PATHOLOGY

بسم الله الرحمن الرحيم

MID – LECTURE 6

INFLAMMATION AND REPAIR

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

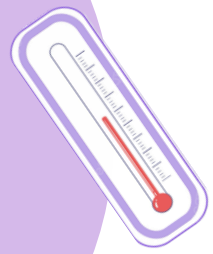
اللهم استعملنا ولا تستبدلنا

Written by:

- Deema Nasrallah
- Leen Mukahal

Reviewed by:

- Rania Nassar



INFLAMMATION AND REPAIR

Mousa Al-Abbadi, MD, FCAP,CPE, CPHQ,FIAC
Professor of Pathology & Cytopathology
University of Jordan
College of Medicine
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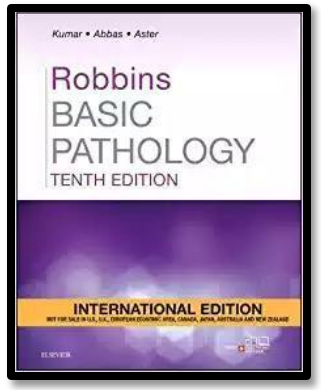
INTRODUCTION

- **6 lectures inflammation**
- **3 lectures repair; revision lecture**
- **Robbins Basic Pathology 10th Edition + lecture contents**



MY DUTIES

- **Simplify**
- **Concepts of pathology**
- **Help U all**
  Understand…understand…
  understand then memorize
- **Answer questions & inquiries**
- **Respect**

UR DUTIES (MY ADVICE)

- **On time attending**
- **Plz…plz…plz…NO CHATTING during lecture**
- **Understand first then memorize and recall**
- **Respect to the process**
- **NO MOBILE**

This will teach you discipline regarding your education process :)

TIPS

- ***"You don't have to be smart to be a good physician; but you need to be thorough"*** ***Thomas Eskin***
- ***"My interest is in the future…bcz Um going to spend all my time there"***

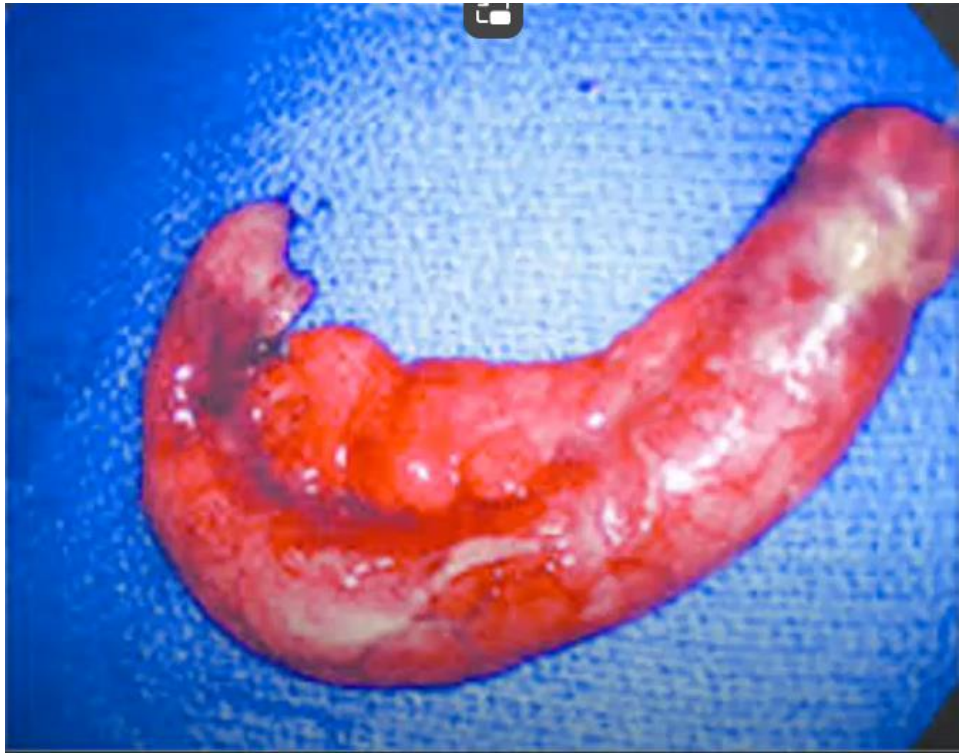
  Charles Kettering

BIG NO

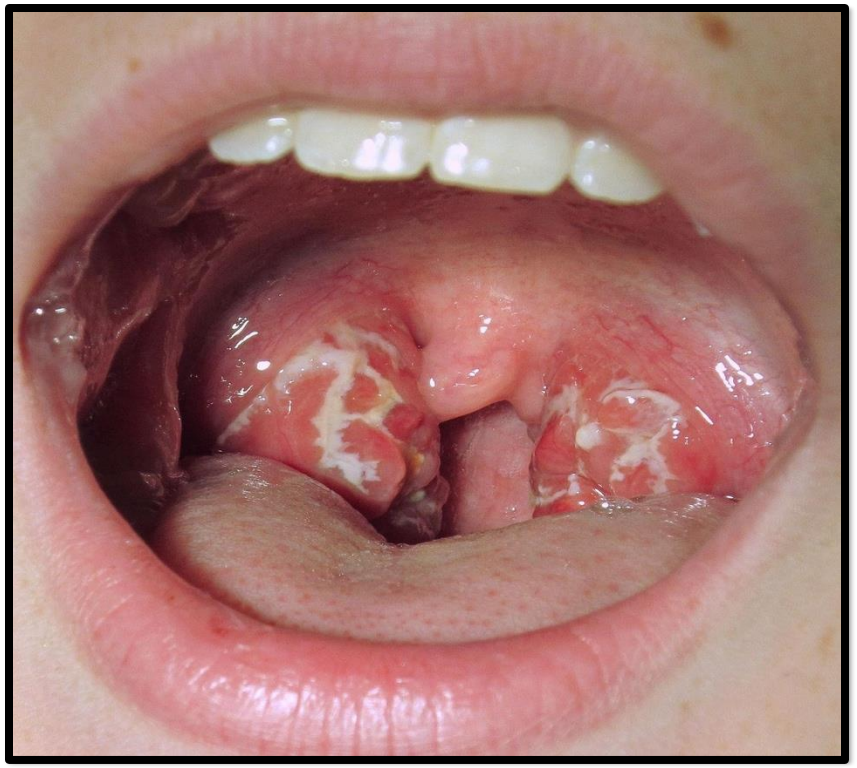
- **I DONNOT answer exam questions to any one before or after the exam**
- **Don’t ask these UNHEALTHY questions:**
  - **Is this important?**
  - **Should I study this?**
  - **How difficult are exam questions?**

E learning 2022 inflammation & Repair Al-Abbadi

1.General review	https://www.youtube.com/wat`ch?v=HrFb0axflGY&ab_channel=MedToday
2. Transudate vs exudate	https://www.youtube.com/watch?v=RE0sT0DYB6k&ab_channel=MEDSCHOOLRADIO
3. Outcomes of A Inflam	https://www.youtube.com/watch?v=Y-xcUN4u_F8&ab_channel=Dr.JohnCampbell
4. AA mediators	https://www.youtube.com/watch?v=PE_D3Os7oWY&t=627s&ab_channel=Dr.JohnCampbell
5. Complement system	https://www.youtube.com/watch?v=BSypUV6QUNw&ab_channel=Kurzgesagt%E2%80%93InaNutshell
6. Granulomatous inflammation	https://www.youtube.com/watch?v=rVaek7-RO0w&ab_channel=MedToday
7. Sarcoidosis	https://www.youtube.com/watch?v=zAq22bbWrNg&ab_channel=DrbeenMedicalLectures
8. Wound healing	https://www.youtube.com/watch?v=TLVwELDMDWs&t=43s&ab_channel=TED-Ed
Tissue repair	https://www.youtube.com/watch?v=KvBt2G4yMx4&t=409s&ab_channel=AnatomyandPhysiologyforParamedics
9. Keloid and HT scars	https://www.youtube.com/watch?v=-VUbBK3K4Ns&ab_channel=djverret
10. Local factors affecting healing	https://www.youtube.com/watch?v=pxOrHRcmeU4&t=22s&ab_channel=Dr.JohnCampbell



This is a red enlarged congested appendix i.e. inflamed appendix or acute appendicitis.
These signs are the three major cardinal signs of inflammation of any organ.



In the recorded lecture, the doctor explained a different image than the one originally included in the slides. We have inserted the image from the recording, but the three major cardinal signs of inflammation can be also seen in the inflamed tonsils.

INFLAMMATION

Most accurate definition of inflammation:

alive/ viable

"Response of vascularized tissue to injury (infections or tissue damage)

→ **recruitment of cells and molecules from**

circulation to the sites of need to eliminate

the offending agent"

or injurious agent which could be an infection (by bacteria/viruses) or tissue damage or trauma

For example: if you have viral tonsillitis your tonsils will have a response to this virus trying to get rid of it.
As a result, for a couple of days you will have swelling, congestion and a lot of cells infiltrating the tonsils getting rid of that virus, then you get back to normal.

INFLAMMATION:

- **Protective**
- **With no inflammation: infections can be fatal, wounds would never heal and injured tissue may sustain permanent damage**

Further explained in the next slide....

Explanation of the previous slide:

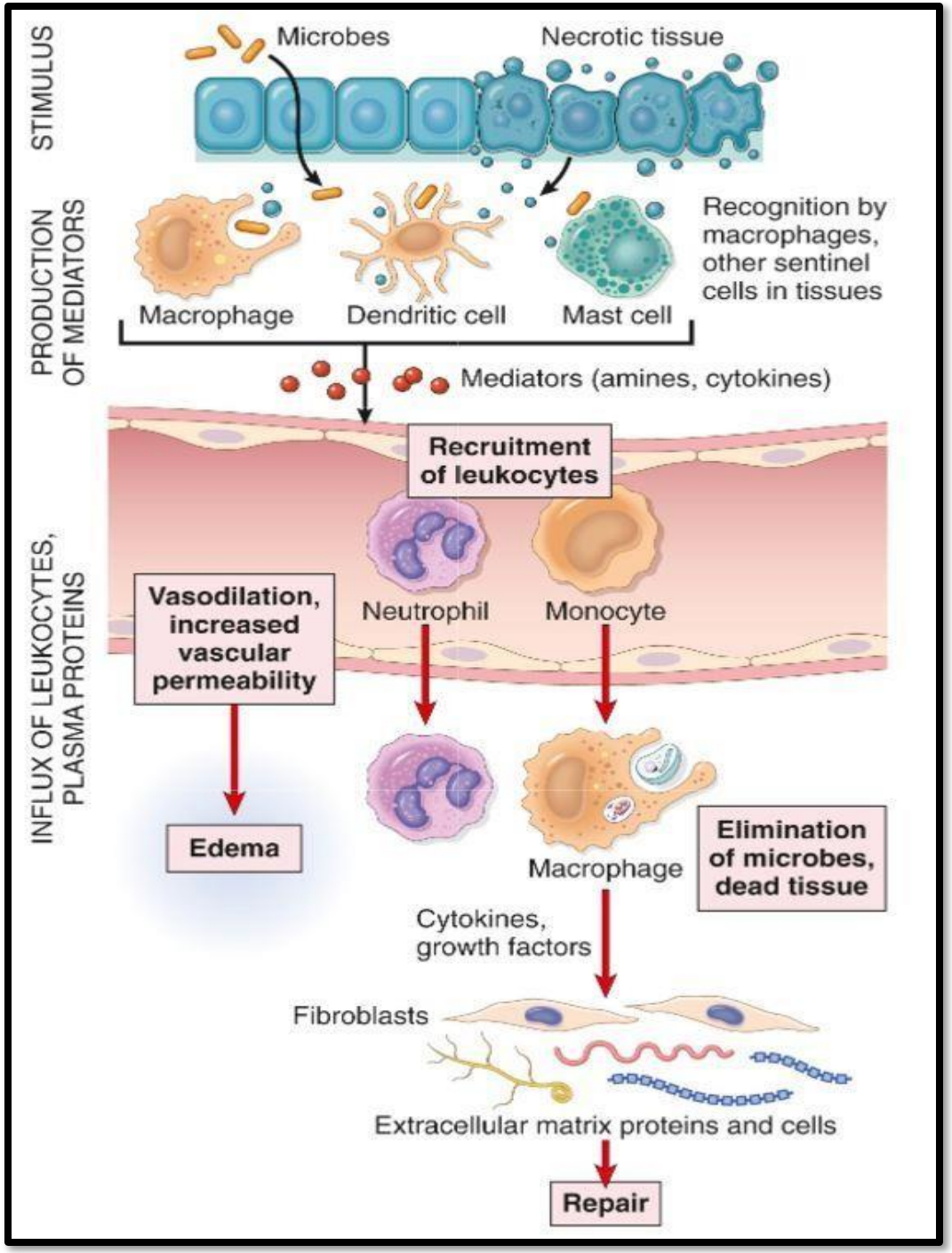
- Inflammation is protective, it is not a normal condition, but it protects you from bad consequences from these offending agents.
- With no inflammation infections can be fatal, in the 30's and 20's before antibiotics were created simple tonsillitis or simple appendicitis used to be fatal.
- Without inflammation your wounds would never heal, and your injured tissue will sustain permanent damage.
- Due to inflammation, we are fighting those fatal consequences, helping our body to heal the wounds and prevent or decrease tissue damage.

To summarize:
Inflammation is protective and without it your life would be exposed to many dangerous fatal events.

This image is a summary of all 5 steps of inflammation. (Part 1)

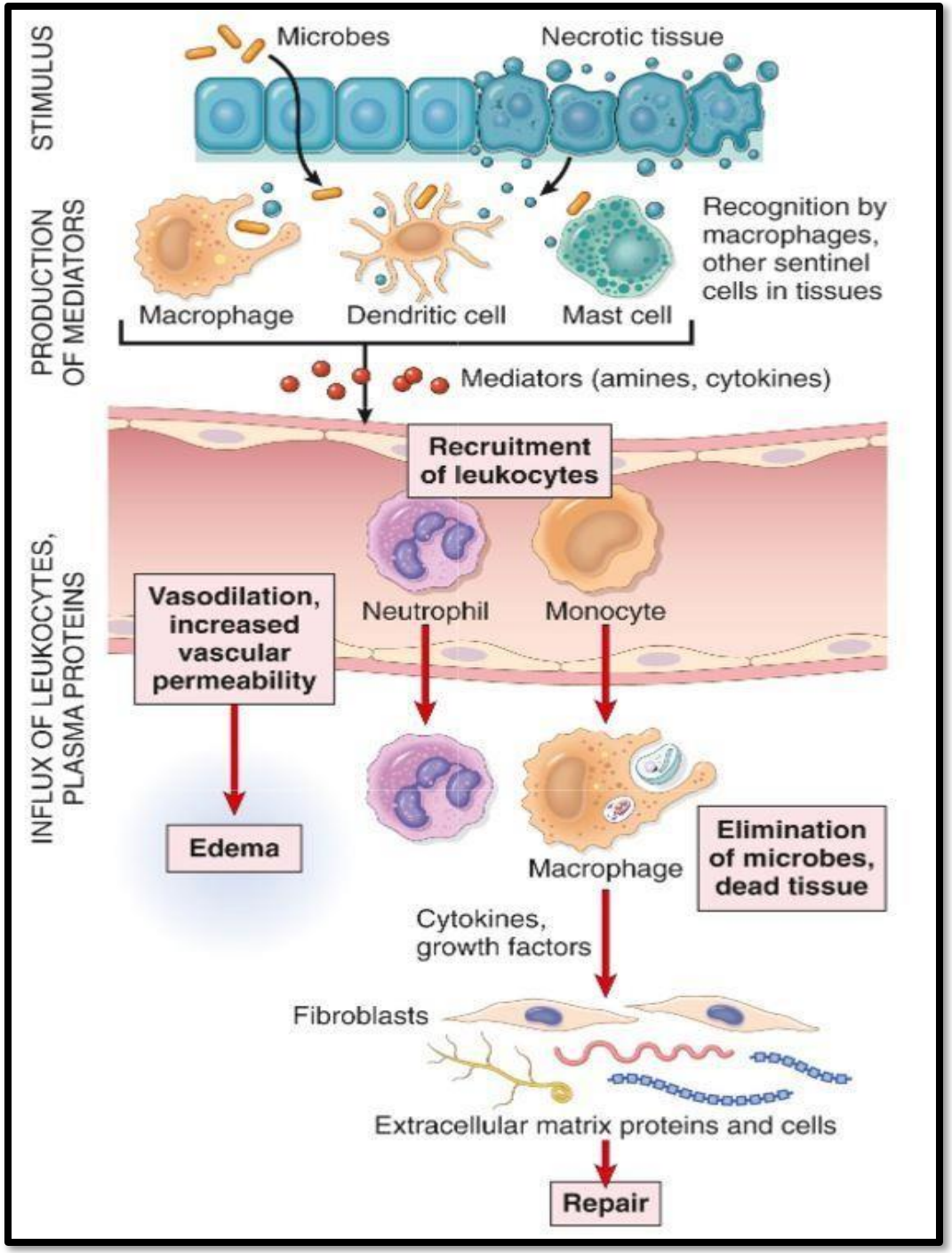
Each step will be explained in a separate lecture

- Here we have an offending microbe or bacteria, bacilli for example as a stimulus which will cause tissue damage.
- Our body cells will first recognize that this is an offending agent or recognize the damaged tissue.
- This will stimulate many inflammatory cells macrophages, mast cells and dendritic cells to secrete a lot of chemical mediators of inflammation, initially we will have predominance of amines that will cause vasodilation and increased vascular permeability. And cytokines



This image is a summary of all 5 steps of inflammation. (Part 2)

- Also, recruitment of inflammatory cells; neutrophils and monocytes into the tissue. Monocytes will be called macrophages as soon as it leaves the blood vessel into the tissue, it will be transformed to activated macrophage monocytes which we call **tissue macrophages** and neutrophils or mickey mouse cells (C3 three lobe nuclei) those cells will also stimulate the secretions of multiple mediators; cytokines and growth factors trying to eliminate the microbe by different mechanisms and intracellular killing.
- Then the reparative process will propagate and start with recruitment of fibroblasts and extra cellular matrix proteins where the reparative process ends.



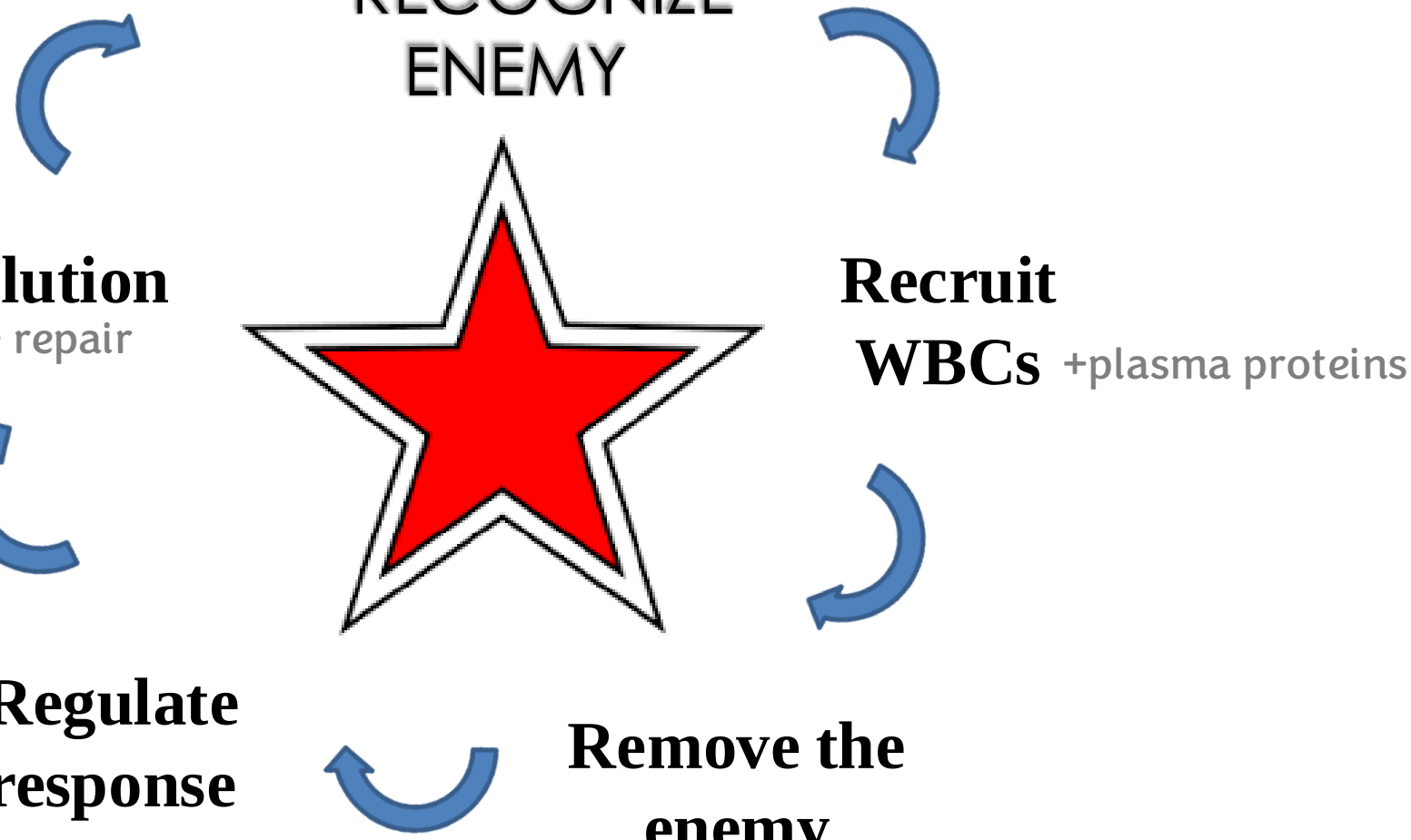
TYPICAL INFLAMM. RX. STEPS:

- **Offending agent recognized by cells and molecules** In addition to the changes which this offending agent causes like change in the structures, proteins or cells.
- **WBCs & Pl. proteins recruited to injury site**
- **WBCs and Pl. proteins work together to destroy and eliminate the enemy** by phagocytosis, intracellular killing
- **Rx. Is then controlled and terminated**

  By the time we eliminate the enemy we don't need all these soldiers WBCs, proteins, chemical mediators to stay because they can cause collateral damage, so we control and decrease the intensity of the response.
- **Repair of damaged tissue (regeneration & fibrosis)** The tissue which has been lost will be replaced by either regeneration if possible or by scar formation (fibroblasts)

THE 5 RS:

These steps are consequential



Which includes controlling and decreasing the intensity of the inflammatory response

This table has clinical implications when you start seeing patients in the clinic, emergency room and operation room!

TABLE 3.1 Features of Acute and Chronic Inflammation

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes + plasma cells
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

Table further explained in the next slide:)

Sometimes we have a situation in which we have both, sometimes we have a baseline of chronic inflammation, and an acute attack comes on top of that. We call it acute on top of chronic or in the stomach for example we call it chronic active gastroenteritis caused by helicobacter pylori bacteria here we see the neutrophils on top of the plasma cells, lymphocytes and macrophages.

Further explanation of the table:

Feature	Acute	Chronic
Onset	If somebody has acute bronchial asthma or acute encephalitis within mins to hours you will start having symptoms, which will push the patient to go seek medical advice. Encephalitis : التهاب دماغ حاد	It is slower, takes days weeks sometimes months to appear and sometimes it doesn't show symptoms until severe damage has happened to the organ. This is why chronic inspiration is insidious (خادع)
Cellular infiltrate	If you have an acutely inflamed appendix and looked at the tissue neutrophils (mickey mouse/ polymorph nuclear cells with 3-5 nuclei WBC) will predominate as they are the whole mark of acute inflammation.	-------
Tissue injury, fibrosis	When you get common cold for example you will have fever/ pain for couple of days. The given treatment is supportive treatment antipyretic for fever, Panadol for pain, antihistamines for congestion.	-------
Local and systemic signs	If somebody has severe acute tonsillitis in 1-2 days will feel pain, sore throat, fever etc.	The signs are much less this is why it is dangerous because the ongoing tissue damage progresses without being noticed.

CARDINAL SIGNS OF INFLAMMATION (Major signs of inflammation) :-

The words written in brackets are in the old latin terminology

- **HEAT (*calor*)** -----> if a patient has inflamed tonsils (enlarged tonsils), you would likely find them warm to the touch
- **REDNESS (*rubor*)** ------> Tissues will be congested with blood.
- **SWELLING (*tumor*)** -----> e.g. swollen tonsils result in difficulty swallowing
- **PAIN (*dolor*)** -----> the inflamed organ will stimulate your pain receptors.
- **LOSS OF FUNCTION (*functiolaesa*)** ---->ultimately the inflamed organ will lose its function (e.g. if you have an inflamed big toe, it won't move or when you have swollen ankle, you can't walk .

CAN INFLAMMATION BE BAD?

The five mechanisms of bad consequences of inflammation

- **Too much…damage**
  - On the other hand, if you don't have proper inflammatory response (your immune system isn't well equipped), you will have exposure to multiple opportunistic infections so too much inflammation isn't good, and for sure too little inflammation is also damaging.
- **Too little… damage** (there will be damage by the offending or endurance agent)
- **Misdirected inflammation…autoimmune diseases and allergies**
- **Chronic inflammation…chronic diseases**

CAN INFLAMMATION BE BAD?

The five mechanisms of bad consequences of inflammation

- **Too much…damage**
- **Too little… damage**
- **Misdirected inflammation…autoimmune diseases and allergies**
  - ❑ The tissue response will be misdirected instead of attacking the virus or the bacteria in your sore throat, they will attack the kidneys, causing Glomerulonephritis or alveolar membranes.
  - ❑ This means your immune response will damage your own tissue (Autoimmune Diseases)
- **Chronic inflammation…chronic diseases**
  - ❑ Most of the chronic diseases (Chronic Hepatitis, Chronic Glomerulitis) will end up damaging the kidney or heart or lungs or liver causing Chronic liver disease end the stage renal disease, end the stage pulmonary fibrosis.

TABLE 3.2 Disorders Caused by Inflammatory Reactions

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts

Listed are selected examples of diseases in which the inflammatory response plays a significant role in tissue injury. Some, such as asthma, can present with acute inflammation or a chronic illness with repeated bouts of acute exacerbation. These diseases and their pathogenesis are discussed in relevant chapters.

- This tables gives you examples of acute and chronic illnesses (you will see them in rotations!)

And sometimes platelets

Acute Syndrome	Main mechanism of injury	More information
Acute respiratory distress syndrome	Neutrophils mediating the injury	is a clinical syndrome, its seen in those patients who are terminally ill with multiple organ failures in the ICUs. The pathologic term is diffuse alveolar damage.
Bronchial Asthma	The mediators of these acute attacks is eosinophils, IgE antibodies.	Patients have atropy, allergy, nasal congestion, severe broncho asthma, bronchospasm, wheezing, difficulty of swallowing
Acute glomerulonephritis	Antibodies and complement system involving monocytes (monocytes tissue injury in the kidneys and neurons)	.....
Septic shock or septicemia	cytokines	Blood poisoning (severe bacterial overgrowth in the blood in association with the impact on your vital functions) Specifically gram-negative bacterial septicemia is lethal

Arthritis is a chronic syndrome

In the musculoskeletal system, we have many examples of this syndrome such as rheumatoid, osteoarthritis, septic, gouty arthritis (you will learn more about them later)

Asthma is a chronic syndrome

You don't need just only to treat the acute attack of asthma, you should have maintenance treatment to prevent the chronic condition of asthma.

Atherosclerosis is chronic inflammatory response

So chronic ischemia can issue with complications in the heart and the CNS in the form of acute myocardial infarction or major strokes in your brain

- Patients sometimes need oxygen supply at home and this chronic condition propagates over months and years

Pulmonary fibrosis

Many diseases in the lungs will end up in idiopathic pulmonary fibrosis or end stage of pulmonary fibrosis

CAUSES OF INFLAMMATION:

INFECTIONS	**Bacteria, fungi, viruses, parasites And their toxins**
NECROSIS	**Ischemia, trauma, physical and chemical injuries, burns, frostbite, irradiation**
FOREIGN BODIES	**Splinters, dirt, urate crystals (gout), Cholesterol crystals (atherosclerosis)**
IMMUNE REACTIONS	**Allergies and autoimmune diseases (Misdirected inflammatory response)**

- Especially bacteria is capable of secreting toxins, endotoxins, exotoxins
- Trauma can cut your artery resulting in physical necrosis and chemical injury like sunburn
- Urate crystals will deposit in your joints especially big toe causing gouty arthritis النقرص
- The position of cholesterol clusters is the main underlying pathogenesis of the development of atherosclerosis which can cause many fatal diseases
- some people are allergic to certain medications and pollens, resulting in the exaggeration of their immune response where sever reactions occur.

RECOGNITION OF MICROBES AND DAMAGED CELLS:

- **First step in inflamm. response**
  - **Cellular receptors: Toll-like R (TLRs); on membranes and endosomes. Recognize Pathogen Associated Molecular Patterns (PAMPs)**
  - **Sensors of cell damage: recognize Damage-Associated Molecular Patterns (DAMPs) such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins gets activated (called inflammasomes)**
  - **Circulating proteins: complement system, mannose-binding lectins and collectins**

✓ Toll is the scientist who discovered TLRs

TLRs recognize something strange, foreign or weird happening by a virus or a microbe

There are sensors that recognize damaged tissues when there is necrosis or radiation or ischemia or dead tissues

Complement system and some body proteins have the ability to recognize those microbes or damaged cells

ACUTE INFLAMMATION

- 3 major components

B V dilatation

Increased V permeability

Emigration of WBCs

- The first phase of acute inflammation is the vascular phase
- The first phase is the vascular dilatation phase. However, some injured patients go through transient vasoconstriction but it continues only for few seconds and the vascular dilatation ensures.
- The second phase is increased vascular permeability where the cells, proteins and fluids will escape from the intravascular compartment to the interstitium, which will lead to edema. In addition, there are many chemical mediators which induce membrane permeability.
- The third phase is the migration or transmigration of WBCs from the intravascular compartment into the interstitium or the tissue site of injury.

Interstitium is a composite of cells, fluids, matrix proteins, and fibrils that form a network

Summary

General Features and Causes of Inflammation

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but also may cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators that are derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five Rs: (1) recognition of the injurious agent, (2) recruitment of leukocytes, (3) removal of the agent, (4) regulation (control) of the response, and (5) resolution (repair).
- The causes of inflammation include infections, tissue necrosis, foreign bodies, trauma, and immune responses.
- Epithelial cells, tissue macrophages and dendritic cells, leukocytes, and other cell types express receptors that sense the presence of microbes and necrotic cells. Circulating proteins recognize microbes that have entered the blood.
- The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

At the end of each session in the book, there are some blue summaries. They are very important brief description (memorize them)

Assess your understanding

Which of the following statements best describes the inflammatory process?

a. It is a damaging process in more than 65% of the cases
b. It is almost always beneficial and harmless
c. It is a response of vascularized tissue to injurious agents
d. It requires innate immunity to be protective
e. Viruses are the causative agents in 75% of the cases

Answer: c

In contrast to chronic inflammatory response; acute inflammatory response is characterized by?

a. Slower time to be noticed
b. More prominent local and systemic signs
c. More tissue damage and fibrosis
d. Tissue infiltration by plasma cells
e. Tissue infiltration by eosinophils

Answer: b

For any feedback, scan the code or clic

CORRECTIONS FROM PREVIOUS VERSIONS:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 20 Slide 21	"exposure to multiple **personalistic** infections" **"In the** stage of **formula** fibrosis"	"exposure to multiple **opportunistic** infections" **"End** the stage of **pulmonary** fibrosis"
V1 → V2	Slide 23 Slide 22	Diffuse **over damage** **Platelets** are mediators involved in **arthritis injury**	Diffuse **alveolar damage** **Platelets** are mediators involved in **atherosclerosis injury**
V2 -> V3	Slide 21	**In the** renal stage	**End the** renal stage

Additional Resources:

Reference Used:

1. ROBBINS and CORTAN Pathologic Basics of Disease pages (71-74)

رسالة من الفريق العلمي:

نسألك اللهم أنْ تقهر من قهر إخواننا في غزة وفلسطين، ولبنان ونسألك أن تنصرهم على القوم المجرمين.

اللهم انصرهم، وارزقهم القوة والصبر، واربط على قلوبهم، وأنزل عليهم من رحماتك.

اللهم حرر فلسطين، والمسجد الأقصى من كيد المعتدين، وكن يا الله عونا لإخواننا في فلسطين.

وصل اللهم وسلم وبارك على سيدنا محمد وعلى آله وصحبه أجمعين طيب الله أوقاتكم بطاعة الله ورسوله