Immunology Of The Cardiovascular System

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Cardiovascular System

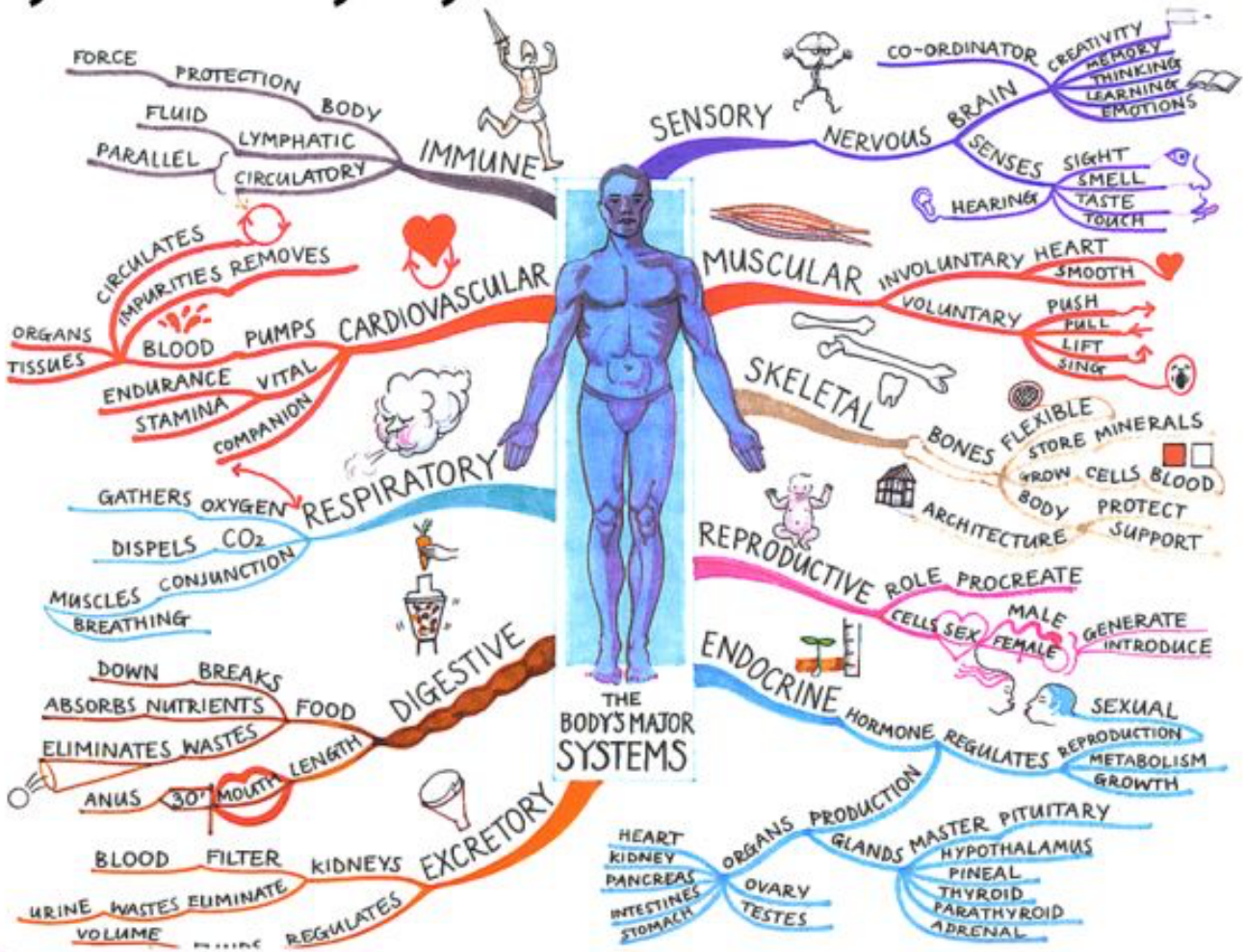
Immunology

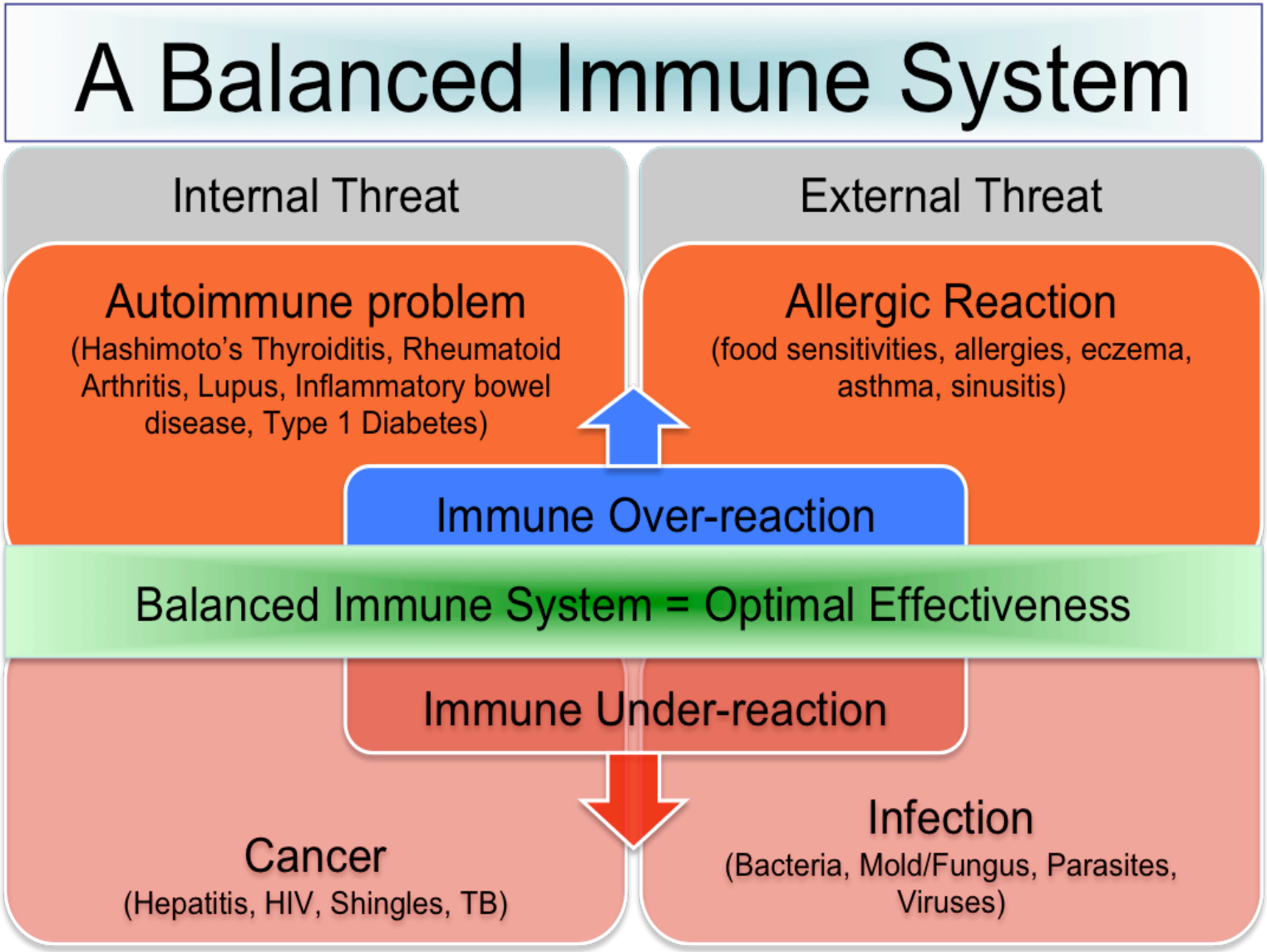
General

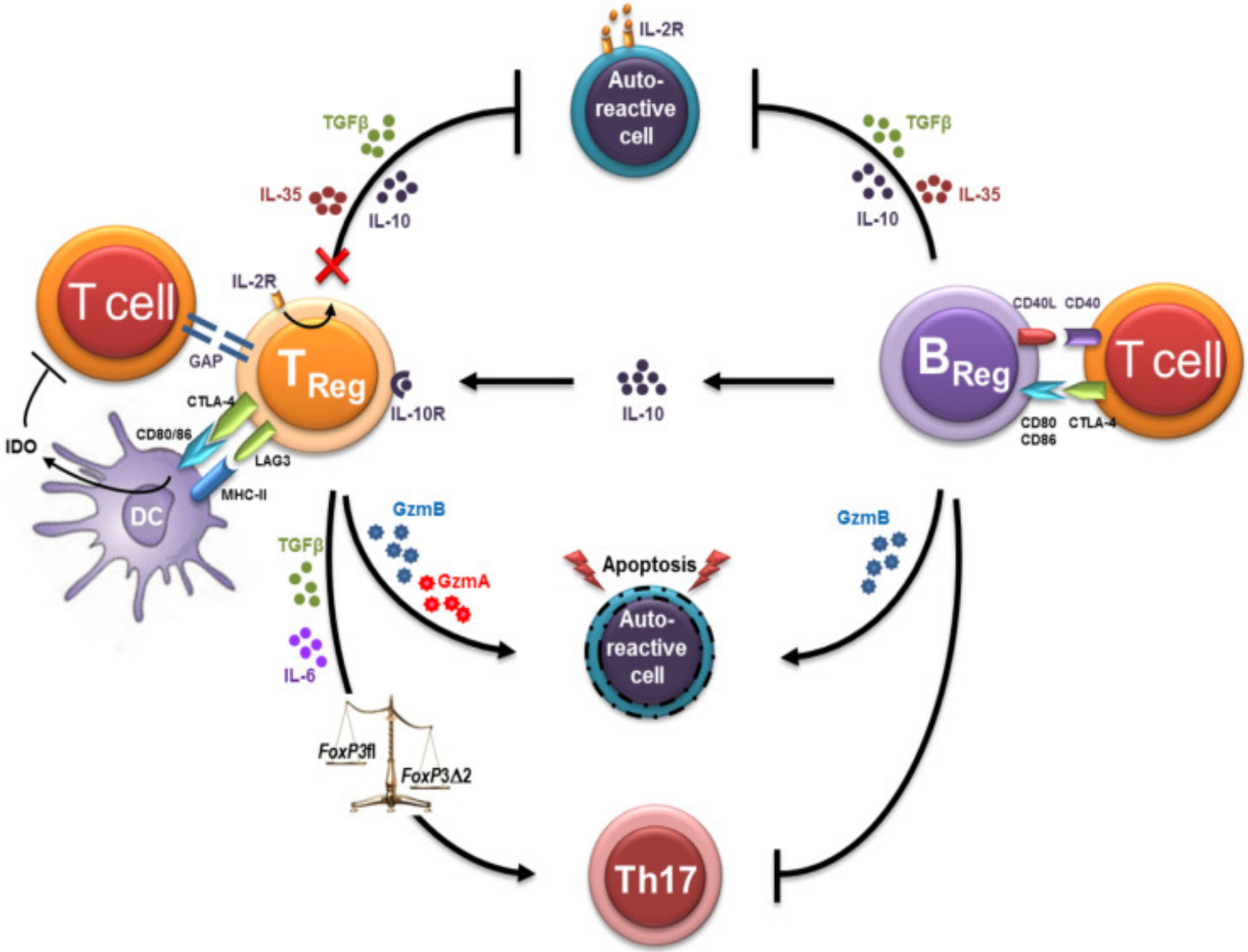
Immunology of the Heart

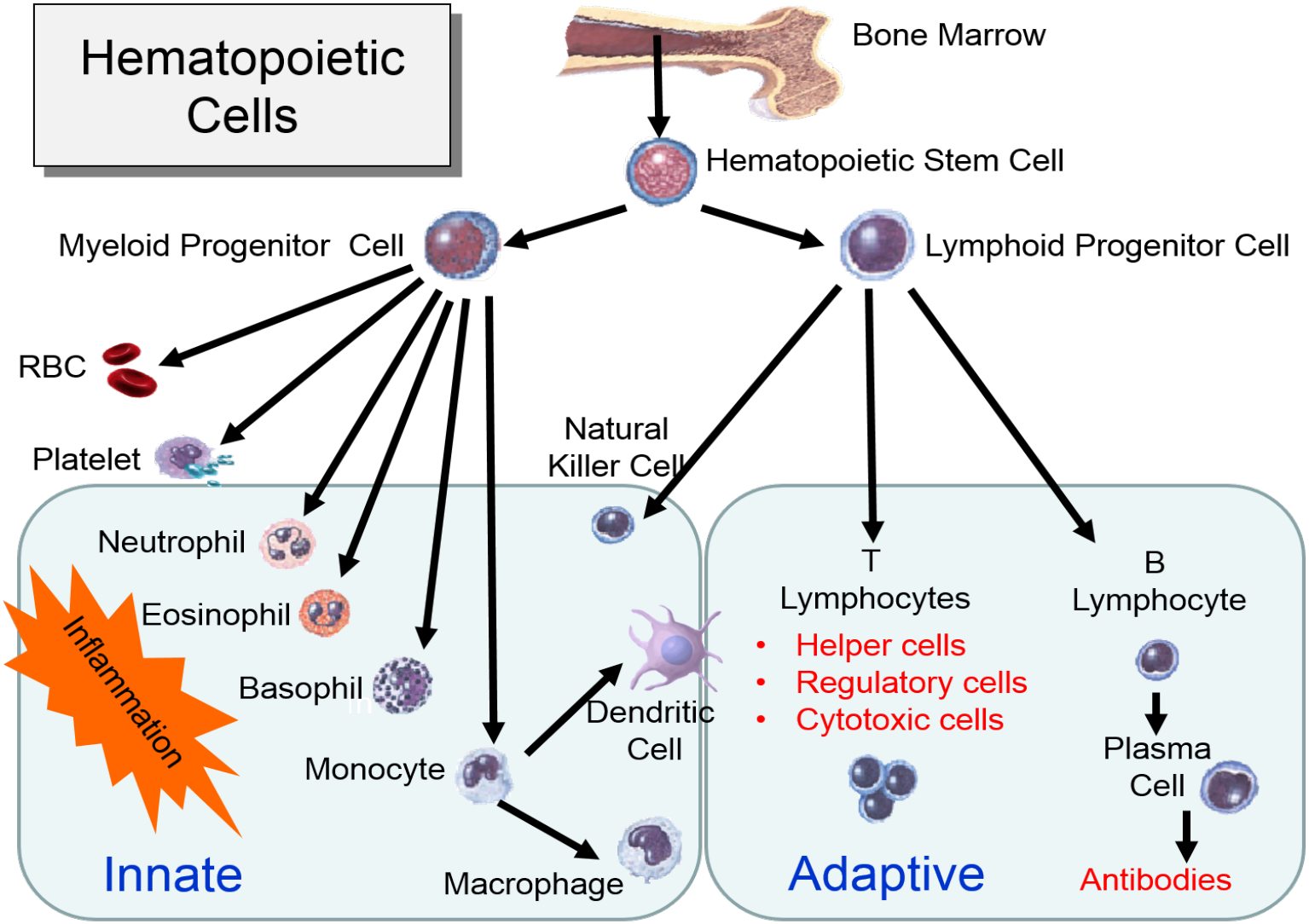
Immunology of the blood vessels

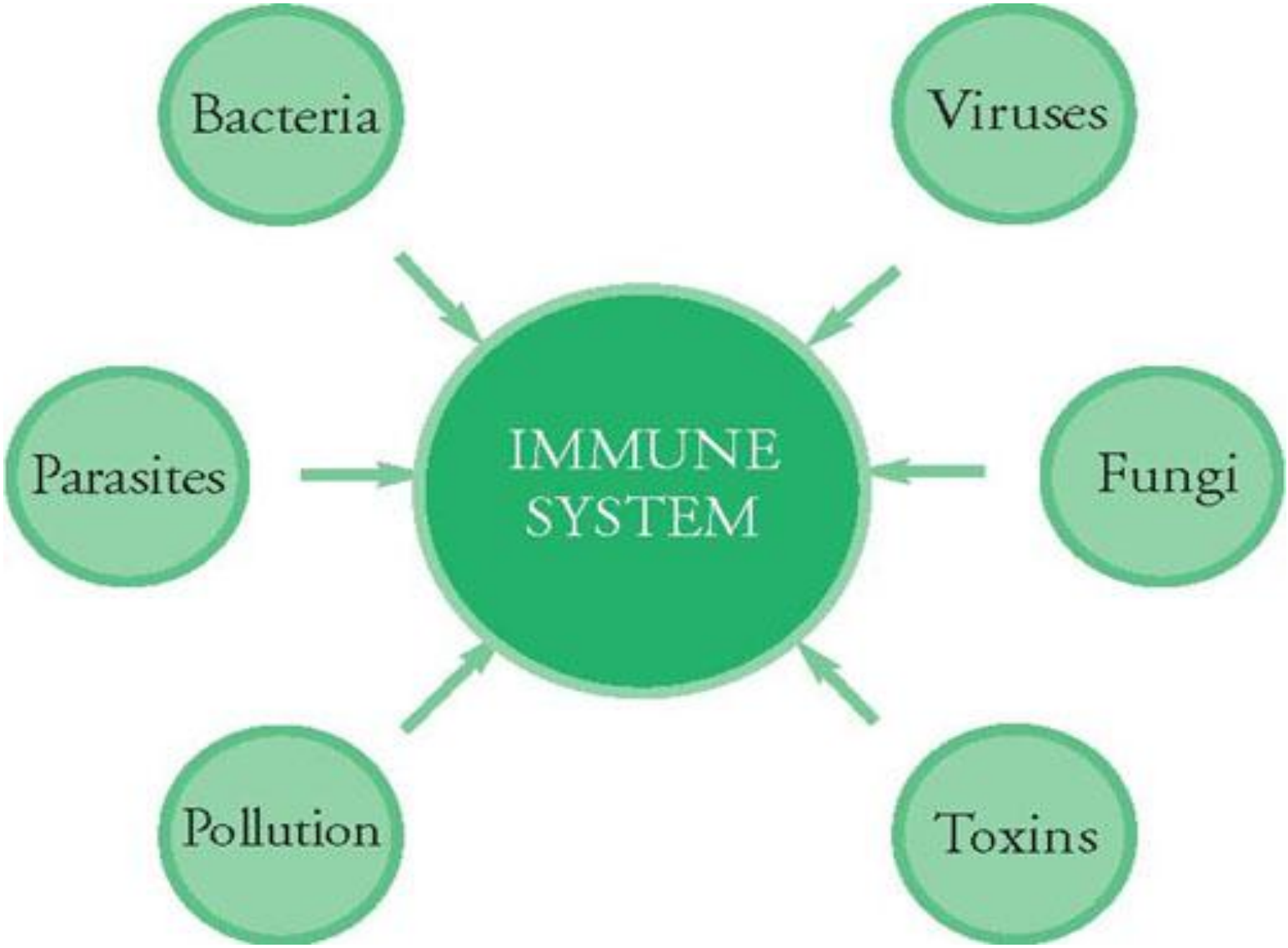
Study of Body Systems




A Balanced Immune System
Internal Threat
External Threat
Autoimmune problem
(Hashimoto's Thyroiditis, Rheumatoid Arthritis, Lupus, Inflammatory bowel disease, Type 1 Diabetes)
Allergic Reaction
(food sensitivities, allergies, eczema, asthma, sinusitis)
Immune Over-reaction
Balanced Immune System = Optimal Effectiveness
Immune Under-reaction
Cancer
(Hepatitis, HIV, Shingles, TB)
Infection
(Bacteria, Mold/Fungus, Parasites, Viruses)


IL-2R
Auto-reactive cell
TGFβ
IL-35
IL-10
TGFβ
IL-10
IL-35
T cell
IL-2R
GAP
T Reg
CTLA-4
CD80/86
LAG3
MHC-II
DC
IDO
IL-10R
IL-10
B Reg
CD40L
CD40
T cell
CD80
CD86
CTLA-4
GzmB
TGFβ
GzmA
IL-6
Apoptosis
Auto-reactive cell
GzmB
FoxP3fl
FoxP3Δ2
Th17

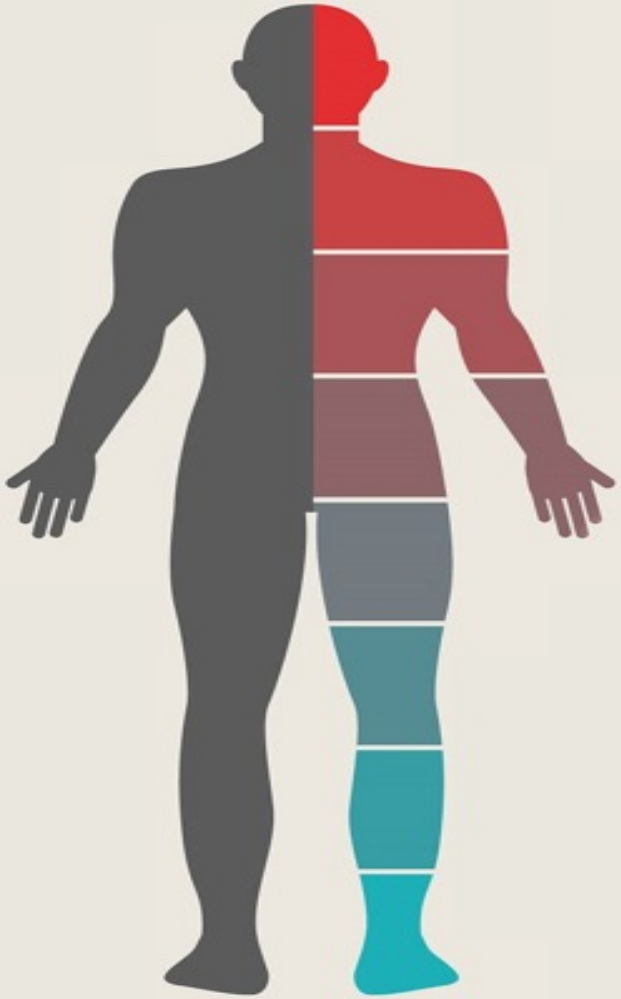

Hematopoietic Cells
Bone Marrow
Hematopoietic Stem Cell
Myeloid Progenitor Cell
Lymphoid Progenitor Cell
RBC
Platelet
Natural Killer Cell
Neutrophil
Eosinophil
Basophil
Monocyte
Dendritic Cell
Macrophage
Inflammation
Innate
T Lymphocytes
Helper cells
Regulatory cells
Cytotoxic cells
B Lymphocyte
Plasma Cell
Antibodies
Adaptive


Bacteria
Viruses
Parasites
IMMUNE SYSTEM
Fungi
Pollution
Toxins


VIRUS
TOXINS
CARCINOGEN
FUNGUS
POLLUTION
BACTERIA
GERMS
PARASITES


Overtime
Sick
Tired
Dread
Health
No Time
Headache
Bills
Payments
Stress
Stress
No Sleep
Debt
Fear
Work
Worry
Job
Anxiety
Retirement
Savings
Anxiety
Expectations
Overdue
Time Management
Fear
Late Nights

The effects of stress on the body



Mood issues including anger, depression, irritability.
Lack of energy, concentration problems, sleeping issues, headaches.
Mental issues including anxiety disorders and panic attacks.

Increased blood pressure, increased heart rate, higher cholesterol and risk of heart attack

In the immune system, there is reduced ability to fight and recover from illness

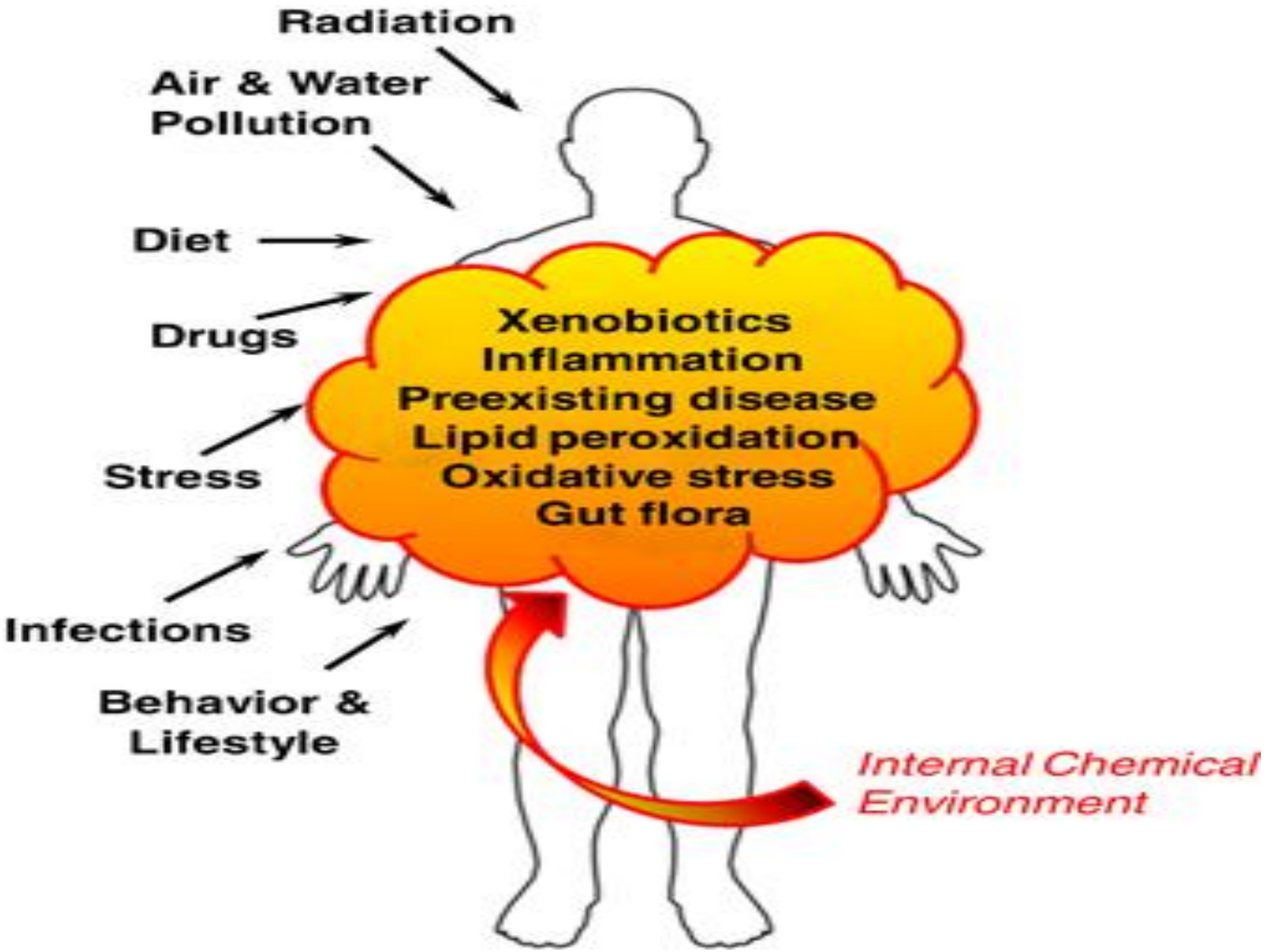
Stomach cramps, reflux, and nausea

Loss of libido, lower sperm production for men, and increased period pain for women

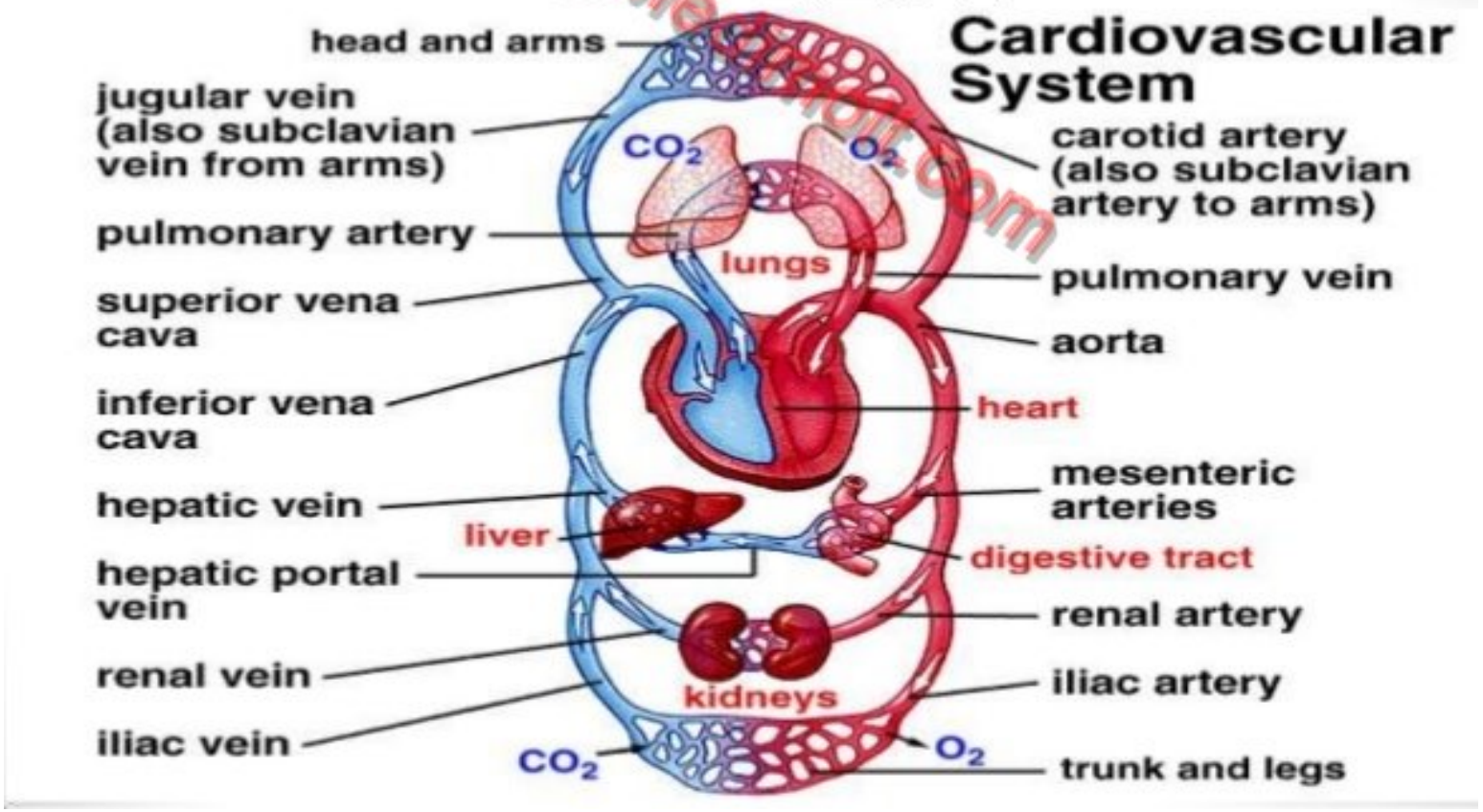
Aches and pains in the joint and muscles

Lower bone density

Holistic Dentistry.ie
Natural & Safe Dentistry. Bray, Co. Wicklow


Radiation
Air & Water Pollution
Diet
Drugs
Stress
Infections
Behavior & Lifestyle
Xenobiotics
Inflammation
Preexisting disease
Lipid peroxidation
Oxidative stress
Gut flora
Internal Chemical Environment

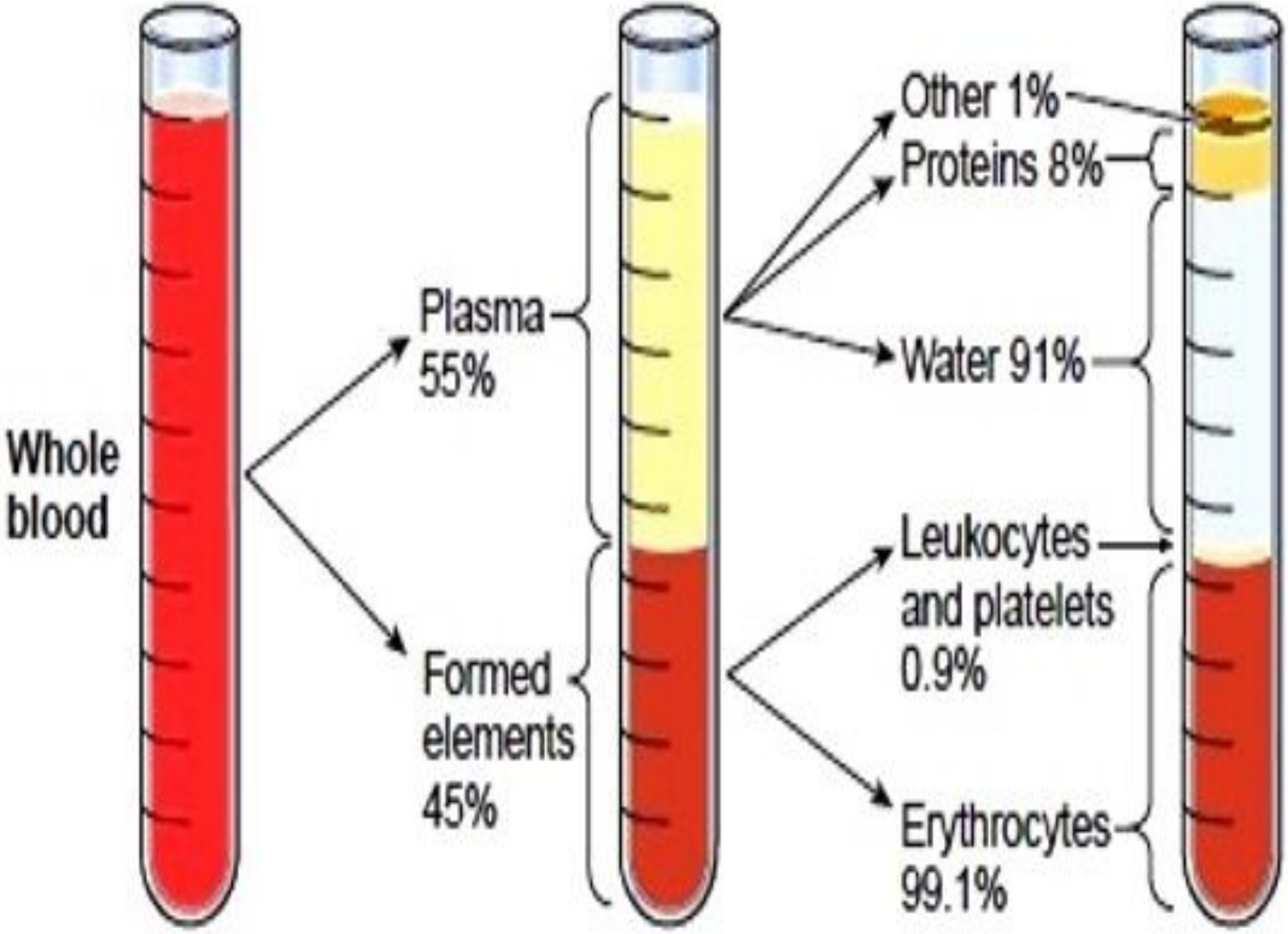
CARDIOVASCULAR SYSTEM

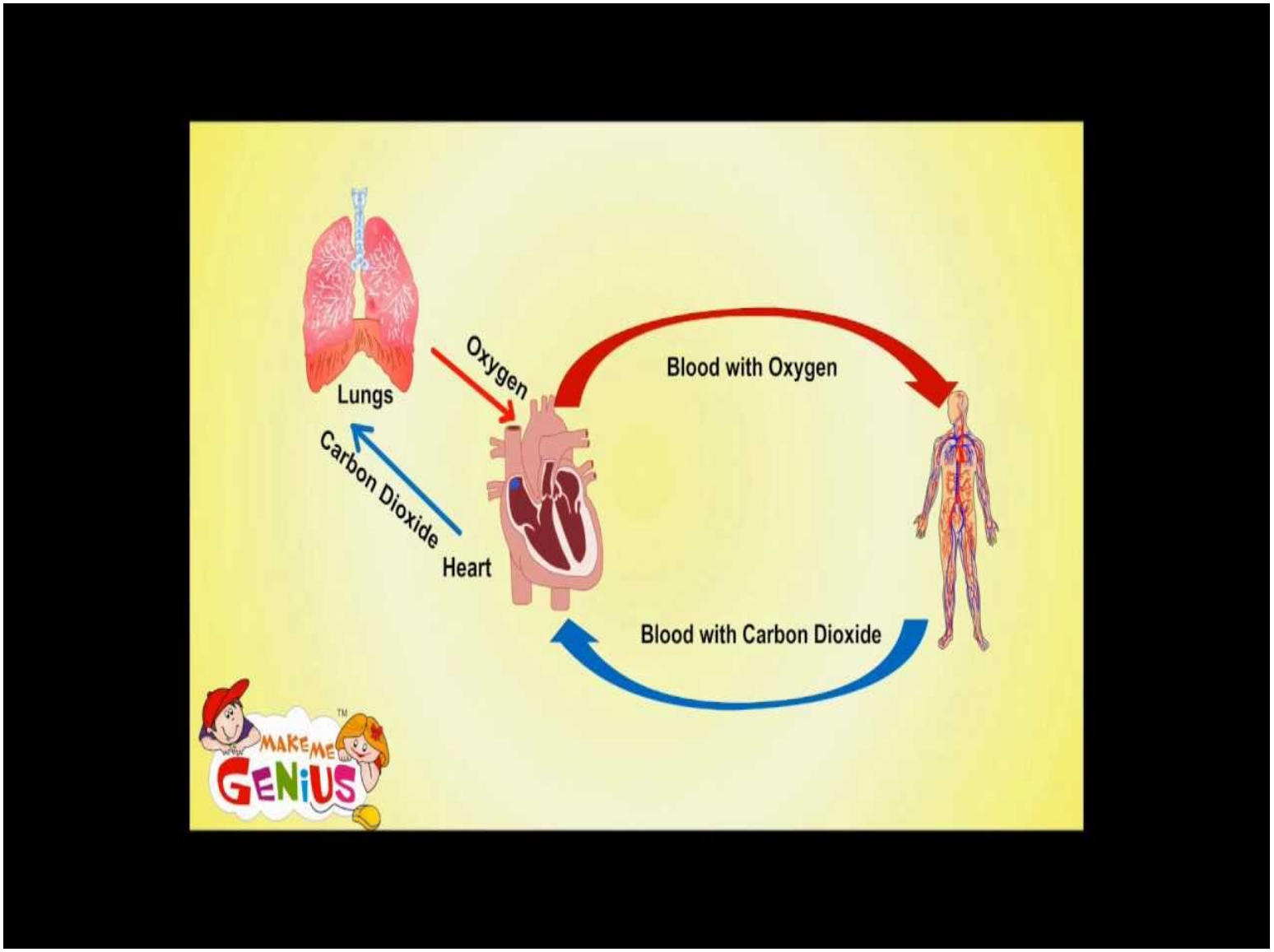


Cardiovascular system

Duration 3 week (3x2=6 hours)

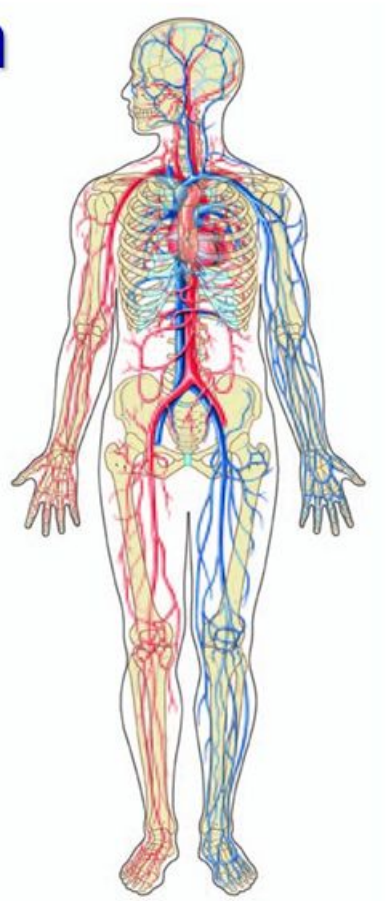
- **The function of cardiovascular system**
- **Human cardiovascular system**
- **Heart**
  - Function and structure
  - Cardiac activity
  - Cardiac circulation and heart nutrition
  - **Blood vessels**
  - Arteries
  - Capillaries
  - Veins
  - The blood movement in the vessels
  - Blood pressure in the vessels
  - Material exchanges between vessels and body cells
  - **Blood**
  - Function of blood
  - Plasma and blood cells
  - Blood types and transmition
- **Types of circulation**
  - Pulmonary circulation
  - Systemic circulation
  - Placental circulation


Whole blood
Plasma 55%
Formed elements 45%
Other 1%
Proteins 8%
Water 91%
Leukocytes and platelets 0.9%
Erythrocytes 99.1%


Lungs
Oxygen
Blood with Oxygen
Carbon Dioxide
Heart
Blood with Carbon Dioxide
MAKE ME GENIUS

The Cardiovascular System

- A closed system of the heart and blood vessels
  - The heart pumps blood
  - Blood vessels allow blood to circulate to all parts of the body
- The function of the cardiovascular system is to deliver oxygen and nutrients and to remove carbon dioxide and other waste products



Functions of the Cardiovascular System?

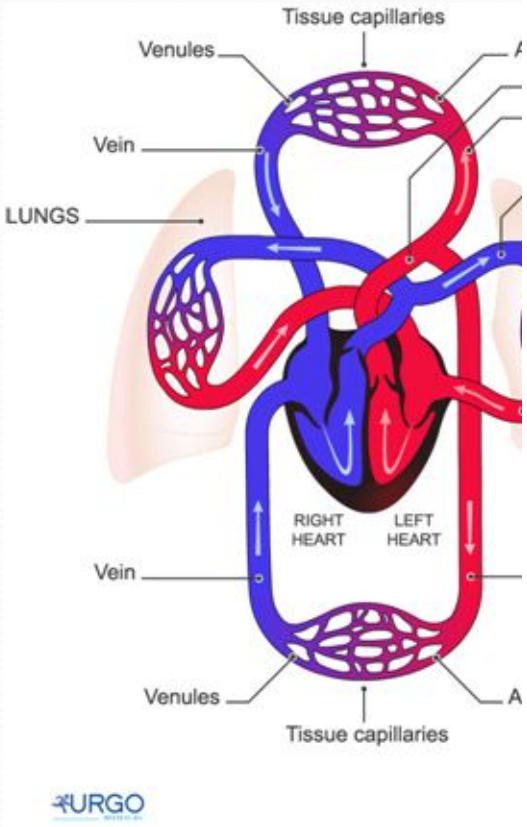
The Cardiovascular system has 2 main function that are both equally important

Function 1. To supply the body and muscles with oxygen

Function 2. To remove waste products like carbon dioxide

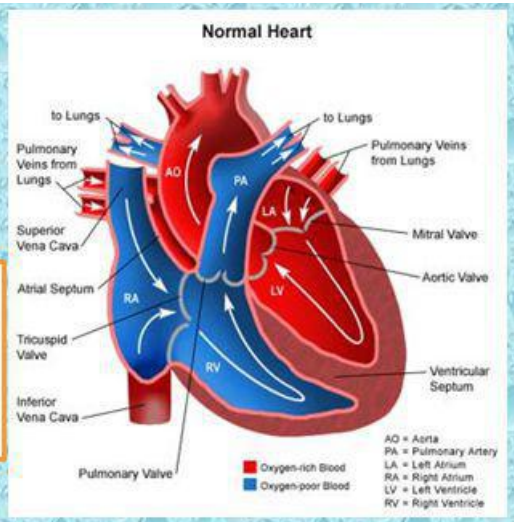
Function of Cardiovascular Syste

- The cardiovascular systems main function is to maintain blood flow to all parts of the body, to allow it to survive. The body takes essential nutrients like oxygen from the blood, and at the same time, the body dumps waste products, like carbon dioxide, back into the blood so it can removed. The Cardiovascular System also plays a role in the immune response and the regulation of body temperature.



General function

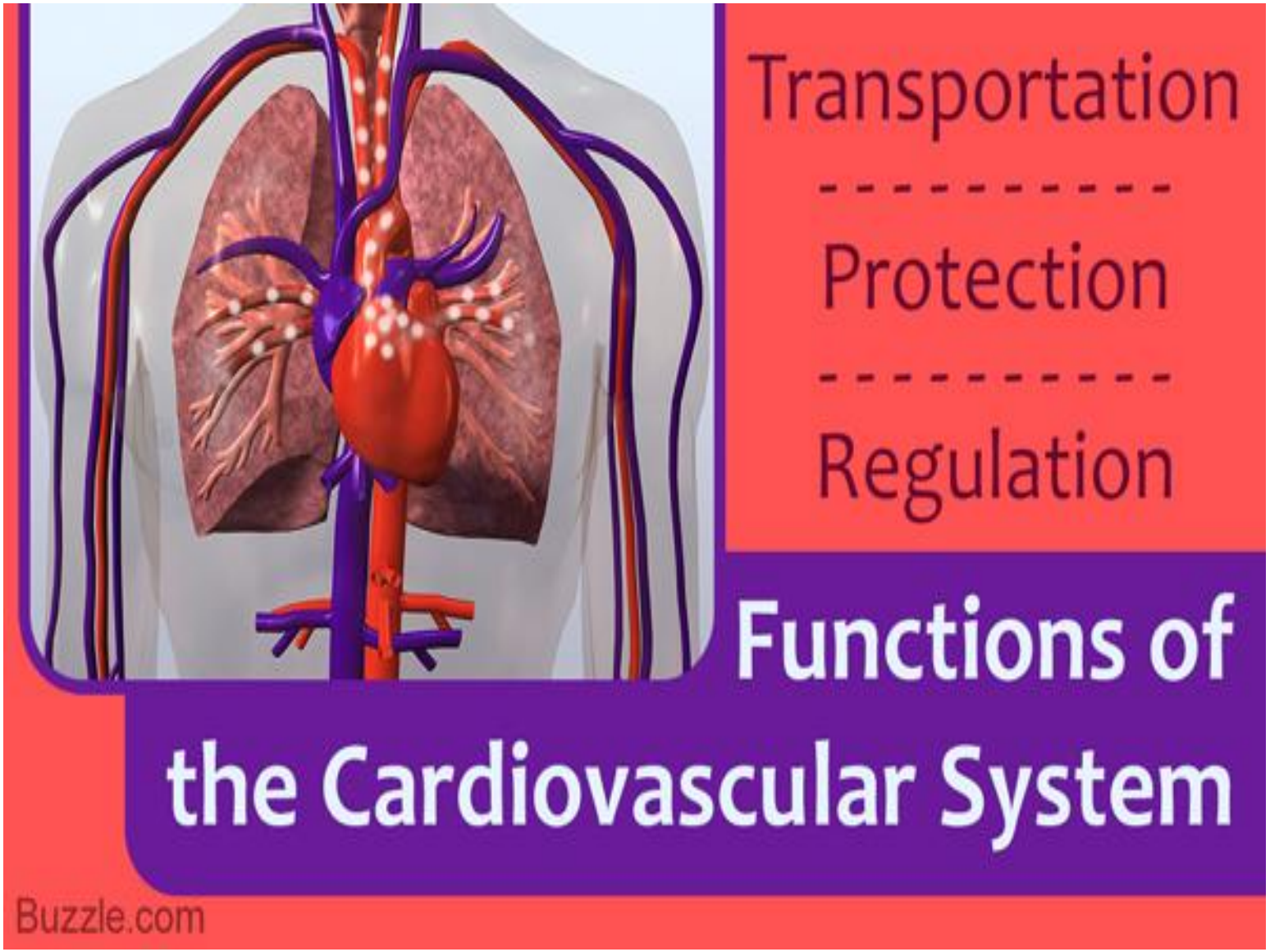
- **The main function of the cardiovascular system is to deliver oxygen and nutrients and remove the waste products of metabolism.**
- **Each part of system has a specific function in helping to do this.**



- Heart
  - Pump – It is designed to push blood out through the arteries.
    - One ventricle pumps blood to the lungs to get oxygen
    - The other pumps blood to the body to deliver Oxygen and nutrients

- Blood vessels
  - Designed to carry the blood. They are hollow, and vary according to their purpose.
    - For example, arteries have thick muscular walls so that they can take the blood at high pressure from the heart, and squeeze it along to the capillaries

- Blood
  - Has a number of functions
    - Red blood cells and their haemoglobin attract Oxygen, so it can be carried around in the blood
    - White blood cells fight infection
    - Platelets help with clotting if we are injured.


Transportation
Protection
Regulation
Functions of
the Cardiovascular System
Buzzle.com

Functions of Cardiovascular System:

I. Primary (main) function of the heart:

- Acts as a muscular pump:
  in order to maintain adequate level of blood flow throughout CVS by pumping blood under press into vascular system.
- Responsible for the mass movement of fluid in body.

Functions of Cardiovascular System (continued)

II. Secondary functions:

1. Transportation:

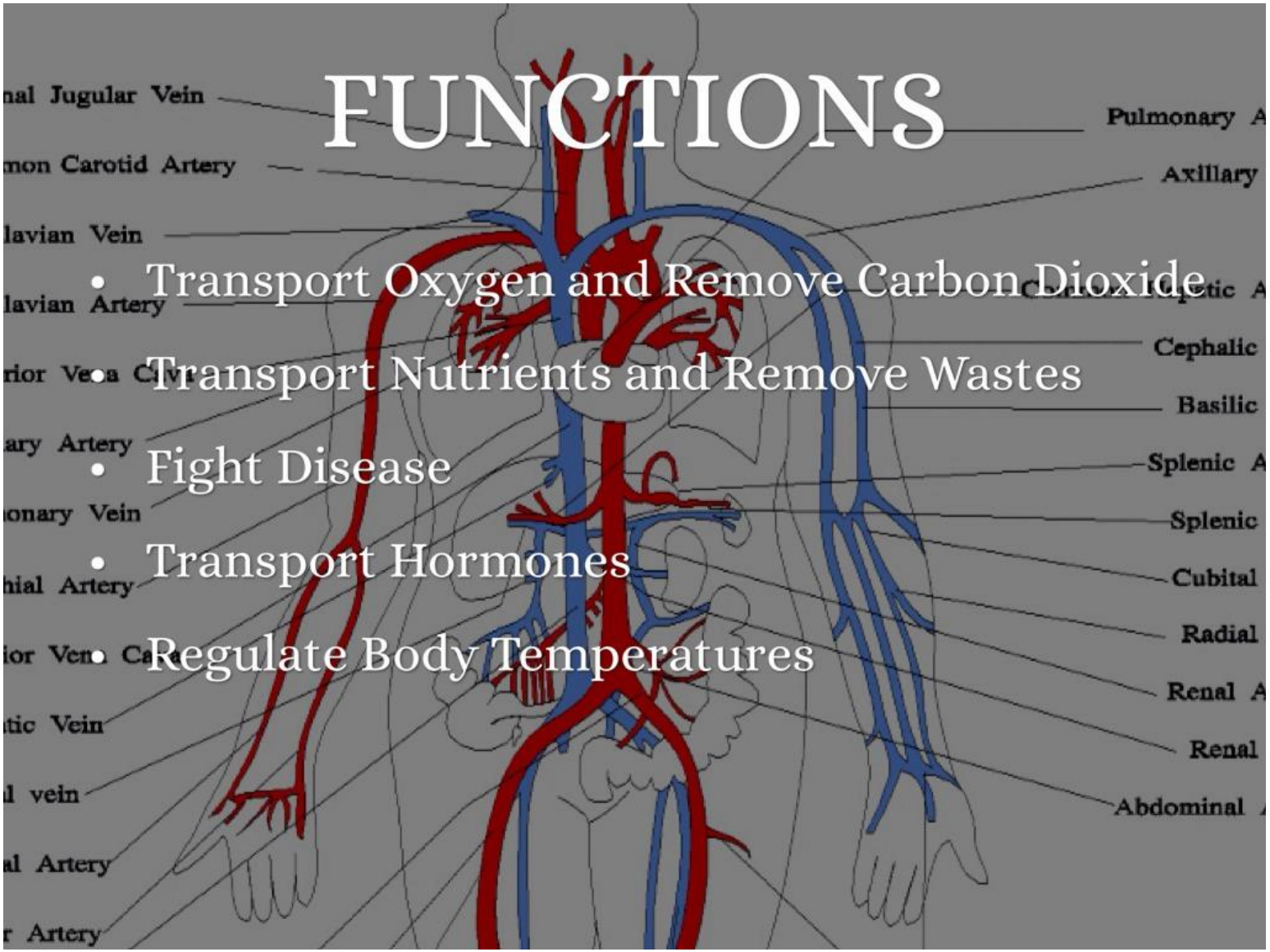
- delivers O_2 to tissues, & brings back CO_2 to lungs.
- carries absorbed digestion products to liver & tissues.
- carries metabolic wastes to kidneys to be excreted.
- distribution of body fluids.

2. Regulation:

- Hormonal: carries hormones to target tissues to produce their effects.
- Immune: carries antibodies, leukocytes (WBCs), cytokines, & complement to aid body defense mechanism against pathogens.
- Protection: carries platelets, & clotting factors to aid protection of the body in blood clotting mechanism.
- Temperature: helps in regulation of body temperature, by diverting blood to cool or warm the body.

Main functions of the circulatory system

1) Transport and distribute essential substances (oxygen and nutrients) to the tissues.
2) Remove metabolic byproducts.
3) Adjustment of oxygen and nutrient supply in different physiologic states.
4) Regulation of body temperature.
5) Humoral communication.



FUNCTIONS

- Transport Oxygen and Remove Carbon Dioxide
- Transport Nutrients and Remove Wastes
- Fight Disease
- Transport Hormones
- Regulate Body Temperatures

P5 describe the structure and function of the cardiovascular system

M2 explain the function of the cardiovascular system

Describe the **Structure** and **Function** of the cardiovascular system

Examine the cardiovascular system and **explain** how it works and how each part of the system is designed to meet its **function**

***Structure** of the cardiovascular system (which you have to find pictures/ label and describe)*:

Heart:

Atria, Ventricles, Bicuspid valve, Tricuspid valve, Aortic valve, Pulmonary valve, Aorta, Vena cava – (superior and inferior), Pulmonary vein, Pulmonary artery

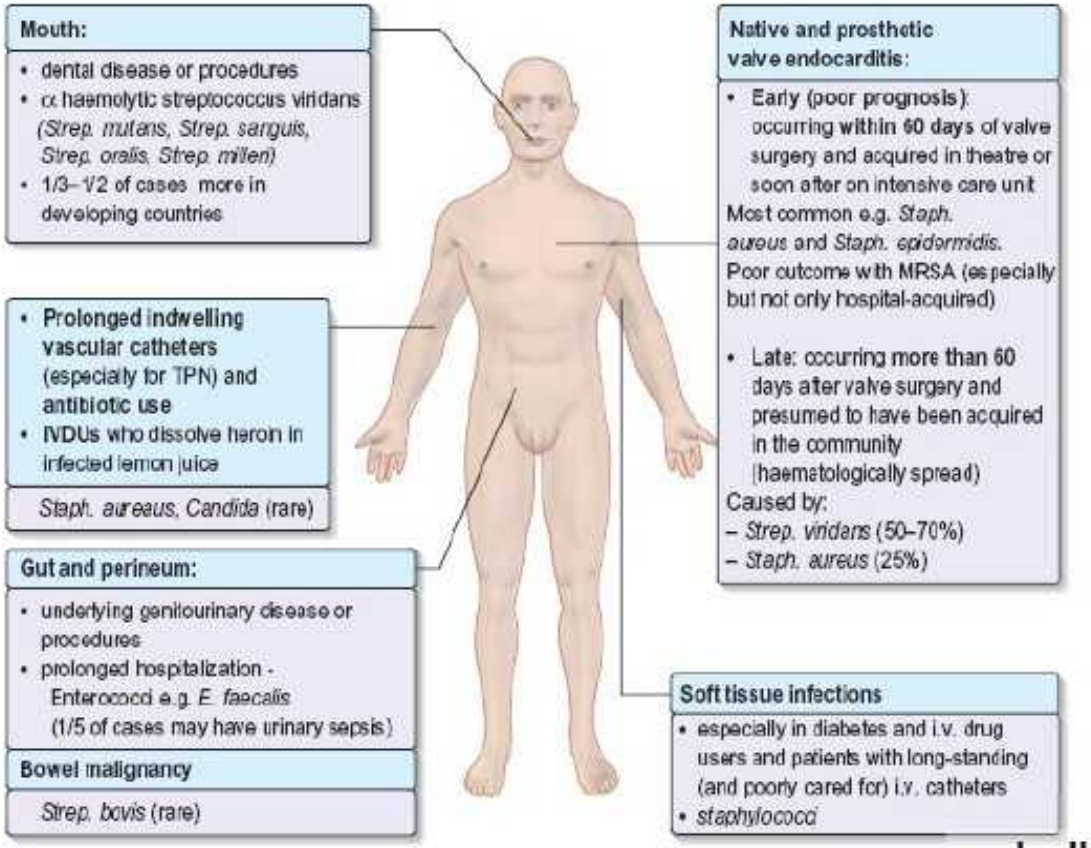
Blood vessels:

Arteries, Arterioles, Capillaries, Veins, Venuoles

Function of the cardiovascular system:

1. *Delivery of oxygen and nutrients*
2. *Removal of waste products*
3. *Thermoregulation* (vasodilation and vasoconstriction of vessels);
4. *Function of blood* (oxygen transport, clotting, fighting infection)

Etiology and sources of infection



Tissue Allostasis

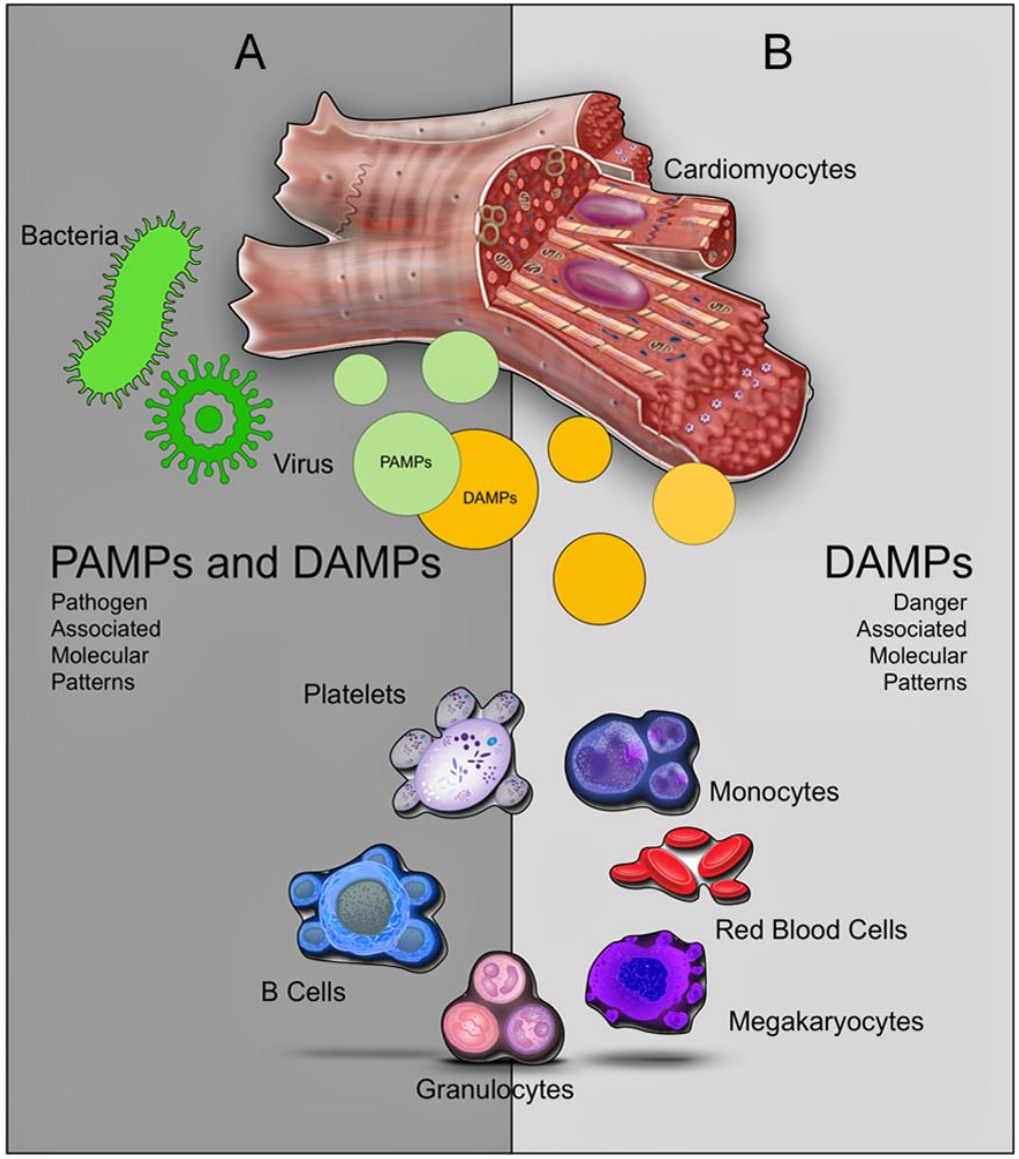
host defense
healing regeneration
angiogenesis

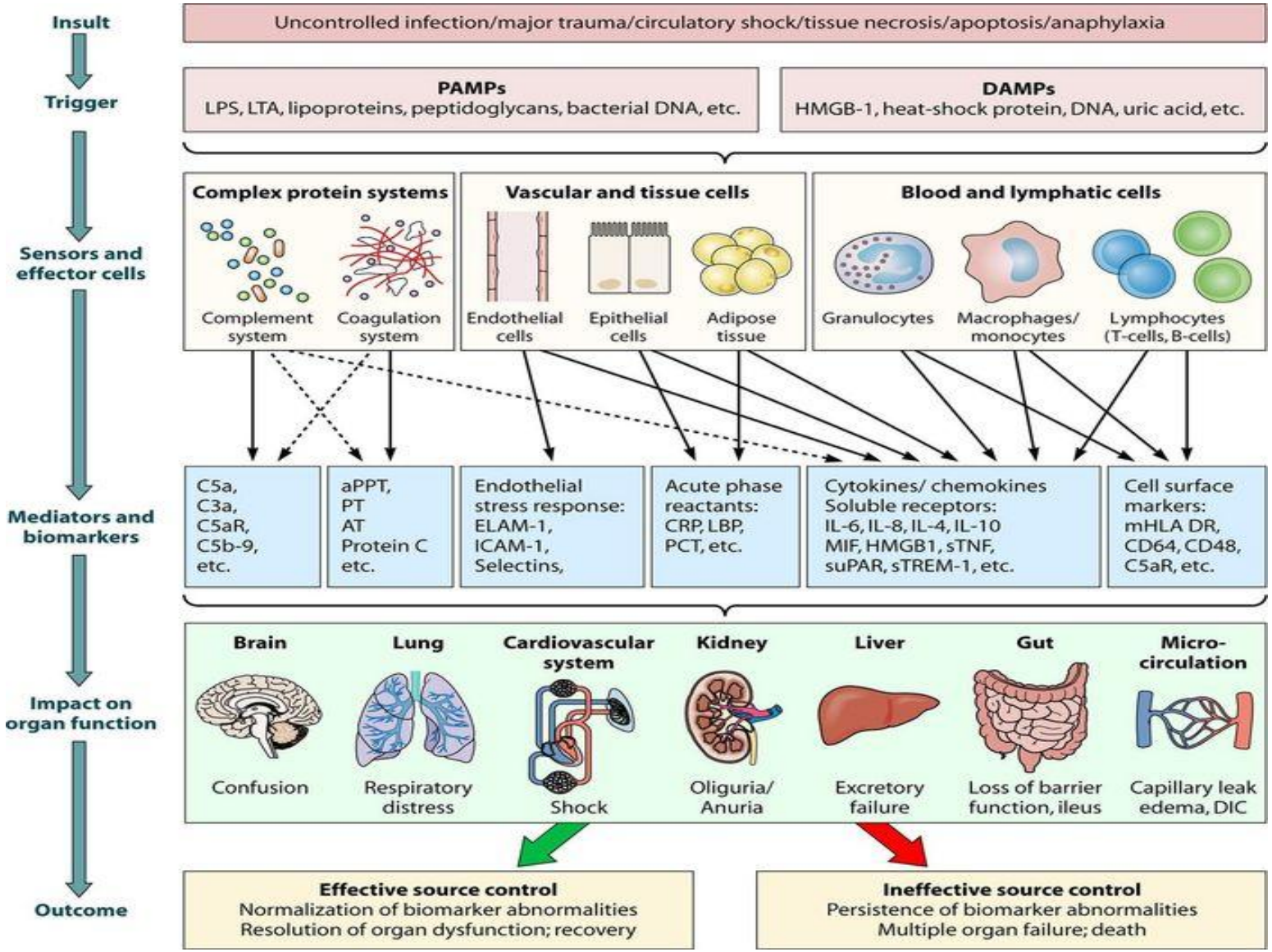
Development

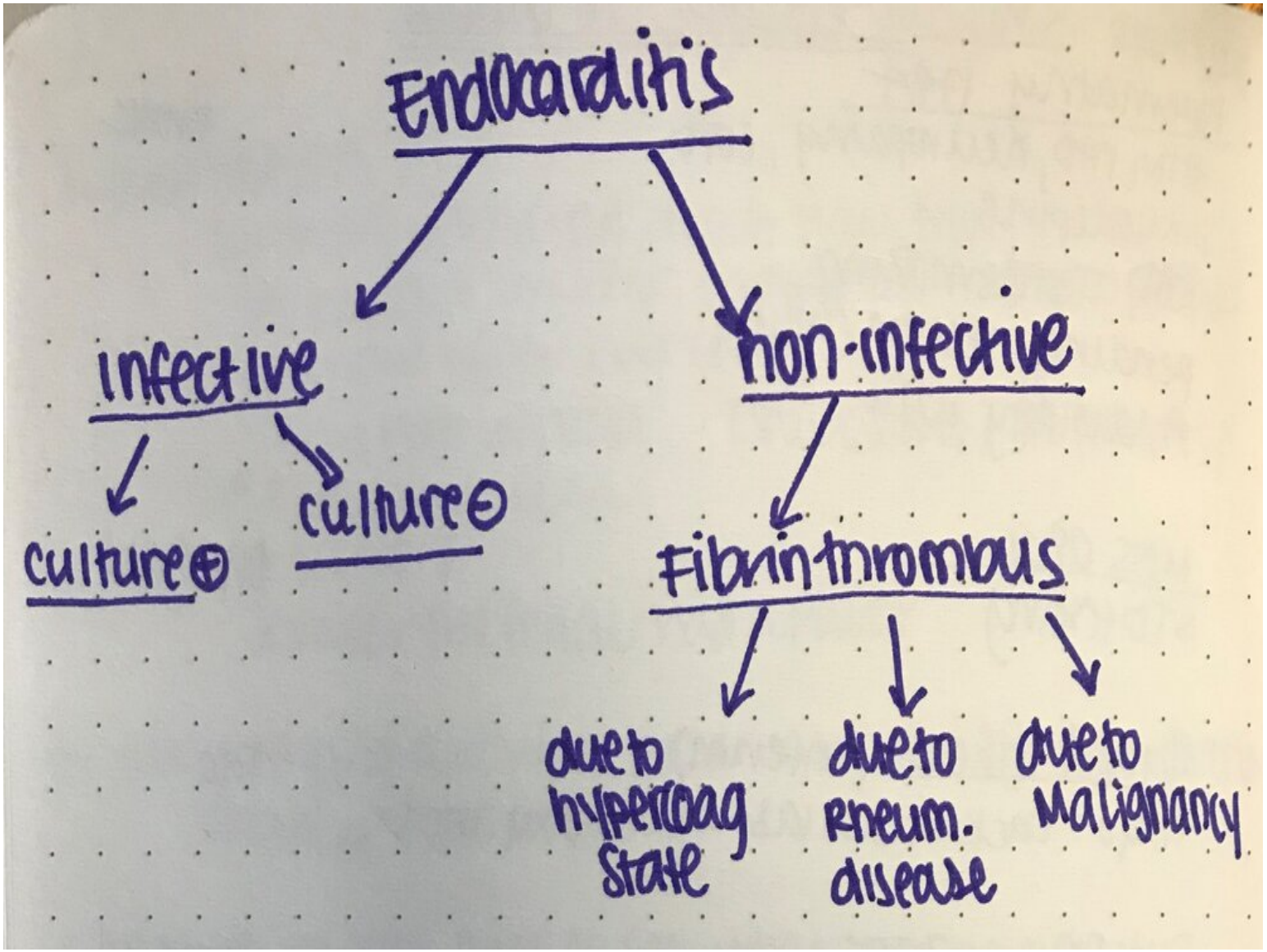
building of organ structures
through developmental apoptosis

Reproduction

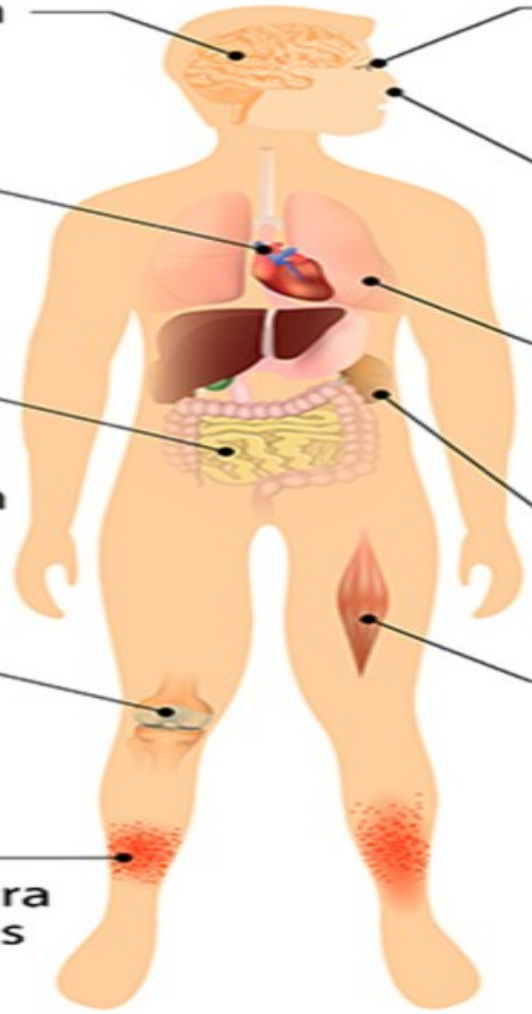
ovulation
fetal-maternal interface
mammary gland development




Insult
Uncontrolled infection/major trauma/circulatory shock/tissue necrosis/apoptosis/anaphylaxia
Trigger
PAMPs
LPS, LTA, lipoproteins, peptidoglycans, bacterial DNA, etc.
DAMPs
HMGB-1, heat-shock protein, DNA, uric acid, etc.
Sensors and effector cells
Complex protein systems
Complement system
Coagulation system
Vascular and tissue cells
Endothelial cells
Epithelial cells
Adipose tissue
Blood and lymphatic cells
Granulocytes
Macrophages/ monocytes
Lymphocytes (T-cells, B-cells)
Mediators and biomarkers
C5a, C3a, C5aR, C5b-9, etc.
aPPT, PT AT Protein C etc.
Endothelial stress response: ELAM-1, ICAM-1, Selectins,
Acute phase reactants: CRP, LBP, PCT, etc.
Cytokines/ chemokines Soluble receptors: IL-6, IL-8, IL-4, IL-10 MIF, HMGB1, sTNF, suPAR, sTREM-1, etc.
Cell surface markers: mHLA DR, CD64, CD48, C5aR, etc.
Impact on organ function
Brain
Confusion
Lung
Respiratory distress
Cardiovascular system
Shock
Kidney
Oliguria/ Anuria
Liver
Excretory failure
Gut
Loss of barrier function, ileus
Micro-circulation
Capillary leak edema, DIC
Outcome
Effective source control
Normalization of biomarker abnormalities
Resolution of organ dysfunction; recovery
Ineffective source control
Persistence of biomarker abnormalities
Multiple organ failure; death


Endocarditis
infective
non-infective
culture⊕
culture⊖
Fibrinthrombus
due to hypercoag state
due to rheum. disease
due to Malignancy

VASCULITIS



Nervous system
- stroke

Heart
- myocardial infarction
- hypertension

Digestive system
- bloody stool
- abdominal pain

Joints
- pain
- arthritis

Skin
- palpable purpura
- livedo reticularis

Eye
- reduced visual acuity

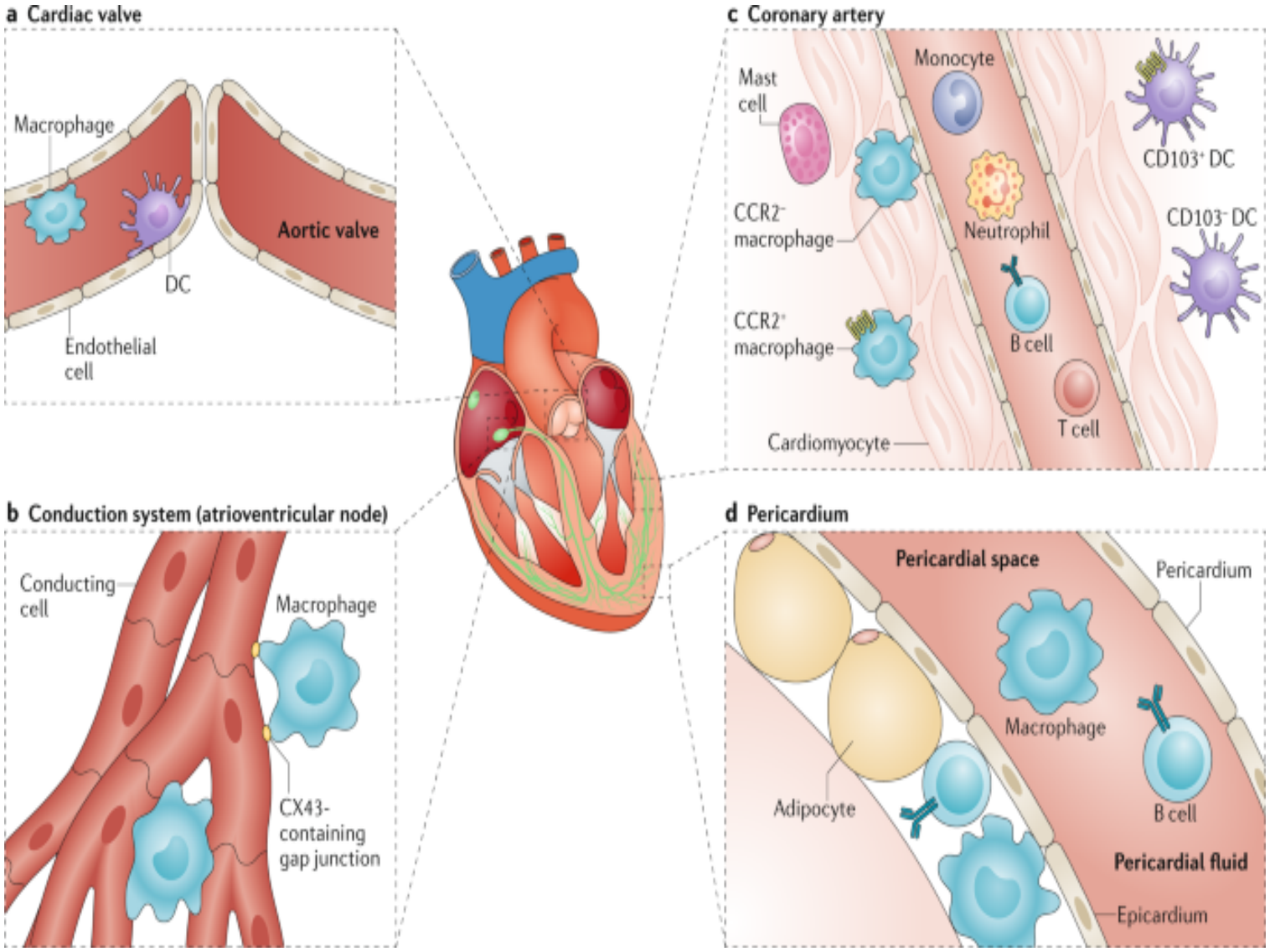
Nose
- bleeds

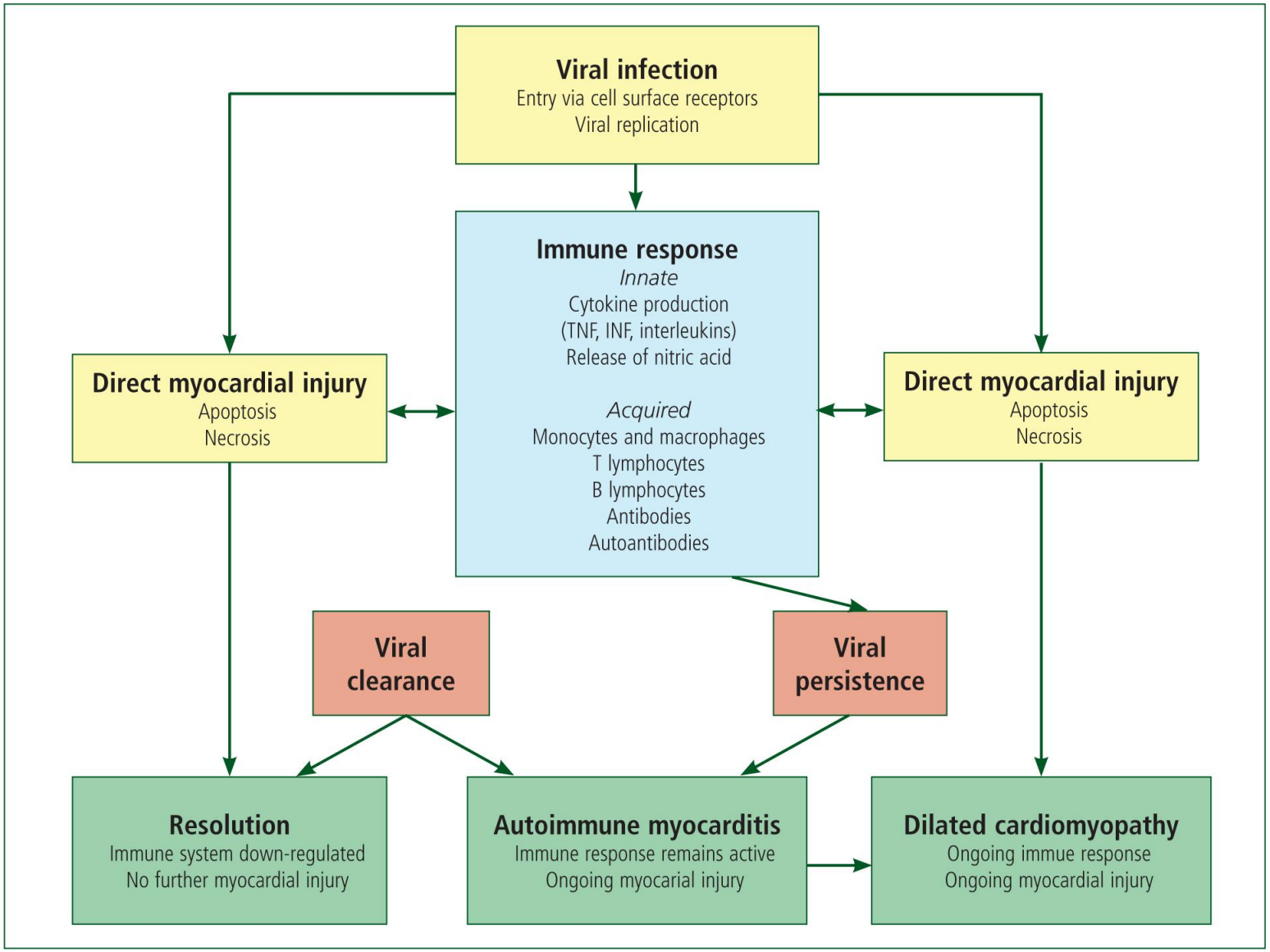
Lungs
- bloody cough
- lung infiltrates

Kidneys
- glomerular nephritis

Muscle
- pain

General symptoms:
- fever
- headache
- weight loss


a Cardiac valve
Macrophage
Aortic valve
DC
Endothelial cell
b Conduction system (atrioventricular node)
Conducting cell
Macrophage
CX43-containing gap junction
c Coronary artery
Mast cell
Monocyte
CD103+ DC
CCR2− macrophage
Neutrophil
CD103− DC
CCR2+ macrophage
B cell
T cell
Cardiomyocyte
d Pericardium
Pericardial space
Pericardium
Macrophage
Adipocyte
B cell
Pericardial fluid
Epicardium


Viral infection
Entry via cell surface receptors
Viral replication
Immune response
Innate
Cytokine production
(TNF, INF, interleukins)
Release of nitric acid
Acquired
Monocytes and macrophages
T lymphocytes
B lymphocytes
Antibodies
Autoantibodies
Direct myocardial injury
Apoptosis
Necrosis
Direct myocardial injury
Apoptosis
Necrosis
Viral clearance
Viral persistence
Resolution
Immune system down-regulated
No further myocardial injury
Autoimmune myocarditis
Immune response remains active
Ongoing myocarial injury
Dilated cardiomyopathy
Ongoing immue response
Ongoing myocardial injury

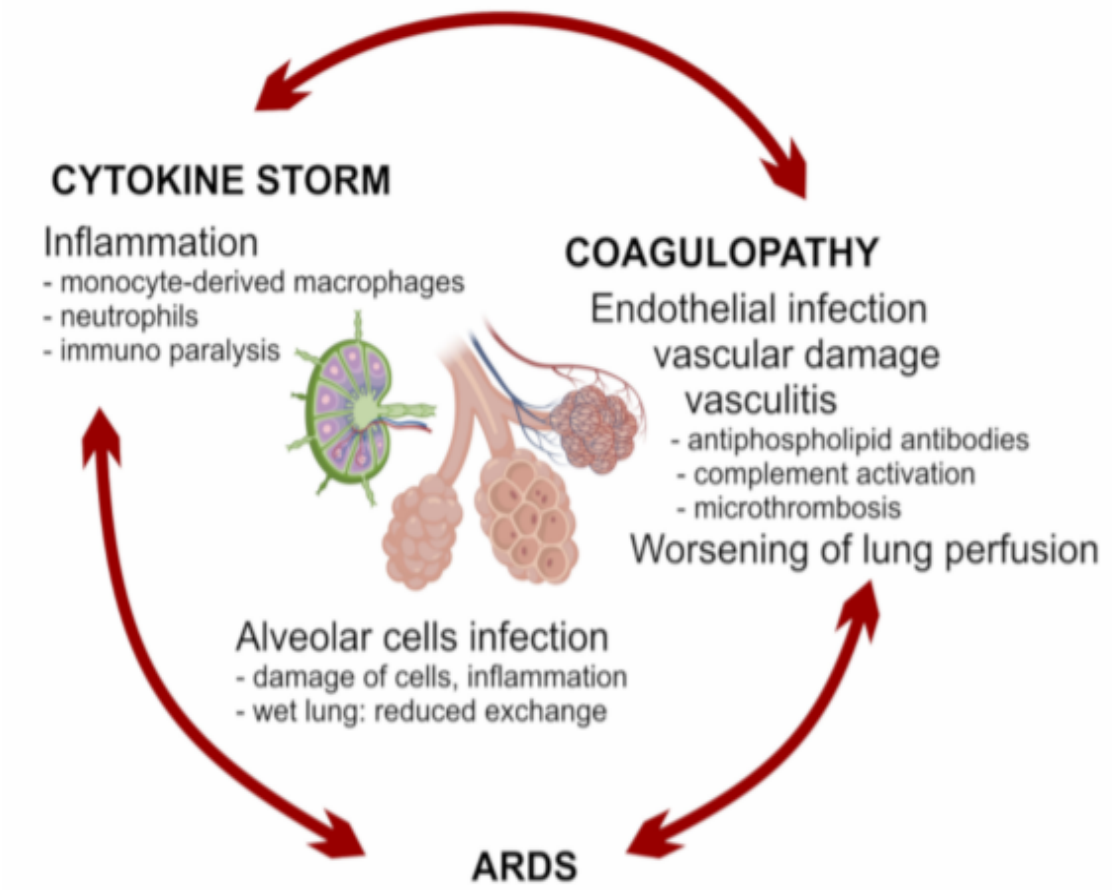
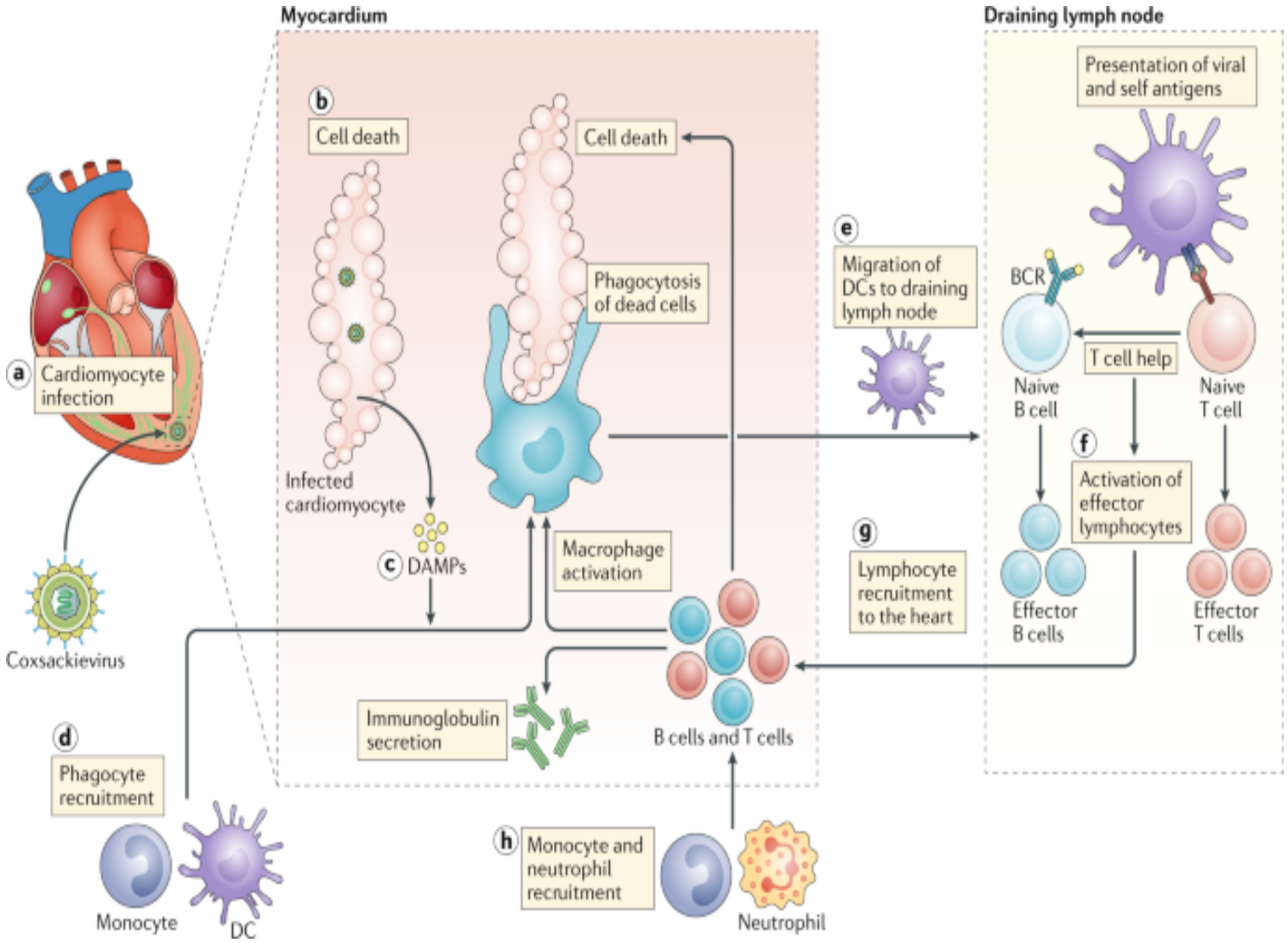
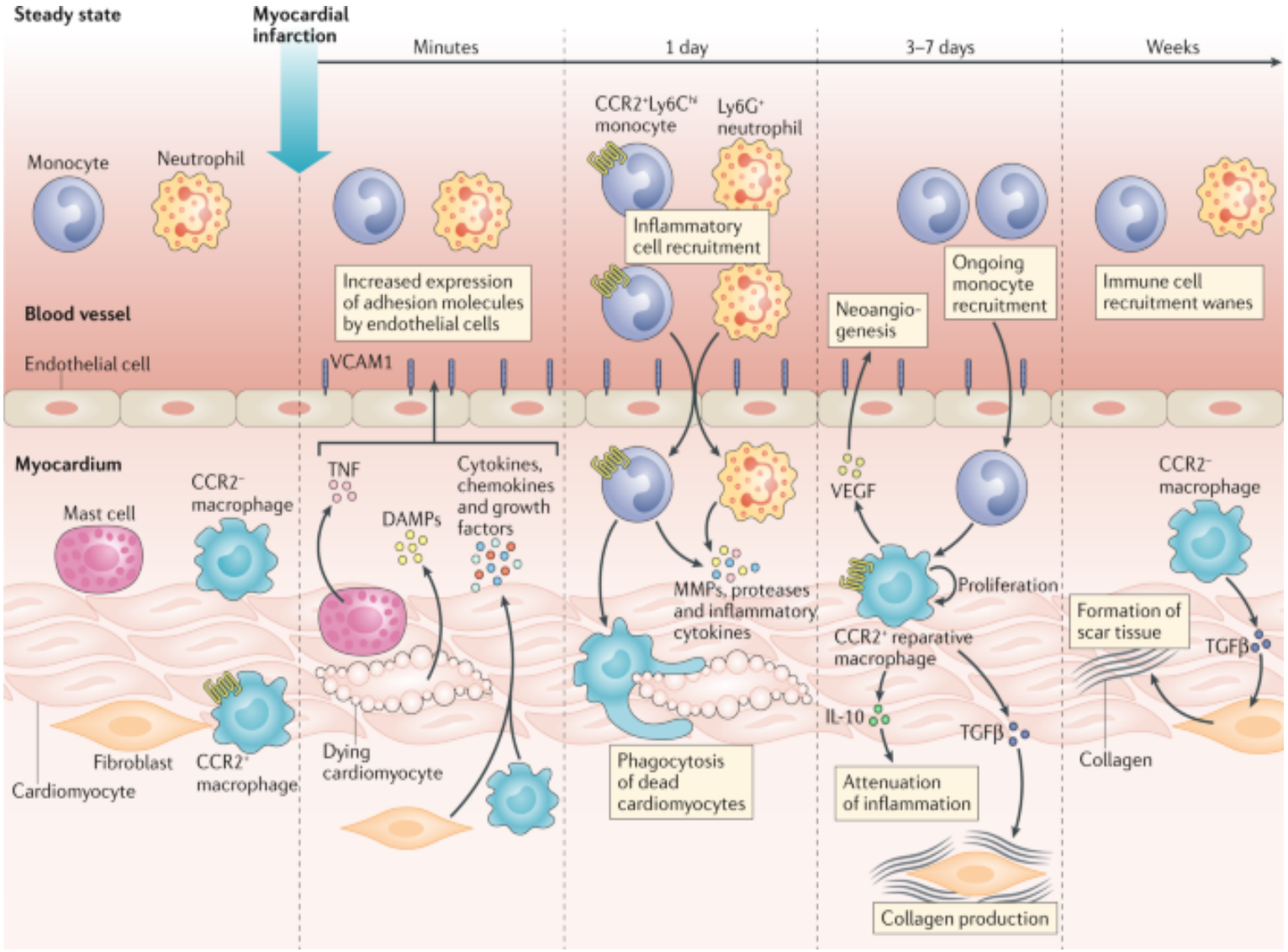


Figure 2. A hypothetical vicious circle between distinct pathogenic mechanisms associated with disease worsening.


Myocardium
Draining lymph node
a Cardiomyocyte infection
Coxsackievirus
b Cell death
Cell death
Phagocytosis of dead cells
Infected cardiomyocyte
c DAMPs
Macrophage activation
d Phagocyte recruitment
Monocyte
DC
Immunoglobulin secretion
B cells and T cells
h Monocyte and neutrophil recruitment
Neutrophil
e Migration of DCs to draining lymph node
Presentation of viral and self antigens
BCR
T cell help
Naive B cell
Naive T cell
f Activation of effector lymphocytes
Effector B cells
Effector T cells
g Lymphocyte recruitment to the heart


Steady state
Myocardial infarction
Minutes
1 day
3–7 days
Weeks
Monocyte
Neutrophil
CCR2+Ly6Chi monocyte
Ly6G+ neutrophil
Inflammatory cell recruitment
Increased expression of adhesion molecules by endothelial cells
Ongoing monocyte recruitment
Neoangio-genesis
Immune cell recruitment wanes
Blood vessel
Endothelial cell
VCAM1
Myocardium
Mast cell
CCR2− macrophage
TNF
DAMPs
Cytokines, chemokines and growth factors
VEGF
CCR2− macrophage
MMPs, proteases and inflammatory cytokines
Proliferation
Formation of scar tissue
TGFβ
CCR2+ reparative macrophage
IL-10
TGFβ
Fibroblast
Cardiomyocyte
CCR2+ macrophage
Dying cardiomyocyte
Phagocytosis of dead cardiomyocytes
Attenuation of inflammation
Collagen
Collagen production

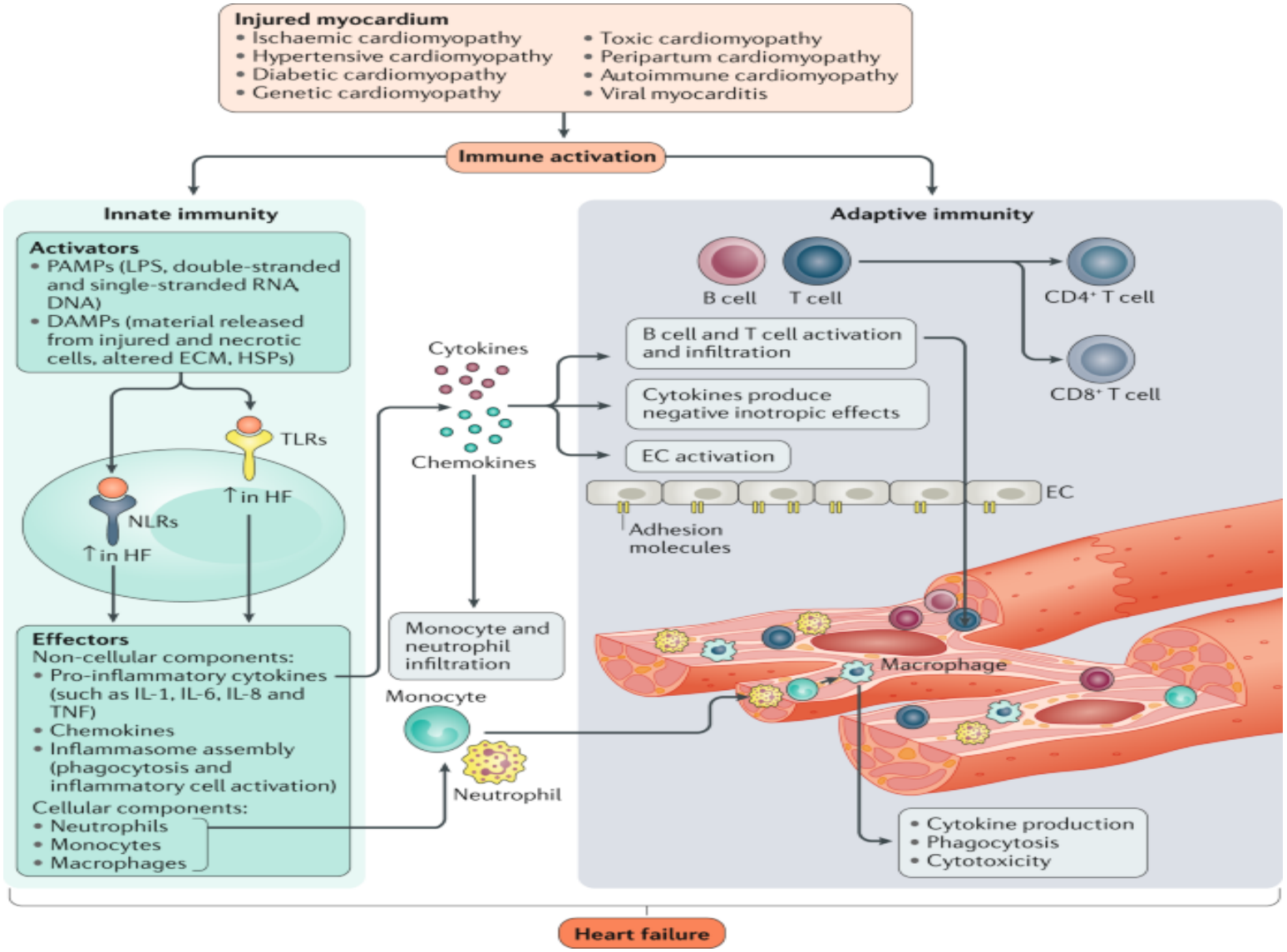
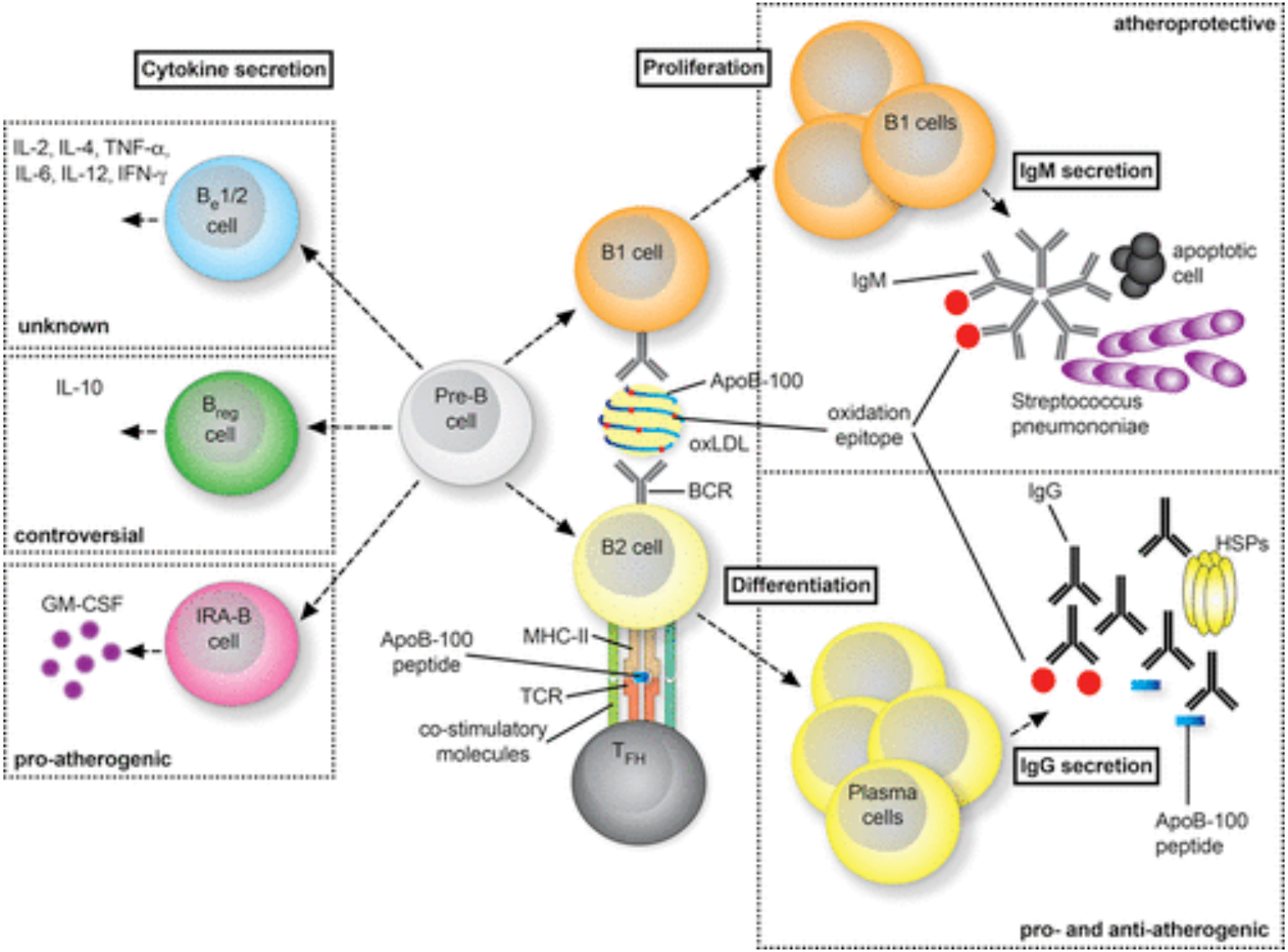
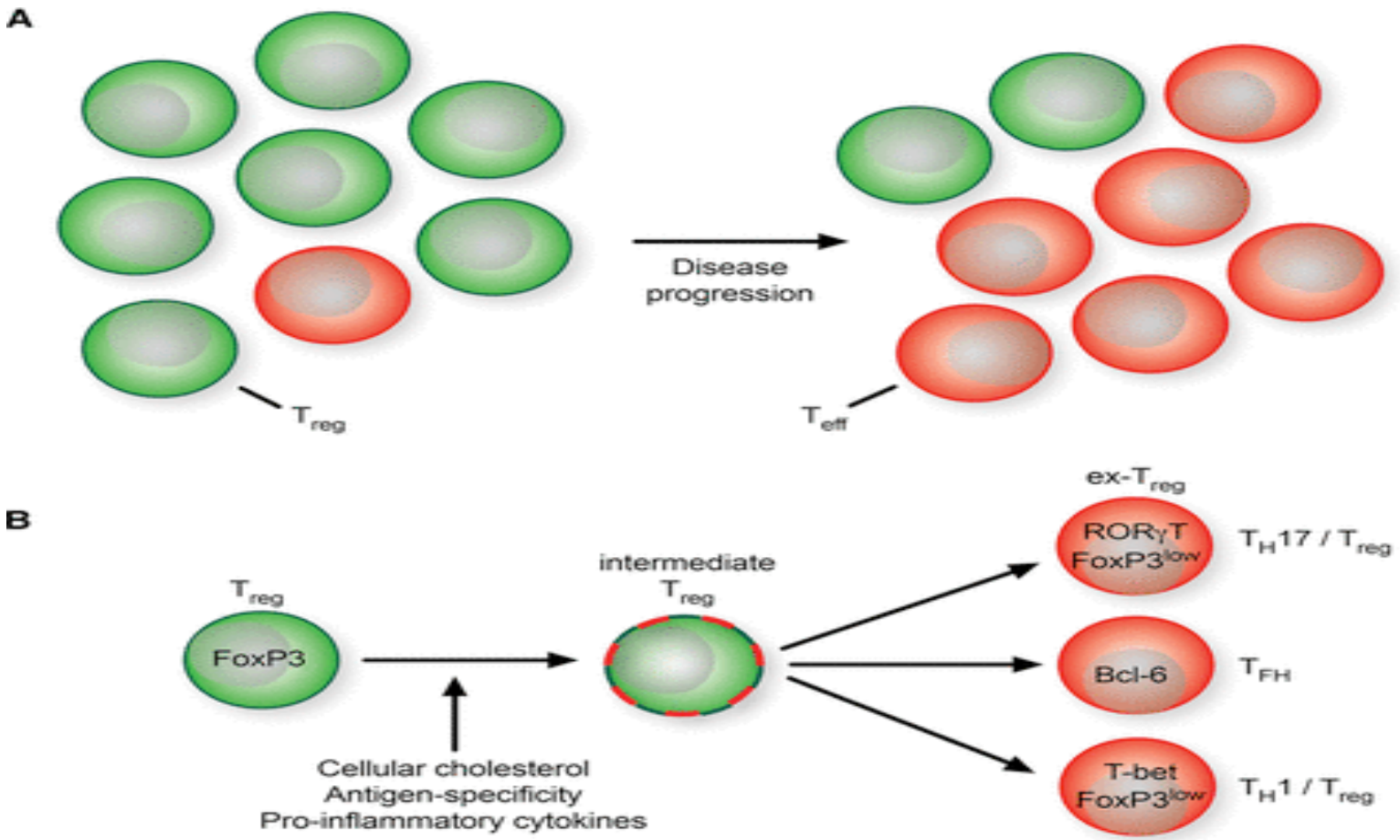
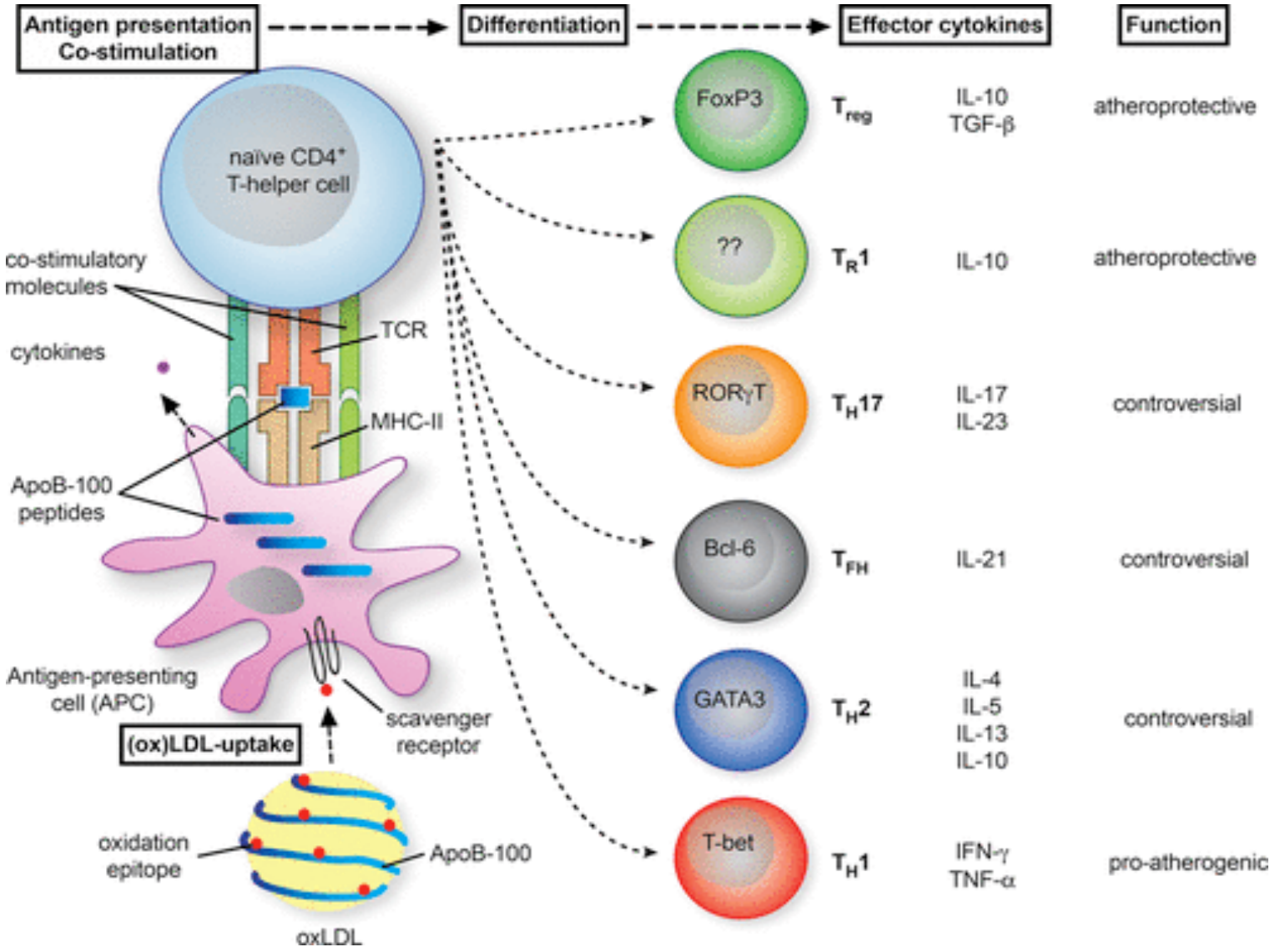

Injured myocardium
• Ischaemic cardiomyopathy
• Hypertensive cardiomyopathy
• Diabetic cardiomyopathy
• Genetic cardiomyopathy
• Toxic cardiomyopathy
• Peripartum cardiomyopathy
• Autoimmune cardiomyopathy
• Viral myocarditis
Immune activation
Innate immunity
Activators
• PAMPs (LPS, double-stranded and single-stranded RNA, DNA)
• DAMPs (material released from injured and necrotic cells, altered ECM, HSPs)
TLRs
↑in HF
NLRs
↑in HF
Effectors
Non-cellular components:
• Pro-inflammatory cytokines (such as IL-1, IL-6, IL-8 and TNF)
• Chemokines
• Inflammasome assembly (phagocytosis and inflammatory cell activation)
Cellular components:
• Neutrophils
• Monocytes
• Macrophages
Cytokines
Chemokines
Monocyte and neutrophil infiltration
Monocyte
Neutrophil
Adaptive immunity
B cell
T cell
CD4+ T cell
CD8+ T cell
B cell and T cell activation and infiltration
Cytokines produce negative inotropic effects
EC activation
EC
Adhesion molecules
Macrophage
• Cytokine production
• Phagocytosis
• Cytotoxicity
Heart failure

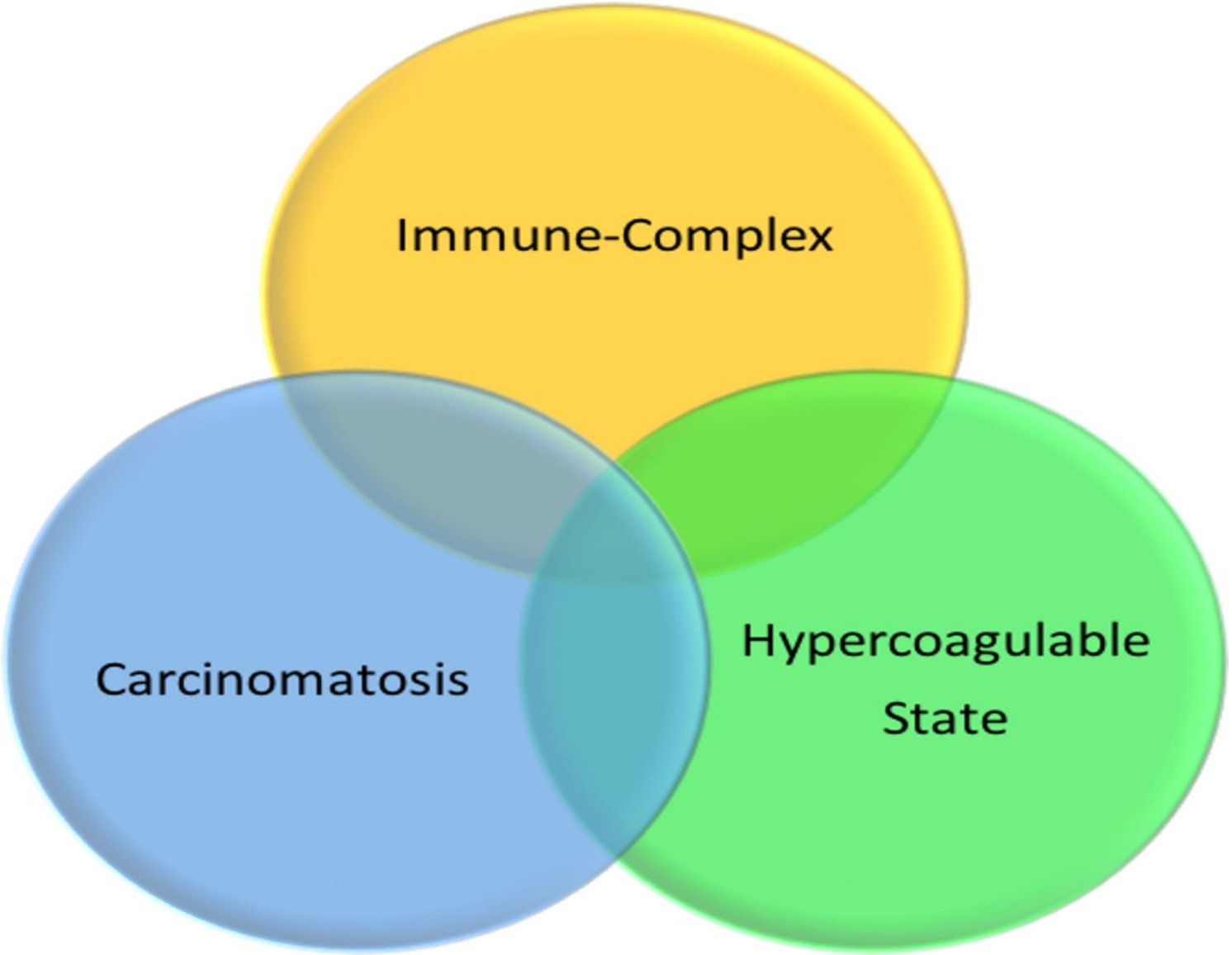
Table 1. Animal Studies Demonstrating Important Roles for Leukocyte Adhesion and Migration in Atherosclerosis

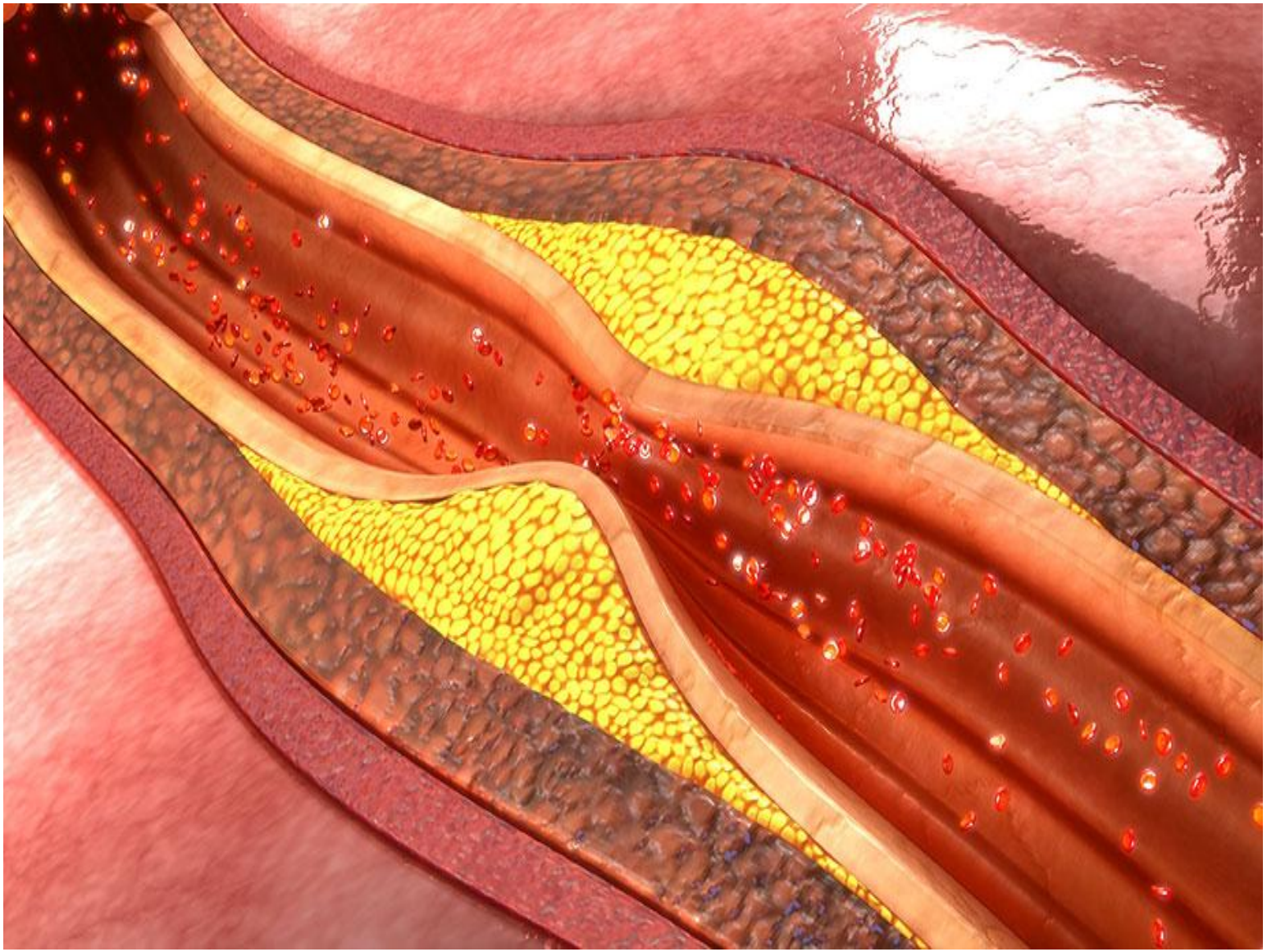
Molecule	Function	Experiment	Atherosclerosis Model	Result	Reference No.
CCR-2 indicates C-C chemokine receptor-2; PMN, polymorphonuclear leukocytes; MC, monocytes; Ly, lymphocytes; rec, receptor; and Tg, transgenic. See text for explanation of other abbreviations.					
P-, E-selectin	Rolling (PMN, MC, Ly)	KO	ApoE-KO	↓ Fatty streaks	34
P-selectin	Rolling (PMN, MC, Ly)	KO	ApoE-KO	↓ Atheroma	35
VCAM-1	Firm adhesion (MC, Ly)	Ab	Rabbit	↓ Postinjury lesion	213
MCP-1	Chemoattractant (MC, Ly)	KO	LDLR-KO, apoE-KO, apoB-Tg	↓ Atheroma	44, 46
CCR-2	MCP-1 rec (MC, Ly)	KO	LDLR, apoE-KO	↓ Atheroma	45

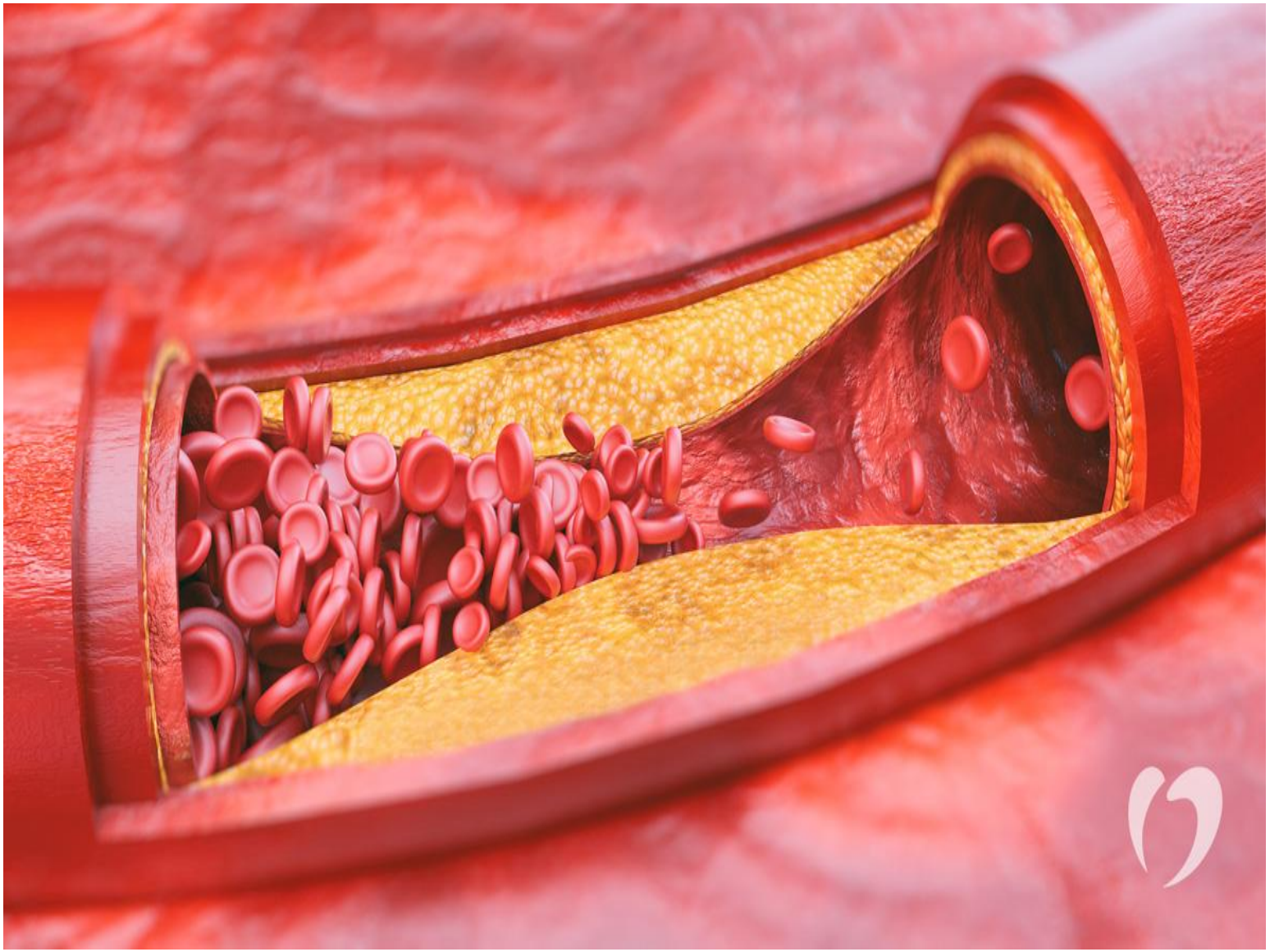

Cytokine secretion
IL-2, IL-4, TNF-α,
IL-6, IL-12, IFN-γ
B_e1/2 cell
unknown
IL-10
B_{reg} cell
controversial
GM-CSF
IRA-B cell
pro-atherogenic
Pre-B cell
B1 cell
B2 cell
ApoB-100
oxLDL
BCR
ApoB-100 peptide
MHC-II
TCR
co-stimulatory molecules
T_{FH}
Proliferation
Differentiation
atheroprotective
B1 cells
IgM secretion
IgM
apoptotic cell
oxidation epitope
Streptococcus pneumononiae
IgG
HSPs
IgG secretion
Plasma cells
ApoB-100 peptide
pro- and anti-atherogenic

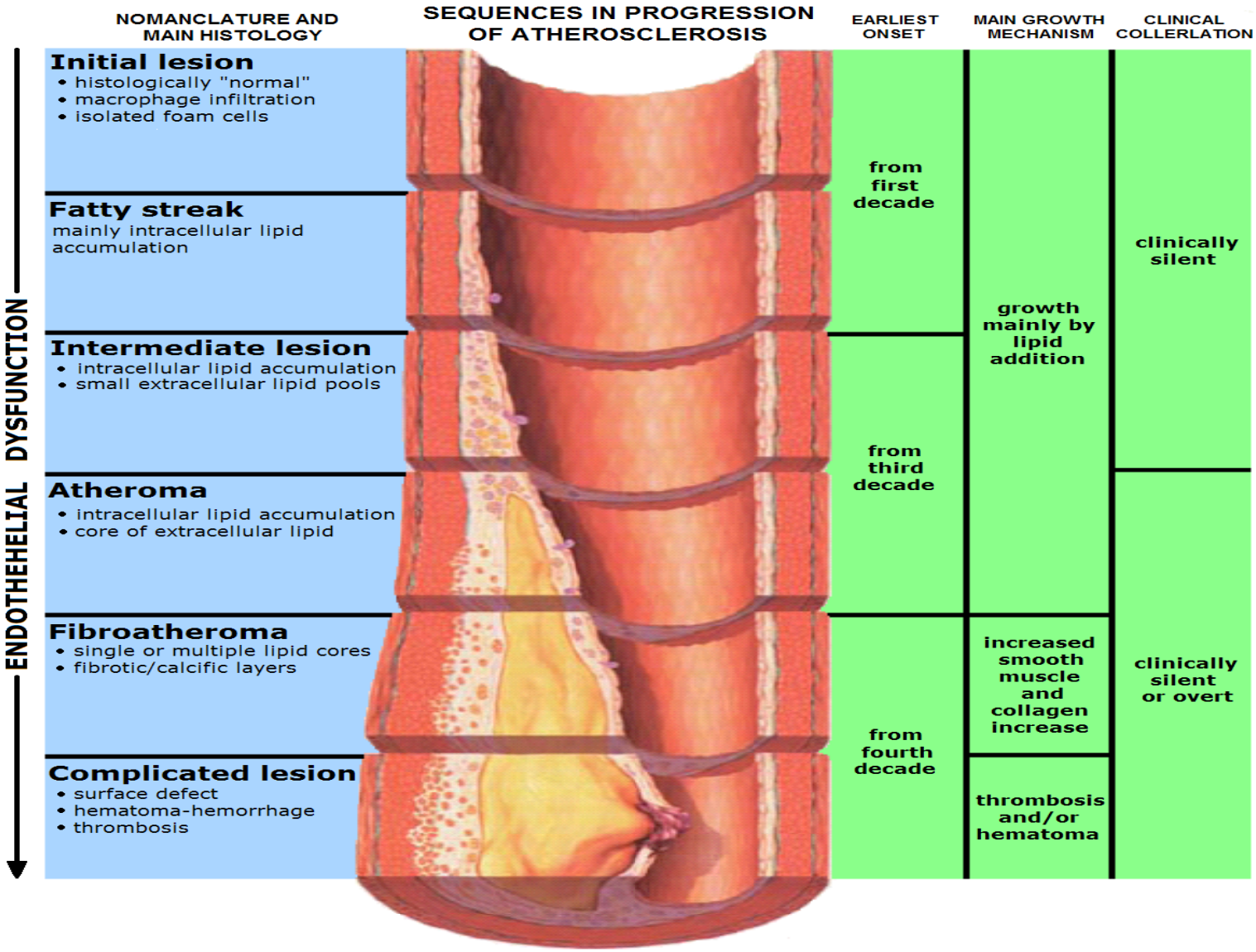

A
Disease
progression
T_{reg}
T_{eff}
B
T_{reg}
FoxP3
intermediate
T_{reg}
Cellular cholesterol
Antigen-specificity
Pro-inflammatory cytokines
ex-T_{reg}
RORγT
FoxP3^{low}
T_H17 / T_{reg}
Bcl-6
T_{FH}
T-bet
FoxP3^{low}
T_H1 / T_{reg}
C
FoxP3
RORγT, T-bet, Bcl-6
atheroprotective
pro-atherogenic

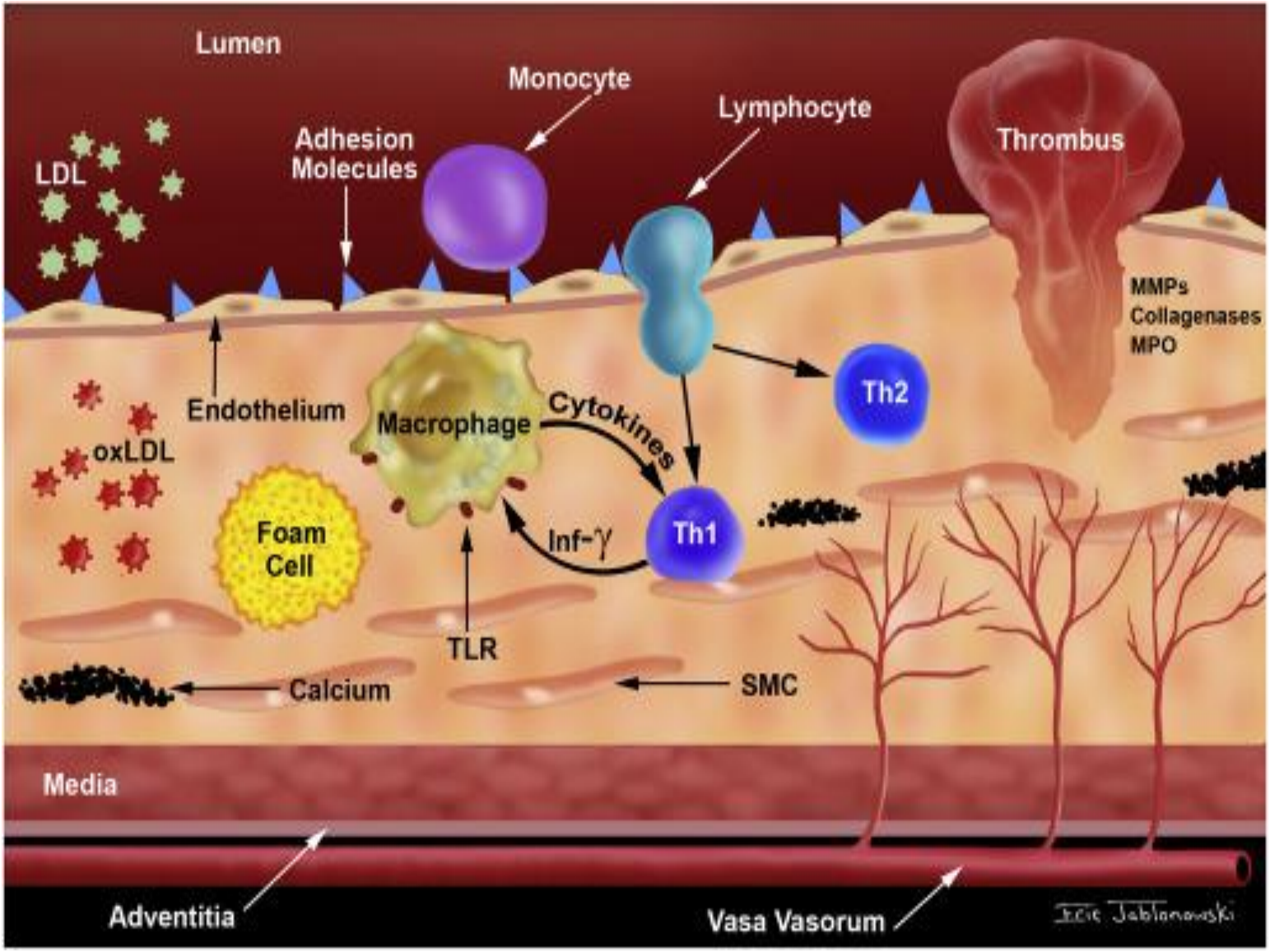

Antigen presentation
Co-stimulation
Differentiation
Effector cytokines
Function
naïve CD4+
T-helper cell
co-stimulatory
molecules
cytokines
TCR
MHC-II
ApoB-100
peptides
Antigen-presenting
cell (APC)
(ox)LDL-uptake
scavenger
receptor
oxidation
epitope
ApoB-100
oxLDL
FoxP3
Treg
IL-10
TGF-β
atheroprotective
??
TR1
IL-10
atheroprotective
RORγT
TH17
IL-17
IL-23
controversial
Bcl-6
TFH
IL-21
controversial
GATA3
TH2
IL-4
IL-5
IL-13
IL-10
controversial
T-bet
TH1
IFN-γ
TNF-α
pro-atherogenic

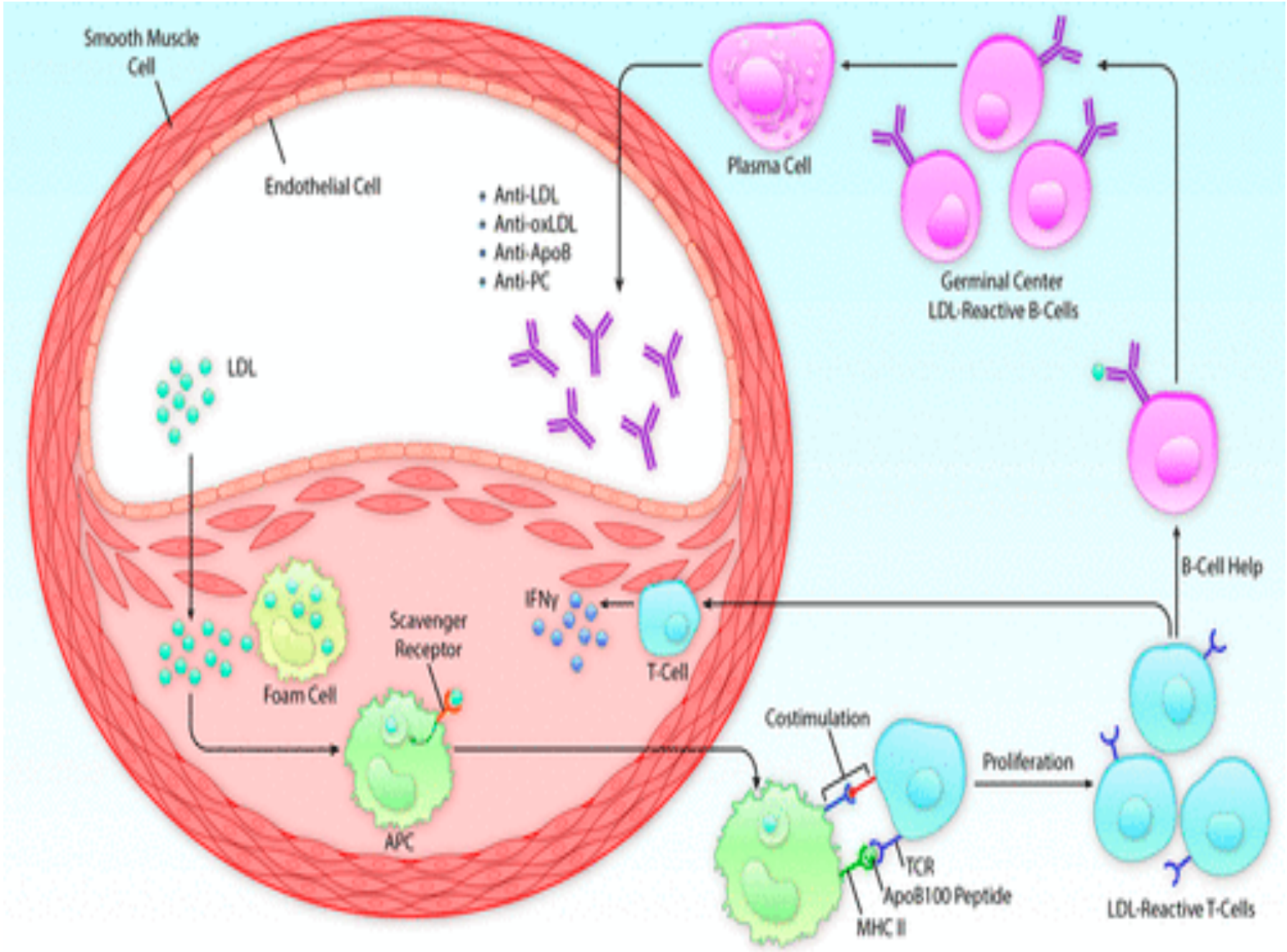

Immune-Complex
Carcinomatosis
Hypercoagulable
State

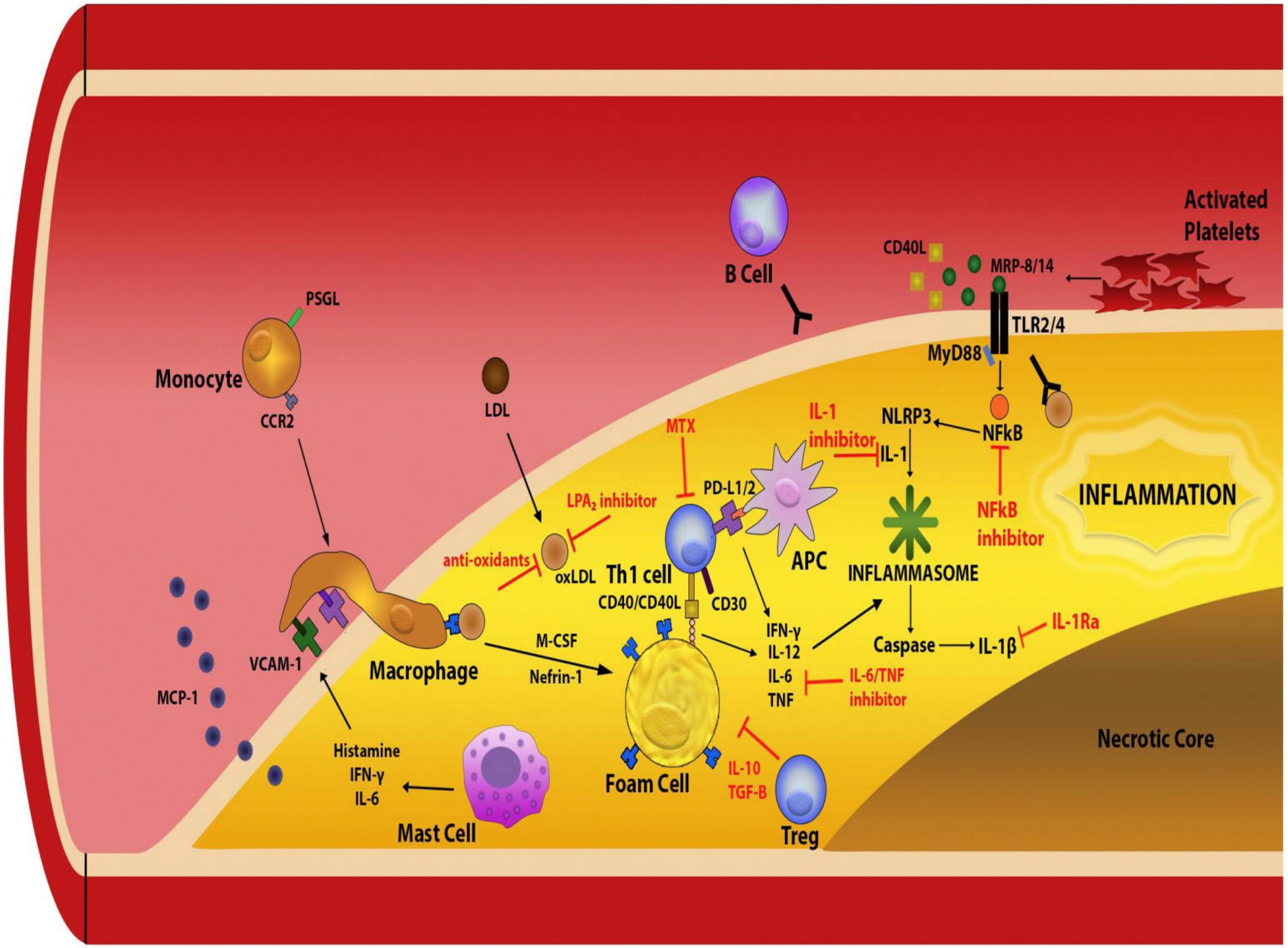


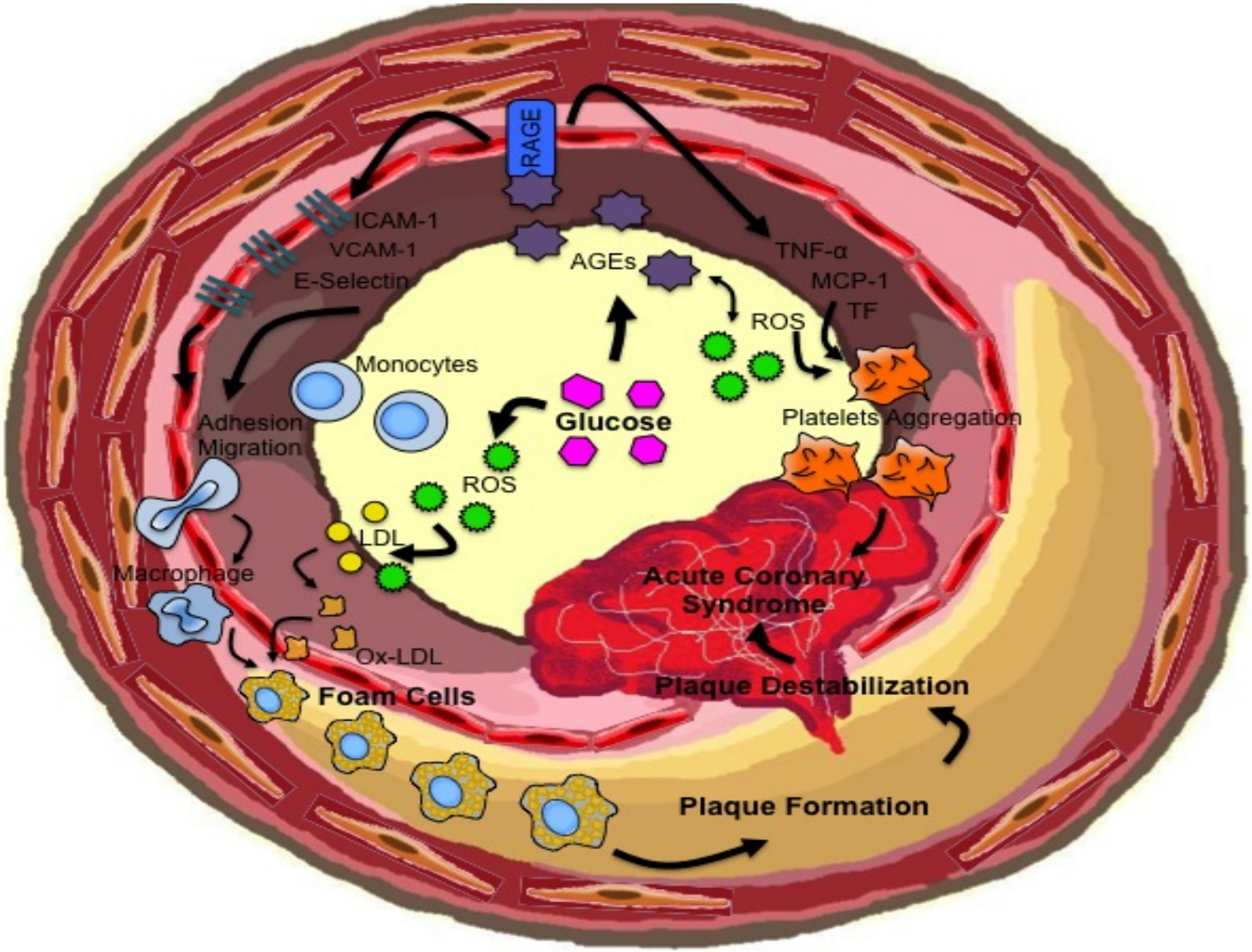



NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt


Lumen
Monocyte
Lymphocyte
Thrombus
LDL
Adhesion Molecules
MMPs
Collagenases
MPO
Th2
Endothelium
Macrophage
Cytokines
oxLDL
Foam Cell
Inf-γ
Th1
TLR
Calcium
SMC
Media
Adventitia
Vasa Vasorum
Jacek Jablonowski


Smooth Muscle Cell
Endothelial Cell
Anti-LDL
Anti-oxLDL
Anti-ApoB
Anti-PC
Plasma Cell
Germinal Center
LDL-Reactive B-Cells
LDL
B-Cell Help
IFNγ
T-Cell
Scavenger Receptor
Foam Cell
APC
Costimulation
Proliferation
TCR
ApoB100 Peptide
MHC II
LDL-Reactive T-Cells


Activated Platelets
B Cell
CD40L
MRP-8/14
TLR2/4
MyD88
PSGL
Monocyte
CCR2
LDL
MTX
IL-1 inhibitor
NLRP3
NFkB
IL-1
INFLAMMATION
PD-L1/2
LPA2 inhibitor
NFkB inhibitor
anti-oxidants
oxLDL
Th1 cell
APC
INFLAMMASOME
CD40/CD40L
CD30
IFN-γ
IL-12
IL-6
TNF
Caspase
IL-1β
IL-1Ra
IL-6/TNF inhibitor
VCAM-1
Macrophage
M-CSF
Nefrin-1
MCP-1
Histamine
IFN-γ
IL-6
Mast Cell
Foam Cell
IL-10
TGF-B
Treg
Necrotic Core

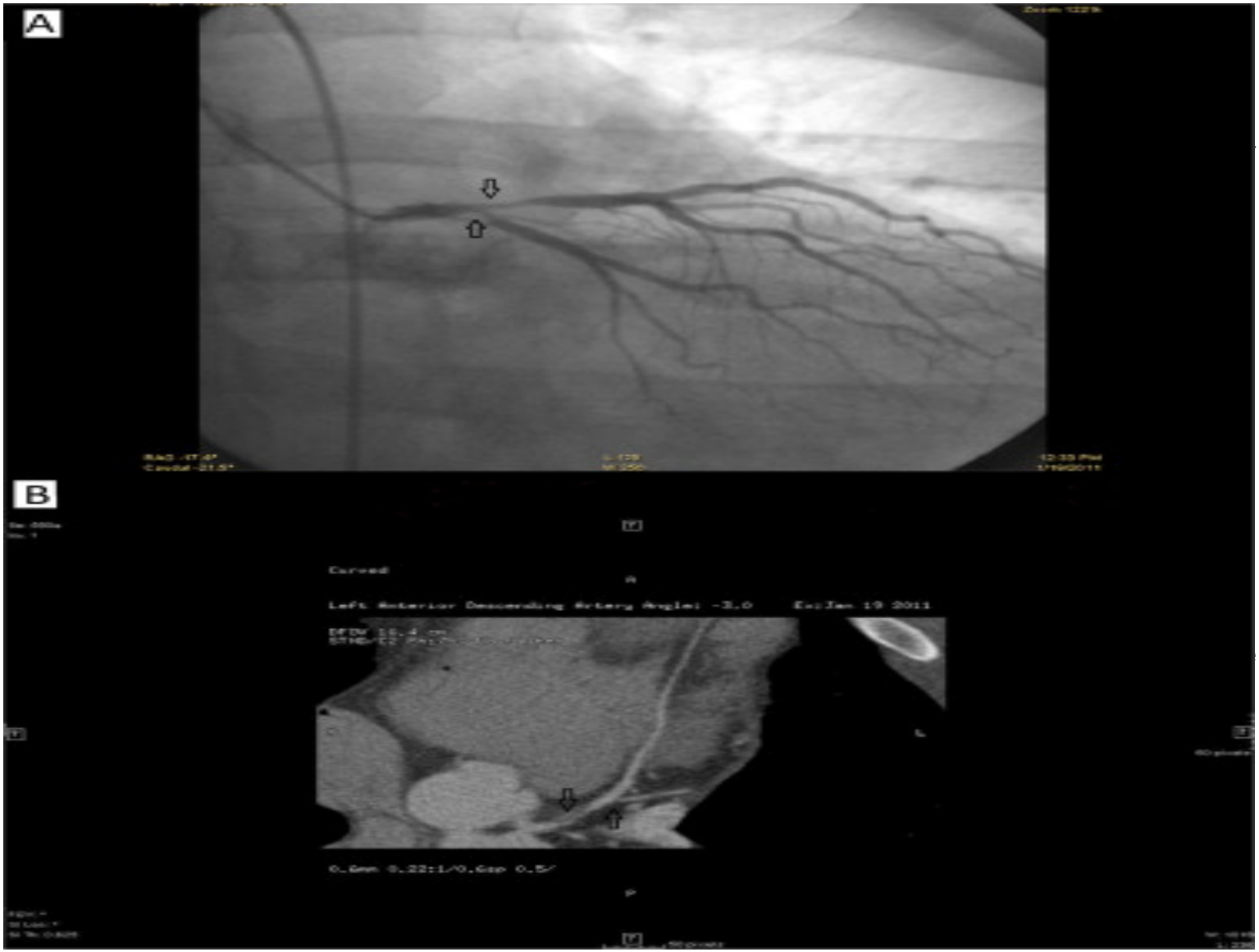

RAGE
ICAM-1
VCAM-1
E-Selectin
AGEs
TNF-α
MCP-1
TF
ROS
Monocytes
Glucose
Adhesion
Migration
Platelets Aggregation
ROS
LDL
Macrophage
Acute Coronary
Syndrome
Ox-LDL
Foam Cells
Plaque Destabilization
Plaque Formation

Case report

A 21-year-old male college student felt heaviness in his chest after walking a slight incline on campus. He was extremely short of breath, and collapsed on a nearby sofa to rest. He was rushed to the hospital where diagnostic tests [electrocardiogram (ECG), chest X-ray, and cardiac enzymes] did not reveal any acute pathology. Vital signs showed elevated blood pressure (BP) of 151/99 mmHg, pulse of 97 beats/minute (bpm), respirations of 20/minute, temperature of 36.6 °C, and oxygen saturation of 98%. The patient was not in acute distress, and his heart showed a regular rate and rhythm without murmurs, S3 or S4. His lungs were clear to auscultation, and the chest discomfort was not reproducible. He was of obese stature, weighing 126 kg and 183 cm tall (BMI 39.7). The patient's extremities were well perfused. He had a 3 pack-year smoking history and a family history of CHD, including his maternal aunt and great grandparents. The clinical diagnosis was stable angina, and the patient was discharged home following short observation. Follow-up laboratory work revealed some insulin resistance and mild dyslipidemia; LDL 78 mg/dL, HDL 30 mg/dL, triglycerides 199 mg/dL, and Lp(a) 68.3 mg/dL.

On follow-up, the patient underwent exercise stress testing; resting ECG showed normal sinus rhythm; vitals included BP of 136/84 mmHg and pulse of 81 bpm. During the peak phase of stress testing, BP reached 196/80 mmHg and pulse was 176 bpm; he exhibited chest pain, dyspnea, and lightheadedness. ECG changes showed nonsustained ventricular tachycardia. During the recovery phase, the patient's chest pain and dyspnea decreased. ST segment depression was shown in V5 and V6, and T wave inversion was shown in aVL. The remaining recovery phase was unremarkable with normalization of the ECG.

The patient underwent echocardiography, which showed mild concentric left ventricular hypertrophy. Computed coronary tomography angiography (CTA) revealed a large soft plaque in the distal left main coronary artery (LMCA) extending into the left anterior descending coronary artery (LAD) (80–90% occluded) and the origin of the left circumflex coronary artery (LCX) (70–80% occluded). The patient subsequently underwent left cardiac catheterization and left ventriculography, which showed normal size and contractility of the left ventricle with an ejection fraction of 65%. The LMCA, LAD, LCX, and right coronary artery (RCA) were of medium diameter. The procedure showed RCA dominance. There was 70% discrete stenosis in the distal LMCA, an 80% long lesion in the proximal LAD, and 70% discrete ostial stenosis in the proximal LCX (see Fig. 1). Due to LMCA involvement and his progressive anginal symptoms, the patient underwent coronary bypass surgery in addition to optimal medical therapy and strict risk factor reduction. The surgery performed was a two-vessel coronary bypass procedure, with left internal mammary artery graft to the LAD and aortocoronary left radial artery graft to the lateral

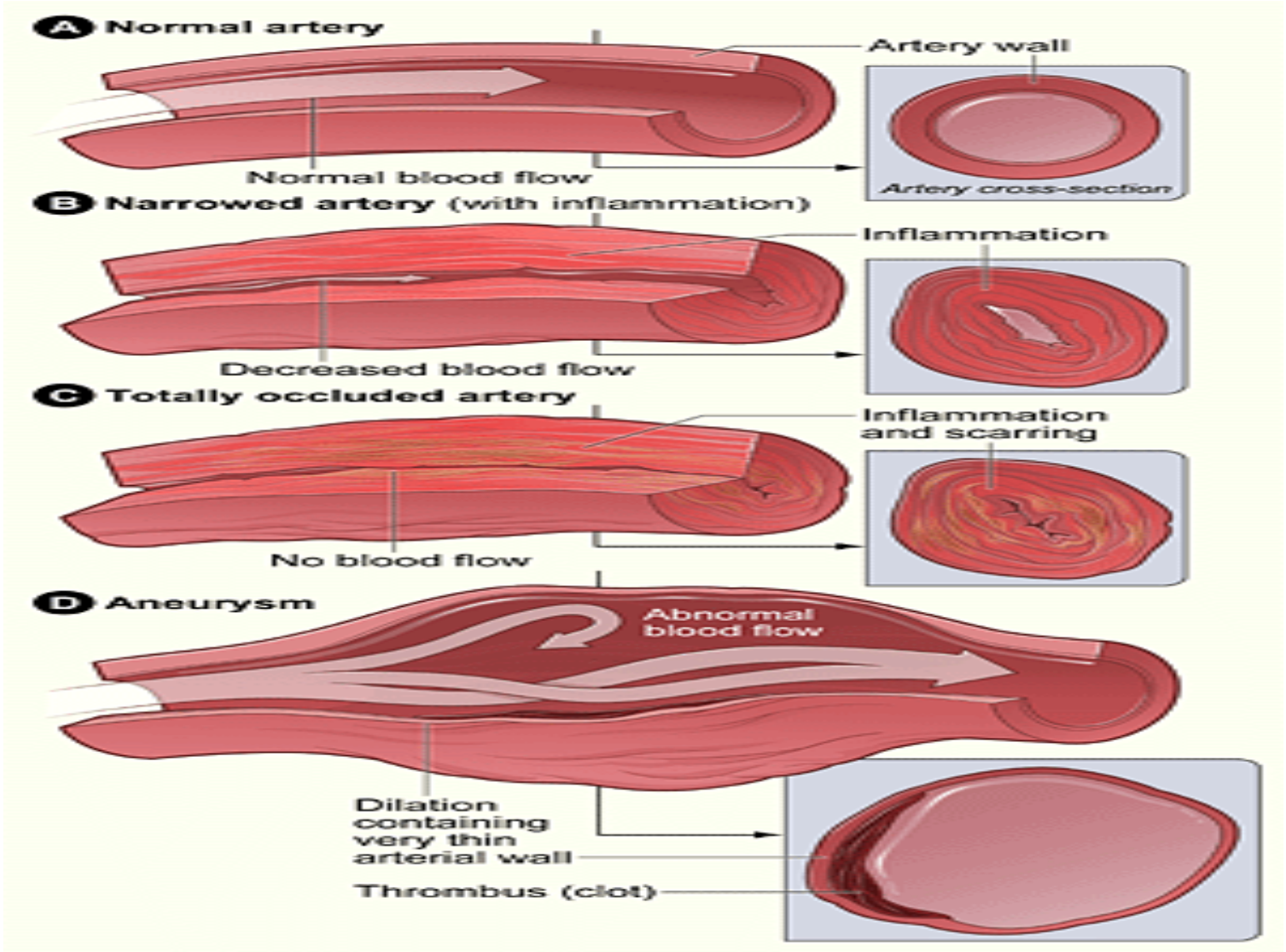

A
B
Curved
Left Anterior Descending Artery Angle: -3.0
Ex:Jan 19 2011

PATHOPHYSIOLOGY AND PATHOGENESIS of Vasculitis

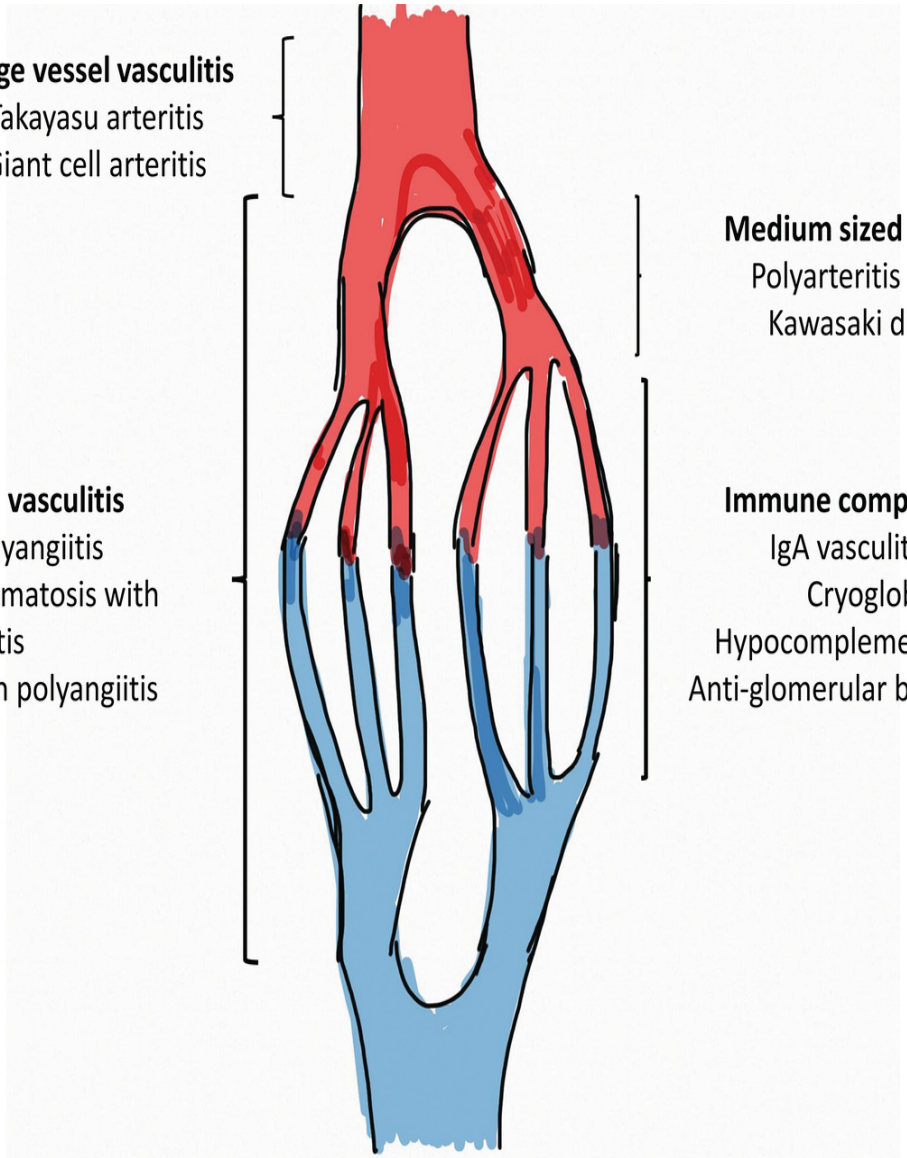
- *Generally, most of the vasculitic syndromes are assumed to be mediated at least in part by **immunopathogenic mechanisms** that occur in response to certain antigenic stimuli*

- *it is unknown why some individuals might develop vasculitis in response to certain antigenic stimuli,whereas others do not.*

- *It is likely that a number of **factors are involved in the ultimate expression of a vasculitic syndrome**. These include the genetic predisposition, environmental exposures, and the regulatory mechanisms associated with immune response to certain antigens.*


A Normal artery
Artery wall
Normal blood flow
Artery cross-section
B Narrowed artery (with inflammation)
Inflammation
Decreased blood flow
C Totally occluded artery
Inflammation and scarring
No blood flow
D Aneurysm
Abnormal blood flow
Dilation containing very thin arterial wall
Thrombus (clot)

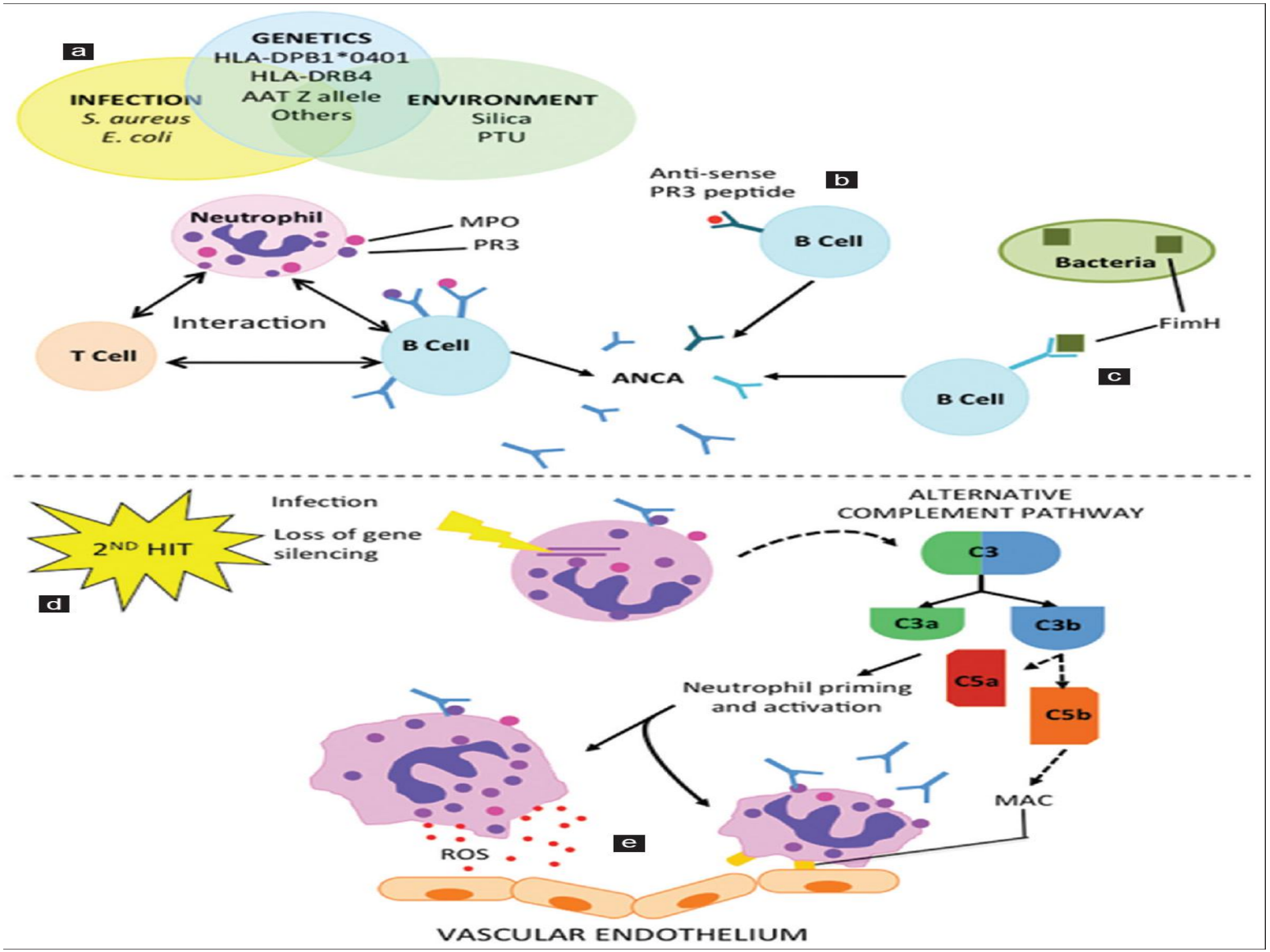
Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis

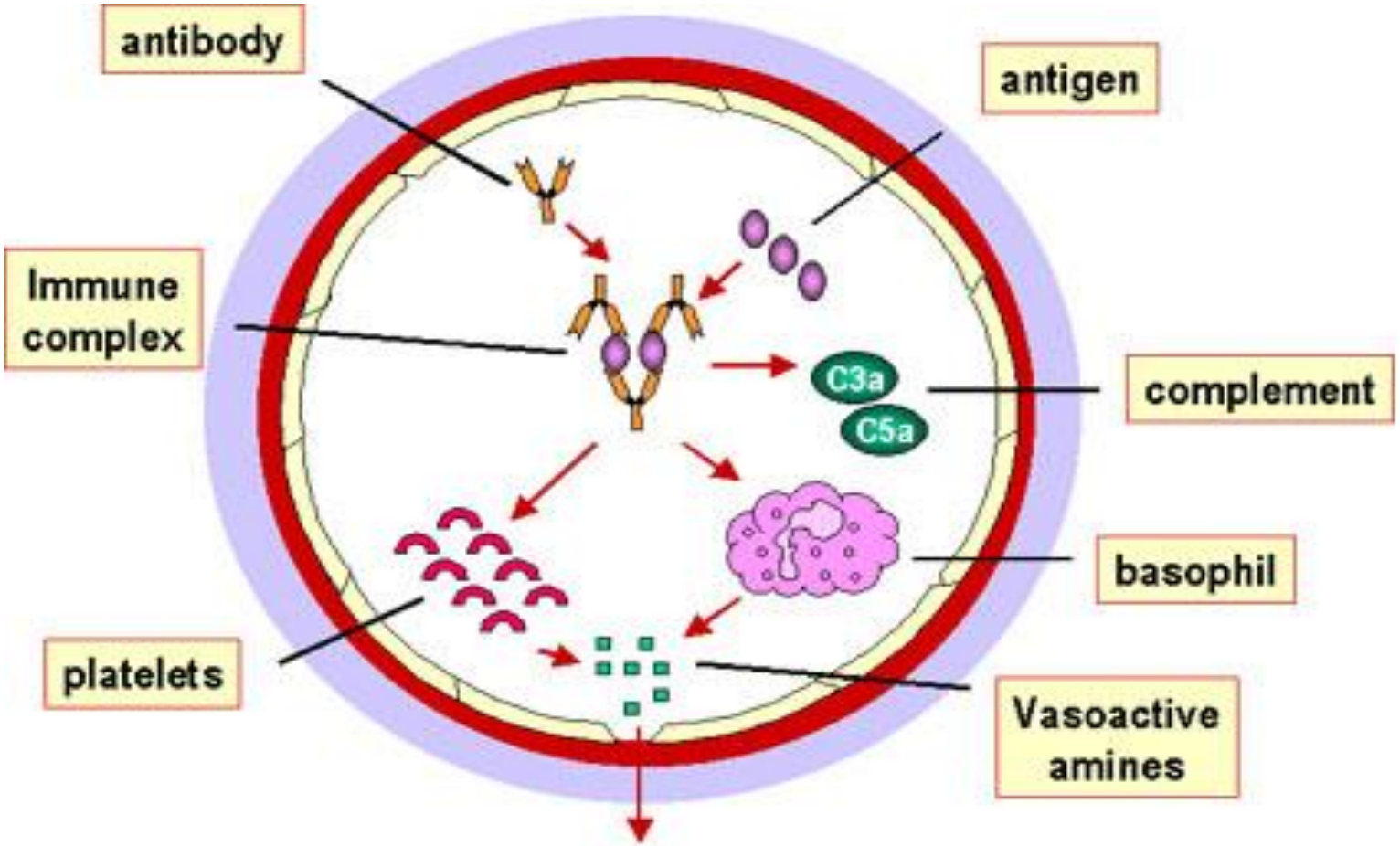


Medium sized vasculitis
Polyarteritis nodosa
Kawasaki disease

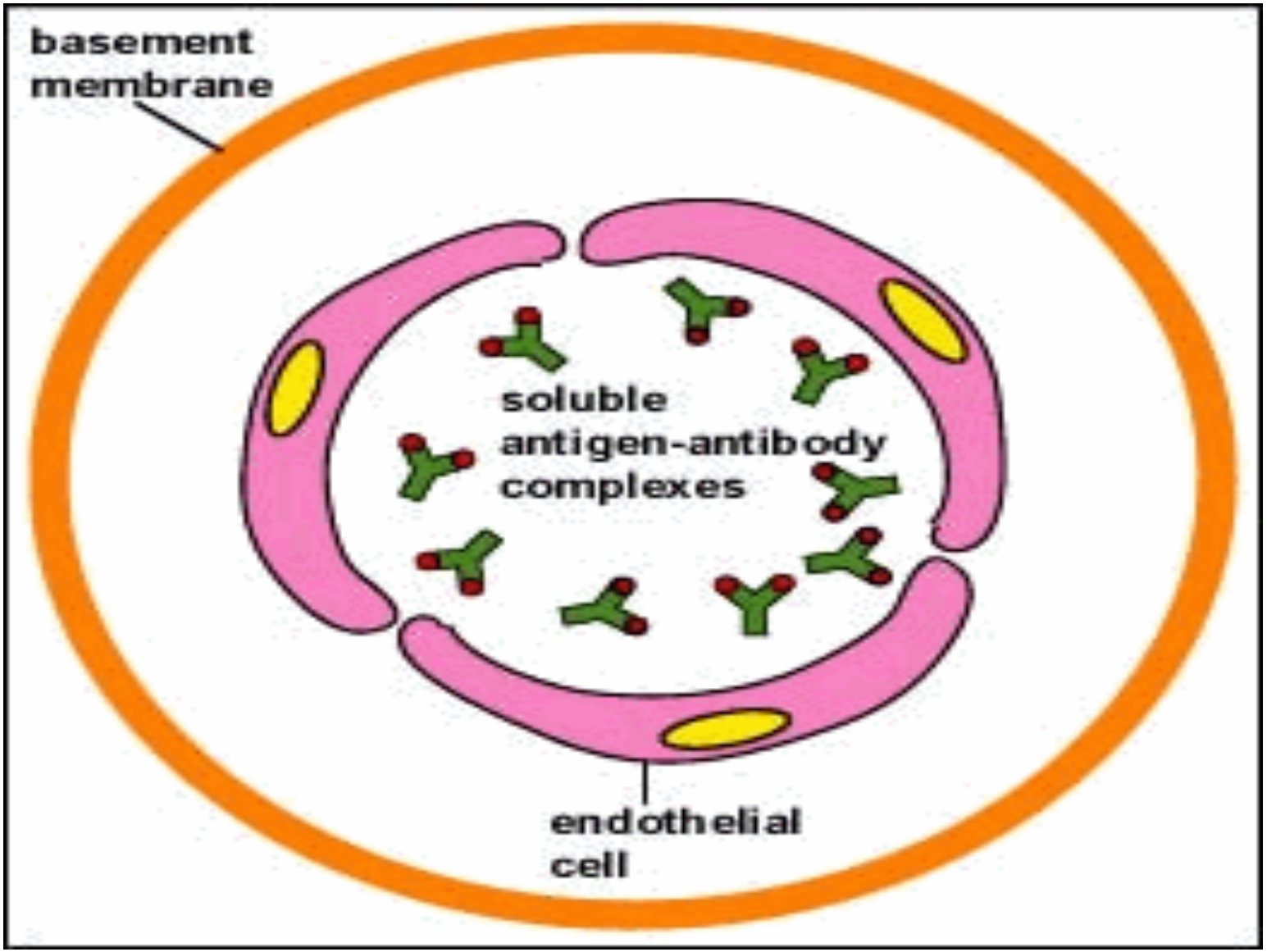
ANCA-associated vasculitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis

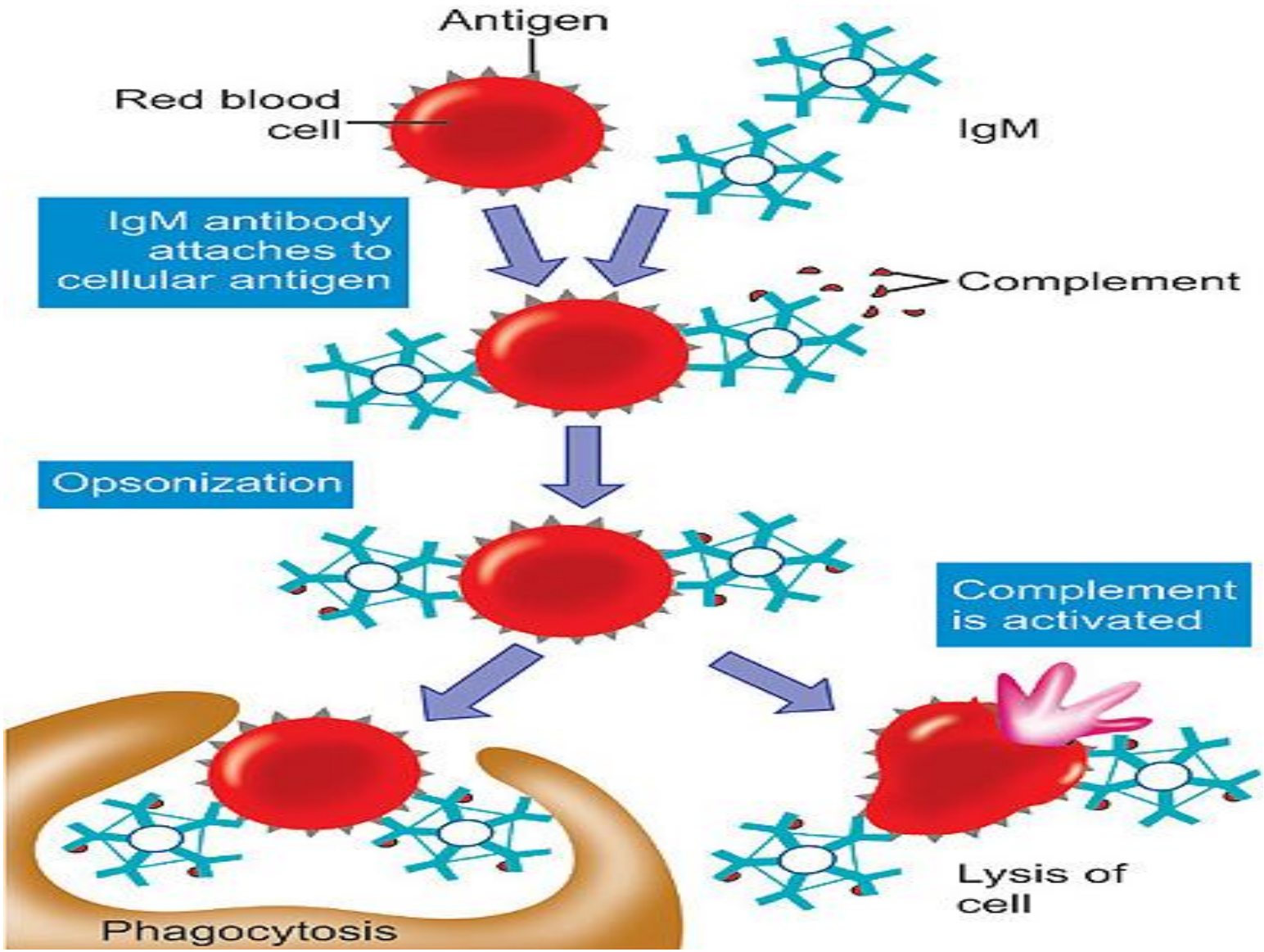
Immune complex small vessel vasculitis
IgA vasculitis (Henoch-Schonlein)
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis
Anti-glomerular basement membrane disease

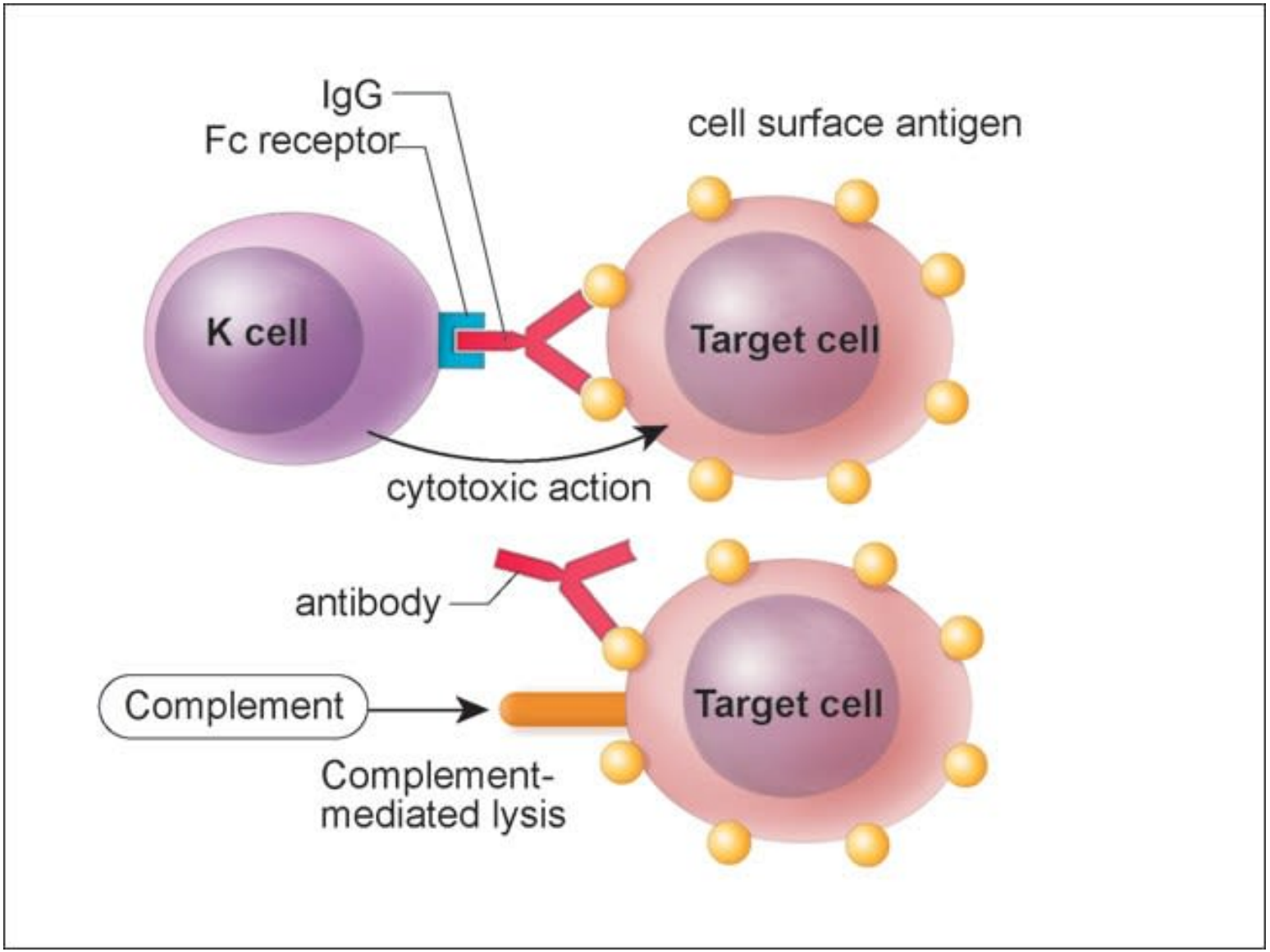

a
GENETICS
HLA-DPB1*0401
HLA-DRB4
AAT Z allele
Others
INFECTION
S. aureus
E. coli
ENVIRONMENT
Silica
PTU
Anti-sense
PR3 peptide
b
Neutrophil
MPO
PR3
B Cell
Bacteria
Interaction
T Cell
B Cell
FimH
ANCA
B Cell
c
2ND HIT
Infection
Loss of gene
silencing
d
ALTERNATIVE
COMPLEMENT PATHWAY
C3
C3a
C3b
C5a
C5b
Neutrophil priming
and activation
MAC
ROS
e
VASCULAR ENDOTHELIUM


antibody
antigen
Immune complex
C3a
C5a
complement
basophil
platelets
Vasoactive amines

RCH


basement membrane
soluble antigen-antibody complexes
endothelial cell

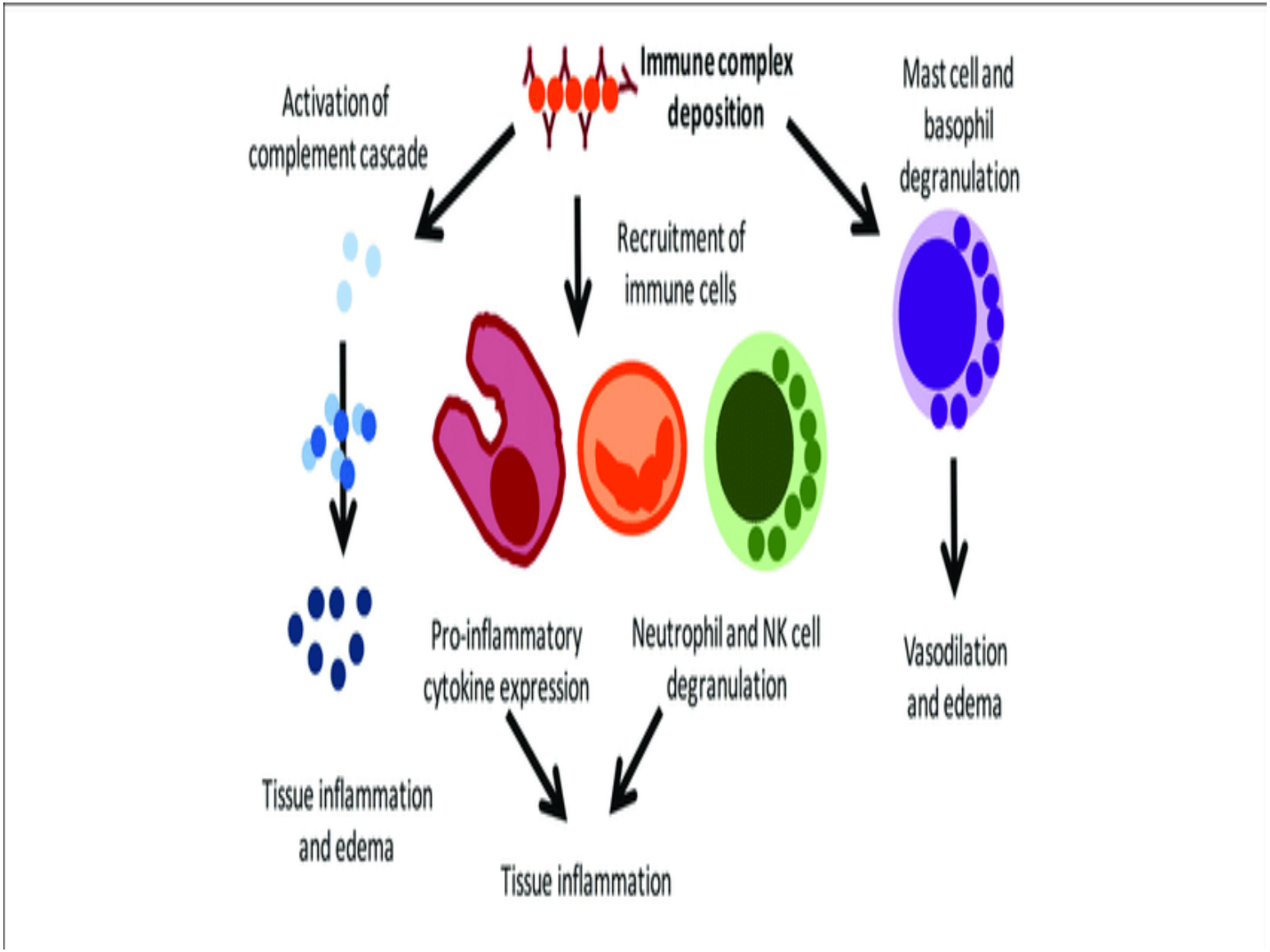

Antigen
Red blood cell
IgM
IgM antibody attaches to cellular antigen
Complement
Opsonization
Complement is activated
Phagocytosis
Lysis of cell


IgG
Fc receptor
cell surface antigen
K cell
Target cell
cytotoxic action
antibody
Complement
Target cell
Complement-
mediated lysis

Type III Hypersensitivity

Antigens Associated with Immune Complex Disorders

ANTIGEN	CLINICAL MANIFESTATION
EXOGENOUS	
Infectious agents:	
Bacteria: *Y. enterocolitica*	Arthritis
Streptococci	GN, Infective endocarditis
T. pallidum	Glomerulonephritis
Viruses: Hep. B, CMV	Polyarteritis nodosa
Parasites: *Plasmodium*	Glomerulonephritis
Schistosoma	
Fungi: *Actinomycetes*	Farmer's lung
ENDOGENOUS	
Nuclear antigens	SLE
Immunoglobulins	Rheumatoid arthritis
Tumor antigens	Glomerulonephritis


Immune complex deposition
Activation of complement cascade
Recruitment of immune cells
Mast cell and basophil degranulation
Pro-inflammatory cytokine expression
Neutrophil and NK cell degranulation
Vasodilation and edema
Tissue inflammation and edema
Tissue inflammation

Phases of immune complex disease

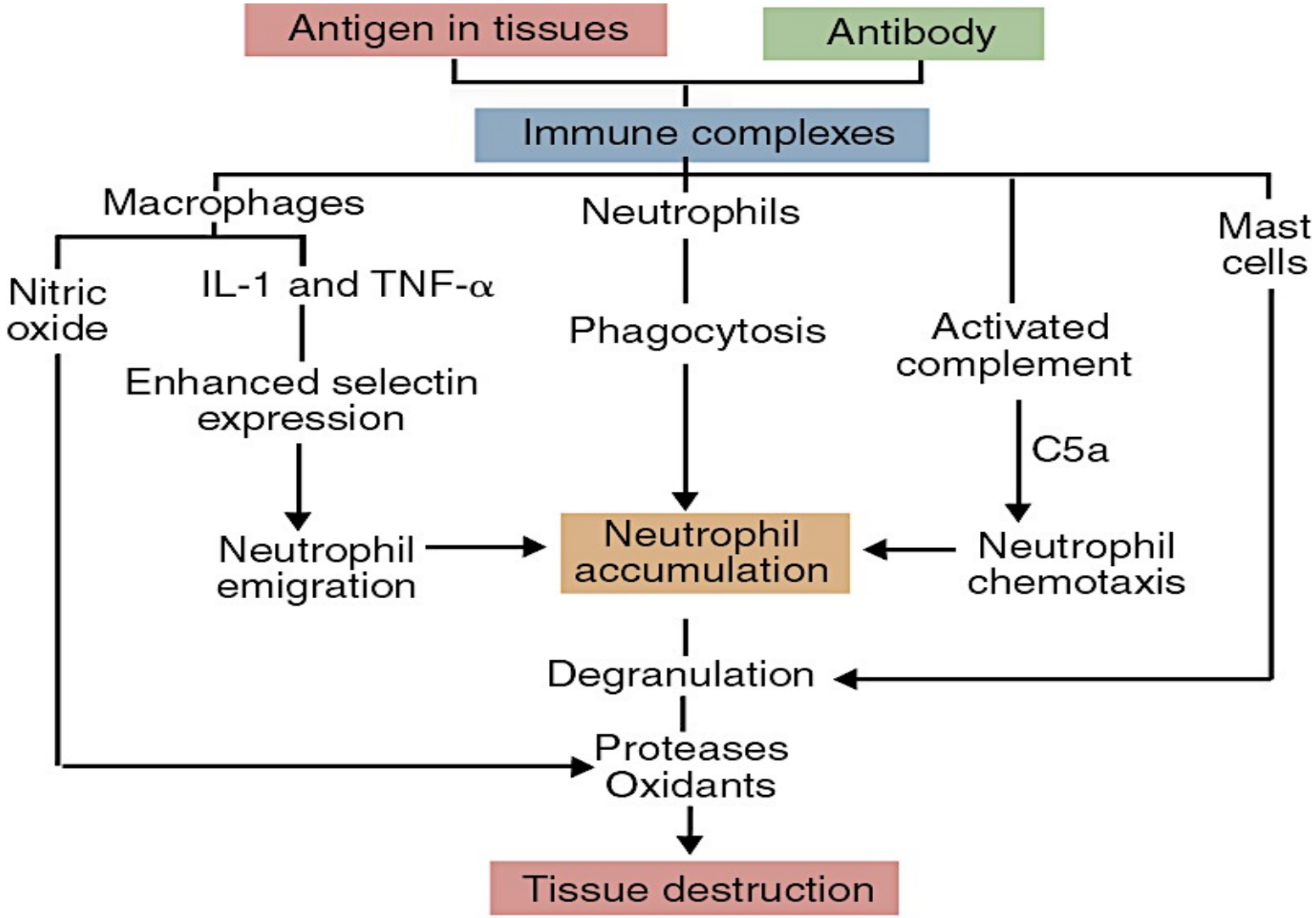
1. formation of AG-AB complexes in the blood circulation
2. deposition of the immune complexes in various tissues, thus initiating
3. an inflammatory reaction at the sites of immune complex deposition

Site of deposition:

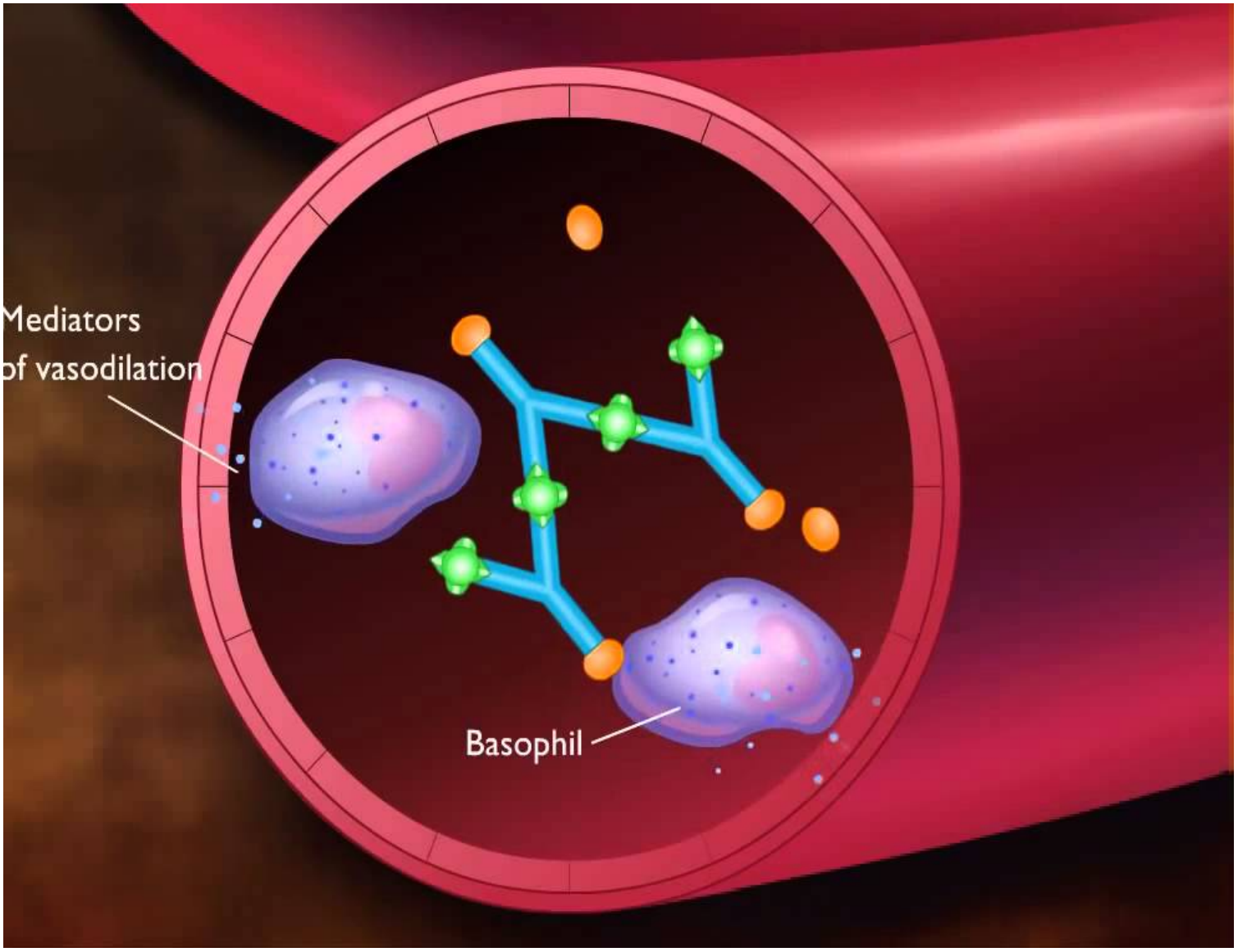
- Complexes accumulate in tissues where filtration of plasma occurs. This explains the high incidence of:
  - Glomerulonephritis (deposition in the kidney)
  - Vasculitis (deposition in the arteries)
  - Arthritis (deposition in the synovial joints)

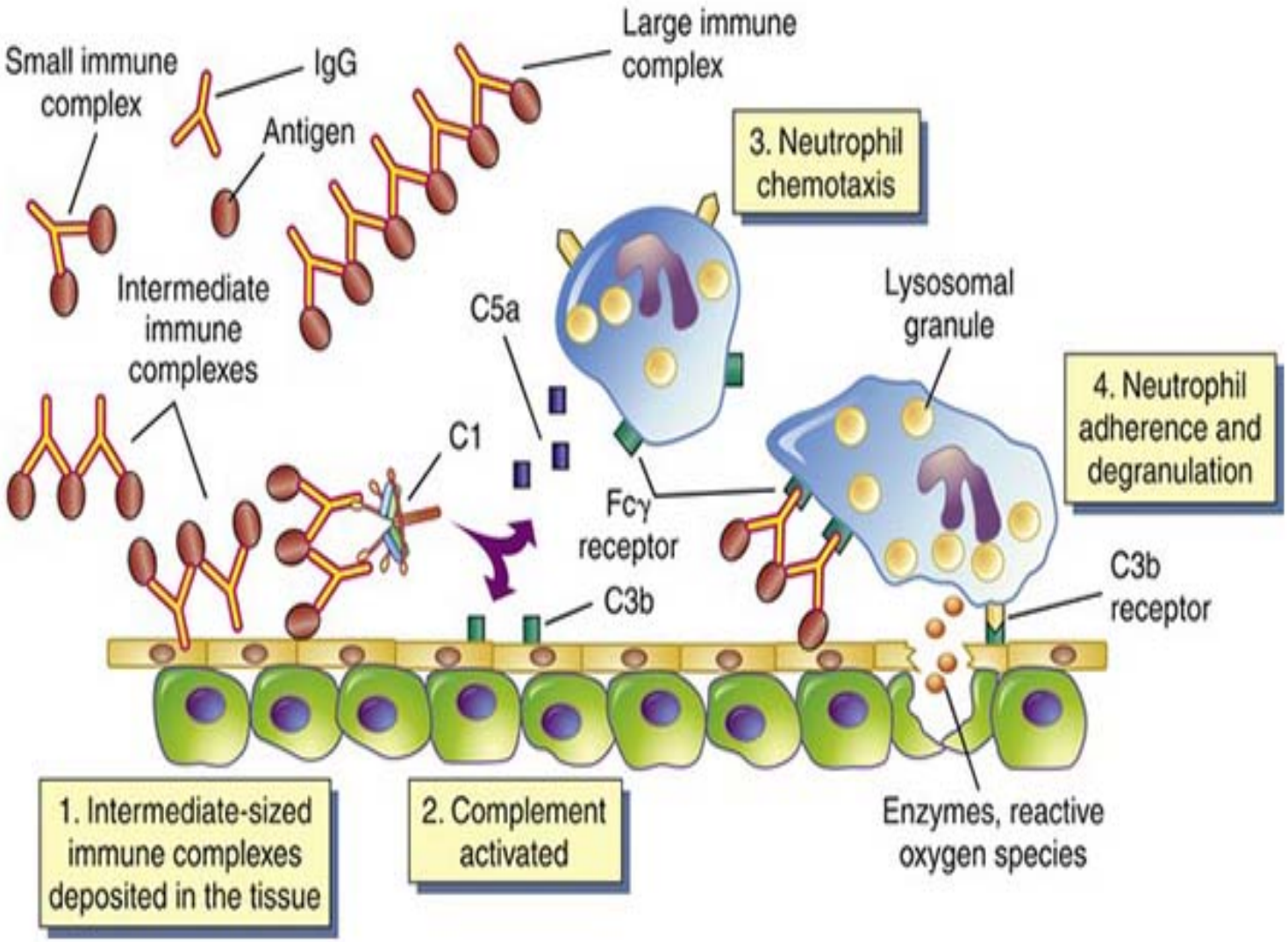
Examples of Human Immune Complex–Mediated Diseases

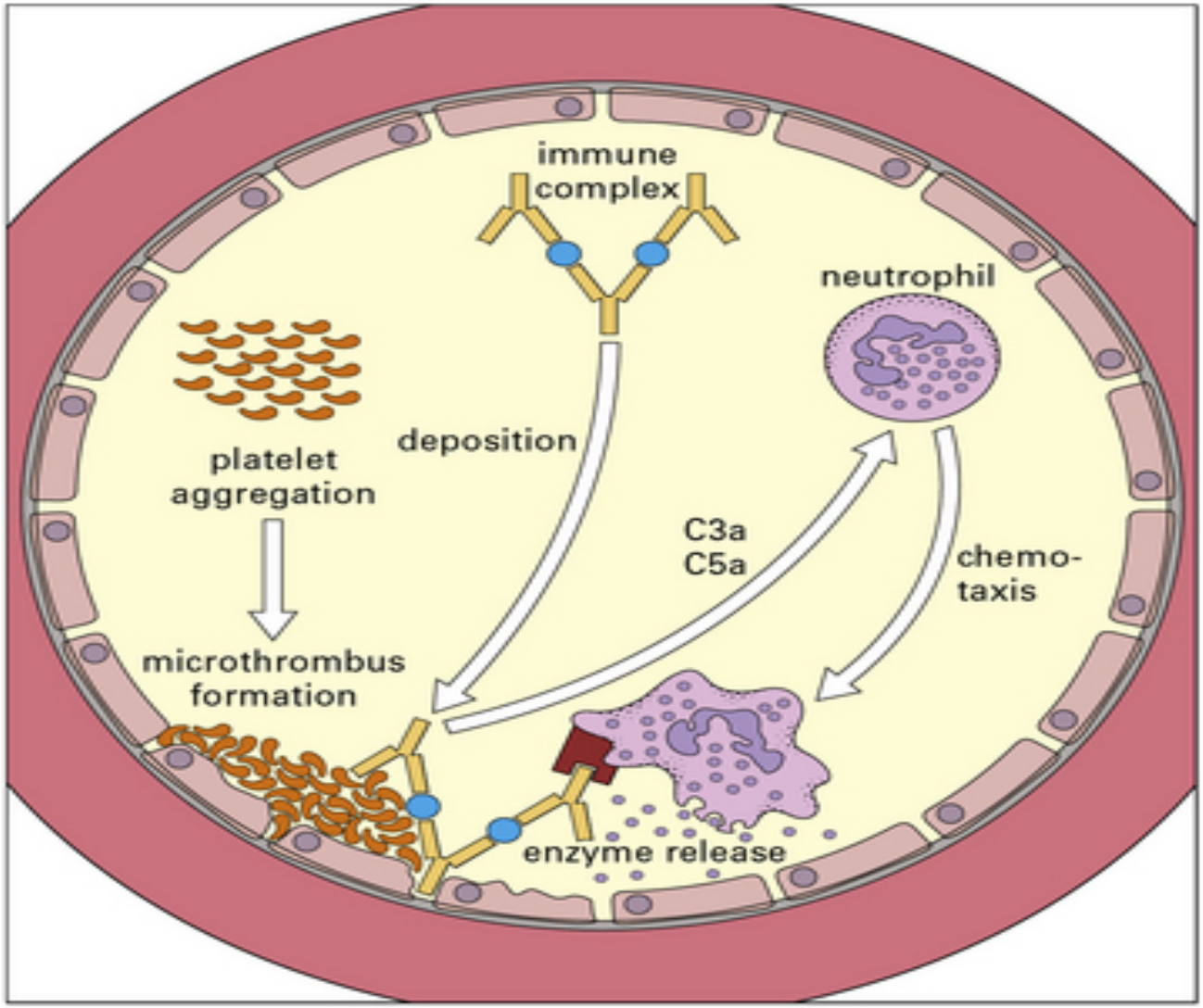
Disease	Antigen involved	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis,vasculitis, nephritis

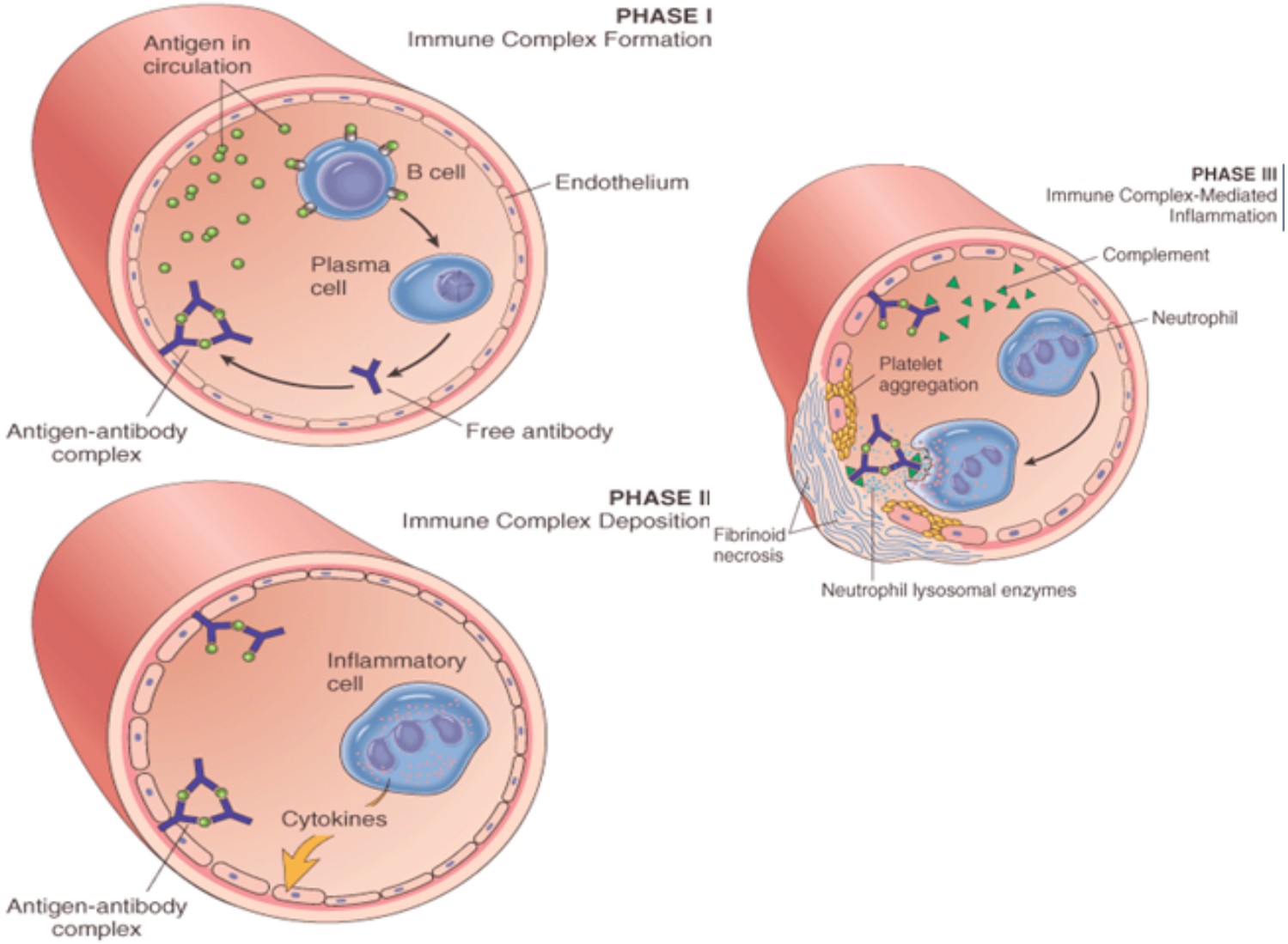


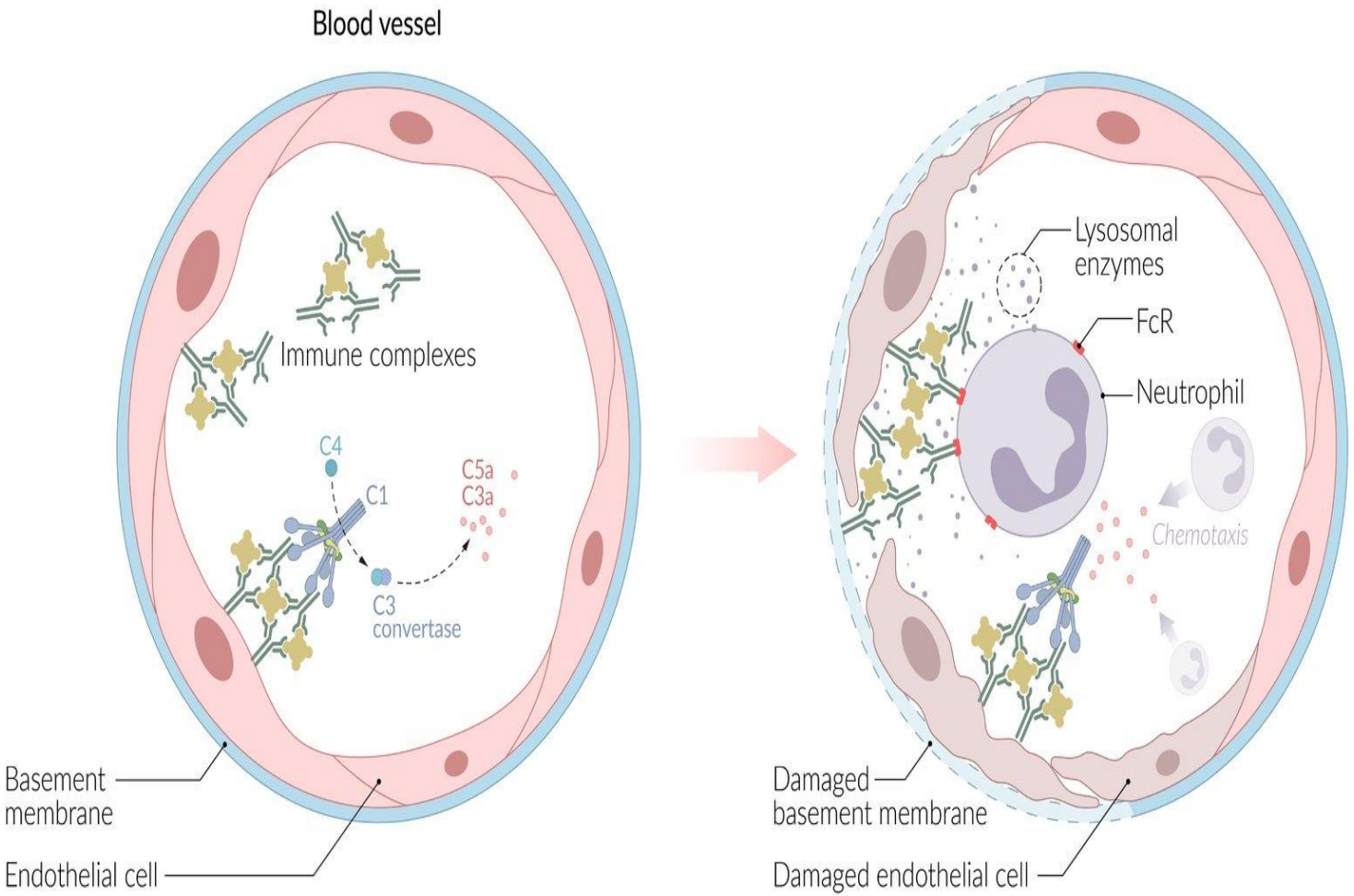
Tizard, Ian R. *Veterinary Immunology*. St. Louis, MO: Elsevier, 2013.

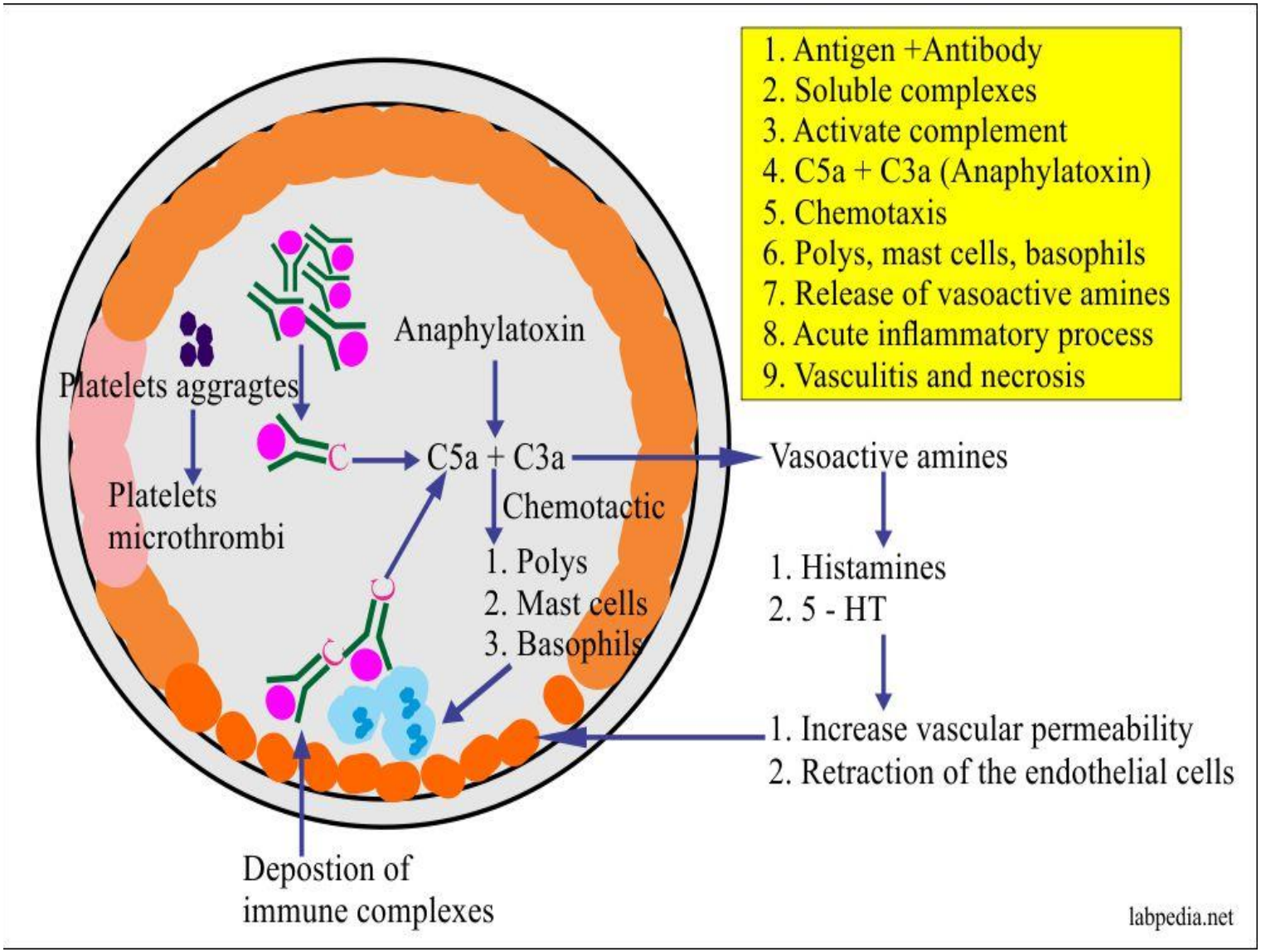

Mediators
of vasodilation
Basophil

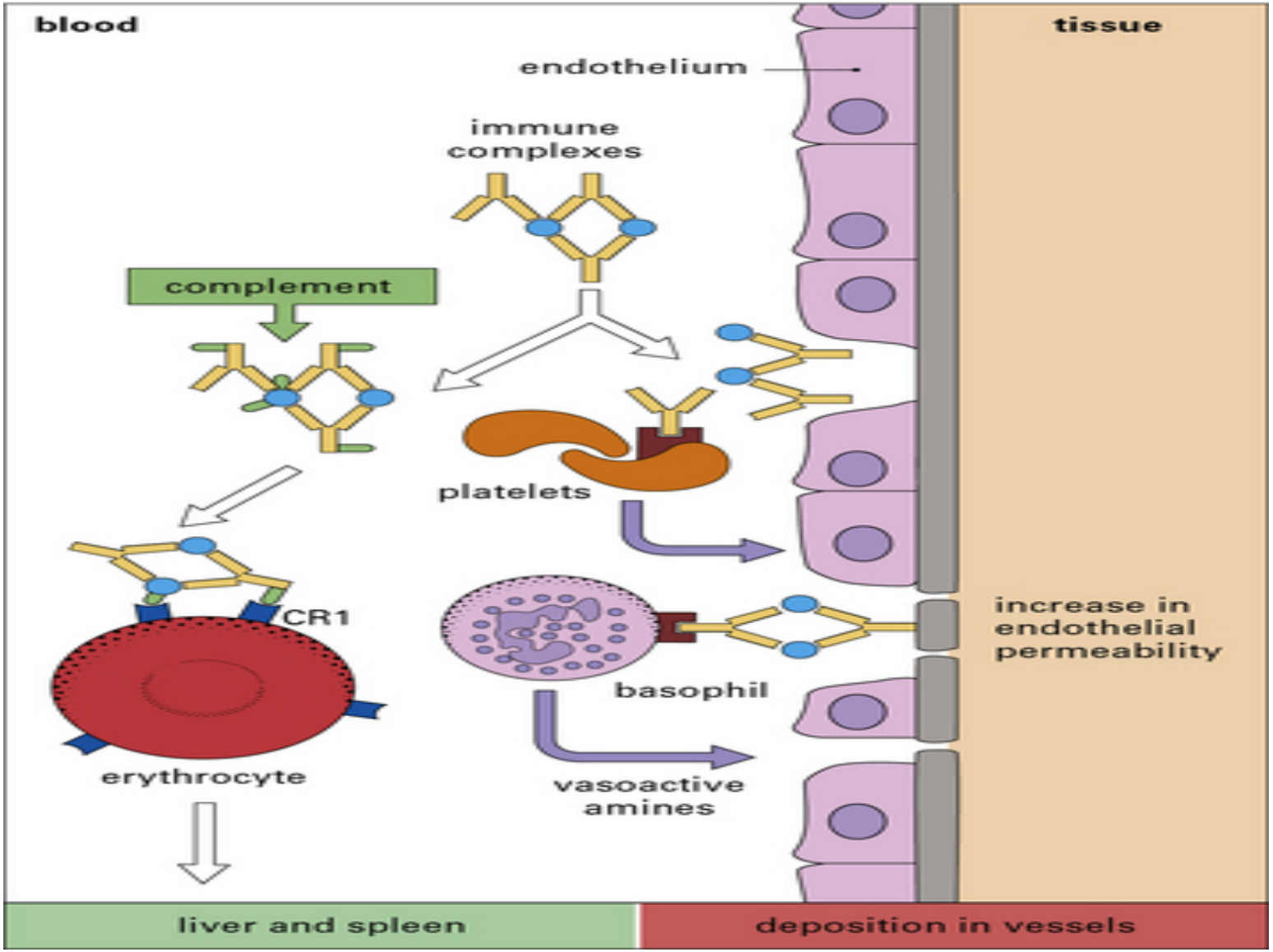

Small immune complex
IgG
Antigen
Large immune complex
3. Neutrophil chemotaxis
Intermediate immune complexes
C5a
Lysosomal granule
4. Neutrophil adherence and degranulation
C1
Fcγ receptor
C3b
C3b receptor
1. Intermediate-sized immune complexes deposited in the tissue
2. Complement activated
Enzymes, reactive oxygen species

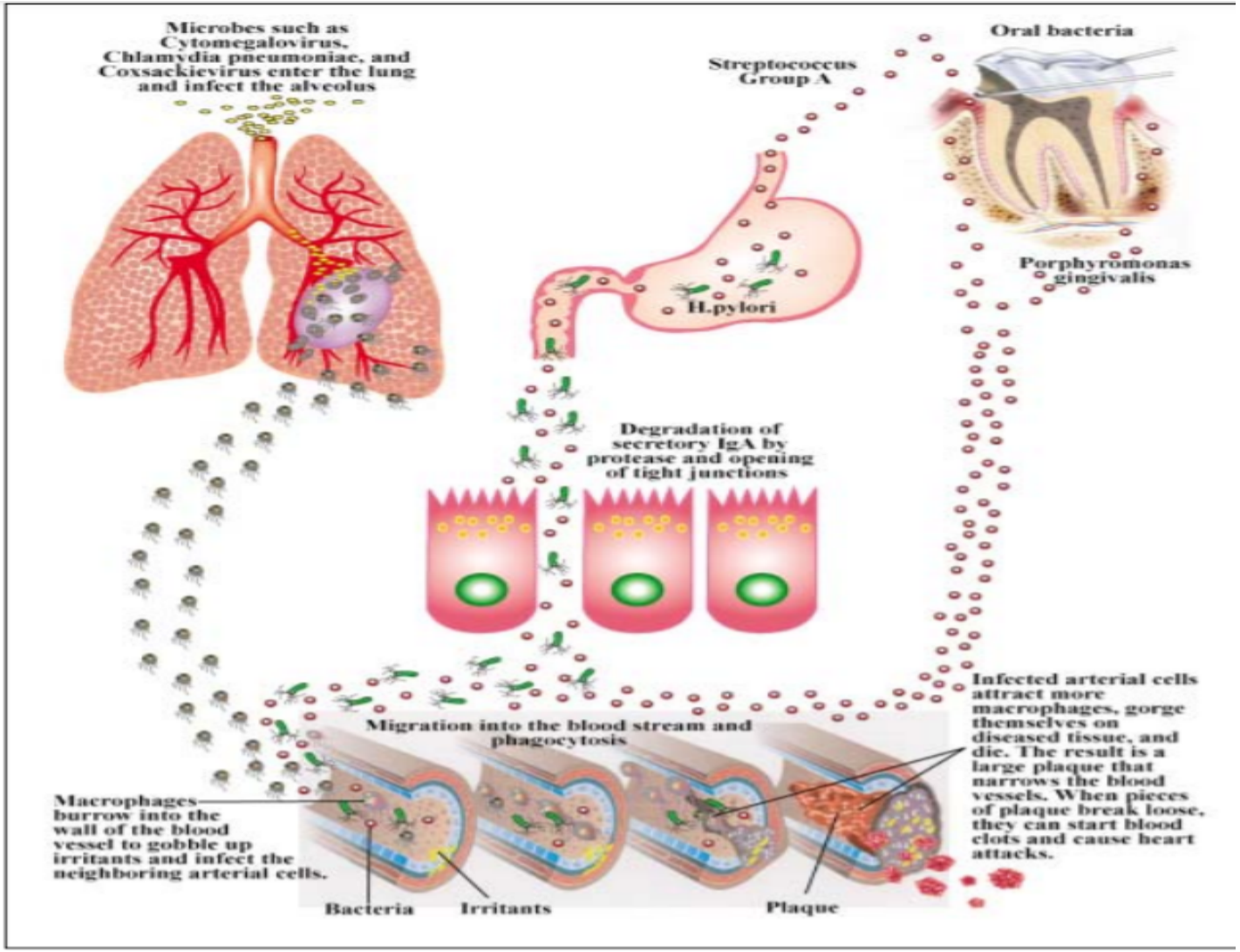

immune
complex
neutrophil
deposition
platelet
aggregation
C3a
C5a
chemo-
taxis
microthrombus
formation
enzyme release


PHASE I
Immune Complex Formation
Antigen in circulation
B cell
Endothelium
Plasma cell
Antigen-antibody complex
Free antibody
PHASE II
Immune Complex Deposition
Inflammatory cell
Cytokines
Antigen-antibody complex
PHASE III
Immune Complex-Mediated Inflammation
Complement
Neutrophil
Platelet aggregation
Fibrinoid necrosis
Neutrophil lysosomal enzymes

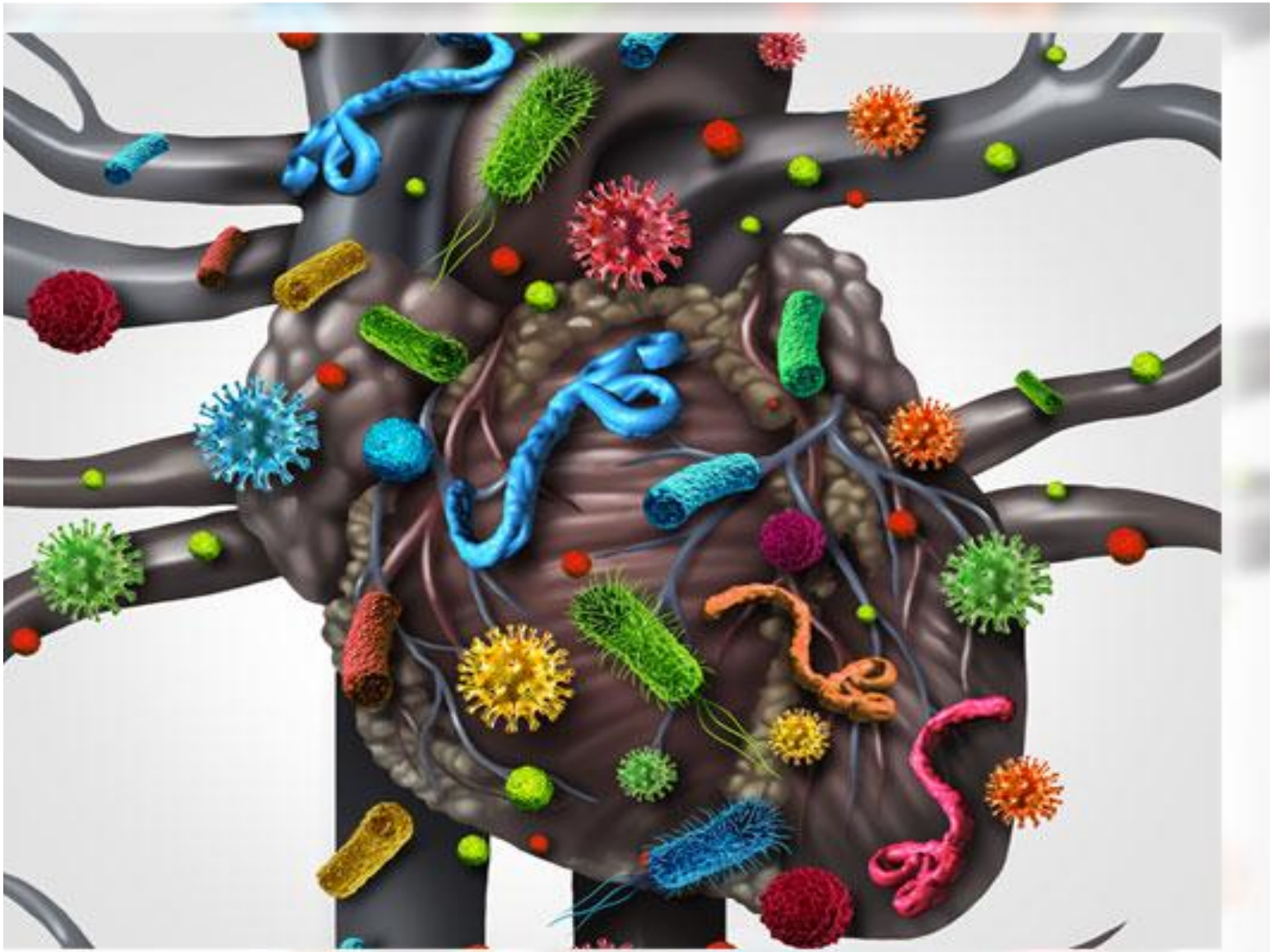

Blood vessel
Immune complexes
C4
C1
C5a
C3a
C3
convertase
Basement
membrane
Endothelial cell
Lysosomal
enzymes
FcR
Neutrophil
Chemotaxis
Damaged
basement membrane
Damaged endothelial cell


1. Antigen +Antibody
2. Soluble complexes
3. Activate complement
4. C5a + C3a (Anaphylatoxin)
5. Chemotaxis
6. Polys, mast cells, basophils
7. Release of vasoactive amines
8. Acute inflammatory process
9. Vasculitis and necrosis
Anaphylatoxin
Platelets aggragtes
Platelets microthrombi
C5a + C3a
Chemotactic
1. Polys
2. Mast cells
3. Basophils
Vasoactive amines
1. Histamines
2. 5 - HT
1. Increase vascular permeability
2. Retraction of the endothelial cells
Depostion of immune complexes
labpedia.net


blood
tissue
endothelium
immune complexes
complement
platelets
CR1
erythrocyte
basophil
increase in endothelial permeability
vasoactive amines
liver and spleen
deposition in vessels



[**F1**] The role of oral, gastrointestinal, and pulmonary pathogens in the induction of atherosclerosis, showing how a bacteria or a virus could set the stage for a heart attack.

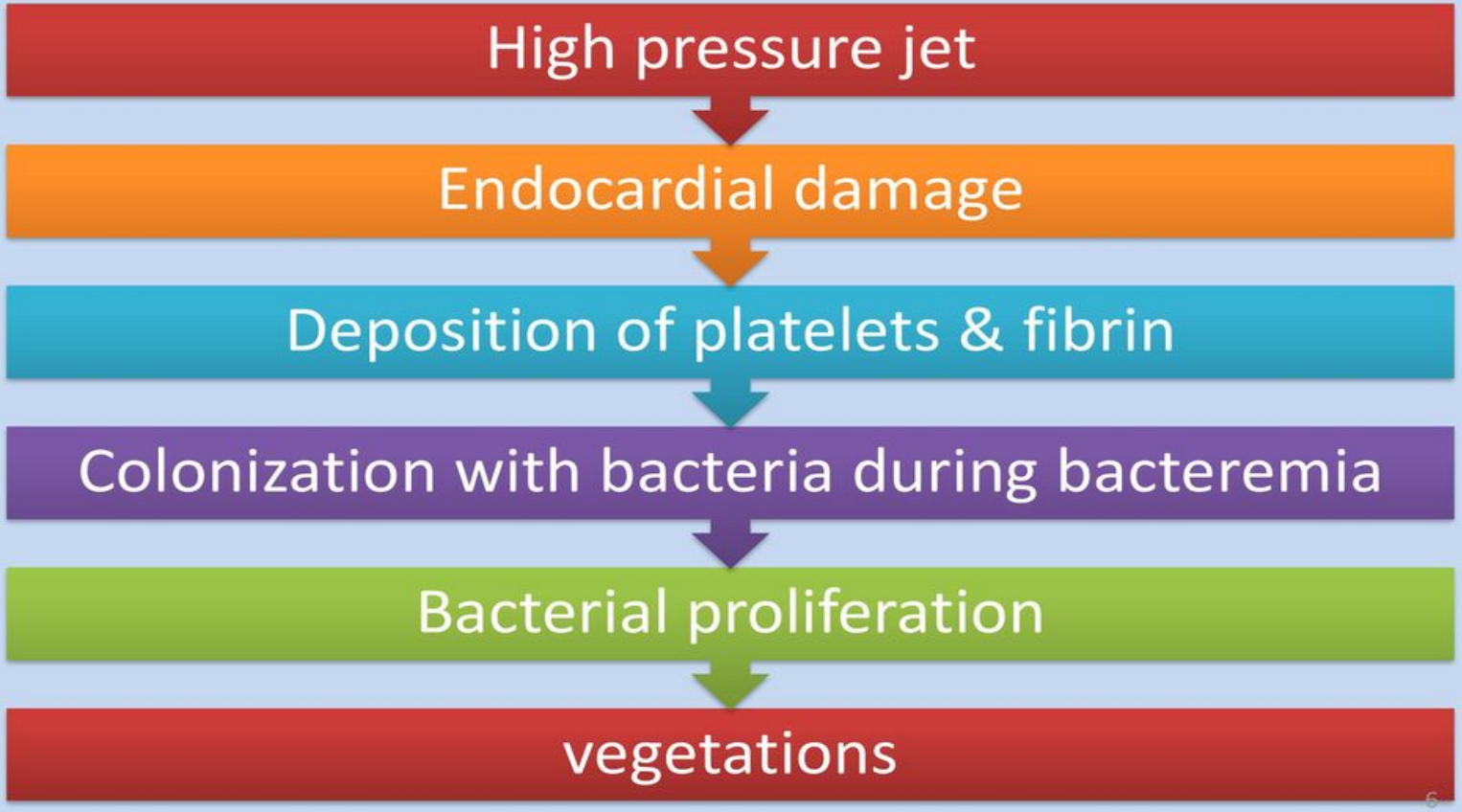


INFECTIVE ENDOCARDITIS: DEFINITION

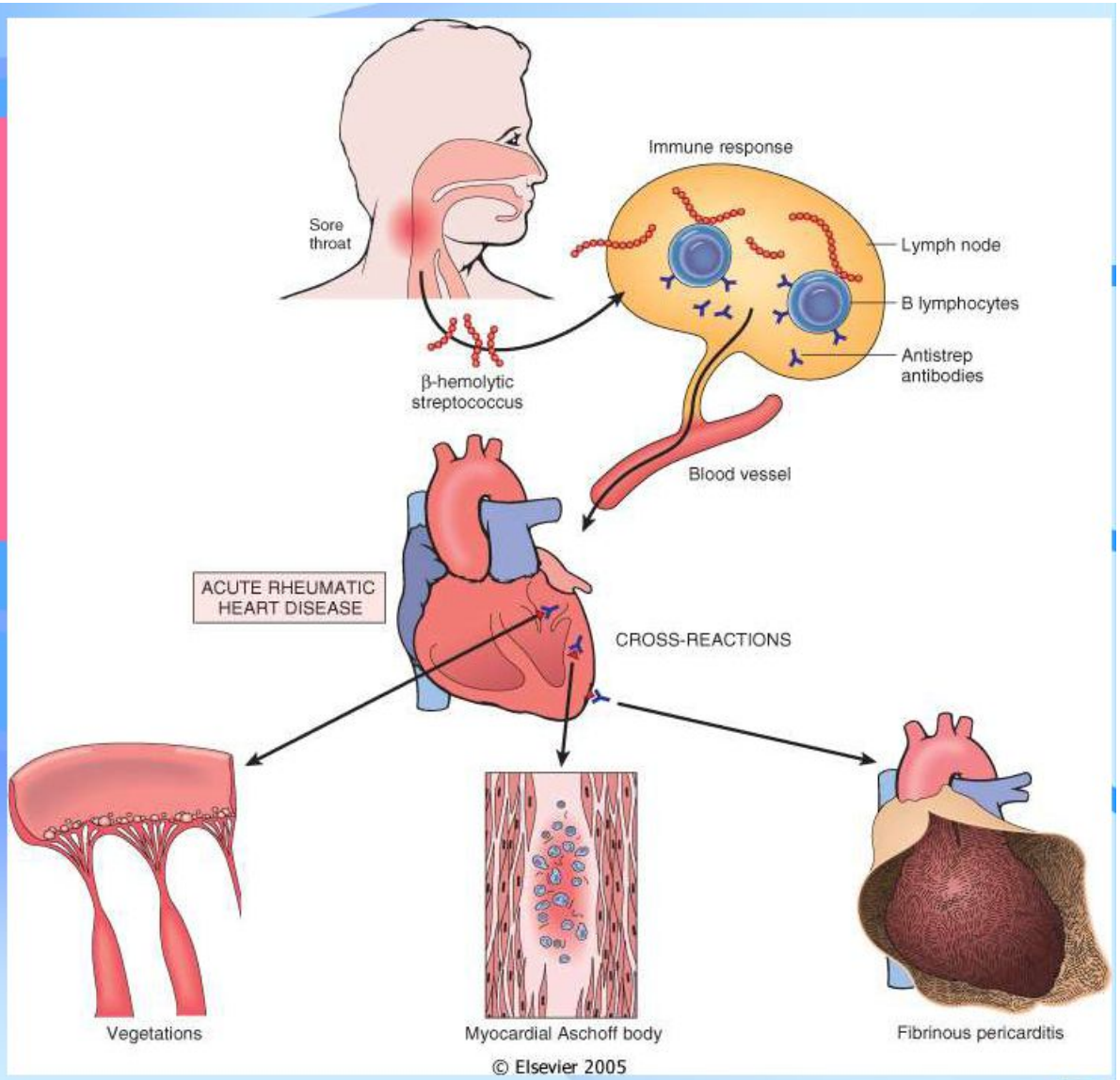
- Causative organism: bacteria, fungi, and rickettsiae

- Most frequent organisms: streptococci, staphylococci, enterococci, and fastidious gram-negative coccobacilli

INFECTIVE ENDOCARDITIS: PATHOGENESIS



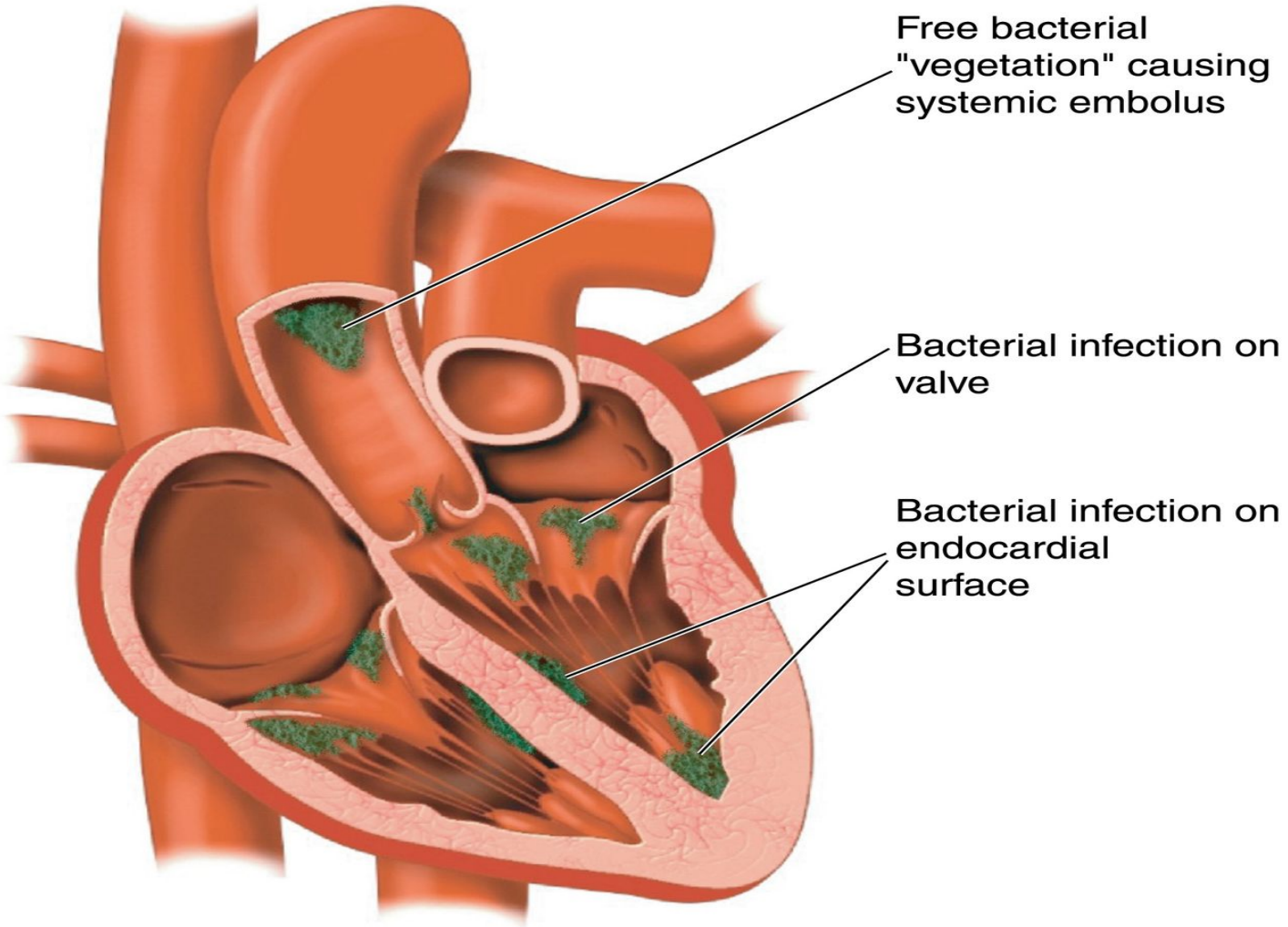
Pathologic sequence and key morphologic features of acute RHD

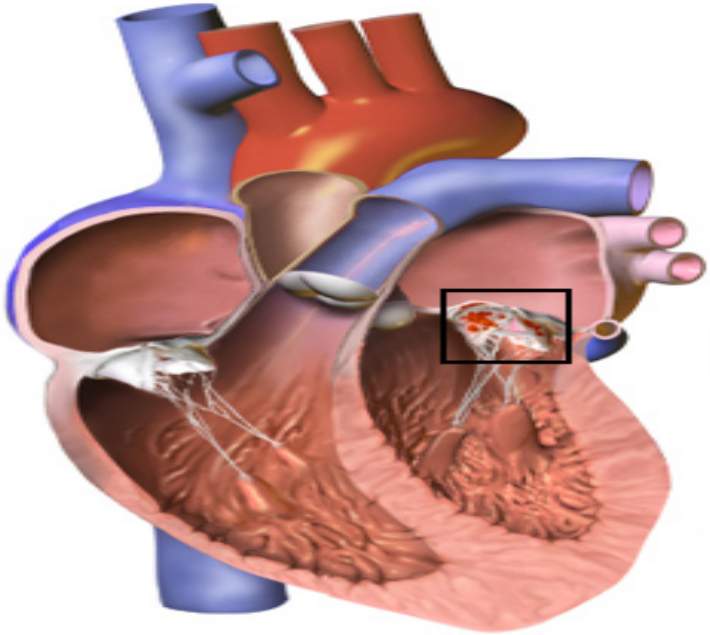


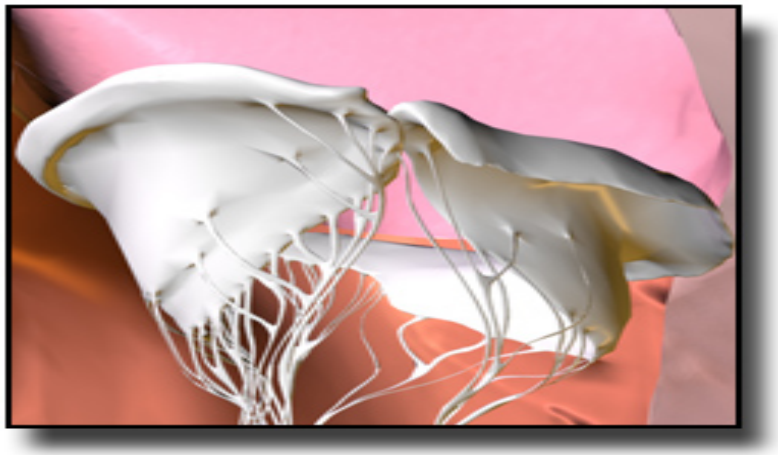
Rheumatic Fever:

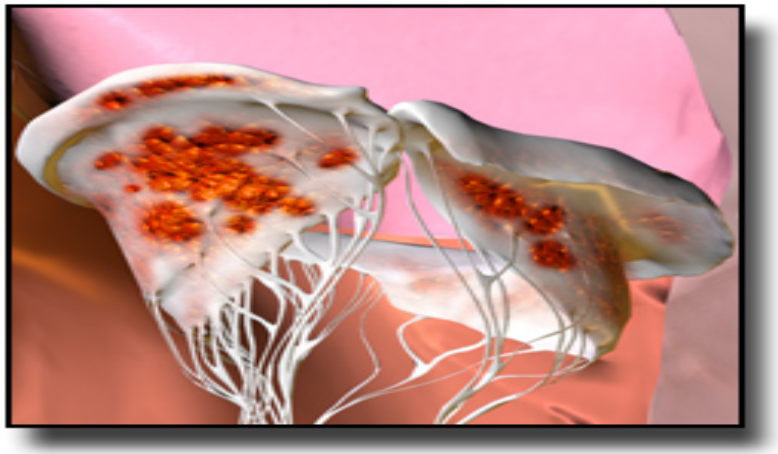
Definition:

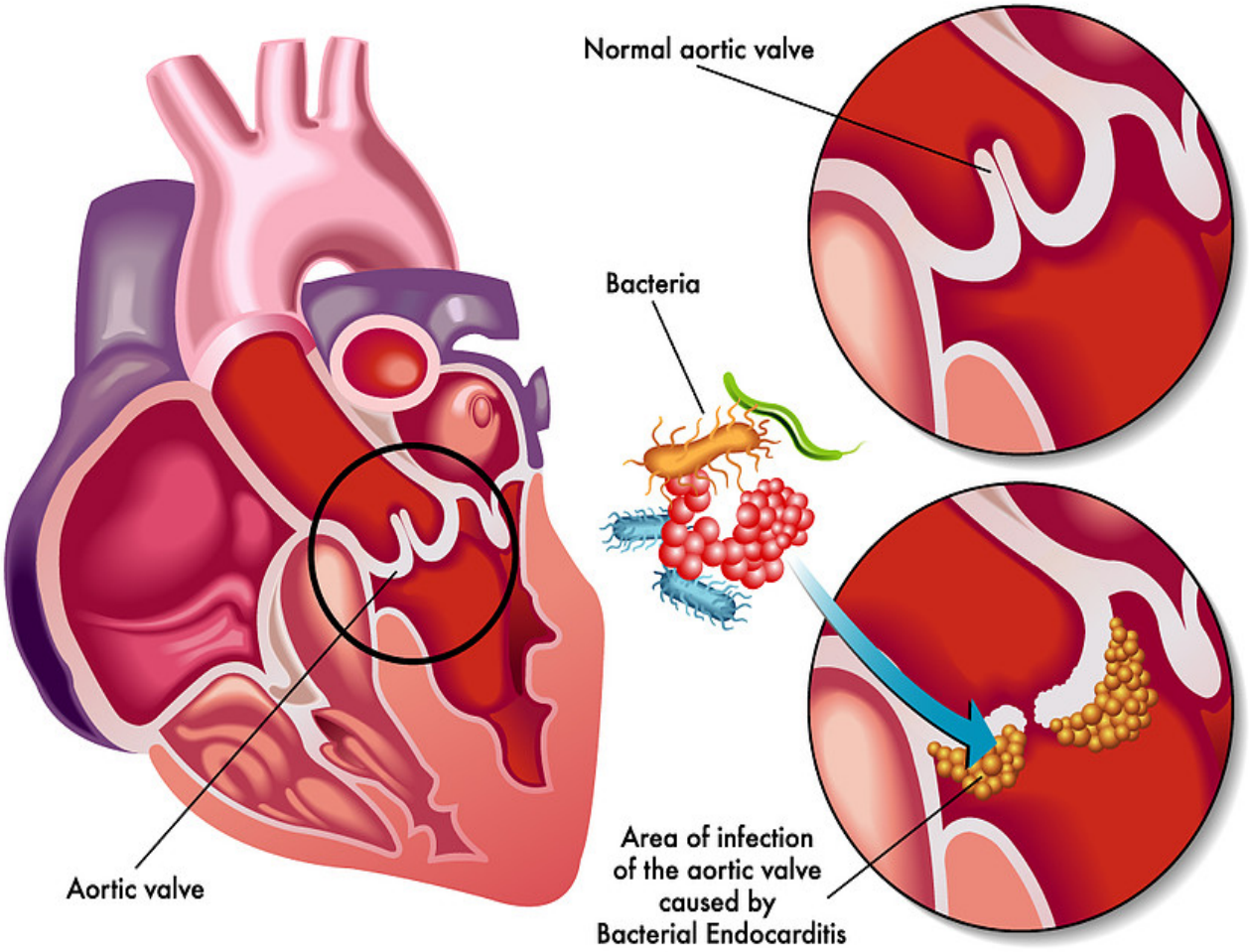
- Autoimmune
- Multisystem
- Inflammatory disorder
- Following group A, (ß-hemolytic) streptococcal pharyngitis.

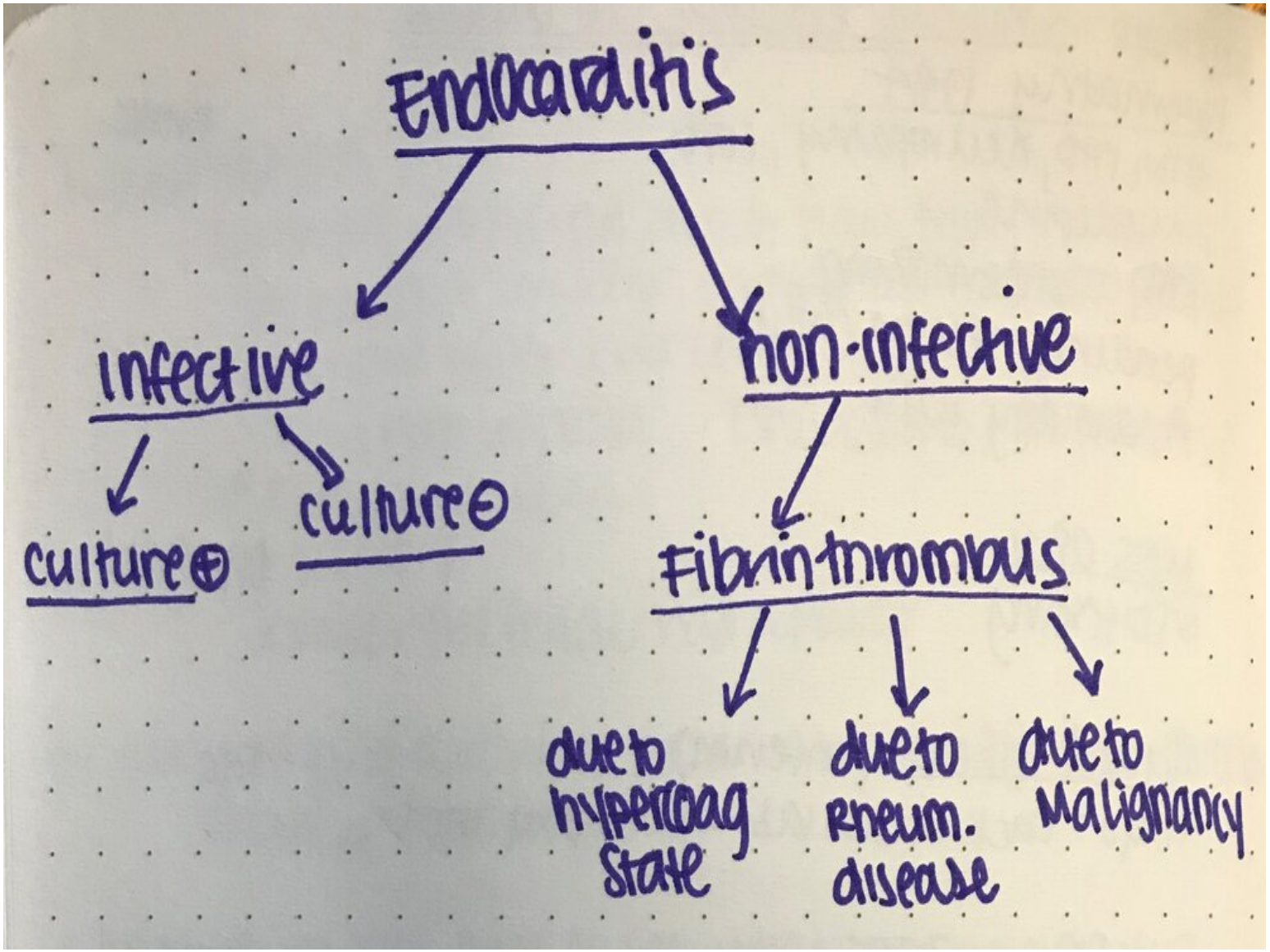

Free bacterial "vegetation" causing systemic embolus
Bacterial infection on valve
Bacterial infection on endocardial surface

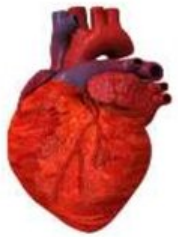




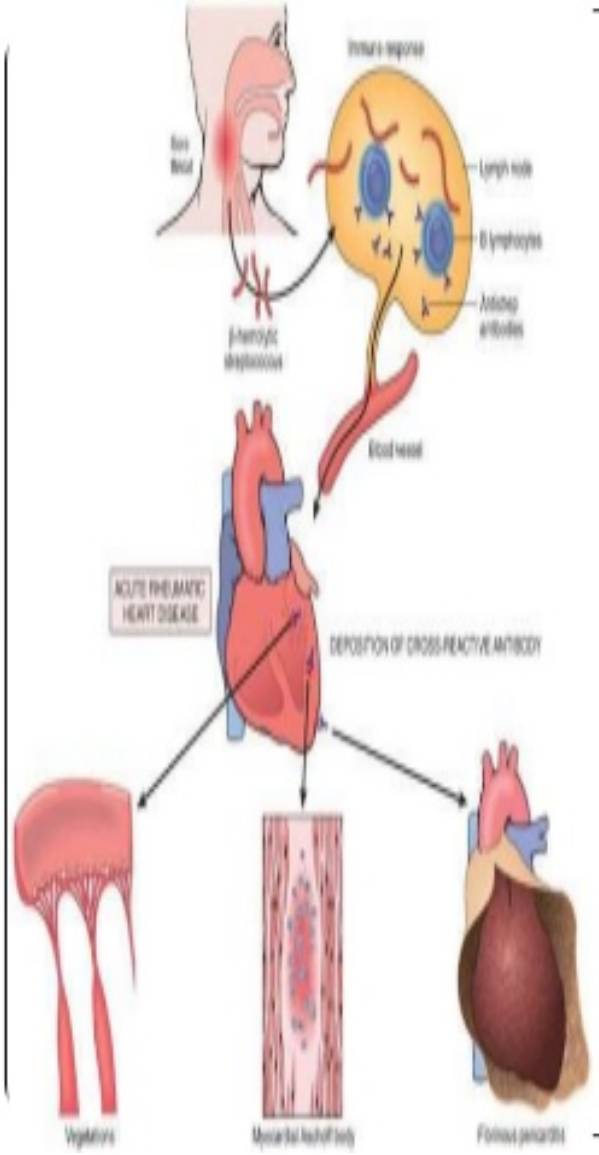



Normal aortic valve
Bacteria
Aortic valve
Area of infection
of the aortic valve
caused by
Bacterial Endocarditis


Endocarditis
infective
non-infective
culture⊕
culture⊖
Fibrinthrombus
due to hypercoag state
due to rheum. disease
due to Malignancy

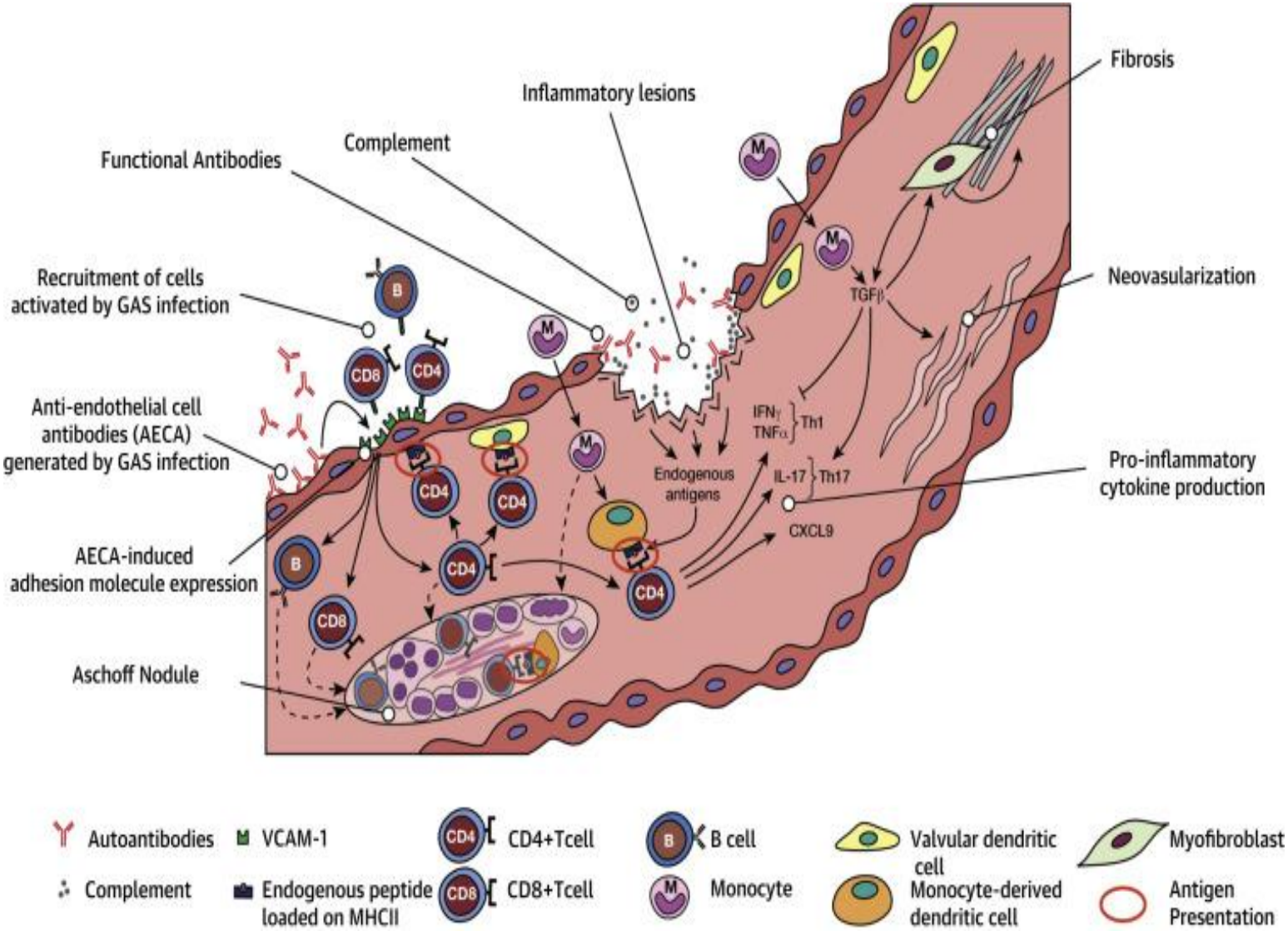


In infective endocarditis, the clots are caused by bacterial or fungal infection, inflaming and damaging the heart cells. The infection reaches the heart through blood that's carrying a concentration of bacteria, a condition called bacteremia. Once the infectious agent reaches the heart via the blood.

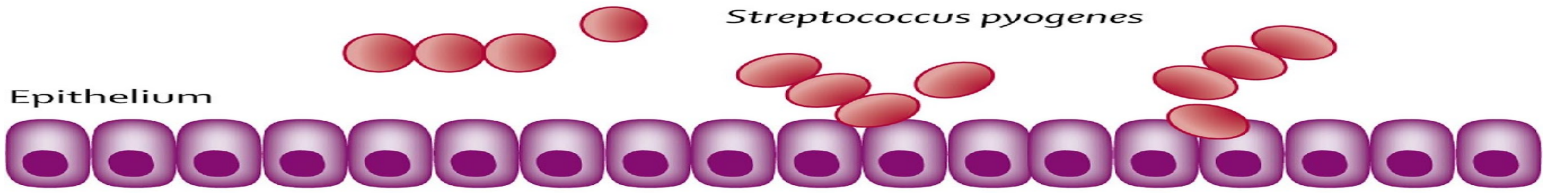


Pathophysiology

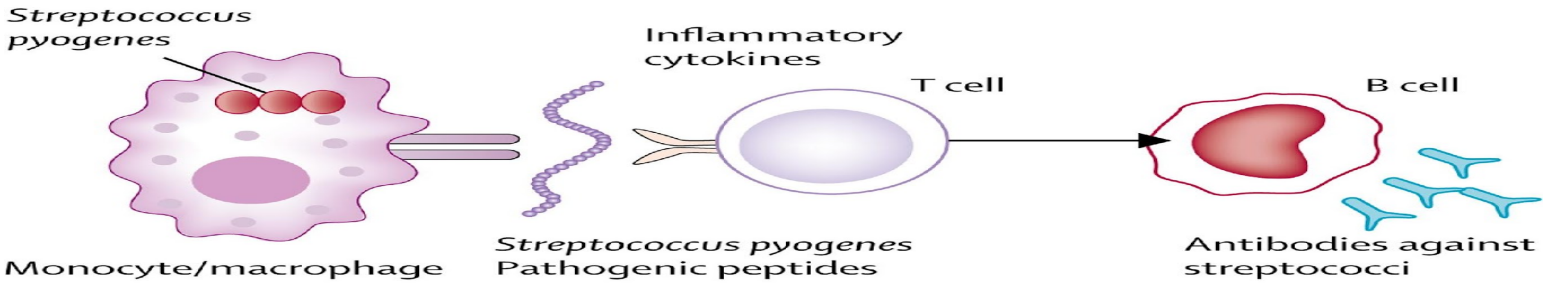
- Rheumatic fever is a sequela to group A beta- hemolytic streptococcal infection that occurs in about 3% of untreated infections. It is a preventable disease through detection and adequate treatment of streptococcal pharyngitis.
- Connective tissue of the heart, blood vessels, joints and subcutaneous tissues can be affected.
- Lesions in connective tissue are known as Aschoff bodies, which are localized areas of tissue


Fibrosis
Inflammatory lesions
Complement
Functional Antibodies
Recruitment of cells activated by GAS infection
Neovasularization
Anti-endothelial cell antibodies (AECA) generated by GAS infection
Pro-inflammatory cytokine production
AECA-induced adhesion molecule expression
Aschoff Nodule
TGFβ
IFNγ
TNFα
Th1
IL-17
Th17
CXCL9
Endogenous antigens
B
CD8
CD4
M
Autoantibodies
Complement
VCAM-1
Endogenous peptide loaded on MHCII
CD4+Tcell
CD8+Tcell
B cell
Monocyte
Valvular dendritic cell
Monocyte-derived dendritic cell
Myofibroblast
Antigen Presentation

Oropharynx

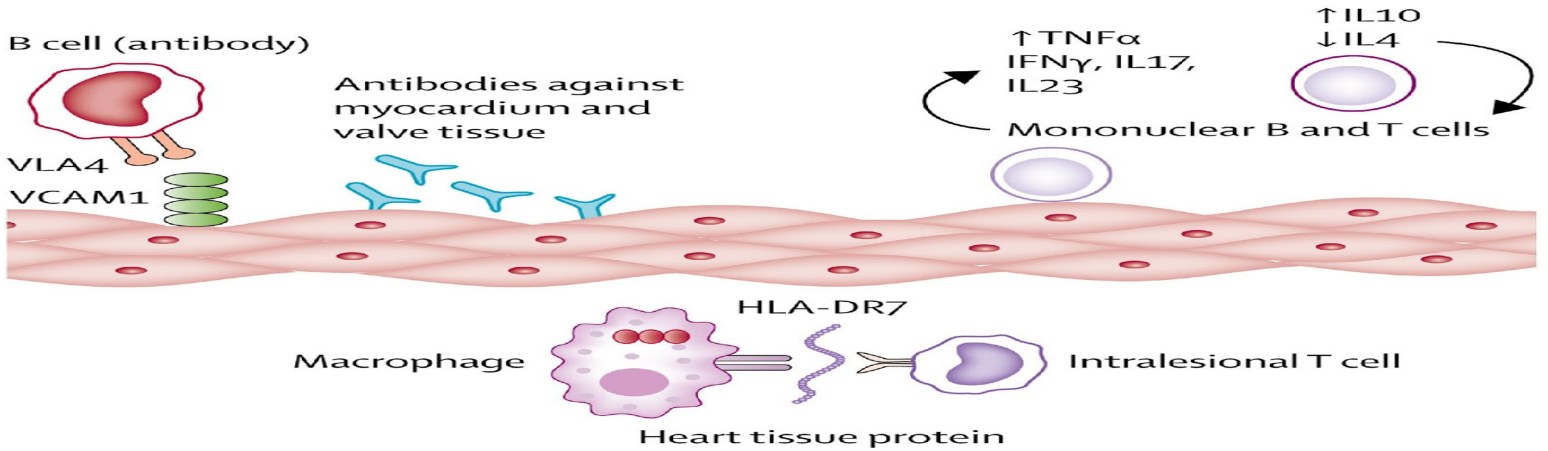


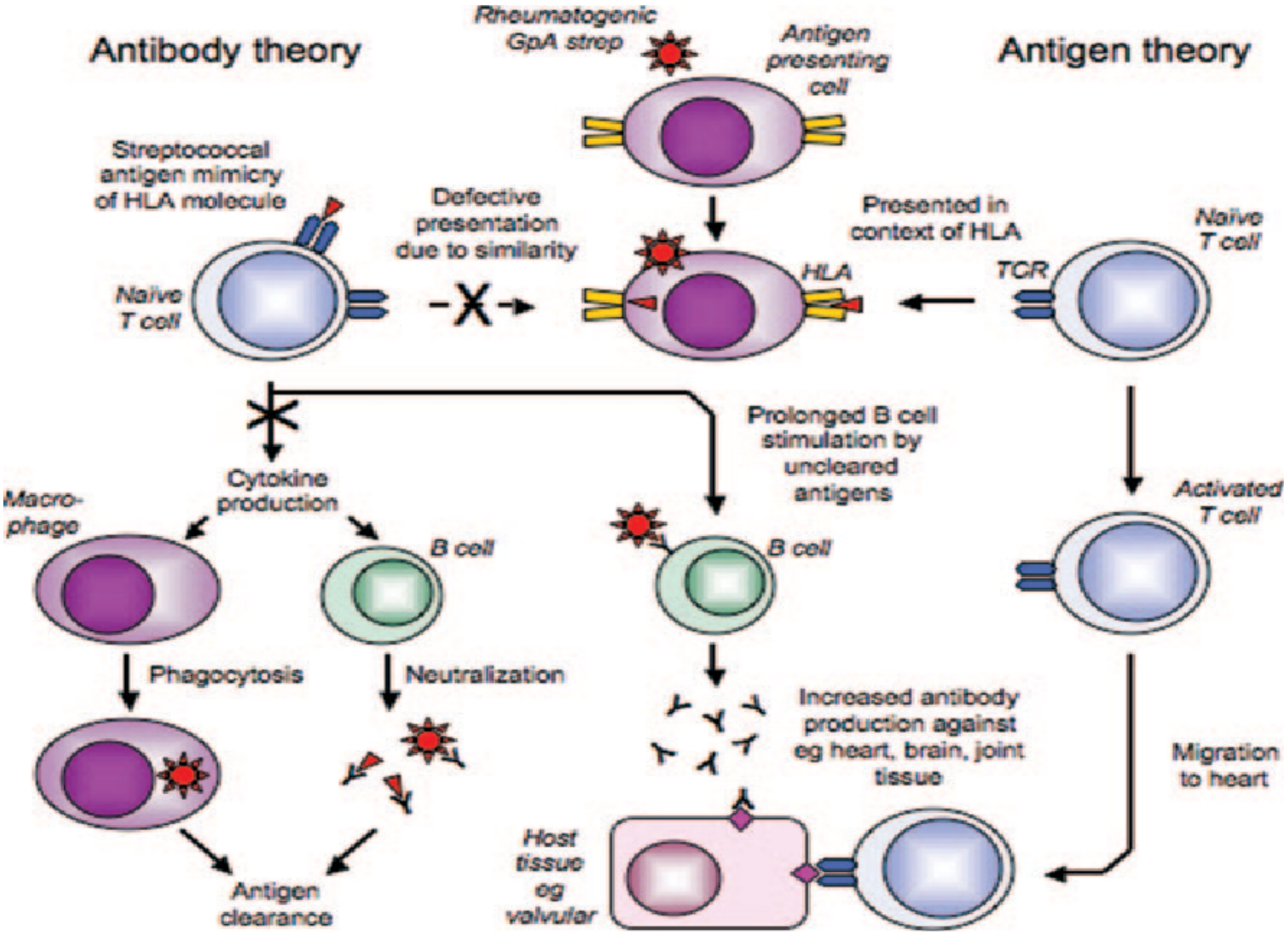
Peripheral blood



Heart

Several heart-tissue proteins in the myocardium and valve tissue are recognised by auto-reactive antibodies and T lymphocytes




Antibody theory
Rheumatogenic GpA strep
Antigen presenting cell
Antigen theory
Streptococcal antigen mimicry of HLA molecule
Defective presentation due to similarity
Presented in context of HLA
Naive T cell
Naive T cell
HLA
TCR
Prolonged B cell stimulation by uncleared antigens
Cytokine production
Macro-phage
B cell
B cell
Activated T cell
Phagocytosis
Neutralization
Increased antibody production against eg heart, brain, joint tissue
Migration to heart
Host tissue eg valvular
Antigen clearance

Pathogenesis

"Damage is mediated both by Abs and T-cells"

Sterptococal antigen
M Protein

B cells	CD4+ cells
Antibodies	Cytotoxic cells
Activation of Complement + Fc recruit Monocytes PMNs	Cytokines
	Activated MØ

Damage to heart tissue

NOTE: M protein and cardiac protein has got structural similarities