

Phthisiology: textbook

КУПИТИ

Professional training of medical professionals of the general practitioners 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. Textbook 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

Kyiv
AUS Medicine Publishing
2018

UDC 616—002.5(075)

LBC 55.4ya73

Ph11

*Approved by the Ministry of Health of Ukraine as a national textbook for students
of higher medical educational establishments (letter No. 1/11-14715, 19 September 2012)*

Authors: V.I. Petrenko — Doctor of Medical Sciences, Professor, Head of the Phthisiology and Pulmonology Department of Bogomolets National Medical University (Kyiv, Ukraine); O.K. Asmolov — Doctor of Medical Sciences, Professor (Odessa, Ukraine); M.G. Boyko — Doctor of Medical Sciences, Professor (Poltava, Ukraine); M.M. Hryshyn — Doctor of Medical Sciences, Professor, Head of the Phthisiology and Pulmonology Department of Georgievsky Crimea State Medical University (Simferopol, Ukraine); L.A. Gryschuk — Doctor of Medical Sciences, Professor of the Internal Medicine Propedeutics and Phthisiology Department of Horbachevsky Ternopil State Medical University (Ternopil, Ukraine); I.D. Duzhij — Doctor of Medical Sciences, Professor, Head of the General Surgery, Radiation Medicine and Phthisiology Department of Sumy State University (Sumy, Ukraine); S.M. Ljepshina — Candidate of Medical Sciences, Associate Professor, Head of the Phthisiology and Pulmonology Department of Gorky Donetsk National Medical University (Donetsk, Ukraine); L.D. Todoriko — Doctor of Medical Sciences, Professor, Head of the Phthisiology and Pulmonology Department of Bukovyna State Medical University (Chernivtsi, Ukraine); O.S. Shalmin — Doctor of Medical Sciences, Professor, Head of the Phthisiology and Pulmonology Department of Zaporizhzhia State Medical University (Zaporizhzhia, Ukraine); O.S. Shevchenko — Doctor of Medical Sciences, Professor, Head of the Phthisiology and Pulmonology Department of Kharkiv National Medical University (Kharkiv, Ukraine); B.M. Puchlykh — Doctor of Medical Sciences, Professor (Vinnytsia, Ukraine); Pierpaolo de Colombani — Medical Adviser of the Infectious Diseases Department, WHO/Europe (Copenhagen, Denmark); Richard Zaleskis — Chairman of the TB Scientific Section of the International Union Against Tuberculosis and Lung Disease (Copenhagen, Denmark); Vaira Laimane — Director of the WHO Collaborating Centre on Research and Training in MDR-TB (Riga, Latvia); Girts Shkenders — Director of the Supranational Reference Laboratory for TB Diagnosis (Riga, Latvia); Alberto Mattelli — WHO Collaborating Centre on Implementation of Joint Actions for TB/HIV Coinfection Management (Brescia, Italy); Giovanni Battista Migliori — Director of the WHO Collaborating Centre on TB and Pulmonary Diseases, Head of the Assembly of European Respiratory Society (Milan, Italy)

Experts: Olena Kheylo — Strengthening Tuberculosis Control in Ukraine Project Manager, Chemonics (Kyiv, Ukraine); Ihor Perehinetz — Infectious Diseases Control Specialist, WHO office in Ukraine (Kyiv, Ukraine)

Reviewed by: D.G. Mjasnikov — Doctor of Medical Sciences, Professor (Kyiv, Ukraine); O.V. Panasjuk — Doctor of Medical Sciences, Professor of the Infectious Diseases, Phthisiology and Pulmonology Department of Private Higher Educational Establishment “Kyiv Medical University” (Kyiv, Ukraine); A.S. Svintsitsky — Doctor of Medical Sciences, Professor, Head of the Internal Medicine Department, Dentistry Faculty of Bogomolets National Medical University (Kyiv, Ukraine)

Acknowledgments: We thank Richard Zaleskis profoundly for his review of the manuscript. His contributions to the edition have been very valuable and much appreciated.

Phthisiology : textbook / V.I. Petrenko, O.K. Asmolov, M.G. Boyko et al. ;
Ph11 edited by V.I. Petrenko. — 2nd edition. — K. : AUS Medicine Publishing, 2018. —
416 p. ; color edition.

ISBN 978-617-505-687-5

Professional training of medical professionals of the general practitioners 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. Textbook 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 of higher medical educational establishments.

UDC 616—002.5(075)

LBC 55.4ya73

© V.I. Petrenko, O.K. Asmolov, M.G. Boyko, M.M. Hryshyn, L.A. Gryschuk,
I.D. Duzhij, S.M. Ljepshina, L.D. Todoriko, O.S. Shalmin, O.S. Shevchenko,
B.M. Puchlykh, Pierpaolo de Colombani, R. Zaleskis, V. Laimane, G. Shkenders,
A. Mattelli, Giovanni Battista Migliori, 2015, 2018

© AUS Medicine Publishing, design, 2018

ISBN 978-617-505-687-5

CONTENT

INTRODUCTION.....	9
KEY TERMS & ABBREVIATIONS	11
Chapter 1. GENERAL BASICS OF PHTHISIOLOGY	15
1.1. History of Phthisiology (V.I. Petrenko)	15
1.2. Basics of TB Control and Elimination (Pierpaolo di Colombani). ...	24
1.3. The Stop TB Strategy (Pierpaolo di Colombani).....	28
1.3.1. TB Control and Styblo's Model	29
1.3.2. The DOTS Strategy.....	29
1.3.3. The Stop TB Strategy	31
1.4. Epidemiology and Control of TB at the Global Level (Richard Zaleskis).....	38
1.4.1. Basics of TB Epidemiology.....	38
1.4.2. TB Epidemiology in the World and in the European Region	40
1.4.3. Combating TB in the World and in the European Region...	45
1.4.4. Achievements in TB Control	46
1.4.5. Main Challenges in TB Control	49
1.4.6. Next Steps in Global TB Control and its Eradication.....	50
1.5. TB Epidemiology and Control in Ukraine (O.S. Shevchenko)....	53
1.5.1. TB Control in Ukraine	53
1.5.2. General Issues on TB Epidemiology	58
1.5.3. Epidemiology of TB in Ukraine	63
1.6. Prevention of TB (Giovanni Battista Migliori)	66
1.6.1. Social Determinants and Noncommunicable Diseases (Giovanni Battista Migliori)	67
1.6.2. Contact Tracing (Giovanni Battista Migliori)	69
1.6.3. BCG Vaccination (Giovanni Battista Migliori, Richard Zaleskis)	70
1.6.4. Psychological Aspects of Stigma and Discrimination of Patients with Tuberculosis and TB/HIV Co-infection (L.D. Todoriko).....	73
1.7. Infection Control (S.M. Ljepshina)	77
1.7.1. Infection Control Rationale (Definition).	77
1.7.2. TB Infection Control in Healthcare Facilities	80
1.7.3. Administrative Control.	82
1.7.4. Environmental Control/Control of Air Indoors.....	88
1.7.5. Personal Respiratory Protection.....	94
1.7.6. Infection Control in TB Patients' Homes.....	97

CONTENT

Chapter 2. ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS	99
2.1. TB Etiology (V.I. Petrenko, O.S. Shevchenko)	99
2.1.1. Causative Agent of TB and Its Types	99
2.1.2. MTB Replication	102
2.1.3. MTB Structure	103
2.1.4. MTB Genetics	105
2.1.5. MTB Resistance to Anti-TB Drugs	106
2.1.6. Environmental Stability of MTB	106
2.1.7. Non-Tuberculosis (Atypical) Mycobacteria	107
2.2. Pathogenesis of Tuberculosis (O.K. Asmolov, V.I. Petrenko)	109
2.2.1. Immunophysiology and Immunopathology of Tuberculosis	109
2.2.2. Pathophysiology of Tuberculosis	115
Chapter 3. DETECTION AND DIAGNOSIS OF TUBERCULOSIS	120
3.1. Case Finding, Diagnosis and Screening (Giovanni Battista Migliori)	120
3.1.1. Case-finding	121
3.1.2. Diagnosis	121
3.1.3. Screening	122
3.1.4. From Diagnosis to Registration	124
3.2. Practical Approach to Lung Health (PAL) (Giovanni Battista Migliori)	127
3.3. Methodology of TB Patient Observation	134
3.3.1. Case History (V.I. Petrenko)	134
3.3.2. Physical Examination (V.I. Petrenko)	137
3.3.3. Haematology (V.I. Petrenko)	140
3.3.4. Biochemistry (V.I. Petrenko)	140
3.3.5. Laboratory Testing for MTB (V.I. Petrenko, Richard Zaleskis)	142
3.3.6. The Role of Tuberculin Skin Test (Mantoux Test) in Diagnosis of TB (Giovanni Battista Migliori, V.I. Petrenko)	148
3.3.7. Other Immunology Testing for Tuberculosis in Ukraine (V.I. Petrenko)	158
3.3.8. Radiological Diagnosis (V.I. Petrenko)	160
3.3.9. Functional Tests (L.A. Gryschuk)	167
3.3.10. Instrumental Diagnostics (V.I. Petrenko)	171

Chapter 4. TREATMENT OF PATIENTS WITH TUBERCULOSIS.....	175
4.1. Brief Historical Overview of the Development of Antimycobacterial Therapy (Vaira Laimane).....	175
4.2. Principles of Treatment of Patients with Tuberculosis (V.I. Petrenko)	176
4.3. Antimycobacterials. Theoretical Basis of Antituberculosis Treatment (V.I. Petrenko, Vaira Laimane).....	177
4.3.1. Antituberculosis Drugs Activity	177
4.3.2. Bacteriologic Bases for TB Treatment (Vaira Laimane) ...	178
4.3.3. Antituberculosis Drugs (V.I. Petrenko, Richard Zaleskis) ...	179
4.3.4. Side Effects of Anti-TB Drugs (B.M. Puchlykh).....	188
4.4. Treatment of Susceptible TB (Vaira Laimane).....	192
4.4.1. The Aims of Susceptible TB Treatment	192
4.4.2. Standardized Treatment Regimens for Active Tuberculosis in Defined Patient Groups (L.D. Todorico).	192
4.4.3. Phases of Treatment of Pulmonary and Extra Pulmonary Tuberculosis.....	193
4.4.4. Evidence Based Recommendations for Tuberculosis Treatment.....	194
4.4.5. Recommended Treatment Regimens for New Pulmonary TB Cases.....	195
4.4.6. Recommended Treatment for Previously Treated TB Cases (Relapses, Treatment after Failure, and Treatment after Default).	196
4.4.7. Monitoring of TB Treatment Response	197
4.5. Adjuvant Therapy in Ukraine	200
4.6. Surgical Treatment of Patients with Tuberculosis (I.D. Duzhij)...	205
4.6.1. Historical Overview on Surgery for Tuberculosis	205
4.6.2. Current Indications for Surgery in TB	206
4.6.3. Contraindications for Surgery in TB.....	207
4.6.4. Types of Surgical Operations	207
4.6.5. Pre- and Post-Surgical Follow-up	212
4.7. Patients' Support and DOT (Vaira Laimane)	212
4.7.1. Importance of Adherence to TB Treatment.....	212
4.7.2. Patient-Centered Approach.....	213
4.7.3. Directly Observed Therapy (DOT)	214
4.7.4. Treatment for TB in Hospital	215
4.7.5. Delivering DOT on Ambulatory Bases.....	216
4.7.6. TB Patient Education.....	219

Chapter 5. CLINICAL FORMS OF TUBERCULOSIS

(V.I. Petrenko, M.G. Boyko).....	221
5.1. Classification of Tuberculosis	221
5.1.1. International Classification of Tuberculosis	221
5.1.2. Classification of TB in Ukraine.....	221
5.1.3. Formulation of TB Diagnosis	225
5.2. The Primary Tuberculosis	226
5.2.1. Overview of Primary TB Forms	226
5.2.2. Tuberculosis of the Nondefined Localization/Primary Site... ..	228
5.2.3. Primary TB Complex	230
5.2.4. TB of Intrathoracic Lymph Nodes Tuberculosis	234
5.2.5. Complications of the Primary Tuberculosis	243
5.2.6. Specific Features of the Primary Tuberculosis in Different Age Groups.....	245
5.3. The Secondary Tuberculosis	247
5.3.1. Disseminated Pulmonary Tuberculosis	247
5.3.2. Focal Pulmonary Tuberculosis	258
5.3.3. Infiltrative Pulmonary Tuberculosis	262
5.3.4. Caseous Pneumonia.....	272
5.3.5. Pulmonary Tuberculoma	274
5.3.6. Fibrotic-Cavitary Pulmonary Tuberculosis.....	281
5.3.7. Cirrhotic Pulmonary Tuberculosis	289
5.3.8. Pulmonary Tuberculosis Associated with Occupational Dust-related Pulmonary Disease (Coniotuberculosis)....	293
5.4. Complications of Pulmonary Tuberculosis	295
5.4.1. Respiratory Insufficiency/Failure	295
5.4.2. Cor Pulmonale	296
5.4.3. Haemoptysis and Pulmonary Bleeding.....	300
5.4.4. Spontaneous Pneumothorax	304
5.4.5. Atelectasis	305
5.4.6. Amyloidosis of Internal Organs	306
5.4.7. Bronchial and Thoracic Fistulae.....	307
5.5. Residual Changes after Pulmonary Tuberculosis.....	308
5.6. Tuberculosis of Respiratory Organs Associated with Other Illnesses and Conditions	312
5.6.1. Pulmonary Tuberculosis and Non-Specific Respiratory Disease.....	312
5.6.2. Pulmonary Tuberculosis and Diabetes Mellitus.....	313

5.6.3. Pulmonary Tuberculosis and Gastric and Duodenal Ulcer...	313
5.6.4. Pulmonary Tuberculosis and Alcoholism.....	314
5.6.5. Pulmonary Tuberculosis and Cancer.....	315
5.6.6. Tuberculosis in Pregnancy and Lactation	316
5.6.7. Tuberculosis in Children	323
5.6.8. Tuberculosis in the Elderly and Aged People	324
5.7. Extrapulmonary tuberculosis	325
5.7.1. Tuberculosis of bronchi, trachea, larynx and upper respiratory tract.....	325
5.7.2. Tuberculosis pleurisy (including empyema)	327
5.7.3. Neuro-tuberculosis and meningeal tuberculosis.....	332
5.7.4. Boneandjoint tuberculosis	336
5.7.5. Genitourinary tuberculosis	338
5.7.6. Tuberculosis of peripheral lymph nodes	343
5.7.7. Abdominal tuberculosis	343
5.7.8. Miliary tuberculosis.....	344
5.7.9. Skin, subcutaneous tissue and ocular tuberculosis.....	348
 Chapter 6. DRUG RESISTANT TUBERCULOSIS AND TB/HIV COINFECTION.....	 352
6.1. Epidemiology of Multidrug Resistant Tuberculosis (Giovanni Battista Migliori)	352
6.1.1. Risk Factors for MDR-TB and XDR-TB Development ...	355
6.2. Diagnostics and Treatment of Drug-Resistant TB (Giovanni Battista Migliori)	358
6.2.1. Clinical Features of MDR-TB and XDR-TB	358
6.2.2. Establishing Diagnosis of Drug-resistant TB	358
6.2.3. New Technologies for Rapid Diagnosis of MDR-TB	359
6.2.4. Conservative Drug Treatment of Drug-resistant TB	360
6.2.5. Failure of Therapy and Retreatment Regimens	363
6.2.6. Treatment Monitoring for Drug-resistant TB.....	364
6.2.7. Risk Factors and Treatment Outcomes of MDR-TB Treatment.....	364
6.2.8. Surgical Treatment for MDR-TB and XDR-TB	365
6.3. Control of MDR-TB and XDR-TB (Giovanni Battista Migliori)...	366
6.3.1. Infection Control Measures and Recommendations	366
6.3.2. Global Recommendations for Prevention and Control of Drug-resistant TB	368
6.4. TB/HIV Co-infection (Alberto Mattelli)	370

CONTENT

6.4.1. Epidemiology.....	371
6.4.2. Diagnosis and Treatment of TB/HIV.....	372
6.4.3. Diagnostics of Tuberculosis among HIV Infected Persons	372
6.4.4. Treatment of TB and HIV Co-infection.....	373
6.4.5. Prevention of TB in HIV-infected People.....	376
6.4.6. Control of TB/HIV Co-infection.....	378
 Chapter 7. TREATMENT OF LATENT TUBERCULOSIS INFECTION (Richard Zaleskis, V.I. Petrenko).....	385
7.1. Introduction.....	385
7.2. Recommended Regimens for Treatment of Latent TB Infection and Their Effectiveness	386
 Chapter 8. NEW PERSPECTIVES IN DEVELOPMENT OF PHTHYSIOLOGY (Giovanni Battista Migliori)	388
8.1. New Technologies in TB Diagnostics	388
8.1.1. The New Diagnostics.....	388
8.1.2. Improving Culture and Drug Susceptibility Testing	390
8.1.3. Looking for Biomarkers: Mycobacterial Lipoarabinomannan (LAM).....	390
8.1.4. Immunodiagnostic Methods: Are They Able to Differentiate TB Infection and Disease?	390
8.1.5. Other New Diagnostic Techniques	391
8.1.6. World Health Organization Policy Statement on Commercial Serodiagnostic Tests.....	393
8.2. New Medications.....	396
8.2.1. Priority Areas for Research in Anti-TB Drugs.....	396
8.2.2. Methodological Issues in Anti-TB Drug Development	397
8.2.3. Anti-TB Drugs Presently Undergoing Clinical Trials	398
8.3. Vaccines.....	401
8.3.1. BCG Vaccine.....	401
8.3.2. The Two Vaccination Strategies: Pre-exposure and Post-exposure	402
8.3.3. The Roadmap for the Future.....	404
 REFERENCES	407

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.

INTRODUCTION

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%).

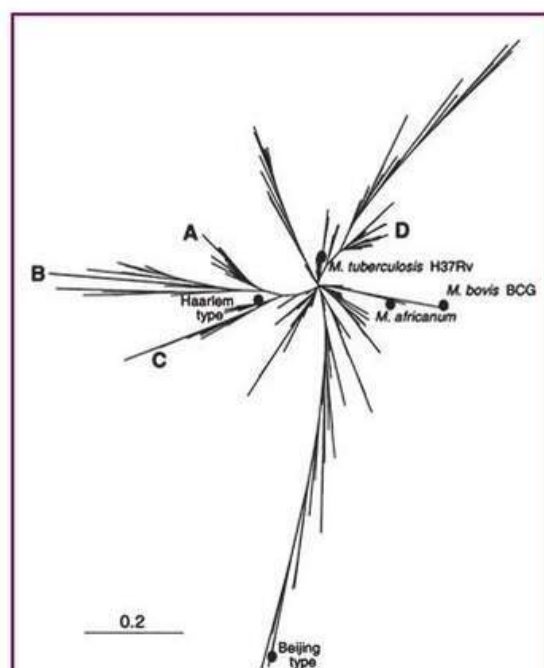


Fig. 2.1.1. Phylogenetic Position of MTB within the Genus *Mycobacterium* (Positions of some reference strains (*M. tuberculosis* H37Rv, *M. bovis* BCG, *M. africanum* group) are shown as well)

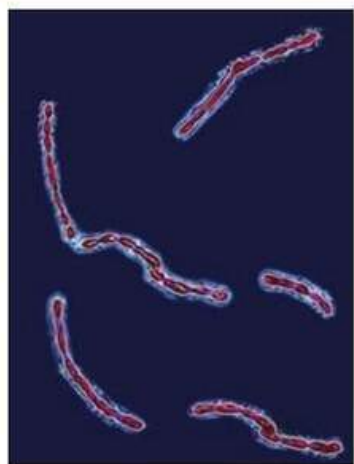


Fig. 2.1.2. Mycobacteria Tuberculosis (Optical Microscopy)

Typical MTB (Fig. 2.1.2 – 2.1.5) are aerobes, non motile, which look like thin, straight or slightly banded 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

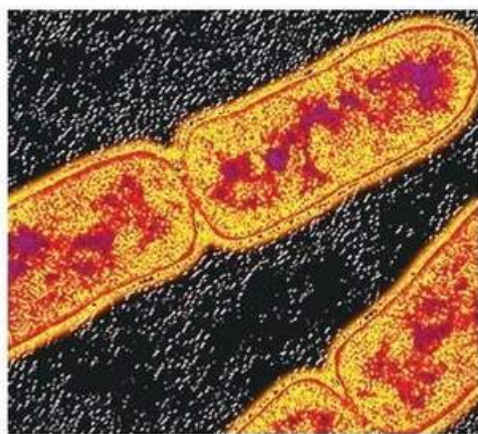


Fig. 2.1.3. Mycobacteria Tuberculosis (Electron Microscopy; $\times 50\,000$)

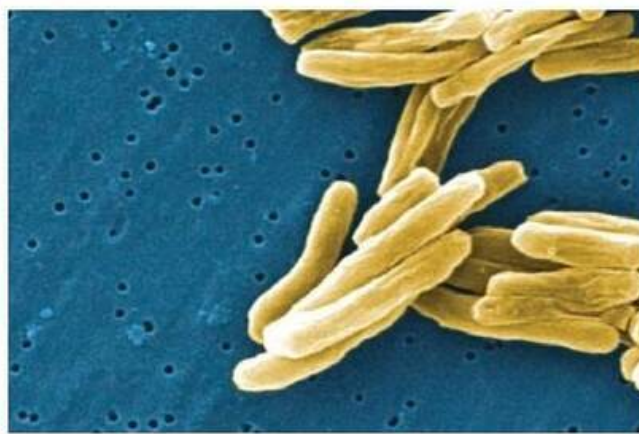


Fig. 2.1.4. Mycobacteria Tuberculosis (Color Electron Microphotograph; $\times 15,594$)



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

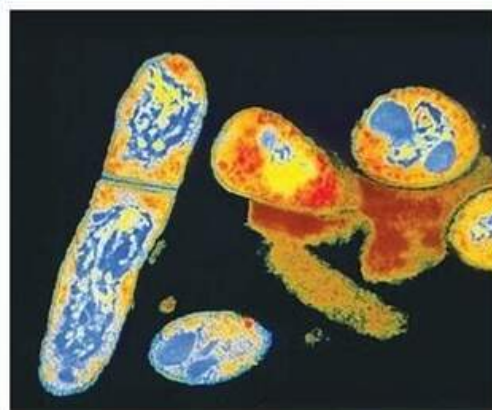


Fig. 2.1.6. Mycobacterium Bovis (Electron Microphotograph)



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

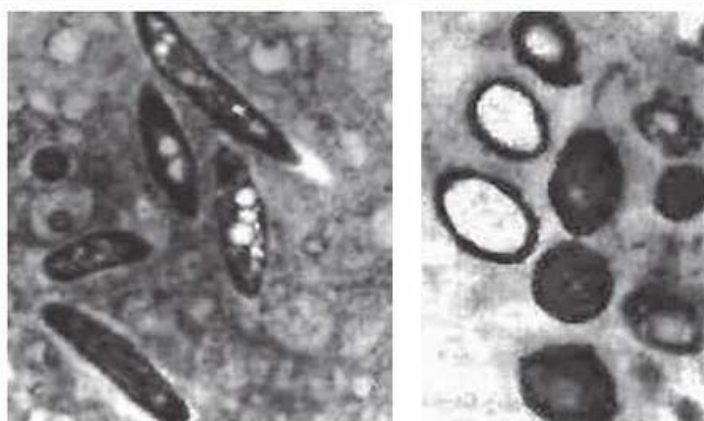


Fig. 2.1.8. Much's Granules in MTB (Optical Microscopy)

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*.

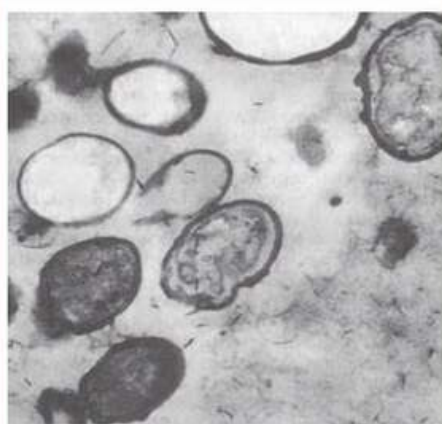


Fig. 2.1.9. Dormant Forms of MTB (Electron Microscopy)

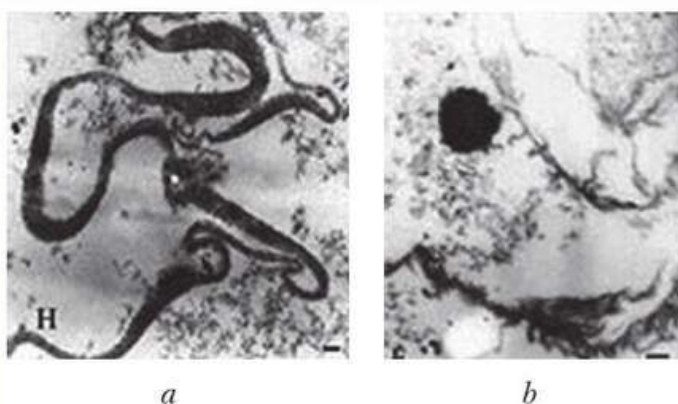


Fig. 2.1.10. Persisting MTB Forms:
a) Thread-like forms of *M.tuberculosis*;
b) Spherical forms of *M.tuberculosis*

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.

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.

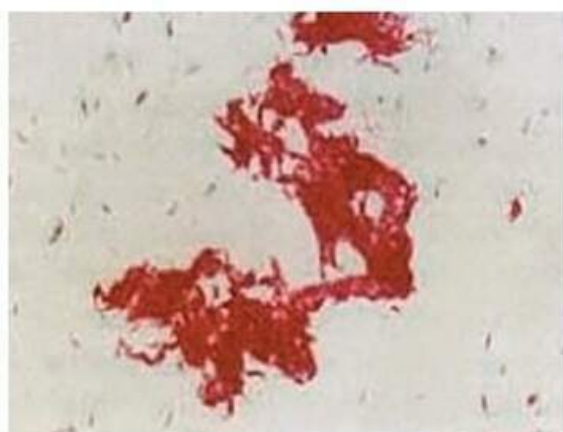


Fig. 2.1.11. MTB Colonies in the Nutrient Medium (Microscopy)

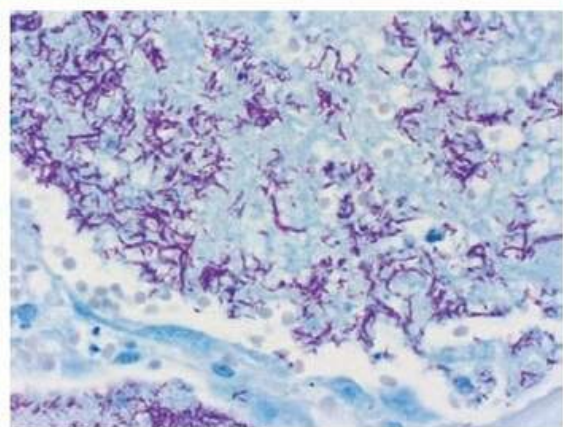


Fig. 2.1.12. M. Tuberculosis in Sputum

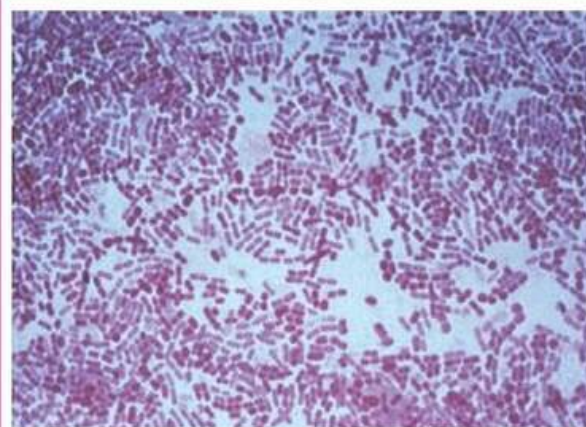


Fig. 2.1.13. M. Bovis in Sputum

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.

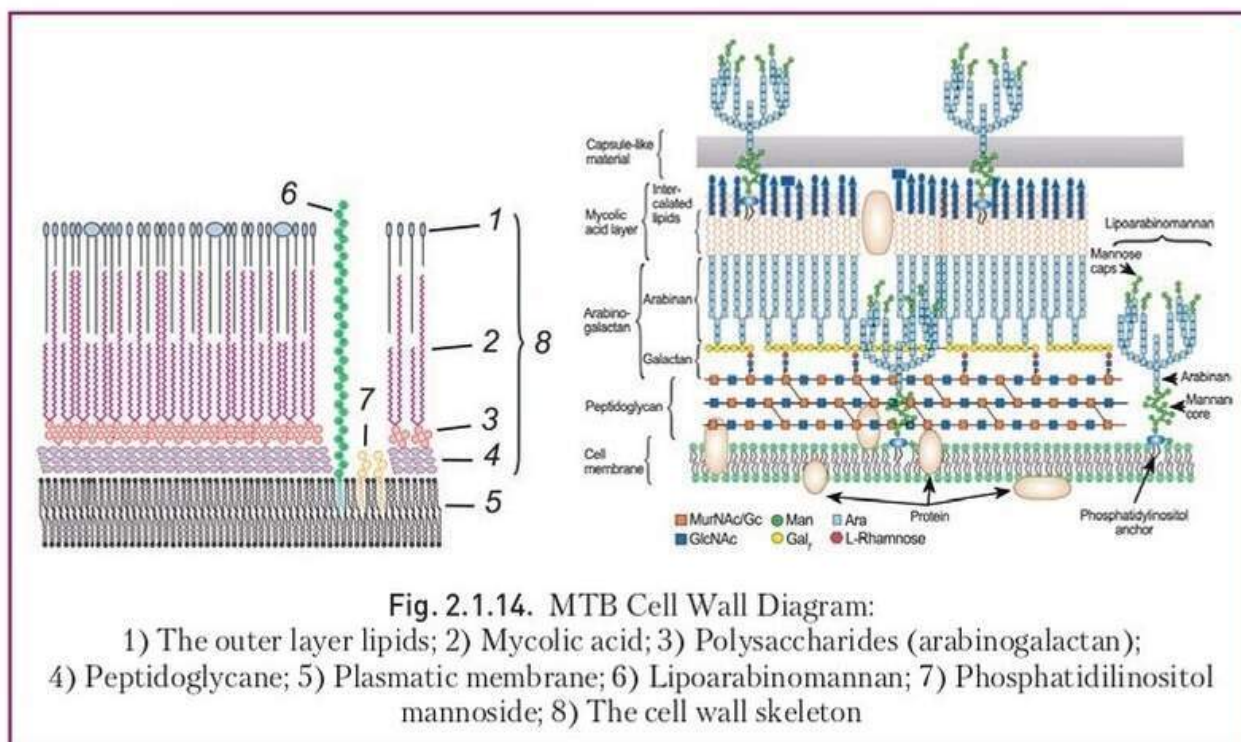


Fig. 2.1.14. MTB Cell Wall Diagram:

- 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



КУПИТИ