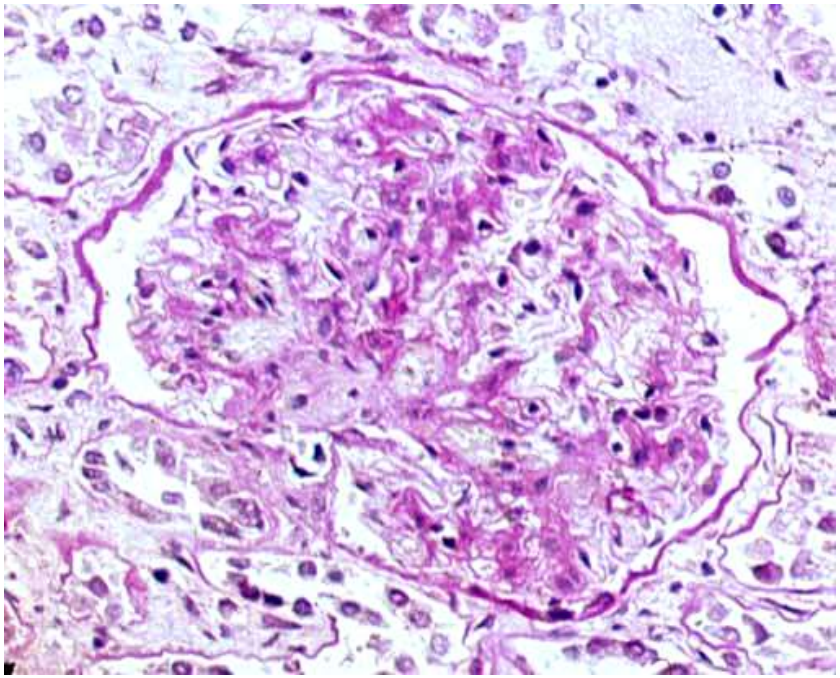


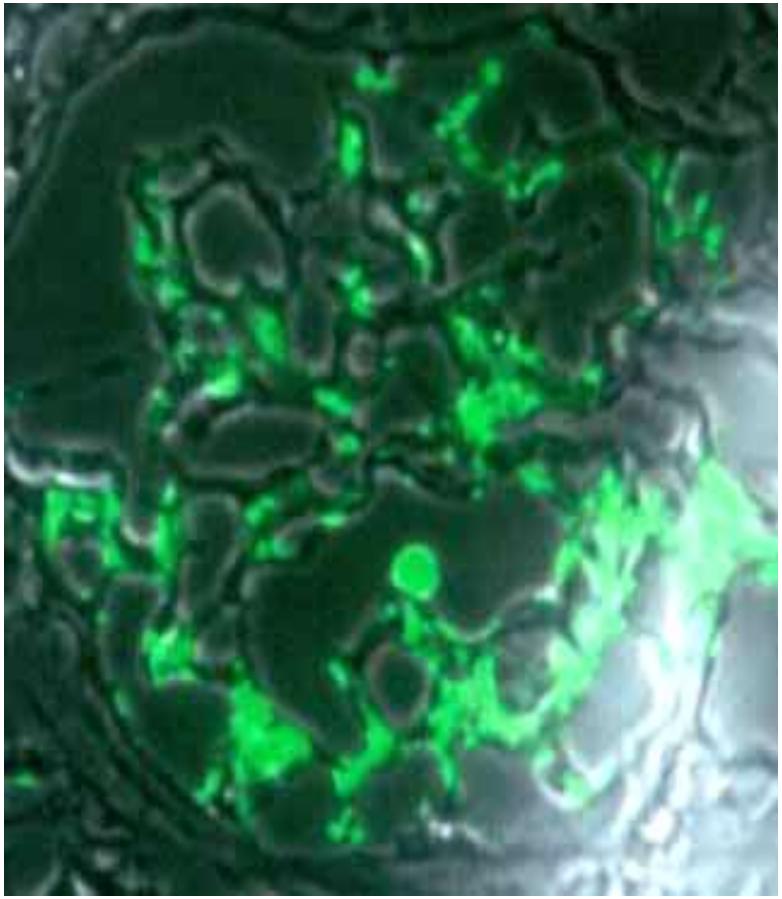
Major finding:

Nekrotising Vaskulitis

III. Patomechanismus

- Chronic: persistent Antigen
- Cause: „autoimmune disease”
- Snake poison Antisera, Mouse anti-human T cell serum, bacterial Streptokinase, iv. Penicillin





Typ IV. Hypersensitivity Reaction

A. Late Hypersensitivity

2. Antigen-Exposition dendritic cell – T Zcell binding (IL-2, TNFa, IFNg)

Lymphocytic accumulation Fibroblast-proliferation Macrophage-Activation

Gefassneubildung epitheloide cells

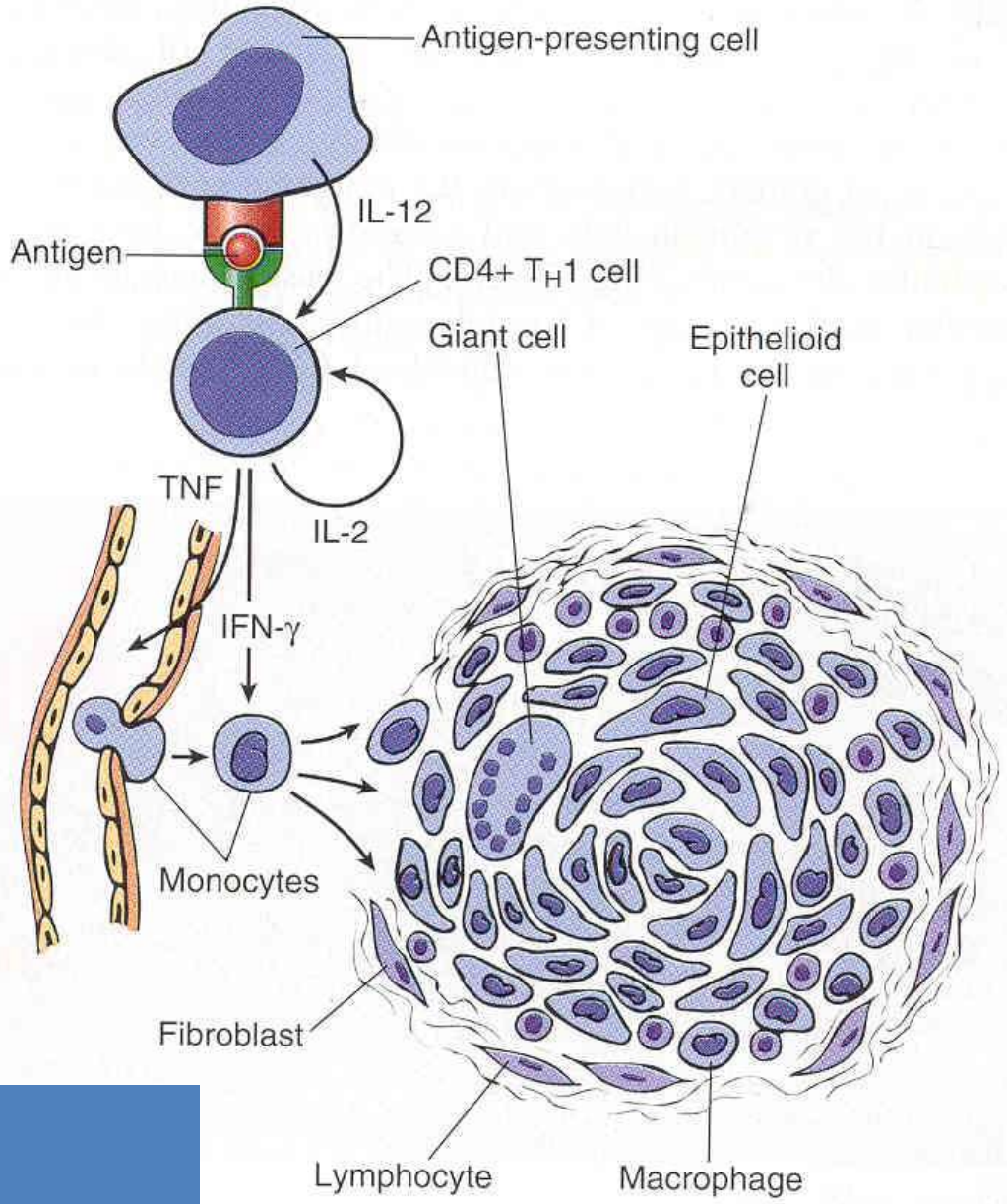
Giant cells –development

(Langhans, foregin body type)

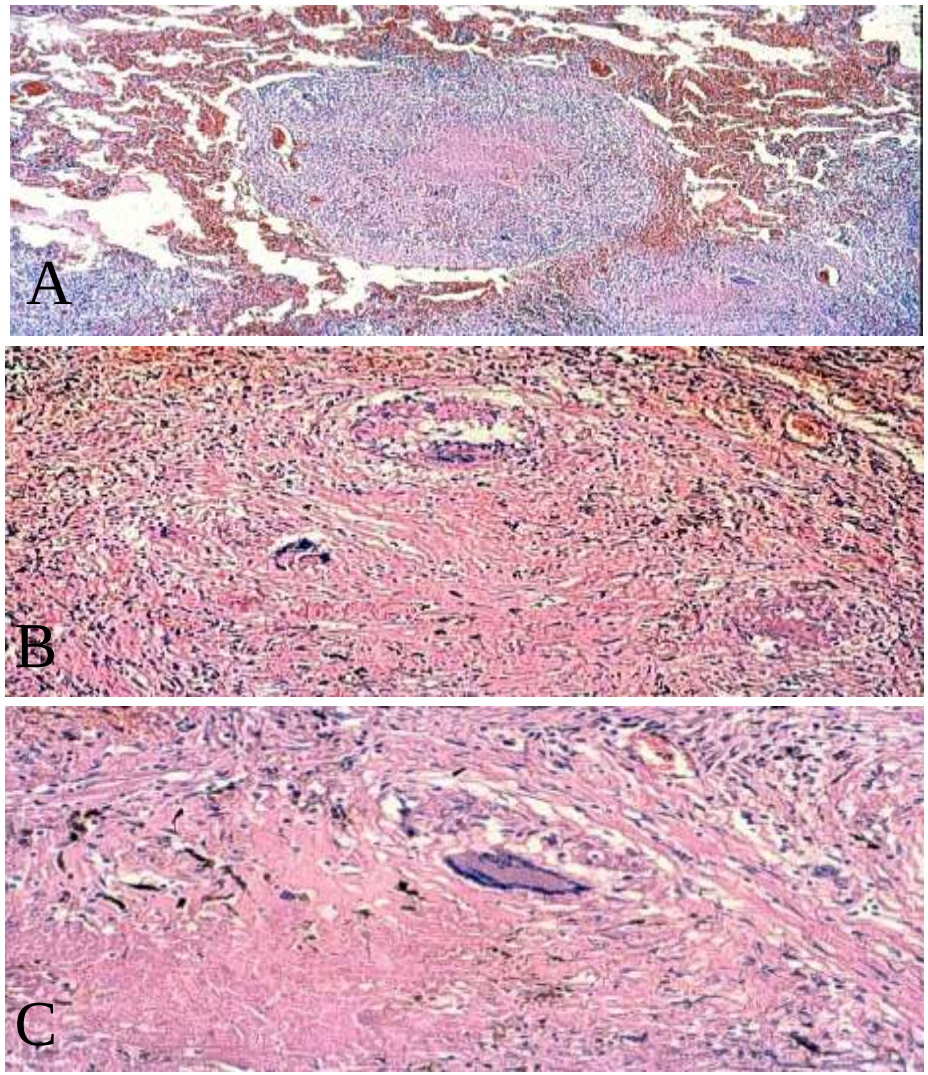
B. T-Zell mediated cellulare Zytotoxicity

Cell carriing foreign-antigen (virus-infiected cells, Allograft)

CD8+ T cell activation



Granulom development



TBC-Lung

Defect immunopathies

developmental

Stemm cell defects → heavy combined Immundeficiency
e.g. Schweizer Type Agammaglobulinemia
thymic Alymphoplasia
Death within the first two years of age

B-Cell-Defects → bacterial Infection
Agammaglobulinemia: missing B-Zell-Area
Selective defects of antiboides - Dysgammaglobulinemias
IgA and IgG-Defect (IgM frequently increased)
IgA-Defect → Sprue. Caution by substitution
IgA is a very robust antigen

T-Cell-Defects → viral and fungal infections
frequenlty by malignant tumors
DiGeorge-Syndrome: Thymus-Aplasia, cardiovaskuläre def.
cause: viral embryopathy
Nezelof-Syndrome: Hypoplasia of the Thymus
missing T-dependent Immunphenom
Tuberkulinreaction, Transplant rejection
Ataxia teleangiectatica (Luis-Bar-Syndrome)
Thymushypoplasia, Teleangiektasia
Degeneration of the Purkinje-cells

Phagocyte-defects, defected production of active O_2-Radicals

Chediak-Higashi-Syndrome

Autosomal recessive inheritance
Giant lysosoms in granulocytes and macrophages
Pyogenic Infections, Lymphomas (85 %)
benefitial effect of vitamin C

Complement defects (hereditary)

C1 Inactivator deficiency → C1 spontaneous activation ihibited, production of C2 Kinine → increased permeability → urticaria, edema

C2-defects associated with Lupus erythematosus disseminatus, Glomerulonephritis
Dermatomyositis

C3-defects → purulent inflammations – tendency for sepsis

defects of terminal components (C5 to C9)

they cause less clinical manifestations

Acquired Immundefects / syndroms
Defects of the humoral systems:

Hypoproteinemia caused by decreased protein uptake
or by lost proteins (e.g. nephrosis sy.)
B-cell-tumors → Gammopathies

Defects of the cellular systems:

disturbed proliferation — Immunsuppression
cytostatics
T-cell-tumors
Abnormal T-cell-function: viruses, AIDS
chronic infections

Immunsuppression = therapeutic suppression of the immunreaction by autoaggressive diseases

prevention and treatment of transplantation associated rejection

Danger: heavy infections, increased risk of tumors

Causes: cytostatics (e.g. Azathioprin) destry the proliferating lymphocytes.

whole body irradiation or central immun organs → lymphopenia

corticosteroids → suppression of the immuncompetent

B- and T-lymphocytes

Antilymphocyte serum → agglutination and cytolysis of the B-cells

cyclosporin A suppresses the syntesis of interleukin-I supported by T-helper cells, further, it makes T-cells unsensitive for interleukin II

Inherited Immundeficiency humoral

- X-bound hypogammaglobulinemia (Bruton), BTK deficiency, only propreB cells

Enteral infections (Viruses, Giardia, Mycopl.)

- Transient hypogammaglobulinemia (T helper cells)
- Hyper-IgM (CD40L deficiency)

No change of isotype, causes: CD4+T cell function is disturbed (IgA, IgE IgG deficiency), pathologic IgM, no germinative centrum...

- Variable hypogammaglobulinemia (B and T cell disturbance)
- Selective IgA deficiency (most common !!)

C4A-del, CD8+T deficiency, isotype change clinics: enteral and skin infections ...

- 5'-nucleotidase deficiency: only preB cells ...

Inherited Immundeficiency cellular

- Di-George sy. (Thymus Aplasia, 22q11del)

Heart developmental diseases+ hypoparathyr.), developmental disorder (3/4 pharingeal ring), only preT cells

- Chr. Mucocutaneous candidiasis

Inherited Immundeficiency mixed

- SCID: CYKR g-chain Mutation

Mostly T cell defect (X-bound, males)

- Adenosine deaminase deficiency (autos.-recessiv)

dATP toxic for T cells ....DNA lesion!!

- Purin nucleotid phosphorilase-deficiency (dGTP toxic, T, DNA!!!)
- Wiskott-Adrich syndrome (X-bound, males)

Xp1123 gene deficiency

Infekctions, thrombocytopenia, ekzema

- Ataxia teleangiectasia .

Thymus hyopolasia,lymph node atrophy, T+IgG/IgA deficiency (DNA Repair Genes)

- Reticular Dysgenesis (Myel., Ly. Stem cell defect)
- Nude Lymph. Syndrom (HLA-II Defizienz), CD4T Problem: CIITA, RFX Transcription factor defect
- Lower HLA-I Expression (Peptidtransporter defect) CD8 defect.....

Acquired Immundeficiency, AIDS

- HIV1/2 infection causes selective CD4 deficiency
- sexual, hematogeous, transplacental transmission
- Target cells: CD4+T (gp120HIV), cytotoxic
- Target cells: macrophages (not toxic, rezervoire, endothel ?
- Solubile gp120+CD4T/anti-gp120 ADCC

A I D S - acquired immune deficiency syndrome –

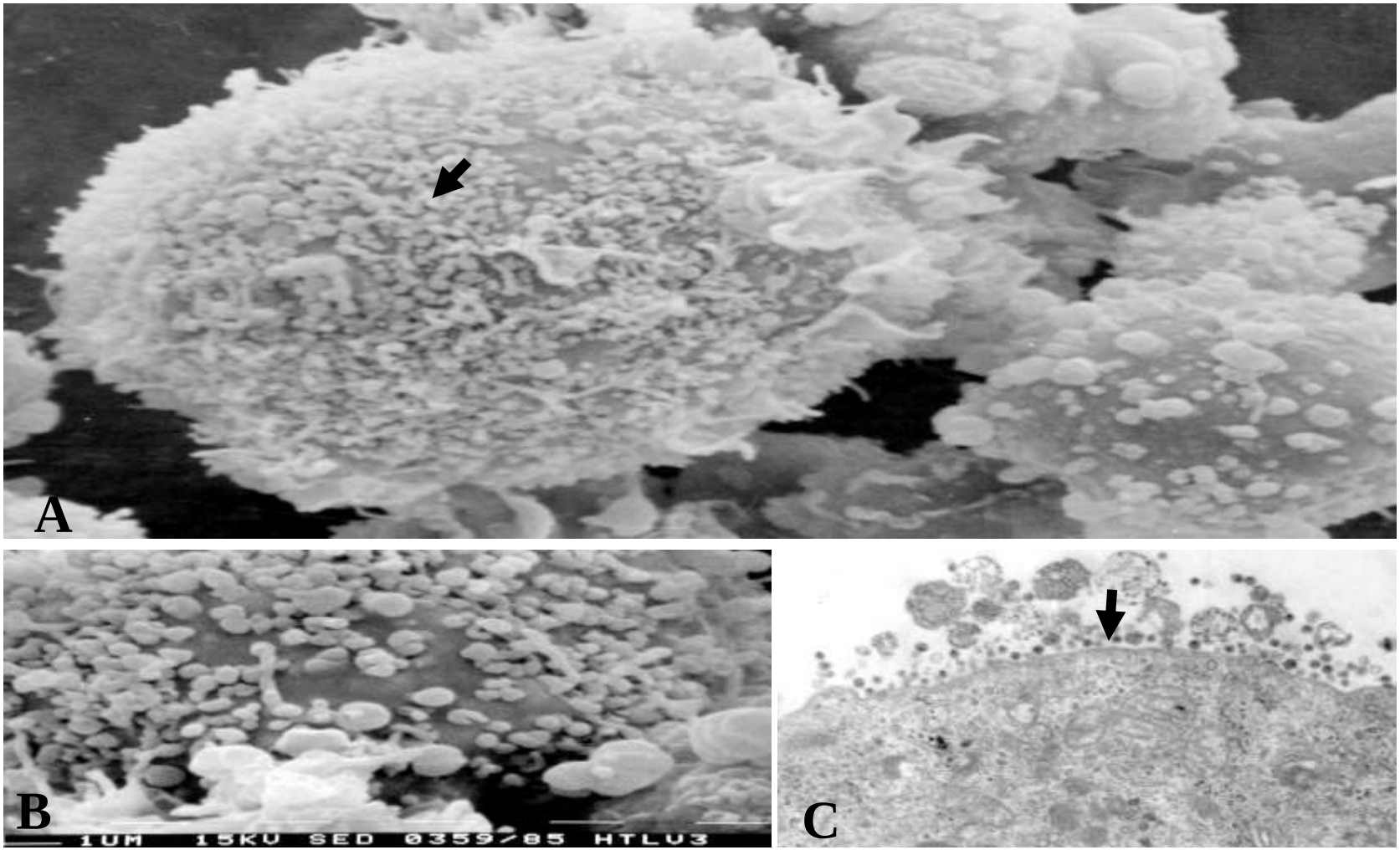
Defect of the cellular immunity → oportunistic infections

causes:: humane Immundefect virus (HIV)

Transmission : with blood
through maternal milk
transplacental
Sperma
Flies, moscitos ?

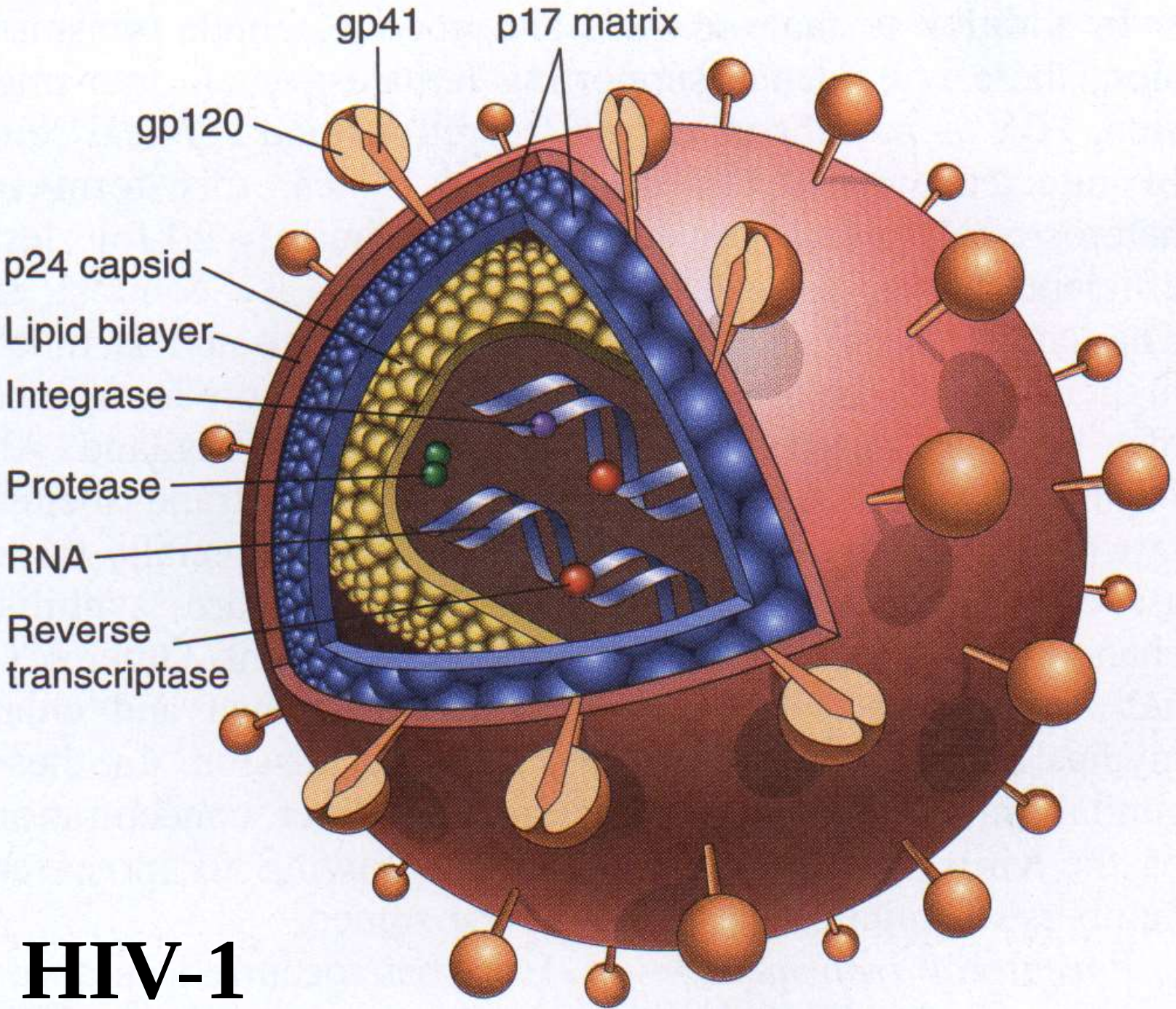
Main receptor: CD4-Antigen of the T4 lymhocytes
for gp120 makrophages
skin -Langerhans-Zellen
follicular retikulum cells

Parallel receptor: Galaktosylzeramid Oligodendrocytes
follikular retikulum cells



CD4/CD8 Verhaltniss: 2-4/1

HIV Infketion: ermindert / umgekehrt

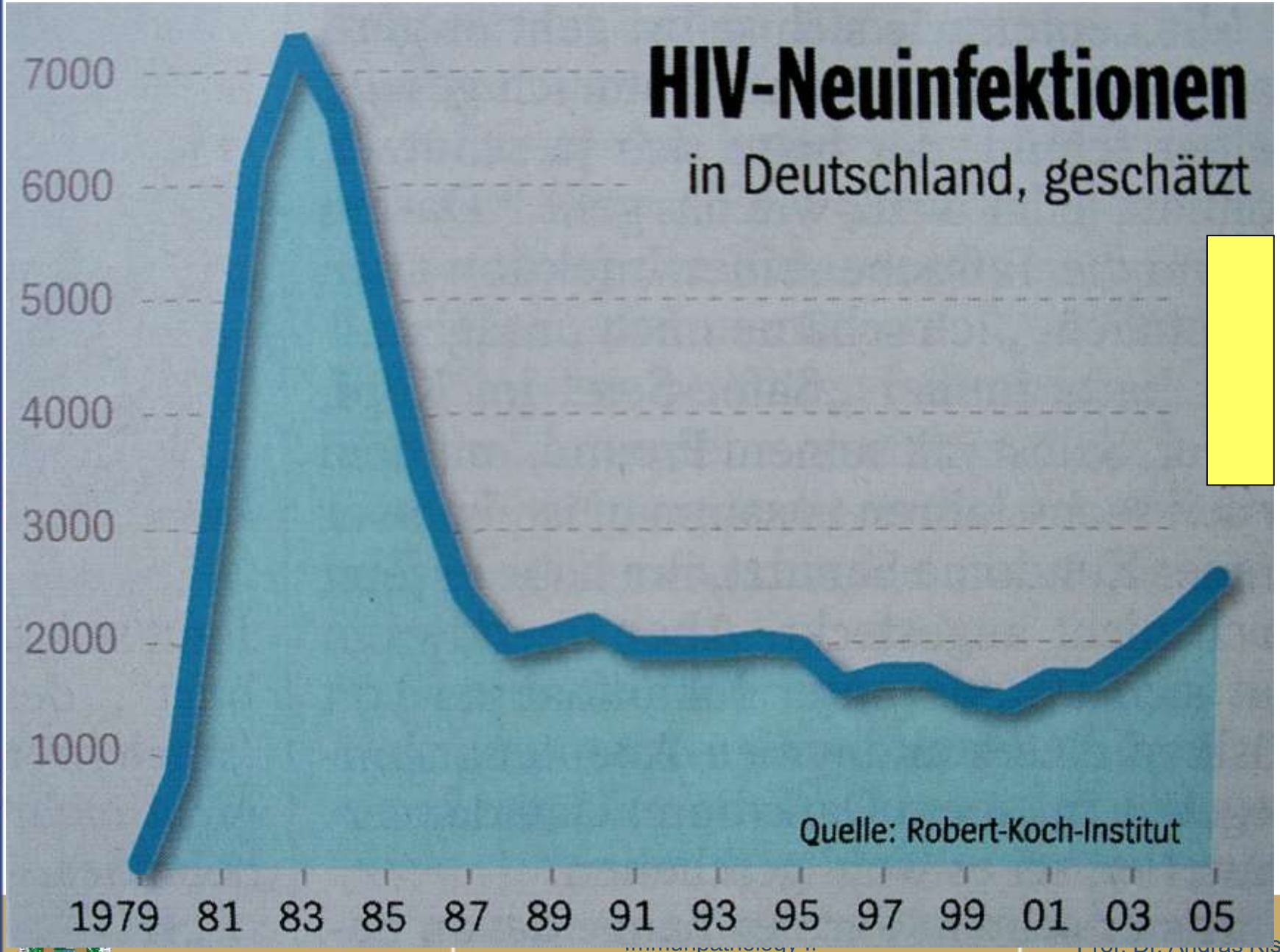

gp41
p17 matrix
gp120
p24 capsid
Lipid bilayer
Integrase
Protease
RNA
Reverse transcriptase

HIV-1

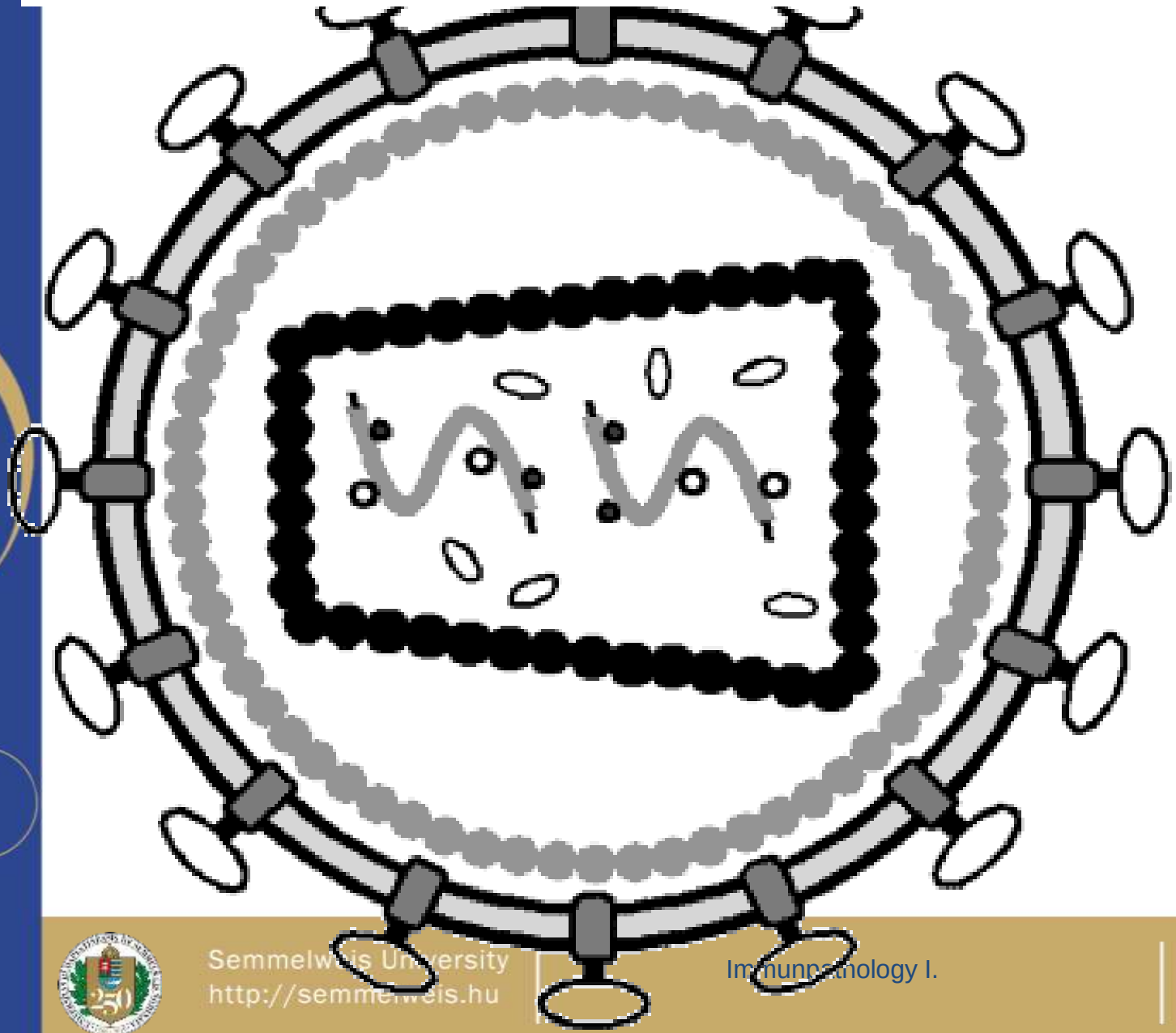

Globale Seuche
HIV-Infizierte 2005, in Millionen
0,72
Europa
1,6
Osteuropa und Zentralasien
1,2
Nordamerika
0,87
Ostasien
0,51
Nordafrika und Naher Osten
0,3
Karibik
7,4
Süd- und Südostasien
1,8
Südamerika
25,8
Schwarzafrika
0,07
Australien, Neuseeland
Quelle: UNAIDS/ World Health Organization

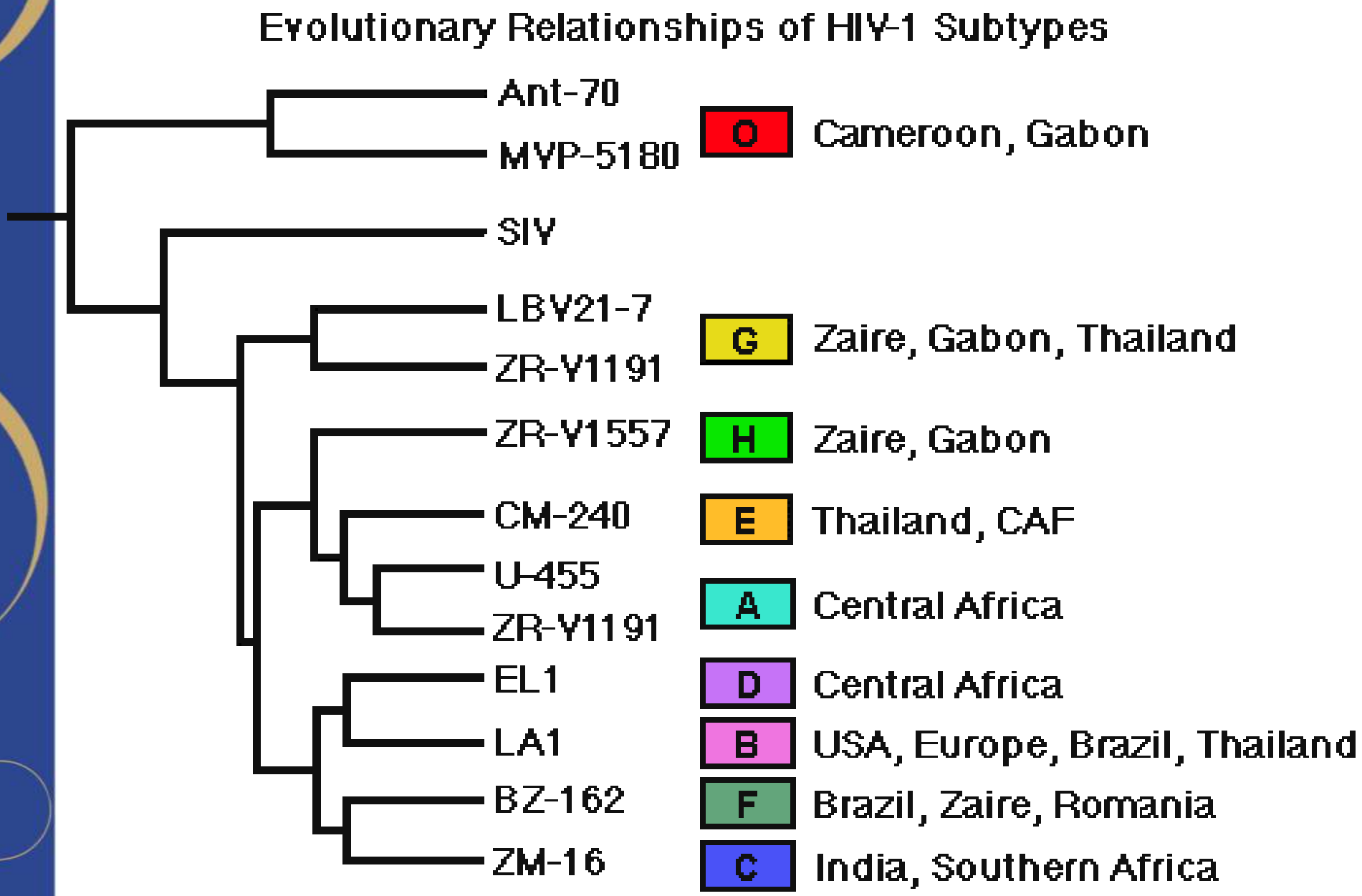
AIDS-Tote in Kenia - apokalyptischer Zustand

in Afrika verheert das Virus Völker und Volkswirtschaften


HIV-Neuinfektionen
in Deutschland, geschätzt
7000
6000
5000
4000
3000
2000
1000
Quelle: Robert-Koch-Institut
1979 81 83 85 87 89 91 93 95 97 99 01 03 05

structural components of human immunodeficiency virus, the key antigenic components are diagrammed here

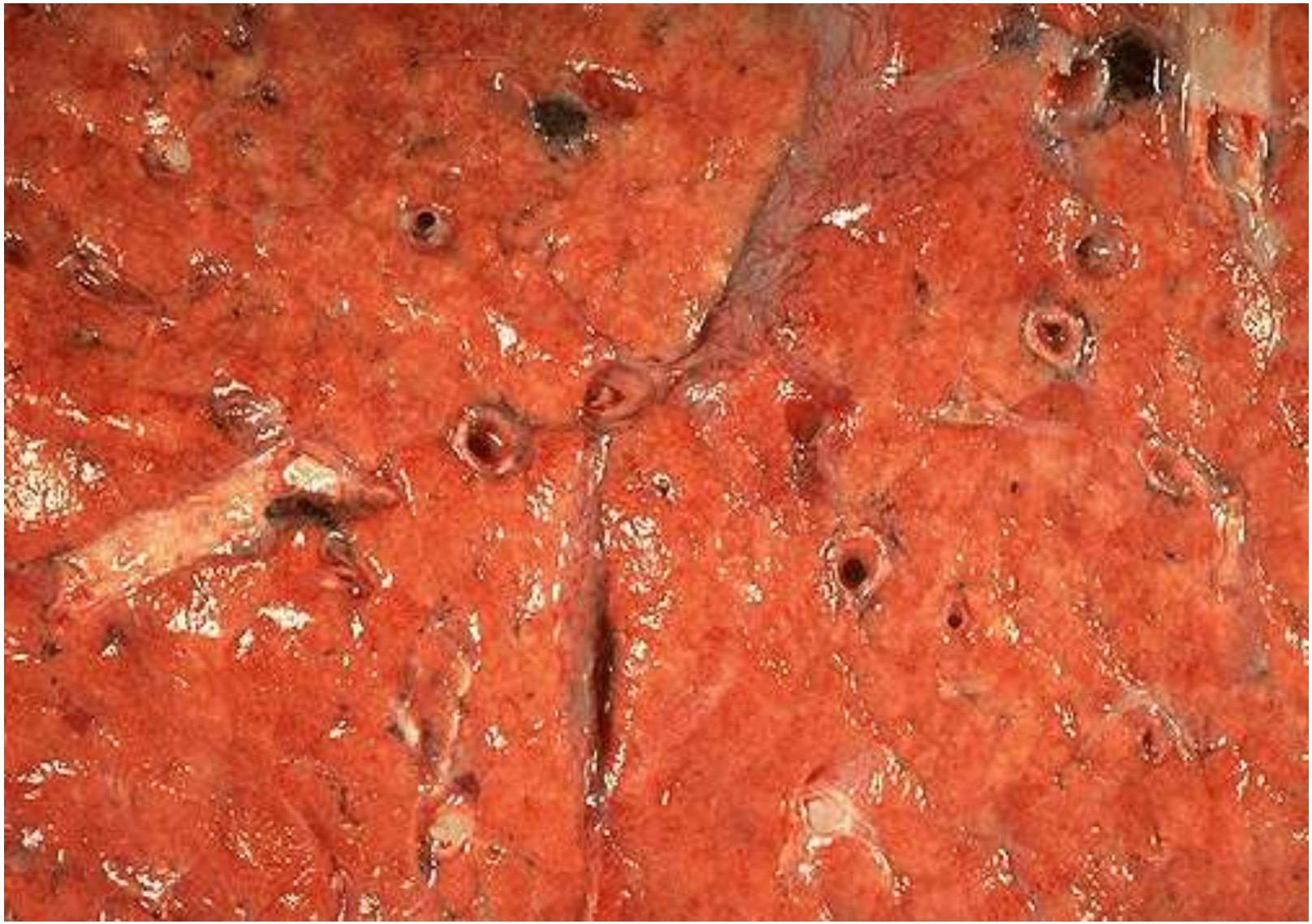




the phylogeny of human immunodeficiency virus (HIV) subtypes and simian immunodeficiency virus (SIV)

Opportunistic Infections in AIDS

Helminths		
	Strongyloides	Gastroenteritis, Sepsis
Protozoa		
	Pneumocystis carinii	Pneumonia
	Toxoplasma gondii	Enzephalitis, disseminnated Form
	Cryptosporidium	Enteritis
	Isospora belli	Enteritis
Fungi		
	Candida albicans	Ösophagitis
	Cryptococcus	Meningitis
	Histoplasmosis	disseminnierte Form
	Coccidiomycosis	disseminnierte Form
Bakteria		
	Mycobacterium avium	disseminnierte Form
	Mycobacterium kansasii	
	Mycobacterium bovis	extrapulmonare Tuberkulose
	Salmonella	Septicaemie
	Bakterille Pneumonie	Rezidivans
Viruses	Herpes simplex	mucocutan
		bronchial
		ösophageal
	CMV	disseminated
Prion	vCJ disease	Leukoencephalopathy

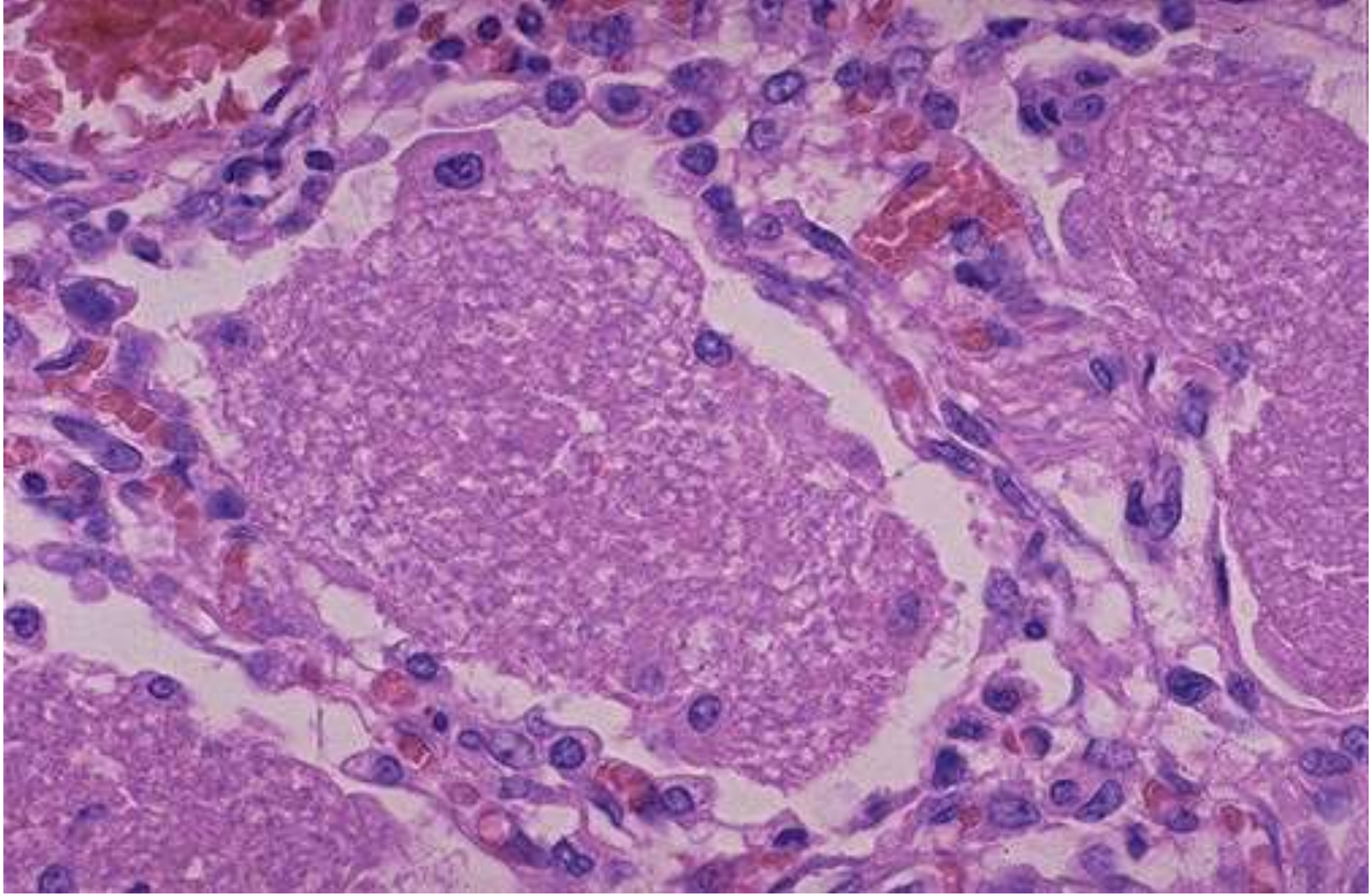


the appearance of Pneumocystis carinii caused extensive pneumonia

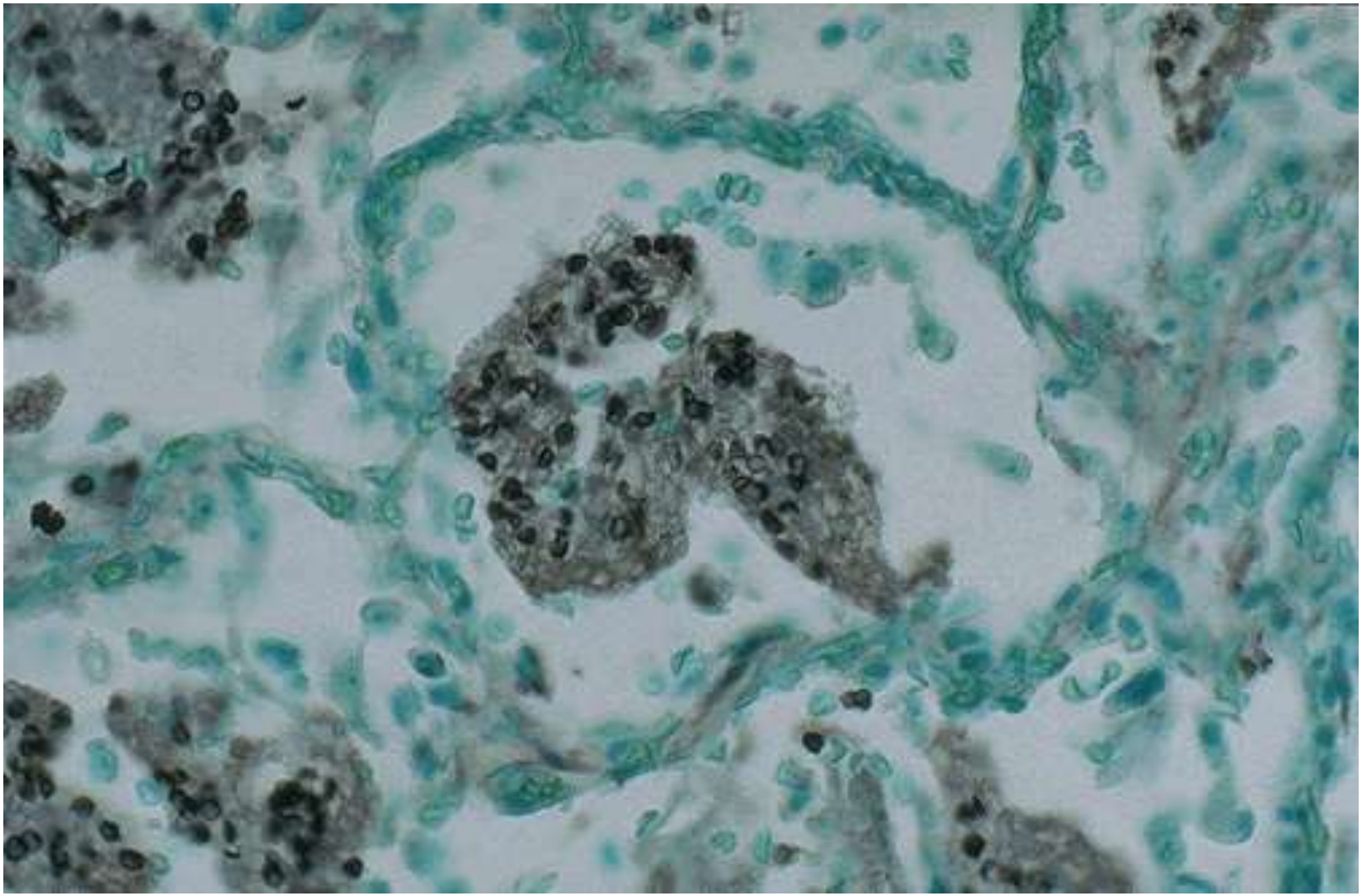
Pneumocystis carinii pneumonia

may produce cavitary change

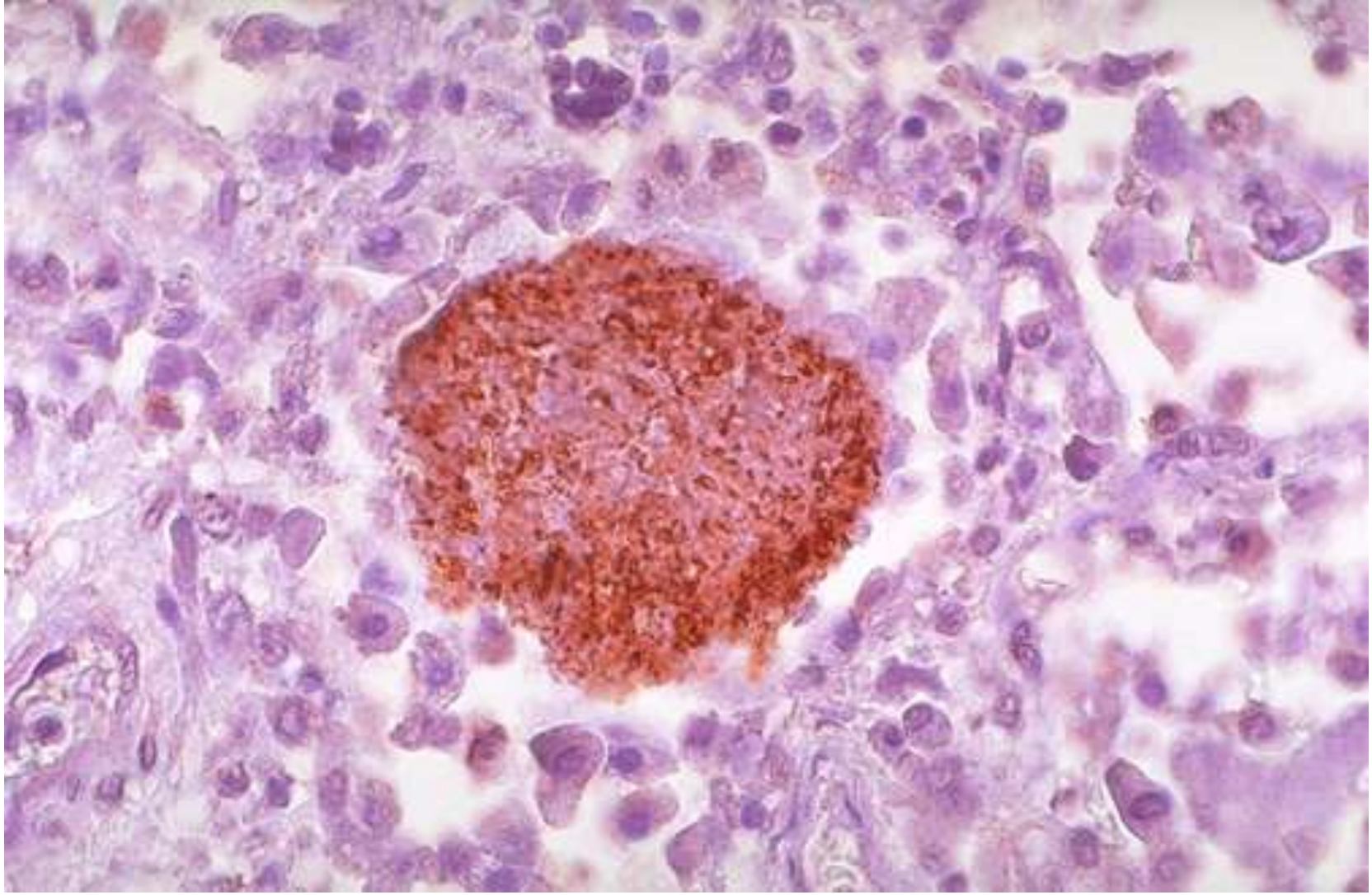
in rare cases



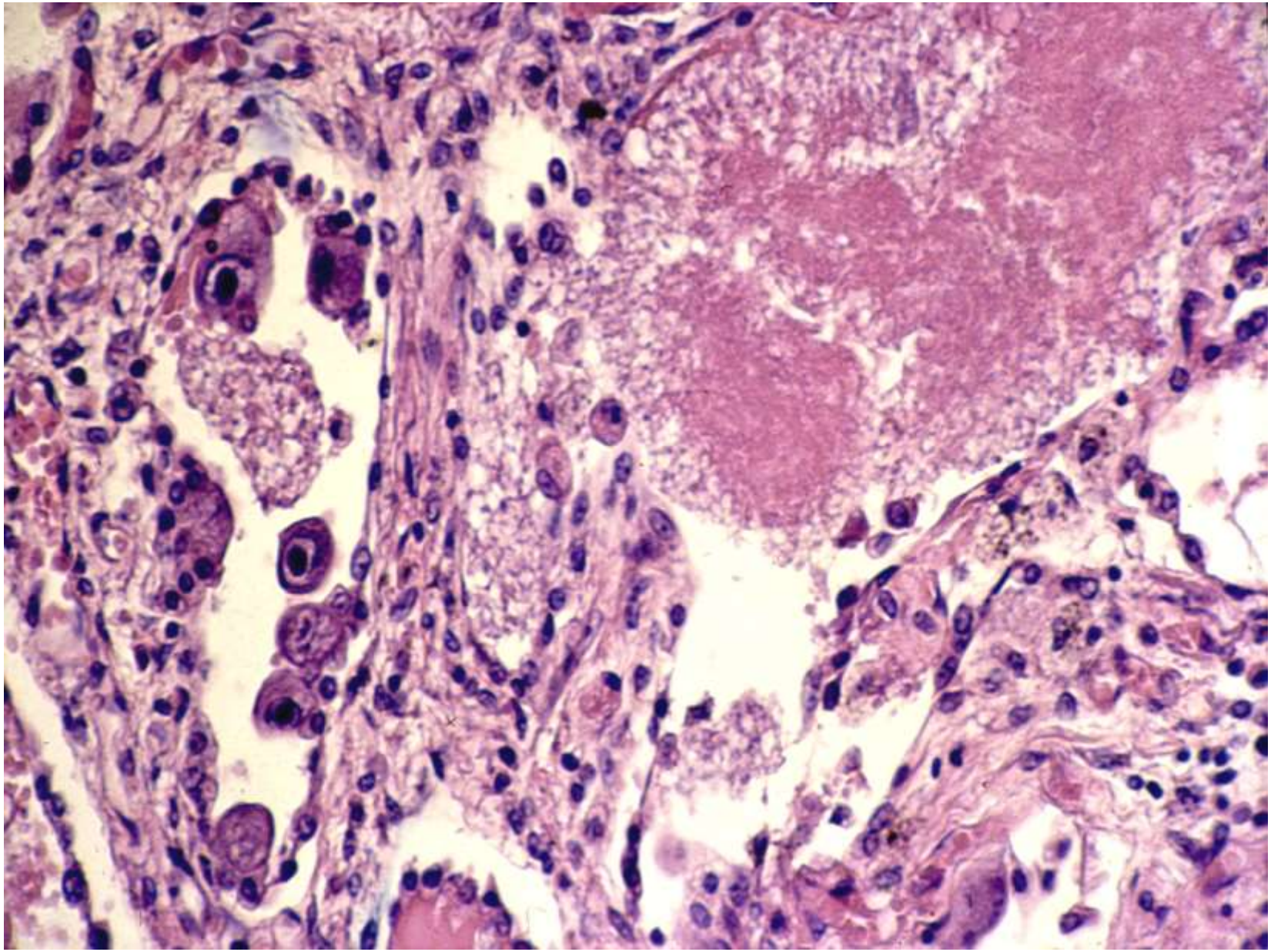
the appearance of Pneumocystis carinii in lung with exudate in nearly every alveolus

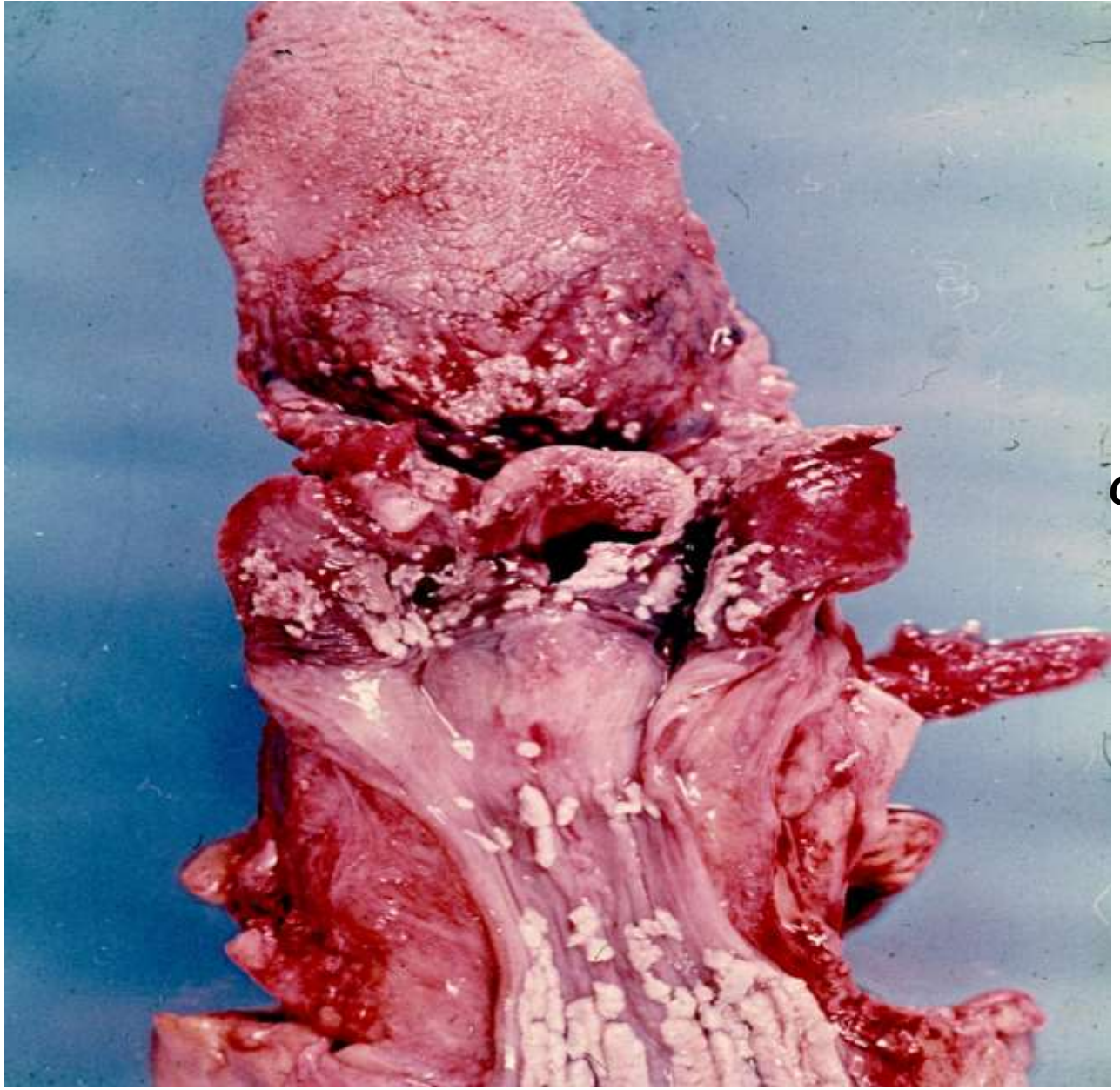


Pneumocystis carinii in lung is demonstrated by the appearance of brown to black cysts in the alveolar exudate - Gömöri stain



immunoperoxidase stain with antibody to Pneumocystis carinii: the brown-red reaction produce is seen highlighting the exudates

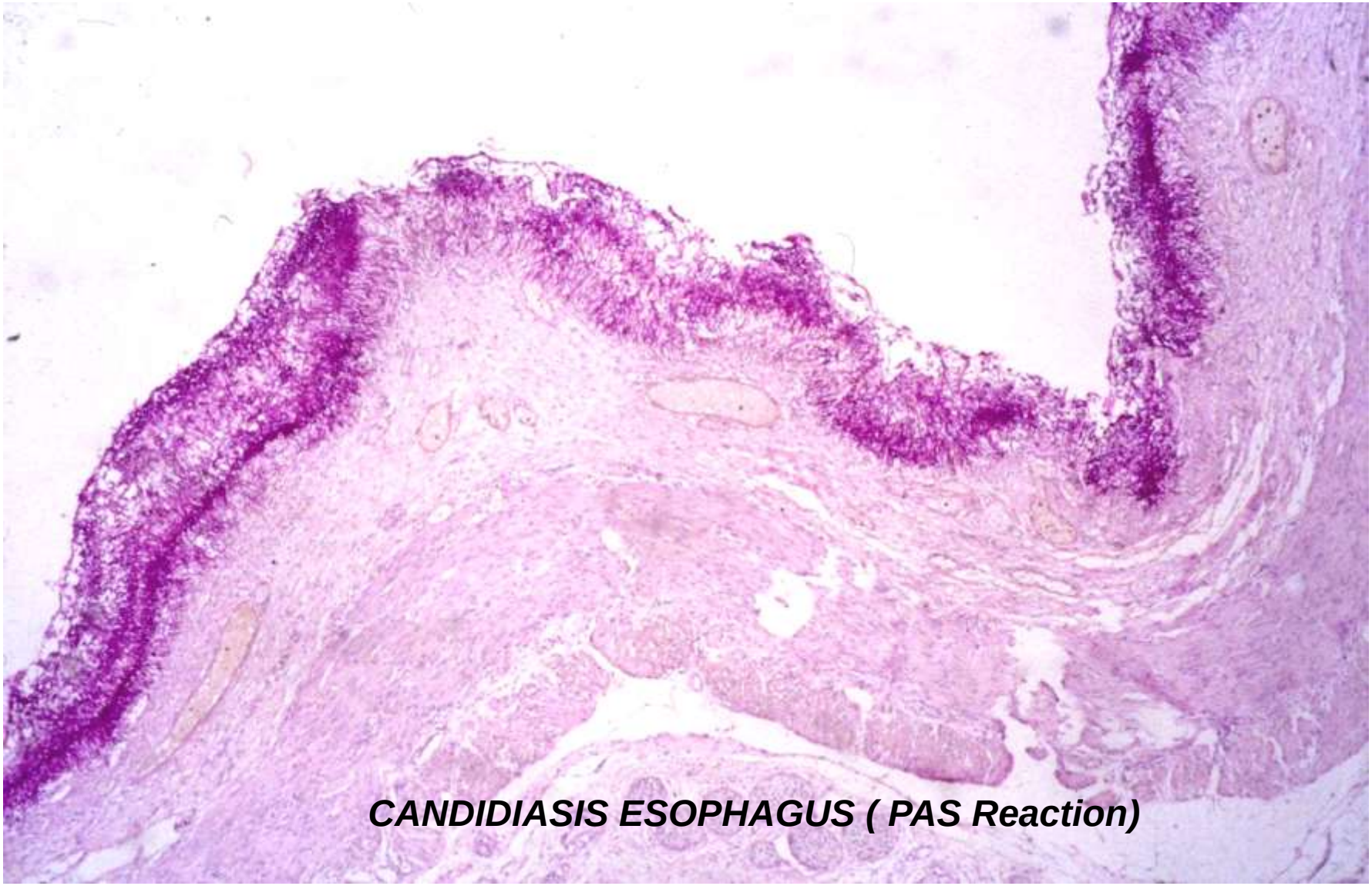




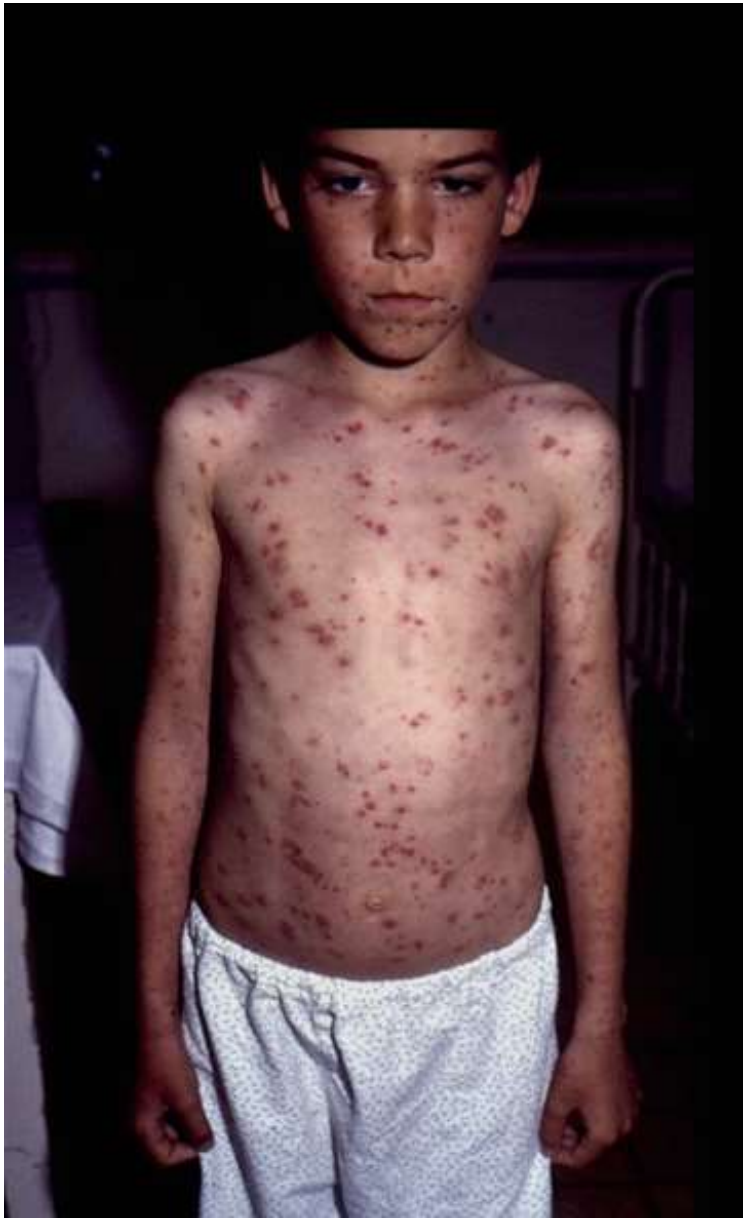
CANDIDIASIS

in

ESOPHAGUS



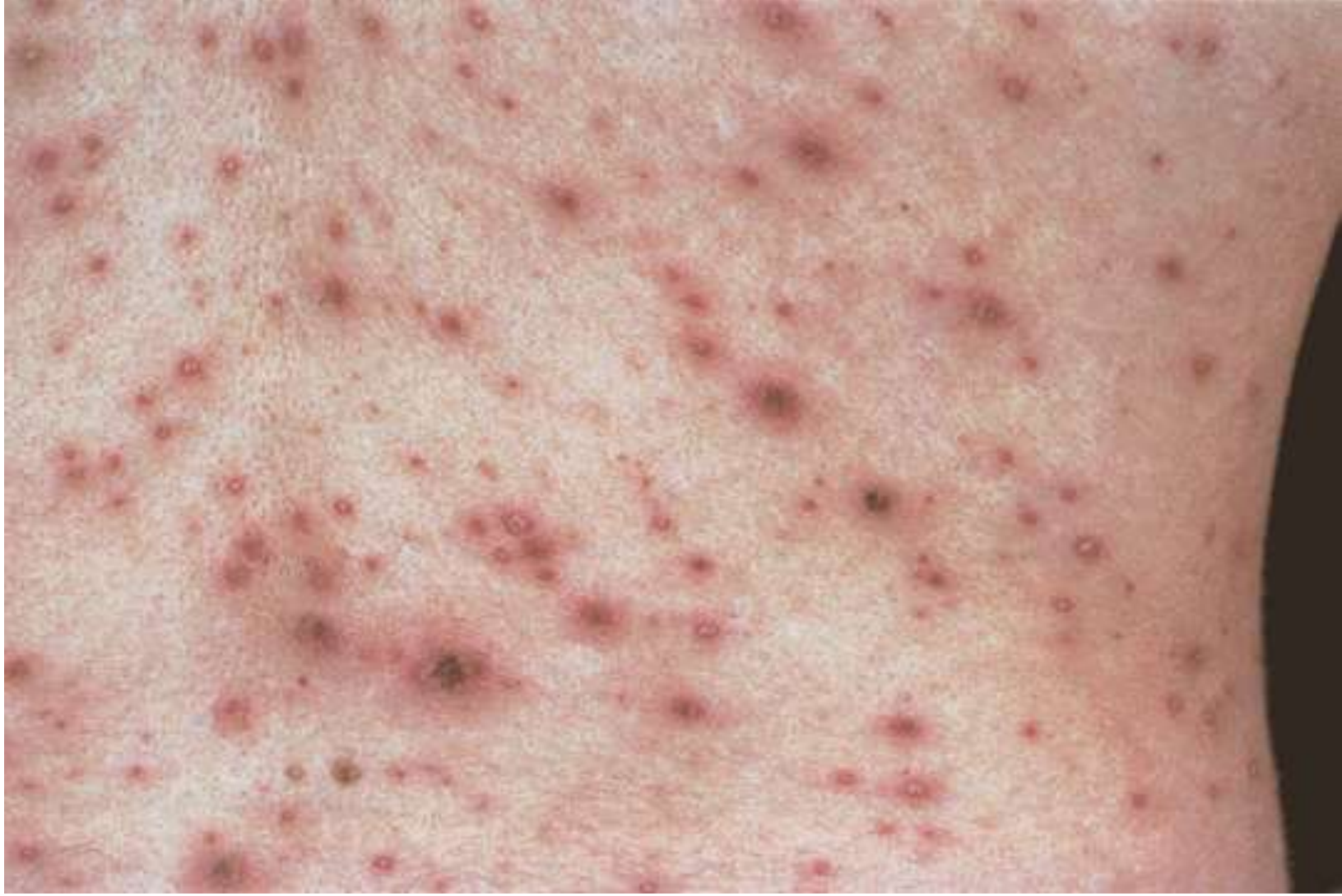
CANDIDIASIS ESOPHAGUS (PAS Reaction)



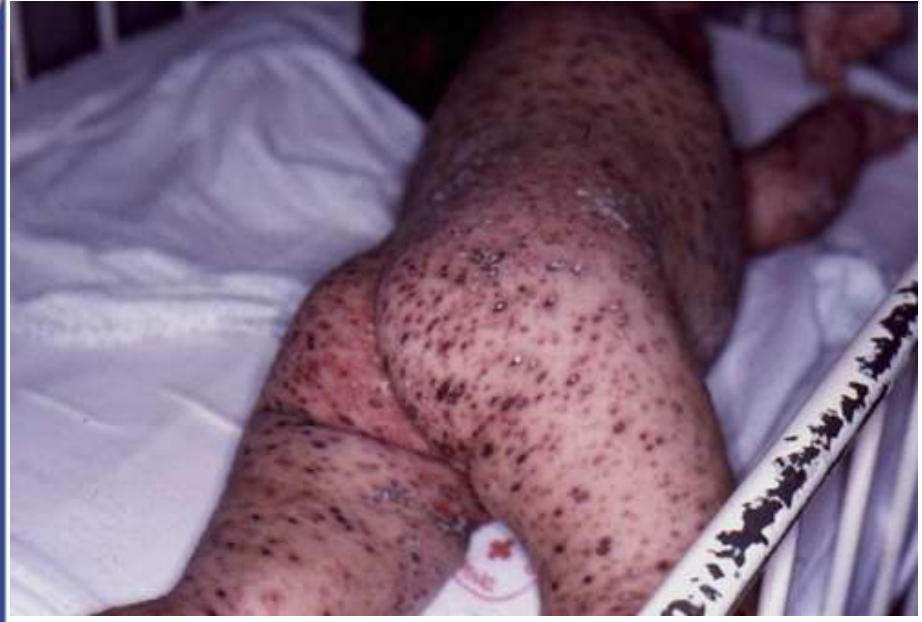
Varicella

Varicella-Zoster-Virus

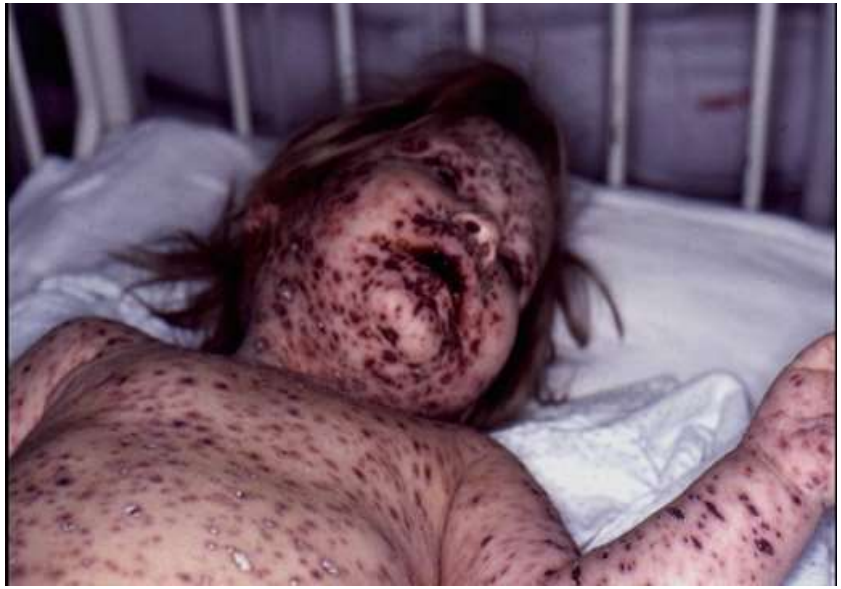
(air born-, rarely contact infection), very infectious !

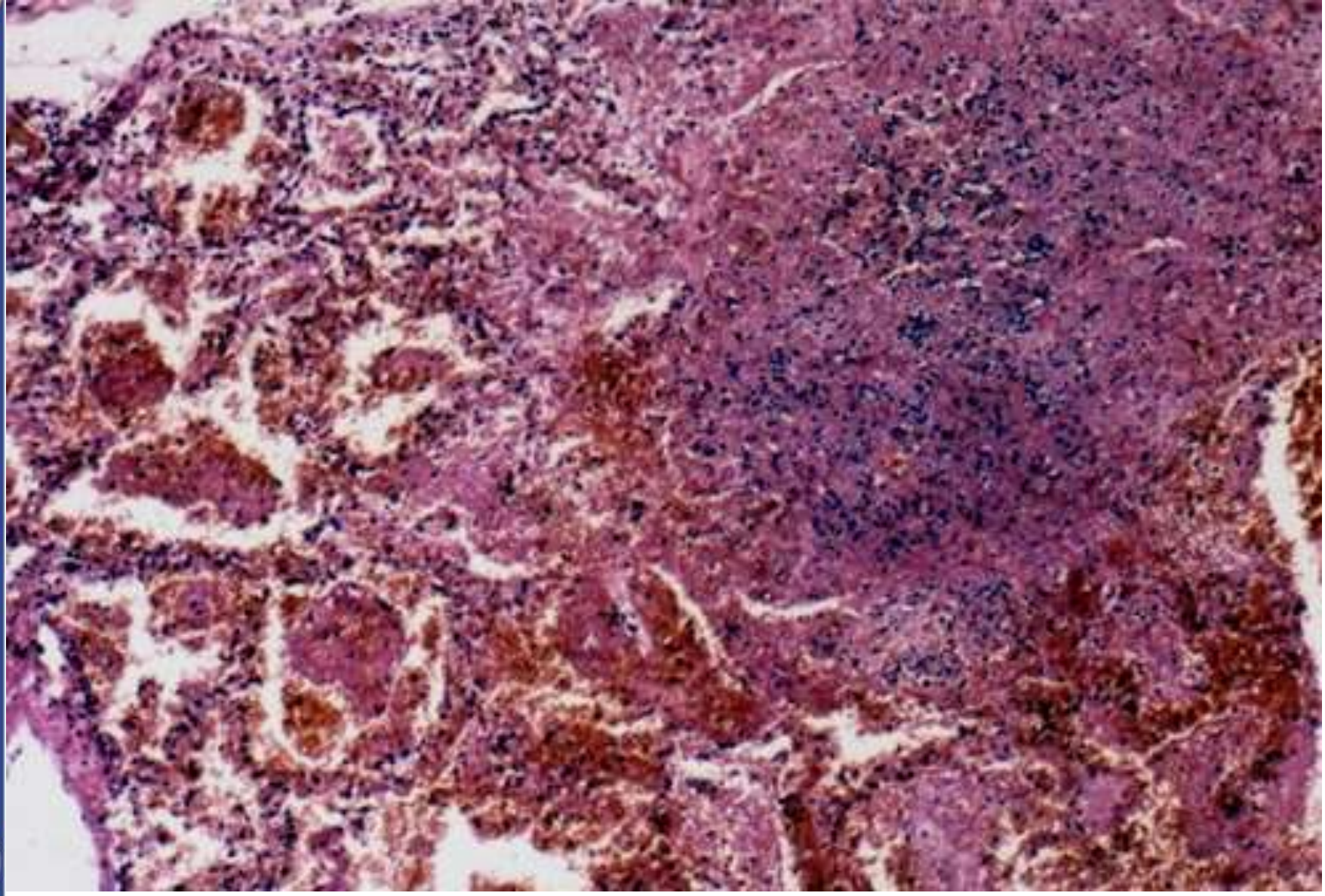


Varicella exanthems an the body

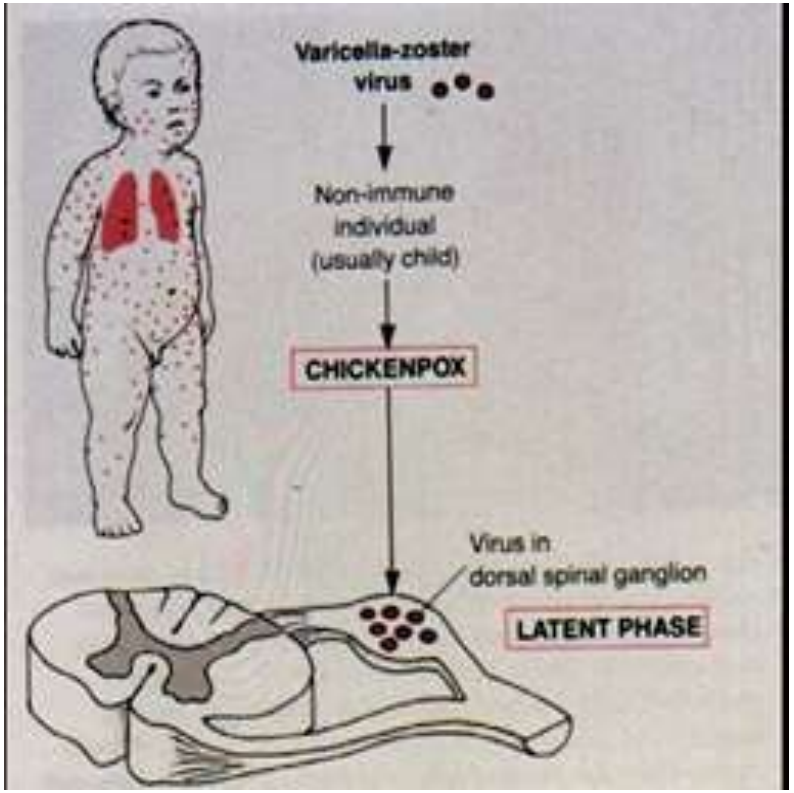


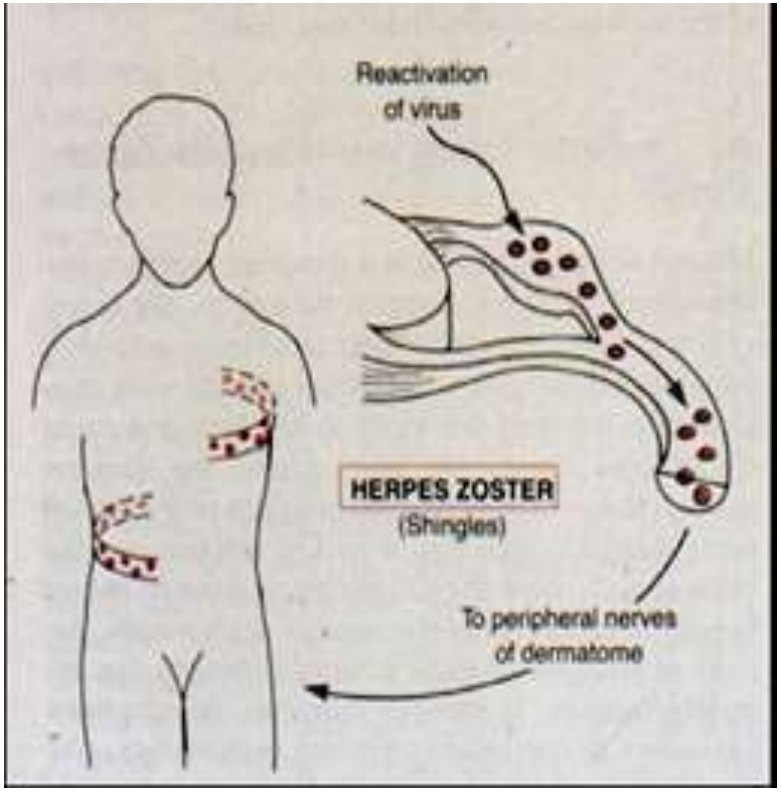
Varoicella and acute lymphoid leukemia - ALL





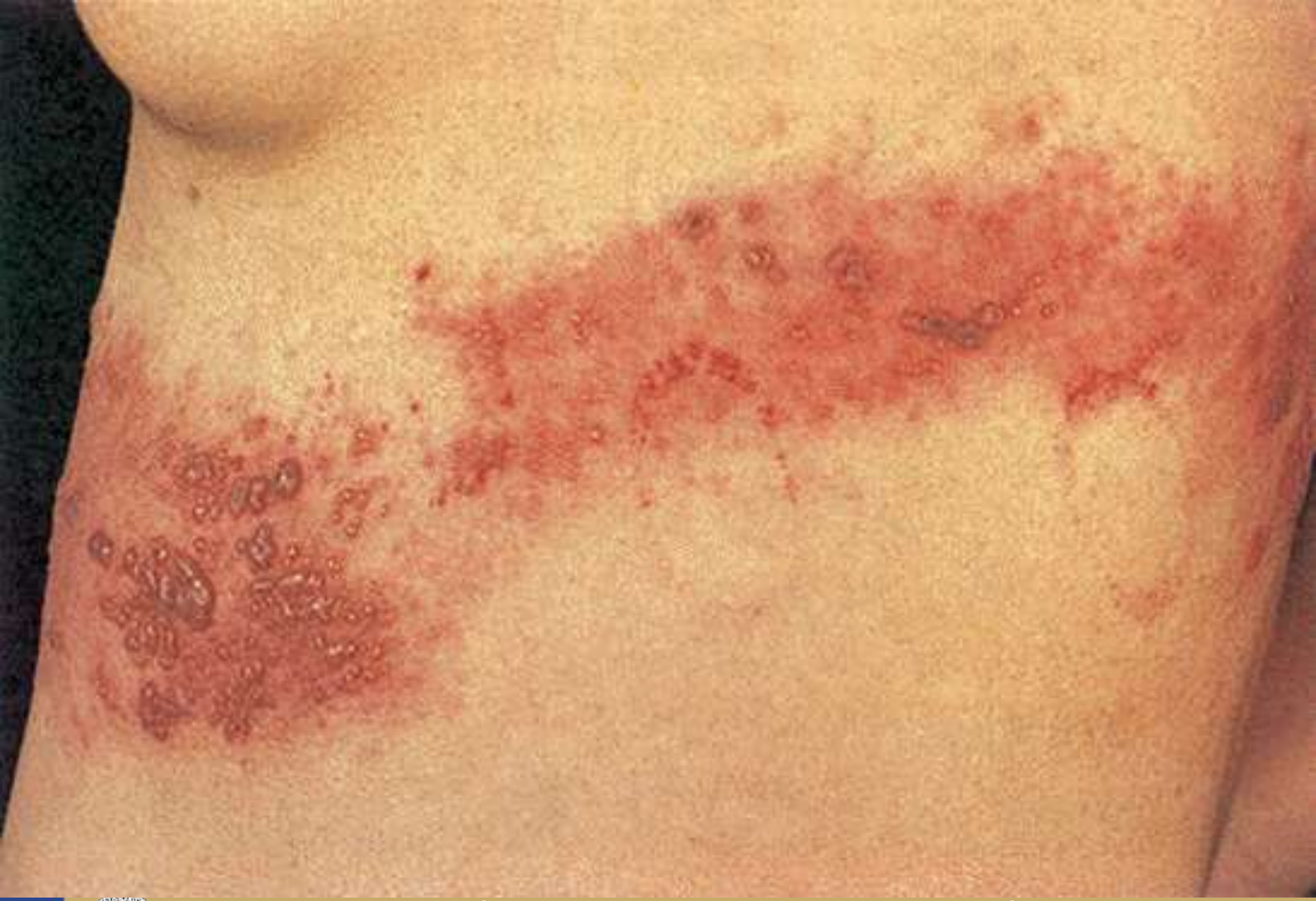
necrotizing pneumonia in varicella generalisata



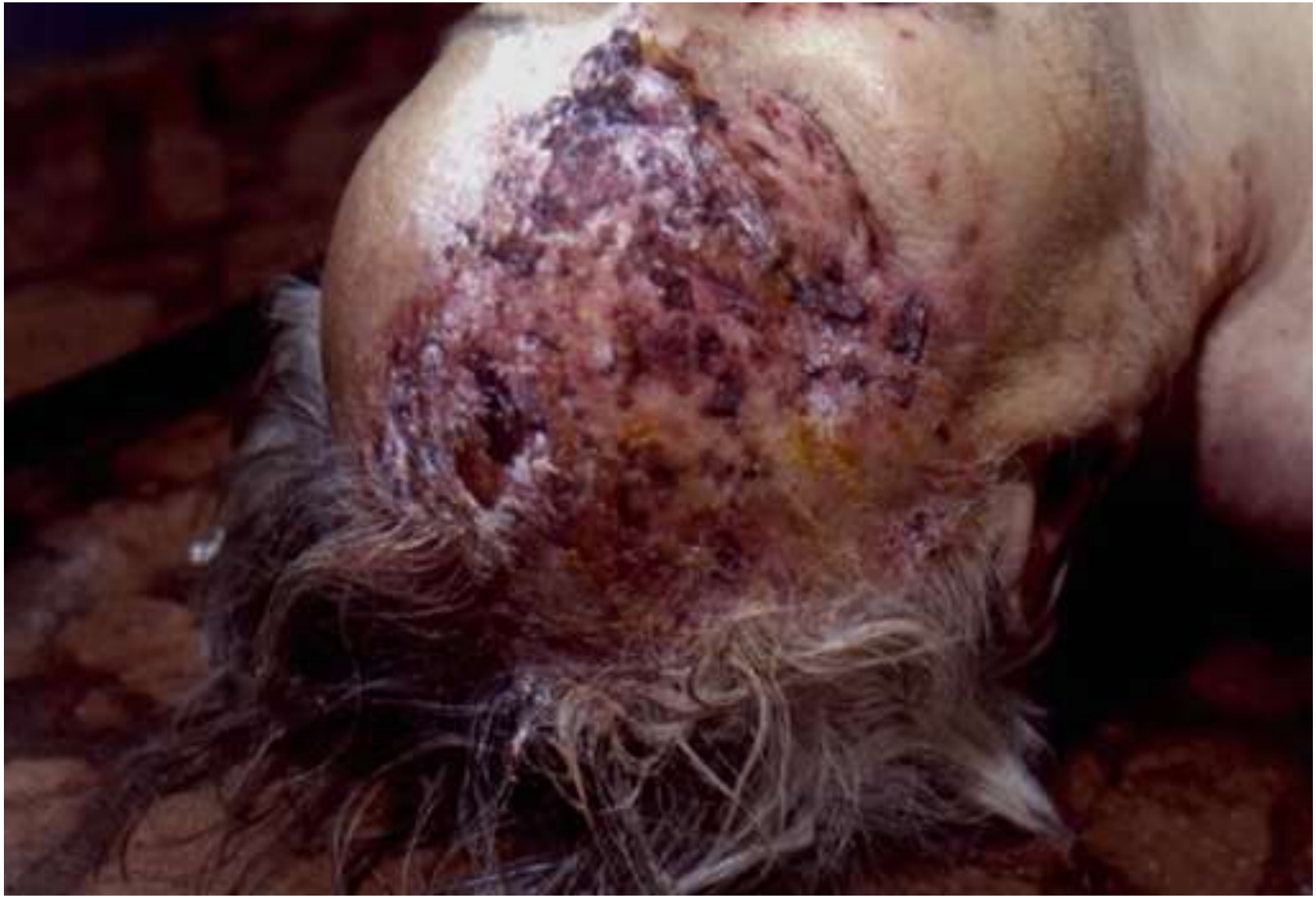


Varicella

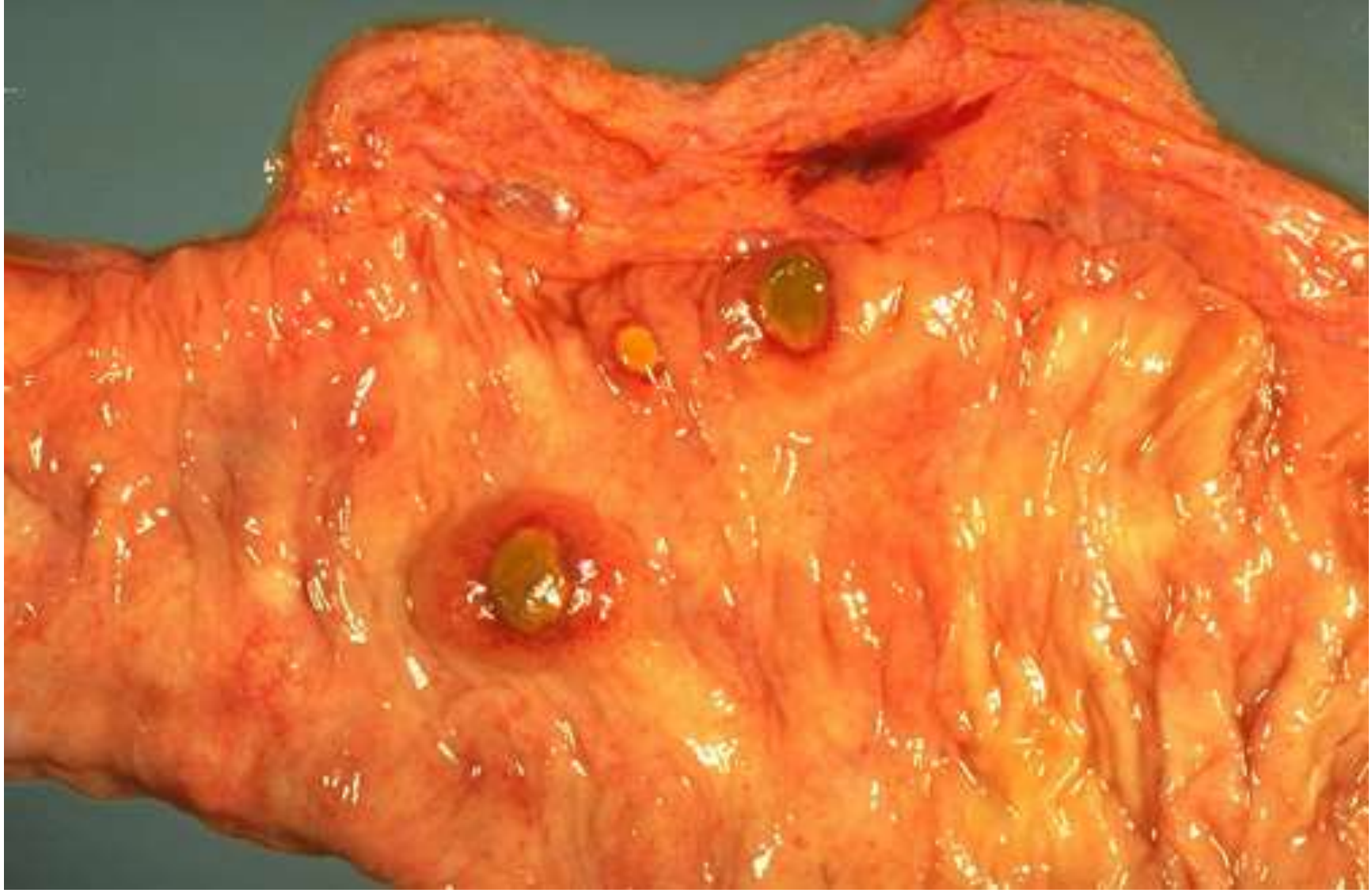
Herpes zoster



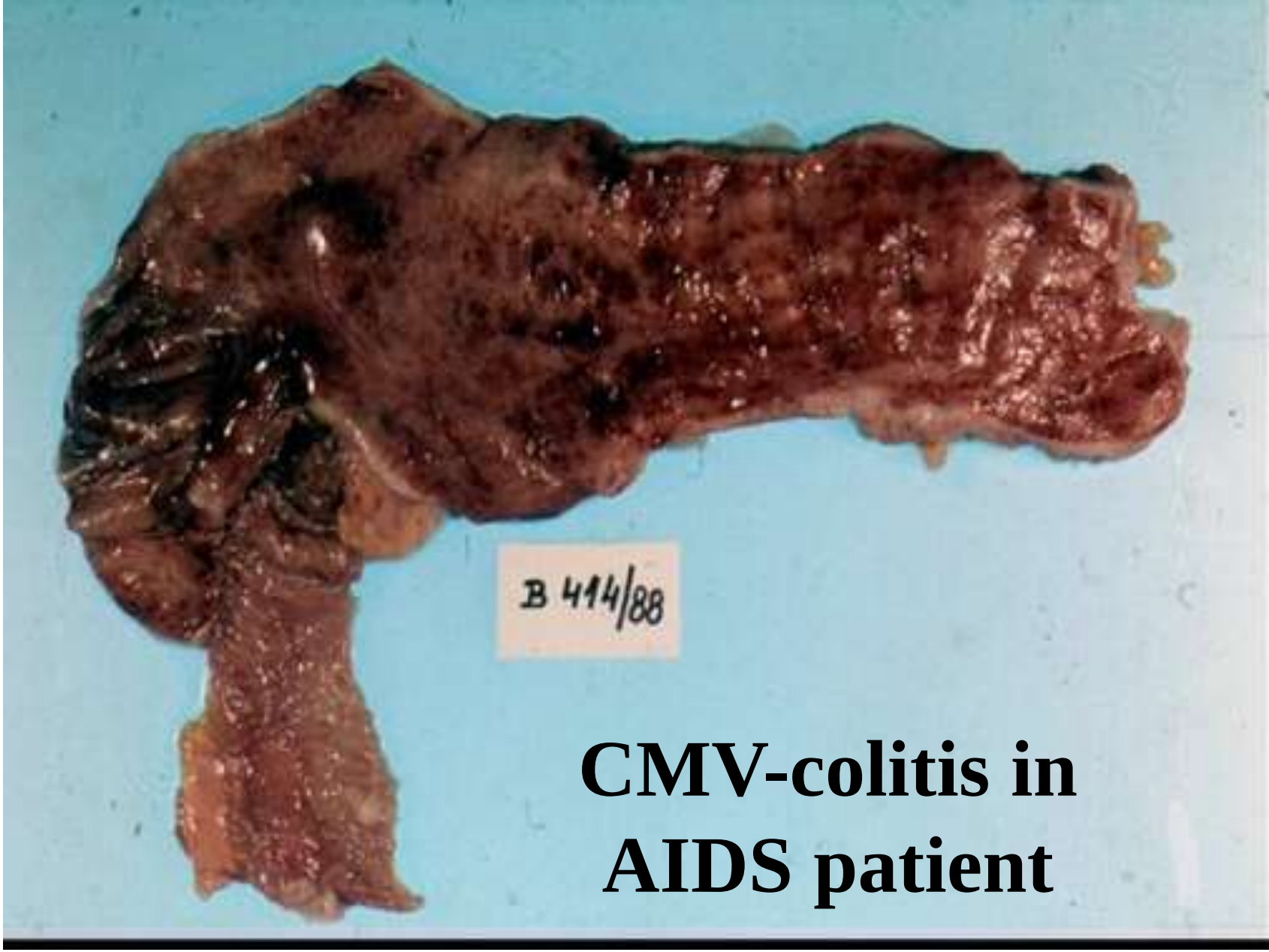
thorakaler Herpes zoster (Zoster intercostalis)



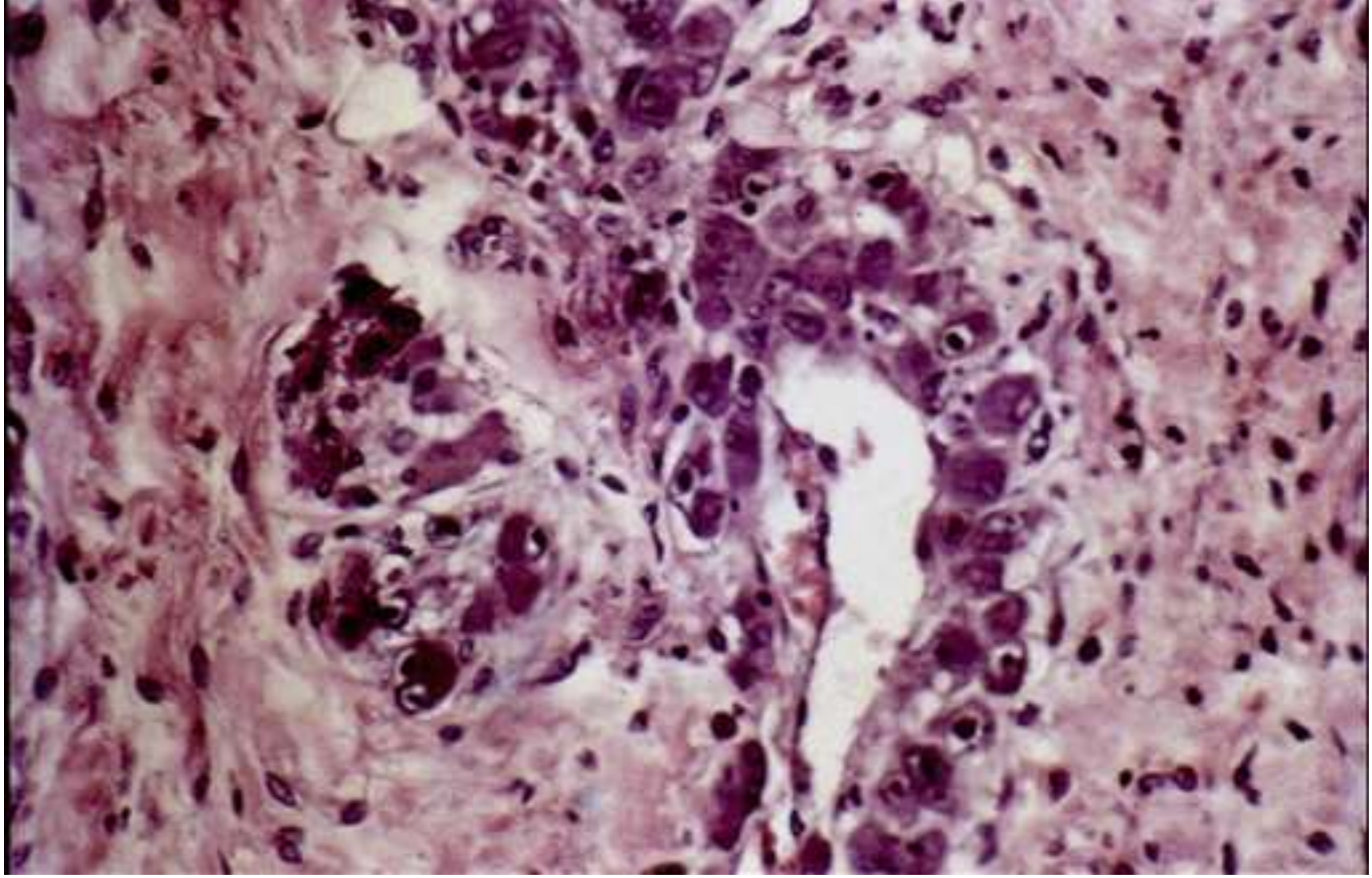
herpes zooster ophtalmicus



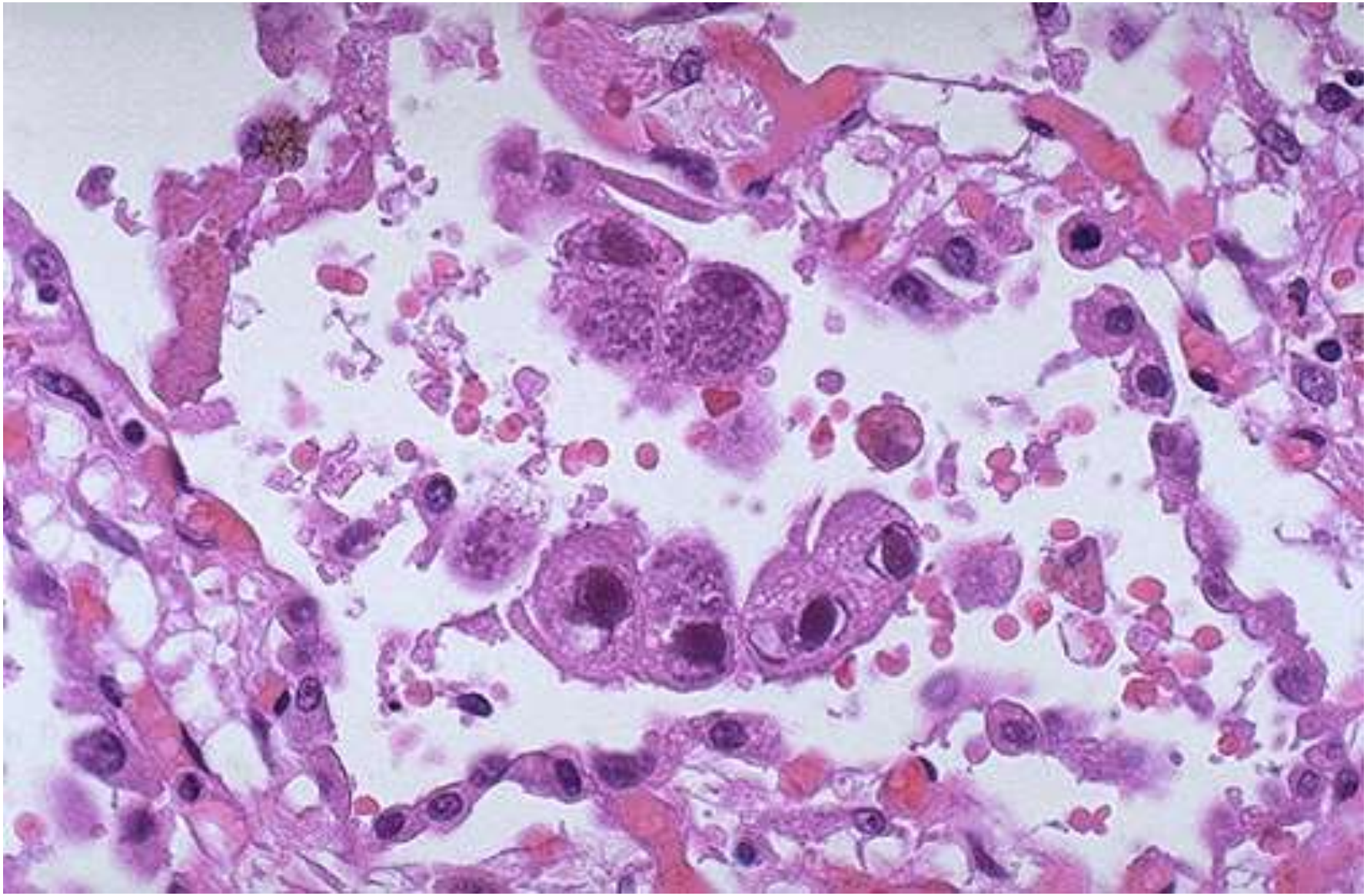
CMV infection has no characteristic gross appearance in any organ - cecal ulceration



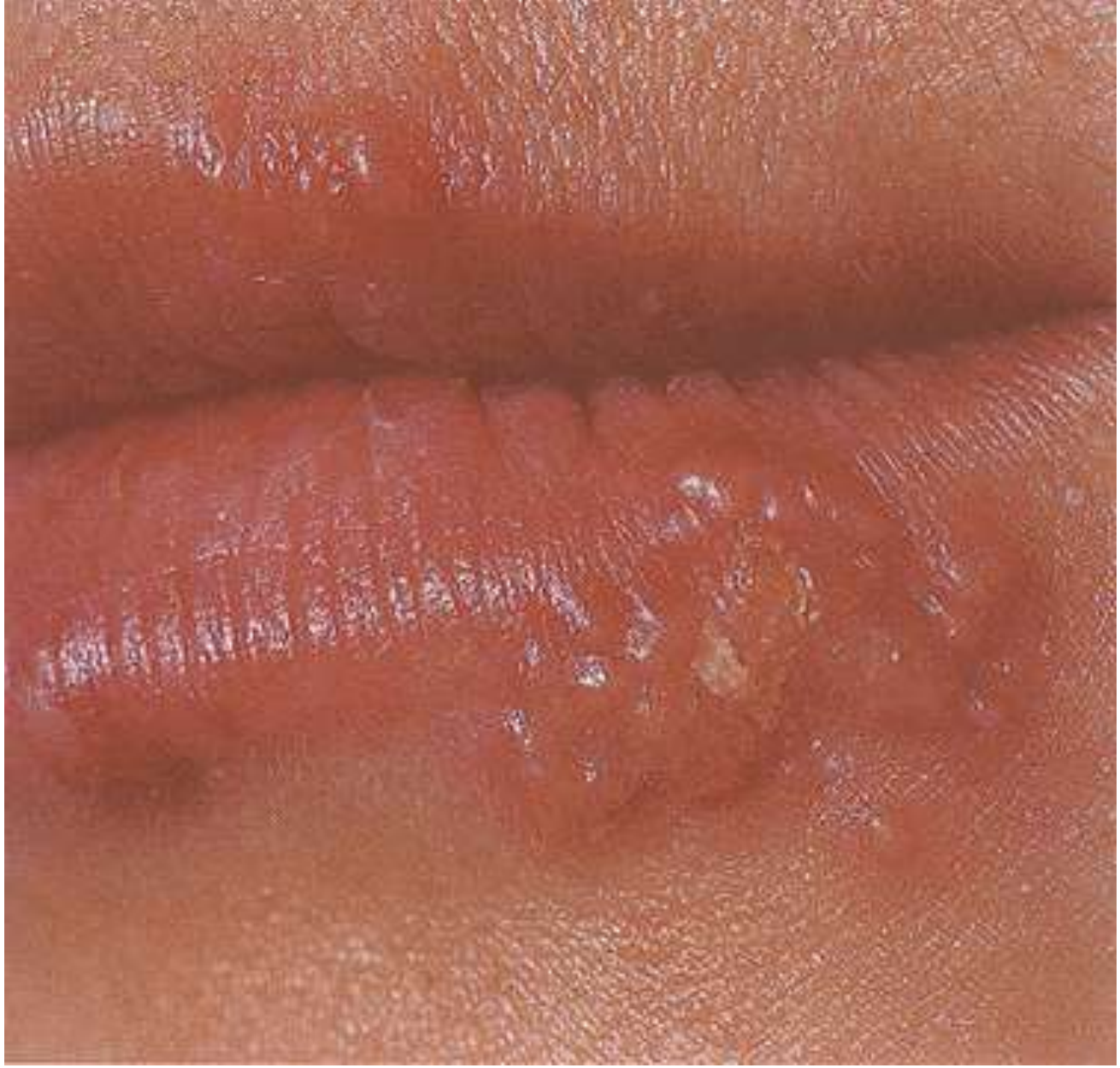
CMV-colitis in AIDS patient



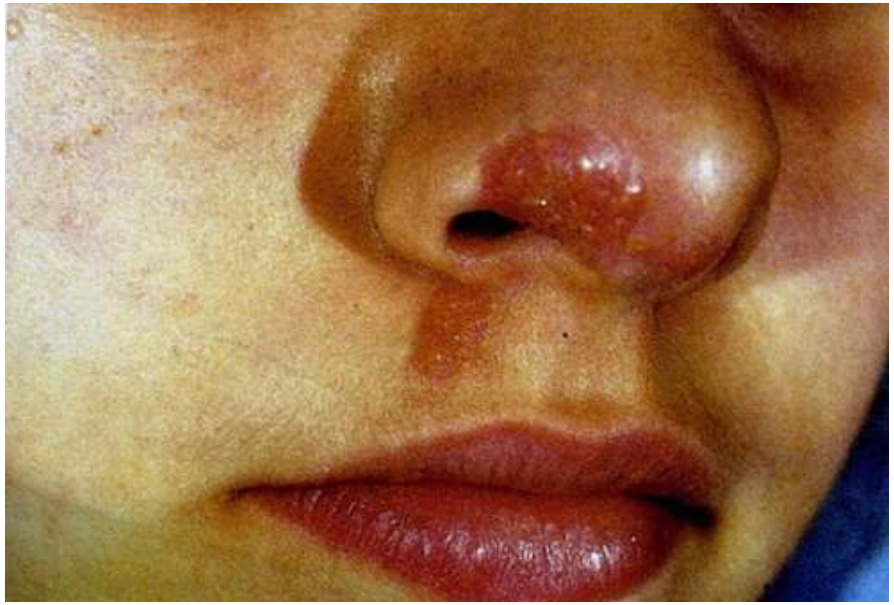
CMV-vasculitis in AIDS patient



CMV often produce a pneumonia - CMV inclusions in lung

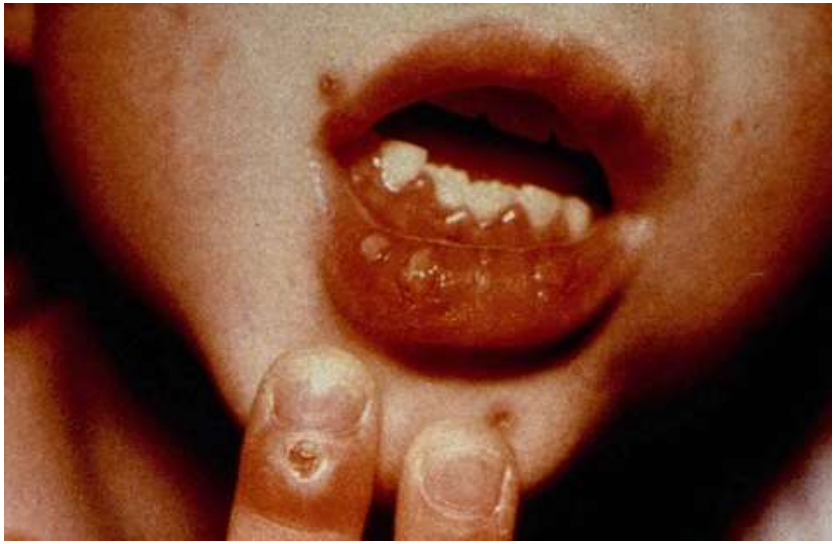


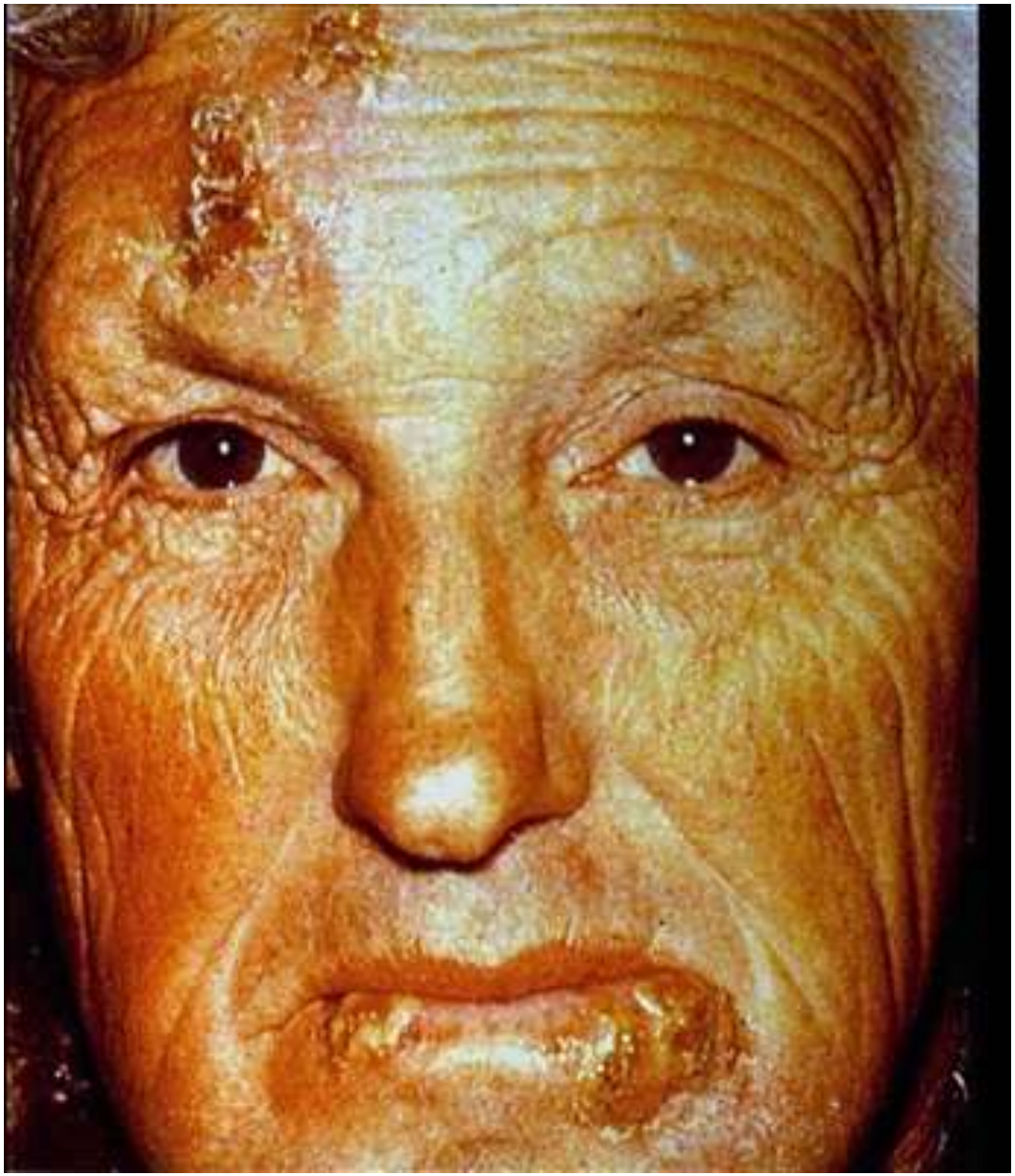
Herpes simplex on the lips



HSV-1 Infection

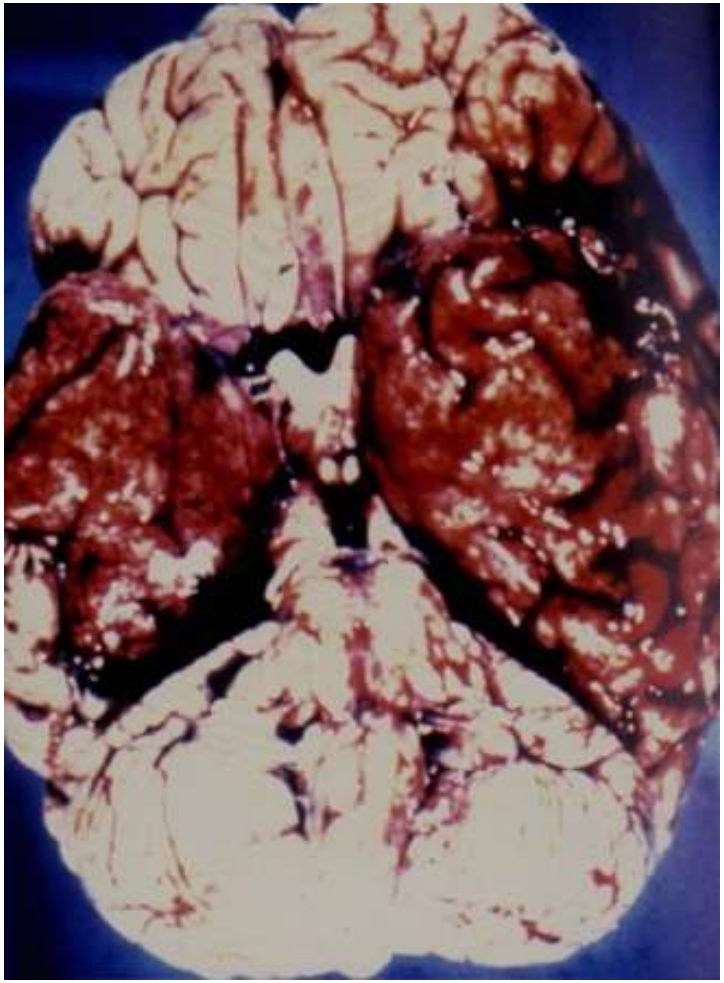
Cold sore

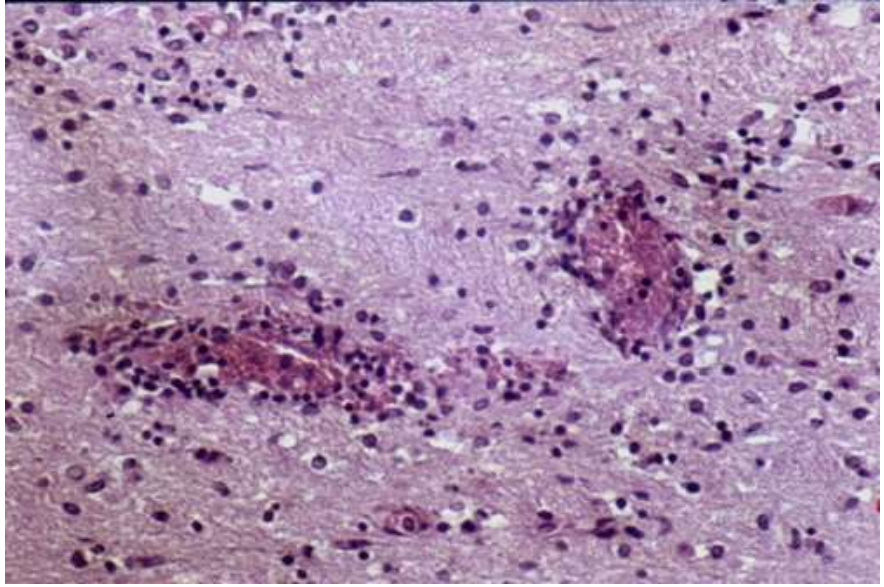


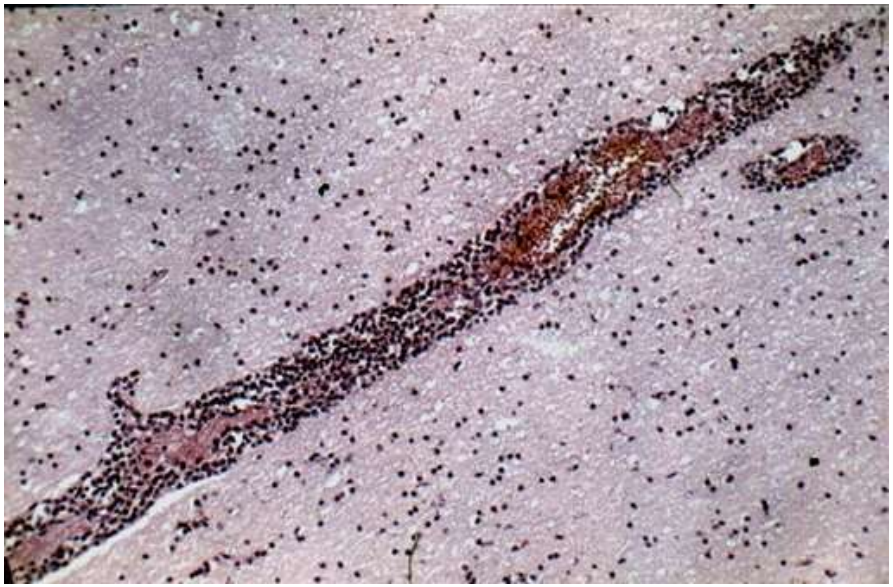


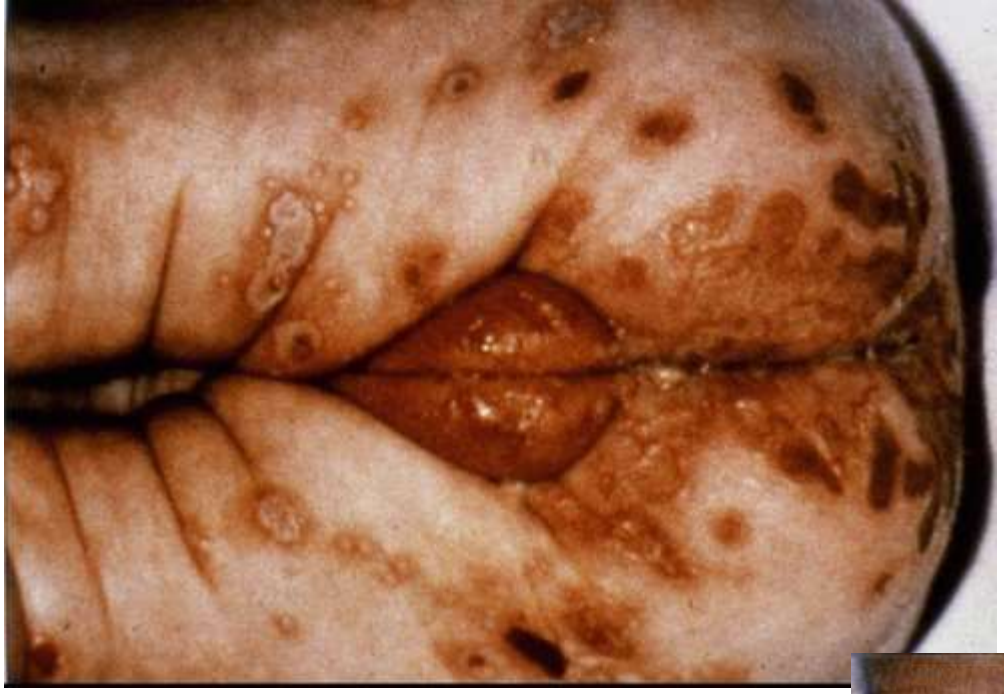
HSV-1 Infektion in Leukamie-Patient

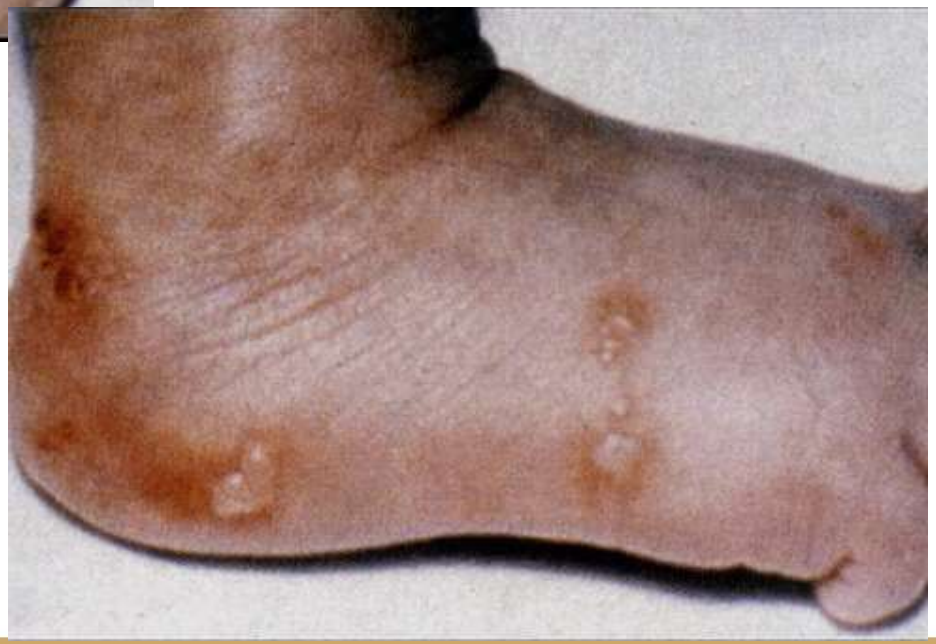
HSV-1 Infektion

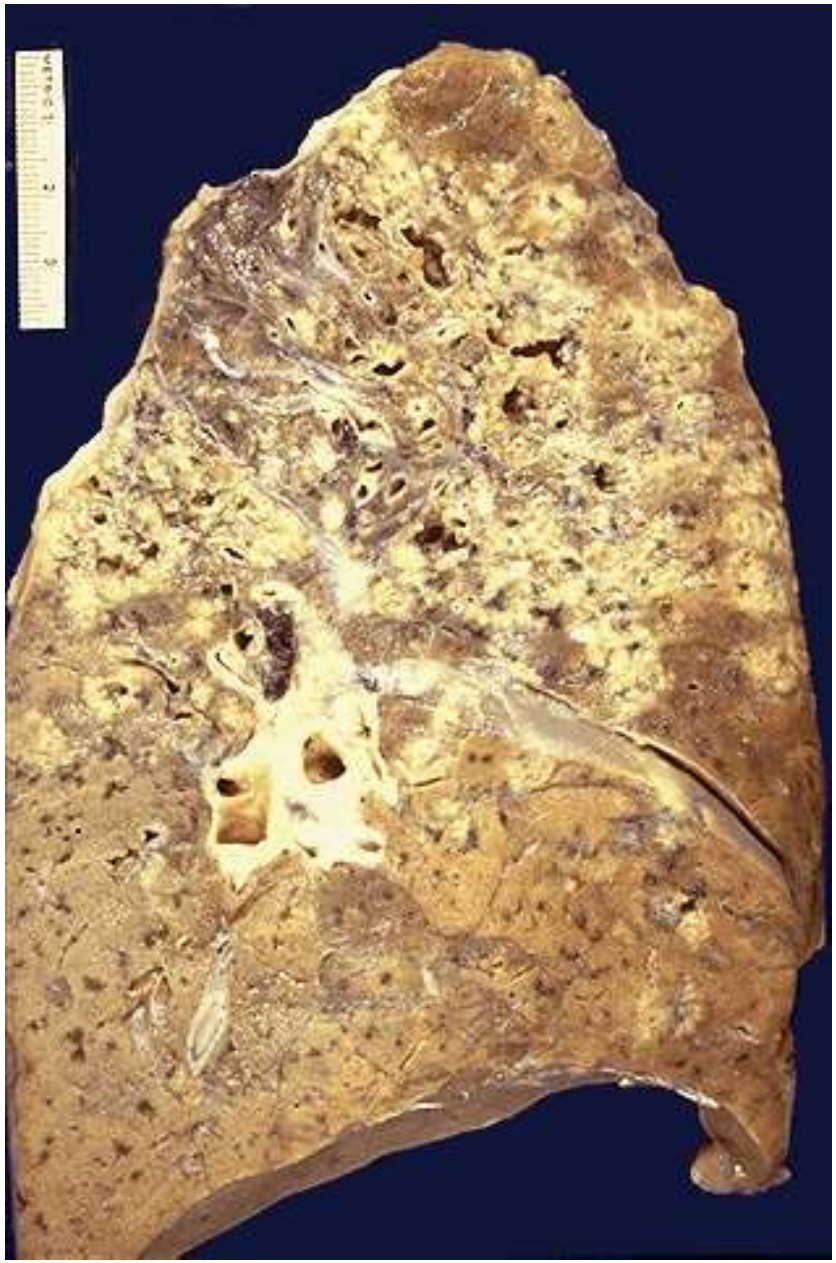




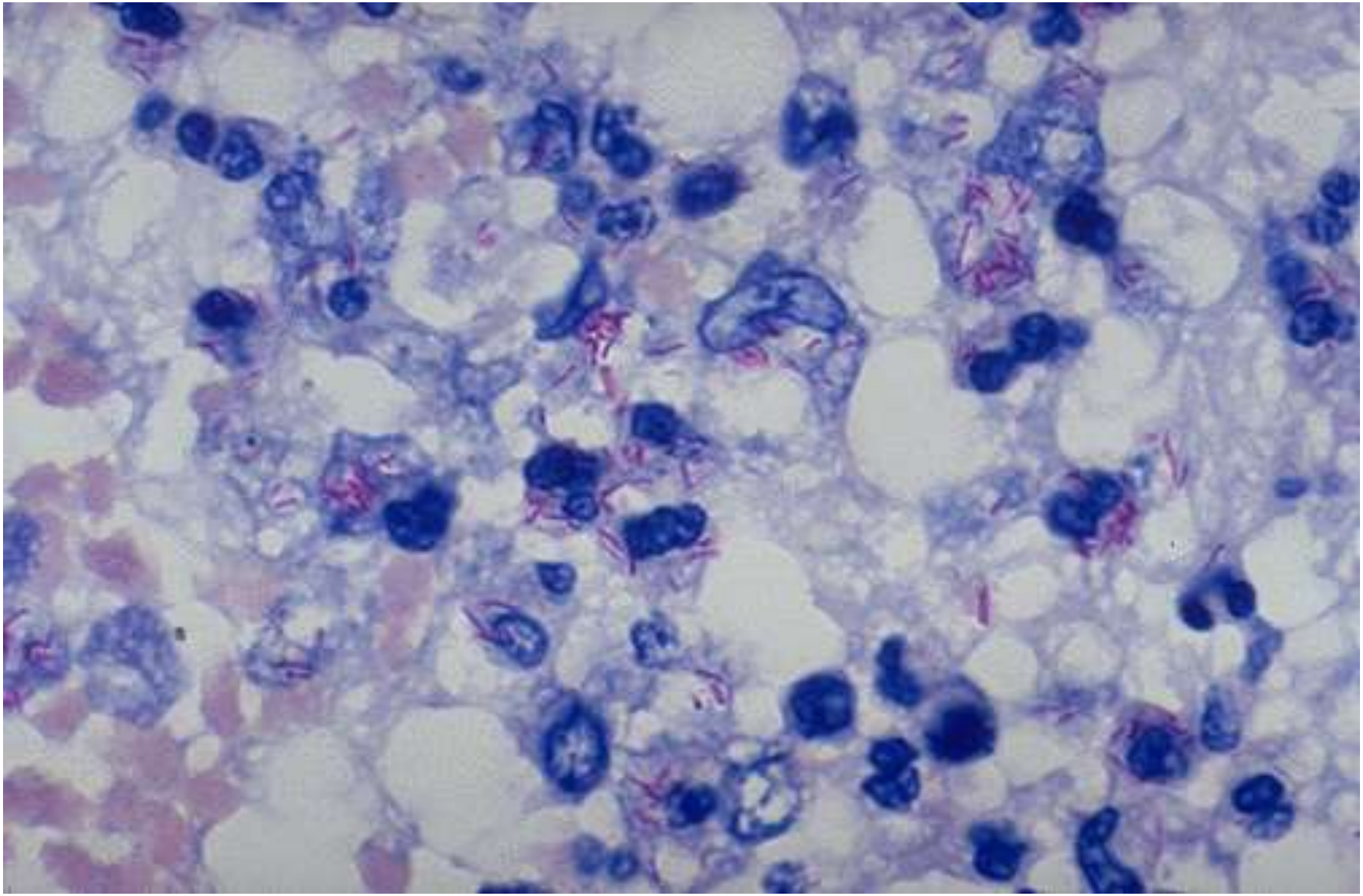








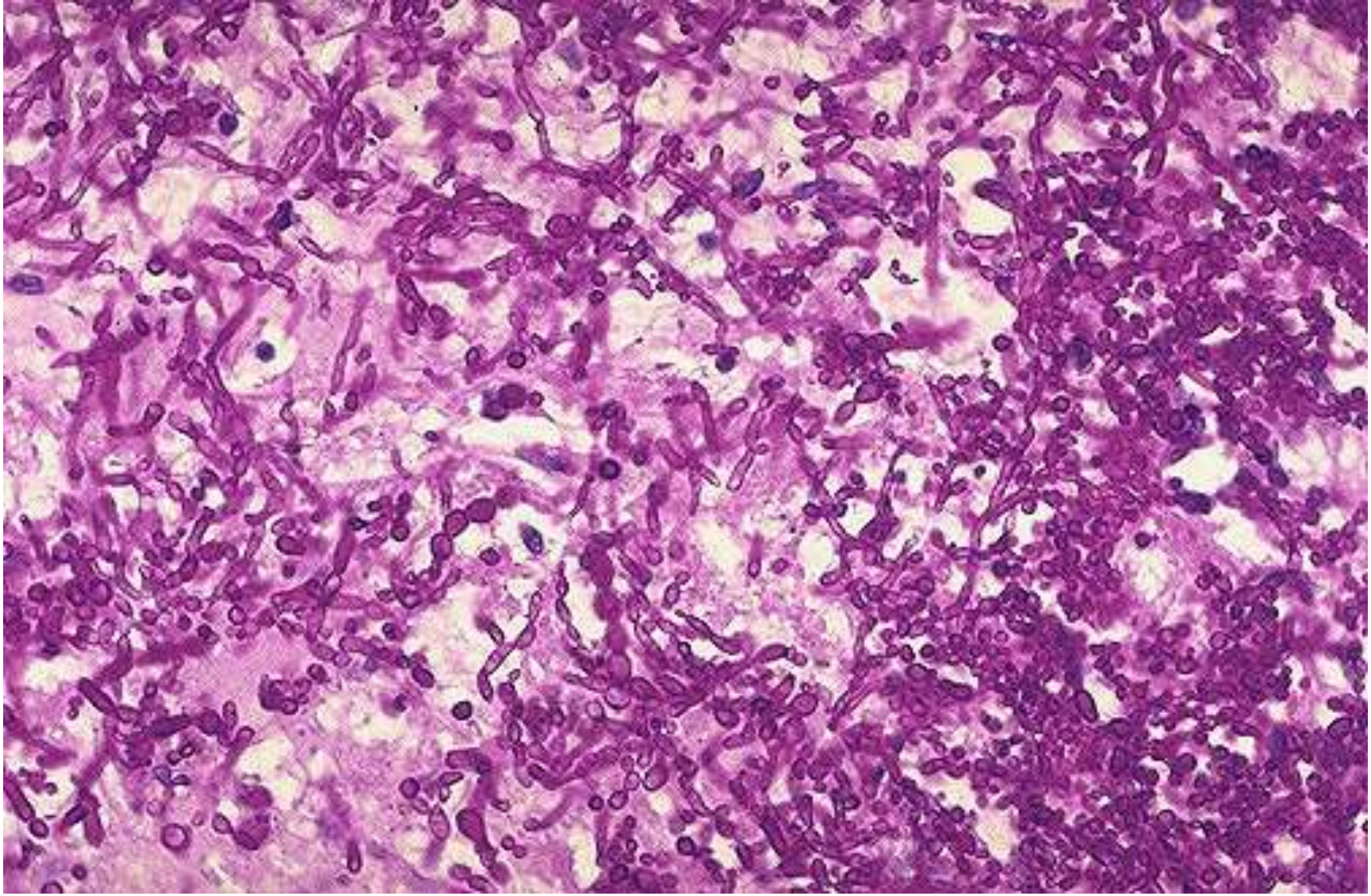
Mycobacterium tuberculosis infection of lung, with upper lung field granulomatous and cavitary disease - AIDS patient



Mycobacterium tuberculosis - Ziehl-Neelsen Färbung

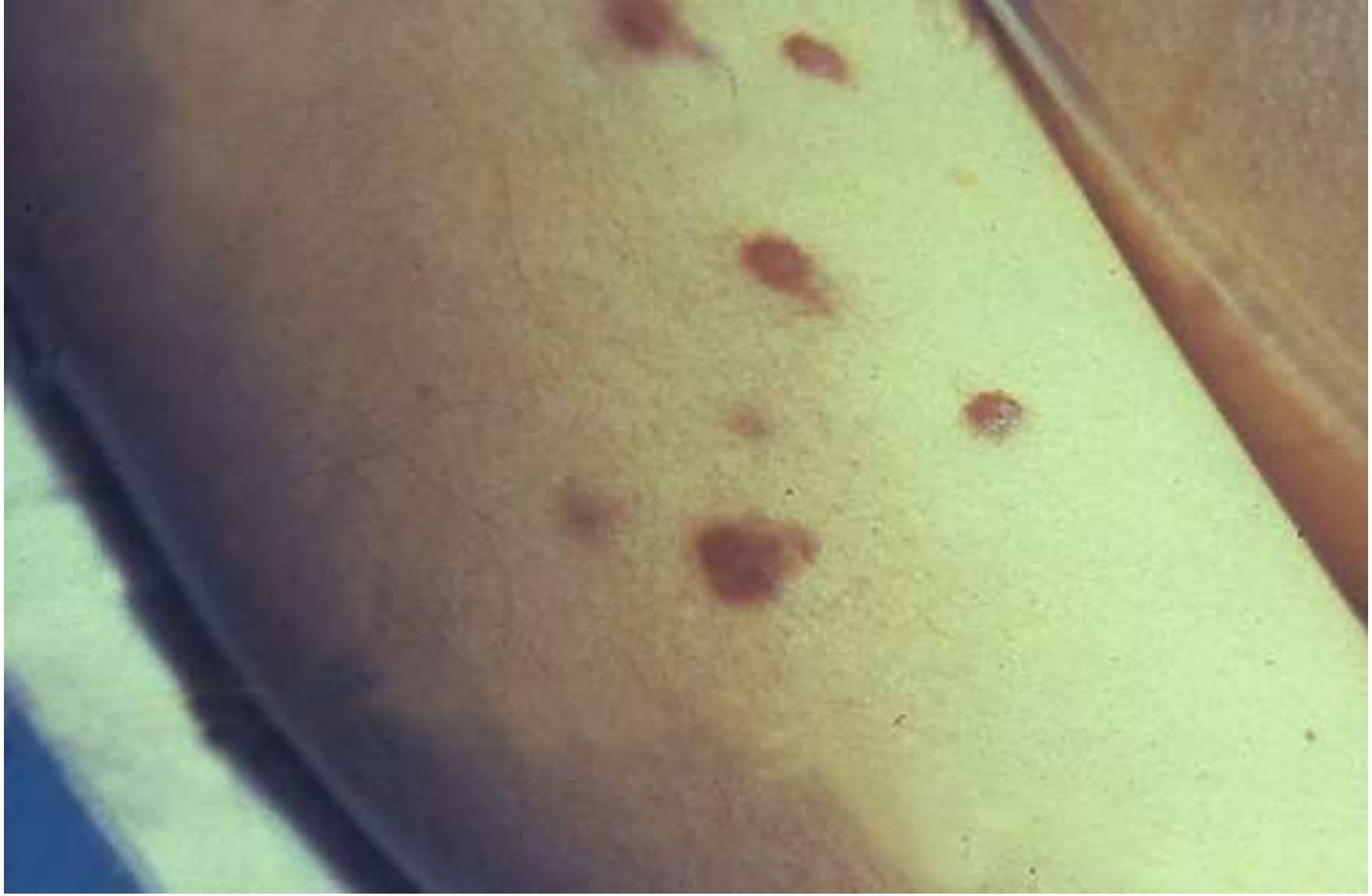
candida infections are common with AIDS, but most often appear as oral thrush, which is a nuisance but not life-threatening.

disseminated infections are uncommon, but here is a rare Candida pneumonia, which resembles a bacterial bronchopneumonia

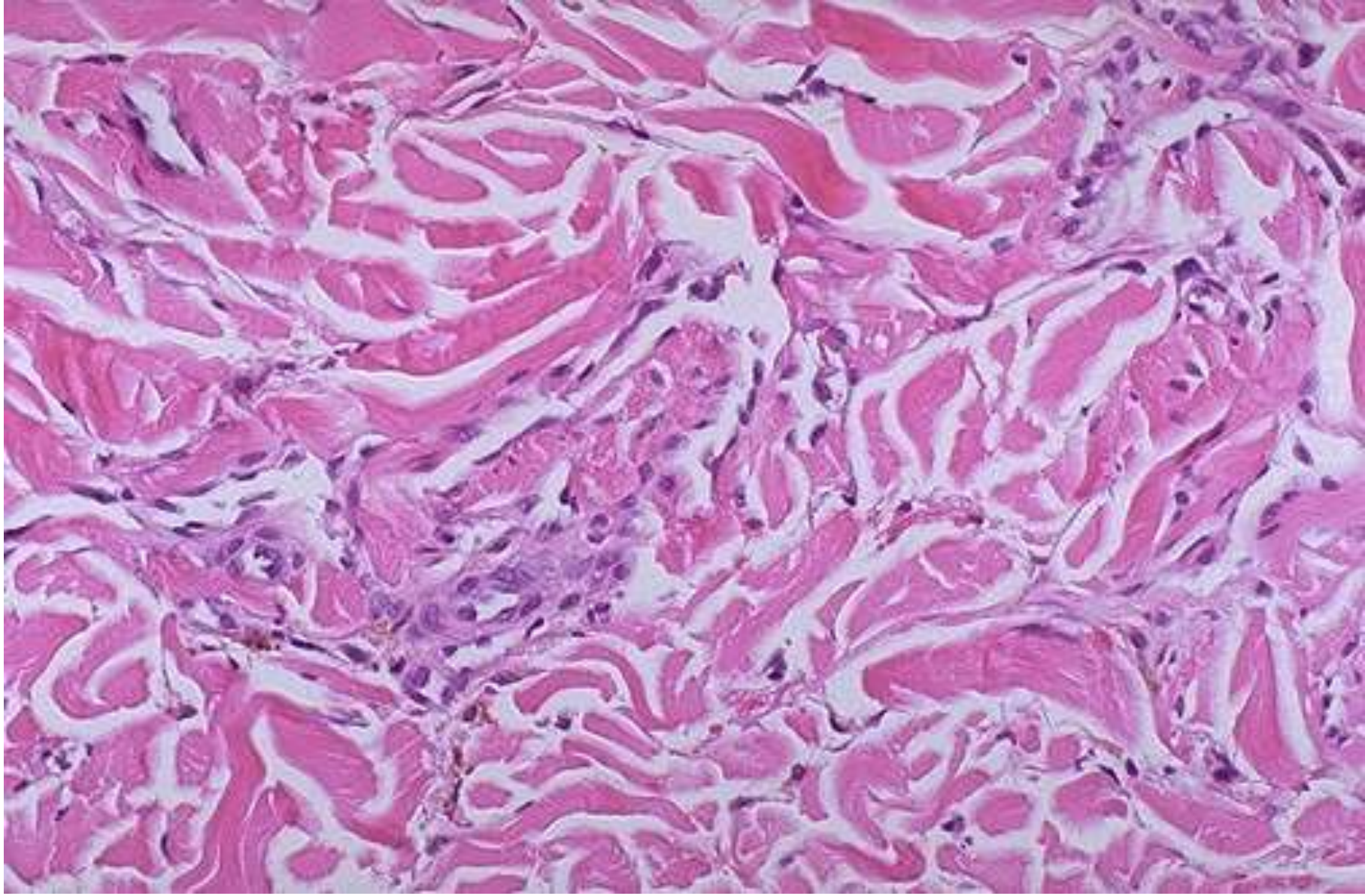


Candida albicans as an invasive process in the esophagus
PAS staining.

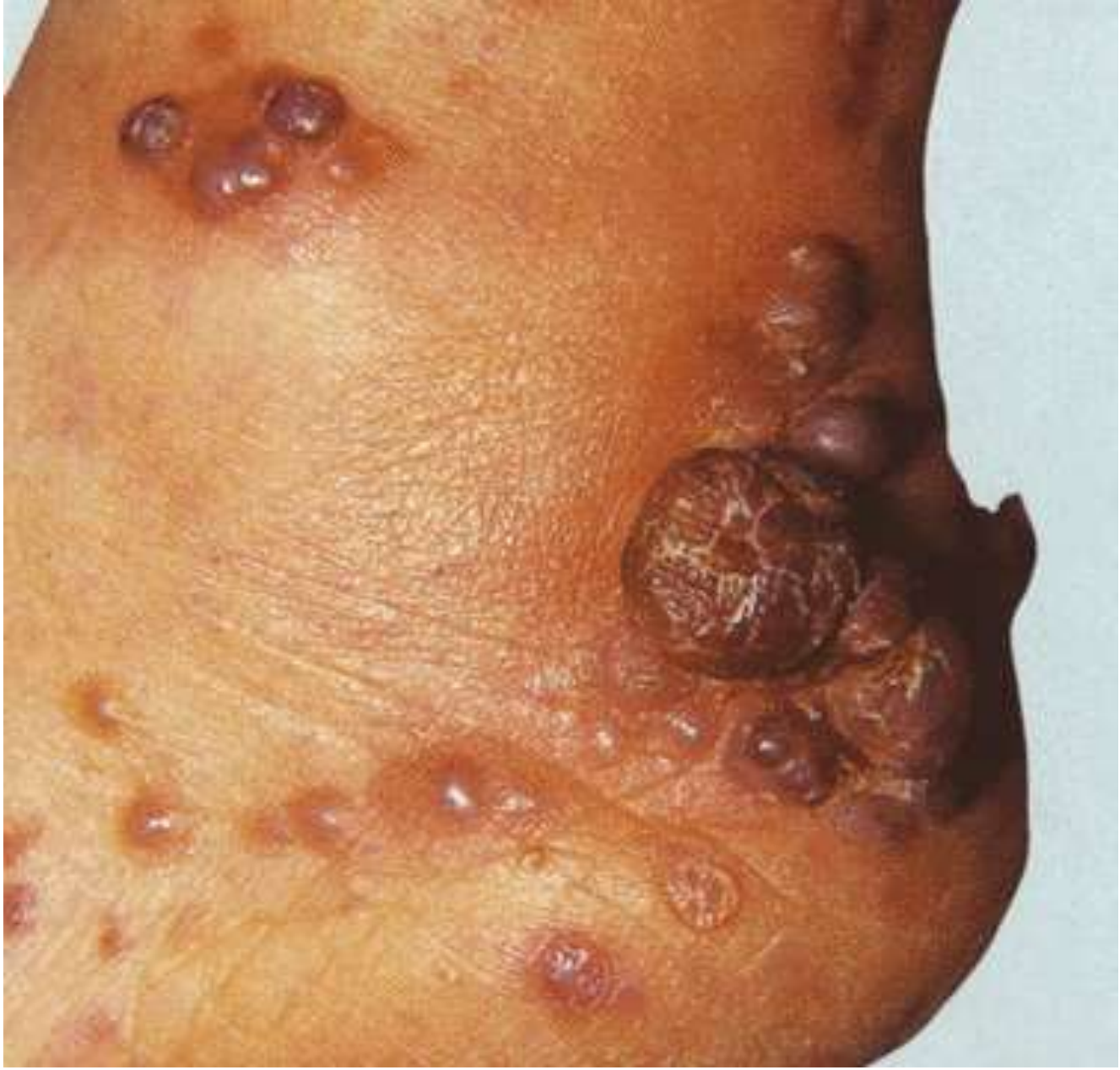
Histoplasma capsulatum may lead to formation of visible granulomas - here in the liver



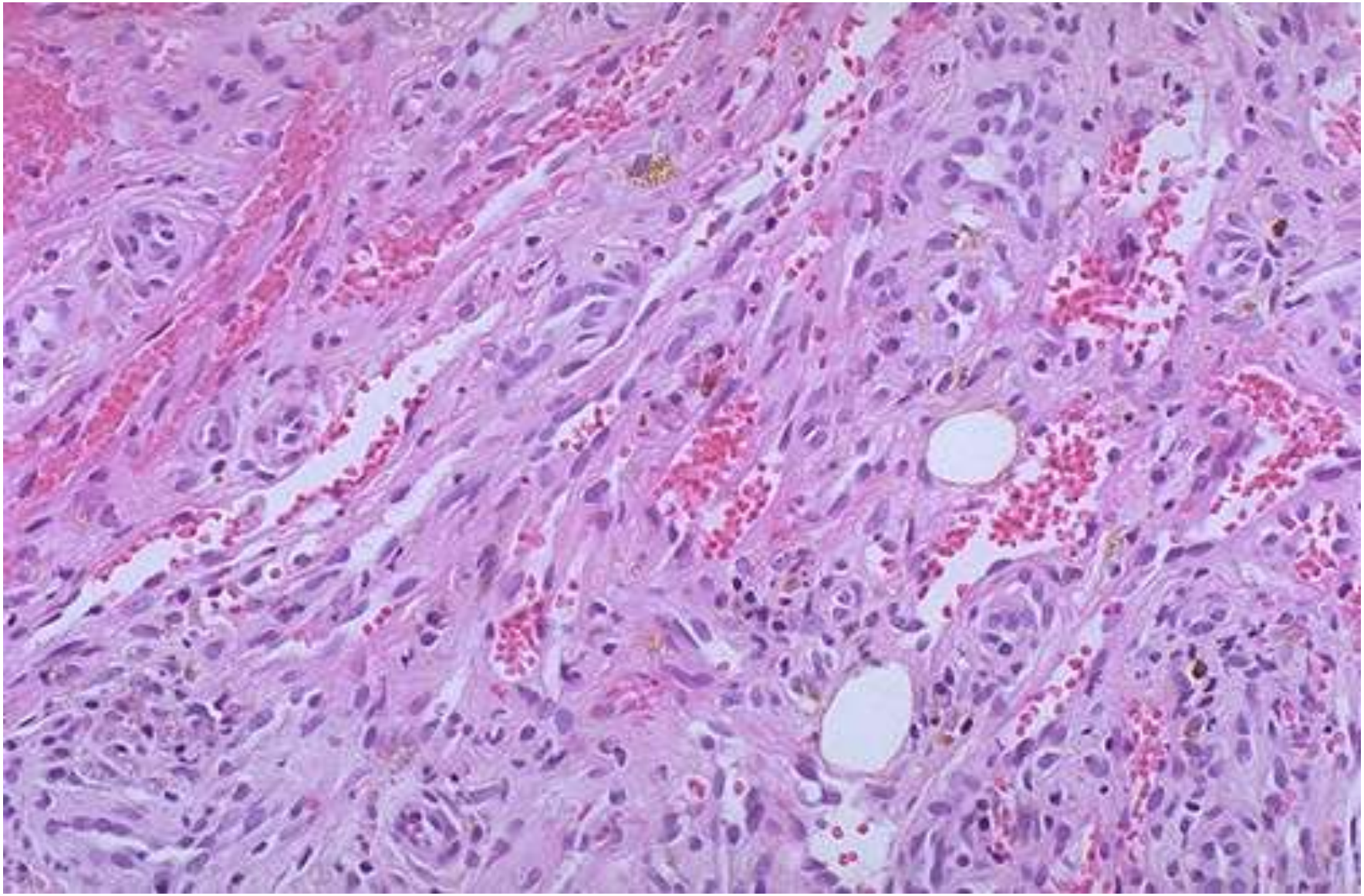
Kaposi's sarcoma: reddish purple nodules on the skin - sarcoma idiopathicum multiplex haemorrhagicum



Kaposi's sarcoma: slit-like vascular spaces in the dermis of the skin



Kaposi sarkoma of the skin

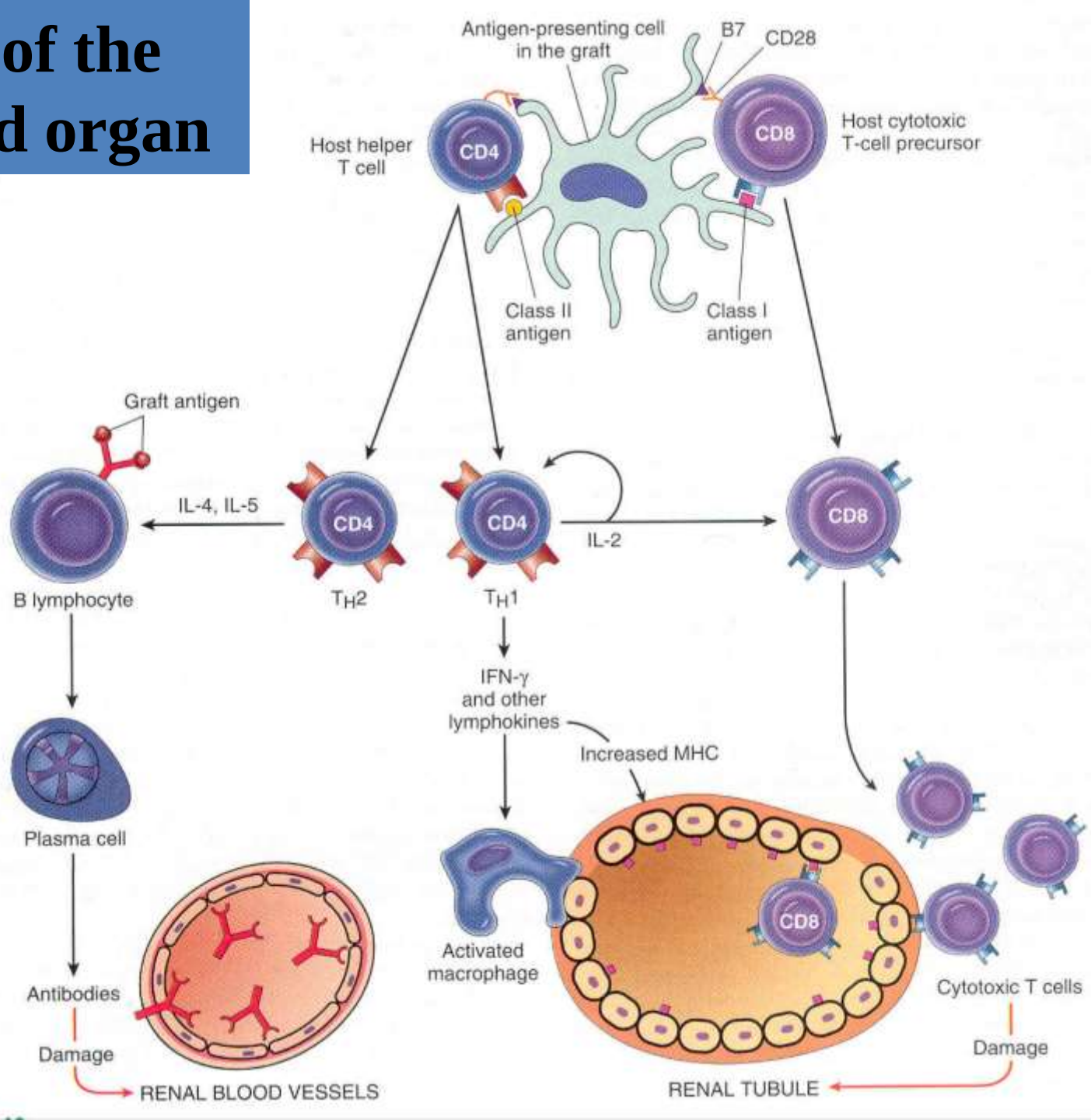


Kaposi's sarcoma: slit-like vascular spaces in the dermis of the skin with extravasation of red blood cells

Transplant-Pathology

- Host-versus Graft: Organtransplantation
- Graft-versus host (Bone Marrow TX)

Rejection of the transplanted organ



Rejection of the TRANSPLANTED ORGAN (Kidney)

HYPERACUTE

in Minutes **(existing ABs in recipient)**

ACUTE

Weeks- Months

sudden Kideny insuffitienty

Therapy!!!

Therapy

resistent!!!

CHRONIC Months-Years

Azotaemia
Oliguria
Hypertonia

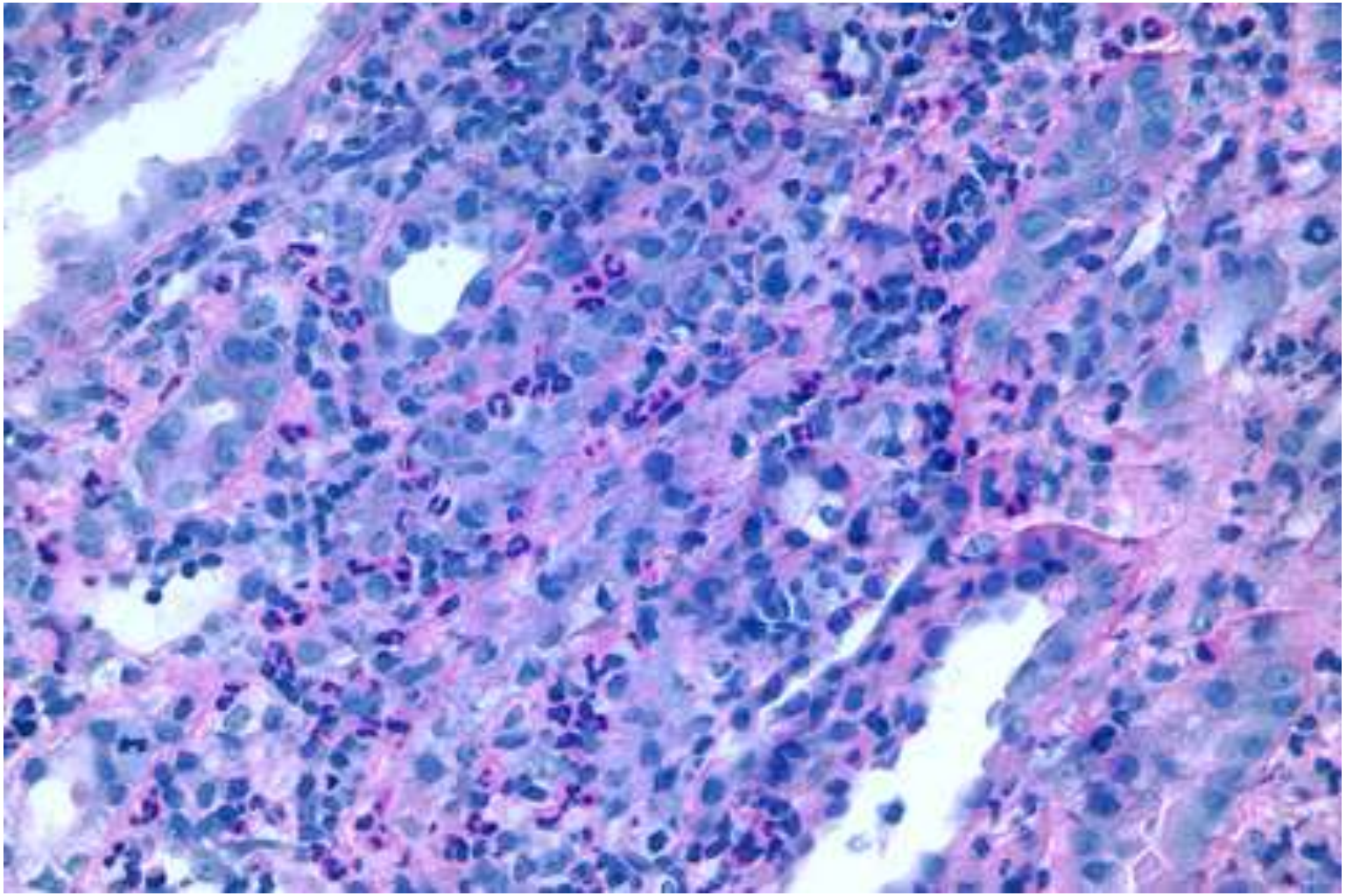
ARTHUS-REACTION fibrinoid necrosis of the wall of the vessel

1./ Cellular
interstit. nephr. II.-IV. h.r. (mononucl., edema) focal necrosis of the tubular epith. Cyclosporin A Toxicity !! **2./ Vascular necrotising vaskulitis Glomerulus necrosis III. h.r. cortex a. thrombosis subacute vasculitis (Intima Prolifer.)**

Changes of the vessel walls
Intima fibrosis sec. Ishaemia

Tubular Atrophy
interstit. fibrosis- end stage kidney !

Acute Rejection



Chronic rejection