Patofisiologi Inflamasi (Allergi)

Inflamasi dan Penyembuhan Luka (Wound Healing)

What is inflammation ?

- Respon dari luka (termasuk infeksi)
- Terjadinya reaksi pada pembuluh darah yg memicu:
  - Akumulasi cairan & Lekosit di jaringan ekstravaskuler
- Lekosit & Pertahanan imunitas pertama menghancurkan zat dr luar tubuh penyebab inflamasi
- Menginisiasi proses "Repair"
- "Protective Response"
- Reaksi Inflamasi yang bisa berbahaya :
  - Hypersensitivity reactions to insect bites, drugs, contrast media in radiology
  - Chronic diseases: arthritis, atherosclerosis
- Terdiri dari 2 reaksi umum :
  - Vascular reaction
  - Cellular reaction
- Melibatkan banyak mediator kimia (mediator inflamasi)
  - Turunan dari plasma proteins
  - Turunan dari sel imun di dalam dan luar pembuluh darah

Tanda Utama Peradangan

- Celsus, a first century A.D. Roman, listed four cardinal signs of acute inflammation:
  - *Rubor* (erythema [redness]): vasodilatation, increased blood flow
  - *Tumor* (swelling): extravascular accumulation of fluid
  - *Calor* (heat): vasodilatation, increased blood flow
  - *Dolor* (pain)

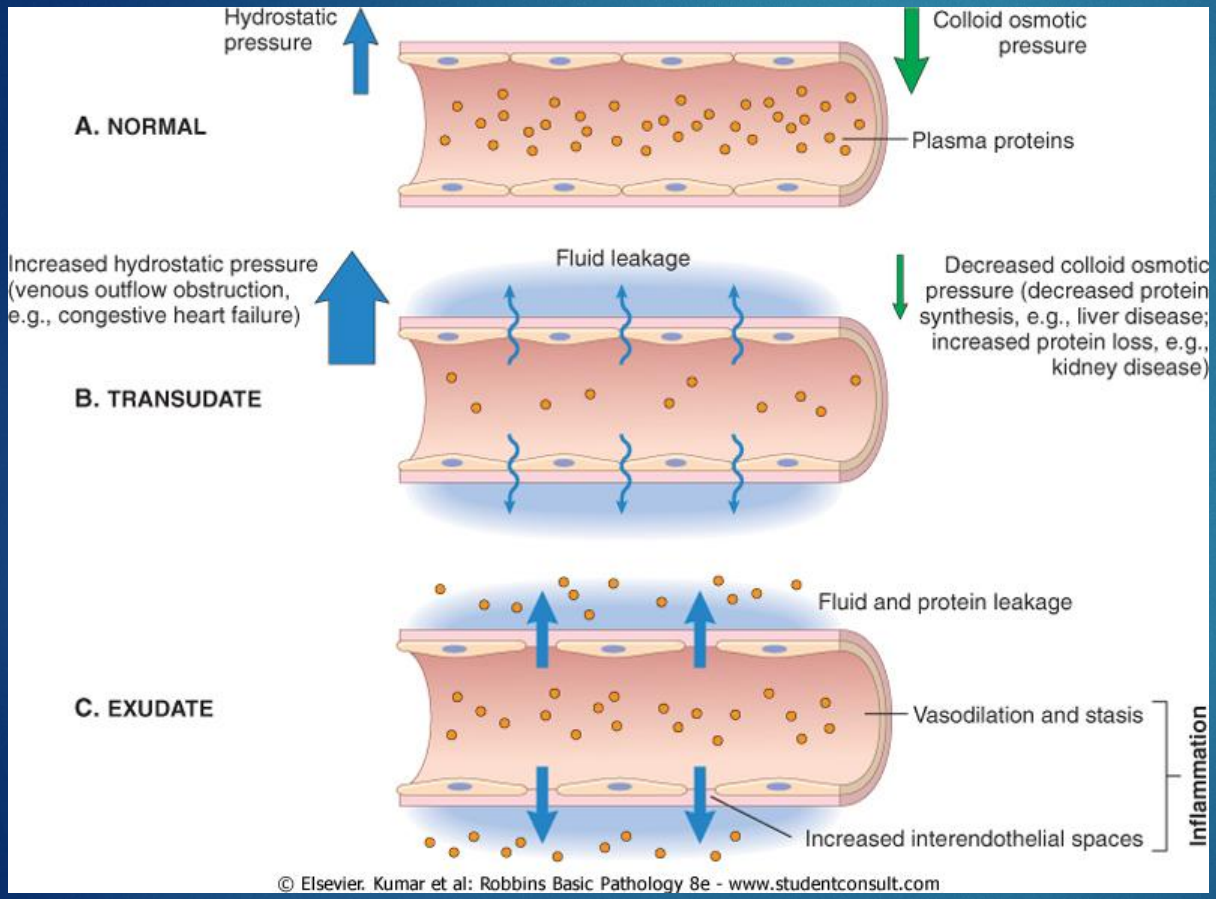
Tipe Inflamasi

- A. Inflamasi Akut
  - Short duration
  - Edema
  - Mainly neutrophils
- C. Inflamasi Granuloma
  - Distinctive pattern of chronic inflammation
  - Activated macrophages (epithelioid cells) predominate
  - +/- Multinucleated giant cells
- B. Inflamasi Kronis
  - Longer duration
  - Lymphocytes & macrophages predominate
  - Fibrosis
  - New blood vessels (angiogenesis)

A. Inflamasi Akut

- Prinsipnya ada 3 tahapan :
  - Peningkatan Aliran Darah (kemerahan & panas/hangat)
  - Timbul Edema yg dihasilkan dari peningkatan tekanan hidrostatik (vasodilatasi) dan tekanan osmotic intravaskuler yang rendah (rusaknya protein)
  - Leukosit bermigrasi dari sirkulasi mikro dan terakumulasi di luka yang mengalami inflamasi
- Pencetus : infections, trauma, physical or chemical agents, foreign bodies, immune reactions

Edema pada Reaksi Inflamasi



Edema is a general term for swelling (usu. due to fluid)

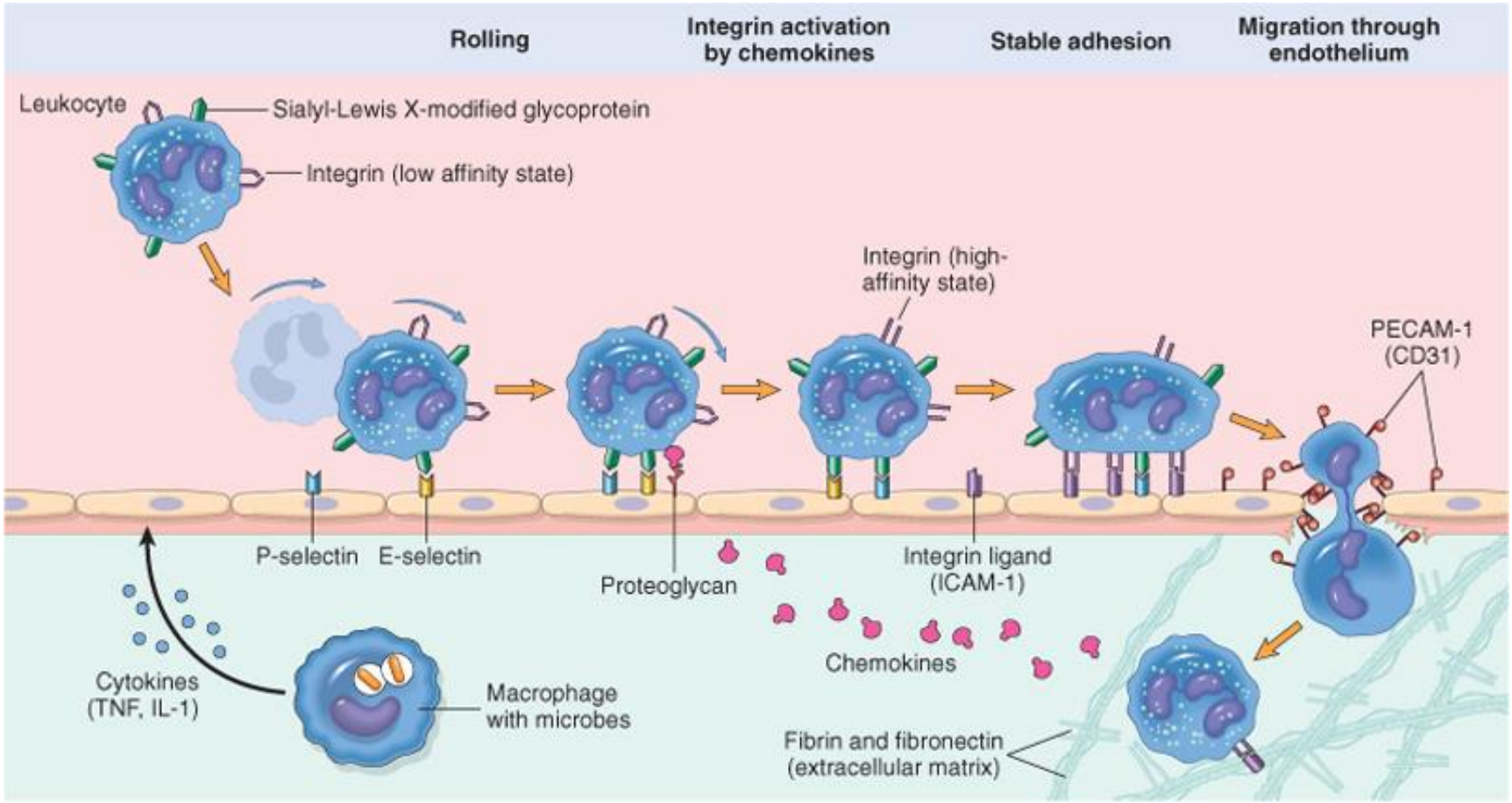
Kondisi Normal. Plasma proteins di aliran darah menjaga tekanan osmotic koloid untuk membantu menarik cairan yang bocor ke jaringan melalui tekanan hidrostatik

Disregulasi tekanan hidrostatik (misal. Gagal Jantung) dan/atau tekanan koloid (karena pengurangan protein plasma) mendorong lebih banyak cairan (transudate) ke dalam jaringan

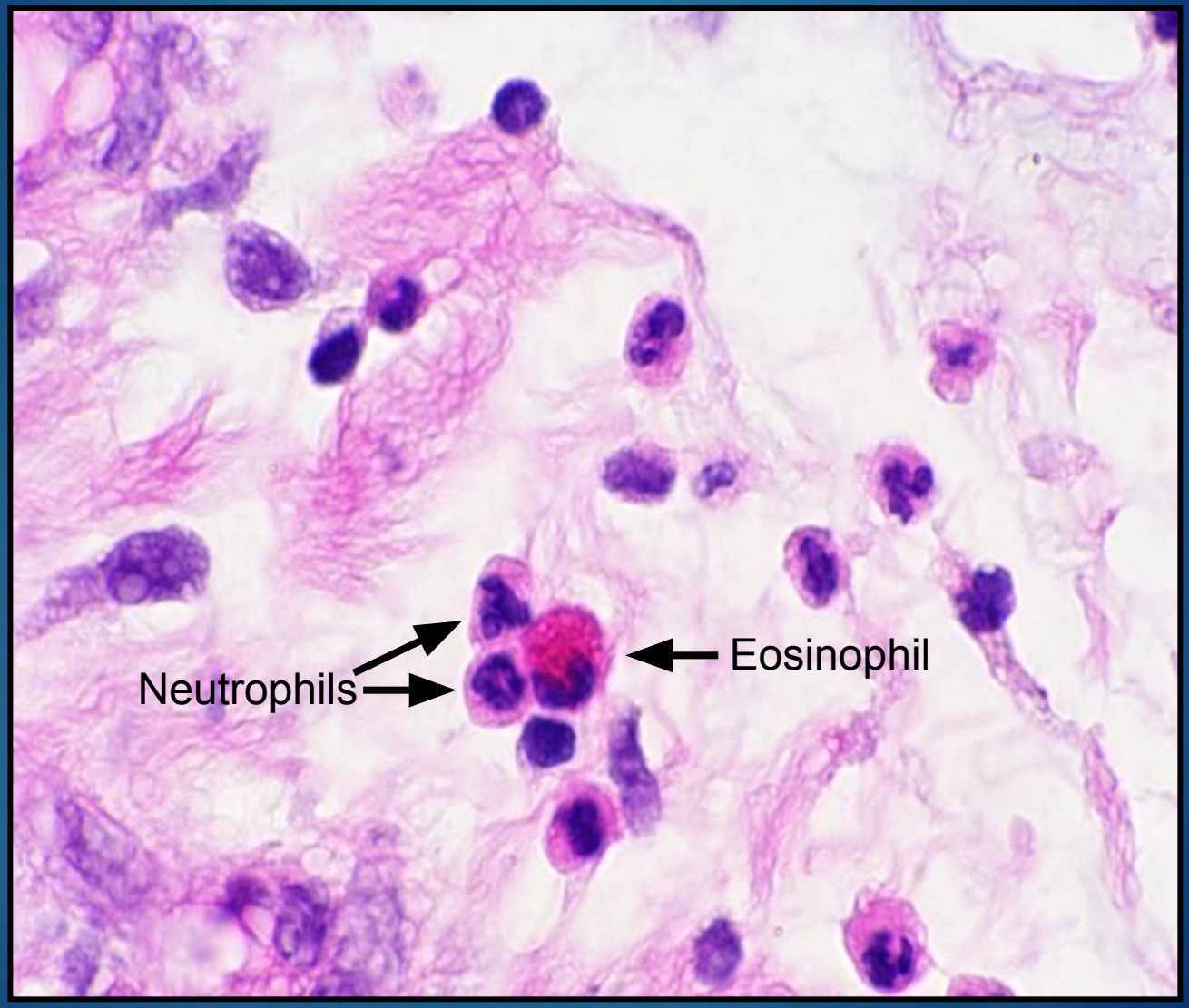
Inflamasi menyebabkan sel endothelial untuk memisah , akibatnya cairan + protein (exudate) dapat masuk ke dalam jaringan

Ekstravasasi Leukosit

- Extravasation: pengiriman leukosit dari lumen pembuluh darah ke
- interstitium (organ dalam jaringan yang berisi cairan suspensi)
  - In the lumen: margination, rolling, and adhesion
  - Migration across the endothelium (*diapedesis*)
  - Migration in the interstitial tissue (*chemotaxis*)
- Leukosit menelan agen penyebab inflamasi (mem-fagositosis), membunuh mikroba, dan mendegradasi jaringan nekrotik dan antigen asing



Neutrophil Morphology

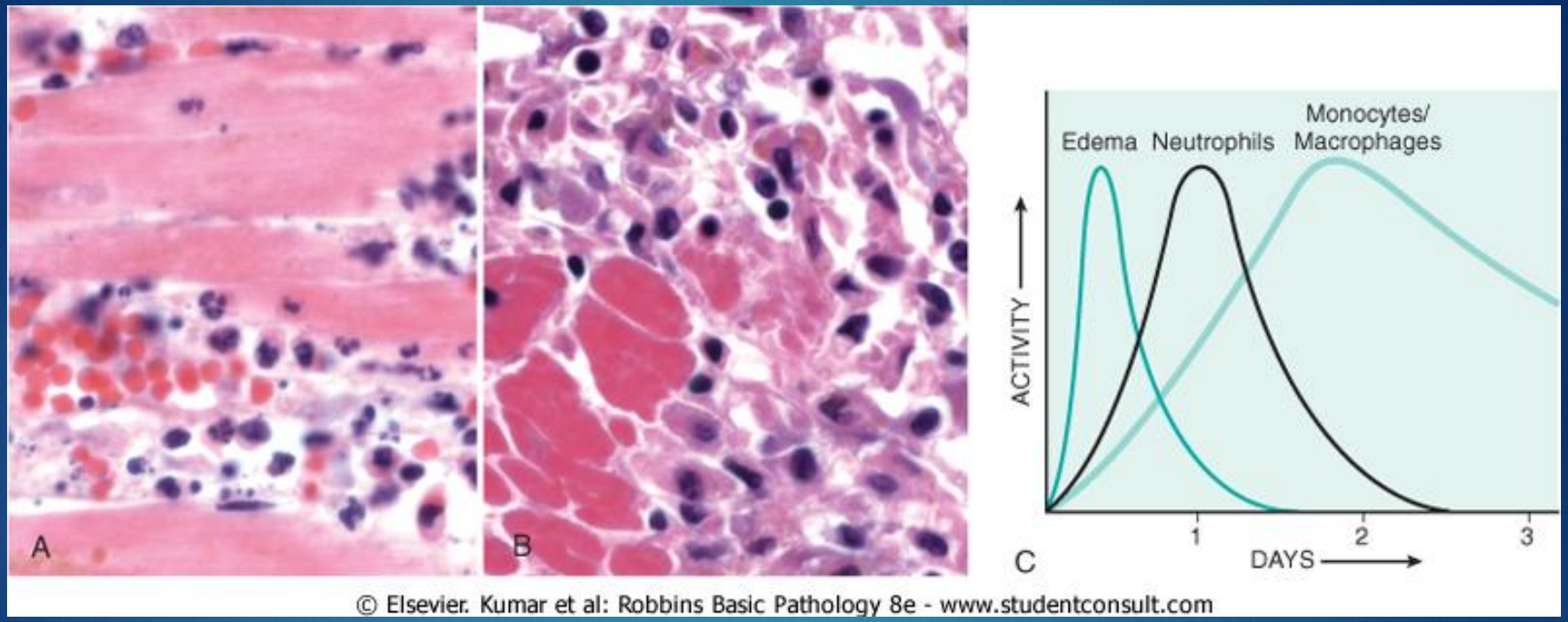


Tahapan Lanjut Proses Emigrasi Leukosit

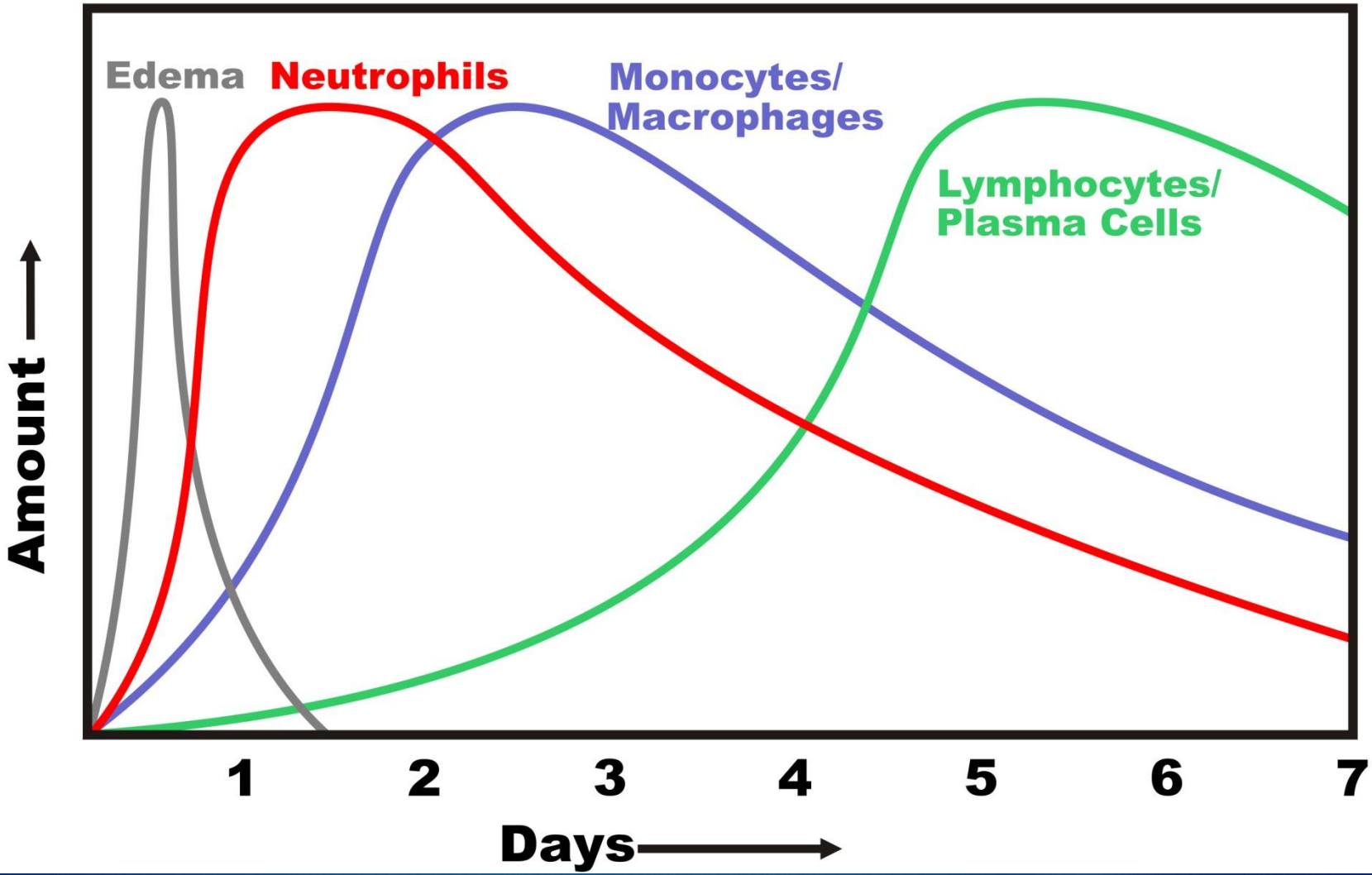
Netrofil meng-infiltrasi selama 6 – 24 jam pertama

Monocytes dalam 24 to 48 hours

Kejadian selanjutnya – Timbul Luka/Kerusakan/inflamasi



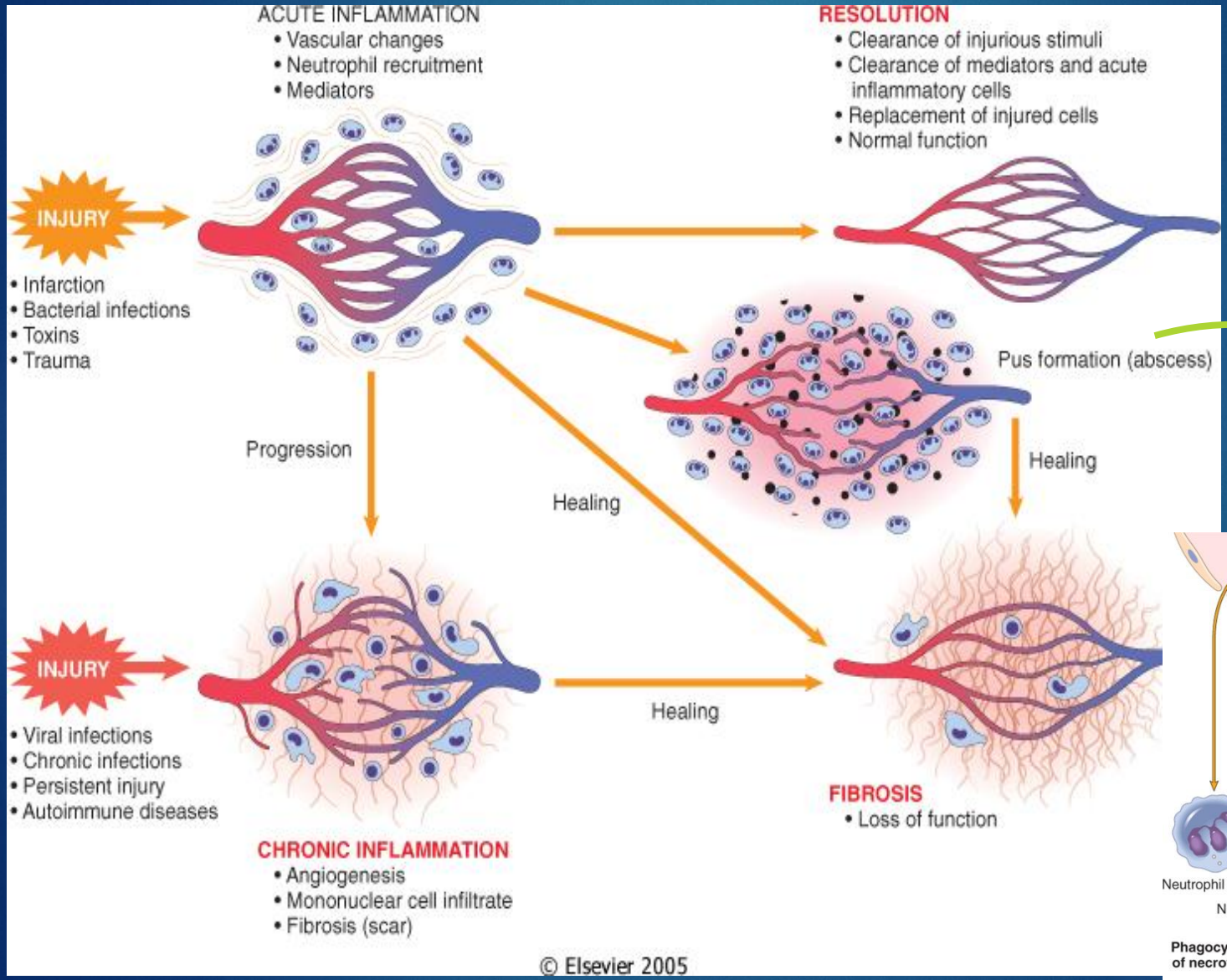
Kejadian selanjutnya – Timbul Infeksi

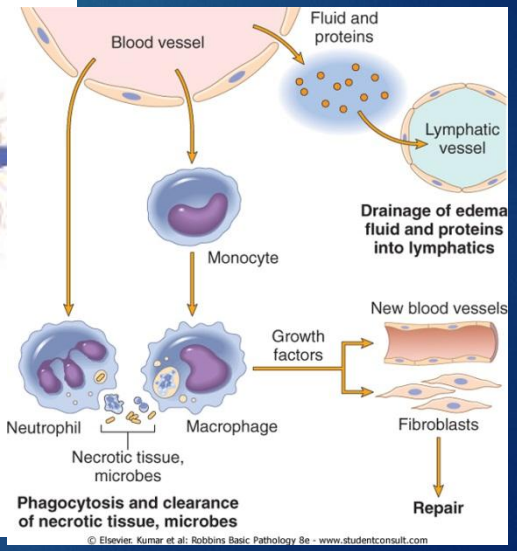


Outcomes dari Inflamasi Akut

- Resolusi Tercapai
- Pembentukan Abses (nanah)
- Pembentukan Fibrosis
  - Setelah destruksi jaringan substantif
  - Pada jaringan yang tidak bisa di regenerasi
  - Setelah eksudasi fibrin yang melimpah, terutama di rongga serosa (pleura, peritoneum)
- Menuju Progres ke inflamasi kronis

Types of Inflammation: acute vs. chronic
Types of repair: resolution vs. organization (fibrosis)





Systemic Manifestations

- Leukocytosis: increased leukocyte count in the blood
  - Neutrophilia: bacterial infections
  - Lymphocytosis: infectious mononucleosis, mumps, measles
  - Eosinophilia: Parasites, asthma, hay fever
- Leukopenia: reduced leukocyte count
  - Typhoid fever, some viruses, rickettsiae, protozoa

B. Inflamasi Kronis

- Inflamasi dalam durasi yang lama (minggu atau bulan)
  - Peradangan aktif, kerusakan jaringan, dan upaya perbaikan berlangsung secara bersamaan
- Dapat terjadi setelah peradangan akut atau dimulai secara diam-diam dan seringkali tanpa gejala
  - Infeksi persisten, paparan agen toksik seperti silika (silikosis), atau oleh autoimunitas

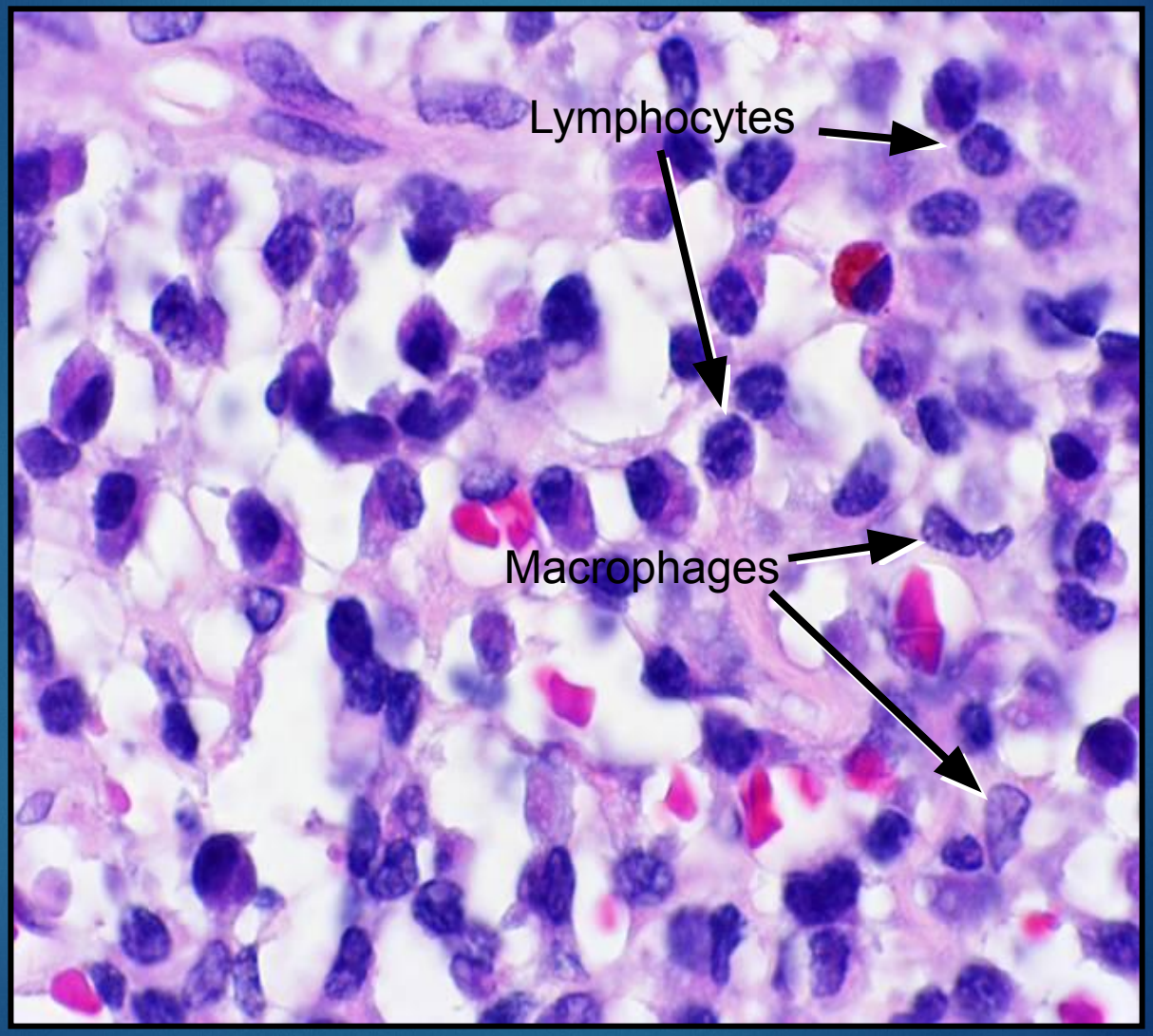
Inflamasi Kronis

- Persistent infections
  - *Treponema pallidum* [syphilis], viruses, fungi, parasites
- Exposure to toxic agents
  - Exogenous: silica (silicosis)
  - Endogenous: toxic plasma lipid components (atherosclerosis)
- Autoimmunity
  - Rheumatoid arthritis, systemic lupus erythematosus

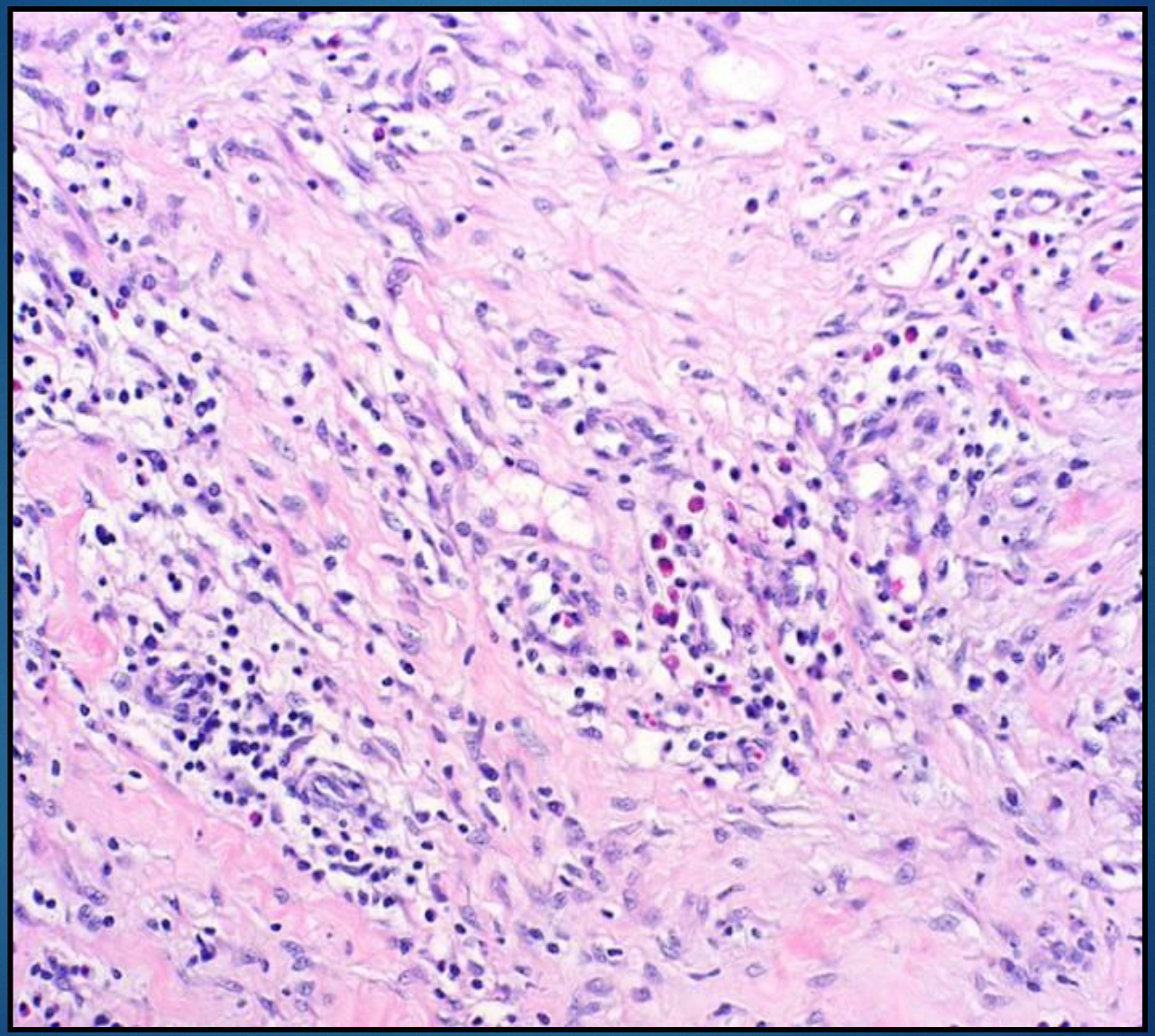
Inflamasi Kronis

- Gambaran Histologi
  - Infiltrasi Sel Mononuklear (macrophages, lymphocytes, and plasma cells)
  - Destruksi Jaringan (induced by the inflammatory cells)
  - Penyembuhan dengan mengganti jaringan yang rusak dengan jaringan ikat (fibrosis) dan pembuluh darah baru (angiogenesis)

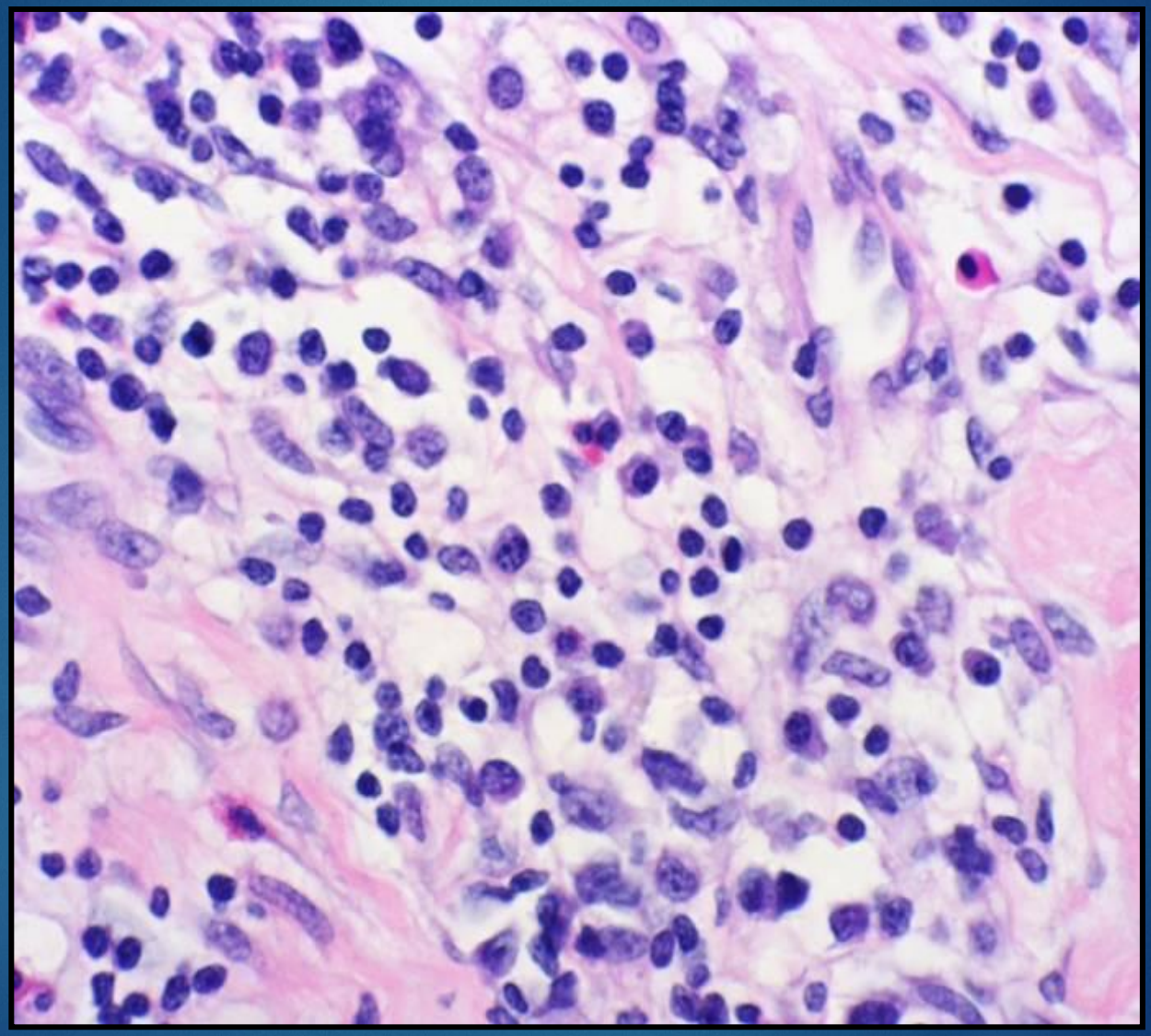
Chronic Inflammatory Cells



Chronic Inflammation

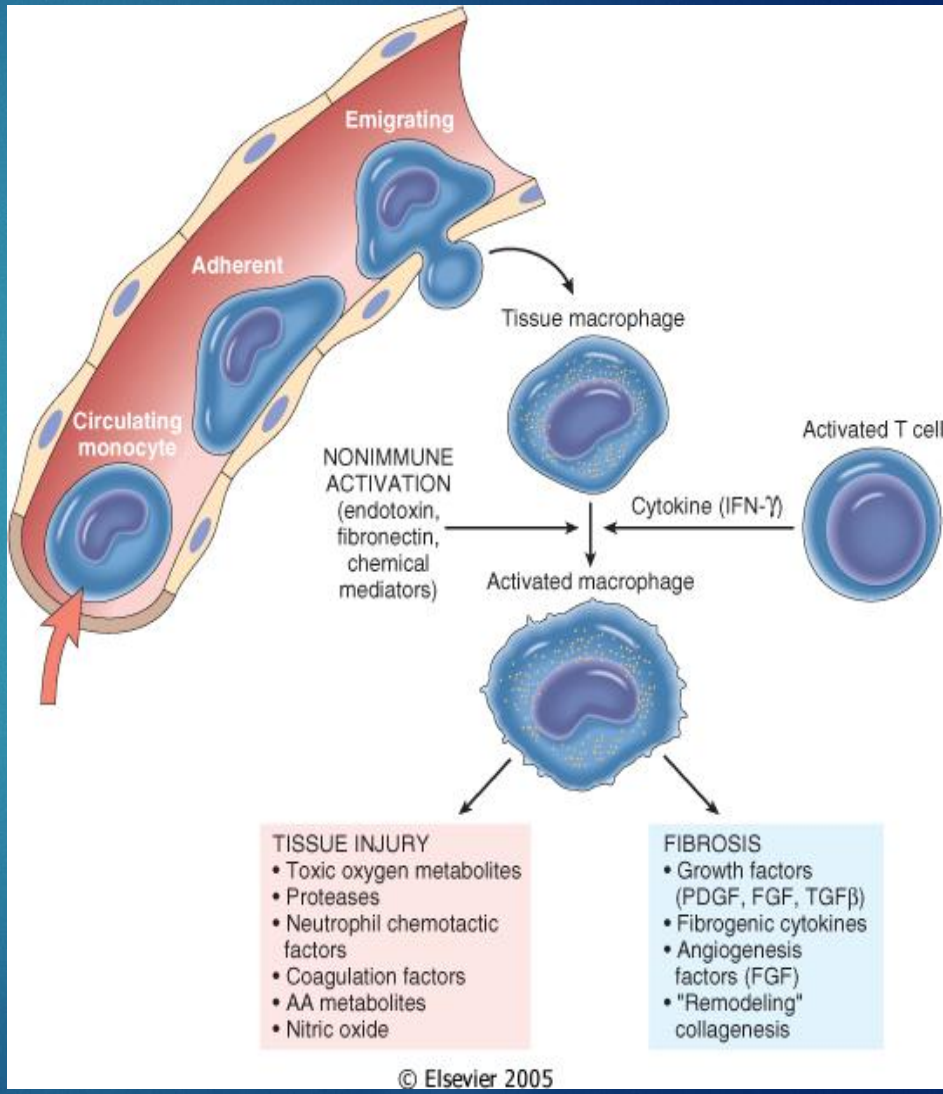


Chronic Inflammation

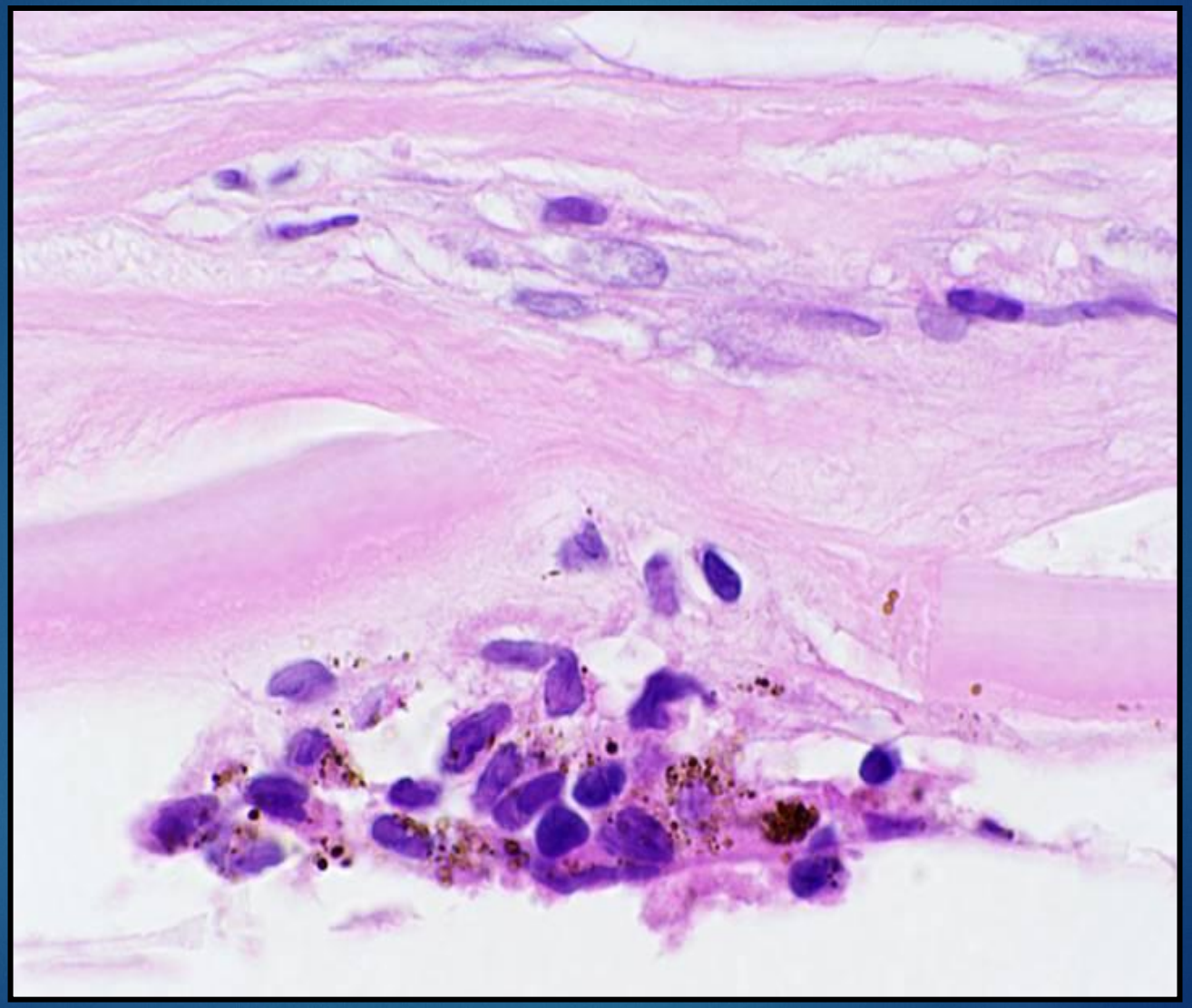


Macrophages

- Monosit mulai beremigrasi ke jaringan di awal peradangan di mana mereka berubah menjadi sel fagositik yang lebih besar yang dikenal sebagai makrofag.
- Macrophages predominate by 48 hours
  - Recruitment (circulating monocytes); division; immobilization
- Aktivasi menghasilkan sekresi produk yang aktif secara biologis



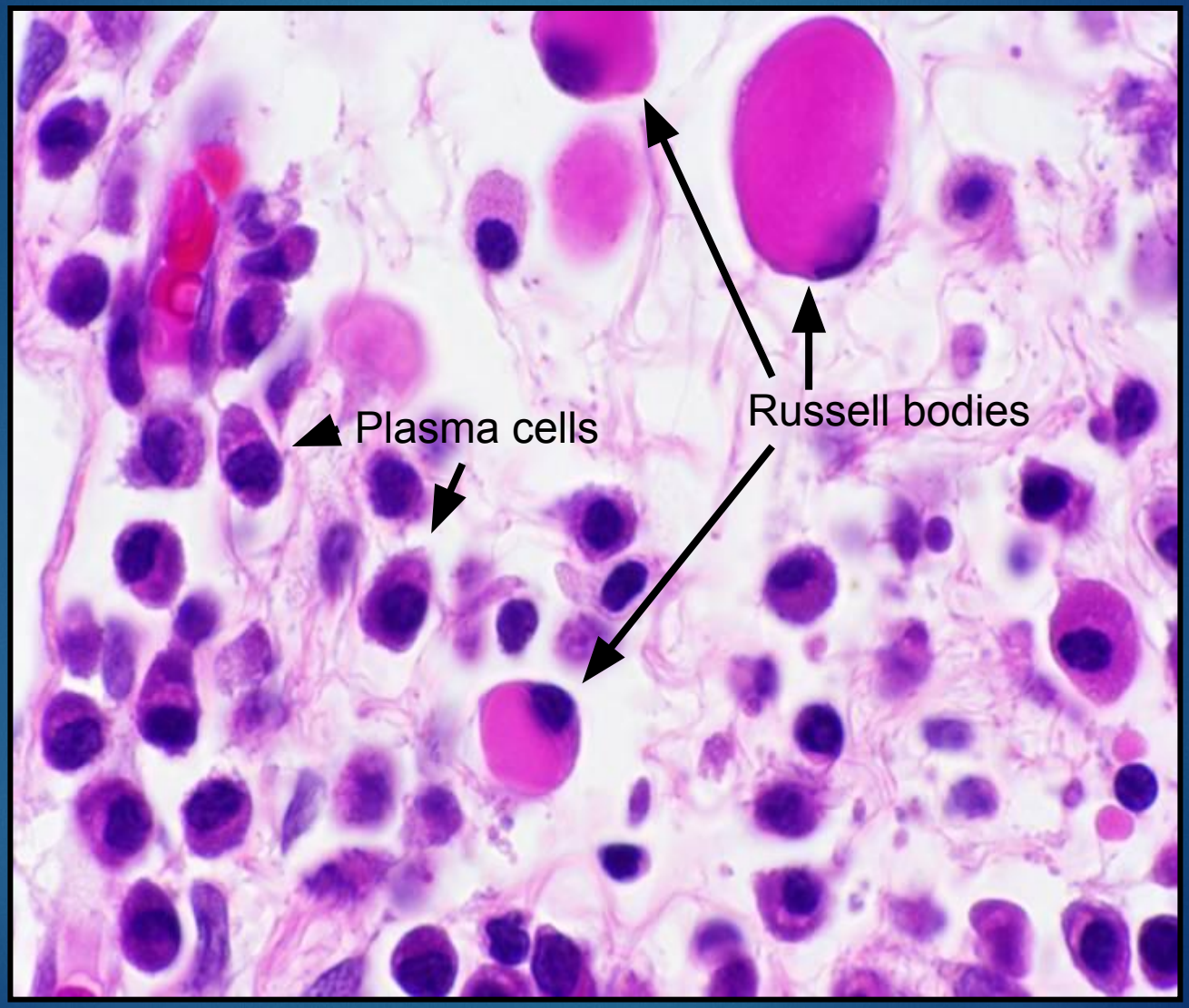
Macrophages



Sel Imun lain yang terlibat pada Inflamasi Kronis

- Limfosit
  - Menghasilkan mediator inflamasi
  - Berpartisipasi dalam reaksi kekebalan yang dimediasi sel
  - Sel plasma menghasilkan antibodi
  - Limfosit dan makrofag berinteraksi secara dua arah

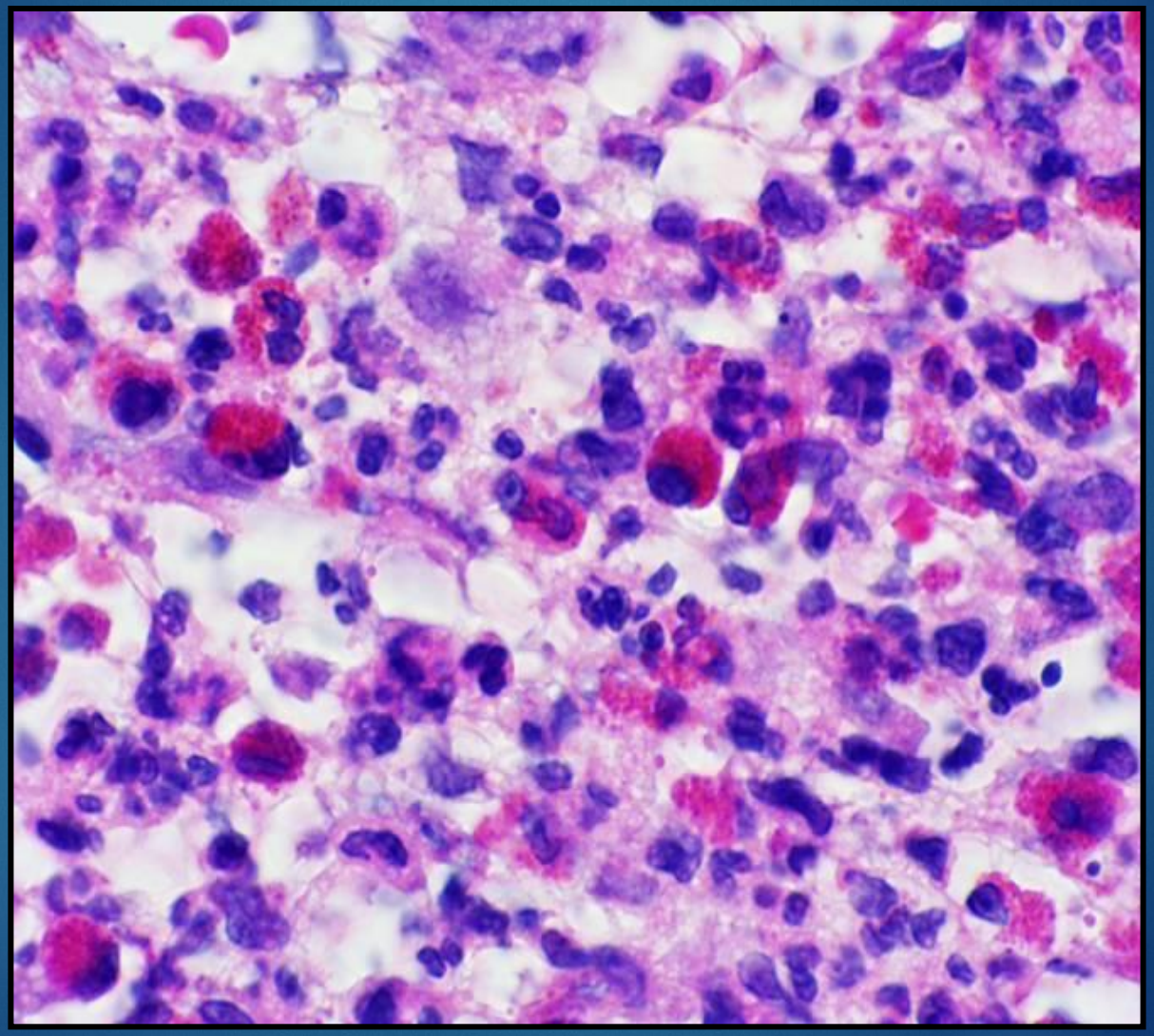
Chronic Inflammatory Cells



Other Cells in Chronic Inflammation

- Eosinofil
  - Reaksi Imun dimediasi IgE
  - Biasanya Muncul pada Infeksi Parasit
    - Butiran eosinofil mengandung protein yang bersifat toksik bagi parasit
- Sel Mast
  - Release mediator inflamasi (histamin) dan sitokin (cytokines)

Eosinophil Morphology

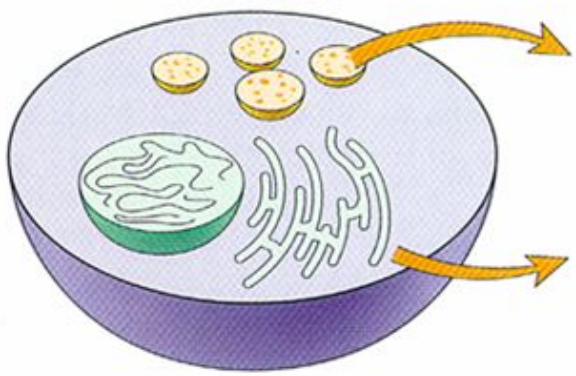


C. Inflamasi Granuloma

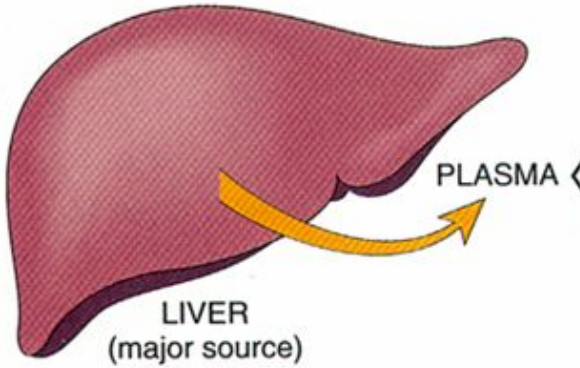
- Pola khas peradangan kronis
  - Jenis sel yang dominan adalah makrofag yang teraktivasi dengan tampilan seperti epitel yang dimodifikasi (epiteloid).
  - Sel raksasa mungkin ada atau mungkin tidak ada
- Granuloma:
  Area fokal peradangan granulomatosa

Mediator Inflamasi

- Prinsip Umum Mediator Kimia (Mediator Inflamasi)
  - Bisa berasal dari plasma atau sel
  - Kebanyakan terikat pada reseptor tertentu pada sel target
  - Dapat merangsang pelepasan mediator oleh sel target, yang dapat memperkuat atau mengubah respons inflamasi
  - Dapat bekerja pada satu atau beberapa sel target, memiliki target yang luas, dan mungkin memiliki efek yang berbeda tergantung pada jenis sel dan jaringan
  - Biasanya berumur pendek
  - Sebagian besar berpotensi menimbulkan efek berbahaya



CELLULAR



PLASMA

LIVER
(major source)

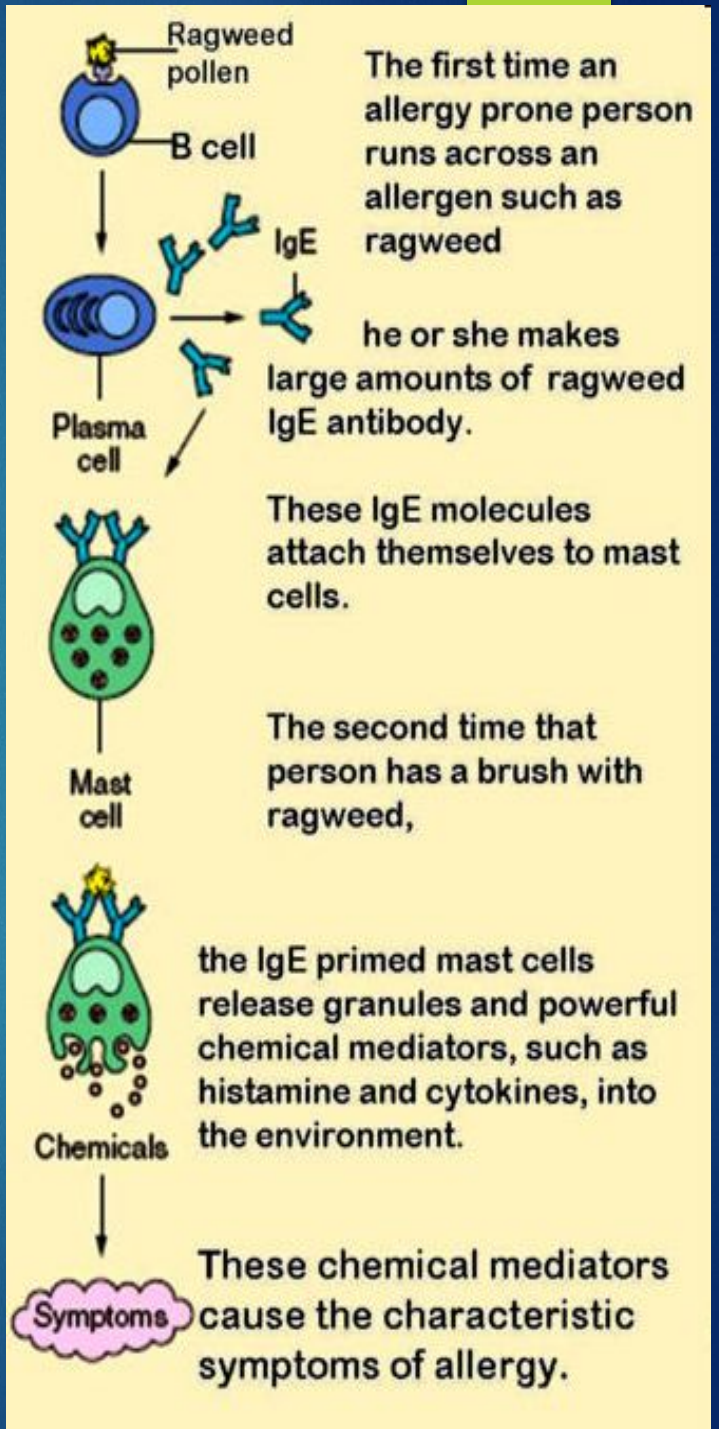
	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	
Complement activation	C_{3a}	anaphylatoxins
	C_{5a}	anaphylatoxins
	C_{3b}	
	C_{5b-9}	(membrane attack complex)

Mediator Inflamasi

- Vasoactive mediators
  - Histamine
  - Bradykinin
  - Complement (C3a, C5a)
  - Prostaglandins/leukotrienes
  - Platelet activating factor
  - Nitric oxide
- Chemotactic factors
  - Complement (C5a)
  - Leukotriene (B4)
  - Platelet activating factor
  - Cytokines (IL-1, TNF)
  - Chemokines
  - Nitric oxide

Histamine

- Mast cells (also basophils and platelets)
- Release mechanisms
  - Pengikatan antigen (alergen) ke IgE pada sel mast melepaskan butiran yang mengandung histamin
  - Dilepaskan melalui mekanisme nonimun seperti dingin, trauma, atau mediator kimiawi lainnya
  - Dilepaskan oleh oleh mediator lain
- Melebarkan arteriol dan meningkatkan permeabilitas venula (reaksi wheal dan flare)



Bradykinin

- Small peptide released from plasma precursors
- Increases vascular permeability
- Dilates blood vessels
- Causes pain
- Rapid inactivation

Arachidonic Acid Metabolites

- Prostaglandins
  - Vasodilators: prostacyclin (PGI_2), PGE_1, PGE_2, PGD_2
  - Vasoconstrictors: thromboxane A_2
  - Pain (PGE_2 makes tissue hypersensitive to bradykinin)
  - Fever (PGE_2)
  - Production blocked by steroids and nonsteroidal anti-inflammatory agents (NSAIDs)
- Leukotrienes
  - Increase vascular permeability: leukotrienes C_4, D_4, E_4
  - Vasoconstriction: leukotrienes C_4, D_4, E_4
  - Leukocyte adhesion & chemotaxis: leukotriene B_4, HETE, lipoxins
  - Production blocked by steroids but <u>not</u> conventional NSAIDs

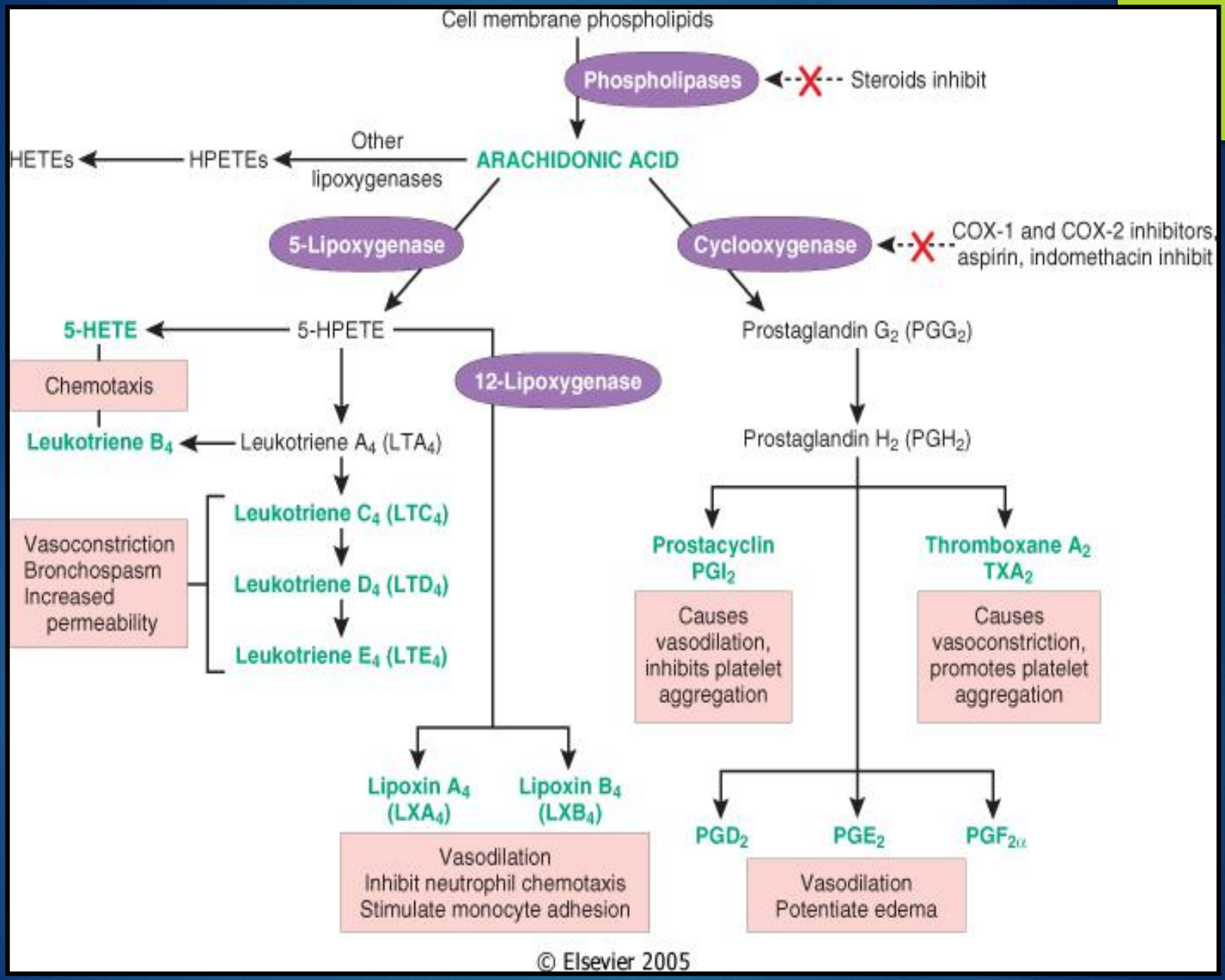


Figure 2-16 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Cytokines (Sitokin)

- Protein yang diproduksi oleh banyak jenis sel (terutama limfosit & makrofag yang diaktifkan)
- Memodulasi fungsi jenis sel lainnya
- Interleukin-1 (IL-1) dan tumor necrosis factor (TNF) adalah sitokin utama yang memediasi inflamasi.

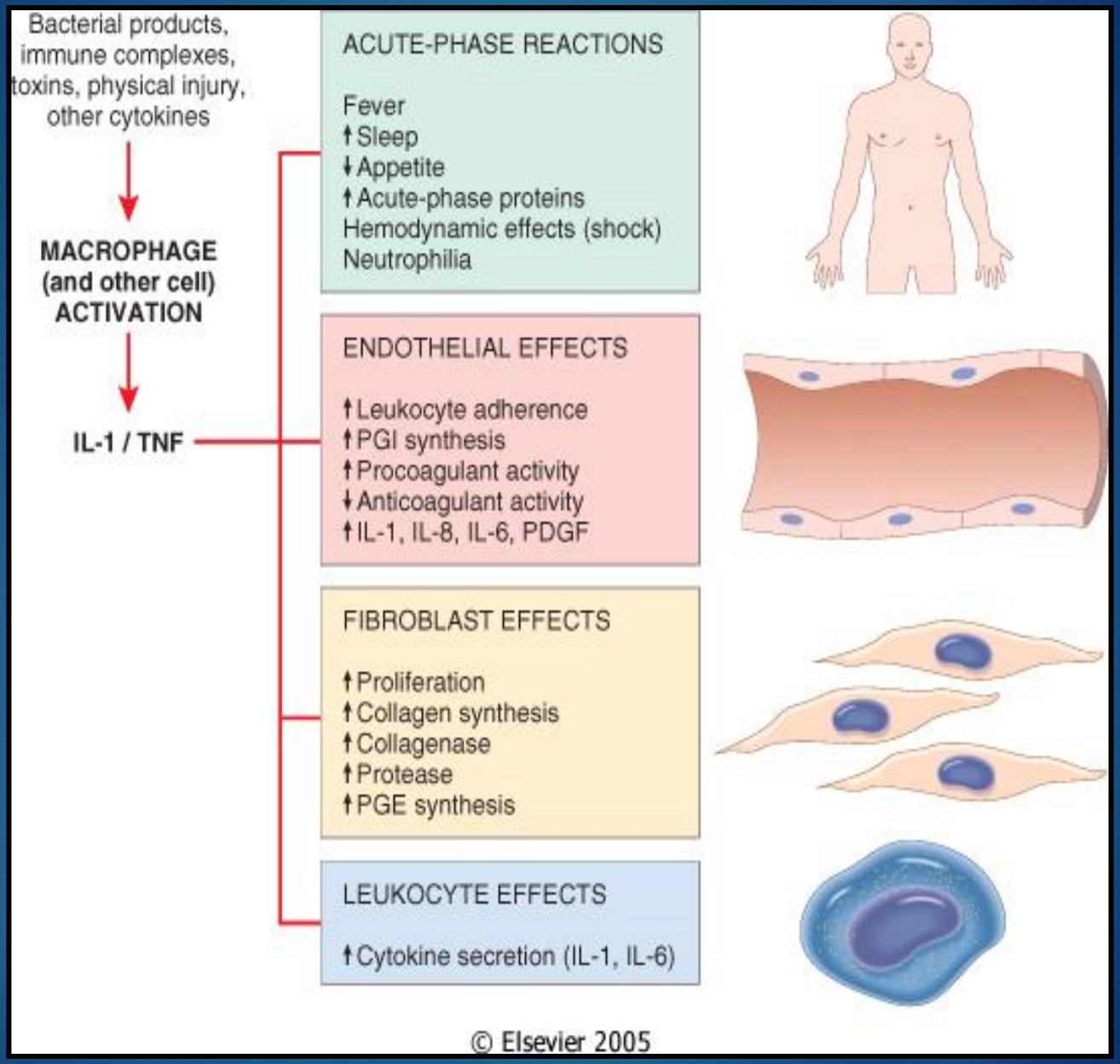


Figure 2-18 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Summary of Inflammatory Mediators

- Vasodilation
  - Prostaglandins
  - Nitric oxide
  - Histamine
- Increased vascular permeability
  - Histamine, serotonin
  - Complement (C3a, C5a)
  - Bradykinin
  - Leukotrienes (C_4, D_4, E_4)
  - Platelet Activating Factor
  - Substance P

Summary of Inflammatory Mediators

- Chemotaxis, leukocyte activation
  - Complement (C5a)
  - Leukotriene B_4
  - Chemokines
  - IL-1, TNF
  - Bacterial products
- Fever
  - Interleukin-1
  - Tumor necrosis factor
  - Prostaglandins

Summary of Inflammatory Mediators

- Pain
  - Prostaglandins
  - Bradykinin
- Tissue Damage
  - Neutrophil and macrophage lysosomal enzymes
  - Oxygen metabolites
  - Nitric oxide

Pathophysiology of Type 2 Diabetes Mellitus

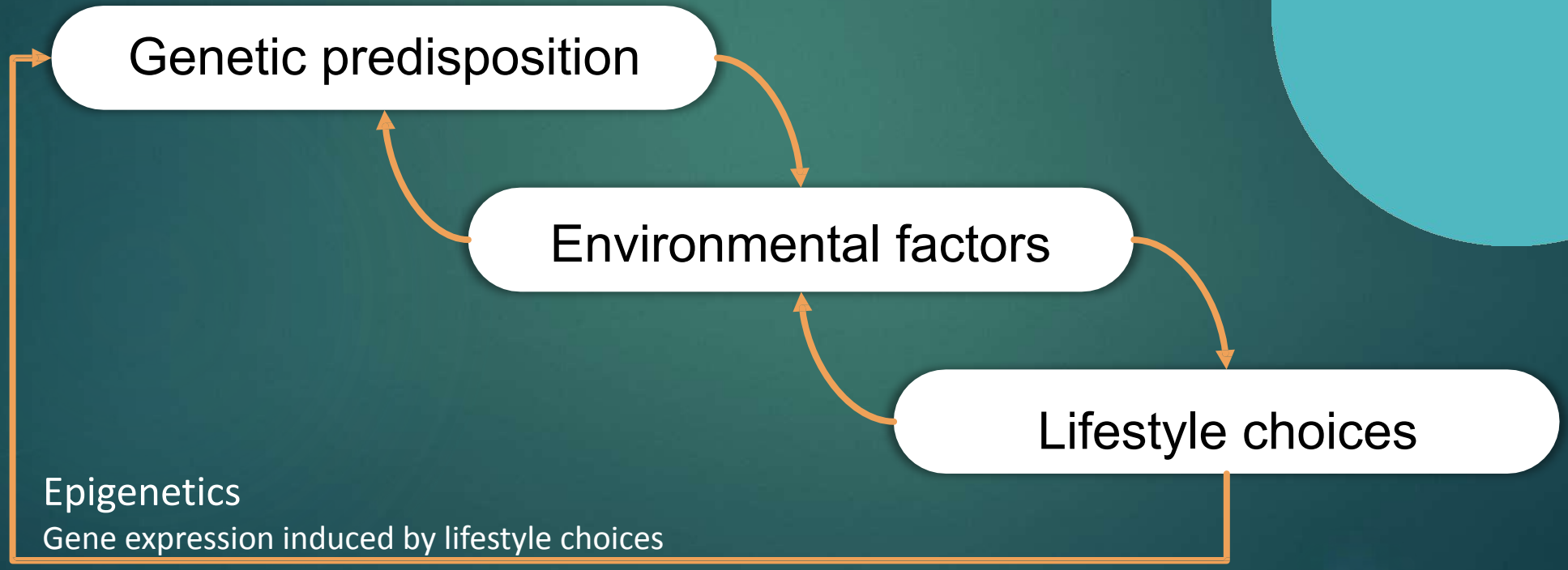
Type 2 diabetes mellitus (T2DM)

- There is an explosion of T2DM prevalence
  - >370 million people with T2DM

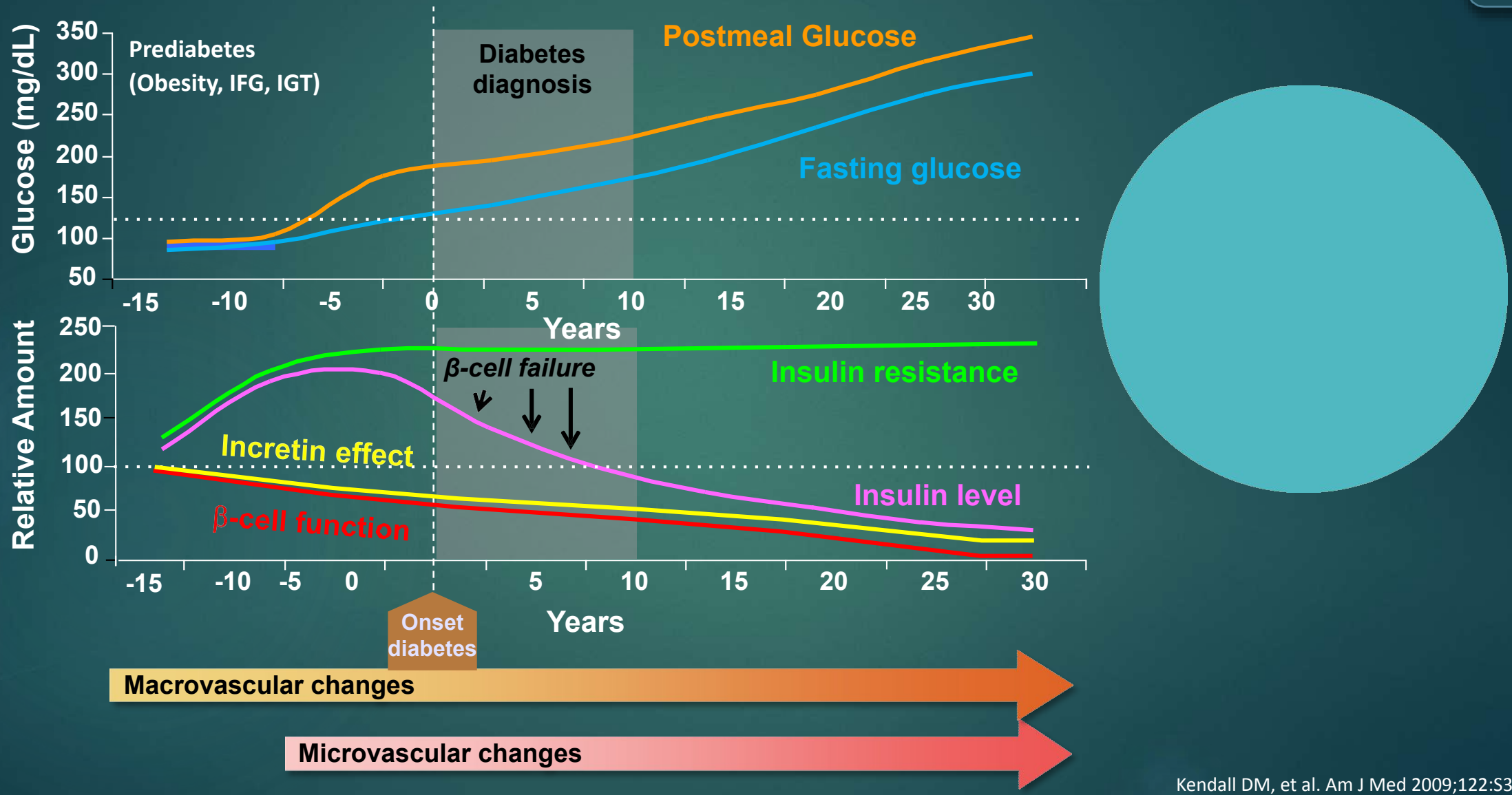
- **Need** to address the pathogenesis and treatment of this syndrome
  - else, macrovascular and microvascular damages of T2DM will remain a major burden for decades to come

Pathogenesis of T2DM

- Multifactorial etiology & complex pathophysiology

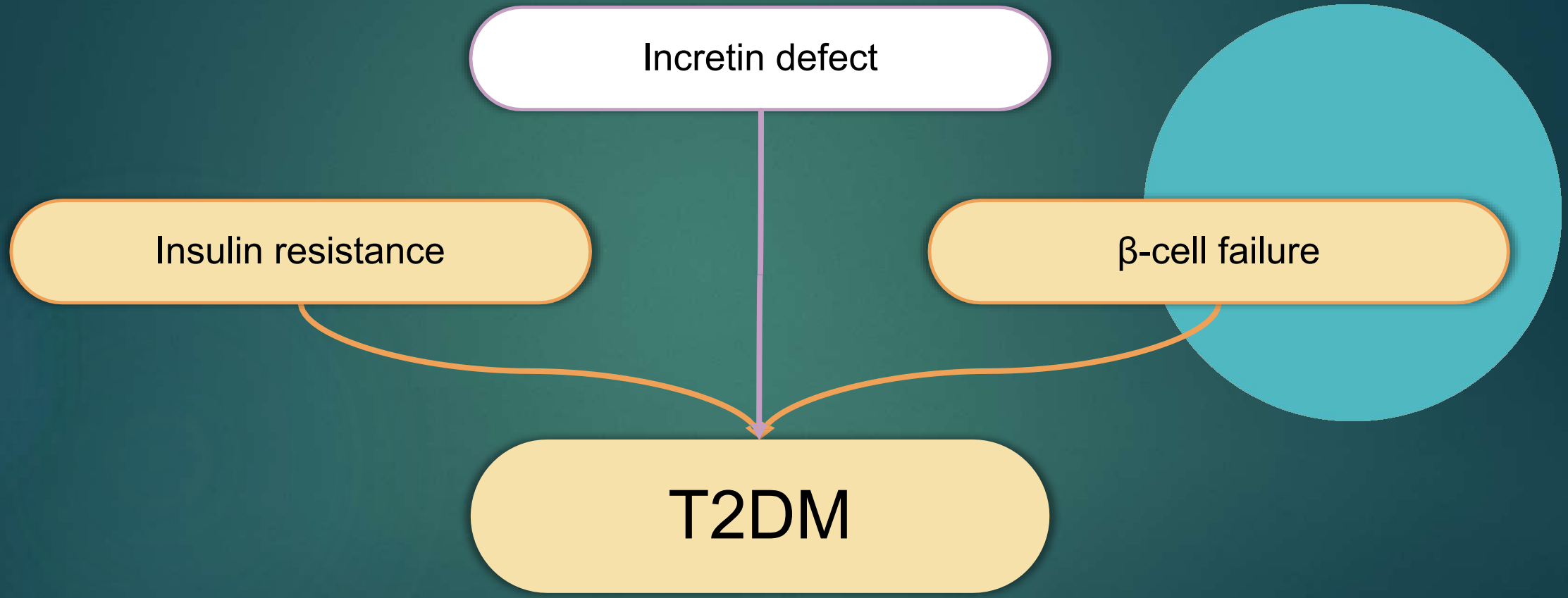


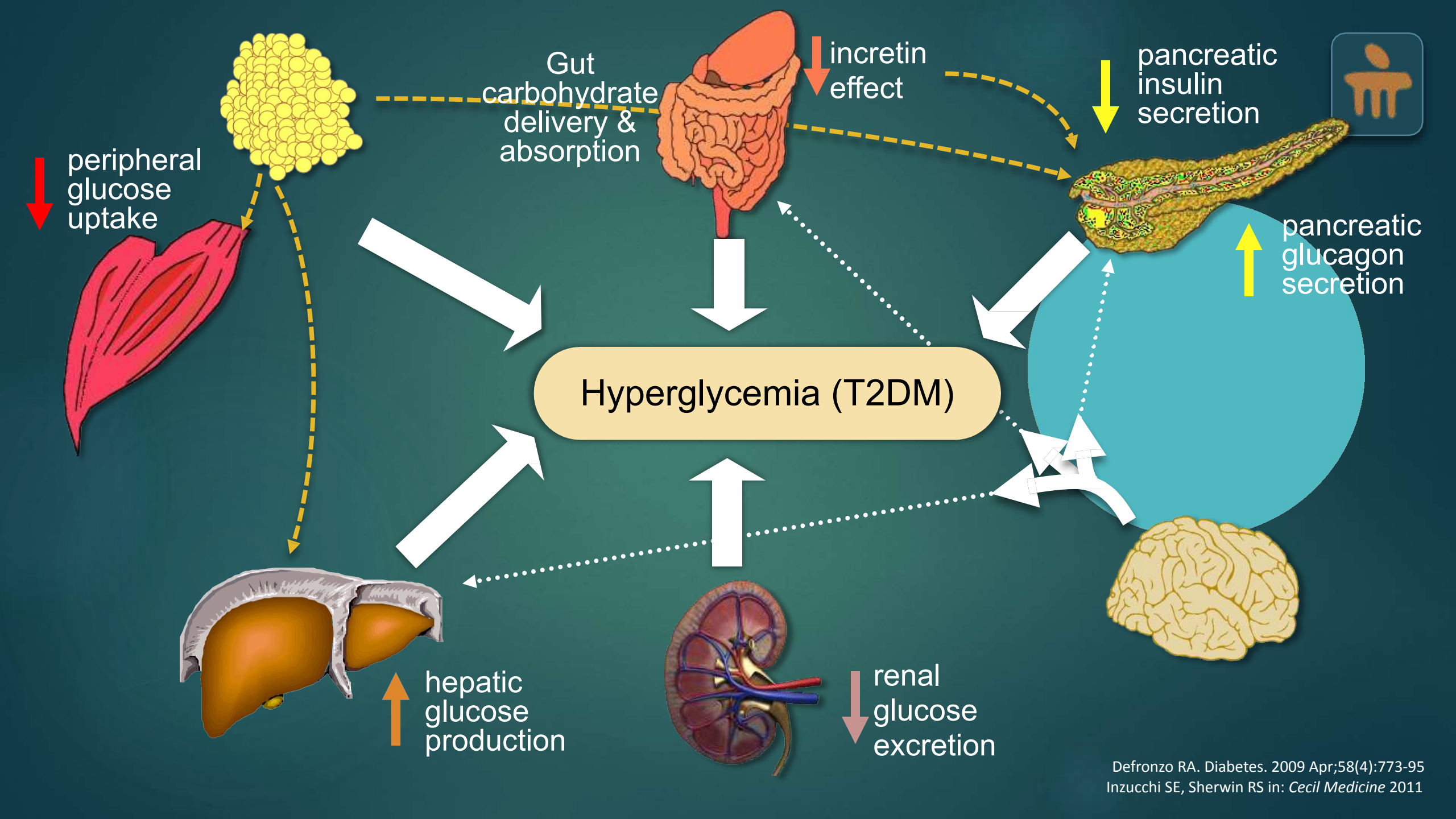
Natural history of T2DM



Kendall DM, et al. Am J Med 2009;122:S37-S50.
Kendall DM, et al. Am J Manag Care 2001;7(suppl):S327-S343.

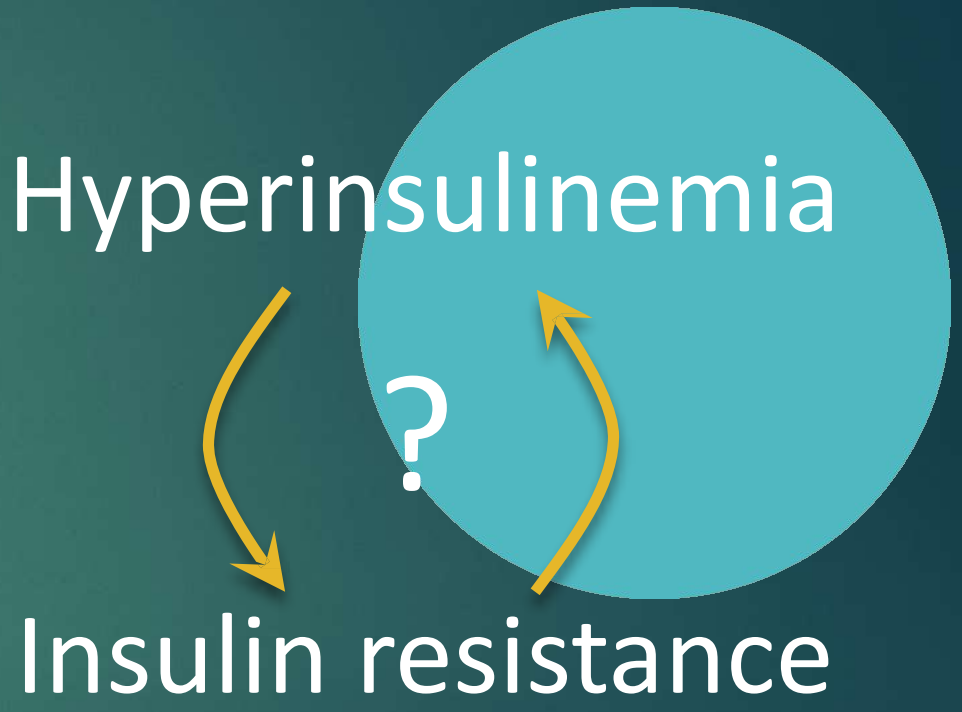
Classic view





Defronzo RA. Diabetes. 2009 Apr;58(4):773-95
Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Which came first?



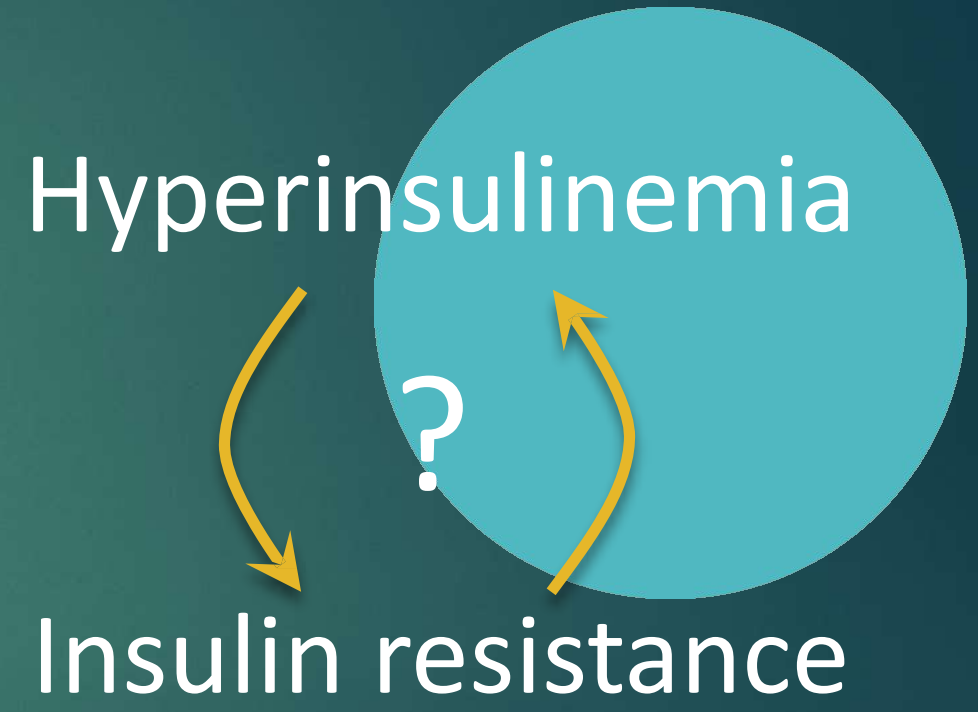
Pories WJ et al. Diabetes Care. 2012 Dec;35(12):2438-42

Diabetes: Have We Got It All Wrong?
Hyperinsulinism as the culprit: surgery provides the evidence

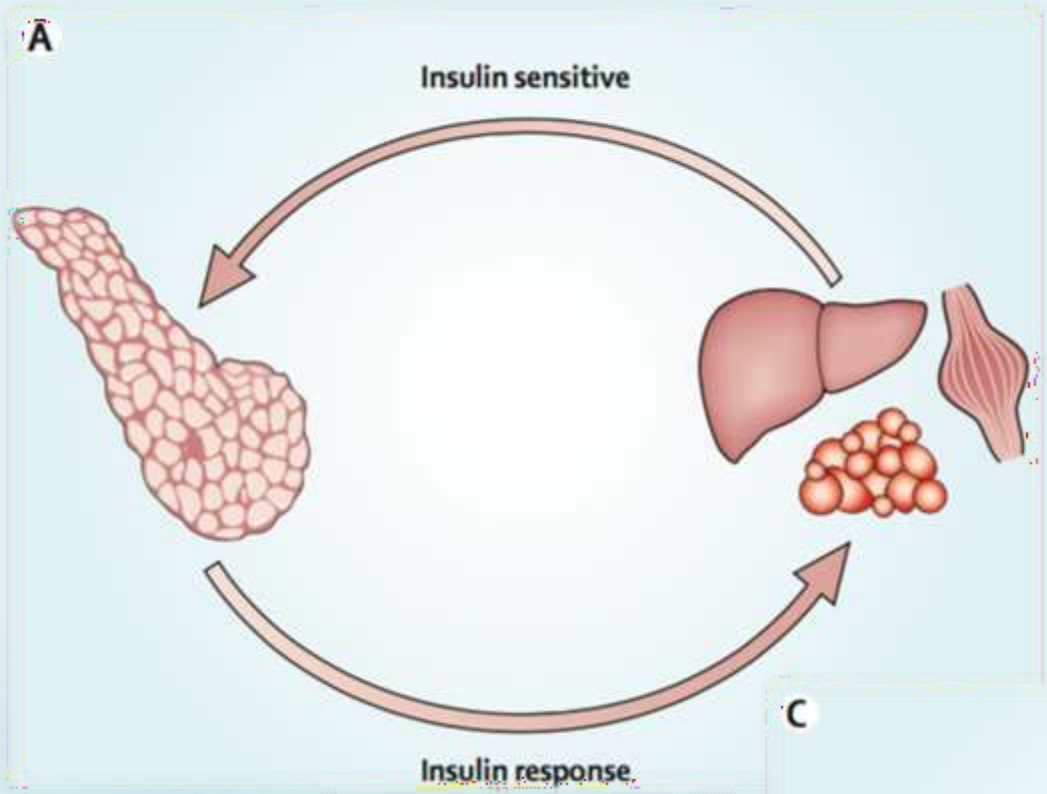
Walter J. Pories, MD, FACS and G. Lynis Dohm, PHD

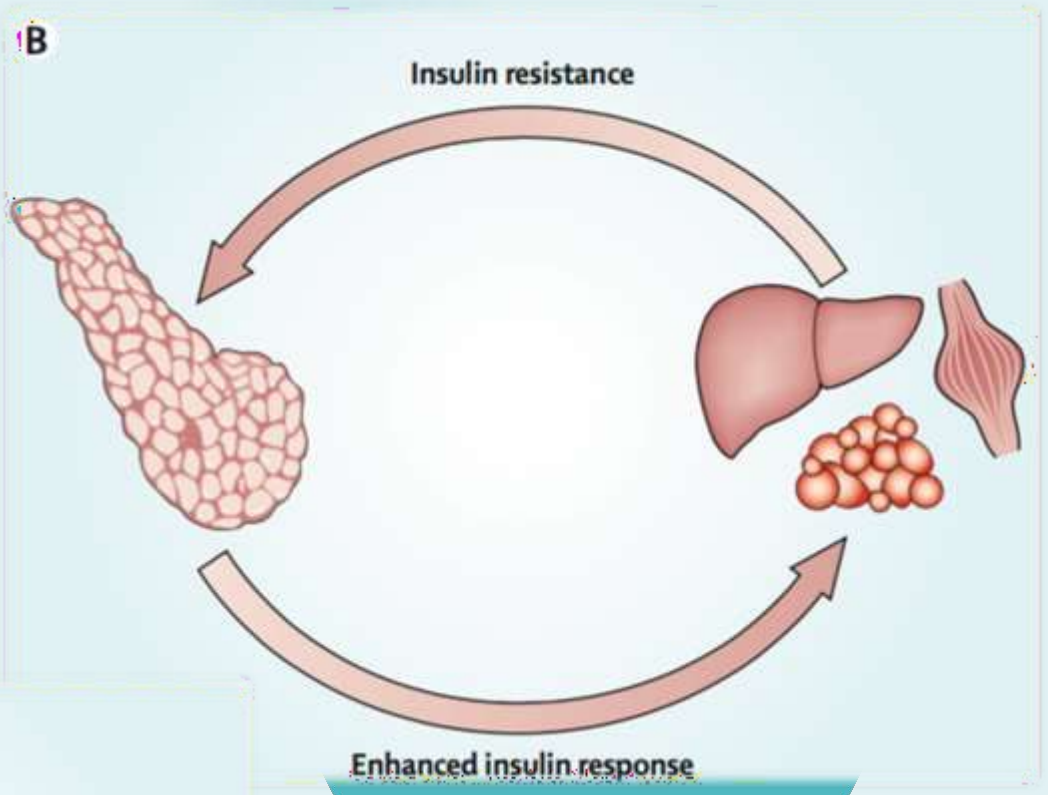
Diabetes: Have We Got It All Wrong?
Insulin hypersecretion and food additives: cause of obesity and diabetes?

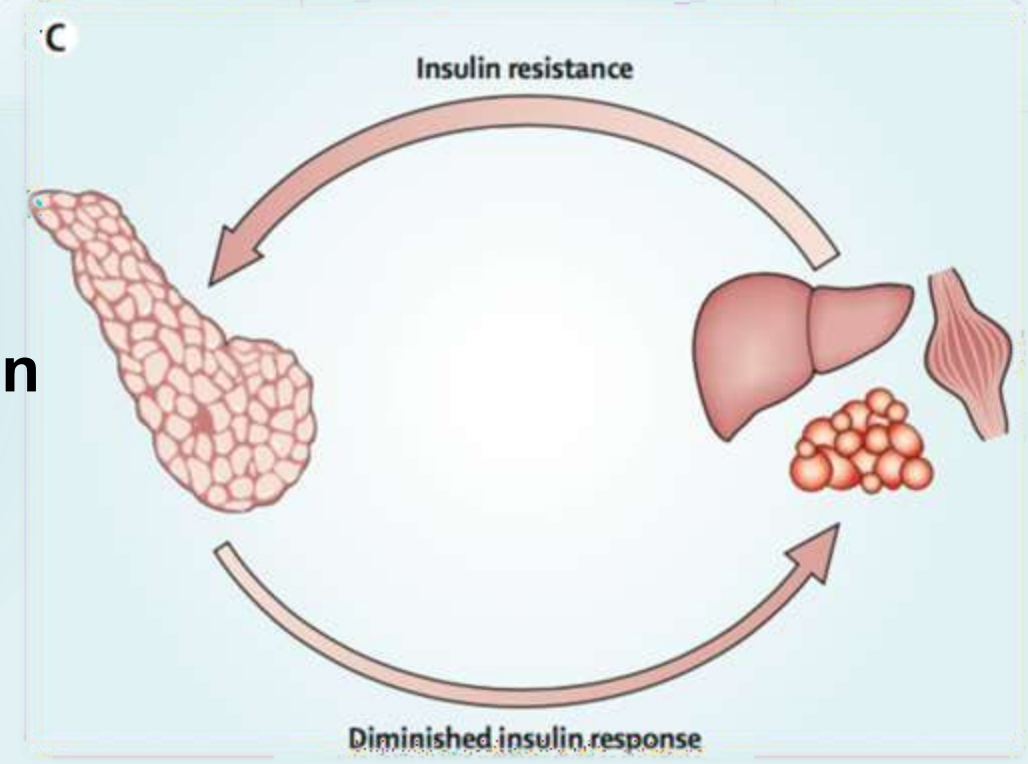
Barbara E. Corkey, PHD



Pories WJ et al. Diabetes Care. 2012 Dec;35(12):2438-42
Corkey BE. Diabetes Care. 2012 Dec;35(12):2432-37





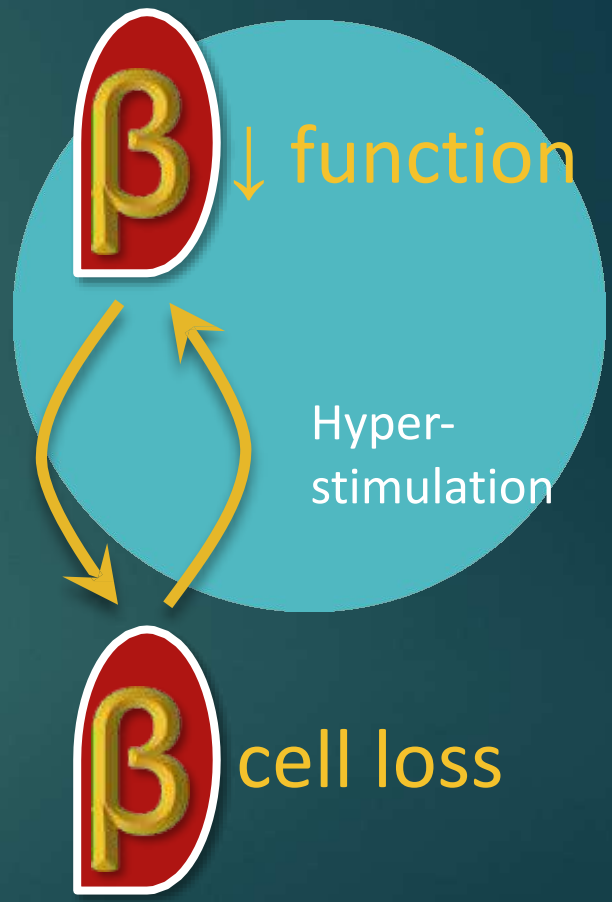


Feedback loop between β-cells and insulin-sensitive tissues

Steven E. Kahn, et al; Lancet. 2014 March 22; 383: 1068–1083

Roles of β-cell loss and α-cell dysfunction

- **Reduction of β-cell numbers in T2DM**
  - **Human pancreas is incapable of renewing β-cells after 30yr of age**
  - Glucolipotoxicity and amyloid deposition result in β-cell apoptosis through oxidative and endoplasmic-reticulum stress
- **Abnormal glucagon release by α-cells**
  - elevated fasting glucagon
  - non-suppression after meal ingestion

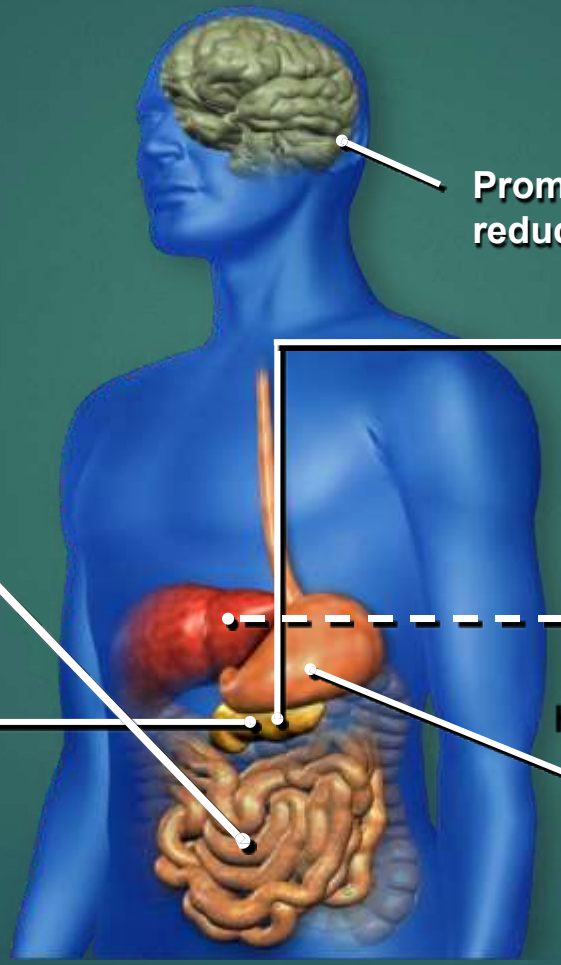


Perl S et al. *J Clin Endocrinol Metab* 2010; **95:** E234–39

Role of Intestines

Numerous functions of GLP-1

GLP-1: Secreted upon the ingestion of food



Promotes satiety and reduces appetite

Alpha cells:
↓ Glucose-dependent postprandial glucagon secretion

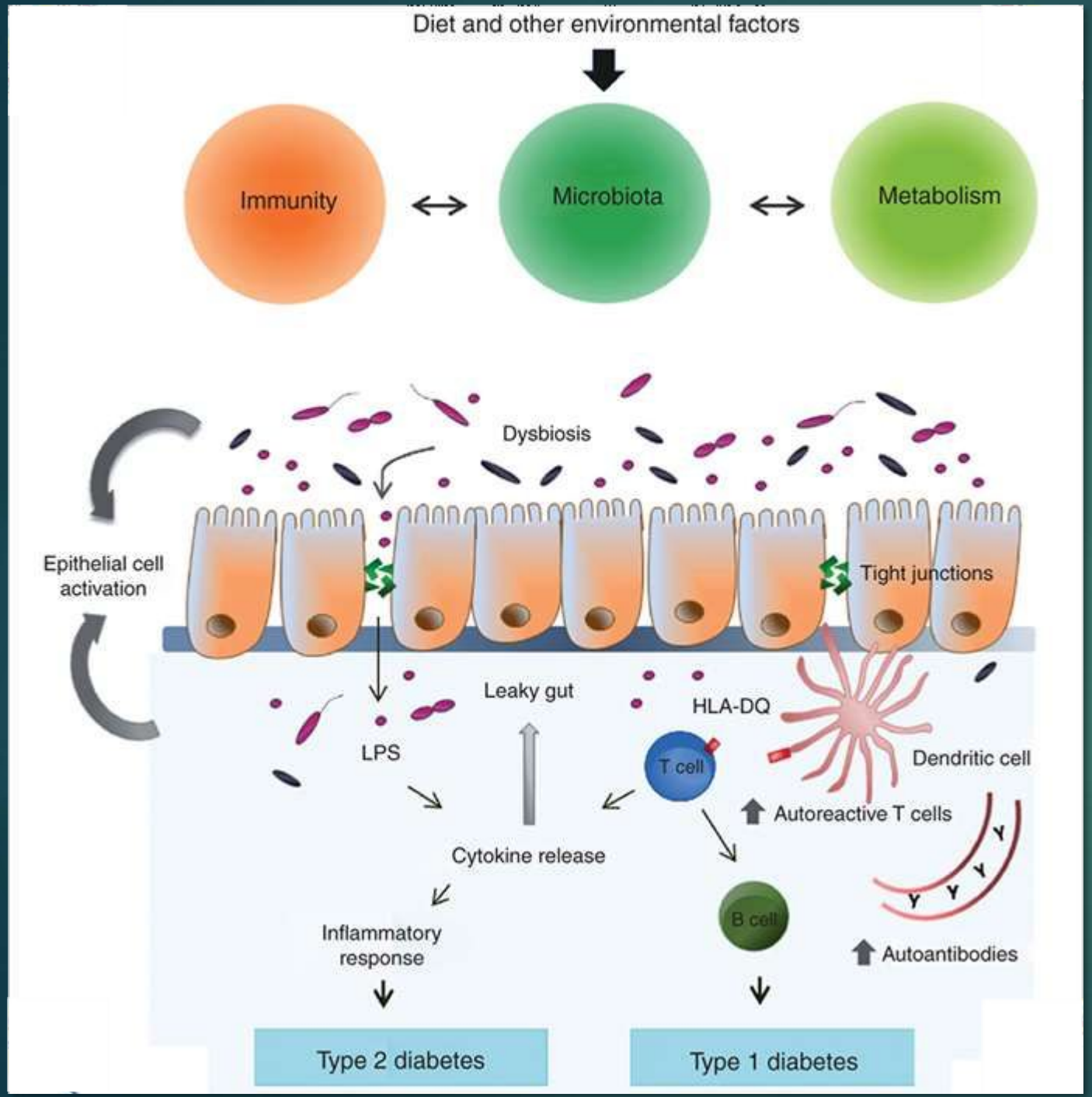
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Incretins
Bile acids

Flint A, et al. J Clin Invest 1998;101:515-520. Larsson H, et al. Acta Physiol Scand 1997;160:413-422. Nauck MA, et al. Diabetologia 1996;39:1546-1553. Drucker DJ. Diabetes 1998;47:159-169.

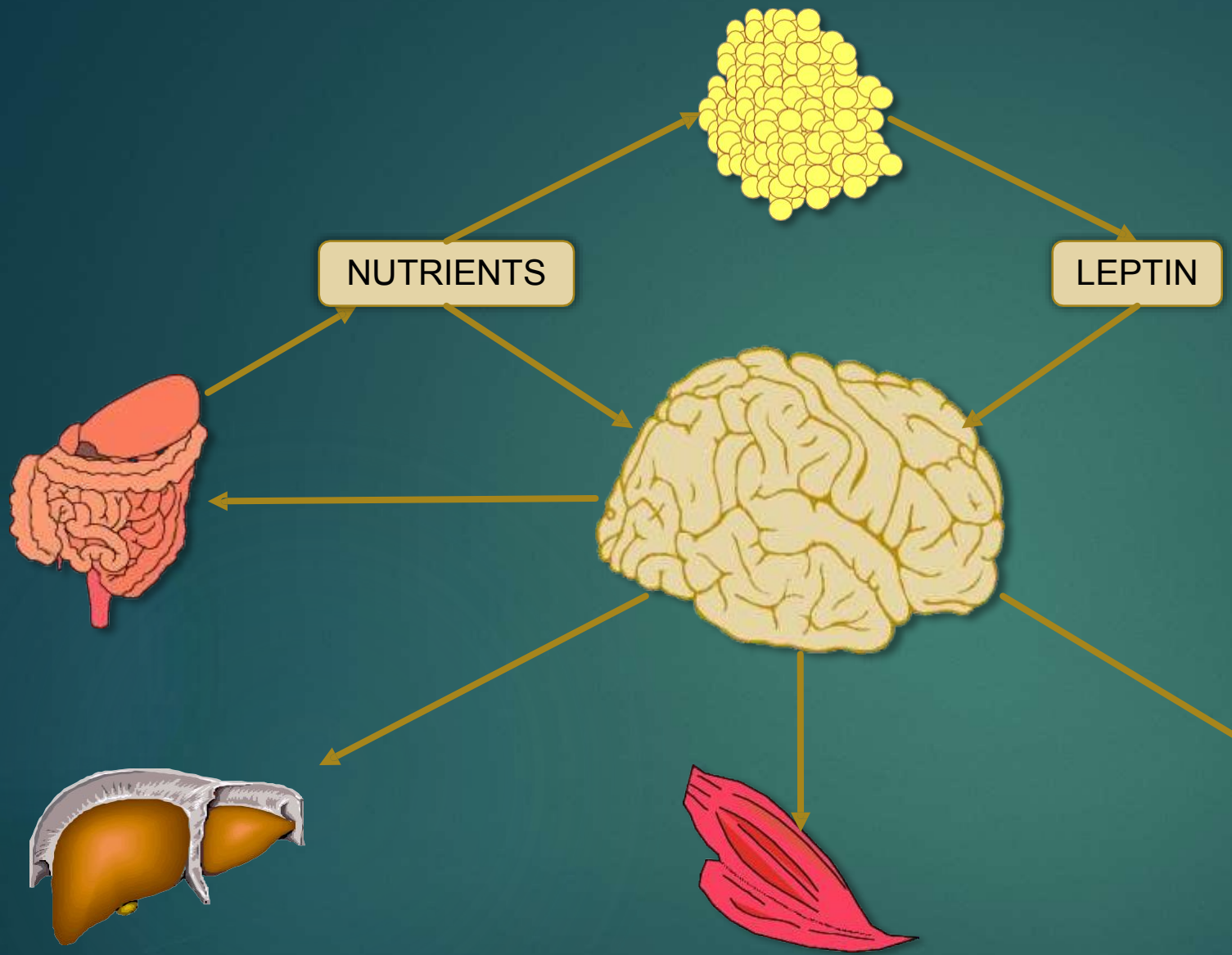


Intestinal microbiome in diabetes

- Gut microbiome has >100 times genetic information than human genome
- Gut genome + Human genome = Human metagenome

Sanz Y et al. *Pediatric Research* (2015) 77, 236–244

Role of Brain



Sympathetic and parasympathetic nervous systems control glucose metabolism

- directly through neuronal input
- indirectly through circulation to affect release of insulin and glucagon and production of hepatic glucose.

Vagus
Hypothalamus

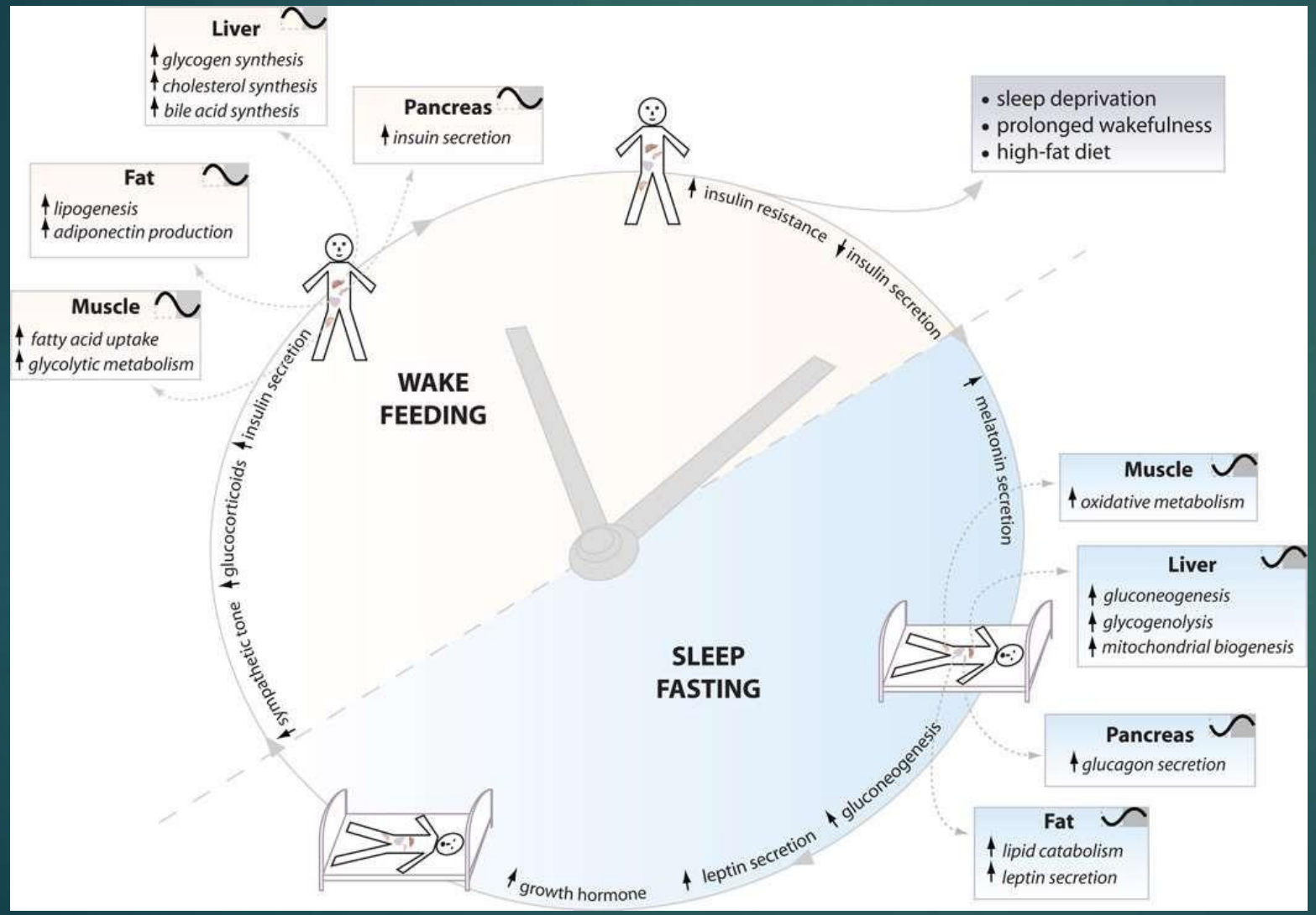
Steven E. Kahn, et al; Lancet. 2014 March 22; 383: 1068–1083

Alzheimer's disease (AD)

- Now proposed as type 3 diabetes (T3DM)
- Insulin resistance in brain
  - Brain has insulin and IGF receptors
  - There is evidence that neurons have insulin and IGF resistance in patients with AD

Suzanne M. de la Monte. Eur Neuropsychopharmacol. 2014 Dec;24(12):1954-60

Role of sleep/ deprivation in diabetes



Changes in diurnal patterns and quality of sleep can have important effects on metabolic processes

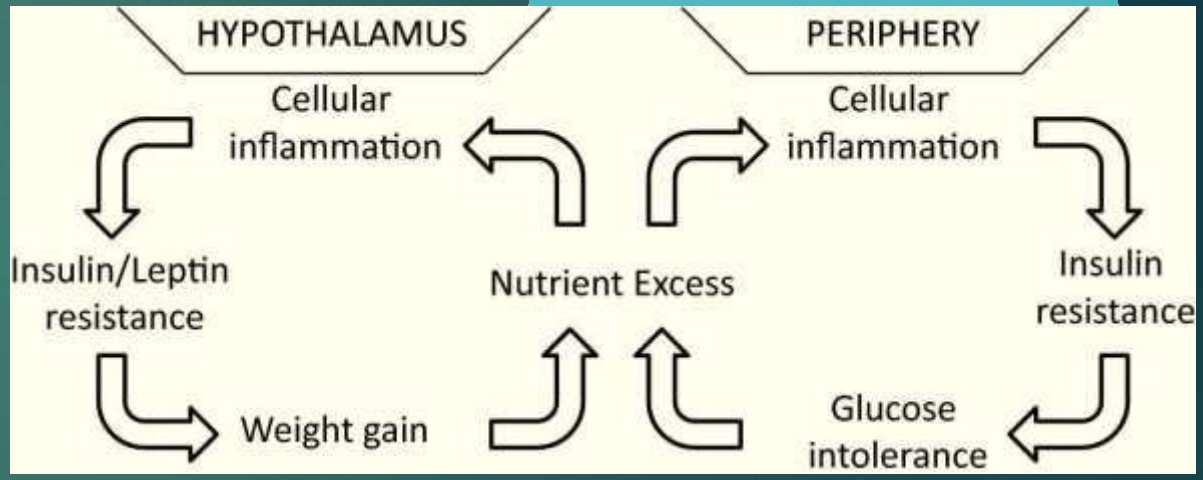
Bass J et al. Science. 2010 Dec 3; 330(6009): 1349–1354.

Role of inflammation

Role of inflammation

- Obesity is characterised by systemic inflammation
- Preclinical evidence links systemic inflammation to β-cell dysfunction
- CRP and its upstream regulator IL-6, are associated with insulin sensitivity and β-cell function
- Circulating concentrations of IL-1β and IL-1 receptor *antagonists* too are increased in T2DM

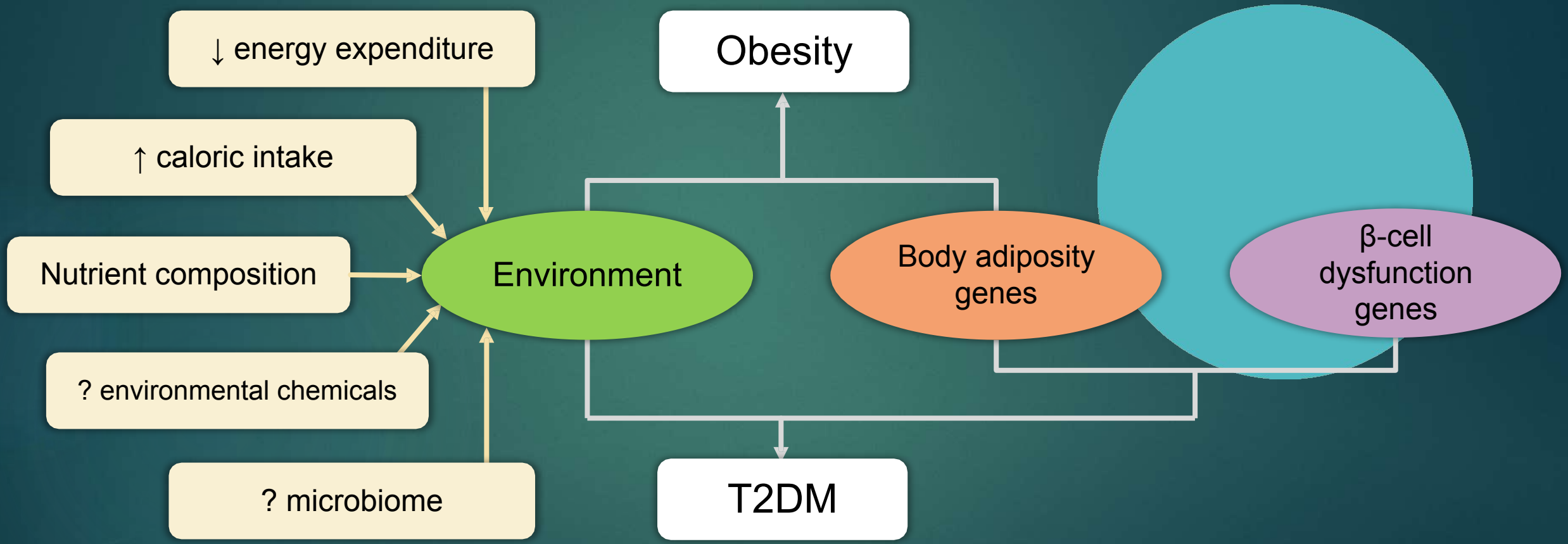
- Hypothalamic inflammation might also contribute to central leptin resistance and weight gain



Luotola K et al. J Intern Med 2011; 269: 322–32.
Thaler JP et al. *Endocrinology* 2010;**151:** 4109–15.

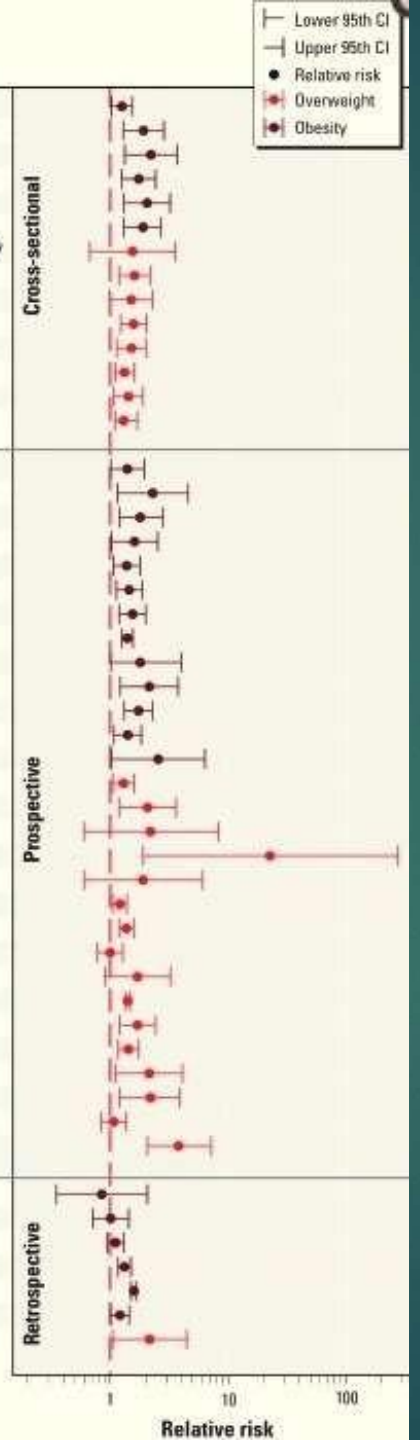
Role of environmental factors

Role of environmental factors



Steven E. Kahn, et al; Lancet. 2014 March 22; 383: 1068–1083

Reference	Study description (*n*)	Relative risk adj OR (95% CI)
Gorog et al. 2009	Europe (6 countries) CESAR, 9–12 year, ♂♀ (8,926)	1.26 (1.03, 1.55)
Toschke et al. 2002	Germany (Bavaria) 5–6.9 year (1997), ♂♀ (8,365)	1.92 (1.29, 2.86)
Toschke et al. 2003	Germany (Bavaria) 5–6 year (2001/2002), ♂♀ (4,974)	2.22 (1.33, 3.69)
Toschke et al. 2007	Germany (Bavaria) 5–6 year (2001/2002), ♂♀ (5,472)	1.75 (1.25, 2.43)
Von Kries 2002	Germany (Bavaria) 5–6.9 year, ♂♀ (6,483)	2.06 (1.31, 3.23)
Von Kries 2008	Germany (Bavaria) 5–6.9 year, ♂♀ (5,899)	1.9 (1.3, 2.7)
Ino et al. 2011	Japan (Kumagaya) 9–10 year, ♂♀ (2,508)	1.55 (0.67, 3.57) [crude prev OR]*
Koshy et al. 2011	UK (Merseyside) 5–11 year, ♂♀ (3,038)	1.61 (1.19, 2.18)
Raum et al. 2011	Germany (Aachen) 6 year, ♂♀ (1,954)	1.51 (0.99, 2.28)
Toschke et al. 2002	Germany (Bavaria) 5–6.9 year (1997), ♂♀ (8,365)	1.58 (1.23, 2.04)
Toschke et al. 2003	Germany (Bavaria) 5–6 year (2001/2002), ♂♀ (4,974)	1.52 (1.14, 2.01)
Toschke et al. 2007	Germany (Bavaria) 5–6 year (2001/2002), ♂♀ (5,472)	1.32 (1.10, 1.61)
Von Kries 2002	Germany (Bavaria) 5–6.9 year, ♂♀ (6,483)	1.43 (1.07, 1.90)
Von Kries 2008	Germany (Bavaria) 5–6.9 year, ♂♀ (5,899)	1.3 (1.1, 1.7)
Al Mamun 2006	Australia (Brisbane, Queensland) 14 year, ♂♀ (3,253)	1.40 (1.01, 1.94)
Bergmann et al. 2003	Germany (multisite) 6 year, ♂♀ (918)	2.3 (1.2, 4.6)
Dubois and Girard 2006	Canada (Quebec) 4.5 year, ♂♀ (2,103)	1.8 (1.2, 2.8)
Durmus et al. 2011	Netherlands (Gen R) 4 year, ♂♀ (5,342)	1.61 (1.03, 2.53)
Montgomery and Ekbom 2002	UK (nat'l) NCDS, 33 year, ♂♀ (4,917)	1.38 (1.06, 1.79)
Power and Jefferis 2002	UK (England, Scotland, Wales) 1958 BBC, 33 year, ♀ (2,921)	1.45 (1.13, 1.87)
Power and Jefferis 2002	UK (England, Scotland, Wales) 1958 BBC, 33 year, ♂ (2,918)	1.55 (1.19, 2.00)
Power et al. 2010	UK (England, Scotland, Wales) 1958 BBC, 45 year, ♂♀ (8,815)	1.40 (1.25, 1.56)
Reilly et al. 2005	UK (multisite) ALSPAC 7 year, ♂♀ (7,758)	1.80 (1.01, 3.99)
Rooney et al. 2010	USA (3 midwestern states) 9–14 year, ♂♀ (777)	2.15 (1.22, 3.78)
Salsberry and Reagan 2005	USA (nat'l) NLSY Child-Mother, 6–7 year, ♂♀ (3,022)	1.74 (1.32, 2.29)
Salsberry and Reagan 2007	USA (nat'l) NLSY Child-Mother, 12–13 year, ♂♀ (3,368)	1.41 (1.08, 1.84)
Suzuki et al. 2009	Japan (Koshu City) 9–10 year, ♂♀ (1,644)	2.56 (1.02, 6.38)
Al Mamun 2006	Australia (Brisbane, Queensland) 14 year, ♂♀ (3,253)	1.3 (1.1, 1.6)
Bergmann et al. 2003	Germany (multisite) 6 year, ♂♀ (918)	2.08 (1.19, 3.63)
Boerschmann et al. 2010	Germany (multisite) GDM offspring study 2 year, ♂♀ (1,420)	2.2 (0.6, 8.3)
Boerschmann et al. 2010	Germany (multisite) GDM offspring study 11 year, ♂♀ (1,420)	22.7 (1.9, 2.8)
Braun et al. 2010	USA (Cincinnati, OH) 3 year, ♂♀ (389)	1.9 (0.6, 6.1)
Chen et al. 2006	USA (multisite) CPP 8 year, ♂ (14,486)	1.21 (1.05, 1.39)
Chen et al. 2006	USA (multisite) CPP 8 year, ♀ (14,612)	1.37 (1.19, 1.58)
Durmus et al. 2011	Netherlands (Gen R) 4 year, ♂♀ (5,342)	1.00 (0.78, 1.28)
Gillman et al. 2008	USA (Boston, MA) Project Viva, 3 year, ♂♀ (1,110)	1.71 (0.90, 3.25)
Iliadou et al. 2010	Sweden (nat'l) milt serv registry 17–24 year, ♂ (124,203)	1.41 (1.34, 1.49)
Koupil and Toivanen 2008	Sweden (nat'l) registries, 18 year, ♂ (6,535)	1.71 (1.21, 2.43)
Kuhle et al. 2010	Canada (Nova Scotia) CLASS 5th grade, ♂♀ (3,426)	1.43 (1.17, 1.75)
Mizutani et al. 2007	Japan (Enzan City) Project Enzan, 5 year, ♂♀ (1,417)	2.15 (1.12, 4.11)
Oken et al. 2005	USA (Boston, MA) Project Viva, 3 year, ♂♀ (2,218)	2.2 (1.2, 3.9)
Tome et al. 2007	Brazil (Ribeirao) 8–10 year, ♂♀ (2,797)	1.07 (0.84, 1.37)
Widerøe et al. 2003	Norway/Sweden (Trondheim/Bergen) 5 year, ♂♀ (482)	3.8 (2.1, 7.2)
Sharma et al. 2008	USA (multisite) PedNSS (Asia/Pacific) 2–4 year, ♂♀ (4,740)	0.85 (0.35, 2.07)
Sharma et al. 2008	USA (multisite) PedNSS (Am Ind/AK Nat) 2–4 year, ♂♀ (2,228)	1.01 (0.71, 1.44)
Sharma et al. 2008	USA (multisite) PedNSS (Hispanic) 2–4 year, ♂♀ (34,378)	1.11 (0.95, 1.31)
Sharma et al. 2008	USA (multisite) PedNSS (Black) 2–4 year, ♂♀ (31,704)	1.32 (1.17, 1.50)
Sharma et al. 2008	USA (multisite) PedNSS (White) 2–4 year, ♂♀ (82,361)	1.59 (1.5, 1.68)
Whitaker 2004	USA (Ohio) WIC, 4 year, ♂♀ (8,494)	1.21 (1.01, 1.45)
Adams et al. 2005	USA (Wisconsin) Am Ind/WIC program, 3 year, ♂♀ (252)	2.16 (1.05, 4.47)

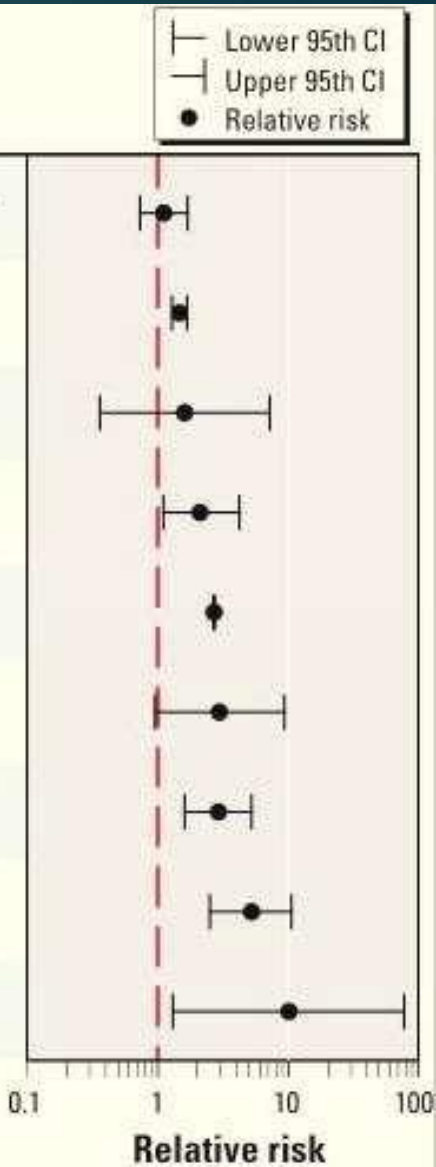


Association between maternal smoking during pregnancy and overweight/obesity in offspring

Thayer KA et al. Environ Health Perspect. 2012 Jun;120(6):779-89

Association between arsenic and diabetes in areas of high exposures

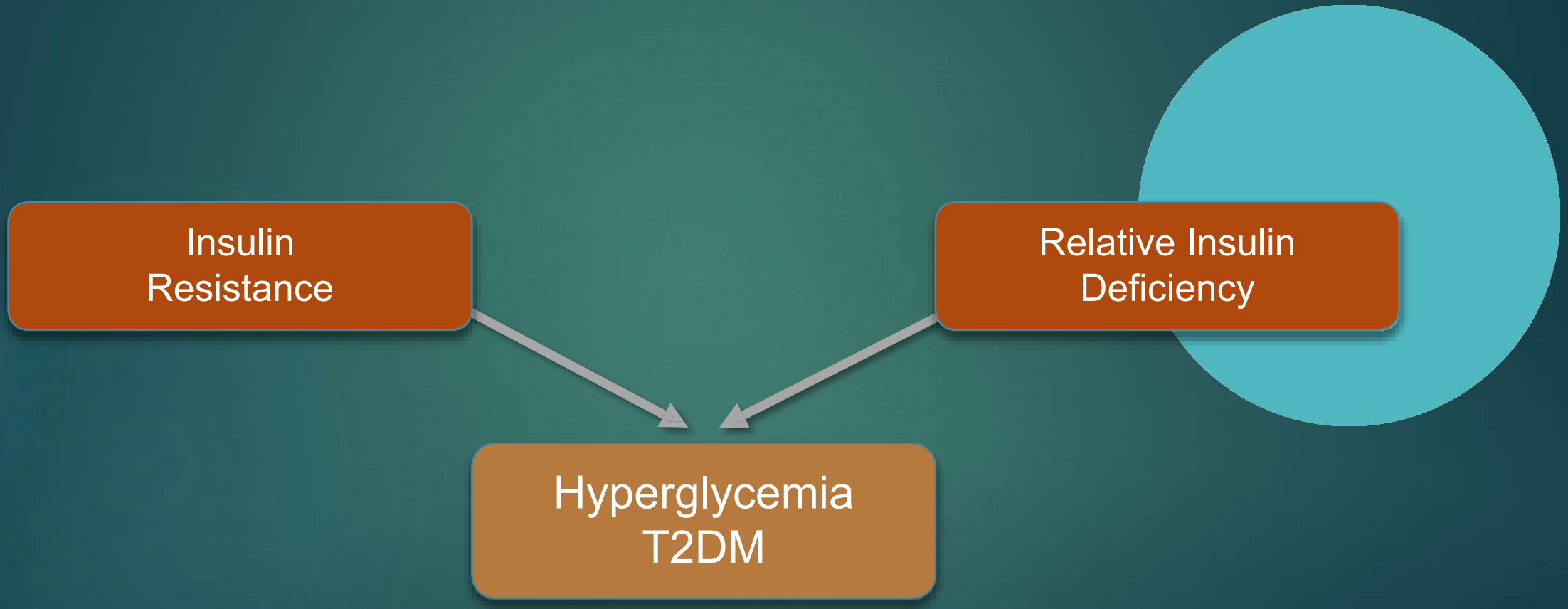
Reference	Study description (*n*)	Diagnostic	Relative risk adj OR (95% CI)	Exposure
Chen et al. 2010	Bangladesh (Araihazar) CS HEALS, ♂♀ (11,319)	Self-report prior to baseline	1.11 (0.73, 1.69)	176.2–864 (Qn5) vs. 0.1-8 (Qn1) µg/L (drinking water, CEI)
Tsai et al. 1999	Taiwan (Chiayi County) Retro blackfoot region, ♂♀ (19,536 deaths)	Death certificate	1.46 (1.28, 1.67) SMR[a]	Blackfoot endemic region vs. national reference
Tollestrup et al. 2003	USA (Ruston, WA) Retro, lived near smelter as children, ♂♀ (1,074 deaths)	Death certificate	1.6 (0.4, 7.2) RR[a]	≥ 10 vs. < 1 year
Tseng et al. 2000a, 2000b	Taiwan (southwestern) Pros industrial region, ♂♀ (446)	FBG, OGGT	2.1 (1.1, 4.2) RR	≥ 17 vs. < 17 mg/L-year (drinking water, CEI)
Wang et al. 2003	Taiwan (southwestern) CS As endemic reg., ♂♀ (706,314)	Insurance claims	2.69 (2.65, 2.73)	Endemic vs. nonendemic region
Nabi et al. 2005	Bangladesh (Chapainowabganj) CC 115 arsenicosis cases, ♂♀ (235)	Glucose, blood	2.95 (0.95, 9.28) OR[a]	218.1 vs. 11.3 (avg) µg/L (drinking water)
Rahman et al. 1999	Bangladesh (multi-site) CS w/skin lesions, ♂♀ (134)	Glucosuria	2.9 (1.6, 5.2) adj PR	> 10 vs. < 1 mg-year/L (drinking water, CEI)
Rahman et al. 1998	Bangladesh (Dhaka) CS 163 keratosis cases, ♂♀ (1,107)	Self-report, OGGT, glucosuria	5.2 (2.5, 10.5) adj PR	Keratosis vs. non-keratosis
Lai et al. 1994	Taiwan (Southern) CS As endemic region, ♂♀ (891)	Self-report, OGGT, treatment history	10.1 (1.3, 77.9)	≥ 15 vs. 0 ppm-year (drinking water, CEI)

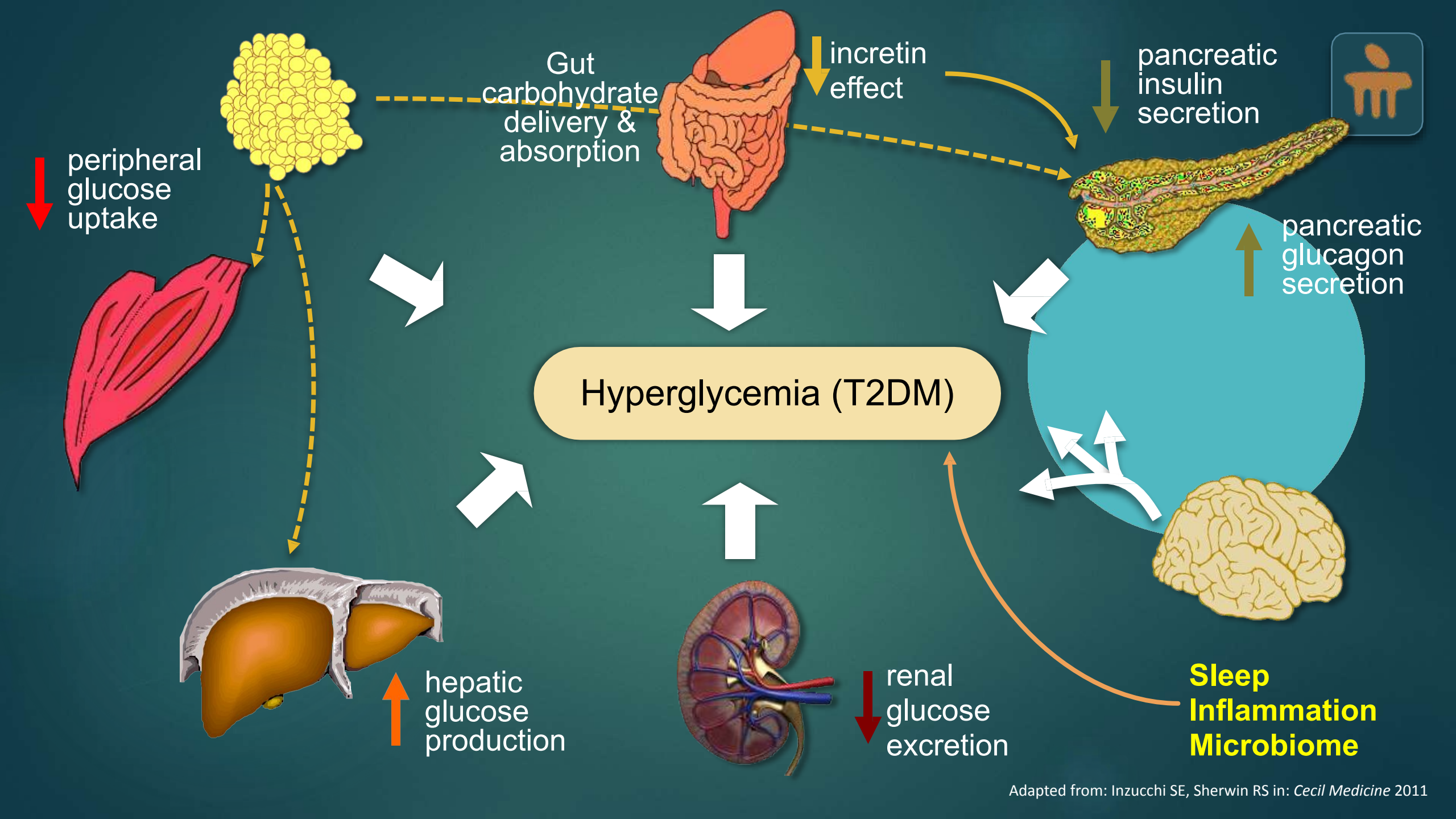


Thayer KA et al. Environ Health Perspect. 2012 Jun;120(6):779-89

Summary

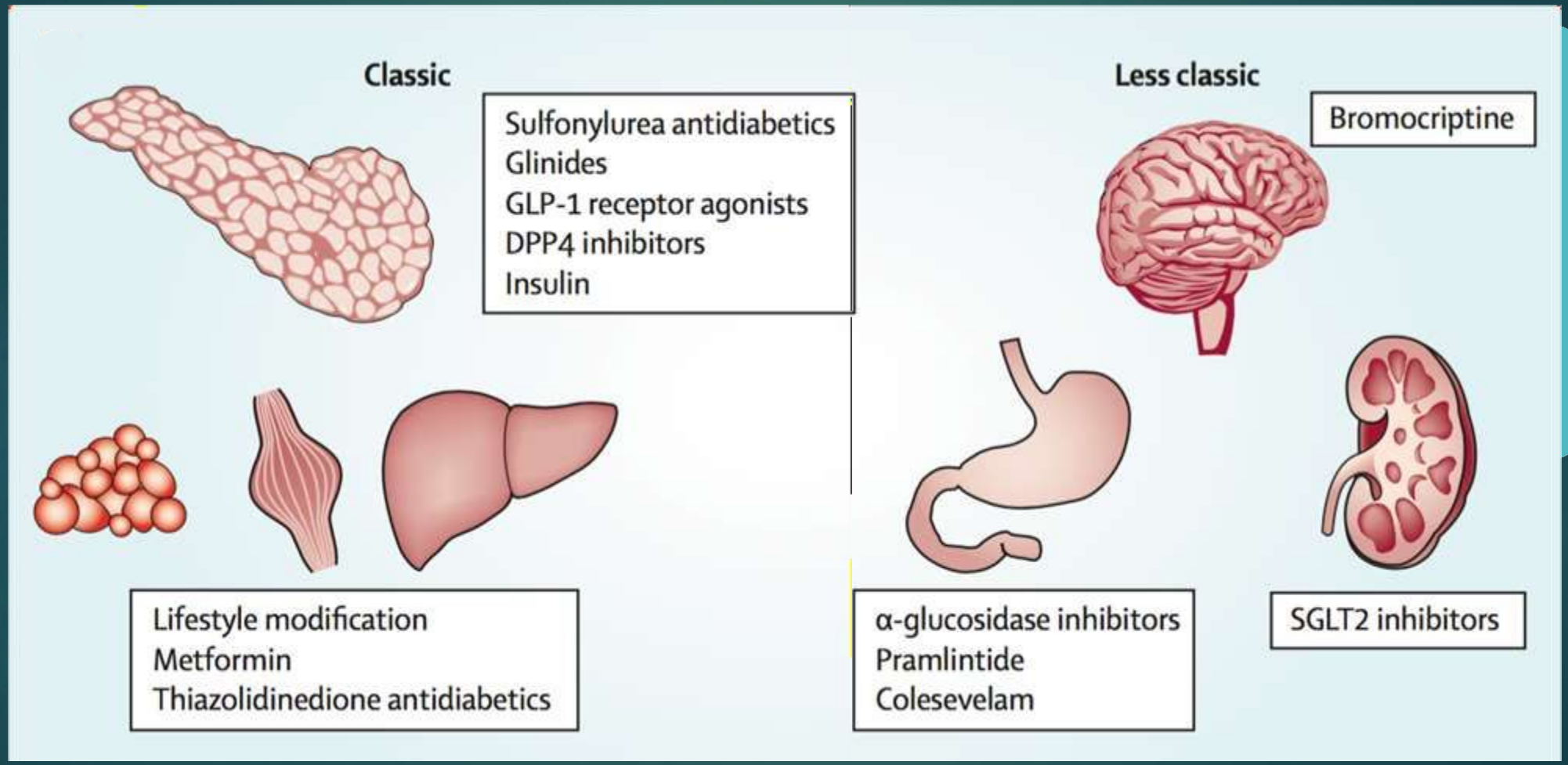
Classic


Insulin Resistance
Relative Insulin Deficiency
Hyperglycemia T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Pathogenesis → Treatment



Pathophysiology of T2DM is not like a simple bicycle with pedal-handle-wheels (IR - βCF - Glucose)

It is much more complex:

Thank you

Question 1

- Which factors determine development of insulin resistance and β-cell dysfunction?

A. Genes, environment and lifestyle together are important determinants

B. Genetic factors alone

C. Obesity alone, by triggering hyperstimulation of β-cells causing their failure

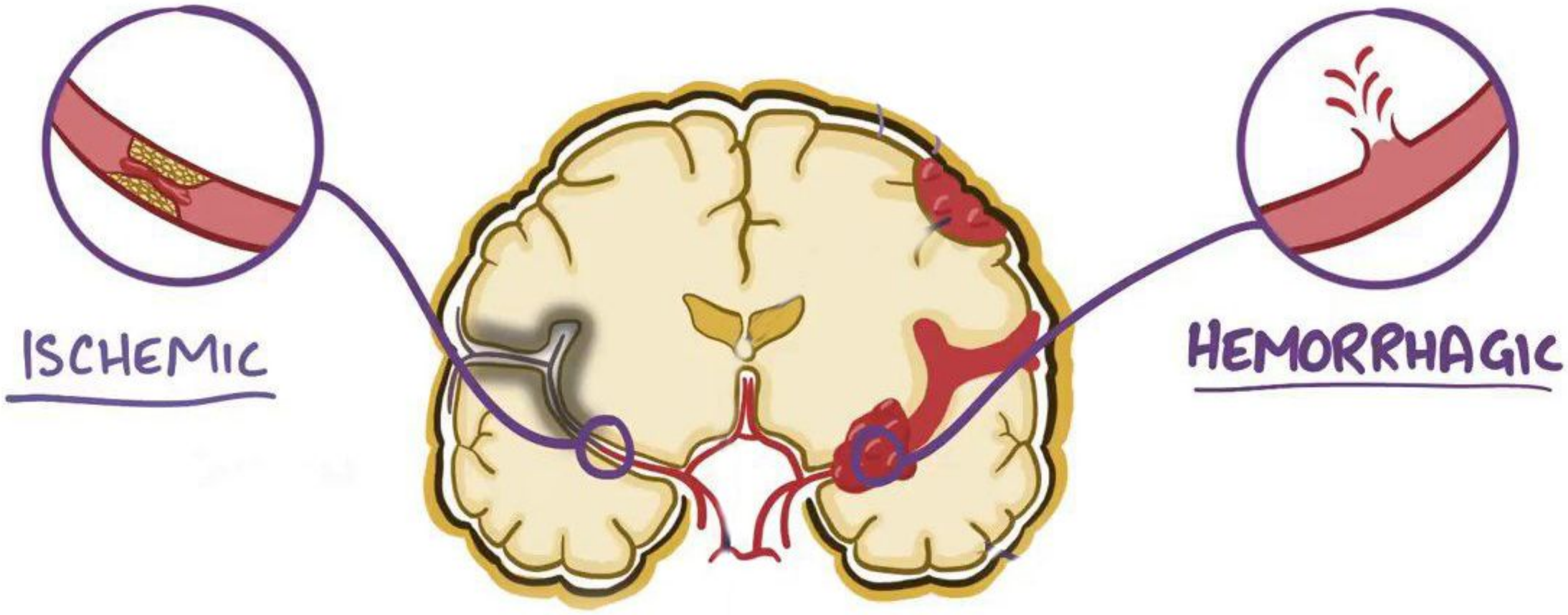
D. None of the above

Question 2

- Example of environmental factors that influence development of T2DM include

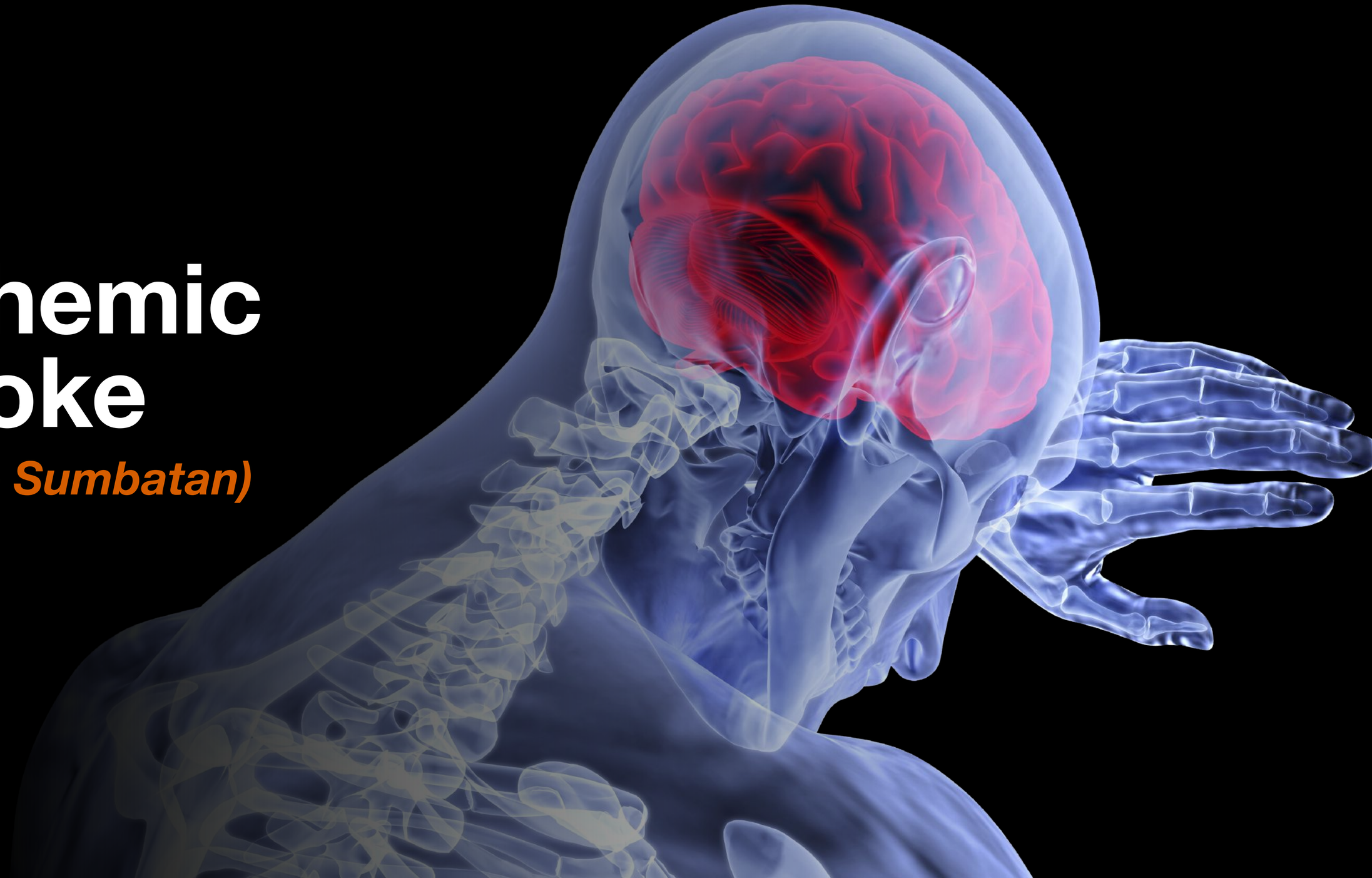
A. Saturated fats in diet
B. Arsenic exposure
C. Gut microbiome
D. All of the above

Ischemic & Hemorrhagic Stroke


ISCHEMIC
HEMORRHAGIC

Ischemic Stroke

(Stroke Sumbatan)



Ischemic Stroke

(Stroke Sumbatan)

Penyebab

1. Hipertensi
2. Diabetes Melitus
3. Kolesterol
4. Infeksi jantung
5. Merokok

Ischemic Stroke

(Stroke Sumbatan)

Stroke Emboli

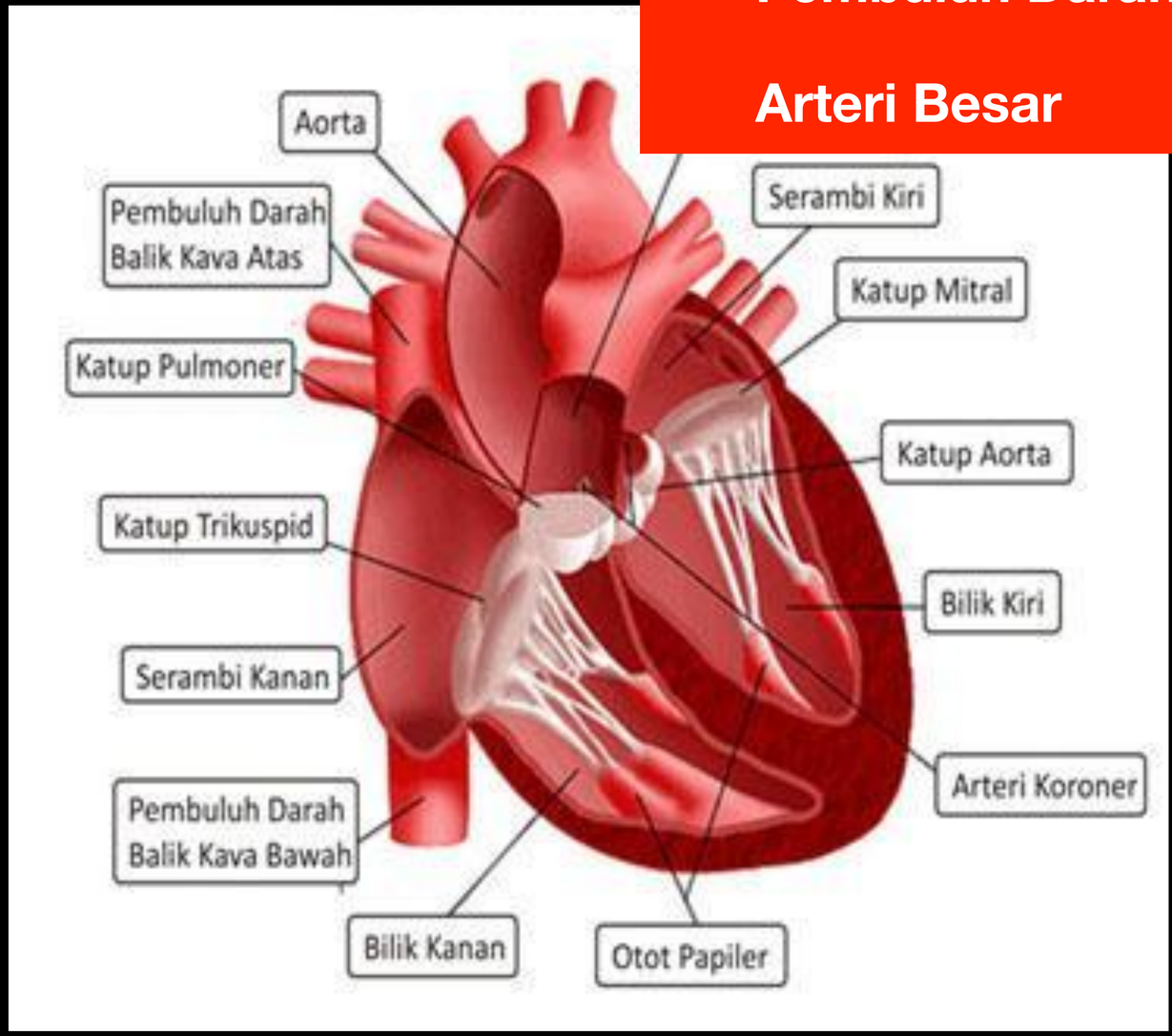
Stroke

Trombotik

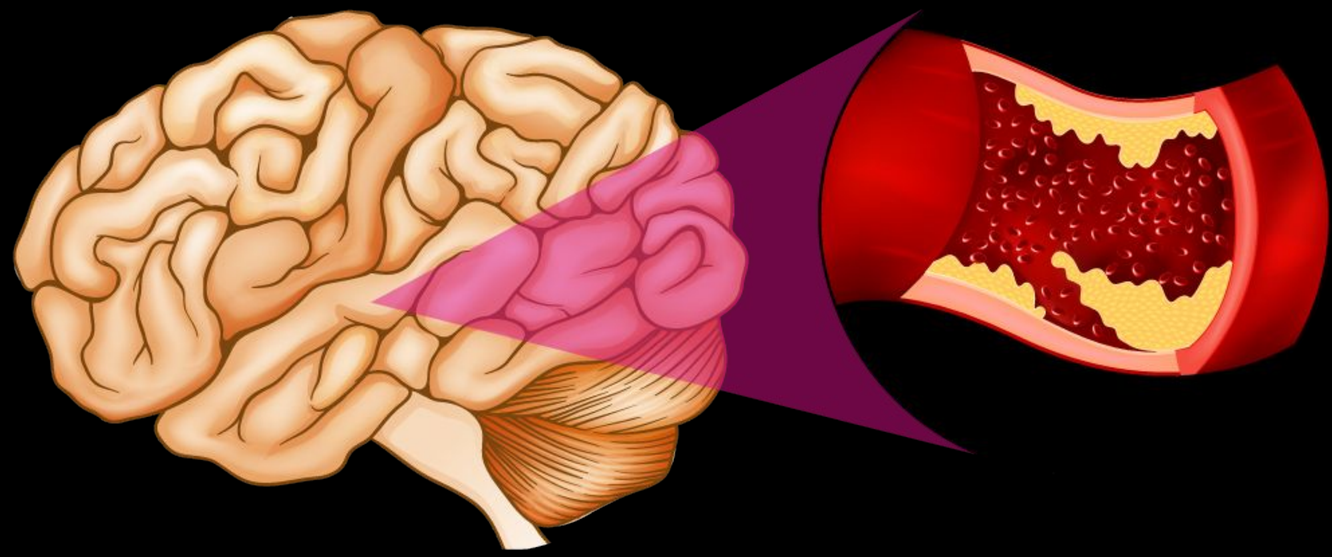
Stroke Embolik

Pembuluh Darah

Arteri Besar



Stroke Trombotik



Pembuluh darah arteri

kecil yang men-suplai darah di otak

Stroke Emboli

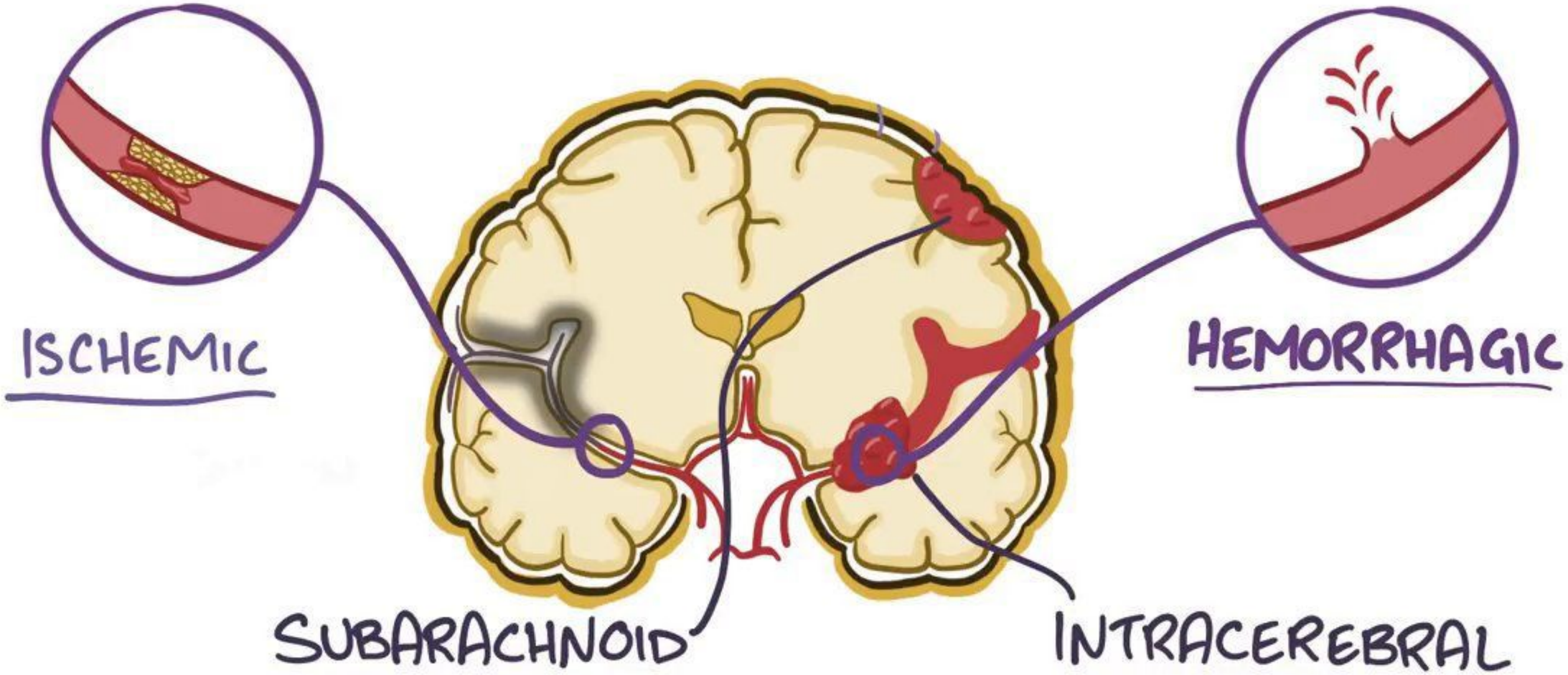
1. Bekuan darahnya/plak *(embolus)* biasanya terjadi di jantung & pembuluh darah (PD) arteri besar
2. Pembuluh Darah terhambat/menyempit
3. Aliran Darah & O2 di otak berkurang
4. *Ischaemia*
5. *Sel mati secara progresif*

Stroke Trombotik

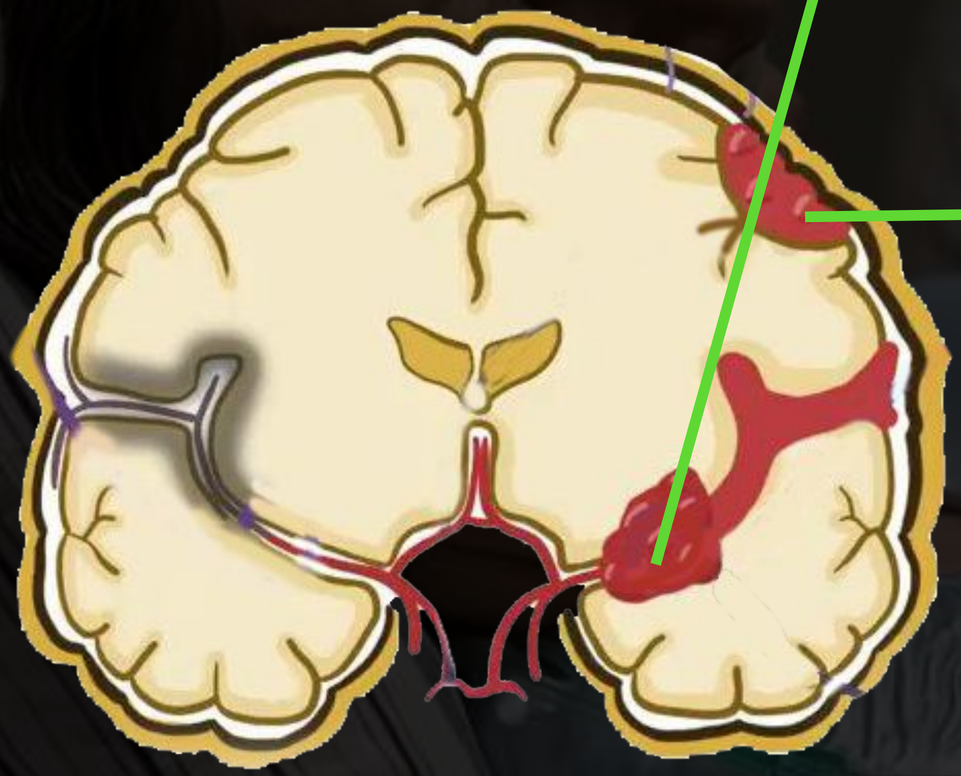
1. Bekuan darahnya/plak *(aterosklerosis)* biasanya terjadi di arteri kecil yang mensuplai darah ke otak
2. Pembuluh Darah terhambat/menyempit
3. Aliran Sarah & O2 di Otak berkurang
4. *Ischaemia*
5. *Sel mati secara progresif*

Hemorrhagic Stroke

(Stroke Perdarahan)


ISCHEMIC
HEMORRHAGIC
SUBARACHNOID
INTRACEREBRAL

Penyebab



Perdarahan

Intraserebral

- Penyebab paling sering = hipertensi tidak terkendali
- Antikogulan (pengencer darah)

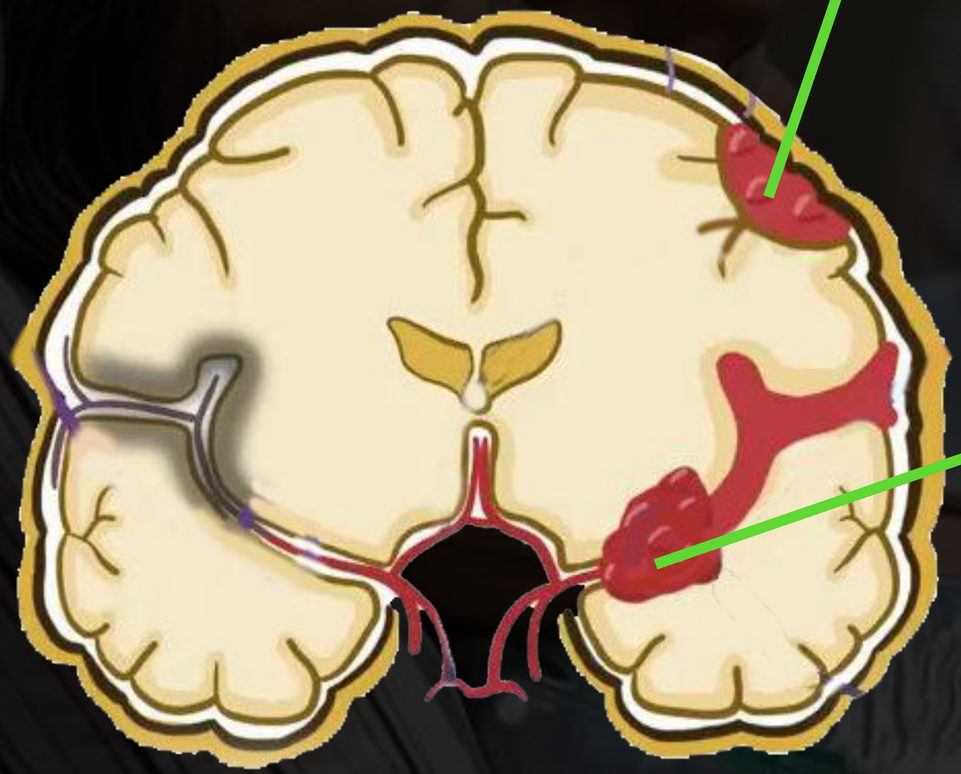
Perdarahan

Subarachnoid

- Penyebab paling sering = Aneurisma pecah —> PD menggelembung seperti balon (karena aliran darah menekan dinding)
- Hipertensi (garam, cafein, alcohol)
- PD lemah wanita > 40 th
- Menopause —> estrogen turun
- Cedera kepala, cocain, ginjal, genetik, kurang Olah raga

Perdarahan subarachnoid

1. PD ada di dekat permukaan otak pecah
2. Darah bocor masuk ke jaringan antara permukaan Otak dengan tulang tengkorak (ruang subarachnoid)
3. Darah dapat terakumulasi
4. Memberi penekanan pada sel-sel Otak
5. Sel-sel Otak mati (nekrosis)
6. Kerja otak mendadak berhenti
7. Mempengaruhi sel Sarah di Otak
8. Stroke



Perdarahan intraserebral

1. PD di Otak pecah (perdarahan/hemorraghic)
2. Darah masuk ke jaringan intraserebral Otak
3. Darah dapat terakumulasi
4. Memberi penekanan pada sel-sel Otak
5. Sel-sel Otak mati (nekrosis)
6. Kerja otak mendadak berhenti
7. Mempengaruhi sel Saraf di Otak
8. Stroke

Thank You!

Questions

?

Patofisiologi Anemia

Your Subtitle Goes Here

Tujuan Pembelajaran

One

Mengenal komponen darah

Two

Mengenal hematopoiesis

Three

Mengenal eritropoiesis & destruksi sel darah merah

Four

Mempelajari patofisiologi berbagai jenis anemia

Pendahuluan

I. FUNGSI DARAH

One

Transportasi

Two

Regulasi

Three

Proteksi

Pendahuluan

Your Subtitle Goes Here

- Darah terdiri dari 45 % *formed elements* (eritrosit, leukosit, dan trombosit), dan 55 % cairan plasma
- Plasma terdiri dari air, protein plasma, elektrolit, gas terlarut, hasil metabolisme, nutrien, vitamin, kolesterol

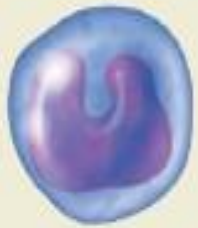
(Lazenby, 2011)

II. KOMPONEN DARAH

Summary of Formed Elements in Blood

NAME AND APPEARANCE	NUMBER	CHARACTERISTICS*	FUNCTIONS
Red Blood Cells (RBCs) or **Erythrocytes** 	4.8 million/μL in females; 5.4 million/μL in males.	7–8 μm diameter, biconcave discs, without nuclei; live for about 120 days.	Hemoglobin within RBCs transports most oxygen and part of carbon dioxide in blood.
White Blood Cells (WBCs) or **Leukocytes**	5000–10,000/μL.	Most live for a few hours to a few days.†	Combat pathogens and other foreign substances that enter body.
Granular leukocytes			
Neutrophils 	60–70% of all WBCs.	10–12 μm diameter; nucleus has 2–5 lobes connected by thin strands of chromatin; cytoplasm has very fine, pale lilac granules.	Phagocytosis. Destruction of bacteria with lysozyme, defensins, and strong oxidants, such as superoxide anion, hydrogen peroxide, and hypochlorite anion.
Eosinophils 	2–4% of all WBCs.	10–12 μm diameter; nucleus usually has 2 lobes connected by thick strand of chromatin; large, red-orange granules fill cytoplasm.	Combat effects of histamine in allergic reactions, phagocytize antigen–antibody complexes, and destroy certain parasitic worms.
Basophils 	0.5–1% of all WBCs.	8–10 μm diameter; nucleus has 2 lobes; large cytoplasmic granules appear deep blue-purple.	Liberate heparin, histamine, and serotonin in allergic reactions that intensify overall inflammatory response.

(Tortora dan Derrickson, 2012)

Agranular leukocytes			
Lymphocytes (T cells, B cells, and natural killer cells) 	20–25% of all WBCs.	Small lymphocytes are 6–9 μm in diameter; large lymphocytes are 10–14 μm in diameter; nucleus is round or slightly indented; cytoplasm forms rim around nucleus that looks sky blue; the larger the cell, the more cytoplasm is visible.	Mediate immune responses, including antigen–antibody reactions. B cells develop into plasma cells, which secrete antibodies. T cells attack invading viruses, cancer cells, and transplanted tissue cells. Natural killer cells attack wide variety of infectious microbes and certain spontaneously arising tumor cells.
Monocytes 	3–8% of all WBCs.	12–20 μm diameter; nucleus is kidney or horseshoe shaped; cytoplasm is blue-gray and appears foamy.	Phagocytosis (after transforming into fixed or wandering macrophages).
Platelets (thrombocytes) 	150,000–400,000/μL.	2–4 μm diameter cell fragments that live for 5–9 days; contain many vesicles but no nucleus.	Form platelet plug in hemostasis; release chemicals that promote vascular spasm and blood clotting.

(Tortora dan Derrickson, 2012)

III. KOMPONEN PLASMA

Substances in Blood Plasma

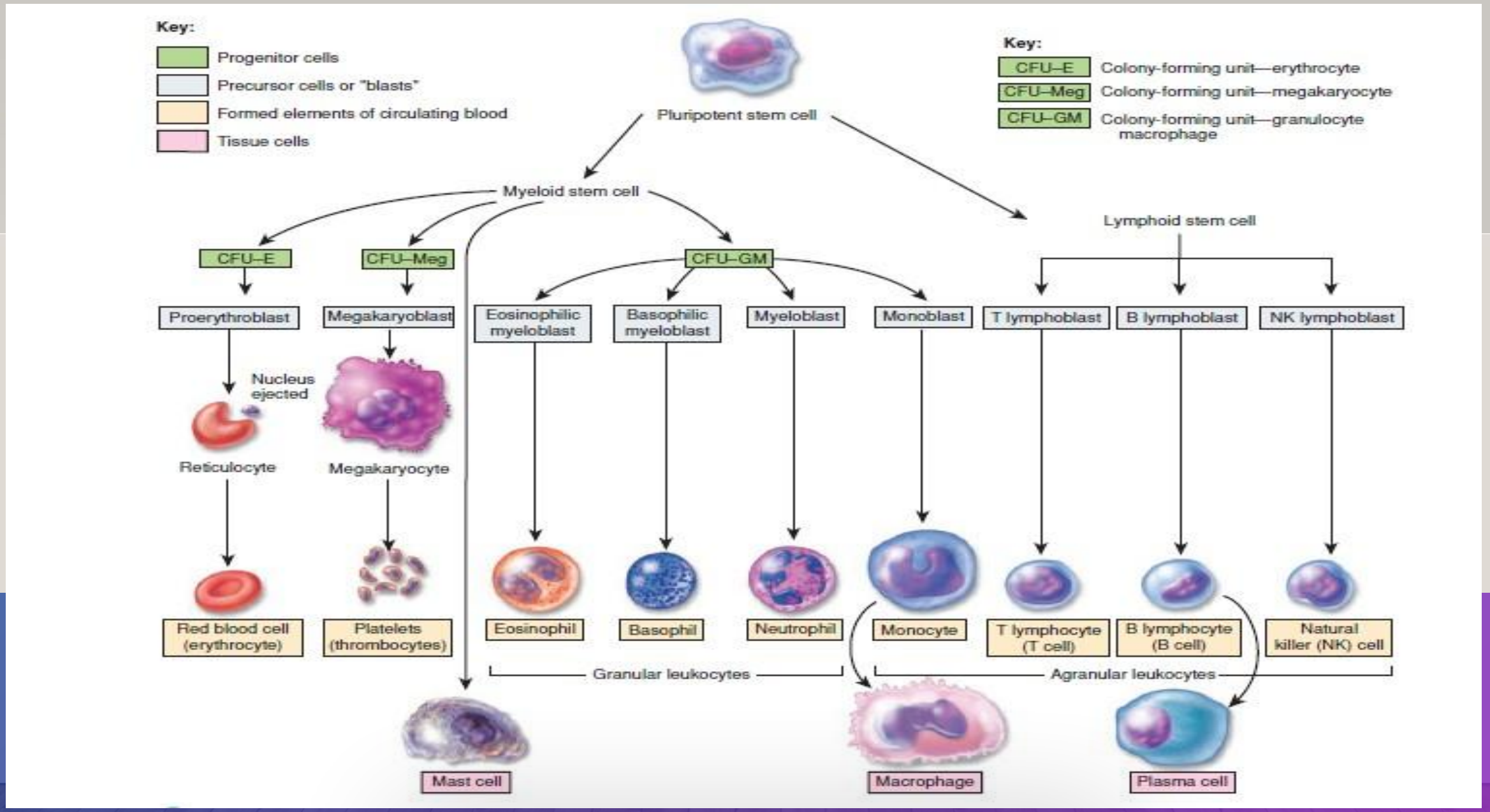
CONSTITUENT	DESCRIPTION	FUNCTION
Water (91.5%)	Liquid portion of blood.	Solvent and suspending medium. Absorbs, transports, and releases heat.
Plasma proteins (7%)	Most produced by liver.	Responsible for colloid osmotic pressure. Major contributors to blood viscosity. Transport hormones (steroid), fatty acids, and calcium. Help regulate blood pH.
Albumin	Smallest and most numerous of proteins.	
Globulins	Large proteins (plasma cells produce immunoglobulins).	Immunoglobulins help attack viruses and bacteria. Alpha and beta globulins transport iron, lipids, and fat-soluble vitamins.
Fibrinogen	Large protein.	Plays essential role in blood clotting.
Other solutes (1.5%)		
Electrolytes	Inorganic salts; positively charged (cations) Na^+, K^+, Ca^{2+}, Mg^{2+}; negatively charged (anions) Cl^-, HPO_4^{2-}, SO_4^{2-}, HCO_3^-.	Help maintain osmotic pressure and essential roles in cell functions.
Nutrients	Products of digestion, such as amino acids, glucose, fatty acids, glycerol, vitamins, and minerals.	Essential roles in cell functions, growth, and development.
Gases	Oxygen (O_2).	Oxygen is important in many cellular functions.
	Carbon dioxide (CO_2).	Carbon dioxide is involved in the regulation of blood pH.
	Nitrogen (N_2).	Nitrogen has no known function.
Regulatory substances	Enzymes.	Catalyze chemical reactions.
	Hormones.	Regulate metabolism, growth, and development.
	Vitamins.	Cofactors for enzymatic reactions.
Waste products	Urea, uric acid, creatine, creatinine, bilirubin, Ammonia.	Most are breakdown products of protein metabolism that are carried by the blood to organs of excretion.

(Tortora dan Derrickson, 2012)

IV. HEMOPOIESIS/HEMA TOPOIESIS

- RBC, WBC, dan platelet pada fetus diproduksi di liver dan limfa, dan setelah lahir baru proses produksi dilakukan di *bone marrow*
- Proses dimulai dari *pluripotent stem cells,* yang dapat berdiferensiasi menjadi berbagai jenis tipe sel

(Lazenby, 2011)



(Tortora dan Derrickson, 2012)

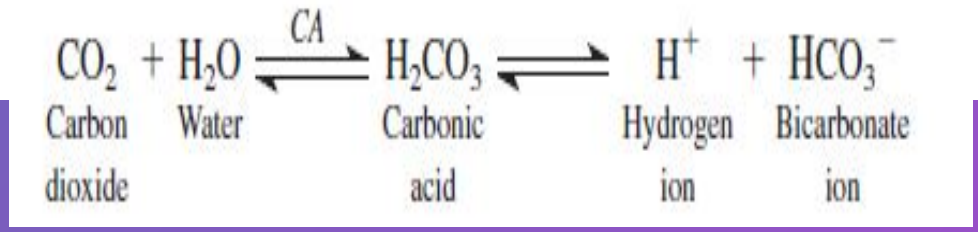
A. SEL DARAH MERAH (RBC)

- Diproduksi di *bone marrow*
- Distimulasi oleh *erythropoietin*
- Retikulosit merupakan bentuk immatur eritrosit (dilepaskan dari *bone marrow*) sebelum mengalami maturasi di aliran darah

(Tortora dan Derrickson, 2012)

A. SEL DARAH MERAH (RBC)

- Tidak berinti, tidak punya mitokondria dan ribosom
- Bentuk *biconcave disk*
- Mengandung hemoglobin (Hb)
- Sintesa memerlukan besi, asam folat, vitamin B12
- Masa hidup 120 hari
- Mempunyai enzim CA (*carbonic anhydrase*)



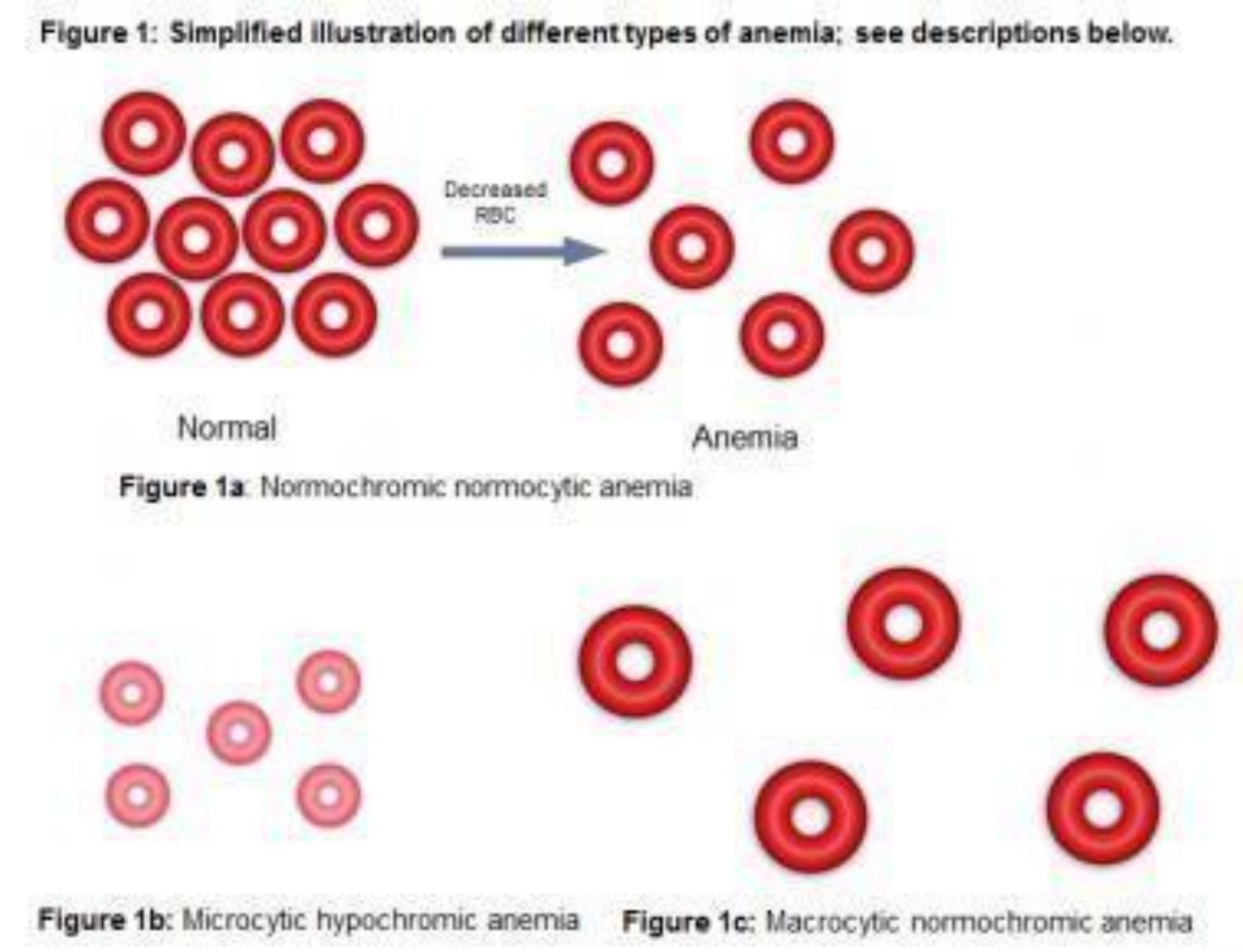
(Ineck *et al.*, 2008)

A. SEL DARAH MERAH (RBC)

- RBC didefinisikan secara klinik dari ukuran dan jumlah Hb
  - normocytic, microcytic, macrocytic
  - Hypochromic, normochromic, hyperchromic

(Ineck *et al.*, 2008)

A. SEL DARAH MERAH (RBC)



(Ineck *et al.*, 2008)

ERITROPOIESIS

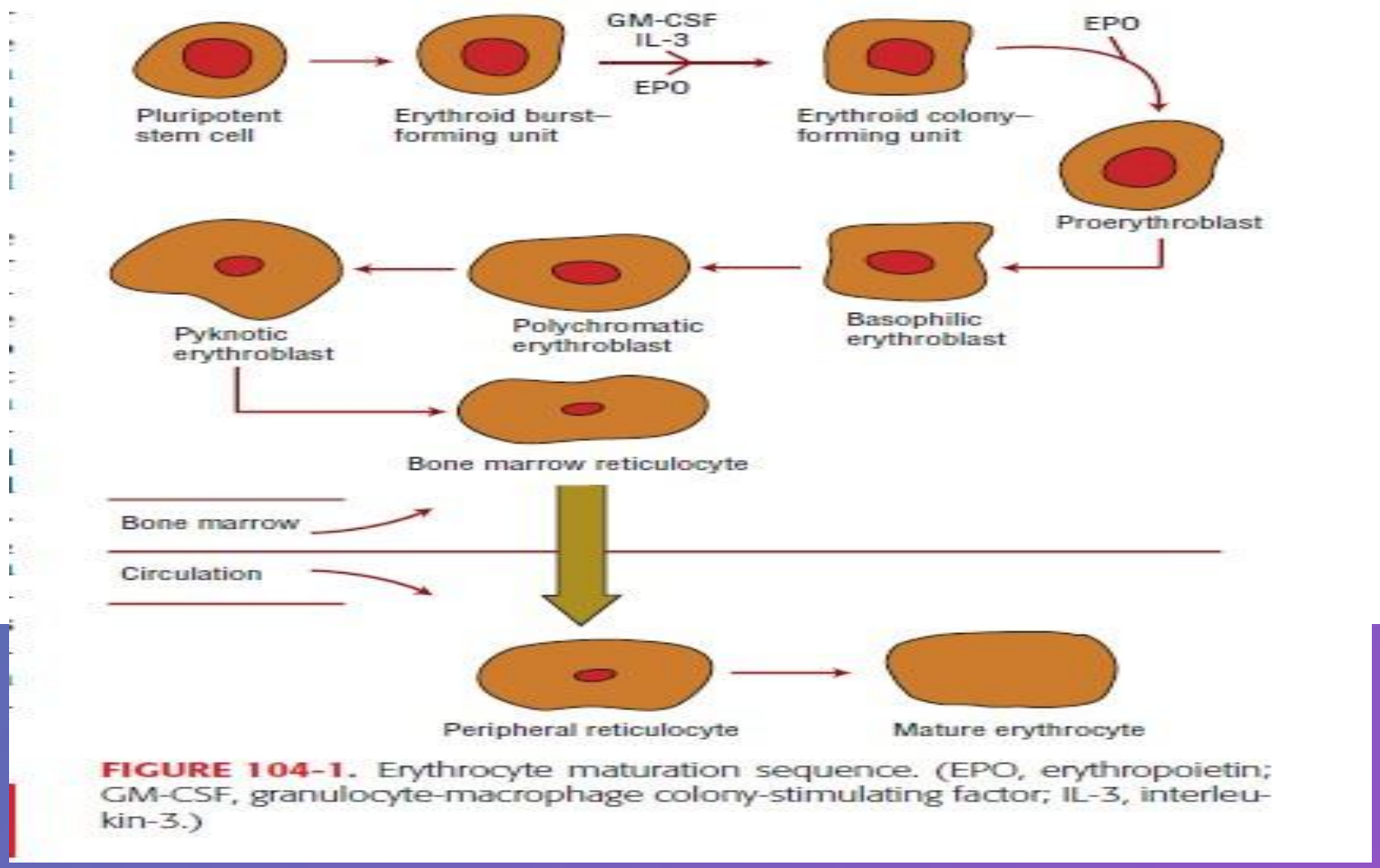


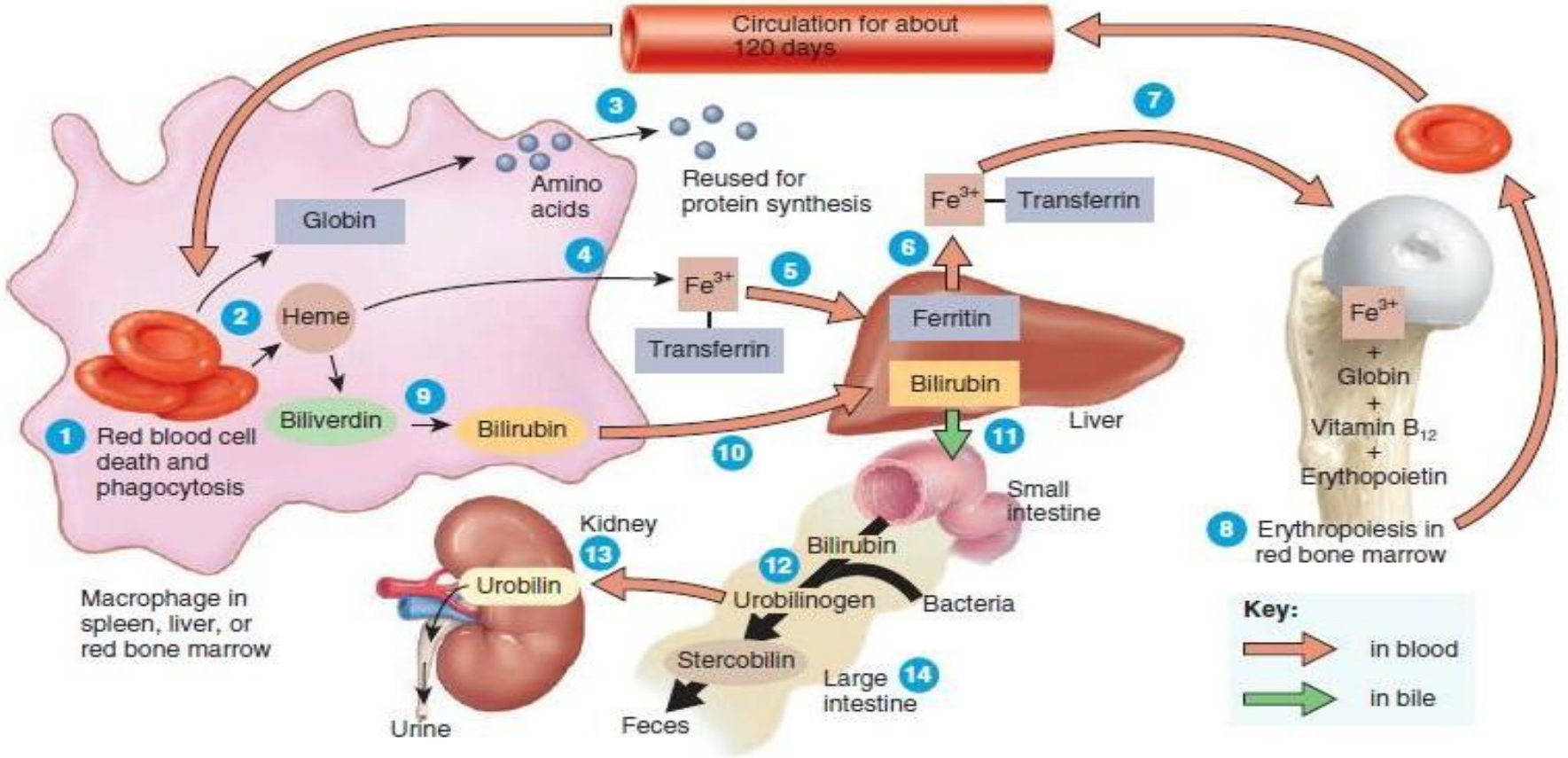
FIGURE 104-1. Erythrocyte maturation sequence. (EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3.)

(Ineck *et al.*, 2008)

ERITROPOIESIS

Figure 19.5 **Formation and destruction of red blood cells, and the recycling of hemoglobin components.** RBCs circulate for about 120 days after leaving red bone marrow before they are phagocytized by macrophages.

The rate of RBC formation by red bone marrow equals the rate of RBC destruction by macrophages.



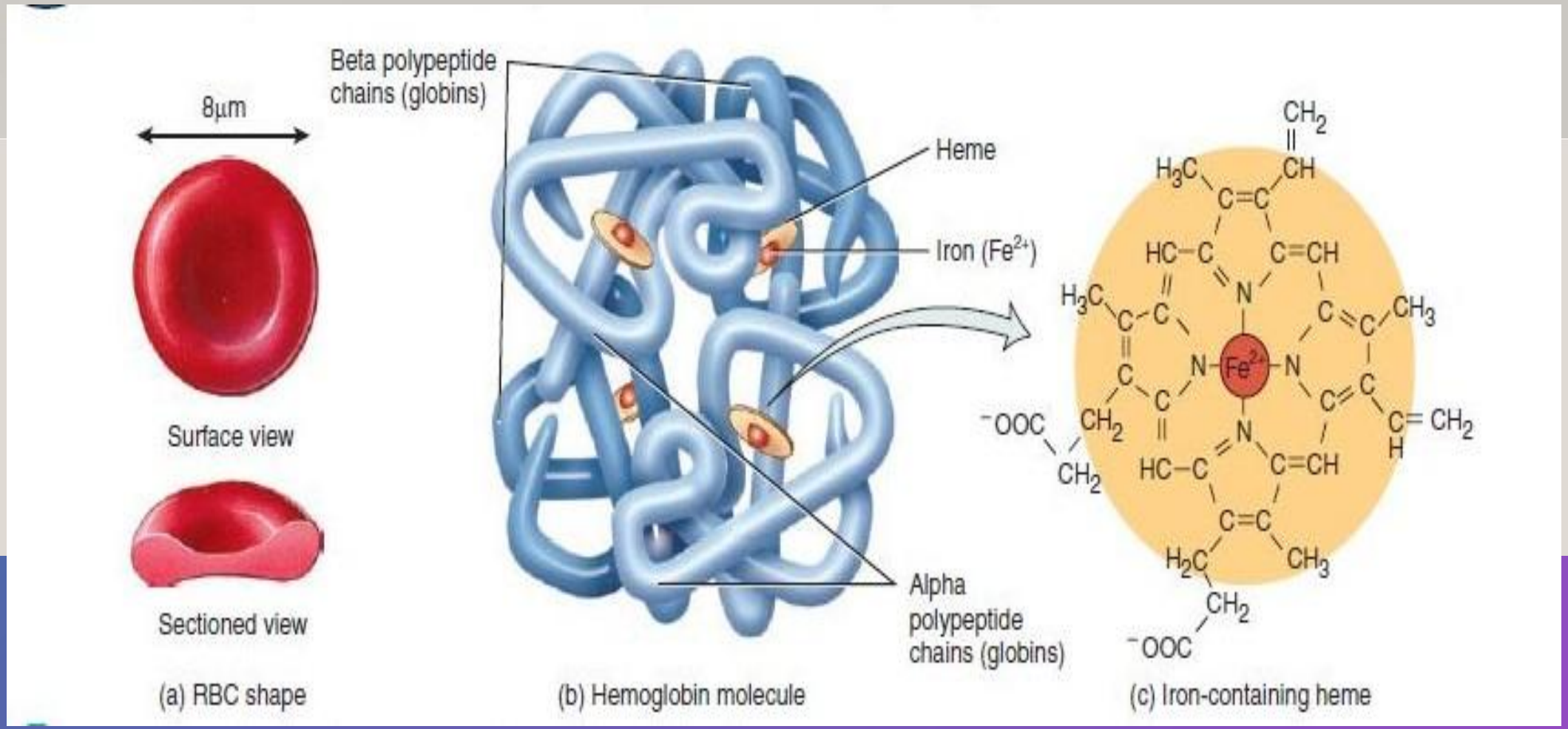
(Ineck *et al.*, 2008)

B. HEMOGLOBIN

- Terdiri dari protein globin
- Ada 4 rantai polipeptida
- Mempunyai heme di setiap rantai
- Ada ion Fe^{2+} yang terikat pada tiap heme, mengikat oksigen secara reversibel
- Dapat pula mengikat karbondioksida (sebagian kecil) dan nitrit oksida (NO)

(Ineck *et al.*, 2008)

B. HEMOGLOBIN



(Tortora dan Derrickson, 2012)

V. ANEMIA

TABLE 12-1 Common Anemias

Common Type of Anemia	Causes
Normocytic	Acute hemorrhage Sickle cell anemia Malaria Aplastic anemia Thalassemia Anemia of chronic disease
Microcytic	Iron-deficiency Slow chronic hemorrhage Anemia of pregnancy
Megaloblastic anemia	Folic acid deficiency Vitamin B deficiency

(Lazenby, 2011)

ANEMIA

- Anemia merupakan kelompok penyakit yang dikarakterisasi oleh penurunan hemoglobin (Hb) ataupun sel darah merah sehingga kapasitas pengikatan oksigen menurun
- Anemia dapat disebabkan karena:
  - Penurunan produksi sel darah merah/ eritrosit/*red blood cell* (RBC)
  - Peningkatan destruksi RBC
  - Kehilangan darah (anemia hemoragik)

(Lazenby, 2011)

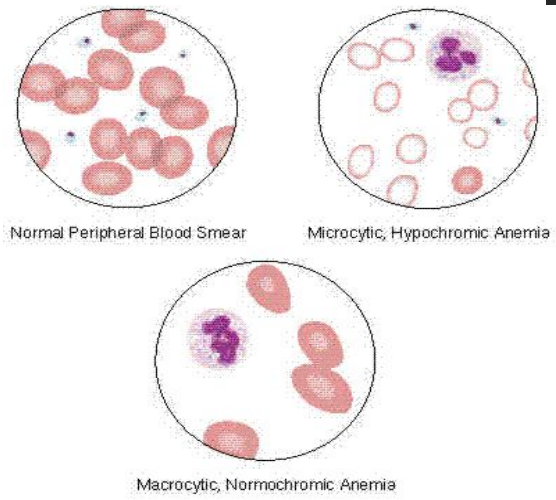
VI. GEJALA DAN TANDA ANEMIA

- Lemah letih lesu
- Pucat
- Hb rendah
- Hematokrit (Hct) rendah

(Lazenby, 2011)

VII. KLASIFIKASI ANEMIA

- Anemia
  - Morfologi
    - Makrositik
    - Mikrositik/Hipokromik
    - Normokromik/Normokromik
  - Etiologi
    - Megaloblastik
    - Anemia Defisiensi Besi
    - Inflamasi
    - Hemolitik
  - Lainnya
    - Usia
    - Perdarahan

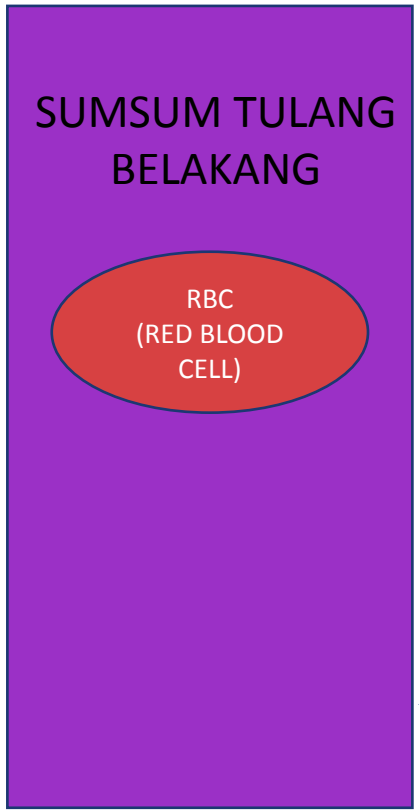


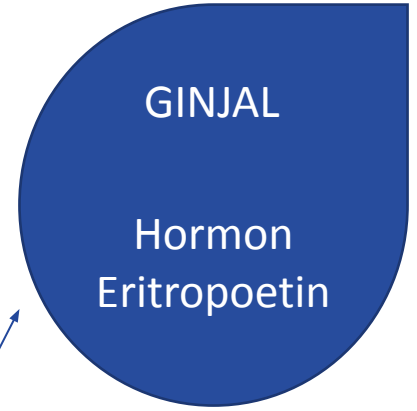
ANEMIA (GAMBARAN UMUM)

Step 3. Bahan baku pembentuk RBC :

- Fe (Zat Besi)
- Vitamin B12
- Asam Folat

- Fe (Zat Besi) → Anemia Defisiensi Besi
- Vitamin B12 → Anemia Pernisiosa
- Asam Folat → Anemia Defisiensi Folat (Anemia Megaloblastik)

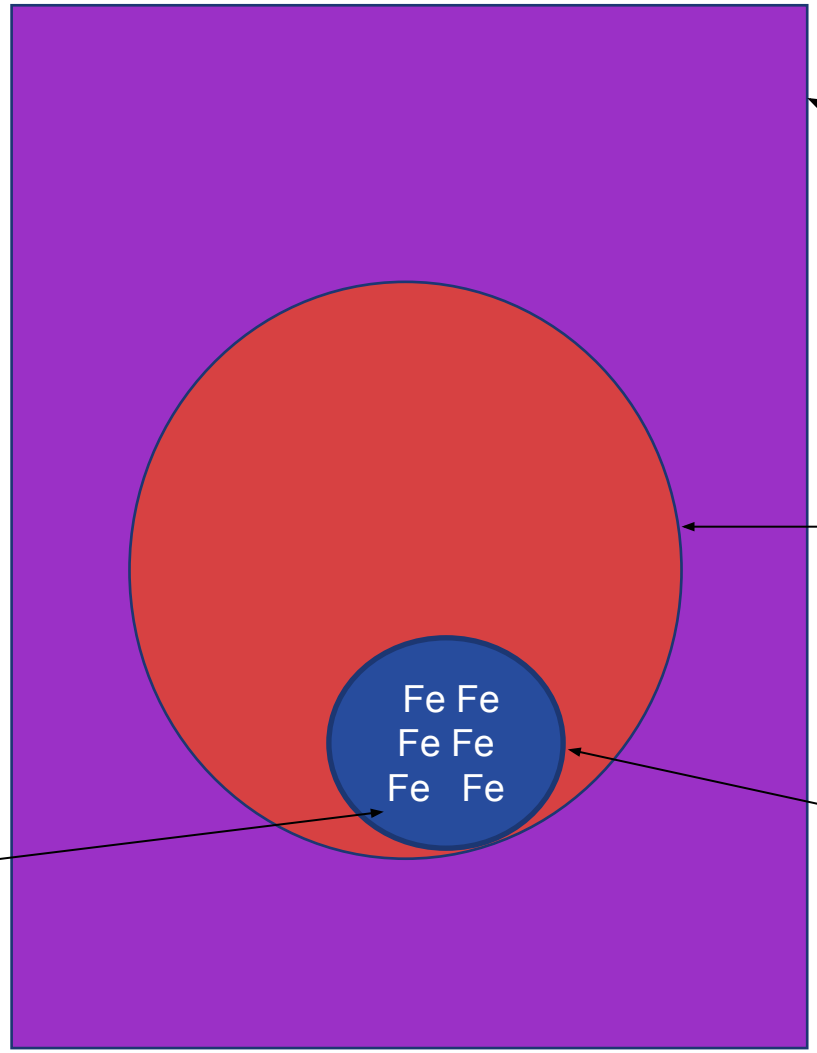




Step 1. Atas dasar rangsangan dari hormone eritropoetin yang dihasilkan oleh ginjal

Step 2.
RBC (Sel Darah Merah) Diproduksi di Sumsum tulang Belakang.
Prosesnya disebut eritropoesis

I. ANEMIA DEFISIENSI BESI



SUMSUM TULANG BELAKANG

RBC
(RED BLOOD CELL)

HEMOGLOBIN (Hb) > Berfungsi mengangkut O2 dan CO2 & Merupakan pigmen pemberi warna merah pada RBC

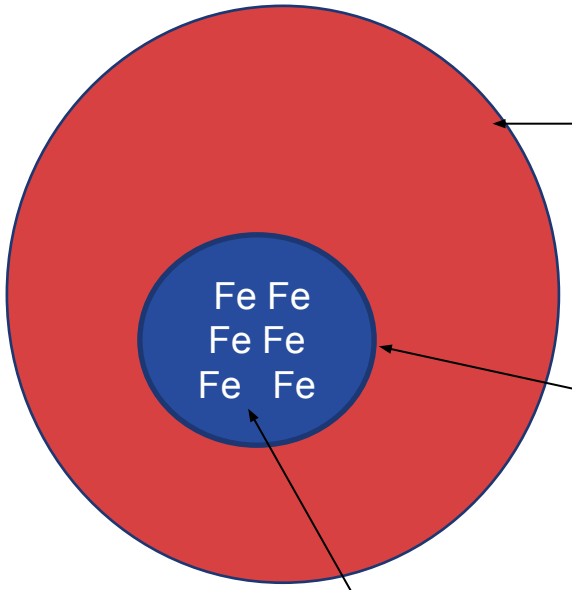
ZAT BESI (Fe)
Porfirin = inti dari Hb = Penahan atom zat Fe

ANEMIA DEFISIENSI BESI

Hemoglobinopati ada 2 kemungkinan :

Hb ↓ = Anemia atau Thalassemia

Fe ↓ = gejala anemia



RBC
(RED BLOOD CELL)

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ZAT BESI (Fe)
Porfirin = inti dari Hb = Penahan atom zat Fe

ANEMIA DEFISIENSI BESI

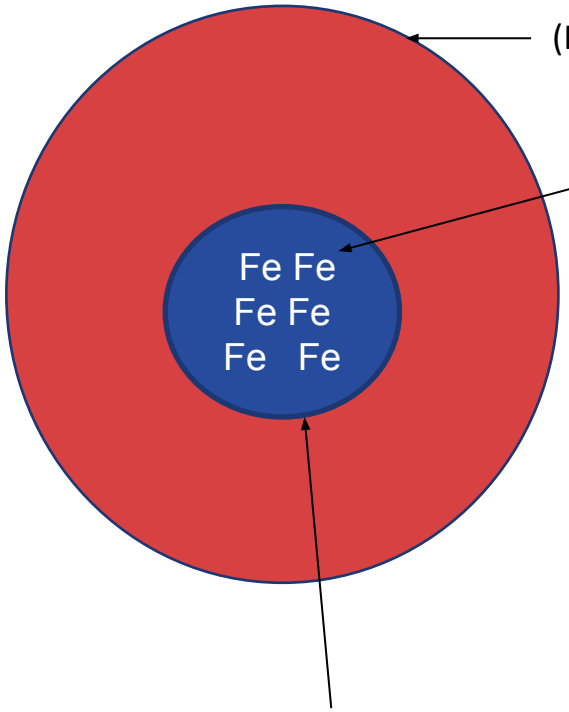
Hb dipengaruhi :

1. Tempat tinggal.
   Orang tinggal di gunung > Hb lebih banyak
   Orang tinggal di pantai. > Hb lebih sedikit
2. Posisi.
   Berbaring, Duduk

Hb ↓ → O2 ↓ → Anemia, sesak nafas, pusing, letih, Lelah, wajah pucat pasi

Hb ↑↑ → O2 ↑↑ → Darah mengental > arteri tersumbat > jantung > stroke

ANEMIA DEFISIENSI BESI



Fe → Anemia Hipokrom = Warna sel darah merah lebih pucat

Anemia Mikrositer = Ukuran sel darah merah lebih kecil dari normal

HEMOGLOBIN (Hb) > Berfungsi mengangkut O2 dan CO2 & Merupakan pigmen pemberi warna merah pada RBC

Penyebab Anemia Defisiensi Besi :

1. Menstruasi
2. Perdarahan
3. Melahirkan (Hamil) > Malnutrisi Fe (Kurang Vitamin)

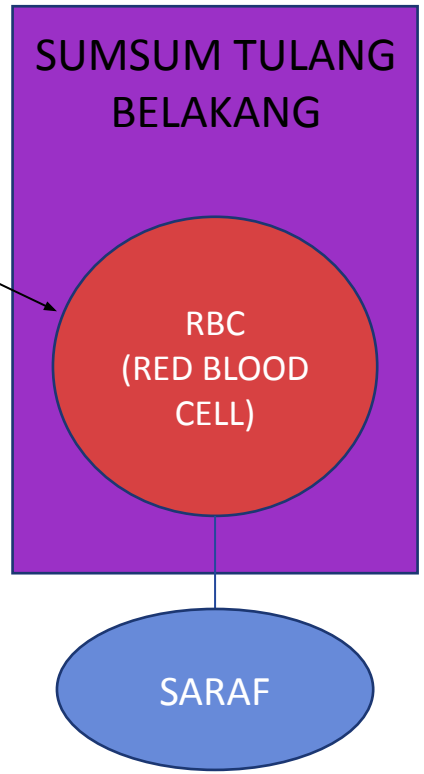
Terapi :

1. Makan makanan kaya Fe
2. Suplemen Fe (Zat Besi)

II. ANEMIA DEFISIENSI VITAMIN B12 = ANEMIA PERNISIOSA

Step 3. Bahan baku pembentuk RBC :

- Fe (Zat Besi)
- Vitamin B12
- Asam Folat



Fungsi Vitamin B12 = Menjaga Kenormalan Fungsi Saraf

Vitamin B12 ↓ → Anemia Pernisiosa → Gangguan Saraf :
Kesemutan
Kebas di tangan atau kaki
Gangguan Daya Ingat
Gangguan Penglihatan

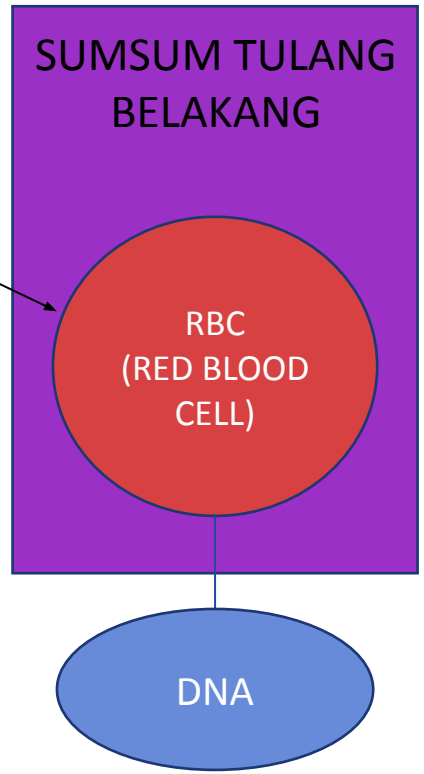
Penyebab : 1. Gangguan Absorbsi
2. Kurangnya asupan nutrisi yang mengandung Vit.B12

Terapi : 1. Makanan kaya Vit.B12 (produk hewani)
2. Suplemen Vit.B12 (mecobalamin)

III. ANEMIA DEFISIENSI FOLAT (VITAMIN B9) = ANEMIA MEGALOBLASTIK

Step 3. Bahan baku pembentuk RBC :

- Fe (Zat Bsi)
- Vitamin B12
- Asam Folat



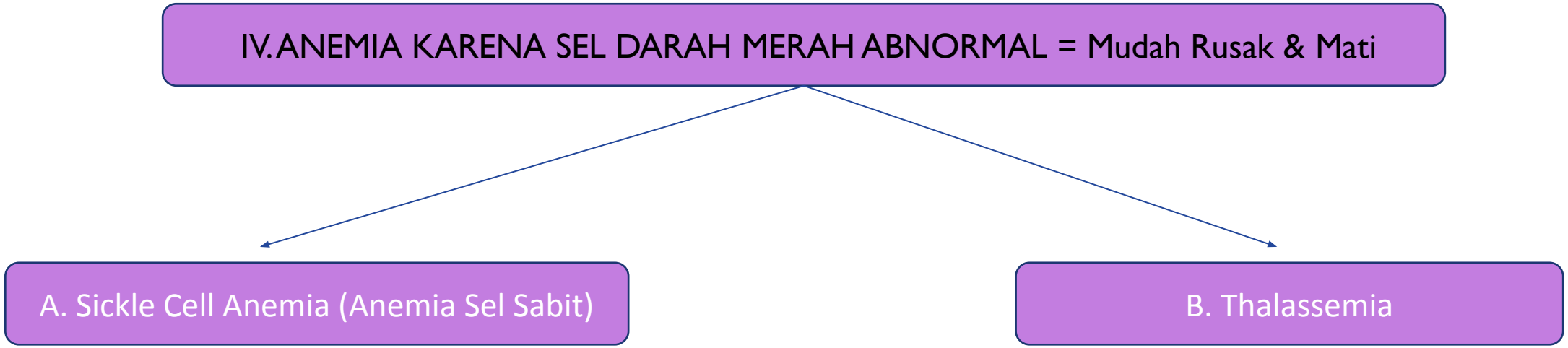
Fungsi Vitamin B9 (Folat) = Memperbaiki DNA & membentuk sel darah merah

Folat (Vit.B9) ↓ → Anemia Megaloblastik → Kulit pucat, mual, kehilangan nafsu makan, Penurunan berat badan, dll

Penyebab : 1. Gangguan Absorbsi
2. Trimester ke 3 kehamilan (Ketika tubuh membutuhkan folat tambahan)

Terapi : 1. Makanan kaya Folat
2. Suplemen Asam Folat

*Anemia Megaloblastik = Dilihat dibawah mikroskop ukuran sel darah merah lebih dari normal



IV.A. SICKLE CELL ANEMIA = ANEMIA SEL SABIT

Pada Hb Normal = Bentuk cakram RBC (seperti donat tidak mempunyai lubang) = memudahkan pergerakan sel dalam darah
Pada Hb Sickle Cell Anemia = Bentuk RBC sabit (akibat adanya Hb S yang kaku)
= Masalah di Hb nya = kelainan gen = yaitu adanya HbS

↓

Akibatnya RBC kaku dan menempel ke dinding arteri

↓

Aliran darah untuk transportasi O2 tidak efektif

↓

Terjadi sumbatan aliran darah

↓

Nyeri

↓

Sel darah mudah hemolisis

↓

Kekurangan Sel darah merah karena banyak yang hemolisis

↓

Anemia

↓

Mudah Lelah, pucat, sulit nafas

↓

Karena sumbatan arteri bisa juga berlanjut ke Infark Miokard dan → Gagal Organ :
Jantung
Tulang
Limpa
Sistem Saraf Pusat

Terapi :
1. Penanganan gejalanya saja (nyeri)
2. Transplantasi Stem Cell (tetapi dengan resiko yang tinggi)

IV. B. THALASSEMIA

Pada Hb Normal = Bentuk cakram (seperti donat tidak mempunyai lubang) = memudahkan pergerakan sel dalam darah RBC
Pada Thalassemia = karena Genetik (keturunan) = Masalah di gen pembentuk Hb nya = kelainan gen pembentuk Hb (mengalami mutase) = Hilangnya fungsi gen rantai globin Beta

Hb supaya normal membutuhkan

- 2 protein Alfa → Jika kekurangan protein Alfa → Menyebabkan kelainan pada Hb → Thalassemia Alfa
- 2 protein Beta → Jika kekurangan protein Beta → Menyebabkan kelainan pada Beta → Thalassemia Beta

Pada Thalassemia = Hb ↓↓ → O2 ↓↓ → Letih, pingsan, susah nafas → Gagal Jantung, Hati, kematian, gagal Organ

Terapi :

1. Transfusi Darah > beresiko > Kelebihan Fe > Bisa merusak jantung dan liver
2. Cangkok sumsum tulang dari donor

V. ANEMIA HEMOLITIK

Pada Hb Normal = Bentuk cakram (seperti donat tidak mempunyai lubang) = memudahkan pergerakan sel dalam darah RBC

Pada Anemia Hemolitik = kadar Hb berkurang karena kerusakan RBC lebih cepat daripada pembentukannya

Penyebab :

1. Intrakorpuskular [Faktor Dalam] : Gangguan metabolism
   Gangguan pembentukan Hb
   Keturunan
2. Ekstrakorpuskular [Faktor Luar] : Autoimun
   Obat
   Infeksi

Terapi :

1. Transfusi Darah
2. Suplemen tambahan asam folat
3. Transplantasi sumsum tulang

V. ANEMIA APLASTIK

Pada Hb Normal = Bentuk cakram (seperti donat tidak mempunyai lubang) = memudahkan pergerakan sel dalam darah RBC

Pada Anemia Hemolitik = Sel-sel darah merah tampak sepi, karena :

1. RBC berkurang > Anemia
2. Leukosit berkurang > Imun kacau
3. Trombosit berkurang > Darah tidak bisa membeku secara normal

Penyebab :

1. Kemoterapi/Leukemia
2. Bahan kimia beracun
3. Obat Osteoarthritis
4. Lupus (autoimun)
5. Infeksi virus
6. Genetik

Terapi :

1. Transfusi Darah
2. Antibiotik
3. Transplantasi stem cell
4. Imunosupresan
5. Stimulan sumsum tulang

PATHOPHYSIOLOGY OF TUMOUR & CANCER

CANCER INCIDENCE

- World wide cancer related death – 20 %
- Most common cancer in ***developed countries*** are lung, breast, prostate and colorectal
- Most common cancer in ***developing countries*** are liver, cervical and oesophageal.
- Following life-style factor attributing cancer worldwide: tobacco use, alcohol abuse, obesity, physical
- inactivity, low fiber diet, unprotected sex, polluted air, indoor household smoke and contaminated injections.

CANCER INCIDENCE

- **Five most common primary cancers in the world (descending order)**

S.No	Men	Women	Children (under 20)
1	Lung	Breast	Acute leukaemia
2	Prostate	Lung	CNS tumour
3	Colorectal	Colorectal	Bone sarcoma
4	Urinary bladder	Endometrial	Endocrine
5	Lymphoma	Lymphoma	Soft tissue sarcoma

EPIDEMIOLOGIC FACTORS

- **I. Faktor Predisposisi**
  - Familial and genetic
  - Racial and geographic
  - Environmental and cultural
  - Age and gender
- **II. Kondisi Non – neoplastic kronik (pre-malignant)**
  - Carcinoma in situ
  - Benign tumour
  - Kondisi lain-lain
- **III. Hormonal**
  - Estrogen
  - Contraceptive hormones
  - Anabolic steroids
  - Hormone-dependent tumor

EPIDEMIOLOGIC FACTORS

I. Faktor Predisposisi

a) Familial and genetic factors:

- Risiko berkembangnya sel kanker pada kerabat tingkat pertama pasien kanker 3 kali lebih tinggi dibandingkan dengan kontrol
- Kanker genetik terdiri tidak lebih dari 5% dari semua kanker.
- Misal: 49% retinoblastoma merupakan warisan (kehilangan gen RB pada kromosom 13),
- 100% familial Polyposis coli berkembang menjadi kanker usus besar,
- neurofibromatosis atau penyakit von Recklinghausen (warisan 50%),
- kanker payudara (2-6 kali lebih tinggi) risiko dari biasanya;
- kanker payudara yang diturunkan- 5-10%,; gen mutan- BRCA-1 dan BRCA-2.)

EPIDEMIOLOGIC FACTORS

I. Faktor Predisposisi

b) Racial and geographic factors

White Europeans and Americans	Lungs, breast and colon; Breast cancer common in Americans but uncommon in Japanese
Black Africans	Skin, penis, cervix and liver
Japanese	5 times higher incidence of carcinoma of the stomach than the Americans
South-East Asians	Chinese- nasopharyngeal cancer
Indians	Higher incidence of carcinoma of the oral cavity and upper aerodigestive tract; female- carcinoma of uterine cervix, breast. Cancer of liver (HBV and HCV viral hepatitis)

EPIDEMIOLOGIC FACTORS

I. Faktor Predisposisi

c) Environmental and cultural factors

- **Cigarette smocking** : cancer of oral cavity, pharynx, larynx, oesophagus, lungs, pancreas and urinary bladder
- **Alcohol and tobacco together**: risk of developing cancer of the upper aerodigestive track
- **Cancer of cervix**: age at first coitus, (senggama), frequency of coitus, multiplicity of partners and parity
- **Penile cancer (kanker penis)** : rare in the Jews and Muslims.

EPIDEMIOLOGIC FACTORS

I. Faktor Predisposisi

d) Age and gender

- Age is most significant factor for cancer (two-third of all cancer occur above 65 yr of age)
- Kanker pada usia lanjut dapat disebabkan oleh perubahan sel inang, paparan efek karsinogen yang lebih lama, atau penurunan kemampuan imunitas inang.
- Tumours in infancy and childhood: Neuroblastoma, nephroblastoma, rhabdomyosarcoma, Ewing's sarcoma, teratoma and CNS tumours.
- Selain bentuk tumor ganas, kebanyakan tumor sering terjadi pada pria dibandingkan pada wanita kecuali kanker payudara
- Breast cancer: throughout the world common for women
- Lung cancer: common for men

EPIDEMIOLOGIC FACTORS

II. Chronic non-neoplastic (pre-malignant) conditions

a) Carcinoma in situ

- Keganasan bisa ditemukan di epitel tanpa invasi melintasi membran basal
- Lokasi umum untuk karsinoma in situ adalah serviks uterus, penyakit Bowen pada kulit, leukoplakia oral, karsinoma payudara intralobular dan intraepitel

b) Benign tumour

- Tumor jinak tidak menjadi ganas kecuali bila berbentuk beberapa vili
- adenoma usus besar
- (adenocarcinoma), neurofibromatosis (neurofibrosarcoma)

c) Kondisi lain-lain

- Pasien kanker kolitis ulserativa yang kronis > kanker kolorektal
- Cirrhosis of liver > hepatocellular carcinoma
- Chronic bronchitis in heavy cigarette > cancer of bronchus
- Old burn scar (Marjolin's ulcer) > squamous cell carcinoma

EPIDEMIOLOGIC FACTORS

- **III. Peran Hormon Dalam Kanker**

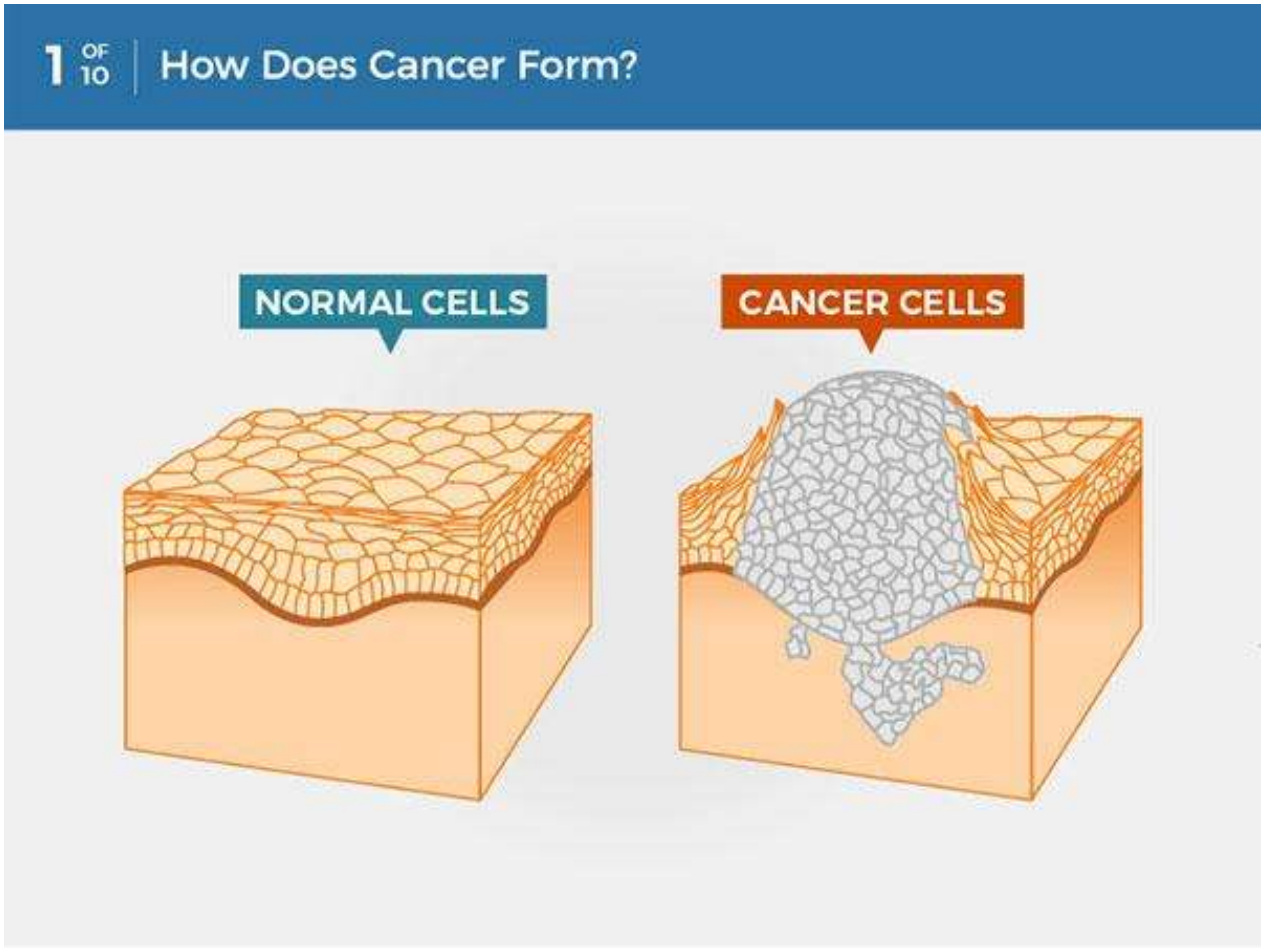
Jaringan yang sensitive terhadap hormone yang bisa memicu tumor adalah jaringan breast, endometrium, myometrium, vagina, thyroid, liver, prostate, dan testis

a) Oestrogen therapy increase the risk of developing endometrial carcinoma

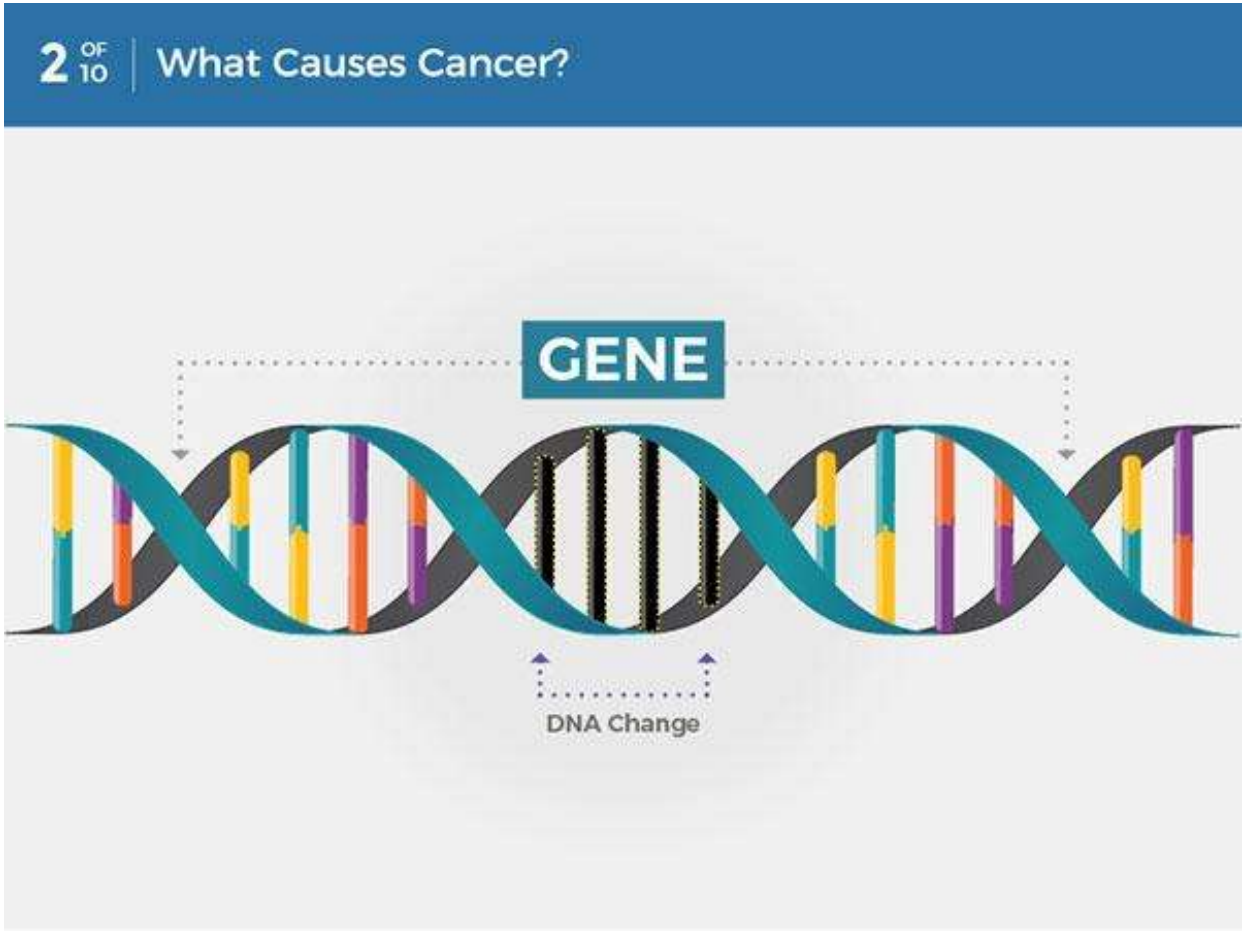
b) Oral contraceptives increase the risk of developing breast cancer

c) Anabolic steroids increase the risk of developing benign and malignant tumours

CARCINOGENESIS

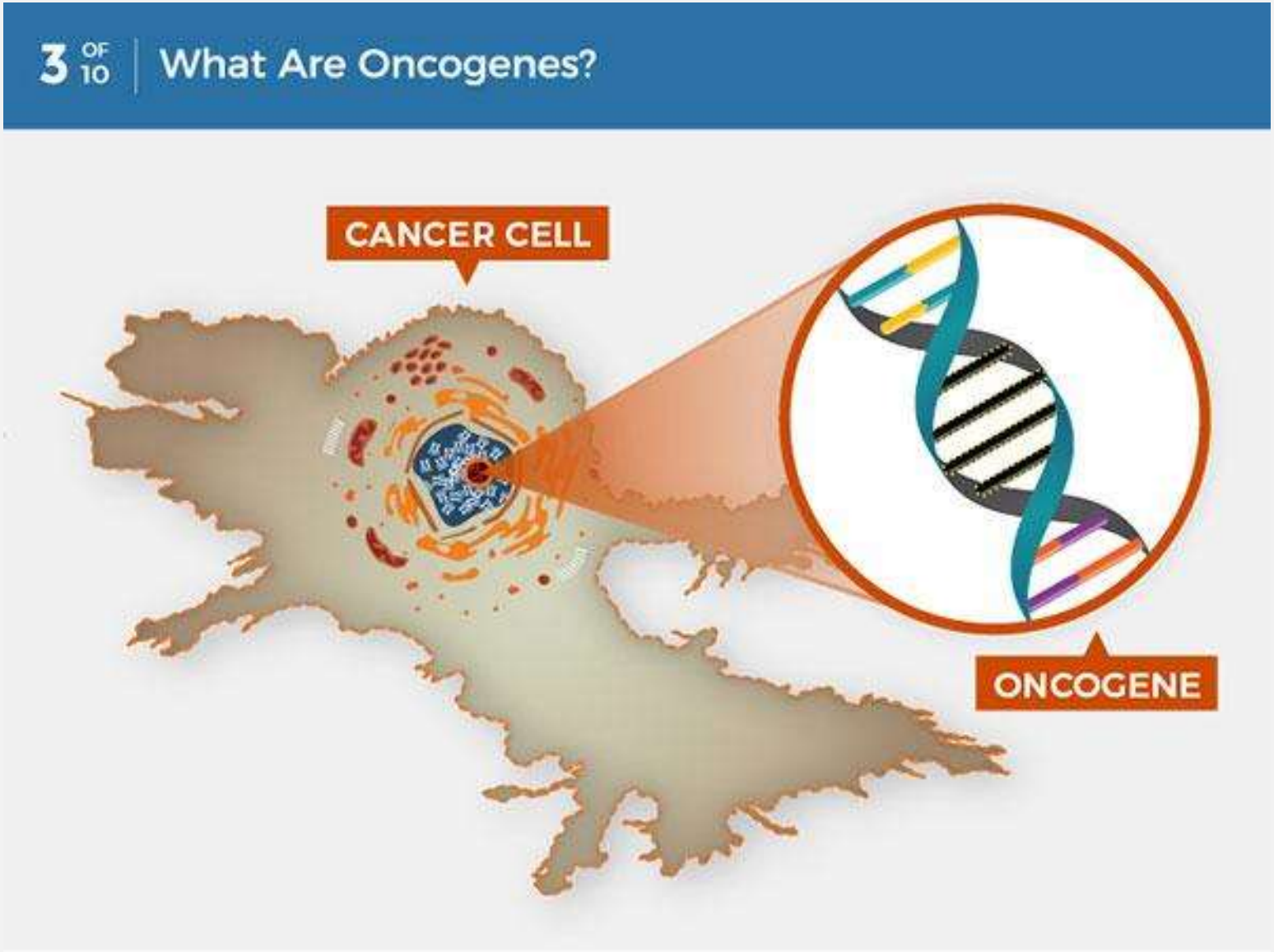


PATHOGENESIS OF CANCER

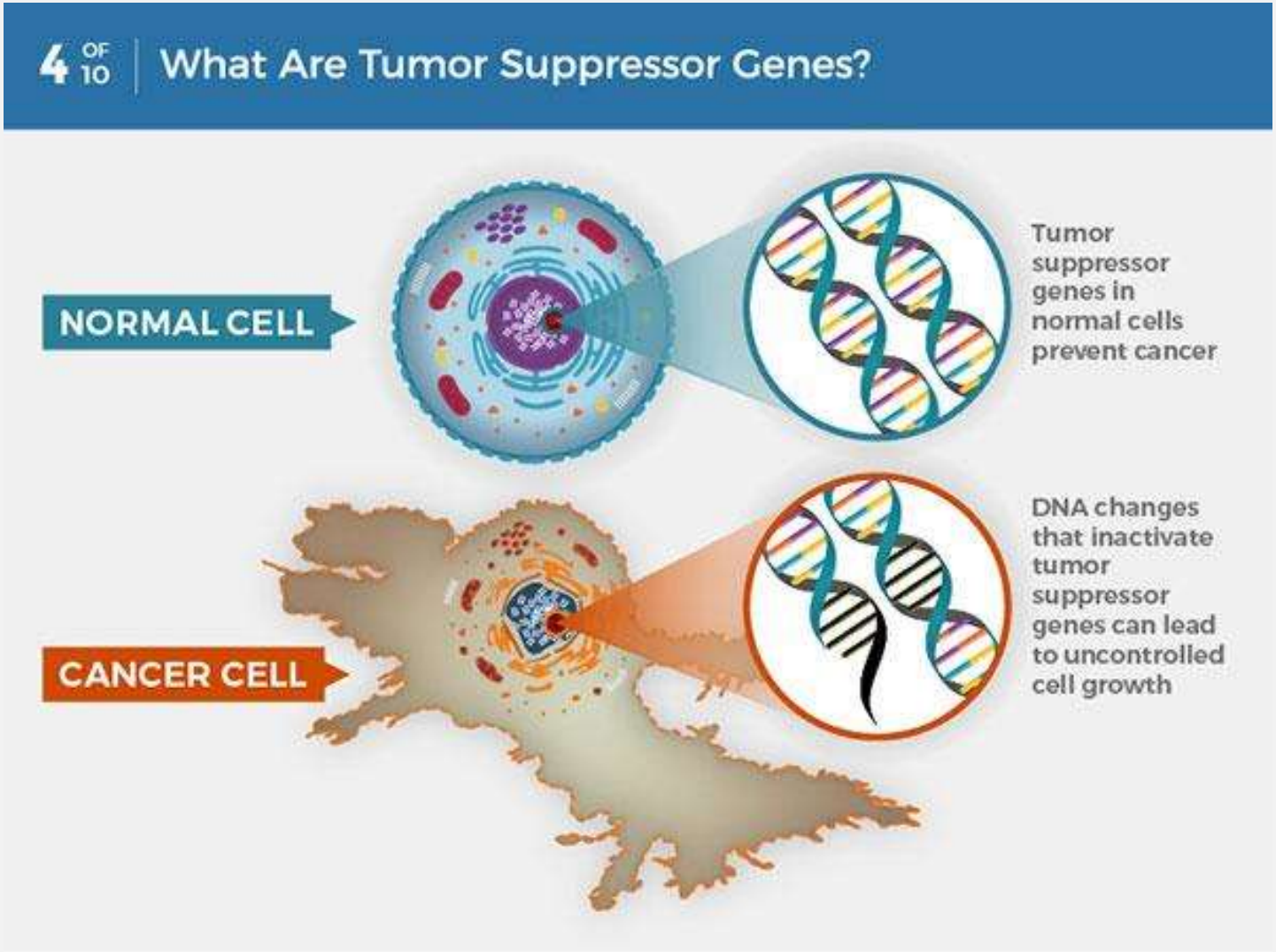


PATHOGENESIS OF CANCER

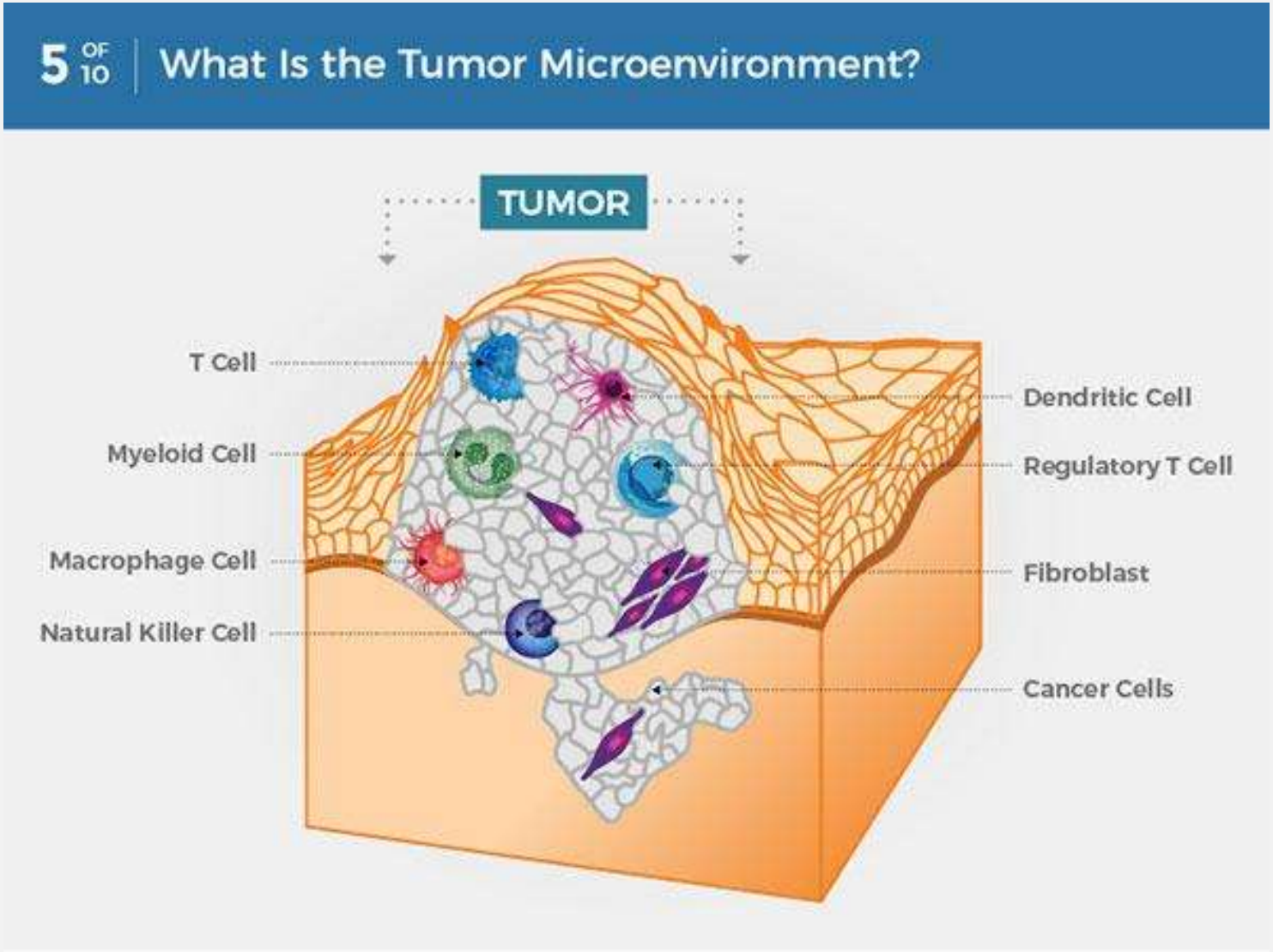
PATHOGENESIS OF CANCER



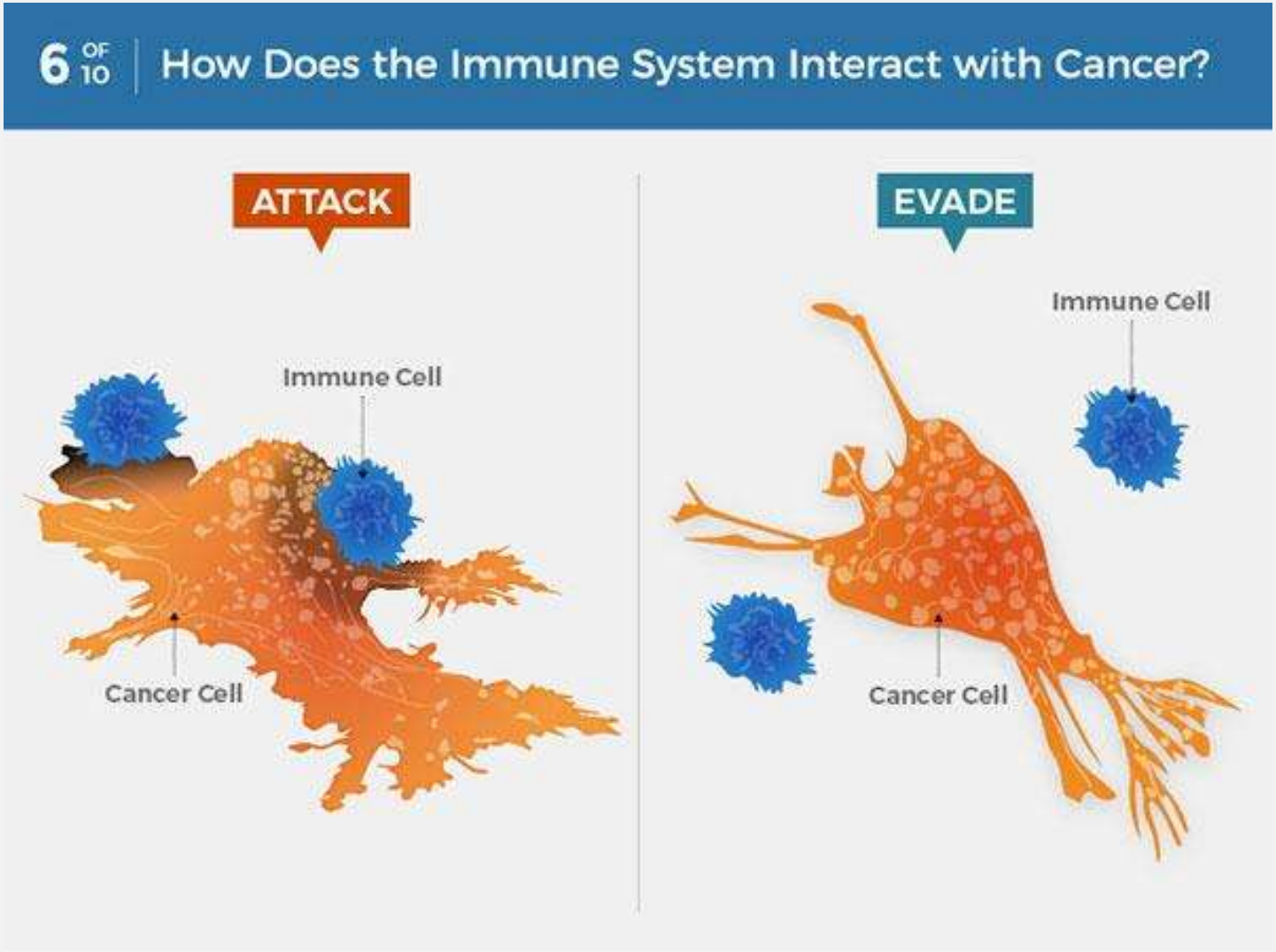
PATHOGENESIS OF CANCER



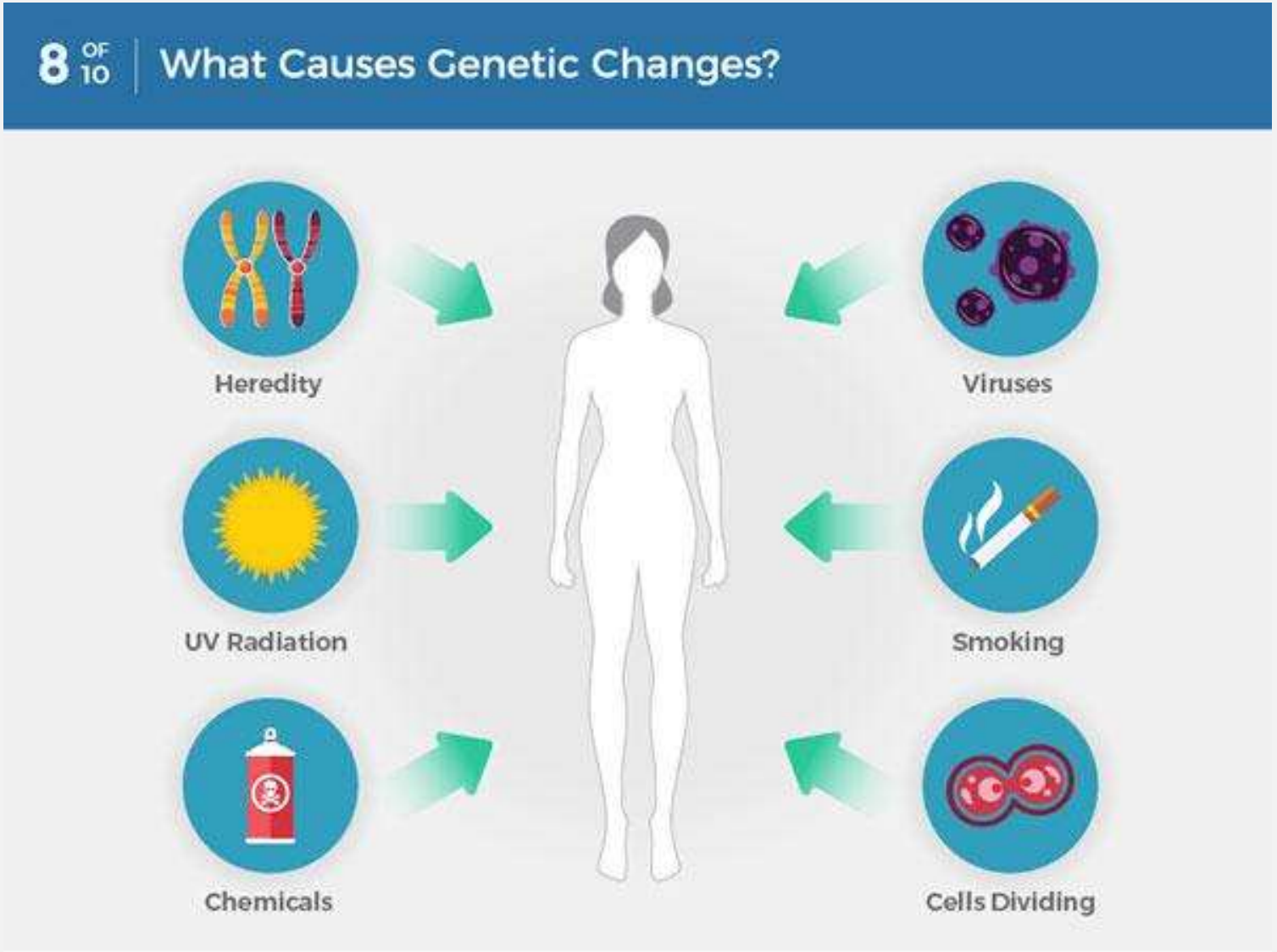
PATHOGENESIS OF CANCER



PATHOGENESIS OF CANCER



PATHOGENESIS OF CANCER



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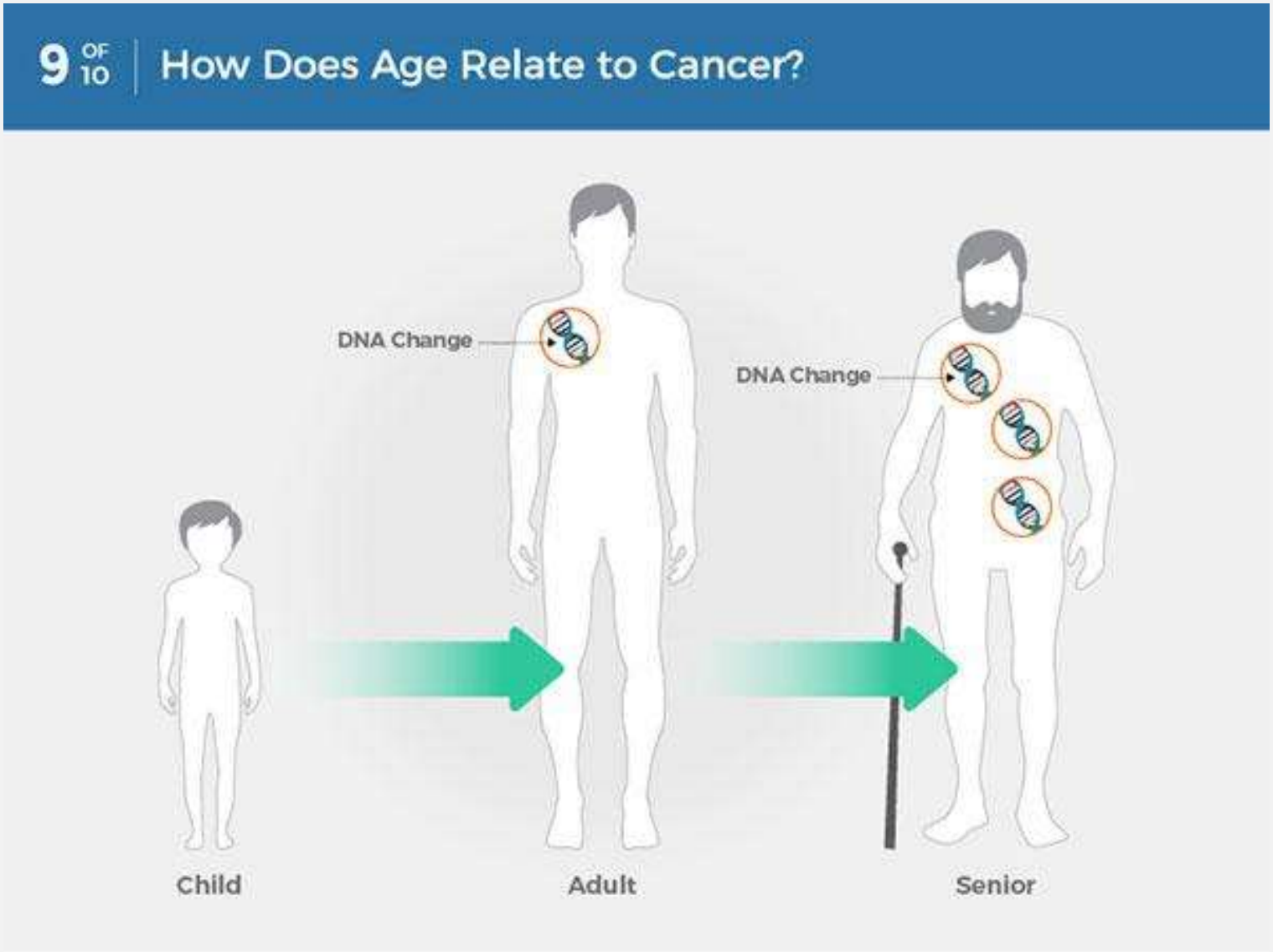
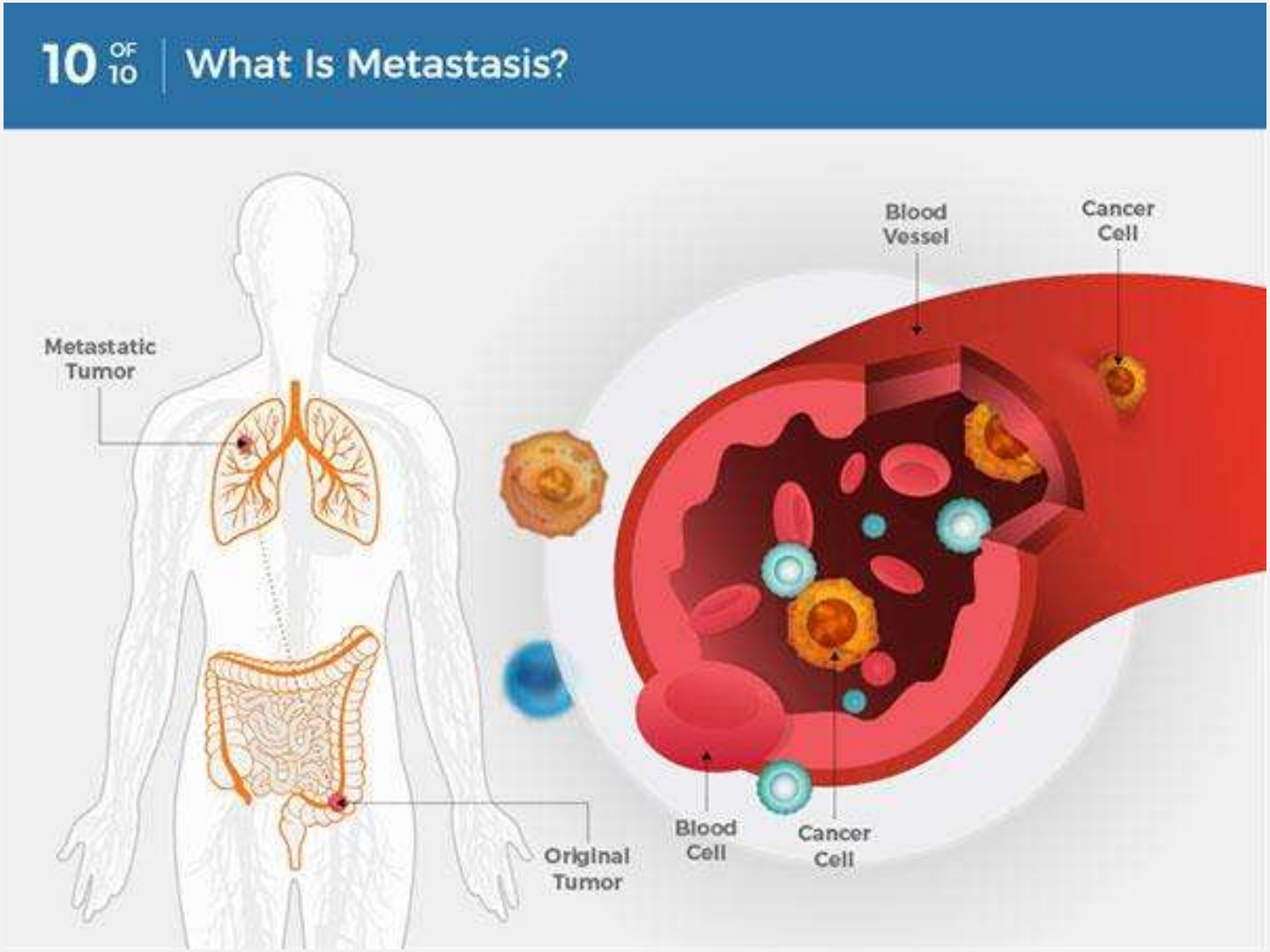
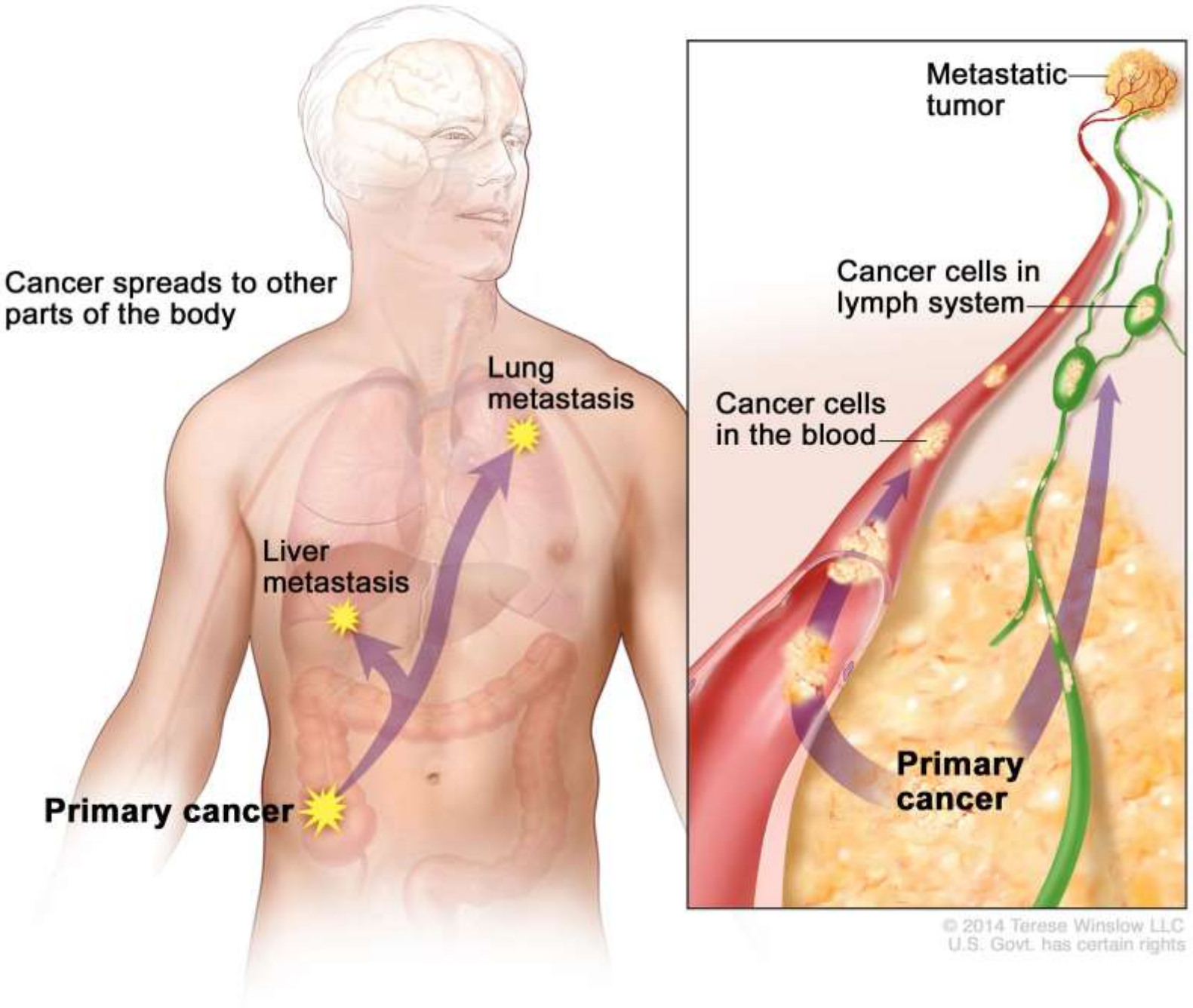
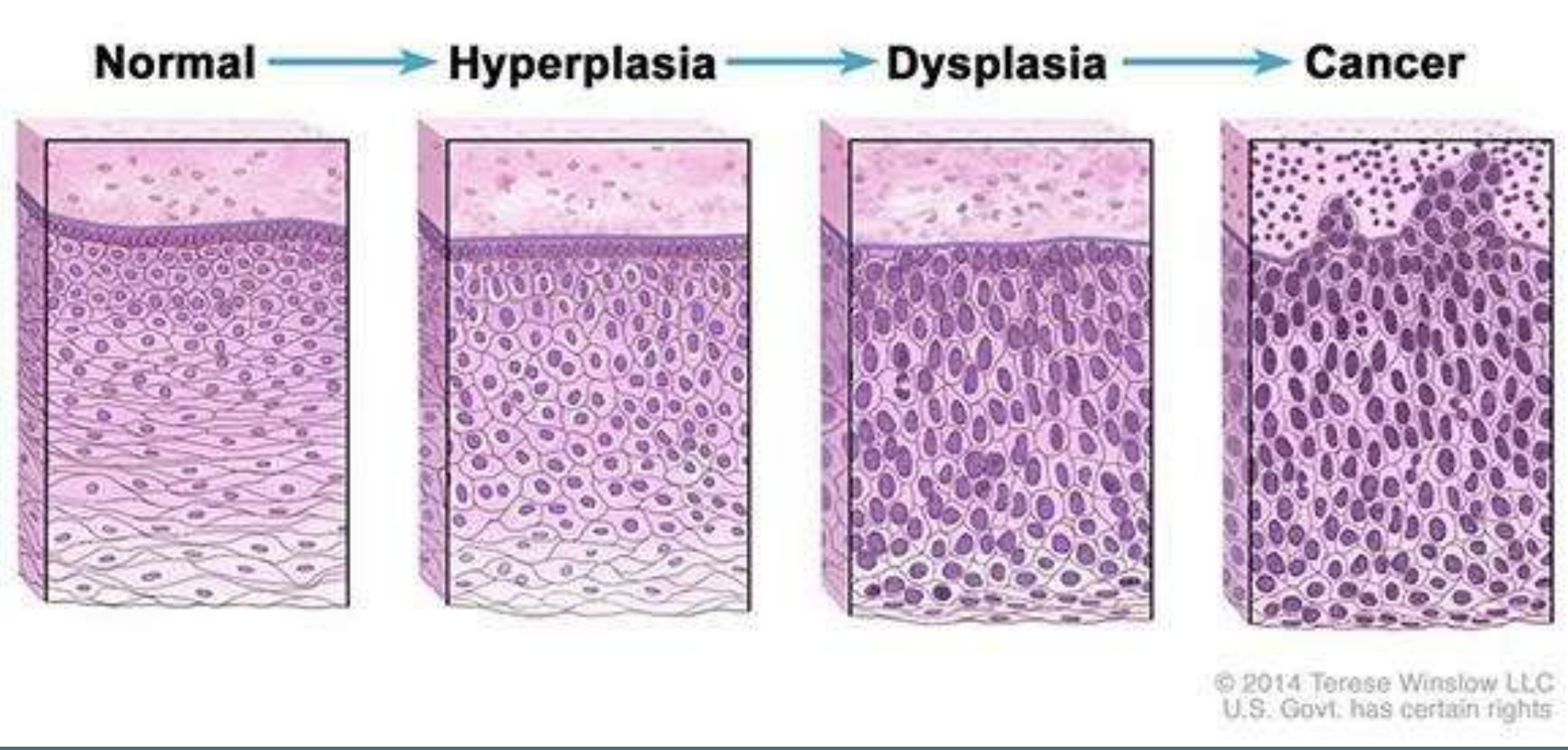


PATHOGENESIS OF CANCER



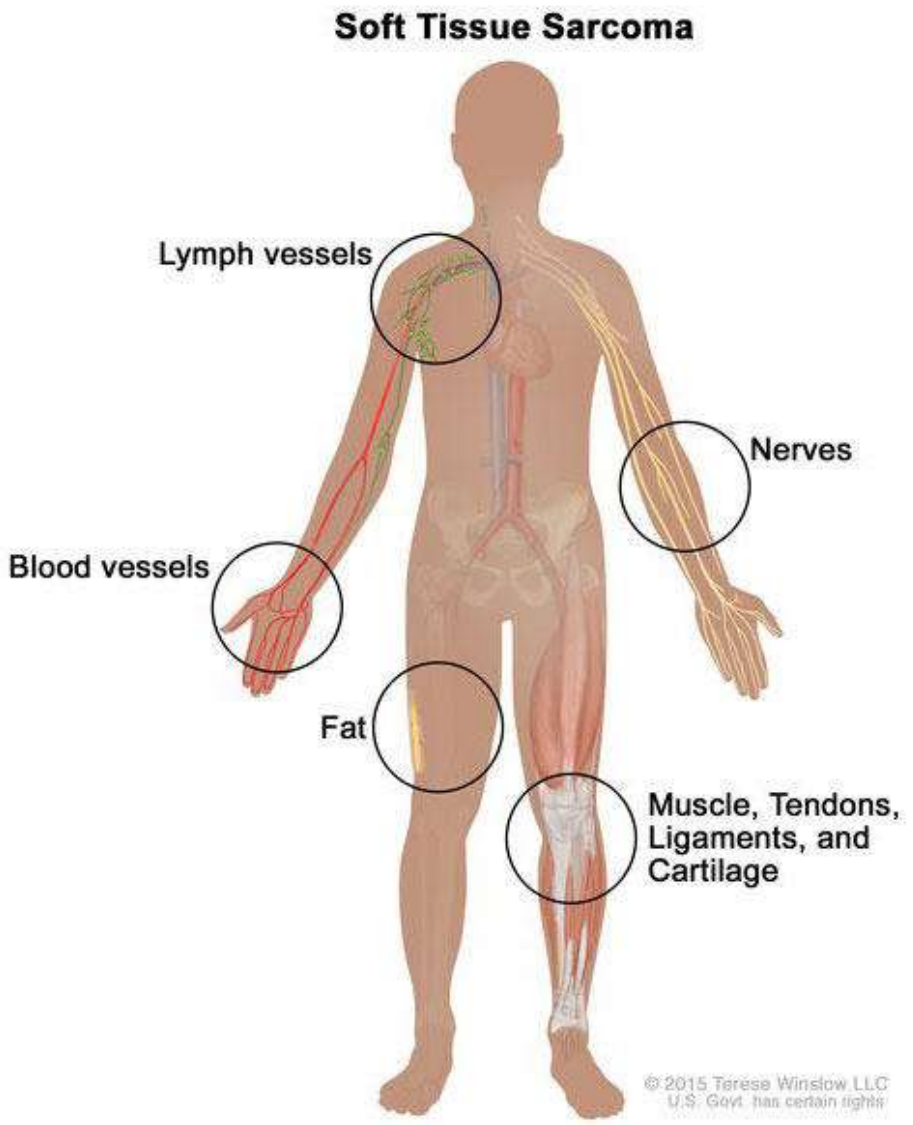
Metastasis



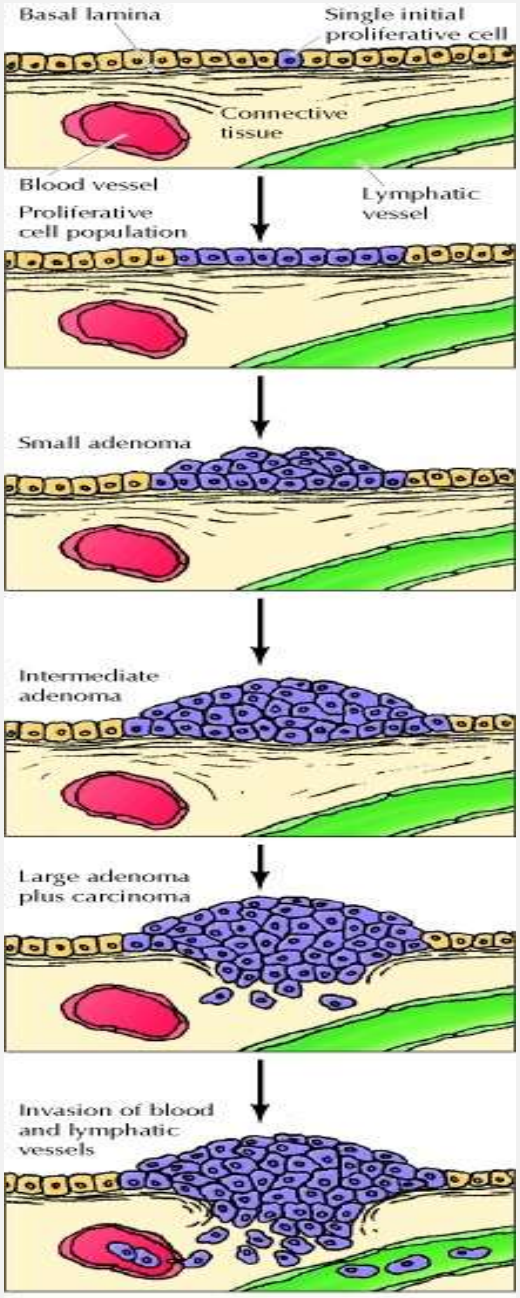


PATHOGENESIS OF CANCER

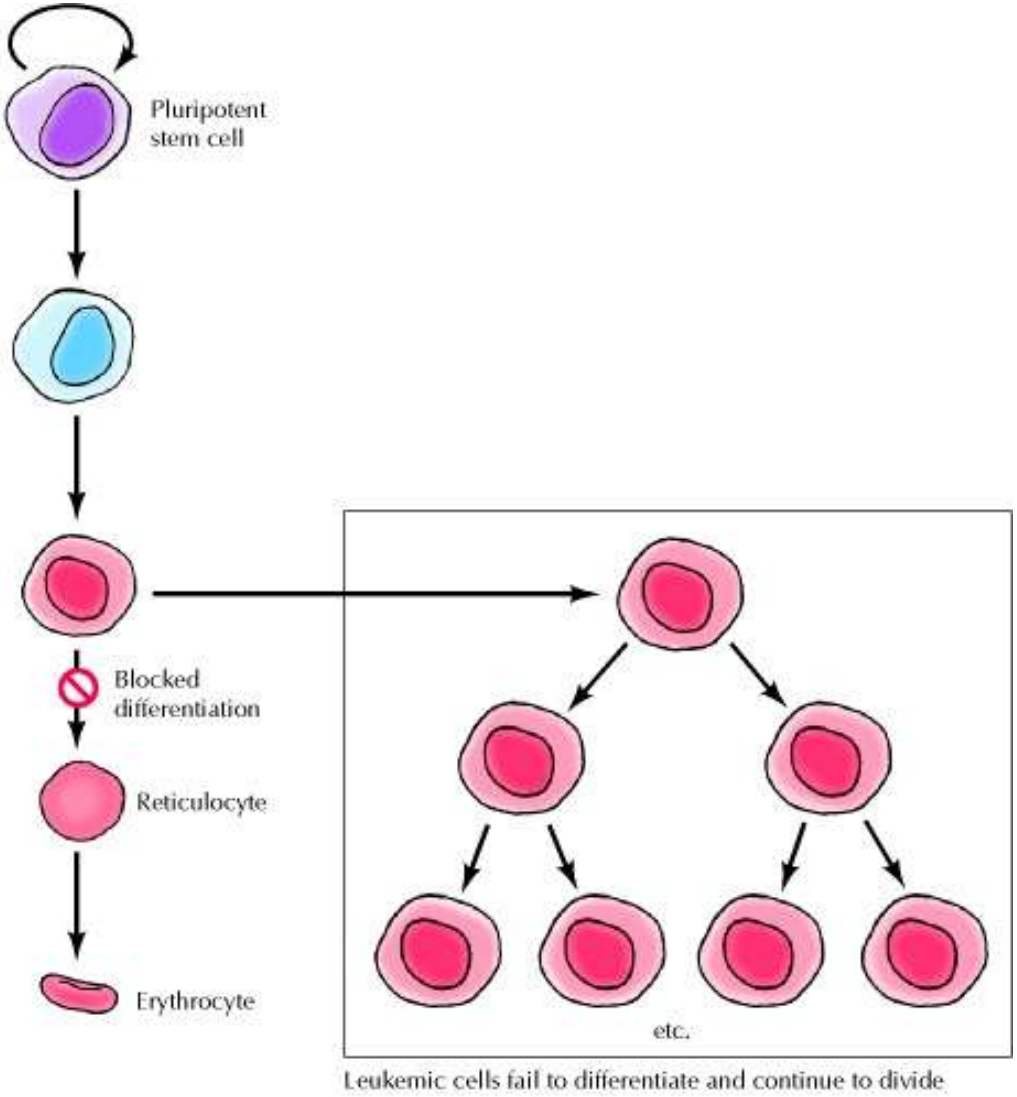
PATHOGENESIS OF CANCER



COLON CARCINOMA



LEUKEMIA



Leukemic cells fail to differentiate and continue to divide

CAUSES/ PATHOGENESIS OF CANCER

- **Carcinogenesis/ oncogenesis or tumorigenesis : mechanism of induction of tumours**
- Three major type of carcinogens
  - I. Chemical carcinogenesis
    - Mutagens
    - Chemical carcinogenesis and their metabolism
  - II. Physical carcinogenesis (radiation)
    - Ultraviolet radiation, Asbestos
  - III. Infectious Pathogens (Viral)
    - Human T-cell leukemia viruses, DNA viruses, Human papillomaviruses
    - Epstein-Barr virus, Hepatitis B virus

I. CHEMICAL CARCINOGENESIS/ MUTAGENS

- **Dua Tahapan/ multistep process**
  - **Initiation : causes permanent DNA damage (Mutation)**
  - **Promotion (Proliferation)**

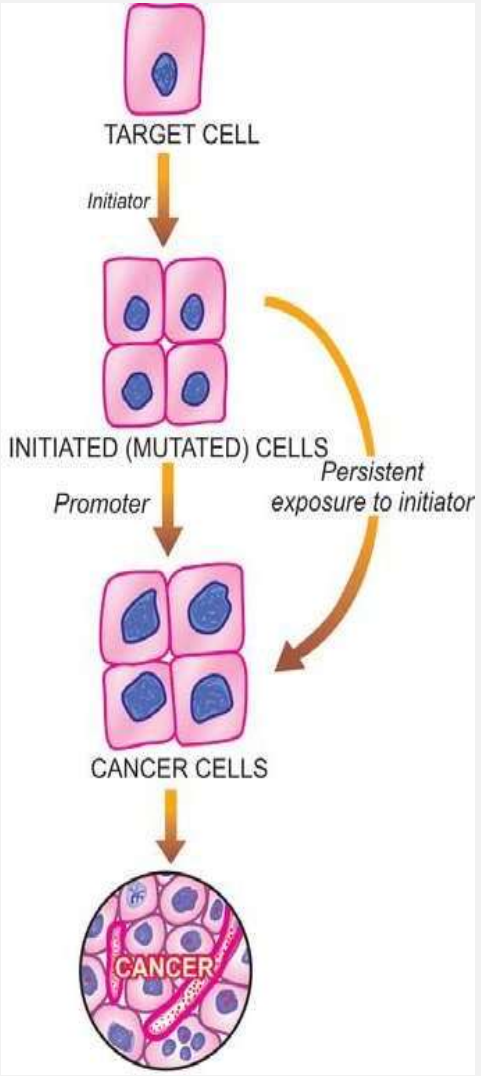
TAHAP INISIASI

- Direct acting compounds: Karsinogen yg kerjanya langsung terikat secara kovalen ke makromolekul seluler.

  E.g. nitrogen mustard, bis(chloro-methyl) ether, benzyl chloride, Epoxides.
- Indirect acting carcinogen (Procarcinogens): Karsinogen yg kerjanya tidak langsung. Memerlukan konversi metabolik untuk membentuk karsinogen akhir yang aktif.

TAHAP PROMOSI (PROLIFERASI)

- Dapat menyebabkan proliferasi sel & menginduksi tumor dalam sel yang diinisiasi, misalnya estrogen tetapi mereka sendiri non tumorigenik.
- Proliferasi sel yang bermutasi dapat menyebabkan akumulasi mutasi tambahan.



I. CHEMICAL CARCINOGENESIS/ MUTAGENS

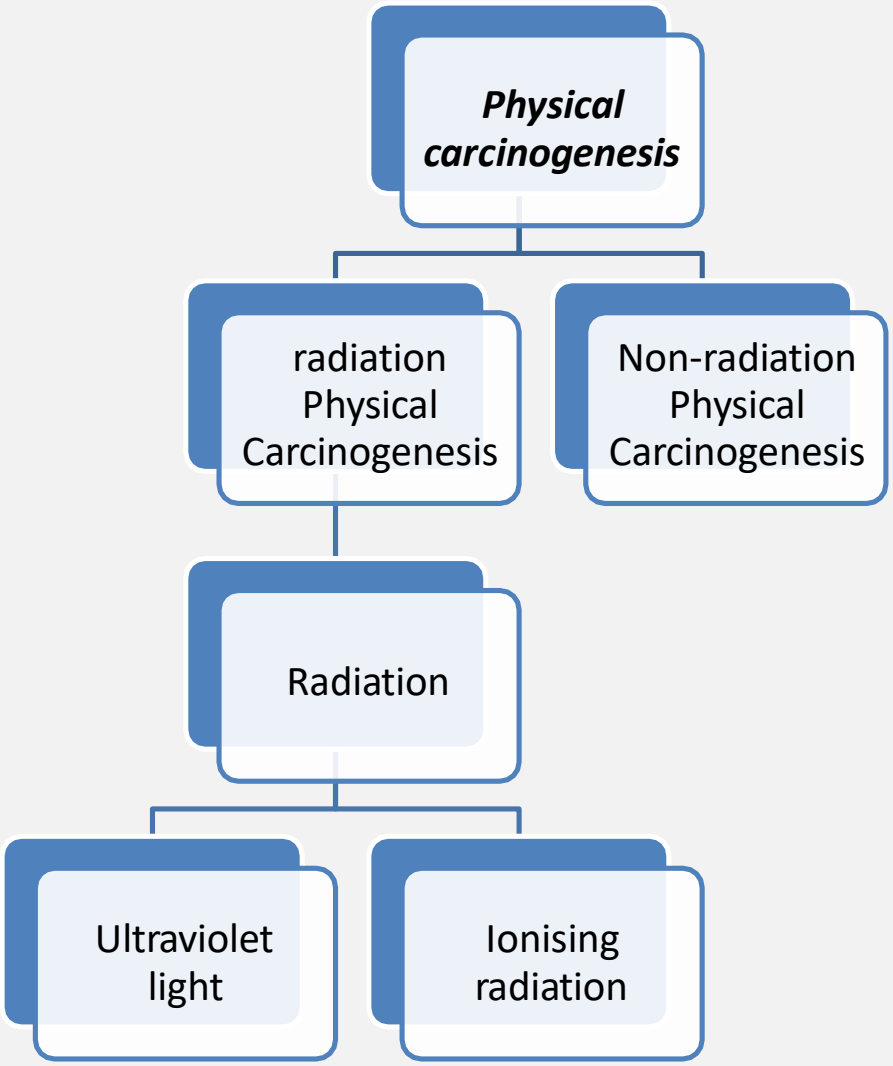
E.g. for indirect-acting chemical carcinogens (procarcinogens)

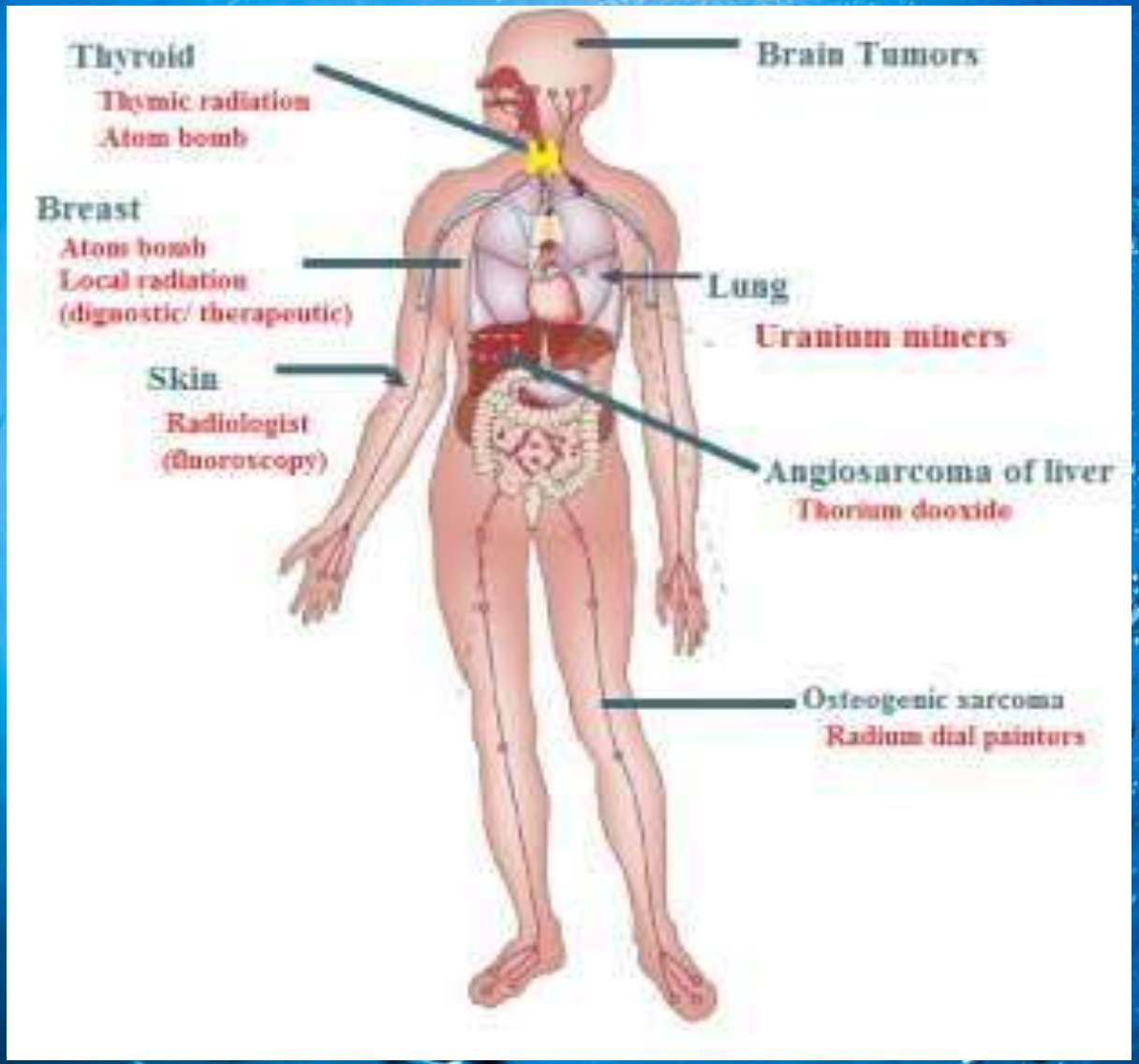
- **Polycyclic aromatic hydrocarbons** → cigarette smoke → lung cancer
- **Aflatoxin B_1** → Fungi *Aspergillus flavus* (contamination of veg. food, peanuts) → liver cancer (Africa and Asia regions)
- **Aromatic amines and Azo dues** → bladder (aniline dye) and liver tumors.
- **Nitrosamines**: Nitrosamines (nitrosamine, dimethyl nitrosamine) are potent carcinogen, produce kidney, liver tumor and gastrointestinal cancers.
- **Metals**: Ni^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+} and Be^{2+}.

FACTORS INFLUENCING CHEMICAL CARCINOGENESIS

- **Metabolisme Karsinogen :** Sebagian besar karsinogen kimiawi membutuhkan aktivasi metabolik.
- **Status Hormonal dan Jenis Kelamin :**
  - Kehamilan dikaitkan dengan penurunan insiden kanker payudara, endometrium, dan ovarium.
  - Wanita yang melahirkan anak pada usia dini memiliki risiko yang lebih rendah daripada wanita nulipara untuk kanker payudara, endometrium dan ovarium.
  - Menarke dini, menopause terlambat, dan usia kehamilan pertama yang lebih tua semuanya meningkatkan risiko kanker payudara.
- **Diet:** Diet rendah protein menurunkan aktivitas hepatic dan menurunkan kepekaan terhadap hepatokarsinogen. Obesitas dikaitkan dengan peningkatan jumlah tumor.

II. PHYSICAL CARCINOGENESIS




Thyroid
Thymic radiation
Atom bomb
Brain Tumors
Breast
Atom bomb
Local radiation
(diagnostic/ therapeutic)
Lung
Uranium miners
Skin
Radiologist
(fluoroscopy)
Angiosarcoma of liver
Thorium dooxide
Osteogenic sarcoma
Radium dial painters

II. PHYSICAL CARCINOGENESIS

- **Radiation- Ultraviolet light**
  - Causes : mutation, inhibits cell division and cell death
  - MOA: formation of pyrimidine dimer
  - Main source of UV light is sunlight, UV lamp and welder's arcs
  - Penetration of UV light protected by **melanin** pigmentation of the skin.

- Sun light > white race > basal cell carcinoma, squamous carcinoma and malignant melanoma
- Sun light > darker races > protected by melanin pigment, which absorbs UV radiation
- Risiko seumur hidup dari 1 rad sinar-X seluruh tubuh atau radiasi sinar gamma adalah satu kematian akibat kanker yang berlebihan per 10.000 orang

II. PHYSICAL CARCINOGENESIS

- **Radiation- Ionising radiation**
  - X-rays, α-, β- and γ- rays, radioactive isotopes, protons and neutrons

    can cause cancer

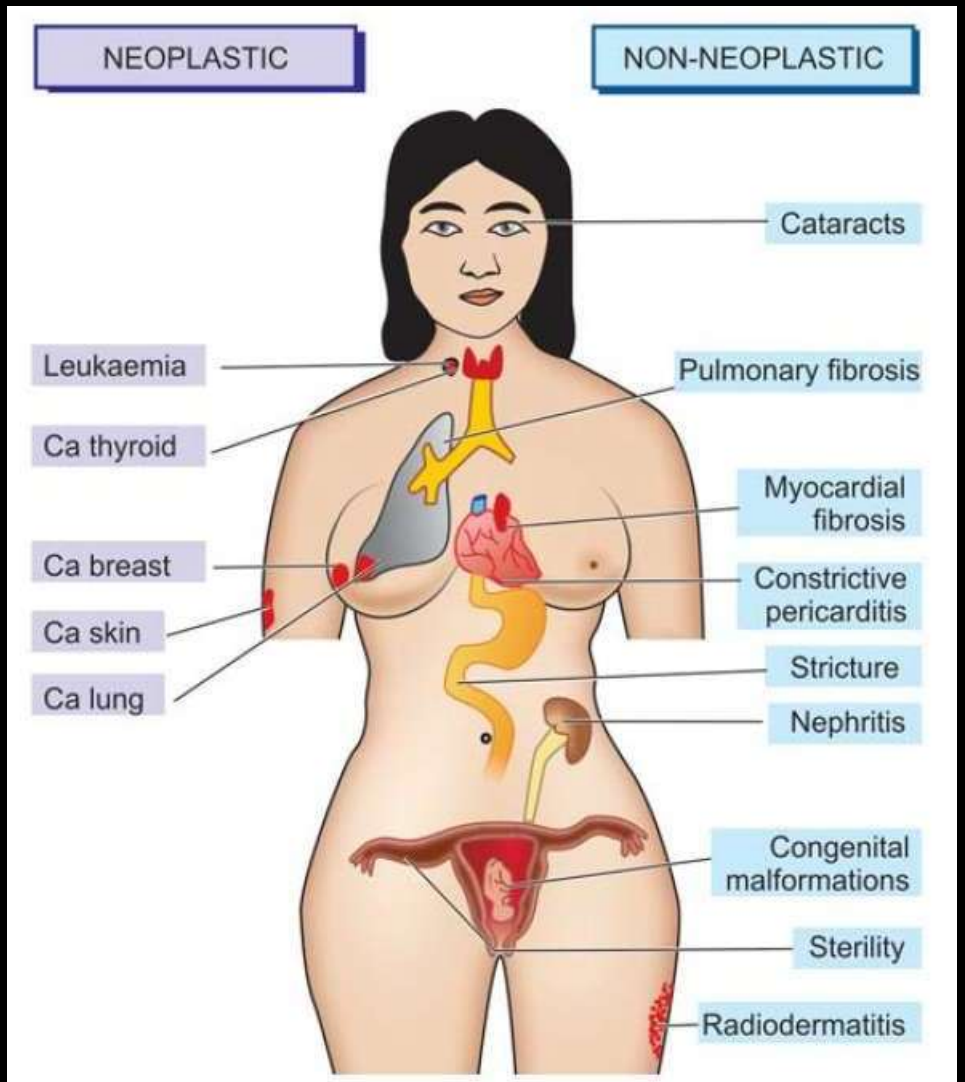


Figure 20.9 Neoplastic (left) and non-neoplastic complications (right) of ionising radiation.

Image form 'Essential Pathology for Dental Students' by Harsh Mohan and Sugandha Mohan, 4th ed. India

II. PHYSICAL CARCINOGENESIS

Non-radiation Physical Carcinogenesis

- Asbestos: A fibrous amphibole; digunakan untuk membuat artikel tahan api
- Inhaling asbestos can cause lung cancer
- Source of inhalation:
  - mining and manufacturing of asbestos
  - pemasangan insulasi asbes
  - udara yang terkontaminasi dalam gedung yang mengalami perbaikan atau pembongkaran
  - clothing of asbestos workers

III. INFECTIOUS PATHOGENS

- Virus
- Viral infection is responsible for 20% of human cancer worldwide
  - RNA retrovirus HTLV-I → T-cell leukemia/ lymphoma (endemic in Japan, Africa, the Caribbean basin and southeastern United States)
  - Human papillomavirus (DNA) → squamous carcinoma of the cervix
  - Hepatitis B and C viruses → primary hepatocellular carcinoma
  - Epstein-Barr virus (EBV) → lymphoma and nasopharyngeal carcinoma
  - Human herpesvirus 8 → kaposi sarcoma

III. INFECTIOUS PATHOGENS

- **Bacteria**
  - *Helicobacter Pylori* (Gastric lymphoma, Mucosal Associated Lymphoid Tumor (MALT) & Gastric carcinoma)
- ***Fungi***
  - aflatoxins produced by *Aspergillus flavus* - hepatocellular carcinoma
- ***Parasites***
  - *Schistosoma* and *Clonorchis sinensis*
- ***Cancer inheritance***
  - Cancer inheritance: Genetic basis. E.g., Breast cancer (associated genes are BRCA-1 and BRCA-2)

THANK YOU

PATOFISIOLOGI GAGAL GINJAL AKUT & KRONIK

OUTLINE

- Epidemiologi
- Mengenal anatomi ginjal
- Jenis gangguan ginjal
- Gangguan ginjal pada anak
- Faktor risiko
- Gejala
- Diagnosis
- Dampak
- Pentingnya deteksi dini dan pencegahan

EPIDEMIOLOGI

Di dunia, **insiden** pada anak yang menjalani opname di rumah sakit sekitar **33,7%** dengan **angka kematian sebesar 13,8%.**

Gangguan Ginjal Kronik

- Amerika Serikat
  - 9.800 anak mengalami gangguan ginjal kronik (2017).
  - 1.399 anak mengalami gagal ginjal (2015).
- Insiden di Eropa sekitar 11-12 kasus/tahun/1juta anak dengan prevalensi sekitar 55-60 kasus/1juta anak.

- Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL. World Incidence of AKI: a meta analysis. Clin J Am Soc Nephrol. 2013 Sept: 8(9); 1482-93. DOI: https://doi.org/10.2215/CJN.00710113.
- CDC. Chronic kidney disease surveillance system: almost 10.000 children and adolescents in United States are living with end-stage renal disease [internet] 2017 Jul. Available from: https://nccd.cdc.gov/ckd/AreYouAware.aspx?emailDate=July_2017.
- Becherucci F, et al. Chronic kidney disease in children. Clin Kidney J. 2016: 9(4); 583-91. doi: 10.1093/ckj/sfw047

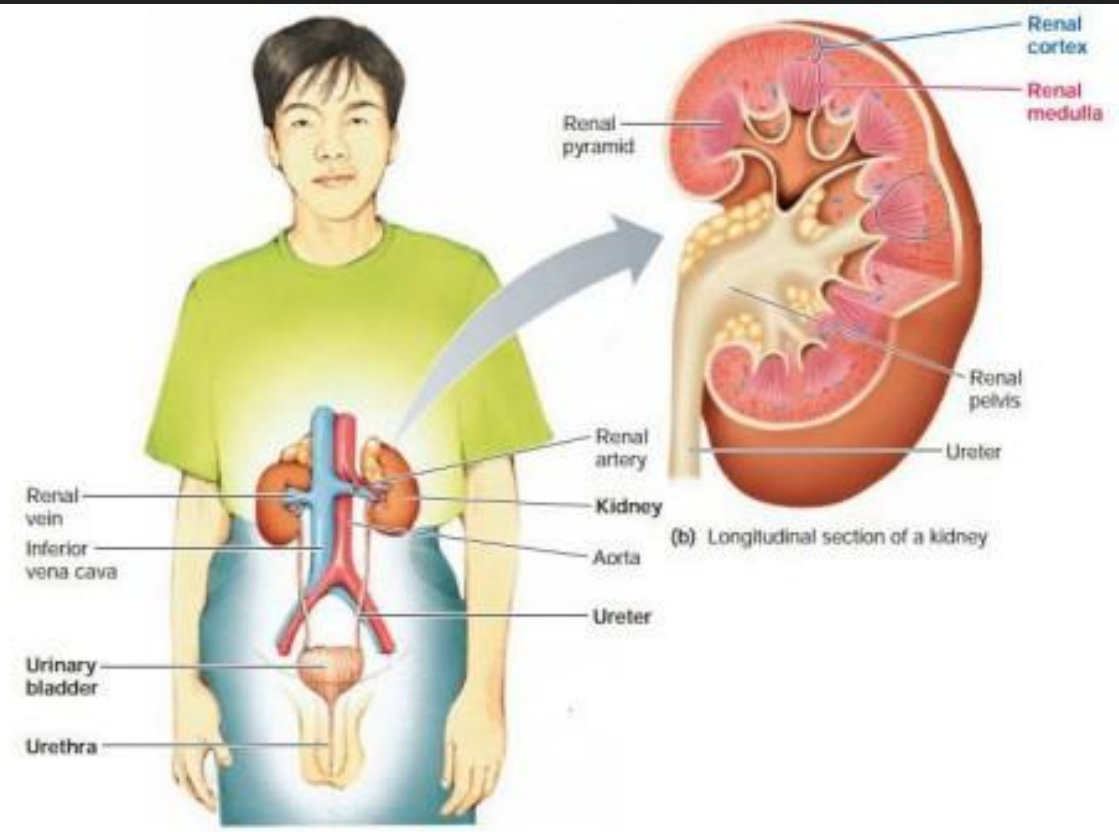
EPIDEMIOLOGI

- Data dari 14 RS Pendidikan dengan Konsultan Nefrologi Anak (tahun 2017)

212 anak mengalami gagal ginjal dan menjalani terapi pengganti ginjal

Angka kematian: 23,6%

MENGENAL ANATOMI GINJAL

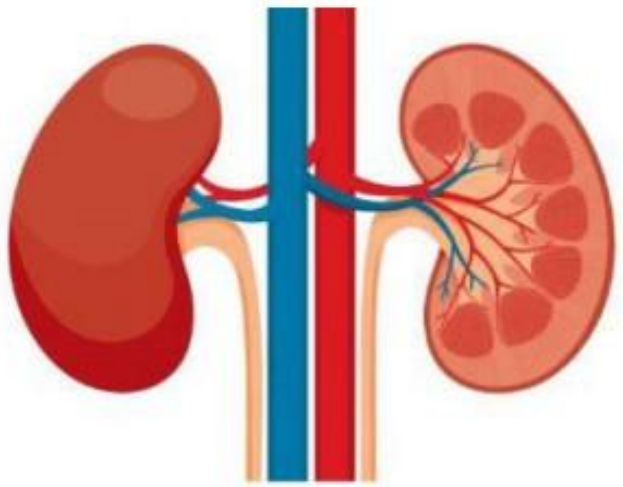


Sepasang organ berbentuk kacang, banyak pembuluh darah

Aliran darah ke kedua ginjal pada keadaan normal mencapai sekitar 22% dari curah jantung

- Sherwood L. Bab 13. The urinary sistem. Dalam: Sherwood L. Fundamentals of Human Physiology. Edisi ke-4. CA: Brooks/Cole; 2012.
- Hall JE. Bab 26. The urinary system: functional anatomy and urine formation by the kidneys. Dalam: Hall JE. Guyton and Hall Textbook of Medical Physiology. Edisi ke-13. PA: Elsevier;2016.

FUNGSI GINJAL



- **Pembuangan (ekskresi)**
  - **Pembuangan zat sisa metabolisme**: Urea, kreatinin, asam urat, bilirubin, dll
- **Pengaturan**
  - Pembentukan **sel darah merah**
  - Keseimbangan **cairan** dan **elektrolit**
  - Tingkat **keasaman** (pH) darah
  - **Tekanan darah**
- **Pembentukan**
  - **Glukosa**
  - **Kalsitriol** (bentuk aktif vitamin D) yang penting untuk metabolisme kalsium dam fosfat

- Hall JE. Bab 26. The urinary system: functional anatomy and urine formation by the kidneys. Dalam: Hall JE. Guyton and Hall Textbook of Medical Physiology. Edisi ke-13. PA: Elsevier;2016.

JENIS GANGGUAN GINJAL

Berdasarkan awitannya, gangguan ginjal dapat dibedakan menjadi 2:

AKUT

(misal *acute kidney injury, infeksi sal kemih*)

Penyakit ginjal yang **timbul mendadak** dan dalam **waktu singkat**.

Gangguan ginjal kronik

(*chronic kidney disease*)

Adanya gangguan pada **struktur** *atau* **fungsi** ginjal selama **>3bulan**

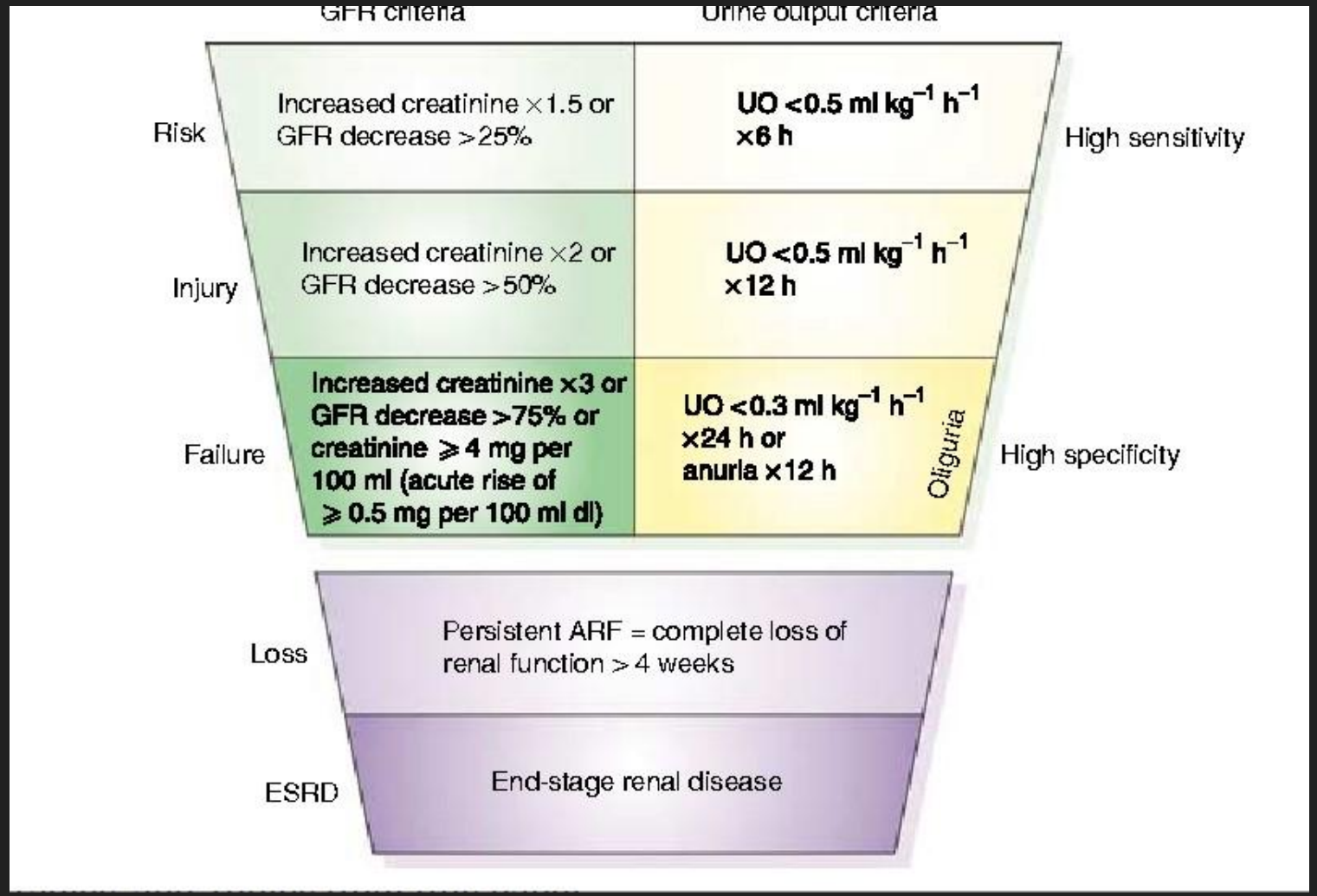
Catatan: kriteria 3 bulan tidak berlaku untuk bayi berusia ≤3bulan.

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3:1.
Alatas H. Bab 24. Gagal Ginjal Akut. Dalam: Alatas H, Tambunan T, Trihono P, Pardede S. Buku Ajar Nefrologi Anak. Edisi ke-2. Jakarta: BP FKUI; 2002.

GAGAL GINJAL AKUT

- Gagal ginjal akut (GGA) adalah penurunan fungsi ginjal yang mendadak dengan akibat hilangnya kemampuan ginjal untuk mempertahankan homeostasis tubuh.
- Akibat penurunan fungsi ginjal terjadi peningkatan metabolit persenyawaan nitrogen seperti ureum dan kreatinin serta gangguan keseimbangan cairan dan elektrolit.
- Kriteria tambahan lain untuk menegakkan diagnosis GGA yaitu terjadinya peningkatan kadar kreatinin darah secara progresif 0,5 mg/dl per hari dan peningkatan kadar ureum darah sekitar 10-20 mg/dl per hari.

KRITERIA RIFLE PADA GAGAL GINJAL AKUT



GAGAL GINJAL KRONIK

Seorang anak dikatakan menderita PGK apabila **selama ≥3 bulan** terdapat salah satu dari kriteria di bawah ini:[1, 3]

- **Abnormalitas struktur atau fungsi ginjal,** dengan/ tanpa penurunan LFG, dengan manifestasi satu atau lebih tanda:
  1. Kelainan pada **Lab.** komposisi darah atau urin
  2. Kelainan pada **Pencitraan** ginjal dan saluran kemih
  3. Kelainan pada **Hasil Biopsi** ginjal
- **Atau : LFG <60 ml/ menit/ 1,73 m^2** dengan/ tanpa kerusakan ginjal seperti yang disebutkan pada kriteria tersebut di atas

STADIUM GAGAL GINJAL KRONIK

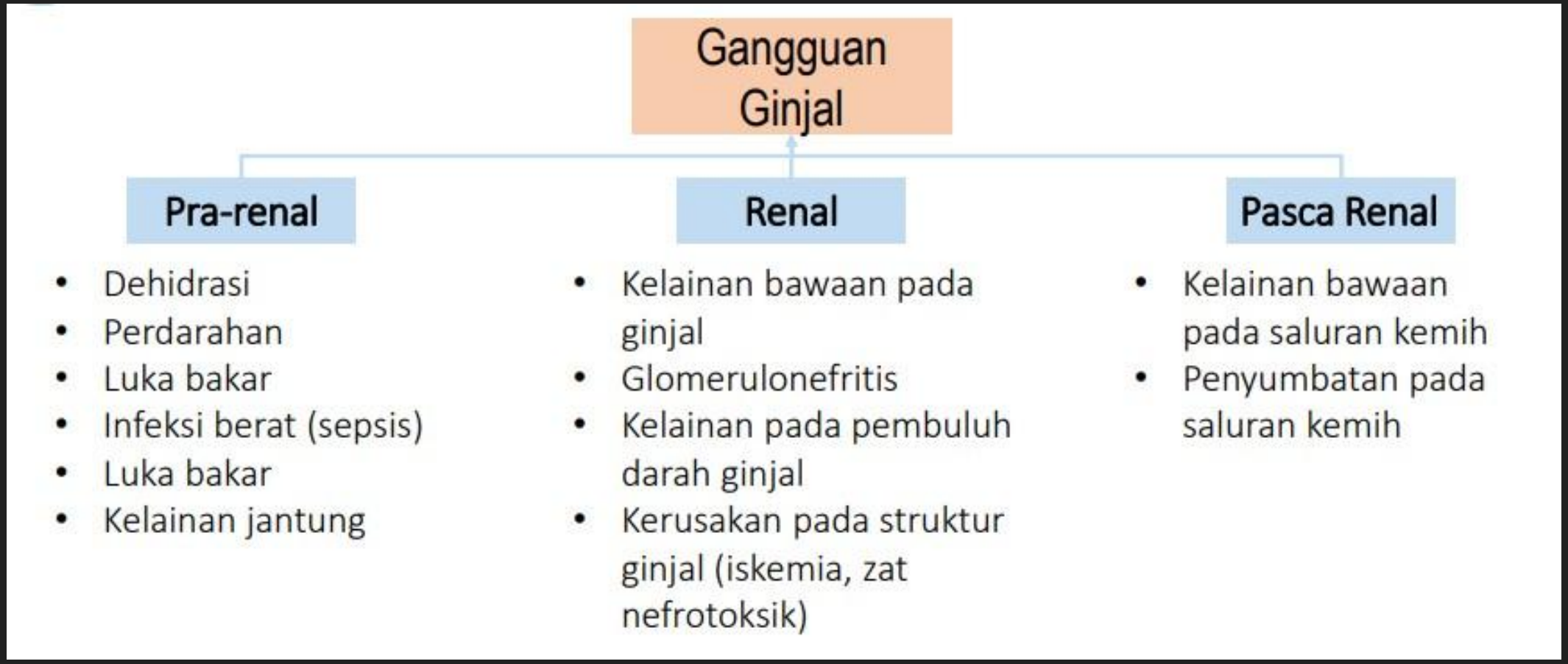
Stadium	Fungsi ginjal	Laju filtrasi glomerulus (ml/menit/1,73m^2)
Risiko meningkat	Normal	> 90 (ada faktor risiko)
Stadium 1	Normal/meningkat	> 90 (ada kerusakan ginjal, proteinuria)
Stadium 2	Penurunan ringan	60-89
Stadium 3	Penurunan sedang	30-59
Stadium 4	Penurunan berat	15-29
Stadium 5	Gagal ginjal	< 15

PERHITUNGAN GFR (SCHWARTZ FORMULA)

GFR (mL/min/1.73 m2) = k x Height / Serum Creatinine

- k = Constant
  - k = 0.33 in Preterm Infants
  - k = 0.45 in Term infants to 1 year old
  - k = 0.55 for Children to 13 years
  - k = 0.65 for adolescent males (because of the presumed increase in male muscle mass
  - K = 0.55 for adolescent females
- Height in cm
- Serum Creatinine in mg/dL

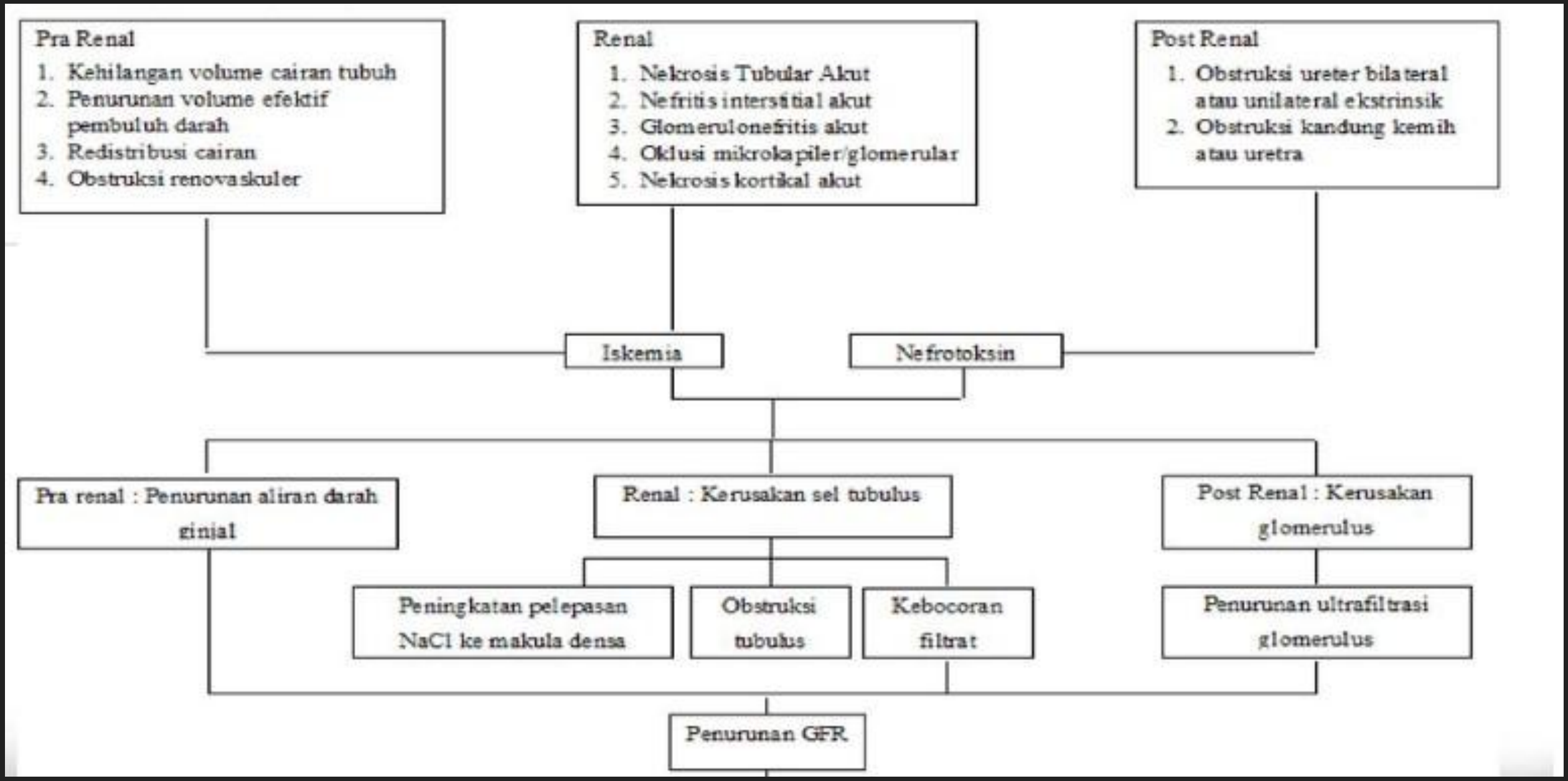
PENYEBAB GANGGUAN GINJAL



PENYEBAB GANGGUAN GINJAL

- UKK Nefrologi IDAI. Kompendium Nefrologi Anak. Jakarta: BP [illegible]
- Wong CG, Warady BA. Chronic kidney disease in children: definition, epidemiology, etiology, and course. UpToDate. 2018 Sep [updated 2018 Oct 18].

PATOFISIOLOGI GAGAL GINJAL



GEJALA GANGGUAN GINJAL

Edema (Bengkak)

Simetris di kiri dan kanan

Hematuria

Adanya **darah dalam urin**, baik makroskopik (**kasat mata**) atau mikroskopik (**tidak kasat mata**).

Leukosituria

Peningkatan jumlah leukosit (sel darah putih) pada urin (>5 sel/LPB).

UKK Nefrologi IDAI. Kompendium Nefrologi Anak. Jakarta: BP FKUI;2011.

GEJALA GANGGUAN GINJAL

- Pardede SO, Chunnaedy S. Penyakit Ginjal Kronik pada Anak. Sari Pediatri. 2009 Okt: 11(3);199-203.
- Wong CS, Warady BA, Srivastava T. Clinical presentation and evaluation of chronic kidney disease in children. UpToDate. 2018 Sept.
- Hidayati EL, Trihono PP. Admission characteristics of pediatric chronic kidney disease. Pediatr Indones. 2011 Jul; 51(4): 192-7.

PEMERIKSAAN PENUNJANG GANGGUAN GINJAL

Laboratorium	Pencitraan	Lain-lain
• Darah lengkap • Ureum, kreatinin • Elektrolit • Profil lipid • Urin lengkap	• USG • CT-Scan • MRI	• Biopsi ginjal

Wong CS, Warady BA, Srivastava T. Clinical presentation and evaluation of chronic kidney disease in children. UpToDate. 2018 Sept.

DAMPAK GANGGUAN GINJAL

- Gangguan pertumbuhan dan perkembangan
- Anemia
- Hipertensi
- Dislipidemia
- Kelainan tulang
- Peningkatan risiko alami penyakit kardiovaskular lebih dini
- Gangguan keseimbangan elektrolit
- Gangguan hormon

- Wong CS, Warady BA, Srivastava T. Clinical presentation and evaluation of chronic kidney disease in children. UpToDate. 2018 Sept.
- Kaspar CDW, Bholah R, Bunchman TE. A Review of Pediatric Chronic Kidney Disease. Blood Purif. 2016:41;211-7. DOI:10.1159/000441737
- Becherucci F, et al. Chronic kidney disease in children. Clin Kidney J. 2016: 9(4); 583-91. doi: 10.1093/ckj/sfw047

RESIKO KEMATIAN GANGGUAN GINJAL

Risiko Kematian Lebih Tinggi

Risiko kematian pada anak dengan **gangguan ginjal kronik stadium akhir** (gagal ginjal),
30 kali lebih tinggi dibanding anak pada populasi umum

Data di RSCM 2007-2009

22% pasien datang pada kondisi stadium akhir

- McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350:2654-62
- Hidayati EL, Trihono PP. Admission characteristics of pediatric chronic kidney disease. Pediatr Indones. 2011 Jul: 51(4); 192-7.

GLOMERULONEFRITIS AKUT

- GNAPS dapat terjadi pada semua usia, tetapi paling sering terjadi pada usia 6 – 7 tahun.
- Rasio ♂ : ♀ = 1, 34 : 1.1
- Angka kejadian GNAPS sukar ditentukan mengingat bentuk asimtomatik lebih banyak dijumpai daripada bentuk simtomatik.

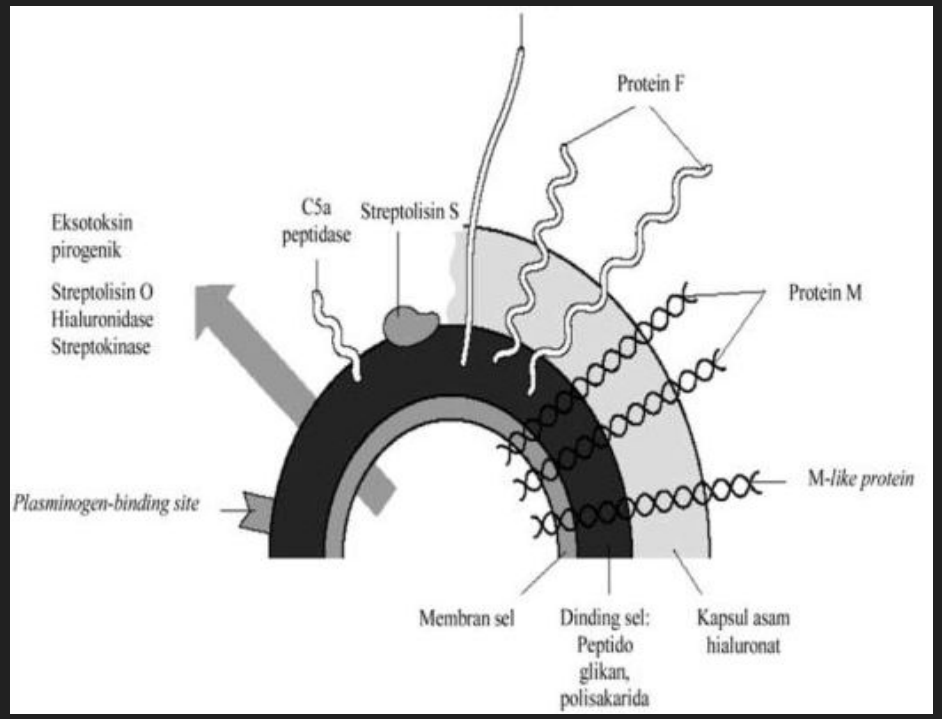
DEFINISI GLOMERULONEFRITIS AKUT

- Suatu proses penyakit yang dikarakteristikan berupa proliferasi & inflamasi sel glomeruli akibat proses imunologik yang ditandai dengan gejala nefritik seperti hematuria, edema, hipertensi, oliguria yang terjadi secara akut.

PENYEBAB GLOMERULONEFIRTIS AKUT

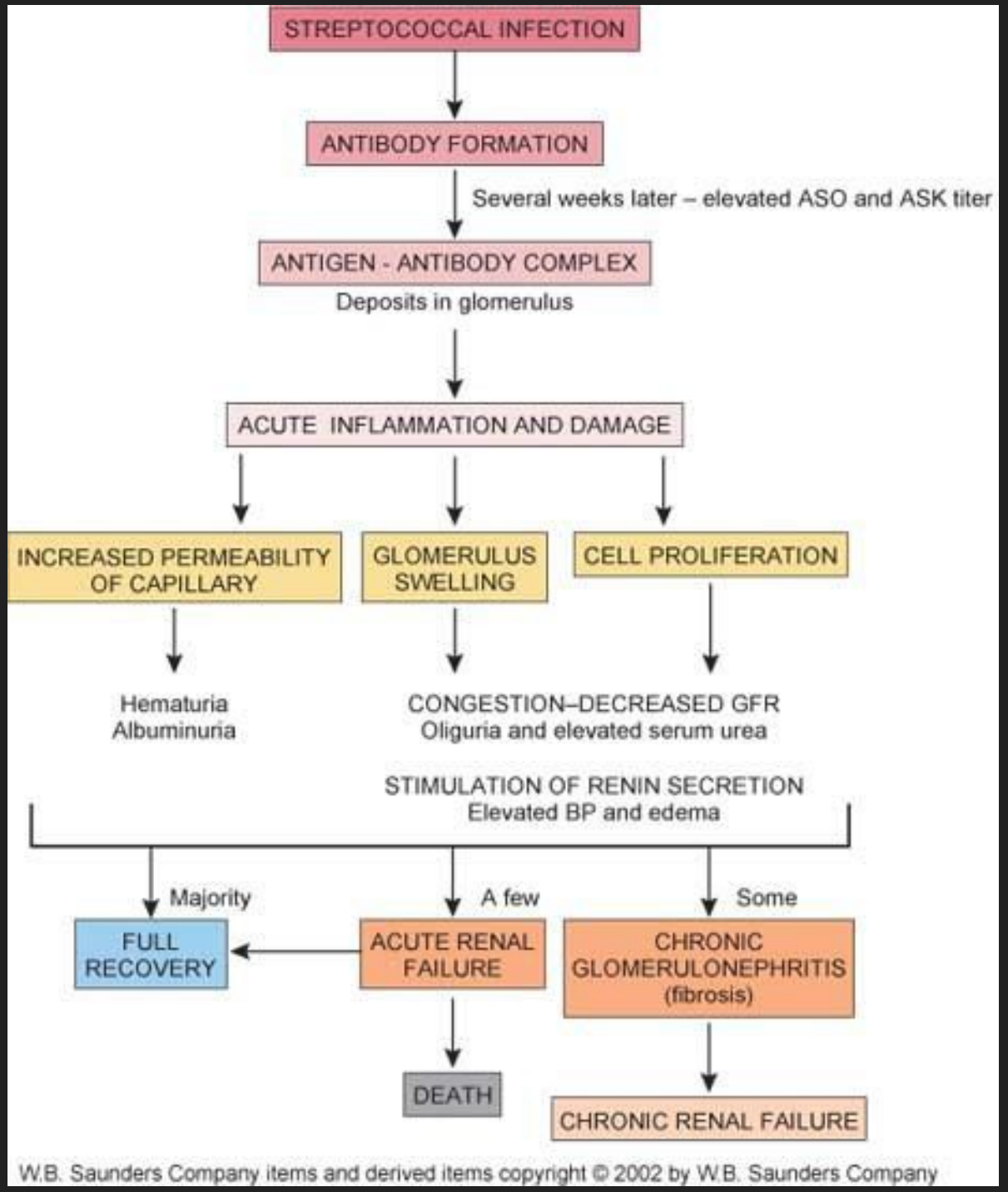
- **Post-streptococcal acute GN**
- **Penyebab Lain:**
  Autoimune disease
  - Ig A nephropathy
  - Henoch Schonlein Purpura
  - Systemic Lupus Eritmeatousus

STREPTOKOKOUS B HEMOLITIKUS



- Group A Streptococcus *β*-hemolitikus (GAS) nephritogenic strain
- Serotipe associated with URI: M types 1,3,4,12,49
- Serotipe associated with pyodermitis: M types 2,49,55,57,60

PATHOGENESIS GNAPS



GEJALA KLINIS

Riwayat Klinis:

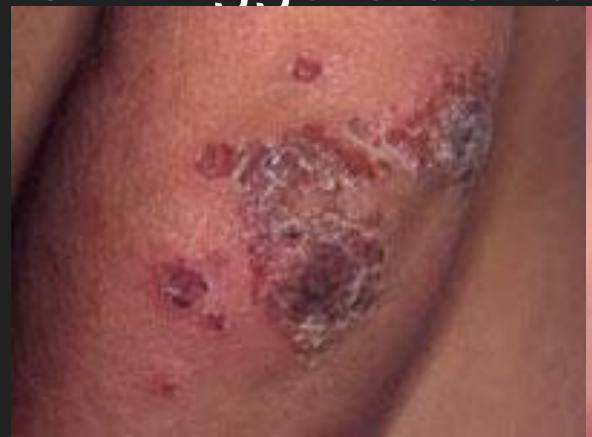
Periode Laten

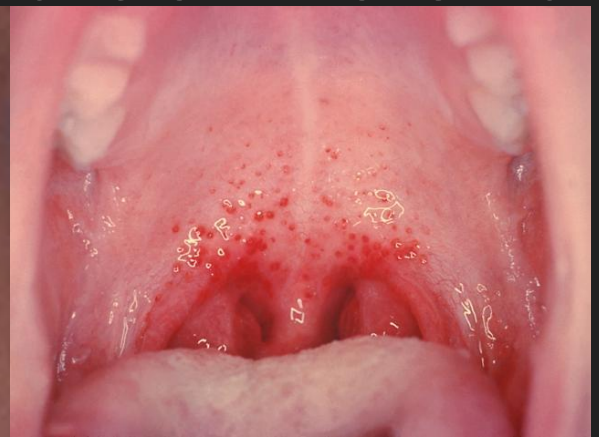
GNAPS yang khas harus ada periode laten yaitu periode antara infeksi streptokokus dan timbulnya gejala klinik.

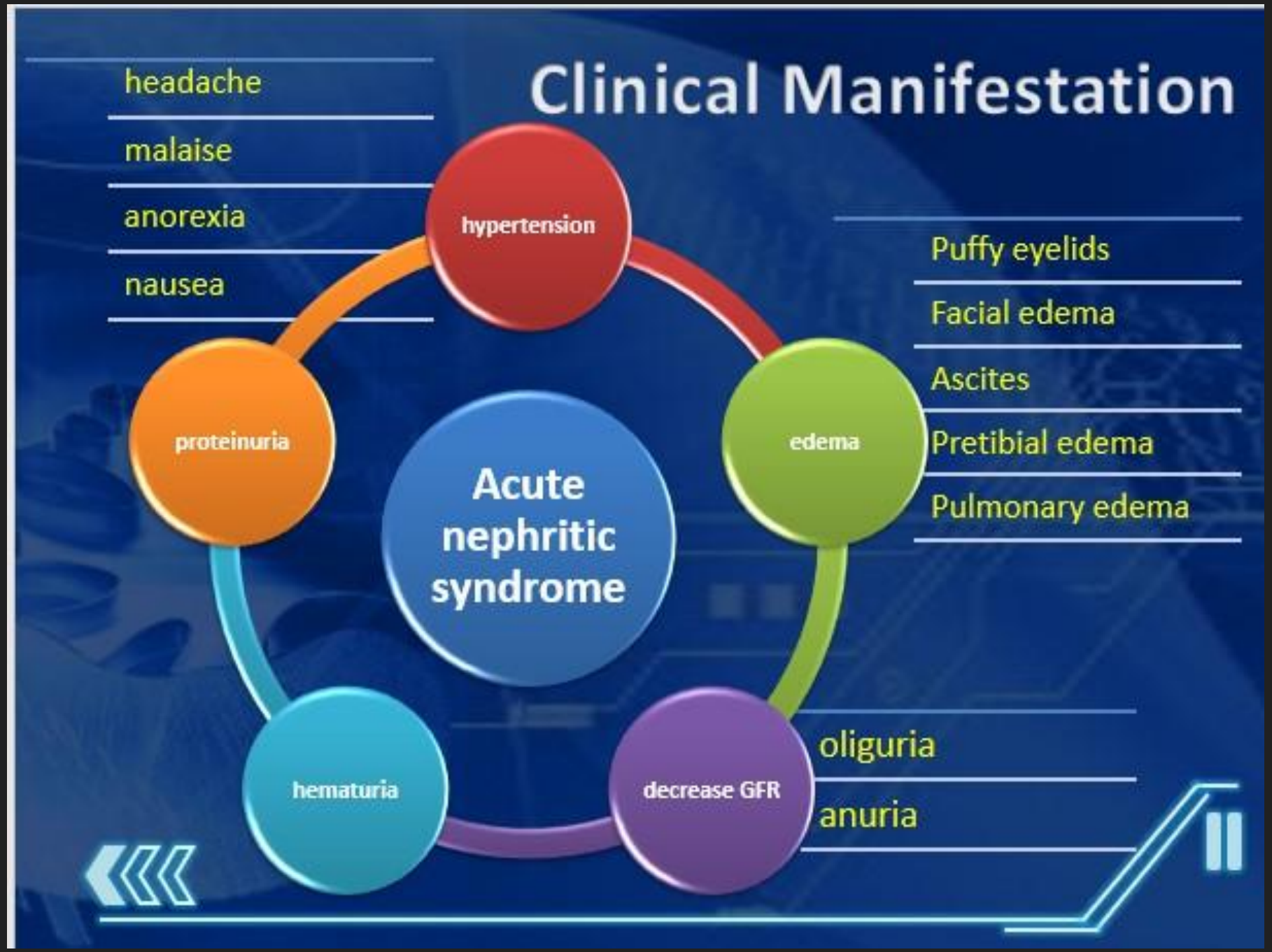
Periode ini berkisar 1-3 minggu;

Periode 1-2 minggu umumnya terjadi pada GNAPS yang didahului oleh ISPA,

Periode 3-6 minggu didahului oleh infeksi kulit/piodermi.






Clinical Manifestation
headache
malaise
anorexia
nausea
hypertension
Puffy eyelids
Facial edema
Ascites
Pretibial edema
Pulmonary edema
proteinuria
Acute nephritic syndrome
edema
hematuria
decrease GFR
oliguria
anuria

DIAGNOSTIC WORK UP

- Urinalysis
  - Dismorphic RBC
  - RBC cast, granular cast
  - Variying degree of proteinuria
  - Pyuria may be found

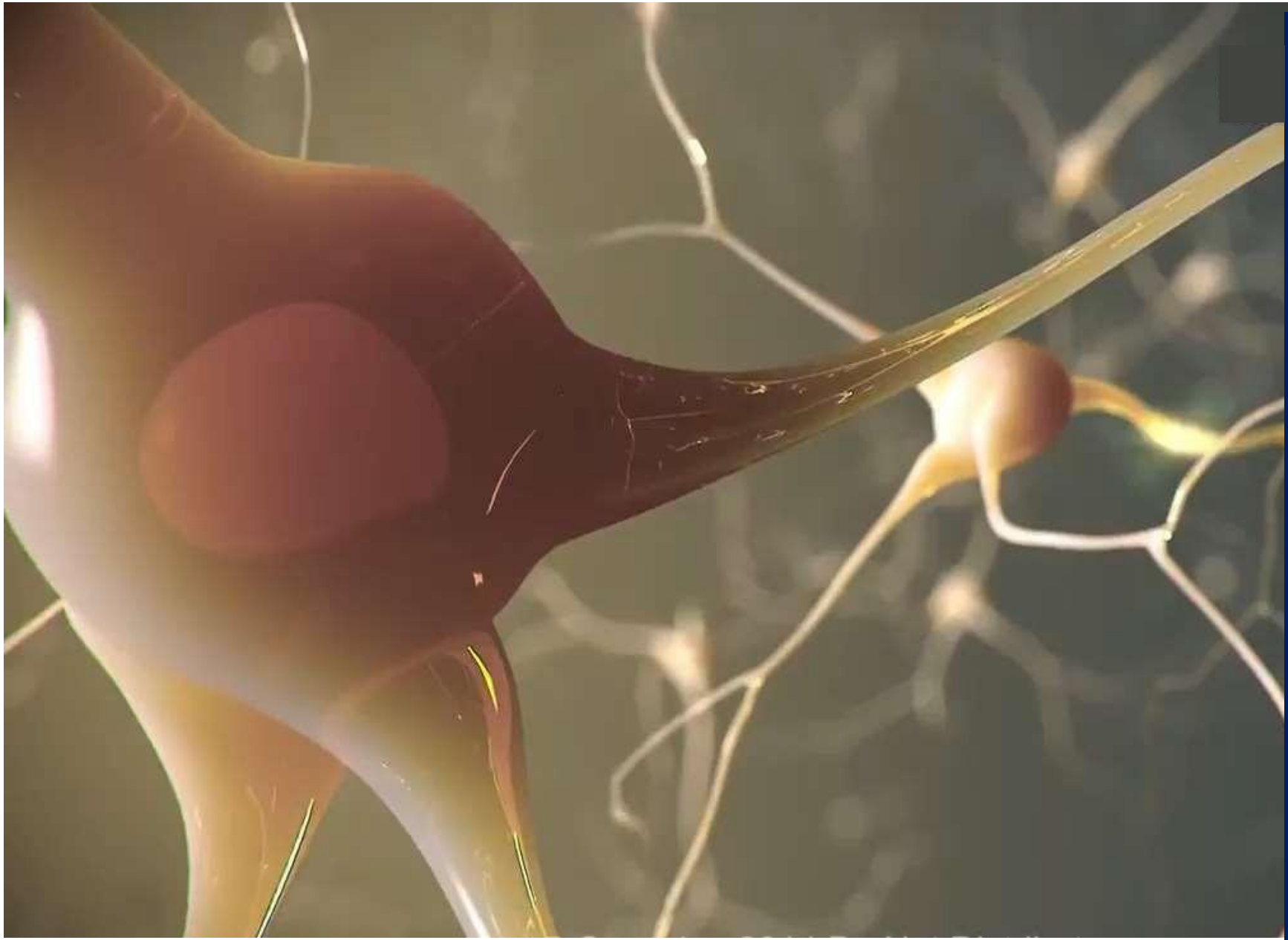
- Renal function: serum creatinin, ureum/ BUN

- C3 complement level
  - 90 % of patients, C3 and CH50 (total complement activity) are significantly low in the first 2 weeks
  - Returned to normal within two months

DIAGNOSTIC WORK UP

- Laboratory evidence of inflammation and a preceding streptococcal infection positive antistreptolysin O (ASTO) titers
  - First noted: 2nd or 3rd week of an acute episode
  - Peaks: 4 to 5 week
  - Its absence does not exclude the diagnosis many nephritogenic strains do not produce streptolysin
  - Gold standard : biakan positif untuk streptokokus ß hemolitikus grup A.

TERIMA KASIH



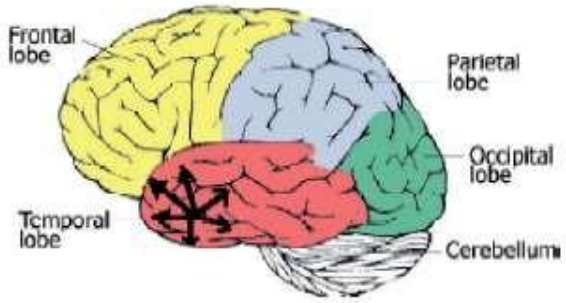
Classification,
Clinical features,
Pathophysiology

Pathophysiology

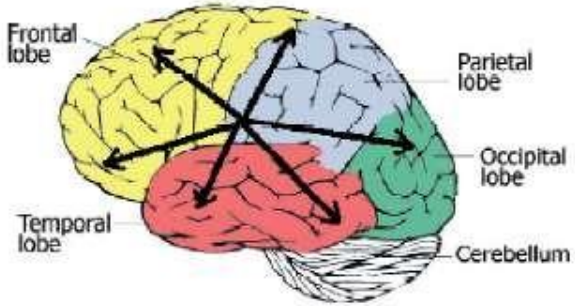
Of

EPILEPSY

Classificatio
n



PARTIAL
Seizure activity starts in one area of the brain.



GENERALISED
Seizure involves whole brain – consciousness is lost at the onset.

Complex
Altered awareness and behaviour e.g. confusion, repetitive movements.

Simple
Patient remains alert e.g. jerking of a limb, déjà vu, nausea, strange taste or smell

May become generalised (spreading from one area to the whole brain).

Tonic Clonic
'grand-mal' or convulsion with loss of consciousness, stiffening of body then jerking of limbs.

Absence
'petit-mal' or staring or trance-like state.

Tonic or Atonic
'drop attack' or abrupt fall, either with stiffening (tonic) or loss of muscle tone (atonic or astatic attacks).

Myoclonic
sudden muscle jerks.

Table 1. Suggested scheme for an etiological classification of epilepsy

Main category	Subcategory	Examples[a]
Idiopathic epilepsy	Pure epilepsies due to single gene disorders	Benign familial neonatal convulsions; autosomal dominant nocturnal frontal lobe epilepsy; generalized epilepsy with febrile seizures plus; severe myoclonic epilepsy of childhood; benign adult familial myoclonic epilepsy
	Pure epilepsies with complex inheritance	Idiopathic generalized epilepsy (and its subtypes); benign partial epilepsies of childhood
Symptomatic epilepsy		
Predominately genetic or developmental causation	Childhood epilepsy syndromes	West syndrome; Lennox-Gastaut syndrome
	Progressive myoclonic epilepsies	Unverricht-Lundborg disease; Dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; sialidosis; neuronal ceroid lipofuscinosis; myoclonus renal failure syndrome
	Neurocutaneous syndromes	Tuberous sclerosis; neurofibromatosis; Sturge-Weber syndrome
	Other neurologic single gene disorders	Angelman syndrome; lysosomal disorders; neuroacanthocytosis; organic acidurias and peroxisomal disorders; prophyria; pyridoxine-dependent epilepsy; Rett syndrome; Urea cycle disorders; Wilson disease; disorders of cobalamin and folate metabolism
	Disorders of chromosome function	Down syndrome; Fragile X syndrome; 4p-syndrome; isodicentric chromosome 15; ring chromosome 20
	Developmental anomalies of cerebral structure	Hemimegalencephaly; focal cortical dysplasia; agyria-pachygyria-band spectrum; agenesis of corpus callosum; polymicrogyria; schizencephaly; periventricular nodular heterotopia; microcephaly; arachnoid cyst

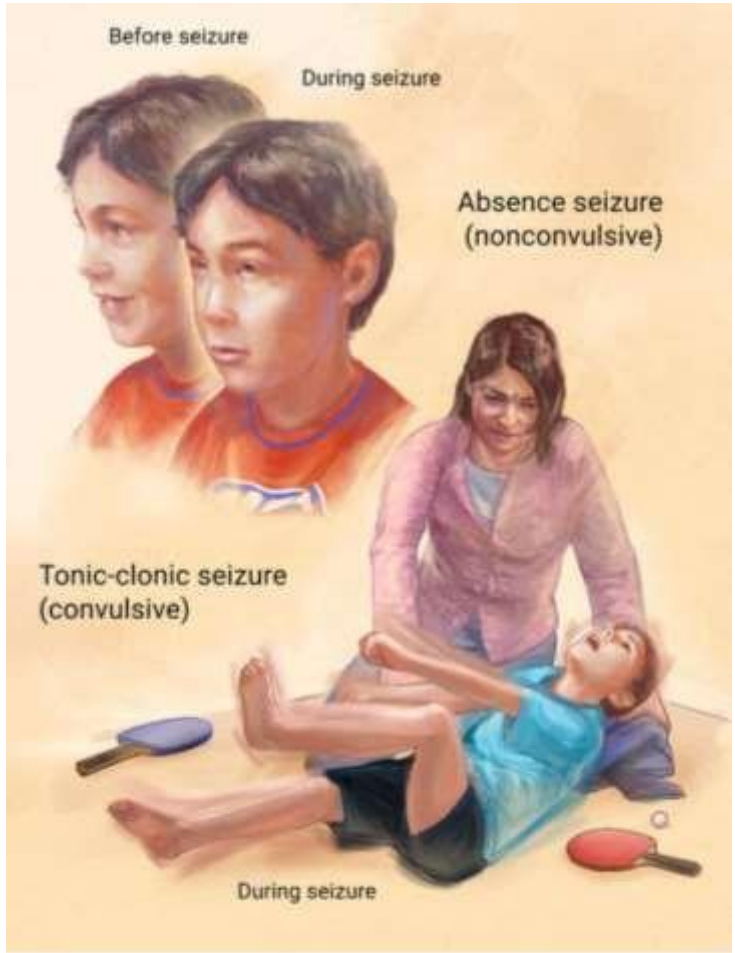
Predominately acquired causation	Hippocampal sclerosis	Hippocampal sclerosis
	Perinatal and infantile causes	Neonatal seizures; postneonatal seizures; cerebral palsy; vaccination and immunization
	Cerebral trauma	Open head injury; closed head injury; neurosurgery; epilepsy after epilepsy surgery; nonaccidental head injury in infants
	Cerebral tumor	Glioma; ganglioglioma and hamartoma; DNET; hypothalamic hamartoma; meningioma; secondary tumors
	Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis, tuberculosis; HIV
	Cerebrovascular disorders	Cerebral hemorrhage; cerebral infarction; degenerative vascular disease; arteriovenous malformation; cavernous hemangioma
	Cerebral immunologic disorders	Rasmussen encephalitis; SLE and collagen vascular disorders; inflammatory and immunologic disorders
	Degenerative and other neurologic conditions	Alzheimer disease and other dementing disorders; multiple sclerosis and demyelinating disorders; hydrocephalus and porencephaly
Provoked epilepsy	Provoking factors	Fever; menstrual cycle and catamenial epilepsy; sleep-wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol and toxin-induced seizures
	Reflex epilepsies	Photosensitive epilepsies; startle-induced epilepsies; reading epilepsy; auditory-induced epilepsy; eating epilepsy; hot-water epilepsy
Cryptogenic epilepsies[b]		

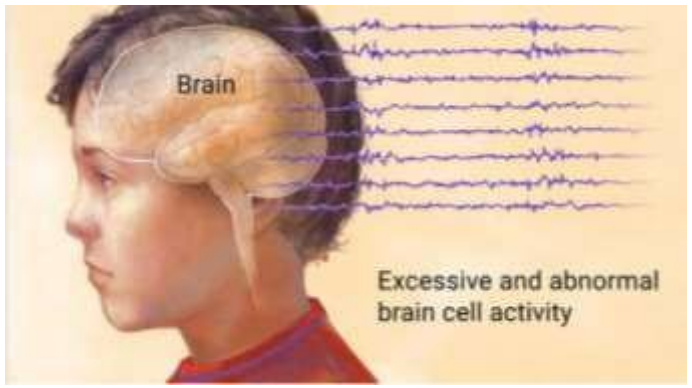
DNET, dysembryoplastic neuroepithelial tumor.

[a]These examples are not comprehensive, and in every category there are other causes.

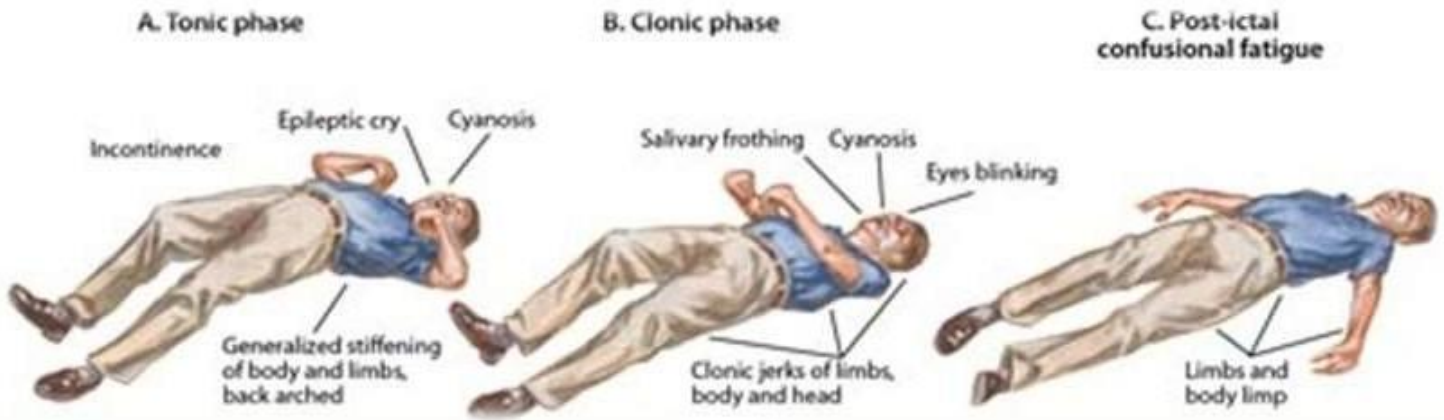
[b]By definition, the causes of the cryptogenic epilepsies are "unknown." However, these are an important category, accounting for at least 40% of epilepsies encountered in adult practice and a lesser proportion in pediatric practice.

This list is derived from the book *Causes of Epilepsy* (Shorvon et al., 2011b).





Generalized Tonic-Clonic Seizure



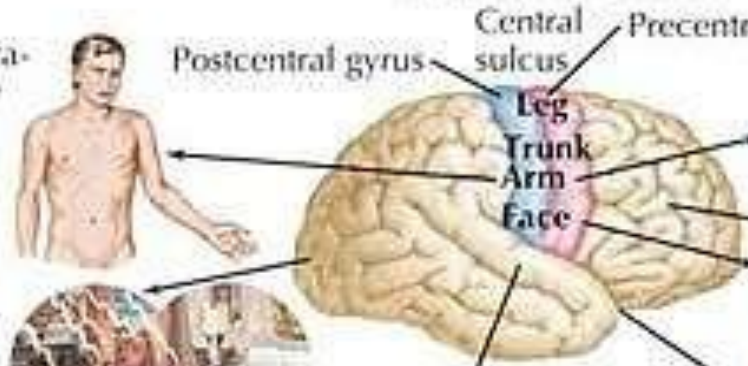
Tonic & Clonic Phases

- Loss of consciousness or fainting – 30 sec to 5 mins.
- General muscle contraction and rigidity (**tonic** phase) – 15-20 sec.
- Violent rhythmic muscle contraction and relaxation (**clonic** phase) – 1-2 mins.
- Biting the cheek/tongue, clenched teeth/jaw
- Incontinence
- Stopped breathing or difficulty breathing during seizure
- Cyanosis

Post-ictal Phase

- Normal breathing
- Sleepiness – 1 hr or longer
- Loss of memory (amnesia) regarding events surrounding the seizure episode
- Headache
- Drowsiness
- Confusion, temporary and mild
- Weakness for up to 24 - 48 hours following seizure (**Todd's paralysis**)

Simple partial seizures



Somatosensory. Tingling of contralateral limb, face, or side of body

Focal motor. Tonic-clonic movements of upper (or lower) limb

Grimacing

Contraversive: head and eyes turned to opposite side

Visual. Sees flashes of light, scotomas, unilateral or bilateral blurring

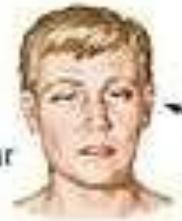
Autonomic. Sweating, flushing or pallor, and/or epigastric sensations

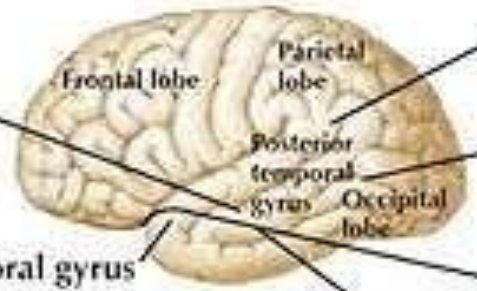
Auditory. Hears ringing or hissing noises

Complex partial seizures

Impairment of consciousness: cognitive, affective symptoms

Dreamy state; blank, vacant expression; déjà vu; jamais vu; or fear





Superior temporal gyrus

Formed auditory hallucinations Hears music etc.

Formed visual hallucinations. Sees house, trees that are not there

Bad or unusual smell

Olfactory hallucinations

Psychomotor phenomena. Chewing movements, wetting lips, automatisms (picking at clothing)

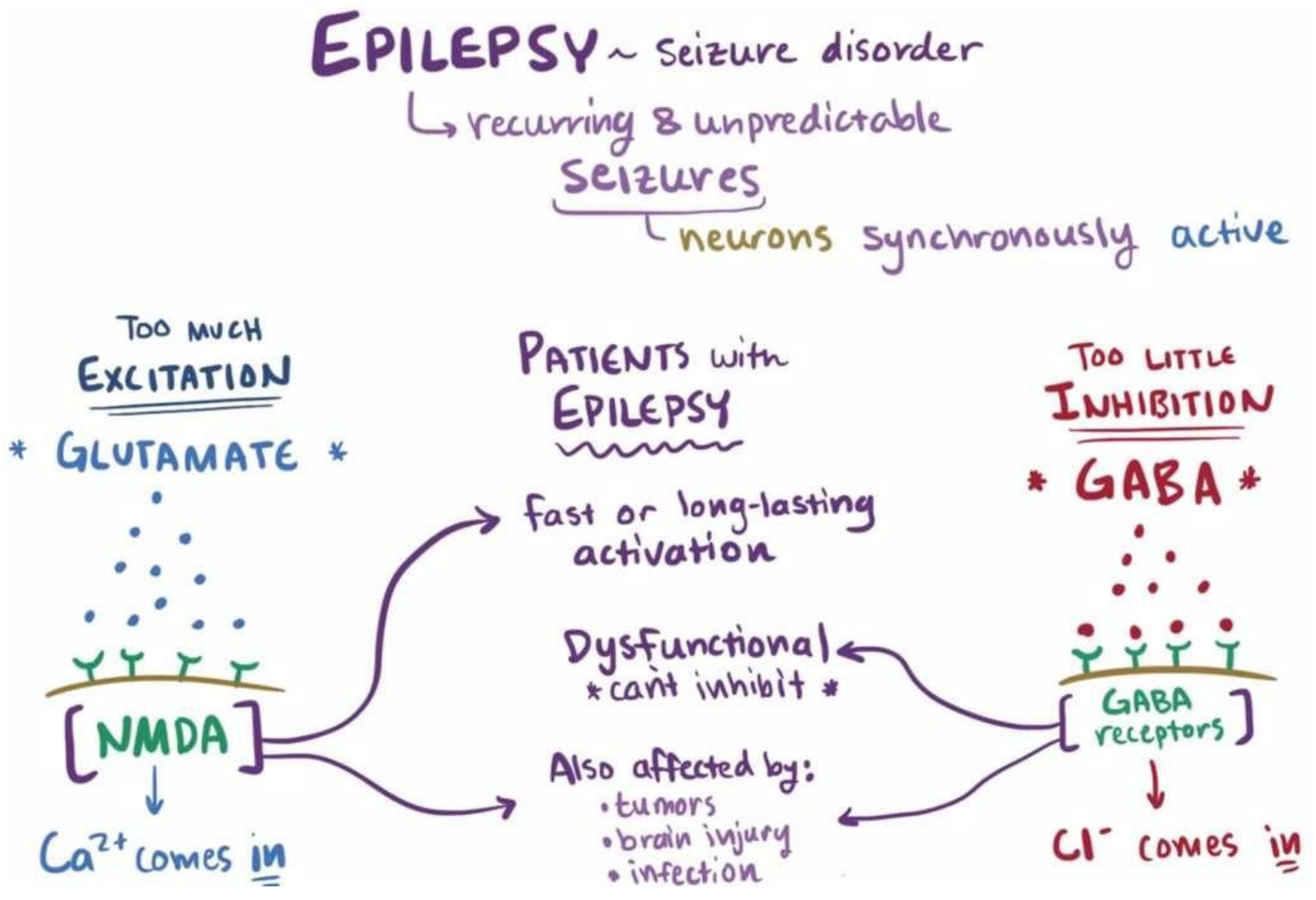
Dysphasia

F. Netter M.D.

Tonic-clonic seizure

Focal partial seizure

Pathophysiology



Infantile spasm

AGE GROUP: 3 mnth -1 YEARS.

MIXED (M.C).
Salaam spells, developmental

retardation. Poor prognosis.

EEG: ***HYPSARRHYTHMIA.***

CHILDHOOD SEIZURES

2- 12
YEARS

BENIGN	INTERMEDIATE	CATASTROPHIC

BENIGN

Benign Rolandic epilepsy

AGE GROUP: 4-10 YEARS.

SIMPLE PARTIAL SEIZURE. USUALLY DURING SLEEP.
ASS W/ ABNORMAL MOVEMENTS OF TONGUE AND

FACE. SECONDARY GENERALISED.

EEG: ***CENTRO-TEMPORAL SPIKES.***

BENIGN

Benign Occipital epilepsy

Any type seizure, no clear clinical course w/ ***visual***

visual aura.

EEG: **OCCIPITAL SPIKE WAVES**

INTERMEDIATE

Childhood absence epilepsy

4-10 years. NEUROLOGICALLY NORMAL.

EEG: ***CLASSIC 3Hz WAVE SPIKES.***

MEDICATION MAY BE UNSUCCESSFUL

OFTEN W/ COAGNITIVE DISORDERS/ LEARNING PROBLEMS.

HYPERVENTILATION TEST.

Childhood absence epilepsy

INTERMEDIATE

Micturational absence

Same as absence seizure. But ass w/ strong detrusor contraction.

Frequent.

MEDICATION MAY BE UNSUCCESSFUL

OFTEN W/ COAGNITIVE DISORDERS/ LEARNING PROBLEMS.

CHILDREN CONSTANTLY WET.

INTERMEDIATE

Myoclonic absence

Same as absence seizure.

CHILD STOPS SUDDENLY, ARMS EXTENDED & RATCHET UPWARD WITH JERKING MOTION.

EEG: 3Hz spike wave

MEDICATION MAY BE UNSUCCESSFUL, VERY RESISTENT.

OFTEN W/ COGNITIVE DISORDERS/ LEARNING PROBLEMS

Myoclonic absence seizure

INTERMEDIATE

Absence w/ eyelid myoclonus

Marked eyelid and upper face jerky movements.

Very resistant to Rx.

Absence w/ eyelid myoclonus

CRYPTOGENIC PARTIAL SEIZURES

TRUE BENIGN.

NORMAL INTELIGENCE.
CANNOT BE CLASSIFIED AS ANYOTHER BENIGN CONDITION.

NO TREATMENT IS USUALLY REQUIRED

CATASTROPHIC

CONTINUES SPIKE -WAVE IN SLOW SLEEP

RESTRICTED TO CHILDHOOD USUALLY.

PARTIAL SEIZURE + COGNITIVE DETIORIATION

EEG: **SPIKES WAVES DURING SLOW WAVE SLEEP.**

THIS MAY PROLONG TO MANY YEARS OR STOPS ABRUPTLY.

CATASTROPHIC

LANDAU-KLEFFNER SYNDROME

1-8 YEARS. PREVIOUSLY NORMAL.

SERIOUS LANGUAGE DETERIORATION, BEHAVIOUR DETRIMENT.

FOCAL OR GENERALIZED SEIZURES. (MIXED GENERALISED SEIZURES)

EEG: HIGH FREQUENCY, HIGH SPIKES.

CATASTROPHIC

Lennox Gastaut syndrome

AKINETIC SEIZURES + MENTAL HANDICAP + SLOW GENERALISED SPIKES ON EEG

NON-CONVULSIVE STATUS – CHILD NON RESPONSIVE, DOESN'T PLAY, INTERACT.

CATASTROPHIC

MYOCLONIC ASTATIC SEIZURES

DROP ATTACKS.

IF SEVERE RESEMBLE *LGS*

- Patofisiologi Mual dan Muntah

Definisi

Mual

Mual merupakan sensasi yang sangat tidak enak pada perut yang biasanya terjadi sebelum keinginan untuk muntah, ini merupakan suatu respon yang berasal dari respon penolakan yang dapat ditimbulkan oleh rasa, cahaya, atau penciuman.

Muntah

Muntah adalah suatu gejala bukan merupakan sebuah penyakit. Gejala ini berupa keluarnya isi lambung dan usus melalui mulut dengan paksa atau dengan kekuatan. Muntah merupakan reflek protektif tubuh karena dapat berfungsi melawan toksin yang tidak sengaja tertelan. Selain itu, muntah merupakan usaha mengeluarkan racun dari tubuh dan bisa mengurangi tekanan akibat adanya sumbatan atau pembesaran organ yang menyebabkan penekanan pada saluran pencernaan.

Etiologi

Muntah diakibatkan oleh stimulasi dari *pusat muntah* di sumsum-sambung (*medulla oblongata)* dan berlangsung menurut beberapa mekanisme, yaitu :

- Secara tak-langsung melalui CTZ
- Melalui kulit otak (*cortex cerebri*)
- Akibat rangsangan langsung dari saluran cerna

Berikut beberapa penyebab mual muntah dari berbagai faktor, antara lain:

Gangguan GI track

Adanya agen yang menyerang atau mengiritasi lapisan lambung, seperti infeksi bakteri H. Pylori, gastroentritis, keracunan makanan , agen iritan lambung (alkohol, rokok, dan obat NSAID). Penyakit peptic ulcer dan GERD juga dapat menyebabkan mual muntah.

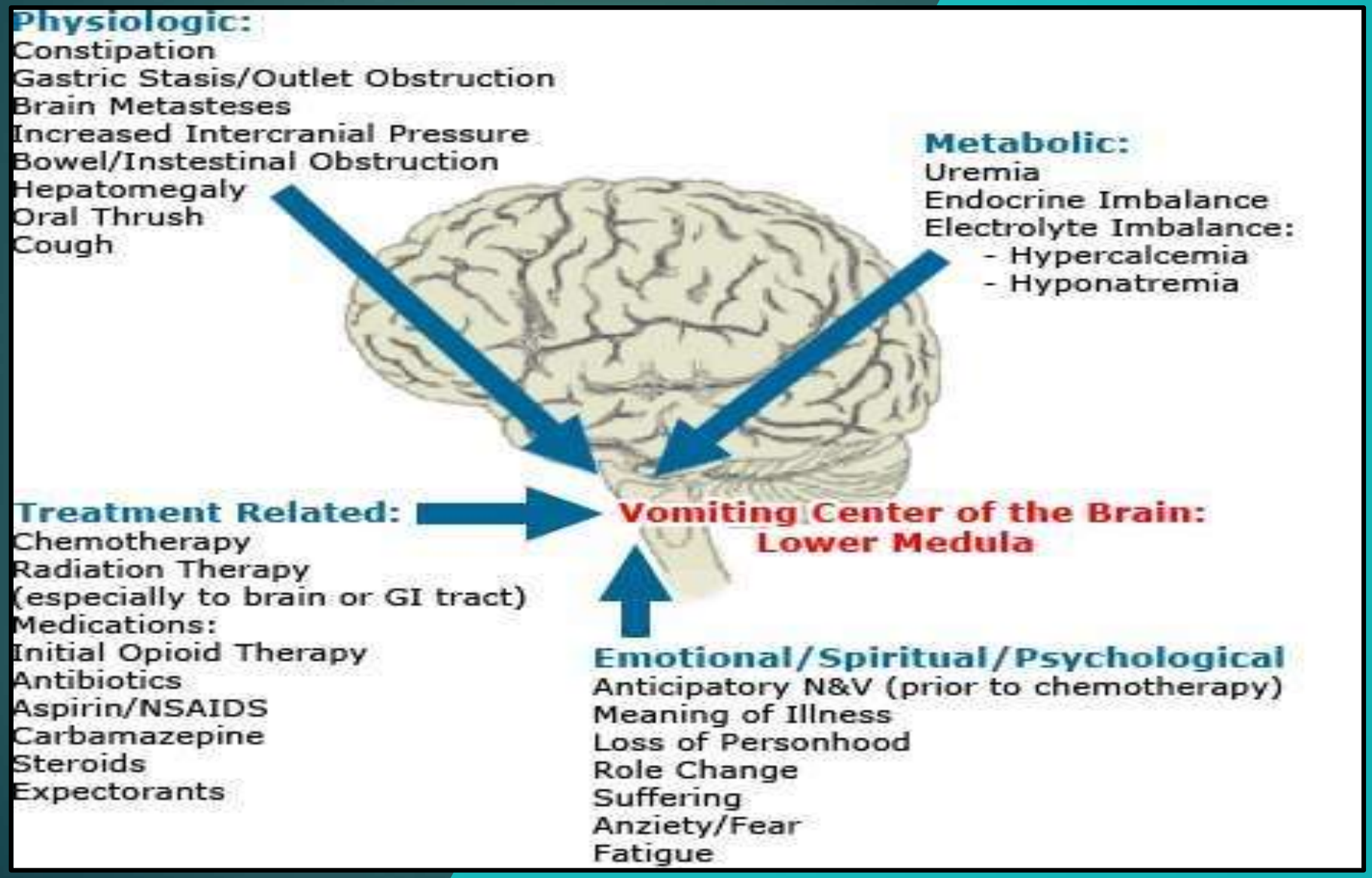
Sinyal dari otak

- Luka pada kepala, pembengkakan otak (gegar otak atau trauma kepala), infeksi (meningitis atau encephalitis), tumor, atau keseimbangan abnormal dari elektrolit dan air dalam aliran darah.
- Noxious stimulus: bau-bau atau suara-suara
- Kelelahan karena panas, terik matahari yang ekstrem, atau dehidrasi.

Terkait dengan penyakit lain

Misalnya pada pasien diabetes dapat mengalami gastroparesis, yaitu kondisi dimana lambung gagal mengosongkan diri secara tepat dan kemungkinan disebabkan generized neuropathy (kegagalan dari syaraf untuk mengirim sinyal yang tepat ke otak).

Penyebab-penyebab tersebut akan menginduksi pusat muntah seperti terlihat pada gambar berikut :



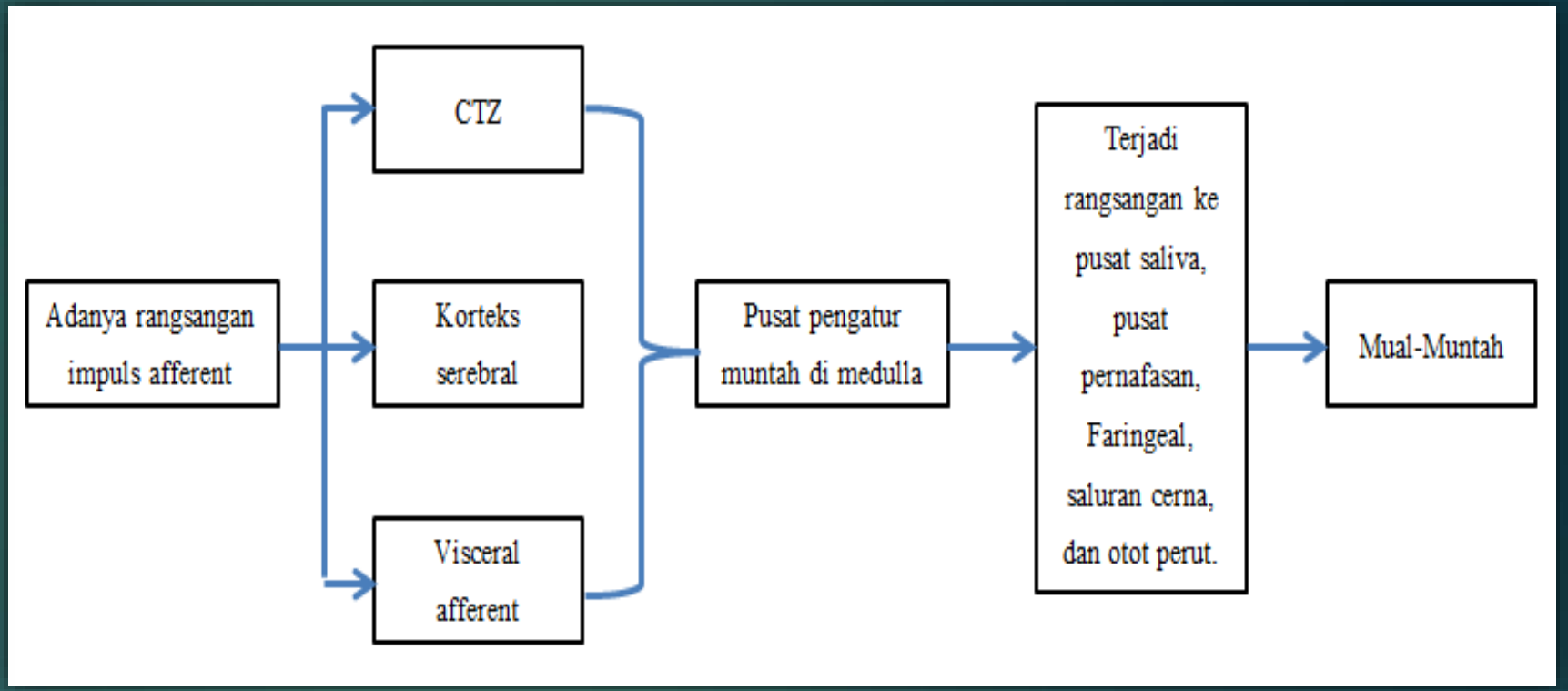
patofisiologi

Terdapat tiga fase emesis, yaitu:

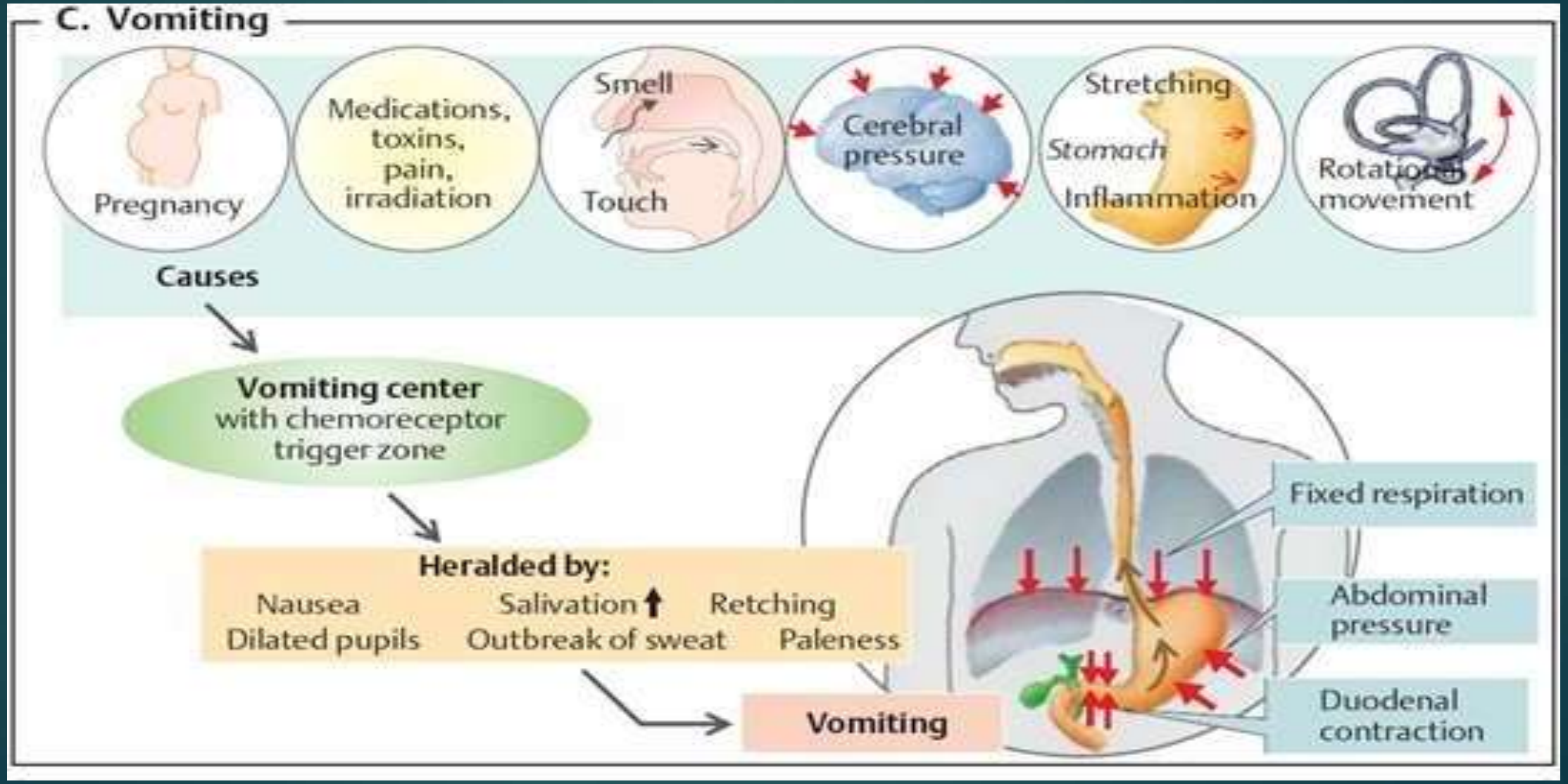
- Nausea, berupa kebutuhan untuk segera muntah atau mual
- Retcing , yaitu gerakan yang diusahakan otot perut dan dada sebelum muntah
- Vomiting atau muntah, yaitu pengeluaran isi lambung yang disebabkan oleh retroperistalsis GI.

Next..

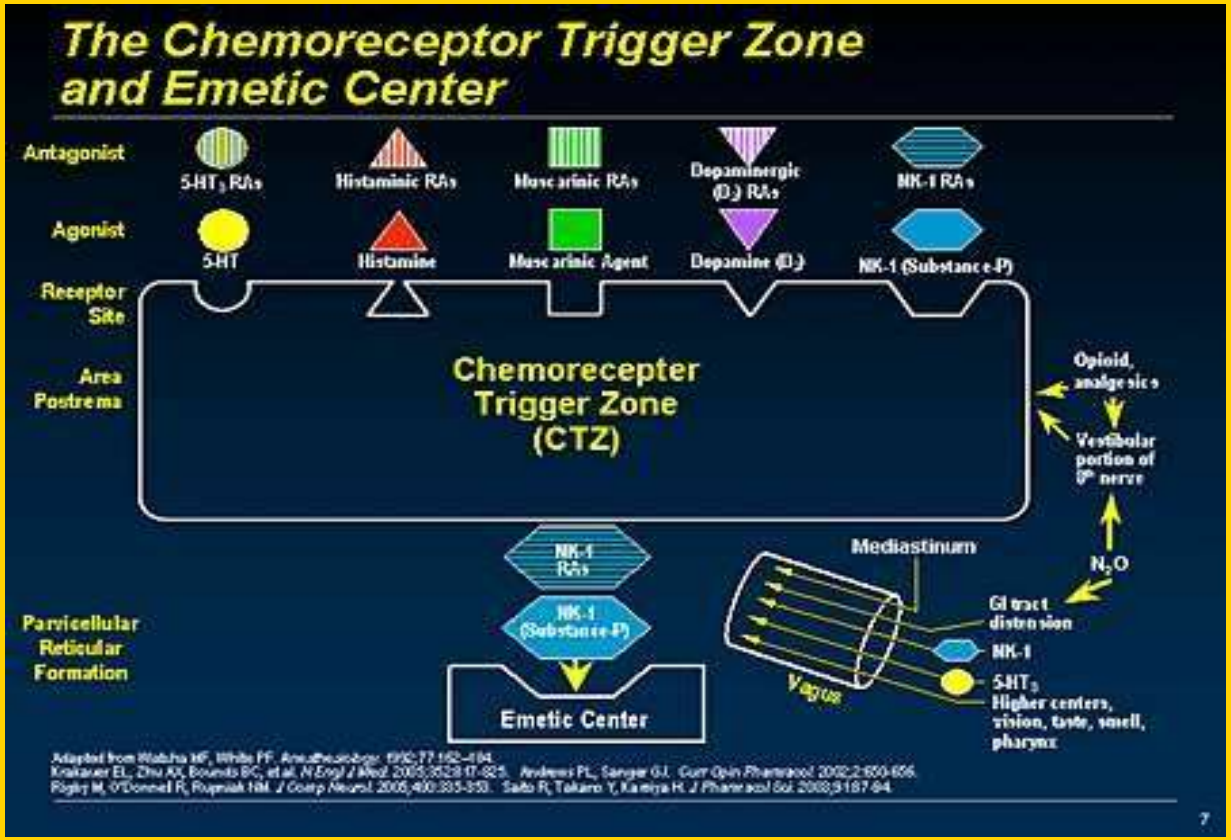
.


Adanya rangsangan impuls afferent
CTZ
Korteks serebral
Visceral afferent
Pusat pengatur muntah di medulla
Terjadi rangsangan ke pusat saliva, pusat pernafasan, Faringeal, saluran cerna, dan otot perut.
Mual-Muntah

Penyebab dan proses terjadinya muntah dapat dilihat pada gambar berikut:



CTZ merupakan daerah kemosensori utama pada proses emesis/muntah dan sering dipicu oleh senyawa senyawa kimia. Obat obat sitotoksik pun memicu emesis melalui mekanisme berinteraksi dengan CTZ. Beberapa neurotransmiter dan reseptor terdapat di pusat muntah, CTZ, dan saluran cerna, meliputi kolinergik, histaminik, dopaminergik, opiat, serotonergik, neurokinin, serta benzodiazepin. Nah dari sini juga terlihat bahwa adanya stimulasi pada satu ataupun beberapa reseptor ini akan memicu muntah. Itulah sebabnya, mekanisme kerja obat antiemetik akan berkutat dalam menghambat ataupun mengantagonis reseptor emetogenik tersebut seperti terlihat pada gambar berikut :



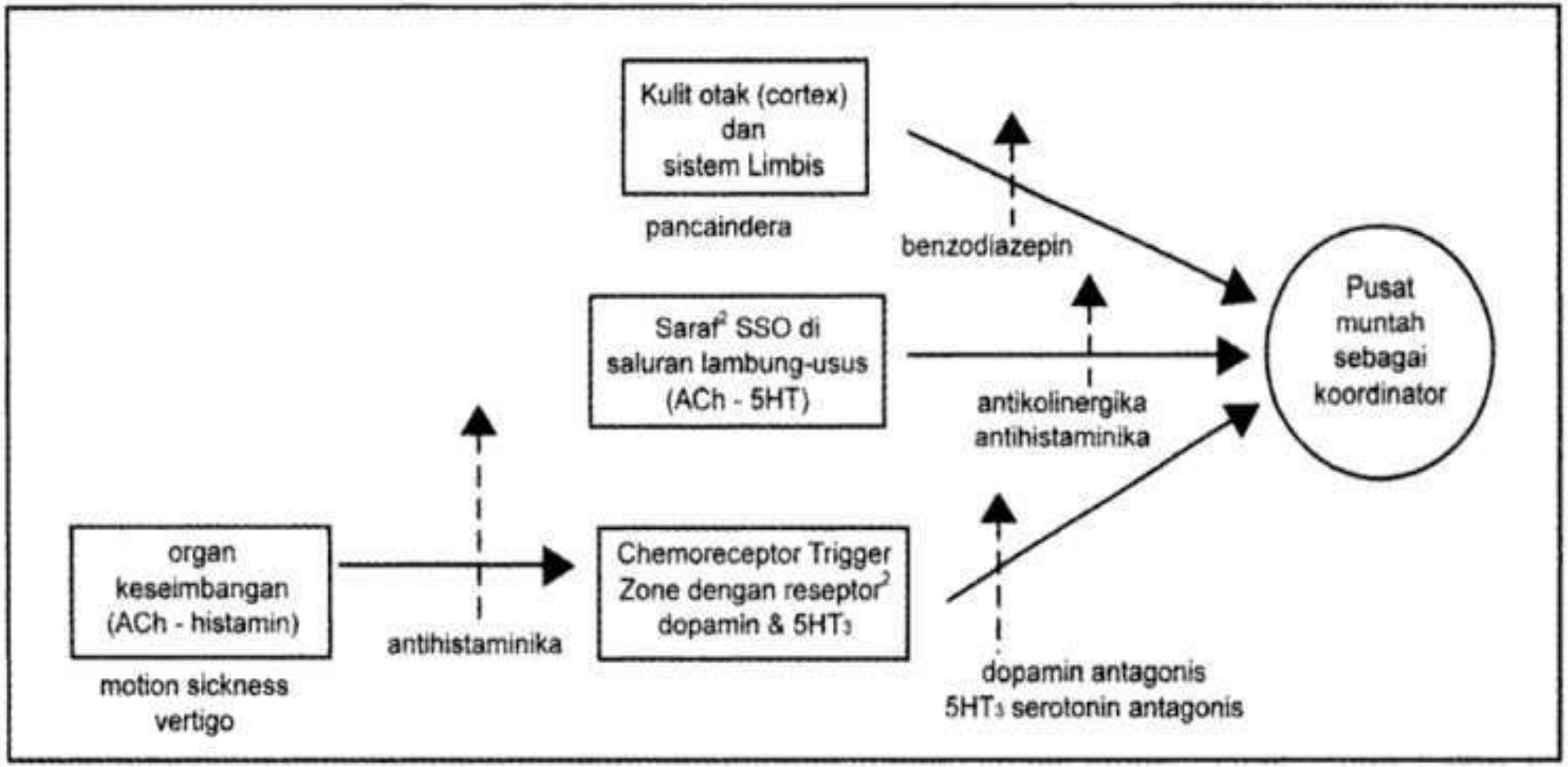
Terapi

Tujuan terapi antiemetik adalah untuk mencegah atau menghilangkan mual dan muntah, tanpa menimbulkan efek samping.

Terapi Non-Farmakologi

1. Pasien dengan keluhan sederhana, menghindari makanan tertentu atau moderasi asupan makanan yang lebih baik.
2. Pasien dengan gejala penyakit sistemik sebaiknya mengobati kondisi yang mendasarinya.
3. Antisipasi mual atau muntah pada pasien terapi kanker dengan memberi profilaksis antiemetik.
4. Intervensi perilaku dan termasuk relaksasi, biofeedback, self-hypnosis.

Mekanisme muntah dan titik-titik kerja antiemetika



PATHOPHYSIOLOGY OF HYPERTENSION

Lectured by
apt. Astri Rachmawati., S.Farm., Apt

Stikes Notokusumo

LEARNING OBJECTIVES

- What is hypertension?
- Different types of hypertension
- Risk Factor
- Pathophysiology of Hypertension
- Further Information

Instruksi Perkuliahan

1. Pre Test (Soal Pretest sudah terupload di google classroom kelas patofisiologi) - 6 menit
2. Menyimak presentasi materi perkuliahan dari dosen tentang Patofisiologi Hipertensi (Listening and Observing)
3. Siswa dibagi menjadi 2 kelompok, masing-masing dalam kelompok menginterpretasi video dengan menuliskan apa yang kalian pahami dari presentasi dosen (interpretating)
4. Sesi diskusi (siswa mengemukakan masalah atau pertanyaan) (expressing the problem)
5. Siswa mencari solusi terhadap masalah (find the solution) - Dosen menyimak masing masing kelompok secara bergantian
6. Siswa melakukan diskusi secara berkelompok untuk menyelesaikan masalah atau pertanyaan secara team (communication) - Dosen menyimak masing masing kelompok secara bergantian
7. Post Test - 6 menit
8. Dosen pengampu mengkonfirmasi tentang materi yang didiskusikan
9. Mahasiswa bersama dosen menyimpulkan hasil pembelajaran

PATHOPHYSIOLOGY OF HYPERTENSION

Primary Hypertension 90%

- Prevalence about 60% (age 60+)
- Prevalence about 15-25% (age 25+)
- Prevalence mean 35%

Secondary Hypertension 10%

- but: may normalize by special treatment (surgery, hormone treatment)!

PATHOPHYSIOLOGY OF HYPERTENSION

I. Primary Hypertension

II. without primary organic cause

CARDIOVASCULAR RISK FACTORS

not modifyable

- Ethnic-genetic risk (black people)
- Age
- Gender

modifyable

- Hypertension
- Hyperlipidemia (Cholesterol, TGs)
- Smoking
- Diabetes
- Overweight
- Inactivity (physical)
- Stress

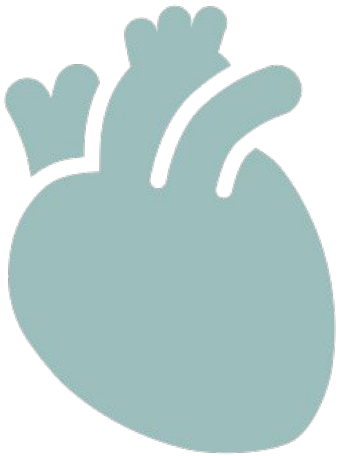
SPECIFIC HYPERTENSION RISKS

- not modifyable
  - Ethnic-genetic risk (black people)
  - Age
  - Gender
- modifyable
  - Diabetes
  - Overweight
  - Alcohol
  - Salt intake
  - combination

FACTORS INDUCING HYPERTENSION

- Renin-angiotensin system RAS, RAAS
- Sympathetic nervous system
- Insuline
- resistance
- Overweight
- Stiff vessel walls (endothelial dysfunction)
- Vasoactive substances (NO, Endotheline)
- Kallikrein secretion

Natriuretic peptides



FACTORS INDUCING HYPERTENSION

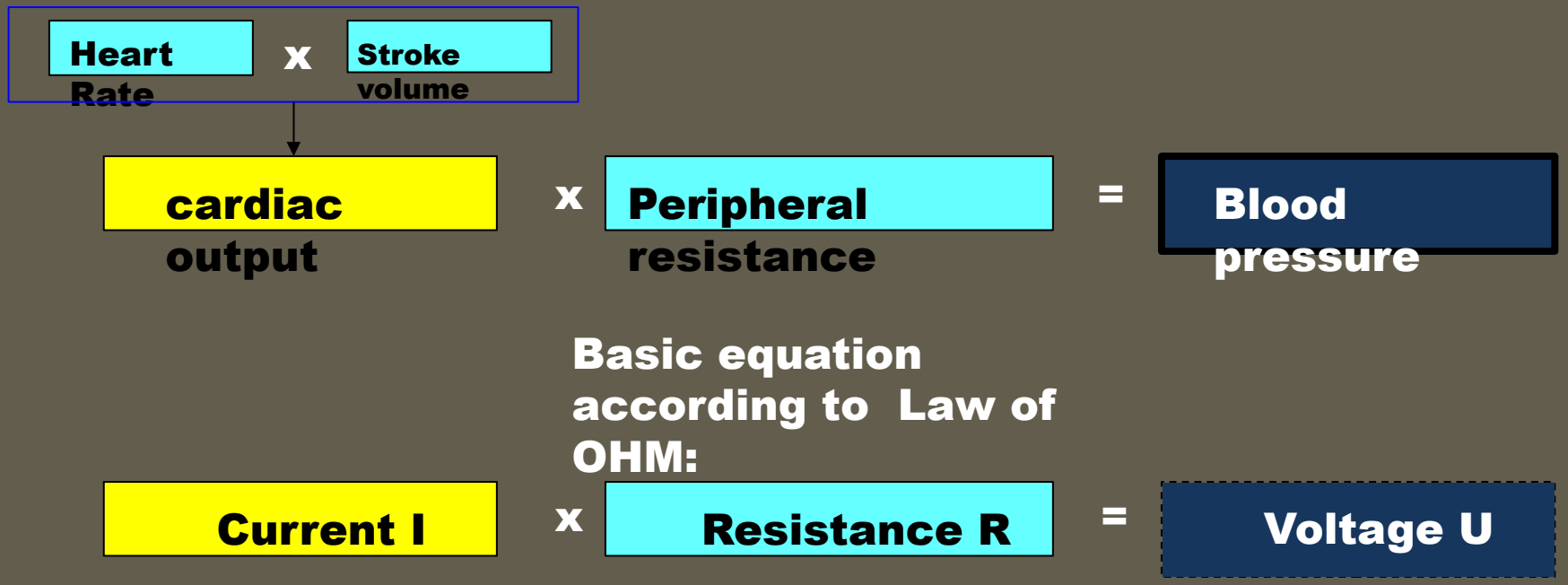
- Neurohumoral system dysbalance

  > Renin-angiotensin system RAS, RAAS

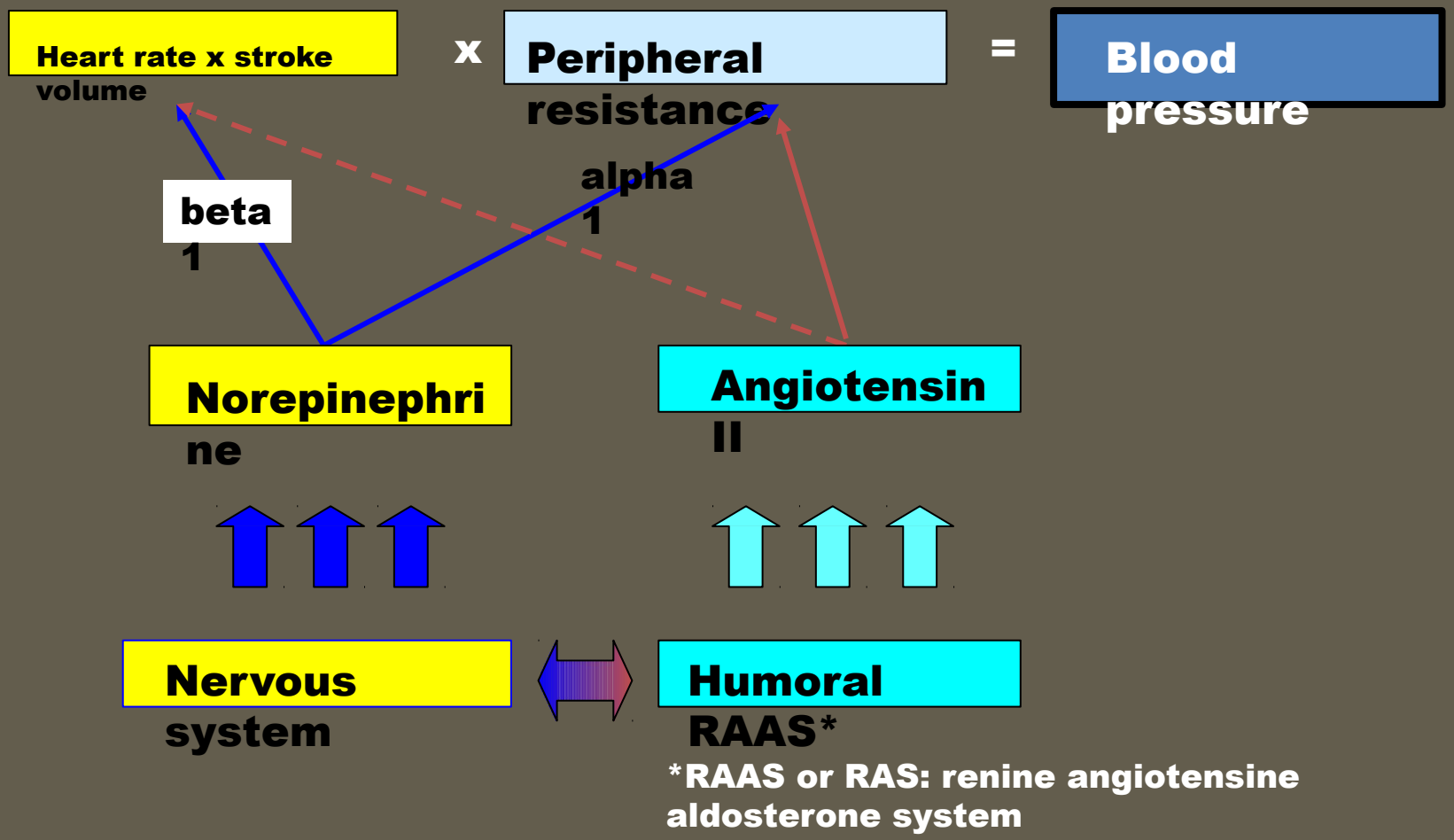
  > Sympathetic nervous system

Most important hypertension cause!

PATHOPHYSIOLOGY OF HYPERTENSION



NEURO-HUMORAL REGULATION OF HYPERTENSION

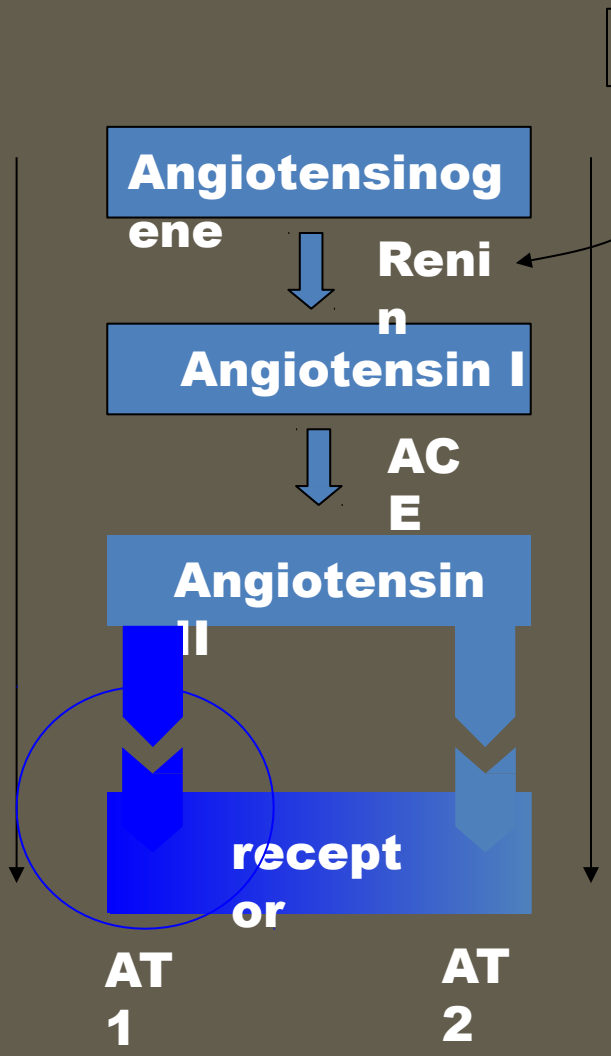


Pathophysiology of Hypertension

The role of endothelium and the RAAS cascade

PATHOPHYSIOLOGY OF HYPERTENSION

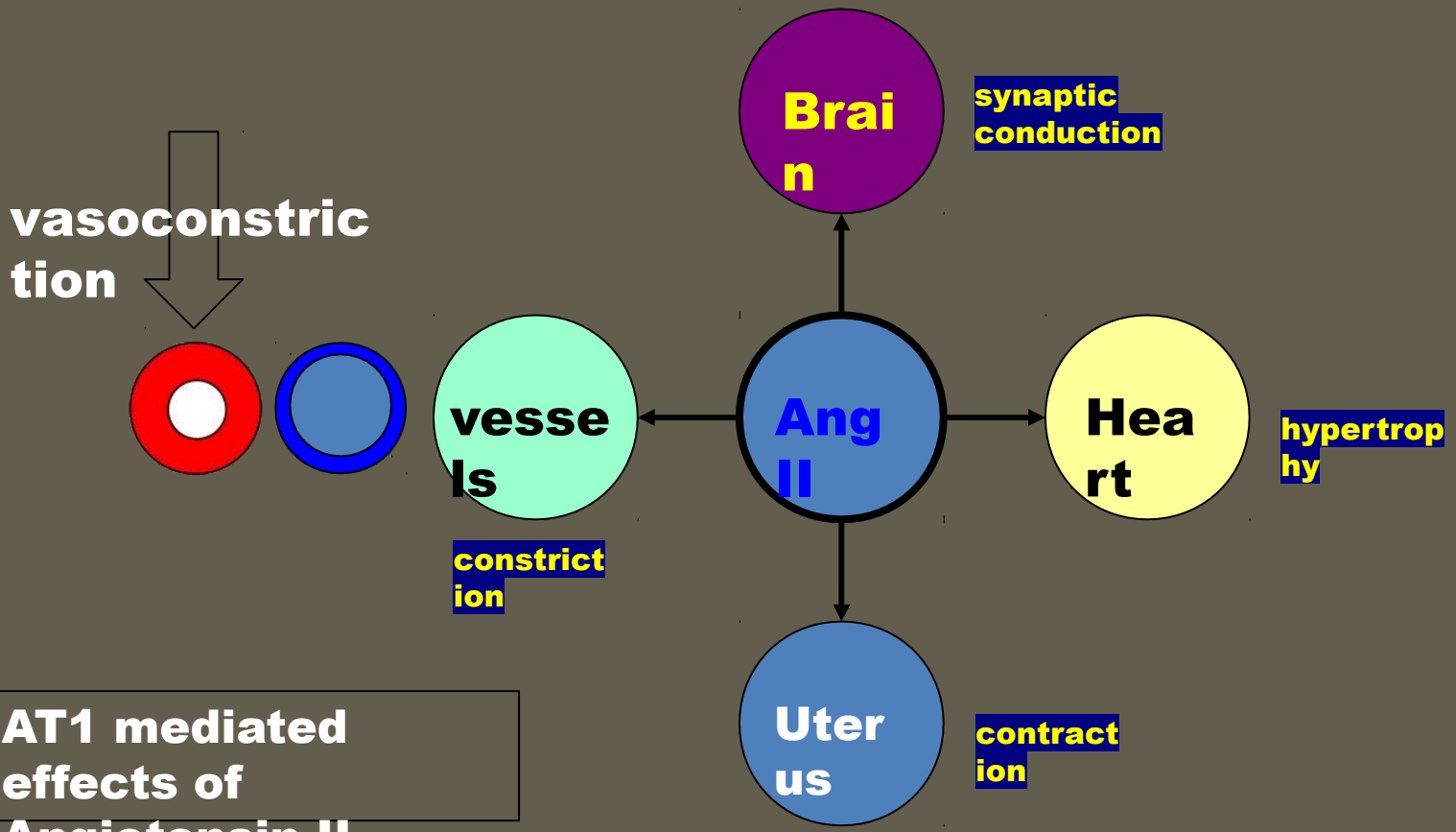
Pathway of RAAS in the Organism (kidney, heart, Vessels) to maintain Fluid volume control, Adjustment of CO and Resistance.
If regulation fails, high blood pressure occurs



Pathway of RAAS in the Tissues: e.g.
Vessel wall

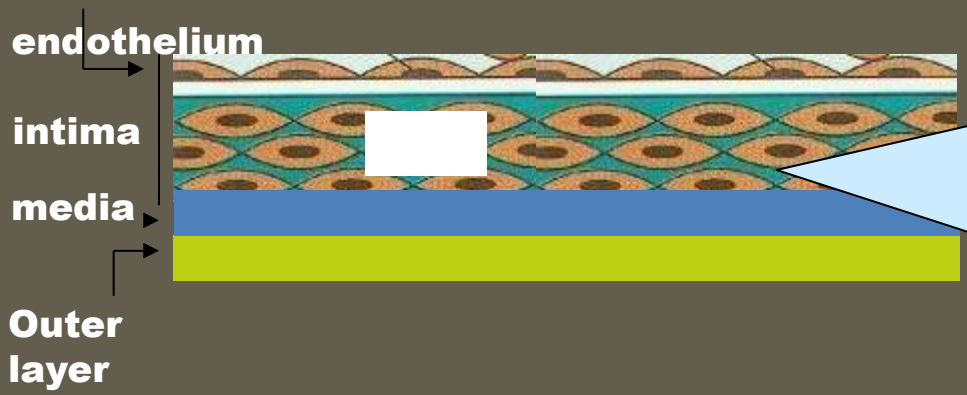
Competition of receptors: AT1 vasoconstriction AT2 vasodilatation

PATHOPHYSIOLOGY OF HYPERTENSION: ANGIOTENSIN II EFFECTS



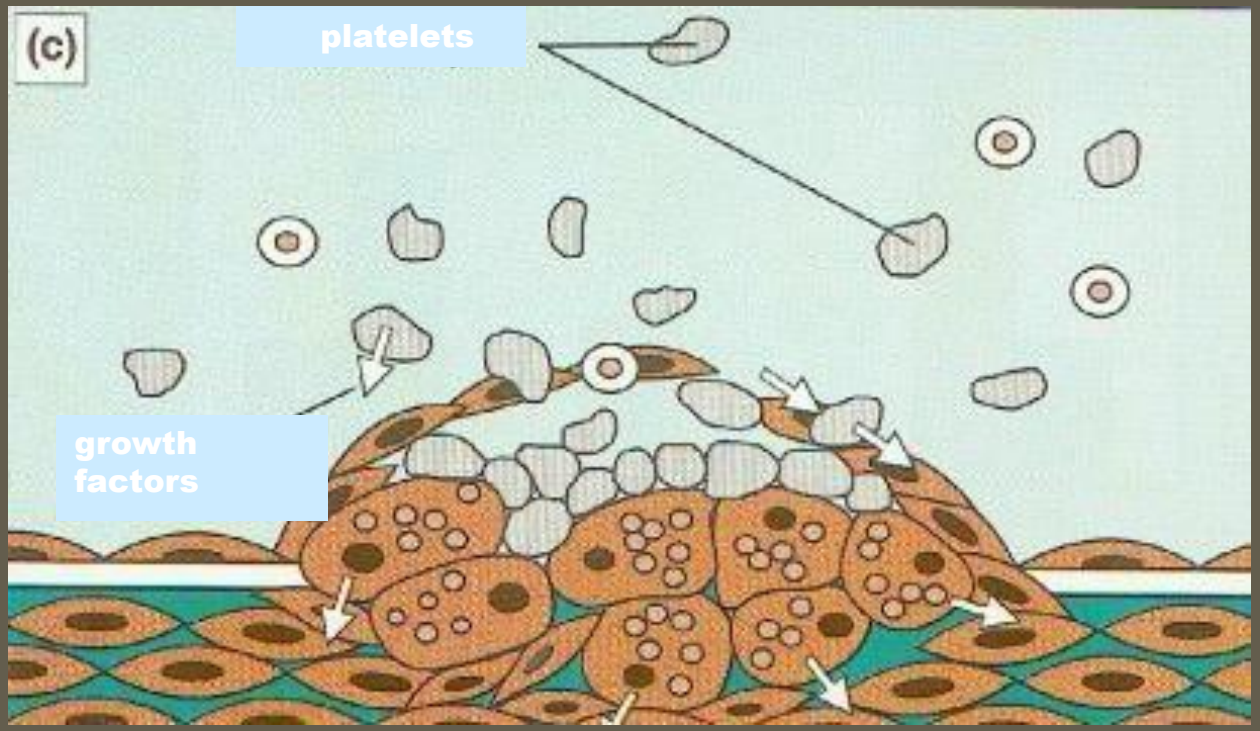
PATHOPHYSIOLOGY OF HYPERTENSION

basic structure and contents of the vessel intima

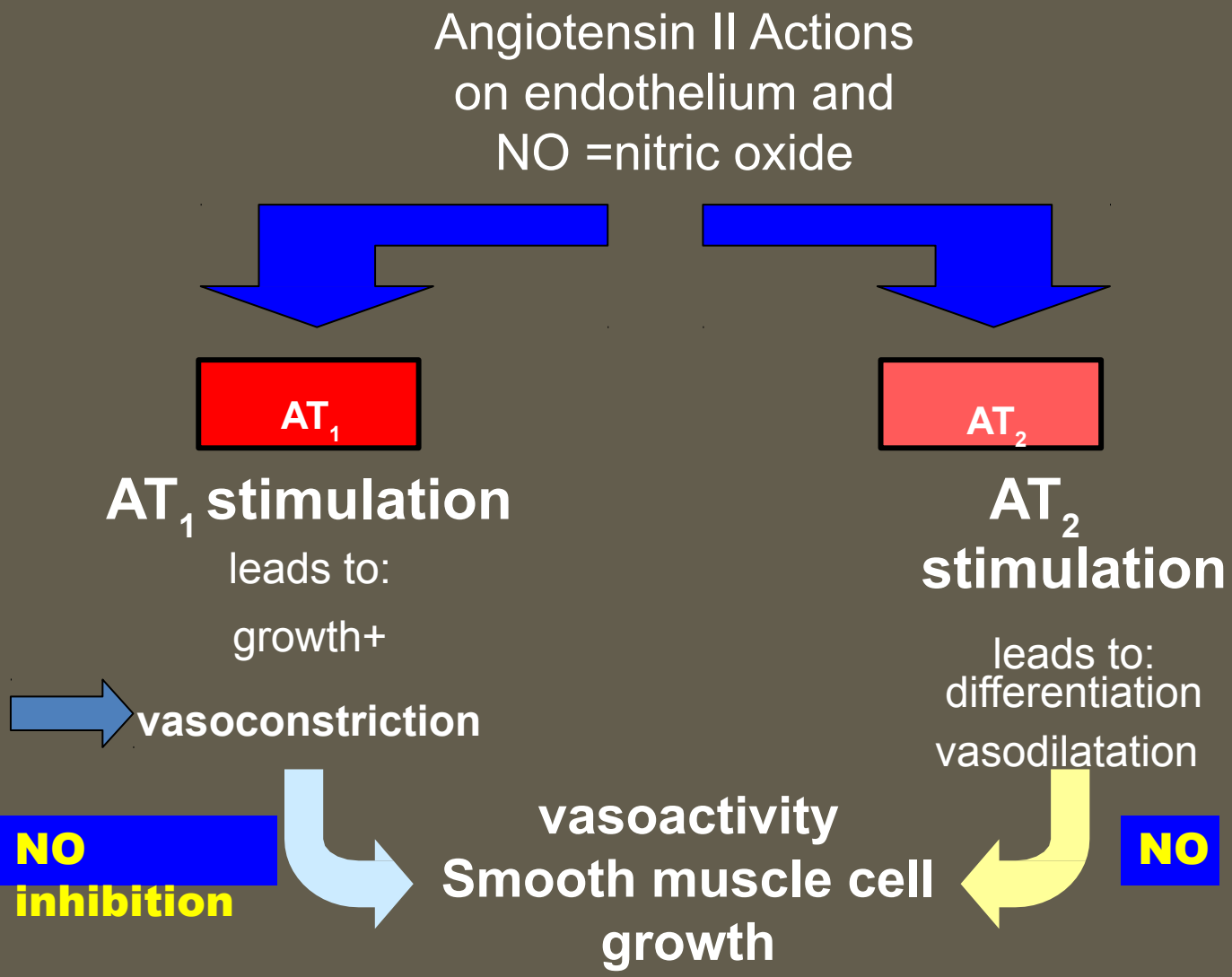


Contents
Smooth muscle cells
SMC
Collagenes
Thrombocytes
Ox-LDL
NO
Kinines
Enzymes
coagulation factors
platelet activation factors

PATHOPHYSIOLOGY OF HYPERTENSION

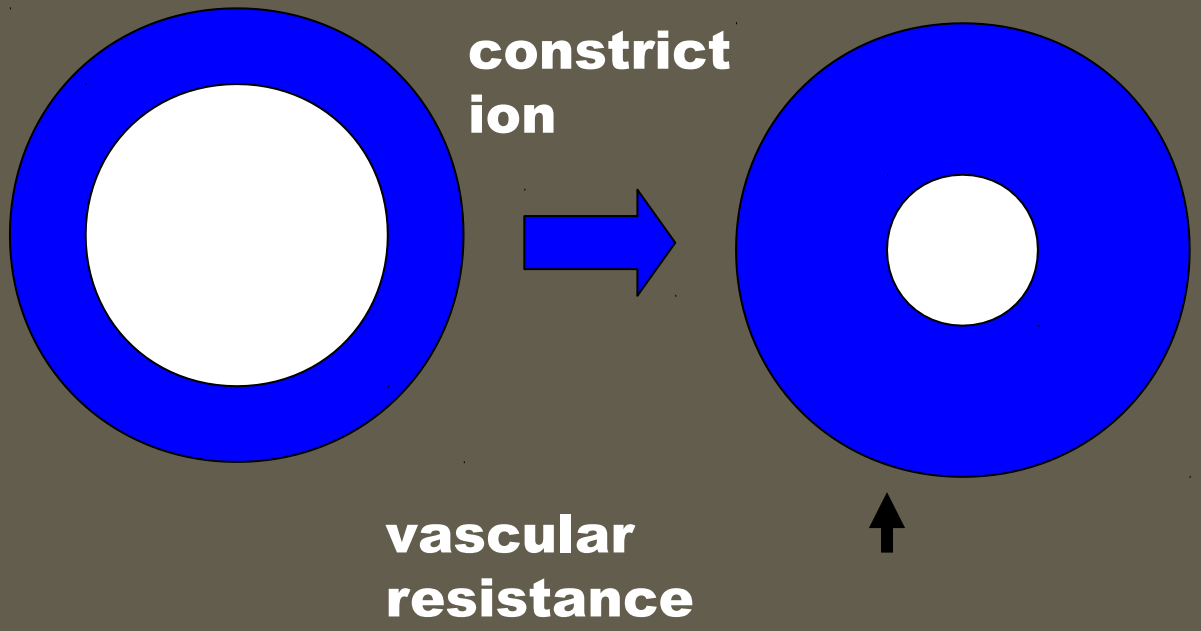


Endothelial dysfunction causing atherosclerosis and vasoconstriction, infarction



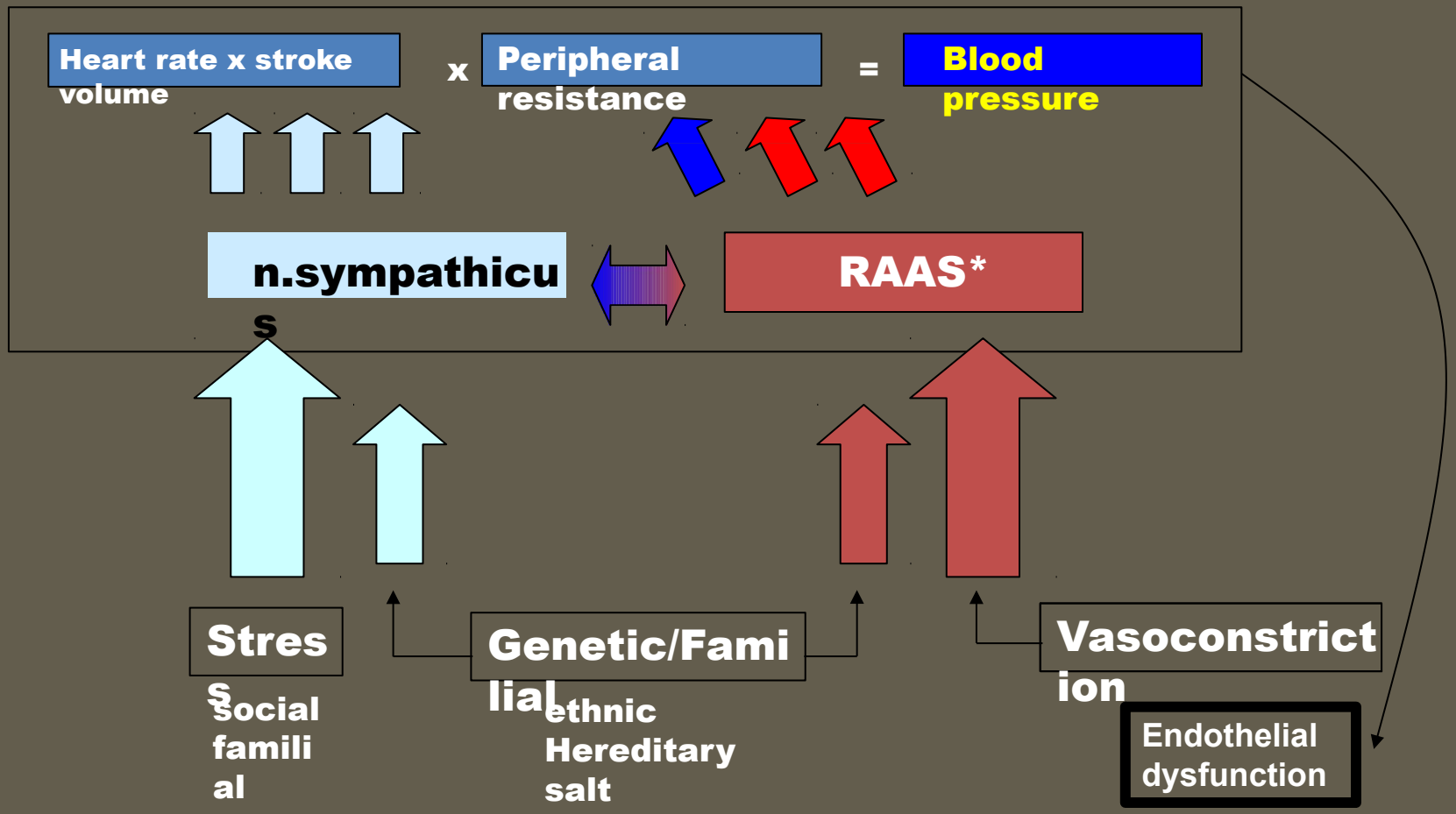
modified acc. to Unger T et al 1996

PATHOPHYSIOLOGY OF HYPERTENSION



Endothelial dysfunction causing hypertension

PATHOPHYSIOLOGY OF HYPERTENSION



*renine angiotensine aldosterone system

PATHOPHYSIOLOGY OF HYPERTENSION

Conclusion:

Primary Hypertension is a target disease mainly of the RAAS - intima - endothelium system!

the endothelium is the major player

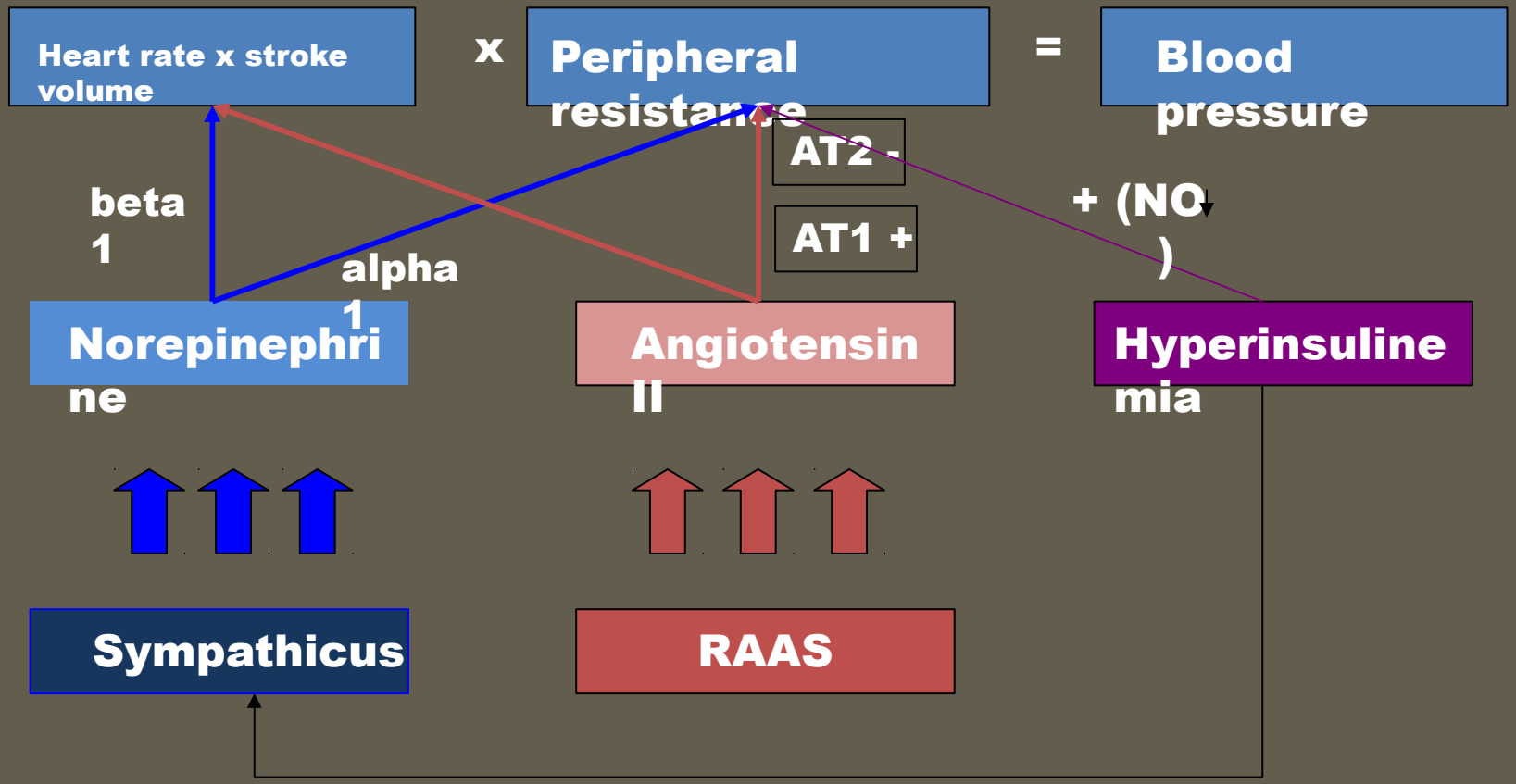
PATHOPHYSIOLOGY OF HYPERTENSION

Trigger example: Obesity,
Hyperinsulinism,
Type-2- Diabetes

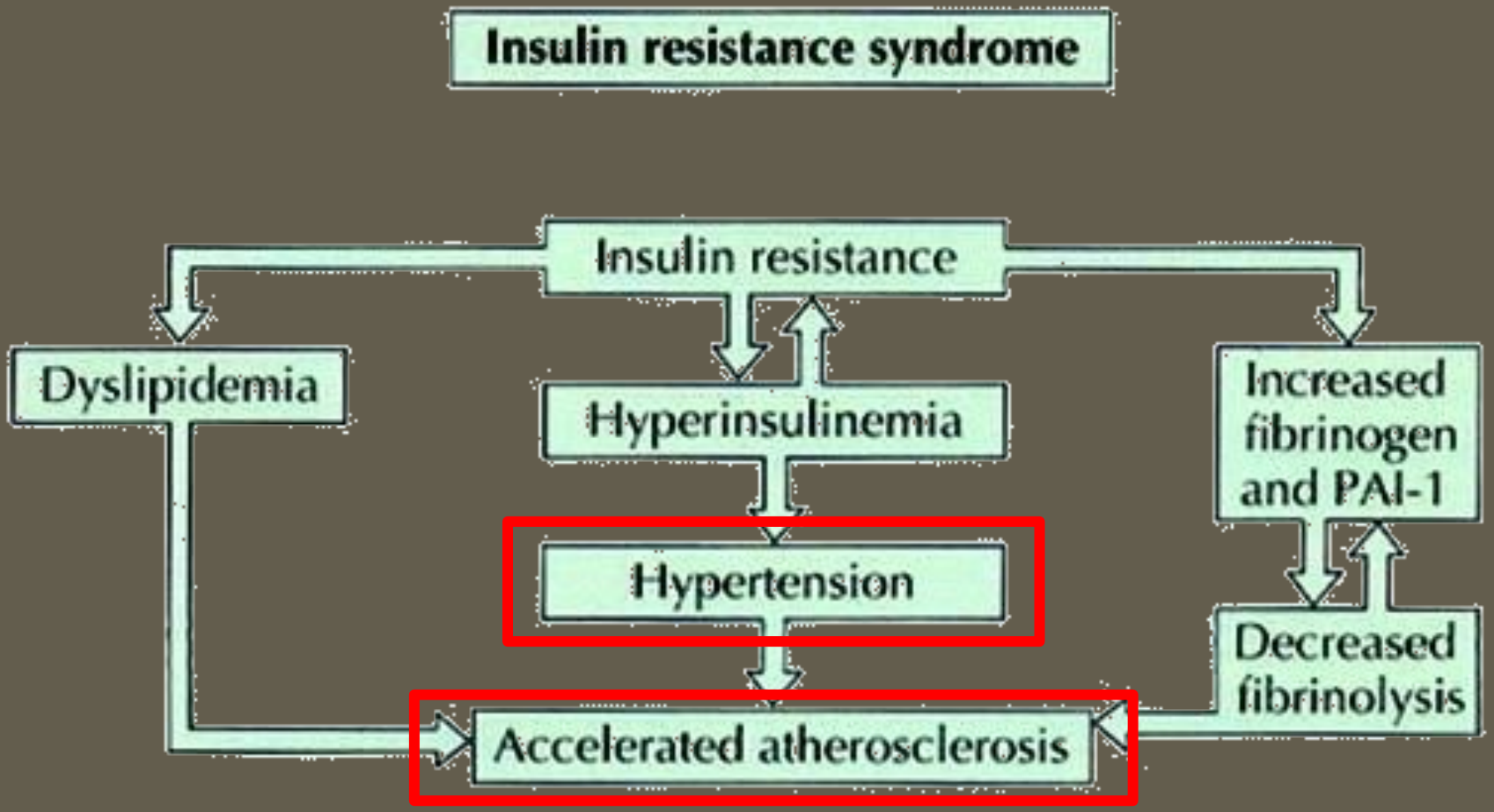
Hypertension

Metabolic syndrome (X)

PATHOPHYSIOLOGY OF HYPERTENSION



PATHOPHYSIOLOGY OF HYPERTENSION



PATHOPHYSIOLOGY OF HYPERTENSION

Target organ damage followed by arterial hypertension

PATHOPHYSIOLOGY OF HYPERTENSION

Target organ damage:

- Brain: Stroke (ischemic, hemorrhagic)
- Heart: CAD, Heart failure (mainly diastolic)
- Vessels:
  - Peripheral arterial disease
  - Central arterial disease: aortic dissection, aneurysm
  - Renovascular disease

PATHOPHYSIOLOGY OF HYPERTENSION

II. Secondary Hypertension

H. with primar

organic cause

PATHOPHYSIOLOGY OF HYPERTENSION:
SECONDARY H.

- Renal 5%
  - Parenchymal
  - **Renovascular (0,3%) (corrected to normal by balloon treatment or surgery!)**
  - Tumors
  - Little‘s disease
- Endocrine
  - Thyroid dysfunction (1%)
  - Adrenal (0,3%)
  - Carcinoid
  - hormones
- Aortic coarctation
- Pregnancy
- Neurogenic (brain tumor, lead, porphyria, sleep apnea)
- Acute stress (including surgery)
- iv. volume increase
- Alcohol abuse

Some may induce primary hypertension, so that the relationships sometimes are weak

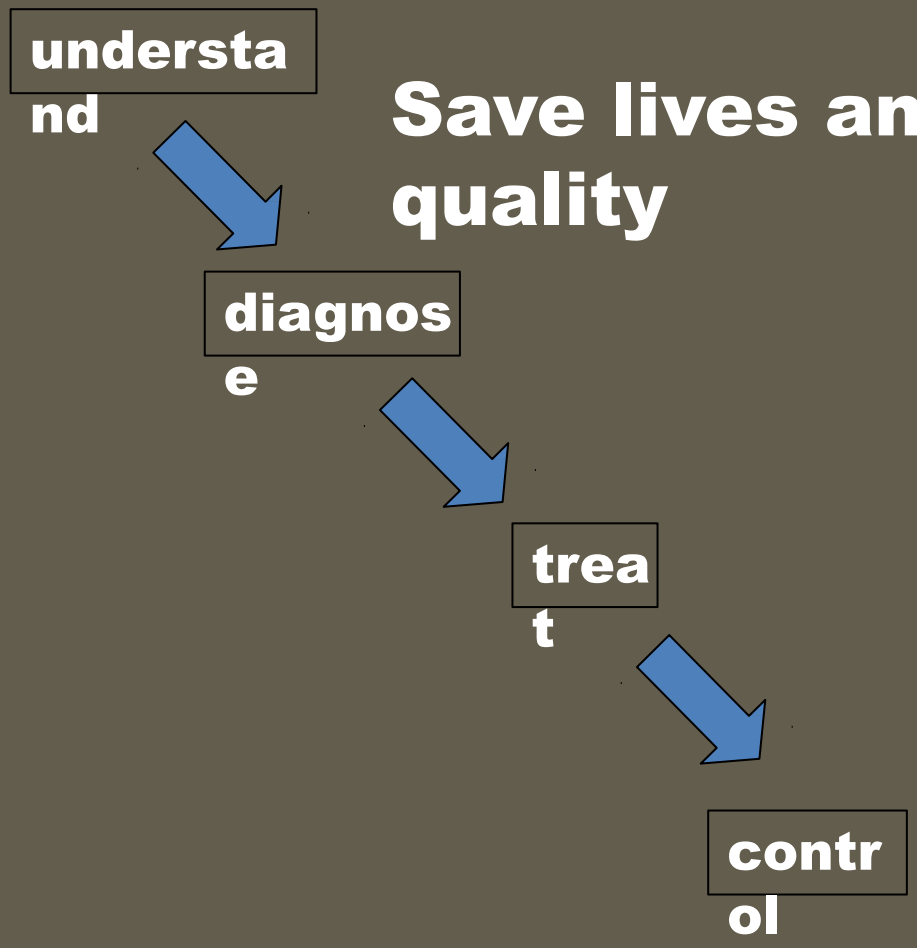
PATHOPHYSIOLOGY OF HYPERTENSION

Systolic Hypertension

↓

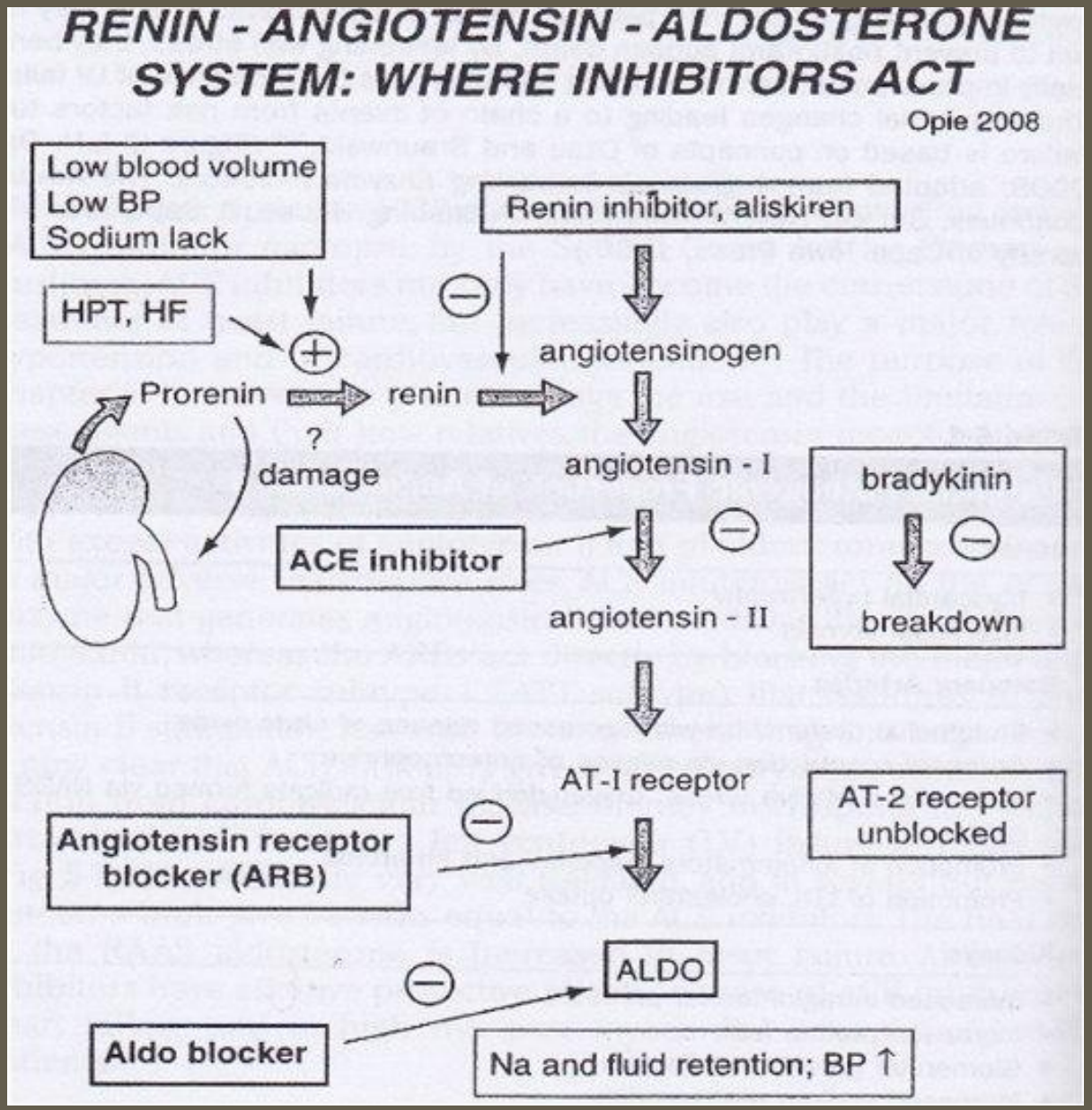
(H. of the aged w. or w/o. diastolic lowering

PATHOPHYSIOLOGY OF HYPERTENSION



Save lives and improve life quality

BAGAIMANA OBAT ANTI HIPERTENSI BEKERJA?



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PATOFISIOLOGI HEPATITIS

PENDAHULUAN

- Hepatitis merupakan penyakit yang berkembang biak, menakutkan, mematikan dan langka
- Definisi : radang hati yang disebabkan oleh aneka virus HAV, HBV, HCV, HDV, HEV, HGV

EPIDEMIOLOGI

- Di Amerika : 600.000 kasus/tahun, kebanyakan adalah hepatitis tipe HAV dan HBV
- 6-10% adalah kasus kronik
- Data WHO > 300juta penduduk terinfeksi HBV dan merupakan penyebab kematian no 9 di dunia
- Indonesia ± 13 juta penduduk terkena hepatitis B, 4 juta hepatitis C (2,4%) paling sering ditemukan di Indonesia tu genotipe 1 (sulit diobati dan disembuhkan).
- Penularan HAV terutama per oral (makanan terkontaminasi feses), transfusi jarang
- Penularan HBV parenteral, menembus membran mukosa, hubungan seksual

ETIOLOGI

Penyebab Utama : aneka virus hepatitis :

- Virus hepatitis A
- Virus Hepatitis B
- Virus Hepatitis C

→ penyebab primer

- Virus Hepatitis Delta
- Virus Hepatitis E
- Virus Hepatitis F
- Virus Hepatitis G

- Hepatits C ada 2 macam :

1. Dapat ditularkan secara parenteral (*parenterally transmitted*)
   PT-NANBH (Non B-Hepatitis), tata nama baru : hepatitis C
2. Ditularkan secara enteral (*enterically transmitted*) ET-NANBH (Non-B-Hepatitis), tata nama baru : hepatitis E

- Virus delta virus RNA yg defektif menyebabkan infeksi hanya bila sebelumnya telah ada HBV dapat timbul bersamaan atau sebagai suprainfeksi pada karier HBV

JENIS-JENIS HEPATITIS

1. Menurut virus penyebabnya

   Hepatitis A, hepatitis B, Hepatitis non A non B (Hepatitis C, Hepatitis E), Hepatitis Delta, Hepatitis F, Hepatitis G

2. Menurut penampilan klinik

   a. Hepatitis akut (< 6 bulan)

   b. Hepatitis fulminan (cepat menjadi fatal)

   c. Hepatitis Kronik (> 6 bulan)

3. Berdasar gejala klinik

   a. Dengan ikterik

   b. Tanpa ikterik

DIAGNOSIS

1. Uji fungsi hati
2. Uji serologi penanda spesifik yang bisa membedakan hepatitis akut dan hepatitis kronik
   - Hepatitis akut tidak memperlihatkan adanya autoantibodi
   - Hepatitis kronik ditemukan autoantibodi

DIAGNOSIS PERBANDINGAN UJI FUNGSI HATI PADA HEPATITIS				
NO	UJI	AKUT	KRONIK	TANDA
		uji diagnostik		
1	Autoantibodi	–	+	
2	Seromaker HBV	+/-	+/-	
3	Seromaker HCV	+/-	+/-	
4	Seromaker HAV	+/-	–	
5	α-Fetoprotein	–	+/-	bila ada hepatoma
		Uji fungsi hepar		
1	Bilirubin	↑	↑	Menandakan fungsi sekresi
2	Transaminase	↑	↔ or ↑	Menandakan destruksi sel
3	Alkaline phosphate	↔	↔ or ↑	Menandakan fungsi sintesis
4	Albumin	↔	↓	Menandakan fungsi sintesis
5	Protrombin time	↔ or ↑	↑	Menandakan fungsi sintesis

HEPATITIS VIRAL AKUT

- Definisi : suatu infeksi viral sistemik selama tidak lebih dari 6 bulan yang mengakibatkan nekrosis-peradangan hati.
- Biasanya sembuh sendiri dan angka kefatalannya rendah
- Etiologi : HAV, HBV, HCV, HDV, HEV dominan HAV

PATOGENESIS

Berdasar marker serologis, dibagi dalam 3 tahap :

1. **Inkubasi** □ dimulai sesaat setelah inokulasi oral/parenteral □ sirkulasi darah □ virus terakumulasi □ internalisasi oleh hepatosit □ replikasi virus di sitoplasma atau sel hepar □ sekresi virus ke darah, empedu, organ lain. Dalam masa ini akan ditemukan virus lengkap/antigen dalam cairan tubuh dan jaringan.

   Masa inkubasi berbeda-beda, tetapi dalam rentang waktu 14-180 hari

PATOGENESIS

2. Hepatitis akut

a. Fase praikterik (sebelum onset jaundice)

Paralel dengan inisiasi respon imun inang dan trjadi sebelum kerusakan sel hati nyata (nilai bilirubin, SGPT-SGOT ± 2x normal)

b. Fase ikterik

Ditandai dengan gejala klinik : demam, nyeri abdomen, mual, muntah, urin gelap, gejala sistemik memburuk. Nilai bilirubin, gama globulin dan transaminase serum nail 4-10 x nilai normal

PATOGENESIS

3. **Pemulihan**

   Sebagian besar pasien mengalami masa pemulihan tanpa komplikasi/ berlanjut ke hepatitis kronis, hal ini terjadi karena faktor regenerasi hepar masih dapat berlangsung.

CLINICAL PRESENTATION OF ACUTE HEPATITIS A

- **Signs and symptoms**
  - The preicteric phase brings nonspecific influenza-like symptoms consisting of anorexia, nausea, fatigue, and malaise
  - Abrupt onset of anorexia, nausea, vomiting, malaise, fever, headache, and right upper quadrant abdominal pain with acute illness
  - Icteric hepatitis is generally accompanied by dark urine, acholic (light-colored) stools, and worsening of systemic symptoms
  - Pruritus is often a major complaint of icteric patients

CLINICAL PRESENTATION OF ACUTE HEPATITIS A

- **Physical examination**
  - Icteric sclera, skin, and secretions
  - Mild weight loss of 2 to 5 kg
  - Hepatomegaly
- **Laboratory tests**
  - Positive serum IgM anti-HAV
  - Mild elevations of serum bilirubin, γ -globulin, and hepatic transaminase (alanine transaminase [ALT], and aspartate transaminase [AST]) values to about twice normal in acute anicteric disease
  - Elevations of alkaline phosphatase, γ -glutamyl transferase, and total bilirubin in patients with cholestatic illness

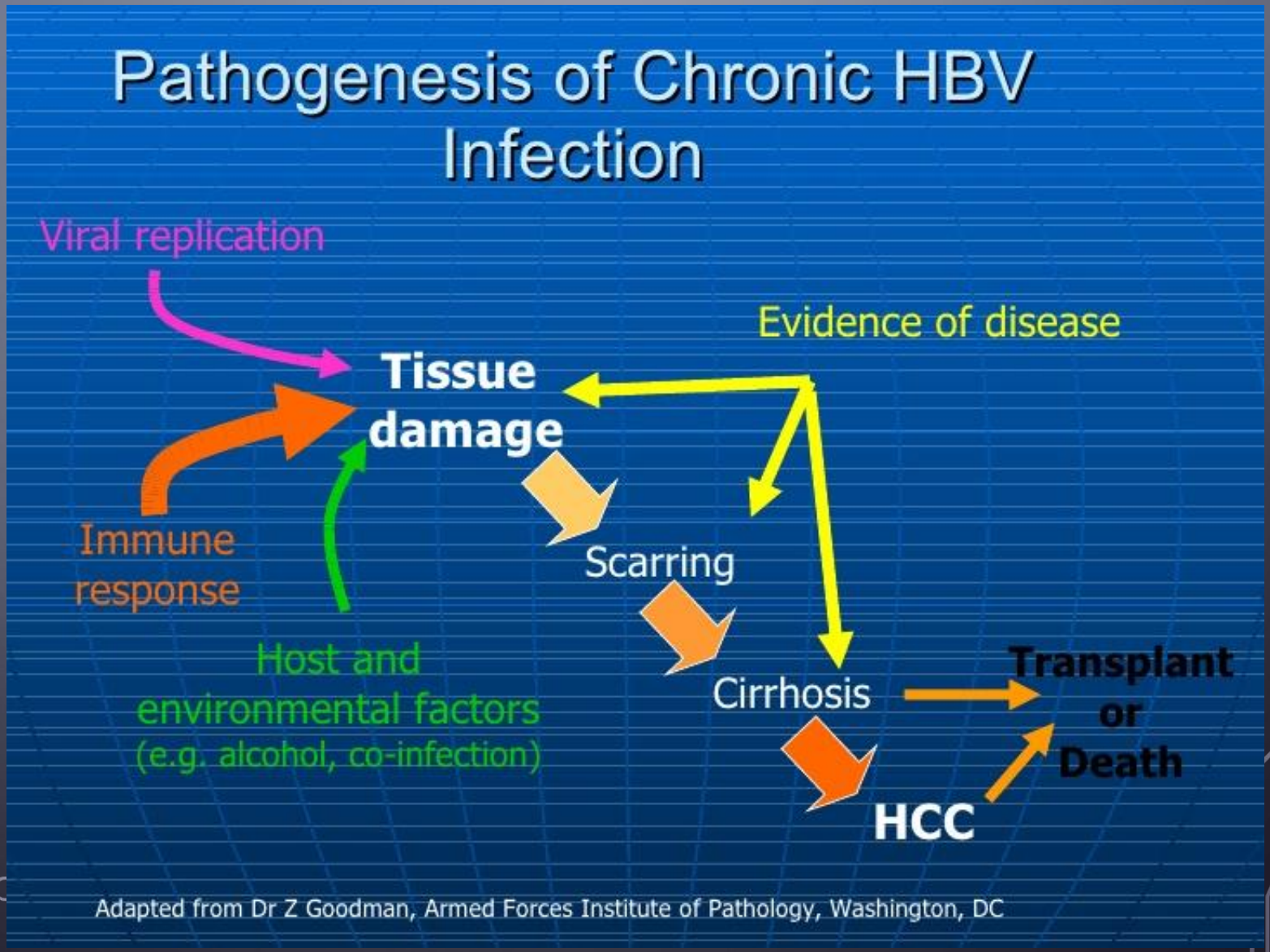
HEPATITIS VIRAL KRONIK (HVK)

- Definisi : Keberlanjutan proses nekroinflamasi hepatik selama 6 bulan atau lebih setelah onset penyakit akutnya

ETIOLOGI

- Terutama HBV dan HCV (60-80%)

PATOGENESIS



GAMBARAN HISTOLOGI

1. Hepatitis kronik persisten (CPH)
2. Hepatitis kronik aktif (CAH) :
   - CAH ringan
   - CAH berat
3. Hepatitis lobular kronik karena infeksi akut > 3 bulan (mirip CPH)

Harapan hidup : 5 th : CPH 97%

CAH tanpa sirosis 86%

CAH dengan sirosis 55%

MANIFESTASI KLINIK

TABLE 40–5. Clinical Presentation of Chronic Hepatitis B[a]

Signs and symptoms
- Easy fatigability, anxiety, anorexia, and malaise
- Ascites, jaundice, variceal bleeding, and hepatic encephalopathy can manifest with liver decompensation
- Hepatic encephalopathy is associated with hyperexcitability, impaired mentation, confusion, obtundation, and eventually coma
- Vomiting and seizures

Physical examination
- Icteric sclera, skin, and secretions
- Decreased bowel sounds, increased abdominal girth, and detectable fluid wave
- Asterixis
- Spider angiomata

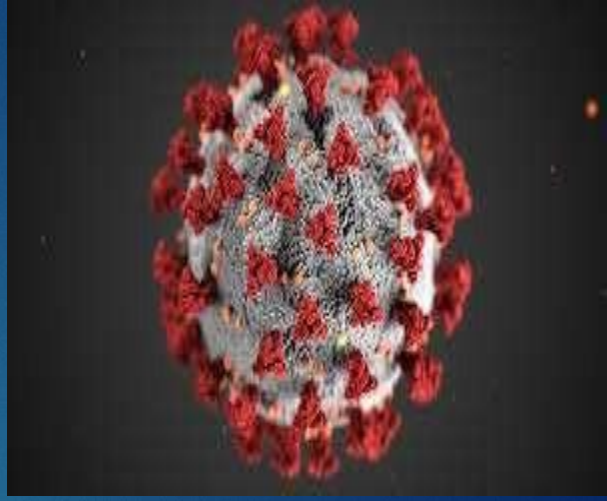
Laboratory tests
- Presence of hepatitis B surface antigen for at least 6 months
- Intermittent elevations of hepatic transaminase (alanine transaminase [ALT] and aspartate transaminase [AST]) and hepatitis B virus DNA greater than 10^5 copies/mL
- Liver biopsies for pathologic classification as chronic persistent hepatitis, chronic active hepatitis, or cirrhosis

[a]Chronic hepatitis B can be present even without all the signs, symptoms, and physical examination findings listed being apparent.

THANK YOU

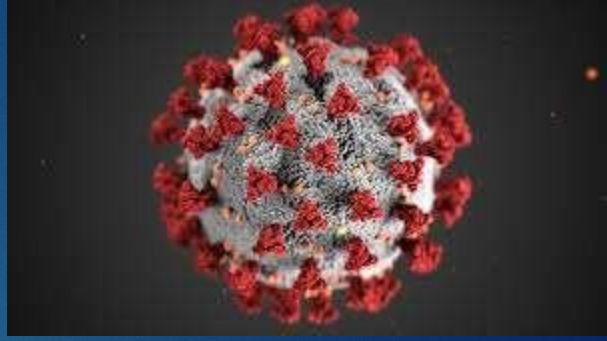
PATHOPHYSIOLOGY OF CORONAVIRUS

Contents



- Introduction
- Epidemiology
- Risk factors and Causes
- Mode of Transmission
- Pathophysiology
- Signs and Symptoms
- Diagnosis
- Complication
- Preventive Measures

Objectives:

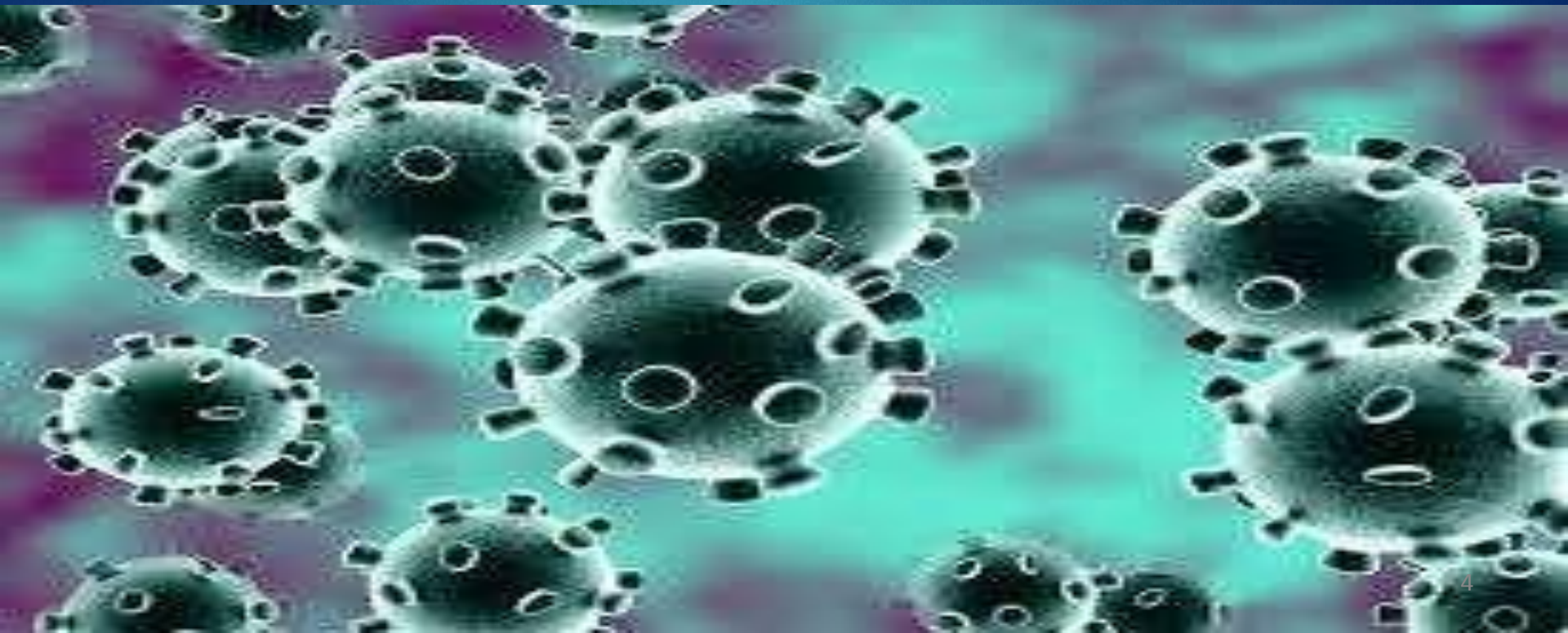


At the end of session, participants will be able to:

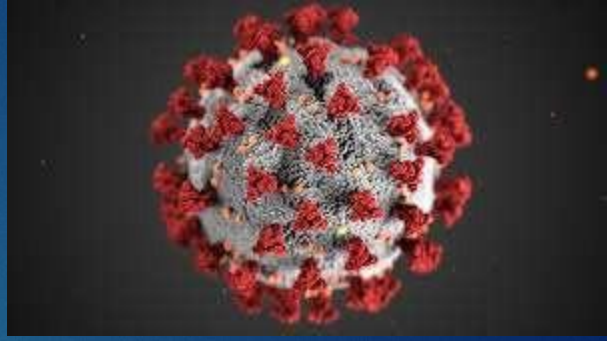
- Introduce about Corona virus
- Enumerate the cause of corona virus
- Enlist the sign and symptoms of corona virus
- Explain the diagnosis of corona virus
- Explain the management of corona virus
- List out the complications of corona virus
- Explain the preventive measures of corona virus.

Introduction

Corona viruses constitute the subfamily ***Orthocoronavirinae*** in the family Coronaviridae



Introduction …



- They are enveloped viruses with a positive-sense single-stranded RNA genome .
- The name *corona virus* is derived from the Latin *corona*, meaning "crown" or "halo", which refers to the characteristic appearance reminiscent of a crown when viewed under electron microscopy, due to the surface covering in club-shaped protein spikes.

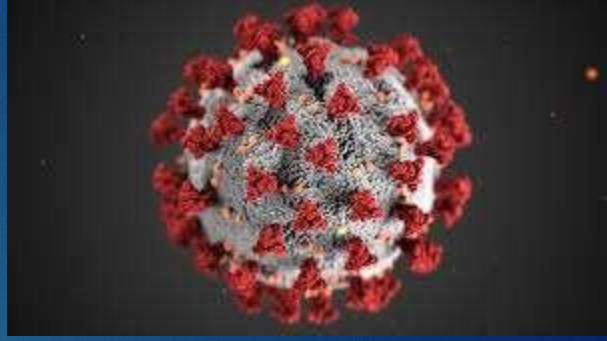
Epidemiology

Epidemiology…

Outbreaks of coronavirus types of relatively high mortality are as follows

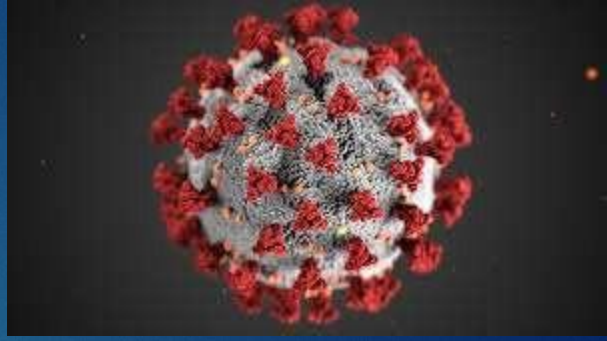
Outbreak	Virus type	Deaths
2003 severe acute respiratory syndrome outbreak	SARS-CoV	774
2012 Middle East respiratory syndrome coronavirus outbreak	MERS-CoV	Over 400
2015 Middle East respiratory syndrome outbreak in South Korea	MERS-CoV	36
2018 Middle East respiratory syndrome outbreak	MERS-CoV	41
2019–21 coronavirus pandemic	SARS-CoV-2	At least more than 5,833

Corona virus disease 2019 (COVID-19) – First Arrival



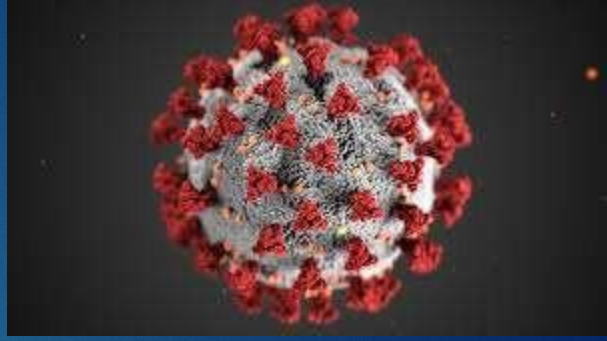
- In December 2019, a pneumonia outbreak was reported in **Wuhan city of China.**
- On 31 December 2019, the outbreak was traced to a novel strain of corona virus, which was given the interim name 2019-nCoV by the World Health Organization (WHO), later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

Corona virus disease 2019 (COVID-19) – First Arrival



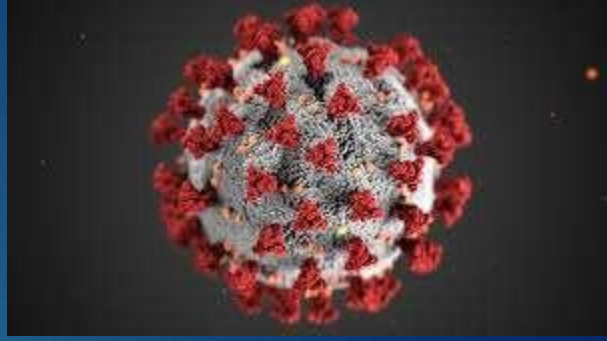
- As of 15 March 2020, there have been at least **5,833** confirmed deaths and more than 156,396 confirmed cases in the corona virus pneumonia pandemic.
- The Wuhan strain has been identified as a new strain of Beta corona virus from group 2B with approximately **70% genetic similarity to the SARS-CoV.**
- The virus has a **96% similarity to a bat corona virus**, so it is widely suspected to originate from bats as well. The **pandemic** has resulted in serious travel

Causes of COVID - 19



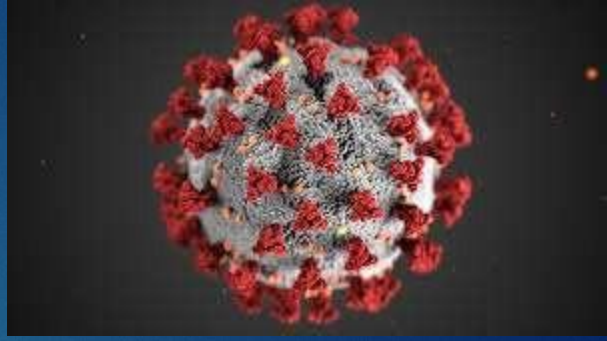
- It is caused by SARS-CoV-2 is closely related to Sever Acute Respiratory Syndrome Corona Virus which was outbreaks in 2003.
- It is thought to have a zoonotic origin.

Mode of Transmission



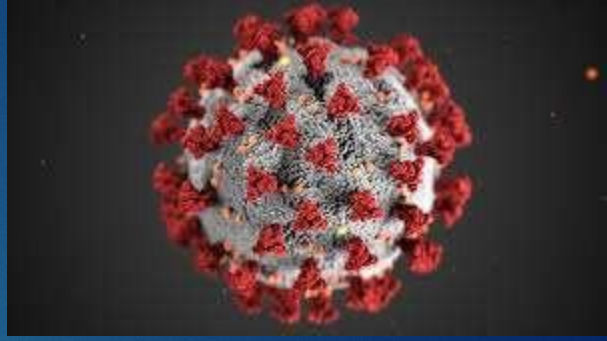
- The primary mode of **transmission** is via **respiratory droplets** that people exhale.
- Droplets only stay suspended in the air for a short time but may stay viable and contagious on a metal, glass or plastic surface.
- **Disinfection** of surfaces is possible with substances such as 62–71% **ethanol** applied for one minute.

Incubation Period



- Ranges from **one to fourteen days**; it is most commonly five days. In one case, it had an incubation period of 27 days

Pathophysiology



Host mechanism is decreased (Impaired gag and cough reflex or

immunocompromized State)
Microorganisms enter the lower respiratory tract

↓

Inflammatory reaction begins

↓

Inflammatory reactions with WBC, neutrophils enter the alveoli and fill normally

air containing spaces

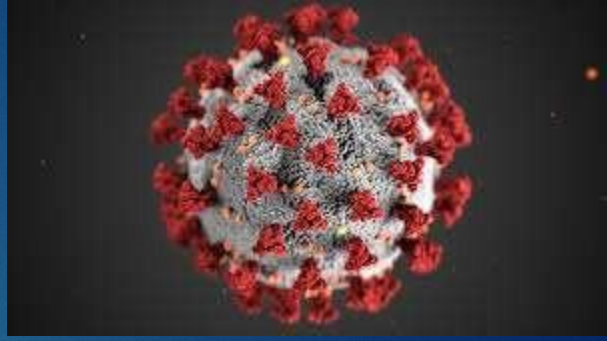
↓

Interfere exchange of O2 and CO2

↓

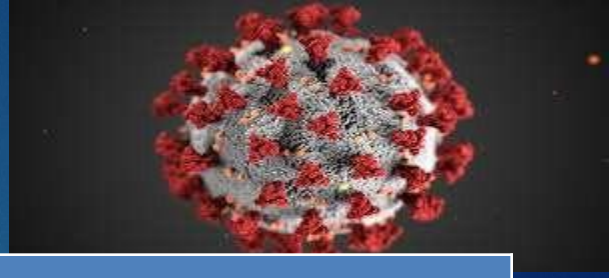
Hypoxemia

Signs and Symptoms



- Symptoms of COVID-19 are **non-specific** and those infected may either be **asymptomatic** or develop **flu like symptoms** such as fever, cough, fatigue, shortness of breath, or **muscle pain**.

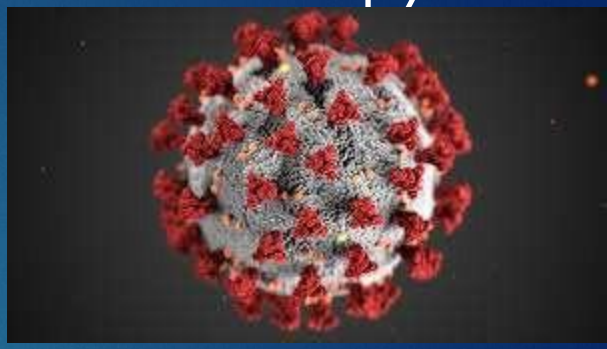
Signs and Symptoms…



Symptom	%
Fever	87.9%
Dry cough	67.7%
Fatigue	38.1%
Sputum production	33.4%
Shortness of breath	18.6%
Muscle pain or joint pain	14.8%
Sore throat	13.9%
Headache	13.6%

Chills	**11.4%**
Nausea or vomiting	5.0%
Nasal congestion	4.8%
Diarrhoea	3.7%
Haemoptysis	0.9%
Conjunctival congestion	0.8%

Clinical Syndrome associated with COVID-19



1. Mild illness
2. Pneumonia
3. Severe Pneumonia
4. Acute respiratory distress Syndrome
5. Sepsis
6. Septic Shock

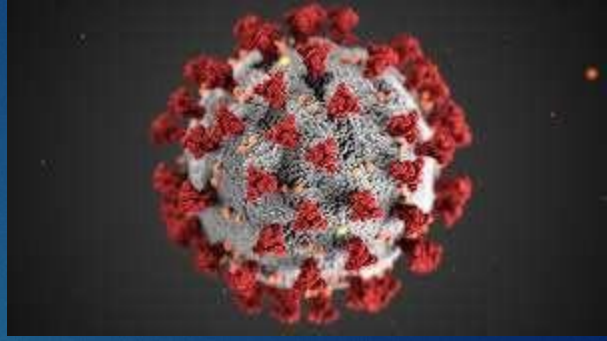
Diagnosis

- Infection by the virus can be provisionally diagnosed on the basis of symptoms, though confirmation is ultimately by **reverse transcription polymerase chain reaction (rRT-PCR**) of infected secretions (71% sensitivity) and **CT imaging** (98 % sensitivity).

Diagnosis…

- 1. Viral testing
  - Reverse transcription polymerase chain reaction (rRT-PCR) is done. The test can be done on respiratory or blood samples.
- 2. Imaging
  - Radiographs and computed tomography.

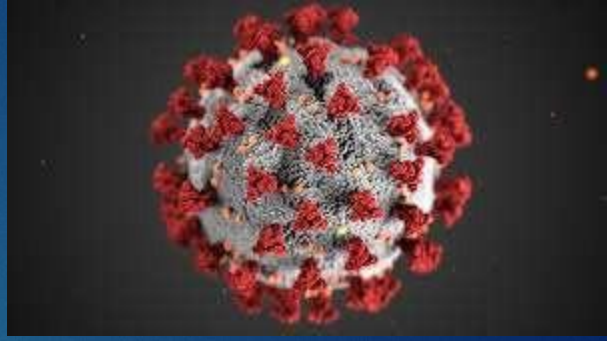
PREVENTION



- **Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Corona virus Disease 2019 (COVID-19) in Healthcare Settings**

  (Centers for Disease Control and Prevention)

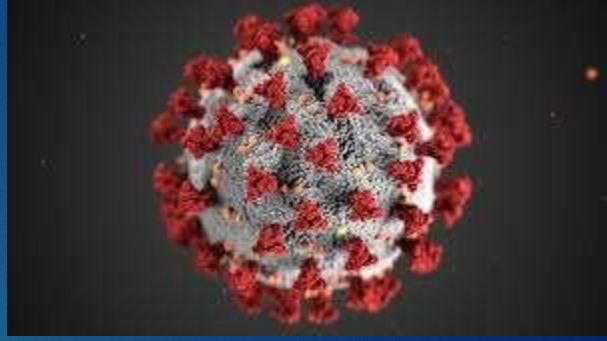
Prevention…



1. Minimize Chance for Exposures

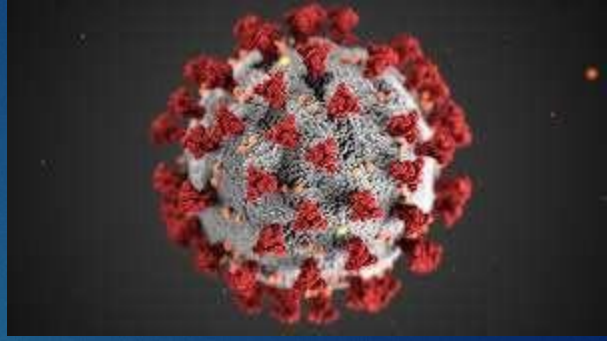
- Measures should be implemented before patient arrival, upon arrival, throughout the duration of the patient's visit, and until the patient's room is cleaned and disinfected.

PREVENTION…



- **Before Arrival**
  - When scheduling appointments for routine medical care (e.g., annual physical, elective surgery), instruct patients to call ahead and discuss the need to reschedule their appointment if they develop symptoms of a respiratory infection (e.g., cough, sore throat, fever) on the day they are scheduled to be seen.

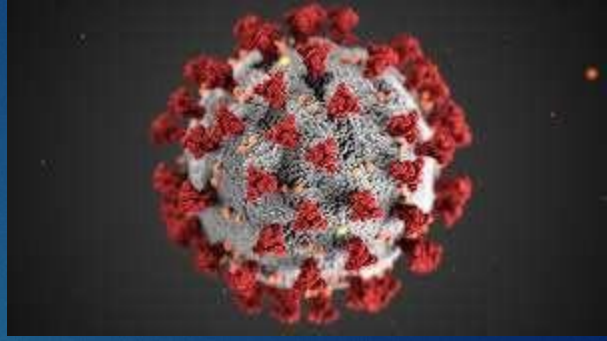
PREVENTION…



- **Upon Arrival and During the Visit**

  Take steps to ensure all persons with symptoms of COVID-19 or other respiratory infection (e.g., fever, cough) adhere to respiratory hygiene and cough etiquette, hand hygiene, etc

Prevention…



2. Adhere to Standard and Transmission-Based Precautions

- Hand Hygiene
- Personal Protective Equipment

HAND WASHING

- Hand washing is recommended to prevent the spread of the disease. The US Centers for Disease Control and Prevention (CDC) recommends that people wash hands often with soap and water for at least 20 seconds.

FOR MAKING HAND SANITIZER

- Ethanol=835 ml
- Hydrogen Peroxide=40 ml
- Glycerol=15 ml
- Sterile water=110ml

Total=1000ml

References

1. **https://www.who/2019-nCoV-clinical-2020.4-eng.pdf retrived on 16th March, 2020**
2. https://www.cdc.gov/coronavirus/2019-ncol-recommendations.htmlov/infection-control/contr **retrived on16th March,2020**
3. https://www.who.int/health-topics/coronavirus**retrived on 16th March, 2020**

thank you