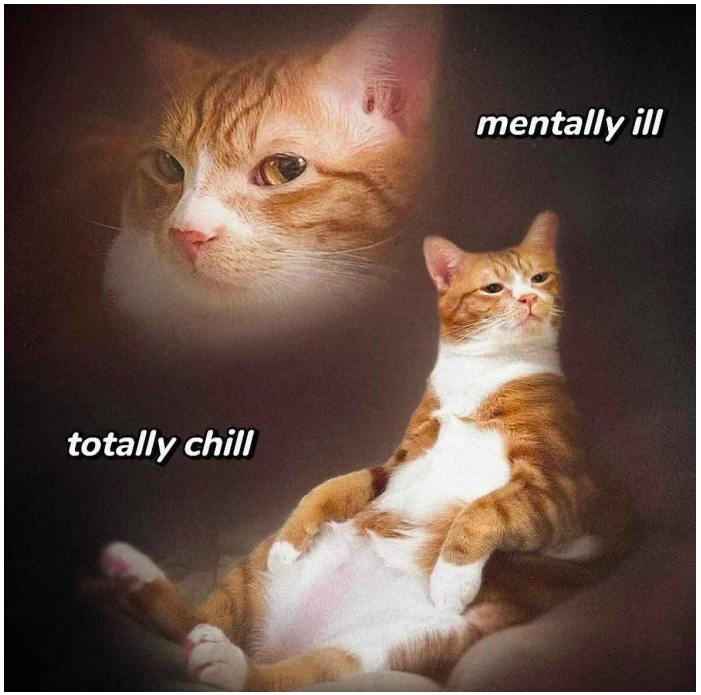

تفريغ سول أكاديمي
اسم المادة: Immunology
المحاضرة: Inflammation & leukocyte Migration
الصيدلانية/ة: Sara Jaber

Inflammation and Leukocyte Migration



Objectives

- Overview of the inflammatory process: initiation, inflammation, resolution, benefits and liabilities
- Major constituents
- Clinically relevant inflammatory processes
- Control of inflammation

Introduction

- "Inflame" – to set fire
- Inflammation is "A dynamic response of vascularised tissue to injury."
- Inflammation: Local defense and protective response against cell injury or irritation or local vascular and cellular reaction, against an irritant.
- It is a protective response.
- It serves to bring defense & healing mechanisms to the site of injury.
- Inflammation is designated by adding the suffix (itis) to the end of the name of the inflamed organ or tissue.

Etiology المسببات

- Microbial infections: bacterial, viral, fungal, etc.
- Physical agents: burns, trauma--like cuts, radiation ⇒ عشان هيك بنخاف على الحروق
- Chemicals: drugs, toxins, or caustic substances like battery acid.
- Immunologic reactions: rheumatoid arthritis.

من اسمه بنعرف انه التهاب

Types

بنصنفه الالتهاب على اساس

1. Time course
   - Acute inflammation: Less than 48 hours
   - Chronic inflammation: Greater than 48 hours (weeks, months, years)
2. Cell type
   - Acute inflammation: Neutrophils
   - Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).

Cardinal Signs of Inflammation

كيف نعرف انه هون في inflammation ؟!

1) • Redness : Hyperemia: increase the amount of the Blood in the vessels in the organ or tissue ← زيادة تدفق الدم
2) • Warm : Hyperemia.
3) • Pain : Nerve, Chemical mediators. ← السوائل بتضغط على الأعصاب فبيصير في ألم
4) • Swelling : Exudation ← كمان بتتسبب زيادة الألم
5) • Loss of Function: Pain

neutrophils بتتجمع وبيجي عليها التهاب فبتتراكم بالمكان

هو مرحلة مهمة من مراحل الالتهاب، وبيعني (الإفراز الالتهابي) *Exudation*:

👉 خروج سوائل + بروتينات + خلايا من الأوعية الدموية إلى النسيج المصاب.

ليش بصير؟
بسبب زيادة نفاذية الأوعية الدموية أثناء الالتهاب (بفعل *mediators* زي الهيستامين)، فبتصير "تسرّب".

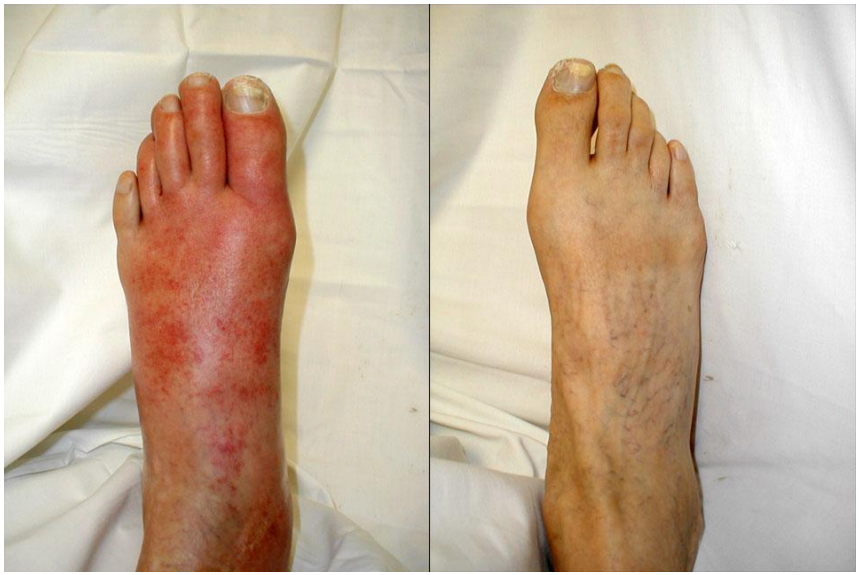
شو اللي بطلع؟

* *Plasma* (سائل)
* *Proteins* (زي *fibrinogen*)
* خلايا مناعية (خصوصًا *neutrophils*)

الهدف منه؟

* توصيل خلايا الدفاع لمكان الإصابة
* التخلص من الميكروبات أو الضرر
* بدء عملية الشفاء

بكلمة بسيطة:
Exudation = "تسريب مواد دفاعية من الدم لمكان الالتهاب"



Pathogenesis

- The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.
- Three main processes occur at the site of inflammation, due to the release of chemical mediators :

1. Increased blood flow (redness and warmth).
2. Increased vascular permeability (swelling, pain & loss of function).
3. Leukocytic Infiltration.

1. Local Vascular Changes

- Initial temporary vasoconstriction for few seconds.
- Active vasodilatation of arterioles and capillaries by chemical mediators like histamine and passive dilatation of venules.
- Slowing of the circulation: outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood (stasis).
- Pavementation: the margination of leukocytes. Neutrophils become oriented at the periphery of vessels and start to stick.

في الالتهاب هي خطوة من خطوات خروج كريات الدم البيضاء من الأوعية.

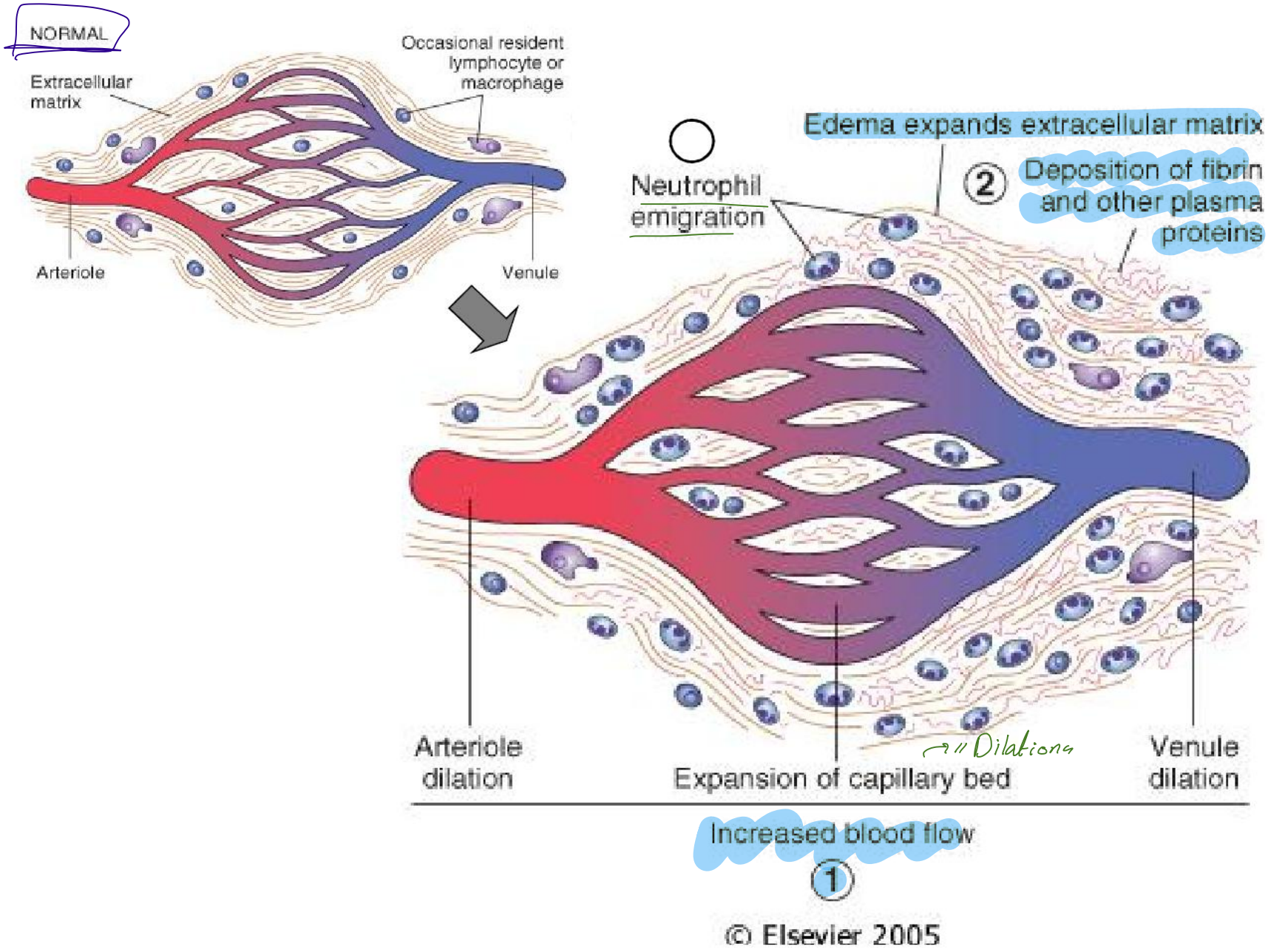
معناها: 👉
التصاق خلايا الدم البيضاء (خصوصًا *neutrophils*) ببطانة الأوعية الدموية (*endothelium*) وكأنها "مرصوفة" على الجدار.

كيف بتصير؟

1. بالالتهاب، الخلايا تبطّئ حركتها داخل الوعاء (*stasis*)
2. تبدأ تلمس الجدار (*margination*)
3. ثم تلتصق بقوة على الجدار = *Pavementation*

ليش اسمها هيك؟
لأن شكل الخلايا وهي ملتصقة جنب بعض على الجدار بيشبه "بلاط مرصوف" 🧱

ببساطة تحفظيها:
Pavementation = white cells "sticking" على جدار الوعاء تمهيدًا للخروج (*diapedesis*


NORMAL
Occasional resident lymphocyte or macrophage
Extracellular matrix
Arteriole
Venule
Edema expands extracellular matrix
Neutrophil emigration
2
Deposition of fibrin and other plasma proteins
Arteriole dilation
Expansion of capillary bed
Venule dilation
Increased blood flow
1
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2. Leukocyte Exudation

- Leukocytes (PMN's , Mphages, lymphocytes, mainly T) circulate in the blood, but often do their work in tissues.
- For T and B cells, circulation increases the chances that you'll meet your antigen.
- For both to do their jobs, however, you often have to leave the blood to enter either the lymph node or the site of damage.
- Once at the site of damage, you want to kill microbes, control the damage, and repair it.

Leukocytes Extravasation

- Neutrophils are usually the first cells to move to site of infections or inflammations
- Neutrophils extravasation involves 4 main stages:

1. Rolling: mediated by selectines
2. Activation by chemoattractant stimulus
3. Arrest and adhesion mediated by Integrins binding to Ig-family members
4. Transendothelial migration

🧩 1. Rolling (التدحرج)

* الخلايا تمشي داخل الوعاء بسرعة
* بسبب الالتهاب، بتصير "تتمسّك وتفلت" بشكل خفيف مع الجدار
* هذا بسبب Selectins

👉 تخيّليها: تمشي وتزحلق شوي شوي على الجدار

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⚡ 2. Activation (التنشيط)

* الخلية تستقبل إشارات من مكان الالتهاب (chemoattractants)
* زي: cytokines أو مواد من البكتيريا
* هذا بخليها "تتحمّس" وتجهّز نفسها للالتصاق القوي

👉 هون الخلية فهمت: "في مشكلة قدّامي!"

🧲 3. Arrest & Adhesion (التوقف والالتصاق)

* الخلية توقف تمامًا
* تمسك بقوة بجدار الوعاء
* يتم عن طريق:
  * Integrins على neutrophil
* ترتبط مع Ig-family على الـ endothelium

👉 هون خلاص: وقفت وثبّتت حالها 💥

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🚪 4. Transendothelial Migration (الخروج)

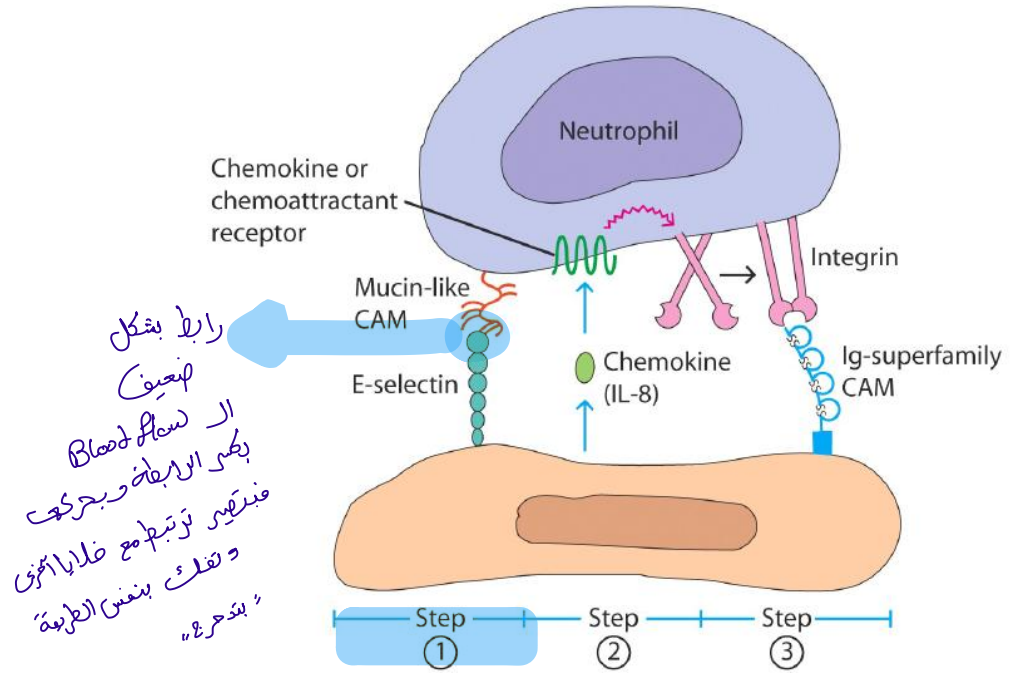
(اسمها كمان Diapedesis)

* الخلية "تزحف" بين خلايا الوعاء
* وتطلع للنسيج المصاب

👉 كأنها طلعت من باب سري بين الخلايا

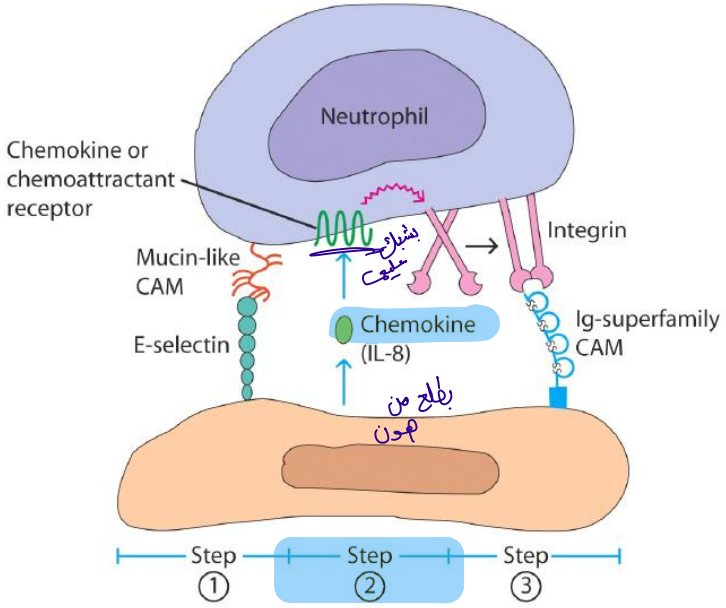
1. Rolling

- In this step leukocytes attached loosely to the endothelium by low affinity selectines-carbohydrate interaction
- This interaction tether the leukocyte briefly to endothelium, but the shearing force of blood flow detached the cells soon
- Selectine molecules on another endothelial cells tether the leukocytes again; this process is repeated so the cells trumble over the endothelium "rolling"



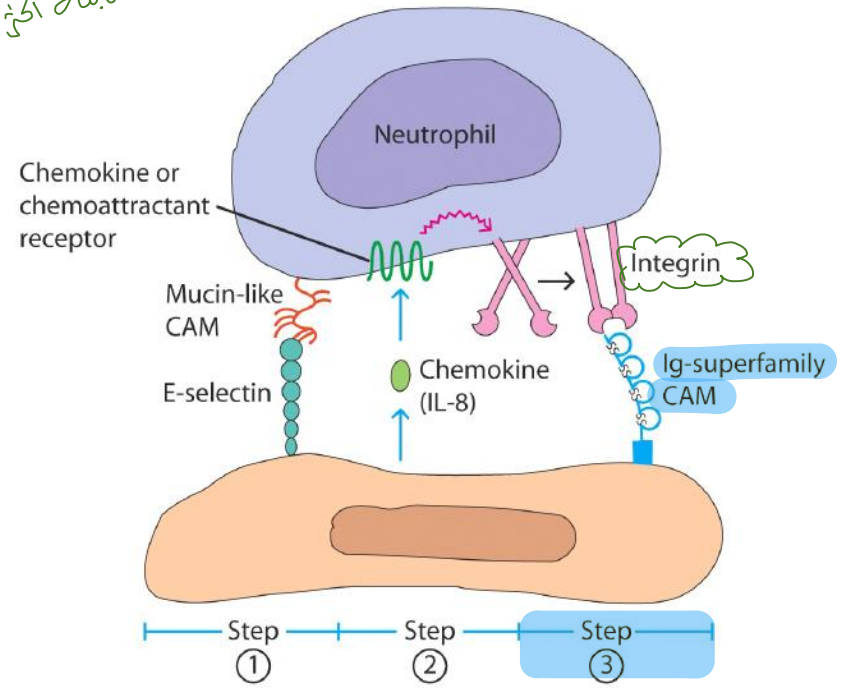
2. Activation

- The process of rolling slow the cells enough to allow interactions between chemokines on the endothelium surface and receptors on leukocytes
- This binding leads to signal transduction events results in change in confirmation and clustering of integrins on leukocytes



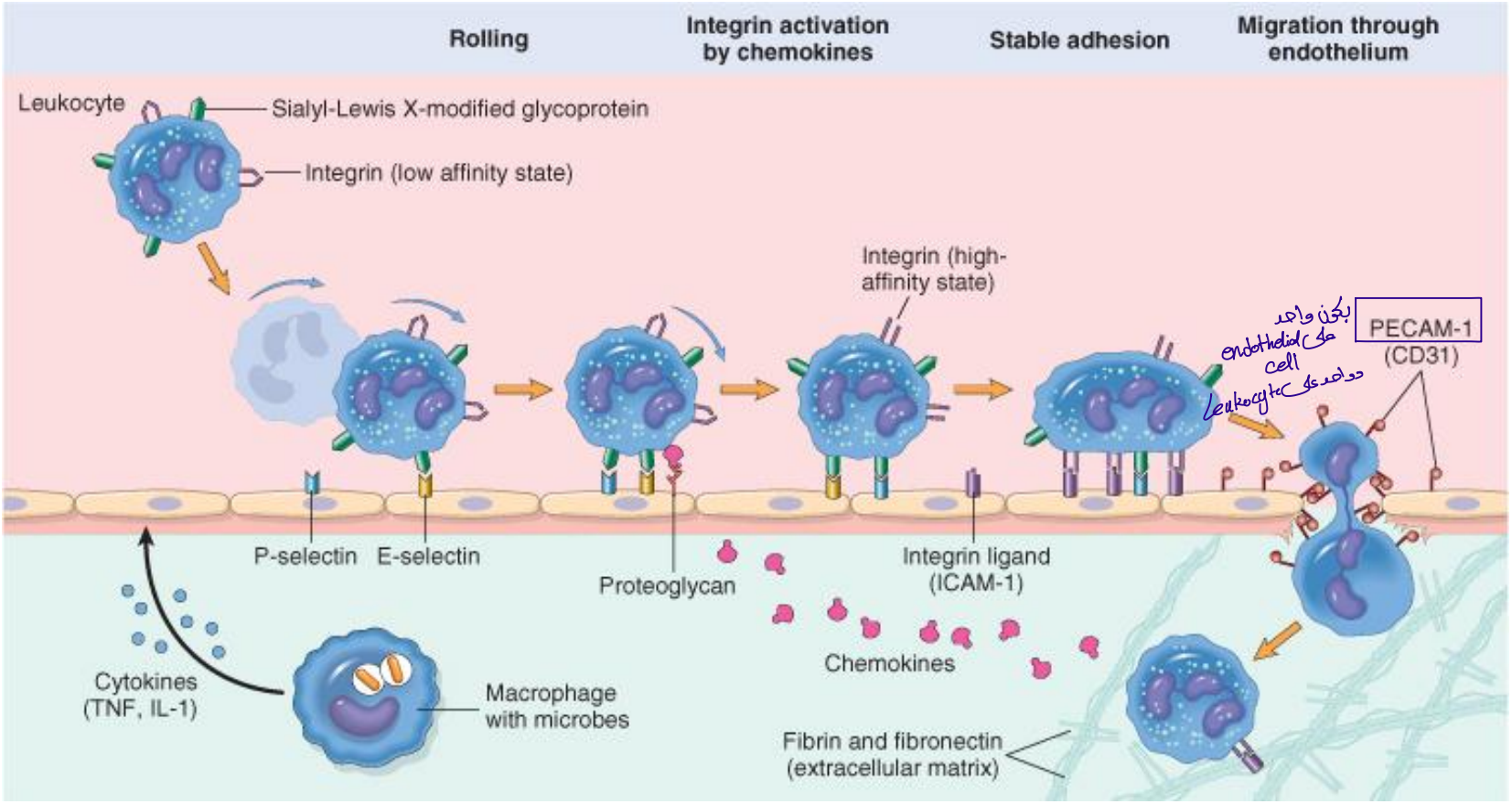
3. Firm Adhesion

- Binding of leukocytes to endothelium and slowing down of leukocytes allow binding of other adhesion molecules including integrins which leads to firm adhesion
- This allowed the leukocytes to binds more tightly to endothelium and it become less likely that blood force will detach them



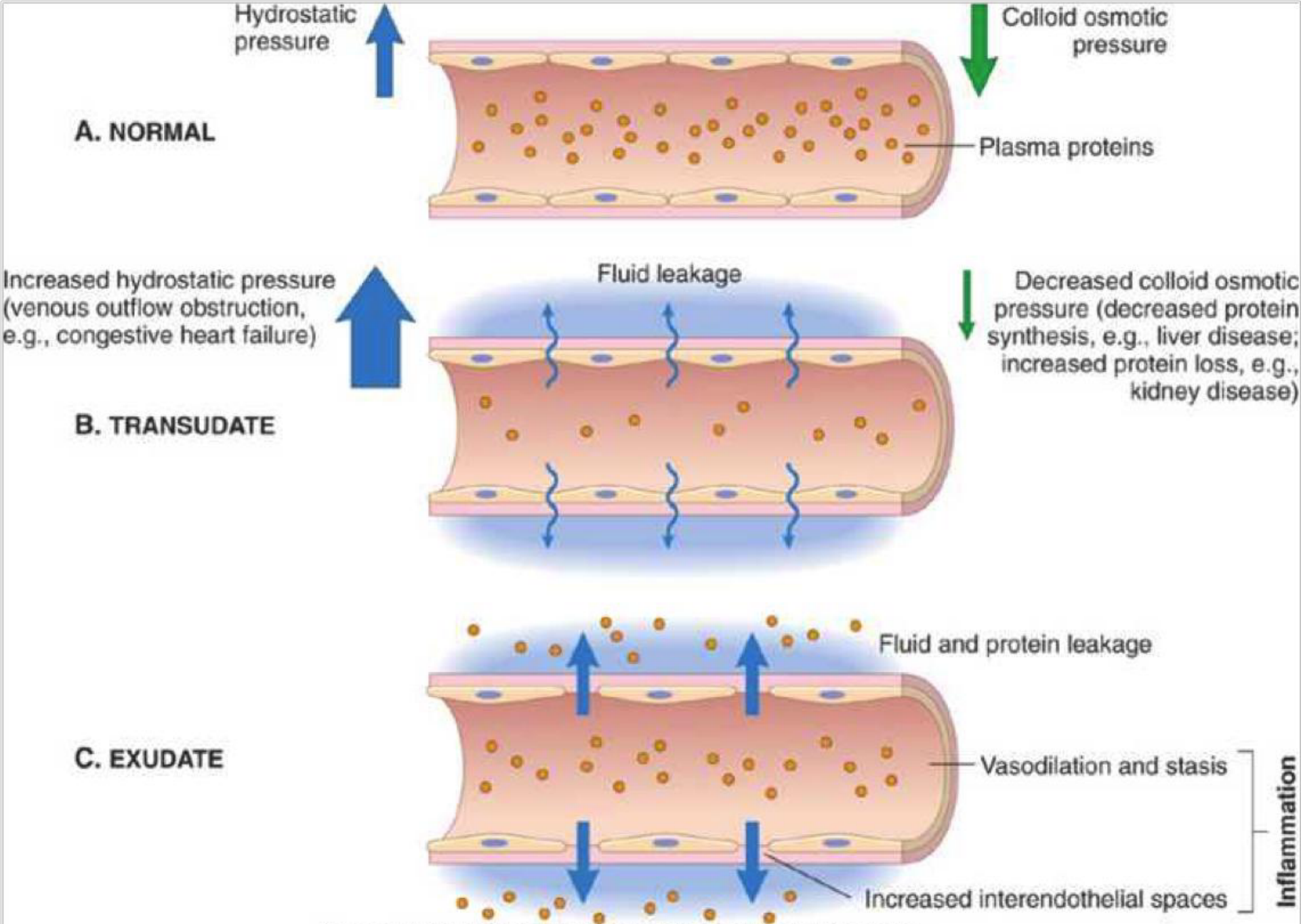
4. Transendothelial Migration

- Leukocyte then squeezes in between two neighboring endothelial cells without disrupting the integrity of these cells
- This is accomplished by binding of platelet endothelial cell adhesion molecule 1 (PECAM-1) on leukocyte with PECAM-1 on endothelial cells



Lymphatics in Inflammation:

- Lymphatics are responsible for draining edema.
- **Edema**: An excess of fluid in the interstitial tissue or serous cavities; either a transudate or an exudate
- **Transudate**: an ultrafiltrate of blood plasma
  - permeability of endothelium is usually normal.
  - low protein content (mostly albumin)
- **Exudate**: A filtrate of blood plasma mixed with inflammatory cells and cellular debris.
  - permeability of endothelium is usually altered
  - high protein content.
- **Pus**: A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.



Function of Inflammatory Exudates

- **Dilute** the invading microorganism and its toxins.
- Bring **antibodies** through the plasma to the inflamed area.
- Bring **leukocytes** that **engulf** the invading microorganisms.
- Bring **fibrinogen** through the plasma, which is converted, to fibrin mesh, helping in **trapping** the microorganism and localize the infection

Inflammatory Mediators:

- Chemical substances synthesised or released and mediate the changes in inflammation.
  1. Histamine by mast cells - vasodilatation.
  2. Prostaglandins – Cause pain & fever.
  3. Bradykinin - Causes pain.
- Cytokines including TNF, IL1, IL6, IL8 → موجودین بشابیٰ از Cytokines
- Lipid mediators: prostaglandins, leukotrienes, and platelet activation factor

Cytokines and Inflammation

- Macrophages or DCs stimulated via innate immune receptors make pro-inflammatory cytokines, especially TNF (Tumor necrosis factor), IL-1, and IL-6
- TNF and IL-1 signal to endothelial cells to make them:
  - Leaky to fluid (influx of plasma; containing antibodies, complement components, etc.)
  - Sticky for leukocytes, leading to influx of first neutrophils, later monocytes, lymphocytes
  - IL-6 promotes adaptive immune responses and has systemic effects ("acute phase response" of liver, including C-reactive protein or CRP; levels used clinically as an indication of systemic inflammation)

الدكاترة بستخدموا هاد الفحص حتى
ليشوفوا إذا في Systemic inflammation
وكان CRP عالي ← في Systemic inflammation

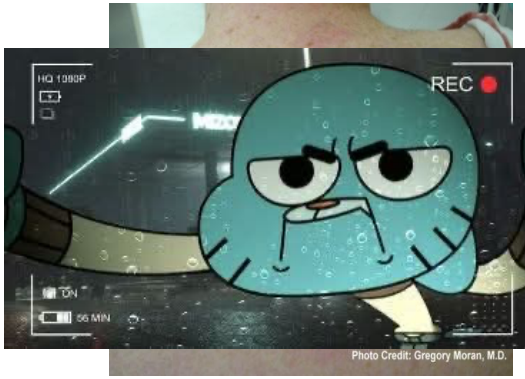
Negative Regulation of Inflammation

- Cells responding to innate stimuli stop making inflammatory mediators after short time period and convert to making anti-inflammatory lipids
- Killing the infectious agent and removal of the dead cells, debris, crystals, will stop stimulation of incoming inflammatory cells
- Systemic elevation of inflammatory cytokines (esp. IL-1) induce production of glucocorticoids, which are anti-inflammatory
- Regulatory T cells are also anti-inflammatory, both by blocking effector T cells and by inhibiting innate cells

Inflammation Outcomes

1. Abscess formation
2. Progression to chronic inflammation
3. Resolution--tissue goes back to normal
4. Repair--healing by scarring or fibrosis
5. Spread through lymphatics or blood or stream

Suppurative or Purulent Inflammation



في صورة
مش لطيفة

- **Pus**: thick fluid containing viable and necrotic polymorph and necrotic tissue
- 1**. Localized**: ex. Abscess: Abscess is the localized collection of pus, commonly seen solid block of tissue - Example: dermis, liver, kidney, brain etc. Pus consists of partly or completely liquefied dead tissue mixed with dead or dying neutrophils and living or dead bacteria, formed of 3 zones
  - Small abscess is called boil or furuncle (الدمل)
  - Large one carbuncle
  - Fistula
- 2. **Diffused**: Spreading of pus to adjacent areas e.g. cellulites occurring in subcutaneous tissue . Usually caused by streptococci.

هو:
سائل سميك يحتوي على: 👉

* *Neutrophils* (حية وميتة)
* نسيج ميت *(necrotic tissue)*
* بكتيريا (حية أو ميتة)

يعني باختصار:
Pus = بقايا معركة الالتهاب 🧬

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أنواع تجمع القيح 🧩

1. 🧱 *Localized* (موضعي)

💥 *Abscess* (الخُراج)

هو:
👉 تجمع قيح بمكان محدد داخل نسيج صلب
مثل:

* الجلد *(dermis)*
* الكبد
* الكلى
* الدماغ

محتواه:

* نسيج ذائب *(liquefied necrosis)*
* *Neutrophils* ميتة أو تحتضر
* بكتيريا

مركز: مليان قيح
طبقة حواليه: خلايا التهابية
طبقة خارجية: *fibrosis* (يحاول الجسم يعزله)

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أشكال الـ *abscess*: 🪄

Boil / Furuncle (دُمّل) 👉 خراج صغير
Carbuncle 👉 خراج كبير ومتصل
Fistula 👉 قناة غير طبيعية تطلع القيح لمكان ثاني أو للجلد

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🌊 *2. Diffuse* (منتشر)

🔥 *Cellulitis*

هو:
👉 انتشار القيح بشكل واسع بين الأنسجة (مش محدد)

غالبًا في *subcutaneous tissue*
ما في حدود واضحة مثل *abscess*

السبب الشائع:
Streptococci بكتيريا 👉

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الخلاصة السريعة (امتحان 🚀): 🧠

Pus = neutrophils + tissue debris + bacteria
Abscess = localized pus (واضح ومحدد)
Cellulitis = diffuse pus (منتشر)
Furuncle = صغير
Carbuncle = كبير
Fistula = قناة تصريف

Pharma-
Cology

Anti-Inflammatory Therapeutics

- **NSAIDs:** inhibitors of inflammation and fever (block prostaglandin synthesis)
- **Glucocorticoids** are also potent anti-inflammatory drugs
- Agents that **block TNF** are effective in treating rheumatoid arthritis, Crohn's disease, etc.
- Agents that **block IL-1** are less effective for these diseases but are useful for some genetic inflammatory diseases (and are currently in clinical trials for more common conditions)