ЗМІСТ

Phthisiology: textbook

Про книгу

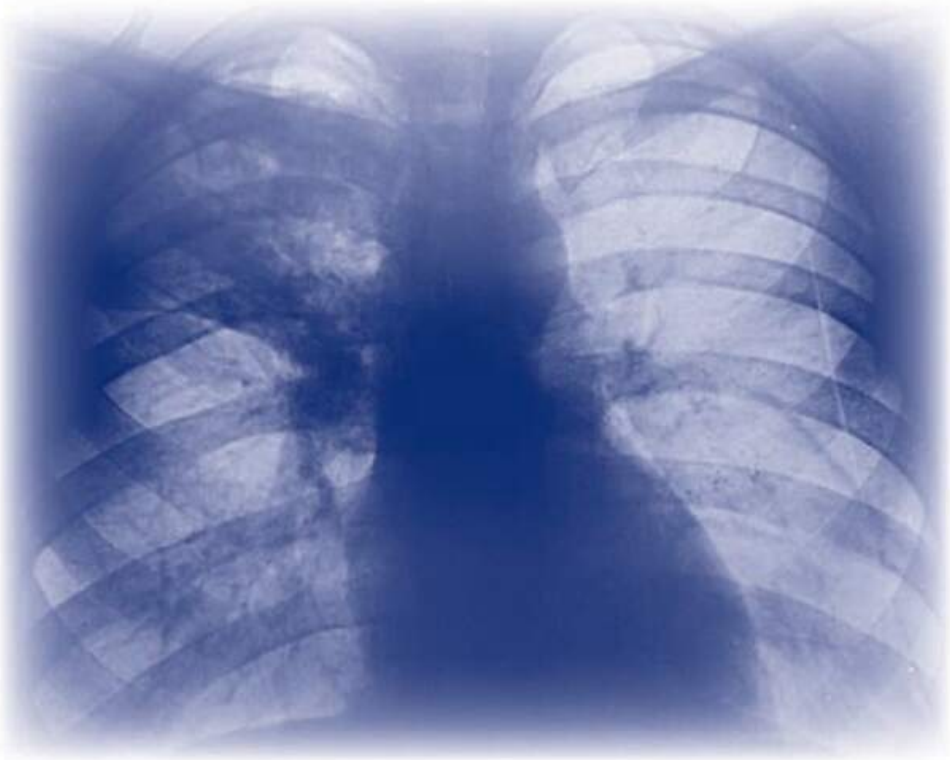
Professional training of medical professionals of the general practicioners network is a very important task, since they are an important element in addressing the TB epidemic. Therefore there was a need for a national textbook of tuberculosis involving Ukrainian and foreign highly skilled professionals in this field, who have invaluable clinical, teaching and research experience. Textbook meets the requirements of the Bologna process. It provides information about the etiology, pathogenesis, clinical presentation, diagnosis, treatment and prevention of tuberculosis. Texbook expounds latest achievements of national and international scientists, WHO standardized protocols in compliance with consistency and volume of standard provision of specialized care for TB patients. For students in higher education institutions.

PHTHISIOLOGY

TEXTBOOK

Edited by Professor V.I. PETRENKO

SECOND EDITION



APPROVED
by the Ministry of Health of Ukraine
as a national textbook for students
of higher medical educational establishments

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CONTENT

INTRODUCTION

Currently tuberculosis (TB) poses one of the major threats for the public health. Weakening of struggle against this disease in many economically developed countries was premature and led to loss of control over the situation and, as a consequence, not a single region of the world has eliminated this disease.

In the 90th of the XX century socio-economic crisis in Ukraine, stress and unbalanced diet, impact of the small doses of radiation after the Chernobyl disaster, environmental pollution, primarily of air, water and food products by industrial emissions, and pesticides led to decreased immunity of many people, as well as insufficient TB control activities, forming a background for an outbreak of tuberculosis to occur. Nowadays TB is widely spread in the post-soviet countries as well as in the poorest countries of Africa and Asia. However, TB much rarely occurs in representatives of indigenous population of economically developed countries. Cases of disease in these countries are mainly associated with HIV-infection or migration of population from TB high burden countries.

TB is first of all a social disease that is why TB morbidity is growing in the countries with poor socio-economic conditions of life, low educational level and sanitary culture of population.

In April 1993 World Health Organization (WHO) proclaimed tuberculosis the global emergency.

Drawbacks in the operations of the healthcare system, spread of the human immunodeficiency virus (HIV/AIDS) and development of forms of tuberculosis resistant to anti-TB drugs have exacerbated the problem.

In the year 2001 Verhovna Rada of Ukraine approved the Law of Ukraine "On Combating Tuberculosis Disease". After that departmental orders regulating operations of the state tuberculosis service of the country were issued.

International organizations, first of all WHO Regional Office for Europe, WHO office in Ukraine and United States Agency for International Development (USAID) have greatly supported organization of anti-TB activities in Ukraine. Dozens of conferences and training workshops have been conducted with participation of international professionals. Collaboration with international organizations provided material support for interventions to combat TB and enhanced the level of knowledge of health professionals. Collaboration with such respected organizations as the World Bank and Global Fund to Fight AIDS, Tuberculosis and Malaria was also useful.

General practitioners being an important link in overcoming TB epidemics, their training seem to be an extremely important process. This necessitated the creation of a national textbook on phthisiology with participation of Ukrainian and top international experts in this field, possessing a valuable experience of clinical, pedagogical and scientific work.

This textbook meets the requirements of Bologna process. It provides information on aetiology, pathogenesis, clinical picture, diagnostics, treatment and prevention of tuberculosis. The most up-to-date developments of both national and international scientists, WHO materials, which have been unified by working protocols with respect to sequence and scope of provision of specialized medical care to TB patients, are presented.

Chapter 2

ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS

2.1. TB ETIOLOGY

2.1.1. Causative Agent of TB and Its Types

On March 24, 1882 R. Koch demonstrated to the scientific community the causative agent of TB under microscope and its pure culture. R. Koch proved its infectious origin by causing disease in animals. In his honor the microorganism was named Koch's bacillum (***bacillum Kochii)***. The current name of the TB causative agent is Mycobacterium tuberculosis (MTB), a pathogen from the *Mycobacterium* genus of the family of fungi ***Actinomicetae*** (See Fig. 2.1.1).

Causative agent of lepra, acid-fast, opportunistic (atypical) mycobacteria and acid-fast saprophytes also belong to the genus of mycobacteria. In certain conditions the atypical mycobacteria can cause mycobacteriosis in humans — disease similar to TB. Acid fast saprophytes are not pathogenic for human beings or animals.

The generic term 'tubercle bacilli' incorporates at least five species belonging to a group termed M. tuberculosis complex: *M. tuberculosis, M. bovis, M. africanum, M. microti, M.canetti.*

Mycobacterium tuberculosis are the human species, causative agent of tuberculosis in human beings.

Mycobacterium bovis *are the* bovine species, causative agent of tuberculosis in cattle;

Mycobacterium africanum — African species, isolated in Western Africa, having the signs of both above types.

A rare TB cases in humans caused by *M. Microti and M. Canetti* have also been reported. Most often the disease in humans is caused by human species of *M. tuberculosis* (92% of cases), seldom — by bovine (5%) and intermediate species (3%).

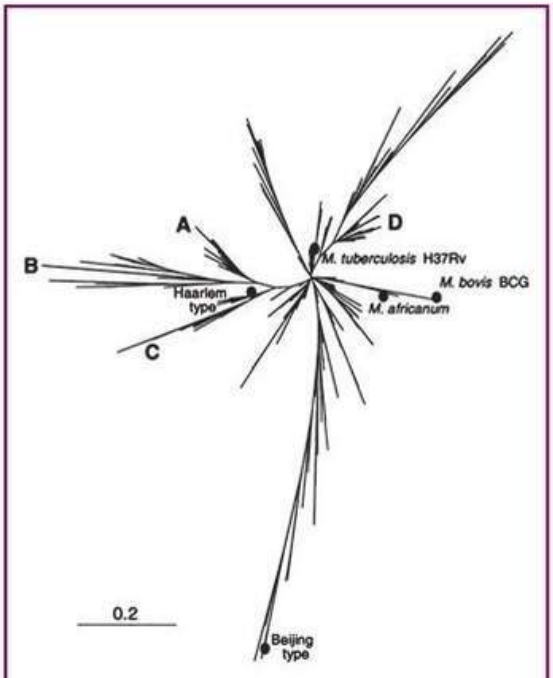


Fig. 2.1.1. Philogenetic Position of MTB within the Genus Mycobacterium (Positions of some reference strains (M.tuberculosis H37Rv, M.bovis BCG, M. africanum group) are shown as well)

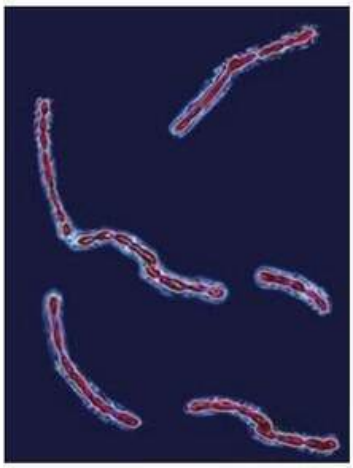


Fig. 2.1.2. Mycobacteria Tuberculosis (Optical Microscopy)

Typical MTB (Fig. 2.1.2 – 2.1.5) are aerobes, non motile, which look like thin, straight or slightly bended sticks/rods, homogeneous or granulated 0,8–5 micrometers in length and 0,3–0,6 micrometers in width, they do not form spores and capsules, they are acid-, base-, alcohol fast and gram positive. The microbial cell has a microcapsule, cytoplasmatic membrane, cytoplasm with organelles (granules, vacuoles, and ribosomes).

In contrast to *M. Tuberculosis, M. bovis* are shorter and thicker, their dimensions are 0,2–0,8 x 1–10 micrometers. At the same time its cocci like L-forms were described (Fig. 2.1.6 – 2.1.7). It is known that globally over 50 mln. of cattle are infected with

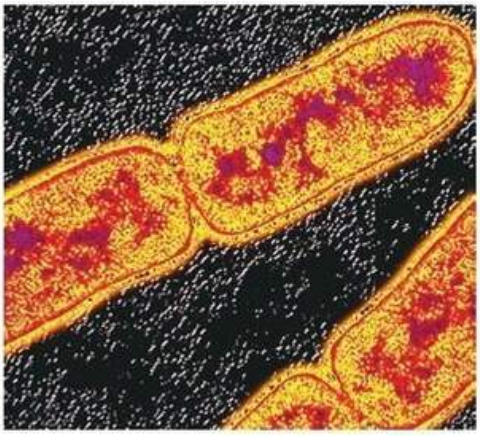


Fig. 2.1.3. Mycobacteria Tuberculosis (Electron Microscopy; × 50 000)

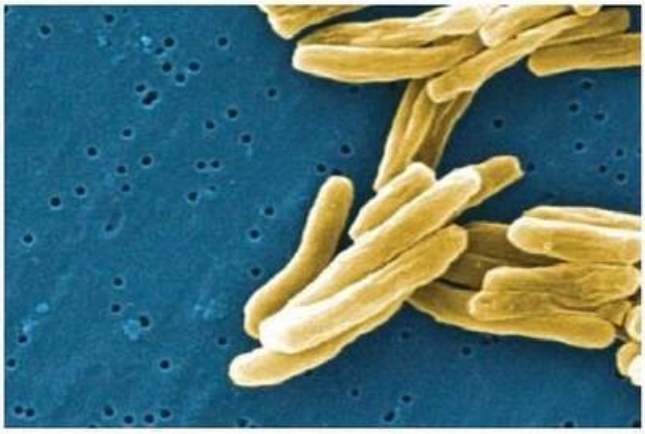


Fig. 2.1.4. Mycobacteria Tuberculosis (Color Electron Microphotograph; × 15,594)

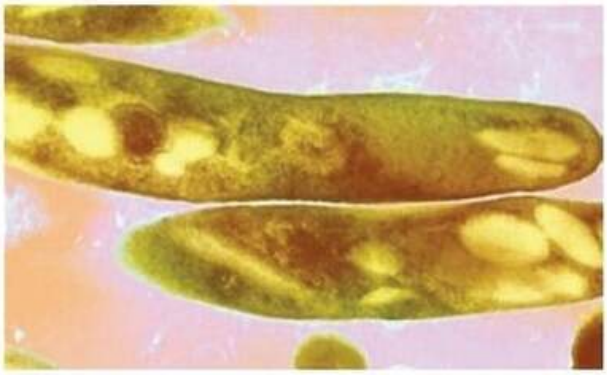


Fig. 2.1.5. Mycobacteria Tuberculosis (Electron Microphotograph Showing Details of MTB Ultrastructure)

Fig. 2.1.6. Mycobacterium Bovis (Electron Microphotograph)

Fig. 2.1.7. BCG Vaccinal Strain (M. bovis) in the Human Macrophage (Green-color Microphotograph; × 11500)

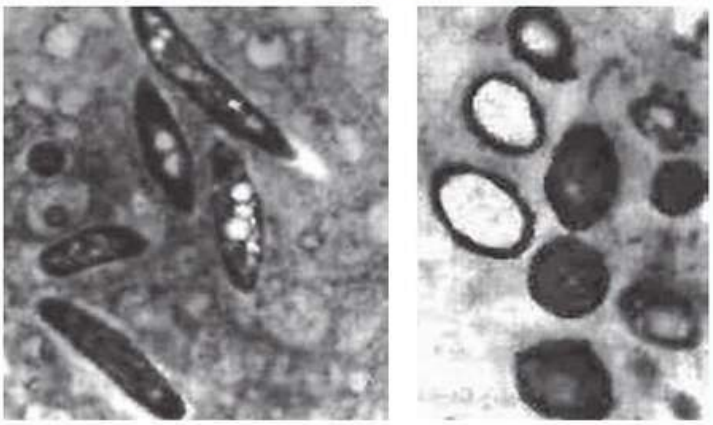


Fig. 2.1.8. Much's Granules in MTB (Optical Microscopy)

M. Bovis, which leads to significant economic losses. *M. bovis* may be pathogenic for humans.

To identify human species MTB niacin test is used (they secrete more niacin — nicotine acid).

Young MTB are homogenous, but with ageing granulation develops (Much's granules), which can be detailed by optical microscopy (see Fig. 2.1.8).

Under the influence of anti-TB drugs change of physical and chemical properties of MTB occurs: they become short, approach coccobaccilli, their acid fastness is reduced (when stained by Zeil-Nilsen they discolorate/poorly stain and cannot be identified) (See Fig. 2.1.9, 2.1.10). The TB causative agent can also exist as *filterable* forms (Fontes, 1910).

Transformation of bacterial form of MTB into dormant forms is called *persistence*. Return of persistent forms into bacterial ones is called *reversion*.

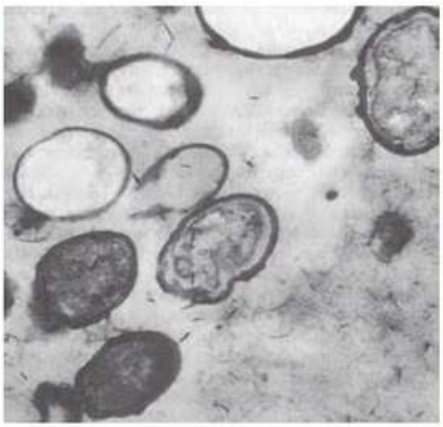
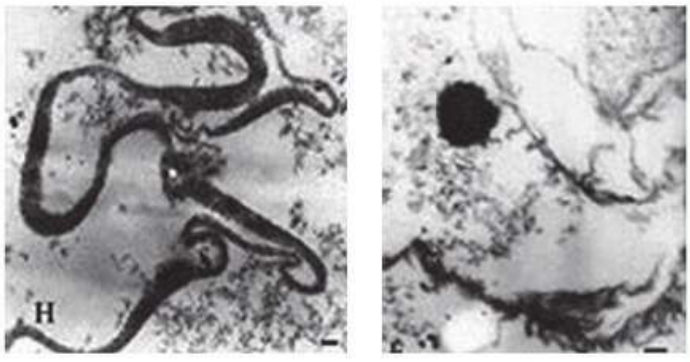


Fig. 2.1.9. Dormant Forms of MTB (Electron Microscopy)



a *b*

Fig. 2.1.10. Persisting MTB Forms:
a) Thread-like forms of M.tuberculosis;
b) Spherical forms of M.tuberculosis

2.1.2. MTB Replication

MTB replicates by transverse splitting, branching or budding of individual granules. This cycle lasts for 20—29 hours.

MTB grow on nutritional media in presence of oxygen, however they are facultative aerobes that is they are able to grow in the absence of oxygen access to the nutritional medium (they obtain oxygen from carbohydrates). That is why growing of MTB requires nutrient medium rich in carbohydrates (E.O.Shkolnikova). Effective solid nutrient media contain eggs, milk, potatoes, glycerin. Most often Lowenstein-Jensen and Fyn-2 media are used; less frequently — of Ogava, Middlebrook (the optimum temperature for growth is 37—38°C).

To facilitate MTB growth 3—6% glycerin is added to the media. MTB grow better on weakly alkaline medium although they can grow in neutral medium. Adding bile to the medium slows down their growth, which was used by Calmette and Guerin when they developed their vaccine.

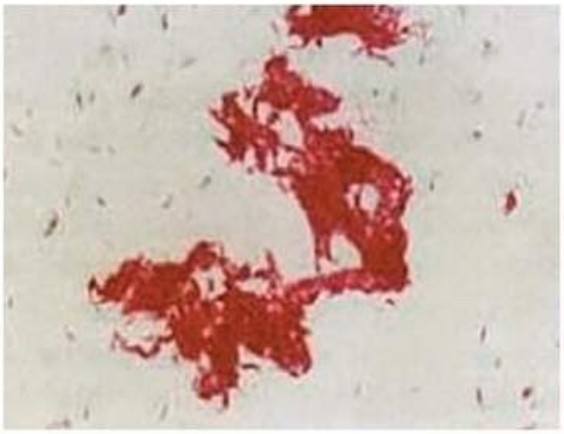


Fig. 2.1.11. MTB Colonies in the Nutrient Medium (Microscopy)

MBT grow slowly. As a rule first colonies appear on liquid nutrient media on day 7, and on the solid ones — in two-three weeks, allowing obtaining the pure culture and identifying the causative agent (Fig. 2.1.11 — 2.1.13). On liquid nutrient media with added glycerol the MTB colonies grow as films. MTB colonies can be rough (R-variants) or rarer — smooth confluent colonies (S-variants). R-variants of MTB are virulent for humans and animals; S-variants most often are non-virulent.

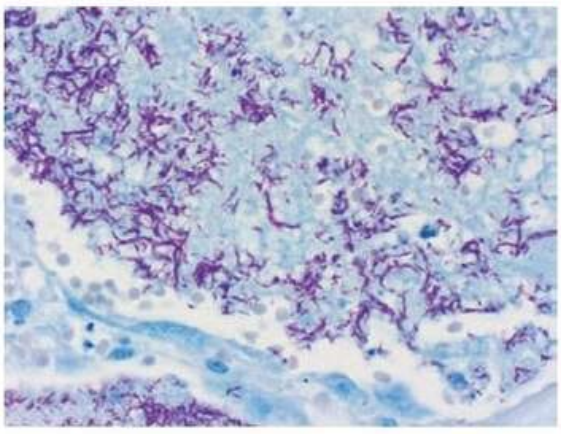


Fig. 2.1.12. M. Tuberculosis in Sputum

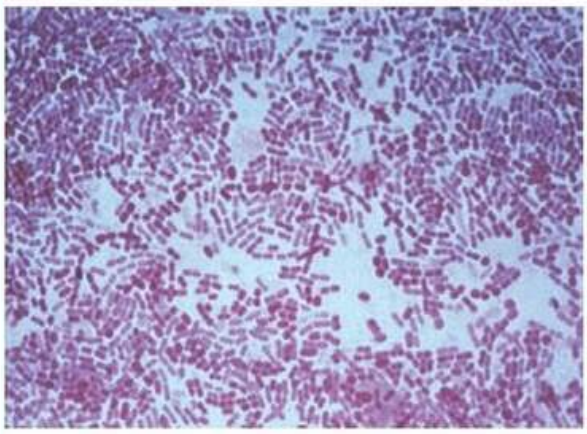


Fig. 2.1.13. M. Bovis in Sputum

2.1.3. MTB Structure

The MTB cell wall has three layers: outer, medium and inner layer. In the virulent MTB it is 230—250 nm thick.

The outer layer surrounding the cell is called *microcapsule*; it is formed by polysaccharides and contains fibrils. It can surround the whole population of MTB and may be located at sites of its contact. The absence or presence of growth, its intensity and composition of the microcapsule depend on which amount of cord-factor is extracted from the cytoplasm into the cell wall. The more cord-factor is extracted, the more pronounced MTB capsule is.

The cell wall participates in the regulation of metabolic processes. It contains the species specific antigens, due to which the cell wall is the locus, in which allergic reactions of hypersensitivity of the slow type and formation of antibodies occur, since it, as well as the surface structure of the bacterial cell is the first to contact with the macroorganism/host tissues.

Beneath the cell wall there are three layers of cytoplasm membrane closely adjacent to cytoplasm and consisting of lipoprotein complexes. Here the processes which condition the specificity of MTB response to environmental factors take place (Fig. 2.1.14).

The MTB cytoplasmic membrane by way of afferent invagination forms the inner cytoplasmic membrane system in the cytoplasm — mesosome. Mesosomes are semifunctional structures containing many enzymatic systems. They participate in the synthesis and formation of the cell wall and play the role of mediator between the nucleus and the cytoplasm of the bacterial cell.

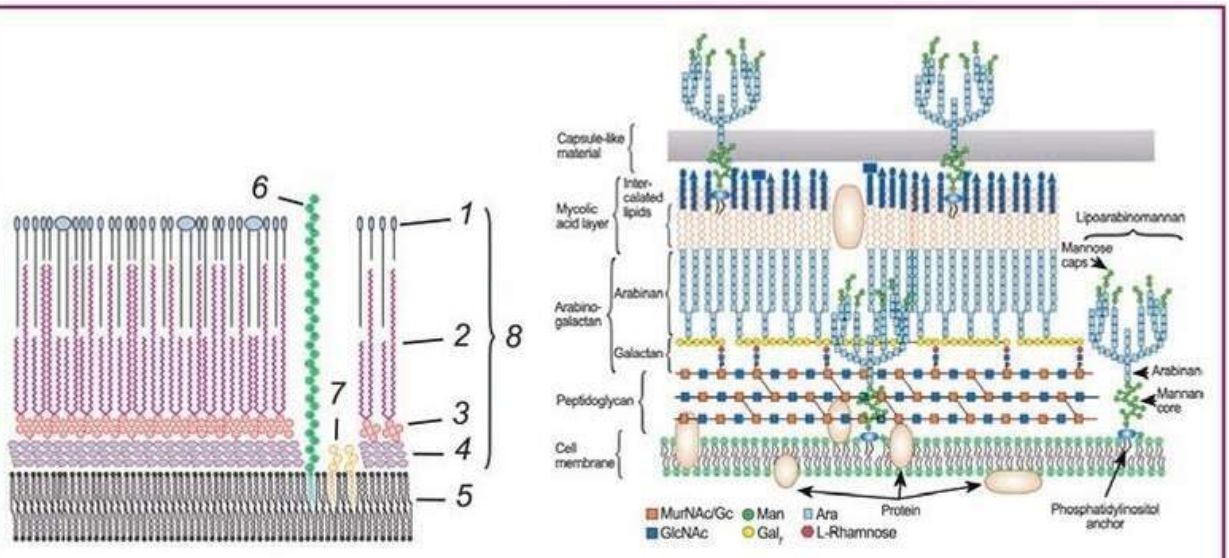


Fig. 2.1.14. MTB Cell Wall Diagram:
1) The outer layer lipids; 2) Mycolic acid; 3) Polysaccharides (arabinogalactan); 4) Peptidoglycane; 5) Plasmatic membrane; 6) Lipoarabinomannan; 7) Phosphatidilinositol mannoside; 8) The cell wall skeleton