ЗМІСТ

Infectious Diseases: textbook (IV a. l.)

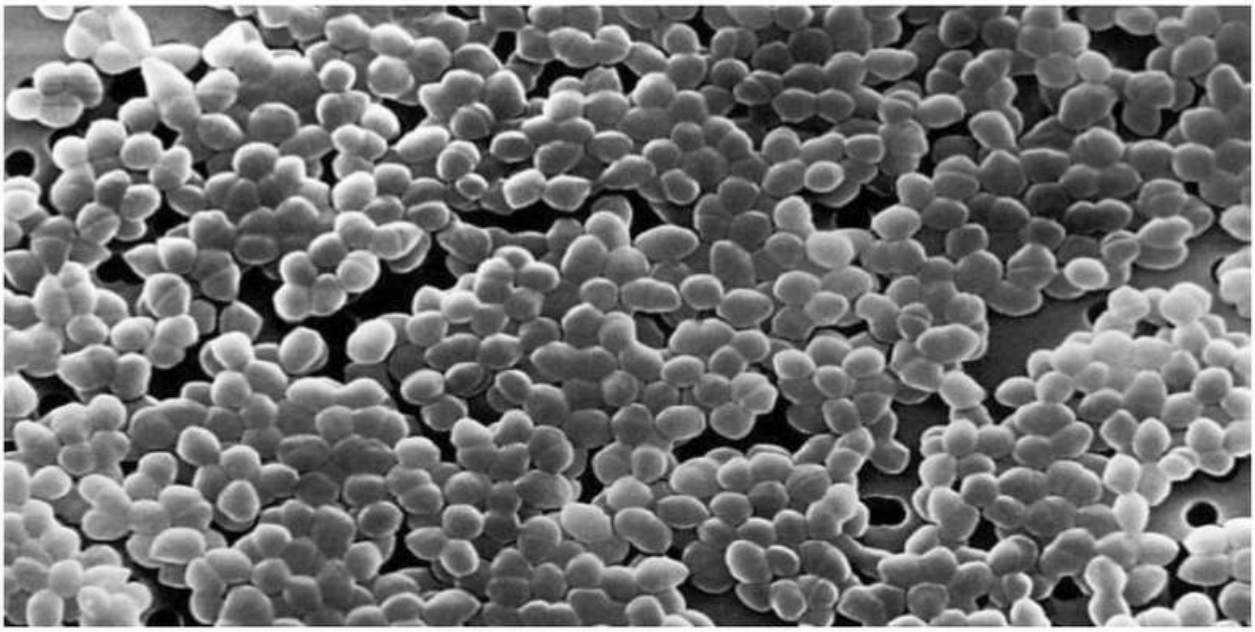
Про книгу

Up-to-date notions of the most widespread infectious and parasitic diseases are stated in the textbook. A particular attention is paid to diseases that occur on the territory of Ukraine, diseases that represent a significant global danger and are regulated by International Health Regulations, infectious and parasitic diseases that can be imported to the territory of our country and represent a problem of travel medicine and tropical medicine. General problems of infectology, principles of classification of infectious diseases, diagnosis, treatment and prophylaxis, including immunoprophylaxis are elucidated. In preparation of the textbook, modern materials and WHO recommendations, foreign publications of leading specialists were used. Classification of infectious and parasitic diseases is given in accordance with International Classification of Diseases of 10th review. Methods of diagnosis, treatment and prophylaxis are stated on the base of international guidelines and consensus. Presented material is well adapted to the content of modules of approved typical programs on the course unit of «Infectious diseases» for prediploma training of specialists on specialities «Medical care», «Pediatrics», «Medical preventive care», «Stomatology», «Medical psychology». All sections of the textbook contain main provisions, questions and tests for self-training according to the principles of the up-to-date educational trend — a credit-transfer system of organization of the educational process. A book is supplied with coloured illustrations of the most widespread infectious diseases. The majority of anatomical terms are given according to International Anatomic Nomenclature approved by IV Congress of anatomists, histologists, embryologists and topographic anatomists of Ukraine. For students of higher medical (pharmaceutical) educational establishments, internship doctors and trainees of faculties of postgraduate education, as well as family doctors, specialists of emergency medicine, infectious disease specialists.

INFECTIOUS DISEASES

TEXTBOOK

Edited by O.A. HOLUBOVSKA



APPROVED
by the Ministry of Education and Science of Ukraine as a textbook
for students of higher medical educational establishments

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

Kyiv
AUS Medicine Publishing
2018

UDC 616.9(075.8)
LBC 54.5;57.33ya73
I-74

Approved by the Ministry of Education and Science of Ukraine as a textbook for students of higher medical educational establishments (letter No. 1/11-8095, 28 May 2012)

Approved by the Ministry of Health of Ukraine as a textbook for students of higher medical educational establishments (letter No. 23-01-8/130, 15 June 2012)

Authors:

O.A. Holubovska, M.A. Andreichyn, A.V. Shkurba, K.I. Bodnia, N.A. Vasylieva, B.A. Herasun, B.M. Dykyi, H.M. Dubynska, I.A. Zaitsev, O.M. Zinchuk, H.M. Koval, V.M. Kozko, V.S. Kopcha, H.B. Mateiko, L.V. Moroz, V.D. Moskaliuk, O.Ya. Pryshliak, O.V. Riabokon, Yu.Yu. Riabokon, V.O. Tieroshyn, T.V. Chaban, M.D. Chemych, L.R. Shostakovych-Koretska, K.V. Yurko, O.V. Bezrodna, V.A. Bodnar, V.V. Ilina, O.L. Ivakhiv, O.M. Iziumska, N.I. Ilina, T.I. Koval, O.Ye. Kondryn, S.M. Kulias, T.M. Kotelevska, N.H. Malysh, O.O. Popovych, B.M. Piasetskyi

Up-to-date notions of the most widespread infectious and parasitic diseases are stated in the textbook. A particular attention is paid to diseases that occur on the territory of Ukraine, diseases that represent a significant global danger and are regulated by International Health Regulations, infectious and parasitic diseases that can be imported to the territory of our country and represent a problem of travel medicine and tropical medicine. General problems of infectology, principles of classification of infectious diseases, diagnosis, treatment and prophylaxis, including immunoprophylaxis are elucidated.

In preparation of the textbook, modern materials and WHO recommendations, foreign publications of leading specialists were used. Classification of infectious and parasitic diseases is given in accordance with International Classification of Diseases of 10th review. Methods of diagnosis, treatment and prophylaxis are stated on the base of international guidelines and consensus. Presented material is well adapted to the content of modules of approved typical programs on the course unit of "Infectious diseases" for prediploma training of specialists on specialities "Medical care", "Pediatrics", "Medical preventive care", "Stomatology", "Medical psychology". All sections of the textbook contain main provisions, questions and tests for self-training according to the principles of the up-to-date educational trend — a credit-transfer system of organization of the educational process. A book is supplied with coloured illustrations of the most widespread infectious diseases. The majority of anatomical terms are given according to International Anatomic Nomenclature approved by IV Congress of anatomists, histologists, embryologists and topographic anatomists of Ukraine.

For students of higher medical (pharmaceutical) educational establishments, internship doctors and trainees of faculties of postgraduate education, as well as family doctors, specialists of emergency medicine, infectious disease specialists.

Reviewers:

S.O. Kramarov — Doctor of Medicine, Professor, Head of the Department of Pediatric Infectious Diseases of Bogomolets National Medical University; *V.P. Malyi* — Doctor of Medicine, Professor, Head of the Department of Infectious Diseases of Kharkiv Medical Academy of Postgraduate Education; *O.K. Duda* — Doctor of Medicine, Professor, Head of the Department of Infectious Diseases of Shupyk National Medical Academy of Postgraduate Education

ISBN 978-617-505-727-8

CONTENTS

INTRODUCTION TO THE COURSE OF INFECTOLOGY

Infectious diseases accompany mankind for as long as one can remember. Total losses of humankind from infectious ailments by hundreds of times prevail the number of victims from all military conflicts in the known history. Pandemics of "Justinian" plague VI century, approximately 100 mln of victims), "Black Death" (XIV century, about 50 mln of perished), ominous pandemic of "Spanish flu" (1916—1920, approximately 50 mln dead), dreadful outbreaks of smallpox, and many other epidemics are well known during human history. Hippocrates, Avicenna, Democritus and other ancient philosophers had been engaged in studying diseases that had an epidemic spread. In Ancient Greece some philosophers, for example, Thucydides, already stated the ideas of live causative agents ("contagium") of infectious diseases but they had no possibility to confirm their assumptions with any reliable facts.

The outstanding doctor of the ancient world Hippocrates (about 460—377 B.C.) had explained the origin of epidemics by the action of "miasmas" — contagious vapors that would supposedly cause a number of diseases.

At last Dutch naturalist Anthony van Leeuwenhoek (1632—1723), at the end of XVII century, had made a very important discovery having detected different microorganisms in dental plaque, stagnant water and extracts of plants under the microscope

Regardless of the fact that the study of causative agents and regularities of the course. In addition, every year 1—2 new causative agents of infectious diseases become known.

Currently, it is established that microbes can cause such diseases as arthritis, atherosclerosis, multiple sclerosis, some forms of cancer and other conditions that earlier were considered traditionally as "non-infectious". So, in 2005, Australian scientists Barry Marshall and Robert Warren had been granted a Nobel Prize for the discovery of the role of Helicobacter pylori in the development of gastric ulcer, and in 2008 a German researcher Harald zur Hauzen had been granted this prestigious prize for the discovery of the role of human papillomavirus in the development of cervical carcinoma.

Infection is the condition of organism's contamination with microorganisms (viruses, bacteria, protozoa). The outstanding German doctor Kristoff Wilhelm Guffeland in 1841 have given a new meaning of "infecting with disease" to the word *"infectio"* (*staining, infiltration, damage)* borrowed from classical Latin.

The founder of pathological anatomy Rudolf Virchow proposed the term "infectious diseases" in 1894 (Fig. 1, see a coloured inset).

Infectious process is a complex of mutual adaptive reactions in response to taking root and multiplying a pathogenic microorganism in the macroorganism intended to restore a disturbed homeostasis and biological balance with the surrounding environment.

Infectious disease is the extreme degree of expression of an infectious process when a disturbance of homeostasis occurs as the result of the prevalence of pathological reac-

tions over the compensatory ones. The infectious disease may run in manifest and subclinical form when clinical symptoms of a disease are absent, but while examination, there are some morphological changes, biochemical and immunological disorders that with the course of time may lead to severe negative consequences. According to the course of the disease, typical and non-typical forms are distinguished. So, for example, in the persons that have undergone vaccination against a louse-borne typhus, this disease runs atypically — in the mild form with a shortened fever period. Infectious diseases are characterized by:

- certain etiology (pathogenic microorganism or its toxins);
- contagiousness, quite often — a tendency to a wide epidemic spread;
- cyclicity of the course;
- formation of immunity.

In 1882 German microbiologist Robert Koch (Fig. 2) on the base of the provisions formulated earlier by German pathologist Frederick Jacob Henle proposed a triad of statements that do not require any proofs (Koch—Henle's postulates) due to which it was possible to determine the role of this or that microbe in the origin of the disease.

Specificity of the causative agent can be proved only when:

1. Microorganism is continually present in sick people (or animals) and isolated in all forms of this disease.

2. Microorganism can be isolated from a sick person (or animal) and grown in pure culture.

3. Axenic pure culture of the causative agent in the experiment reproduces a disease that has a similar clinical picture.

Further, the fourth postulate was added to the above triad — a microorganism must be isolated repeatedly from the experimentally infected animals or people. It is quite obvious that in certain diseases, some of these postulates do not operate, but on the whole, they are acceptable for the estimation of the causative agent role in causing an infectious disease. Koch—Henle's postulates have not lost their significance even up to the present day and remained fundamental postulates in microbiology and infectology, correspondence to which is the necessary condition to substantiate a hypothesis of infectious etiology of any disease.

Properties of the microorganism that are able to cause an infectious process are defined by its pathogenicity and virulence.

Pathogenicity (from Greek *"pathos"* — sufferings and *"genes"* — birth) is the ability of the microorganism to cause an infectious process and infectious disease. Pathogenicity is a species trait that originated and ingrained in microorganisms in the process of evolution. A degree of pathogenicity of the same microbe may be changed by the long-term influence of various conditions of the environment. This degree or a measure of pathogenicity is accepted to call virulence.

Virulence (Lat. "*virulentus*" — poisonous) is a measure or degree of pathogenicity. It is not a species trait but a common feature of a specific strain of this or that causative agent unlike pathogenicity. Virulence can change depending on many factors that have an influence on the micro- or macroorganism.

In order to start and maintain the infectious process, microorganisms have to penetrate into the susceptible organism, where they meet with a number of factors that offer resistance to a destructive action of the microbe.

Pathogenic microorganisms have factors of pathogenicity to overcome these factors. The basic factors of pathogenicity are:

- adhesiveness ("*adhaesio*" — adhesion) — the ability of the microorganism to fix on the surface of cells;
- colonization;
- invasiveness — the ability to penetrate and spread in the macroorganism is implemented through enzymes of pathogenicity (hyaluronidase, fibrinolysin, and neuraminidase, etc.);
- aggressiveness — the ability of microbes to live, multiply and spread in the organism and to counteract the organism's protective factors;
- toxin production;
- resistance to the action of the macroorganism's protective factors.

Some microorganisms produce poisonous substances (toxins) that are released from the microbial cell into the environment. Microorganism's toxigenicity is designated as its ability to produce toxin of this or other strength.

Circulation of microorganismal toxins in the blood (for example, in diphtheria, tetanus, botulism) is called toxaemia; it causes a number of disorders in the organism.

The most important feature of infectious diseases is the fact that a direct cause of their occurrence is the penetration of pathogenic microorganisms into the macroorganism. The causative agents can get into the body by different mechanisms and ways: through the skin, tonsils, mucous membranes of the respiratory tract, digestive tract, etc.

The site of initial penetration of microorganism into the macroorganism is called *infection porta*. However, this single factor is not usually sufficient to develop the infectious disease. Human or animal organism should be *susceptible* to this infection and must respond to infection with a specific pathophysiological and morphological reaction that determines a clinical picture of the disease and all other its manifestations.

In some infectious diseases, a pathogenic microorganism may have only one infection porta (for example, in shigellosis — GIT), in some other — it may have several infection portae (for example, in tularemia — skin, tonsils, mucous membranes of the upper respiratory tract, GIT and conjunctivas).

The result of infectious disease may be a complete recovery, death or formation of the carriare state and development of the chronic course of the disease.

A characteristic feature of infectious diseases is their *cyclicity*, i.e. the presence of the incubation period, prodromal period, a period of active manifestations of the disease and convalescence. The *incubation period* lasts from the moment of pathogenic microorganism's penetration into the organism up to the emergence of the first clinical signs of the disease. Taking into account epidemiologic data and duration of the *incubation period*, a number of problems are in await of the decision as to establishing quarantines, diagnosis of nosocomial infections, etc.

Duration of incubation period varies within significant limits from a few hours (botulism, food poisoning) to several weeks and even months (tetanus, rabies, HIV-infection). As a rule, the most number of causative agents are released into the environment at the end of the incubation period and at the start of clinical manifestations of the disease (flu, ARVI, the majority of intestinal infections). But there are some exclusions, for example, a sick person with typhoid fever is the most contagious on 2—3 weeks of the disease due to certain peculiarities in the pathogenesis of this disease.

First symptoms of the disease are revealed in the prodromal period. Most of them are nonspecific: a headache, malaise, insignificant elevation of temperature and the like. However, characteristic symptoms of the disease can be already determined in the prodromal period in some infectious diseases. For example, Koplik's spots can be revealed on the mucous membrane of the oral cavity in the prodromal period of measles (the pathognomonic symptom of this disease).

The height of the disease lasts from several days (intestinal infections, ARVI) to a few weeks and even months (acute viral hepatitis); it may take the undulating course with alternations of periods of aggravation and improvement of the condition. To know the period of the disease is very important both for establishing the diagnosis by its clinical symptoms and with the purpose of isolation of the causative microbe from the patient for laboratory studies. For example, the causative agent of typhoid fever can be isolated from the blood of a sick person during the whole fever period, but most successfully in the early terms of the disease.

Fever reactions of the organism are typical for a prevailing majority of infectious diseases. Fever is defense and adaptation response. Several types of temperature curves are distinguished that can be drawn marking on the paper the patient's morning and evening temperature.

1. Continuous fever (*febris continua*) — the difference between the morning and evening temperatures does not exceed 1°C (typhoid fever, louse-borne typhus).

2. Remittent fever (fever that weakens) (*febris remittens*) — the difference between the morning and evening temperatures most often reaches 2—2.5 °C (for example, brucellosis).

3. Intermittent (alternate) fever (*febris intermittens*) is characterized by the same high swings, but they are separated between themselves by 2—3-day intervals (for example, sepsis, malaria).

4. Hectic fever (*febris hectica*) is characterized by sharp fluctuations between the morning and evening temperatures — within 3—4 °C (sepsis).

5. Wave-like or undulating fever (*febris undulans*) runs with wave-like elevations and reductions of temperature during several days or maybe weeks (brucellosis).

6. Recurrent fever (*febris recurrens*) a period of temperature elevation lasts 4—7 days, it quickly starts and in the same way quickly ends, then after a few days of normal temperature, fever repeats again (relapsing fever).

7. Irregular type of fever is characterized by the absence of any regularity. It occurs in case of administration of antipyretic drugs.

These or other types of curves can occur both in pure form and in combinations. So for example, a period of sharp oscillations between the morning and evening temperatures (amphibola) can follow a period of continuous fever in sick persons with typhoid fever.

Fever period in infectious diseases can end in a different way. The temperature may decrease to normal from high values within 2—3 hours in case of critical drop (for example, in relapsing fever).

In patients with tularemia, the temperature usually decreases very slowly in the course of 4—6 days; this decrease is called lysis. The accelerated lysis is also singled out, when the temperature drops within 1—1.5 day, for example, in louse-borne typhus.

After a past infectious disease, the immunity is formed.

CLASSIFICATION OF INFECTIOUS DISEASES

Owing to the great number of microorganisms that cause diseases, a variety of mechanisms and routes of infection transmission, there are certain difficulties in the classification of infectious diseases that would satisfy infectionists, epidemiologists and microbiologists.

At present, all infectious diseases are divided into three classes: anthroponoses, zoonoses, and sapronoses.

1. Anthroponoses (from Greek word *anthropos* — human, *nozos* — disease) — a group of infectious and parasitic diseases, the causative agents of which are able to parasitize in natural conditions only in the human organism and a human is a single source of infection (measles, chickenpox).

2. Zoonoses (from Greek word *zoo* — "animal" and *nozos* — disease) — a group of infectious and parasitic diseases, the causative agents of which parasitize in the organism of some animals, when animals are a natural reservoir and the source of infection (or invasion) for humans (tularemia, foot-and-mouth disease).

3. Sapronoses (from Greek word *sapros* — putrid, *nozos* — disease) — a group of infectious diseases, for causative agents of which abiotic (non-vital) objects of the environment are the main natural reservoir (legionellosis, tetanus).

In all classes, every group is divided into infectious diseases that are caused by viruses, bacteria, pathogenic fungi, protozoa, helminths, prions. In the world practice classification of infectious diseases are often given according to the etiological factor that reflects the absence of consensus as to the classification of infectious diseases. Such situation cannot satisfy clinicians due to the fact that different by their manifestations diseases fall into the groups only according to the etiological principle that causes some mess. There are also classifications based on organs principle (infectious diseases of skin, eyes, lungs et al.) or syndromic (infectious diseases that run with jaundice or diarrheal syndrome). But the sufficient number of causative agents of infectious diseases can cause complex, generalized damages (for example, typhoid fever), that is why it is difficult to relate them to these or other "organs" classifications.

Therefore, in 1947, the outstanding Soviet and Ukrainian epidemiologist Lev Vasylyovich Gromashevsky (Fig. 3) had suggested the classification of infectious diseases that is based on the clinicoepidemiological principles: place of primary localization in the organism and mechanisms, routes of infection transmission from the source to the healthy organism. Thus, we distinguish:

- **intestinal infections** (fecal-oral mechanism of transmission, a focus of primary localization — GIT);
- **infections of the respiratory tract (**airborne mechanism of transmission, a focus of primary localization — respiratory tract);
- **blood infections** (transmissible mechanism of transmission, a focus of primary localization — blood circulatory system and blood elements);
- **skin infections** (contact mechanism of transmission, a focus of primary localization — skin and hypoderm);

Diseases with multiple mechanisms of transmission are also distinguished (and, accordingly, to the specific mechanism of transmission) — plague, tularemia, anthrax and other, with **vertical mechanism of transmission** (from mother to child, including a trans-

placental route) — TORCH, **blood-borne infections** (due to artificial parenteral intervention) — viral hepatitis et al. This classification also has certain shortcomings but allows to single out groups of different by their etiology diseases with common pathogenetic features.

GENERAL PRINCIPLES OF DIAGNOSIS OF INFECTIOUS DISEASES

Diagnosis of infectious diseases uses all clinical diagnostic methods and ways that are applied in the internal medicine and known from the course of propaedeutics, however, there are certain of their own features. In that case, in the clinic of infectious diseases while examining a sick person, in addition to other types of anamnesis, *epidemiologic anamnesis* is taken — information as to the possibility of infection transmission from the source of infection to the sick, about possible factors (routes) of transmission of the causative agent and duration of the possible incubation period. Availability of revealed factors of epidemiological anamnesis permits, in suspected cases of certain infectious diseases (botulism, tetanus, rabies, etc.) to suggest a diagnostic judgement (often, final) of the presence of such infectious disease according to the clinicoepidemiological factors. Thus, for example, in the patient with the probable occurrence of tetanus, in addition to its clinical signs, the establishment of the presence of contaminated wound (epidemiological factor) is sufficient to transfer a provisional diagnosis to the gradation of the confirmed event.

Methods of nonspecific laboratory and instrumental diagnosis are, in the whole, common with other fields of medicine. But the presence of a certain causative agent in the development of infectious disease enables to reveal it or its particle (antigens, toxins, etc.) or immunologic reactions in response to its penetration into the organism (production of antibodies, reactions of hypersensitivity et al.). In the clinic of infectious diseases, the following methods of specific diagnosis are applied:

For detection of the causative agent itself:

- Microscopic (direct and indirect light microscopy, electron microscopy, bacterioscopy, parasitoscopy, including ovo- and helminthoscopy, virusoscopy);
- Bacteriologic (inoculations of blood, feces, urine, sputum and other fluids of the organism on artificial nutritional media, cell cultures or tissue cultures to detect bacterial causative agents);
- Virologic (chicken embryo inoculation, inoculation of cell cultures or tissue cultures);
- Biologic (administration into the organism of laboratory animals of various fluids taken from a sick person with the purpose to reproduce a development of infection in them, to isolate a causative agent in great amount with the aim of its identification and study of its properties);
- *For detection of antibodies, antigens, genomes of the causative agent, by-products of its vital activity:*
- Serologic (detection of antibodies in (AT, CFT, IHAT, RIA, EIA, ELISA, etc.);
- Detection of antigens, nucleic acids, immunofluorescence test (IFT, EIA, RIA, PCR, molecular cloning et al.);
- Gas chromatography;
- Immunochromatography tests (express-diagnosis);

- Delayed cutaneous hypersensitivity test (intra-cutaneous test in tularemia, etc.);
- Toxin neutralization test in botulism that is carried out on laboratory mice.

For detection of the causative agent itself of the infectious disease, in some cases a microscopic method is applied. In so doing, it is necessary a direct or indirect detection of a pathogenic microorganism in the tissues of the affected macroorganism. A direct microscopic study of fluids, exudates and tissues is simultaneously simple and one of the most informative laboratory techniques that are applied in the diagnosis of infectious diseases. In many cases, this investigation allows carry out the exact, highly specific identification of the etiologic agent. As the example is the identification of plasmodia in blood smears taken from patients with malaria. Innumerable techniques are used in the direct microscopy. If a microorganism has rather large sizes or typical morphology, one can prepare unstained native preparations from the investigated material and study them in the light field, in the dark field or with the help of phase-contrast microscopy. More often, for direct microscopy, dried smears are prepared — this permits apply various staining that facilitates to detect and identify a microorganism.

Native preparations are often used to diagnose fungal and parasitic infections. Studies of the native preparations of feces or duodenal content are also the initial stage in the establishment of the diagnosis of intestinal parasitic infections, helminthiases (ovo- and microscopy of bodies or fragments of helminths themselves). On the base of revealing typical motions of microfilariae and trypanosomes in the blood and other fluids of the organism, trypanosomiasis and filariasis can be identified.

Even after a century passed, Gram's staining remains the best and single widely available method of rapid diagnosis of bacterial infections. In fact, it is used in the examination of all kinds of clinical materials, being most valuable in in the investigation of exudates, aspirates and tissue fluids, including cerebral fluid and urine. Bacteria are defined as dark-blue (Gram-positive) or as pink-red (Gram-negative) bodies. Their staining and morphological features often allow carry out preliminary identification of the microorganism's genus and sometimes even a species. A number of specific microorganisms can be detected while staining, using other techniques (with fluorochromes, by Romanowsky—Giemsa, etc.).

Electron-microscopic studies are used to identify those viruses that have no cytopathic effect in the cell culture but have typical structural features (rotaviruses, *Norwalk* virus).

Regardless of the complexity of performance and need in a certain period to obtain the result, the isolation of etiologic agent with the help of cultivation in artificial nutrient media, in tissue cultures or in experiments on animals is, as a rule, the most reliable method.

However, a diagnostic value of the material examined by the method of inoculation depends, to a great extent, on the fact whether it was contaminated while sampling with concomitant microorganismal flora and delivered to the laboratory, maintaining the conditions that guarantee a survival of finical microorganisms. The sensitivity of the bacteriological method depends on the volume of material studied. Differential-diagnostic artificial nutrient media can be used for isolation of causative agents (medium with potassium tellurite for isolation of Corynebacteria diphtheria, 1 % alkaline peptone water for isolation of Vibrio cholerae, etc.). Special conditions of cultivation are sometimes required for isolation of yersinia (keeping a nutrient medium at the temperature of thermostat 4 °C during 2—3 days, prolonged waiting through a slow growth of causative agents, etc.).

A selection of material for the diagnosis of viral diseases depends both on the stage of disease and on its clinical manifestations. If the sick is examined at the earlier stages of the disease, one often succeeds to reveal a virus, using the appropriate virologic technique. The nature of the material that is subject to virologic investigation and method of its transportation to the laboratory depends, to some extent, on the nature of the disease. Virologic method is rarely effective for the isolation of viruses from the blood except for arbovirus infections.

Sometimes, it is not possible to isolate causative agents by means of nutrient media or cell, or tissue cultures. Then experimental infection of various laboratory animals can be used — biological method.

In case of biological isolation of causative agents, their growth is possible in various organs depending on the way of inoculation and its further biochemical, morphological and other identification.

In the practice of diagnosis of infectious diseases, *detection of antibodies, antigens, genomes of the causative agent, its vital activity by-products* are widely used. In order to detect a specific for a particular infectious disease result of human contact with a microorganism that leads to the immune response and antibody production, a serological method is used. But the detection of antibodies in the patient's blood serum that react with the certain antigen points only to the fact that this particular sick person has a contact with the antigen. In this connection, clinical interpretation of serologic tests, with a rare exception, depends on the results of serial determinations. If the antibody titer is significantly increased or decreased, the appropriate reaction can be regarded as a fresh contact with the antigen. In any patient with an unclear disease, a sterile sample of serum taken at the start of investigation should be stored in the frozen state, in order to have a possibility, if needed, to compare it with the serum taken in the later period (the so-called paired sera). A contact with the antigen can occur as the result of previous vaccination or immunization that quite often makes the interpretation of serum antibodies titers difficult.

The so-called anamnestic reaction, non-specific stimulation of antibodies to other causative agents in this or other infection, occurs only in case of the antigenic similarity of causative agents; this can lead to certain diagnostic errors, and that is why it is necessary to carry out the examination of paired sera to detect the increase of antibody titers to the antigen of the true causative agent. The anamnestic reaction will be characterized by a monotonic titer or its decrease. Results of serological tests should be interpreted taking into account additional information about the patient including such factors as previous immunizations and diseases, a possibility of the impact of chemical, but etiologically foreign antigens, the presence of changing titer in the performance of serial reactions in contrast to a single result. Different groups of antibodies arise against the causative agent (agglutinins, opsonins, complement-fixing antibodies, hemagglutinins, etc.) that are accordingly revealed in AT, CFT, HAT, IHAT and other. While carrying out these tests, pseudo-positive results are possible. EIA that is widely used gives the opportunity to divide antibodies to antigens of the causative agent into classes IgM, IgG that allows carry out the differentiation of the acute process (prevail IgM) from results of vaccination, chronic course of the infectious disease (prevail IgG).

In the diagnostic process of revealing infectious diseases, a number of technical procedures are applied intended to detect microbial antigens, genomes, causative agent by-

products. While using immunofluorescence test (IFT), smears that are hypothetically contain viral, bacterial, fungal or parasitogenic microorganisms, are stained with the aid of preparations that include prepared specific monoclonal antibodies, labelled with fluorescent dyes and studied in the luminescent microscope. A direct fluorescent staining of impression-smears from the epithelium of the nasal cavity can be used for a rapid diagnosis of influenza, ARVI.

A countercurrent immunoelectrophoresis is the most widely applied technique to detect antigens. In this variant of diffusion, a material examined for the presence of the antigen is placed into the well, made in agar, and specific antiserum — into the other (adjacent) well. Then an electric current is applied to the agar, as the result of which a rapid, within a few minutes, drawing together of antigen and antibody occurs and their fusion with the precipitate formation. Agglutination test of corpuscles is used for the same purposes as a countercurrent immunoelectrophoresis, but is characterized by greater sensitivity, though there may be false positive results caused by thermolabile components of serum and rheumatoid factor.

RIA can be applied for a visual or spectrophotometric detection of microbial antigens. ELISA, as the variant of EIA, is based on the fact that specific monoclonal antibodies react with the enzyme-labelled antispecies conjugate. After treatment with the appropriate substrate, a change of staining appears that can be seen under a common light microscope.

IHAT is a highly sensitive method and by using commercially available test-kits, results can be obtained in the course of a few hours. In this method, a radioisotope-labelled test-antigen competes with the antigen in the patient's serum for specific antibodies in the test-mixture. Free and bound antibodies are removed by washing. Then, with the help of gamma-counter, the reactivity of antigen-antibody complex is analyzed.

Usage of recombinant DNA-technique of amplification (PCR or molecular cloning) enabled isolation, reproduction and labelling of microorganisms with a strictly determined unique arrangement of nucleotides in the genome that represents the strain, species, genus or group. The advantage of recombinant DNA-techniques of amplification consists in their unique specificity, ability to detect a single pathogen among innumerable others and to identify microorganisms that are very difficult or even impossible to detect by means of other techniques.

Immunochromatographic (ICHG) express-tests are based on the rapid determination of certain antigens in the samples with the help of dissolvable monoclonal antibodies on the test strips. Visible coloring appears in case of availability of the appropriate antigen in the examined substrate. The tests mentioned above can be carried out by persons having a minimal technical qualification and require a few minutes to be performed. At this stage of development of medicine, such studies have certain shortcomings but are widely used for purposes of screening investigation of people. In order to confirm the results of express-tests in uncertain cases, PCR and other tests are used.

Method of gas-chromatography lies in the direct study of clinical materials by means of gas-liquid chromatography with the aim to reveal typical by-products of microorganisms' metabolism. The method is effective in the differentiation of aerobic and anaerobic microorganisms in the pus and blood.

The impact of antigens of certain types by different ways and due to some circumstances, not always completely clear, leads to the development of sensitivity of various