IMUNOPATOLOGI S3

ERYATI DARWIN

PROGRAM PASCASARJANA S2 BIOMEDIK

FAKULTAS KEDOKTERAN UNIVERSITAS ANDALAS

TOPIK

- HIPERSENSITIVITAS
- DEFISIENSI IMUN
- AUTOIMUN
- IM UNOLOGI KANKER
- APOPTOSIS
- TRANSPLANTASI

HIPERSENSITIVITAS

FUNGSI SISTIM IMUN

1. **PERTAHANAN (DEFENCE)**

   IMUNITAS SELULER ⟶/ INVASI MIKROORGANISME

   HIPOAKTIF ⟶ DEFISIENSI IMUN

   HIPERAKTIF ⟶ HIPERSENSITIVITAS/ALERGI

2. **HOMEOSTASIS**

   MEMPERTAHANKAN KESERAGAMAN DARI JENIS SEL TERTENTU UNTUK MEMENUHI SEGALA KEBUTUHAN UMUM ORGANISMEMULTISELULER

   PENYIMPANGAN AUTOIMUN

   ⟶

3. **PENGAWASAN (SURFEILANCE)**

   MEMONITOR PENGENALAN JENIS-JENIS SEL ABNORMAL (MUTAN)

HIPERSENSITIVITAS

- **BILA RESPON IMUN ADAPTIF TERJADI SECARA BERLEBIHAN SEHINGGA MENIMBULKAN KERUSAKAN JARINGAN**
- **BERSIFAT INDIVIDUAL**
- **REAKSI TIMBUL PADA KONTAK KEDUA DENGAN ANTIGEN YANG SAMA**
- **MENURUT COOMBS & GELL TDP 4 TIPE:**

  1. TIPE I (ANAPHYLACTIC HYPERSENSITIVITY)

  2. TIPE II (ANTIBODY-DEPENDENT CYTOTOXIC HYPERSENSITIVITY)

  3. TIPE III (IMMUNE COMPLEX-MEDIATED HYPERSENSITIVITY)

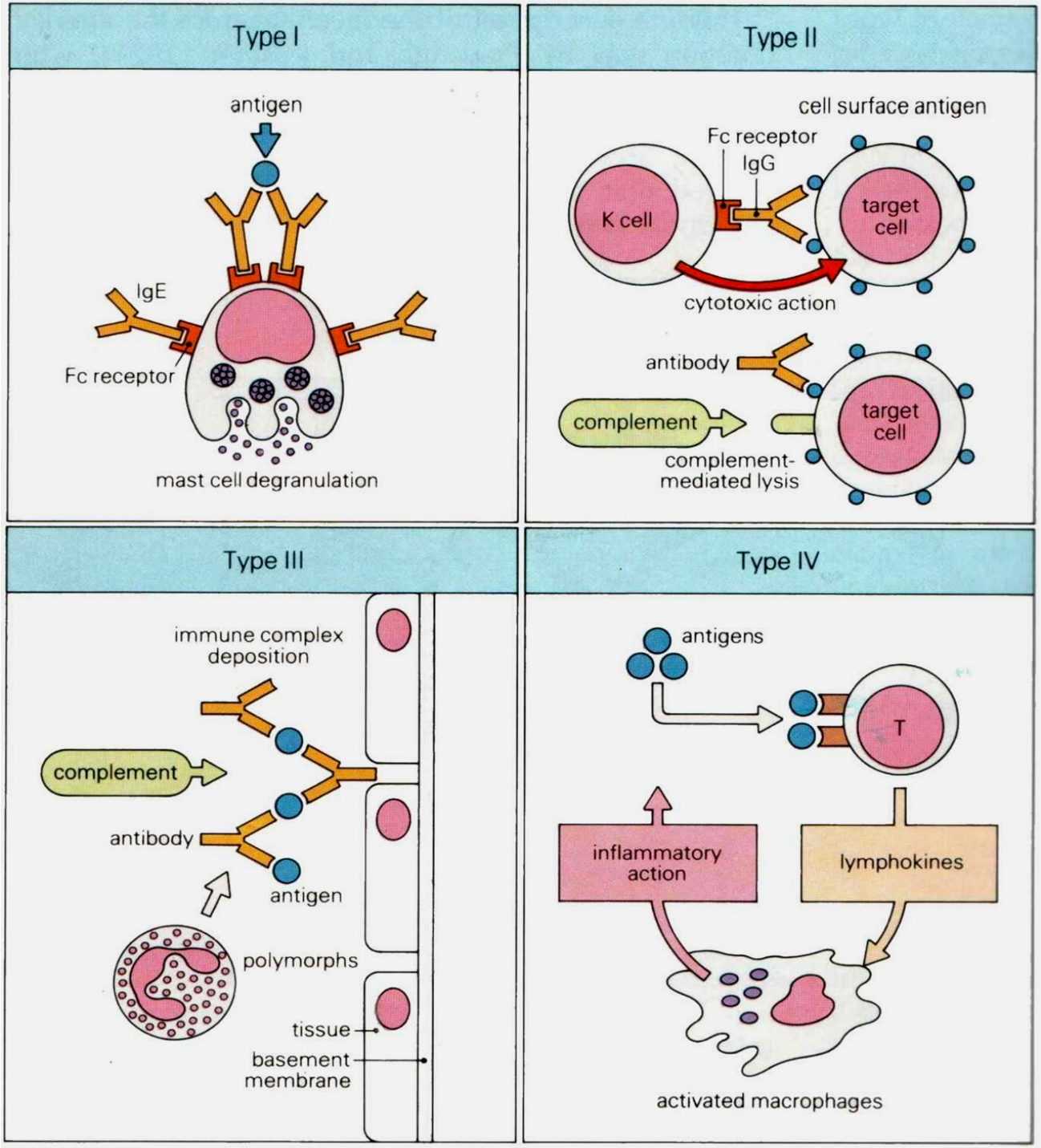
  4. TIPE IV (CELL- MEDIATEDHYPERSENSITIVITY)

  5. TIPE V (STIMULATORY HYPERSENSITIVITY)

  6. INNATE HYPERSENSITIVITY REACTION

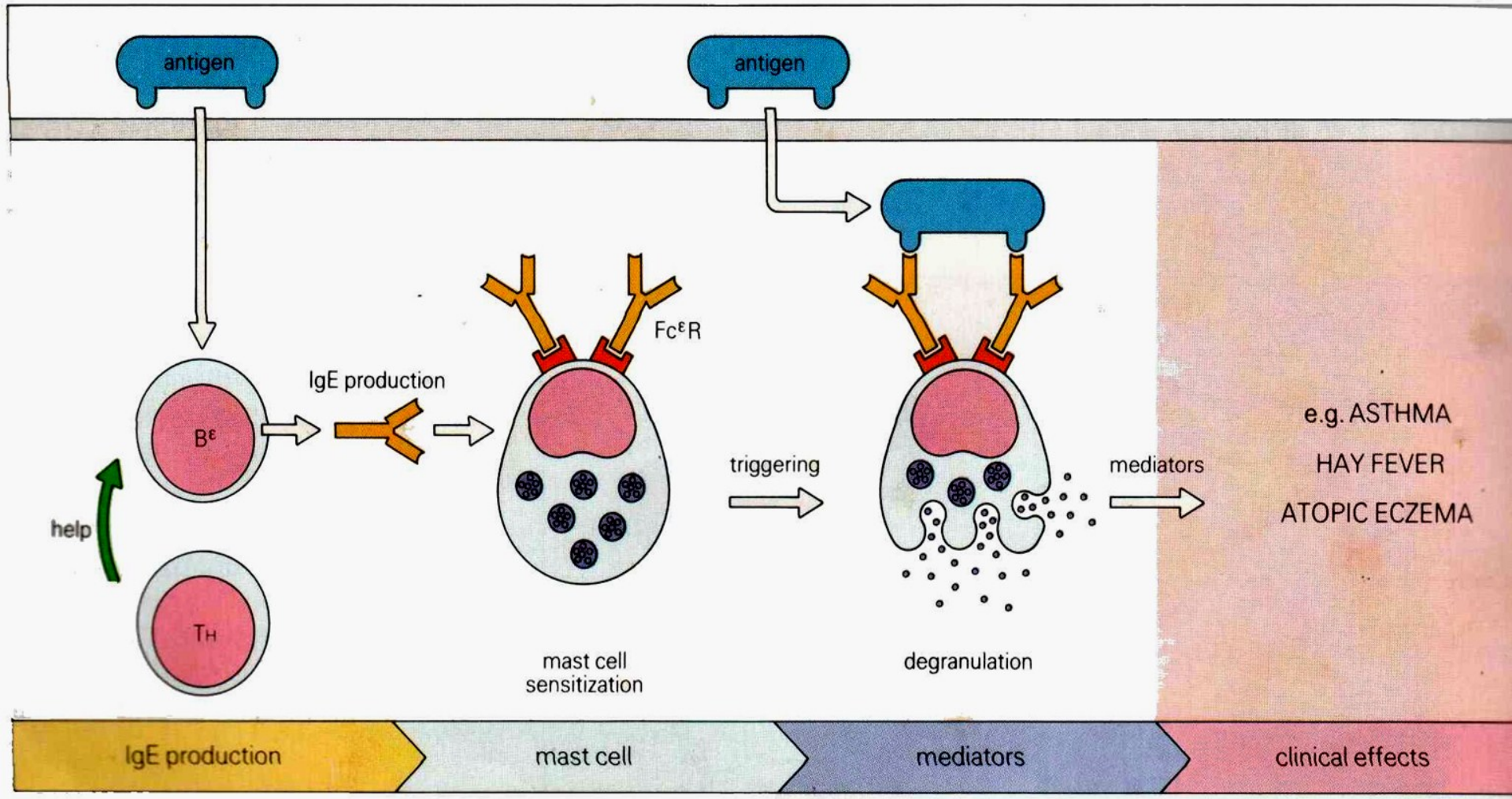
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement Phagocytes	Macrophage activation	Eosinophil activation	Cytotoxicity
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Chronic urticaria (antibody to FαRIα)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Figure 12.2 The Immune System, 3ed. (© Garland Science 2009)


Type I
antigen
IgE
Fc receptor
mast cell degranulation
Type II
cell surface antigen
Fc receptor
IgG
K cell
target cell
cytotoxic action
antibody
complement
target cell
complement-mediated lysis
Type III
immune complex deposition
complement
antibody
antigen
polymorphs
tissue
basement membrane
Type IV
antigens
T
inflammatory action
lymphokines
activated macrophages

HIPERSENSITIVITAS TIPE I

- **DISEBUT IMMEDIATE HYPERSENSITIVITY**
- **DITANDAI OLEH REAKSI ALERGI SEGERA SETELAH KONTAK DENGAN ANTIGEN (ALERGEN)**
- **PORTIER & RICHERT : RX ANAFILAKSIS PD BINATANG TDK SAMA DG MANUSIA**
- **ISTILAH ALERGI: VON PIRQUET 1960: PERUBAHAN REAKSI PADA HOST BILA TERJADI KONTAK KEDUA DENGAN 'AGENT'**
- **AGENT → IgE → MELEKAT PD RESEPTOR IgE**
- **PRAUSNITZ & KUSTNER (1921): TRANSFER PASIF FK SERUM (REAGIN) DAPAT MENYEBABKAN RX KULIT**
- **ISHIZAKA : REAGIN ATOPIK = IMUNOGLOBULIN E**
- **REAKSI TERGANTUNG PADA RGS SPESIFIK TERHADAP SEL MAST YANG SUDAH DISENSITISASI OLEH IgE, SHG MENGAKIBATKAN PELEPASAN MEDIATOR FARMAKOLOGI → INFLAMASI**


antigen
antigen
IgE production
Fc$^{\varepsilon}$R
B$^{\varepsilon}$
help
T$_H$
mast cell
sensitization
triggering
degranulation
mediators
e.g. ASTHMA
HAY FEVER
ATOPIC ECZEMA
IgE production
mast cell
mediators
clinical effects

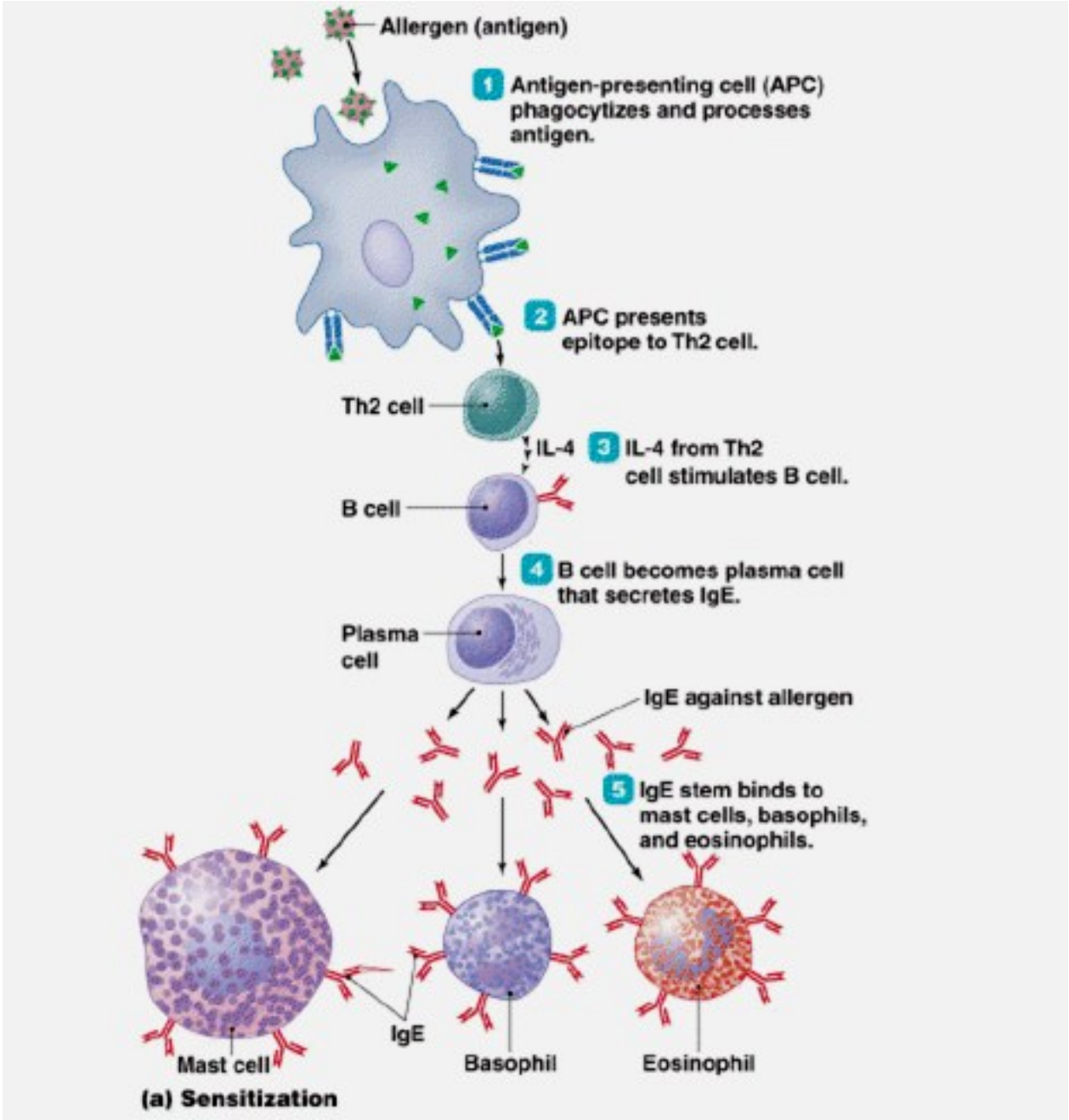
ALERGI

- **BERASAL DARI BAHASA YUNANI *ALLOS ERGOS* →ALTERED REACTIVITY (MUCH ABUSED)**

- **IMUNOLOGI:**
  - **REAKSI YANG BERLEBIHAN DARI SISTEM IMUN TERHADAP BAHAN ASING**
  - **REAKSI YANG TERJADI BILA SEL MAST YANG BERIKATAN DENGAN IgE, BERINTERAKSI DENGAN DENGAN ANTIGEN TARGET YANG DISEBUT ALERGEN**

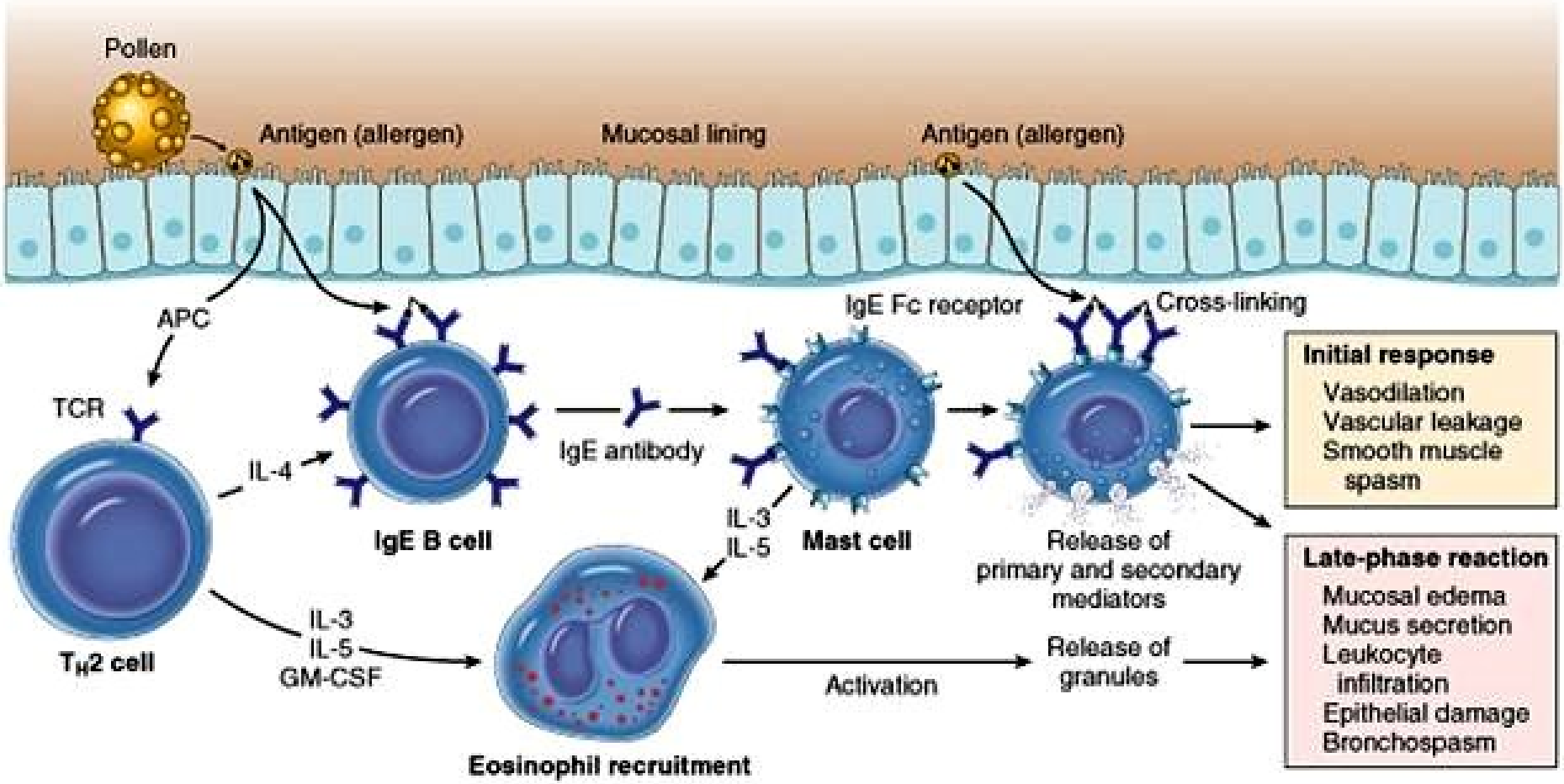
- **MENURUT KATEGORI GELL DAN COOMBS 1970 → HIPERSENSITIVITAS TIPE I**

MEKANISME HIPERSENSITIVITAS TIPE 1



Hipersensitivitas tipe I pada mukosa

Histamin, heparin dan serotonon pada granul sel mast
Degranulasi→ vasodilatasi dan vasopermeabilitas



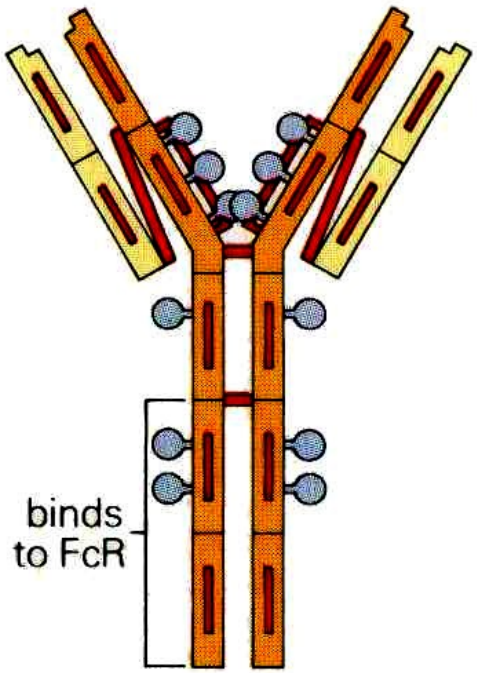
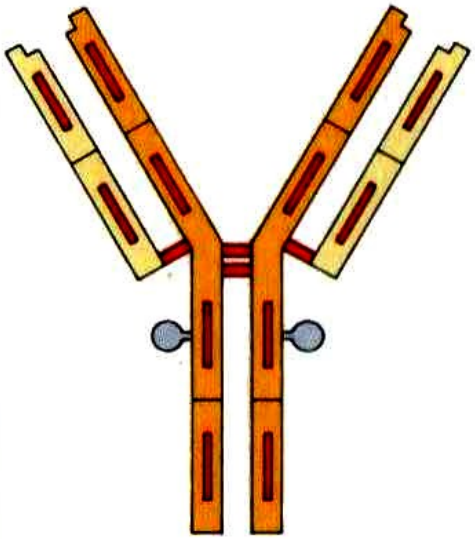
FENOMEN ANAFILAKSIS

- **ANAFILAKSIS >< PROFILAKSIS**
- **MUNCULNYA SENSITIVITAS TERHADAP BAHAN YANG SEMULA TIDAK MEMBERIKAN RESPON**
- **PERCOBAAN BINATANG: (ALBUMIN, GLICERIN)**

  SUNTIKAN ANTIGEN KE 2 MENIMBULKAN GEJALA ANAFILAKTIK: KONTRAKSI OTOT POLOS, DILATASI PEMBULUH DARAH→ VASOKONSTRUKSI BRONKHUS/OLUS
- **PADA MANUSIA:**
  - **SENGATAN SERANGGA**
  - **SUNTIKAN PENICILIN**
- **ANTIBODI ANAFILAKSIS PADA MANUSIA: IgG**

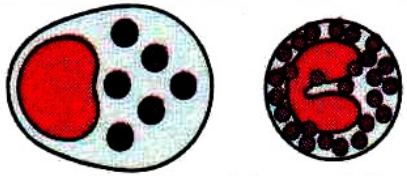
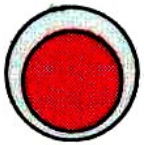
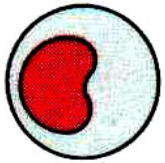
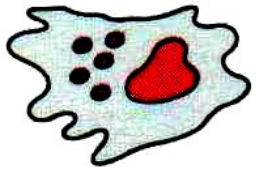
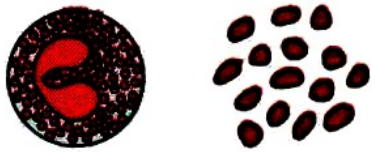
IMUNOGLLOBULIN E

- **KONTAK PERTAMA DENGAN ALERGEN → IgE LOKAL (MUKOSA / LIMFONODUS)**
- **DIPRODUKSI OLEH SEL B MELALUI APC, T-HELPER**
- **BERIKATAN DG RESEPTOR PD SEL MAST DAN BASOFIL**
- **HALF LIFE: 2 1/2 HARI**
- **MENSENSITISASI SEL MAST: 12 MINGGU**
- **BM: 188.000 (IgG:146.000)**
- **HEAVY CHAIN 5 DOMAIN (IgG:4)**
- **LABIL PADA > 56^{o}C**

	IgE	IgG1
		
heavy chain domains	5	4
molecular weight	188,000	146,000
carbohydrate	12%	2-3%
half-life (serum)	2½ days	21 days

SEL-SEL YANG MERUPAKAN RESEPTOR IgE

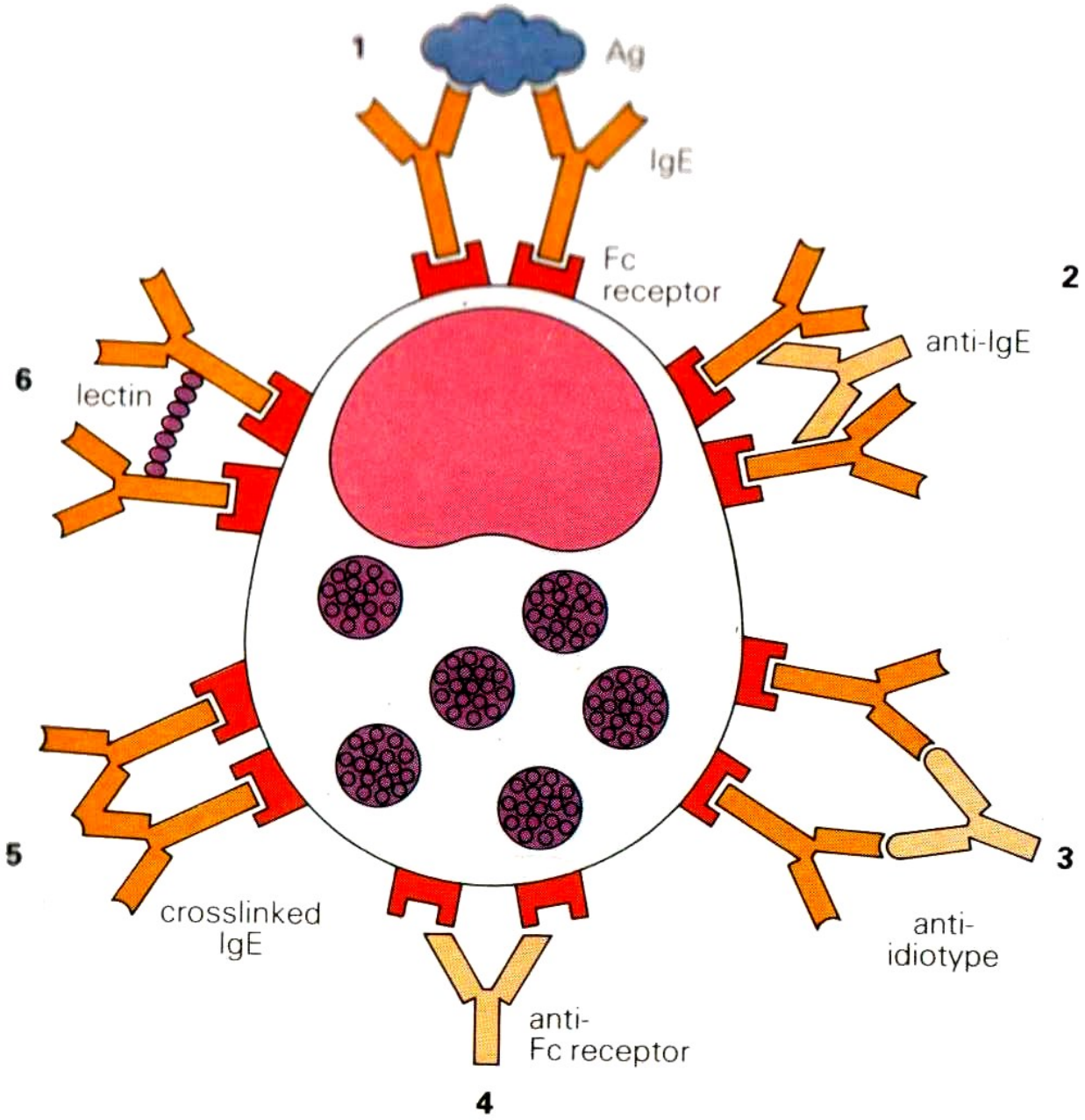
- **SEL MAST DAN BASOFIL (EFEKTOR UTAMA)**
- **SEL T DAN B**
- **MONOSIT**
- **MAKROFAG**
- **EOSINOFIL DAN TROMBOSIT**

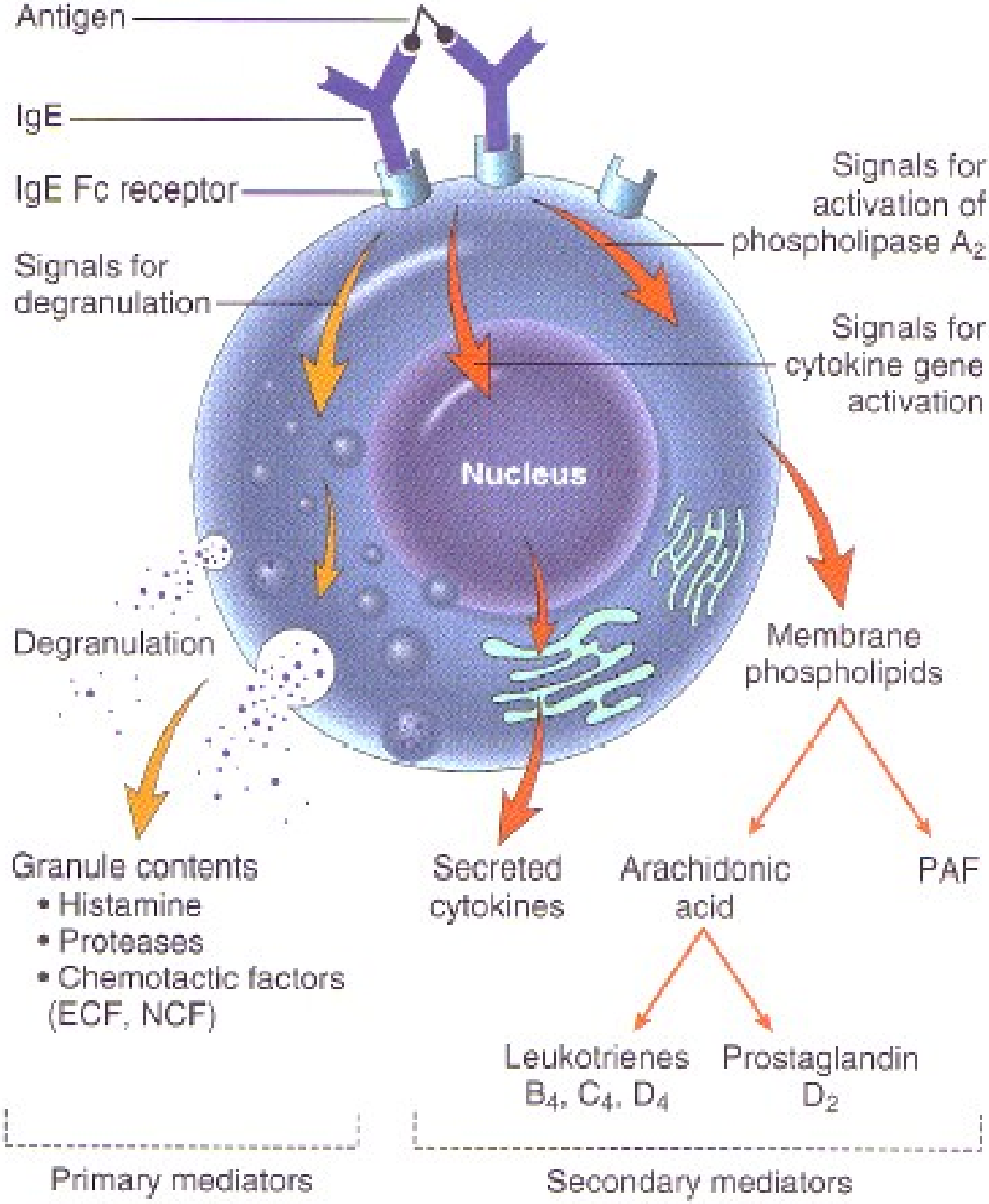
cell type	comment
 mast cell and basophil	main effectors of IgE-mediated reactions
 T cell and B cell	T cells: about 1% $Fc^{\varepsilon}R$ positive, increase in atopics during pollen season B cells: about 30% $Fc^{\varepsilon}R$ positive increasing as above
 monocyte	about 2% $Fc^{\varepsilon}R$ positive increasing up to 20% in some allergic disorders
 alveolar macrophage	receptors demonstrated by IgE-mediated enzyme release
 eosinophil and platelets	effectors of IgE-mediated damage to schistosomes

SEL MAST

KARAKTERISTIK	CONECTIVE TISSUE MAST CELL	MUCOSAL MAST CELL
HISTOLOGIS	- SITOPLASMA BIRU TUA - GRANUL KECOKLATAN	- SITOPLASMA BIRU MUDA - GRANUL BIRU
DISTRIBUSI	SEKITAR P.DRH, PERITONEUM, KULIT	MUKOSA GIT DAN PULMO
STIMULUS PROLIFERASI	FAKTOR FIBROBLAS	IL-3
RESEPTOR Fcε	$2X10^5$/SEL	$3X10^4$/SEL
GRANUL: -PROTEASE -PROTEOGLIKA	 TRIPTASE & CHYMASE HEPARIN	 TRIPTASE KONDROITIN SULFAT
DEGRANULASI	-HISTAMIN++ -DIHAMBAT DISODIUM KROMOGLIKAT/TEOFILIN	HISTAMIN+ –

FAKTOR-FAKTOR YANG MEMICU DEGRANULASI




Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for activation of phospholipase A_2
Signals for cytokine gene activation
Nucleus
Degranulation
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

MEDIATOR YANG DILEPAS OLEH SEL EFEKTOR

1. HISTAMIN

VASODILATASI, PENINGKATAN PERMEABILITAS KAPILER, KEMOKIN, BRONKHOKONSTRUKSI

2. HEPARIN

ANTIKOAGULAN

3. ENZIM

PROTEOLITIK, C3 CONVERTASE, RESIDU GLUKOSAMIN

4. FAKOR KEMOTAKTIK & AKTIVATING

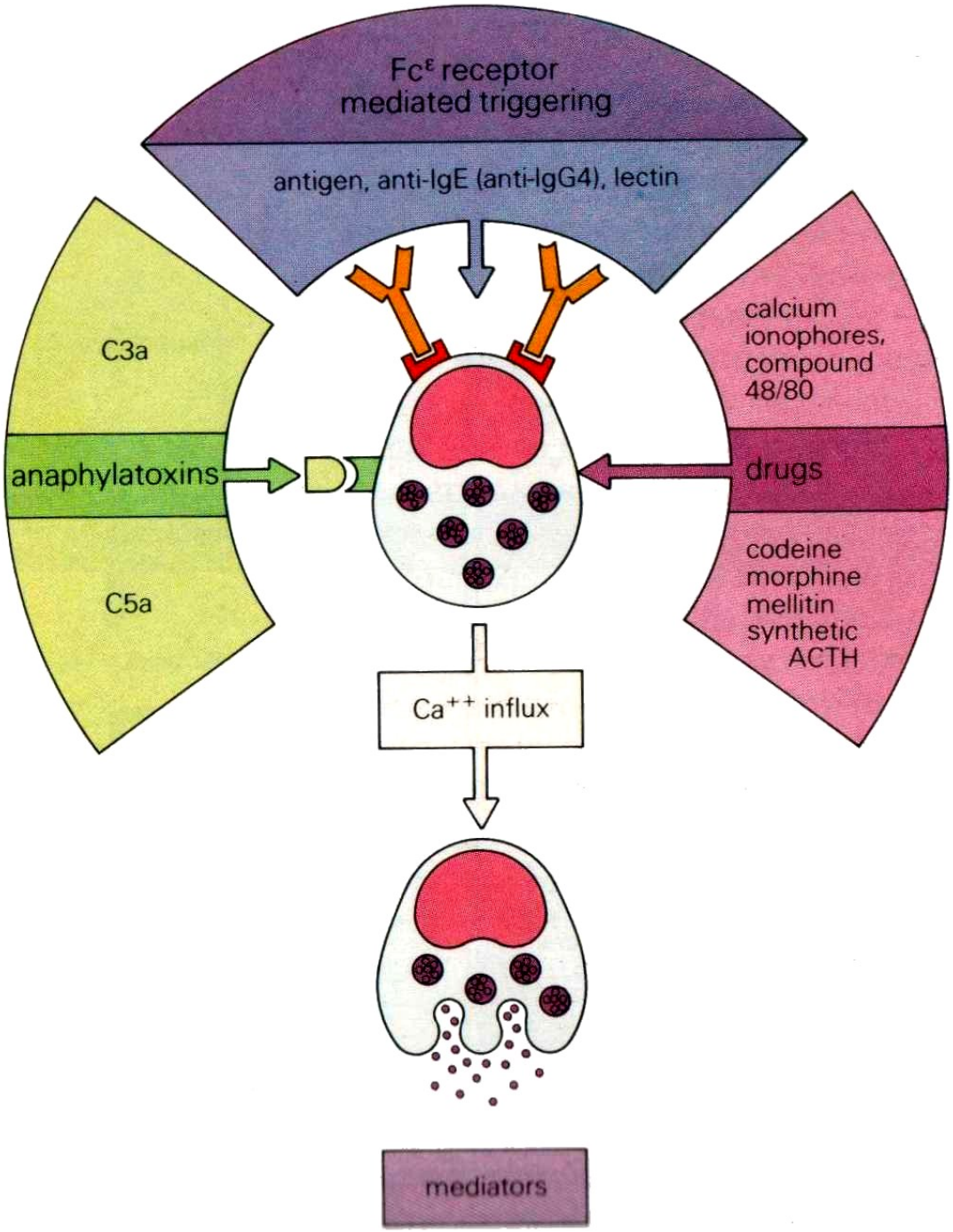
KEMOTAKSIS DARI EOSINOFIL DAN NETROFIL, AKTIVASI TROMBOSIT

5. LEUKOTRIN

VASOAKTIF, BRONKHOKONSTRUKSI, KEMOTAKTIK/ KEMOKINETIK

6. PROSTAGLANDIN DAN TROMBOKSAN

KONTRAKSI OTOT BRONKHIAL, AGREGASI TROMBOSIT, VASODILATASI

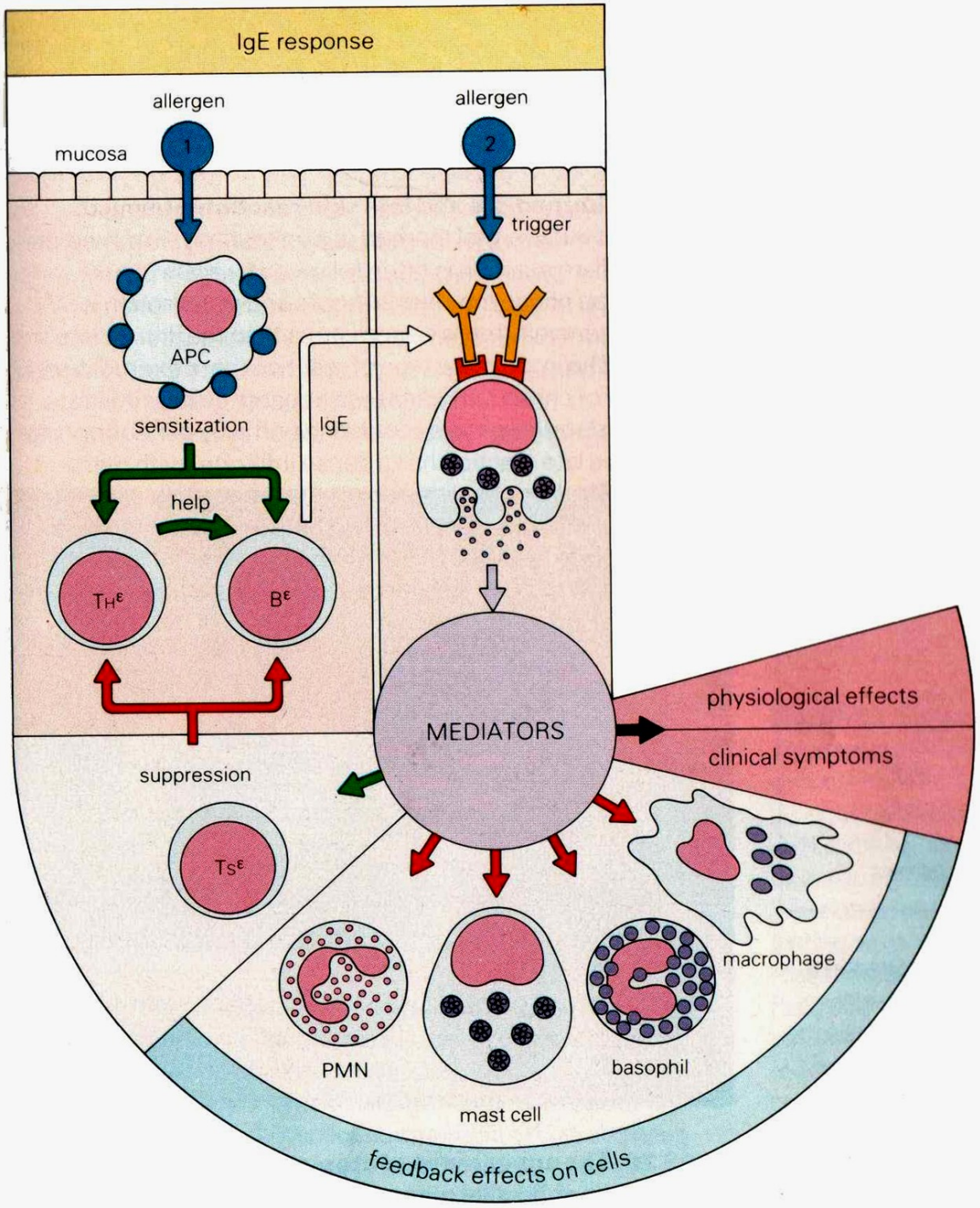

Fcε receptor
mediated triggering
antigen, anti-IgE (anti-IgG4), lectin
C3a
anaphylatoxins
C5a
calcium
ionophores,
compound
48/80
drugs
codeine
morphine
mellitin
synthetic
ACTH
Ca++ influx
mediators

GAMBARAN KLINIK HIPERSENSITIVITAS TIPE I (COCA & COOKE 1923) : ATOPY

- **ASMA BRONKIAL**
- **RINITIS ALERGIKA / HAY FEVER**
- **EKSIM**
- **URTIKARIA**
- **ANAFILAKSIS GENERAL**
- **RIWAYAT KEL. DG RX KULIT WHEAL & FLEAR THD INHALASI ALERGEN**

PENYEBAB ALERGI

- **DEFISIENSI SEL T**
- **FEEDBACK MEDIATOR YG ABNORMAL**
- **FAKTOR LINGKUNGAN**
- **FAKTOR-FAKTOR NON-GENETIK:**
  - ► **JUMLAH EKSPOSURE**
  - ► **NUTRISI**
  - ► **PENYAKIT INFEKSI KRONIK**
  - ► **PENYAKIT VIRUS AKUT**


IgE response
allergen
allergen
mucosa
1
2
trigger
APC
sensitization
IgE
help
T_H^ε
B^ε
MEDIATORS
physiological effects
clinical symptoms
suppression
T_S^ε
macrophage
PMN
basophil
mast cell
feedback effects on cells

Sitokin pada alergi

- Limfokin: IL-2, IL-3, IL-4, IL-5, IL-13, IL-15, IL-16, IL-17.
- Sitokin Pro-inflammatory : IL-1, TNF, IL-6, IL-11, GM-CSF, SCF.
- Sitokin Anti-inflammatory : IL-10, IL-1ra, IFN-γ, IL-12, IL-18.
- Chemotactic cytokines (chemokines):
  - RANTES(Regulated on Activation, Normal T cell Expressed, and Secreted)
  - Monocyte chemoattractant protein (MCP-1)
  - MCP-2, MCP-3, MCP-4, MCP-5
  - Macrophage inflammatory protein (MIP-1α)
  - Eotaxin
  - IL-8
- Growth factors: PDGF, TGF-β, FGF, EGF, IGF.

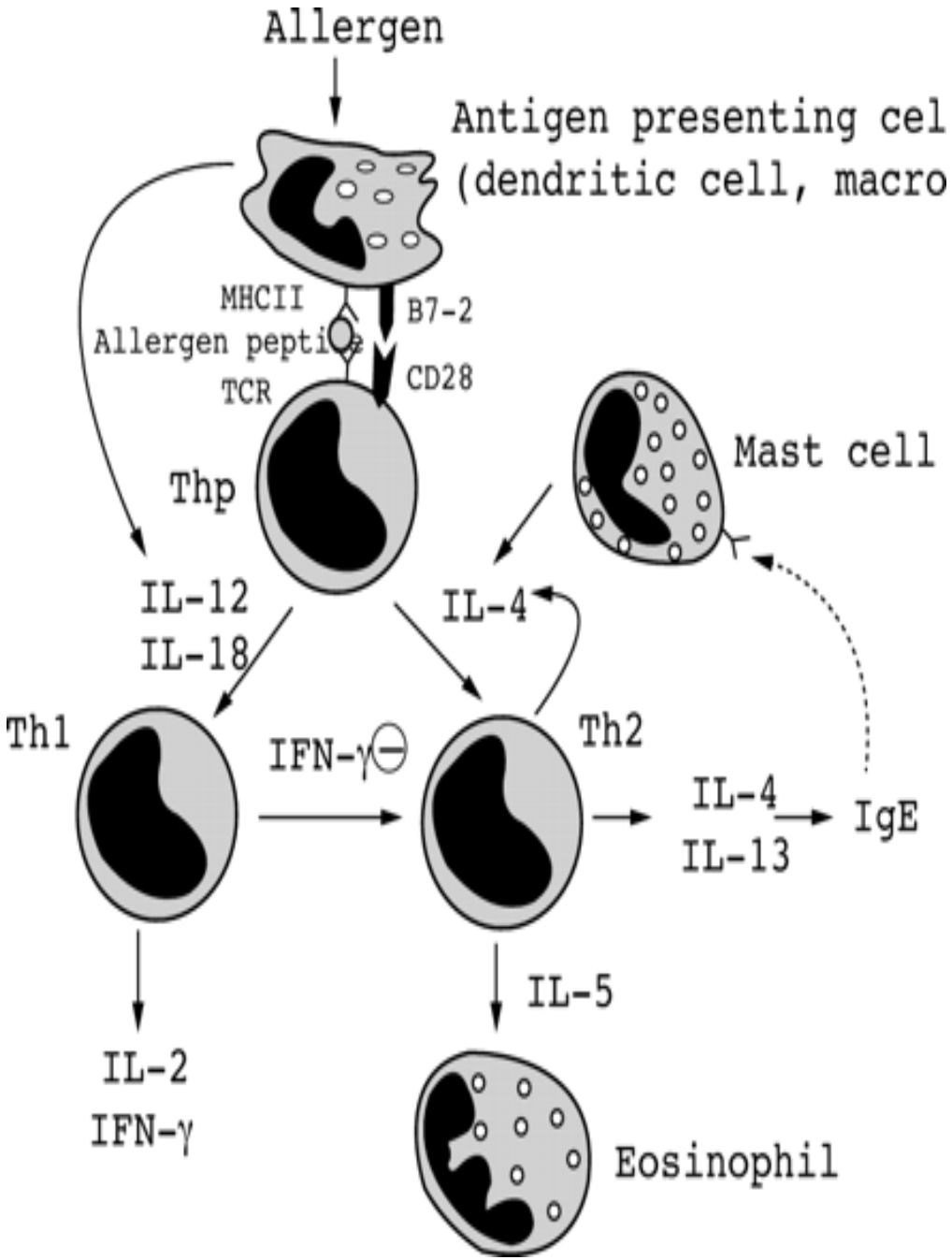
chemokin (**chemo**tactic cyto**kines)**

Fungsi:

- Hemostatik: migrasi leukosit

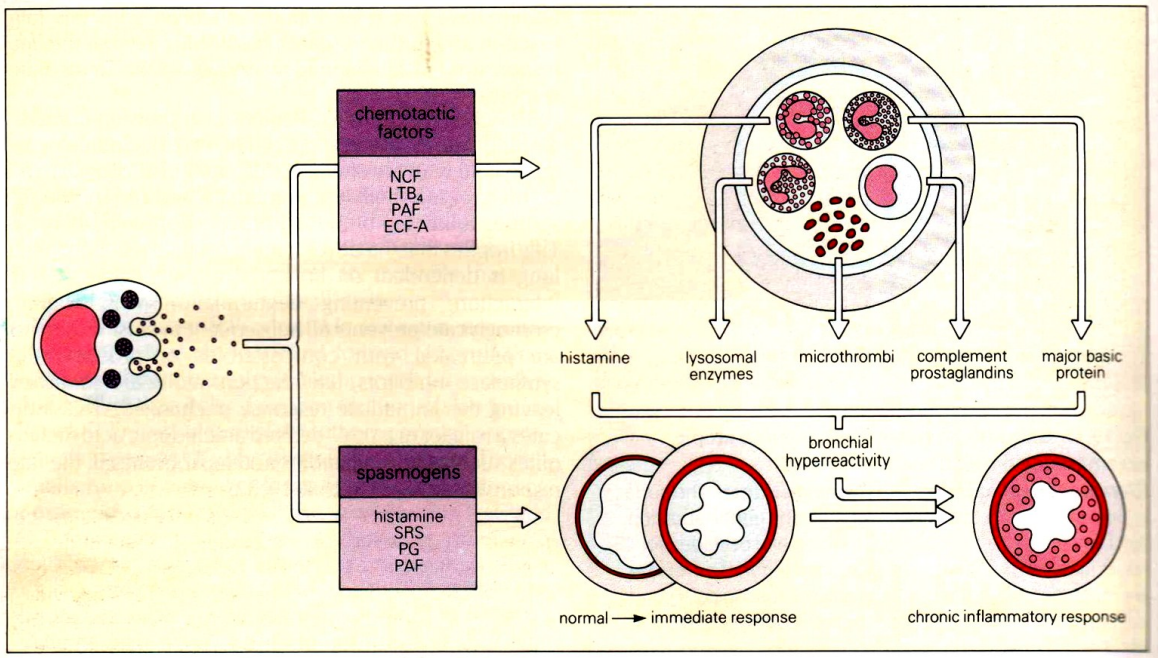
  CCL14, CCL19, CCL20, CCL21, CCL25, CCL27, CXCL12 and CXCL13. (klasifikasi tdk baku→ contoh : CCL20 → pro-inflammatory chemokine.
- Inflamasi: patologi→stimulus IL-1, TNF,LPSVirus

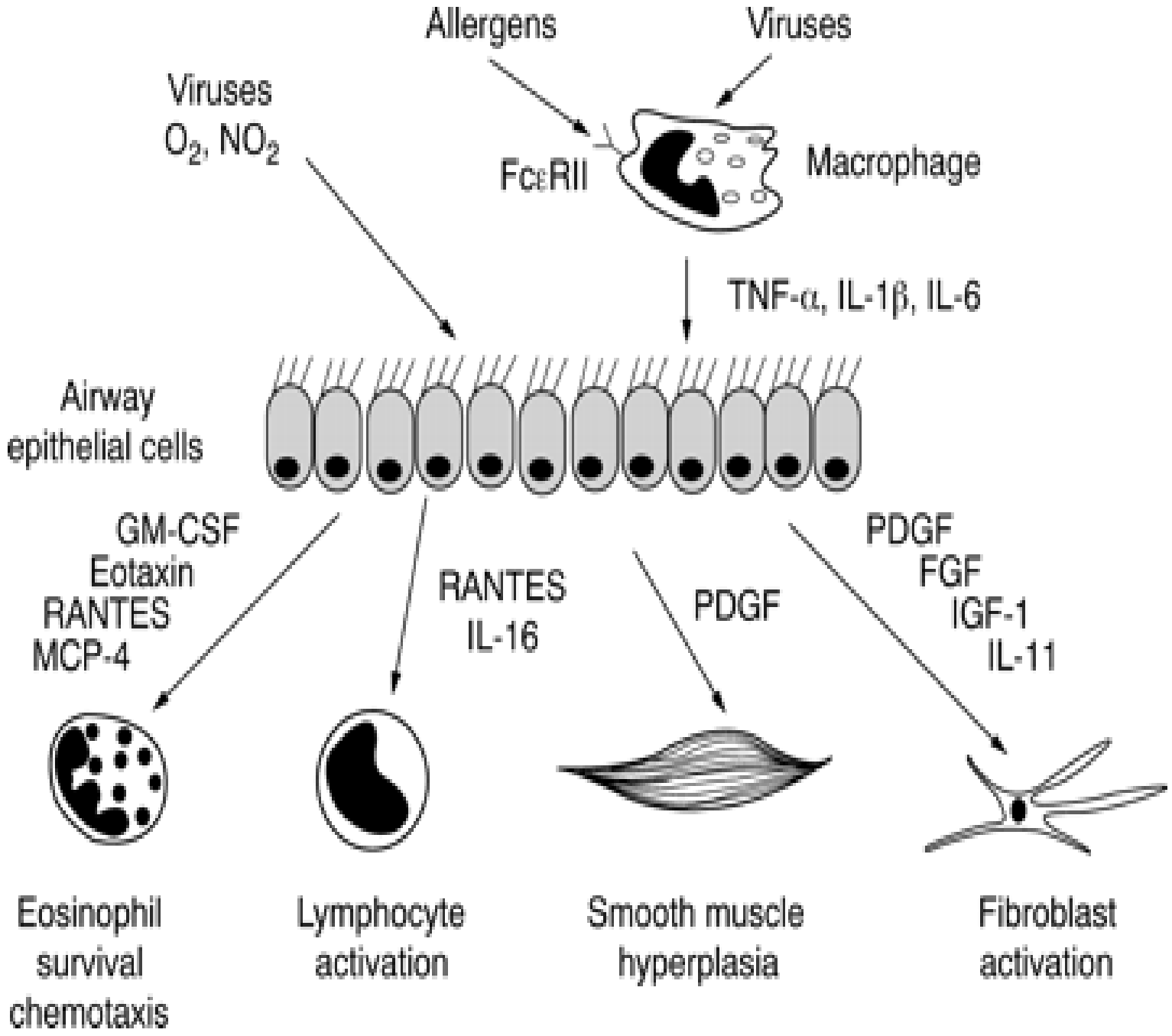
  CXCL-8, CCL2, CCL3, CCL4,CCL5, CCL11, CXCL10.


Allergen
Antigen presenting cel
(dendritic cell, macro
MHCII
B7-2
Allergen peptide
CD28
TCR
Thp
Mast cell
IL-12
IL-18
IL-4
Th1
IFN-γ
Th2
IL-4
IL-13
IgE
IL-5
IL-2
IFN-γ
Eosinophil

Mekanisme alergi pada saluran nafas

- Stimulus→ sitokin disekresikan epitel tr.resp dan makrofag
- Efek sitokin→ terhadap sel-sel tr.resp
  - eosinofil
  - limfosit
  - otot polos tr.resp
  - fibroblas




Allergens
Viruses
Viruses
O_2, NO_2
FcεRII
Macrophage
TNF-α, IL-1β, IL-6
Airway
epithelial cells
GM-CSF
Eotaxin
RANTES
MCP-4
RANTES
IL-16
PDGF
PDGF
FGF
IGF-1
IL-11
Eosinophil
survival
chemotaxis
Lymphocyte
activation
Smooth muscle
hyperplasia
Fibroblast
activation

GENETIKA ALERGI

- **STUDI EPIDEMIOLOGI (1920)**
- **ANAK DARI ORTU ALERGI, MENDERITA ALERGI > TIDAK ALERGI**
- **KEDUA ORTU ALERGI: 50% ANAK ALERGI**
- **SALAH SATU ORTU ALERGI: 30% ANAK ALERGI**

MEKANISME GENETIK YANG MENGATUR RESPON ALERGI

1. LEVEL IgE TOTAL

makin tinggi level IgE serum, makin besar resiko atopi

2. RESPON HLA-LINKED

HLA-B8 dan HLA-Dw3

3. GENERAL HYPERRESPONSIVE

Kromosom	Kandidat Gen	Fenotipe
Kromosom 5 **•5q31-33**	**•IL-3** **•IL-4** **•IL-5** **•IL-9** **•IL-13** **•GM-CSF** **•*glucocorticoid receptor* 1 (GRL1)** **•β-2-*adrenergic receptor* (ADRB2)**	**☞kadar Ig E serum** **☞hiperreaktifitas bronkus** **☞sirkulasi eosinofil**
Kromosom 6 **•6p21.3**	**TNF-α**	**Asma**
Kromosom 11 **•11q13**	**$Fc_{\epsilon}I\beta$**	**Asma** **hiperreaktifitas bronkus** **Ig E total** **Ig E spesifik** **Dermatitis atopi**
Kromosom 12 **•12q13-q24**	**Interferon-γ**	**hiperreaktifitas saluran napas kadar eosinofil** **kadar Ig E**
Kromosom 13 **•13q14.3-qter**	***tumor protein translationally controlled*-1 (TPT-1) mengkode *human histamin-releasing factor* (HRF)**	**atopi** **kadar Ig E serum**
Kromosom 14 **•14q11**	**TcR-α**	
Kromosom 16 **•16p11.2-16p12.1**	**IL-4Rα**	**asma dan atopi**
Kromosom 17 **•17q11.2-q21**	**RANTES**	**asma**
Kromosom 20 **•20p13**	**ADAM-33**	**remodeling saluran napas pada pasien asma**

TES KLINIK ALERGI

- **SKIN TEST**

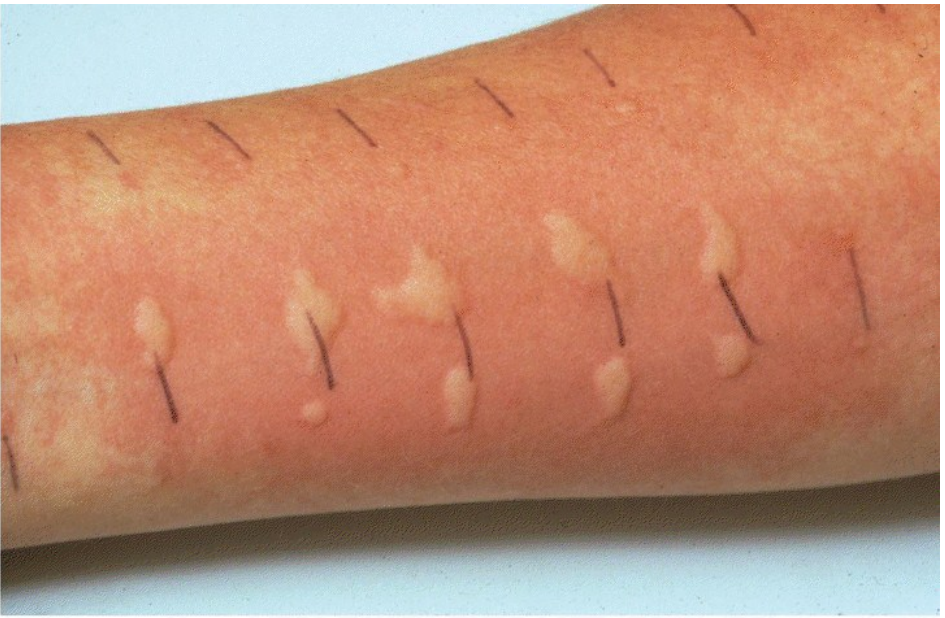
  1. SKIN PRICK TEST

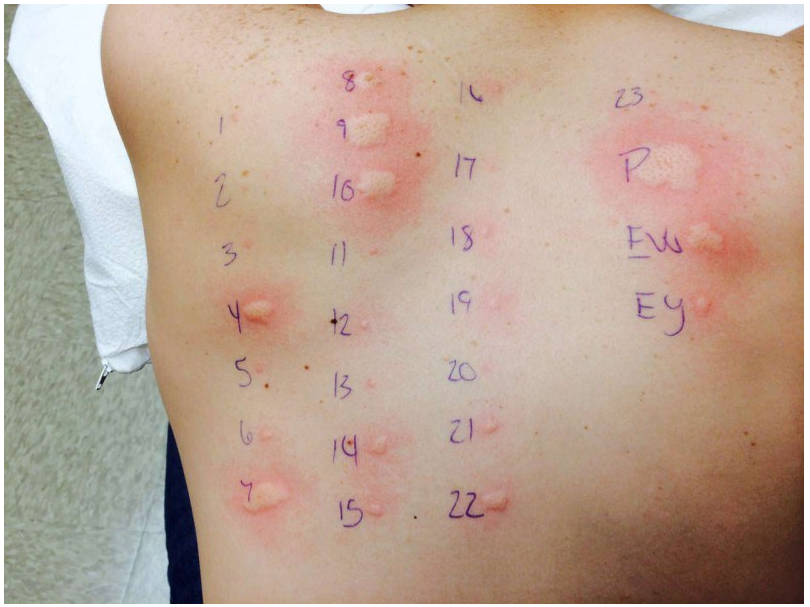
  2. SKIN PATCH TEST

  - KONTAK ALERGEN LANGSUNG PD KULIT IgE BERIKATAN DG SEL MAST PADA KULIT (CTMC) →PELEPASAN MEDIATOR

  - RESPON SKIN TEST KLASIK PADA ATOPIK: WHEAL&FLARE

- **PROVOCATIVE TEST**



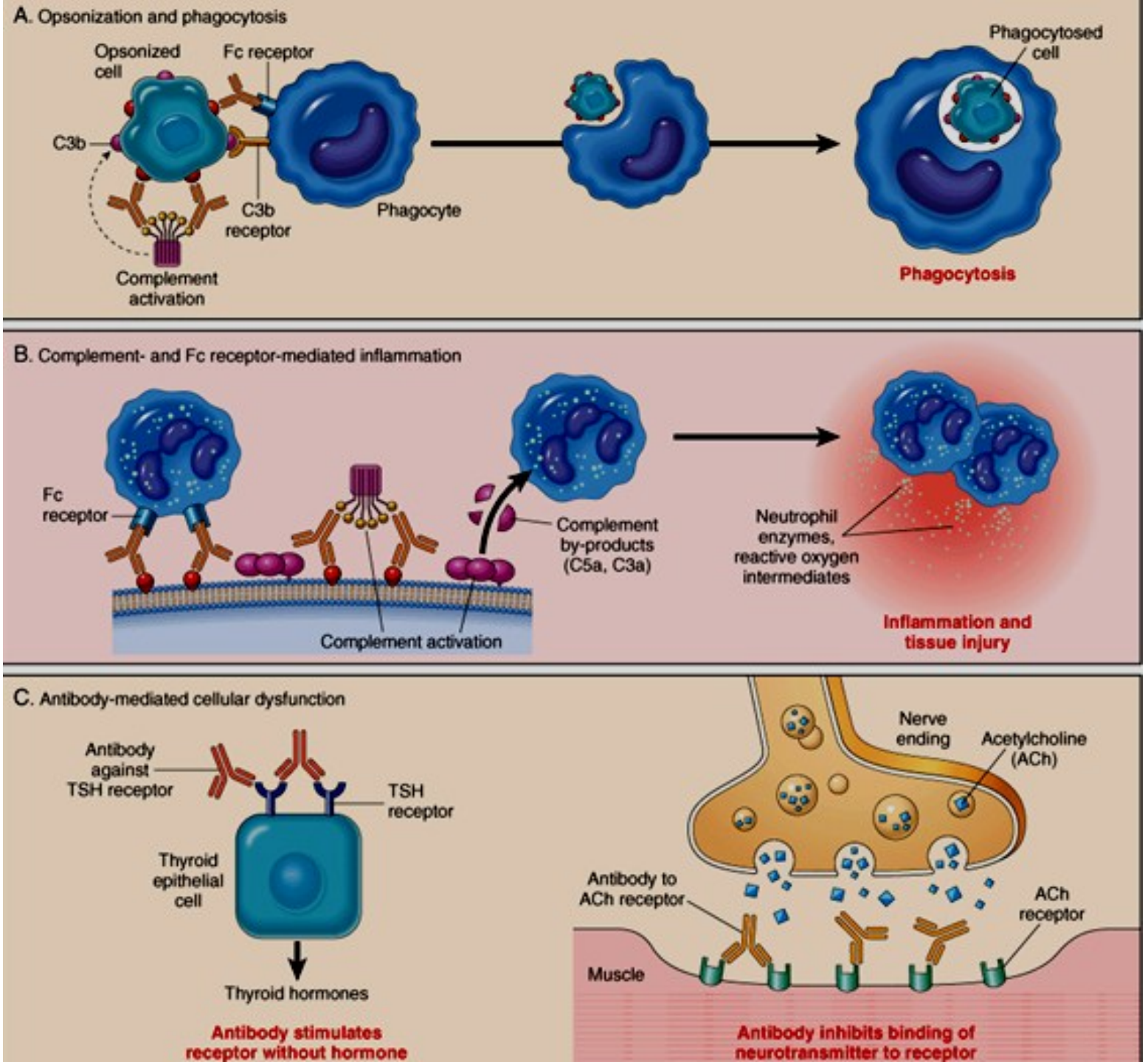


PENGOBATAN ALERGI

- **ALLERGEN AVOIDANCE**
- **FARMAKOLOGIS**
- **HIPO SENSITISASI / DESENSITISASI**

HIPERSENSITIVITAS TIPE II

- **DISEBUT RX SITOTOKSIK,**
- **PRODUKSI IgG DAN IgM BERIKATAN DENGAN ANTIGEN PADA TARGET ATAU JARINGAN TARGET**
- **FAGOSITOSIS ATAU LISIS SEL TARGET OLEH AKTIVASI KOMPLEMEN ATAU RESEPTOR Fc → REKRUTMEN LEUKOSIST**
- **KOMPONEN DARI PENYAKIT AUTO IMUN**
- **MEKANISME:**
  1. **Fagositosis: komplemen dan reseptor Fc→ fagositosis**
  2. **Opsonisasi : komplemen dan reseptor Fc→ fagositosis**
  3. **Antibodi→ disfungsi sel→ tipe V**


A. Opsonization and phagocytosis
Opsonized cell
Fc receptor
C3b
C3b receptor
Phagocyte
Complement activation
Phagocytosed cell
Phagocytosis
B. Complement- and Fc receptor-mediated inflammation
Fc receptor
Complement by-products (C5a, C3a)
Complement activation
Neutrophil enzymes, reactive oxygen intermediates
Inflammation and tissue injury
C. Antibody-mediated cellular dysfunction
Antibody against TSH receptor
TSH receptor
Thyroid epithelial cell
Thyroid hormones
Antibody stimulates receptor without hormone
Nerve ending
Acetylcholine (ACh)
Antibody to ACh receptor
ACh receptor
Muscle
Antibody inhibits binding of neurotransmitter to receptor

Peran Antibody-dependent cellular cytotoxicity (ADCC) pada hipersensitivitas tipe II

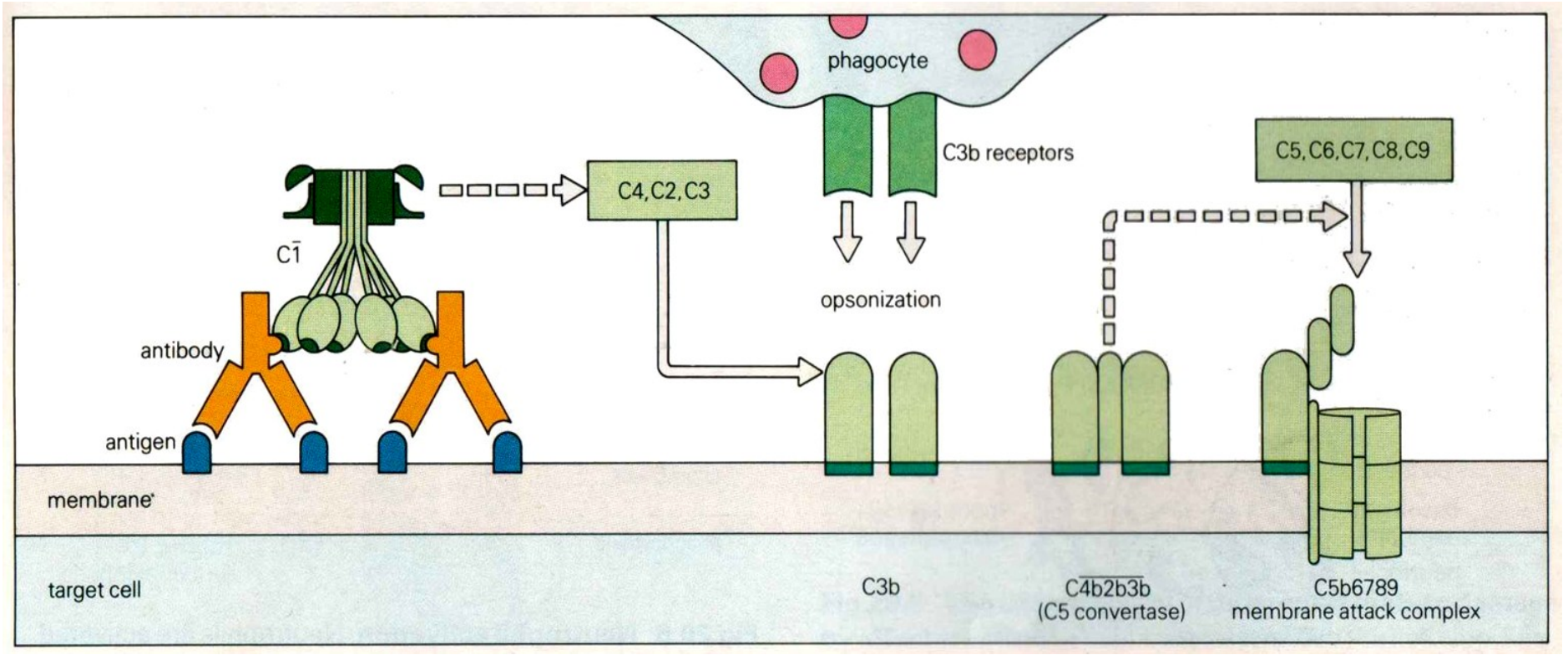
- Sel dilapisi IgG level rendah
- Sel efektor (Mo,Net.Eo,NK) berikatan dengan IgG melalui FcγR
- Sel melepas perforin dan granzim→ lisis

KLINIS HIPERSENSITIVITAS TIPE II

- Inkompatabilitas ABO
- HDNB
- AIHA
- Rx obat
- Myastenia gravis

KOMPLEMEN + RESEPTOR Fc→ FAGOSITOSIS

- **Komplemen;**
  -Jalur klasik→ lisis membran sel yang sudah disensitisasi Ab
  -Aktivasi c3 melalui sel efektor→ aktivasi C56789→ kerusakan jaringan
- **Frustrated Phagocitic**



MEKANISME HIPERSENSITIVITAS TIPE II PD RX TRANSFUSI

- TERJADI KARENA KETIDAK COCOKAN TRANSFUSI GOL.DARAH ABO
- RESEPIEN MEMBENTUK ANTIBODI TERHADAP ERITROSIT DONOR SEGERA SETELAH TRANSFUSI
- IGM MENGAKTIFKAN KOMPLEMEN, AKTIVASI C5,6,7,8,9 MENGHANCURKAN (LISIS) ERITROSIT INTRAVASKULER
- ANTI BODI YANG TERBENTUK PD I NKOMPATIBILITAS SISTEM ABO: IgM

  SISTEM LAIN:IgG
- DESTRUKSI ERI MENYEBABKAN SHOCK SIRKULASI
- BAGIAN ERI YANG HANCUR MENYEBABKAN ATN PADA GINJAL

system	gene loci	antigens	phenotype frequencies	
ABO	1	A, B or O	A	42%
			B	8%
			AB	3%
			O	47%
Rhesus	3 closely linked loci: major antigen = RhD	C or c D or d E or e	RhD^+	85%
			RhD^-	15%
Kell	1	K or k	K	9%
			k	91%
Duffy	1	Fy^a, Fy^b or Fy	$Fy^a Fy^b$	46%
			Fy^a	20%
			Fy^b	34%
			Fy	0.1%
MN	1	M or N	MM	28%
			NN	50%
			MN	22%

	Caucasians	African American	Hispanic	Asian
O +	37%	47%	53%	39%
O -	8%	4%	4%	1%
A +	33%	24%	29%	27%
A -	7%	2%	2%	0.5%
B +	9%	18%	9%	25%
B -	2%	1%	1%	0.4%
AB +	3%	4%	2%	7%
AB -	1%	0.3%	0.2%	0.1%

system	gene loci	antigens	phenotype frequencies	
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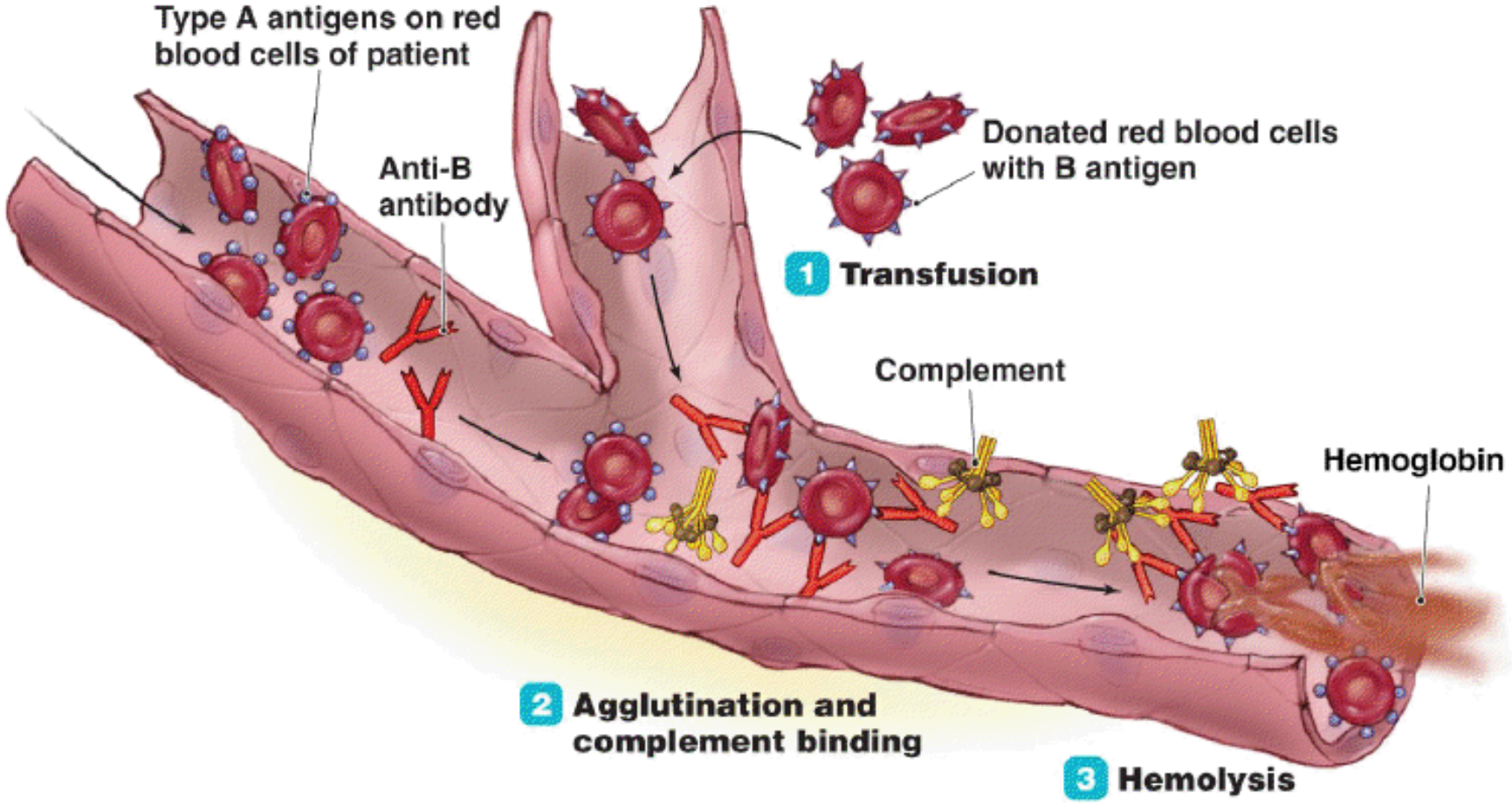
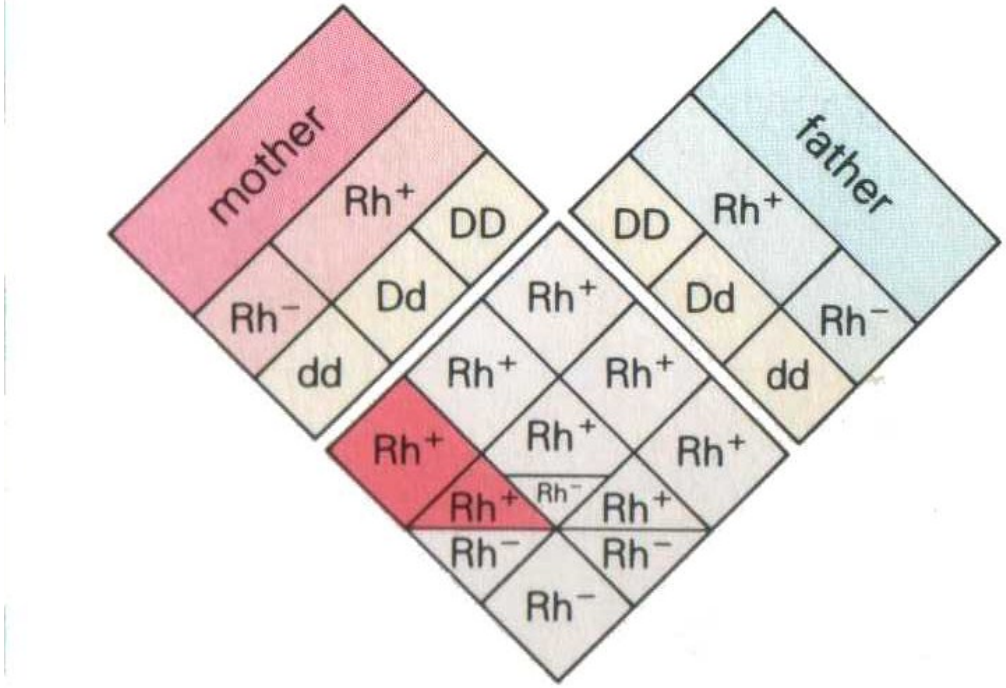
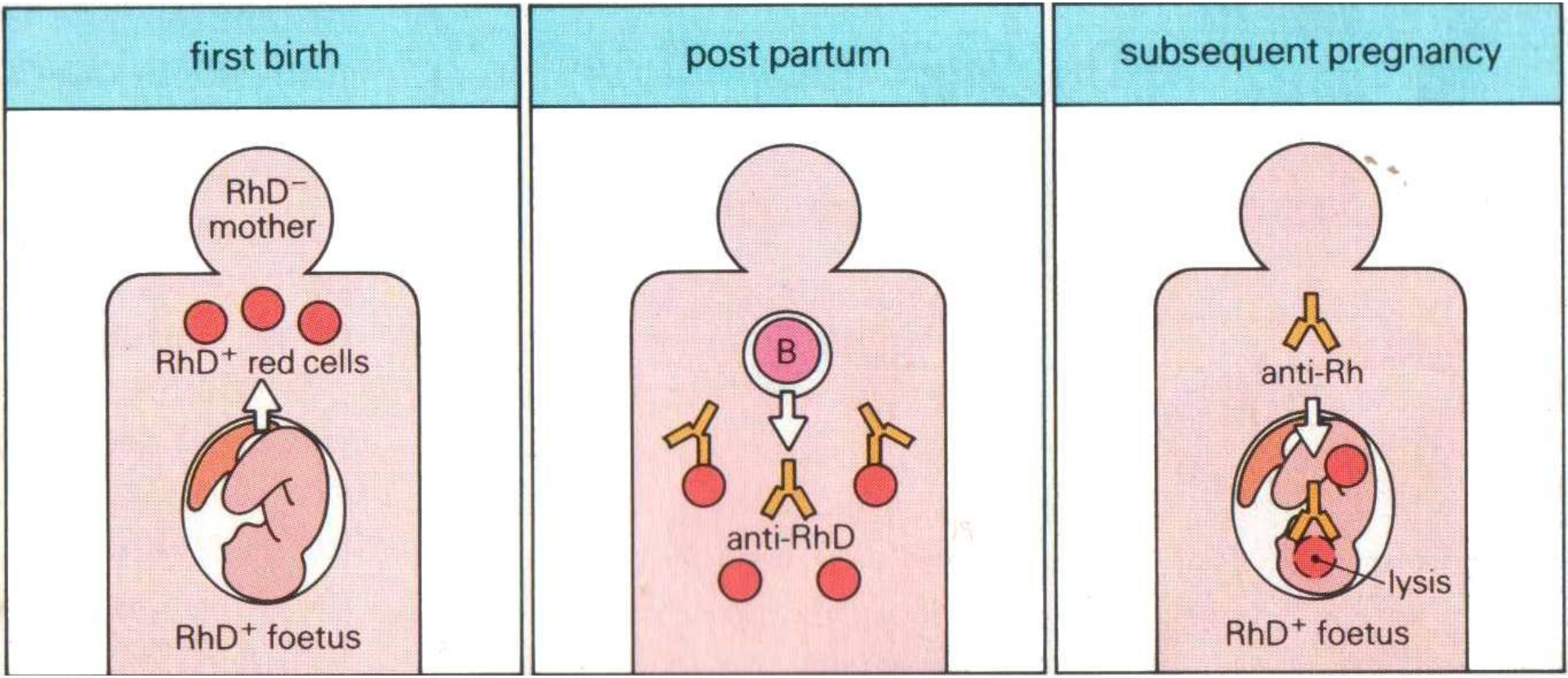
PROSES HEMOLISIS



MEKANISME HIPERSENSITIVITAS TIPE II PDHDNB

- **TERJADI PADA BAYI BARU LAHIR (PADA ANAK KE II)**
- **KARENA INKOMPATIBILITAS RHESUS (IBU RhD-, JANIN +)**
- **DARAH IBU DISENSITISASI OLEH ANTIGEN ERI JANIN SEHINGGA TERBENTUK IgG → DESTRUKSI ERI JANIN**
- **SENSITISASI TERJADI SELAMA PROSES PARTUS (DARH ANAK KEMBALI KE IBU MELALUI PLASENTA)**



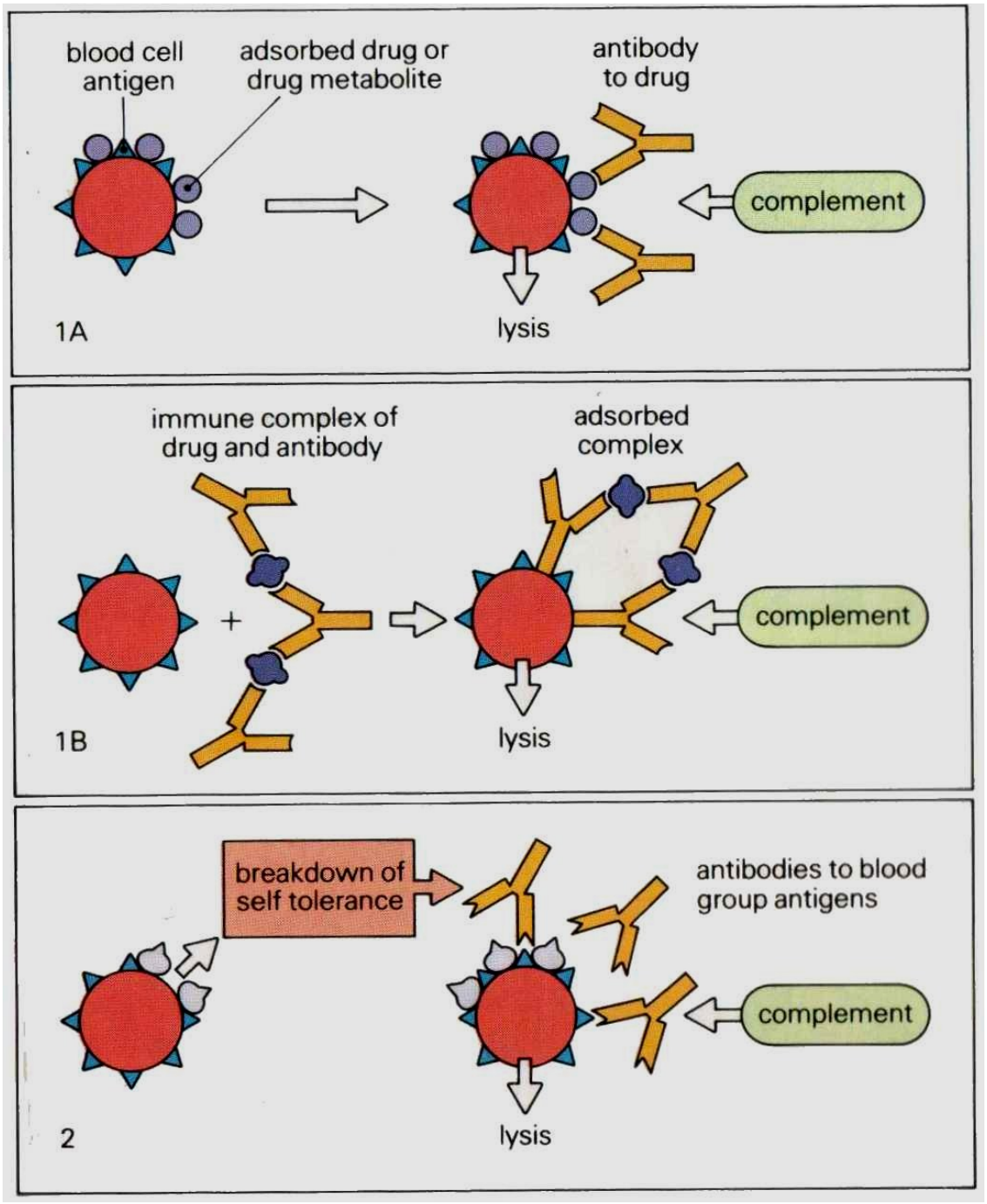

first birth
RhD⁻ mother
RhD⁺ red cells
RhD⁺ foetus
post partum
B
anti-RhD
subsequent pregnancy
anti-Rh
lysis
RhD⁺ foetus

MEKANISME HIPERSENSITIVITAS TIPE II PD AIHA:

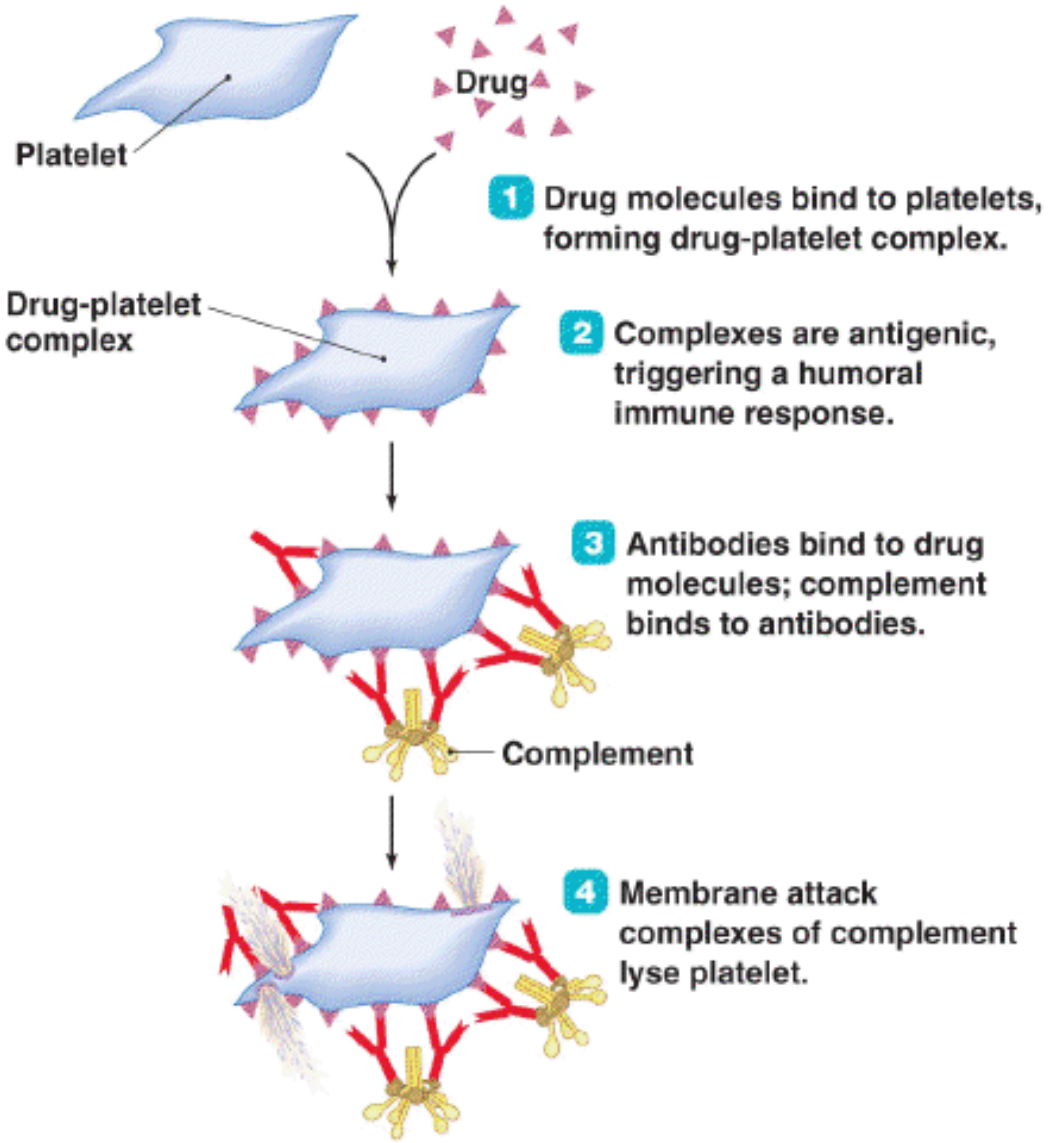
- **Rx Ab dg eri self**
- **Lisis eri → fagositosis via reseptor Fc dan C3b**

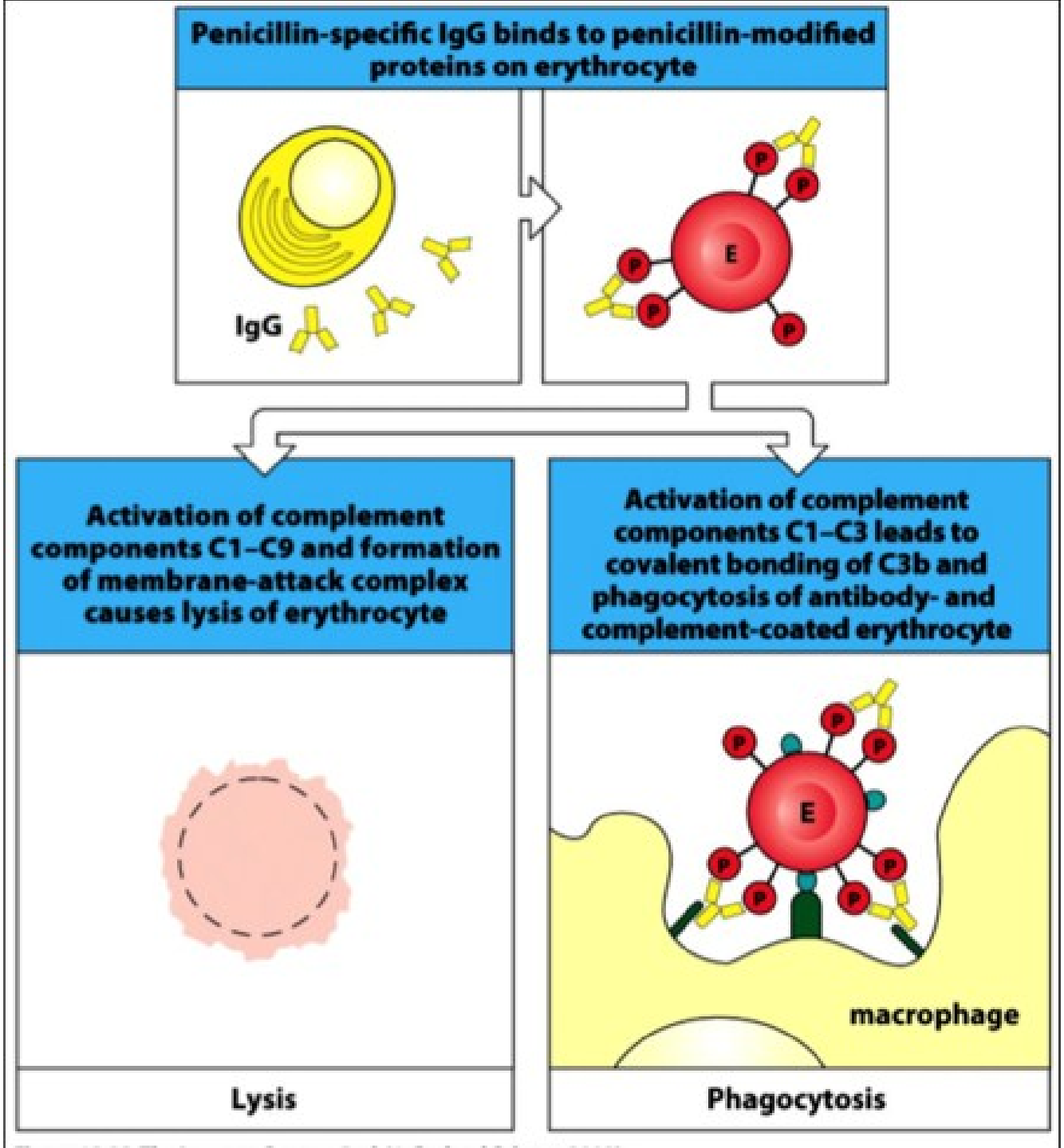
REAKSI INDUKSI OBAT TERHADAP KOMPONEN DARAH:

- **Bahan kimia obat berikatan dengan komponen permukaan eritrosit atau trombosit → epitop "asing"**
- **Produksi IgG atau IgM→ lisis**
- **Jenis obat:**
  - **Penisilin**
  - **Quinidin**
  - **metildopa**
  - **Sedormid→ mingikat trombosit→ purpurta**
  - **Fenasetin dan CPZ→ mengikat eri**
  - **klorampenikol→ mengikat eri**


blood cell antigen
adsorbed drug or drug metabolite
antibody to drug
complement
lysis
1A
immune complex of drug and antibody
adsorbed complex
+
complement
lysis
1B
breakdown of self tolerance
antibodies to blood group antigens
complement
lysis
2

ITP


Platelet
Drug
1 Drug molecules bind to platelets, forming drug-platelet complex.
Drug-platelet complex
2 Complexes are antigenic, triggering a humoral immune response.
3 Antibodies bind to drug molecules; complement binds to antibodies.
Complement
4 Membrane attack complexes of complement lyse platelet.

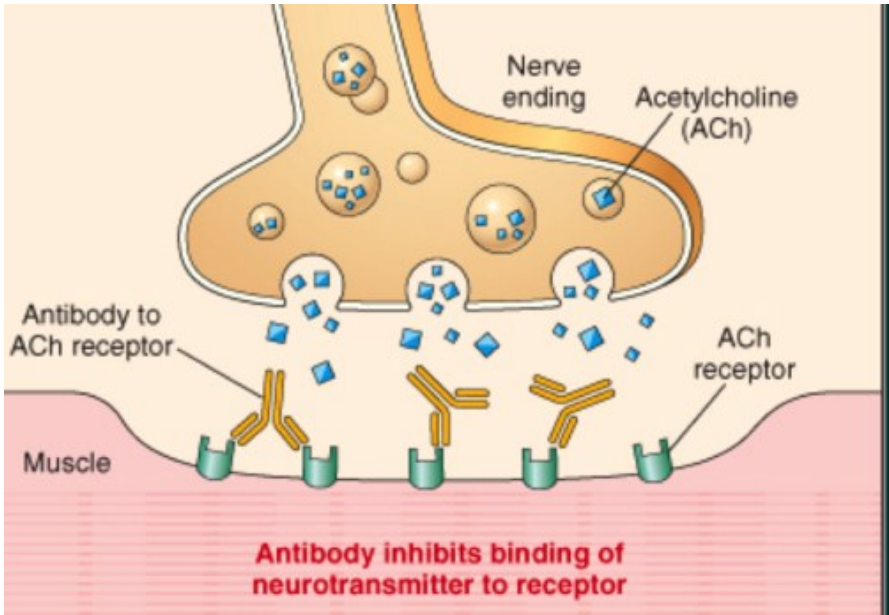

Penicillin-specific IgG binds to penicillin-modified proteins on erythrocyte
IgG
E
P
Activation of complement components C1–C9 and formation of membrane-attack complex causes lysis of erythrocyte
Activation of complement components C1–C3 leads to covalent bonding of C3b and phagocytosis of antibody- and complement-coated erythrocyte
macrophage
Lysis
Phagocytosis

Komplemen+Reseptor Fc→ Inflamasi

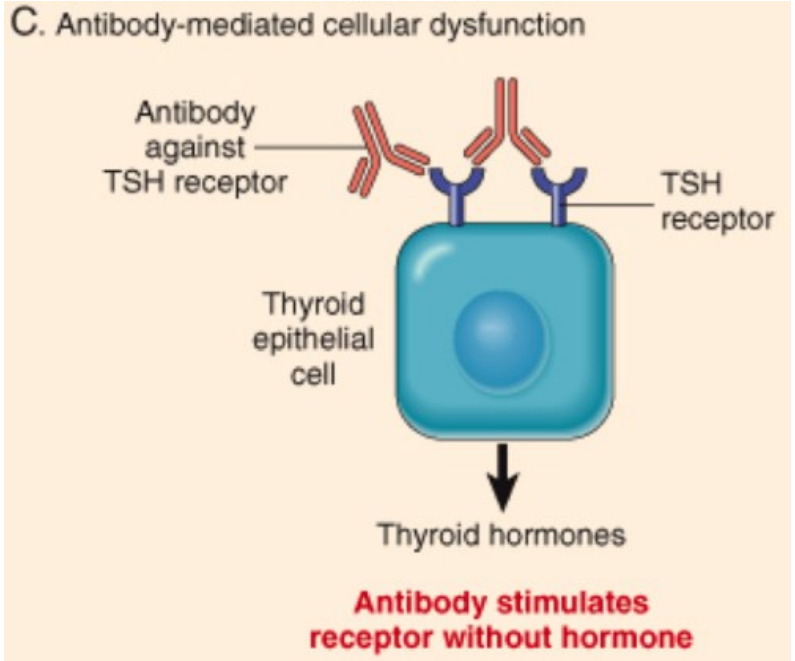
- Ab dideposit pada jaringan ekstrasel spt membrana basalis dan matriks→ aktivasi komplemen→ enzim degradasi → inflamasi → kerusakan jaringan
- C5a sebagai faktor kemotaktik→ rekrutmen netrofil dan monosit→ berikatan dg Ab
- C3a dan C5a sebagai anafilatoksin→ meningkatkan permeabilitas vaskuler
- Sel yang teraktivasi melepas prostaglandin, peptida vasoaktif, kemotaktik faktor,, degradative enzymes, ROS> kerusakan jaringan

Antibodi→ Disfungsi seluler

- Ab berikatan langsung dengan molekul reseptor permukaan → Gangguan fungsi protein tanpa menyebabkan cedera sel atau induksi inflamasi.
- Myastenia gravis
  - Ab terhadap reseptor asetilkolin
  - menghambat ikatan asetilkolin dg motor en plate pada otot lurik→ kelemahan otot progresif
  - Autoimun



- **Antibody mediated cellular dysfunction: Pemphigus vulgaris**
  - Ab terhadap desmosom
  - ganggua intercellular junctions epidermis
  - vesicles pada kulit
- **Antibody mediated cellular dysfunction: Graves disease**
  - Receptor agonis
  - Antibodi terhadap TSH / reseptor pada sel-sel epitel tiroid→ stimulasi sel
  - hyperthyroidism



- **Antibody mediated cellular dysfunction: Acute Rheumatic Fever (ARF)**

  - ab thd protei M dari Strep

  - interaksi dg katub jantung

  - miokarditis, artritis

- **Antibody mediated cellular dysfunction: Goodpastures syndrome**

  - Ab thd protein non-kolagen pada membrana basalis glomerulus ginjal dan alveoli paru

  - nefritis , hemoragi paru→ hemoptoe

PENOLAKAN PENCANGKOKAN HIPERAKUT

- **TERJADI BILA RESEPIEN MEMBENTUK ANTIBODI LANGSUNG TERHADAP JARINGAN YANG DICANGKOKAN (GINJAL)**
- **RX TERJADI DAL BEBERAPA MENIT-48 JAM**
- **RX TERLIHAT PADA JAR.CANGKOKAN BERUPA TERJADINYA REVASKULARISASI SEGERA SETELAH PENCENGKOKAN**
- **DL 1 JAM DISUSUL DENGAN INFILTRASI NETROFIL, KERUSAKAN KAPILER GLOMERULUS DAN HEMORAGIA**

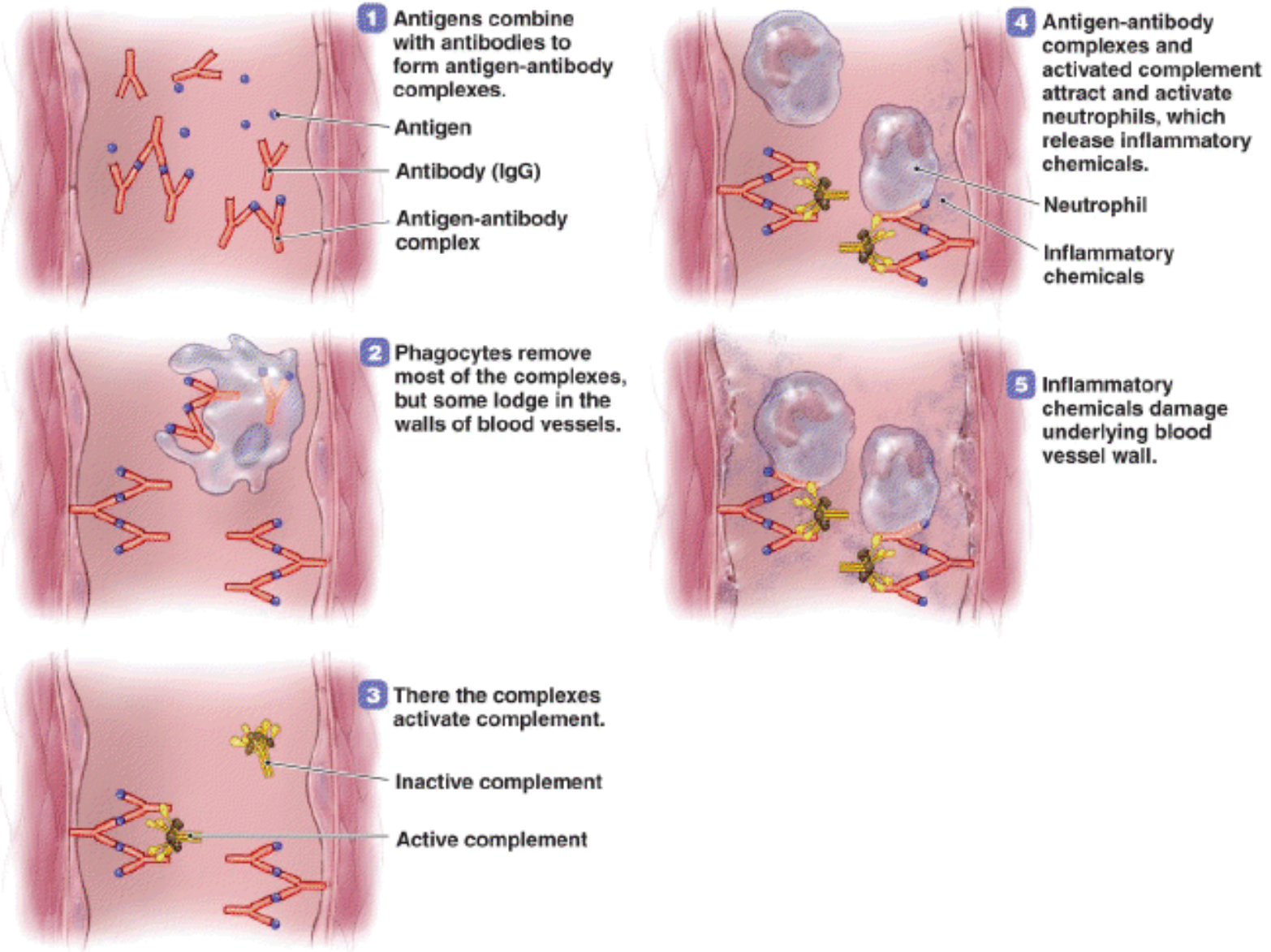
Human antibody-mediated diseases.

Examples of human diseases caused by cell- or tissue-specific antibodies			
Disease	**Target antigen**	**Mechanisms of disease**	**Clinicopathologic manifestations**
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Goodpasture s syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor-mediated inflammation	Nephritis, lung hemorrhages
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetycholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	Thyroid stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B12	Abnormal erythropoiesis, anemia

Hipersensitivitas Tipe III

- **Rx kompleks imun**
- **Ag eksogen atau endogen→ Ab IgM atau IgG**
- **Kompleks Ag-Ab dalam sirkulasi tidak dieliminasi→ deposit pd dinding p.darah di jaringan→ inflamasi→ kerusakan jaringan**
- **Penyebab:**
  - **Ag menetap dl sirkulasi ok Autoimun atau infeksi persisten dari Streptokokus, stafilokokus, plasmodium vivax, virus hepatitis**
  - **proses hemodinamik**
  - **peningkatan permeabilitas p.darah**
  - **menembus endotel**
  - **Aktivasi komplemen**
  - **kompleks imun pada permukaan paru: inhalasi berulang dari Ag→ IgG**

MEKANISME HIPERSENSITIVITAS TIPE III



Kompleks imun

1. Lokasi Deposit

    - Kidneys (glomerulonephritis)
    - Joints (arthritis)
    - Skin
    - Heart
    - Serosal surfaces
    - Small vessels (vasculitis)→ SLE

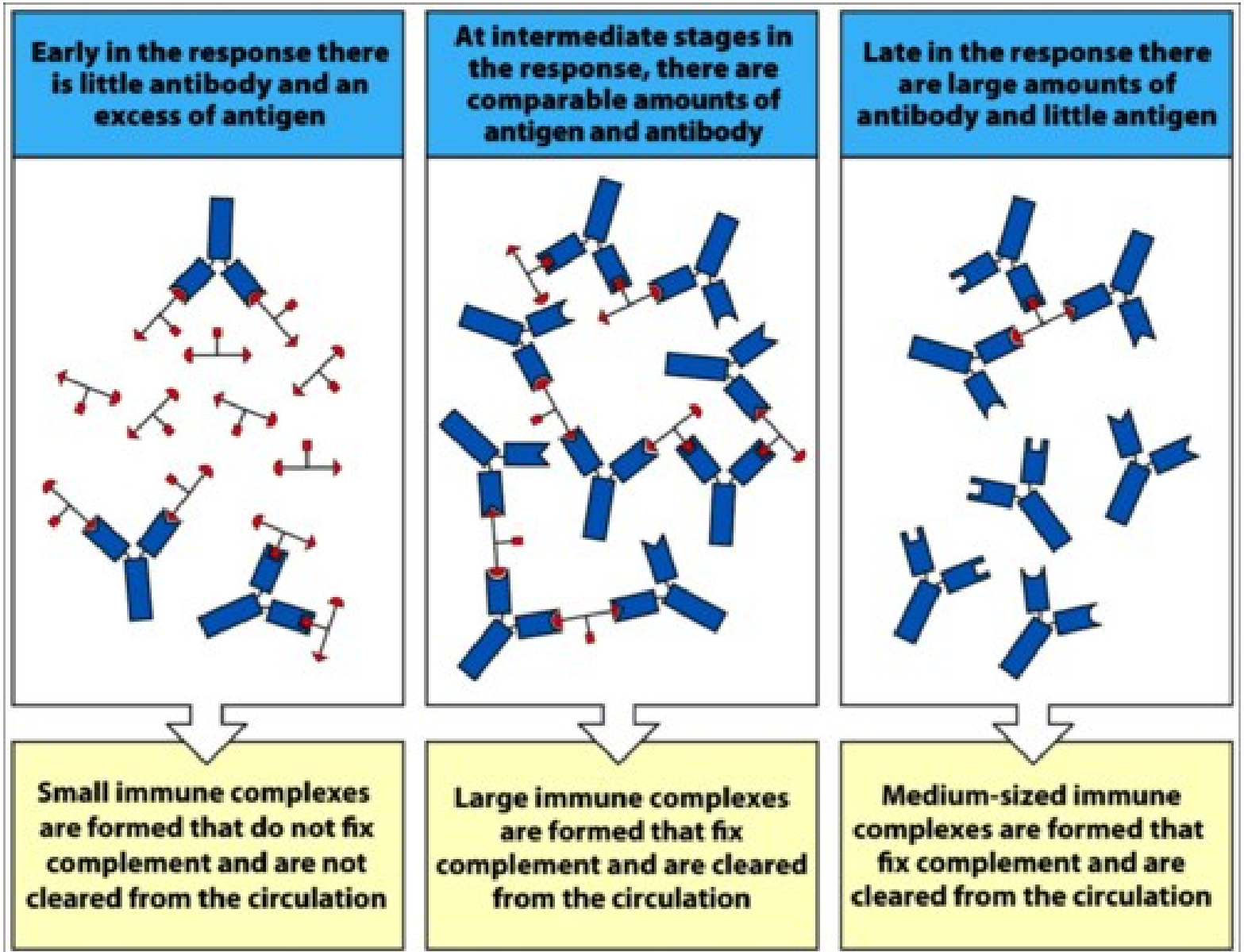
2. Proses dari sirkulasi→ jaringan

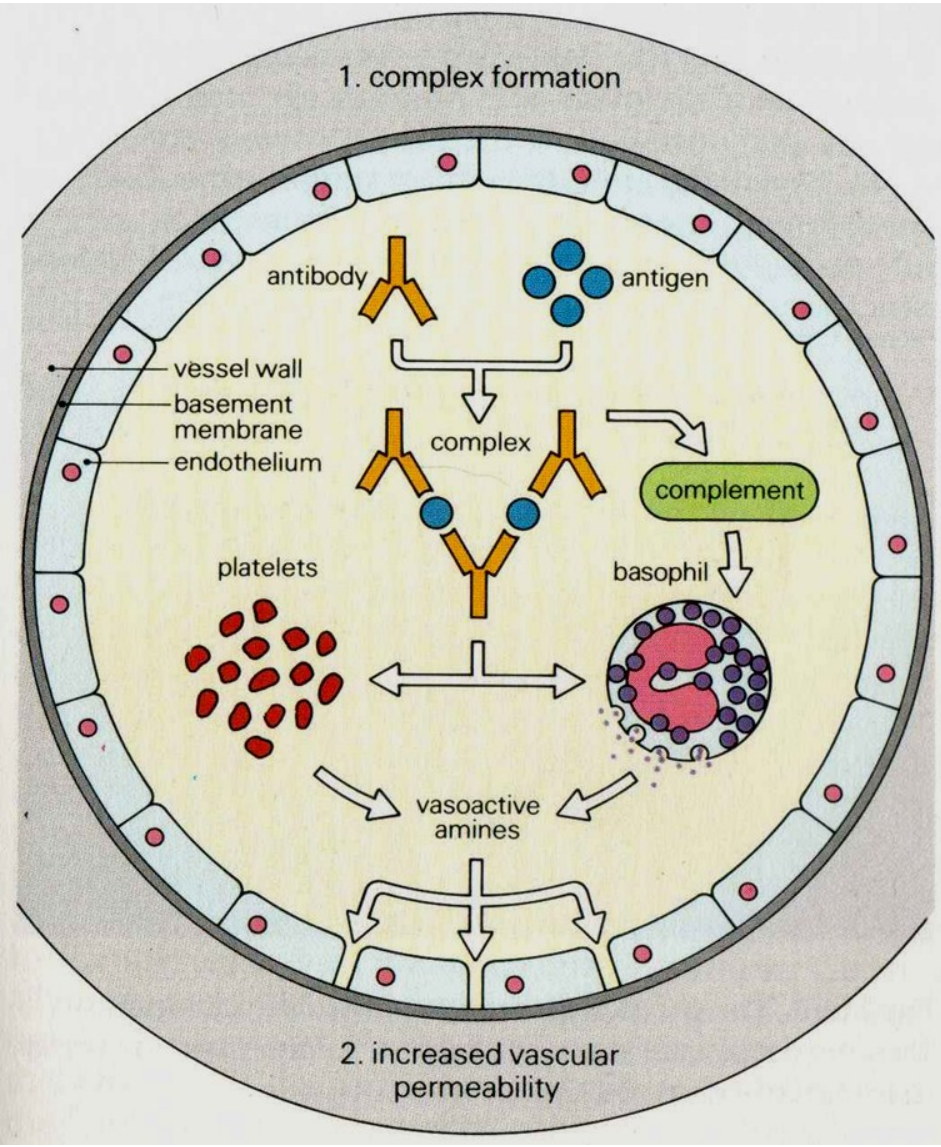
    Kompleks imun berikatan dengan sel-sel inflamasi via FcR atau C3bR→pelepasan amina vasoaktif dan sitokin → Permeabilitas kp.darah

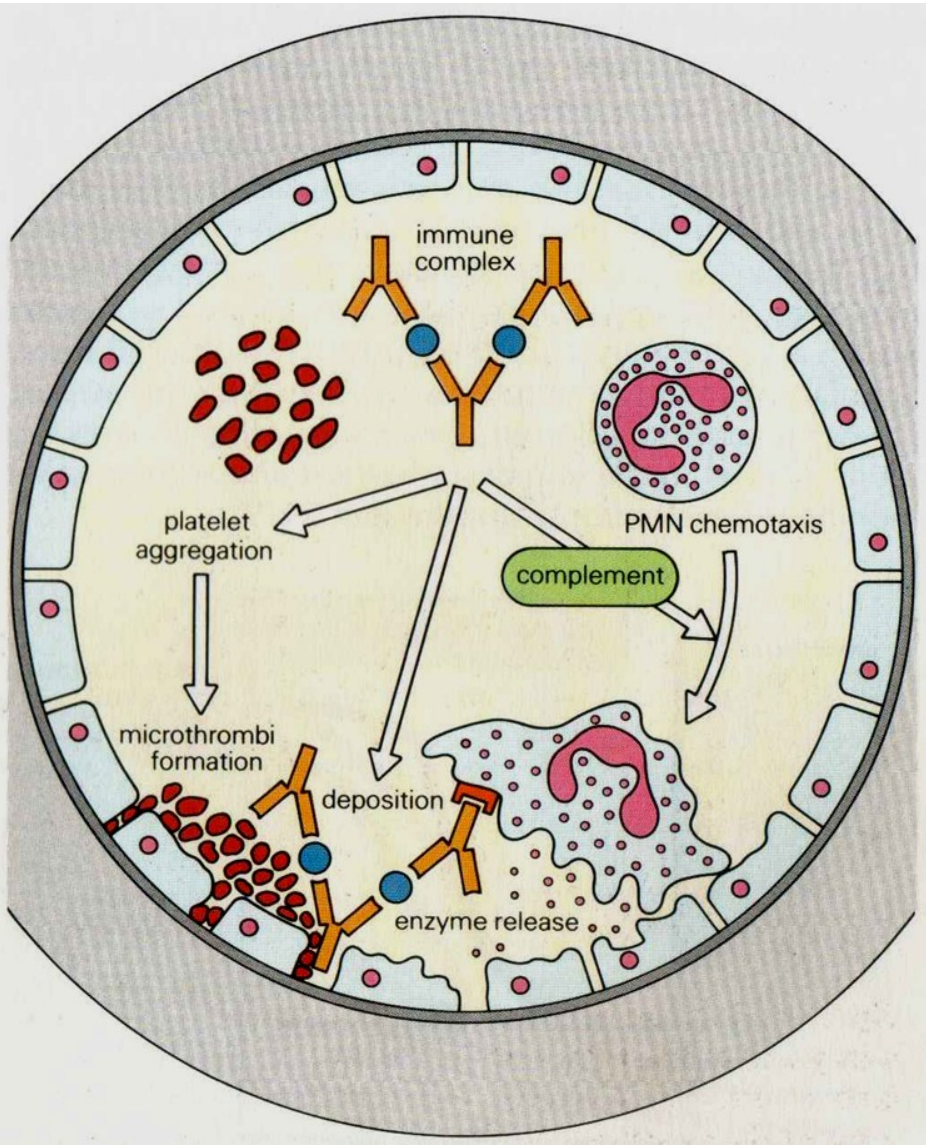
3. Sekali kompleks imun dideposit di jaringan → inisiasi inflamasi akut

   → gejala klinis (Fever- Urticaria- Arthralgias- Lymphadenopathy- proteinuria)

Pembentukan Kompleks Imun (Early, Intermediate, Late Response)

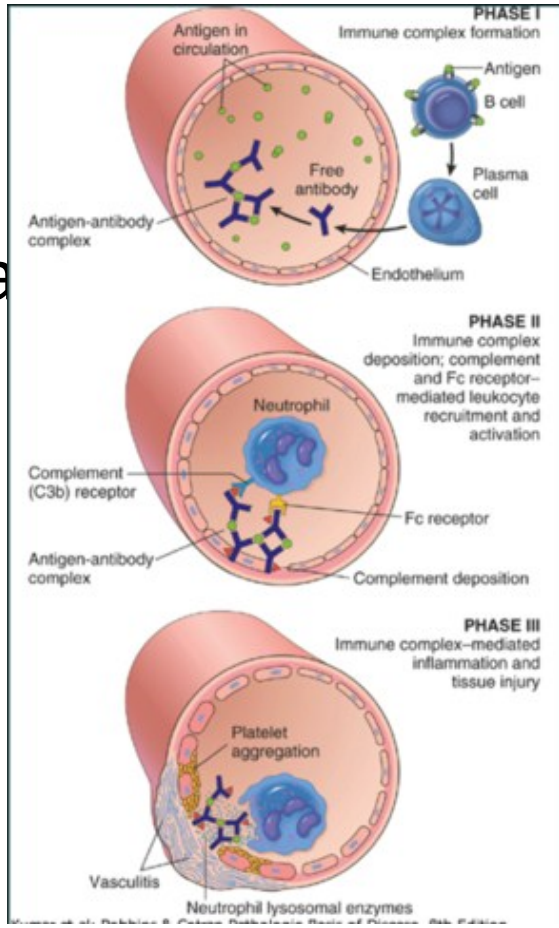



1. complex formation
antibody
antigen
vessel wall
basement membrane
endothelium
complex
complement
platelets
basophil
vasoactive amines
2. increased vascular permeability


immune complex
platelet aggregation
PMN chemotaxis
complement
microthrombi formation
deposition
enzyme release

Klasifikasi rx Hipersensitivitas tipe III

- **Sistemik**
  - -Serum sickness→ prototipe
  - - jarang
  - - kompleks imun dideposit di banya organ
  - - terdiri dari 3 tahap
  1. pengenalan Ag→ pembentukan kompleks imun
  2. Deposit kompleks imun
  3. Inisiasi rx inflamasi akut
- **Terlokalisis**

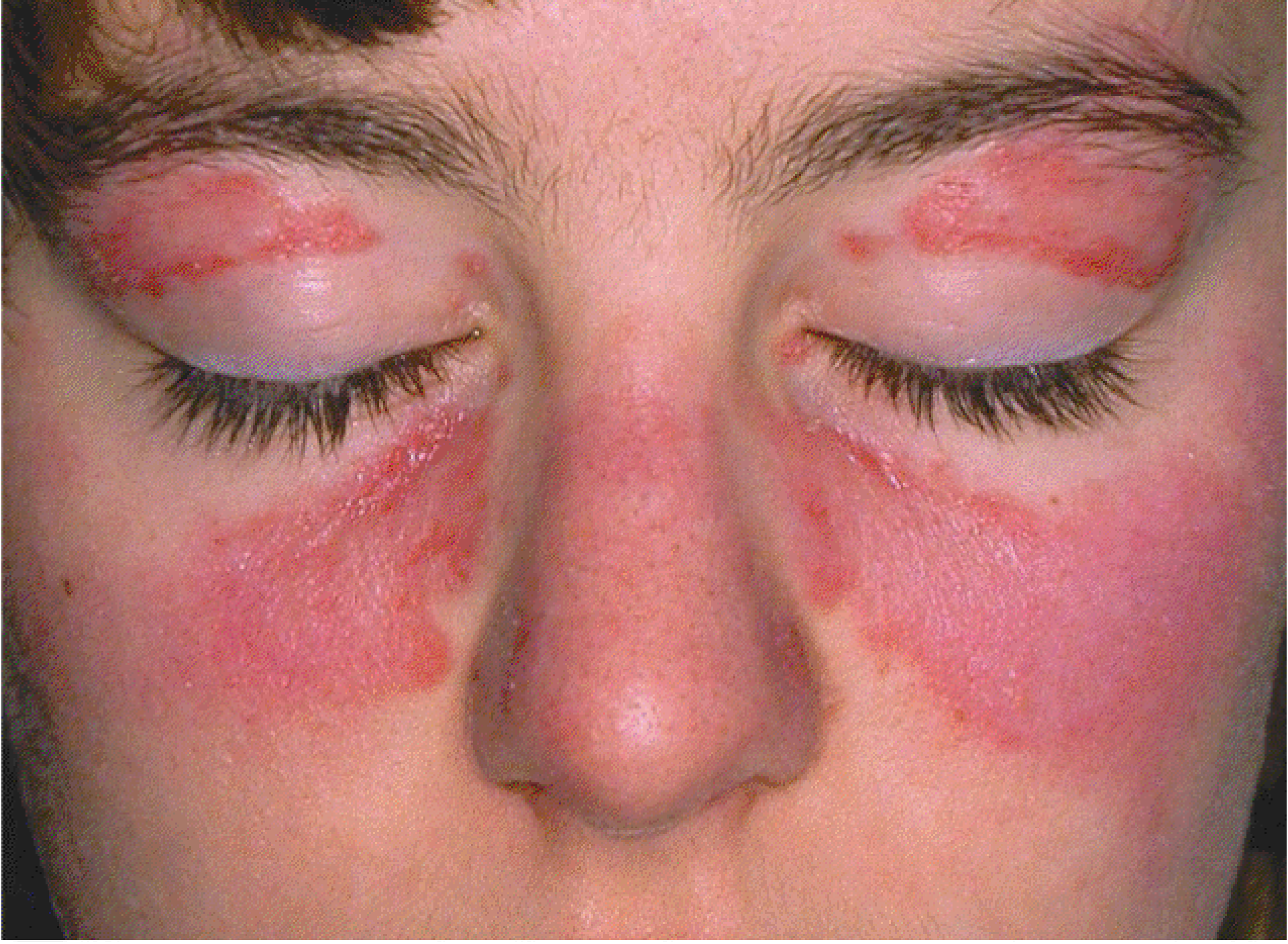


Hipersensitivitas tipe III terlokalisir

- Reaksi artus
- deposit kompleks imun terlokalisir pada organ tertentu spt: ginjal, sendi, p.darah kecil dan kulit
- Inhalasi antigen (fungi, animal feces) dapat menyebabkan reaksi pada paru paru
- ‘Farmers lung’ and ‘piegeon-breeder’s lung
- Ab: IgG

KLINIS HIPERSENSITIVITAS TIPE III

- PNEUMONITIS: INHALASI ANTIGEN→ IMUN KOMPLEKS
- GLOMERULONEFRITIS: IMUN KOMPLEKS DARI SIRKULASI DIDEPOSIT PADA DINDING GLOMERULUS→ GAGAL GINJAL
- ARTRITIS REUMATOID: IMUN KOMPLEKS DIDEPOSIT DI JARINGAN SENDI
- SLE:DEPOSIT IMUN KOMPLEKS AKIBAT AUTOANTIBODI TERHADAP DNA



Kerusakan Jaringan Akibatinflamsi

Mekanisme

1. Aktivasi kaskade komplemen

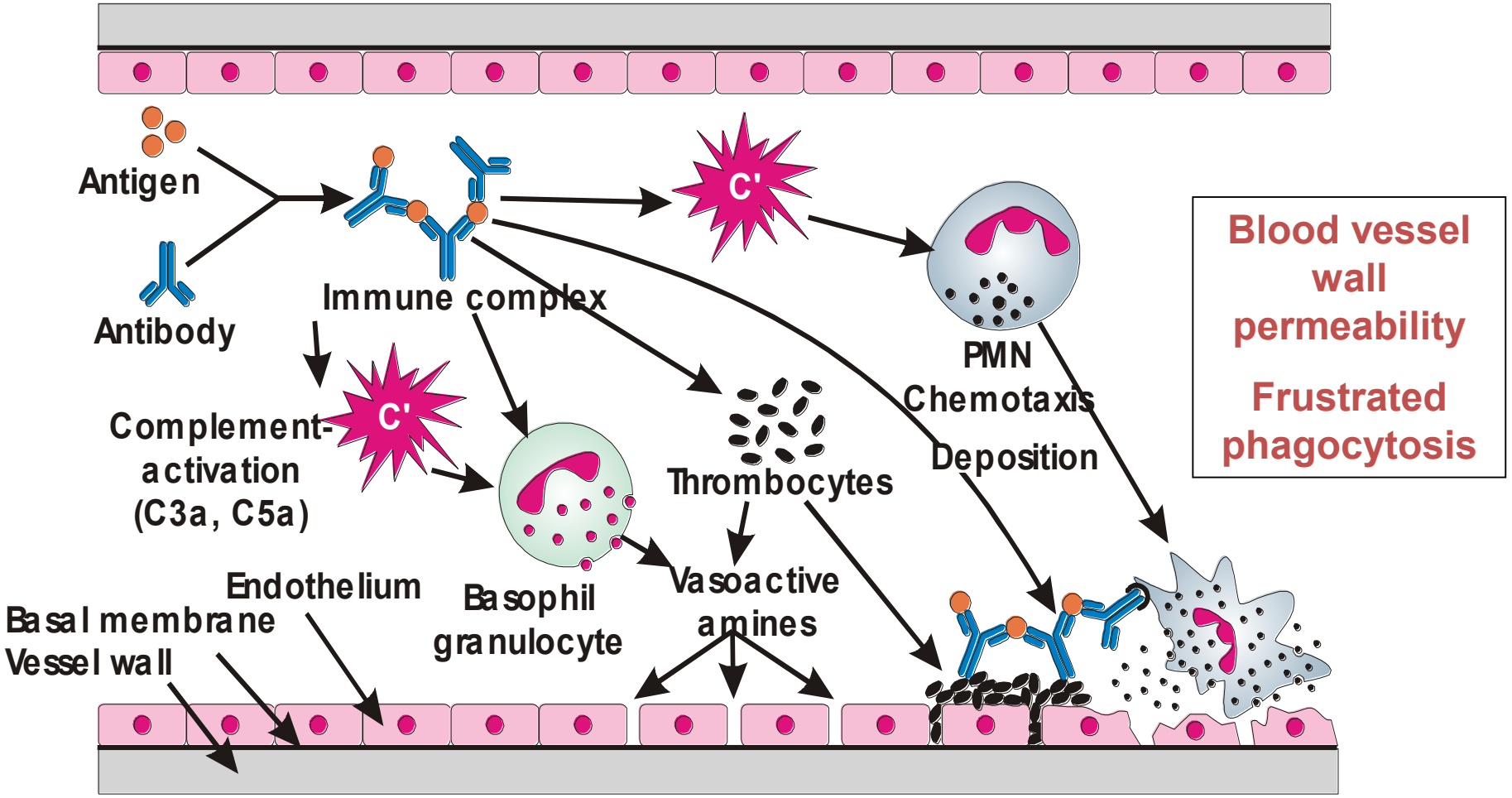
   Faktor kemotaktik→ migrasi PMN dan makrofag

   C5a dan C3a→ anafilatoksin→ permeabilitas p.darah

2. Aktivasi netrofil dan makrofag via FcR→ melepaskan substan pro-inflamasi:

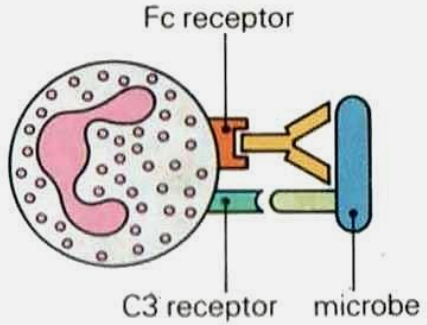
- Prostaglandins
- Vasodilators
- Chemotactic factors
- Lysosomal enzymes
- oxygen free radicals

THE PROCESS OF TISSUE DAMAGE CAUSED BY IMMUNE COMPLEXES

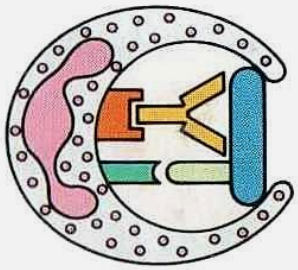


Immune complexes activate the complement system, neutrophils, basophils and thrombocytes

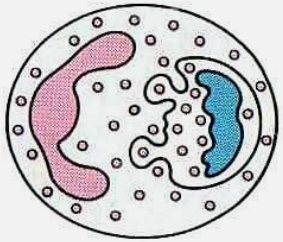
normal anti-microbial action



1. neutrophil

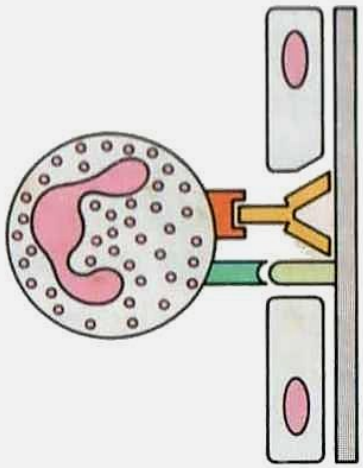


2. phagocytosis

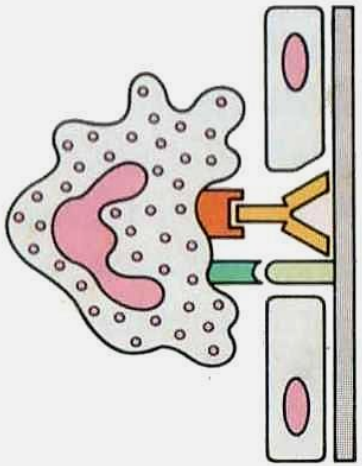


3. lysosome fusion

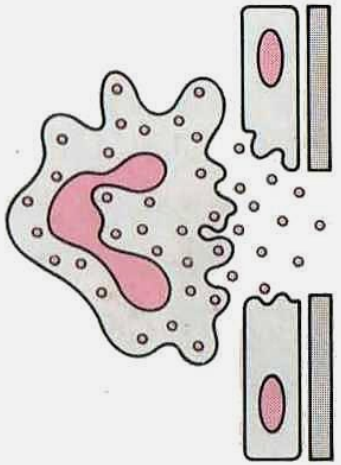
hypersensitivity reaction



4. neutrophil



5. 'frustrated phagocytosis'

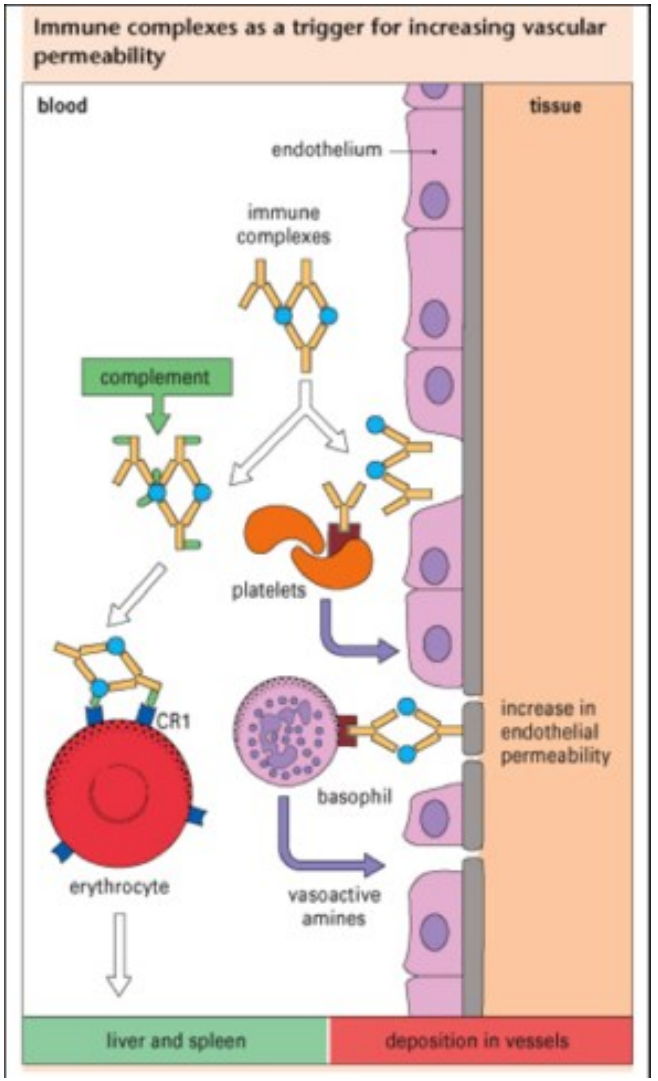


6. extracellular enzyme release

Efek kompleks imun yang lain

Agregasi trombosit→ pembentukan mikrotrombus

→ perdarahan → hematuri



HIPERSENSITIVITAS TIPE IV

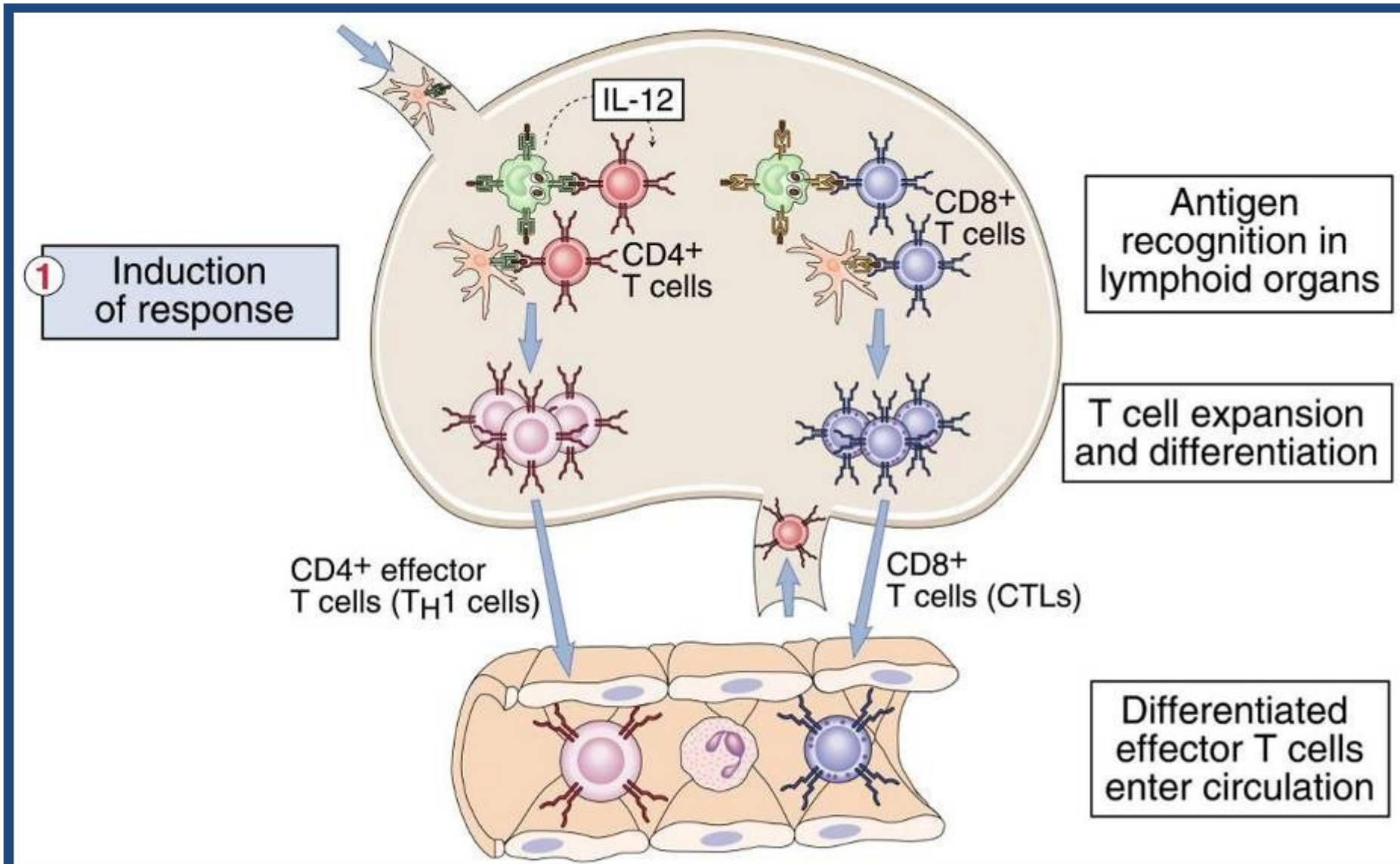
- **DISEBUT REAKSI HIPERSENSITIVITAS TIPE LAMBAT/ CELL MEDIATED IMMUNITY/ DELAYED HYPERSENSITIVITY**
- **TIMBUL RX SETELAH 24 JAM**
- **RX TERJADI KARENA RESPON SEL T YANG SUDAH DISENSITISASI Ag TERTENTU (2 MINGGU) MELALUI APC**
- **RX TERGANTUNG PADA SITOKIN (LIMFOKIN)**

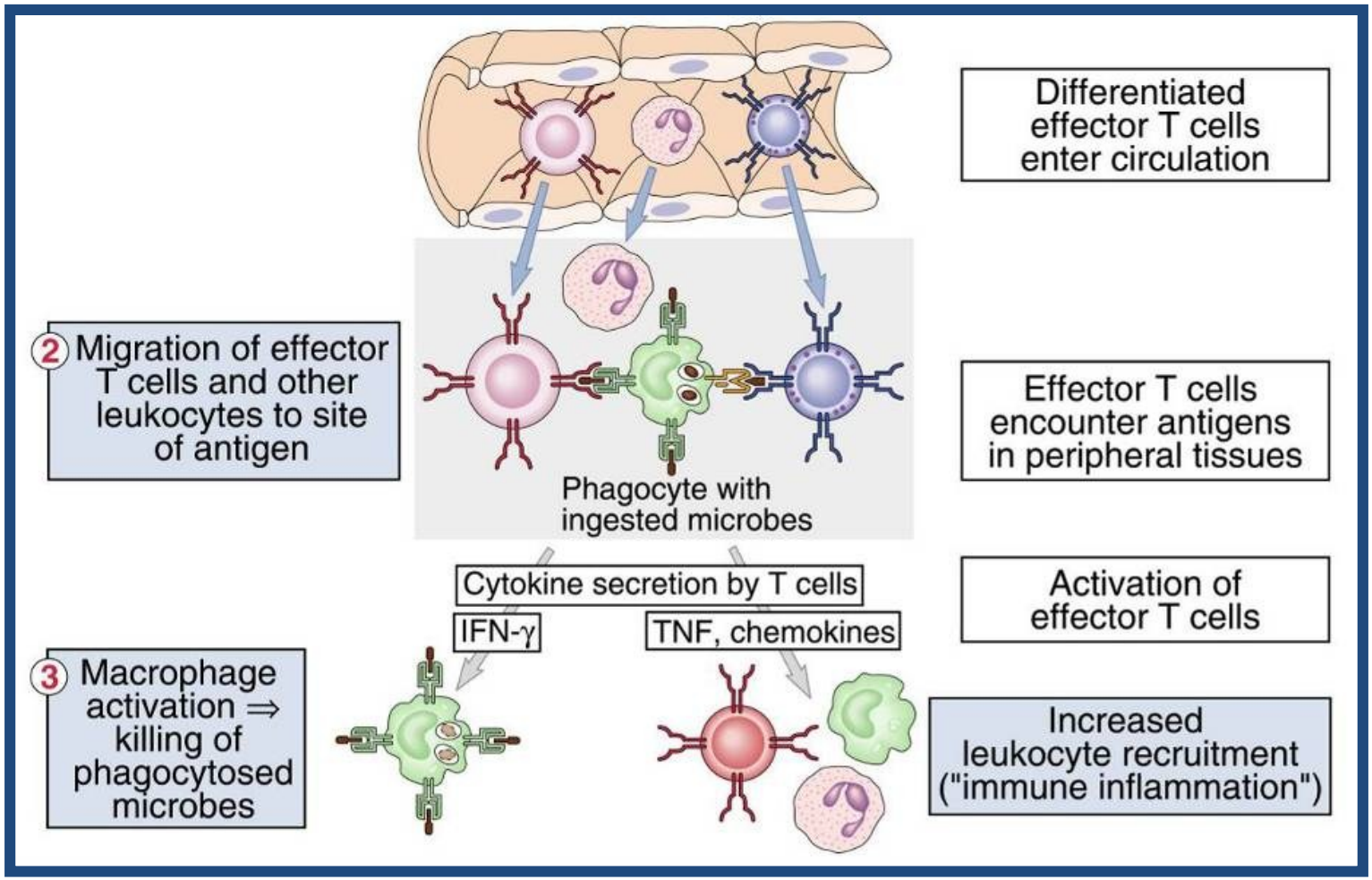
REAKSI	WAKTU MAKSIMAL
JONES-MOTE	24 JAM
CONTACT	48-72 JAM
TUBERCULIN	48-72 JAM
GRANULOMATOUS	>14 HARI

Hipersensitivitas tipe VI dimediasi oleh sel T

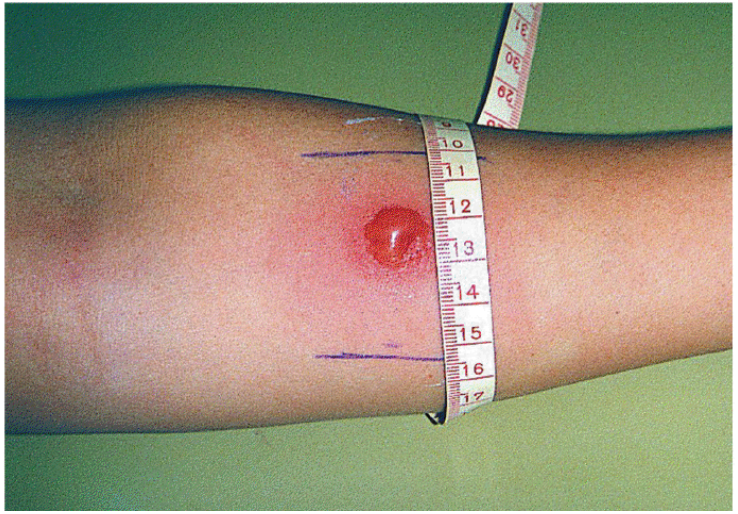
Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells		
Syndrome	**Antigen**	**Consequence**
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitive enteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

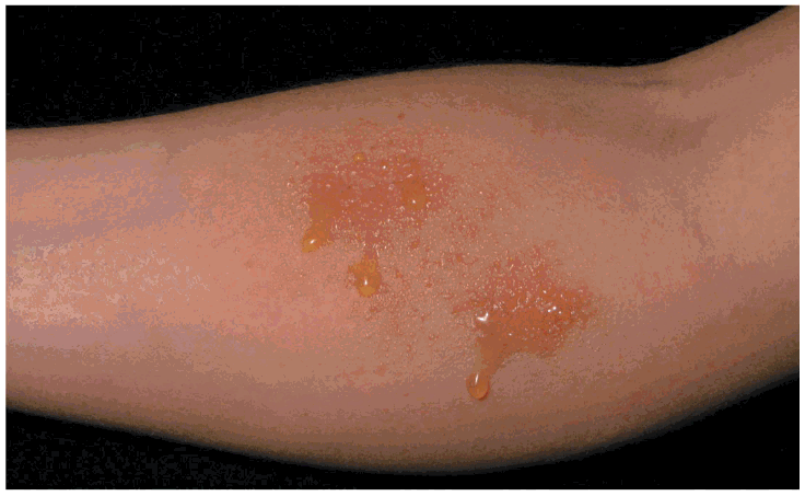
Mekanisme Hipersensitivitas Tipe IV



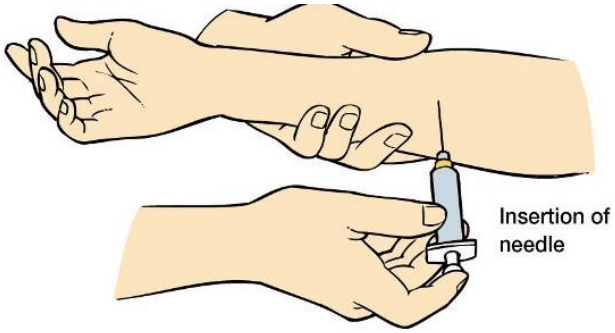

Differentiated effector T cells enter circulation
2 Migration of effector T cells and other leukocytes to site of antigen
Effector T cells encounter antigens in peripheral tissues
Phagocyte with ingested microbes
Cytokine secretion by T cells
IFN-γ
TNF, chemokines
Activation of effector T cells
3 Macrophage activation ⇒ killing of phagocytosed microbes
Increased leukocyte recruitment ("immune inflammation")

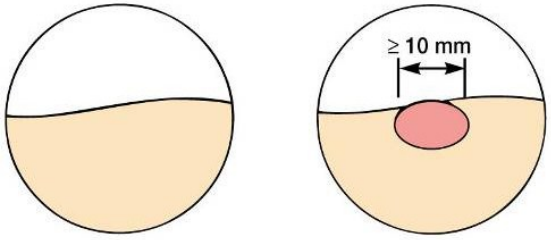
- REAKSI TUBERKULIN
- DERMATITIS KONTAK
- REJEKSI GRAFT
- GRAFT VS HOST





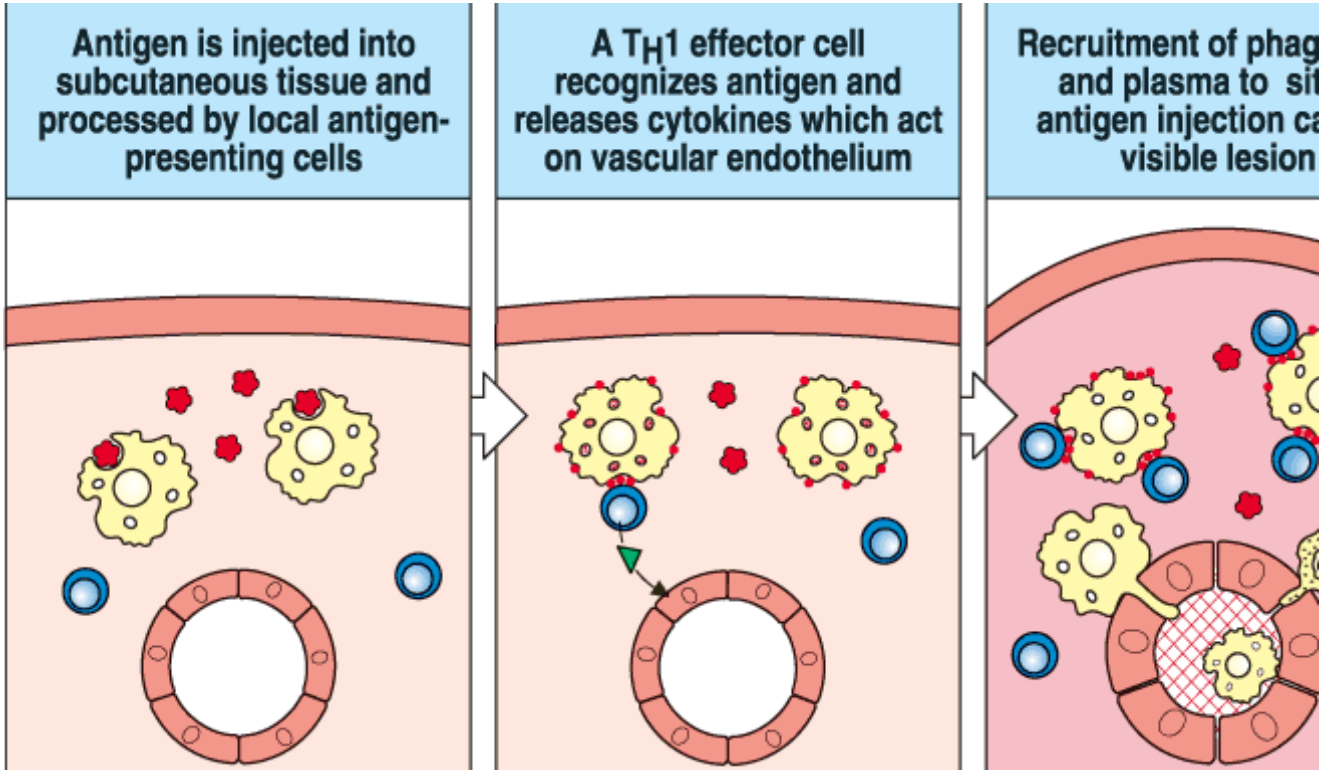
Reaksi Tuberkulin





Negative reaction

Positive reaction (size of induration)



Dermatitis Kontak

Agen yang merupakan kontak biasanya merupakan molekul kecil yang dapat menembus kulit→ berikatan dengan protein “self”→ terlihat seperti non-self