A brief history of tuberculosis in development of its diagnosis and treatment

Tuberculosis (from Latin, Tuberculum – tubercle) – general infectious disease caused by Mycobacterium tuberculosis. From the Greek word (phthisis – consumption –“exhaustion of a body” the word phthisiology is derived – scientific study of tuberculosis. The numerous historical documents and medical data testify to universal distribution of tuberculosis in the far past. The most ancient discovery indicating tubercular disease among people, settled in the ancient times in Europe, belongs to Bartels. In 1904 at inspection of the skeleton, found near to Heidelberg, of the man living in stone century (approximately for 5000 B.C.), he has established a tubercular defeat of chest vertebra with hump formation.

During foreseeable historical time already for a long time stimulate attention dependence of tuberculosis on socio economic conditions of life, of various groups of the population. Hunger and unemployment, the economic crisis, as a rule, were accompanied by mortality growth from tuberculosis. Especially significant were the drastic raise of tuberculosis prevalence at time of numerous wars.

Hippocrates – 400-350 B.C. The first systemic description of the clinical manifestations and epidemiological features of phthisis was recorded in the «Hippocratic Collection». In his book «The causes and symptoms of chronic diseases» Hippocrates gave a very accurate description of the disease, which later refer to tuberculosis and mentioned that fever, sweating, fatigue and lassitude were symptoms of tuberculosis.

The supposition about infectiousness of consumption stated by still Aristotle (384-322 B.C.), pointing out, that in air around consumptive patient there is a morbid source. From that time the huge amount of evidences were collected that the basic source of consumption distribution is the patient allocating sputum, which particles infect air, linen, plates and dishes, furniture, habitation. At those times, many doctors connected to infection comparatively more often morbidity among spouses and persons living in one dwelling with consumptive patients, among students and doctors making postmortem examinations of persons died from this illness.

Girolamus Fracastorius (1483-1553) for the first time raised the “germ theory” and believed that consumption was contagious. He systematically described three major modes of transmitting infection in his book “De contagionii”:
1. spread by direct contact;
2. spread by intermediary subjects (fomites) being in contact with pathogenic microorganisms;
3. infection at a distance.

He also mentioned about need of antiseptics for consumption prevention. Benjamin Marten (1704-1782) in his book “A new theory of consumption” conjectured that the disease could be caused by “certain species of micro organism (virus)”, which, once they enter in the body, could generate the lesions and symptoms of the disease.

Jean Antone Villeman french physician of military service began a series of experiments in 1865 that before 20 years of Koch’s discovery of Mycobacterium tuberculosis. Taking lung tissue and blood and pus from cavities of tuberculous patients, Villemin inoculated rabbits and was able to demonstrate disseminated tuberculosis in all.
In parallel to study of a role of infectious cause of tuberculosis, the data were collected, about peculiarities of clinical and pathomorphologic displays of tuberculosis.

The long empirical period of observation and diagnostics of the disease, when, on words of Hippocrates, "... the judgments are done by means of eyes, ear, nose, mouth and other ways, known for us, i.e. by sight, touch, hearing, smell and taste ", was replaced by a clinical-anatomical direction, which promoted rational understanding of the illness.

Andreas Vesalius (1514-1564) made the pioneering efforts of postmortem examinations. This method of diseases study facilitated the understanding of the pathological findings such as lung cavities, empyema among others.

Franciscus Sylvius de la Boe (1614-1672) for the first time associated small hard nodules discovered in various tissues at autopsy with the symptoms of consumption.

John Jacob Monget in 1700 gave the description of classical miliary tuberculosis.

Gaspard Laurent Bayle (1774-1816) performed a prodigious number of autopsies on phthisic patient. Notably, the necropsies were accompanied by detailed antemortem histories of the illness, enabling physicians to make clinical-pathological correlations.

Rene Theophile Hyacinthe Laenec (1781-1826), the french doctor carried out numerous clinical–anatomical studies and stated in 1819 the doctrine about tuberculosis in “Treatise about auscultation or recognition of lung and heart diseases”. In the Treatise he for the first time has entered the term “tuberculosis”. Laenec gave the description close to our conception about tuberculum as a source of tuberculosis, noted existence of isolated “infiltrative tuberculum”. He united various morphological displays in the uniform doctrine about phthisis. To these displays he referred scrofulous [tuberculous] changes of lymphatic nodes, contact disease of bronchi, the cavity formed as a result of tissue softening and which is looking like cheese (caseosis). Laenec managed to see connection existing between various displays of tubercular character in organs, and to combine into one disease, known in that time damage of the lung and lymphatic system.

The Russian surgeon, brilliant physician and scientist N.I.Pirogov (1810-1881) had played an important role in development and broadening of conception about tuberculosis as a systemic disease. N.I.Pirogov had described a clinical pathological picture of acute generalized tuberculosis, has noted an opportunity of simultaneous existence of miliary eruptions and of confluent changes at the same patient. He first had paid attention to gigantic cells in tubercular nodules, received then name of Pirogov-Langhance.

brief history of tuberculosis in development of its diagnosis and treatment (part 2)

On 24th March 1882 Robert Koch announced the discovery of the tubercle bacillus (bacterium of Koch). So, it was Robert Koch – German scientist who finally demystified the secret of the cause of tuberculosis. Koch represented proof that tuberculosis is brought about by the tubercle bacillus – mycobacterium tuberculosis (MBT).

Afterwards Koch’s discovery served as the scientific ground in development of methods for diagnosis and prevention of tuberculosis as infectious disease. These are:

1. Koch’s development of tuberculin and its application as an immunological diagnosticum for definition of tuberculosis infection;
2. improvement by Ziehl and Neelsen of staining of MBT at microscopy;
3. creation by Calmette and Guerin, human vaccine (Bacillus Calmette-Guerin, BCG).

It was proved, that mycobacteria of tuberculosis concerns to a sort Mycobacterium. Mycobacteria are widely distributed in an environment, among them pathogenic and non pathogenic forms are met. For the humans, basically, pathogenic (capable to cause a tuberculosis) are being mycobacterium type (humanus) and (bovinus).

Soon after Koch’s discovery of typical Koch’s mycobacterium the Russian scientist Mechnikov I.I. has informed, that in cultures, there are polymorphic forms of mycobacterium tuberculosis. The polymorphism becomes apparent by development of rode like, granular and coccus forms. Thereby Mechnikov I.I. has specified the ability of MBT to variability.
From this time the conceptions about tuberculosis were already based on exact knowledge of methods of diagnostics of the causative agent and localization of tuberculosis in various organs. With the discovery of X-rays by W.C. Roentgen in 1895 the technique of radiological imaging of different organs became available including the lungs. Thus began accessible to compare pathomorphological manifestation of tuberculosis to lifetime tubercular changes in various organs.

Even long before discovery of mycobacterium tuberculosis the various methods were applied for treatment of this disease.

The medicine of ancient times was based on a belief that disease was a natural phenomenon and its remedies are derived from natural sources. Dietary enrichments of various forms were popular, including milk from various sources. Generally recognized remedies were used at those times such as bleeding, purging, emetics, or other interventions.

Various chemical preparations were empirically used such as combinations of mercury, silver, copper, calcium, bismuth, iodine, anti-infective agents, dyes etc. For the tuberculous patients they often were morbid at best and mortal in the extreme.

Koch’s discovery of tuberculous pathogen stimulated development of specific methods of treatment, with application of active antibiotics and chemical compounds against mycobacterium tuberculosis.

Introduction in 1950s and 1960s of numerous anti-tuberculosis drugs: isoniazid, aminglycosides, viomycin, capreomycin, pyrazinamid, ethionamide, cycloserine, ethambutol and rifampicin, ensure effective and predictable treatment of tuberculosis.

Now phthisiology is armed with a number of treatment methods, effective at various forms of tuberculosis. Simple or more complex schemes, based on various principles and simultaneous assignment of several anti-tuberculosis preparations strengthen therapeutic effect and prevent development of drug resistance of mycobacteria.

The chemotherapy of tuberculosis expanded indications to surgical methods of treatment of the disease. To those are concerned: extra pleural pneumothorax, oleothorax, thoracoplasty, surgery on the peripheral nerves. Widely applied lung resections are: limited cuneiform resections, segmentectomy, lobectomy and pulmonectomy – removal the whole lung.

But such only medical means of fight with tuberculosis could not be successful because of large quantity of the patients. An obstacle for the tuberculosis prevention is its long and chronic course and many factors such as conditions of life, economic, of moral and psychological order connected to the large material spending. During all history of fight with tuberculosis, the necessity realized of conducting of effective widespread measures of public, sanitary and personal prevention under conditions of communal life, development of specialized anti-tuberculosis service.

The tuberculosis dispensaries were organized to carry out some of these measures. Such establishments were organized in France (in Lille) under the initiative Kallmette, in Edinburgh under the initiative R. Philip, etc. However quantity of such establishments was insufficient earlier and remains the same now. Those treatment facilities did not play the role of organizational establishments.

Long before, when the etiology of the disease was unknown, but as the infective nature of tuberculosis suspected, has ripened necessity for wider sanitary – preventive measures. In some countries, for example in Persia and Italy, because of significant distribution of tuberculosis attempts were made to isolate the patients forbade to them to communicate with the population, to enter a marriage. Further in Spain in 1751, in Italy in 1782, and then in Portugal and in other countries the laws were issued on obligatory registration of all patients with phthisis and their hospitalization, disinfection of their dwellings, annihilation of clothes, home belongings.
1. ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS

1.1. Characteristics of the Tubercle bacilli

**Mycobacterium tuberculosis (MBT)** – facultative intracellular parasite. **Mycobacterium tuberculosis (MBT)** belongs to the family of Mycobacteriaceae, of order Actinomycetaceae, and genus Mycobacterium. Etymologically, "mycobacterium" is derived from the Greek words 'myces’ for fungus and ‘bakterium’ meaning small rod. The name "fungus" derives from the tendency of these microorganisms to spread diffusely over the surface of liquid medium in a mold like growth pattern.

According to the modern concept of clinical medicine, the term "Mycobacterium tuberculosis” which was discovered by the German scientist Robert Koch in the year 1882, unites the complex of four kinds of mycobacterium including: M. tuberculosis (MBT), M.bovis and its Bacilli Calmette-Guerin (BCG) variant, M.africanum and M.microti. There is a high degree of genetic relatedness in this group.

Mycobacterium tuberculosis is the major cause of tuberculosis in man. M.bovis and M.africanum can cause a disease clinically indistinguishable from classical tuberculosis. M.microti is not considered to be pathogenic for human beings but it can cause a disease resembling tuberculosis in rats. BCG strain is not a pathogenic for humans.

The given material about “Tuberculosis” in this textbook refers only to the disease caused by M. tuberculosis (MBT) or tubercle bacilli of Koch (BK), Typus humanus.

The natural reservoirs of MBT are – human, domestic and wild animals, birds.

MBT are slender, curved rods that are resistant (fast) to acids, alkalis, and dehydration. The cell wall contains complex waxes and glycolipids.

**MBT can multiply within macrophages, and also extra-cellular.**

**Multiplication of MBT is comparatively slow,** with means of simple cell division. In the enriched media, double multiplication lasts from 8 to 24 hours. Clinical strains of MBT may require 4 to 6 weeks to grow in the medium.

**Genetic structure of MBT.** The sequence and annotation have been published in the international databases. The sequence of MBT is 4,411,529 b.p. long.

![Fig 1.1.2. Genome of MBT](image)
The MBT is not motile. The temperature borders or growth are between 29-42° C (optimum between 37-38° C). **MBT is resistant to physical and chemical agents. MBT can endure very low temperatures and resist temperatures as high as 80° C for duration of 5 minutes.**

MBT can survive for about 150 days in wet environment. When dry, MBT can cause TB in Guinea Pigs after an incubation period of 1 – 1.5 years. MBT in the lyophilized and frozen state has a viability of about 30 years. 

MBT's viability is significantly reduced under intensive sunlight and under a high temperature environment. However, its viability remains significantly high when submitted to a damp and dark environment. MBT remains viable for several months when exposed outside host organism, especially in dark and damp rooms.

MBT has acid resistance (acid-fastness) that differ them from many other causative agents of the infection. Ziehl and Neelsen in 1883 developed a special method of MBT staining, based on acid-fastness of MBT.

A film preparation stained by carbol-fuchsine dye is decolorized by sulphuric acid and washing with water is processed by finish dyeing with methylene blue (Ziehl–Neelsen method). In contrast to not acid-resisting bacteria MBT becomes apparent (having red color) at preservation of the coloring even after discoloration by acids and well stand out against blue background at microscopy. Ziehl–Neelsen method is still employed today.

Resistance of MBT to acids, alkaline and spirits related with lipid fraction of external layer of MBT membrane. The construction of the MBT cell wall consists in several layers. External
layer (description top down) contains lipids. The primary frame of the cell wall consists in peptidoglycans. The layer of arabinolactans has points of connection with the layer of peptidoglycans and structures for fastening mycolic acids and their derivatives. The mycolic acids presents in a form of free sulfolipids and cord-factor. The layers of cell membrane and layers of cell penetrated be channels and pores providing controlled diffusion and transport of energy dependent substances. Terminal fragments unspecifically suppress activation of T-lymphocites and leucocytes of peripheral blood. This process cause disturbance of immune reaction of the host on mycobacterium.

![Fig. The MBT cell wall](image)

**Morphological changes of MBT.** The morphology and the sizes of MBT are not constant, depending on the age of bacteria and, especially, on the condition of their environment and content of their nutrient medium.

**The cord-factor.** The lipids of the external membrane of MBT determine its virulence and formation of plait-like congestions (cord-factor) in nutrient medium. (see Fig. 1.1.5. Cord factor)

Koch noted about cord-factor in his initial report on the etiological agent of tuberculosis. First of all cord-factor related with virulence of M. tuberculosis. Formation of plait-like congestions was subsequently observed to occur among other mycobacterial species of lesser or having no virulence. Cord-factor was later identified as a highly unusual biological compound, trehalose 6,6-dimycolate, was observed to cause highly virulence, often lethal consequences when injected into experimental animals. However, the role of this compound in the pathogenesis of tuberculosis is unclear.

**L-forms.** One of the important features of MBT is its ability to produce L-forms. The L-forms are characterized by reduced level of metabolism and weak virulence. Remaining viable L-forms can survive for a long time and produce anti-tubercular immunity.

**The L-form** differs from usual MBT by the expressed functional and morphological alterations. It has been discovered, that the transformation of MBT into the L-forms accelerated under long anti-bacterial therapy and under other factors, which inhibit the MBT growth, duplication and cell membrane formation.

It has been established, that **L-forms** can be found in the sputum of "MBT-negative" patients with destructive form of tuberculosis, **capable, under the appropriate conditions, to be modified in rode-like variant which may cause reactivation of the tubercular process.** Hence, elimination of MBT from cavities of such patients yet does not mean their sterilization from MBT.

**MBT is resistant (tolerant) to many antibiotics.** This property is connected first of all with highly hydrophobic cell surface, which serves as a physical barrier for chemical agents and antibiotics. The main reason of resistance is coded in the MBT genome.

MBT can become resistant to anti-tubercular drugs. Combined resistance of the MBT to several drugs considerably reduces efficiency of treatment of tuberculosis for last years.
Fig 1.1.6. Drug resistance of MBT

A **wild strain** is defined as a strain of Mycobacterium tuberculosis which has never been exposed to any antimycobacterial drug. Naturally resistant strains are wild strains with species-specific constitutional resistance to a specific drug, such as Mycobacterium bovis resistance to pyrazinamide or Mycobacterium tuberculosis resistance to penicillin.

**Wild-type resistance** is the result of random mutation in naturally susceptible strains before any exposure to antituberculosis drugs. **Resistant strains** differ from sensitive strains in their capacity to grow in the presence of higher concentration of a drug.

**Acquired (secondary) resistance** results from exposure of the strain to the drug and the consequent selecting out of resistant mutant bacilli.

**Primary resistance** when the persons infected by someone who has tubercle bacilli with acquired to one or more antitubercular drugs.

**Multi-drug resistant tuberculosis (MDR-TB)** is defined as TB that is resistant at least to isoniazid (INH) and rifampicin (RMP). Isolates that are multiply-resistant to any other combination of anti-TB drugs but not to INH and RMP are not classed as MDR-TB.

**Combined resistance** - The World Health Organization sums primary and acquired to determine the overall or combined prevalence of resistance.

**Monoresistance** - strains of MBT that are resistant to only one of the five first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin).

**Poliresistance** resistance - strains that are resistant to two or more drugs but not to both isoniazid and rifampicin.

As a result, the modern public health services deals not only with the dangerous infection of tuberculosis agent but also with the whole set of strains which are resistant against different drugs. In practice, for organizing of effective tuberculosis treatment, it is important not only to discover MBT, but in parallel (fast enough) to promptly determine its resistance – within two-three days in order to on time prescribe an effective chemotherapy.

During the late 80s of the last century a new method was discovered shortening the analysis process mentioned above. The new diagnostic test is based on selective amplification of nucleic acids (DNA or RNA) in vitro with the help of polymerase chain reaction (PCR).

This PCR method has a wide spectrum (the large opportunities) and serves as the base of exact DNA-diagnostics, which allows to identify any strain of MBT and to define the reason of the drug resistance.
The laboratory researches have shown that the occurrence of MBT resistance is connected with nucleotide replacements (mutations) in genes, encoding various enzymes, which directly influence with drugs. Mutations in the gene katG, resulting in replacement of some amino acids in enzymes catalase and peroxidase are associated with resistance of some MTB strains to Isoniazid. The resistance of MBT to Streptomycin is connected with missens mutation in a gene rpsL, coding S12 mitochondrial protein, or with nucleotide replacements in a gene rrs, coding 16S RNA. The above submitted mutations in MBT genome are the only limited examples of formation of its resistance to anti-tuberculosis drugs. On this basis it is possible to make the following conclusion: introduction of new drugs in chemotherapy of tuberculosis leads to new mutations in MBT, resulting to resistance without exception of all used drugs and in this circumstance it is necessary to constantly take into consideration the tactics of tuberculosis treatment.

1.2. WAYS AND MEANS OF TRANSMISSION OF TUBERCULOSIS INFECTION

The source of infection. The basic source of MBT is the tuberculous patient, spreading MBT (bacillary expectorator/case).

The focus (place) of tubercular infection becomes dangerous in case when the patient is suffering from the “Open form” of TB that is when the patient expectorates MBT. Infection occurs with direct, long duration and close contact with a MBT positive patient. Infections mostly occur within families, apartments or communities where a tiberculous patient has been coughing MBT for a long time. The danger of dissemination of the infectious agent is eliminated if MBT expectorator is detected and isolated on time.

Occurrence and course of the infection depend not only from the virulence of the agent, but also on the condition of resistance and reactivity of the host.

The place of MBT penetration into the host is most important because in this site the primary contact between MBT and a host takes place (entrance gates of infection). The following channels of tuberculosis infection transmission are distinguished:

1) air-born;
2) alimentary (digestive);
3) contact;
4) intrauterine tuberculosis infection.

Air-born tuberculosis infection

MBT are distributed in the air with cough droplets, sneezing and conversation by a patient with active TB. Inhalation of these infected droplets can penetrate into healthy lungs. This type of infection is known as air-droplet infection (Air-born infection)

![Fig.1. The patient with TB generates aerosol that contains MBT. Small particles of aerosol dry out to form droplet particles. Droplet particles containing bacilli are inhaled by potential host](image-url)
Depending on the force of cough impulses and of the droplets sizes MBT can be dispersed with air on different distances from the patient, upon coughing – up to 2 m, upon sneezing – up to 9 m. The basic movement of sputum throwing particles occurs on distance of 1 m directly in front of the patient.

**Dust infection**

Tubercular sputum droplets, accumulated on floors, dry up and turn to dust particles. MBT being inside of the motes for some time remains viable. It has been established, that on the 18-th day of dried up sputum, and there are still about 1% of viable bacteria. Intensive air flow, floor sweeping, daily locomotion and any other type of movements will raise the MBT containing motes in the air, which can potentially penetrate into lungs and cause infection.

**Infection through digestive tracts**

Special experiments on animals show, that much more MBT are necessary for alimentary way of transmission compared to air-born infection. For infection of the host through air-tracts it is needed only one or two mycobacterium tuberculosis, but for infection per os hundreds of MBT are needed.

The way of MBT dissemination in a host at alimentary infection by tubercular culture was demonstrated by the results of post-mortem examinations published in connection with judicial **process in Luebeck**. By mistake 252 infants at vaccination through feeding with the tubercular culture (Kiel strain) instead of BCG was entered. Owing to infection 68 children died from tuberculosis and 131 children were ill; 53 children had remained healthy.

At post mortem examinations of 20 children who were dead, it was discovered that in the majority of cases, the damage was in peritoneal cavity. Therefore, the entrance of infection was the digestive organs.

One of the features of this way of infection of infants is frequent damage of mesenterial lymphatic nodes by tuberculosis.

It is necessary to take into consideration that MBT penetration into the intestine can occur at swallowing by the lung tuberculous patients own sputum that proved by the presence of MBT in significant quantity in stomach flush waters.

**Contact ways of MBT penetration into the host**

Cases of infection through a conjunctiva were observed among children and adults; acute conjunctivitis and inflammation of the lachrymal sac were sometime seen in these patient.

**The tuberculous infection through the skin is rare.** The cases of tuberculosis infected milkmaids are described, at MBT penetration through the injured skin of hands from the cows infected by tuberculosis.

**Intrauterine tuberculosis infection**

The possibility of tuberculosis of the fetus in the intrauterine period was proved on section, of newborns died during the first days after birth. The infection occurs at tuberculosis lesion of placenta or at affection of injured placenta during delivery by the tuberculosis-infected mother. Such way of tubercular infection occurs very rare.
1.3. ETIOLOGY AND IMMUNITY

The morphological and biochemical components of microbial cells cause various reactions in the host.

The basic biochemical components of MBT are:

- proteins;
- carbohydrates;
- lipids.

Proteins (tuberculoproteids) is the basic carrier of MBT antigenic properties.

Delayed-type hypersensitivity (DTH)

The substances, which are included in the MBT wall structure, induce tissue specific inflammation reaction and granuloma formation, with the development of the delayed-type hypersensitivity (DTH), which could be detected by a positive tuberculin test reaction, and a weak antibody formation.

In general, term DTH is used for characteristics of a type IV immune response (induration at the site of intradermal injection of tuberculin develops after 48 hours) among individuals who are infected with Mycobacterium tuberculosis. DTH is to be concerned as an immune response from the damaged tissue factors.

Relationship between the immune response and pathogenesis

Local and general tuberculosis lesions can be determined by the host’s immune response against the MBT.

In the description of this most complex process, we will limit ourselves to the simple enumeration of the events, proceeding from the moment of primary penetration of MBT into the alveoli, to the results of actual battle between the macroorganism and the MBT. This process determines the fate of at least one third of the world population infected with mycobacterium tuberculosis.

The cycle of tuberculosis development from MBT contamination till the occurrence of its clinical manifestations and distribution of MBT in environment conditionally is classified into 5 stages.

Stages.
1. Spreading of infection (contamination).
2. Beginning of infection, proliferation and dissemination in an infected host.
3. Formation of immune reaction in the host.
4. Formation of caseous necrosis, and proliferation of bacteria.
5. Secondary spreading of infection (ability to infect).

Brief description of each stage
Stage 1. Spreading of infection.

1.1. Patient produces MBT-containing aerosol.

1.2. Smaller particles of aerosol dehydrate and form droplet particles.

1.3. Mycobacterium-containing droplet particles are subsequently inhaled.

1.4. Droplet particles penetrate into bronchi and deposit into alveoli.

1.5. Mycobacterium is swallowed by the alveolar macrophages of the non immunized organism.

1.6. If alveolar macrophages are able to kill the MBT; Infection will not occur.

Stage 2. Beginning of infection, proliferation and dissemination.

2.1. MBT survives within alveolar macrophages and proliferates.

2.2. Proliferating MBT kills the alveolar macrophages and the latter consequently release chemokines, freed chemokines interact with the new cells.

2.3. New alveolar macrophages and monocytes activate and ingest MBT.

2.4. Killer cells and T lymphocytes begin to accumulate in the lesions.

2.5. MBT continues to proliferate, killing host cells and spreading locally.

2.6. MBT is transported to the intrathoracic lymph nodes and from there they spread systemically.

Stage 3. Formation of immune response of the host. Formation of process of tuberculosis in the Stage 3 can occur in two ways.

1st variant: Most patients who enter Stage III develop sufficient immunity to control the tuberculosis for lifetime.

3.1.1. MBT proliferation halted and the bacillary population falls substantially.

3.1.2. The primary lesion and metastatic foci involutes, leaving minimal residuals.

3.1.3. The tuberculin skin test becomes reactive.

2nd variant (unfavorable). In the case of insufficient immune response, a progressive tuberculosis process will develop. This situation is often observed among children, AIDS patients and those who have a predisposition to tuberculosis.

However, some undergo reactivation of latent infection: which may occur at extrapulmonary site(s) or in the lung. Reactivation of disease may end into tissue lesions, cavity formation and secondary MBT proliferation.

On the cell level unfavorable variant of the Stage 3 is characterized by the following processes.
3.2.1. Immune response of macro organism: macrophages submit tuberculosis antigens to T lymphocytes; T cells release cytokines.

3.2.2. Cytokines recruit and activate macrophages; resulting in immune response that includes protective cellular and tissue-lesions.

3.2.3. These responses limit proliferation and/or kill, MBT, resulting into involution of the primary lung lesion and the remote, extrapulmonary foci, or

3.2.4. If the host is unable to respond effectively against MBT, progression of primary disease proceeds.

Stage IV: Caseation and accelerated MBT proliferation.

4.1. Pulmonary focus reactivates and undergoes necrosis (caseation) resulting into cavity formation.

4.2. MBT located in the extracellular space exponentially multiplies.

Stage 5. Retransmission of the infection.

5.1. Patient expectorates MBT in sputum; another person inhales them. In that way, the process of tuberculosis infection with subsequent MBT expectoration into external environment is accomplished, thereby the spreading of MBT prolong into the surrounding.

Conclusion. A whole set of contributing factors predispose the development of the clinical manifestations of TB. It is known that virulent tuberculosis mycobacterium can be found among healthy individuals and those manifesting tuberculosis clinical symptoms are more than in mere carriers. Conditions in which various adverse external and internal contributing factors, cause a sharp decrease of the host’s resistance, tuberculosis infection can proceed into a disease, namely tuberculosis. At the same time, the tuberculosis contamination can be terminated as so called latent infection without serious consequences.

The latent infection

The latent infection is such infectious process, at which there are no clinical displays of the illness when mycobacteria is present in the host. The existence of the process at latent infection can be established by means of pathomorphological examination or with the help immunobiological reactions.

The tuberculosis latent infection is a consequence:

1. of the undeveloped primary infection, at which MBT continue to remain in the host;
2. of the unfinished process of the transferred tuberculosis in past.

In any case, MBT exists in a host, but conditions of the latent infection occurrence are different. In the first situation the latent infection arises at presence of some inherent of the host’s resistance, due to which the infectious focus does not develop. In second – it is a consequence of developed immunity during illness, when there is a latent focus. In both cases the reaction of the host is insufficient to destroy MBT.
Hence, the occurrence of the tuberculosis latent infection depends both on a degree of MBT virulence, and from a condition of host’s tolerance and immunobiological reactivity. The influence of external environment has also been proved important.

**Pathogenesis Mechanism:** The pathogenesis of tuberculosis begins when a droplet nucleus, generated by an index case, is inhaled by a contact and is carried via the airstream to a site in the lung. This droplet nucleus is ingested by an alveolar macrophage at the site of implantation, and after a lag period of a few days, the bacillus multiplies intracellularly.

The macrophage eventually dies and the bacilli are released and ingested by other macrophages. As this process continues, a primary lesion forms which can be identified after calcification. Because a single droplet nucleus (which may contain 1-10 tubercle bacilli) is sufficient to initiate the development of the primary lesion, the infectious dose in TB is exceedingly low. In addition, in most individuals only a single primary lesion is observed.

As the primary lesion enlarges, some organisms are transported to the lymph nodes draining the area containing the primary lesion. The lymph nodes enlarge as the bacilli multiply intracellularly, creating a situation in which bacilli escape from the leaky, swollen lymph node.

The term progressive primary tuberculosis is often used to describe disease arising directly from either the parenchymal or the lymph node component of the primary complex, disease which commonly occurs within 3-8 months after tuberculin conversion (Balasubramanian et al., 1994).

**1.3.1. The tubercular inflammation**

The tubercular inflammation, like any other inflammation is a manifestation of alteration, exudation, proliferation, leading to the formation of tubercular granuloma (tubercular tumor). The term granuloma is derived from the diminutive of the Latin term for a grain, granulum, which was first used by Rudolf Virchov [1818] to describe tumors that may ulcerate and give rise to granulation tissue.

The tubercular granuloma is not a mere collection of inflammatory cells but is an active site of action of numerous enzymes and cytokines in the very complex process of removing the causative agent MBT.

Hematogenic elements (lymphocytes, monocytes, polymorphonuclear leucocytes) and histiogenic elements (histocytes, macrophages, fibroblasts, reticular cells, endothelium of blood vessels, plasmatic and mast cells), participate in the formation of tubercular granuloma.

The tubercular granuloma has the following structure. The center consists of amorphous tissue detritus (due to alteration and necrosis), the peripheral region contains several layers of...
epithelial cells. Lymphoid and plasma cells are present in the external layers of the tuberculum. Giant multinucleated Pirogov – Langhans cells can be seen among the epithelial cells.

The tuberculum histogenesis depends on the development of the inflammation process, which is either progressive or regressive. When there is a decreased host resistance to tuberculosis, Fig 1.4.2.6. Progres vs reverse of the tubercular inflammation takes place.

Photomicrograph. Showing the progression of tubercular inflammation. Focuses of cheesy necrosis are formed of various intensity and illegible counters, on the background of the tissue exudative reaction. Cheesy necrosis develops in granuloma and in surrounded tissue, is impregnated by serous-fibrinous exudates.
At chronic development takes place the reverse development of inflammation process (regression). The epithelium cells are turned into fibroblasts, granuloma turns to scarring. In the further development the focus of necrosis can dissolve, undergo fibrosis, calcification and ossification.

The focuses are mainly of productive character, with the well outlined borders. Around of the focuses significant perifocal signs of inflammation are not present.

The tissue exudative reaction develops with the formation of **cheesy necrosis** which might develop within the tuberculum and surrounding tissues. These tissues will generally be impregnated with serous-fibrinous exudates.

Various foci of different sizes of cheesy necrosis arise during the further progression of specific tubercular inflammation. Foci of cheesy necrosis can spread and merge into bigger foci from which foci with sites of caseation (infiltrates) are formed. Caseation is diluted under the action of proteolytic enzymes and is coughed out through the bronchi. Cavities of disintegration appear in these sites of the lungs but ulcers appear on the mucous membrane and skin. The cavity formed during the disintegration of caseation will be the source of dissemination of MBT in other parts of the lungs and formation of new foci and cavities.

*Fig. 1.4.3.1.* **Basic phasis** of inflammatory process at tuberculosis (1 — **Tuberculum** / granuloma; 2 — **Focuses**; 3 — scar; 4 — focuses with cavities of disintegration; 5 — fibrotic focuses; 6 — infiltration; 7 — infiltration with cavities; 8 — tuberculoma; 9 — cavity; 10 — cirrhosis; 11 — cavities, fibrosis).
The particular danger is represented by vascular blood erosion supplying sites of lungs where caseous degeneration occurred. During cavity formation, blood from the damaged vessels penetrates the bronchi and from there, either penetrates other parts of lungs or is expectorated externally.

Reversible development of process (regression) occurs during high resistance of the organism the tuberculum will be substituted by fibrosis and calcification.

1.4.1. PATHOLOGIC ANATOMY OF TUBERCULOSIS

The lungs are the basic organs affected by tuberculosis.

The lungs are comprised of lobes. The right lung has 3 lobes, (superior, medial, inferior), left – 2 lobes (superior and inferior). The lobes are dividing into segments. In the right lung there are 10 segments and in left lung there are 9. The segments are comprised from lobules. In both lungs, there are about 1000 lobules. In general the size of lobule is 1 – 1.5 cm. The collection of the lobules comprise sub-segment. Several sub-segments form a segment.

Each lung segment contains a bronchus and artery that are almost arranged in a parallel order. The bronchi-lung segments have a triangular shape with the apex facing medially and the base facing peripherally. Each lung segment is separated from one another by a layer of connective tissue.

**Bronchial Airways.** The two bronchi proceed from the bifurcation of the trachea opposite to the 4-th thoracic vertebra to their corresponding lungs. Upon entering the lungs, the bronchi divide into branches in which each of these branches divide and subdivide dichotomously to their ultimate termination (smallest bronchi)

**The structure of the lung parenchyma.** The finniest, independent functional unit of the lung parenchyma is an acinus. It is a miniature lung about 1,5 mm in diameter.

The acinus is ventilated by the smallest bronchioles (bronchiolus or bronchulus terminalis) – finniest branching of the bronchial tree.

The group of acinus forms lobulus, whose diameter reaches 1 – 1.5 cm.

The mucous membrane lining the bronchi has a ciliated columnar epithelium as far as their termination. However, in the alveolar passages and air-cells the mucous membrane becomes thin and transparent coated with a squamous epithelium.

**The lung blood vessels.** The pulmonary artery, conveying the venous blood to the lungs, accompanies the bronchi to the lung, and divides along with the bronchi. The branches terminate into a thick capillary network around the alveoli. Air exchange occurs between the alveoli and venous blood. Consequently, oxygenated blood returns to the left auricle of the heart through the Pulmonary vein. In their course through the lung, the artery is commonly found above and behind the bronchial tube, while the vein is below and anterior.

**Pleura.** Each lung is enclosed and its structure supported by a serous membrane, the pleura, which invests it as far as the root, and is then reflected on the parietals of the chest. That portion of the membrane which is in relation with the lung is called (pleura visceralis s. pleura pulmonalis), and that in contact with the parietes, pleura costalis, pleura diaphragmatica and (pleura mediastinalis). The pulmonary pleura is very thin, elastic, and inseparably connected with the structure of the lung; the costal pleura is thick and strong, has very little elasticity, and can be readily stripped off the ribs and intercostal muscles which it covers.

The lymphatic lung system. The lung surface is formed of a thin sub-pleural network of lymphatic vessels that communicate with the pleural cavity by a system of pores.

The lung parenchyma consists of 2 types of lymphatic structures.

The 1\textsuperscript{st} type forms an elaborate network located beneath the bronchi’s mucous membrane.

The 2\textsuperscript{nd} type originates in the capillaries between alveolar ducts and alveolar sacs.
Lymphatic vessels of both types terminate in the broncho-pulmonary nodes in the hilus of the lung. These numerous and large nodes are located around the bronchi and within the tracheal bifurcation.

The lung nerves are derived from the parasympathetic and sympathetic nervous system. They form 2 plexuses:

1. Anterior pulmonary plexus, which is located in the anterior part of the hilus and is mainly composed of the filaments of the deep cardiac plexus;
2. Posterior pulmonary plexus, which is located in the posterior part of the hilus and is composed principally of branches of n.vagus.

The branches from both plexuses follow the course of the bronchi, and are then distributed within the walls of the alveolar ducts and alveolar sacs.

Mediastinum. The two pleural sacs do not communicate with each other, but have between them a space which contains all the viscera of the chest (thorax) with the exception of the lungs. This is called the intra-pleural space or mediastinum. The mediastinum is divided into: anterior, middle, posterior, and superior portions (parts).

Lung function. The functions of lungs are closely connected to the features of their structure. Due to the presence of hundreds and millions of alveoli, the total surface of which reaches 100 m² and the network of capillaries with a surface area up to 80 m², together with the components of alveolar-capillary membrane. The lungs do not only play a role in the breathing but also in expectoration and in the maintenance of a constant body temperature. The lungs also produce substances which participate in the regulation of blood coagulation, protein, fat and carbohydrates metabolism.

1.4.2. Pathological anatomy of the primary pulmonary tuberculosis

Primary tuberculosis develops after the first contact of macroorganism with MBT. MBT fill in the peripheral parts of the lungs when tiny particles containing MBT are inhaled through the superior respiratory tract. The mycobacterium remains there and reproduces slowly forming the primary pulmonary affection (focus). In this way, mycobacterium falling into the lymph through which they are transported to the lymph nodes. The classical form of morphological manifestation of primary tuberculosis is the primary tuberculosis complex. In 90% of cases, the formation of the primary tuberculosis complex are located in the superior and middle parts of the lungs but can be found in the small intestine, bones, etc.

In the primary lung focus, alveolitis develops, which is quickly replaced by the typical development of caseosis necrosis. In the centre of primary focus, caseosis forms but in the periphery – elements of non specific inflammation occur. The primary lung affect localizes more often just under pleura, therefore frequently pleura is involved in the inflammation process.
The lymphatic vessels expand, their walls becoming infiltrated and tubercles appear. In the regional lymphatic nodes, there are elements of inflammations converting into specific caseous changes with necrosis.

**Perifocal inflammation** around the lymph nodes will spread in the mediastinum and surround the lung tissues. The inflammation process within the lymph nodes is most intense in the primary affection area. Therefore, reparative changes in the lymph nodes will be slower.

The dynamic study of primary pulmonary processes among children has allowed to allot 4 phases of the **primary tuberculosis course**:

1. pneumonic;
2. phase of dissolving;
3. phase of condensation;
4. formation of Gohn’s focus.

**Phase 1 (pneumonic) of primary complex formation (explanation in the text)**

<table>
<thead>
<tr>
<th><img src="image1.png" alt="Image" /></th>
<th><strong>In the first phase (pneumonic)</strong> the focus of broncho-lobular pneumonia (3) is determined with a size of 1.5-2 till 5 cm. The form of the lung focus (3) is round or irregular, with heterogenous character and dim contours. Enlarged regional lymphatic nodes (1) are determined simultaneously (the picture of infiltrative bronchoadenitis) and there is an amplification of bronchial vessels picture – <strong>lymphangitis (2)</strong> between the focus and the lung root. The inflammative changes in the lung and in the lymph nodes (lymphadenitis) and lymph paths (lymphangitis) are together known as the <strong>Primary tuberculosis complex</strong>. Thus, the picture of primary tubercular complex consists of three components: <strong>changes in the lungs (3), lymphangitis (2) and lymphadenitis (1)</strong>. (See Fig. 5.)</th>
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**Phase 2 of dissolving (bipolarity)**

In the second phase of dissolving (bipolarity) the reduction of the perifocal zone of inflammation (3) is observed. The centrally located caseous focus becomes more prominent. The signs of inflammation in regional lymphatic nodes (1) and in the zone of bronchopulmonary vessels are decreasing.

**Phase 3 – condensation**

**In the third phase**, the phase of condensation: the primary focus is well outlined (3), its contours are cleared, on periphery of the focus there is the beginning of calcification as fine pieces; at peripheral regional bronchial lymphatic nodes calcification is also present (1).

**Phase 4 - formation of Gohn’s focus**

**In the fourth phase**, in the place of broncho-lobular pneumonia (3) calcification become compact, the focus is round with regular precise contours, its size does not exceed 3-5 mm. This formation is called **focus**.

Outcomes of the primary tubercular complex may be in the following way:

1. healing with encapsulation, calcification or ossification;
2. **progression** and **generalization** of the inflammation process. It may be accompanied with complications such as atelectasis, pneumosclerosis, etc.
There are 2 types of generalization of the tubercular complex progression:
1) hematogenic;
2) lymphogenic
3) bronchogenic

Hematogenic generalization develops when MBT penetrates blood circulation. A prerequisite for hematogenic generalization to occur is hyperergia. Two types of early generalization process have been identified depending on the condition of the primary tubercular complex:

1. generalized miliary tuberculosis with massive dissemination of the productive or exudative nodes in all organs;
2. focal tuberculosis with formation of caseous foci, with the size up to 1 cm.

The foci of hematogenic generalization might become a source for the development of tuberculosis in different organs.

At progression of hematogenous disseminated tuberculosis the cavities are formed. The formation of cavities is the result of cheesy disintegration and dissolution of necrotic masses. The cavities are usually thin-walled, multiple and settled down symmetrically in both lungs. In an origin of such cavities, important role plays damage of blood vessels, their thrombosis and obliteration. The blood supply of these focuses is disturbed in lungs and destruction is formed resembling trophic ulcers. During the formation of the cavities, the possibility of bronchogenic dissemination of healthy regions of lungs can appear.

Hematogenic dissemination of mycobacterium is always combined with lymphogenic. Thus MBT not necessarily penetrate into the blood at one time at the destruction of the large focal necrosis. They can penetrate repeatedly by small portions, passing in the beginning through the lymphatic vessels. Such genesis gives different clinical and X-ray display of hematogenic disseminated forms with various courses, duration of the disease and with heavy outcome or recovery.

The tubercular focuses in lymphatic nodes are poorly accessible to action of antibacterial drugs, but they are the source of serious complications: such as distribution of the tubercular process on the mediastinum organs; joining of a secondary infection; development of amyloidosis of internal organs.
More commonly, the primary lesion remains inactive (quiescent) and may remain so for decades or for the whole individual’s life. The precise mechanisms underlying this phenomenon have not yet been clarified. However, reactivation or reinfection of tuberculosis may occur due to malnutrition, malignant disease, HIV infection, use of immunosuppressive drugs, concomitant infection and non-infection diseases.

The inflammative changes in the lung (1) and (2) in the lymph nodes (lymphadenitis) and lymph paths (lymphangitis) are together known as the Primary tuberculosis complex.

1.4.3. Pathological anatomy of secondary tuberculosis

The progression of tuberculosis is divided into 2 separate consecutive periods reflecting different clinical and pathomorphological picture of the disease.

Post-primary (secondary) tuberculosis – this definition is used for tuberculosis, which has been developed in organism with old post primary lesions, which were partially healed. Occurrence and development of secondary tuberculosis can rise in two ways:

1) endogenous super infection – reactivation of the residual post primary focuses (partially calcified lymphatic nodes);

2) exogenous super infection (reinfection) – repeated tuberculosis infection.

Secondary tuberculosis (90% of most cases) – is pulmonary tuberculosis. The tubercular changes of the secondary period in lungs quite often are detected at fluorography or X-ray, that are made during preventive checkup without any complaints of the patients. This tendency is one of the indirect proofs that the patient does not feel the illness as it developed asymptotically. In such cases, X-ray tubercular affections appear as a medium-sized foci in lungs or in the other organs. However, in lungs they seen more often.

During the secondary tuberculosis the spread of infection as a rule proceeds through the bronchial airways.

The most important event that determines if the patient, especially the adult patient, will have significant clinical tuberculosis is the softening and liquefaction of the caseous necrotic material. During liquefaction, there is a massive increase in the number of bacilli which grow extra cellular in this situation.

Evolution of secondary tuberculosis is possible to divide into phases:

- lesion formation in upper parts of lungs in adults. It is often in the upper part of the lung. The lesions in the hilar lymph nodes usually absent (though sometimes – among
Africans, Asians or patients with HIV infection – the nodes may be greatly enlarged). The lung and lymph node lesions often heal and may later be calcified;

- **gradual enlargement of the lung lesions**;
- **caseation (necrosis)**. Liquefied caseous material may be coughed up. This results in a cavity. Spread of TB from the cavity to produce further lesions in the same and in the opposite lung with a further cavity developing in that lung;
- after a year or two of effective treatment (if the patient survives) in the places of specific lesions **fibrosis (scarring) of cavities** develops which pulls up the hilum and the trachea to the side of biggest damage.

**Calcification starts to occur** during the beginning stages of tubercular foci development in apical lesions. But the cavities can be still open. This type of chronic tuberculosis is a major source of infection.

### 1.4.3. Pathological anatomy of secondary tuberculosis

#### 1.4.3.1. Focus pulmonary tuberculosis

The **focus pulmonary tuberculosis** referred to the manifestation of secondary tuberculosis. It is the initial form of pulmonary tuberculosis in an adult. To this type of tuberculosis refer: fresh or soft focal tuberculosis; fibrotic focal tuberculosis; long-standing tuberculosis with foci of less than 1 cm in diameter.

**Soft focus pulmonary tuberculosis** morphologically represented by the development of endo- and peri-bronchitis of the fine apical branches (1-st and 2-nd order of the segmental bronchi). There is subsequent caseous necrosis in the bronchial walls. The involvement of the nearby alveoli results in the formation of caseous acinus or lobular bronchial pneumonia.

For a long period of time, the process within the lungs will be limited within the acini or lobules. As the process progresses, new foci will appear near the original focus, developing by contact within the limits of the same lung segment. Lymphostasis will develop in the lymphatic vessels, fibrotic tissue layers, peribronchial and perivascular tissues, passing on the lung hilum.

The typical path of the lung focal tuberculosis progression is a bronchogenic progression. New bronchial pneumonic foci will form from this progression. However damage of lymph nodes is not characteristic.

At favorable course the bronchopneumonic focuses are exposed to encapsulation, calcification, fibrosis or hyalinosis.

The focuses («re-infects») have character of latent development at the fibrotic focus pulmonary tuberculosis, but under adverse conditions, their aggravation possible with exudative reactions and growth of a zone of necrosis.

At tubercular damage of bronchial tree with MBT expectoration the destructive (cavitary) form of pulmonary tuberculosis develops.

At reverse tubercular process quite often diffuse sclerosis develops of the top segments.
1.4.3.2. Infiltrative-pneumonic pulmonary tuberculosis and caseous pneumonia

The infiltrative pulmonary tuberculosis known for a long time. T.H. Laenec [1781-1926] on the basis of the section data has described it as gelatinous pneumonia.

The infiltration develops because of exacerbation of encapsulated focuses, which can be not only in lungs, but also in the intrathoracic lymphatic nodes. When an infiltrative focus develops in the unaltered tissue, then around fresh tubercular focus or fused several focuses perifocal inflammation is developed.

Infiltrative pulmonary tuberculosis characterized by the presence in lungs inflammatory changes, mainly of exudative character with caseous necrosis and with the presence or absence of lung tissue destruction.

The etiology of infiltrative pulmonary tuberculosis can be of various origins. In some groups of patients, infiltrative focuses are developed as a result of bronchogenic dissemination of MBT to healthy pulmonary tissue from inflamed latent apical focuses. While in other groups of patients the infiltrations represent a perifocal inflammation of small infiltrative focuses of older origin, which consequently radiographically difficult to be determined.

The pathological-anatomical picture of the infiltrative pulmonary tuberculosis is characterized by presence one or several fine focuses of cheesy necrosis, with different time duration with a zone of perifocal inflammation, which volume exceeds their sizes in several times.

The character of the exudate is various at this form: serous, serous-fibrinous, sometimes as desquamative alveolitis, caseous infiltration. According to extent the process can be limited by lobule, but can occupy the whole lobe of a lung.

Proliferative reaction comes to an end by development of a connective tissue, giving the appearance interstitially indurative fibroid fields.

Outcomes of the infiltrative pulmonary tuberculosis:

1. Complete resorption of the perifocal zone or carnification of the damaged focus with encapsulation and calcification (transition to fibrotic focus form).

2. Caseation of the perifocal zone of inflammation, joining of disintegration, sequestration and transition into the acute caseous pneumonia or cavernous pulmonary tuberculosis.

3. At predisposition of infiltration to development of caseous necrosis the infiltration is exposed to complete or partial disintegration. As a result of caseous mass discharge the pneumogenic cavity is formed which size depends on a volume of infiltrative pneumonic focus and necrosis.

Caseous pneumonia

The caseous pneumonia arises more often as a result of progression of the infiltrative pulmonary tuberculosis, but can aggravate the development of any form of pulmonary tuberculosis. The basic morphological attribute of the caseous pneumonia is prevalence of caseous changes above unspecific perifocal. Depending on the size of the lung volume the following caseous pneumonia are distinguished:

1. acinous;
2. lobular confluent;
3. segmental;
4. lobar caseous.

During the progression of caseous pneumonia, the pulmonary tuberculosis develops with numerous cavities.

1.4.3.4. Cavernous and fibrotic-cavernous pulmonary tuberculosis

Cavernous tuberculosis is characterized by the presence of a thin-walled cavity, without perifocal inflammation, with solitary focuses in surrounding tissue.

Cavernous pulmonary tuberculosis originate from:

1. discharge of the caseous masses, from the tuberculous infiltrative-pneumonic focus in lungs (the pneumogenic acute cavity);
2. from the focus with a capsule (tuber-culoma), due to discharge of caseous masses).

Lung cavities have:

1. an external fibrotic capsule and
2. an internal capsule consisted of regions of not tear away caseous necrosis.

Complications of the cavernous tuberculosis. For the cavernous pulmonary tuberculosis bronchogenic way of progressing is typical. Concerning complications of the cavernous tuberculosis it is necessary to note an opportunity of the profuse hemorrhage. The cavernous tuberculosis at the further development converts into the fibrotic-cavernous one.

Fibrotic-cavernous pulmonary tuberculosis

Fibrotic-cavernous pulmonary tuberculosis develops from any progressing form of pulmonary tuberculosis with formation of the cavity, in which the wall expressed by fibrotic component. Certainly, it is not easy to define which process was a source and served as the reason for development of far advanced fibrous-cavernous pulmonary tuberculosis.

At fibrotic-cavernous tuberculosis three layers begin clearly to be defined in the wall of the cavity:

1. an internal necrotic layer;
2. middle – as the layer of tubercular granulation tissue;
3. the external, layer of a cavity wall consists of a fibrous connecting tissue.

The transition from sharp cavernous to fibrotic-cavernous tuberculosis morphologically consists in development of sclerotic changes as in the cavity wall, so in surrounding lung tissue. With time the structure of a wall and a cavity appearances change. The external layer can be of various thickness, as its structure can comprise of adjacent atelectatic lung tissue.

For fibrotic-cavernous tuberculosis, the focuses of repeated bronchogenic dissemination of various remoteness of events are characteristic. As a rule, the cavity drainage bronchus is damaged. Other morphological changes develop also in lungs such as pneumosclerosis, emphysema bronchoectasia.
The way of **progression of the fibrotic-cavernous pulmonary tuberculosis** is developed by contact along bronchi in direction from the top of the lungs to their base. The damage of the bronchial tree reveal in all cases of fibrotic-cavernous pulmonary tuberculosis.

**The damage extent in lungs** can be various. The process can be unilateral and bilateral with presence of one or multiple cavities.

### 1.4.3.6. Tubercular pleurisy

The **pleurisy**, is the inflammation of pleura. Two basic forms of pleurisy are distinguished: dry or fibrinous (pleuritis sicca, fibrinosa), and exudative (pleuritis exudativa).

**During** tuberculosis the pleura is involved in the process of inflammation at penetration in it infection by the contact way, through the lymph or the blood. The involvement of pleura in various pathological processes is conditioned by close anatomic topographical connections of visceral and parietal pleura with lung tissue, intrathoracic lymphatic nodes. The pleura, having barrier function, reacts to various pathophysiological changes of the body. Therefore, the developments of inflammative or allergic processes take place.

**Exudative inflammative reaction of the pleura** is connected with increased permeability of the blood and lymphatic capillaries of the lung cortical layer and pleura itself. These capillaries make way for a liquid part of blood into intra tissue fissures, superficial layers of pleura and there from, with the help negative pressure, into pleural cavity.

**Lymphagenic pleurisy.** The tubercular infection can affect subpleural lymphatic nodes. Accumulating in the nodes Mycobacterium tuberculosis, some are bricked up and are eliminated and the rest of MBT, keeping their virulence, are distributed along lymph vessels cause subpleural cortical lymphangitis or the exudative pleurisy.

**Hematogenic pleurisy.** The hematogenic spreading of MBT into the pleural cavity promotes development of tubercles on the pleura. The initial focus is an active tubercular process in mediastinum lymphatic nodes.

**The contact way of MBT dissemination** arises at active tuberculosis of lymphatic mediastinum nodes, with defeat of visceral pleura.

**Fibrinous pleurisy** (dry pleurisy). At the fibrinous pleurisy on the pleura at first, gentle layer occurs, of fibrinous structure, which could easily remove. Further the fibrinous pellicle of yellowish or yellowish-gray color is formed.

**Purulent pleurisy (empyema)** from the very beginning arises as purulent very rare, but more often it develops after serous-fibrinous inflammation of the pleura. The process usually happens unilateral and mainly settles down in basal or posterior part of the pleural cavity. The purulent pleurisy is observed at bursting out of caseous masses from lung into the pleural cavity, broncho-pleural fistulas and etc.

**Hemorrhagic pleurisy** accompanied by penetration of exudates containing a significant impurity of erythrocytes into pleural cavity.
Outcome of pleurisy

In overwhelming majority of cases the fibrinous exudates dissolves only partially, and basically is subjected to transformation, that leads to development of commissural joints, fibrotic thickening of the pleura, to obliteration of the pleural cavities.

Purulent exudate seldom is exposed to complete dissolution; more often the encapsulation of the inflammatve effusion is developed. The inflammatve process at pleural empyema can pass on interstitial lung tissues (purulent pneumonia).

Chronic pleurisy

More often chronic course of the pleurisy is observed at pleural empyema. In these cases exudates condense, dissociate, turn in cheesy mass or thin gruel with presence of cholesterol crystals; the microorganisms can disappear. The pleural membranes are considerably thickened and dense, sometimes with focal petrification and even ossification. The significant sediments of calcified masses are especially typical for tubercular empyema. The pleural empyema can lead to purulent – resorption fever, sepsis, exhaustion, amyloidosis of internal organs. Sometimes long, chronic current is observed at serous-fibrotic and fibrotic pleurisy.

During acute and chronic pleurisies the significant accumulation of exudates in the pleural cavity causes the atelectasis in appropriate lung and the mediastinum organs are displaced in the opposite side.

1.4.3.7. Tuberculosis of bronchi, trachea, upper respiratory tract

Tuberculosis of bronchi, trachea, upper respiratory tract and other organs: (nose, buccal cavity, pharynx) are the complications of primary and secondary pulmonary and of intrathoracic lymph nodes tuberculosis. Sometimes these forms especially bronchi tuberculosis can be isolated.

Pathologoanatomic changes in tuberculosis of bronchi, trachea, upper respiratory tract etc. (nose, oral cavity, and pharynx) are characterized by formation of typical epithelioid tubercles with Langhance gigantic cells with proliferation of connective tissue. The formation of the foci of necrosis, cheesy disintegration, edemas with MBT existence, revealed at histological investigations, characterizes predominantly exudative type of the reaction. The epithelioid tubercles are located more often superficially and directly under the epithelium. Owing to cheesy disintegration at progressing development of infiltrates, tubercles arranged under an epithelium there comes formation of ulcers.

Pathomorphology of healing processes are characterized by intensive development of fibrous connective tissue grows through tubercles and encapsulating them.

1.4.4. Conclusion.

Tuberculosis is infectious disease. No case of tuberculosis can be without mycobacteria tuberculosis. But if the disease arises it develops not only in the place of direct contact of pathogen with host's tissues. The study of tubercular morphology of various manifestations shows the existence of not only injuries and destructive processes caused by tuberculosis, but number of events typical for modified reactivity of the patient and for recovering.
So, healing or exacerbations are antagonistic, but interrelated phases of tuberculosis development. In any of these phases each process can transfer into another and the reasons of this transition locate not only in the focus, but based on general vital functions of the host.

Any tubercular focus aroused in the host could not consider as isolated formation. The processes having place during tuberculosis recovery such as dissolution, encapsulation, organization of hyaline capsule, calcification, ossification do not isolate the focus from a host, but are the signs of the inseparably linkage.

Hence, manifold clinical course of tuberculosis represents complicated but common uninterrupted process of MBT interaction with the human organism. All systems of the human body participate in this process.

1.5. EPIDEMIOLOGY OF TUBERCULOSIS

Tuberculosis infection and disease patterns among different populations are heterogeneous. Understanding the epidemiology of this disease is, therefore, vitally important as an aid to diagnosis, prevention, and public health program development.

Tasks of tuberculosis epidemiology:

1. Identifiable populations at risk.
2. The scope and impact of the infection.
3. Temporal trends in infection patterns.
5. Reservoirs and mechanisms of transmission.
6. Risk factors – why do some become infected and/or diseased and others not?

Epidemiological definitions (terms)

Epidemiological situation concerning tuberculosis is characterized by the following statistical data: infection; incidence; prevalence; mortality.

Infection (infected/contaminated) – percentage of persons with positive tuberculin reactions, if the reactions are not due to vaccination.

Incidence Rate (incidence of new cases). The incidence rate is the number of new cases of active disease (events) occurring in an identified population over a time period. Generally, tuberculosis morbidity is referred to in events per 100,000 populations per year.

Prevalence of tuberculosis. Prevalence is the number of patients with active forms of tuberculosis in a population at the end of the year per 100000 population, the special importance has the prevalence index of active (MBT positive cases of pulmonary tuberculosis). Prevalence thus reflects the cumulative morbidity from tuberculosis. If all new cases were promptly «cured» by treatment, the incidence and prevalence of disease would be closely approximate. But if patients are lost from therapy or partially treated, cases of chronic tuberculosis will accumulate, causing gross disparities in the incidence and prevalence values.

Mortality from tuberculosis – number of patients died because of tuberculosis per 100000 populations.
**Smear-Positive (Bacillary, MBT+) case of pulmonary tuberculosis**, this refers to a patient with tuberculosis of the respiratory tract whose airway secretions, when examined by special stains and microscopy, demonstrate tubercle bacilli. Some authorities refer to these as "bacillary" cases.

**Smear-Negative Pulmonary Case (MBT-).**

This refers to a patient with pulmonary disease whose sputum microscopy examination fails to demonstrate bacilli. The diagnosis of disease is established by symptomatology, positive cultures, progressive changes on chest radiograph deemed to reflect disease activity, and/or other supporting data such as positive tuberculin skin test reactivity, epidemiological features, and – for infants and children – a history of exposure to tuberculosis.

**Extra pulmonary disease.** This is the case of a patient whose clinical illness presents with active inflammatory tuberculosis in organs outside the lungs. Depending on age, race, and immunological competency, 5% to 70% of patients who develop active tuberculosis will manifest it primarily in the organs other than the lungs. Most patients have either pulmonary or extrapulmonary tuberculosis; a minority manifests simultaneous disease in both systems. Although extrapulmonary and smear-negative pulmonary cases are both clearly components of the overall morbidity of tuberculosis, they are less significant epidemiologically than sputum smear-positive cases, which act as the primary vectors of transmission to others.

**Annual Rate of Infection (ARI).** The annual rate of infection (ARI) is yearly incidence of new tuberculous infections among "eligible" (tuberculin-negative, not previously infected) members of a population, manifested primarily by tuberculin skin test conversion rates.

The ARI has been employed as indirect or inferential marker of the prevalence of sputum smear-positive (communicable) cases; within a population. By following a group individuals known to be non reactive to tuberculin and observing the frequency with which their skin tests become reactive through time authorities have attempted to estimate the total tuberculosis morbidity within that community by comparison with established data bases. This technique has been employed primarily in developing nations that lack the resources for consistent diagnosis and case tabulations.

**Tuberculosis infected.** This is the state of harboring viable tubercle bacilli within one's body without manifesting signs or symptoms of overt disease. The great majority of normal individuals who are exposed to and infected with MBT enjoy this status throughout their entire lives.

**Diseased tuberculous patients.** This is the state of suffering from active, progressive invasion of an organ or organs by MBT. This typically is manifested by constitutional symptoms or signs or symptoms that relate to a specific organ system. In most cases, a tuberculin skin test is reactive, but this test is neither specific nor sensitive for disease status. The most important bacteriological confirmation is cultivation of MBT from the sputum, or from the tissues of different organs.

Largely for public health communication and reporting, **World Health Organization** recommends a system to classify persons with known or suspected disease and individuals being evaluated in contact investigations surrounding new cases.

Information gathered in this system forms the backbone of case reporting in the world. As a morbid case of tuberculosis – is accepted a disease confirmed by detection of mycobacterium tuberculosis, allocated from the affected focus, (with sputum, urine etc.) or received from tissues by biopsy.
According to this classification the patients are divided into 6 groups.

**Group 0.** No known exposure to TB and a negative tuberculin test.

**Group 1.** Tuberculosis exposure, with no evidence of infection. Person known to have been exposed but tuberculin test is negative. If infant, may also include negative chest x-ray. May require follow-up at 3 months to confirm the disease.

**Group 2.** Tuberculous infection, without disease. Persons with significant tuberculin reaction but without clinical, radio-graphic, or bacteriologic evidence of disease.

**Group 3.** This group includes all patients with clinically active tuberculosis whose diagnostic studies is adequate to confirm the diagnosis; if inconclusive, should list as class 5.

**Group 4.** Tuberculosis, not clinically active.

A history of previous episode(s) of tuberculosis or abnormal but stable chest x-ray, positive tuberculin test, negative bacteriology (if done), and no clinical or radiographic signs of disease. Until active disease is excluded, should list as class 5.

**Group 5.** Tuberculosis suspects (diagnosis pending).

Persons in whom active tuberculosis is suspected on basis of clinical, radiographic, and/or epidemiologic factors. Use this status for up to 3 months while complete evaluation is pending.

**Global and continental epidemiology.** The profile of tuberculosis in the world today has been developed by a mix of direct observations and inferential means such as the annual risk of infection (ARI), as detailed above. Because tuberculosis is most extensive in impoverished nations, which typically have inadequate health information systems, much of the information is indirect. Because of deficiencies in reporting in the areas where tuberculosis is most prolific, these numbers are far lower. Looking at longitudinal trends for tuberculosis, it could be noted a clear divergence between the industrialized nations, where incident case numbers and rates steadily and substantially declined, and the developing world, where the number of reported cases remained stable or rose. In the developing nations, if incidence rates declined, they did so only as a result of the dilution effects of explosive population growth.

In general, infected and tuberculous patient’s pool grows in the world.

**2. THE METHODS OF TUBERCULOSIS DIAGNOSTICS**

**2.1. SETTING QUESTIONS**

The majority of cases of tuberculosis generally discovered when the patient visits his/her general practitioner.

The patient feeling some type of discomfort does not immediately refer to the doctor. Patient complains of a somewhat constant sub-febrile temperature up to 37.5°C. Dry cough with occasional presence of sputum appears in case of advanced TB. Heavy smokers do not pay adequate attention to their coughing and relates their coughing to smoking rather than TB.

Medical professionals whatever their specialty must be aware of the TB prevalence. Here is a set of questions that are to be addressed in the case a doctor is faced with a tuberculous patient:

1. Whether the given patient was prior infected by tuberculosis?
2. Whether his/her relatives were infected by tuberculosis?
3. Whether the patient had contact with tuberculous patients or animals (household, professional, industrial contact)?
4. Whether the patient is registered in a tuberculosis dispensary due to: tuberculin testing or hypersensitive reaction to the test, contact with tuberculous patients, and no clear diagnosis of tuberculosis.
5. When the patient had the X-ray examination?
6. Whether the patient was invited after the X-ray examination for additional research?
7. Whether he was in a prison or lived with someone who was in a prison.
8. Whether the patient is homeless, a refugee, migrant or being in unfavorable social conditions?

In the recent years, AIDS has become one of the most powerful increasing factors, of TB infection. Patients simultaneously infected with HIV and MBT, have a 50% increased chance of developing TB.

A thorough anamnesis must be performed, as it is necessary to pay attention to the frequency of repeated respiratory infections. The respiratory infections will usually be described as the common cold. If a patient contracted influenza and still has a long-standing sub-febrile body temperature accompanied with coughing, then we should not suspect Influenza but rather one of TB’s manifestations.

If a patient had suffered from exudative or dry pleuritis, this might be an indication for the presence of tuberculosis in past.

Upon gathering anamnesis among teenagers, adults and elderly patients, it is very essential to obtain the following information whether they had suffered from chronic conjunctivitis; erythema nodosum; other poorly displayed signs of tubercular intoxication.

Upon gathering anamnesis, it is also necessary to find out, when the tuberculin test reacted positive for the first time.

After a well-collected anamnesis, it is easier for the doctor to confirm his assumption of presence of tubercular process.

2.2. SYMPTOMS OF TUBERCULOSIS

If a patient has any of the following, consider him a 'Tuberculosis Suspect':

1. Cough for over 3 weeks.
2. Haemoptysis.
3. Pain in the chest for over 3 weeks.

4. Fever for over 3 weeks.
   All these can be due to some other diseases but sputum must be tested if any of the symptoms are present.

   Cough and sputum is very common everywhere. Much of this is due to acute respiratory infections and lasts only a week or two.

   There is also much chronic cough due to chronic bronchitis (sometimes called 'Chronic Obstructive Pulmonary Disease' (COPD or other names). This is mostly due to tobacco smoking, but may also occur from atmospheric pollution (either due to cooking or heating fires or in some places due to industrial pollution).

   As we shall see, certain additional symptoms may suggest tuberculosis. However, often this is not obvious: the only way to confirm the diagnosis is to examine the sputum for MBT presence at least 3 times, in everyone who have had a cough for more than 3 weeks.

   Here are some guidelines for the proper diagnosis of pulmonary tuberculosis.
General Symptoms:
++ Loss of weight.
++ Fever and sweating.
+ Loss of appetite.
+ Breathlessness.

Respiratory Symptoms:
+++ Cough.
+++ Sputum.
++ Blood-spitting.
+ Tiredness.
+ Chest wall pain.
+ Localized wheeze in lungs.
+ Frequent colds.

(The number of plus (+) sign show which symptoms are most important for tuberculosis.)

It is important to remember that all the symptoms could be due to other illnesses.

One of the most important signs, that should raise suspicion of possible tuberculosis, is that the symptoms have developed gradually over weeks or months.

Cough, of course, is a common symptom after acute respiratory infections. It is also common in smokers. It is common in some areas where the houses or huts have no chimneys and the houses are often full of smoke when fires may be used for heating as well as cooking.

Both tobacco and domestic smoke lead to chronic bronchitis. Cough may develop gradually in a patient with lung cancer, which is becoming commoner in countries with increasing cigarette smoking.

Bronchiectasis is common in some countries: the patient may have had a chronic cough with purulent sputum since childhood. However, if a patient has had a cough for more than 3 weeks you must get his sputum examined for TB to make sure that the cough is not due to tuberculosis.

There is nothing in the sputum which itself suggests tuberculosis: it may be mucoid, purulent or contain blood. In tuberculosis, blood in the sputum may vary from a few spots to a sudden coughing of a large amount of blood. Occasionally this blood loss is so high that the patient quickly dies, usually from asphyxia due to aspirated blood.

Presence of blood in sputum calls for sputum examination for MBT.

Pains in the chest occur often in tuberculosis. Sometimes it is just a dull ache. Sometimes it is worst on breathing in (due to pleurisy). Sometimes it is due to muscle strain from coughing.

Breathlessness in tuberculosis is due to general infection of the lung tissues, or to pleural effusion complicating the lung tuberculosis.

Sometimes patients seem to have developed acute pneumonia. However, such pneumonia may not get better with routine antibiotics. The cough and fever may persist. The patient remains ill. If you question him closely, you may find that he has had cough and loss of weight for weeks or months before the pneumonia developed.

One should remember that, in an older smoker, cough and loss of weight, which comes on gradually, may be due to lung cancer. However, one must check for tuberculosis by examining the sputum.

Women who develop tuberculosis may stop having menstruation (amenorrhea).

Physical signs. Often these do not help much. But do examine the patient carefully. The pathognomonic signs could be revealed.

1. General condition. Sometimes the patient appears to be in good health despite advanced disease.

2. There may be different type of fevers. There may be only slight rise of temperature in the evening. The temperature may be high or irregular. Often there is no fever.

3. Pulse is usually raised in proportion to fever.
4. **Finger clubbing.** This symptom may be encountered, especially in patients with extensive disease. One should keep in mind that clubbing is common in lung cancer.

5. **Examination of chest.** Often there are no abnormal signs. The commonest is **fine crepitations** (crackles) in the upper part of one or both lungs. These are heard particularly on taking a deep breath after coughing. Later there may be **dullness to percussion** or even **bronchial breathing** in the upper part of both lungs. Occasionally there is a **localized wheeze** due to local tuberculous bronchitis or pressure by a lymph node on a bronchus. In chronic lung tuberculosis, with much fibrosis (scarring), the scarring may pull the trachea or the heart over to one side. At any stage the physical signs of pleural effusion may be present.

However, often you will find nothing abnormal in the chest.

2.3. **LABORATORY METHODS OF MYCOBACTERIUM TUBERCULOSIS DETECTION**

Laboratories serve major roles in the diagnosis and management of tuberculosis – to detect presence of MTB in a patient. The laboratory MTB identification consists of the following methods:

1) sputum collection and processing;
2) microscopic identification of MTB in secretions or tissues;
3) culture techniques;
4) drug susceptibility testing;
5) serological testing;
6) performance of new molecular biological methods of MTB identification, including polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

**Collection of sputum specimens with MTB** performs in specially equipped medical institutions or in ambulatory services. The collected specimens immediately send for laboratory examination.

Special sputum containers should be used. They must be rigid to avoid crushing in transit and possess a wide-mouthed screw top hermetically scalable cover to prevent desiccation and to minimize contamination by leakage.

There are two acceptable types of container. One available from UNICEF (UN Children’s fund), is plastic with a black bottom, a translucent lid, and is readily destroyed by burning; the patient’s identification must be made on the container (not on the lid). The other is a heavy glass, screw-capped jar that may be reused after disinfection by boiling (10 min.) and thorough cleaning.

The risk of infection is very high when the patient coughs, therefore specimens must be collected as far away as possible from other people in specially prepared room.

**Additional procedures for MTB collection**

**Laryngeal swabs.** The operator should wear a mask and gown when taking a swab. The patient’s tongue pulled out using a piece of lint and the swab pushed down behind the tongue towards the larynx. The patient will cough and the swab will catch some mucus. The swab placed back into the sterile bottle and send to the laboratory for culture.

**Bronchial flush waters.** In modern diagnosis of lung tuberculosis and other organs, early detection of infected bronchi plays an important role. For this purpose, bronchial flush water examinations are applied in practice. The technique of bronchi flush waters is not difficult, but it is necessary to remember the contra-indications of its application. This technique should be applied with large care to the people of senile age. The procedure is contra-indicated for patient with bronchial asthma and those with heart-lung insufficiency.
To obtain bronchial flush waters, first anesthesia is performed of the upper airways. Physiological solution (15-20 ml) warmed up to 37°C is administered with a larynx syringe. This procedure will increase secretion from the bronchial mucosa. The patient will cough up the flush water. The flush water collected in a sterile flask and sent for bacterioscopy and for MBT culture. The examinations performed for a separate bronchus or for the whole branch. The method of bacterioscopy of bronchial flush waters and especially the MBT culture increases the possibility of MBT detection up to 11-20%.

**Gastric suction (Gastric flush waters).** Gastric suction usually used among children who are not able to cough out sputum, and for those adults, who have poor amount of sputum. The method is not difficult and gives rather a high percentage of detection of MBT not only with lung tuberculosis, but also with tuberculosis of other organs (skin, bones, joints etc.).

For reception of gastric flush waters, the patient in the morning should drink a glass of water. Then through a gastric tube, the stomach fluids collect in sterile flasks. The fluid is then centrifuge treated. Smears produced from the purulent elements processed as regular sputum (staining etc.).

**Examination of cerebrospinal fluid.** Upon suspicion of tubercular meningitis it is necessary to make a cerebrospinal fluid analysis as early as possible. When the cerebrospinal fluid is obtained, attention should be paid to the degree of pressure, under which it is discharged from the cerebrospinal canal. The liquid flowing by a continuous jet under the large pressure indicates an increased intracranial pressure. If the liquid expectorates by large often drops, it is a sign of normal pressure, and in the case of rare small drops – about a lowered pressure or about some obstruction to discharge.

Material for examination is placed in two sterile tubes. One tube is placed in a cold environment and after 12-24 hours film is formed on the surface of the liquor. Liquor collected in the second tube is used for the biochemical and cytological examinations.

**Bronchoscopy.** When other methods have failed to give a proper diagnosis, it is possible to collect bronchial material by a trap specimen through a bronchoscope. Biopsy of the lining of the bronchi may sometimes show typical changes of tuberculosis when histologically examined.

**Pleural fluid.** MBT may occasionally be seen in centrifuged pleural fluid, but usually are only found on culture. The larger the amount of fluid cultured the more likely to obtain a positive result.

**Pleural biopsy.** Pleural biopsy can be useful when there is pleural effusion. But it needs a special biopsy needle (Abrams punch), facilities for histology and trained personal.

**Lung biopsy.** Only experienced surgeon should use this method. A diagnosis may be made by histology or by finding MBT in the sections.

**Sputum microscopy.**

The simplest and fastest method of revealing acid-fast bacilli (AFB) used for over 100 years: sputum microscopy. AFB – mycobacterium that remain stained even after they washed in an acid solution and could be detected under a microscope in a stained smear. Mycobacteriums differ from other microorganisms by characteristic structure of their cell wall consisting of mycolic acids, which, due to absorption properties, cause ability for staining on techniques revealing AFB.

The resistance to standard dyes and the ability with which the mycobacterium retain certain dyes, once impregnated, are both due to the high lipid content of their cell walls. Generally, gram-positive bacteria have about 5% lipid or wax content in their cell walls, gram-negative organisms around 20%, and the mycobacterium roughly 60%.

Sputum microscopy or other separate material with MBT carried out by a "simple" method and method of flotation.

In the simple method, a smear is prepared with a sputum lump or drops from liquid substance (exudates, flash waters etc.). The material is placed between two glass slides. One of
smears is processed for Gram’s staining, in order to reveal the general flora, and the second smear – for MTB detection.

Main techniques that are still employed today – the carbol-fuchsin methods of Ziehl – Neelsen. The fundamental principles of this method relate to the ability of the cell wall to absorb carbol-fuchsin dye. The mycobacterial cell walls absorbing the red carbol-fuchsin are becoming so impregnated, that they resist decolorization even with a potent hydrochloric acid-ethanol solution (acid-alcohol). So, when the slide is counterstained with methylene blue, the MTB appear as red rods on the blue background.

Since 1989, immunofluorescent microscopy has largely supplanted the older, acid-fast methods in modern laboratories. Fundamentally, this technology relies on the same lipid-related affinity for dyes, but the stain in this case is auramine-rhodamine. The mycobacteria absorb this agent and resist decolorization with acid-alcohol, however, the auramine-rhodamine-stained bacilli fluorescents when excited with UV or other specially filtered light frequencies. The mycobacteria appear as bright yellow rods against an inky black background in the UV system.

Culture MBT examination
Isolation of MBT from clinical samples by culture still is main method tuberculosis diagnosis. At present, mycobacterial culture can be performed on conventional egg based solid medium such as Lowenstein-Jensen medium and agar based ones, such as Middlebrook 7H10 or 7H11 and liquid media.

Both types of media contain inhibitors to keep contaminants from out-growing MTB. The major constraint of culturing mycobacteria in conventional media is its slow growth which necessitates a mean incubation period of at least 4 weeks. The drug susceptibility tests to anti-tuberculosis drugs require additional 4 weeks.

MBT molecular-genetic diagnostic methods
Deciphered MBT genome has opened unlimited prospects, in development of the genetic-molecular tests, including the study and revealing of MBT and its diagnostics in the host.

The classical methods used for detection of MBT presence in host, such as bacterioscopy, cultural, serological, cytological are rather effective, but differ in either their insufficient sensitivity, or duration of revealing MBT. Development and the perfection of molecular-diagnostic methods have opened new prospects for fast revealing MBT in clinical samples.

Polymerase Chain Reaction is mostly used (PCR).
Polymerase chain reaction entails amplification of characteristic fragments of bacillary DNA that found in diagnostic specimens. This test used for detection of MBT in sputum or identification of species that are growing in culture medium.

The PCR allows carrying out MBT identification in a diagnostic material within 5-6 hours (including processing of a material) and has high specificity and sensitivity (in a range from 1-10 MBT cells in a sample).

2.4. THE IDENTIFICATION OF MBT DRUG RESISTANCE
Mycobacterium strains are considered to be sensitive to a given drug when the drug administered in the critical drug concentration (criteria of resistance) shows a bactericidal or bacteriostatic action.

Tolerance (resistance) is defined as the decrease in sensibility to the degree/extent that the given mycobacterium strains is capable of multiplying under the action of a drug having a critical or much higher concentration. Presently, besides the concepts of “sensitivity” and “resistance” to anti-tuberculosis drugs, other concepts determining the qualitative and quantitative characteristics of the drugs are also considered.

Characteristics of drug resistant tuberculosis
**Acquired (secondary) resistance** – it is in the case of such types of tuberculosis when the strain of tubercle bacilli change from a susceptible into resistant phenotype during or after a course of chemotherapy. In these cases, «inadequate» treatment leads to the selection of drug-resistant mutants.

The secondary resistance suspects among patients, whose anamnesis shows that they were under the treatment of anti-tuberculosis drugs for 1 or more months, and originally it was known, that at the beginning of the treatment, the MBT strain was sensitive to the anti-tuberculosis drug.

**Primary resistance.** In some instances, during initial medical encounter patients harbor a strain of MBT involving significant resistance to a single drug or resistance to several anti-tuberculosis drugs.

Primary resistance occurs when a person infected by MBT already resistant to one or more types of anti-tuberculosis drugs.

**Combined resistance.** The World Health Organization sums up primary and acquired resistance to determine the spread of a resistant strain.

**Monoresistance** – MBT strains that resistant to only one of the five first-line anti-tuberculosis drugs: rifampicin, isoniazid, ethambutol, pyrazinamide, streptomycin.

**Multidrug resistance (MDR)** – MBT strains that resistant to both isoniazid and rifampicin simultaneously there may be additional resistance to other anti-tuberculosis drugs.

**Polyresistance (combined) resistance** – MBT strains resistant to two or more anti-tuberculosis drugs without resistance to isoniazid and rifampicin.

**MDR (Multi-Drug Resistant) bacilli and MDR tuberculosis** is the most severe form of bacterial resistance today. MDR tuberculosis raises a serious concern for tuberculosis control in many countries.

Since the early 1990s, several outbreaks of MDR tuberculosis reported in different regions of the world, as consequence of inappropriate use of essential anti-tuberculosis drugs. Usually MDR tuberculosis occurs in chronic cases, after failure of standard scheme of chemotherapy suggested by WHO and other schemes of treatment. MDR tuberculosis represents a significant proportion of tuberculous patients with acquired resistance.

**Criteria for drug resistance**

The level of given strain resistance is expressed by the maximal concentration of a preparation (microgram quantity in 1 ml of media), at which the duplication of the MTB (according to number of colony formation on dense media) can still be observed.

The critical concentration established for different anti-tuberculosis drugs. The critical concentration is of clinical importance, as it indicates the concentration of drug in which MBT duplication would be sensitive.

Method of absolute concentrations in Lowenstein-Jensen inspissated egg media is widely used to determine MBT drug resistance.

**The drug resistant microorganisms** are capable to multiply in such concentrations of the drug in the media, which has bacteriostatic or bactericidal effect still take place.

**Genomic analysis of the MBT sensitivity to drugs.** The genetic loci of resistance mutations to isoniazid, rifampin, ethambutol, streptomycin, and the fluoroquinolones identified. Based on this type of methodology, molecular-biological techniques are rapidly improved and offer quick identification of the drug sensitivity of the clinical MBT strains.
2.5. SEROLOGICAL METHODS FOR DIAGNOSIS OF TUBERCULOSIS

Serological tests for tuberculosis develop throughout the twentieth century. Particular interest focused on patients with extrapulmonary forms of tuberculosis, since they generally do not have readily accessible diagnostic targets such as chest radiography or sputum. However, unlike many infectious diseases for which serologic diagnosis has proven a highly valuable tool, tuberculosis has largely defied efforts at developing a methodology that is sensitive, specific, and practical for clinical use.

Analysis of the many studies of the serological diagnosis of tuberculosis indicates that there is a diversity of antigens potentially involved, and a wide array of immune responses associated with different forms of tuberculosis disease (cavity pulmonary, noncavitary pulmonary and extrapulmonary).

The latest scientific research is directed to following c seroantigens and techniques:
- antigen of 38 Kilodaltons;
- antigen 5;
- antigen A60;
- antigen of 88 Kilodaltons;
- multiantigen analysis.

The application of modern methods of biochemical research enables to increase the sensitivity and specificity of individual proteins. They directly participate in all physiological and pathophysiological processes within the host.

On character of functions and number of individual properties these proteins can conditionally be divided into several groups:
2. Proteins, reactants of a sharp phase of an inflammation: C-reactive protein, alpha1 – acidic glycoprotein, alpha1 – antitrypsin.
4. Proteins entering in the host, mainly, in process of nutrition: transferrin, ferritin, pre-albumin.

Thus, serological methods do little to enhance the diagnostic yield above the current, very economical standard diagnostic tool, microscopy and conventional MBT detection. However, rapid progress of virtuoso molecular biology will bring new effective and cheap, serological tests. If one or more of the above tests were employed and interpreted in a manner that maximized their sensitivity, "clearly negative" results might effectively "rule out" tuberculosis in given patients. This could prove to be of considerable clinical and public health utility.

2.6. BLOOD AND URINE ANALYSIS

Red blood elements, as a rule, do not suffer serious changes in tuberculosis. Only after acute blood loss (i.e. lung or intestines) can cause anemia. The small downturn of hemoglobin is markedly increased in chronic forms of fibrotic-cavernous tuberculosis.

One of the parameters indicating activity of tubercular process is the ESR (erythrocyte sedimentation rate) reaction. Raised ESR not only demonstrates activity and volume of an ongoing fresh process, but also the volume of a chronic process, especially the fibrotic-cavernous process.

White blood cells have a more sensitive reaction to tubercular process.
Conditionally three different phases of white blood cells changes differ connected with characteristic changes of tubercular damage of the lungs:
1. Neutrophilic – phase of struggle. The number of neutrophiles increases in the blood results in a shift of blood formula to the left. Eosinophiles absent, the quantity of lymphocytes and monocytes reduce.
2. Monocytic – phase of overcoming the infection. In blood the quantity of lymphocytes is increased, there is a shift to the left and the number of neutrophiles decrease, single eosinophiles are present.

3. Phase of recovery. The number of lymphocytes and eosinophiles is increased. The Blood index normalizes gradually.

Such grouping on phases represents only general blood reactions.

**The analysis of urine**

Excretion of urine in tuberculosis patients is usually normal. Pathological changes could be revealed in tubercular infection of kidneys or in urinary tract. Signs of amyloidosis can be detected among patients with purulent chronic forms of lung and bones tuberculosis.

**2.7. RADIOGRAPHIC METHODS OF TUBERCULOSIS DIAGNOSIS**

**Introduction**

On the diagnostics of lung tuberculosis most frequently are applied the following X-ray methods:

1. x-ray;
2. radiography;
3. tomography;
4. fluorography.

**Rontgenoscopy (X-raying, X-ray examination, radioscopy, sciagraphy)** is the cheapest method of examination used for diagnostics. At rontgenoscopy the image of an organ is examined on the screen at the moment of X-raying. The disadvantage of this method is that it does not give the objective documentation of examination, badly reveals fine pathological formations, particularly in focuses of the size 2-3 mm and fine linear components. In lung tuberculosis, X-ray is applied to preliminary, orienting examination. This method is useful for revealing of exudations in pleural cavity, pathological formations hidden on radiograph behind the shadow of mediastinum and diaphragm, vertebra, and for specification of the process localization.

**Radiography (radiographic imaging, rontgenography).** This method displays details of pathological process more full. Standard radiograph is a projection of «shadows» of human organ on X-ray film. On passage through chest, the X-ray beam is non-uniform and proportionally weakened by the density of organs and tissues. This changed beam gets on a film containing brome silver, and film changes its property. The picture of restoration of film is seen after display and fixings. At those places where the exposition of X-rays on the film was stronger, the more silver was restored, so these places of the film are darker. At those places where the beams penetrate through dense formation – bones, calcifications etc. – less silver is restored and in this places the film is more transparent. This is mechanism of negative formation; the places treated by X-rays more intensively become darker. Therefore tumor, infiltrations, bones – are almost transparent on a film, and empty chest cavity in spontaneous pneumothorax – almost black.

The rigidity of X-ray film is estimated on a shadow of the vertebra. On the film of soft X-ray irradiation, the thoracic portion of the vertebral column presented as a continuous shadow. On the film of intensive irradiation every vertebra is seen well. On optimum X-ray irradiation the first 3-4 thoracic vertebra are visible. Other shadows of chest cavity in posterior – anterior (PA) projection have no decisive importance at in estimation of irradiation intensity.
Series of radiographs, made during the whole period of disease, allows to carry out dynamic supervision of the proceeding course in lungs. Radiography – is the basic X-ray method used now for diagnostics of lung tuberculosis. It is accepted to make direct (posterior – anterior / general view X-ray) and left or right profile radiograph depending on prospective localization of the lesion.

**Tomography** (body section radiography) is obtained by level snapshots through special devices to the X-ray installation. Radio-tomography of the chest cavity enables to get X-ray films without summation effect. «Spreading» of interfered tissues is reached by movement of X-ray tube and cartridge in opposite directions. Tomography applies to specify the character of process, its topography and study of details in the focus of damage, such as deep disintegration, to reveal borders and volume of damage more precisely.

**Fluorography** – is photographing of the x-ray image from fluorescent screen. Fluorograms could be with size of 34\times34 mm, 70\times70 mm and 100\times100 mm and electronic. The electronic fluorograms carry out with the help of special fluorography installations, equipped with a computer. Fluorography applies for massive preventive X-ray examinations of the population, with the purpose of revealing of latent forms of lung diseases, mainly lung tuberculosis and tumors.

**X-ray appearances of lung tuberculosis**

On radiograph tubercular lesions of lung parenchyma, stroma is revealed as shadows (densities, consolidations). At the description of these shadows it is necessary to take into account their:

1. quantity;
2. size;
3. form;
4. contours;
5. intensity;
6. structure;
7. localization.

The quantity of a shadow can be single or multiple, its size – fine, average, large, its form – rounded, oval, polygonal, linear, and irregular. The contours of shadows can be precise and indistinct. The intensity of shadows – weak, average, high; structure – homogeneous or non-homogeneous. Localizations of the shadows are indicated according lobes or segments of lungs.

The changes of lung picture are:

1. rod and
2. net character.

The tension bar appears as linear shadows going in parallel or of a «fanlike» arrangement of the lung markings. Net like lung shadows are defined by intertwine linear shadows. These shadows can be of various widths, from 1-2 up to 5-6 mm. Quite often they merge in wide strips, especially in lungs roots areas. Their contours are precise or dim. The intensity is average or high. Large or fine loops are formed at a net like arrangement of shadows.

**Rod-like and net-like** changes in the lung picture reflect inflammatory processes the scar and the fibrous changes in lymph vessels or in interlobular connective tissue. Usually for
inflammatory process (lymphangitis) large width, indistinct contours and average intensity of linear shadows are typical. For fibrotic and the scars are typical shadows of minor width, clear contours and high intensity. However, it is not an obligatory attributes. Repeated radiographic examinations are needed in order to distinguish fresh changes from the old in the connective tissue of lung. The fresh changes decrease or increase depending on the course of process (recovering or progressing), but old ones remain stable.

Focus shadows are the most often display of lung tuberculosis. They are defined as spots of size from 2-3 mm up to 1,0 cm in diameter. They can be single, but more often multiple. According to their sizes, the focuses are divided into three groups: fine – 2-4 mm, average size – up to 5-9 mm and large – up to 1-1,2 cm. The form of the foci can be rounding, polygonal, irregular and wrong. Contours can be precise or dim. Linear shadows are visible, rod-like, departing from a contour of the focus into surrounding lung parenchyma. The intensity of the foci could be weak, when it corresponds to the intensity of a longitudinal shadow of a vessel, average, corresponding to the intensity of transverse shadow of a vessel, high intensity corresponds to intensity of a rib, mediastinum.

The structure of the foci can be homogeneous and non-homogenous. The non-homogenous structure is observed usually at their irregular condensation and calcification, and at presence of disintegration. At irregular condensation and calcifications of the focuses the intensity of its shadow will be various in different parts; the intensity of an average degree settles down closely to the site of the large intensity. The disintegration is defined as enlightenment with a precise contour inside the shadow of the focus.

The infiltrations (infiltrative focuses) are shadows with the size more than 1,5 cm in diameter. Infiltrative focuses, according to their sizes are divided into fine – 2 cm, medium – up to 3 cm and large 4 cm and more. The infiltrations are usually formed at merge of the focuses or fine and medium infiltrations. Mainly infiltrations are single. Their forms could be round, oval, and irregular. Large infiltrations usually occupy segments or lobe and usually repeat the form of the lung subunit. Their contours are more often precise, the intensity is medium or high and structure is more often non-homogenous

Tuberculous cavities may be classified under three types:

1. forming (acute);
2. fresh;
3. old.

X-ray diagnosis of all kinds of cavities is based on detection of two attributes:

1. presence of closed ring-like shadow of various form and size inside the shadow;
2. internal contour of a cavity never repeats its outer contour.

The acute (forming) cavity is defined by enlightened irregular and distinct inlet contours A forming cavity is localized in the center (or eccentrically) of the area of caseation.

The fresh cavity is defined by a round ring like shadow with smooth thin fibrous wall, which develops more slowly within a small area of tuberculous infiltration. The width of the cavity wall is various, usually 5-10 mm. The fresh cavities could be with rounded, smooth, thin-walled «stamp-like cavities», which may develop because of check valve action of granulations at the bronchial communication.
If the fresh cavity arises among old tubercular changes (scars, fibrotic focuses), its form can be extended and even irregular. Characteristic sign of fresh cavities is the presence of two wide pair strips, going from its bottom poles to the lung root. This is the condensed wall caused by inflammation of draining bronchus.

The old cavity is defined as ring-like shadow with oval or irregular form, with precise internal and external contours formed as a result of chronic process. Its wall width usually reaches several millimeters, with high intensity. The multiple linear and rod-like densities of fibrosis are found around the shadow of the cavity. Frequently the walls of draining bronchus are visible, but these shadows are thinner and more intensive, than in fresh cavity.

The described attributes of different kinds of cavities are relative. They meet in significant percentage of cases, but not necessarily in all. Therefore, the possibility to make a final conclusion about freshness or chronicity of a cavity can be done only after dynamic supervision.

Statistically more frequently the lesions of secondary lung tuberculosis localize in I, II, VI segment and sometimes in X. Upper and dorsal departments, subclavicular area are the favorite locations of fresh tubercular lesions. In supraclavicular, areas and upper parts of lungs old specific tubercular densities are frequently determined.

The artifacts or defects on radiographs are named shadows or enlightenments caused by technical errors and which do not connected with the shadows of body tissues. The linear white strips can be simply scratches, round transparent stain or smudges – consequence of hit on the not shown film of a fixative substance. The branch-like or, similar figure of lightning black shadows arise at the electrostatic discharge due friction between films.

Techniques of description of the X-ray lung shadows. At the investigation of the lung’s X-ray it is convenient to use the consecutive order of their description.

1. **Localization** of process. Specify distribution on lobes and segments.
2. **Number**, quantity of shadows. Specify individual or multiple.
3. **Form**. Specify rounded, oval, polygonal, linear and irregular.
4. **The size of a shadow**. Specify fine, average, and large.
5. **The intensity**. Specify weak, average and high.
6. **The pattern** (spotty and linear), structure of a shadow (homogeneous or non-homogenous).
7. **The contours**. Specify precise and indistinct (dim).
8. **Displaysness**. Specify a position deviation of lung structures from their normal arrangement.
9. **Condition** of surrounding lung tissue.

Radiographic classification of tubercular lesions in lungs

In order to have a common ground of clinical understanding, the following classification is used mostly in **English literature** to denote the extent and degree of pulmonary involvement. From the X-ray standpoint the essential features of this classification are as follows:

**Extent of pulmonary lesions:**

1. **Minimal.** Slight lesions without demonstrable excavation confined to a small part of one or both lungs. The total extent of the lesions, regardless of distribution, shall not exceed the
equivalent of the volume of lung tissue, which lies above the second chondrosternal junction and the spine of the fourth or the fifth thoracic vertebra body on one side.

2. Moderately advanced. One or both lungs may be involved, but the total extent of the lesions should not exceed the following limits.

2.1. Slight disseminated changes that may extend through not more than the volume of one lung, or the equivalent of this in both lungs.

2.2. Dense and confluent changes that may extend through not more than the equivalent of one-third the volume of one lung.

2.3. Any gradation within the above limits.

2.4. Total diameter of cavities, if present, should not to exceed 4 cm.

3. Far Advanced. Lesions more extensive than moderately advanced.

2.8. ENDOSCOPIC METHODS FOR THE DIAGNOSIS OF TUBERCULOSIS


Thoracoscopy (pleuroscopy) Endoscopic biopsy.

All set forth above methods of research are accessible in equipped, specialized medical establishments staffed with the adequately trained personnel.

Tracheobronchoscopy.

The examination of bronchi and trachea executes in combination. For bronchoscopy a rigid (metal) or flexible bronchoscope with fiber glass optics (bronchofiberscope / fiber-optic bronchoscope) are used. On examination of bronchi to estimate the condition and ability of bleeding of the mucous membrane, character of bronchial contents, diameter of a bronchi lumen, elasticity, tone and mobility of a bronchial wall are estimated. Other deviations from norm are fixed also. An endoscopic picture is photographed. The examination is finished (if it necessary) by sampling of material pieces for bacteriological and pathology-anatomical examinations.

Bronchoscopic lavage.

During bronchoscopy getting of the lavage fluid allows to receive a material for diagnosis for histological verification for the diagnosis of TB at negative bacteriological data. Sometimes from the lavage waters, it is possible to reveal MBT, when it is impossible to reveal by other ways.

Thoracoscopy (pleuroscopy).

The investigation consists of by examination of pleural cavity. It is possible to use other optical devices, for example bronchofiberscope.

Transebronchial biopsy.

The direct indication of its realization is the presence of a pathology in main, lobe, segmental or subsegmental bronchi. For biopsy, various techniques are used: snap off (biopsy forcepsing), erasure by a curette, brush (spongy or brush biopsy), pressing by porolone sponge (sponge biopsy), puncture and aspiration.

Transthoracic needle biopsy.

Is used for getting:

- materials for the histological and cytological investigation from the pleura and lung tissues
• the biopsy material of lungs, pleura and lymphatic nodes by operation – opening of the chest cavity.

**Pleurocentesis (thoracocentesis) and paracentetic biopsy of pleura.**
By method of aspiration [needle] biopsy, it is possible to take a material from the pleura and the pleural fluid. From the fluid obtained at pleurocentesis, in sterile tubes select probes for laboratory research. The relative density of a fluid, cell composition of liquid etc are defined. Pleurocentesis is carried out with a special needle under the control of rontgenoscopy. Usually two samples of biopsy material are prepared, one sample for hystological investigations and another – for MBT presence.

### 3. CLINICAL FORMS OF TUBERCULOSIS
#### 3.1. CLINICAL CLASSIFICATION OF TUBERCULOSIS

**Clinical classification of tuberculosis is based on the following principles:**
1. Clinico-radiological features of tuberculosis disease process (including localization and extent).
2. Phases of the tubercular process.
3. Presence of bacterial emission.

**The classification consists of four main sections.**
2. The characteristics of tubercular process.
3. The complications of tuberculosis.
4. Residual changes after recovery of tuberculosis.

**Clinical forms of tuberculosis** differ according to localization and clinical-radiological features taking into consideration pathogenetic and pathomorphological characteristics of tubercular process.

**Tuberculosis of the respiratory organs:**
- Primary tuberculosis complex.
- Tuberculosis of the intra thoracic lymph nodes.
- Disseminated pulmonary tuberculosis.
- Miliary pulmonary tuberculosis.
- Focal pulmonary tuberculosis.
- Infiltrative pulmonary tuberculosis.
- Caseous pneumonia.
- Pulmonary tuberculoma.
- Cavernous pulmonary tuberculosis.
- Fibrotic-cavernous pulmonary tuberculosis.
- Cirrhotic pulmonary tuberculosis.
- Tuberculous pleurisy (including empyema).
- Bronchus, trachea, upper respiratory tract tuberculosis.

**Tuberculosis of the respiratory organs combined with professional lung diseases (Coniotuberculosis).**

**Non-pulmonary tuberculosis.** (Tuberculosis of other organs and systems):
- Meningleal and central nervous system tuberculosis.
- Tuberculous colitis, peritoneal and mesenteric lymph nodes tuberculosis.
- Tuberculosis of bones and joints.
- Genitourinary tuberculosis.
- Cutaneous and subcutaneous tuberculosis.
- Peripheral lymph nodes tuberculosis.
- Tuberculosis of the eye.
- Tuberculosis of other organs.
Tubercular process description specifies localization, clinical-radiological findings, presence of Mycobacterium tuberculosis (MBT) in diagnostic material of a patient.

Localization and extent are specified:
– by lobes and segments for lungs;
– by localization of lesions in other organs.

Phase:
a) infiltration, disintegration, dissemination;
b) resolution, induration, scarring, calcification.

Bacterioexcretion:
a) with mycobacterium tuberculosis discharge (MBT+)
b) without mycobacterium tuberculosis discharge (MBT-).

Complications of tuberculosis:
– hemoptysis and bronchial hemorrhage, spontaneous pneumothorax, cardiopulmonary insufficiency, atelectasis, amyloidosis, fistula and others.

Residual changes after recovery.

a) for respiratory apparatus:
– fibrous, fibrotic-focal and bullous-dystrophic changes, calcification in lungs and lymphatic nodes, pleuropgenic pneumosclerosis, cirrhosis, condition after surgery and others.
b) for other organs:
– scarring changes in different organs and their consequences, calcification, condition after surgery.

3.2. CLINICAL CLASSIFICATION OF TUBERCULOSIS OF THE RESPIRATORY ORGANS

3.2.1. PRIMARY TUBERCULOUSIS COMPLEX

Clinical pattern. In infants with massive tuberculous infection, the primary tubercular complex proceeds as pneumonia, with extensive damage of thoracic lymph nodes. The disease develops with high fever and temperature rise up to 39-40 C°, dry cough or cough with mucous sputum, chest pain.

Pneumonia (lobar or segmental) changes into diffused form that depends on hyperergic reactions and incomplete differential process in lungs of small children. Elder children have small primary foci in lungs, where as others have various complications of primary tubercular complex.

During the examination of a child enlarged peripheral lymph nodes (cervical, axillary) dense, mobile, without perifocal inflammation are found out in surrounding tissues. If the pneumonic focus is large, the corresponding half of thorax lags in breathing. Dullness of percussion tone and fine moist rales are heard above the focus. If lung focuses are small, there are no physical changes.

Mycobacterium tuberculosis can be found in lavage waters of bronchi and stomach. They get into lavage waters not only from infiltrative pneumonic lung foci, but also from specific changes in bronchi.

Blood examination reveals moderate leucocytosis with shift of neutrophil formula to the left, eosinopenia, monopenia and increased of ESR.

Diagnostics. An anamnesis is very important for making the diagnosis of primary complex especially indicating contact with an eliminator of bacilli and positive tuberculin tests. The
conversion of tuberculin tests is especially valuable. When the primary complex is latest and active, the conversion shows hyperergic tuberculin reactions.

It is very important to examine presence of mycobacterium tuberculosis in sputum and lavage waters from bronchi and stomach.

X-ray examinations reveal fresh pulmonary foci with accompanying adenitis.

**Radiographic picture of a primary tubercular complex.** The classical primary complex consists of three basic components: pulmonic, lymphadenitis and lymphangitis connecting them. However a phase of infiltration passes before bipolarity becomes distinct on anterio-posterior radiograph. An infiltration represents rather intensive opacity connected to a lung root, sometimes it is deposited on the lung root. As a rule, infiltration is not homogeneous. It’s borders are dim. The vessels and bronchi appear through infiltration. The sizes of infiltrations are various and depend on a degree of lung’s damage; they can be lobar, segmental and bronchopulmonary. The primary complex is located in the top and middle lung segments more often. At dissolving the sub-pleural localization of infiltration more distinctly is visible.

**The primary complex has four stages of development:**

**I a stage - pneumonic.** On X-ray general view three components of a complex are visible:

1) **the focus** in lung tissue by the size 2-4 cm. in diameter or more, of oval or irregular form, various intensity (more often - average and even high), with an indistinct, obscure contour;

2) **the flow out to a root - lymphangitis**, which is defined as linear tension bars from focus to the root;

3) **in a root - enlarged infiltrated lymphatic nodes.** The root is represented to be extended, it’s structure is blurry, the intensity is increased. The contours outlining lymphatic nodes, or are dim, or more precisely depict the increased nodes.

![X-ray The primary complex (pneumonic stage)](image)

**II stage - resorption.** The size of the focus in lung tissue decreases, its intensity raises, the contours become precise. The flow out to a root and infiltration of lymphatic nodes decreases.
Fig. 2.9.1.2. Rn. II stage - resorption. The size of the focus in lung tissue decreases, its intensity raises, the contours become precise. The flow out to a root and infiltration of lymphatic nodes decreases.

**III stage - condensation.** On a place of focus area remains with the size up to 1 cm, inside of it inclusions of calcinations appear as fine spots of sharp intensity. Same spots of calcinations are noticeable and in lymphatic nodes of the lung root. Thin tension bars are determined between the focus and the root.

Fig. 2.9.1.3. Rn III stage-condensation. - On a place of focus area remains with the size up to 1 cm, inside of it inclusions of calcinations appear as fine spots of sharp intensity. Same spots of calcinations are noticeable and in lymphatic nodes of the lung root. Thin tension bars are determined between the focus and the root.

**IV stage - calcination.** The focus in lung tissue becomes even smaller, more densely, of high intensity, with distinct contour, frequently rugged and rough. Calcinations are intensified also in root lymphatic nodes. Calcinations in certain cases are represented by solid, dense formations, in others - they have less intensive shadows of inclusions, which testify about incomplete calcifications of the focus and preservation of caseous regions in it.
The focus in lung tissue becomes even smaller, more densely, of high intensity, with distinct contour, frequently rugged and rough. Calcinations are intensified also in root lymphatic nodes. Calcinations in certain cases are represented by solid, dense formations, in others - they have less intensive shadows of inclusions, which testify about incomplete calcifications of the focus and preservation of caseation regions in it.

At favorable course of primary tuberculous complex with time calcification increases up to ossification at the place of former caseosis located in peripheral parts of lungs. This is Gohn's focus.

The lesion is small and usually cannot be detected during its active stage; not until calcium salts are deposited in the healed lesion can its presence be detected. In a large majority of instances healing takes place with fibrosis and calcification (Gohn's focus pointed be arrow).

When primary complex is revealed in time and the patient receives valuable treatment, frequently could be achieved complete dissolution of pathological changes in lung tissue and in root, with complete restoration of their initial structure.
Fig. 2.9.1.6. Outcome of primary tuberculosis - When primary complex is revealed in time and the patient receives valuable treatment, frequently could be achieved complete dissolution of pathological changes in lung tissue and root, with complete restoration of their initial structure (a - at moment when tuberculosis was revealed, b - after 4 years).

The greatest difficulties arise at diagnosing tubercular intoxication and small forms of lymphatic nodes tuberculosis. At absence on chest x-ray obvious pathological signs of lymphatic nodes high profile is given computer tomography, allowing to visualize insignificantly increased lymphatic nodes and deposits of calcium salts.

3.2.2. Tuberculosis of intrathoracic lymphatic nodes.

A tubercular disease of the lung root lymphatic nodes and mediastinum are named bronchoadenitis. Bronchoadenitis at tuberculosis are unilateral and bilateral. The unilateral bronchoadenitis meets more often. Infiltrative and tumor-like bronchoadenitis are discerned.

**Infiltrative bronchoadenitis.** On chest x-ray the shadow of the lung root is extended on the damaged part, the outside contour is dim, the structure is blurred and intensity is increased. Shadows of enlarged lymphatic nodes are clearly come to light on x-ray tomogram.

Fig. **Infiltrative bronchoadenitis.** On chest x-ray the shadow of the right lung root is extended the outside contour is dim, the structure is blurred and intensity is increased.
**Tumor-like bronchoadenitis.** The shadow of the root looks same, as an infiltrative form, but its exterior contour is distinct, regular or polycyclic. The shadow of the upper part of mediastinum is expanded at a defeat of para-tracheal and tracheo-bronchial lymphatic nodes. Its contour remains distinct, as a rule. The defeat of bifurcation lymphatic nodes is revealed usually on the chest x-ray or tomograms.

![Image of Tumor-like bronchoadenitis]

| Fig. | Left side tumorous lymphadenitis. Massive enlargement of broncho-pulmonic lymphatic nodes. (Chest x-ray and tomogram). |

**Outcomes of bronchoadenitis.**

**Full dissolvement** – is most often outcome, when the process is revealed in good time and after effective treatment.

**Progressing exacerbation of bronchoadenitis**

**Scarring condensation of the root.** The tension bars could be revealed in the field of the root on a chest x-ray, their intensity is raised.

**Calcinations.** Calcinations could be as seeds, lumpy, shell-shaped and solid. Solid calcinations could be revealed as large, intensive, oval shadows.

![Image of Calcinations]

| Fig. | Calcinations in lymphatic nodes. |
3.2.3. Disseminated lung tuberculosis

To this form miliary, sub acute disseminated and chronically proceeded disseminated lung tuberculosis is referred.

Miliary lung tuberculosis. On the chest x-ray multiple, fine (1-2 mm) of the same type focuses, rich and in regular intervals distributed in all lung fields. The focuses are precisely outlined, do not merge. Their intensity is average. Picture of lung vessels is not seen because of a big number of focuses.

Rn 2.9.3.1. Miliary TB.

Miliary tuberculosis. High-resolution CT scan obtained with lung windowing demonstrates numerous fine, discrete nodules bilaterally in a random distribution. (Harisinghani et al Tuberculosis from Head to Toe1 RadioGraphics 2000; 20:449–470)

Focuses can completely dissolve or calcify at reverse development of tubercular process. The quantity of calcified focuses is less, than in the period of dissemination, because of partial dissolving of focuses. Dissemination of focuses is settled down symmetrically, as a rule, in all lung fields, on a background of pneumosclerosis and is kept on for all life.

Disintegration of lung tissue appears as thin-walled cavities, at progression of process, owing to trophic changes in lungs. Usually cavities are multiple, oval, identical in a form and in sizes. Therefore they are named "stamped". Sometimes they are located by a chain, quite often are symmetric in both lungs. They are named as system cavities in such cases.
**Subacute disseminated tuberculosis.** Subacute disseminated tuberculosis on chest x-ray is characterized by representing larger and merged focuses; lymphangitis in the form of peribronchial "couplings" along with multiple fine focuses in both lung fields. Cavities are the same, as at miliary tuberculosis, thin-walled, "stamped".

![Subacute disseminated tuberculosis - Disseminated TB of lung with accompanying chest X-ray](http://granuloma.homestead.com/TB_miliary_gross.html)

**Chronic disseminated tuberculosis.** On chest x-ray chronic disseminated tuberculosis is characterized by presence of the focuses of various size and intensity, places of formed conglomerates, and also net like fibrosis of the upper lobes. The roots and the vessels of the upper lobes are displaced up. The process is bilateral, but frequently asymmetrical - one lung can be struck more than another. Cavities are thin-walled, but usually deformed. Exudative pleuritis is observed quite often at disseminated tuberculosis.

![Chronic disseminated tuberculosis - chronic disseminated tuberculosis in a phase of condensation.](#)

**3.2.4. Focus lung tuberculosis.**

Two forms of focus lung tuberculosis are distinguished, according to clinical and radiographic point of view: soft focus – more fresh and fibrous focus – in the stage of remission

On a chest x-ray focuses have sizes up to 1 cm in a diameter, oval or irregular form at soft focus form. Their contours can be distinct or dim, intensity - weak or average. The focuses are single and multiple, more often are settled down in one lung, mainly in the upper lobes: in I, II and VI segments; quite often are merged. Wide linear bound shadows - lymphangitis are visible around focuses. At progression the increases of quantity of the fresh tubercular focuses, aggravation of lymphangitis are defined, a field of disintegration appears.
After effective antibacterial treatment the fresh tubercular focuses and lympangitis dissolve usually in 12 months, more often with complete restoration of lung tissue. Less often the fresh focuses are not dissolved after treatment but becoming encapsulated.

So-called productive form is observed at subacute current of the process. The focuses are of average size and fine (3-6 mm), oval or irregular, their forms are precisely outlined, average and high intensity. The focuses settle down separately, do not merge.

At treatment these changes slowly dissolve, during 1,5 and more than years. Frequently focuses are encapsulated, around of them large fibrosis remains. The damaged sites of lungs considerably decrease in volume in result of lung tissue shrinking, up to cirrhosis development.

(Chest x-ray and tomogram)/ A focus tuberculosis in segments 1 and 2 in phase of infiltration of the left lung. In these segments multiple focuses are presented of minor and medium sizes, weak and average intensity.

3.2.5. Infiltrative-pneumonic lung tuberculosis

On chest x-ray most often focuses infiltrative are defined in the upper lung lobes of various size: from 1,5 cm in a diameter up to defeat of the whole segment of lobe.

Intensity of focuses is various. Frequently they are bordered by an indistinct, dim contour, having wrong form, not homogeneous structure.

According to localization of extent of process infiltrative-pneumonic lung tuberculosis is divided into the following forms: limited and oval with near lung root localization, cloudy infiltrations, periscissuritis, and lobitis.

The contours of infiltration are precise at tubercular damage of a segment or lobe. Focuses of various sizes, architectural distortion of the lung tissue, and inflammation "path" to a root are defined in contiguous areas of lungs.
Infiltrative-pneumonic lung tuberculosis is complicated by disintegrations with formation of a cavity. The cavity is found out as enlightenment in infiltration, having oval or irregular form, with precise internal contour.

The types of infiltration in lung tuberculosis:

1 - broncho-lobular; 2 - rounded; 3 - cloudy; 4 - cloudy in a phase of disintegration; 5 - lobitis; 6 - periscissuritis

Infiltrative lung tuberculosis (chest x-ray + tomogramm). The focus of infiltration is presented of irregular form, with size of 6x7 cm in upper left lobe. Intensity of the focus is average, without distinct contours.
Infiltrative lung tuberculosis (general view + tomogram). In the top of the right lobe 2 focuses, are defined with sizes of 3x3 cm., with irregular contours, of non-uniform structure. Numerous fine shadows, of average intensity take position around.

A chest x-ray + tomogram. Infiltrative lung tuberculosis in the upper lobe of the right lung. In the upper lobe of the right lung two focuses are presented 3x4 and 2.5x 3 cm, of average intensity with irregular, indistinct contours, heterogeneous structure owing to disintegration cavities. Multiple minor focuses distributed around.

The focus of infiltration, with irregular and indistinct contours with cavity of disintegration is presented in cortical region of the right lung. The focus is connected by "path" with the lung root. Multiple focuses of bronchogenic dissemination are presented in both lungs.
A tubercular infiltration. An infiltrative shadow occupies the upper lobe of the right lung (lobitis) with accented lower border. The interlobe fissure is shifted upward.

3.2.6. Fibrous cavernous lung tuberculosis.

On chest x-ray the picture of fibrosis of shrinking of a lung, old fibrous cavity (one or several), pleural depositions are defined. At fibrous cavernous lung tuberculosis the cavity settles down among rough lung fibrosis, its walls are deformed, are dense, are thick more often. Quite often at the bottom of the cavities the small level of a liquid is defined. At an aggravation and progressing of the process, the sites of infiltration are visible around a cavity. Sometimes fibrous cavity comes to light only at tomography, as on chest x-ray the shadow of a cavity can be closed by layering shadows of the focuses, fibrosis and pleural stratifications. The picture of fibrosis and shrinking of lungs are found out in the upper lobes, with a predominant defeat of one of them. Mediastinum and trachea are shifted to the site of biggest defeat. The upper lobes are reduced in volume, their transparency is sharply lowered because of hypoventilation. Architecture of the lung tissue is sharply distorted because of rough fibrosis. The transparency of lungs is often increased owing to inflation. Usually in both lungs groups of focuses of various intensity are visible.

The roots, as a rule, are displaced up. The large vessels are defined as direct, equal regular — a so-called symptom « of the tense string ».

Fibrous cavernous lung tuberculosis. Gigantic cavity.
Fibrous cavernous. A destructed right lung.

3.2.7. Tubercular pleurisy

The pleurisy, is the inflammation of pleura. Two basic forms of pleurisy are distinguished: dry or fibrinous (pleuritis sicca, fibrinosa), and exudative (pleuritis exudativa).

During tuberculosis the pleura is involved in the process of inflammation at penetration in it infection by the contact way, through the lymph or the blood. The involvement of pleura in various pathological processes is conditioned by close anatomic topographical connections of visceral and parietal pleura with lung tissue, intrathoracic lymphatic nodes. The pleura, having barrier function, reacts to various pathophysiological changes of the body. Therefore, the developments of inflammatve or allergic processes take place.

Exudative inflammatory reaction of the pleura is connected with increased permeability of the blood and lymphatic capillaries of the lung cortical layer and pleura itself. These capillaries make way for a liquid part of blood into intra tissue fissures, superficial layers of pleura and there from, with the help negative pressure, into pleural cavity.

Lymphagenic pleurisy. The tubercular infection can affect subpleural lymphatic nodes. Accumulating in the nodes Mycobacterium tuberculosis, some are bricked up and are eliminated and the rest of MBT, keeping their virulence, are distributed along lymph vessels cause subpleural cortical lymphangitis or the exudative pleurisy.

Hematogenic pleurisy. The hematogenic spreading of MBT into the pleural cavity promotes development of tubercles on the pleura. The initial focus is an active tubercular process in mediastinum lymphatic nodes.

The contact way of MBT dissemination arises at active tuberculosis of lymphatic mediastinum nodes, with defeat of visceral pleura.

Fibrinous pleurisy (dry pleurisy). At the fibrinous pleurisy on the pleura at first, gentle layer occurs, of fibrinous structure, which could easily remove. Further the fibrinous pellicle of yellowish or yellowish-gray color is formed.
**Purulent pleurisy (empyema)** from the very beginning arises as purulent very rare, but more often it develops after serous-fibrinous inflammation of the pleura. The process usually happens unilateral and mainly settles down in basal or posterior part of the pleural cavity. The purulent pleurisy is observed at bursting out of caseous masses from lung into the pleural cavity, broncho-pleural fistulas and etc.

**Hemorrhagic pleurisy** accompanied by penetration of exudates containing a significant impurity of erythrocytes into pleural cavity.

**Outcome of pleurisy**

In overwhelming majority of cases the **fibrinous exudates** dissolves only partially, and basically is subjected to transformation, that leads to development of commissural joints, fibrotic thickening of the pleura, to obliteration of the pleural cavities.

**Purulent exudate** seldom is exposed to complete dissolution; more often the encapsulation of the inflammatative effusion is developed. The inflammatative process at pleural empyema can pass on interstitial lung tissues (purulent pneumonia).

**Chronic pleurisy**

More often chronic course of the pleurisy is observed at pleural empyema. In these cases exudates condense, dissociate, turn in cheesy mass or thin gruel with presence of cholesterol crystals; the microorganisms can disappear. The pleural membranes are considerably thickened and dense, sometimes with focal petrification and even ossification. The significant sediments of calcified masses are especially typical for tubercular empyema. The pleural empyema can lead to purulent – resorption fever, sepsis, exhaustion, amyloidosis of internal organs. Sometimes long, chronic current is observed at serous-fibrotic and fibrotic pleurisy.

During acute and chronic pleurisies the significant accumulation of exudates in the pleural cavity causes the atelectasis in appropriate lung and the mediastinum organs are displaced in the opposite side.

### 3.2.8. TUBERCULOSIS OF MENINGES AND CENTRAL NERVOUS SYSTEM

**Tuberculosis of meninges and the central nervous system (CNS)** begins from the moment of haematogenic dissemination of MBT to the nervous system and structures surrounding the brain or spinal cord and causing meningitis.

**Tuberculous meningitis** – It is the inflammation of meninges. Up to 80% of patients with tuberculous meningitis either have traces of early acquired tuberculosis of other localizations, or active tuberculosis of other site.

**Pathogenesis of the tuberculous meningitis**

The main route of MBT infiltration into the meninges is the hematogenous route. At the same time the damage of meninges proceeds in **two phases**:

1. **During the first phase**, in primary tuberculosis, the sensibilization of an organism develops, MBT break through blood-brain barrier (hematoencephalic barrier) and infection of vascular plexuses of the piamater takes place.
2. **During the second phase** MBT from vascular plexuses, penetrate into the liquor, invoke specific inflammation of piamater at the base of brain – bacillary meningitis.

During distribution of MBT from primary tuberculous focus, or as manifestations of miliary tuberculosis tiny tubercles arise in the tissues of the brain and meninges. Sometimes tubercles may also settle in the bones of the skull or the vertebrae.
These tubercles may cause:

1. **inflammation of the meninges**;
2. **formation of a grey jelly-like mass at the base of brain**;
3. **inflammation and narrowing of the arteries providing blood supply to the brain** which may cause local brain damage.

**These three processes cause the clinical picture of tuberculous meningitis.**

The pathological process involves not only meninges of the brain and the spinal cord, but also the vessels. All layers of the vessels’ walls are damaged, but intima is affected to the greatest degree. These changes are considered by pathologists to be a display of hyperergic inflammation. Therefore, **when there is cerebral tuberculous meningitis, the membranes and vessels are first damaged.** The brain parenchyma is less considerably involved in the tuberculous process. In cerebral cortex, subcortex and spinal cord, the foci of the specific inflammation are located near and around the injured vessels.

**Mainly children become sick with meningitis**, especially at the early age, and much less often adults are affected.

### Clinical signs of the tuberculous meningitis

The main forms of tuberculous meningitis according to localization are:

- basilar meningitis;
- meningoencephalitis;
- spinal meningitis.

**Three periods in development of the tuberculous meningitis are distinguished:**

1. **Prodromal**
2. **Irritation**
3. **Terminal (pareisis and paralyses)**

#### 1. Prodromal period of tuberculous meningitis is characterized by its gradual development (during 1-8 weeks). Headache, dizziness, nausea, sometimes vomiting, fever (sub febrile, less often – high temperature), ischuria, constipation, appear first. However, cases of development of illness with normal temperature have been reported.


By the end of the first week of this period (on 5-7th day) indistinctly expressed meningeal syndromes appear (rigidity of occipital muscles, Kerning's sign).

**Characteristic manifestations of the symptoms during the second period depend on localization of the inflammatory tuberculous processes are:**

**At inflammation of the meninges,** headache, vomiting and rigidity of occipital muscles appear.

**Due to accumulation of the serous exudates at the base of the brain,** irritation of the cranial nerves can appear producing the following signs: deterioration of vision, paralysis of eyelid, squint, unequal dilation of pupils, and deafness. Papillodema is present in 40% of patients.

Loss of speech or weakness in extremities **can appear after involvement of the brain arteries** in the pathological process. Here, any area of the brain can be damaged.

**Due to hydrocephalus** of some degrees the blockage caused by exudates of some cerebrospinal connections within the brain. Hydrocephaly is the main reason for loss of consciousness. The resulting damage may be permanent and accounts for the bad prognosis in the patients as they are found in an unconscious state.
Spinal block by exudates may cause motor neuron weakness or paralysis of the lower extremities.

3. Terminal period (period of paresis and paralyses 15-24th day of illness). In the clinical picture, signs of encephalitis prevail: lack of consciousness, tachycardia, Cheyne–Stokes respiration, temps. 40 °C, paresis, paralyses of central nature.

In spinal form at 2 and 3 period, in the surrounding, very strong nerve root [radicular] pains, flabby paralyses, bedsore are observed.

The diagnostics. The ascertainment of diagnosis:

- intime – during 10 days from onset of irritation period;
- late diagnosis – after 15 days.

Simultaneous presence of the following diagnostic peculiarities, indicate high probability of tubercular meningitis:

1. Prodrome.
2. Syndrome of intoxication.
3. Functional distresses of pelvic organs (constipations, ischuria).
4. The scaphoid abdomen.
5. Craniocerebral symptoms.
6. Specific character of the cerebrospinal fluid.
7. Corresponding clinical dynamics.

Tuberculous infection can potentially spread to any part of the body and therefore special attention should be given to the following:

1. tuberculosis of the lymph nodes;
2. X-ray evidence of lung disease especially miliary tuberculosis;
3. enlargement of liver and/or spleen;
4. choroidal tubercles visible on examination of the retina.

The tuberculin test may be negative especially in the advanced stages of the disease.

Diagnostic signs of the tuberculous meningitis at the cerebrospinal fluid (CSF) examination:

1. The pressure in cerebrospinal channel usually raises (the cerebrospinal fluid flows as rapid drops or stream).
2. Appearance: the CSF, at first, looks clear but may form a 'spider's web clot on standing. May be yellowish if there is spinal block.
3. Cells: 200-800 per mm3 (Normal = 3-5).
4. Protein content raised to (0,8-1,5-2,0 g/l), normal 0,15-0,45 g/l.
5. Glucose: low in 90% of patients, but may be normal in the early stage of the disease or in AIDS. This is very helpful in differentiating from viral meningitis in which the glucose is normal.
6. At the bacteriology examination MBT are revealed only in 10% cases if volume of CSF is sufficient (10-12 ml). The method of centrifuge flotation during 30 minutes on high speed can reveal MBT in CSF in 90% cases.

Tuberculosis of meninges and the central nervous system (CNS) in adults remains a major cause of death.

Treatment. If there is a suspicion of tuberculous meningitis, it is necessary to send the patient immediately to a hospital where X-ray, lumbar puncture, laboratory examinations and specific methods of anti-tubercular therapy are carried out.

Differential diagnosis. The main conditions to be differentiated are bacterial meningitis, viral meningitis, and HIV-related cryptococcal meningitis. In the first two, the onset is much more acute. Cryptococcal meningitis may have a much slower onset. A family history of tuberculosis, or the finding of tuberculosis somewhere else in the body, makes tuberculosis meningitis much more likely. But the best evidence comes from examination of the cerebrospinal fluid (CSF) obtained by lumbar puncture.
Prognosis. Fatal outcome is certain if the patient does not receive treatment. The earlier meningitis is diagnosed and treated, the more likely is the patient to recover without serious permanent damage. The clearer the state of consciousness when treatment is started, the better the prognosis. If the patient is in coma, the prognosis for complete recovery is poor.

Granulomatous tuberculous meningitis, ventriculitis, and spinal arachnoiditis. Sagittal paramedian magnetic resonance imaging after intravenous gadolinium injection reveals:

- irregular lumpy enhancement of the tentorium cerebelli suggestive of granulomatous meningitis.
- enhancement of the walls of the lateral ventricle and spinal canal are consistent with ventriculitis and spinal arachnoiditis.

4. TUBERCULOSIS, HIV (HUMAN IMMUNODEFICIENCY VIRUS) INFECTION AND AIDS (ACQUIRED IMMUNODEFICIENCY SYNDROME)

The rapid growth of HIV infection spread in most parts of the world is causing great problems in the diagnosis and treatment of tuberculosis. It is also causing difficulties of fight against tuberculosis.

AIDS (Acquired ImmunoDeficiency syndrome) is due to HIV (Human ImmunoDeficiency Virus). In countries with high prevalence of tuberculosis, 30-60 per cent of adults have been infected with tuberculosis. Most people's immune defenses prevent the MTB causing disease. But if their defenses have been damaged by HIV the tuberculosis may no longer be kept under control, MTB may multiply and cause disease. In the same way, people with HIV infection, even if not yet ill, may not be able to resist new infection with MTB from other patients with mycobacterium positive sputum. So there are likely to be many more cases of tuberculosis in countries where there is increasing HIV infection.

4.1. HIV (Human Immuno Deficiency Virus)

The HIV can be spread in different ways:

1. By heterosexual activity.
2. By homosexual activity.
3. Through blood by:
   blood transfusion with HIV contaminated blood.

   In countries where many people are being infected with HIV, even screened blood can be dangerous. There may be virus in the blood before antibodies can be detected;
3.2. use of needles which have not been properly sterilized. This is common in drug abusers.

However health staff who are known to be HIV-infected, even if healthy, should not care for patients with tuberculosis. They have a much greater risk than normal people of being infected with tuberculosis and eventually developing disease.

There is a long period, often several years, between infection with the HIV virus and developing AIDS. This period is shorter in children under five and in patients aged over forty. During this 'incubation period' the patient may feel quite well (though he/she remains infectious). The development of tuberculosis is often the first sign that he/she has HIV infection.

In about 50% of patients with HIV and tuberculosis there is no other evidence of HIV infection. The only way to make the diagnosis is to do a HIV test.

Diagnosis and testing. The HIV antibody test is the only certain way of making the diagnosis.

Effect of HIV on the efficiency of the fight against tuberculosis

Prevalence of tuberculosis. Among people already MBT infected (being tuberculin positive) lifetime risk of clinical tuberculosis is about 50 per cent if they have been infected with HIV in comparison with 5-10 per cent risk if they are HIV negative. The result is that considerable increase of tuberculosis take place in populations in which HIV rate becomes high.

Reaction to drugs. Drug reactions are very common among the patients with tuberculosis and HIV. This may increase the default rate from treatment.

Needles. Great care must be taken in multiple using of injection needles. For this reason streptomycin is no longer used for tuberculosis in many countries with high HIV prevalence.

Clinical picture of patients with tuberculosis in combination with HIV infection

The following differences from the usual clinical picture of tuberculosis of non-HIV infected patients in comparison with the patients who are infected with HIV:

1. Extra-pulmonary disease, especially in the lymph nodes, is more common. There is often enlargement of the lymphatic nodes, which is rare in other forms of tuberculosis.

2. Increased rate of miliary tuberculosis. MBT can be isolated from blood culture (which never occurs in ordinary tuberculosis).

3. X-ray. In the early stages of HIV infection with pulmonary tuberculosis there is often little difference in the X-ray from the usual appearances. In the later stages there are often enlarged mediastinal lymph nodes. Cavitation may be less frequent. Pleural and pericardial effusions are more common. The shadows in the lungs may change rapidly.

4. Tuberculosis may occur at unusual sites, e.g. tuberculoma of the brain, abscesses of the chest wall or elsewhere.

5. Sputum smears may be negative despite of considerable changes in the chest X-ray.

6. The tuberculin test is often negative (anergy).

7. Fever and weight loss are more common in HIV-positive tuberculosis than in HIV-negative.

In a patient with tuberculosis, suspect the possibility of accompanying HIV infection if there is:

1. Generalized lymph node enlargement. In late stages of HIV the nodes may be tender and painful, as in acute infection.

2. Candida infection (painful white patches of fungus in the mouth).

3. Chronic diarrhea for more than a month.

4. Herpes zoster (shingles).

5. Kaposi's sarcoma: small red vascular nodules on the skin, and particularly on the palate.


7. Burning sensation in the feet (due to neuropathy).

8. Persistent painful ulceration of genitals.
4.2. Treatment of tuberculosis of HIV-positive patients

Standardized course of treatment. Modern standardized treatment of tuberculosis in an HIV-positive patient is as effective as in HIV-negative patients. The sputum becomes negative very quickly. Relapse rates are not so often. Weight gain may be somewhat less than in HIV-negative patients. Long term 'standard' treatment, not including rifampicin, is less successful and relapse occurred quite often. Some of the relapses may have been due to super infection because of the patient's lowered defenses due to HIV.

Mortality. There is a higher mortality from tuberculosis HIV infected patients. Most of it is due to other complications of HIV infection. But some deaths seem to be directly due to tuberculosis.

The long term prognosis is therefore poor, as in all HIV patients. But treatment of tuberculosis of such patient usually gives him/her a longer period of improved health and is well worth doing. Moreover treatment stops the spread of tuberculosis to others.

Side-effects. Side-effects of drugs are more common in HIV-positive patients. In particular thioacetazone is liable to cause severe skin reactions which may be fatal in up to 25 per cent of cases. If a patient develops a reaction to thioacetazone never use it again. Some countries with high prevalence of HIV, thioacetazone is no longer used.

Preventive treatment with isoniazid is used in HIV patients without the evidence of clinical tuberculosis.

Tuberculosis speeds up the progress of HIV disease. Therefore tuberculosis and HIV patients may develop other common complications of HIV infection.

Protection of medical staff from infection by HIV.

1. While taking blood wear gloves. Afterwards put used needle and syringe into special 'Sharp Box'. Put gloves and swabs into leak-proof plastic bag.
2. On doing manipulations in which there is contact with blood (e.g. surgery or delivering a baby) wear gloves and apron. Protect your eyes with glasses.
3. If blood or other bodily fluid is spilled, clean up as soon as possible. Use an antiseptic, e.g. phenol or sodium hypochlorite.
4. If doing resuscitation one must not implement direct mouth-to-mouth breathing. Use a bag and mask.
5. LUNG TUBERCULOSIS AND DIABETES MELLITUS

In the combination of Diabetes Mellitus (DM) and lung tuberculosis, in overwhelming majority of cases (up to 90 %) DM is a primary disease, on the background of which tuberculosis develops in different time periods. If both diseases come to light simultaneously, that means obviously that DM was latent and has become aggravated under the influence of concomitant tuberculosis.

There is no one common reason to explain the accelerated tuberculosis morbidity among DM patients. No doubt that the tuberculosis in some forms of the diabetes develops in conditions of reduced immunity of a host to the infection, which is determined by exhaustion of immunobiological properties caused by reducing the ability to develop antibodies and antitoxins. Development of the lung tuberculosis in such cases promotes uncompensated or uncured DM.

Clinical signs of tuberculosis among the DM patients. If tuberculosis is revealed in early stages then more favorably proceeding forms of disease are observed even in the combination with DM. The malignant, severe course of tuberculosis predispose to fast progression and disintegration mainly at wrong treatment of DM or at late revealing of tuberculosis.

The first clinical signs of tuberculosis during DM are: increasing weakness; decrease of appetite; weight loss, increase of diabetic symptoms. The disease can proceed at the beginning in a latent manner; therefore lung tuberculosis is quite often diagnosed during mass fluorography or routine X-ray examinations.

Tuberculin tests are usually highly positive. However with the development of chronic forms of tuberculosis (fibrous-cavernous, hematogenic spreading) – there comes an exhaustion of the host’s protective forces and the tuberculin sensitivity is reduced.

The process of tuberculosis in combination with DM differs by slow normalization of the disturbed metabolism, longer period of the tuberculosis intoxication and slow healing of cavities of disintegration.

The reasons for the progression of even small forms of tuberculosis (focus and small tuberculoma) is the underestimation of activity for the first time revealed tuberculosis, hence, untimely start of the therapy of tuberculosis, wrong diet and anti-diabetic treatment, that results in absence of DM compensations.

The course of DM is aggravated on the background of joined tuberculosis. The level of sugar in blood raises, diuresis and glycosuria are increased, acidosis can appear. The worsening of metabolism is characterized by the prominent fluctuations of sugar content in blood within a day, which allow the patient to feel sensation of dryness in the mouth, feeling of thirst, often urination. The loss of weight progresses. The given data have the large practical importance: any sudden deterioration of the DM course should attract the doctor’s attention to the development of tuberculosis.

The features of tuberculosis course in the DM patients and adverse influence of tuberculosis on DM demand skillful combination of all medical measures from the doctor. In the past half of the patients died from tuberculosis accompanied with DM. Clinical cure became possible for tuberculosis and DM patients with introduction of physiological diet, insulin and chemotherapy in medical practice.

Increased tuberculosis incidence among the DM patients demands the special attention that should be taken for tuberculosis prevention. The persons of young age, at which DM proceeds usually severe and frequently is complicated by tuberculosis, require careful supervision and regular check-ups for tuberculosis.

Anti-diabetic therapy of the tuberculous patients should be complex and depending on individual host’s condition, form and phase of tubercular process and severity of DM.

Chemotherapy of the tuberculosis combined with DM should be carried out continuously for a long time using various combined preparations, which have been individually chosen for particular patient.
Each DM patient in whom tuberculosis has been revealed for the first time should be hospitalized.

6. TUBERCULOSIS AND ALCOHOLISM

The problem of alcoholism in connection with tuberculosis is very important.

The persons with combined pathology (tuberculosis and alcoholism) represent strong epidemiological danger not only because of high prevalence among them but also due to severe destructive forms of the tuberculosis with massive MBT expectoration which occur due the following reasons:

1) personal degradation;
2) low level sanitary education;
3) non-observance of elementary rules of hygiene;
4) late request for medical help;
5) neglecting the recommendations of the doctors;
6) refusal of radical therapy.

Thus, becoming dangerous for the surrounding especially when the MBT becomes resistant to drug.

The prevalence of drug resistance of MBT is twice higher, and multidrug resistance six times higher among the patients having tuberculosis combined with alcoholism than among those tuberculous patients who are not suffering from alcoholism. It indirectly testifies that the treatment of such patients was undertaken more than once and many of them avoided it.

Alcohol abuse is 3-5 times more among the patients registered in tuberculosis dispensary, than among those registered for the first time. The reason for this accumulation in the dispensary of such patient is due to the low efficiency of their treatment. The prevalence of alcoholism is high especially among the patients with chronic destructive lung tuberculosis.

The lung tuberculosis in the overwhelming majority of patients develops on the background of alcoholism, rather than precede to it. It characterizes the majority of the persons with combined pathology of alcoholism with accompanying tuberculosis.

Lung tuberculosis combined with alcoholism can have various course and clinical signs. The process in lung of the alcoholic patients sometimes gets acute and results to lethal outcome. Complications of lung tuberculosis combined with alcoholism are: lung hemorrhage and hemoptysis, which more often give rise to pneumosclerosis and increased permeability of blood vessels under influence of alcohol.

After treatment of tuberculosis among alcoholic patients, the expressed residual changes in lungs are observed, that creates conditions for occurrence of relapses of tuberculosis. The main reason of relapse occurrence is the ineffective treatment of the patients during the realization of the basic course of chemotherapy in hospital because of a prescheduled discharge of them caused by violation of rules. In the alcoholic patients, during relapses the course of tuberculosis proceeds more unfavorable rather than that at the initial stage of the disease.

The course alcoholism is sharply worsened at onset of tuberculosis; its severe stages develop quickly with expressed personal psychopathological degradation and social inadequate adaptation. The syndrome persists and aggravates in heavy drinkers especially in the morning. The tuberculous infection is the additional aggravating factor, promoting occurrence of alcoholic psychosis. The basic role in their development is played by the intensification of the tubercular process.

The principles of treatment. One of the basic reasons of adverse tuberculosis course combined with alcoholism is an ineffective treatment because of a non-discipline behavior of such patients. Without active anti-alcoholic therapy the treatment of the persons with combined pathology (tuberculosis and alcoholism) cannot be successful.
Using highly effective and adequately chosen combinations of anti-tuberculosis drugs allow carrying out simultaneously active anti-alcoholic therapy without serious complications. Such approach in treatment allows to prolong time of stay of the patients in hospital for the account of alcoholism remission and by that to increase effectiveness of tuberculosis chemotherapy.

Chemotherapy of lung tuberculosis of the alcoholic patients is essential and necessary to carry out in hospital according to the standard principles. Frequently such patients avoid chemotherapy, therefore it is necessary to organize strict control of the chemotherapy regularity: the drugs are advisable to be administered using parenteral introduction, and if internal, in daily single dozes.

It is necessary to take care during administration of hepatotoxic drugs: rifampicin (especially together with isoniazid), pyrazinamide, etionamid, protionamide and tyoacetozone for alcoholic patient, patient with alcoholic liver cirrhosis, patient having virus hepatitis and continuing the alcohol abuse.

Multiple somatic diseases combined with alcoholism limit the choice of effective combinations of anti-tuberculosis drugs, because of contraindications to their administration. Therefore at the combined diseases the individualization of chemotherapy is necessary according to the character of accompanying somatic pathology.

7. TUBERCULOSIS UNDER PREGNANCY

Tuberculosis in pregnant woman can be expressed in several ways. Pregnant women may have a past history of tuberculosis. Occasionally, the disease may be diagnosed in a pregnant woman when she develops symptoms and signs suggestive of tuberculosis or incidentally by screening tests.

Atypical presentation of tuberculosis in pregnant women makes difficulties in confirmation of the diagnosis. Tuberculosis in pregnancy, thus, has an important role for mother as well as for the child.

Influence of pregnancy on tuberculosis. It is currently believed that pregnancy neither predisposes to the development of tuberculosis nor results in the progression of the disease. However, clinical investigations show a small but definite risk of relapse and deterioration in the postpartum period.

Effect of tuberculosis on pregnancy. Clinical observation does not suggest any adverse affect of tuberculosis during the course of pregnancy or labor.

MBT penetration through placenta.

Endometrial infection can be an important source for trans-placental transmission of disease in patients with congenital tuberculosis. Placental transmission of tuberculosis infection has now been conclusively proven by a number of case reports. A case has been reported where a child had mycobacterium in umbilical lymph nodes indicating umbilical vein as the route of transmission. MBT has also been detected in placental specimens and tissues from stillborn infants.

Congenital tuberculosis can be as result of hematogenous spread from infected placenta, through umbilical vein, or by aspiration by a fetus of the infected amniotic fluid. Liver is a major site of involvement reflecting hematogenous spread via fetal circulation.

It is important to identify pregnant women suffering from tuberculosis infection. It may help to prevent transmission of the disease to the newborn and close contacts.

Chest X-ray. A routine chest x-ray is advised during pregnancy in order to detect active and inactive tuberculosis. Concerns about radiation exposure of fetus do not justify the policy of routine chest x-ray examination during pregnancy. When indicated, the chest X-ray should be performed with abdominal shielding, preferably after the first trimester of pregnancy. Therefore, a chest x-ray carried out during pregnancy does not seem to carry a measurable risk to the fetus if it is done with all measures of precaution.
**Tuberculin skin test** serves as an important screening test during pregnancy. Tuberculin test identifies persons infected by MBT but does not define activity or extent of disease. Patients with active tuberculosis may not have a positive skin test as a result of anergic state.

**Microbiological methods.** Presence of MBT in sputum, body fluids or material stained by Ziehl-Nielsen and Lowenstein-Jensen culture confirms the diagnosis of tuberculosis disease.

**Treatment of active tuberculosis during pregnancy.** Pregnant women with tuberculosis should be treated immediately when diagnosed. Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does the treatment of disease. Administration of chemotherapy remains the basic method in the management of active tuberculosis in pregnancy.

The analysis of consolidated data on the teratogenic risk of the first line anti-tuberculosis drugs (isoniazid, rifampicin, streptomycin and ethambutol) showed that despite the fact that all these drugs pass across the placenta, none of these drugs appear to be teratogenic or toxic to the fetus with the exception of streptomycin having auto-toxic affect.

The decision of continuing the pregnancy lies in the hands of both the woman and the treating doctor. The treating doctor should insist in interruption of pregnancy at: fibrous-cavernous, chronic disseminated or widespread cirrhotic tuberculosis complicated by lung-heart insufficiency; in the newly revealed progressing tuberculosis; a combination of tuberculosis with diabetes or other chronic diseases.

**Exemplary management of the newborn child of the tuberculous mother:**

1. The child should not be separated from the mother unless she is desperately ill.
2. If the mother is smear-negative, the infant should be BCG vaccinated immediately.
3. If the mother is sputum positive during pregnancy or is still so at the time of delivery:
   3.1. if the infant is ill at birth and congenital tuberculosis is suspected full anti-tuberculosis treatment should be administered;
   3.2. if the child is healthy, isoniazid 5 mg/kg in a single dose daily for 2 months should be prescribed.

5.1. **Principles and methods of treatment of tuberculous patients**

The **aim of treating tuberculosis in adults** is to eliminate the clinical features of tuberculosis and promote a stable healing of the tubercular lesions; with restoration of the working capacity and social status of the patient.

Whereas the **goal in treating tuberculosis in children** is to cure without any residual changes or with minimal changes.

Among some patients, it is impossible to achieve these goals because there are objective limitations of treatment. In these cases it is necessary at least to achieve prolongation of the patient’s life, improvement of his condition, if possible to terminate or reduce MBT expectoration and to preserve partial work capacity.

**Criteria of effectiveness in the treatment of tuberculous patients are:**

1. the disappearance of clinical and laboratory signs of tubercular inflammation;
2. the stable termination of MBT expectoration, confirmed by microscopic and cultural examinations;
3. the regression of radiographic signs of tuberculosis (focal, infiltrative, destructive);
4. the restoration of functional and work capacity.

The peculiarities of tubercular process determine the complexity of treatment. Therefore, this disease requires a rational combination of various medical measures like:

1. chemotherapy;
2. sanitary-hygienic regime and therapeutic nutrition;
3. hormonal drugs;
4. tuberculin therapy;
5. collapse therapy and surgical interventions;
6. treatment of concomitant diseases.

Chemotherapy. Chemotherapy is the method of etiotropic treatment of tuberculosis with the help of the chemical agents. Chemotherapy is directed to one agent – mycobacterium tuberculosis with the purpose of suppressing the MBT reproduction (bacteriostatic action) or eliminating MBT in the host (bactericidal effect). The major factor to choose a chemotherapy regimen is the resistance of MBT to anti-tuberculosis drugs.

Based on the wide experiences the following principles should be considered during chemotherapy of tuberculosis.

1. The type of specific sensitivity of MBT which determines Minimal Inhibitory Concentration (MIC) of the drug in tissues. MIC is considered as a conditional constant.
2. MBT drug resistance that constantly varies and requires control with bacterial inoculation on specific media.
3. Patient’s drug tolerance increases the vulnerability of the host’s organs and systems.
4. Ways and methods of drugs administration, effective dose and speed of release from its pharmaceutical form.
5. Degree of penetration into the damaged tissue and physiological solution.
7. Degree of the patient’s cooperation with the medical personnel.

Treatment of tuberculosis is defined by various standard schemes comprising several groups of patients which are categorized according to the form and phase of their tubercular process. Within standard schemes, individual medical tactics are applied according to: the dynamic of the disease; the MBT drug sensitivity; the pharmacokinetics of the drugs used and their interaction; the drug tolerance of the host; the presence of concomitant diseases. Such principle allows combining standard treatment of tuberculosis with individual treatment strategy.

Staging. The treatment of tuberculosis varies according to the patient’s condition, character of process and its phases, thus the treatment may be:

1. in the outpatient department;
2. domicile treatment under the supervision of the assigned doctor of dispensary;
3. in hospital;
4. in sanatorium or in health resorts.

The treatment is known as staging as the doctor changes the mode of it according to the different stages of the disease.

A balanced regimen of work, rest and physical exercise are the prerequisite in treating tuberculosis at all its stages.

The term regimen means such the daily routine of a patient that provides comfort condition for his health. For that, the patient will require an increased amount of sleeping hours with an additional 2-hour rest in the afternoon; a prolonged exposition in open air; frequent strolls sleep in open air during both summer and winter; oxygen treatment in oxygenated room for more severe cases.

Hospitalization is a difficult period for the patient and for that matter it is useful not to restrict him to realize physical efforts or some kind of labor. Adequate, time-limited physical loads, educational and scientific work, are recommended to patients who are receiving treatment in medical establishments.

In well-organized tubercular establishments, patients may work in hospital workshops, kitchen and participate in gardening activities within the hospital’s territory. Such physical activity stimulates normalization of emotional state of the patients. These establishments also
offer educational programs for children, teenagers and high school students who had interrupted their studies due to illness.

A rational diet is an integral part of modern therapy of tuberculosis. It plays the role of a pharmacodynamic action that normalizes the body’s destructed physiological functions. Therefore, the diet should be strictly individualized for each patient. The food should contain fibers, fats and carbohydrates in an optimal amount and proportion according to the patient’s needs.

A nutritional diet in case of tuberculosis should contain an increased amount of proteins preferably of animal origin and a moderate amount of carbohydrates. The ratio between these ingredients should be the following: 15-20% of proteins; 25-35% of fats; the remaining – carbohydrates.

Tuberculous patients with weight deficiency should be provided with a diet exceeding the norm by 15-20%. Multi-vitamins intake is a cardinal part of a dietary regimen in tuberculosis. Multi-vitamins are prescribed in the form of drinks, fruits and drugs (intra muscular or per os). The quality, variety and taste of food are very important. Various and tasty foods should be served 4-5 times a day.

Sanatorium treatment and treatment in health resorts of the tuberculous patient in the Russian Federation is organic form of modern therapeutic methods and is mostly helpful in patients with freshly detected tubercular processes. The purpose of sanatorium treatment is to achieve complete clinical healing. It helps to eliminate exacerbation and to prevent relapses in patients with chronic process.

Sending patients to climatic resorts should be recommended only after the acute stage of inflammation process has been eliminated.

Taking into account that tuberculosis is a social disease, its treatment should be maximally standardized and should correspond to regulations and instructions of the public health services, regardless of whether there is specialized phthisiatric service in the given country or not.

8. THE STANDARD CHEMOTHERAPY REGIMES

Theoretical basis for chemotherapy in tuberculosis. According to the theoretical model of tuberculous infection, four different populations of MBT distribute in tuberculous focuses of a human organism.

1. Population of MBT, which actively grow because of high oxygen content and neutral pH in the liquefied caseous material that covers the cavity wall. These populations are the source of MBT in sputum and environments therefore are highly contagious to the surrounding.

2. Population of MBT, which exists in an acidic pH and are located mainly intracellular. These MBT, are thought to grow very slowly.

3. Population of MBT located in solid caseous content. This population of MBT multiplies slowly or intermittently.

4. Population of completely inactive MBT also exists.

Sensitivity of MBT populations to anti-tuberculous drugs.

1. Population of MBT, which actively grow in the liquefied caseous material and neutral pH are particularly vulnerable to isoniazid, and to a lesser extent, to rifampicin, streptomycin and ethambutol.

2. Against population of MBT, which exists in an acidic pH, pyrazinamide is particularly effective in killing this population.

3. Population of MBT contained in solid caseous areas is killed most efficiently by rifampicin.
At chemotherapy of tuberculosis, simultaneous existence of different MBT populations against which the anti-tuberculosis drugs have various activities proves application of combinations of anti-tuberculosis drugs in the initial (intensive) phase of treatment.

As the risk of selection of resistant mutants exists, the bacterial population is not significantly reduced; anti-tuberculosis treatment needs to be administered for a prolonged period.

**Anti-tuberculosis chemotherapy aims are to:**
1. prevent the selection of drug resistant mutants;
2. eliminate MBT in sputum;
3. assure complete cure.

All these objectives are achieved by simultaneously administering several drugs to which the MBT is susceptible.

The chemotherapy course according to the recommendations of the Ministry of Health of the Russian Federation consists of two phases with different tasks:
1. **phase of intensive chemotherapy**;
2. **phase of continuation (maintenance) of chemotherapy**.

**Phase of intensive chemotherapy** is directed on elimination of clinical manifestations of the disease:
1. to provide maximal effect on MBT population, with the purpose to stop MBT expectoration and to prevent drug resistance development;
2. to reduce infiltrative and destructive changes in organs.

**The phase of intensive therapy can be as a part of preparation to surgical operation.**

**The phase of continuation (maintenance) of chemotherapy is directed on:**
1. suppression of MBT population in a host;
2. reducing of the inflammatory changes and involution of tubercular process;
3. restoration of the functional abilities of the patient.

**Regime of chemotherapy consists of:**
1. selected combination of anti-tuberculosis drugs;
2. duration of their intake;
3. periods and contents of control examinations;
4. organized forms of treatment which are defined depending on groups, to which the tuberculous patient is regarded.

The following method is now generally accepted by WHO.

Each standard drug is indicated by a capital letter. They are as follows;
- Isoniazid (H)
- Ethambutol (E)
- Rifampicin: (R)
- Streptomycin (S)
- Pyrazinamide (Z)
- Thioacetazone (T)

When the drugs are given daily a figure before the drug combination shows for how many months that combination is given, e.g. **2HRZE** indicates that Isoniazid, Rifampicin, Pyrazinamide, Ethambutol are given in a single dose daily for 2 months.

Similarly **4HR** indicates that Isoniazid, Rifampicin are given in a single dose daily for 4 months.

One of the standard regimens is **2HRZE/4HR**. This indicates that Isoniazid, Rifampicin, Pyrazinamide, Ethambutol are given for the first 2 months (known as the 'initial' or 'intensive phase') followed by Isoniazid, Rifampicin for another 4 months (known as the 'continuation phase'), making 6 months in all.
8.1. MANAGEMENT OF ADVERSE EFFECTS CAUSED BY ANTI-TUBERCULOSIS DRUGS

Management of adverse effects to anti-tuberculosis drugs is important because they cause discomfort to patients and as a result they may interrupt the treatment.

Hypersensitivity (allergic) reactions rarely occur in the first week of treatment. They are common in the second to fourth week. They are much less frequent with isoniazid, rifampicin and ethambutol than with streptomycin and thioacetazone. Very rarely patients become allergic to all three drugs in a regimen.

There are various degrees of allergic reactions:
1. Mild itching of the skin is often the only sign of rifampicin allergy.
2. Moderate: fever and rash. The rash is often mistaken for measles or scarlet fever. If severe, the skin looks blistered and resembles urticaria.
3. Severe. In addition to fever and rash there may be generalized swelling of the lymph nodes, enlargement of liver and spleen, swelling around the eyes and swelling of the mucous membranes of the mouth and lips.
4. High fever, a generalized blistering rash and ulceration of the mucous membranes of the mouth, genitals and eyes (Stevens-Johnson syndrome). This is a rare but dangerous reaction, particularly to thioacetazone, and in patients with HIV infection.
5. Very rarely there may be chronic eczema involving the limbs occurring after the eighth week. This is almost due to allergy to streptomycin.

Treatment of allergic reactions can be immediate and desensibilizing.

Immediate treatment of allergic reactions.
1. If the only complaint is mild itching, it is possible to continue anti-tuberculosis treatment, making prescription of anti-histaminic drug.
2. If there is fever and rash, it is necessary to stop receiving of all drugs and to prescribe anti-histaminic drug.
3. If there is a very severe reaction, it is necessary to stop receiving of all the drugs.
4. If the patient seems seriously ill, it may be necessary to admit the patient in a hospital for active desensibilization therapy.

8.2. Surgical methods of treatment

The surgical methods have big importance in combined treatment of tuberculosis. The modernizations of methods of operative invasion, modern anesthesia, considerably expanded the application of the surgical help for the patient with the various forms of lung tuberculosis.

Modern anti-bacterial therapy allows to carry out preparation of the patients for operation so that in post operative period minimize possibility of tuberculosis process complication. Thus, it is necessary to take into account, that tuberculosis is quite often a bilateral disease and in postoperative period, it is possible that the process progress to the other lung.

To surgical methods of treatment concern except for described above collapse therapeutical operations: extrapleural pneumothorax, oleothorax, thoracoplasty, surgery on the peripheral nerves. Widely applied lung resections are: limited cuneiform resections, segmentectomy, lobectomy and pulmonectomy – removal the whole lung, if it is completely destroyed by tubercular process.

Pneumolysis (Pneumonolysis). Stripping of the pleura from the fascia of thoracic wall results in pneumolysis – an artificial cavity between intrathoracic fascia and parietal pleura is created. In the surgically formed cavity, as air is entered, gas bubble is formed and then repeated pumping is performed, as in intrapleural pneumothorax. The operation has little effect on function of external breathing, but now it is rarely applied, due to successes of anti-bacterial therapy and development of resection surgery of the lungs.
Extrapleural thoracoplasty does not have wide application. During thoracoplasty, ribs above the tuberculous focus are resected with the pathological part of the thorax; the lung is pressed inside of the thorax, making its collapse. Thoracoplasty causes irreversible changes: deformation and narrowing of thoracic cavity, shrinking of collapsed lung, and large functional loss. Thoracoplasty is recommended at fibrous cavernous processes with large cavities, at lung hemorrhages threatening life of the patient and when the condition of the patient does not allow applying modern methods of surgical treatment of lung tuberculosis.

The operations on the peripheral nerves are carried out on cervical part of phrenic nerve, thus changing the blood and lymph circulation of lungs. This operation provides infringement of phrenic nerve functions and rise of diaphragm. The operation leads to collapse of the lower parts of the lungs. For that during operation the phrenic nerve is cut (phrenectomy), or crushed (phrenicexision or phrenicotreption). To prevent complete damage of phrenic nerve, it is possible to introduce alcohol in it – phrenicoalcoholisation. After such method, function of the nerve is restored with time. In case of necessity alcoholisation can be repeated.

Lung resection. Lung resections are used more often in connection with introduction of effective methods of chemotherapy in practice, development of the methods of intratracheal anesthesia and improvement of methods of processing of the lung roots. Now it is one of the routine methods of lung tuberculosis treatment. Lung resections mainly perform within the limits of one-two segments, less often – lobectomy and pneumoectomy.

On the basis of modern experience the following absolute indications to lung resection are established:
1. Fibrous-cavernous lung tuberculosis with mainly unilateral localization.
2. Stenosis of bronchi with atelectasis in lung tuberculosis.
3. Progressing lung tuberculoma.
4. Combination of lung tuberculosis with bronchectasis and abscesses.
5. Empyema of pleura with pleuro-bronchial fistula, with cavity in collapsed lung and MBT expectoration.
6. Caseous pneumonia, resistant to chemotherapy.

The relative indication for mainly partial resection is the presence of cavernous lung tuberculosis.

Decortication and pleuroectomy. In certain cases of chronic tuberculous empyema of pleura, stone condensation of visceral and parietal pleura, pleuro-pulmonic fistulae develop. In these cases decortication is performed – removal of fibrotic stratifications on visceral pleura – and pleuroectomy – removal of all pleural «sac» with both layers of pleura.

A cavity resection is an opening, cleaning and drainage of a cavity through thoracic wall. The basic indications to open a cavity are the presence of large or huge cavity in lung, when the functional insufficiency of the respiratory and cardio-vascular systems excludes performing lung resection. The plastic operations are applied to close residual cavities in the lung: thoracoplasty, muscle-plasty, skin-muscle plasty.

Surgical intervention – is one of stages of treatment of the patient, therefore is necessary after operation to continue treatment with anti-bacterial drugs, it is desirable in conditions of sanatorium. It results in reduction of the number of aggravations and relapses in the post operative period.
8.3. TREATMENT OF HEMORRHAGES DURING LUNG TUBERCULOSIS

According to modern statistical data lung hemorrhages and hemoptysis of tubercular aetiology, constitute about 80-90% of all lung hemorrhages.

Conservative, therapeutic measures have wide application in mild and moderate hemorrhages.

The treatment of lung hemorrhages consists of:
1. patient is assigned to rest and be in half-sitting position;
2. reduction of blood pressure in bronchial artery or pulmonary artery;
3. increase coagulation property of blood.

Reduction of blood pressure in bronchial arteries could be achieved by:
1. intravenous injection of Sodium Nitroprusside;
2. intravenous injection of arphonade (quick action ganglio blockers).

Systolic blood pressure should not be lower than 90 mm Hg.

Pressure in system of pulmonary artery could be reduced:
1. by applying venous tourniquet on extremities for not more than 40 min.
2. by intravenous injection of eophylline (theophylline).

For amplification of blood coagulation intravenous introduction:
1. 10% solution of sodium chloride or Calcium gluconate;
2. intravenous 1% solution of protamine sulfate;
3. intravenous fibrinolis inhibitor – 5% solution of aminocapronic acid.

At profuse bleedings there can be a necessity of partial replacement of the lost blood.

It is necessary to assign additional methods during lung hemorrhages for prevention of aspiration pneumonia and worsening of the condition:
1. antibiotics of a wide spectrum;
2. anti-tuberculosis drugs.

Performing artificial pneumothorax or pneumoperitoneum help to stop hemorrhage as soon as possible in tuberculous patients. Artificial pneumothorax is necessary to apply in patients, for whom bleeding arises in fresh cavities, without expressed fibrosis. If a source of bleeding is fresh and destructive processes located in the lower lobes, then it is recommended to impose pneumoperitoneum.

Treatment with the above mentioned medical measures allow stopping hemorrhages in up 80-90% of the patients. Surgical intervention is indicated during inefficiency of these methods, and life threatening condition.

The operations on lung hemorrhages can be done during:
1. extreme cases – at moment of blood loss;
2. urgent need – after arrest of bleeding;
3. scheduled or planned – after stopping of hemorrhage, fulfilled special investigation and full preoperational preparations.

Emergency surgical methods

To stop hemorrhage it is necessary to organize immediate surgical help, perform resection of a part or the entire lung. Depending on the form, prevalence of tubercular process, and functional data segmental resections, lobotomy or pulmonectomy can be performed. Blood transfusion is obligatory during preparation of the patients for surgery in case of massive bleeding.

Occlusion of a bleeding vessel is the most effective method to stop hemoptysis.

During occlusion of bronchial artery, it is possible to catheterize immediately after bronchial arteriography and refinement to topical diagnostics of bleeding. For this purpose through catheter enter slices of Teflon velour, silicon balls, fibrin sponge, clots of own blood, and in a case of a very wide vessel – a special metal spiral with a loop from Teflon strings. It is possible to use other materials, which promote thrombosis and to stop bleeding from bronchial arteries.
8.4. Spontaneous pneumothorax

The reason for spontaneous pneumothorax can be perforation of sub pleural localized focus, cavernous, and emphysematous bullas. The size of a gas cavity depends on presence of pleural adhesions, which considerably complicates the ability of lungs for compression; therefore, limited closed spontaneous pneumothorax is formed. If the pleural adhesions are not present, the formation of large gas cavity is possible with subsequent squeeze of the lung. Thus, the quick stoppage of one lung function can result in the stopping of respiratory function and then give rise to lung-heart insufficiency. The first hours are most dangerous after spontaneous pneumothorax to the patient. If the perforation is not closed, it causes open spontaneous pneumothorax.

At formation of pleural – pulmonic fissure, valvular (gated) pneumothorax is formed. Limited closed spontaneous pneumothorax can proceed asymptotically if the gaseous balloon is small and hemodynamic disturbance is not observed. The perforation is quickly closed, the gas is absorbed, and spontaneous pneumothorax disappears without leaving any trace.

Clinical signs. At spontaneous pneumothorax, the patients complain of pain in the side of spontaneous pneumothorax, especially during cough and physical stress, dyspnoea occurs. Large and fast lung shrinking cause collaptoid state: weakness, pallor, cold sweat, frequent and thread pulse. On auscultation of the patient above the area of spontaneous pneumothorax, there is decrease in breathing.

On X-ray, gas bubble is found in the pleural cavity. Open and valvular spontaneous pneumothorax is complicated sometimes with exudative pleurisy resulting in prolonged duration of illness and severe than in closed pneumothorax.

Closed limited pneumothorax without damage of heart-lung function is preserved without intrapleural interventions. Gradually gas is absorbed, and the lung expands.

9. SPECIFIC PREVENTION OF TUBERCULOSIS. VACCINATION. CHEMOPROPHYLAXIS

Worldwide methods of tuberculosis specific prevention include the following BCG (Bacilles-Calmette-Guerin) vaccination, revaccination and chemoprophylaxis.

The BCG strain is used for vaccination and revaccination. This strain has the following properties: it is harmless, has specificity, immunogenicity, keeps residual virulence, has limited multiplication in vaccinated organism, being in lymphatic nodes. For immunization in Russian Federation a dry BCG vaccine is applied as most stable, and capable for considerable time to keep required quantity alive MBT.

The duration and stability of post-vaccinated immunity is determined by character of immuno-morphological changes and vegetation of BCG in inoculated organism. BCG strain introduced in organism, multiply within the cells, and stimulates the development of antituberculosis immunity.

After two weeks of vaccination BCG strain begin to transform into L-forms. In such situation MBT of BCG strain can exist in organism for a long time, maintaining antituberculosis immunity.

The efficiency of BCG vaccinations is shown by the fact that among vaccinated and revaccinated children, teenagers and adults incidence of new tuberculosis cases and mortality is lower, than among not vaccinated.

The duration of post-vaccination immunity is maintained minimum up to 5-7 years after intradermal BCG vaccination.

Method of administration of BCG vaccine and its dose. In the territory of Russian Federation intradermal BCG vaccination is used as the most effective and economic method of vaccination.
BCG vaccination of newborn is carried out on 4-7-th day of life without preliminary tuberculin test.

BCG revaccination or repeated inoculation against tuberculosis will be carried out in decreed (approved) periods at presence of negative reaction on Mantoux test with 2 TU PPD-L.

The first revaccination is carried out at the age of 7 years (1-st school class), second at 11-12 years (5-th school class), third – 16-17 years (10-th school class).

Subsequent revaccinations will be carried out with an interval 5-7 years up to 30-years of age. Method of revaccination is the same as the vaccination.

**Chemoprophylaxis**

The term chemoprophylaxis has been applied to two distinct types of preventive therapy of tuberculosis.

1. **Primary chemoprophylaxis** where the drug is given to individuals who have not been infected (with negative tuberculin test) in order to prevent development of disease (e.g. infant being breastfed, being in contact with bacillary patient).

2. **Secondary chemoprophylaxis** where the anti-tuberculosis drugs is used to prevent development of disease in people who have already been infected but being in condition of repeated infection or relapse of tuberculosis.

**The groups of population’s eligible for chemoprophylaxis**

Chemoprophylaxis is carried out for the prevention of tuberculosis in the following groups of population:

1. children, teenagers and adults who are being in constant contact with tuberculous patients;
2. healthy children without clinical signs, teenagers and persons of young age till 30 years of age who for the first time are MBT infected;
3. persons with constant hyper allergic reactions to tuberculin;
4. newborn (BCG vaccinated in the maternity hospital), born from tuberculosis suffering mother;
5. people with newly positive tuberculin reactions;
6. the persons with the signs of earlier transferred tuberculosis and now in the presence of the adverse factors (acute forms of diseases, operation, traumas, pregnancy etc.). capable to cause an aggravation of tuberculosis, and also in persons who were earlier treated from tuberculosis but with large residual changes in lungs, being in a dangerous environment;
7. the persons with signs of old tuberculosis but at present having concomitant diseases capable to activate tuberculosis (diabetes, collagenosis, silicosis, sarcoidosis, ulcer of stomach, stomach resection etc.).

Among the persons who had undergone chemoprophylaxis, the number of incidence of tuberculosis is 5-7 times less in comparison with the appropriate groups of the persons without chemoprophylaxis.

**Drugs.** For chemoprophylaxis isoniazid or ftivaside are used for 3 months, and if epidemic danger remains, chemoprophylaxis is repeated 2 times per year for 2 months. For the persons with hypersensitivity to tuberculin test, prophylaxis is recommended with two preparations – isoniazid and pirazinamide (ethambutol).

**Doses.** For adults and teenagers the daily doze of isoniazid for daily administration is 0,3 g., for children 8-10 mg/kg. If intolerance to isoniazid occurs, it is possible to do chemoprophylaxis with ftivasid. Ftivasid prescribed for the adult is 0,5 g 2 times per day, children 20-30 mg/kg. Both adults and children should necessarily take vitamin B6 and C.

The application of secondary chemoprophylaxis is most justified by seasonal courses (in a autumn-spring season) for 2-3 month 2 times per year.
10. SOCIAL AND SANITARY PREVENTION OF TUBERCULOSIS

The basic principles of carrying out tuberculosis control are based on state struggle against tuberculosis as a social disease. The organization concerned with the fight against tuberculosis includes establishments of public health services together with specialized anti-tuberculosis system.

The purpose of anti-tuberculosis measures:
1. to prevent MBT infection of healthy people;
2. to limit and to assure safety of contacts active tuberculous patient (especially MBT sputum positive) with the healthy people living together or at work.

Major component of sanitary prevention is the realization of social, epidemiological and medical measures in family and in the residence (infection focal point) of tuberculous patient.

The realization of preventive measures in the infection focal point begins with its visit by phthisiatrist, epidemiologist and medical nurse of the local dispensary immediately from the moment of detecting MB in the sputum of patient or detection of destructive tuberculosis in lung. Depending on the results of the examination of the infection focal point the plan of its improvement (sanitation) is made.

The plan should reflect:
1. disinfection of the focal point;
2. treatment of the patient;
3. isolation of children;
4. registration of the inhabitants in dispensary;
5. frequency and extent of regular investigation of all members of a family, realization of chemotherapy prevention, supply of disinfectants.

The criteria of epidemic danger of the place of tuberculous patients’s residence (tuberculous focus) are:
1. massive and constant expectoration of MBT by the patient;
2. patient’s life style;
3. behavior, general standards of cultural habits and sanitary awareness of the patient as well as persons surrounding him.

On the basis of these criteria the tuberculous focuses depending on degree of epidemic danger are divided into three groups. According to this grouping volume and contents of preventive measures in the tuberculous focus are defined.

The 1-st group of tuberculous focus – most unfavourable:
1. the patient with chronic destructive tuberculosis living in bad housing conditions constantly expectorates MBT;
2. in family of the patient there are children, teenagers, pregnant women;
3. the patient and the people around him do not observe hygienic rules.

The 2-nd group of the tuberculous focus – relatively unsuccessful:
1. the patient has poor bacterial expectoration, stable tuberculous process, lives in satisfactory housing conditions;
2. in family of the patient there are only adult persons, adverse factors are absent;
3. the patient and the persons around him do not observe hygienic rules.

The 3-rd group of the tuberculous focus – potentially dangerous:
1. the patient is conditional MBT expectorator;
2. in family of the patient there are only adults;
3. the patient and the persons, around him, carry out all necessary sanitary – hygienic measures of tuberculosis prevention.
Realization of preventive measures in the focus of infection

The important section of the plan is educating the patient and members of his family about sanitary – hygienic skills.

The room of the patient is to be cleaned and disinfected every day.
When the patient is going from the house for treatment in a hospital, in a sanatorium or in case of his death, a final sanitary – epidemiological service should be carried out.

It is very important to train the patient to be careful with sputum, plates and dishes, subjects of personal use that practically makes him safe for persons around him.

The MBT expectorator should have spittoon for sputum collection, which content must be boiled, with the purpose of MBT elimination; it is possible to use chloride of lime.

The clothings of the patient and especially handkerchiefs, towels should be collected in a separate bag, before washing the linen is soaked in 5 % of chloramin solution over night and boil in 2 % solution of soda during 30 minutes.

Plates and dishes of the patient are washed and are wiped by a separate towel.

The clothes of the tuberculous patient should be exposed to the sun often, weekly ironed and disinfected not less than 2 times per year in steam or in steam-formalin chambers.
The cleaning of clothes should be done outside the inhabited room.

The floor cleaning must be conducted with a damp cloth dipped in 2 % soda solution.

All these measures forming part of the concept of the current disinfection, which is carried out by the patient or adult members of his family under the management and control of the medical nurse of tuberculosis dispensary.

Measures on tuberculosis prevention among persons, being in contact with the tuberculous patients and working in tuberculosis establishments

In anti-tuberculosis establishments the personnel communicate with the tuberculous patients, including those who are secreting bacteria. These contacts take place in out-patient reception of the patients, at service in clinics and in the apartments, where the transmission of the infection is possible through dust, contact, drops and alimentary ways.

Incidence of tuberculosis among medical staff of anti-tuberculosis establishments is 8-10 times higher, than in all population.

In every anti-tuberculosis establishment, there are rules with the purpose to minimize the danger of infection by tuberculosis and to create the most favorable working conditions for the personnel. These rules should be strictly observed.

Individual means of protection of respiratory organs

The general regulations. Individual means of respiratory organ protection (respirators, gauze bandages) serve for medical workers as "last boundary of defense" against concomitant MBT distribution.

Respirator’s use is limited in places of high risk, namely:
1) in boxes of the tuberculous patients or MDR-TB;
2) at stimulation of sputum expectoration or other procedures causing cough;
3) at bronchoscopy;
4) at section halls;
5) at spirometry;
6) during emergency surgery on the potentially infectious tuberculous patients.
**Surgical masks.** Between a surgery mask and respirator there are important differences. Surgical masks for example (made of cloth or of paper):

1. really provide prevention of distribution of microorganisms from their source (for example, tuberculous patient) to other persons by retention of large particles separated near nose and mouth;
2. do not provide protection of the user (for example, medical worker, patient, member of family) from inhalation of the infectious agent in air droplets.

**Means and methods of disinfection**

**Means of disinfection.** Now there is a wide spectrum of disinfectants. However at application it is necessary to check their activity to disinfect contaminated MBT material. From these preparations chloride of lime and chloramin are most widely used in Russian Federation.

1. **Chloride of lime** – white powder containing 28,0-35,0 % of active chlorine.
2. **Chloramin B and XB** – powder of cream color, contents of active chlorine 27,0-28,0 %.

For preparation of 5 % chloramin disinfectant solutions 500 g. of chloramin powder dissolve in 10,0 liters of water.

**Disinfection of objects of personal and public use**

**Spittoons.** Plates and dishes with remains of food. The remains of food. Wash basin, urinals, lavatory pans, taps. Subjects of patient’s care: bedpans, urinals, tips for clysters.

**Methods of disinfection.**

1. Boiling in soda solution.
2. Immersing in a pan with a cover containing chloramin solution.
3. Autoclaving.
4. To cover with chloride of lime.

**Service rooms (wall, floor, doors, furniture) in wards, in procedure units, in places of common usage.**

**Methods of disinfection.**

1. Wiping with tatters moistened in the activated solutions of chloramin.
2. Washing with hot soap-soda solution.
3. Immersing in a vessel with a cover containing solution of chloramin.
4. To cover with chloride of lime.

**Linen (bed, from dining rooms, underwear, furniture cases, gauze masks, respirators, handkerchiefs, personal linen and bed cloths).**

**Methods of disinfection.**

1. Boiling in soda solution.
2. Ironing by a hot iron.
3. Disinfection in gas-chamber.

**Soft furniture.** Fine objects of use, toy (metal, rubber, wooden, plastic). Books, notes, paper etc.

**Methods of disinfection.**

1. Immerse in disinfection solutions and disinfect according to regimes.
2. The objects of little value are burnt, and valuable ones are disinfected in gas chamber.
3. Cleaned by a brush moistened in one of disinfectant solutions.
In anti-tuberculosis hospitals at reception of the patients, and then regularly sanitary –
educational work with the patients should be carried out. With the purposes of protection of the
personnel from infection, special attention should be paid to the rules of behavior, obligatory
for the patients.

When discharged, the patient must receive explanations about the rules of his behavior at
his place of living and in public places, warning him about the spread of tuberculosis infection
to the surrounding.

Sanitary education is part of preventive work in dispensary. In the plan epidemiological
measures directed on struggle against tuberculosis, anti-tuberculosis propagation should play an
important role. The sanitary – educational work is necessary for carrying out first of all among
the tuberculous patients.

The propagation of knowledge about the origin of tuberculosis, its sources, and distribution
is the important part of struggle with this illness. The knowledge of methods of personal and
public preventive measures of tuberculosis has the practical importance for the population.

Anti-tuberculosis activity of general medical establishment’s network

Prevention of tuberculosis and detection of the patients with tuberculosis in a population is
the function of treatment-preventive establishments of a general medical network. This work is
carried out under organized and methodical management of the tuberculosis dispensary and
organs of sanitarian-epidemiological surveillance.

The basic tasks of general medical establishment of polyclinic type are to perform proper
investigations in the patient in whom tuberculosis is suspected and to send him to tuberculosis
dispensary.

The polyclinics of common profile carry out, after investigation of the tuberculosis
suspects, a clinical minimum: lung fluorography, sputum examination for MBT, tuberculin test,
analysis of blood and urine.

Measures of sanitary and epidemiological surveillance of the Republic Moldova
in prevention and revealing of tuberculosis

The work of committee of sanitarian and epidemiological surveillance and its divisions on
prevention of tuberculosis in territory of their responsibility includes the following:
1. specific prevention and early detection of tuberculosis, improvement of bacteriological
service for strengthening of the effectiveness of epidemiological situation on
tuberculosis;
2. to controll sanitary situation of the industrial enterprises, children's and teenage
establishments, epidemiological regime in anti-tuberculosis establishments and in the
focuses of tuberculosis infection;
3. to carry out retrospective epidemiological forecast and participation in planning of anti-
tuberculosis measures.
Standards, publications on TB

1) WHO publications
- Global TB Control Report 2011
- The Global Plan to Stop TB 2011-2015
- Treatment of TB: guidelines
- The Stop TB Strategy

2) TB data
- Tuberculosis country profiles
- WHO's global TB database

3) ATS Documents: Statements, Guidelines & Reports
- Microbiology, Tuberculosis and Pulmonary Infections
- Pulmonary Function and Exercise Testing
- Diagnostic standards and classification of TB in Adults and children (2000)

4) National Institute for Health and Clinical Excellence (NHS)
- Tuberculosis. Clinical diagnosis and management (2011)