Ministry of Health of Ukraine
Poltava State Medical University
Department of internal medicine №3 with phthisiology

LECTURE 1. DETERMINATION OF TB AS SCIENTIFIC AND PRACTICAL PROBLEM. HISTORY OF DEVELOPMENT OF PHTHISIOLOGY. EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS OF THE TB. IMMUNITY AT TB.

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Lecture plan
Introduction
Definition of TB as a medical and social problemHistory of phthisiology
Epidemiology of TB
Etiology of TB
Pathogenesis of tuberculosis
Clinical classification of TB

- **1. The theme topicality**: Tuberculosis is one of the infectious diseases. It is known since ancient times. This disease is produces typical tubercular changes in the lungs and other organs. The clinical manifestations of tuberculosis are described by Hippocrate, Avizenna many centuries ago. However, today the World Health Organization has proclaimed the tuberculosis as the global dangerous disease. Every year the level of sickness and mortality (death-rate) are increasing in all the world. That is why the knowledge of tuberculosis is necessary for the doctors of any specialty.

A phthisiology is science, studying of reasons, mechanisms of development, pathomorphological, clinic, diagnostics, treatment and prophylaxis of tuberculosis.

- **Tuberculosis is an infectious disease the patogen of which is mycobacterium of tuberculosis (MBT), characterized the granulom with caseous and necrotic-destruction impression of tissue, with wide clinical polymorphism, shows social dependence, the temporal loss of capacity for work and requires the protracted treatment and rehabilitation of sick.**

- **1. EPIDEMIOLOGY OF TUBERCULOSIS**
- Annually in the world find out near 10 millions patients are with fresh tuberculosis and 3—4 millions of them die every year. The third of the population of Earth are infected the pathogen of TB which ground to forecast considerable growth of morbidity on TB in the future.
- The greatest level of morbidity on TB is in the African, Asiatic regions and countries of the Pacific coast. An epidemic situation is worsened from TB in countries to East Europe.
- After the criteria of WHO in accordance with the level of morbidity on TB, up-diffused on three categories:

- **countries with the low level** of distribution of TB, where level of morbidity below 10 cases on 100 thousands populations;
- **countries with the middle level** of the distribution TB. For them is the level of morbidity makes from 10 to 30 cases on 100 thousands of population;
- **countries with the high level** of distribution of TB, where the index of morbidity is more high 30 cases on 100 thousands of population.

- **The epidemic chain** of tuberculosis have consists of three links: source of pathogen of tuberculosis, ways and methods of infecting and the sensitive to tuberculosis contingents.
- **The source of MBT** more frequent is a patient with the opened form of TB, or animal illness on tuberculosis (mainly cows). They forming *reservoir* of tubercular infection in an environment.
- A TB patient can excreting in an environment from 4 to 7 milliards bacillus of MBT every days, that substantially influences on forms of the epidemic of TB.

- ***Basic epidemiology indexes****:* infection, morbidity, death rate and sickliness.
- ***The infection*** is determined as a percent of people in which sensitiveness appeared to the tuberculin, from the number of inspected during a year.
- The systematic study of this index is conducted only for children and annually in Ukraine and other countrys it grows on 5-7%.

- **Morbidity** is an index amounts sicks first of discovered during a year in a calculation on 100 thousands of population. From data of WHO **(2011**) morbidity on TB folds in Svazilend- 1200, in South Africa - 960, Zimbabve - 760, Namibia - 750, to Botswana - 710, Lesotho - 640, Dgibuty- 620, Sierra Leone - 610, to Cambogia - 490, Habon - 450, Togo - 440, Congo - 390, Central African Republic - 340, Kenya - 330, Uganda - 310, Nigeria - 300, Somalia - 290, Fillipine - 280, to Liberia - 280, Pakistan - 230, Tadjikistan - 200, Kamerun - 190, Indonesia - 190, Kazakhstan - 180, India - 170, Uzbekistan - 130, Sudan - 120, Russia - 110, Azerbaygan - 110, China - 97, Morocco - 93, Armeny - 73, Yemen - 60, Turkmenistan - 68, to Iraq - 64, Bulgaria - 43, to Turkey - 30 on a 100 thousand population. This index is relatively subzero in: Japan - 22, Syria - 22, Iran - 20, Saudovsky of Arabia - 19, to Spain - 17, to England - 12, to Italy - 7, to Greece - 6, to France - 6, to Germany - 5, the USA - 5, to Canada - 5 on 100 thousands.

- In Ukrain the morbidity on TB is 62 on 100 000 of population.

  Morbidity on TB exceeded 50 patients on a 100 thousand population is epidemic threshold.
- On achievement of children of 15-years-old age this index is 35%, among a persons attained 40-60 old-years this index composed 90 - 100%. People, infected MBT, are not always illness of tuberculosis. Only in 5-10% of infected MBT may be develop active of tuberculosis and possibly contagious form. It is predefined by the immune system, which can brake reproduction of MBT in organism.
- If the immune system is depressed, the chances of this man illness on tuberculosis is considerably grow.

- ***Morbidity*** is an index amounts sick first of discovered during a year in a calculation on 100 thousands of population.
- A 1,4% population are stands on an account in the anti tubercular dispensaries of Ukraine. Morbidity on tuberculosis among medical workers are in 2 times, among the workers of anti tuberculosis establishments in 4—5 times exceeds this index among a population.

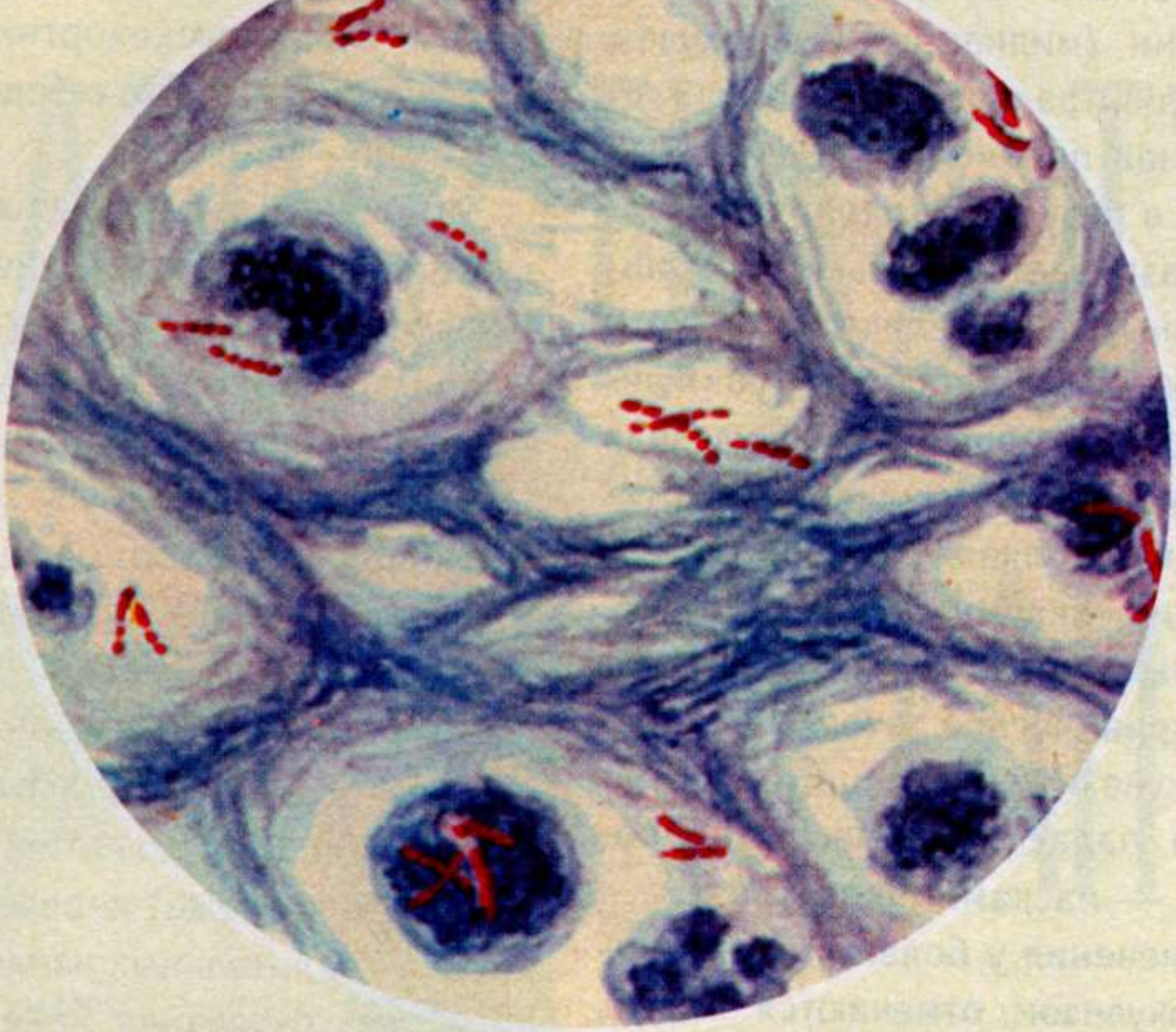
- The thorny of medical problem is permanent growth of the polyresistant tuberculosis, related to the loss sensitivity of MBT to anti tubercular drugs.
- In the world over 54 millions people is infected of MBT, not sensible to anti tubercular preparations.
- A substantial role in forming of the epidemic of tuberculosis in world is expansion of the VIH-infection, which forming a cellular immune deficit, assists development of AIDS-associated of tuberculosis.

- ***A death rate (mortality)*** is an index amounts dying from of tuberculosis during a year in a calculation on 100 thousands of population. From data of WHO tuberculosis is principal reason of death rate from one pathogen of illness. 95% cases of disease on tuberculosis are in countries with a weakly economy. 80% patients are made by the people of capable of working age (19—59 years).

- A death rate among them is 25%. This index is high in the countries of Asia and arrives at 70 on 100 thousands population. In the countries of Western Europe it is within the limits to 2,5 on 100 thousands population. In Ukraine a death rate from tuberculosis for the last 10 years was doubled and makes near 12 on 100 thousands population.

- **2. ETIOLOGY OF TUBERCULOSIS**
- **The reason of development disease of tuberculosis** is mycobacterium of tuberculosis (MBT), which was discovered by R.Koch in 1882. The group of mycobacterium is made by over 30 forms of mycobacterium, but pathogenic for a man are only MBT of human, bovine and African types.
- MBT have a bacillus kind long 1-6 mkm and breadthways 0,2-0,5 mkm, immobile, have large polymorphism. Reproduction MBT realize by a simple division of cells, transversal division, branch out. The spores MBT is not generates. They grows slowly, optimum temperature of growth is 37-38°C. Doubling of MBT comes in 24—48 hours. At the decline of temperature to 29°C, or increase to 45°C growth of MBT is halted. After growling properties select MBT, which are grow quickly or slowly and MBT, that are in the latent state.

РОБЕРТ КОХ (1843–1910) — немецкий бактериолог, один из основателей современной микробиологии. В 1891–1904 годах — директор созданного им Института инфекционных заболеваний в Берлине (позднее Институту было присвоено его имя). В 1882 году Роберт Кох известил об открытии возбудителя туберкулеза. За это открытие, которое принесло ему мировое признание, ученый был удостоен Нобелевской премии. В 1893 году была опубликована еще одна классическая работа Роберта Коха — о возбудителе холеры. Этот выдающийся успех был достигнут в результате изучения эпидемий в Египте и Индии. Одна из выдающихся его заслуг заключается в том, что он создал мировую школу бактериологов, представленную именами многих выдающихся ученых, среди которых Э. Беринг, Ф. Леффлер, Р. Пфейфер, С. Китасато, А. Вассерман и другие.



Микобактерии туберкулеза (окраска по Цилю–Нильсену)

- MBT is resistant to acids, alkalis and alcohols.
- In composition MBT are tuberculin protein, lipids and polysaccharides. Tuberculin protein is the transmitters of immunogenic specificity; to them the reaction of hypersensitiveness of slow type is related. Large content of lipids distinguishes MBT from other types of microorganisms and predetermines such properties:

- MBT is firmness against ordinary disinfection matters;
- In the natural conditions of MBT are resistens to the factors of external environment and keep viability during a few months. In a liquid environment MBT perish at boiling in 5 minutes, and in a dry sputum at the temperature of 100°C— in 45 minutes. Under act of sun ray they perish in 3-4 minutes, and in a sputum — in 4 hours. Under act of disinfection facilities (desacting, chlorantin) MBT are perish during 3-5 hours.

- Under act of unfavorable conditions and anti tubercular preparations of MBT can be changeability: they are transformed in more firmness, not sensible forms to these conditions (filtration, L-form and others like that) is **persistent** of MBT,but at favorable conditions they are **reversion** to acquire classic form of MBT with pathogenic properties. In this way can be formed resistance MBT to anti tubercular drugs (ATD).
- Resistance may be: primary, secondary, monoresistence, poliresistence, multiresistence.

- *Primary medicinal firmness* is resistance MBT, which found out in patients with first diagnosed TB which not treatment by anti tubercular preparations (ATP) never.
- *The secondary medicinal* is resistant of MBT, which found out for patients which accepted ATP more than 4 weeks.
- *Monoresistance* is firmness of MBT against 1 from 5 drugs of I-st of row ATP.
- *The poliresistance* is firmness of MBT against 2 and anymore ATD.
- Multiresistance is a variety to poliresistant, namely is firmness of MBT only against combination of isoniasidum+rifampicinum or with to other preparations.

- ***The reasons of medicinal firmness (resistance) are:***
- biological – it is an insufficient concentration of preparation, individual features of organism of patient (speed of inactivate preparations);
- conditioned by present contact with patients on drugs resistant TB, irregular reception of drugs, premature stopping of reception of drugs, unsatisfactory combination of drugs, inadequate treatment, not awareness of importance of treatment;
- the conditions illness are the plenty of MBT in the areas of affected organs, the pH in areas affected, which changes the active action of drugs;
- the conditions of the treatment are inadequate appoint of treatment, monotherapy is treatment by one drug, under doses or short duration of treatment and use of drugs to which MBT are resistence.

- 3. PATHOGENESIS of TUBERCULOSIS

The infection of MBT may be 2 ways: aerial (92-95%) or alimentary (5-8%), described also cases of infection through the wounds of skin, mucus shells and antenatal. Antenatal infection is *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 is very rare.

- ***Factors of infecting*** are contact with a patient with the opened form of tuberculosis (domestic, professional), apartments, things, objects are infected and food products are infected (especially milk).
- Conditions which assist development of tuberculosis are VIH/AIDS, chronic stresses, diabetes mellitens, ulcerous illness of stomach, treatment immunosuppressive drugs, harmful habits (alcoholism, drug addiction), all of it predetermines development of immundeficiency.

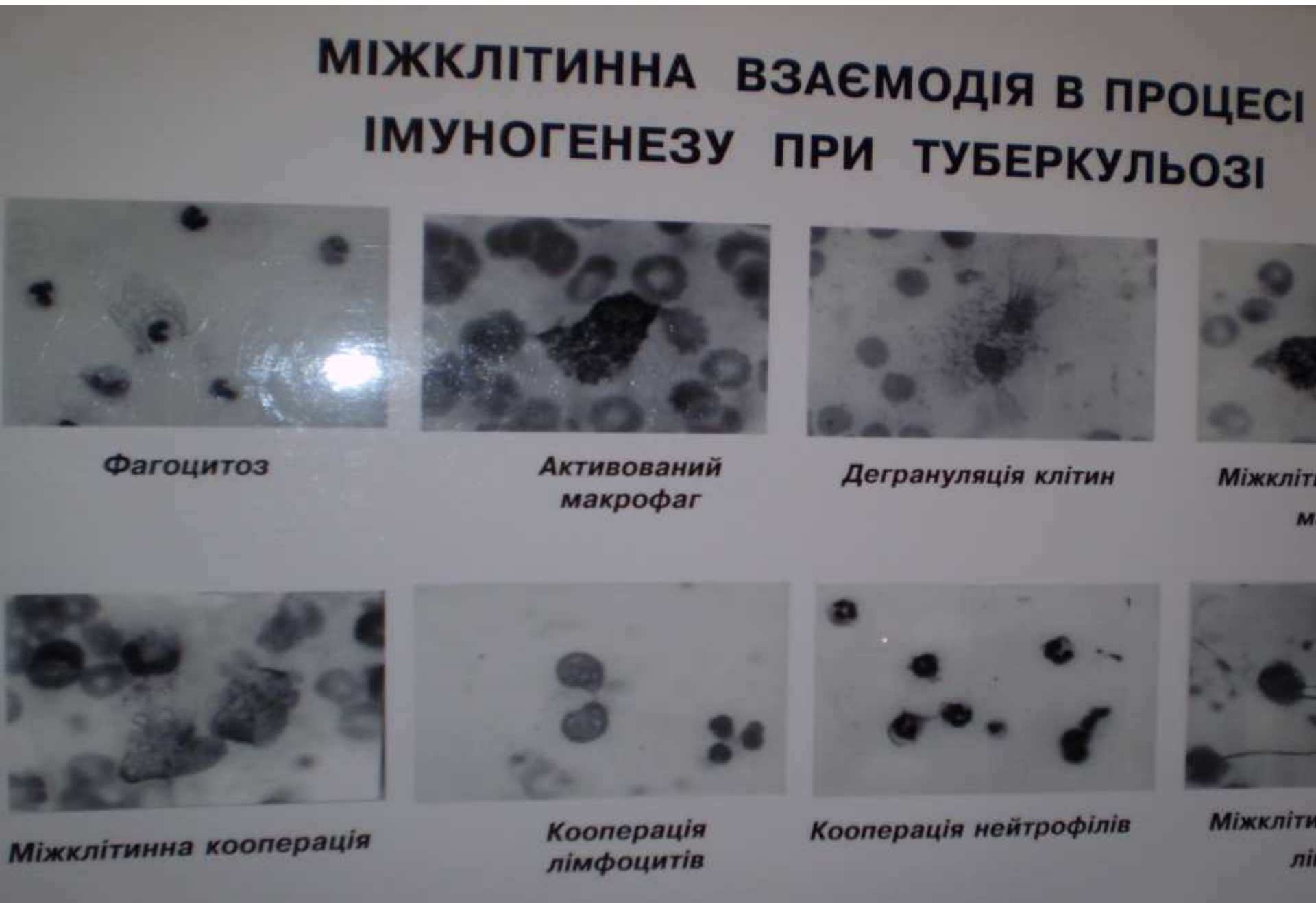
- Differenced the primary and secondary infection.
- **The primary infecting** is penetration of MBT in the organism is not infected before. In most cases the primary infecting does not result a disease if the reaction of the protective systems of organism is adequate. At decreased of immune defense, massiveness and high virulence of infection by MBT the primary infection may be causes development of disease.

- **In pathogenesis of the primary infecting select 4 phases:**
- I phase is characterized of bacillhemia and hematogenic distribution of MBT in an organism;
- II phase is characterized of immune-morphological reactions of tissues of organism on penetration of MBT;
- III phase is characterized of clinico-pathomorphological displays of illness;
- IV phase is characterized of completion of tuberculosis and formation remaining changes in affected tissues or passing disease to the chronic forms TB.

- **Phase of bacillhemia it is** short-term and lasts 4-6 hours, during what MBT get to the sub mucous layer, in lymphatic and of the circulatory system vessels carried on all of organism. At this time there is elimination of MBT in tissues of different organs, the book-mark of tuberculosis of different localization is formed as a result: pulmonary, osteoarticular, urinal, nervous system, skin, organs of abdominal region, pelvic organs, eyes and other organs.

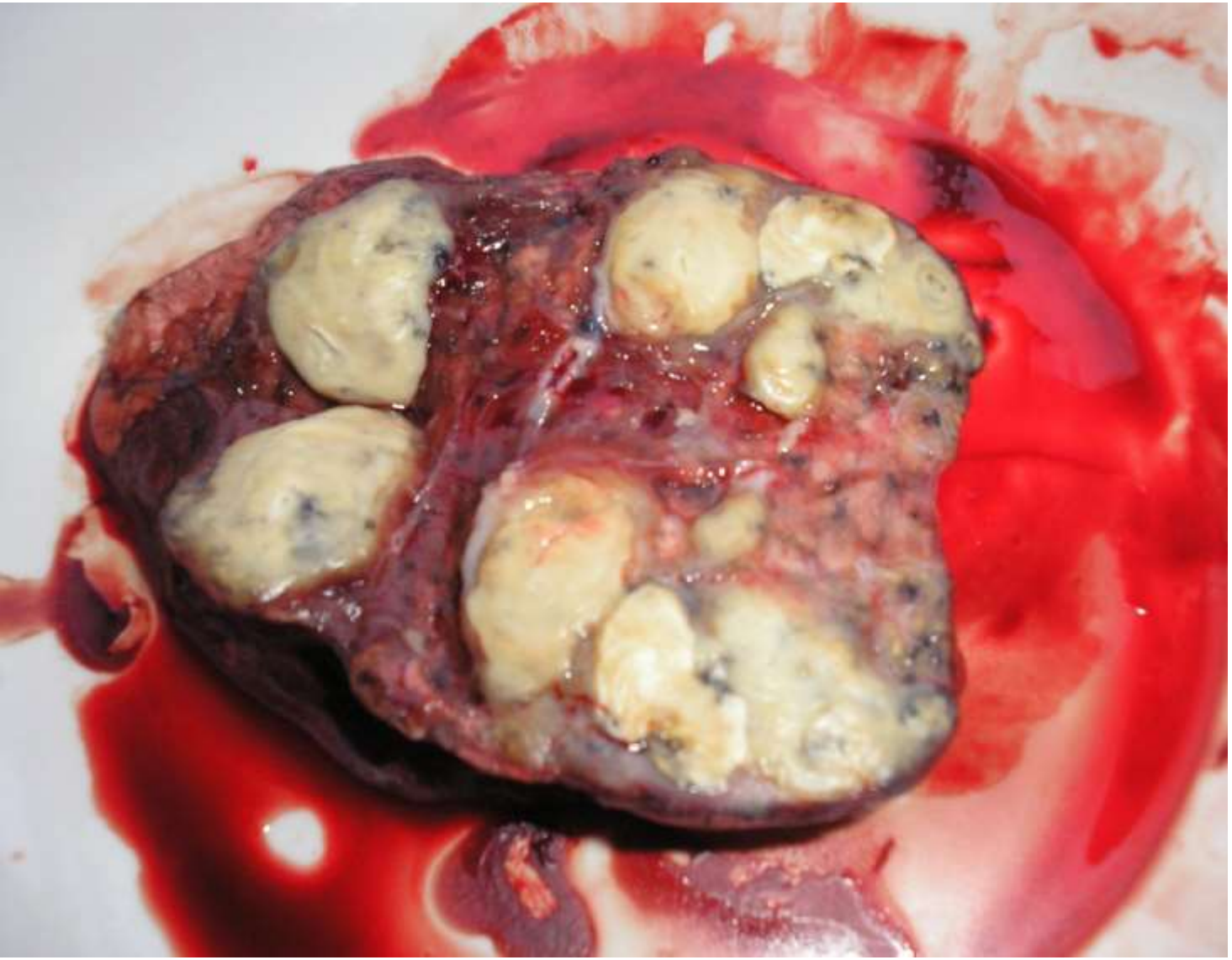
- **The phase of immune-morphological reactions of tissues** is begun with phagosytosis of MBT by tissue macrophages. MBT is living and multiply in macrophages. The macrophages identify the antigen signs of MBT, excreting monokines (factor of chemotaxis and activating of immunological alteration of organism), forms at first heterospecific epithelioid granulomes, and later – tubercular granulome, from which appear the hump of the impression in tissues. Immunological alteration in organism is activated and carried out during 6-8 weeks. Character of immunological reactivity determines the subsequent fate of infectious process. If the immune system is not decrease and forms adequate reactivity (normergic), an infectious process can acquire reverse development without the clinical displays and an organism acquires to the tuberculin sensitiveness.

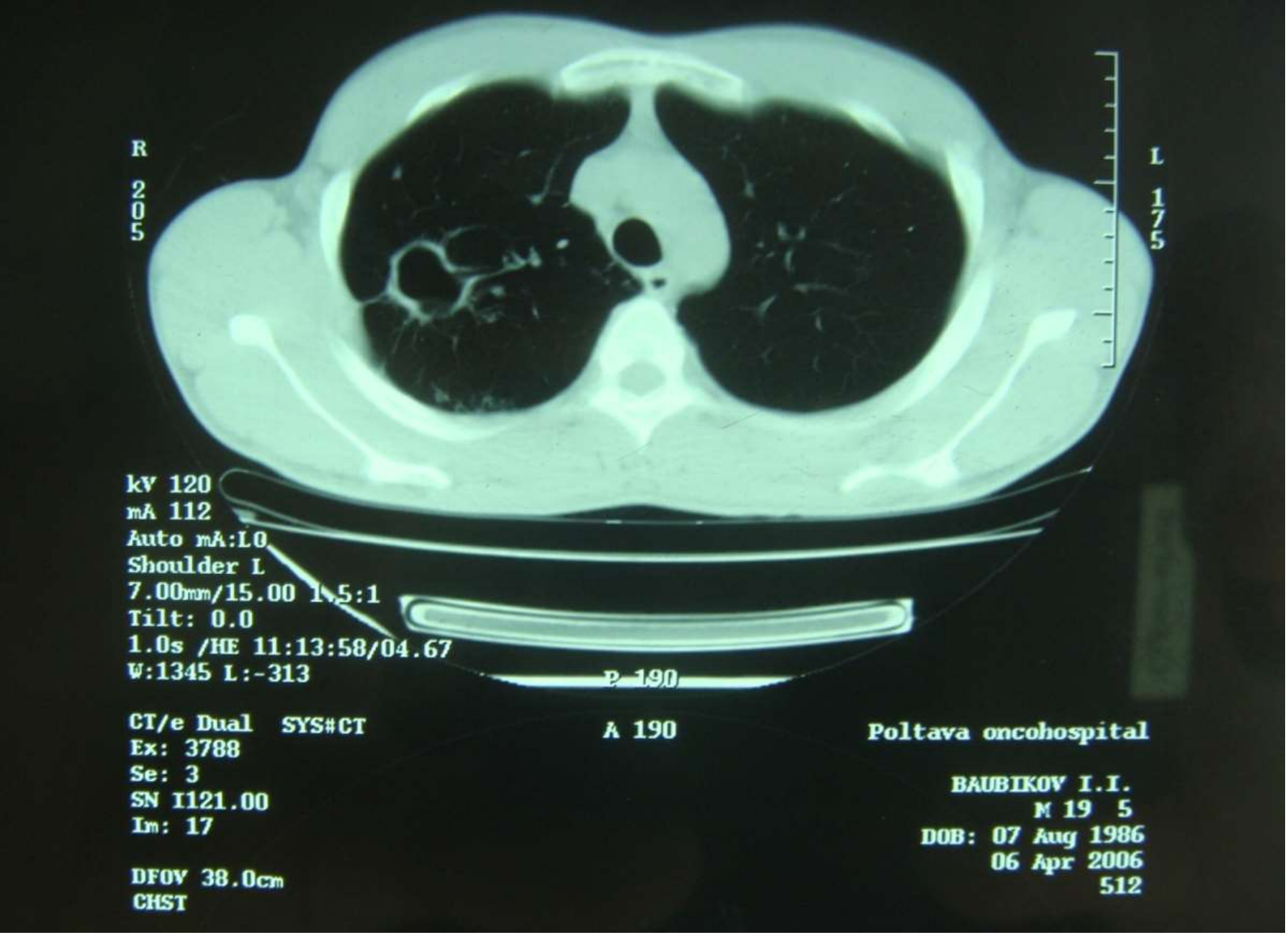
- Interaction of the cells



- If immunological defense is decreased (anergy) or inadequately enhanceable (hyperergy), local changes in tissues is acquire progressing character and passes to **the lll phase of clinic-pathomorphological changes** the expressed of which stipulates the general and local clinical displays of tuberculosis.
- At the normergy reactivity the productively or productive-caseous changes are without in tissues or with small destructions.
- At hyperergic reactivity exudates-destructive processes with forming of the cavities are prevail.

- At anergy aTB process can acquire lympho-hematogenic dissemination with forming of the productive, productive-caseous and exudates-necrotic changes in different organs and tissues. A TB process development to the phase of clinico-morphological manifestations, when the symptoms of the local impression the expressed of which are determined prevalence of infiltration and caseous-destructive changes in tissues and develop on a background the general clinical symptoms of the intoxication.

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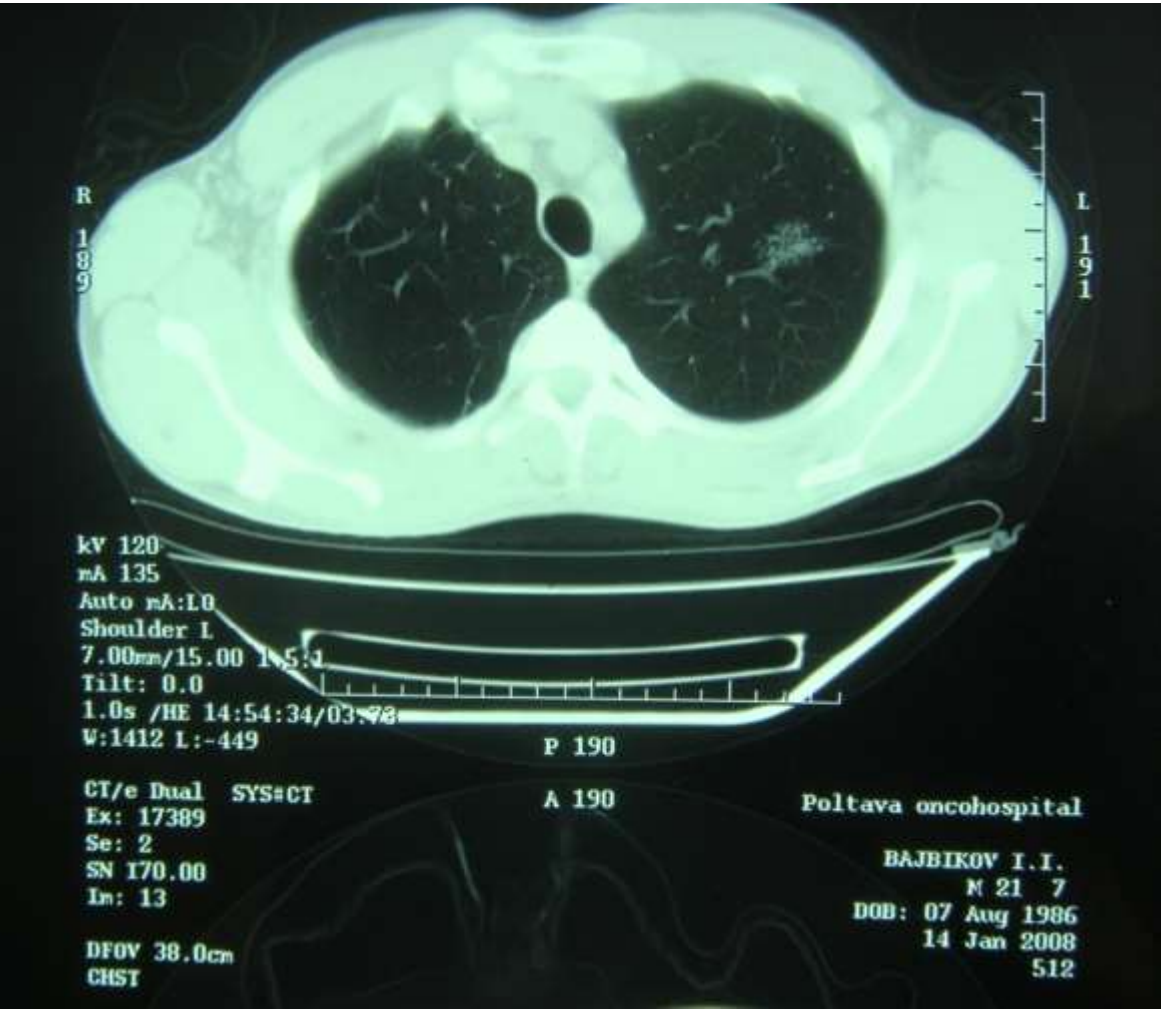
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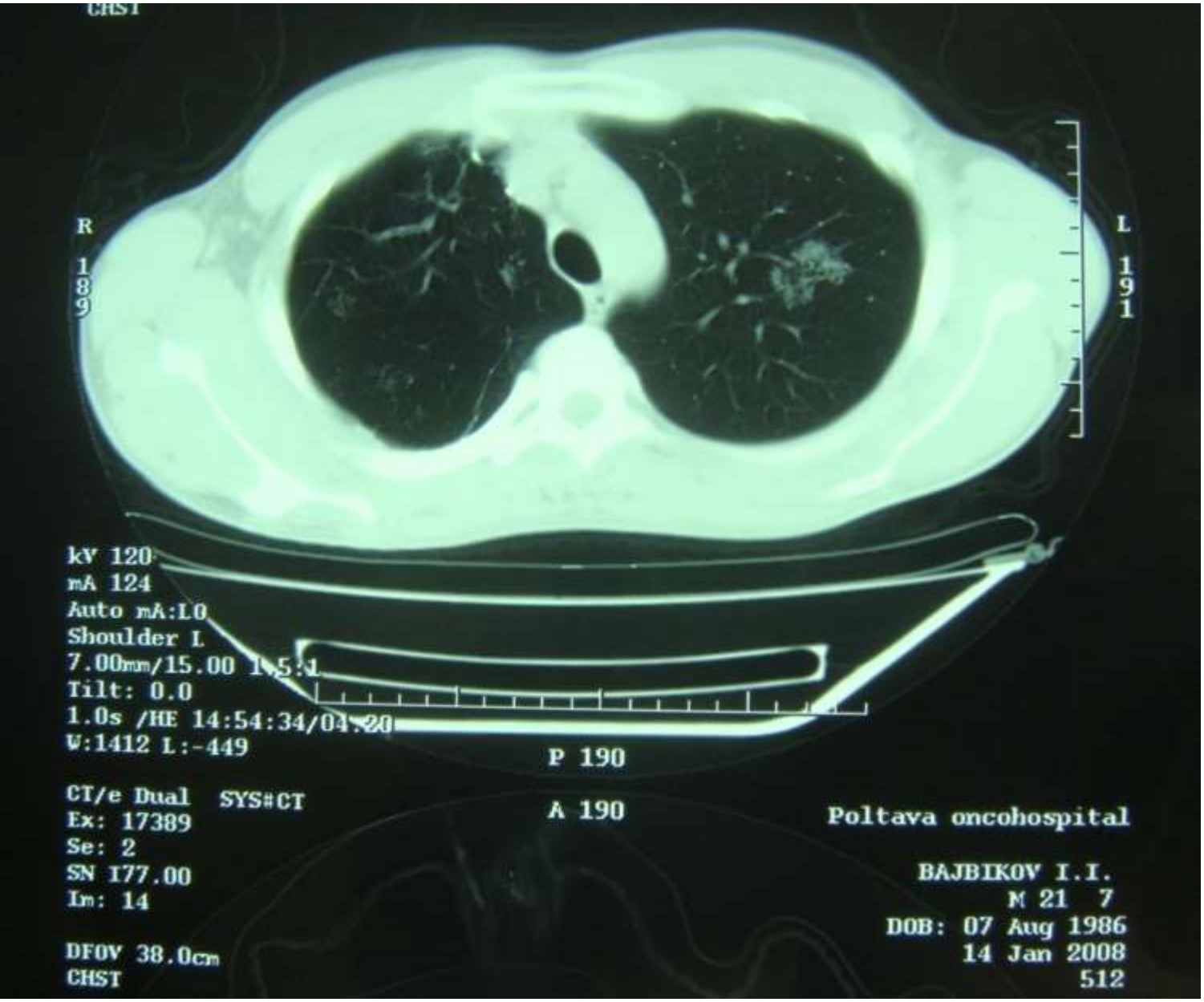
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- Under act of treatment or spontaneously illness can accept reverse development with resolved of exudates infiltration in tissues, closing of cavities and forming of remaining changes (**IV phase)** as hearths (focus), scars, fibrous, to the cirrhosis of lungs, deformations and others like that. In majority cases of illnesses there are indurations of TB caseous, which afterwards calcinated. In the cases of ineffective treatment a process can be acquire making progress motion with passing to chronic tuberculosis.

- The secondary infecting can develop in two ways:
- One of them is the repeated infection of MBT of man which carried the primary infecting (exogenous super infection);
- Other way is reactivation of remaining post tubercular changes (endogenous relapse). The secondary tuberculosis from data of WHO near 80% cases has an endogenous origin and near 20% is as a result of the repeated infection by the exogenous MBT. The features of the secondary tuberculosis are mainly pulmonary localization and propensity to gradually making progress motion.

- STATISTICAL CLASSIFICATION OF TUBERCULOSIS
- According to the recommended by WHO the tuberculosis is separated five headings:
- A 15. Tuberculosis of respiratory organs confirmed bacteriologically or histologically.
- A 16. Tuberculosis of respiratory organs not confirmed bacteriologically or histologically
- A 17. Tuberculosis of brain tunics and the central nervous system
- A 18. Tuberculosis of other organs and systems
- A 19. Milliary tuberculosis

- CLINICAL CLASSIFICATION OF TUBERCULOSIS (in Ukrain)
- 1. Type of tubercular process
- (indicating the date and year of detecting):
- 1.1. First diagnosed tuberculosis – FDT
- 1.2. Tubercular relapse - TR
- 1.3. Chronic tuberculosis - ChT

- **2. Clinical forms**
- **PULMONARY TUBERCULOSIS**
- A.15-16. Primary tubercular complex
- A.15-16. Disseminated lung tuberculosis
- A.15-16. Focal lungs tuberculosis
- A.15-16. Infiltration lungs tuberculosis
- A.15-16. Caseous pneumonia
- A.15-16. Lungs tuberculome
- A.15-16. Lung fibrotic-cavernous tuberculosis
- A.15-16. Lung cirrhotic tuberculosis
- A.15-16. Tubercular pleurisy (including empyema)
- A.15-16. Tuberculosis of respiratory organs combined with dust professional diseases (coniotuberculosis)

- **A.18. Tuberculosis of other organs and systems**
- A.15-16. Tuberculosis of bronchi, trachea and upper respiratory tract
- A.15-16. Tuberculosis of intrathoracic lymphatic nodes
- A.17. Tuberculosis of brain tunics and the central nervous system
- A.18. Tuberculosis of intestine, peritoneum, mesenteric lymphatic nodes
- A.18. Tuberculosis of bones and joints
- A.18. Tuberculosis of urinary and sexual organs
- A.18. Tuberculosis of skin and hypodermic tissue
- A.18. Tuberculosis of peripheral lymphatic nodes
- A.18. Eyes tuberculosis
- A.18.Tuberculosis of other organs (unspecified localization)
- A. 18. Children tuberculosis intoxication (TB of undetermined localization)
- A. 19. Milliary tuberculosis

- **4. CHARACTERISTIC OF TUBERCULAR PROCESS**
- 1.Localization and spreading: in lung according to the numbers (names) of segments, names of lung section, and other organs systems IS according to anatomical names of localization of a wound.
- 2. Phase (stages):
- infiltration, destruction, sowing
- suction, induration, scarring, calcinations.
- 3. Method of confirmation of the diagnosis TB
- (MBT+) confirmed bacteriologically (cipher A 15)
- (MBT-) not confirmed bacteriologically (cipher code A 16)
- (HIST+) confirmed histologically (cipher A 15)
- (HIST-) not confirmed histologically (cipher code A 16)
- If histological examination was not done, so HIST is not written down in an extensive diagnosis.

- **COMPLICATION**
- Tuberculosis of respiratory organs: haemoptysis, lung haemorrhage (bleeding), spontaneous pneumothorax, lung insufficiency, chronic lung heart, atelectasis, bronchus stenosis, pleural empiema, fistulae (bronchial, thoracic), amyloidosis.
- Tuberculosis of other organs: renal insufficiency, sterility etc.
- **Consequences of tuberculosis**
- Residual changes after healed tuberculosis:
- 1. In respiratory organs: fibrous, fibrous-focus, cystic-dystrophic changes , calcinates in lung and lymphatic nodes, pleuropneumosclerosis, cirrhosis, consequences of surgical intervention (with the indication of the type and date of an operation) etc.
- 2. In other organs: cicatricial changes in various organs and their consequences, calcinosis, consequences of surgical intervention (with the indication of the type and date of an operation).

- Diagnosis formulation is recommended in the following consistency:
- the type of tubercular process (date of diagnosis),
- localization,
- clinical form,
- the phase of process (Destr±) MBT± HIST± RESIST 1± Category 1-4 Cogorte 1-4
- **Examples of diagnosis formulation:** FDTB (first diagnosis tuberculosis, 10.01.2006), tuberculosis of the lung (dissemination, S1-6 (segment, section 1-6 of both lungs) Destr+ MBT+ (10.01.2006) Resist 1 – Resist 2- Category1 Cogorte1, lung haemorrhage.
- ChTB (1.12.2000) Tuberculosis of the lung (left upper section, exacerbation) MBT+ Resist 1 +(streptomycin, isoniazidum, rifampicinum) Cat 4 Cog 1

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

2.1. Limited dissemination 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 extensive. Lesions are more extensive than moderately.

Thank you very much