Immunpathology I.

2017/2018

– Autumn semester
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Med. habil., Ph.D., D.Sc.

The purpose of the immunsystem to

Maintain the integrity of human organism

Warrant the individulaity

Protect against infectious diseases

Protect against tumors

***Unspecific immunity* –**

Resistence: *e*pithelial 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

LOCAL SIGNS OF INFLAMMATION ACCORDING TO CELSUS
„ cardinal symptomes ”

CALOR

RUBOR

TUMOR

DOLOR

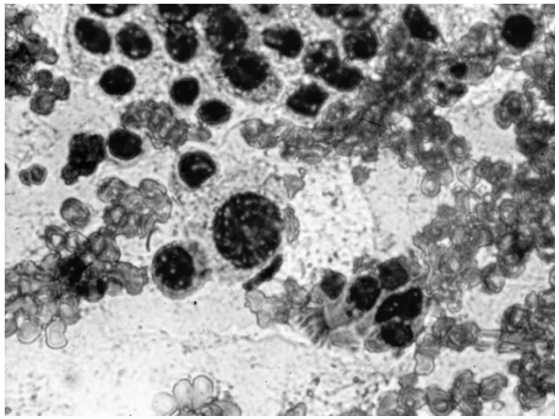
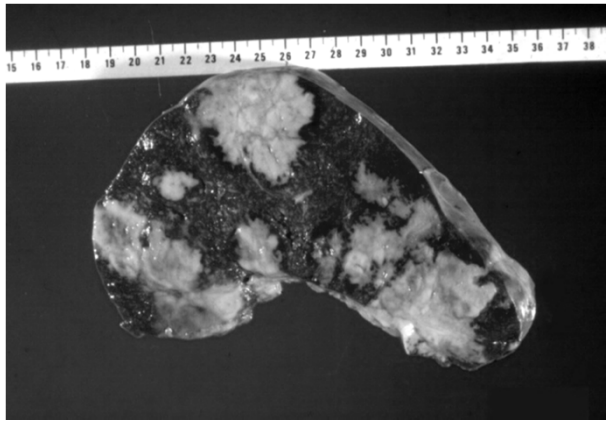
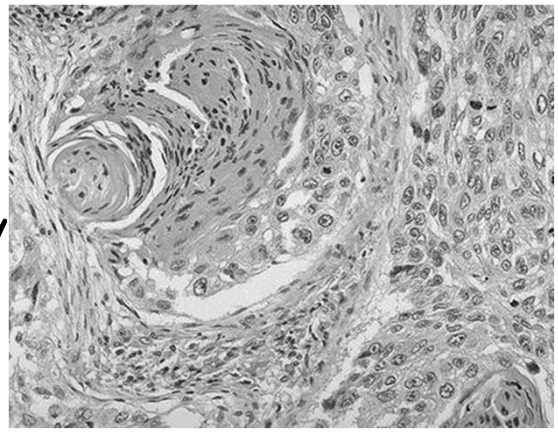
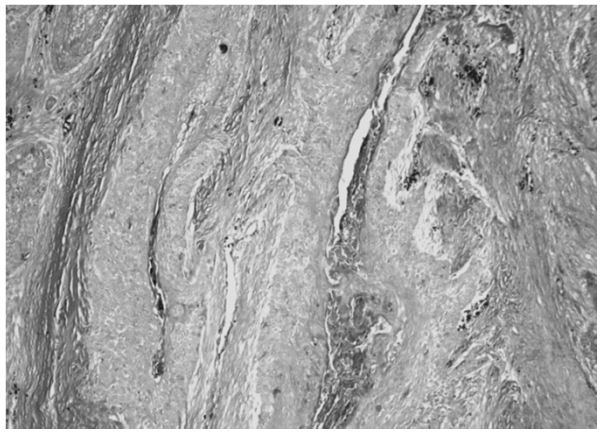
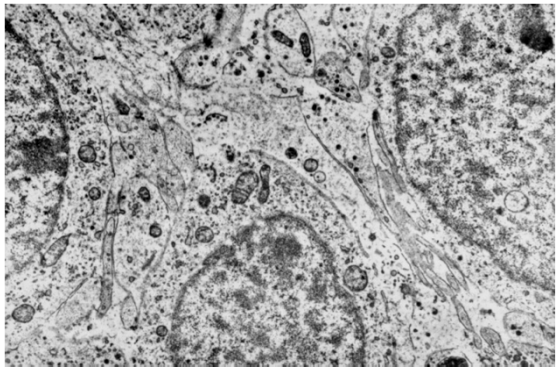
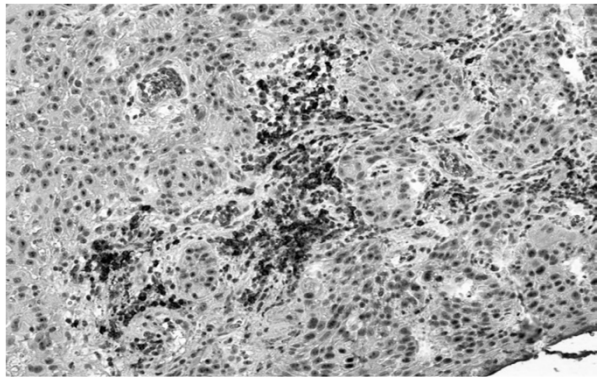
FUNCTIO LAESA (added by Rudolf VON VIRCHOW)

GENERAL OR SYSTEMIC SIGNS OF INFLAMMATION

FEVER
TACHYCARIDA
LEUKOCYTPSIS
INFECTIOUS ANEMIA

XX. Century Technologies

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

Clinical Course of Inflammation

HYPERACUTE (Peracute)

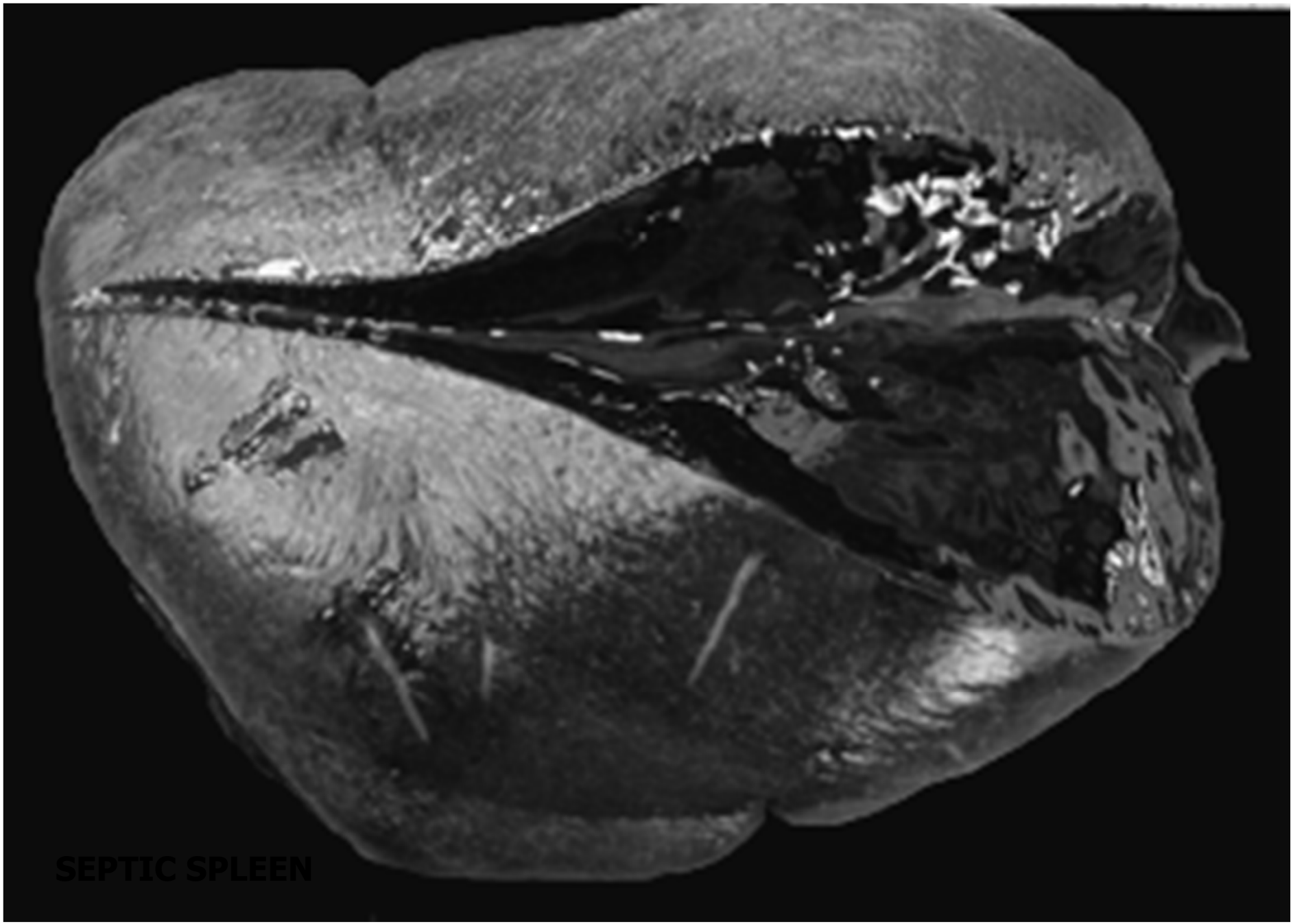
ACUTE

SUBACUTE

SUBCHRONIC

PRIMARY CHRONIC (e.g. PCP)

SECONDARY CHRONIC


SEPTIC SPLEEN

MORPHOLOGY

ACUTE: NEUTROPHILS, EOSINOPHIL GRANULOCYTES

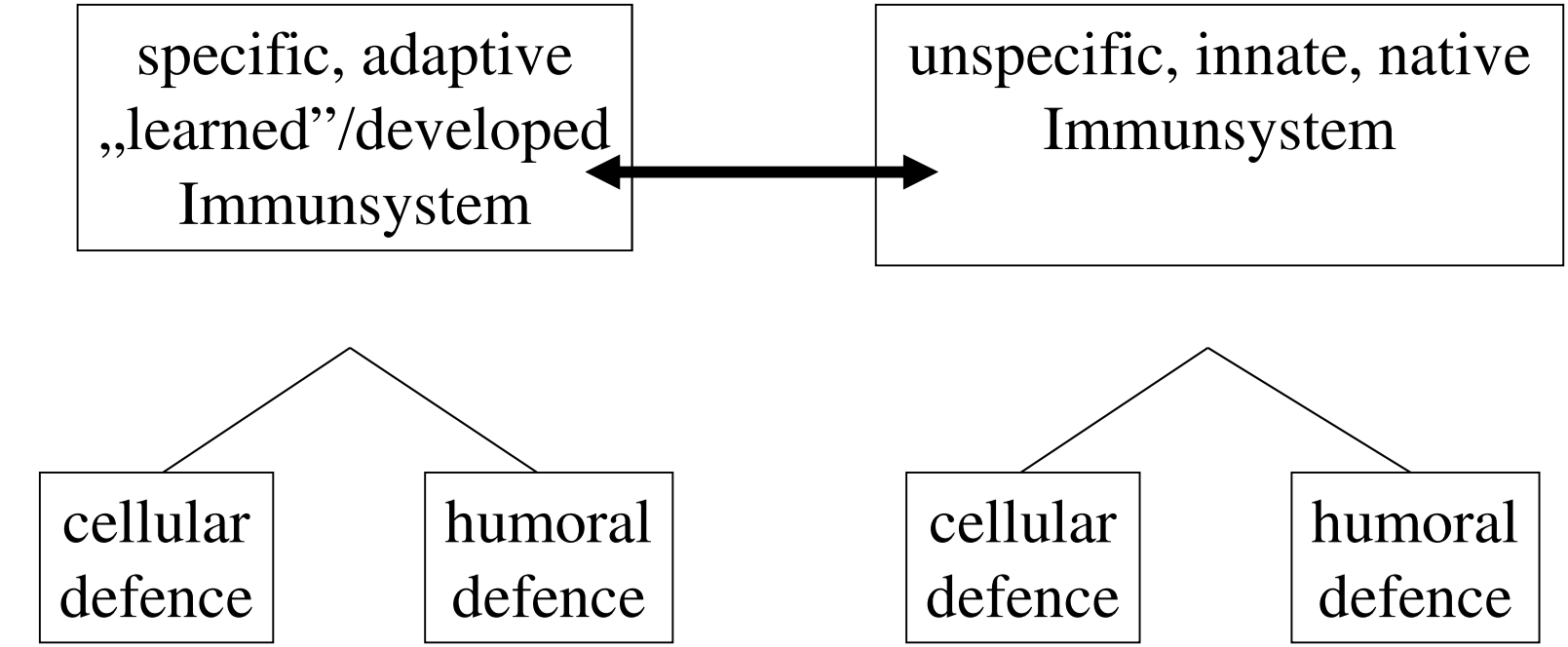
AFTER SOME TIME REPLACED BY „ ROUND CELLS ” : MONOCYTES, MACROPHAGES, LYMPHOCYTES

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)

Immunsystem to defend from noxa



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

CELLULAR COMPONENTS

NEUTROPHIL GRANULOCYTES
AKUTE BAKTERIELLE ENTZÜNDUNGEN

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

BASOPHYL GRANULOYTES: (Histamin, Heparin)

TISSUE MAST CELLS (MACROPGHAGES): (Heparin, Histamin

LYMPHOZYTEN BEVORZUGT BEI VIRALEN INFEKTIONEN
UND CHRONISCHEN ENTZÜNDUNGEN
BEI MASERN: WARTHIN-FINKELDEY RIESENZELLEN

CELLULAR COMPONENTS

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

NUCELI: „footstep" form nuclei

Fusion of macrophages, eventuelly epitheloid cells results in:

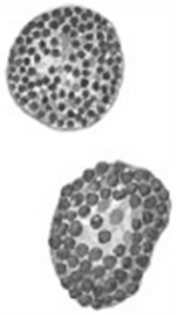
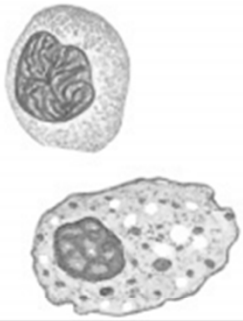
GIANT CELLS: mostly in granulomas
(nodule like growth made of granulation tissue)

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

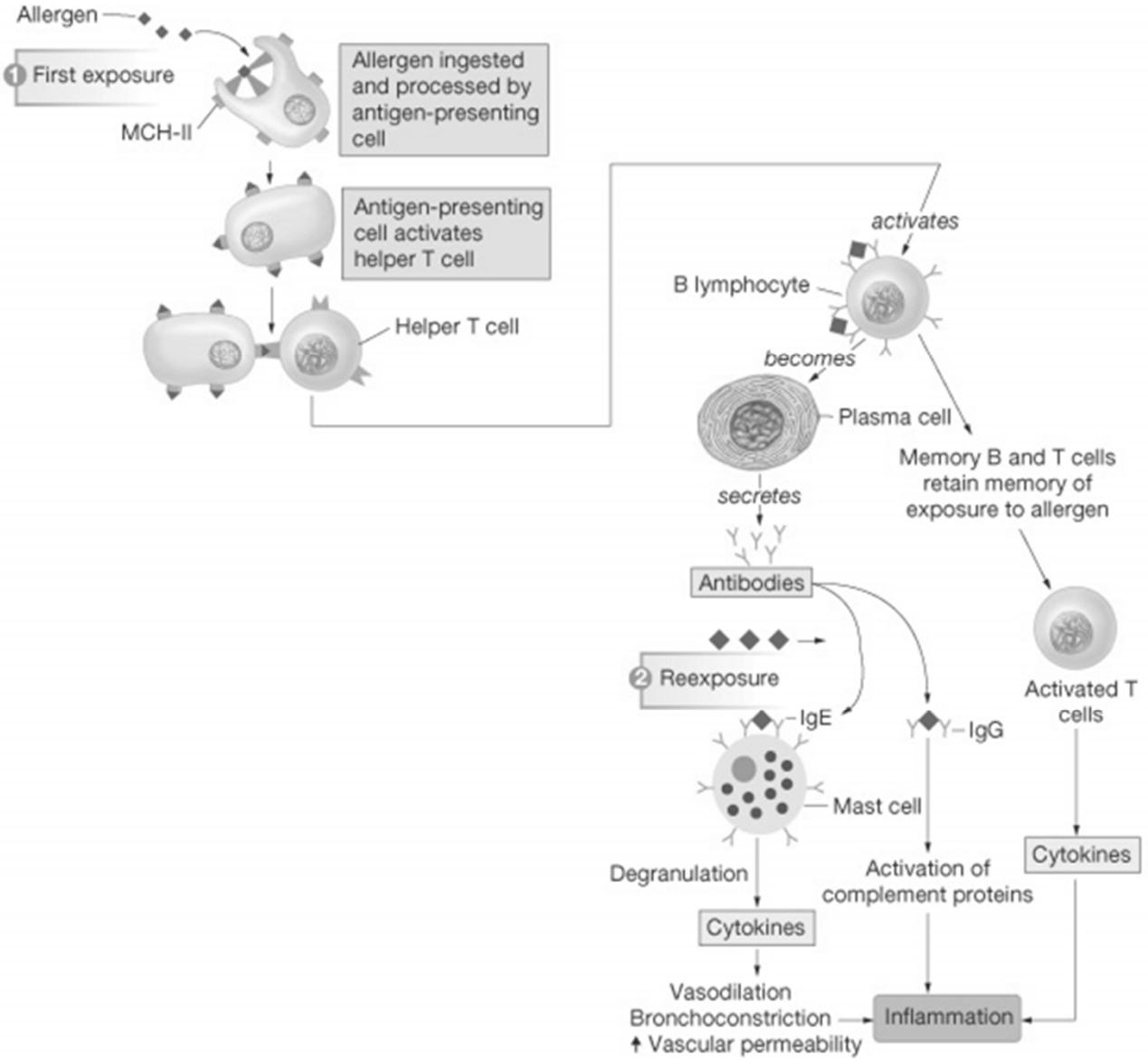
Foregin body type Giant Cell :

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	

Allergic inflammation on non-pathogenic noxa



CYTOGENIC MEDIATORS

HISTAMIN in ALLERGIC (hypersensitivity) INFLAMMATION

SEROTONIN:

PROSTAGLANDINE:

LYMPHOKINE:

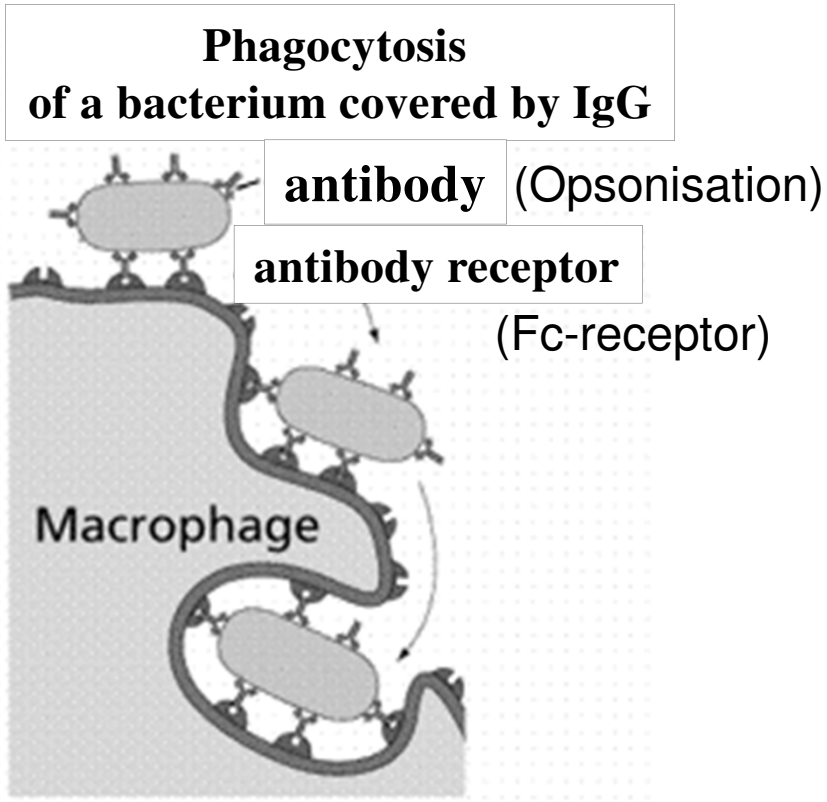
LEUKOTRIENE:

PLATELE ACTIVATIONS FAKTOR (PAF):

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

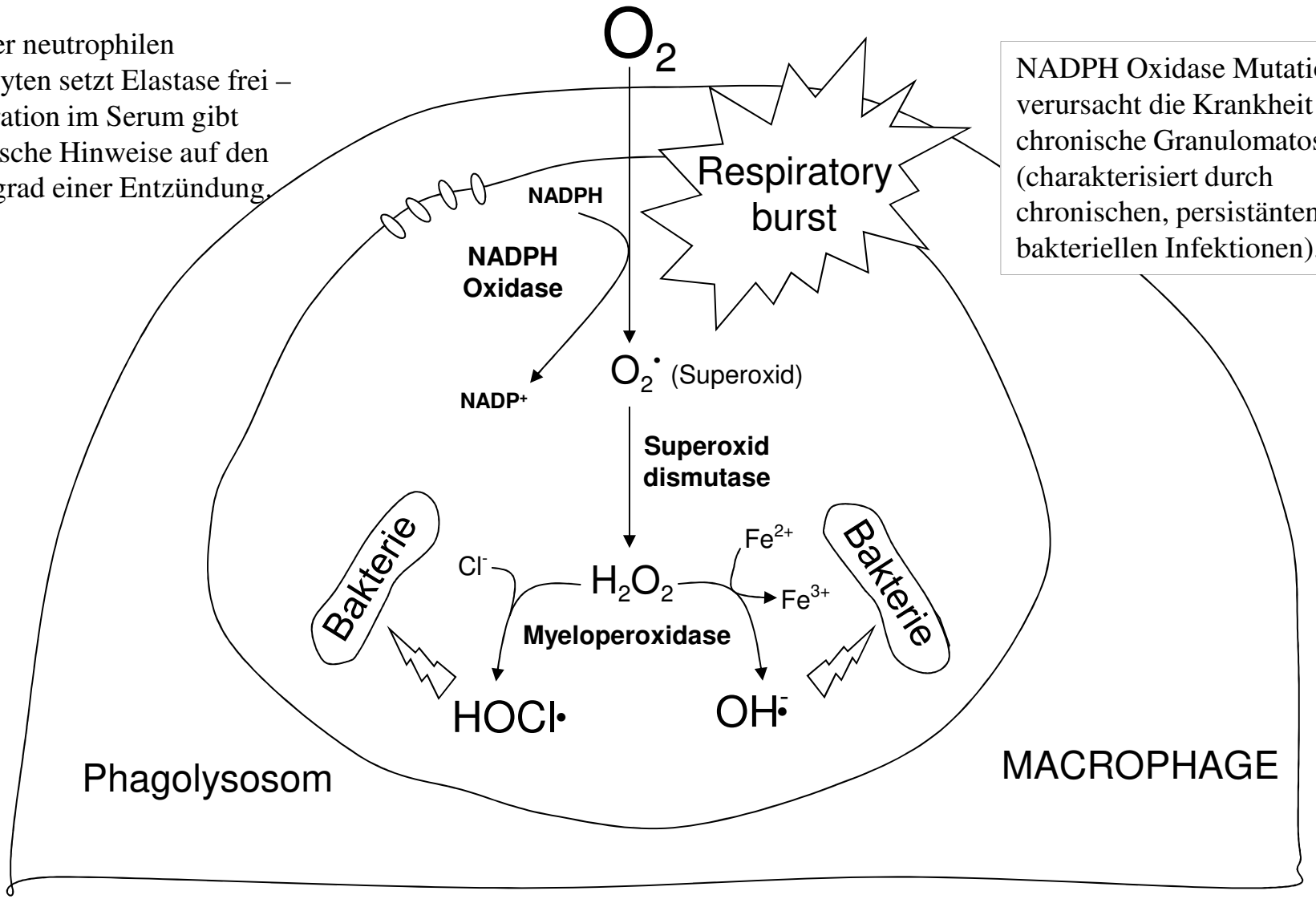
Cells of unspecific immune system

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



Phagocytosis by macrophages and neutrophile leukocytes

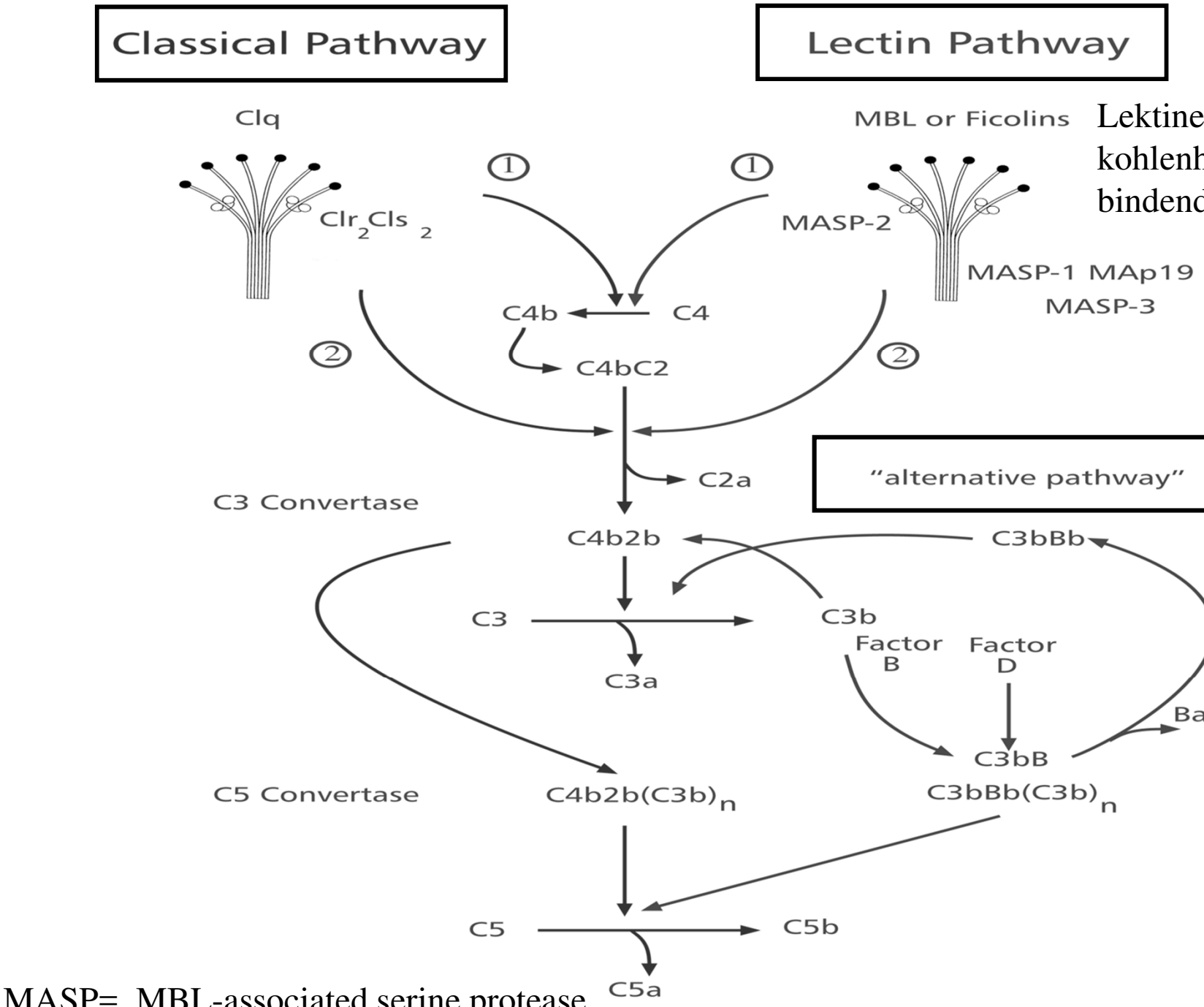
Zerfall der neutrophilen Granulozyten setzt Elastase frei – Konzentration im Serum gibt diagnostische Hinweise auf den Schweregrad einer Entzündung.



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

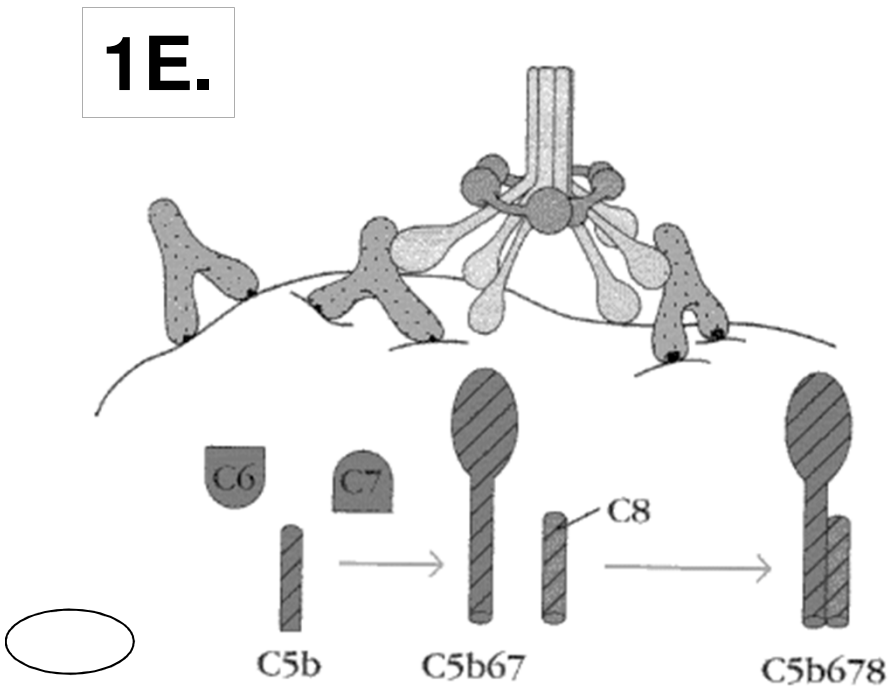
NK - natural killer cells

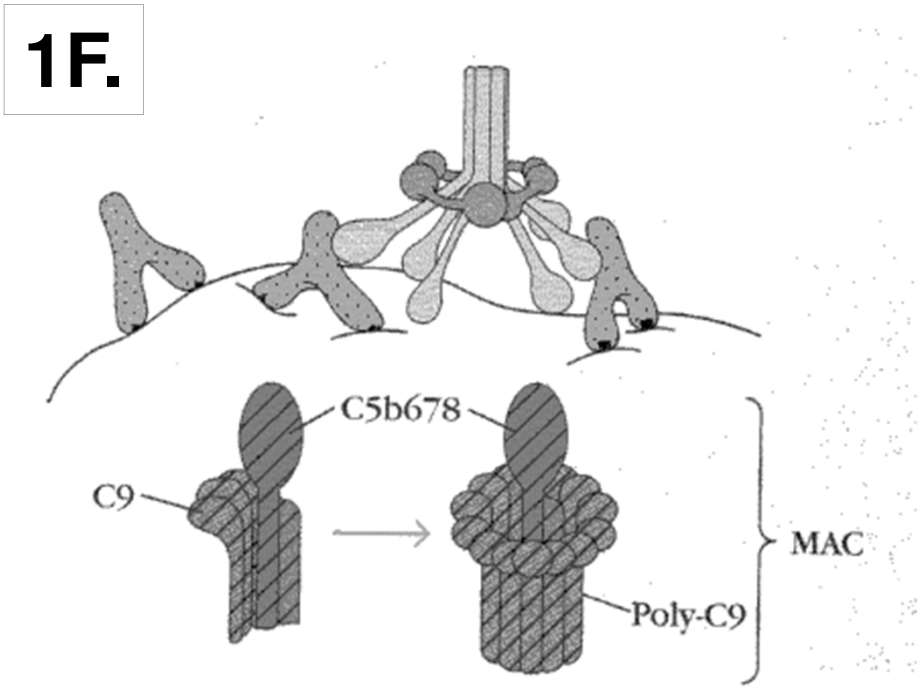
- Originally described as anti-tumorcell
- Important role in rejection of an implant, in elimination of virus infected cells as in certain bacterial and fungal infections
- Target cells: MHC class I-negative cells („immune evasion“)
- No activation by APC is necessary (activated by cytokines IL-12, IFNγ)
- 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



MASP= MBL-associated serine protease

Complement activation: classic pathway

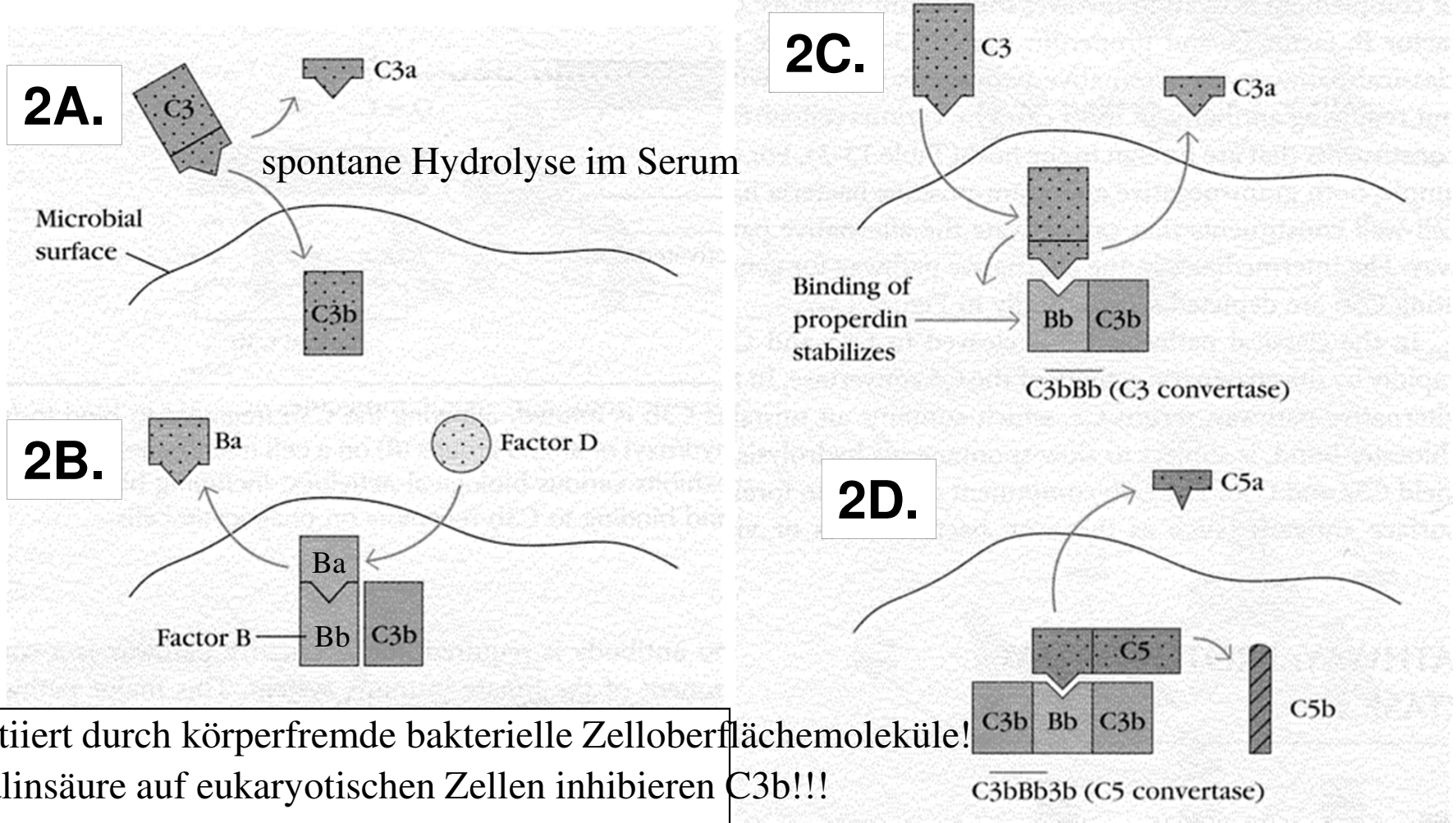




MAC-membrane-attack complex

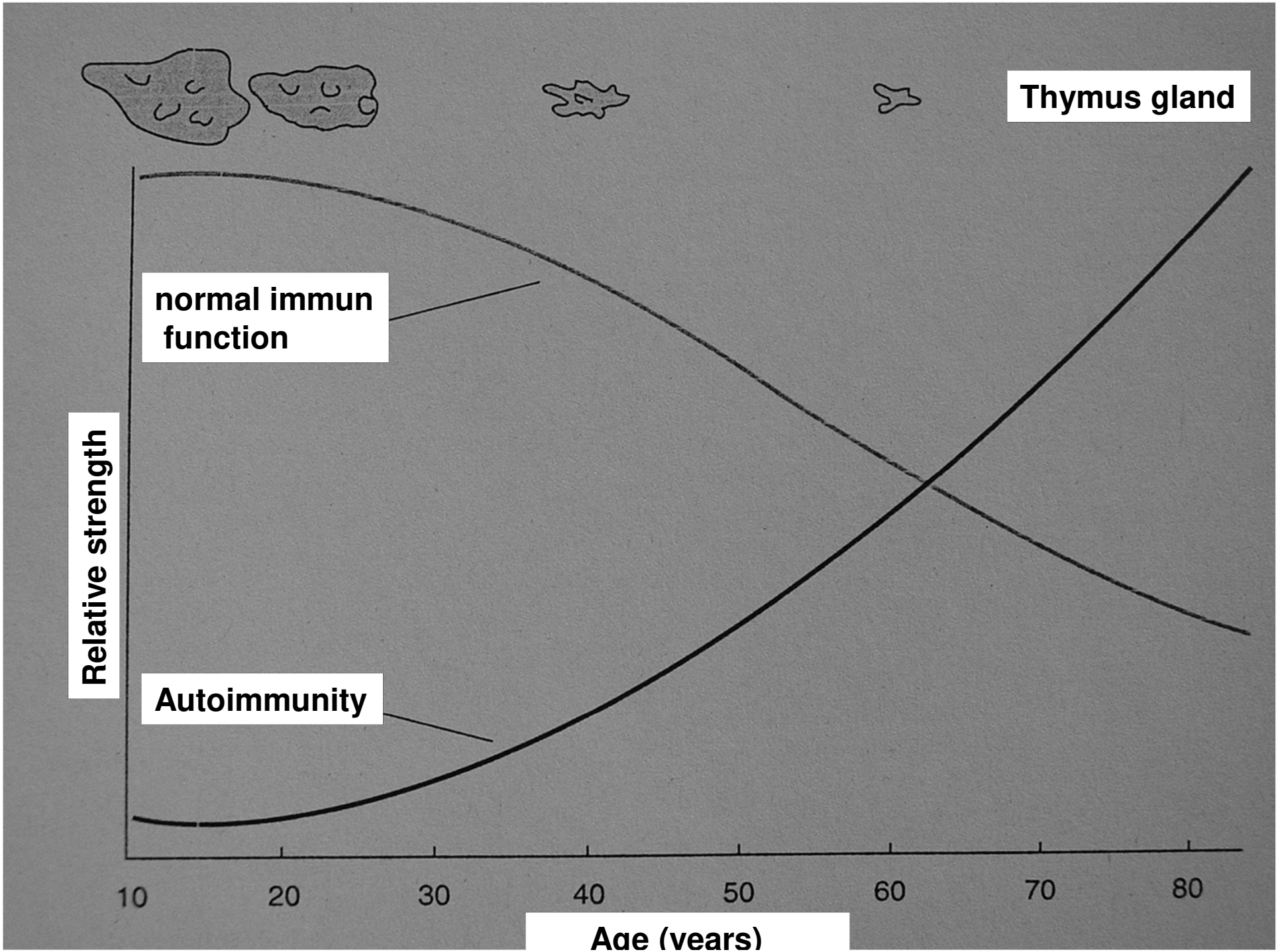
Quelle: Kuby Immunology, W.H. Freeman and Company

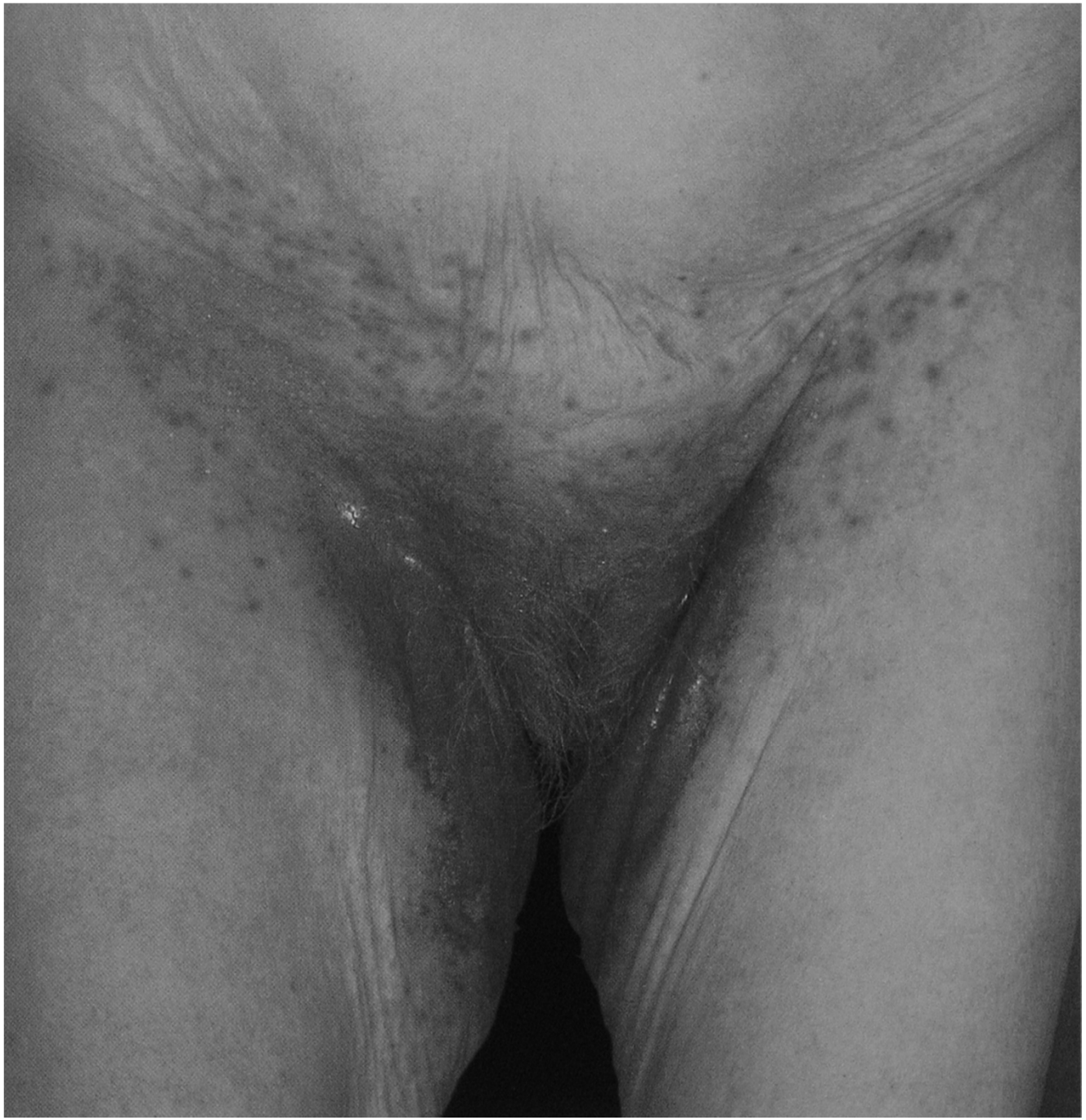
Complement activation: alternative pathway (independent of antibodies)



Initiiert durch körperfremde bakterielle Zelloberflächemoleküle!
Sialinsäure auf eukaryotischen Zellen inhibieren C3b!!!

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


Thymus gland
normal immun function
Autoimmunity
Relative strength
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.

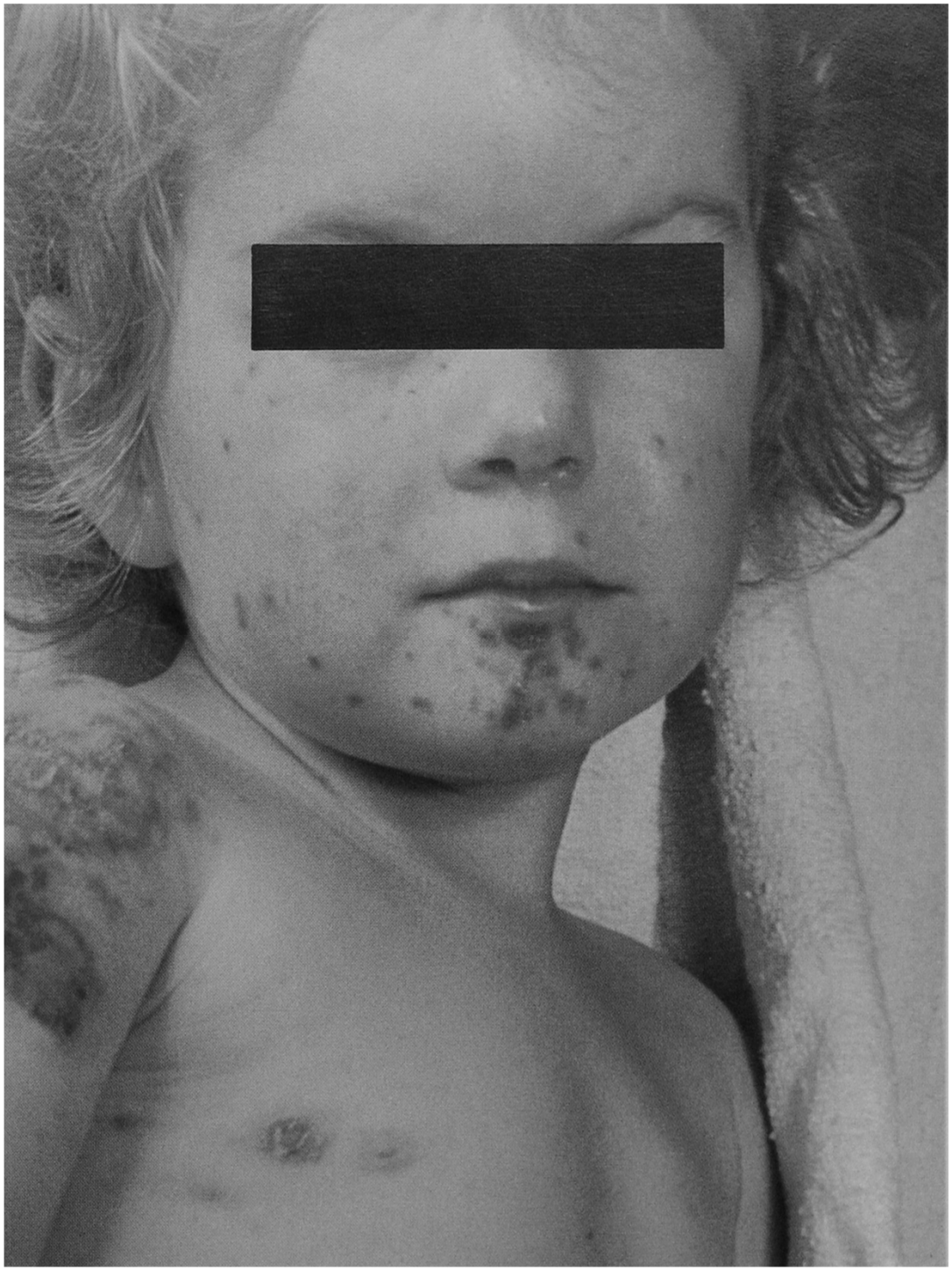
Differentiation between »self«)and „foreign"/ »not-self« might be lost later for certain „tolerogenes", therefore, this can lead to autoaggressive diseases.

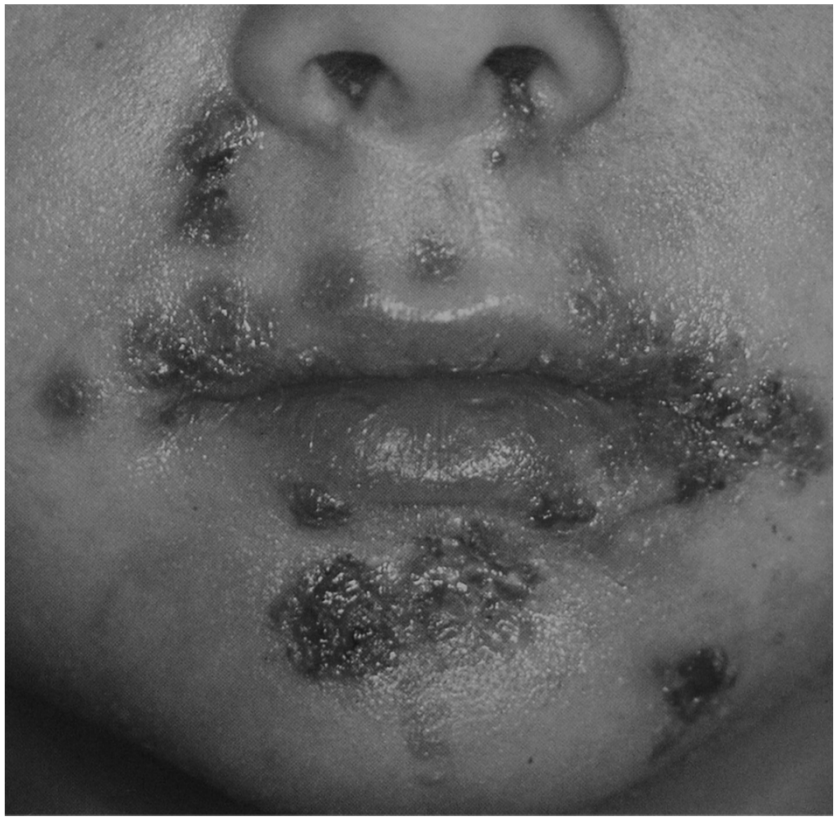
Angeborene: gegenüber körpereigene Antigene (Autoantigene)

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)



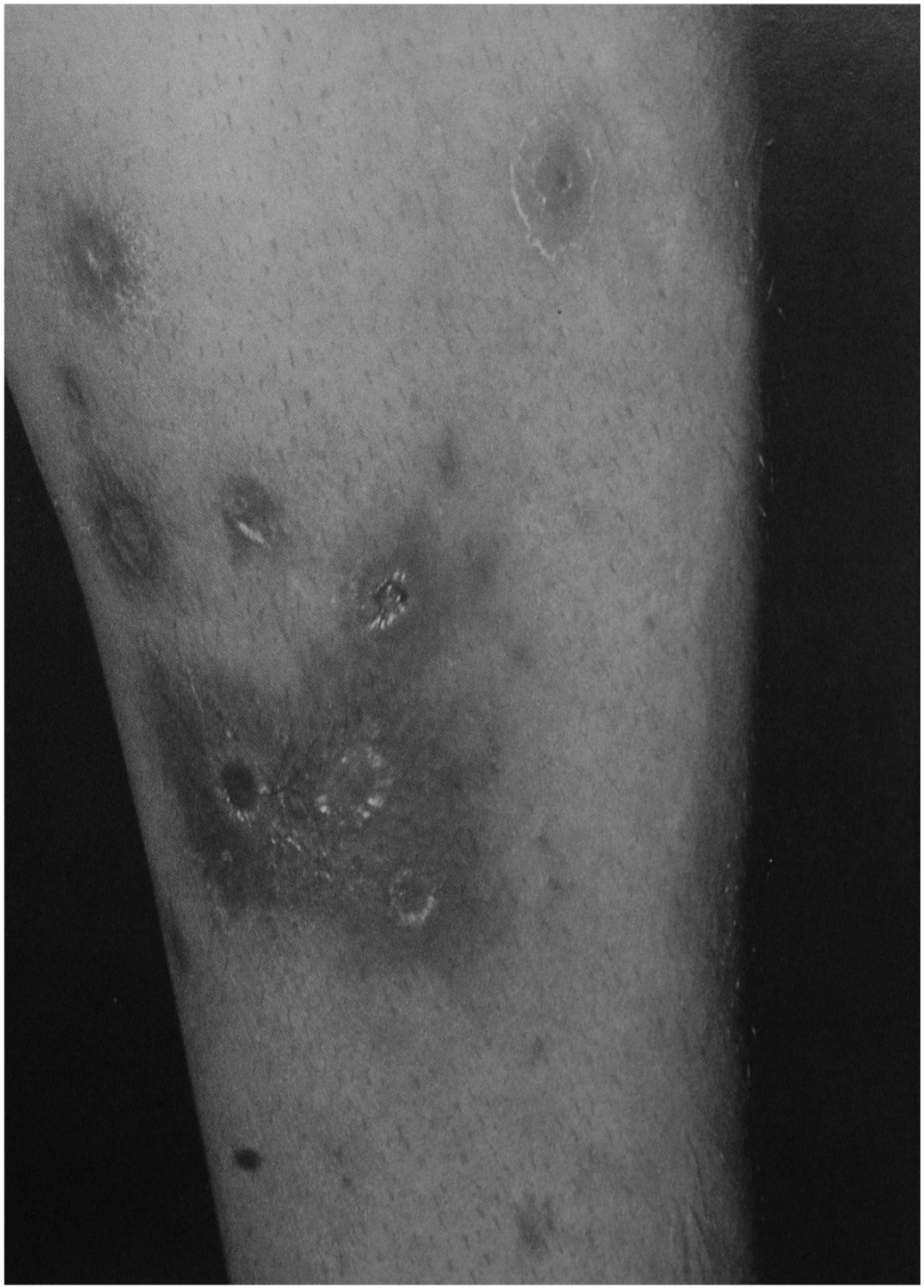


Impetigo contagiosa

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

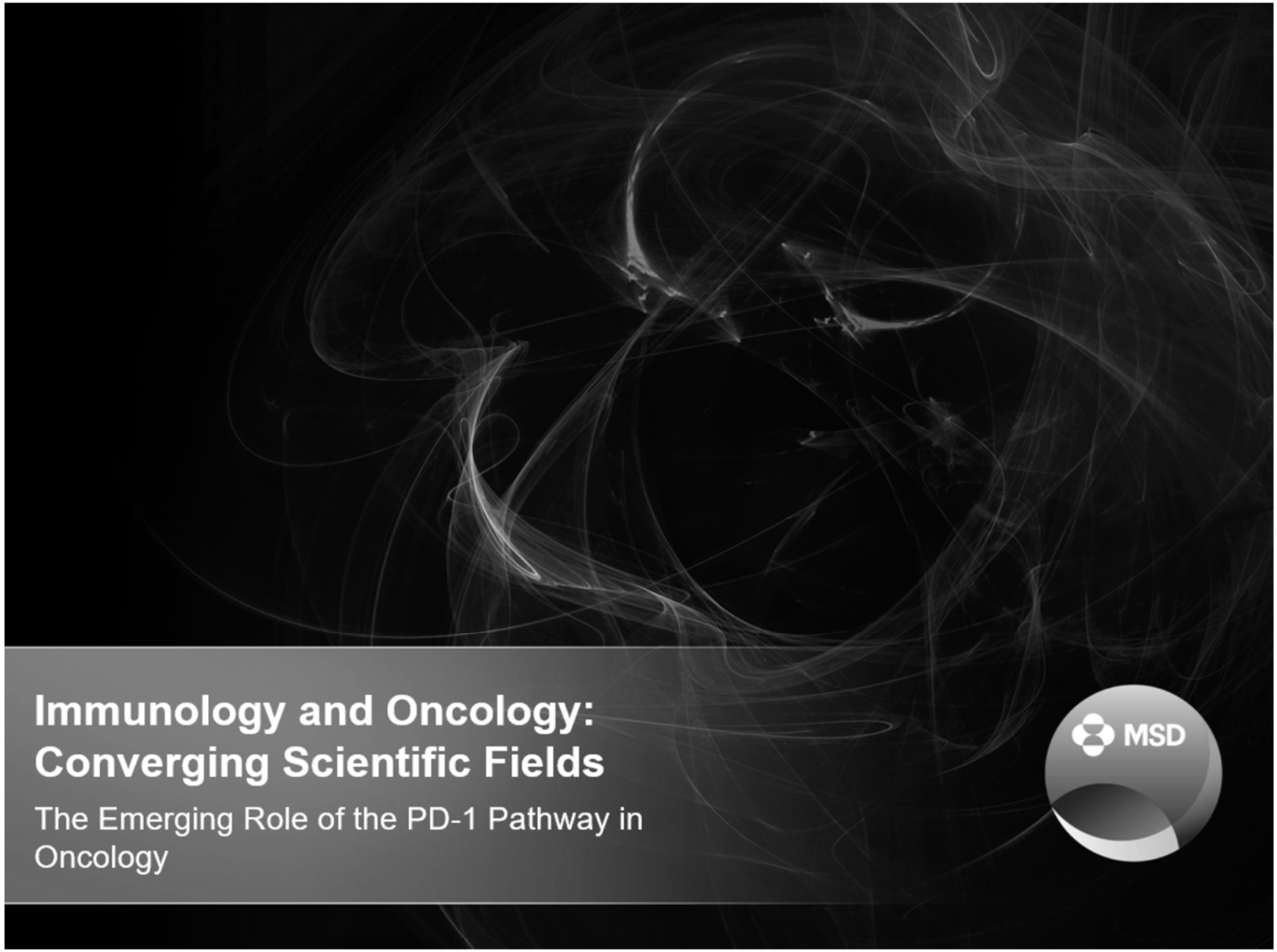
directed againts epidermal growth factor receptor: EGFR

Receptor protein C-Kit (Thyrosin kinase function) CML, GIST

overexpressed ,e,bran associated receptores - Herceptin (Erbb2)

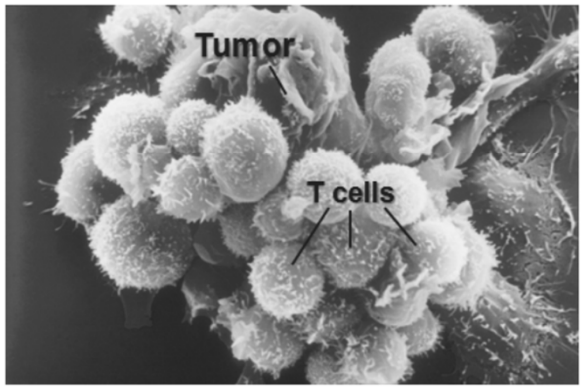
To raise antigeneicity by infaction with apathogenic viruses

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


Immunology and Oncology:
Converging Scientific Fields
The Emerging Role of the PD-1 Pathway in Oncology
MSD

Could the Immune System be an Important Ally in the Fight Against Cancer?

- The presence of immune cells (such as T cells) within a tumor has been correlated with better clinical outcome in some tumor types[1–3]
  - Less advanced stage
  - Absence of signs of metastasis
  - Increased survival
  - Reduced risk of relapse

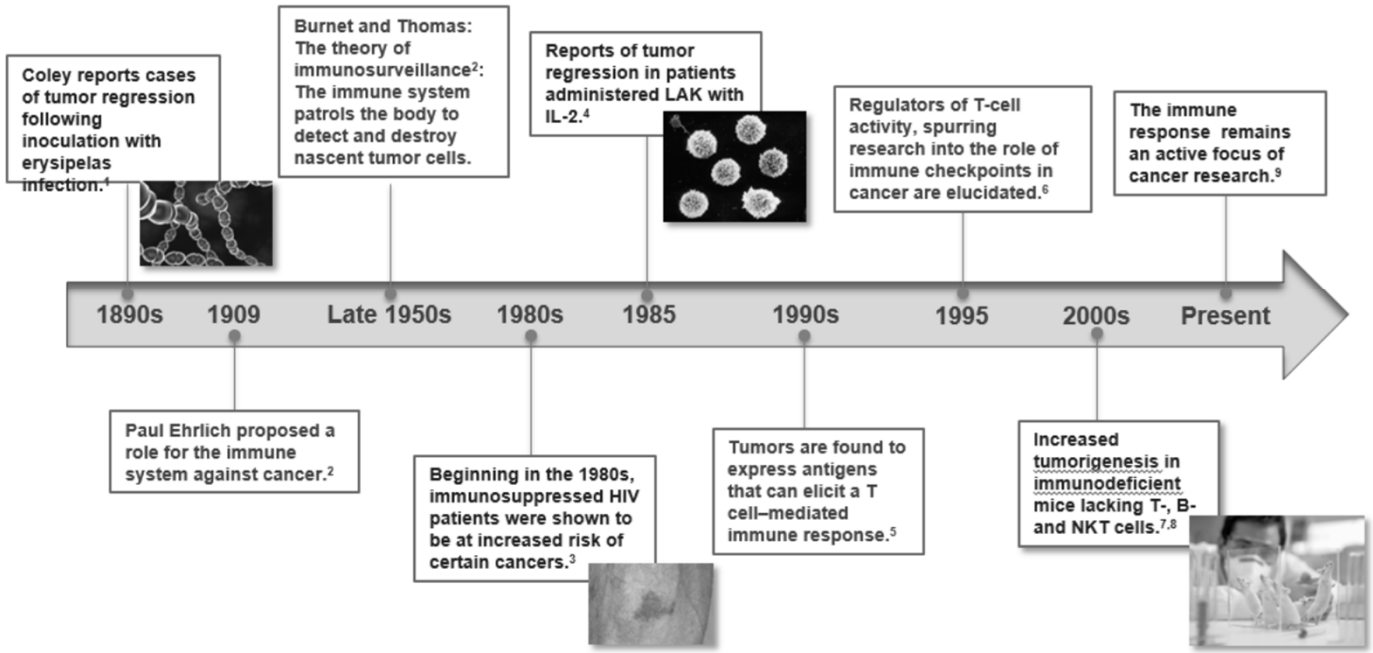


- When the immune system is suppressed, the risk of developing certain cancers increases
  - HIV patients[4]
  - Transplant patients treated with immunosuppressants[5]

HIV = human immunodeficiency virus.

1. Hwang WT et al. *Gynecol Oncol.* 2012;124:192–198. **2.** Pages F et al. *N Engl J Med.* 2005;353:2654–2666. **3.** Loi S et al. *J Clin Oncol.* 2013;31:860–867. **4.** Engels EA et al. *Int J Cancer.* 2008;123:187–194. **5.** Grulich AE et al. *Lancet.* 2007;370:59–67.

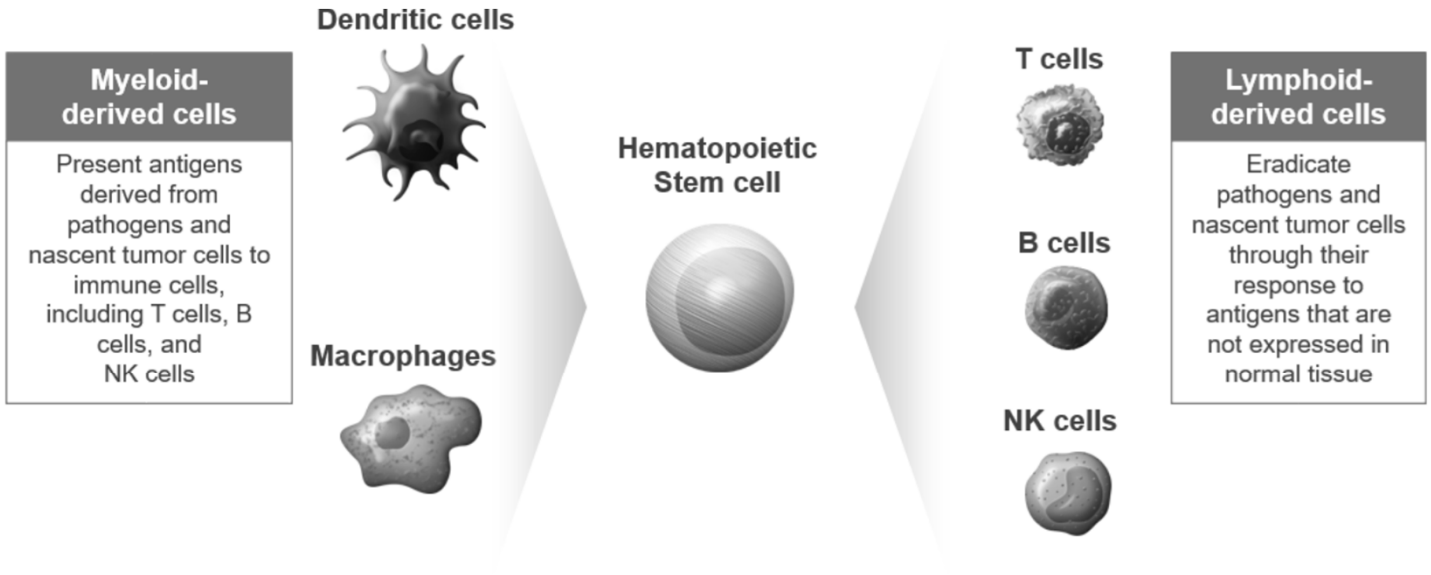
What Have We Learned About the Role of the Immune System in Oncology?



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 Can Fight Tumors Via a Variety of Functionally Specialized Cells[1]



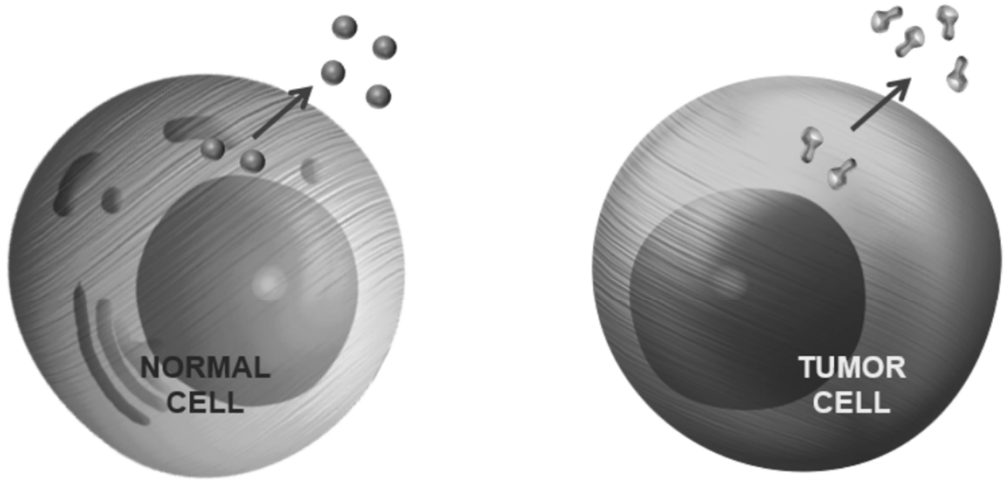
NK = natural killer.

1. Norvell A. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:11–24.

Some Tumor Cells Express Multiple Antigens That Are Not Expressed by Normal Cells[1]

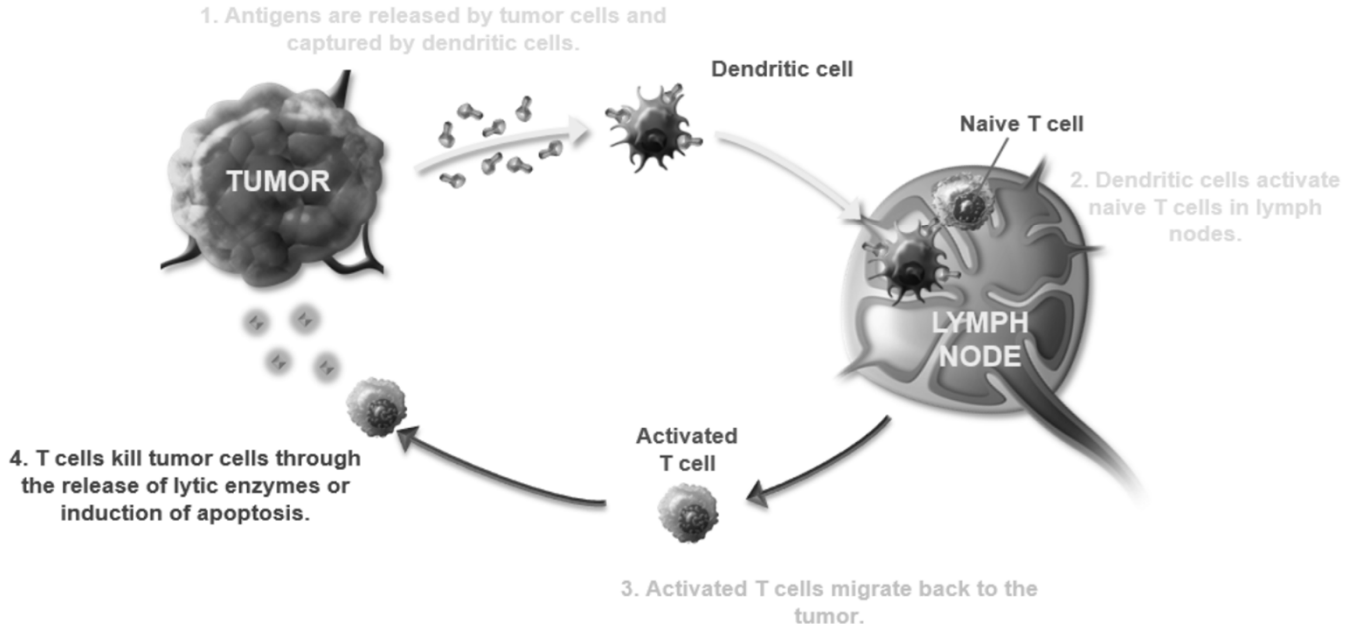
Normal cells release molecules that are captured by antigen-presenting cells, but they don't elicit an immune response.

Tumor cells release differentially expressed antigens that cause them to be recognized as foreign entities and therefore elicit an immune response.



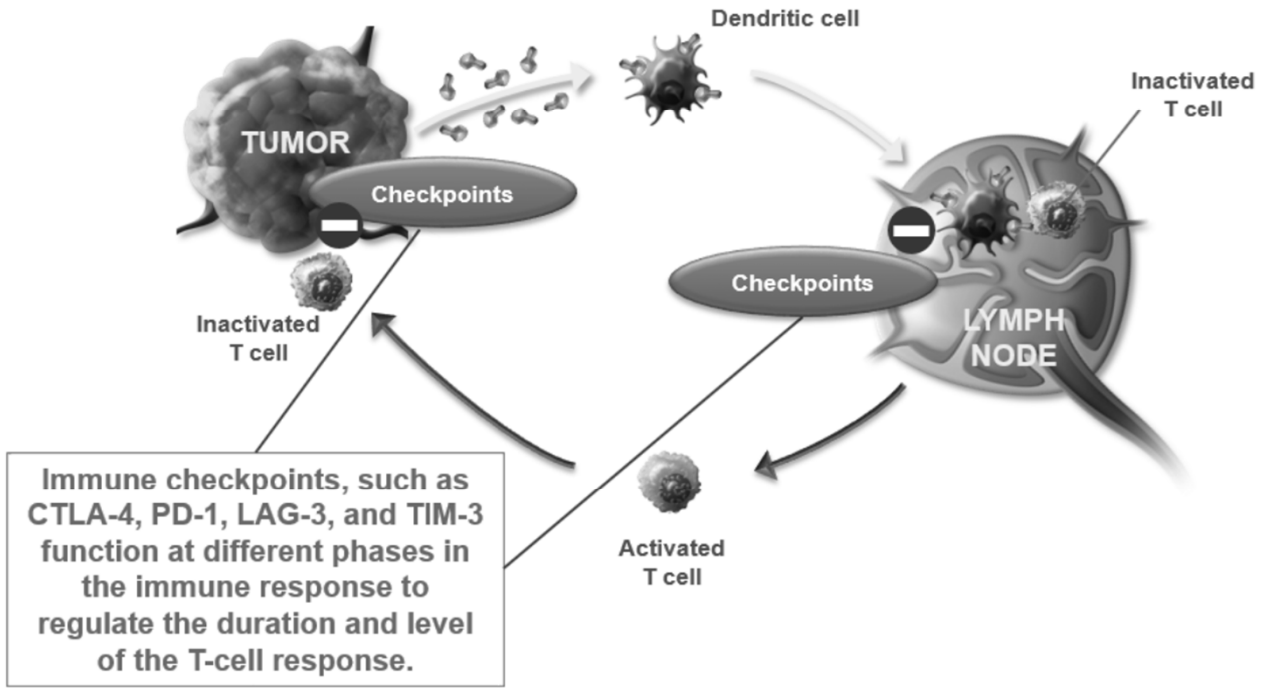
1. Finn OJ. *N Engl J Med.* 2008;358:2704–2715.

T cells Are Important in the Ability of the Immune System to Detect and Destroy Tumor Cells[1]



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

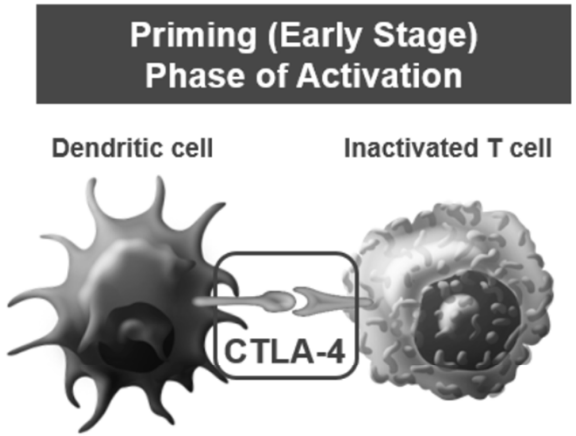
T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]



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.

CTLA-4 Is Thought to Affect The Priming Phase of T-Cell Activation[1]

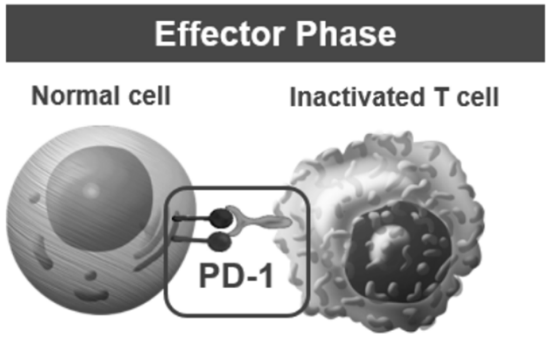


- In healthy tissues, CTLA-4 is thought to function as a dominant "off switch" broadly shutting down T-cell activity to prevent autoimmunity[1–3]

CTLA-4 = cytotoxic T-lymphocyte antigen 4.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264; **2.** Ribas A. *N Engl J Med*. 2012;366:2517–2519; **3.** Topalian SL et al. *Curr Opin Immunol*. 2012;24:207–212.

PD-1 Is Thought to Primarily Regulate the Effector Phase of T-Cell Activity

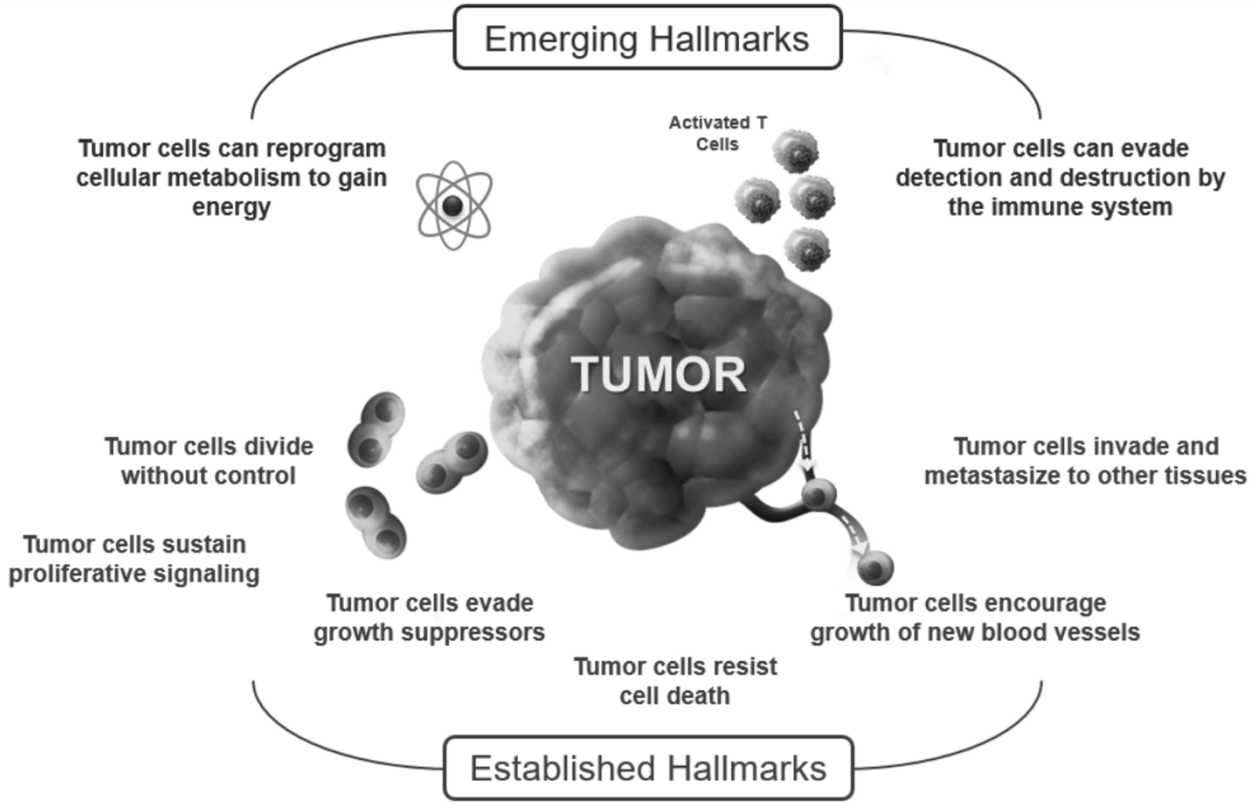


- The PD-1 immune checkpoint pathway primarily functions during the effector phase of the T-cell response in the peripheral tissue[1]
- In healthy tissues, PD-1 is thought to limit the activity of antigen-specific T cells to prevent collateral tissue damage during infection[1]
- In cancer, the PD-1 pathway can be exploited by some tumor cells to inactivate T cells[1]

PD-1 = programmed cell death protein 1.

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

Evasion of the Immune Response Is One of the Emerging Hallmarks of Cancer[1]



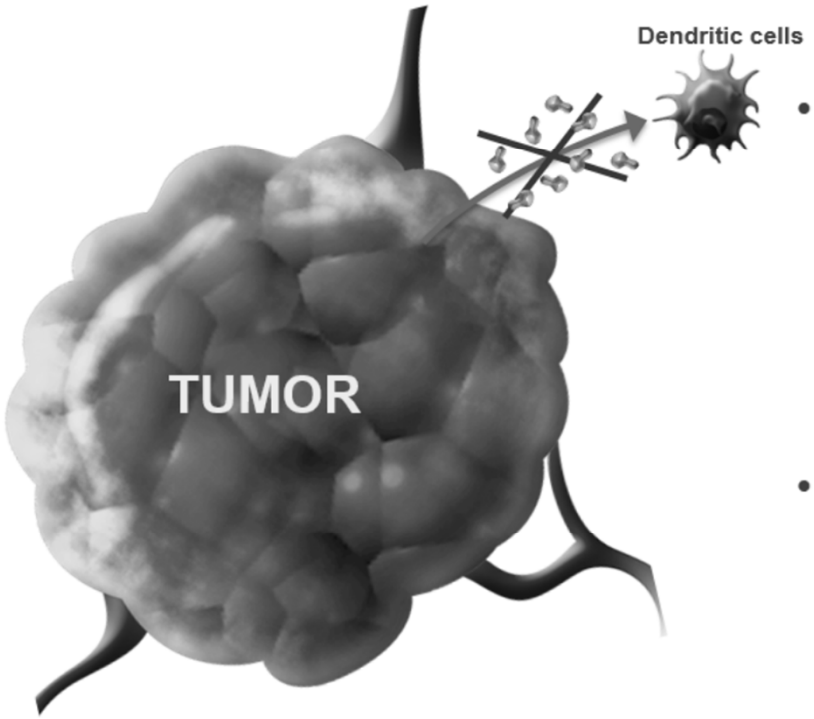
Tumor Cells Can Evade the Body's Immune Response Via Different Mechanisms

1. Loss of antigen expression[1]
2. Secreting immunosuppressive cytokines and recruiting immunosuppressive cells[2,3]
3. Exploiting immune checkpoint pathways, such as the PD-1 pathway[4]

PD-1 = programmed cell death protein 1.

1. Ahmad M et al. *Cancer Immunol Immunother*. 2004;53:844–854; **2.** Zou W. *Nat Rev Immunol*. 2006;6:295–307;
3. Finn OJ. *N Engl J Med*. 2008;358:2704–2715; **4.** Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

1. Loss of Antigen Expression

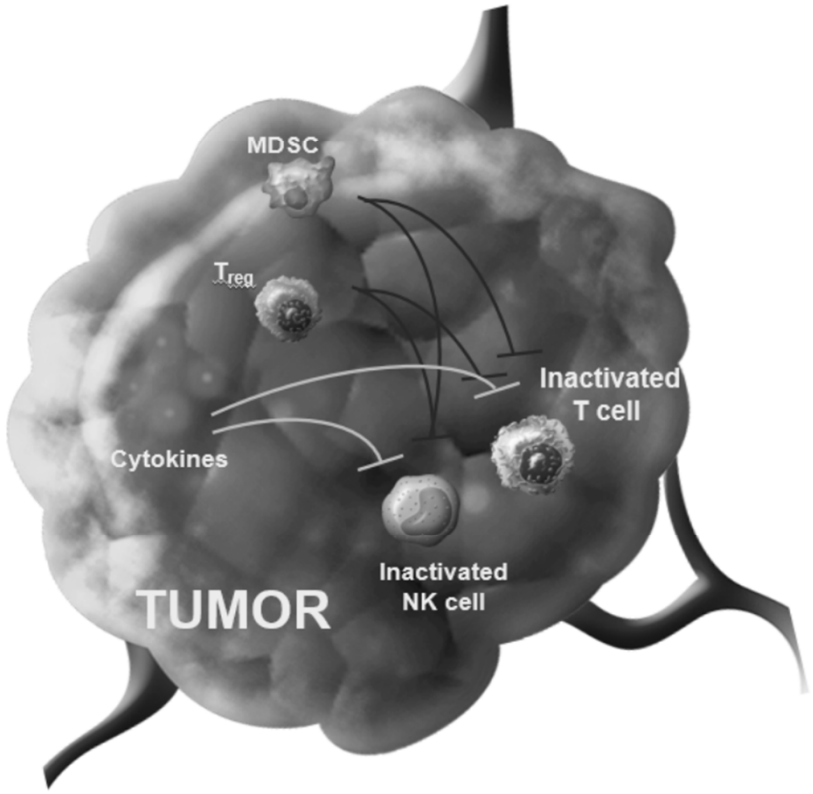


- In the adaptive immune response, the first step of tumor cell detection is antigen capture and presentation by dendritic cells[1]
- Tumors can escape detection by decreasing or completely shutting down antigen expression[2]

1. Pinzon-Charry A et al. *Immunol Cell Biol*. 2005;83:451–461.
2. Ahmad M et al. *Cancer Immunol Immunother*. 2004;53:844–854.

2. Secreting Immunosuppressive Cytokines and Recruiting Immunosuppressive Cells

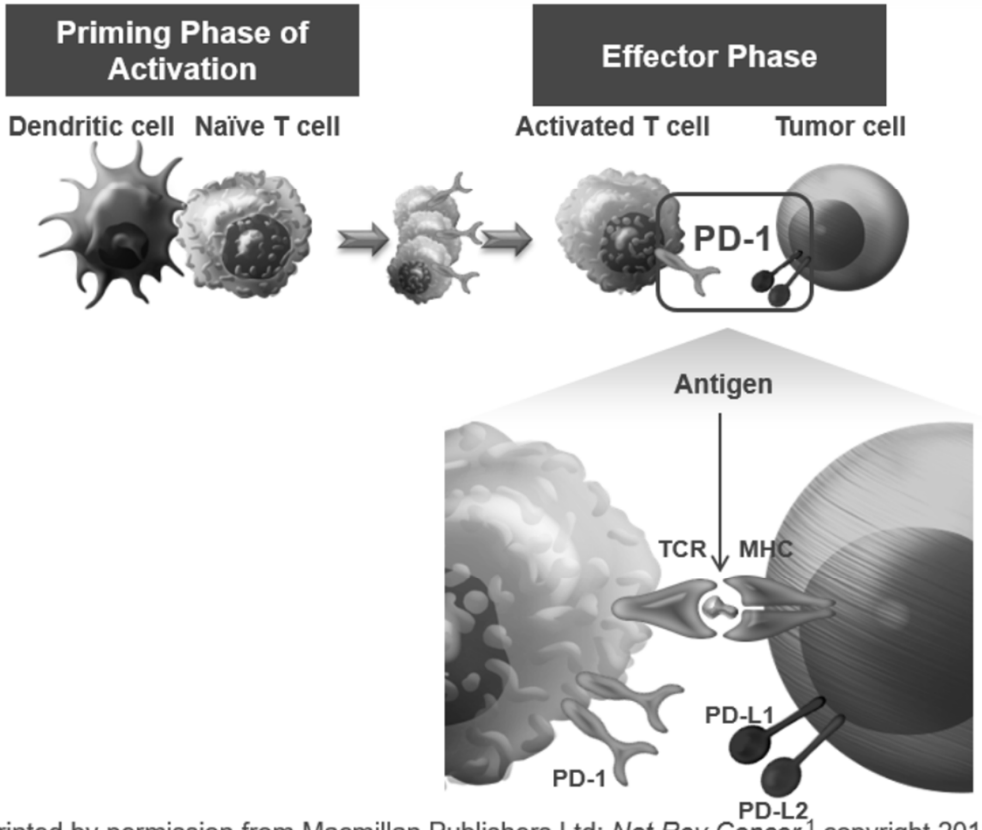
- Tumor cells can secrete cytokines (TGF-β, IL-10, VEGF) that have an inhibitory effect on T and NK cell function[1]
- Tumor cells can be infiltrated by immunosuppressive cells that can inhibit T cell function[2]:
  - T_{reg} cells
  - MDSCs



TGF-β = transforming growth factor β; IL-10 = interleukin10; VEGF = vascular endothelial growth factor; NK = natural killer; T_{reg} = T regulatory; MDSCs = myeloid-derived suppressor cells.

1. Zou W. *Nat Rev Immunol.* 2006;6:295–307; **2.** Finn OJ. *N Engl J Med.* 2008;358:2704–2715.

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



- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

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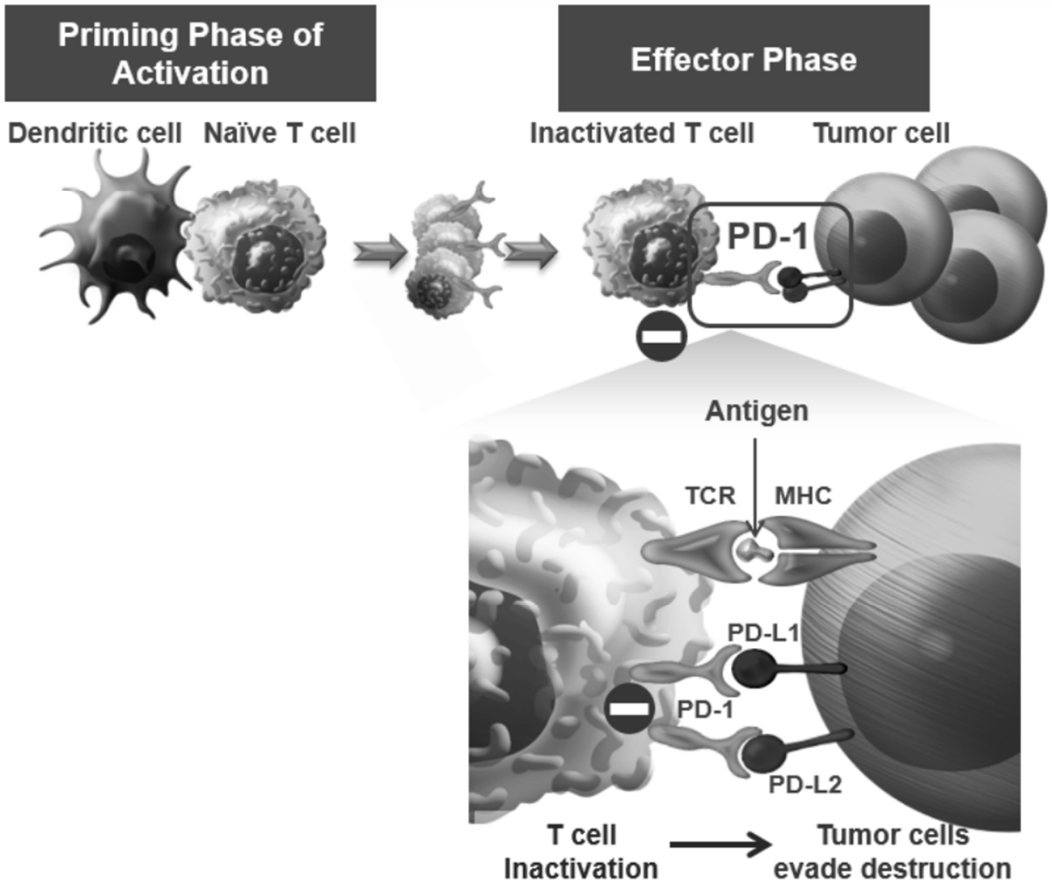
PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

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.

PD-L1 and PD-L2 Can Be Expressed on Some Tumor Cells

- PD-L1 is expressed on some tumor cells and may downregulate tumor-specific T-cell activity by binding to PD-1 in the tumor microenvironment[1–5]
  - In some tumors, high PD-L1 expression based on immunohistochemistry has been associated with a poor prognosis[6–8]
- PD-L2 may also play a role in helping tumor cells evade the immune response[8–10]
- The role of immunology in cancer, including PD-1 and its dual ligands PD-L1 and PD-L2, is a significant focus in oncology research[11]

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

1. Hino R et al. *Cancer*. 2010;116:1757–1766; **2.** Wintterle S et al. *Cancer Res*. 2003;63:7462–7467; **3.** Konishi J et al. *Clin Cancer Res*. 2004;10:5094–5100; **4.** Hamanishi J et al. *Proc Natl Acad Sci U S A*. 2007;104:3360–3365; **5.** Inman BA et al. *Cancer*. 2007;109:1499–1505; **6.** Loos M et al. *Ann Thorac Surg*. 2011;91:1025–1031; **7.** Thompson RH et al. *Cancer Res*. 2006;66:3381–3385; **8.** Nomi T et al. Clin Cancer Res. 2007;13:2151–2157; **9.** Chapon M et al. J Invest Dermatol. 2011;131:1300–1307; **10.** Karim R et al. Clin Cancer Res. 2009;15:6341–6347; **11.** Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Summary

- The body's immune system can detect and destroy tumor cells through T-cell activity[1]
- T-cell activity is regulated by various immune checkpoints in order to limit collateral tissue damage during the immune response[2]
- One way tumor cells may evade the body's immune response is by exploiting the PD-1 immune checkpoint pathway[2]

PD-L1 = programmed cell death ligand 1.

1. Finn OJ. *Ann Oncol*. 2012;23 (suppl 8): viii6–viii9; **2.** Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

Immunhistochemistry

- Deparaffinization

- Antigen Retrieval / Microwave treatment (proteases, pressure cooker, etc,)

- Blocking Serum

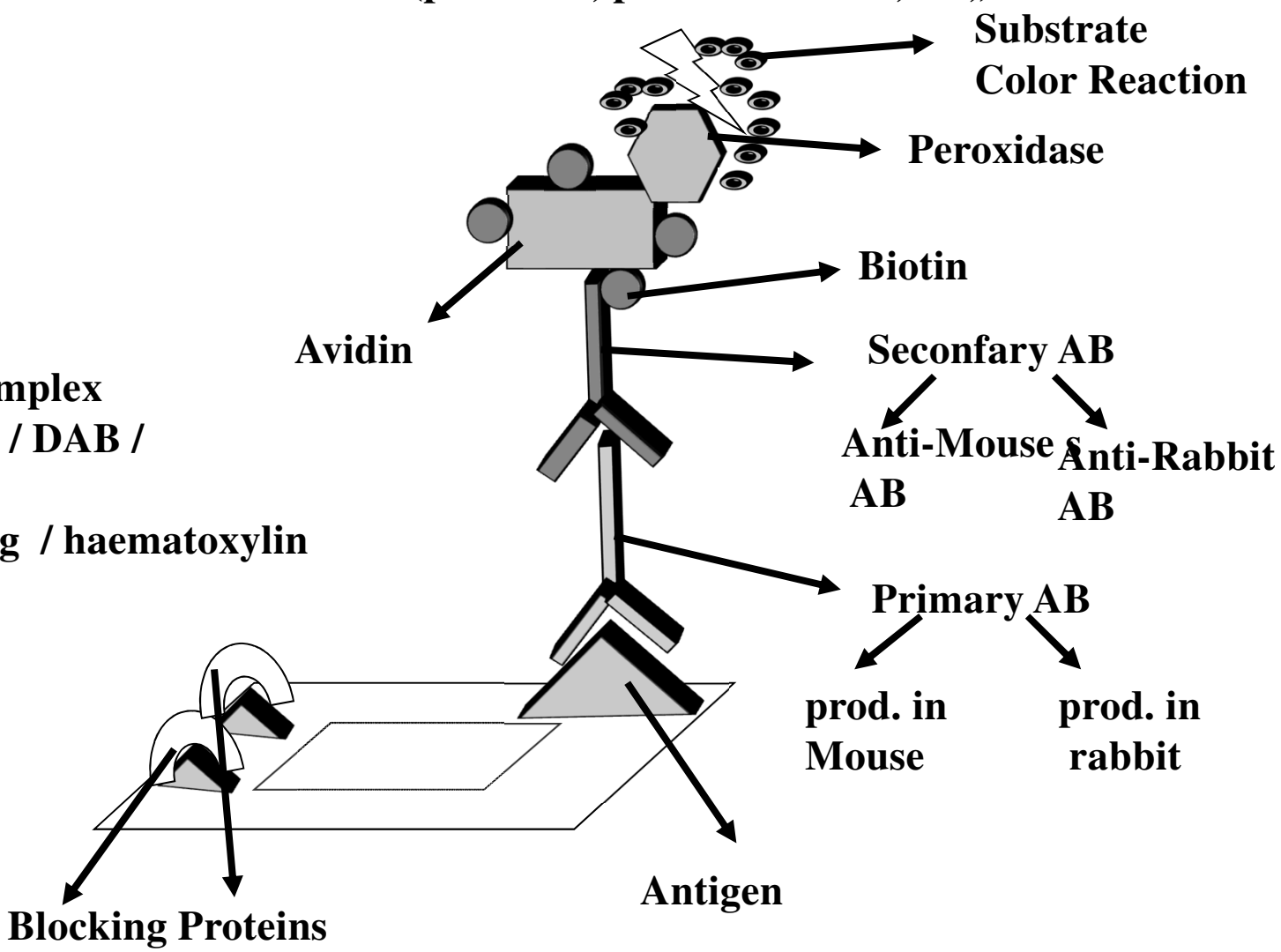
- Primayr AB

- Secondary AB

- Avidin - Biotin - Complex

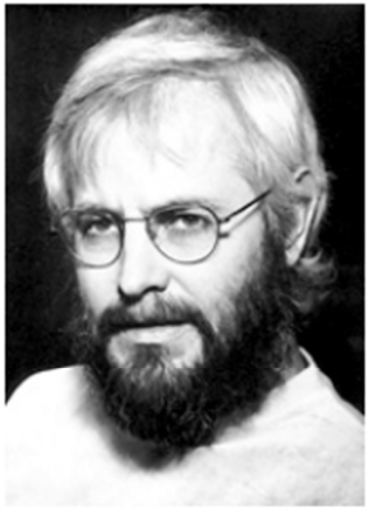
-Peroxidase Reaction / DAB /

- Backgorund staining / haematoxylin
  (Nuclei are blue)



The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne

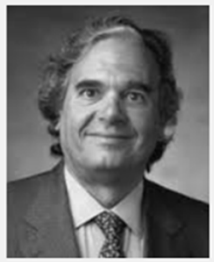


Georges J.F. Köhler

César Milstein

The Nobel Prize in Physiology or Medicine 1984 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"*.

Carlo M. Croce









Education and career

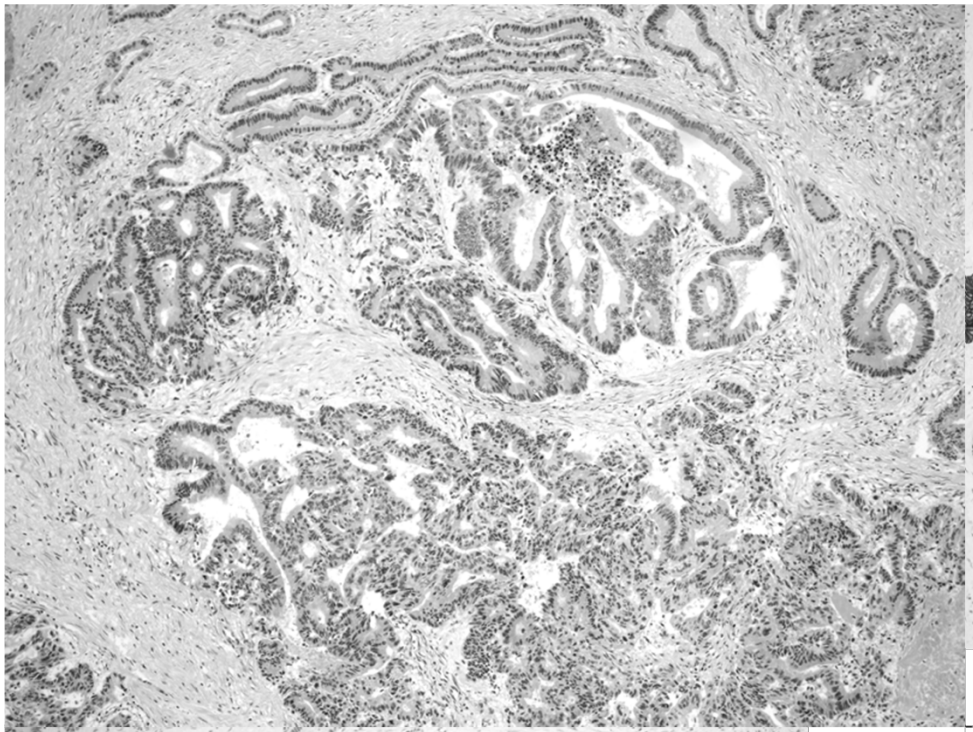
Croce was born on December 17, 1944 in Milan, Italy to a housewife and a mechanical engineer. At age 2, Croce moved to Rome with his family. In 1963 Croce entered the school of medicine of La Sapienza University of Rome and graduated in 1969 with "summa cum laude" in medicine and Latin. In his late 20's, Croce moved to Philadelphia to work at Temple University, moving to Thomas Jefferson University shortly thereafter (1990), where he stayed for more than 15 years.

Dr. Croce earned his medical degree, summa cum laude, in 1969 from the School of Medicine, University of Rome. He began his career in the United States the following year as an associate scientist at the Wistar Institute of Biology and Anatomy in Philadelphia. In 1980, he was named Wistar Professor of Genetics at the University of Pennsylvania and associate director of the Wistar Institute, titles he held until 1988. From 1988-91, he was director of the Fels Institute for Cancer Research and Molecular Biology at Temple University School of Medicine in Philadelphia. In 1991, Dr. Croce was named Director of the Kimmel Cancer Center at Jefferson Medical College at the Thomas Jefferson University, in Philadelphia. While at Jefferson, he discovered the role of microRNAs in cancer pathogenesis and progression, implicating a new class of genes in cancer causation. In 2004 he moved to The Ohio State University. Under his direction at Ohio State faculty within the Human Cancer Genetics Program conduct both clinical and basic research. Basic research projects focus on how genes are activated and inactivated, how cell-growth signals are transmitted and regulated within cells, and how cells interact with the immune system. Clinical research focuses on discovering genes linked to cancer and mutations that predispose people to cancer.

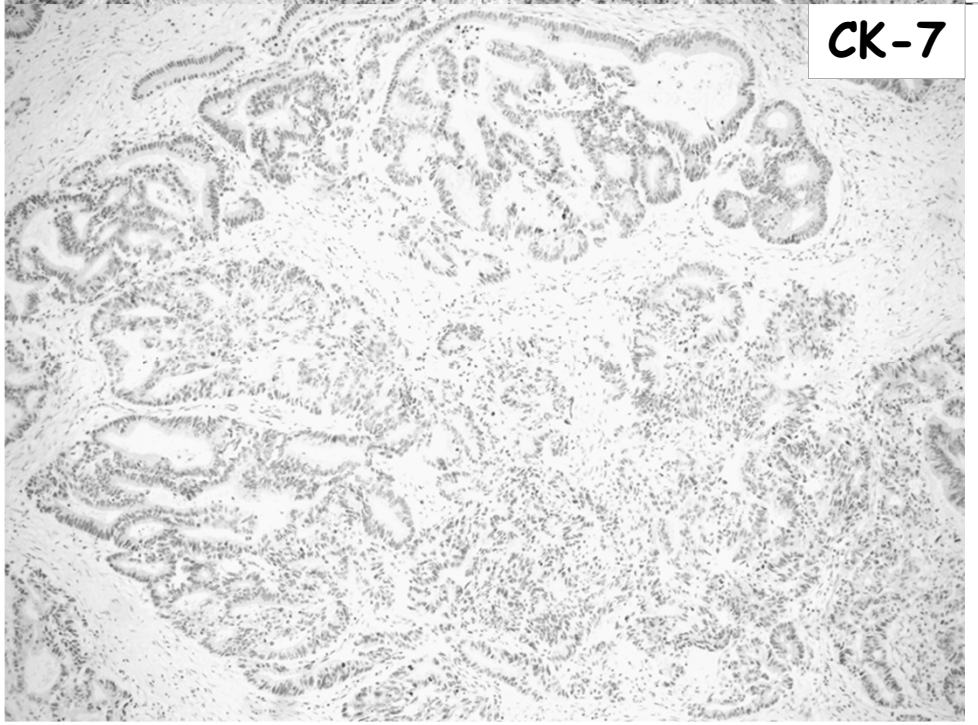
Discoveries and awards

A brilliant researcher whose work has revealed cancer is the result of somatic genetic changes, he has received the 30th Annual Jeffrey A. Gottlieb Memorial Award. He has discovered the juxtaposition of the human immunoglobulin genes to the MYC oncogene and the deregulation of MYC in Burkitt lymphoma, the MLL gene involved in acute leukemias, the TCL1A gene associated with T-cell leukemias, and cloned, named and characterized the BCL2 gene involved in follicular lymphoma. Dr. Croce has also uncovered the early events involved in the pathogenesis of lung, nasopharyngeal, head and neck, esophageal, gastrointestinal and breast cancers. His discoveries have led to revolutionary innovations in the development of novel and successful approaches to cancer prevention, diagnosis, monitoring and treatment, based on gene-target discovery, verification and rational drug development.

Dr. Croce, a member of the National Academy of Sciences in the US and the Accademia Nazionale delle Scienze detta deiXL in Italy, has received almost every significant award for cancer research that one can earn. He was awarded two Outstanding Investigator awards from the National Cancer Institute, the Richard and Hinda Rosenthal Foundation Award and the G.H.A. Clowes Memorial Award from the American Association for Cancer Research, the John Scott Award, the Robert J. and Claire Pasarow Foundation Cancer Award, the GM Cancer Research Foundation - Charles S. Mott Prize, the Scanno Prize for Medicine, the AACR-Pezcoller Award, the Raymond Bourgine Award and Gold Medal of Paris and President of the Republic Prize, the iwCLL Binet-Rai-Medal for Outstanding Contribution to CLL Research, the Henry M. Stratton Medal from the American Society of Hematology, the Albert Szent-Györgyi Prize for Progress in Cancer Research, the Leopold Griffuel Prize awarded by the French Association for Cancer Research, The Ernst W. Bertner Memorial Award, The University of Texas M. D. Anderson Cancer Center and most recently, an Elected Member of The American Academy of Arts and Sciences. He is principal investigator on seven federal research grants and has more than 875 peer-reviewed, published research papers. [3]

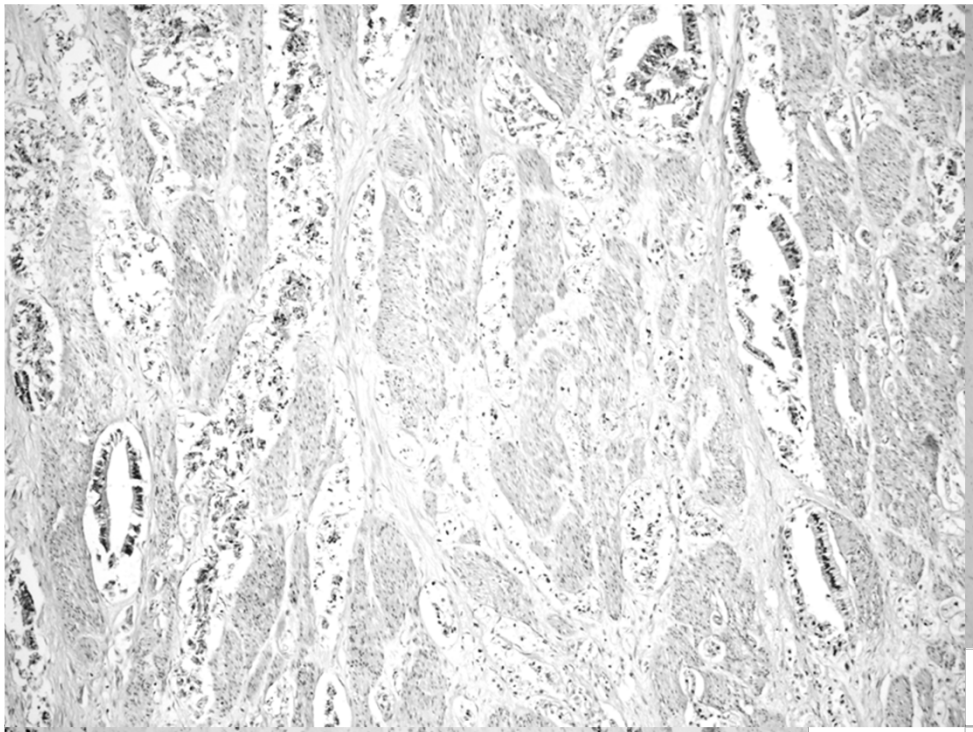


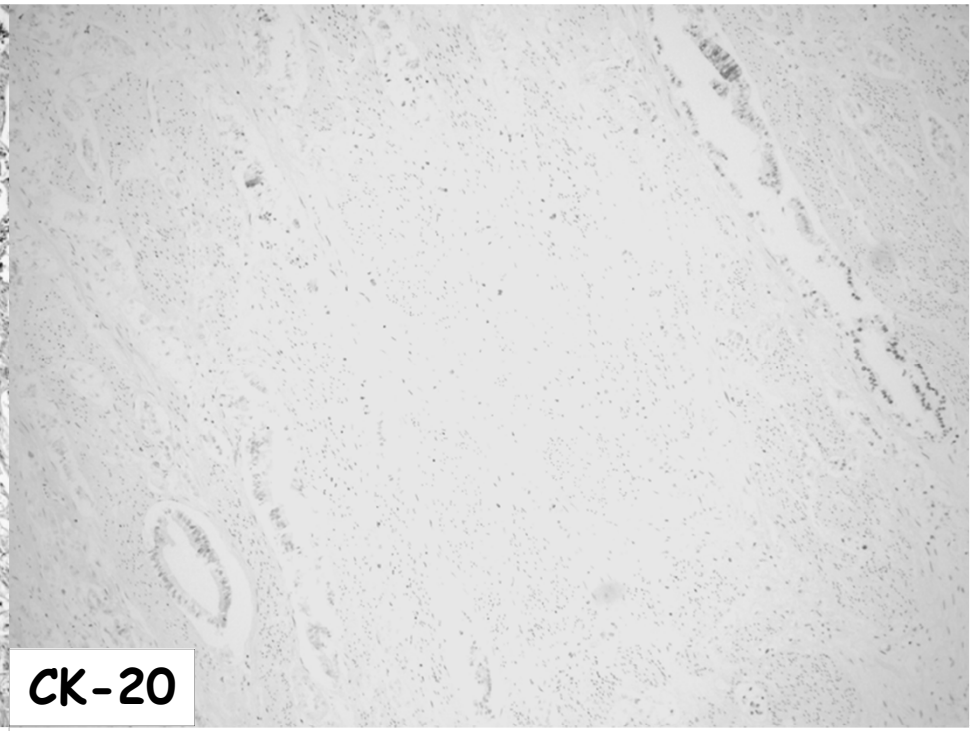
CK-20



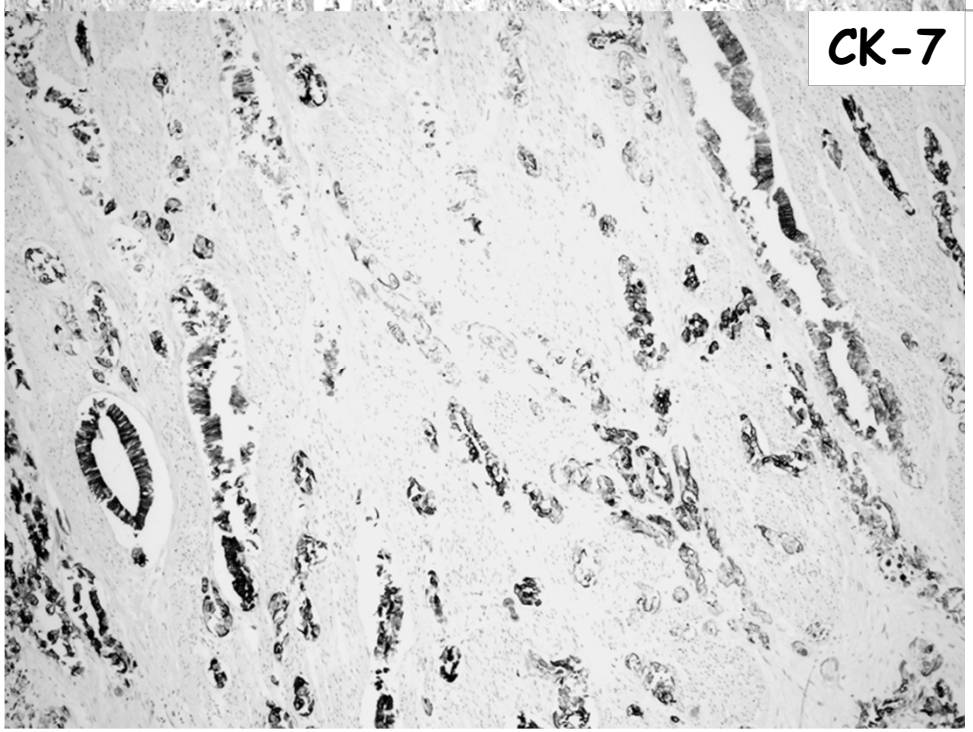
CK-7

Large Int. – Sigma carcinoma



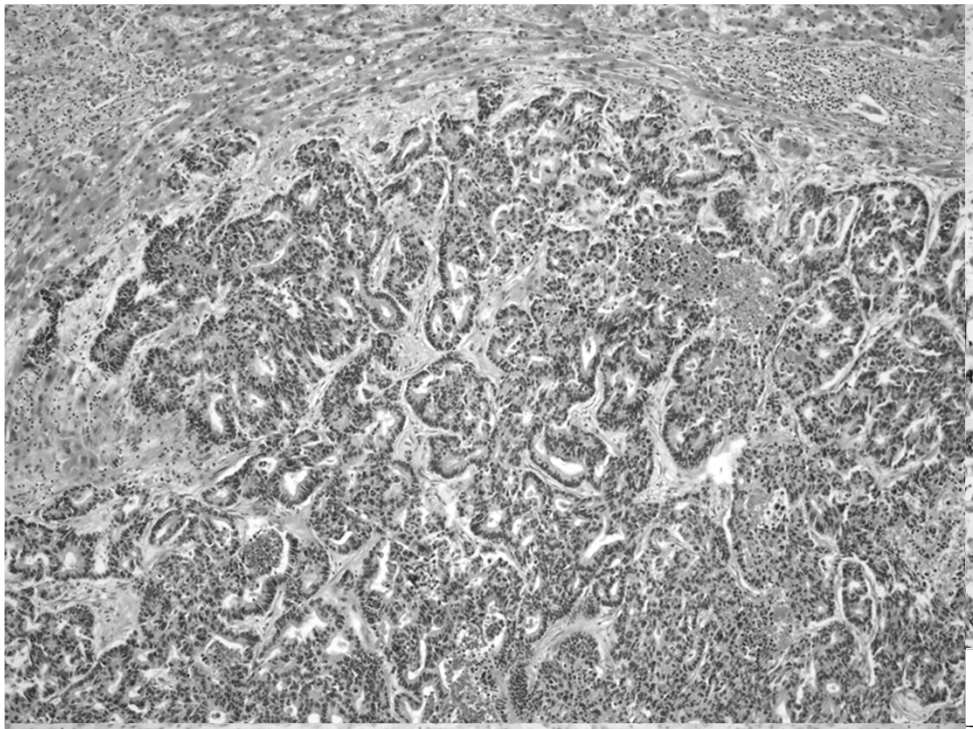


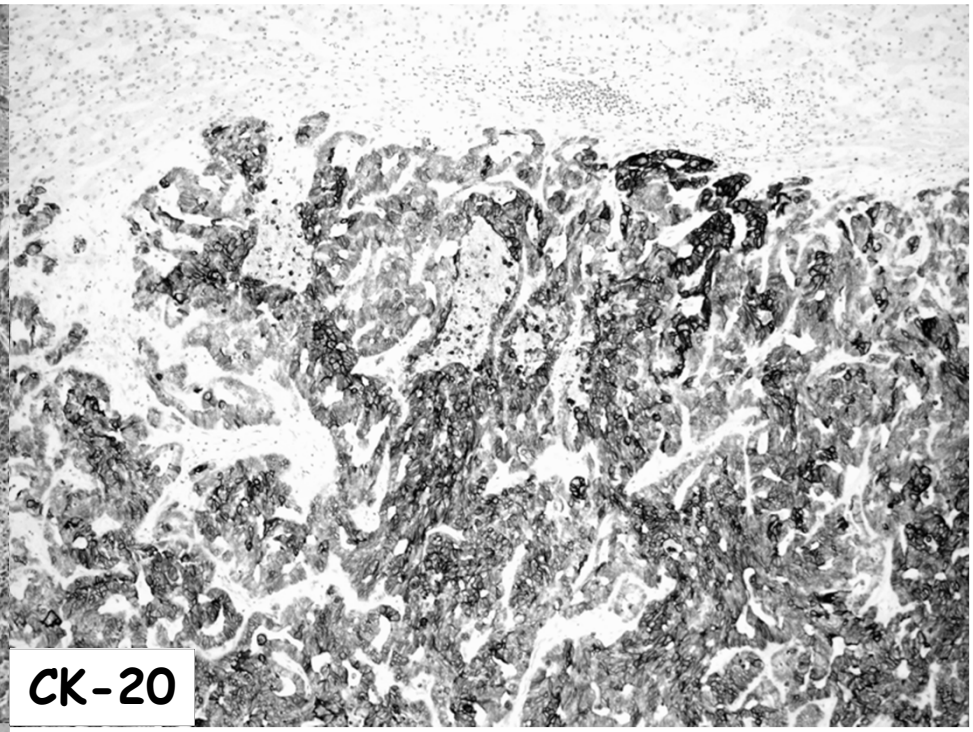
CK-20

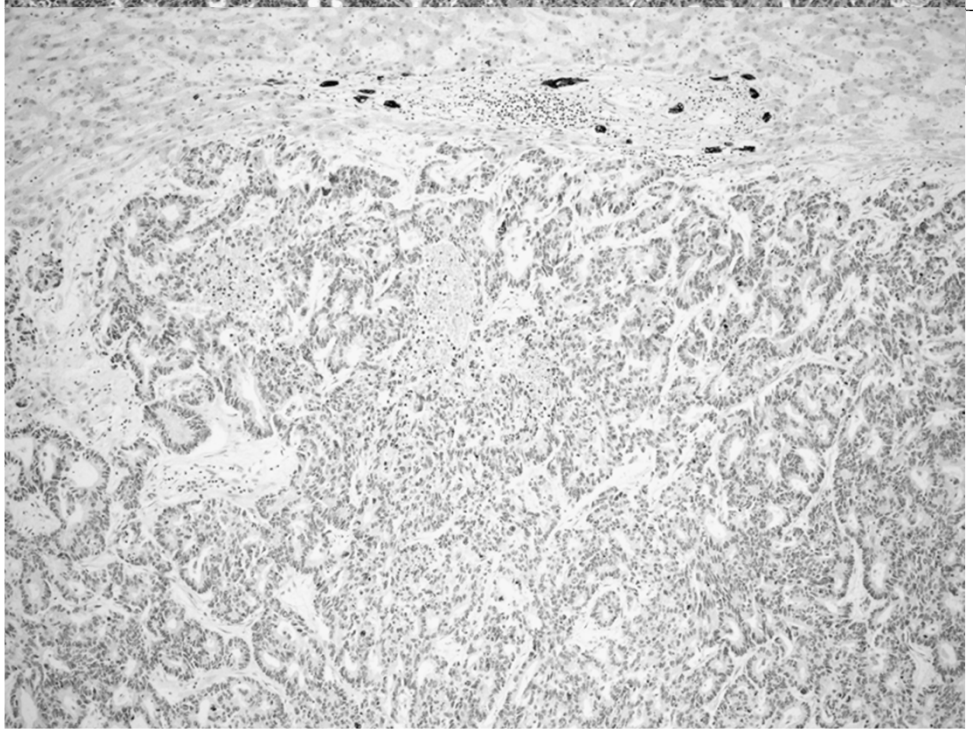


CK-7

STOMACH - gastric carcinoma







Liver – Liver metastasis

THEREFORE, the liver metastasis derived from the sigma tumor but the gastgric cancer.

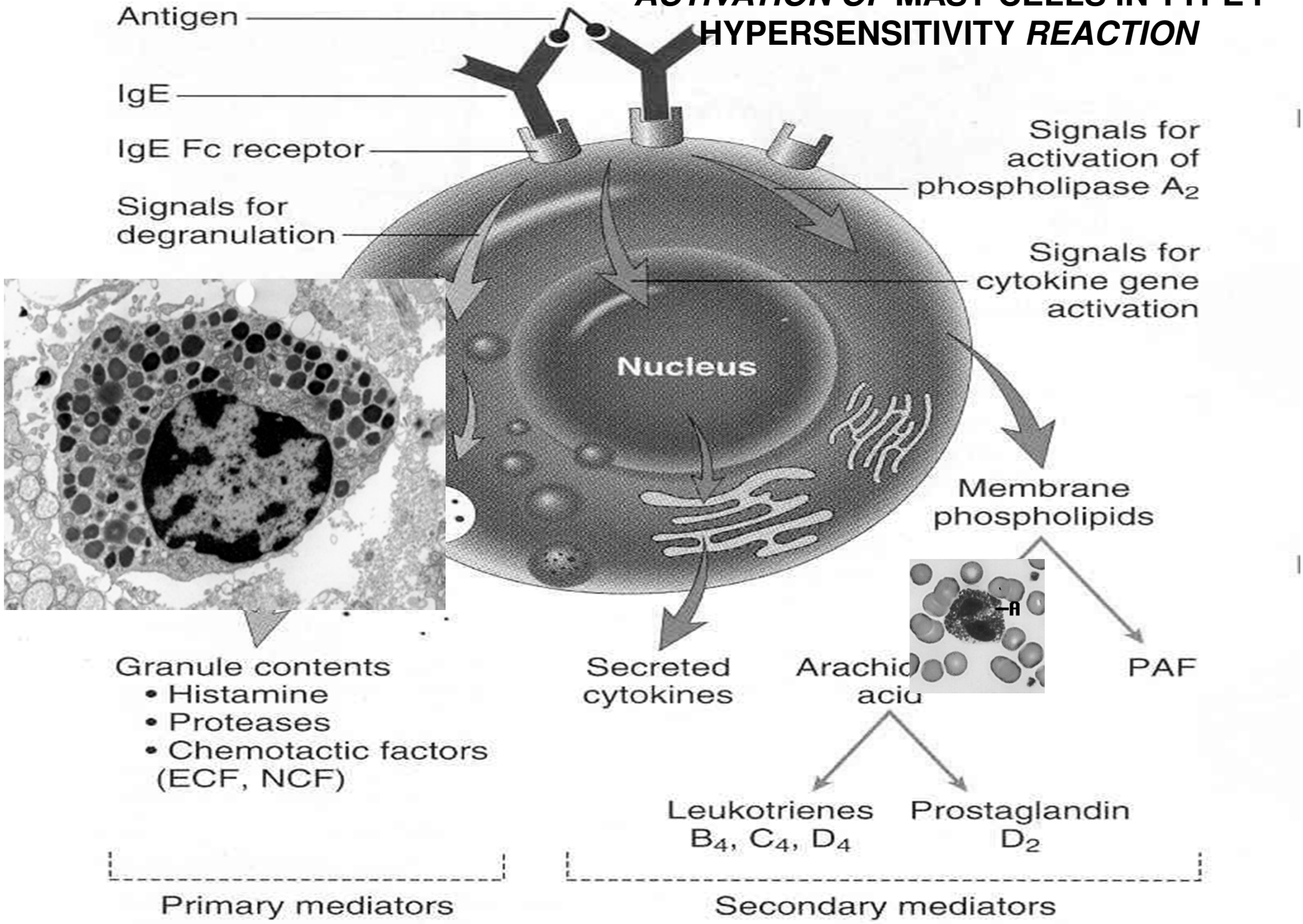
Typ I. Hypersensitivity Reaction

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

DEGRANULATION

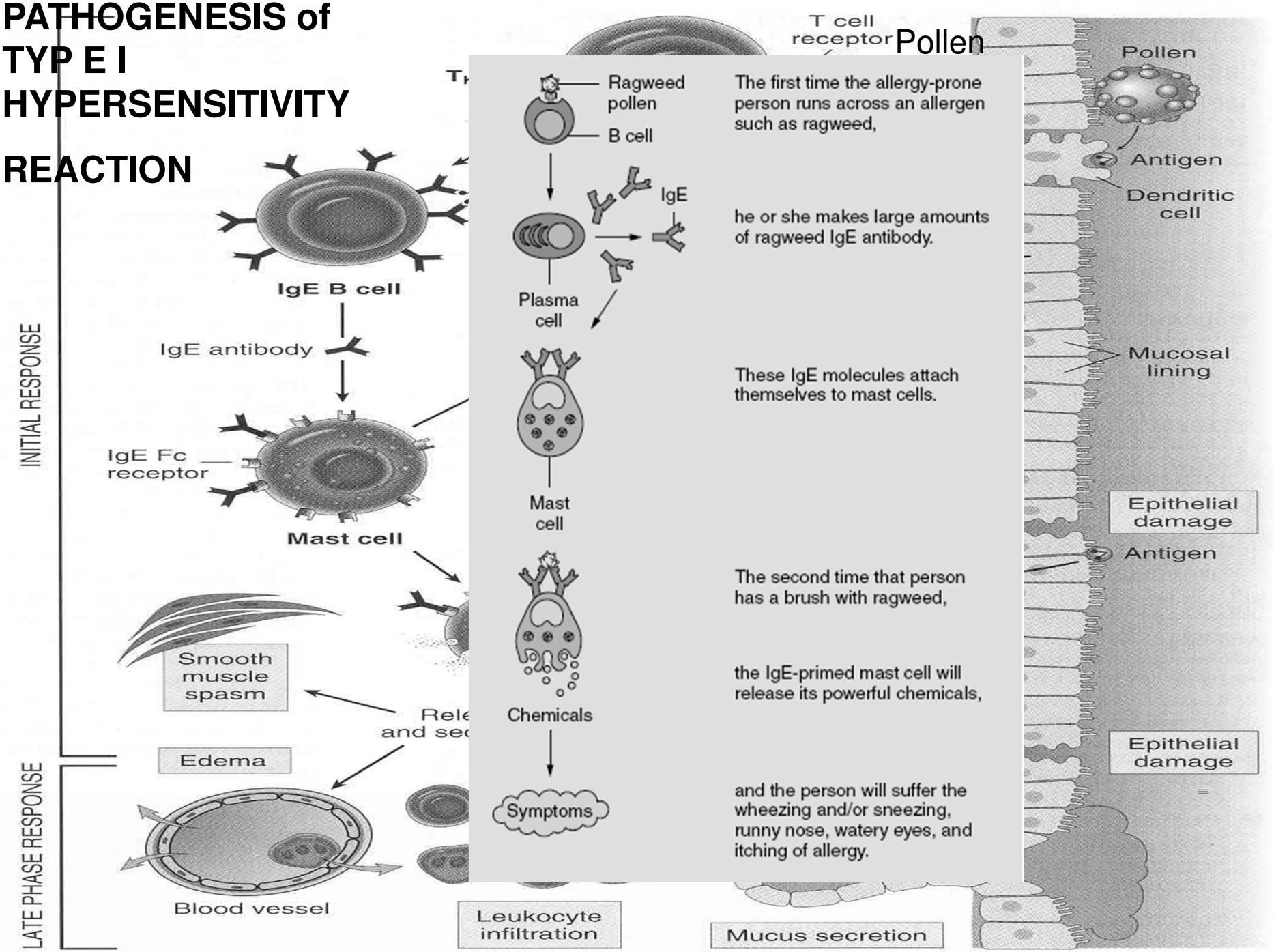
LTB4	Histamin	Histamin
Chemotactic	PAF	LTD4
Faktors		
Zytokine	PGE2	PE
	LTD4E4	PAF
Chemotaxis/Exsudation	Vasodilatation	Spasmus of smooth muscles
Glattmuskulatur		
	increased permeability of the vessels	
Eosinophile		
Mckrophage	EDEMA	

ACTIVATION OF MAST CELLS IN TYPE I HYPERSENSITIVITY *REACTION*



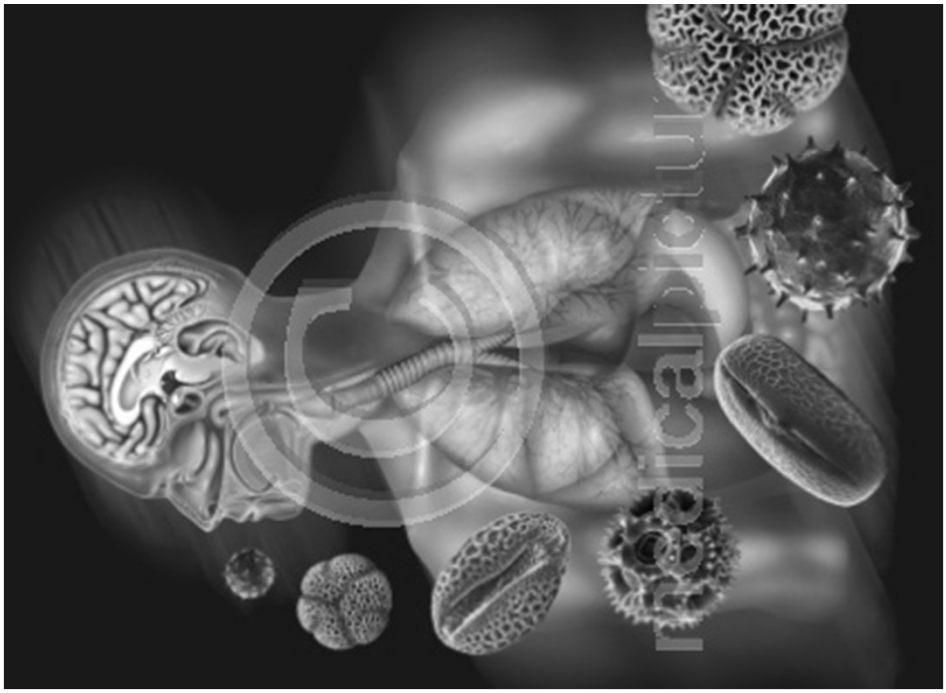
PATHOGENESIS of TYP E I HYPERSENSITIVITY

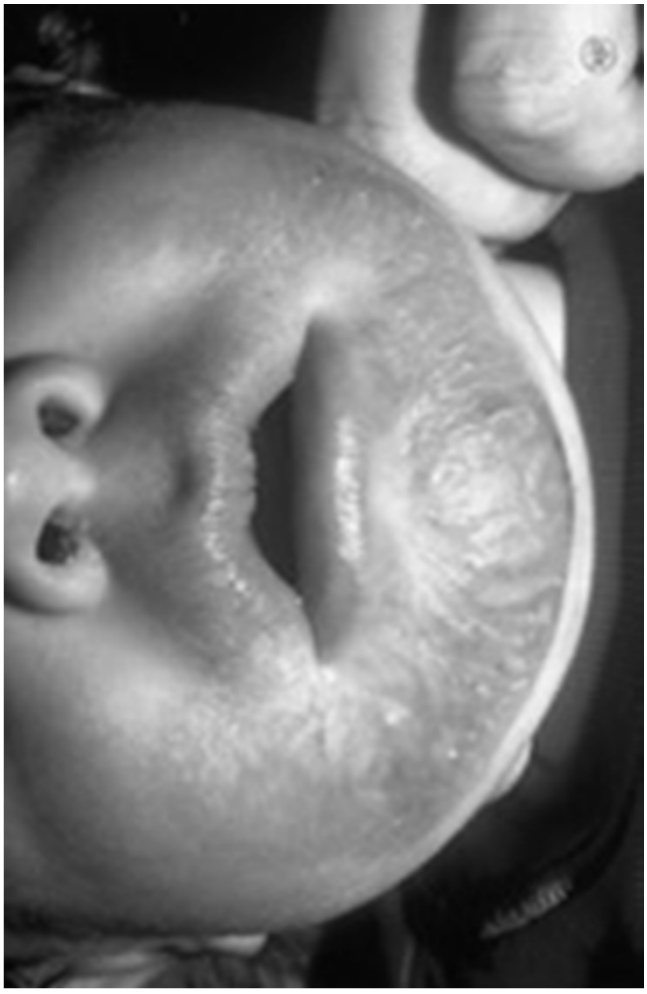
REACTION



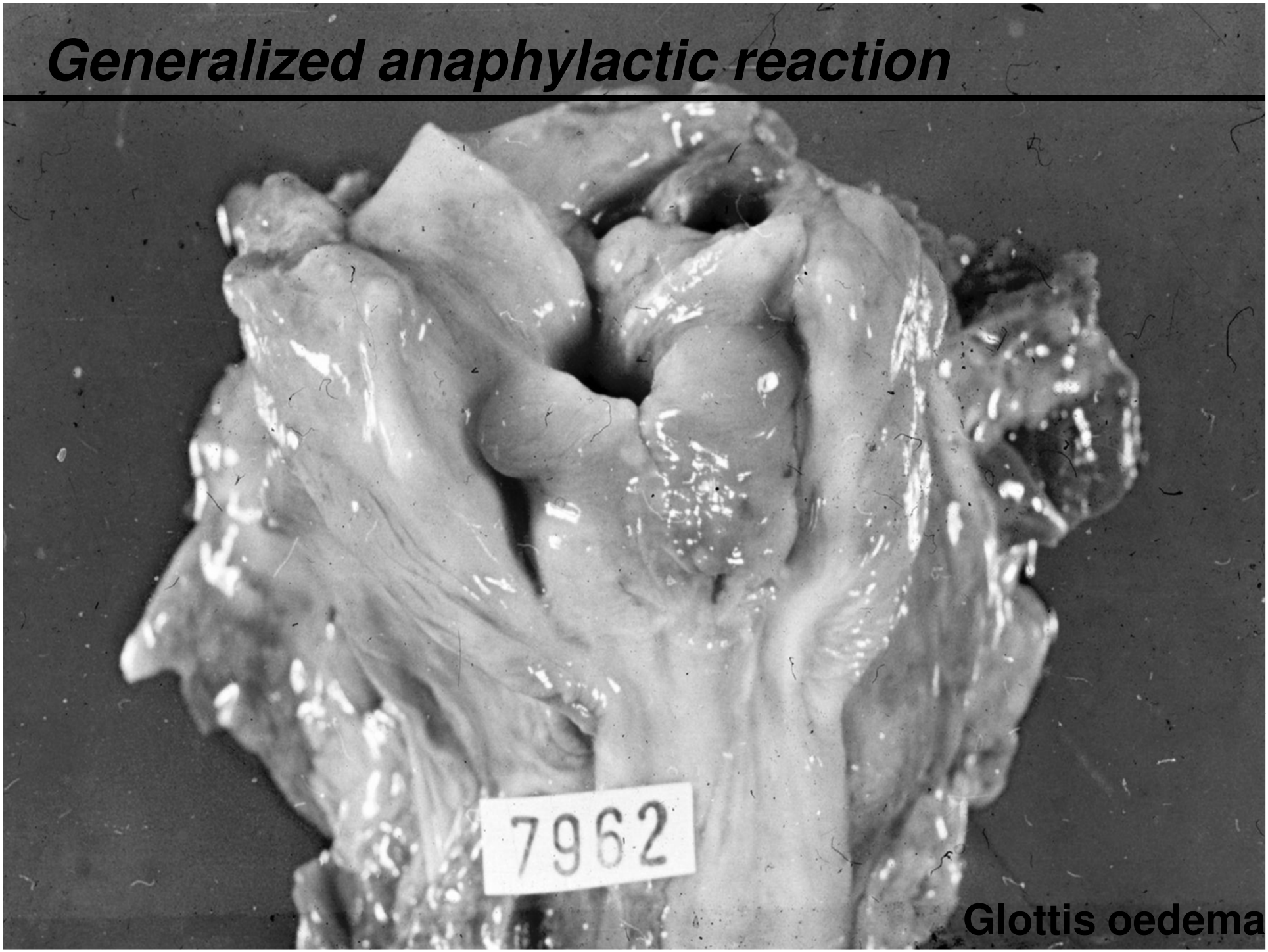
Allergy

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





Generalized anaphylactic reaction



Glottis oedema

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

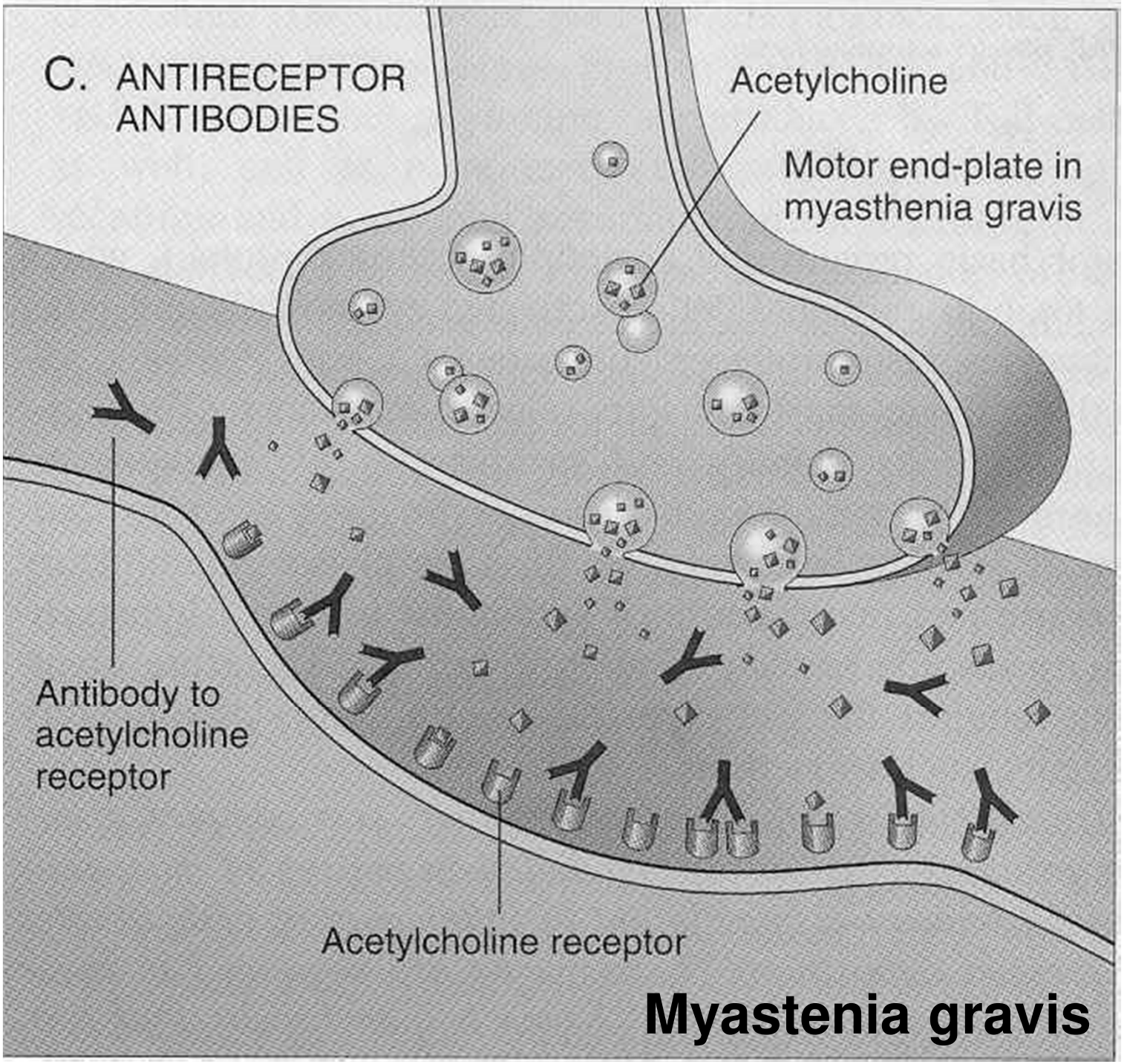
Anti Receptor AB mediated

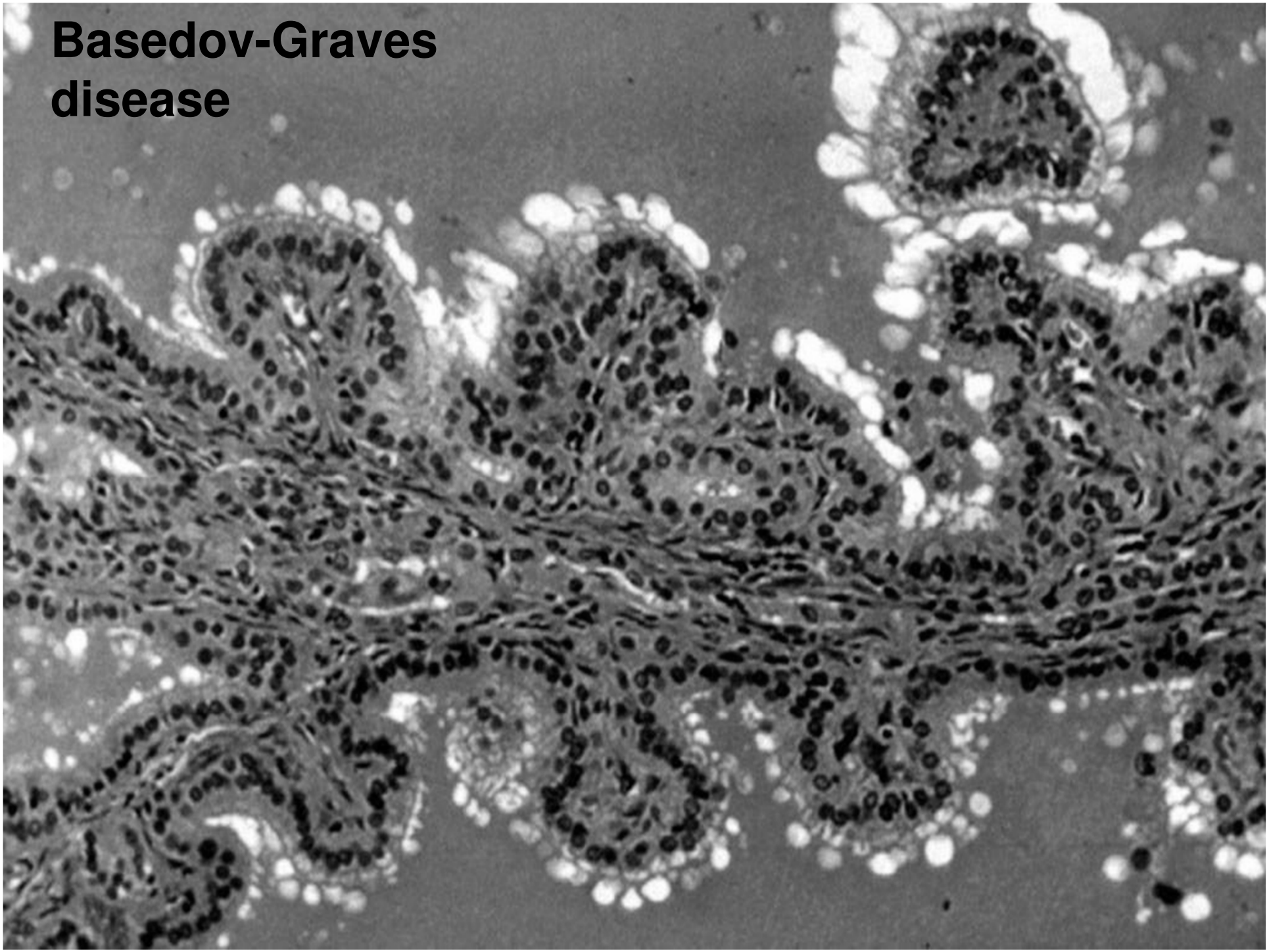
Anti-receptor-AB Production

Target cell AB Binding

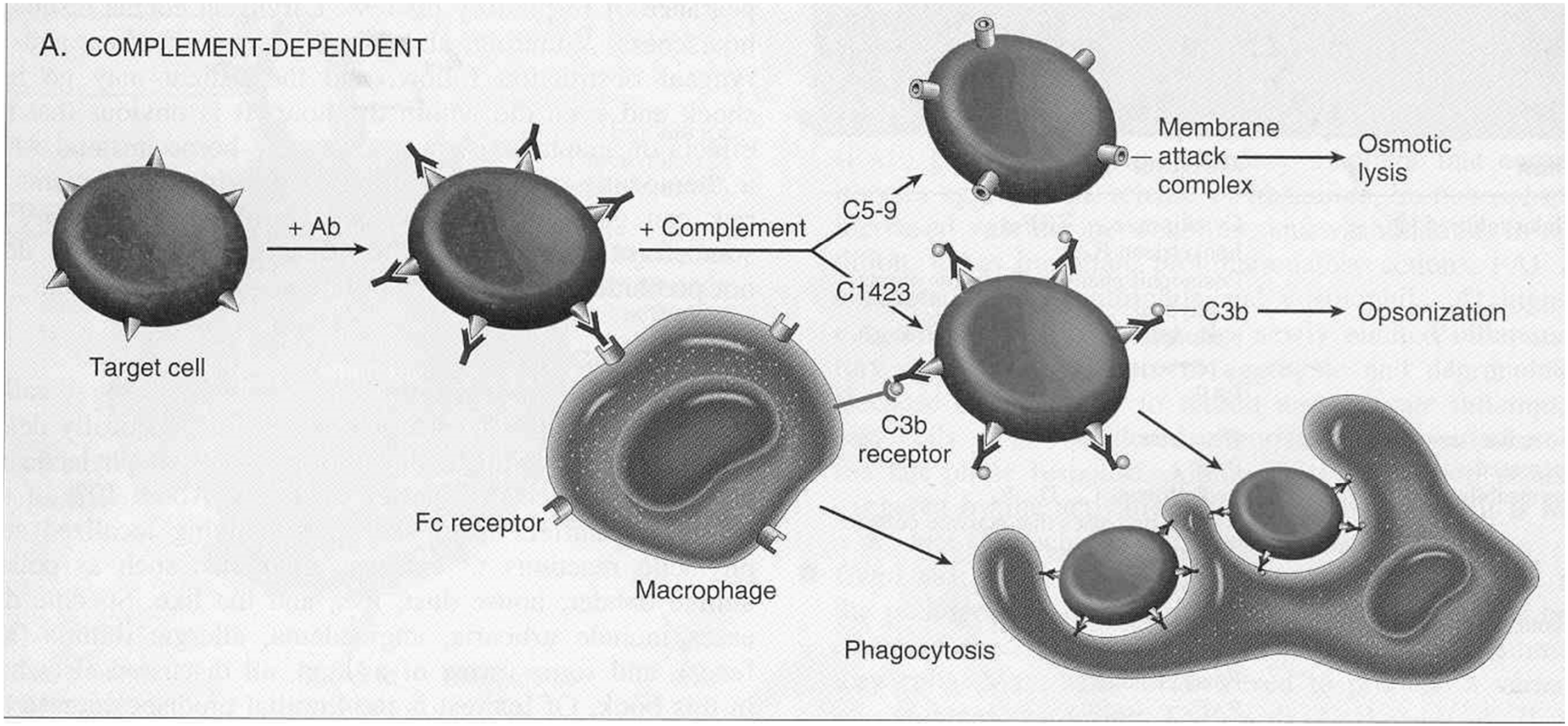
Receptor-Inhibition Receptor-activation

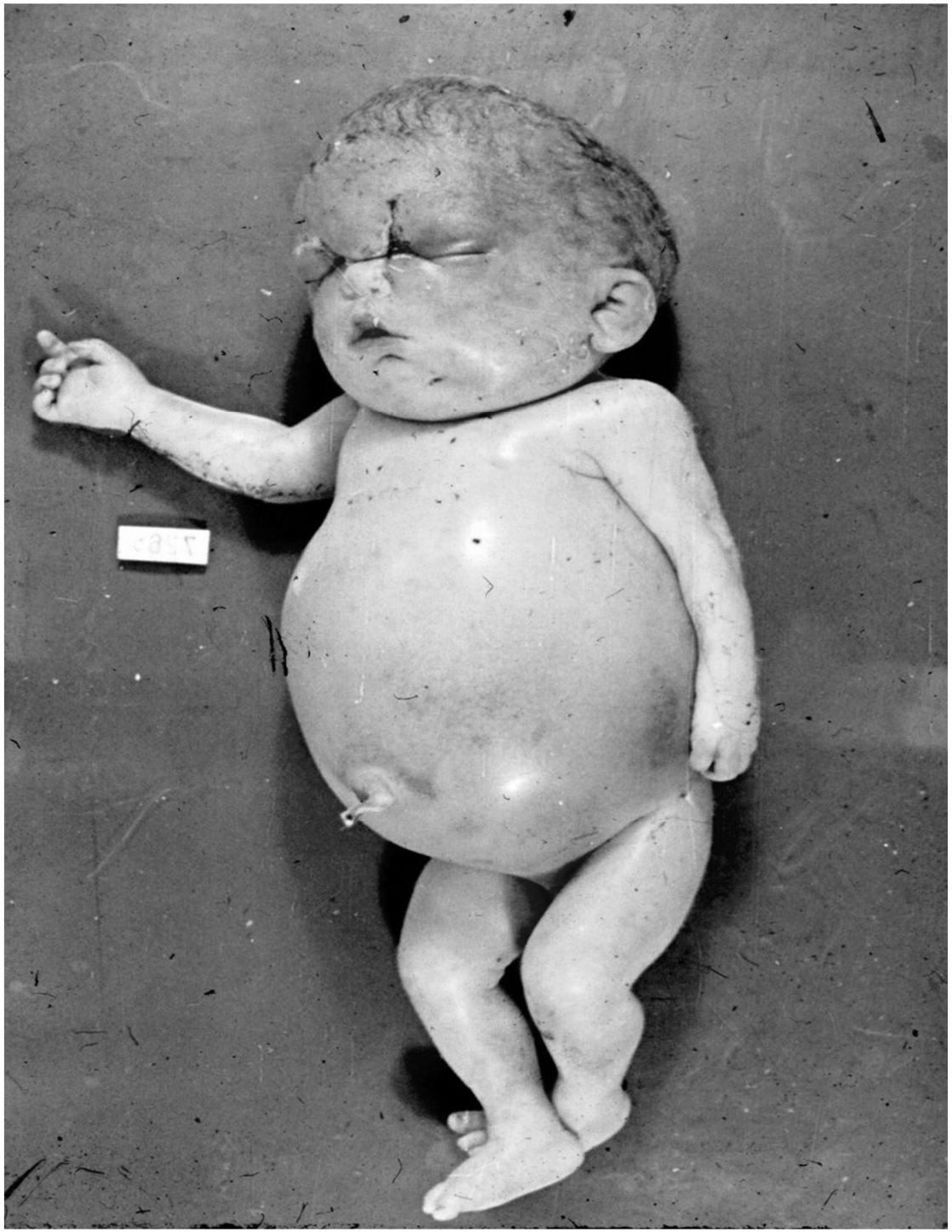
(AchR, myasthenia gravis) (TSHR, Hyperthyreosis)


C. ANTIRECEPTOR ANTIBODIES
Acetylcholine
Motor end-plate in myasthenia gravis
Antibody to acetylcholine receptor
Acetylcholine receptor
Myastenia gravis


Basedov-Graves
disease

Typ II. Hypersensitivity Reaction *(cytotoxic)*

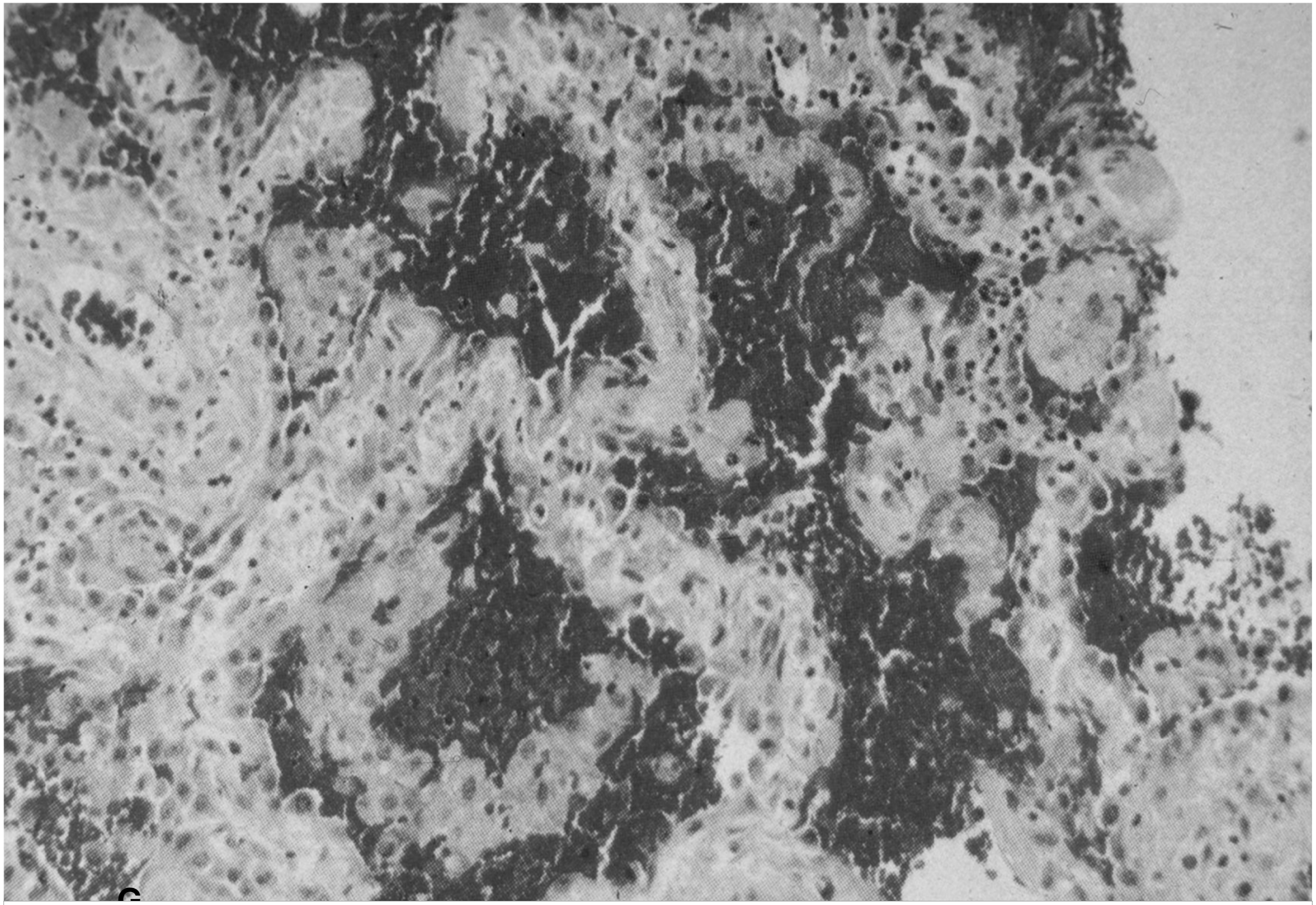




Hydrops foetus universalis

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

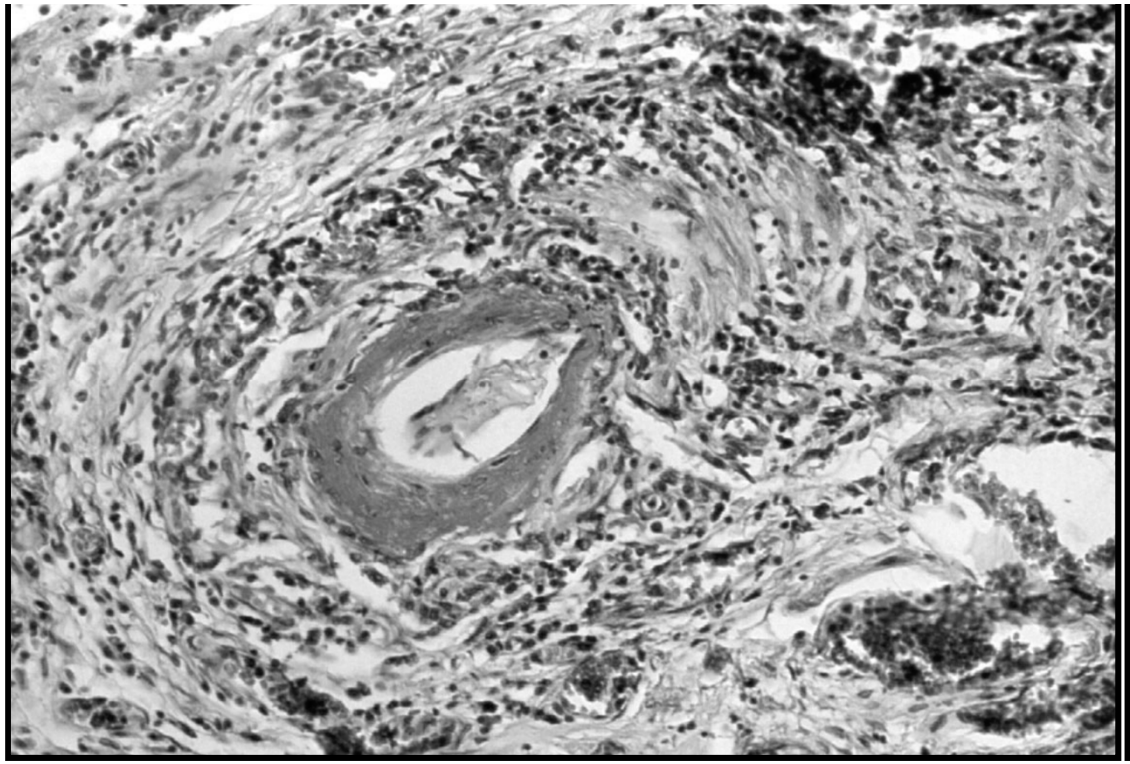
Edema — Ischemia

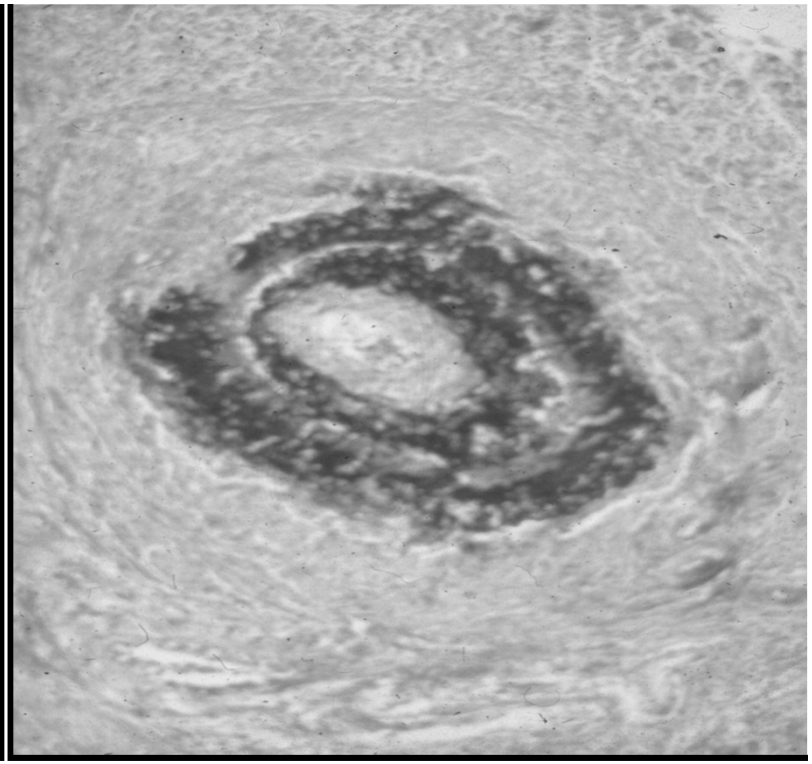
tissue necrosis

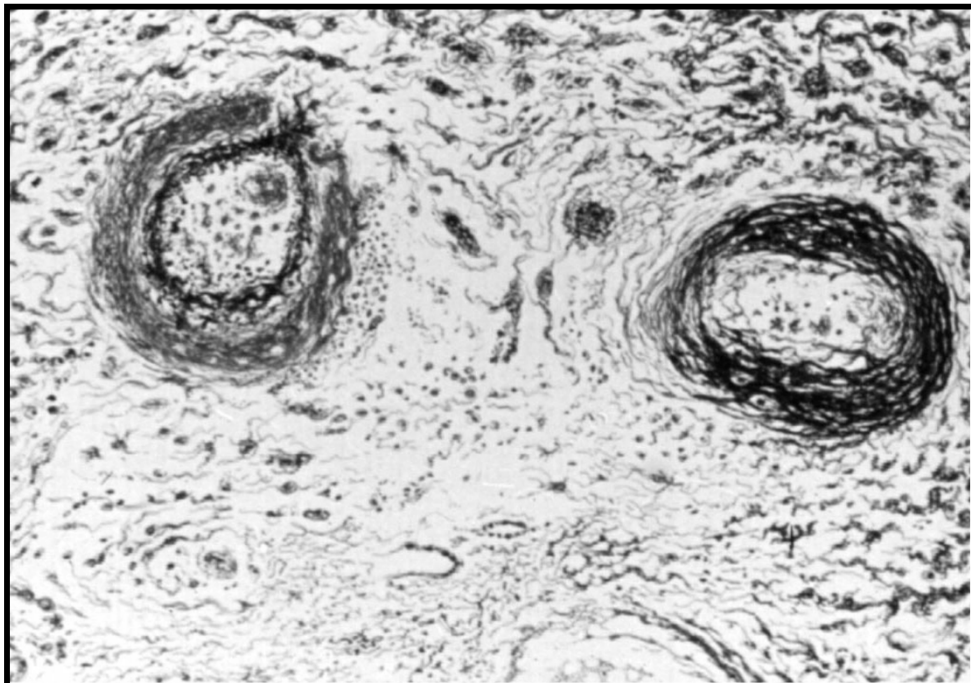
Patomechanismus

- 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)





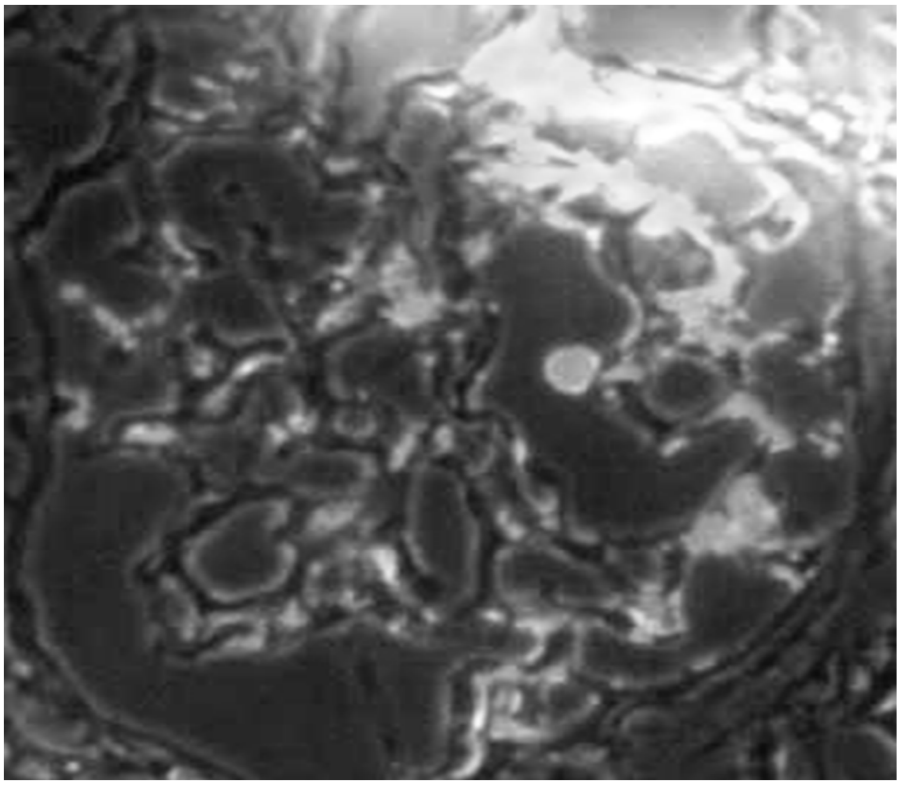


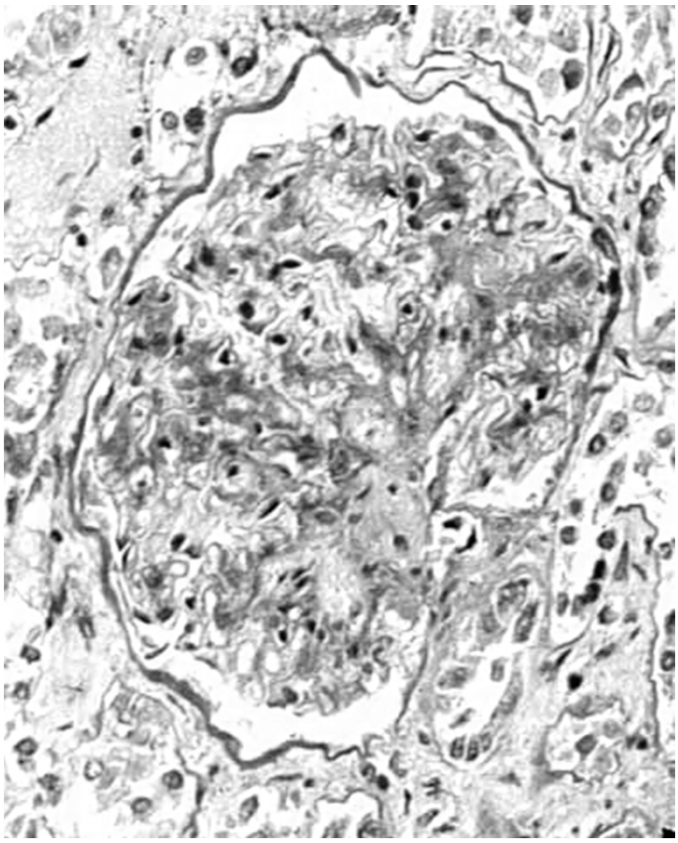
Major finding:

***Nekrotising Va*skulitis**

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

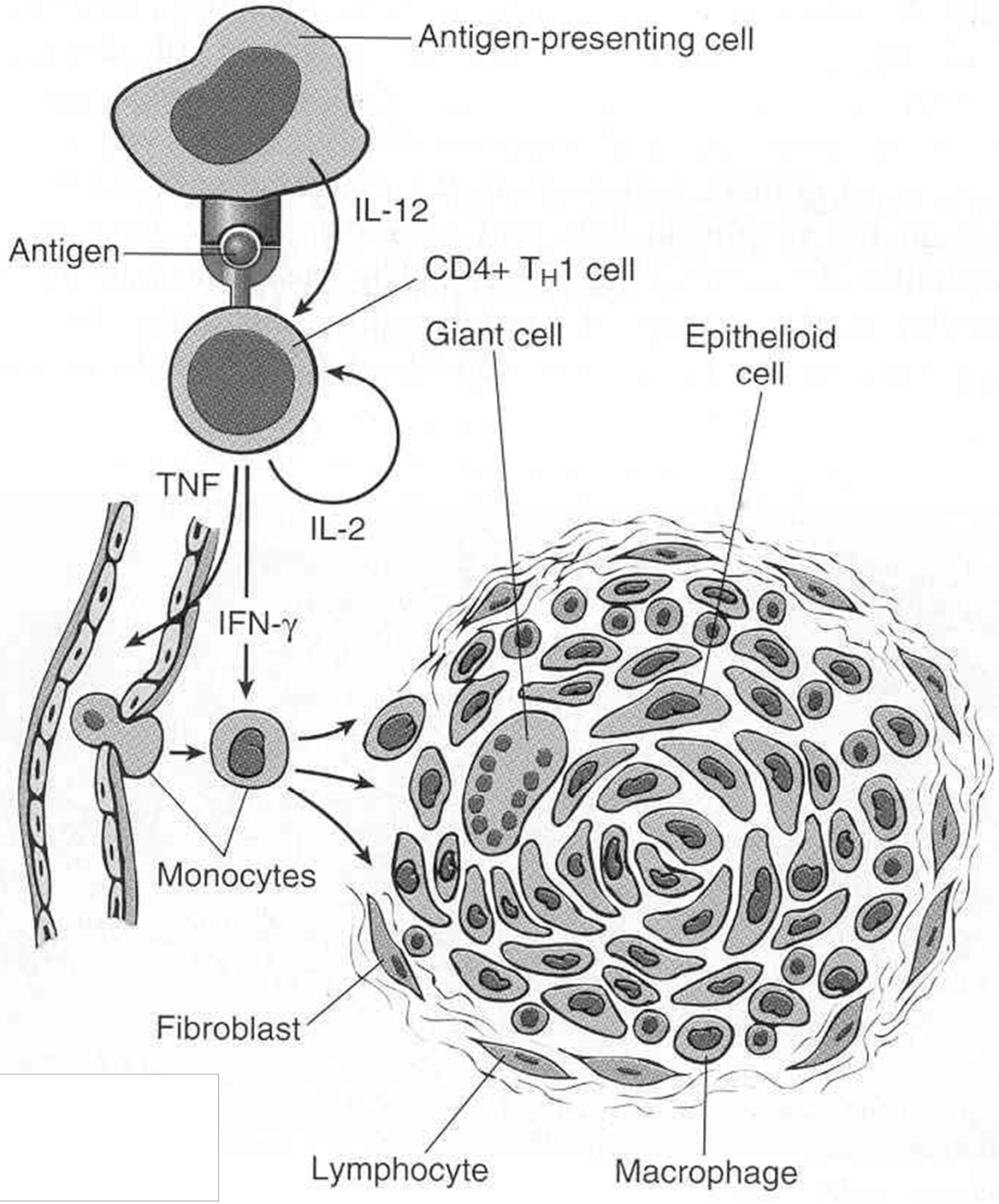
Giant cells –development

(Langhans, foregin body type)

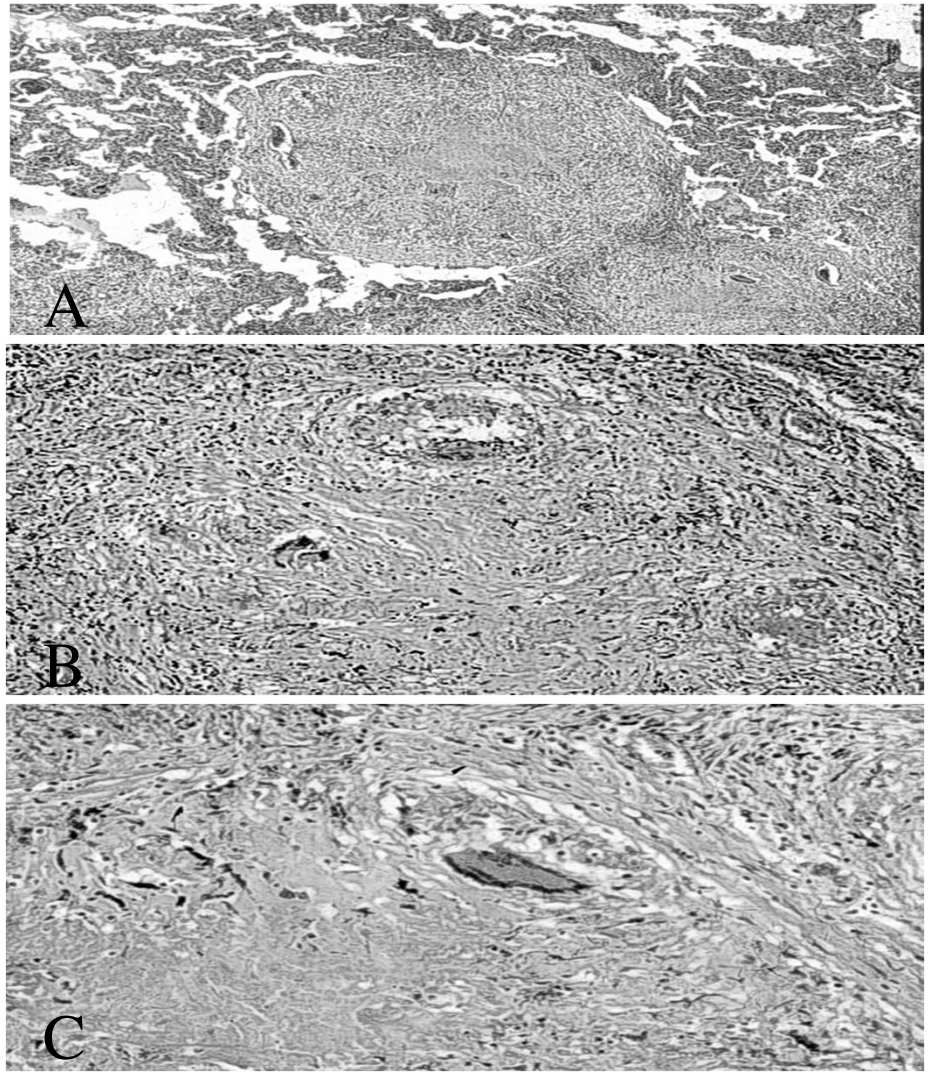
B. T-Zell mediated cellulare Zytotoxicity

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+ ypoparathyr.), 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 –

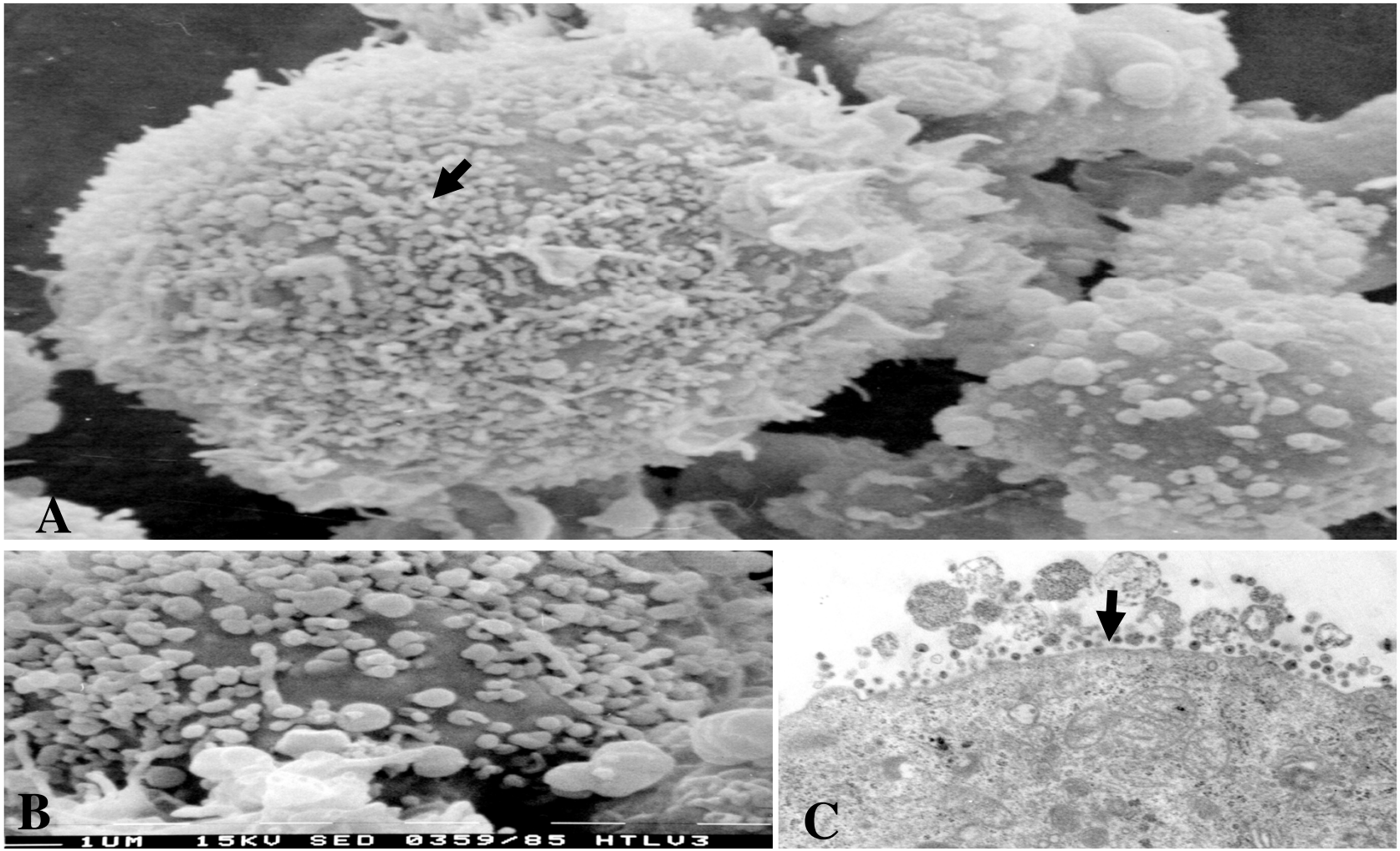
Defect of the cellular immunity → oportunistic infections

causes:: humane Immundefect virus (HIV)

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

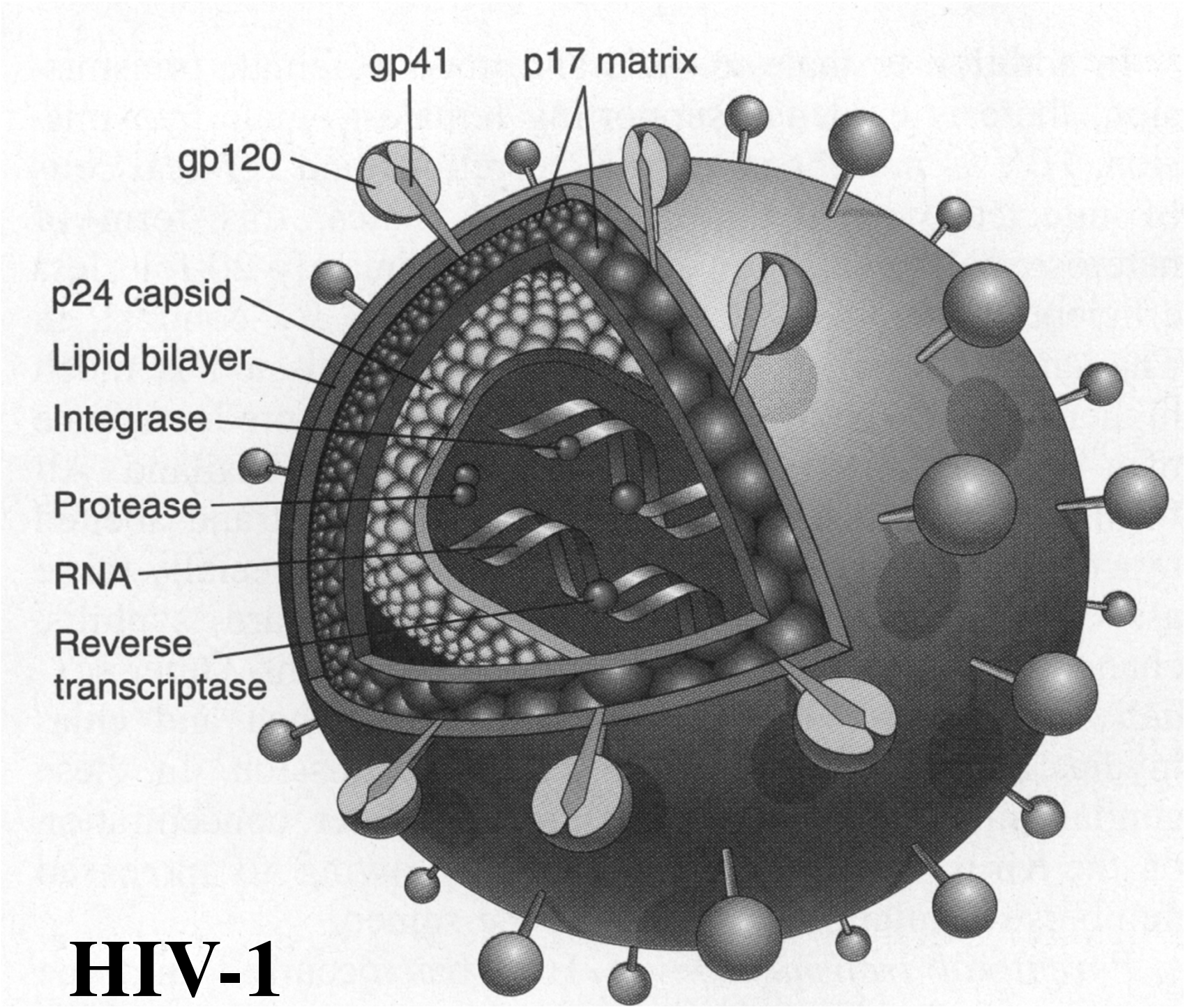
Main receptor: CD4-Antigen of the T4 lymhocytes
for gp120 makrophages
skin -Langerhans-Zellen
follicular retikulum cells

Parallel receptor: Galaktosylzeramid Oligodendrocytes
follikular retikulum cells



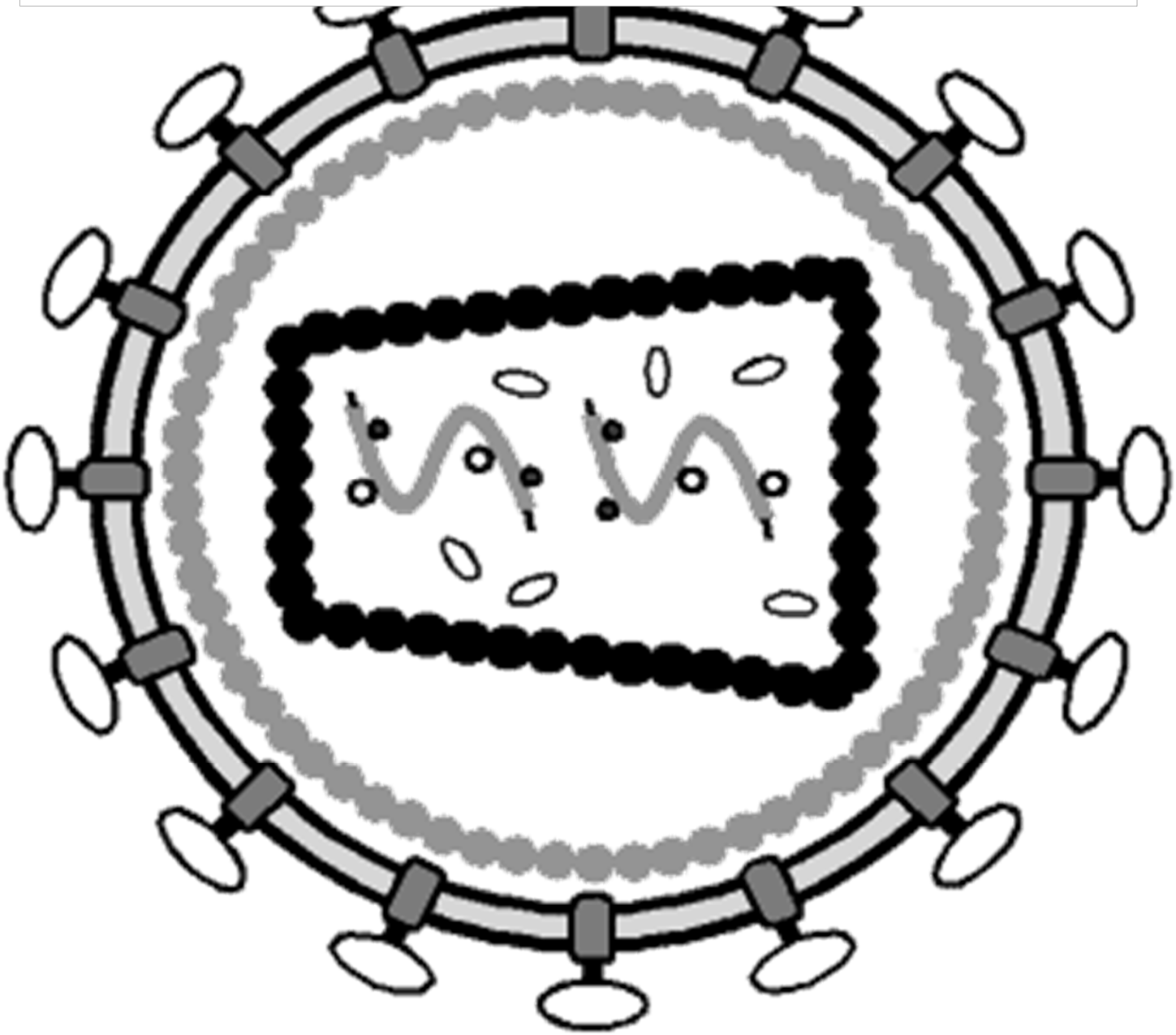
CD4/CD8 Verhaltniss: 2-4/1

HIV Infketion: ermindert / umgekehrt


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

HIV-1

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



env

gp 120

gp 41

gag

p 17

p 24

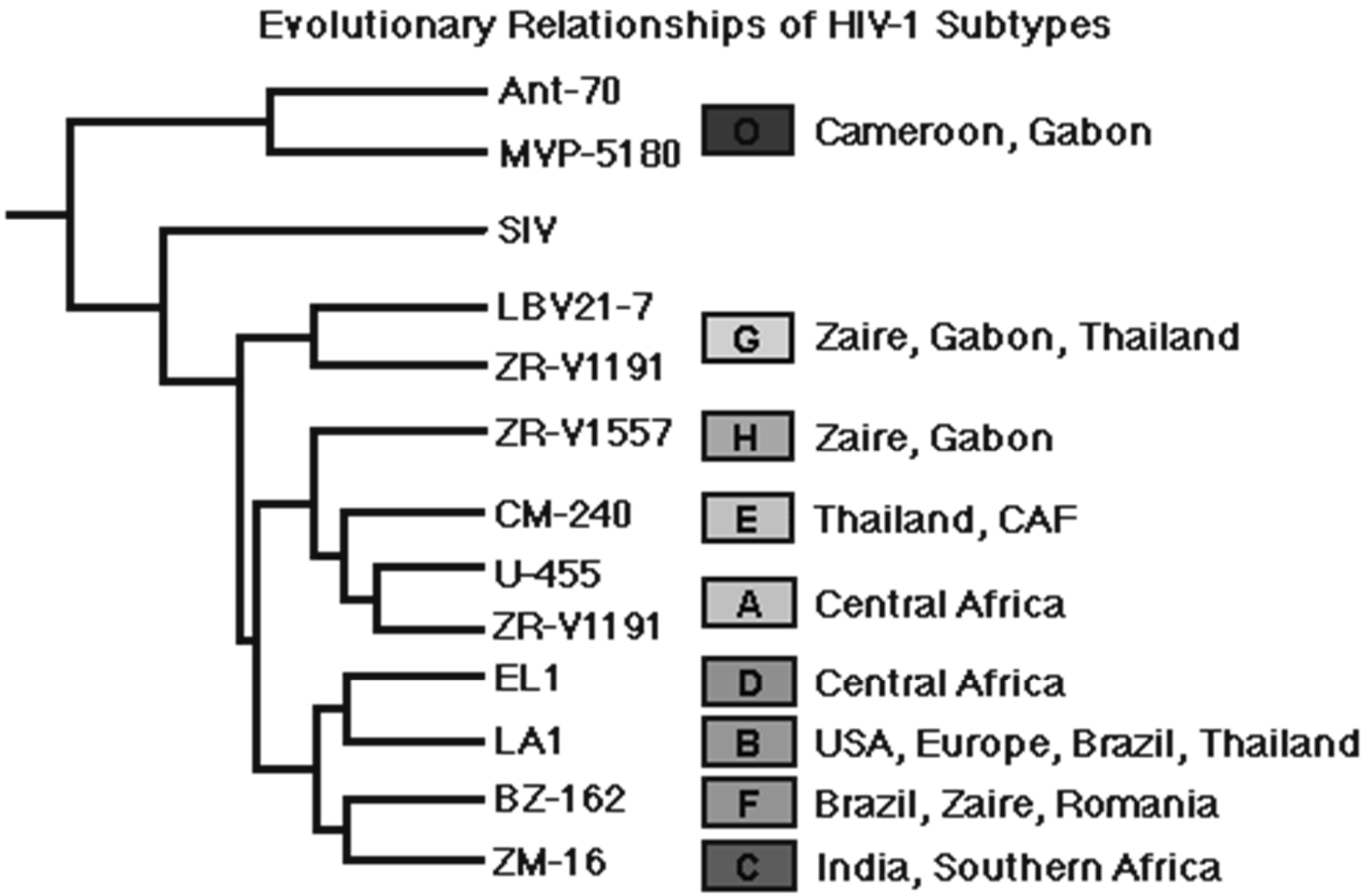
p 7

pol

p 66/51

p 32

p 11



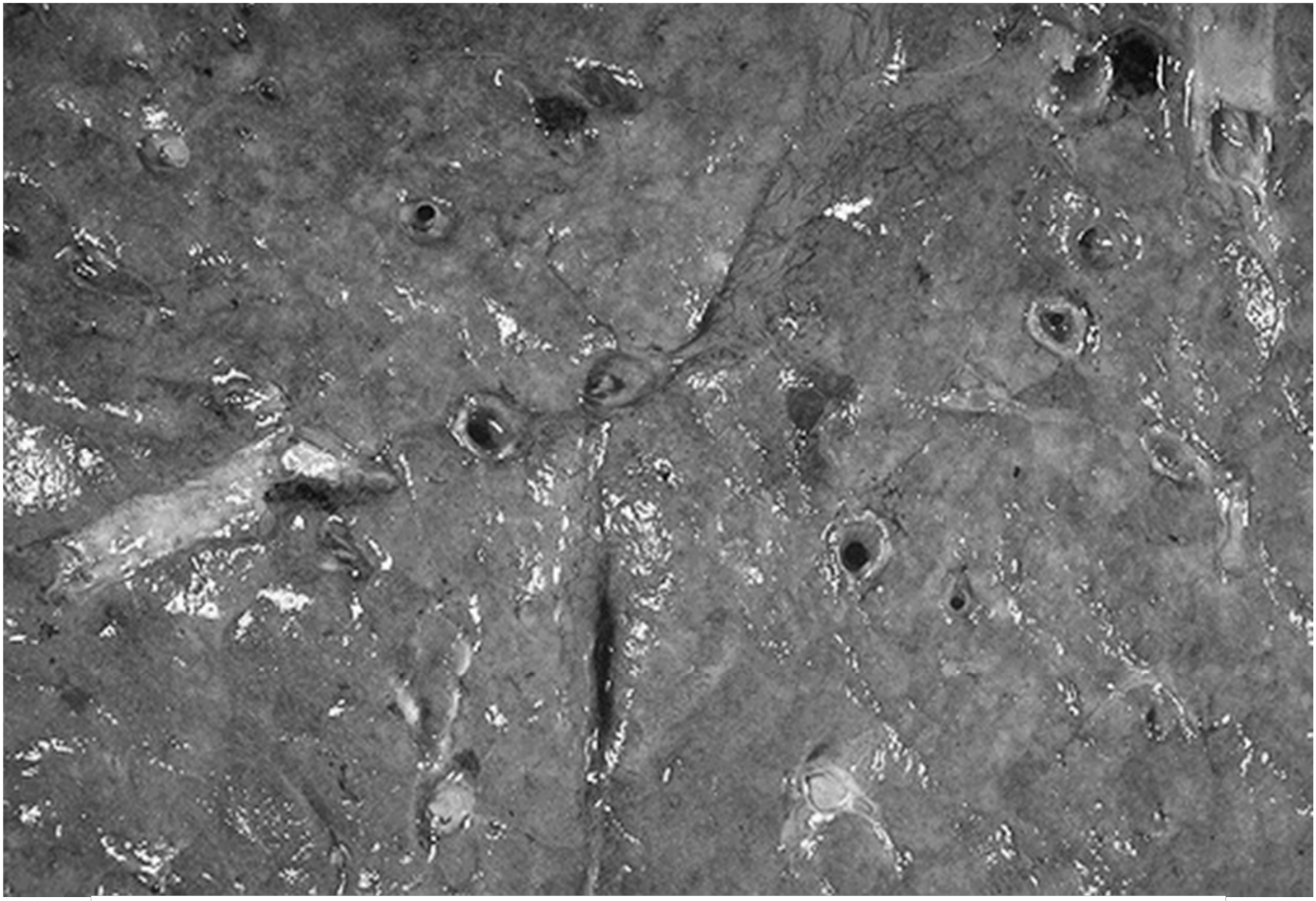
the phylogeny of human immunodeficiency virus (HIV) subtypes and simian immunodeficiency virus (SIV)

AIDS-Tote in Kenia - apokalyptischer Zustand

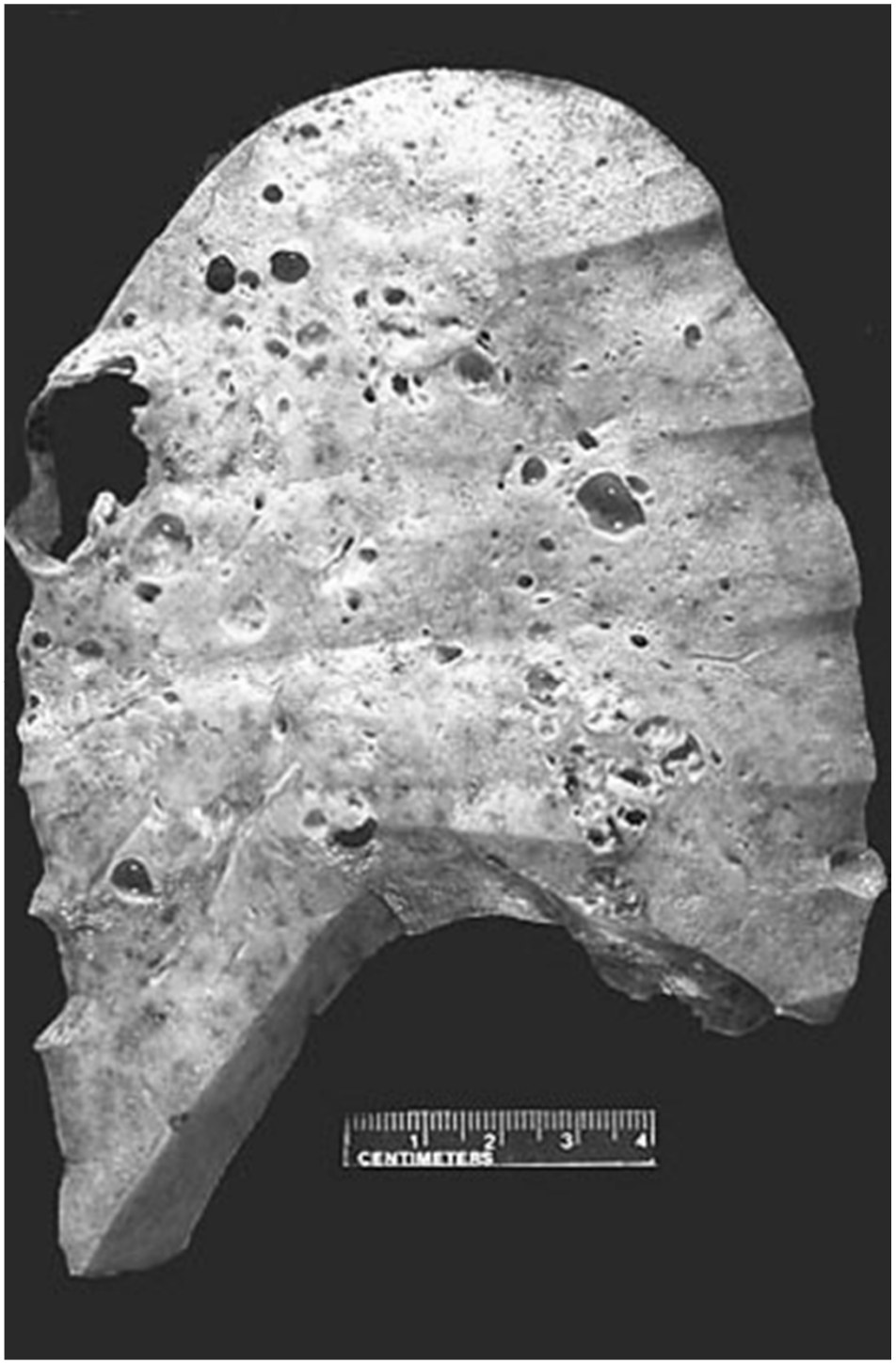
in Afrika verheert das Virus Völker und Volkswirtschaften

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	dissemiiniert
Prion	vCJ betegség	Leukoencephalopathie



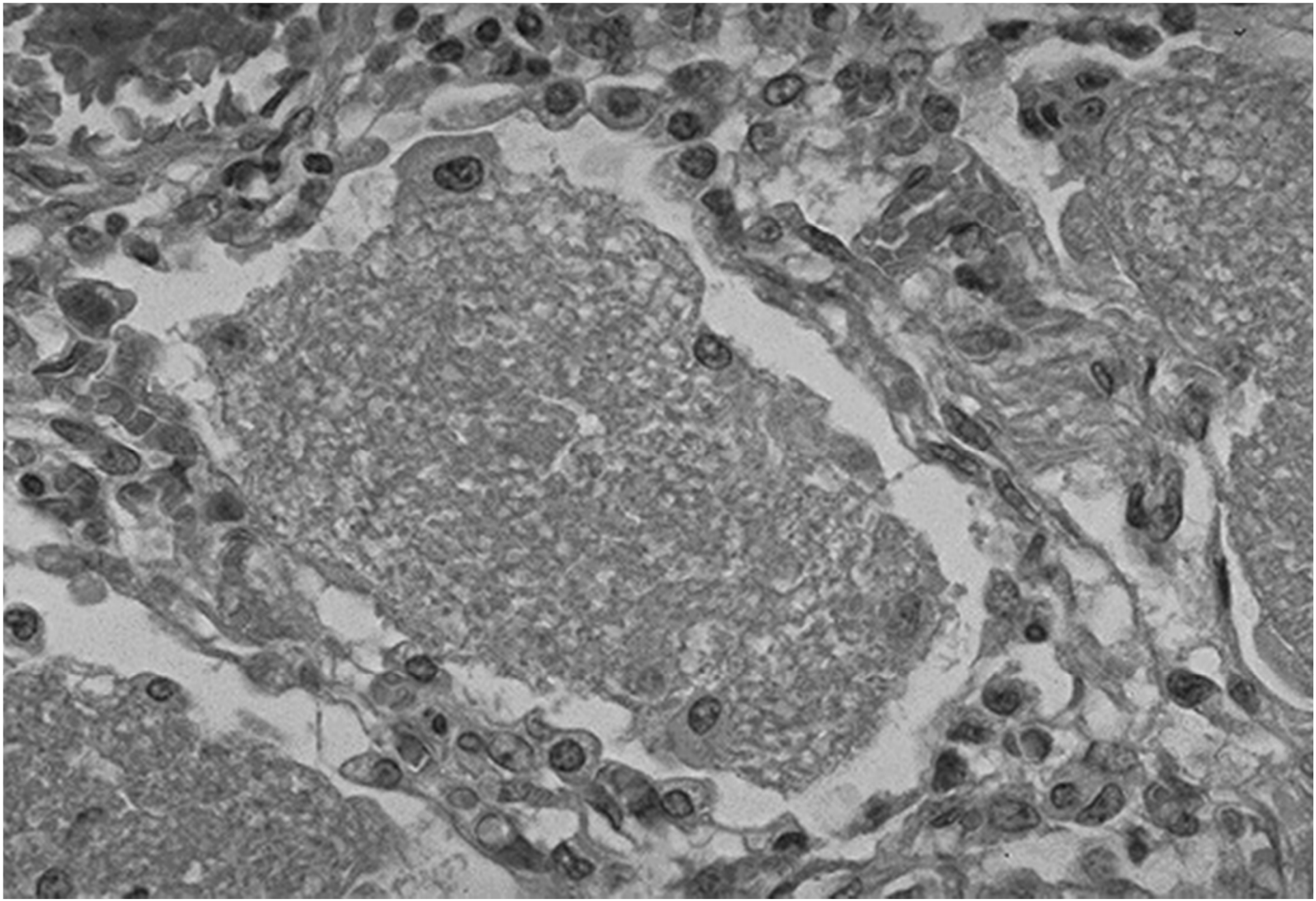
the appearance of Pneumocystis carinii caused extensive pneumonia



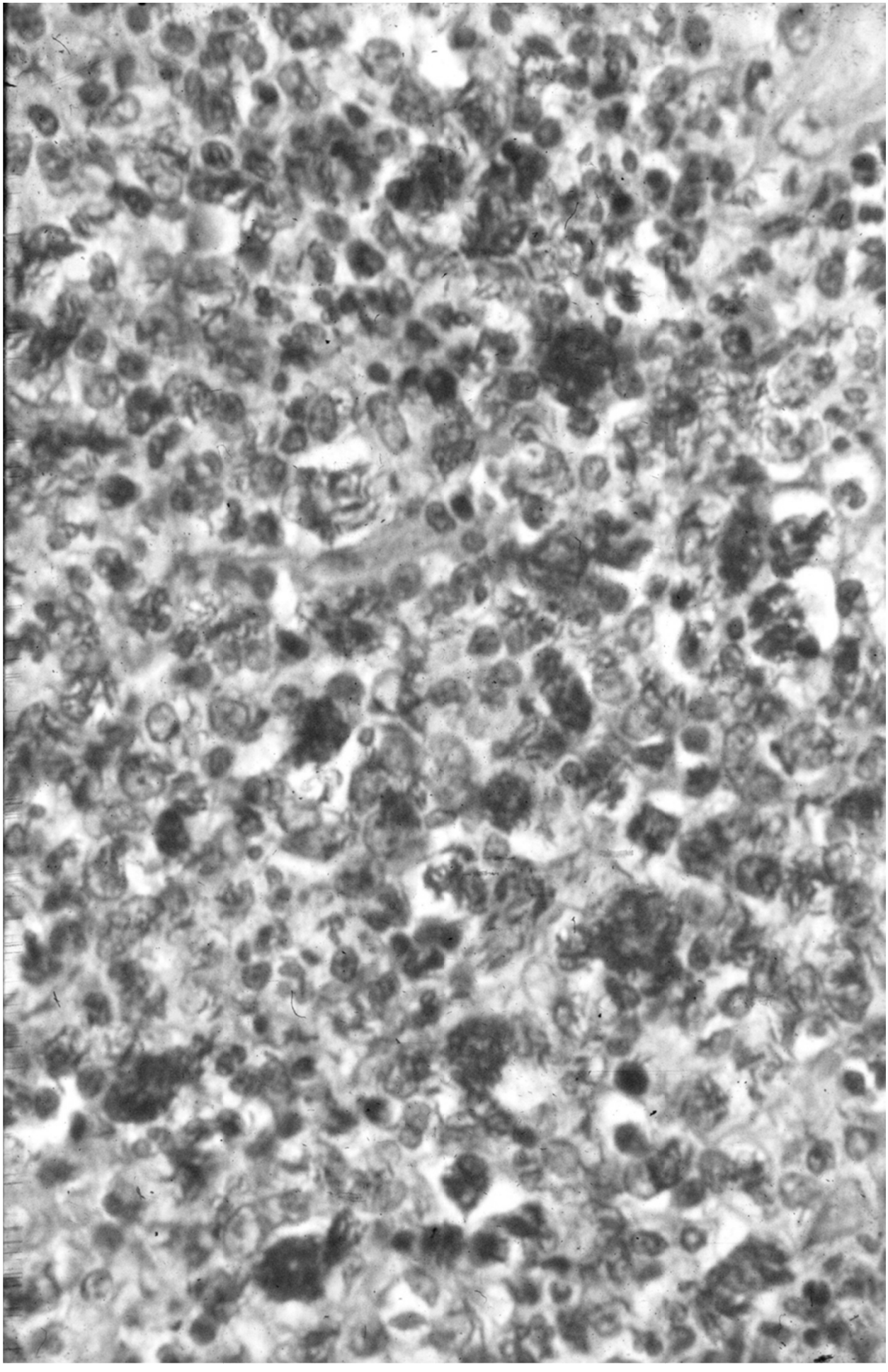
Pneumocystis carinii pneumonia

may produce cavitary change

in rare cases



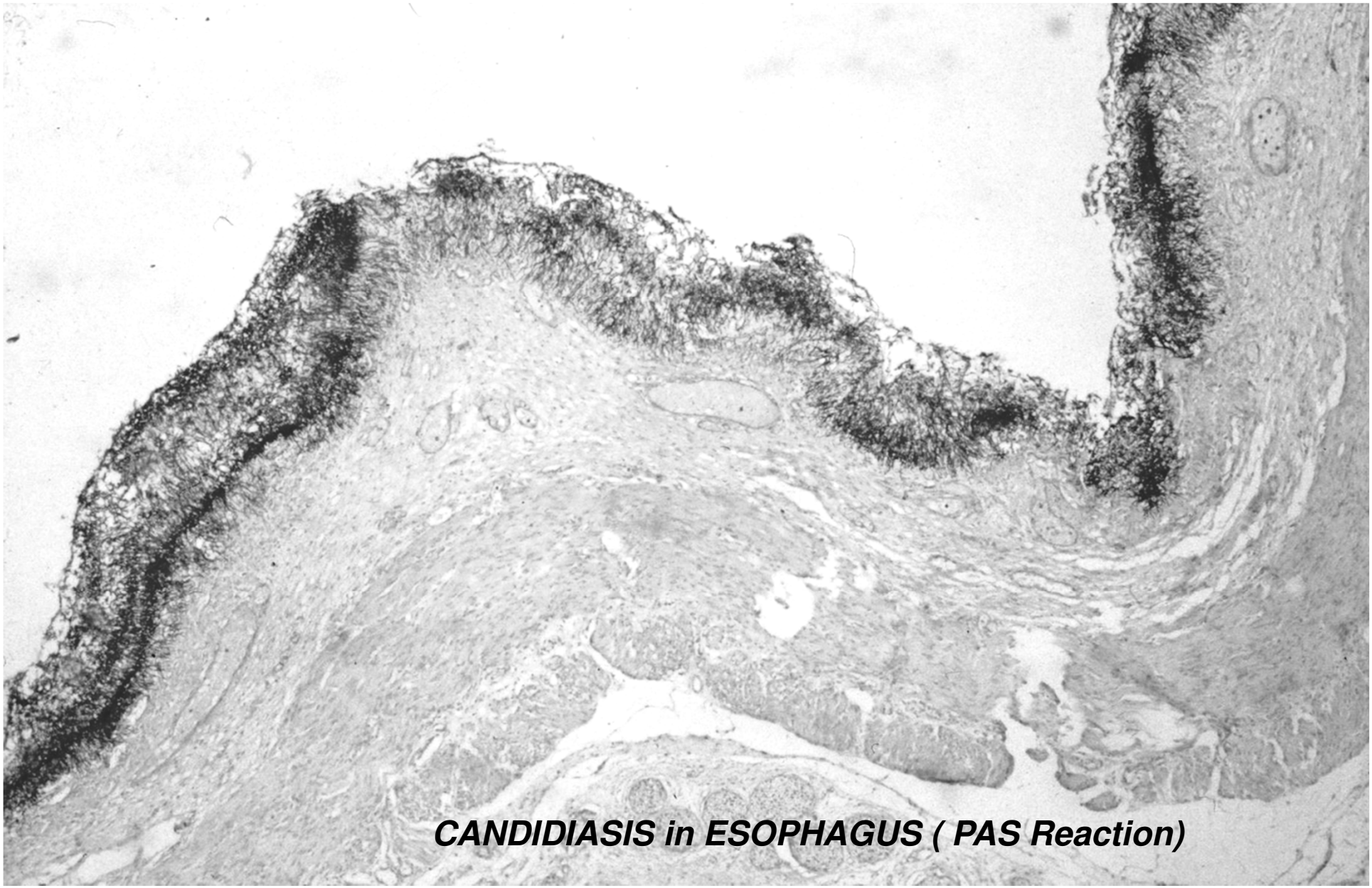
the appearance of Pneumocystis carinii in lung with exudate in nearly every alveolus



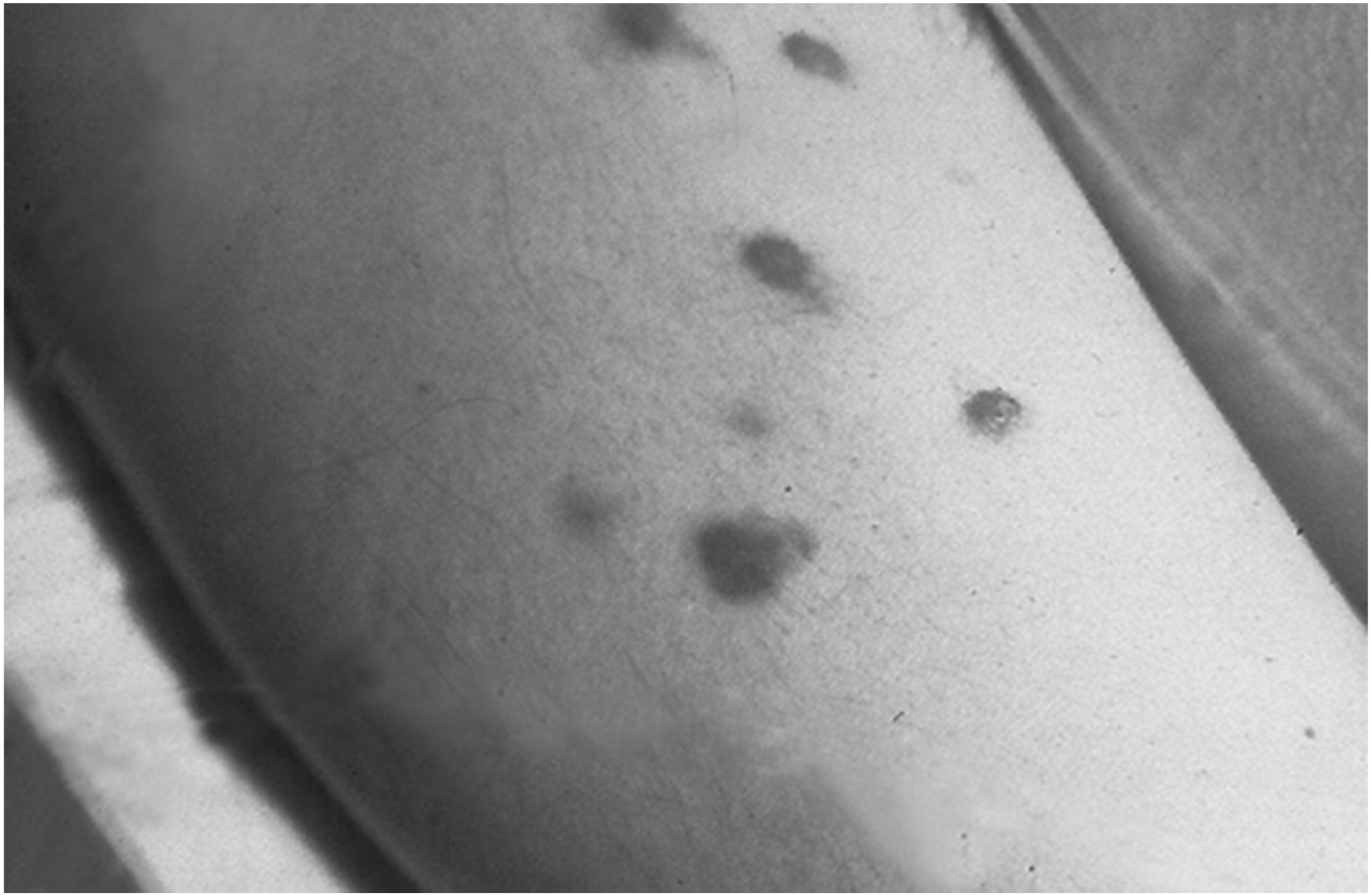
CANDIDIASISIS

in

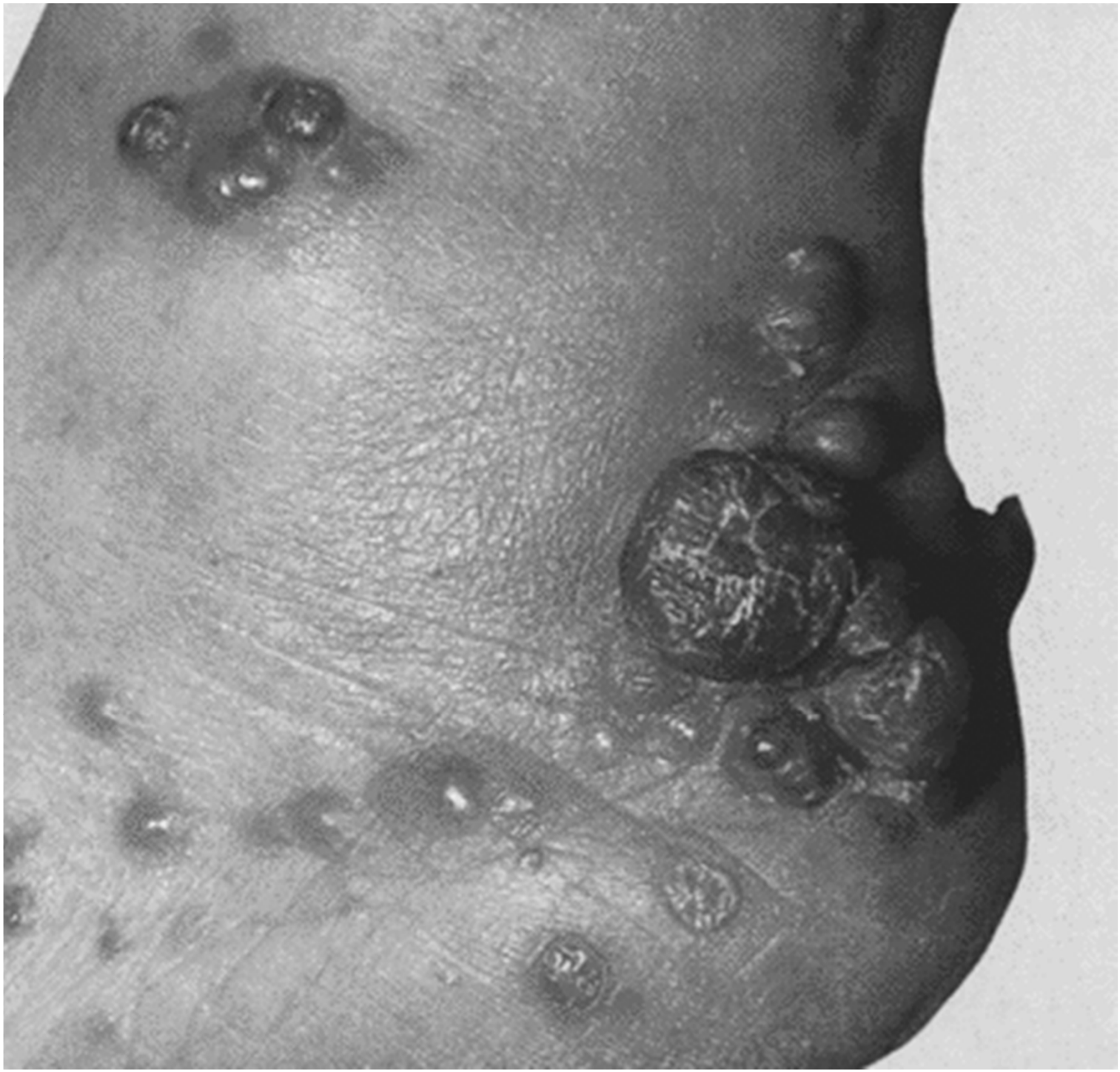
ESOPHAGUS



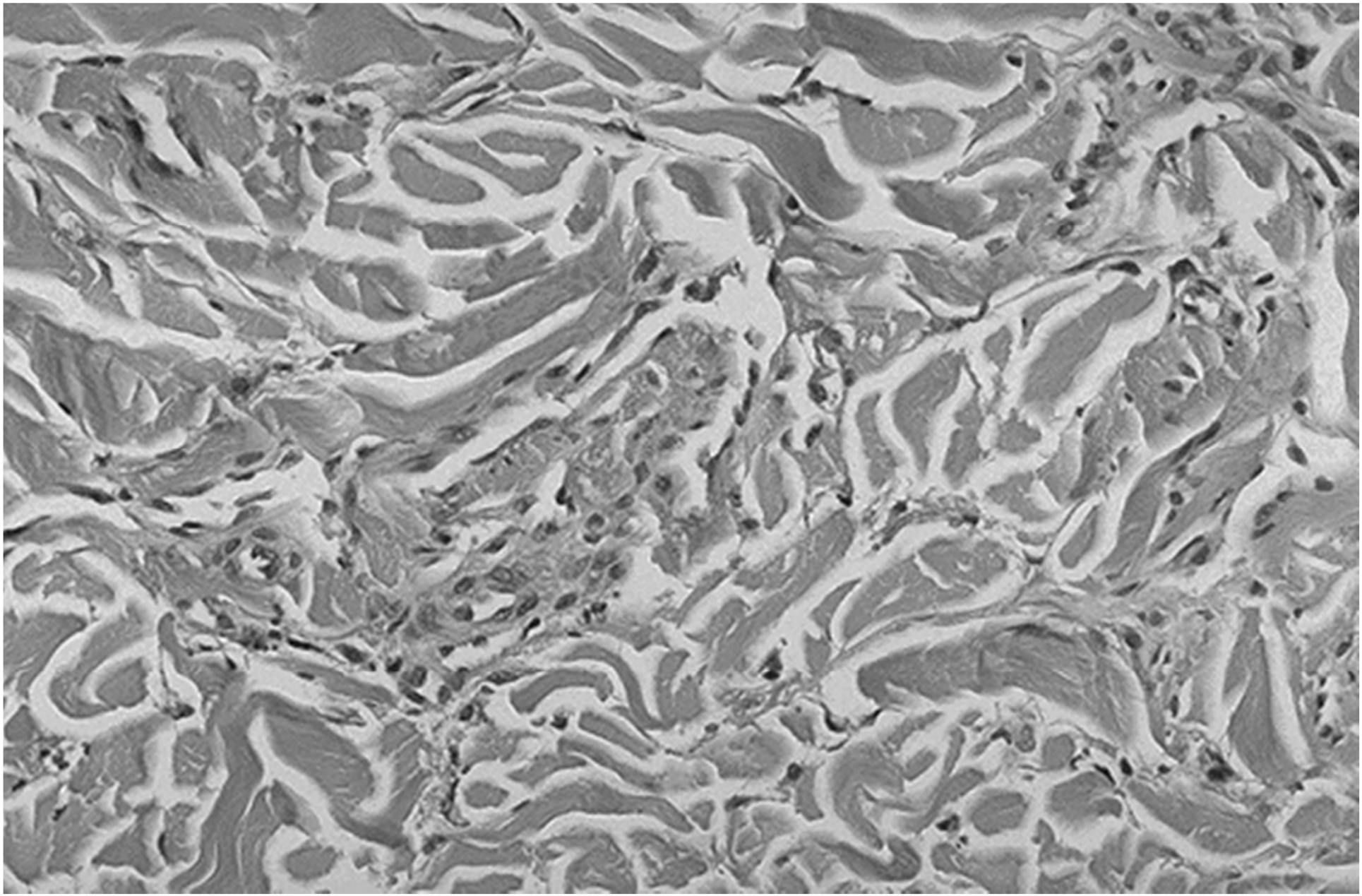
CANDIDIASIS in ESOPHAGUS (PAS Reaction)



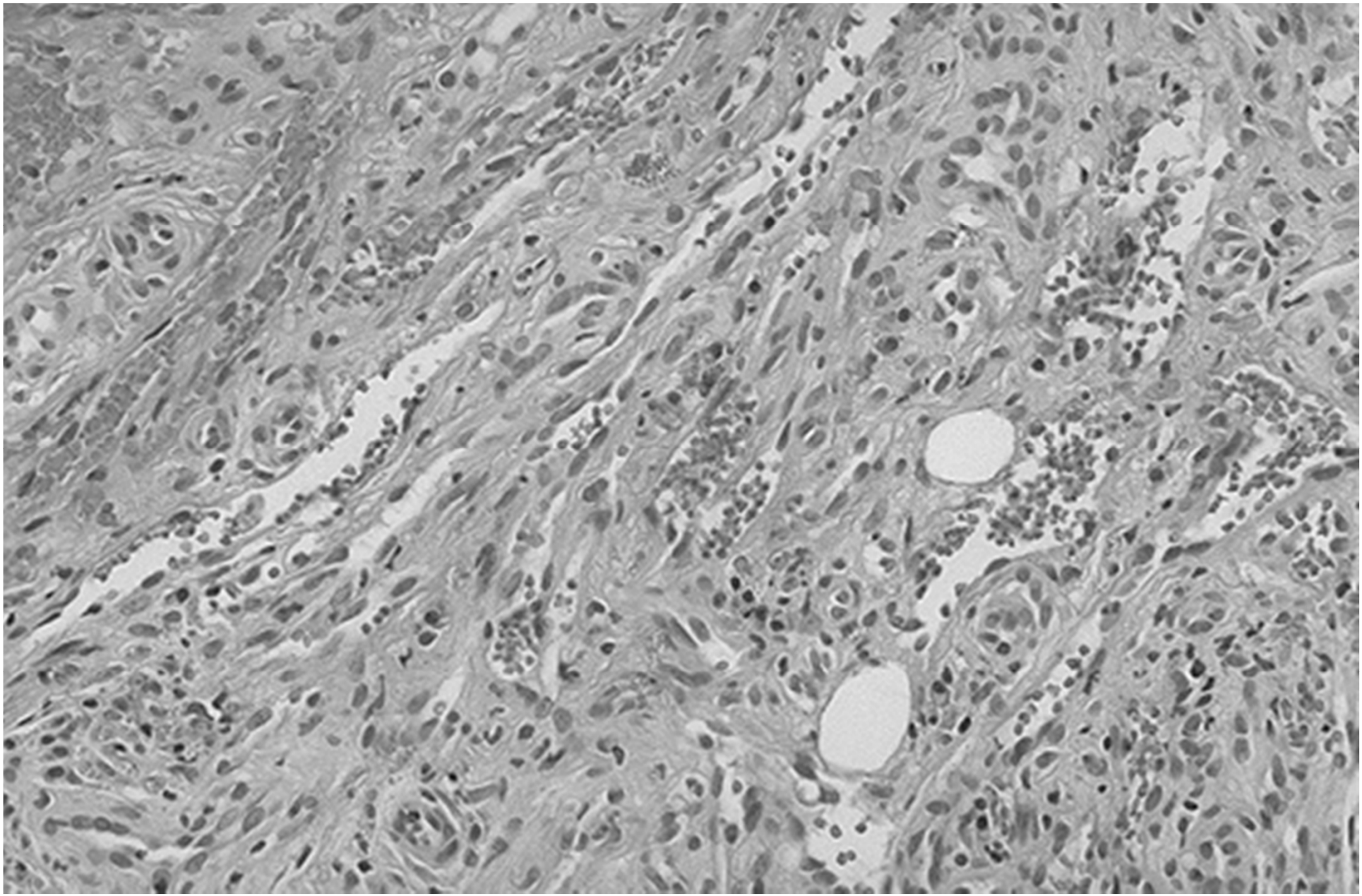
Kaposi's sarcoma: reddish purple nodules on the skin - sarcoma idiopathicum multiplex haemorrhagicum



Kaposi sarkoma of the skin



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



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

Transplantation-Pathology

- Host-versus Graft: organ transplantation
- Graft-versus host (bone marrow TX)