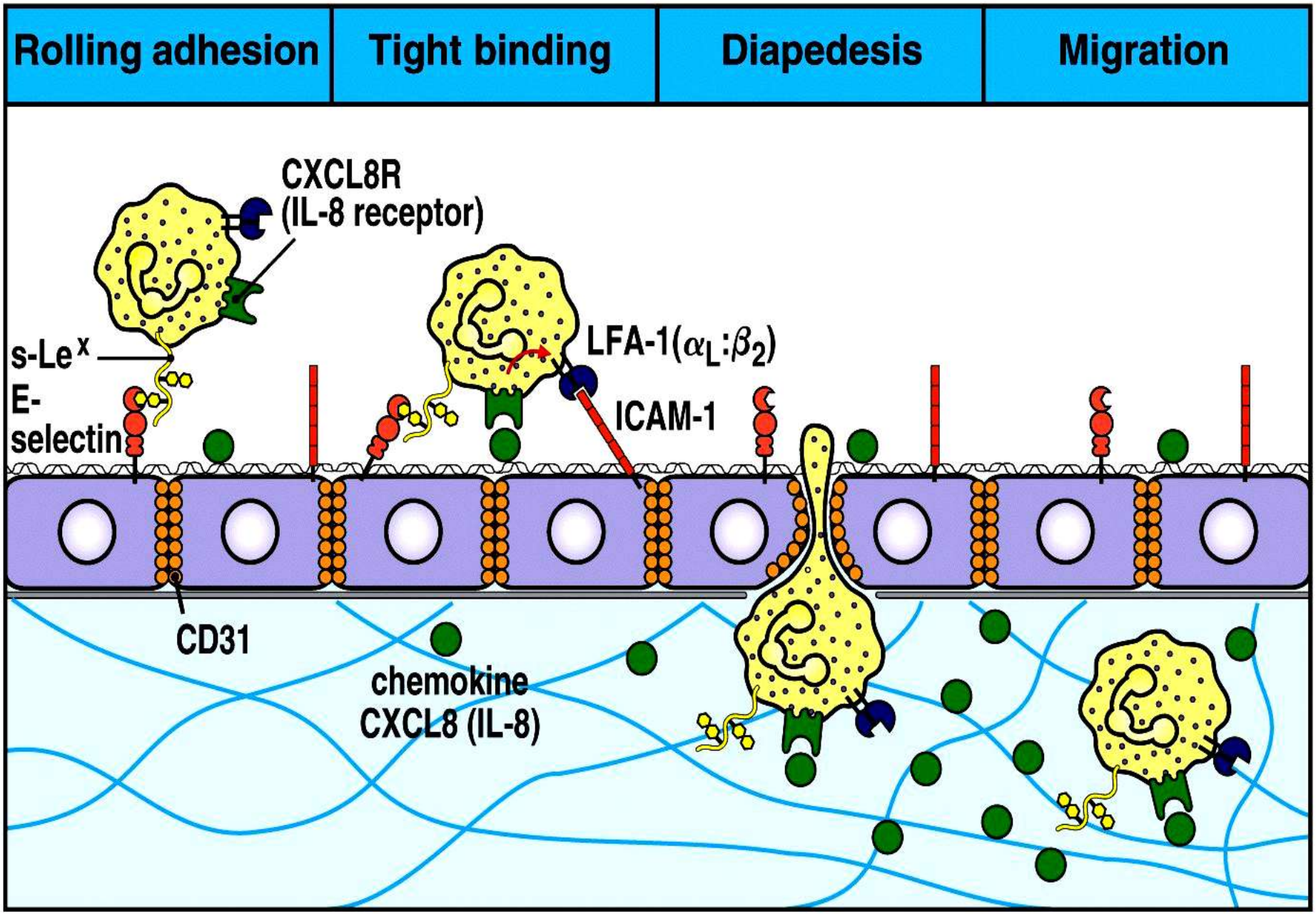
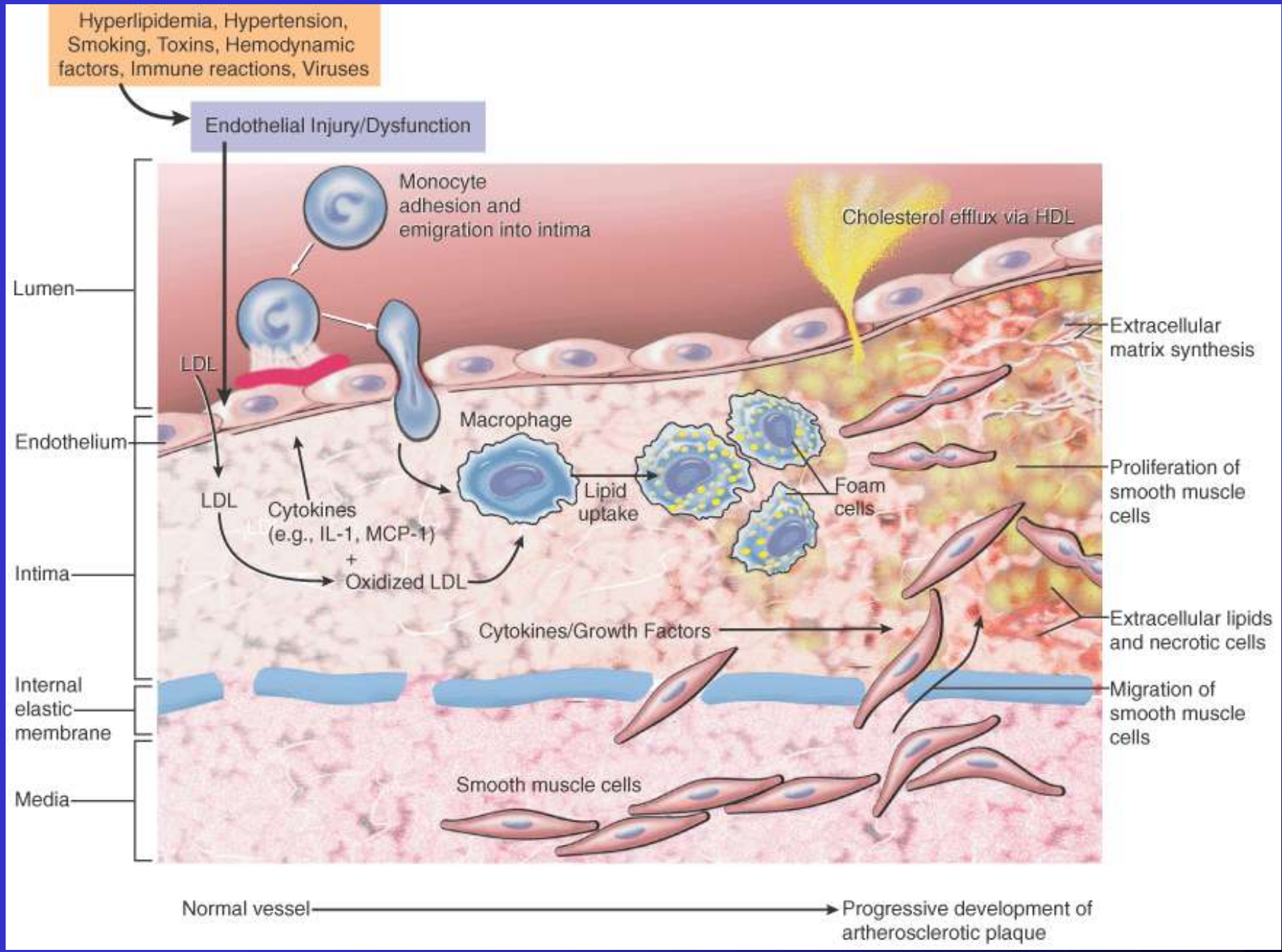
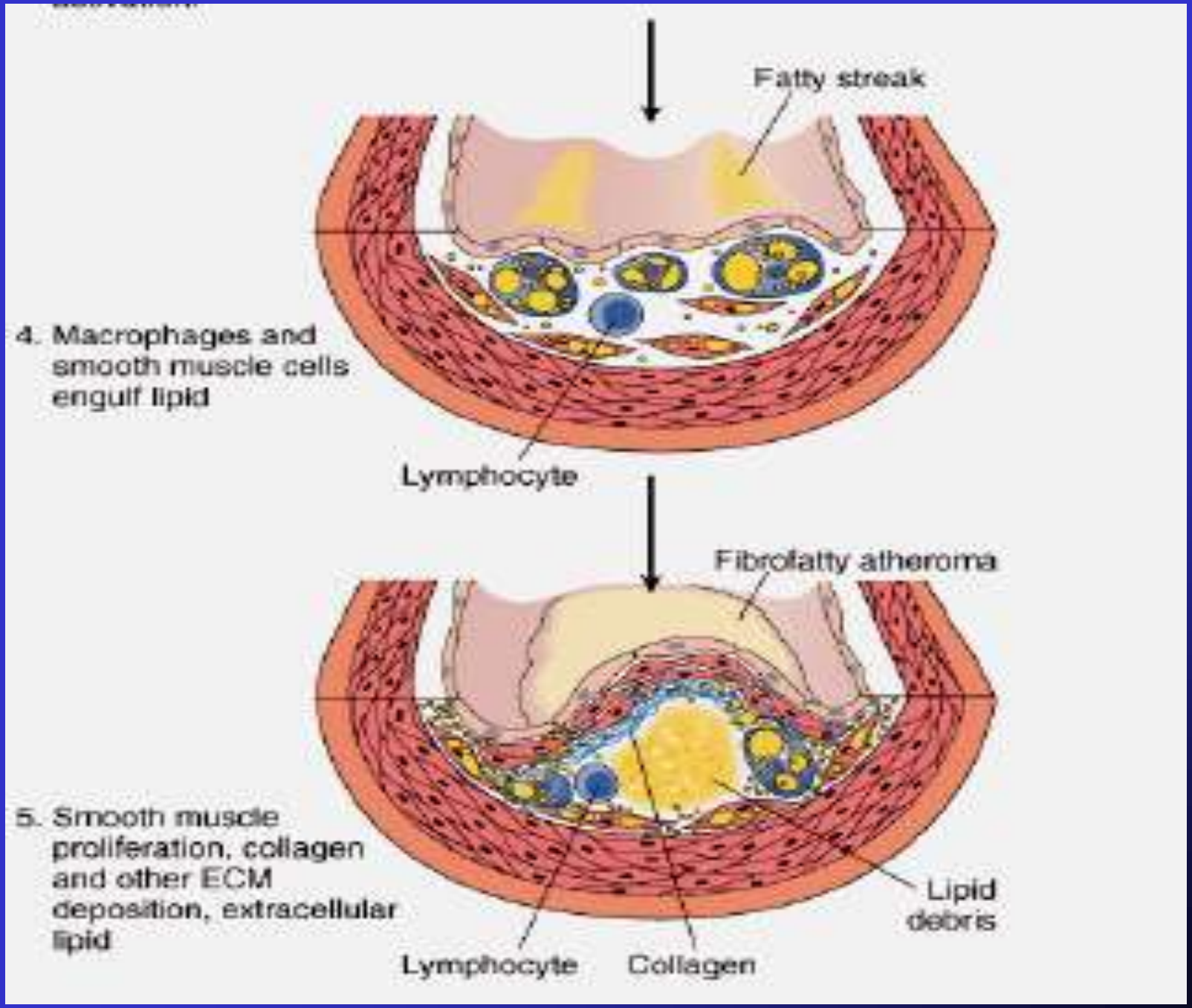
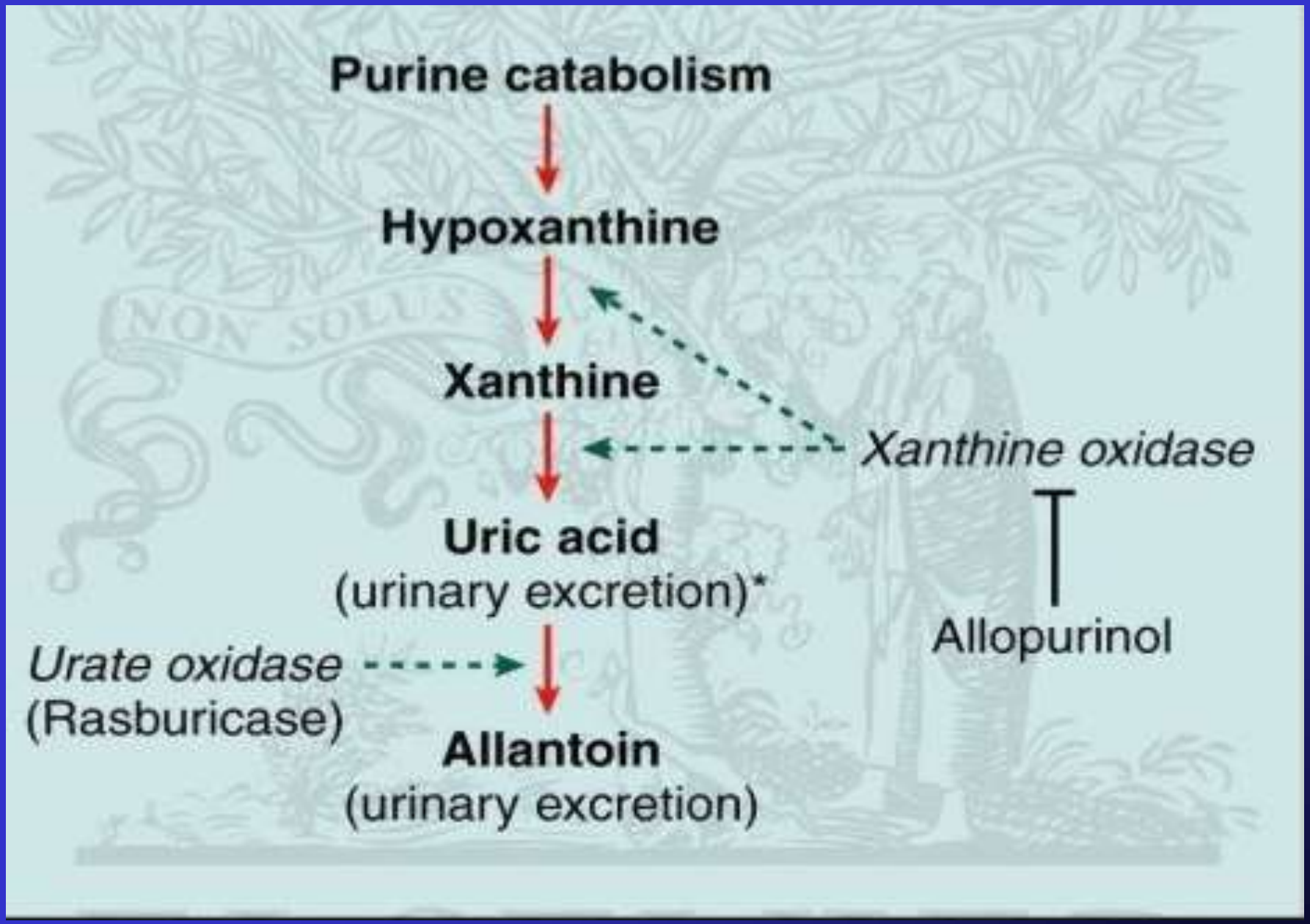


Figure 2-44 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)


Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Cholesterol efflux via HDL
Lumen
LDL
Extracellular matrix synthesis
Endothelium
Macrophage
Lipid uptake
Foam cells
Proliferation of smooth muscle cells
LDL
Cytokines (e.g., IL-1, MCP-1) + Oxidized LDL
Intima
Cytokines/Growth Factors
Extracellular lipids and necrotic cells
Internal elastic membrane
Migration of smooth muscle cells
Media
Smooth muscle cells
Normal vessel
Progressive development of artherosclerotic plaque

Robbin, 2005


Fatty streak
4. Macrophages and smooth muscle cells engulf lipid
Lymphocyte
Fibrofatty atheroma
5. Smooth muscle proliferation, collagen and other ECM deposition, extracellular lipid
Lipid debris
Lymphocyte
Collagen



Blood 2001;97:2998–3003. © The American Society of Hematology.)

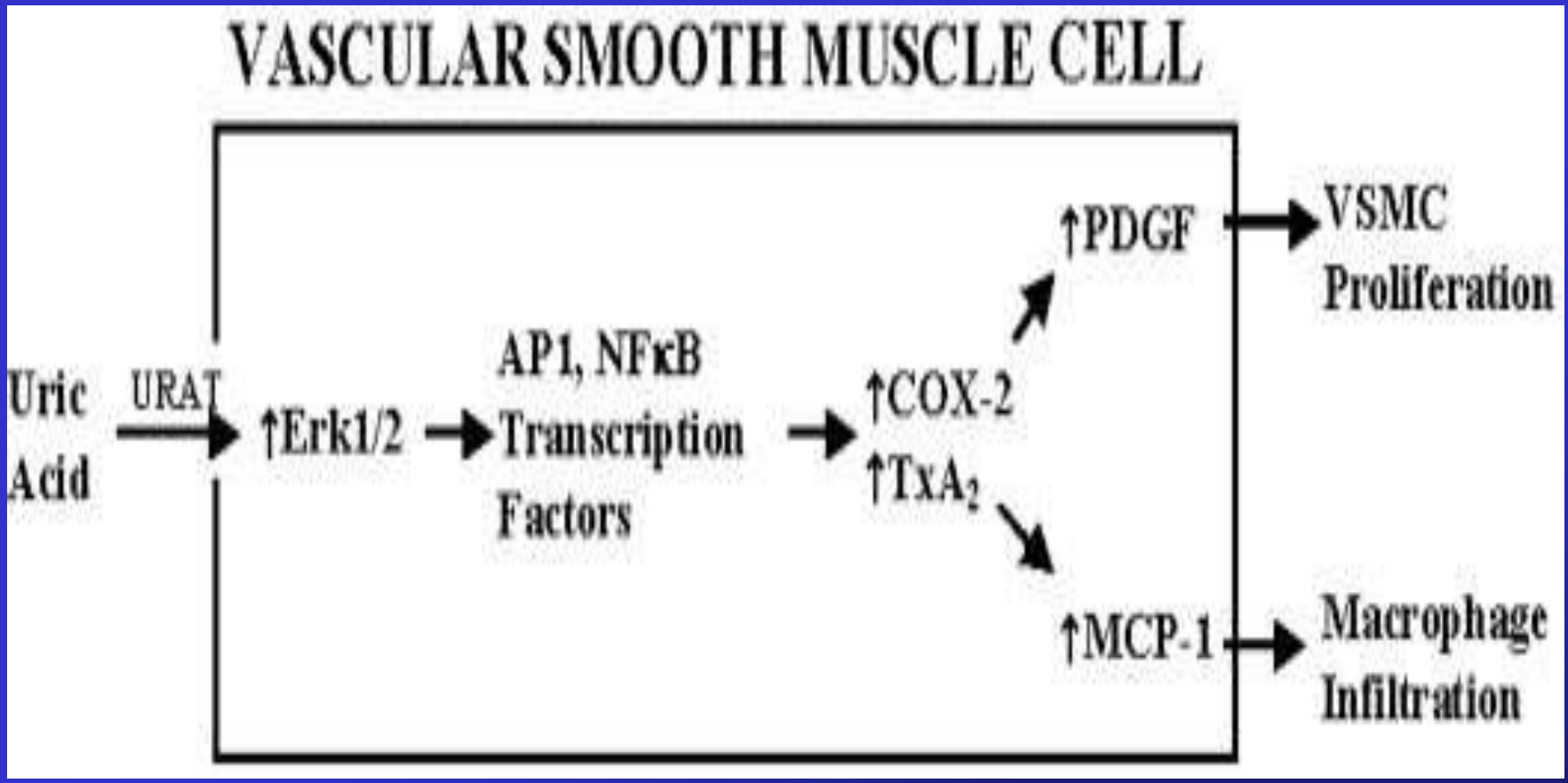
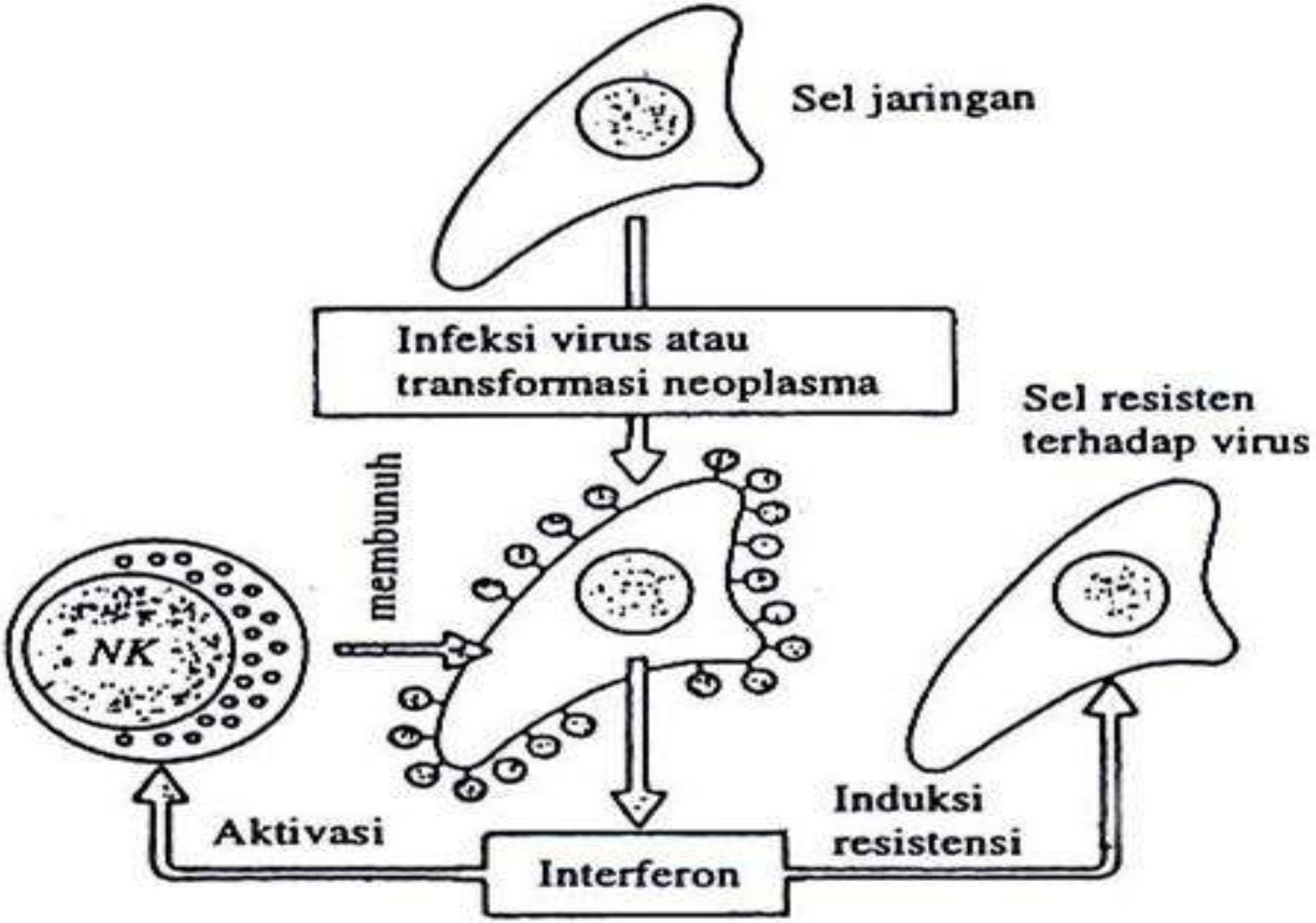
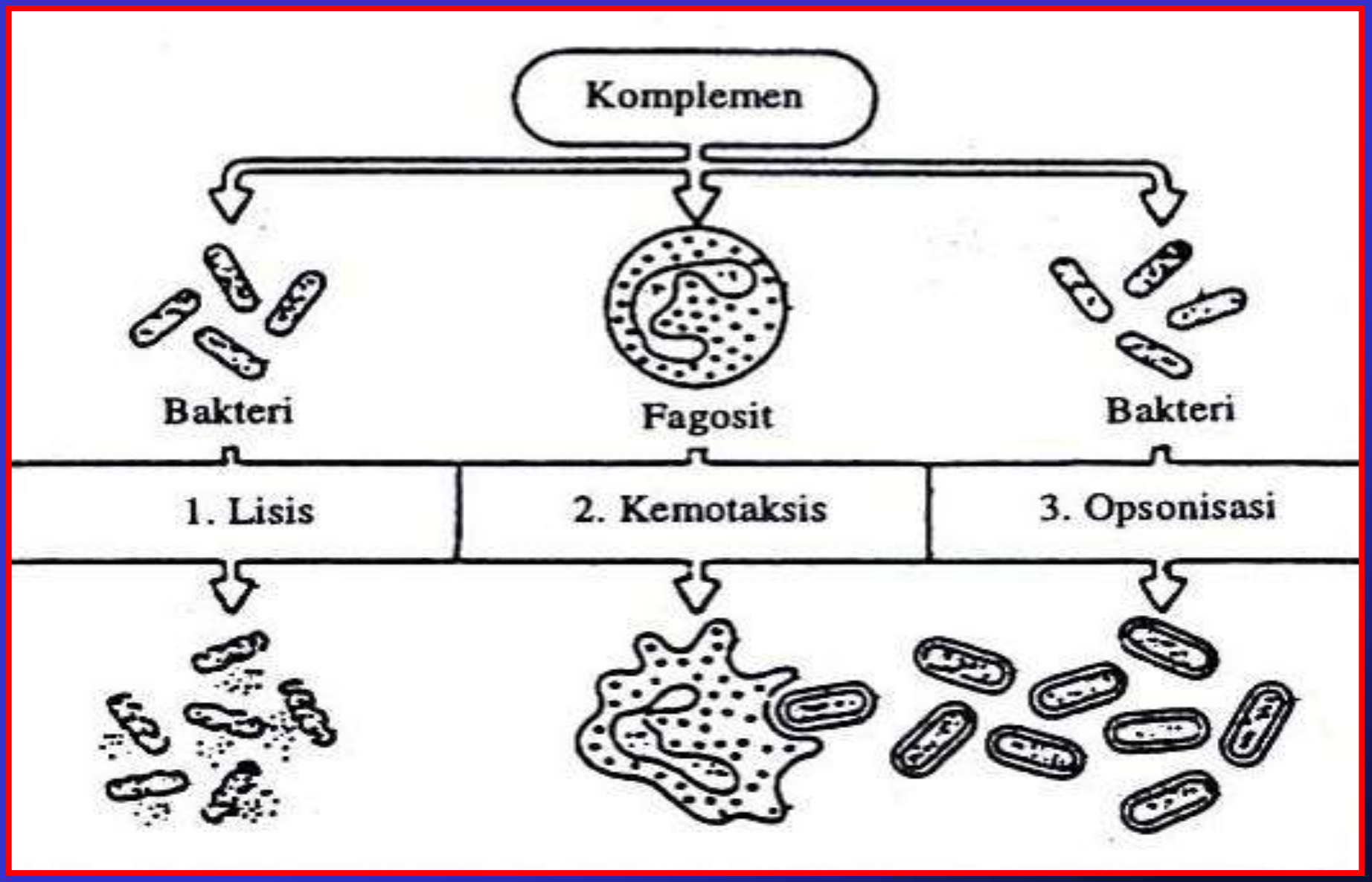


Figure 1. The effect of uric acid on vascular smooth muscle cells (VSMC). Uric acid is taken up through the probenecid-sensitive urate-transport channel URAT1. This leads mitogen-activated protein kinase activation and extracellular signal–regulated kinase 1 and 2 (Erk 1/2) phosphorylation. In turn, transcription factors NF-B and AP1 are activated leading to increased cyclooxygenase- 2 (COX-2) expression and activity. The COX-2 product Thromboxane A2 mediates increased expression and elaboration of platelet derived growth factor (PDGF) and monocyte chemoattractant protein-1 (MCP-1), which induce VSMC proliferation and macrophage infiltration, respectively (13,18 –20).

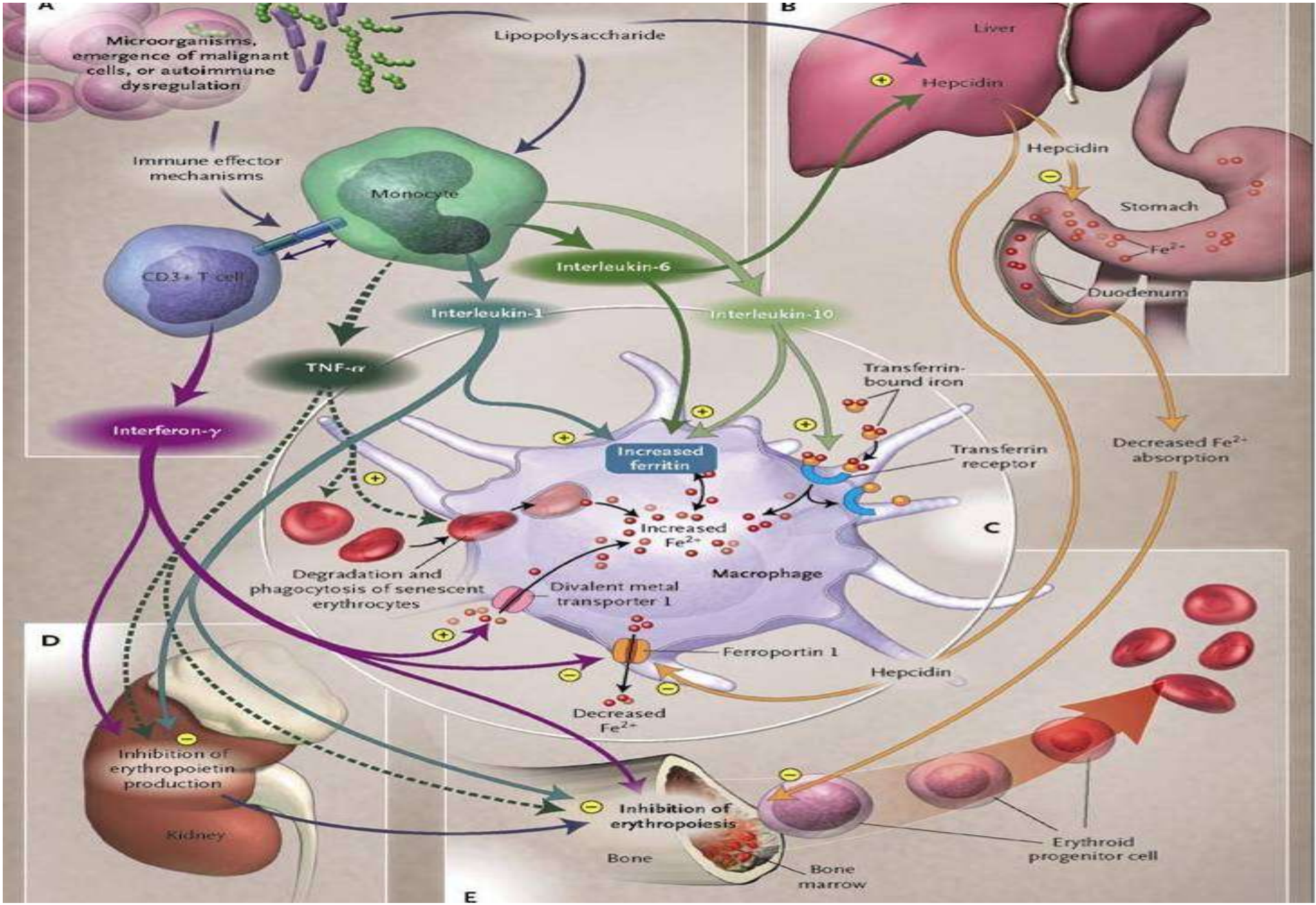
J Am Soc Nephrol 17 : S69-S73, 2006



Interferon dan sel *NK*



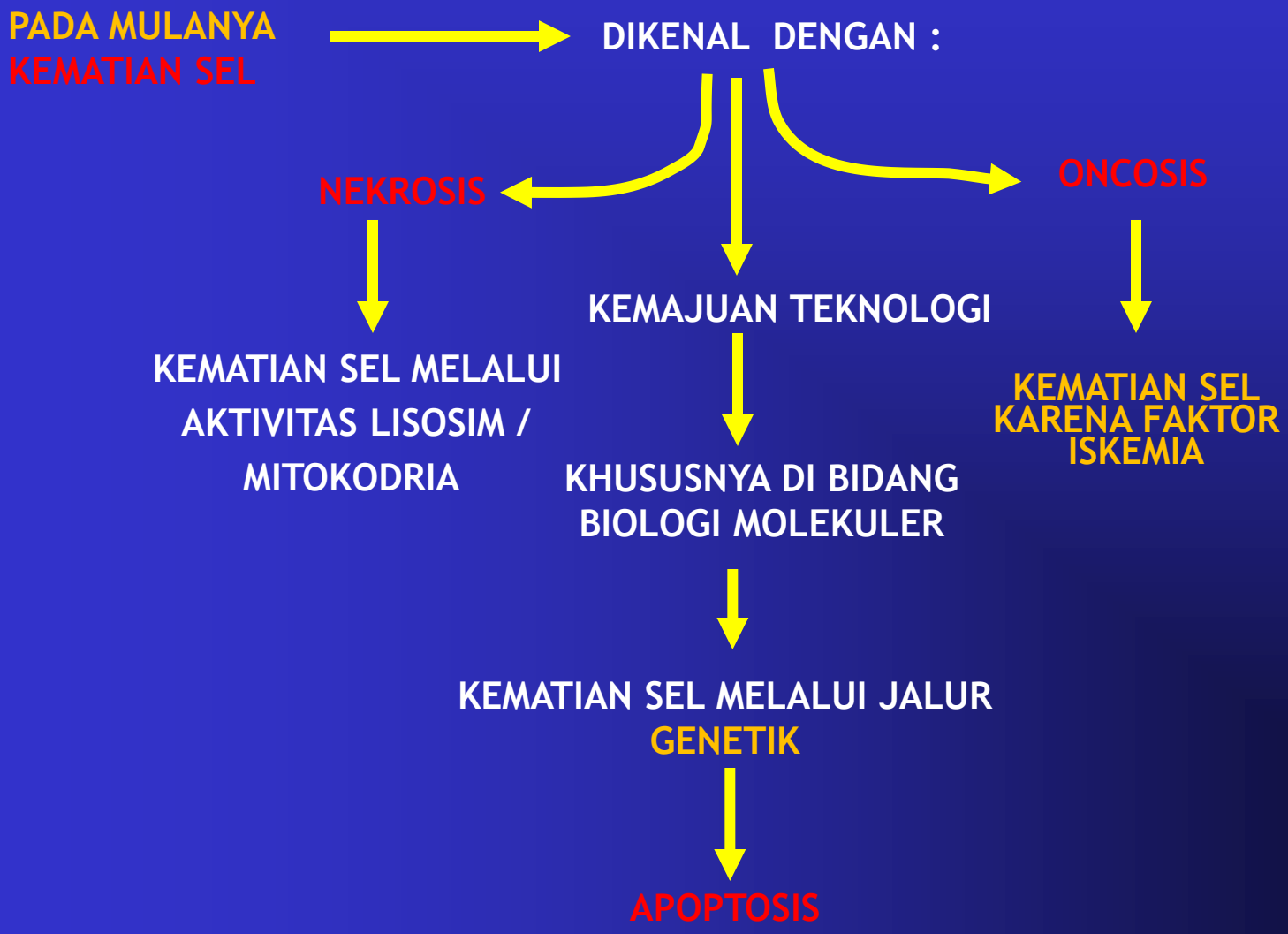
Fungsi Komplemen



ANEMIA PADA PENYAKIT KRONIS

N Engl J Med 2005;352:1011-23.

PROSES KEMATIAN SEL EUKARYOTA



MEDICAL-RESEARCH QUESTIONS

- What genes underlie susceptibility to disease ?
- What is the triggers ?
- What are the effector system lead to disease ? (Organ and cell competence)
- What are the target molecule ?
- How about the sequences of the disease process ?

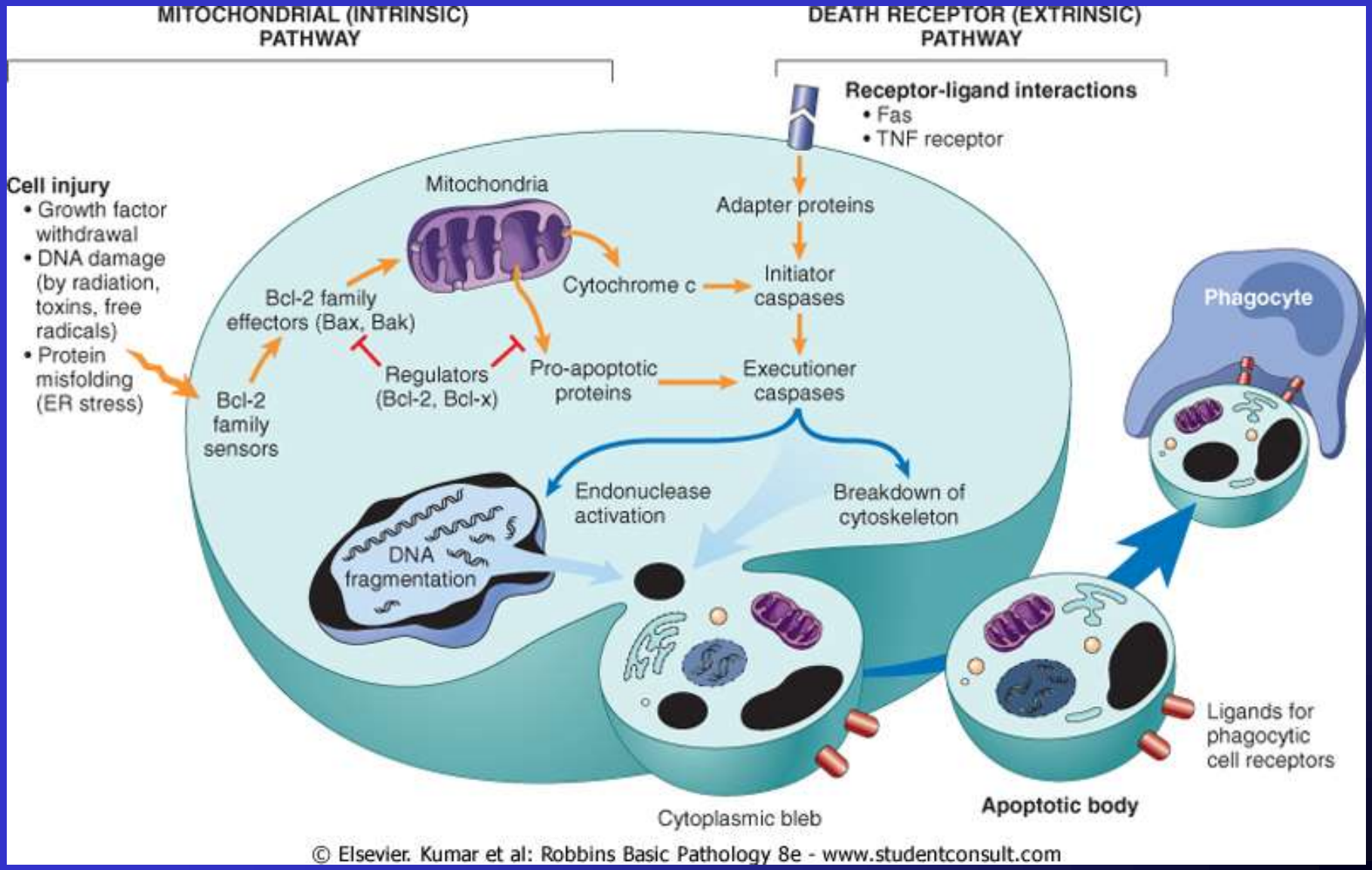
SINDROM METABOLIK

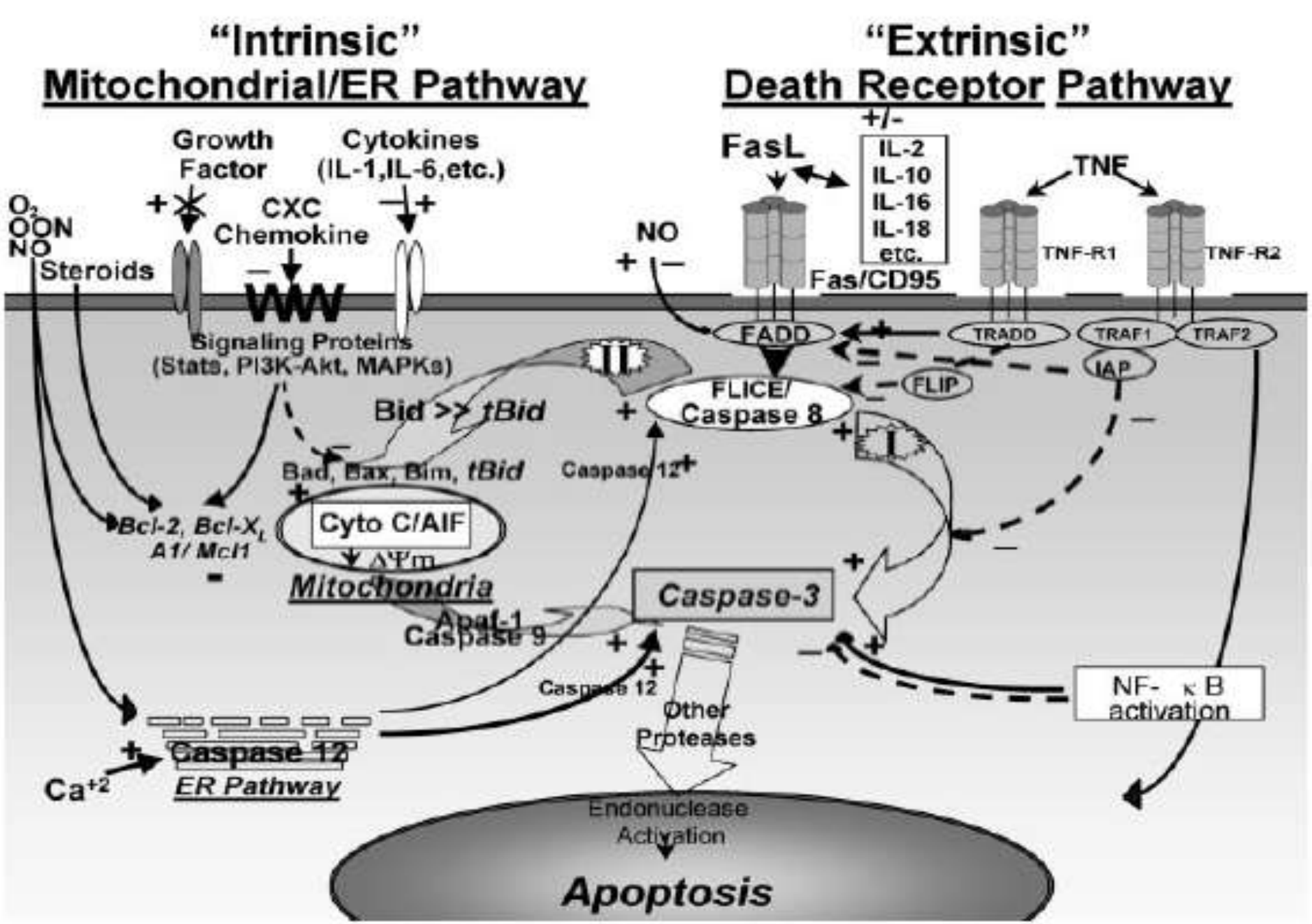
- Tensi ≤ 130/85 mmHg
- Gula darah puasa < 110 mg%
- Lingkar perut
  - laki laki < 102 cm
  - wanita < 88 cm
- Trigliseril < 150 mg %
- HDL → laki > 40 mg %
  → wanita > 50 mg %
- LDL → < 100 mg %

- Olah raga
- Obat ↓ kolesterol

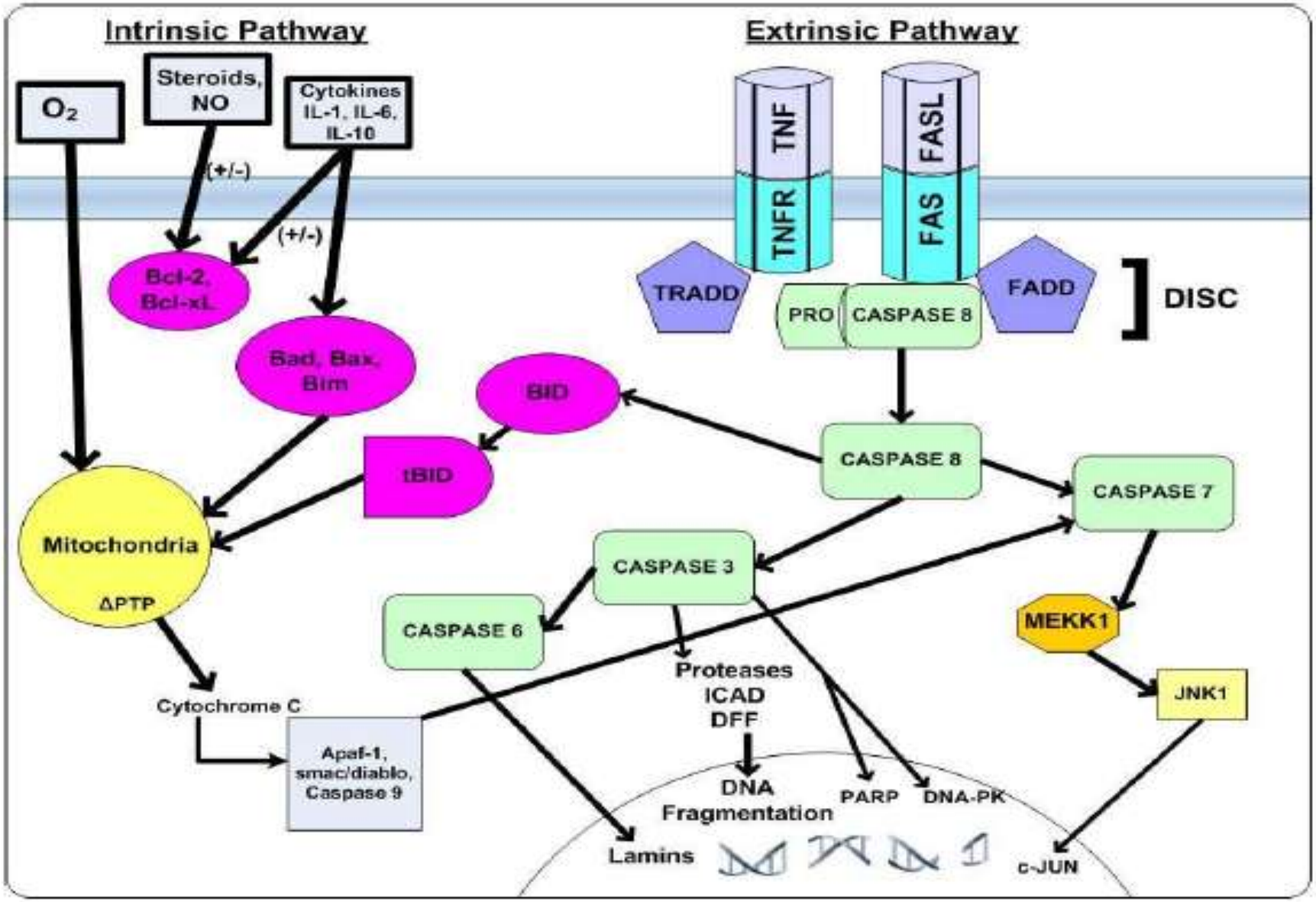

photo by Yuri Tand | www.tandi.nl

Apoptosis


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adapter proteins
Cytochrome c
Initiator caspases
Bcl-2 family effectors (Bax, Bak)
Regulators (Bcl-2, Bcl-x)
Pro-apoptotic proteins
Executioner caspases
Bcl-2 family sensors
Endonuclease activation
Breakdown of cytoskeleton
DNA fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Cytoplasmic bleb
Apoptotic body
© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com


"Intrinsic"
Mitochondrial/ER Pathway
"Extrinsic"
Death Receptor Pathway
Growth Factor
Cytokines (IL-1,IL-6,etc.)
CXC Chemokine
O_2
OON
NO
Steroids
Signaling Proteins (Stats, PI3K-Akt, MAPKs)
+/-
FasL
IL-2
IL-10
IL-16
IL-18
etc.
Fas/CD95
TNF
TNF-R1
TNF-R2
NO
FADD
TRADD
TRAF1
TRAF2
IAP
FLIP
FLICE/ Caspase 8
Bid >> tBid
Bad, Bax, Bim, tBid
Caspase 12
Bcl-2, Bcl-X_L, A1/ Mcl1
Cyto C/AIF
$\Delta\Psi m$
Mitochondria
Apaf-1
Caspase 9
Caspase-3
Caspase 12
Other Proteases
NF- κB activation
Ca^{+2}
Caspase 12
ER Pathway
Endonuclease Activation
Apoptosis

Apoptosis


Intrinsic Pathway
Extrinsic Pathway
O2
Steroids, NO
Cytokines IL-1, IL-6, IL-10
(+/-)
(+/-)
Bcl-2, Bcl-xL
Bad, Bax, Bim
BID
tBID
Mitochondria
ΔPTP
Cytochrome C
Apaf-1, smac/diablo, Caspase 9
TNF
TNFR
FASL
FAS
TRADD
PRO
CASPASE 8
FADD
DISC
CASPASE 8
CASPASE 7
CASPASE 3
CASPASE 6
MEKK1
JNK1
Proteases ICAD DFF
DNA Fragmentation
PARP
DNA-PK
Lamins
c-JUN

Research Activities &Philosophical Approach

(Judajana, 2008a)

Berdasarkan prinsip ***ONTOLOGY*** :

- Kerusakan ginjal → dimulai pemberian DXR → berikatan dengan reseptor membran sel tubulus proksimal → merangsang enzim NADPH (mitokondria) → membentuk ROS proses ini sesuai → ***initial stage (Incubation Period/ Sub Clinical*)**.

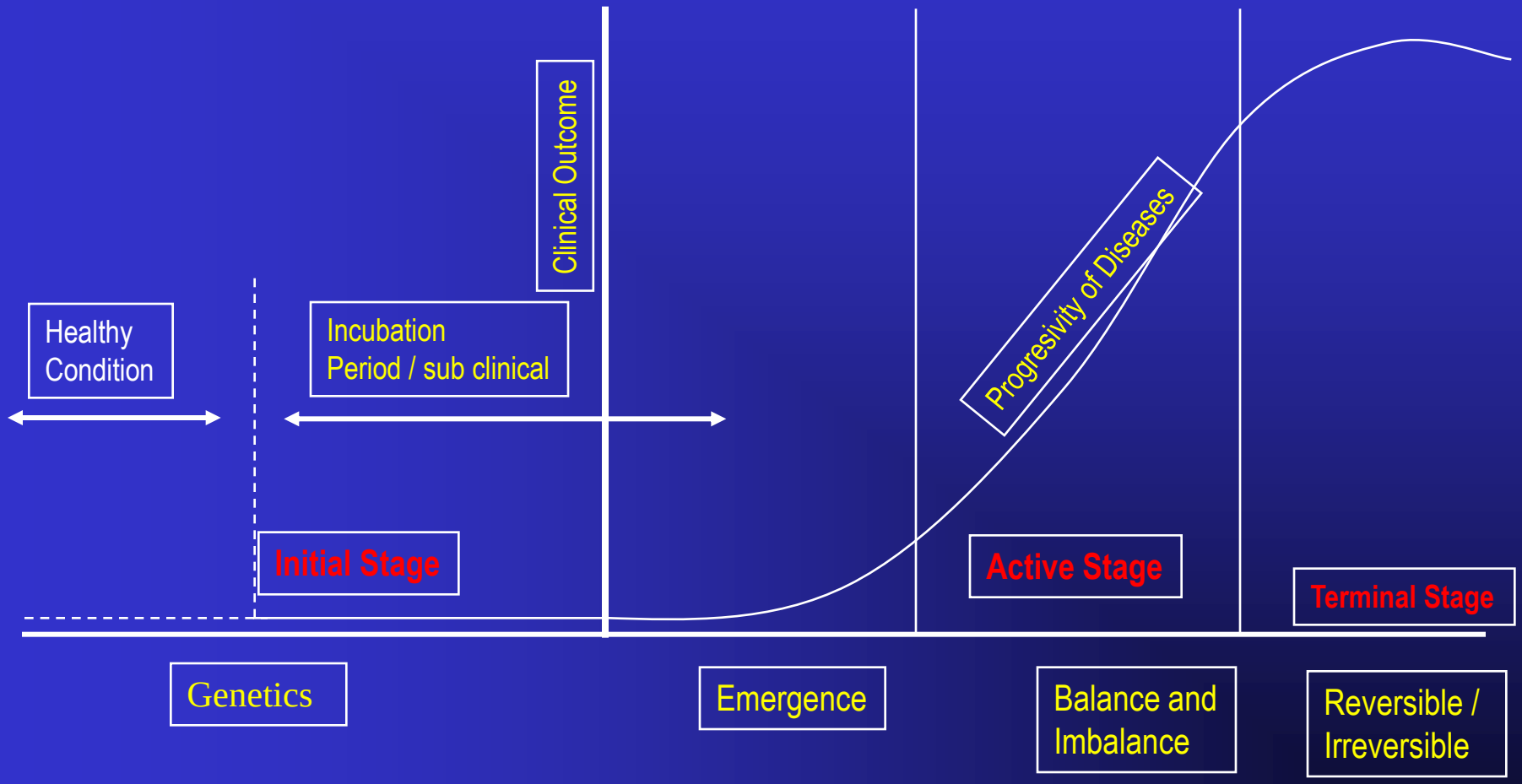
- ROS merusak sel tubulus, endotel dll, → terbentuk debris. Debris merangsang makrofag → makrofag mengekspresikan TNF-α, TGF-β1, IL-1, IL-6 dan IL-8. Proses ini sesuai → kondisi ***Emergence*.**

- TGF-β1 merangsang sel mesangial glomerolus → mengekspresikan kolagen IV, dan merangsang fibroblast → mengekspresikan kolagen I. TNF-α merangsang endotel → e -selektin, e-selektin menarik PMN, → PMN mengekspresikan MMP-9, MMP-9 berfungsi → mendegradasi kolagen I dan IV. Ekspresi TGF-β1 dan MMP-9 sampai terbentuknya dan degradasi kolagen I dan IV, terjadi ***Imbalance*****.** Dimana pengaruh TGF-β1 lebih dominan, proses sesuai → ***Active Stage .***

- PTX akan → ↓Ekspresi TGF-β1 dan meningkatkan Ekspresi MMP-9 → tujuan memperbaiki ***Imbalance***.

- Ekspresi kolagen IV → glomerulosklerosis, ekspresi kolagen I → interstisial fibrosis. Terjadi kondisi ***Irreversible*** proses ini sesuai → ***Terminal Stage***

The Sequences of The Disease Process



(Judajana, 2008b)

Berdasarkan Prinsip ***EPISTEMOLOGY*** :

- Hasil penelitian kami mengenai pengaruh DXR sebagai obat nefrotoksik dengan variabel TGF-β1, MMP-9, Kolagen I, kolagen IV, Glumerulosklerosis, Interstisial Fibrosis, dan Albuminuri, sesuai → penelitian Tamaki *et al*., 1994, tetapi penelitian kami ditambah → PTX sebagai obat nefroprotektif, dengan → menurunkan ekspresi variabel tersebut diatas, dan penurunan ekspresi variabel tersebut signifikan.

Berdasarkan Prinsip ***AXIOLOGY*** :

- Manfaat penelitian kami → PTX mencegah progresivitas glomerulosklerosis, interstisial fibrosis dan albuminuri, akibat pemberian DXR. Pencegahan progresivitas glomerulosklerosis, interstisial fibrosis dan albuminuri tersebut → mengurangi komulatif sisa metabolisme protein → mencegah terjadi sindroma uremia.

NILAI KEBARUAN

Invention : penemuan baru yang sebelumnya belum pernah ada

Discovery : penemuan yang pernah diciptakan sebelumnya, ex.: Colombus

(Judajana, 2005)

FASE UJI	KETERANGAN
Studi Preklinik	Invitro utk menguji efikasi, toksisitas dan farmakokinetik
Fase 0	Uji pertama pada manusia (10-15 org) Farmakodinamik dan kinetik
Fase I	20-100 org Uji keamanan, dosis, efikasi obat
Fase II	Konfirmasi dari fase I dg subyek lebih besar (20-300 org) Uji keamanan, dosis, efikasi obat
Fase III	RCT, multicenter, 300-3000 org Perbandingan dengan gold standar tx
Fase IV	Post Marketing Surveillance Trial Efek jangka panjang

Adapted from Clinicaltrials.gov, 2009

Matur Nuwun