

وَقُلْ رَبِّ زِدْنِي عِلْمًا



RESPIRATORY SYSTEM

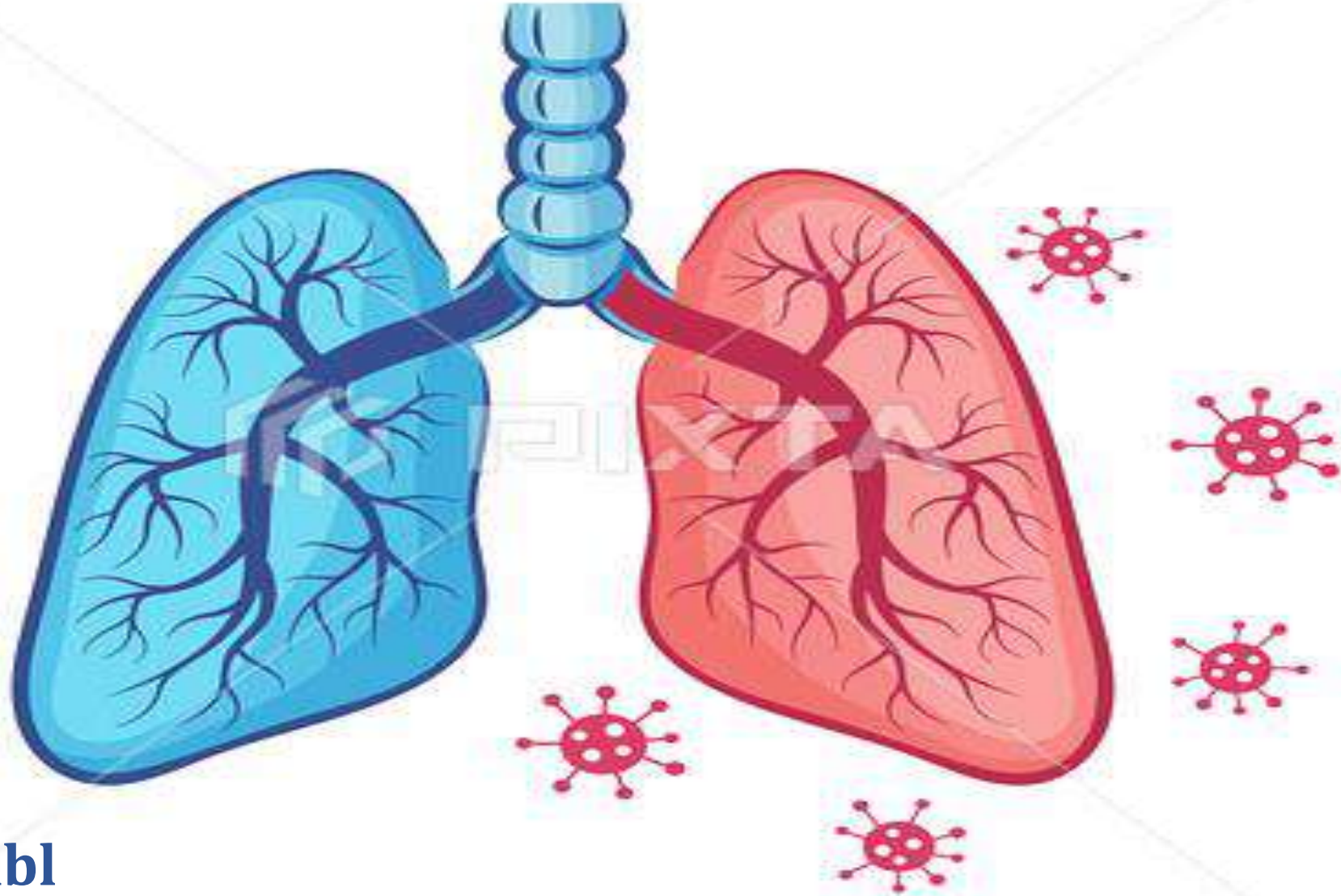
HAYAT BATCH

SUBJECT : _____

LEC NO. : 4 _____

DONE BY : Tabark Aldaboubi
Raneem Azzam

RESPIRATORY TRACT INFECTIONS - IV



By
Prof. Hala Tabl

Mycobacteria

Mycobacteria
Mycobacteria
Mycobacteria

لما بزرها على Fluid media بتكون زي شكل ال Fungi بس هي بكتيريا
سموها صلب لأنها Strict aerob

Medically important Mycobacteria

**M. tuberculosis*

**M. bovis*

السَّلح
Causative agents of tuberculosis in man

**M. Leprae*

→ Causative agent of

الجَنَام

**Atypical mycobacteria*

جَطْعَة شَغْف
نكمل بها ما تبقى من الحياة

General characters of Mycobacteria:

bacilli

➤ Slender rods, non-spore forming, strictly aerobic.

Cell wall مكون من Lipid بنسبة (40-60%) بتخليق hydrophobic من بكتل مويك انما تنصبغ بال gram stain ليعتصها صبغات خاصة

➤ Difficult to stain with ordinary stains (e.g. Gram stain) because of a **high lipid content (mycolic acid)**

(40-60%) in the cell wall.

لها 3 خطوات: [1] يستخدم Primary stain لونها احمر
[2] Acid decolorization with acid يستخدم يزيل اللون المشترك
[3] Counter stain صبغة لونها ازرق

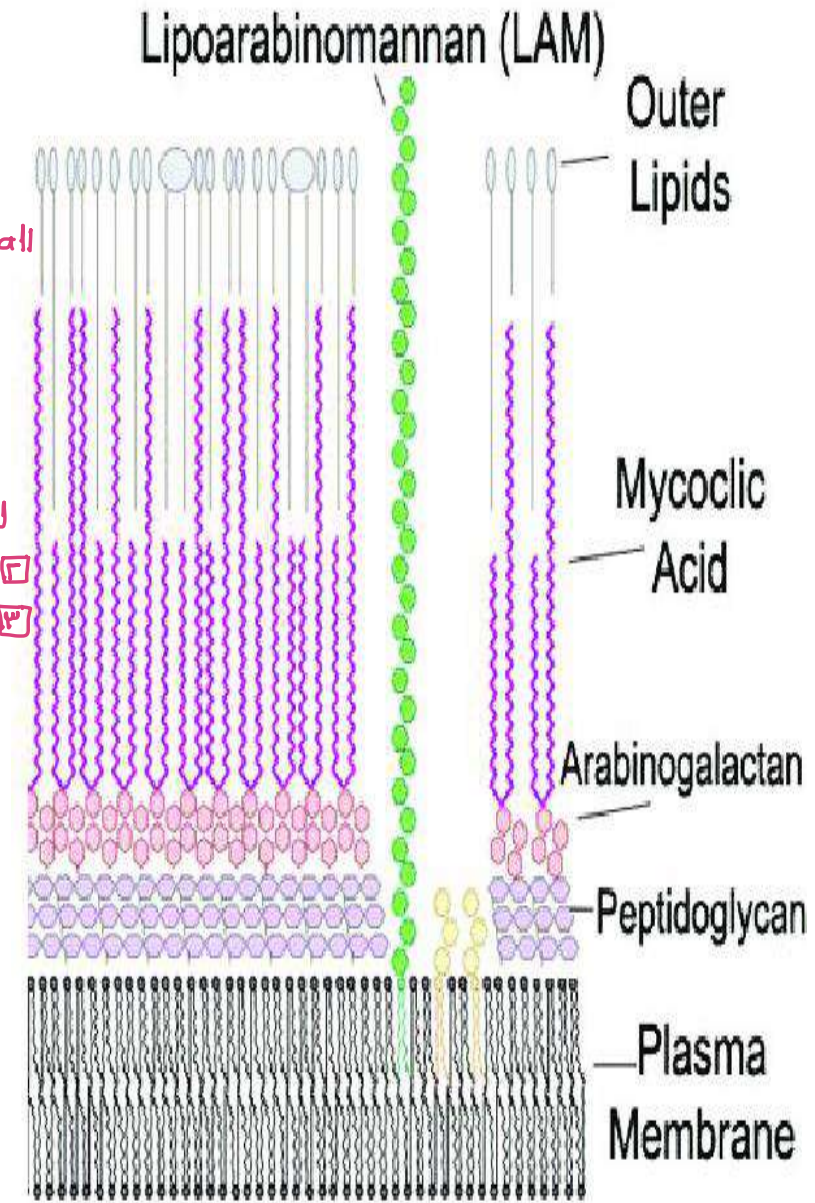
➤ Stained with special stain **Ziehl-Neelsen (Z.N)** that depend on application of heat and concentrated dye.

يعتمد على الحرارة وتركيز الصبغة فيزيدوا ال penetration of stain across lipid layer

➤ Once stained , they retain the stain and resist decolorization with acids, that is why described as

بهاي الخضوة كل الشريحة بتولئ اللوك ويتصبغ

“ **acid fast bacilli** “ (AFB). بمصبغة ال Counter واعدا ال organism نفسه بقبل احمر



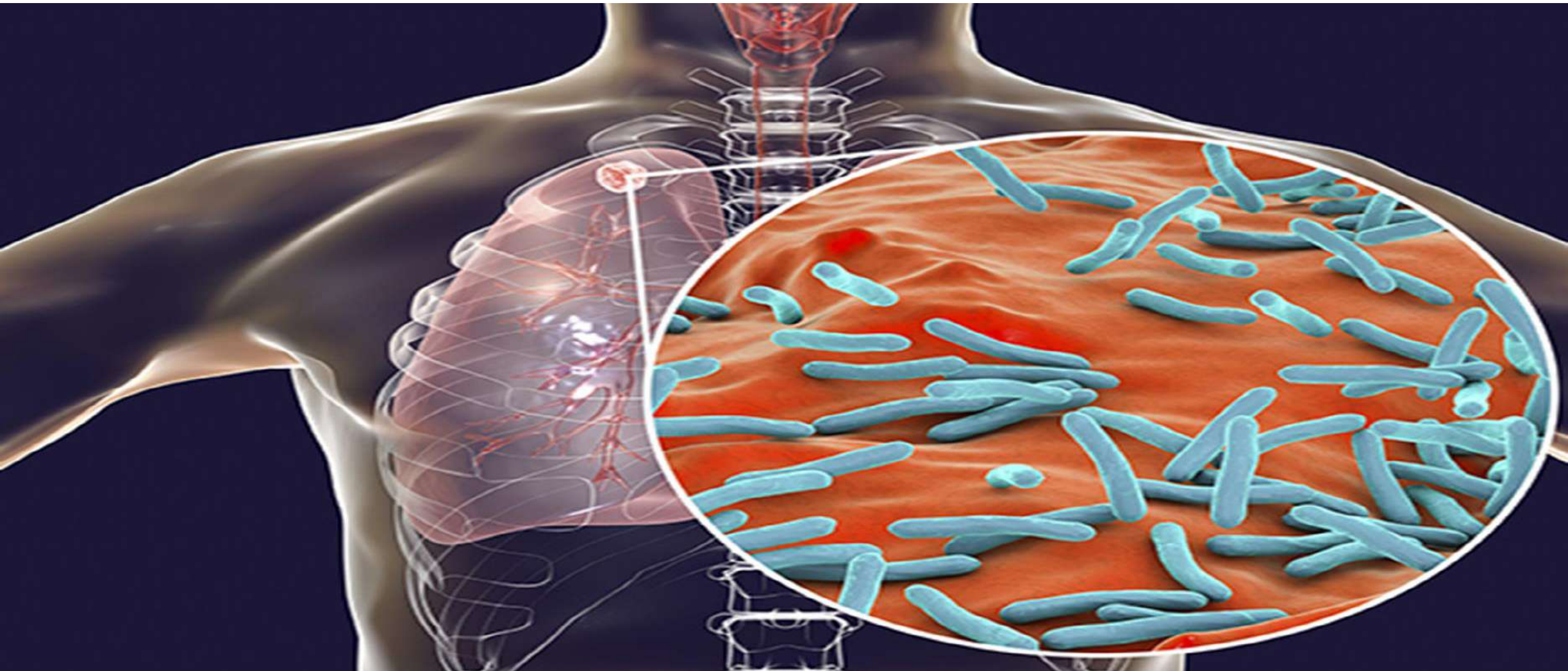
ال organism بتخزن يمسكها decolorization ويتمسك بلونها.

MYCOBACTERIUM TUBERCULOSIS

اسم العالم الحي وصفها هي البكتيريا

← “Tubercle bacillus” “Koch bacillus”

Small Swelling
Granuloma بنوع



Morphology:

التي محافظة على لونها وما حار لها discoloration هي البكتيريا

➤ Thin straight or slightly curved rods.

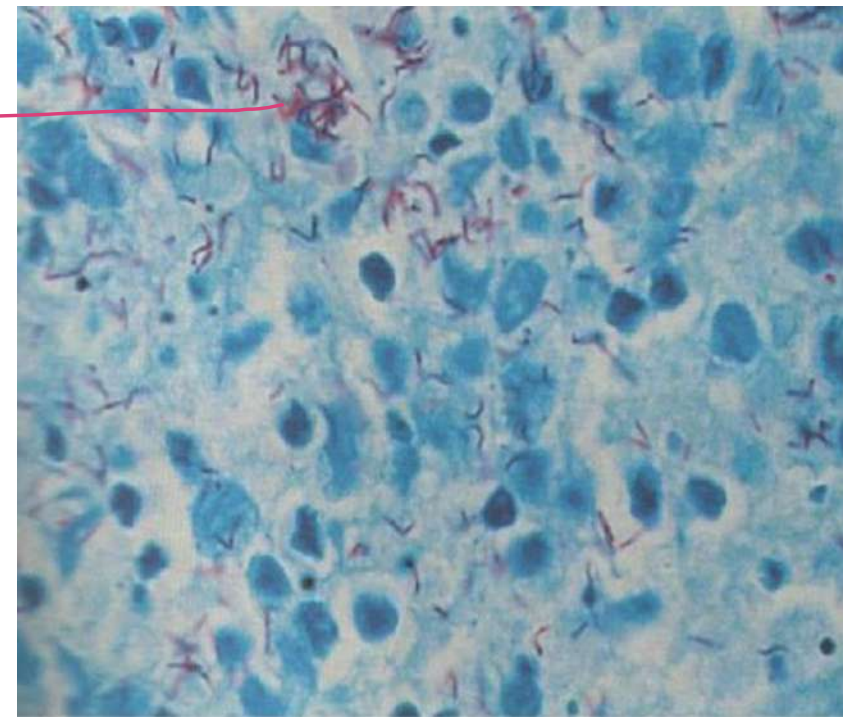
➤ Non motile, non-sporing and non-capsulated.

بدل عن صبغة ال Z.N بين لتفرقة عن ال Z.N انما هي بتستخدم درجات حرارة منخفضة

➤ They stained by **Z.N (Hot)** or **Kinyoun (Cold)** stain and appear as thin **pink rods** arranged singly or in small groups **in a contrasting blue background.**

هي المصبغة بتصبغ البكتيريا بلون اصفر وال background اسود ويتونها بال
Fluorescent microscope

➤ They can be stained by **fluorochrome** (fluorescent) stains (e.g. auramine, rodamine).



Cultural characters:

(oxygenated area) infection to upper lobe ← *مناطق الأكسجين نفسها ليشن بتعمل*

➤ They are **obligate aerobe** (upper lobe of the lung).

➤ They are **slow growers**, growth appears after 4-6 weeks
بدها وقت طويل حتى تنمو بعد زراعتها (ليش عكس باقي البكتيريا الي بدها يوم او اقل) لانها بدها 18 ساعة حتى يصير لها تخماعات
(doubling time 18 hs in contrast to <1 hour in most bacteria).

➤ Types of media: → *ما بنوع على ال media ordinary*

مكونت من البيض

1) Egg based media such as **Lowenstein-Jensen (L-J)** medium & Dorset's egg medium.

اسرع من ال media لكي فوق بدها 3 اسابيع

2) ↑ Agar based media e.g. Middlebrook's 7H10, 7H11 agar.

3) Fluid media e.g., Middlebrook's 7H9.



L-J medium

Resistance & Sensitivity:

*They are highly resistant to :

سبب ال lipid الي بال cell wall
الي يتمنع ال diffusion تاخذ المواد

• Dryness (survives in dried sputum for long periods). →

لصليق بنلاقي ال organism بقل survives

خارج الجسم حتى بعد ما ال sputum ينشف لمدة طويلة

• Chemicals, many acids and alkalis.

• Antibiotics.

*They are killed by:

• Sunlight →

لهيكن اي بين في مريضنا سئل ينصحوهم بفتحوا المشابيل ، والنقوس للشمس → الاشعة اليرنيا

• U.V. rays

• 5%phenol , Chlorine

• Heat (60°C for 20 min.) (Pasteurization can kill them in milk).

خطوة مهمة ب prevention of these disease خصوصا اننا bovin strain

Virulence Factors:

1. **High lipid of cell wall (Mycolic acids)**, responsible for:

Resistance to: Antibiotics, acidic and alkaline compounds, Osmotic lysis via complement.

ال lipid يمنع ال diffusion تام اغلب المواد وال Antibiotics

2. **Cord factor:** Virulent strains grow in a characteristic

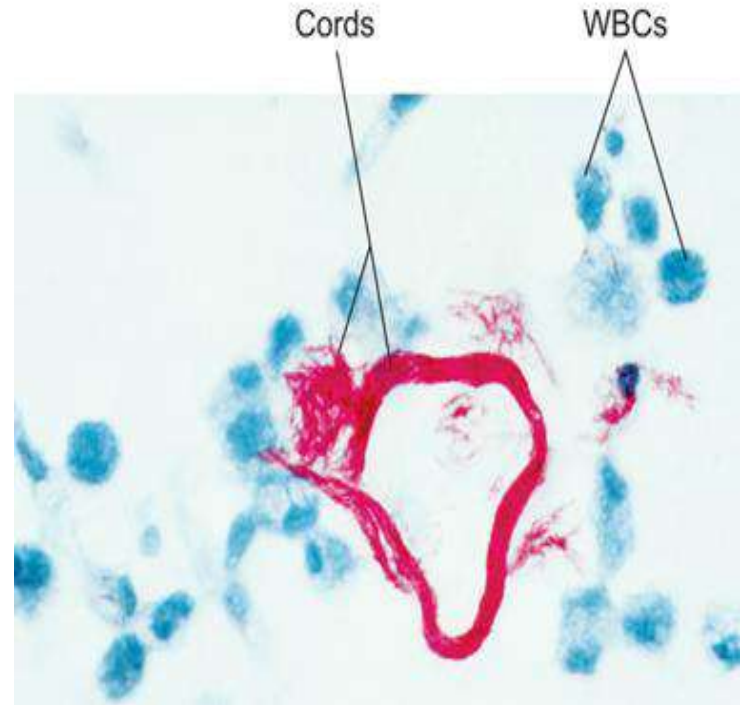
“Serpentine” cordlike pattern.

بخلي ال organism تنمو في تجمعات ، تكتلات .
يقوم بنفس العملية وجود ال lipid (يمنع دخول المواد)

3. **Exported repetitive protein Erp & PkAg:**

Inhibit phago-lysosomal fusion.

→ The main pathogenesis of TB



Pathogenesis:

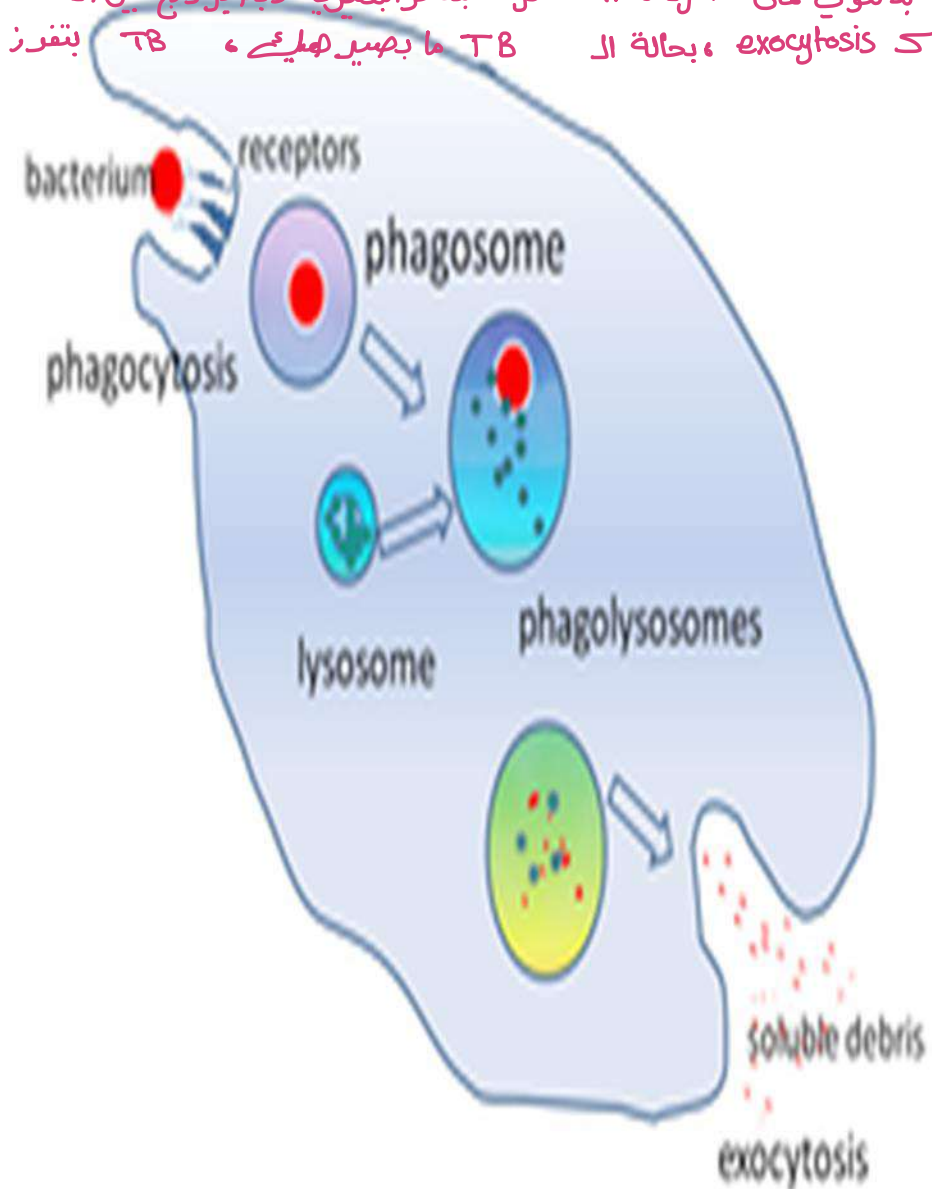
بتعمل engulfment للبكتيريا بتدخلها جوانها ب vacule (phagosome) ونز vacule صيغة اسمها lysosome
بتحتوي على lysosomal enzyme بتكسر البكتيريا وبصير دمج بين الـ 2 vacule مشمن phagolysosome بتكسر البكتيريا وبنتظفها
كـ exocytosis بحالة الـ TB ما بصير هليجى ، TB بتفوز بروتينان معينات بتمنع الـ 2 vacule ان تجتمع بالتالي بتعمل جوال phagosome

➤ Tubercle bacilli do not contain or produce toxins.

فاعدتها endotoxin بل الـ cell wall ناعها .

➤ Their pathogenicity depends upon the fact that the organism **survives and multiplies in macrophage** within a vacuole called a phagosome as it produces a specific protein that prevents phago-lysosomal fusion and so, escape the degradation by lysosomal enzymes.

➤ It is an intracellular organism.



Immunity Against Tuberculosis:

اول ما تدخل قلايتي - phagocytic organism او paralysis وفتش بتقدر عليه
 لما قتل بالقتل عليه بتروح تنادي خلية اقوى منها (الماستوترو) T-cell
 بتروح تفرز Cytokines بعمل more activation و TNF و phagocytic cell بصيغ تزداد و Killing power
 و بمرضها بتعمل complet clearance و بمرضها ال immune system بتروح تنادي و ييجو ال lymphocyte
 ليفوا حوالين ال Macrophage

• On primary infection, the patient develops:

انواع ال immunity هيا الهم باء immunity against to TB

1- Cell mediated immunity (CMI) (Delayed-type

تعتمد على الخلايا تاع ال immune system

اله بتؤخذ وقتا حتى تتكون

= type IV hypersensitivity) (Granuloma formation)

الهدف من هيا ال عملية :

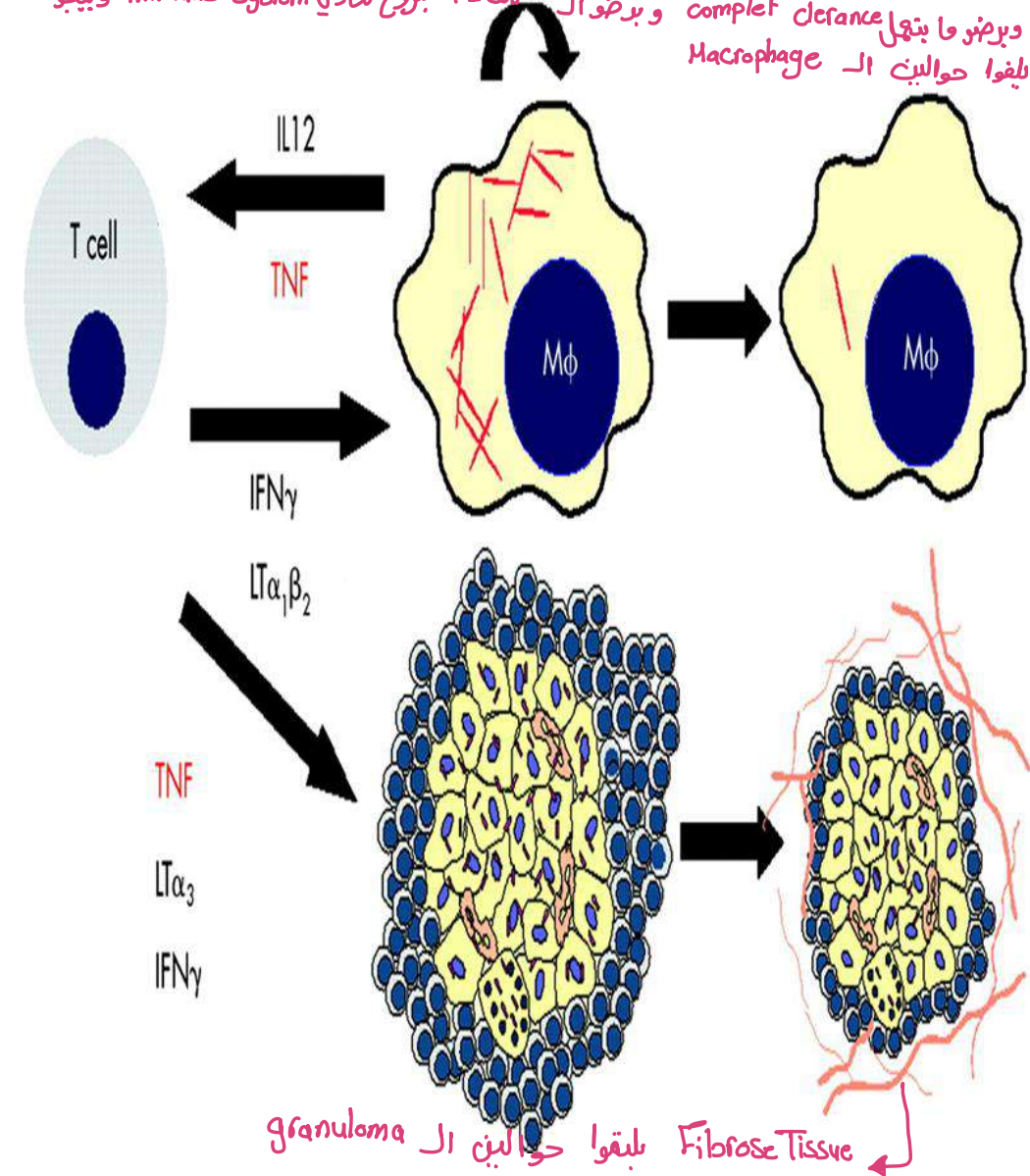
that leads to localization of tubercle bacilli, retards their multiplication, limits their spread.

Patients deficient in cellular immunity, such as AIDS patients, are more susceptible to disseminated (miliary) tuberculosis.

بمضرب خلية ال T cell

2- Circulating antibodies forms but has little role.

يعتمد على انتاج ال Antibodies .



بلقوا حوالين ال granuloma Fibrose Tissue

Human Tuberculosis (TB)

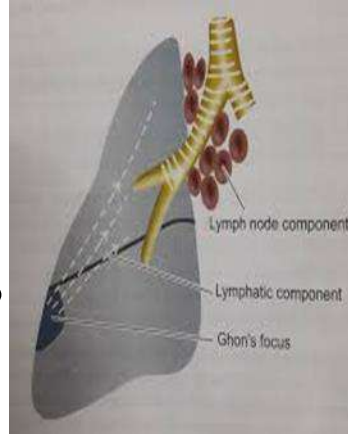
- Caused mainly by the **human** and **bovine** types.
- **Human** type is transmitted airborne by **inhalation** of respiratory aerosol (droplet nuclei $<5\mu\text{m}$) which expelled from active TB patient when cough, speak, sneeze,.. These nuclei remain **suspended in air for several hours**. Its ^{primary} initial site of infection is the lung.
- **Bovine** type is transmitted mainly by **ingestion** of unpasteurized milk of infected cattle (zoonosis) and its **initial site of infection is the intestine**.

Primary pulmonary tuberculosis:

يدخل ال organism ← للعرق الاول

➤ Characterized by a small lesion called **“Primary complex”** which consists of:

- * Ghon focus (T.B. granuloma) in the lung (mid-zone). ¹
- * Lymphangitis and lymphadenitis of the draining lymph nodes. ²



➤ The T.B granuloma become surrounded by fibrous tissue (Tubercle), undergone central caseation necrosis (cheese like). ^{(Tubercle) Fibrous} بتكون حواليها ^{Caseatione necrosis ← Center} وبمير بال ^{Thick و Cheesy} بتكون

➤ **Fate of primary lesion:**

- In most cases, it is asymptomatic and tubercles **heal** by fibrosis and calcification leaving the person immune and hypersensitive (**tuberculin positive**). ^{90-95%} بتكون تكونت عند المريض Cell mediate immunity لو غلت Skin test ← بطوع Positive
- Small foci containing **dormant viable** organisms (**Simon foci**) may be formed and often become sites of reactivation (**Latent TB**). ^{dormant ← organism} يضل ال ^{reactivation to dormant} بمرحلة ما يهيبولوا
- **Only small % (immunocompromised)** progress into active or disseminated T.B. ^{diffrent system} بتنتشر

Secondary pulmonary tuberculosis:

➤ Is the most common form of **clinical** tuberculosis.

بتصير نتيجة :

➤ It may be: reactivation of old primary lesion or reinfection.

عدوى جديدة

غالبا بتكون عند الناس :

➤ Occurs mainly in **immunocompromised**, **debilitated** or **diabetic** patients.

ببلش ينتشر بطريقتين

➤ **Spread of the organism occurs by two mechanisms:**

ببلش يعمل infection لبارت ثاني من الlung وغالبا بميل يعمل infection of upper lobe، ليه؟
لأنها more oxygenated

① Local spread: -To other parts of the lungs (upper lobe), OR

② -A tubercle cavitate, erode a bronchus, empty its contents, and spread the organism to other persons if expectorated (Open TB).

فنسي لهاي الحالة

هسا هون بصير عنا necrosis في الtubercle بعمل cavities ، وهاي الcavity بتروح تفتح على الbronchus وبتبلس البكتيريا تنتشر في الairway، واذا قح المريض او عطس او وهو بحكي وطلع منو sputum (يحتوي على بكتيريا) بتنتقل لشخص ثاني

نستقل عن هالايق الدم

② Hematogenous spread: which result in miliary T.B.



Symptoms of active TB disease:



Cough lasting 3+ weeks



Coughing up blood or sputum (*phlegm from deep inside the lungs*)



Chest pain



Weakness or fatigue



No appetite



Weight loss



Fever and/or chills



Night sweats

هيك في العادة يكون

Note that the sputum is yellowish green or may be coughing blood: (hemoptysis).

و يمكن يكون مصعبا

Laboratory Diagnosis

**في البداية اخذ عينة من ال sputum

Specimens: Sputum (3 consecutive days) or broncho-alveolar lavage.

لما النتيجة تطلع بوسيتيف بكون تشخيص مبدي ل TB، بس مش معناه اذا طلع سلبي يعني مش مصاب، لالا مرات يضطر نعيدو ٣ مرات مختلفة على ٣ ايام

1- Direct microscopic examination:

حبفة نوع ١

why

***Z.N stain & Kinyoun:** low sensitivity? (Require large number of bacilli). بدي اعداد كبيرة
حق اقدر اشوف

-Positive film is highly suggestive, **negative film does not exclude T.B.**

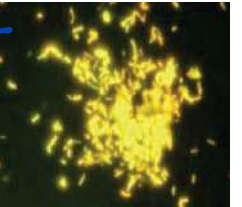
حبفة نوع ٢

* * *

***Flouochrome stain:** More sensitive and allow more rapid screening than Z.N.

2- Culture: مشكلتها بطيئة

← هيك بتبين وضوية



-Culture is the **gold standard and the most conclusive** method.

بدي ٨ اسابيع حتى ابعث تقرير انو نيجاتف

طريقة اسرع من ال قبل خلال ٣ اسابيع

-L.J medium (**up to 8 weeks**) or more rapid Middlebrook 7H9 (~3 weeks).

3- Polymerase Chain Reaction (PCR): Rapid & sensitive.

هاي اسرع ايشي ممكن خلال ساعة تبين النتيجة

Tuberculin Test “Mantoux test”

اختبار حساسية بدني اعمل اختبار للشخص هل هو عندو

Principle: It is skin allergic test used to detect cell mediated immunity to tubercle bacilli which become detectable few weeks after natural infection or BCG vaccine.

طب متى جسمي بتعرف على هاي الorganisms؟ لما يكون شايفها، طب متى بشوفها؟ يا من مطعوم، او يكون انصاب من قبل

Procedure:

Intradermal injection of 0.1ml of PPD (Purified Protein Derivative).

بحقن جزء بسيط 0.1 من T bacilli، بحكي للبيشنت روح وتعال بعد 48-72 ساعة وبعدها منحدد، يا رح الاقي صار رياكشن او ما صار

Read the test **48-72 hours**.

الرياكشن الي بصر الو كراكتير معين، انو يكون بصورة induration وهاي معناها localized hard papule وهي granuloma

Measure the diameter of the induration using mm ruler.

“Only the induration”, which is localized hard papule, is measured, even if there is surrounding erythema).

جافة/مخش شريط

تشوفها ممكن تبقي حاسما [يكون عندي مسطرة حتى اقيس قطرها (ما الي علاقة بالاحمرار الي حوله في القياس)



Interpretation of Tuberculin test

١٥ → ٥

<p>An induration of <u>5</u> or more mm</p> <p>هون كمان ما يعتبره نيجاتف لانو ممكن يكون بوساتف في حالات ال high-risk</p>	<p>An induration of <u>10</u> or more mm</p> <p>ما بقدر اعتبره نيجاتف لانو بكون بوساتف في هاي الحالات الي منحكيلها moderate risk</p>	<p>An induration of <u>15</u> or more mm</p> <p>قولاً واحداً</p>
<p>Considered <u>positive</u> for:</p> <ol style="list-style-type: none"> 1. People with previous history of TB. 2. Close contacts of TB patients. 3. People with HIV infection. 	<p>Considered <u>positive</u> for:</p> <ol style="list-style-type: none"> 1. People in endemic areas where TB is common. 2. Healthcare workers. 3. People with certain medical conditions such as diabetes. 4. Unvaccinated children younger than 4 years old. 	<p>considered <u>positive</u> even in absence of any risk factor for TB.</p>

✦ ✦ ✦ **Positive Tuberculin dose not differentiate between active or latent T.B**

← هو بس مساعداً الي في التشخيص

➤ Negative Test:

A negative test means that there is no infection at all or a very old healed one.

Tuberculin is a good negative test. ✖

➤ False Negative Test: يكون عندو TB بس اعطى نتيجة نيجاتف بشوفها عند مين؟

1. **Anergy:** is the inability to react because of a weakened immune system, e.g.

Severe T.B, HIV infection, Some viral infections or cancer.

2. **Recent T.B:** it takes 2-10 weeks for tuberculin test to become positive. او لسا لقط العدوى جديد، يكون لسا ما تكون antibody ←

➤ False Positive Test: ما عندو TB بس (خفه) بين الفحص عند

1- Infection with other non-tuberculous mycobacteria.

مع الوقت تفتد

2- BCG vaccine (The test reactivity induced by vaccine wanes with time).

أخذ مطعوما

Treatment:

➤ **First line anti-tuberculous drugs:** more effective with less side effects.

Isoniazid (INH), Rifampicin, Pyrazinamide, Ethambutol.

➤ **Second line anti-tuberculous drugs:** less effective with more side effects.

Fluorquinolones, Streptomycin, Amikacin, ...

➤ **Second line drugs can be used in patients whose infecting strains are resistant to the first line drugs.**

بسن في هاي الحالة

Treatment of TB should be: يعتمد على فكرتين رئيسيتين

1-Long Duration: ليه لفترة طويلة؟ والسبب؟

Response of tuberculosis to treatment is slow, this is due to the facts that:

- Intracellular location of the organisms. **antibiotics** في صعوبة بوصول ال
- Caseous material interferes with penetration of the drugs. **interferes** مع ال **drug** الي تكونت من ال **caseous necrosis**، المادة هاي بتكون تشيزي وبتعمل
- The slow growth of the organism. **تضاعفه بطيئ والاسجابة بطيئة**
- Metabolically inactive “persisters” within the lesion in chronic cases which may not be eradicated easily by anti-tuberculous drugs (source of reactivation in the future). **ال organism** عندو القدرة على تحول ال **metabolically inactive** يعني بوقف ال **multiplication** بتاعه (بعمل نفسو ميت) وهاي طريقة بتبعها حتى يكتسب **resistant of antibiotic**، وخلينا مفكرين إنه ال **antibiotic** بشتغل على **active metabolic**

2- In Combination: 2-4 drugs simultaneously to:

- ➤ Reduce development of resistance. **لانوكال دوا بمتنقل بطريقة مختلفة**
- ➤ Reduce toxicity of the drugs. **بتقل ال side effect**

↓
بستفدم في علاج ال
في نفس التوقيت
- طب سواله هدف؟

Resistant mutants Worldwide problem

➤ **Multidrug resistant TB (MDR-TB)**: means tubercle bacilli resistant to both isoniazid (INH) and rifampicin.

➤ **Extensively (Extremely) drug resistant TB (XDR-TB)**: It is defined as MDR + resistance to fluorquinolones and at least one second-line injectable drugs. Results from inadequate treatment of MDR-TB.

المشكلتين لنفس السبب يكون المريض نفسو مش منتظم في
اخذ العلاج او بوقف و يرجع هيك

➤ Because drug resistance is a problem, antibiotic sensitivity testing should be performed for all isolated organisms.

← لازم اعلمه قبل ابدا العلاج
+ اثناء فترة العلاج بين الوقت
و الثاني اعلمه

Prevention:

اسماء العلماء الي حضروه

Vaccination: BCG “Bacillus of Calmette-Guérin” vaccine:

بتحضيون

- This is a **living attenuated** vaccine prepared from a **bovine** strain.
- It is given as a **single dose** of 0.1 ml **by** intradermal injection in the left deltoid region.
جرعة واحدة فقط
- It is given to all children during the first month of life. ← اجباري
- It is also given to **adults exposed to infection e.g. nurses, doctors and contacts of the case.** ← عن الكنت السعال علم مكان التلاميذ
- It should **NOT** be given to **immunocompromised people.** ← منعيه للتبار
- It loses its effectiveness over time, usually **within 5 to 15 years**

ATYPICAL MYCOBACTERIA

اسم افر
اسم افر
Non-tuberculous mycobacteria "NTM"
Mycobacteria other than tuberculosis "MOTT"

- They normally found in soil and water.
- Transmission is from the environment. NO person to person transmission.
- They are of low pathogenicity for man but occasionally they cause opportunistic infections especially in immunocompromised persons.
- They cause pulmonary diseases which are indistinguishable clinically, radiologically and histologically from that caused by the human tubercle bacilli, but tend to be more chronic and difficult to be eradicated. عالمی مستوی قابلیت ایزولہا
- e.g. M. Avium Complex (MAC) (M. avium¹, M. intracellulare², M. chimera³).