



MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Pathology

teamwork 437

Granulomas Inflammation.

Color Index :-

- **VERY IMPORTANT**
- Extra explanation
- **Examples**
- **Diseases names: Underlined**
- **Definitions**



*{عاشي حكيماً، فما قيمة العلم إن كان سهواً تيسراً}

OBJECTIVES:

- **DEFINE A GRANULOMAS INFLAMMATION**
- **RECOGNIZE THE MORPHOLOGY OF GRANULOMAS , AND LIST THE CELLS THAT ARE FOUND IN IT**
- **UNDERSTAND THE PATHOGENESIS OF GRANULOMAS**
- **IDENTIFY THE TYPES OF GRANULOMAS :**
 1. **FOREIGN BODIES**
 2. **IMMUNE GRANULOMAS**
- **COMMON CAUSES OF GRANULOMAS**

GRANULOMATOUS INFLAMMATION

• Definition :

- Granulomatous inflammation is a form of **chronic inflammation** characterized by collections of **activated macrophages**, often **with T lymphocytes**, and sometimes associated with **central necrosis** (Especially in TB you see Caseous necrosis always)

-Granulomas are encountered in certain specific pathologic states. So the Recognition of the granulomatous pattern is important . **Why?** because it is limited to number of conditions (some of which are life-threatening).

-granulomas are usually 0.5 to 2.0 mm aggregations of epithelioid macrophages surrounded by a rim of lymphocytes. Epithelioid macrophages have an appearance suggestive of squamous epithelial cells due to their abundant pink cytoplasm.

• Cellular constitutes of granulomas :

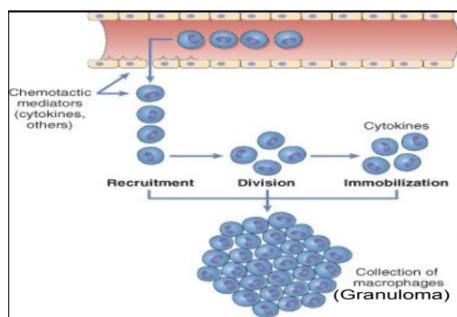
- A granuloma is a nodular collection of **epithelioid macrophages** surrounded by a **rim of T-lymphocytes**.
- Activated macrophages develop abundant pink cytoplasm and begin to resemble epithelial cells (squamous-like appearance) **epithelioid cells**
- Some activated macrophages may fuse, forming **multinucleate giant cells** (Langhans Cells most of the time).

What are **multinucleated giant cells?**

They form from the cytoplasmic **fusion** of **macrophages**.

What are **Langhans cells?**

Langhans giant cells are large cells found in **granulomatous conditions**. They are formed by the fusion of **epithelioid cells (macrophages)**, and contain nuclei arranged in a **horseshoe-shaped** pattern in the cell periphery.



لماذا تحدث ال granuloma؟ تحدث لما يدخل للجسم foreign Body وما يقدر الجهاز المناعي انه يتخلص منه، فتروح ال lymphocytes تنادي جيش من ال macrophages عشان يحدون من انتشار المايكروب ويحاولون التخلص منه، وممكن يندمجون مع بعض ويصيرون giant cells عشان يصيرون أقوى .

PATHOGENESIS

Neutrophils ordinarily remove agents that incite an acute inflammatory responses

However, there are circumstances in which reactive **neutrophils** cannot **digest the substances that provoke acute inflammation.**

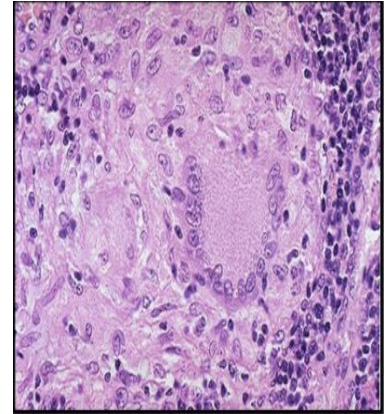
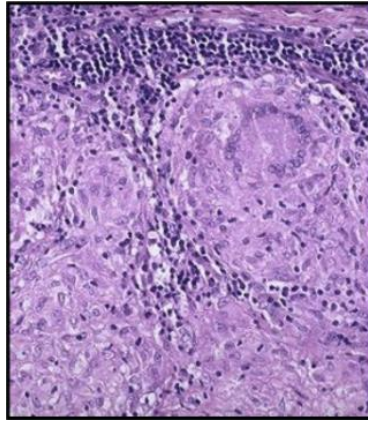
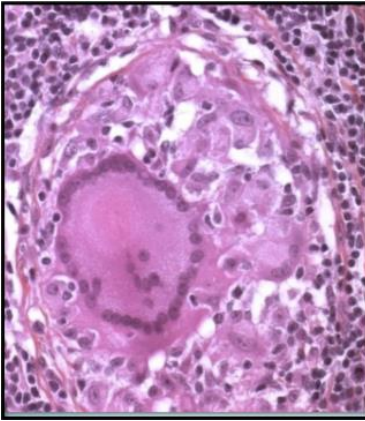
Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate.

It occurs when:

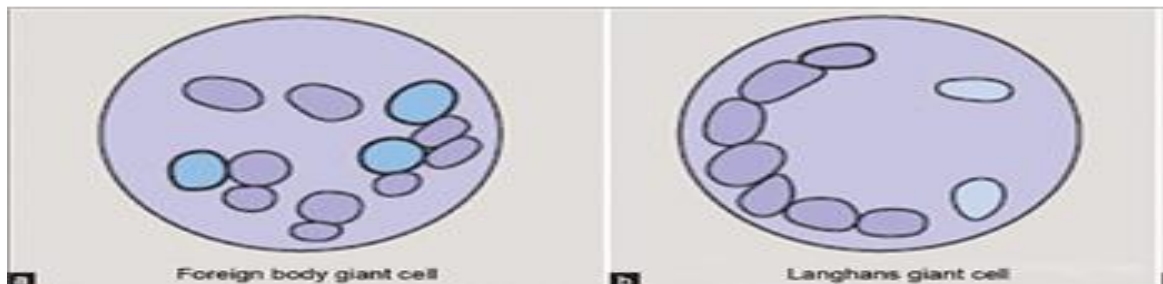
- 1) **macrophages** **phagocytose** the injurious agents but they **survive inside them.!**
- 2) an active **T-lymphocyte** mediated cellular immune response
- 3) production of **lymphokines** that inhibit the migration of macrophages and cause them to aggregate in the area of injury and form granulomas.

Granulomas inflammation is associated with Type 4 (IV) Hypersensitivity

Langhans giant cell

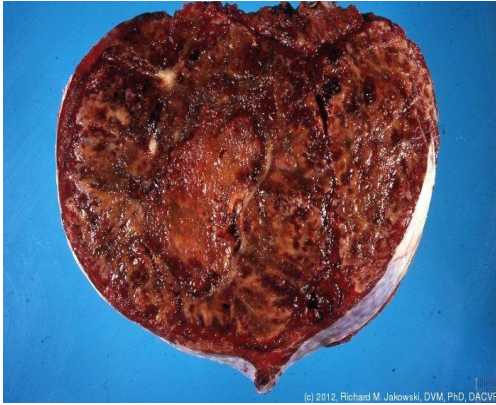


- The nuclei of **giant cells** are arranged either peripherally (**Langhans-type giant cell**) or haphazardly (**foreign body-type giant cell**).



- Granulomas associated with certain infectious organisms (classically ***Mycobacterium tuberculosis***) often contain a central zone of necrosis.
- Grossly, this has a granular, **cheesy appearance** and is therefore called **caseous necrosis**.
- Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with loss of cellular details.
- The granulomas in **Crohn disease, sarcoidosis**, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating.
- Healing of granulomas is accompanied by **fibrosis** that may be extensive.

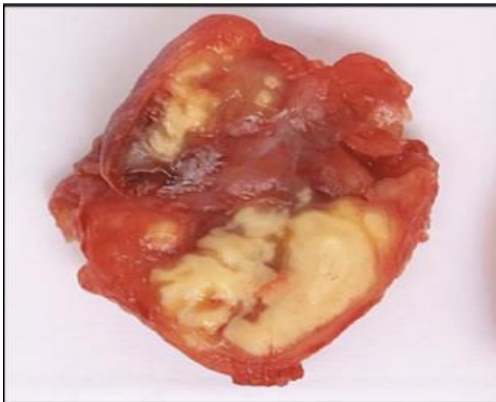
non-caseating
granulomas of the
spleen



Caseous necrosis of the
lung



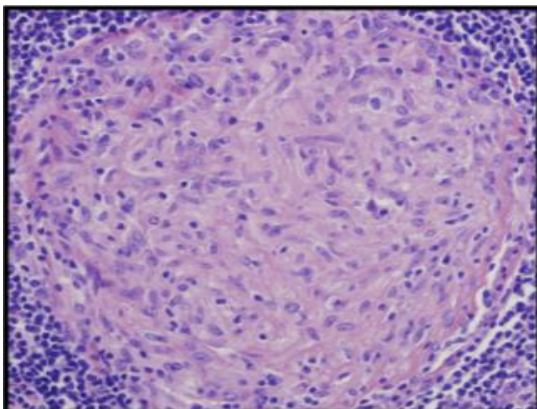
Lymph node



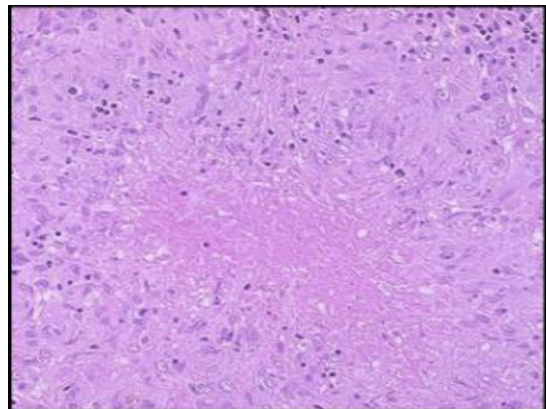
Adrenal gland



Noncaseating granuloma

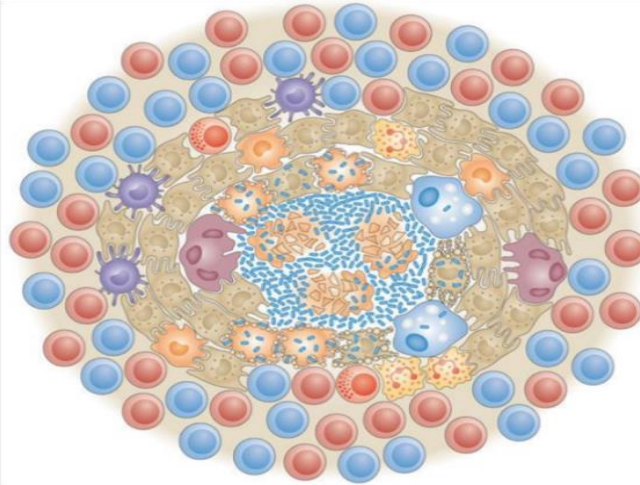
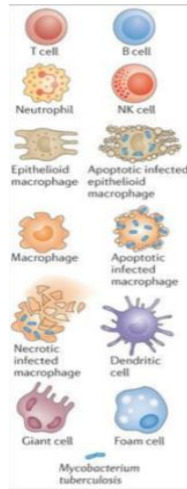


Caseating granuloma



DISTINCTIVE CELLS FOUND IN GRANULOMA

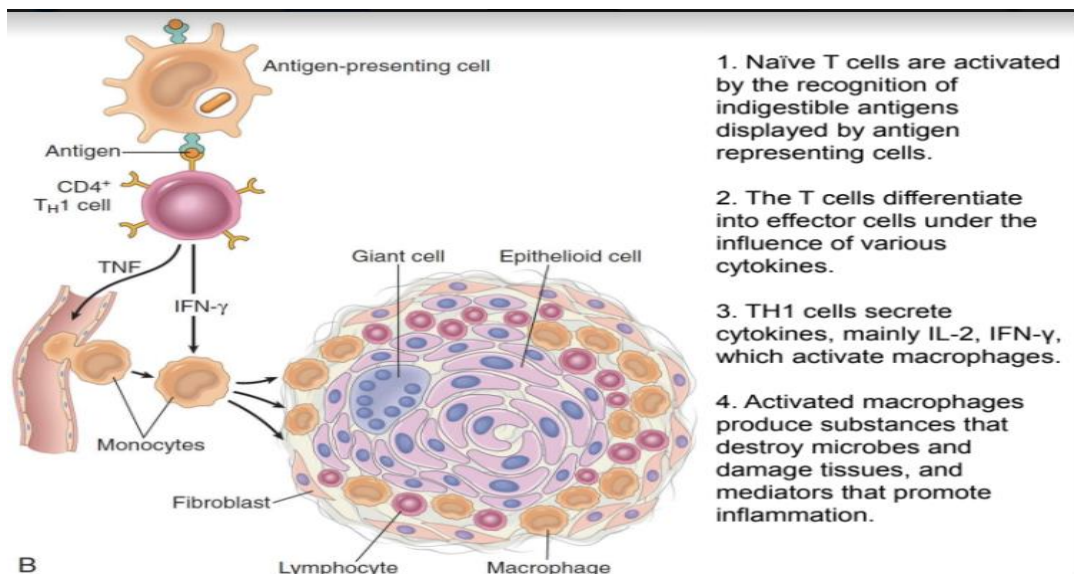
- **Epithelioid histiocytes** (Epithelioid cells): are **activated macrophages** that resemble an essential characteristic of granuloma and are surrounded by a rim of lymphocyte.
- **Lymphocytes**: mediate cellular immune response.
- **Macrophages**: phagocytose the injurious agent



Granuloma of TB Nature Reviews | Immunology

The macrophages have different name in different tissues but basically all are Macrophages.

Macrophages In Granulomas called - **Epithelioid cells**



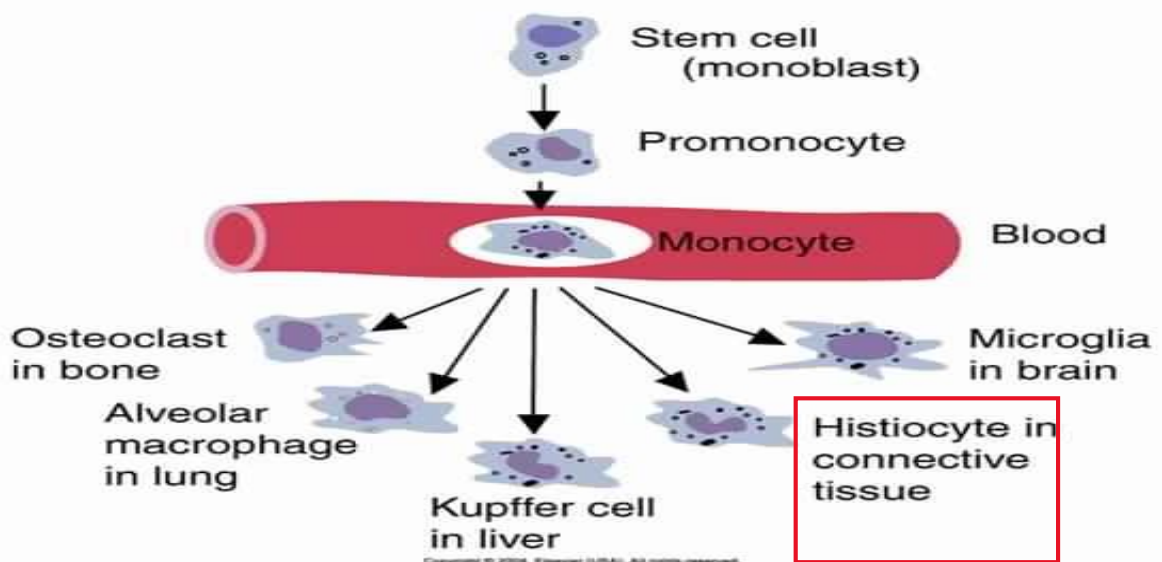
The difference between macrophage and histiocyte

is that macrophage is (immunology|cytology) a white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink it presents foreign antigens on MHC II to lymphocytes part of the innate immune system while histiocyte is a macrophage, derived from bone marrow, found in connective tissue.

The difference between macrophage and lymphocytes.

A macrophage is the first cell to recognize and engulf foreign substances (antigens). Macrophages break down these substances and present the smaller proteins to the \longrightarrow T lymphocytes. (T cells are programmed to recognize, respond to and remember antigens).

Origin and Development of Macrophages



TYPES AND CAUSES OF GRANULOMAS:

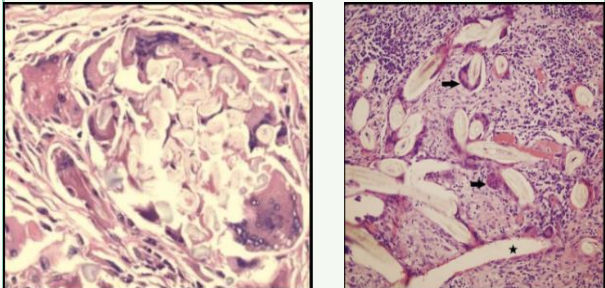
Immune granuloma	Foreign body granuloma
<ul style="list-style-type: none"> They are caused by a variety of agents that are capable of inducing a persistent T cell-mediated immune response. It occurs when the inciting agent cannot be readily eliminated, such as a persistent microbe or a self antigen. Macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which activates the macrophages. 	<ul style="list-style-type: none"> They are seen in response to relatively inert foreign bodies, in the absence of T cell-mediated immune responses they do not incite a specific immune response. They form around materials such as talc (associated with intravenous drug abuse), sutures, or other fibers that are large enough to preclude phagocytosis by a macrophage. The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it may appear refractile.
<ul style="list-style-type: none"> Bacteria <ul style="list-style-type: none"> <u>Tuberculosis</u> <u>Leprosy</u> <u>Actinomycosis</u> <u>Cat scratch disease</u> Fungi <ul style="list-style-type: none"> <u>Blastomycosis</u> <u>Histoplasmosis</u> Parasites <ul style="list-style-type: none"> <u>Schistosomiasis</u> <u>Leishmaniasis</u> Metals/Dust <ul style="list-style-type: none"> <u>Berylliosis</u> Others <ul style="list-style-type: none"> <u>Crohn's disease</u> <u>Sarcoidosis</u> 	<ul style="list-style-type: none"> Talc شيء غريب يستخدم في شم المخدرات Sutures Graft material Hair shafts
	

Table 2-8 Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	<i>Mycobacterium leproe</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease	Immune reaction against intestinal bacteria, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

TUBERCULOSIS AND GRANULOMA

Tuberculosis (TB) is an infectious disease caused by the bacterium **Mycobacteria tuberculosis bacteria**(MTB).

Tuberculosis generally affects the lungs, but can also affect other parts of the body.

• **Mycobacterium tuberculosis :**

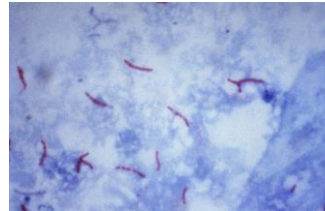
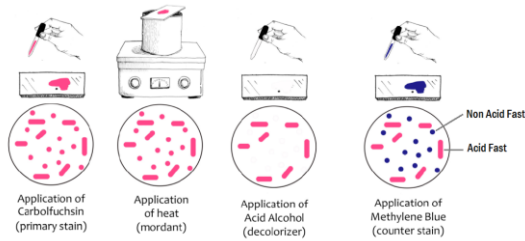
-Mycobacteria – ‘fungus like are slender rods.. (اول شيء كانوا يحسبونها فطريات)

-called: **acid fast bacilli** [AFB] (i.e., they have a high content of complex lipids that readily bind the **Ziehl-Neelsen** [carbol fuchsin] **stain** and subsequently resist decolorization).

الـ TB له staining خاص فيه اسمه Acid Fast bacilli (or ZN stain)

الـ Mycobacterium tuberculosis ما يصير لها Decolorization زي الـ Gram + ولا يصبغها الـ Crystal violet زي الـ Gram -

بس عندها glycolipids في الـ cell wall ترتبط مع الـ ZN stain فاللون بالنهاية يطلع pink للبكتيريا و blue لكل شيء حولها



• **Pathogenesis of TB :**

- **Cord factor is a glycolipid molecule** found in the cell wall of Mycobacterium tuberculosis and similar species.

-It protects M. tuberculosis from the defenses of the host and prevents fusion between phagosomal vesicles.

-Cord factor presence increases the production of the cytokines:

• **interleukin-12 (IL-12)** • **IL-1 β** • **IL-6** • **TNF**

which are all pro-inflammatory cytokines important for granuloma formation



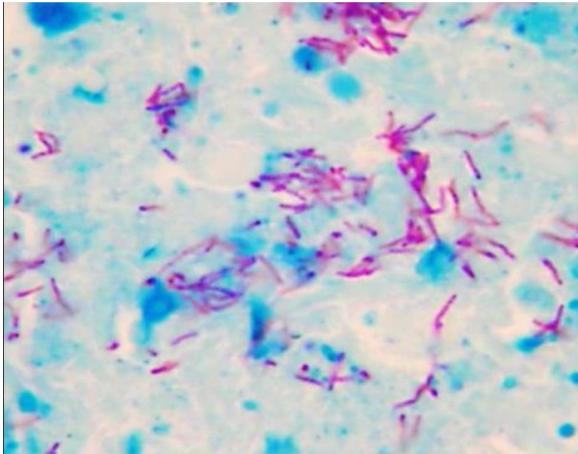
Gross pathology



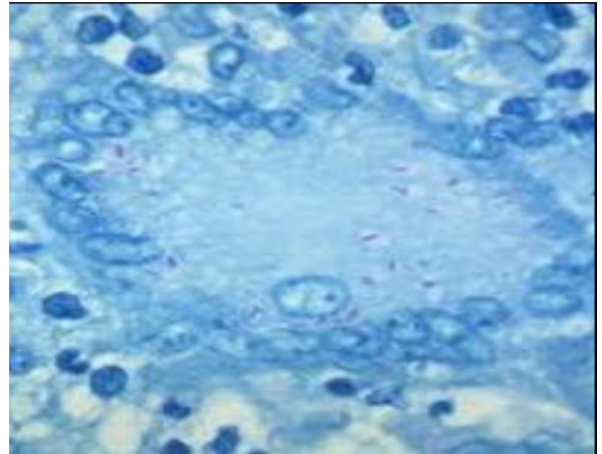
Chest X-ray



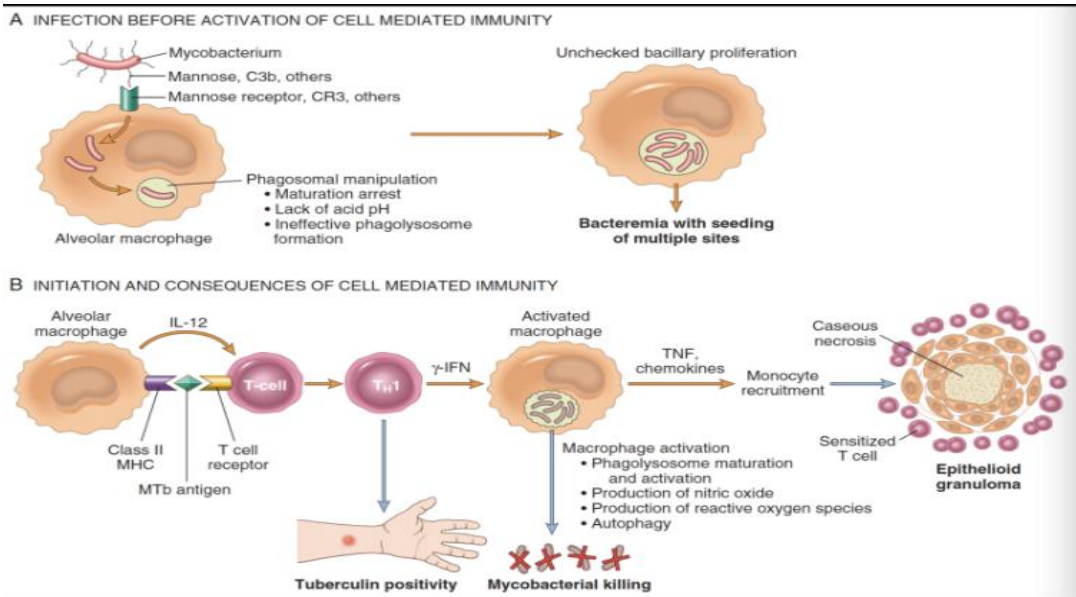
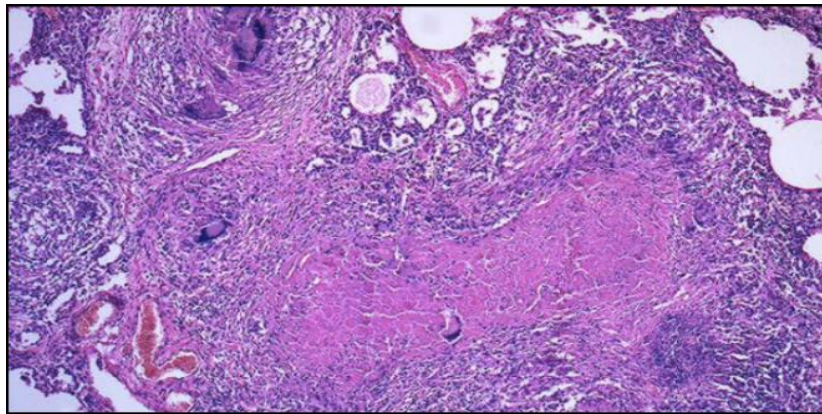
M. Tuberculosis in tissue section



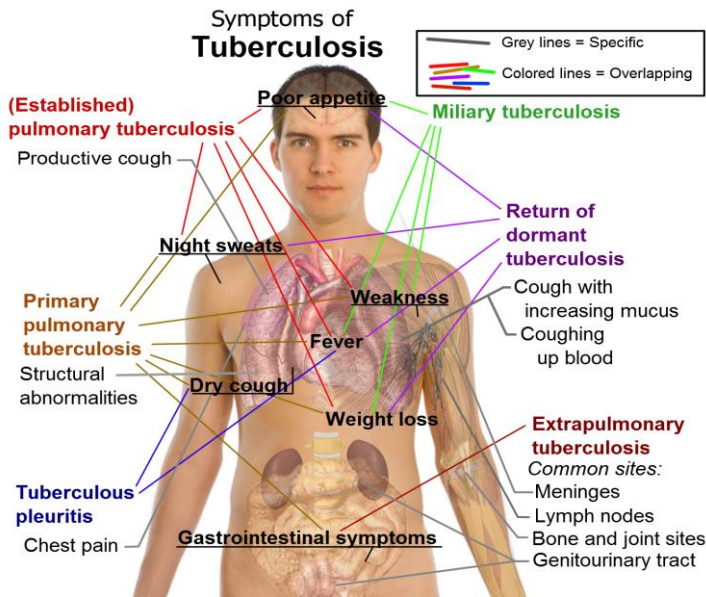
M. Tuberculosis in tissue section



Tuberculosis



- Signs and Symptoms of TB (Organized in the new few slides)



Any long-standing cough with or without fever could be Tuberculosis (TB)!

Do you have...



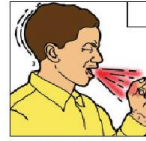
...a cough longer than 14 days?



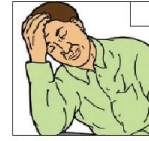
...fever of long duration?



...shortness of breath?



...blood in your cough?



...tiredness?



...chest pain?



...loss of appetite?

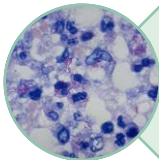


...weight loss?



...night sweats?

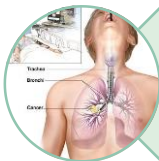
- Diagnosis of TB :



Sputum smear

- Acid fast stain (>10,000 CFU/ml)

• هذا الـ ZN stain



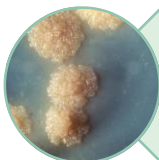
Bronchoscopy



Chest X-Ray



Tuberculin skin testing (TST)



Culture

FIG. 3.15

Estimates of the case fatality ratio (CFR), (including HIV-negative and HIV-positive people), 2015

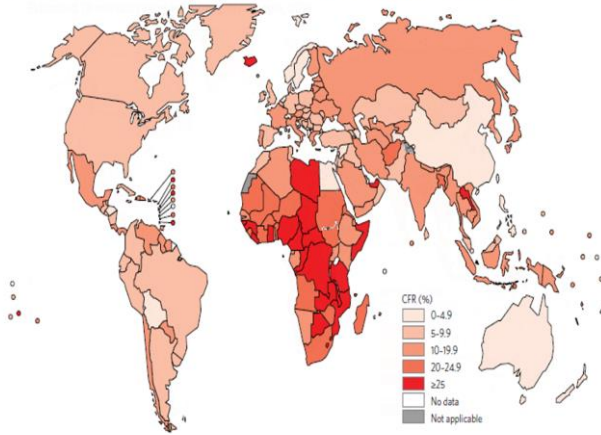
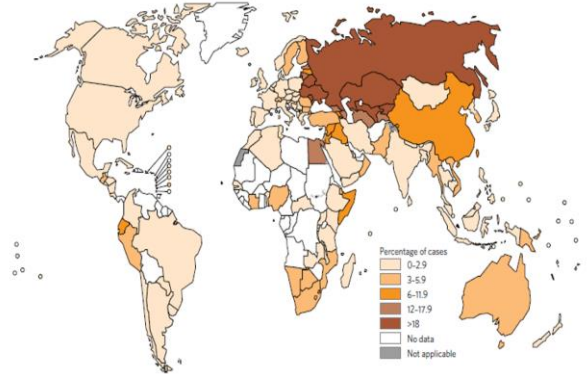


FIG. 3.18

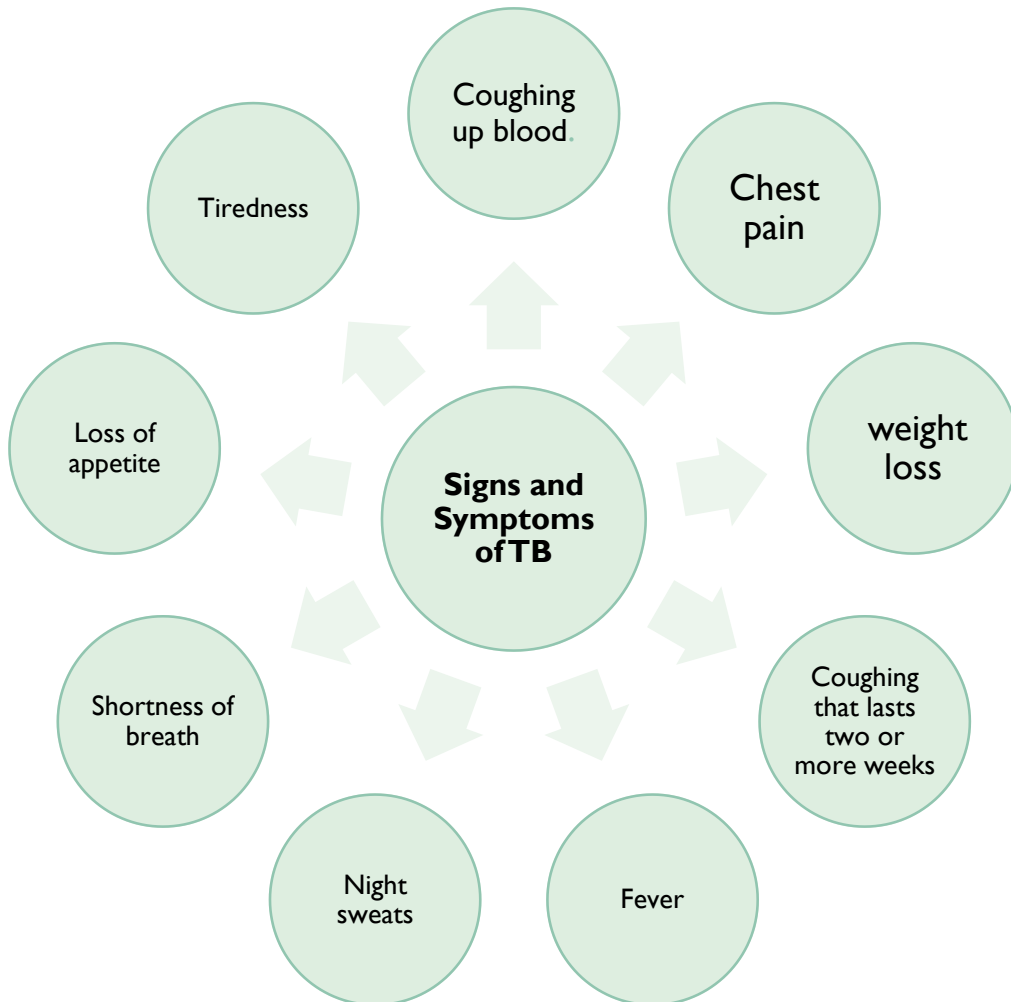
Percentage of new TB cases with MDR/RR-TB*



* Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2001 are not shown.

This is just to appreciate the prevalence of TB , no need to look at it 😊

Symptoms and signs of TB



The next slides are just to appreciate the prevalence of TB in KSA
 ..Which is important for you! As a doctor ☺

PREVALENCE OF TB IN KSA AND WORLDWIDE

Cases :

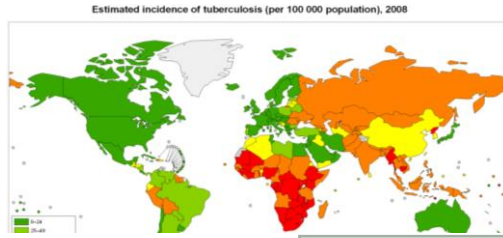
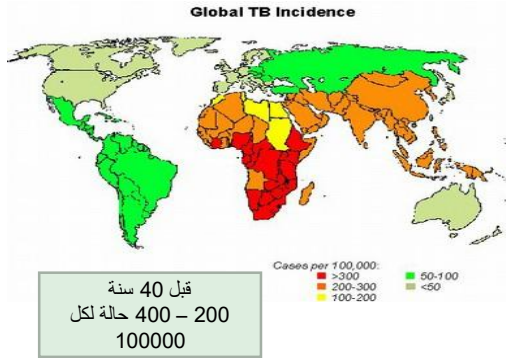
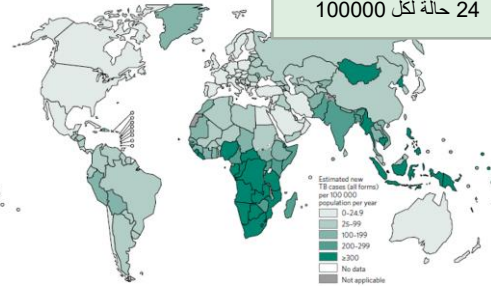


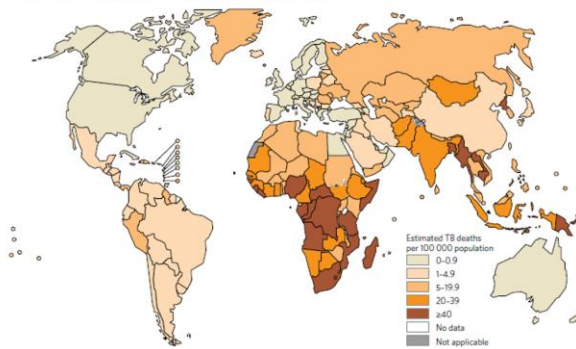
FIG. 3.3
 Estimated TB incidence rates, 2015



في 2008 و 2015 اقل من
 24 حالة لكل
 100000

Case fatality :

FIG. 3.12
 Estimated TB mortality rates in HIV-negative people, 2015

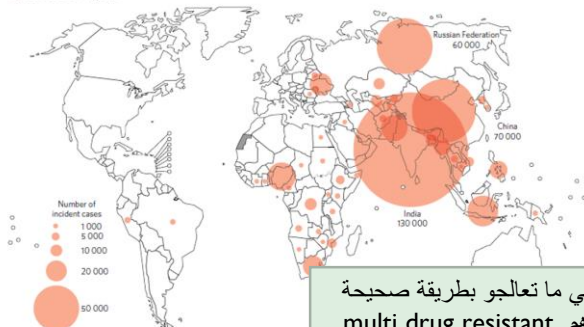


1- 4.9 اشخاص يموتون
 بسبب الـ TB من 10000

تعتمد على

- التشخيص الصحيح و وقته (مبكر - متأخر)
 - جودة العلاج و تحديده وطريقة اعطائه للمريض

FIG. 3.20
 Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.



المرضى الي ما تعالجو بطريقة صحيحة
 يصير عندهم multi drug resistant
 هنا يوريك اماكنهم ونسبتهم (لا تخاف ما
 فيه عندنا حتى هذه اللحظة)

عند معالجة المصاب بالـ TB بشكل خاطئ (يقوله فيك
 التهاب عادي و يعطيه Antibiotics) يصير للبكتيريا
 المسببة للـ TB مقاومة ضد كل Antibiotic ياخذ
 المريض
 و بالاخير بيطلع لنا بكتيريا مقاومة لكل انواع المضادات
 تسبب TB (Multi drug resistant)
 التشخيص مهم جدا علشان يعطى الطبيب مريضه كورس
 مناسب يعالجه

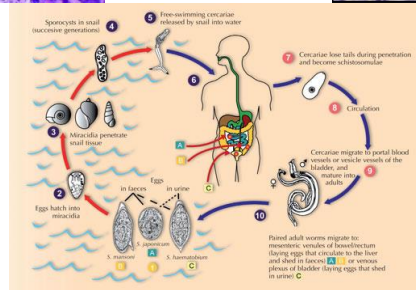
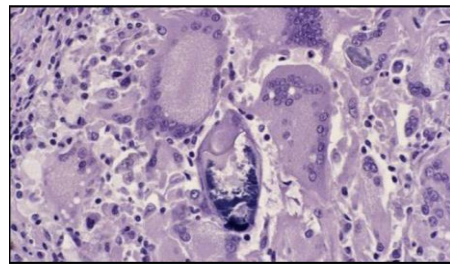
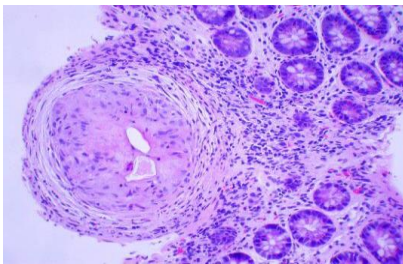
OTHER DISEASES ASSOCIATED WITH GRANULOMAS

- **Schistosomiasis**

- most commonly found in Asia, Africa and South America.

- **Schistosoma mansoni** parasites penetrate the **skin** but eventually **localize in blood vessels** of the **portal system** and **mesentery**, damaging the liver and intestine.

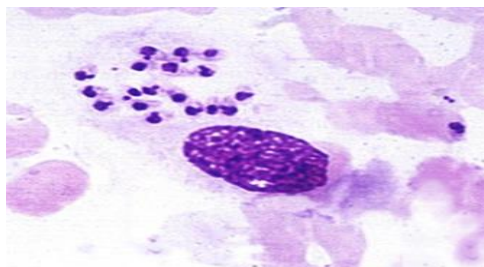
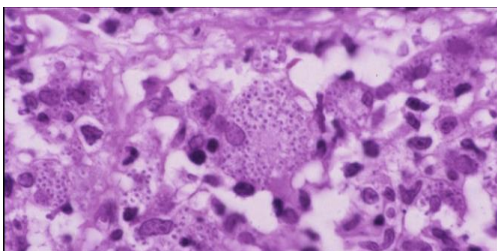
- Schistosoma haematobium also penetrates the skin, but localizes to the urinary bladder and causes cystitis



- **Leishmaniasis**

- common in all tropical countries.

- It causes a cutaneous, mucocutaneous or visceral disease.

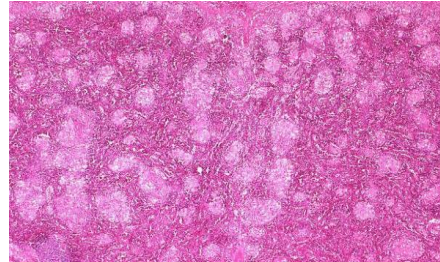


- **Leprosy**

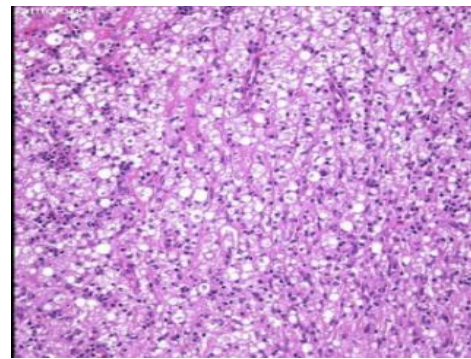
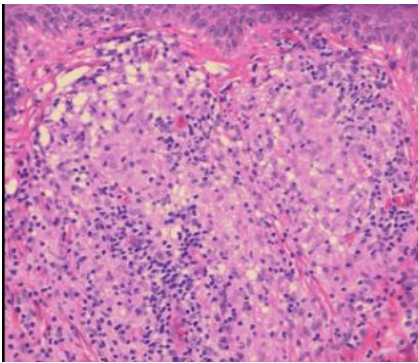
- endemic in tropical countries.
- It causes a chronic cutaneous infection.
- It is transmitted by nasal discharges and dermal contact.



Tuberculoid leprosy

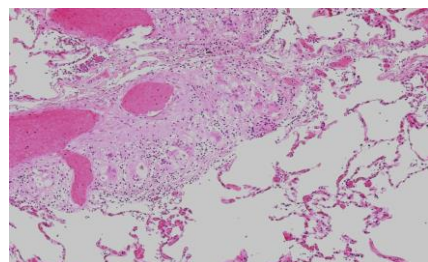
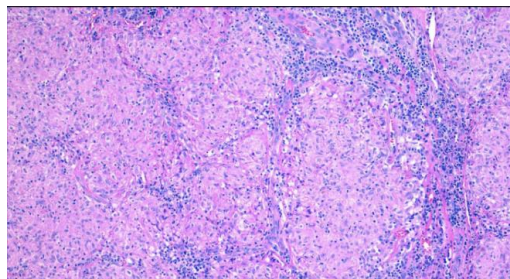


Lepromatous leprosy



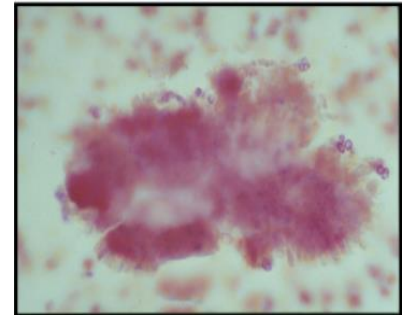
- **Sarcoidosis**

- A multisystem disease of unknown origin that involves lung or bilateral hilar lymph nodes in 90% of cases
- It causes **noncaseating epithelioid granulomas**.



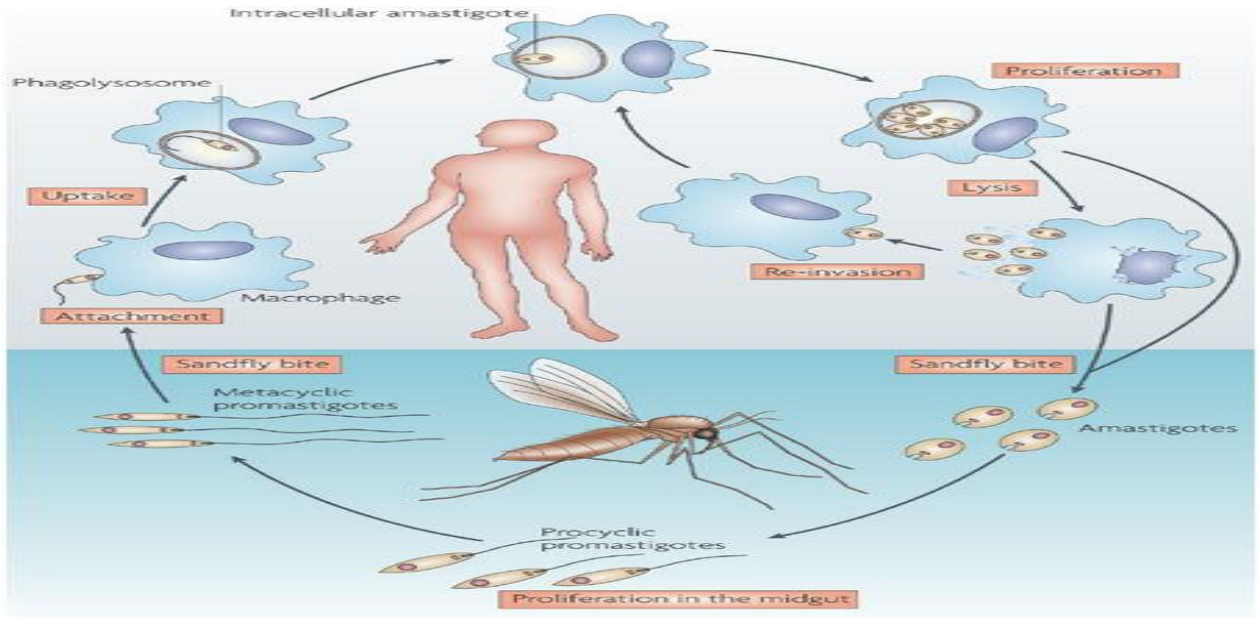
Actinomycosis:

- a long-term (chronic) granulomatous bacterial infection.
- It is caused by filamentous, gram-positive, non-acid-fast, anaerobic-to-microaerophilic bacteria.
- It commonly affects the face and neck.
- Examination of drained fluid from an abscess under a microscope shows "sulfur granules" in the fluid. They are yellowish granules made of clumped organisms.



Schistosomiasis	Leishmaniasis	Leprosy	Sarcoidosis	Actinomycosis
<ul style="list-style-type: none"> • most commonly found in Asia, Africa and South America. • Schistosoma mansoni parasites penetrate the skin but eventually localize in blood vessels of the portal system and mesentery, damaging the liver and intestine. • Schistosoma haematobium also penetrates the skin, but localizes to the urinary bladder and causes cystitis. 	<ul style="list-style-type: none"> • common in all tropical countries. • It causes a cutaneous, mucocutaneous or visceral disease. 	<ul style="list-style-type: none"> • endemic in tropical countries. • It causes a chronic cutaneous infection. • It is transmitted by nasal discharges and dermal contact. 	<ul style="list-style-type: none"> • A multisystem disease of unknown origin that involves lung or bilateral hilar lymph nodes in 90% of cases. • It causes noncaseating epithelioid granulomas. 	<ul style="list-style-type: none"> -a long-term (chronic) granulomatous bacterial infection. - It is caused by filamentous, gram-positive, non-acid-fast, anaerobic-to-microaerophilic bacteria. - It commonly affects the face and neck.

Leishmaniasis pathogenesis



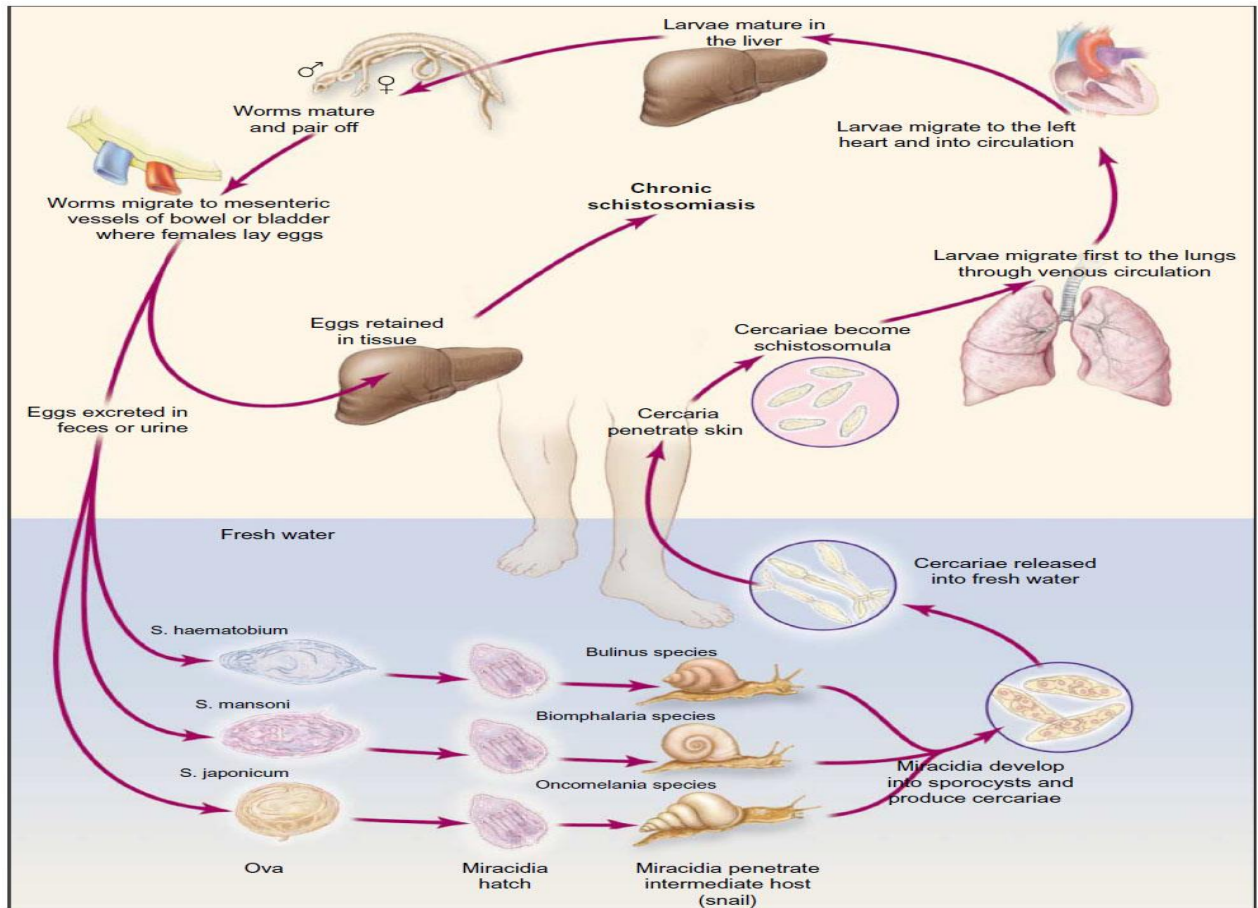
Nature Reviews | Microbiology

فيديو يشرح كل شيء نحتاجه عن TB و زيادة



Schistosomiasis pathogenesis

CURRENT CONCEPTS



MCQ'S (TEST YOURSELF !)

- **1) are incited by relatively inert foreign bodies.?**
 - a) Immune granuloma
 - b) Foreign body granuloma
 - 4) granuloma in Leprosy is very similar to the one in Tuberculosis expect for ?
 - a) Necrosis
 - b) Lymphocytes
 - c) Epithelioid histiocytes
 - d) Multinucleated cell
- **2) fungi that have the ability to cause granuloma?**
 - a) Histoplasmosis.
 - b) Blastomycosis
 - c) Leprosy
 - d) A&B
 - 5) type of granuloma associated with intravenous drug abuse?
 - a) talc
 - b) Blastomycosis
 - c) Leprosy
 - d) Cat-scratch disease
- **3) type of granuloma that is caused by sand fly?**
 - a) Leishmaniosis
 - b) Blastomycosis
 - c) Leprosy
 - d) Tuberculosis
 - 6) Which of the following diseases does not cause a granulomatous inflammation?
 - a) Cat-scratch disease
 - b) Actinomycosis
 - c) Sarcoidosis
 - d) Leishmaniasis
 - e) Staphylococcus infection

1-b
2-d
3-a
4-a
5-a
6-e

MATCHING THE NUMBER WITH LETTER

- 1. The most important cell in granulomatous inflammation?**
- 2. A cytokines that is important inactivating macrophages and transforming them into epithelioid cells**
- 3. Multinucleated cells in TB**
- 4. Antigen presenting cells**
- 5. Pathogenesis of immune type granulomatous inflammation**
- 6. Microscopic finding of TB**
- 7. Found In the cell wall of mycobacteria**

- a) IFN- γ .**
- b) Langhans cells**
- c) Epithelioid histiocytes**
- d) Cord factor**
- e) Langerhan's cells**
- f) Type IV hypersensitivity reaction**
- g) Caseating granuloma**

1-c
2-a
3-b
4-e
5-f
6-g
7-d

- 1- What are the common causes of a caseous necrosis?

Tuberculosis, leprosy, and fungal infections.

- 2- What is the origin of epithelioid cells?

They are transformed (activated) macrophages.

- 3- How does a caseous necrosis differ from a coagulative necrosis under the microscope?

In caseous necrosis, there is total loss of tissue structure, whereas in coagulative necrosis, the cell outlines are retained.

- 4- What is the difference between granulation tissue and granulomatous inflammation?

Granulation tissue contains new small blood vessels, fibroblasts, and mononuclear cells in an edematous extracellular matrix; it is part of the repair response. A granuloma is a circumscribed collection of epithelioid cells, usually surrounded by lymphocytes and it is a form of chronic inflammation.

- 5- What are the common causes of granulomatous inflammation?

Bacterial (e.g. *Mycobacterium tuberculosis*, *M. leprae*, *Treponema pallidum*)

Parasitic (e.g. Schistosomiasis)

Fungal (e.g., Histoplasmosis, Blastomycosis)

Inorganic dusts (e.g. Silicosis, Berylliosis)

Foreign body

Unknown (e.g. Sarcoidosis)

- 6- How are giant cells formed in granulomas?

Giant cells are formed by fusion of macrophages.

- 7- What are the other cells in a granuloma?

Lymphocytes, mainly CD4+, that caused the granulomatous reaction, are present. Healing granulomas are surrounded by fibroblasts.

- 8- In tuberculosis infection do granulomas in different organs look different?

No, all granulomas look similar.

MEMBERS :

Females:

-Leader : بثينة آل ماجد

- روان الربيعي
- وفاء العتيبي
- الجوهرة الشنيفي
- رزان الزهراني
- رهف الشمري
- روان مشعل
- منيرة المسعود
- لميس السويلم
- نوف العتيبي
- رزان الزهراني
- هديل عورتاني
- فاطمة بالشرف
- ابتسام المطيري
- رناد الفرهم
- غرام جليدان
- بلقيس الرزجي
- نورة القاضي
- آلاء الصويغ
- ريم القحطاني
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- أحمد الراشد
- عبدالله بالعبيد
- عبدالله السرجاني
- أحمد الربيعي
- أنس السيف
- داود إسماعيل
- خالد الدوسري
- فهد الفايز
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Kindly contact us if you have any questions/comments and suggestions:

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*** TWITTER: [@pathology437](https://twitter.com/pathology437)**

GOOD LUCK! 😊

Resources:-

- 1- Females slides
- 2- Robbins reference book

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