INFECTIOUS DISEASES

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The manual reveals etiology, pathogenesis, clinic, diagnosis, medical treatment, and prophylaxis of widespread infectious diseases considering modern data. The authors of the book generalized experience of this subject being tought at home and foreign medical universities and academies, as well as infectious diseases departments, where they work. Attention is paid to presentation of material, which has important clinical value.

This manual corresponds to the program of Ministry of Health of Ukraine and is designed for the students of medical higher education institutions of III-IY accreditation levels.

У підручнику, з урахуванням сучасних відомостей, висвітлено етіологію, патогенез, клініку, діагностику, лікування та профілактику розповсюджених інфекційних хвороб. Узагальнено досвід викладання цього предмету у вітчизняних і зарубіжних медичних університетах та академіях, а також кафедр інфекційних хвороб, на яких працюють автори книги. Акцент зроблено на подання матеріалу, який має важливе клінічне значення.

Підручник відповідає програмі, затвердженій Міністерством охорони здоров'я України, й адресується студентам медичних навчальних закладів III-IV рівнів акредитації.

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INTRODUCTION
OF INFECTIOUS DISEASES

Nowadays there are about 2,500 well-known microorganisms that cause infectious diseases. About 300 nosological forms have been distinctly described ("nosos" means "disease" in Greek). According to the international classification the infectious diseases relate to 13 classes and 975 rubrics. They constitute up to 60-70 % of the total morbidity. In polyclinics 4-6 patients out of 10 suffer from infectious diseases. The responsibility for the exposure of the infectious morbidity is taken by the physicians of the "first line" – therapeutists, surgeons, gynecologists and other specialists. Now it is distinctly ascertained that the infectious agents are the basic or leading ethiological factor of the different branches of the medical science.

Such fields of the internal diseases as rheumatology, pulmonology or hepatology cannot be conceived without taking into consideration the infectious factor. The infectious factor often determines the outcome of the surgery. The gynecological, urological and eye diseases cannot be treated without considering it. The association of the viral hepatitis B and C with the primary liver cancer is undoubted, there is a certain connection between the cancer of the cervix of the uterus and the virus of the herpes simplex, leucosis and Bercet's lymphosarcoma. The significance of the infections agents in bronchial asthma, arthritis, meningoencephalitis is undoubted.

Besides these many new earlier unknown discuses have appeared. Only during the last years such infections diseases as HIV, Legionnaires disease, cryptosporidiosis, SARS, hemorrhagic fevers, caused by Marburg or Ebola virus, hantavirus and others have appeared, they are responsible for the development of the ulcer disease of the stomach, pneumonia, meningoencephalitis, cutaneous diseases, lymphoadenopathy, heart and vessels diseases. Many researchers think that the world is standing on the verge of the T-cell leucosis epidemic, which is already widely spread in Japan and in some regions of Latin America. That is why a physician of any speciality will more or less often encounter with the infectious pathology.

The origin of the infectious diseases dates back from the ancient times. The old archives that contain the man's first descriptions of his thoughts with the help of signs tell us that he already suffered from such diseases as leprosy, hydrophobia, malaria, trachoma, fungous, helmintic and some other diseases.

Although the infectious diseases exist as long as life itself, their studying started comparatively not long ago. It is one of the youngest branches of science.

The scientific history of the infectious diseases started at the end of the 19th century when the term "infectious diseases" was introduced, and it was determined that they were caused by the microorganisms i.e. the organisms that could be found only with the help of a microscope.

The common feature of the majority of the infectious diseases is the possibility of transmission from the affected organism to a healthy one, and the ability of massive (epidemic) spreading. During the study of the infectious diseases the terms "infection" and "infectious process" are usually used. They both originate from the Latin words – "*infectio*" – "*pollution*", "contamination" and "*infecio*" – "*to pollute*". At the modern level of the science development it is impossible to give an exhaustive definition of the terms "infection" and "infectious process" which would open all the sides of this conception. The term "infection" means the penetration of a microorganism into another organism and their following interaction under various conditions connected both with the microbe itself and the qualities of the organism which receives it at the various stages of the development of the organic world.

The term "infectious process" means the totality of the physiological, defensive and pathologic reactions, which appear under the certain conditions of the environment as an answer to the affection of the pathogenic microorganisms.

An infectious disease is the extreme stage of the infectious process development, which manifests in different signs and changes of the biological, chemical and epidemiological order.

According to all of these definitions it is obvious that the term "infection" cannot be identified with the "intectious process". The contents which we put into the term "infectious process" does not let us make a complete image of the infection as a general biological phenomenon. The concept "infection" is much wider as infection is common to all the beings. The infectious process includes the patterns common to the complicated organisms. The term "infectious process" is used to identify all the dynamics of the pathologic changes connected with the infection irrespective of the fact that they develop into a special qualitative condition called an infectious disease or not.

The origin of the infectious diseases and their nature were discovered owing to the brilliant success of bacteriology. That is why for a long period of time the infectious process was identified only with the activity of the microorganism without any consideration of the physiological aspects of the macroorganism.

Later when the scientists started to pay more attention to the study of pathogenesis i.e. the mechanism of the sickness processes development, they advanced a thesis of the domination of the macroorganism in the infectious process. It was a second mistake as it is impossible to separate something that is by the nature closely connected and can be understood only in correlation. Besides, the pathological process also has to be examined under the influence of

the environment. So if the disease develops as a result of the violation of this certain form of the organism's adaptation to the environment at the change of its conditions, then the infectious disease develops as the result of the influence of the part of environment which belongs to the living organisms. In other words, all the participants of the pathologic process are noted for the biological activity, functional mobility and the ability to develop.

The penetration of a certain number of microorganisms into the macroorganism is necessary for the infectious disease to develop. Besides, it has to be of a certain quality i.e. pathogenicity and virulence. However, the development of the pathological process depends on the general condition of the macroorganism and its immune status. In case of the weak immune status the pathologic process develops rapidly and the disease takes a severe course, in case of the comparatively strong immune status the disease takes a mild course or may not develop at all. Spreading of the disease and its severity depends on the environment – both on the geographical position (in the tropics – overheating, in cold countries – supercooling), and on the social sphere (a luxury villa and overcrowded facilities). All these processes can be expressed in the formula: the infectious disease is pro rate to the number and quality of the microbe (pathogenecity, virulence) and invasively to the immune status and the environment. Each of the mentioned factors is variable and they should be considered as dynamically developing with the changing of the cause and effect.

Comparing an infectious disease with a non-infectious one we can point out their mutual signs – intoxication and functional disorders of the organs and systems, morphological changes and others. However, with all the similarities we should mention the peculiarities of the infection diseases. This is, first of all, the cyclical course with expressed periods (incubative, prodromal, high point, fading healing). The second peculiarity is that the pathogen that caused the disease as a living agent has its own "interests" – it lives, multiplies as it tries to preserve its species – at the same time it adjusts, changes or remains in its constancy – the death of the macroorganism is not "profitable" for it as the pathogen can die with it as well. The third peculiarity is that the affected organism can become a source of infection for healthy people. The common feature of the majority of the infectious diseases is the possibility of transmission from the affected organism to healthy one and the ability of massive (epidemic) spreading. The fourth peculiarity consists of the immune processes which make the organism insensible to the later affections in case of the same etiologic factor.

Different interrelations occur when organisms contact with one another, it happens in nature all the time. To understand the infectious diseases we should mention the basic types of such interrelations.

1. The meeting and contact of the organisms do not have any consequences, any reaction. No symbiotic relations appear after it. In such cases we talk about species inherited immunity. For example, a human immunity to the horned livestock's plague, to the hemorrhage septicemia of cats and others.

2. The meeting of the organisms results in the symbiotic commonwealth (in Greek „symbiosis" means state of living together). There may be no reaction at all on the part of both partners, the condition called saprophytosis („saprobe" means microorganism that lives in the dead organic remains) appears. Some researchers consider symbiosis to be any form of living together between the representatives of different species. To this symbiosis they refer:

a) synoikia (Greek) − neutral living together during which one species uses the other one as a place to live without harming it;

b) mutualism − the symbiosis that is profitable for both organisms;

e) commensalism (Lat. "*com*" − with, "*mensa*" − table) also (French − "commensa" − dependent) interrelation when one organism gets a benefit from the other without harming it;

d) parasitism − a microorganism feeds with the saps or tissues of the master harming it. Most of the infectious diseases belong to this kind of symbiosis.

Analyzing the pathogenic processes scientists divide the infectious diseases into endogenous and exogenous ones. The endogenous diseases or autoinfections develop from their own microflora which is situated on the skin, respiratory and alimentary tracts, conjunctive, genital tracts. Because of the disorder of the regulatory processes which provide the physiologic symbiotic balance, there develop local, widely spread or even general infectious processes. Such microorganisms are called conditionally pathogenic or half-parasites.

The diseases caused by the penetration of the microorganisms from the environment and to which a macroorganism is not resistant are called exogenous infectious diseases.

Such division is pretty relevant and only relatively right. Sometimes the endogenous infectious disease becomes dangerous to the others because of itself and because the symbionit acquires new biological qualities.

If the infectious disease is caused by one species of microorganism it is called simple. If two or more microbe agents participate in the disease, then we talk about mixed-infection. Joining one infection to the other may affect the infectious process in different directions sometimes intensifying it, sometimes decreasing its activity and manifestations. So while studying the infectious pathology we should consider not only the pathogen itself but their associations. Salmonella infection especially bent to join other infectious diseases and start the secondary pathological process, this phenomena is called nosoparasitism (in Greek "nosos" − disease).

The growing number of the diseases caused by the conditionally-pathogenic pathogens is mostly connected with the changed reactivity of the organism and especially immune response which as a rule in such cases forms very slowly and is not valuable. The autoimmune processes activate and take a leading role in pathogenesis and clinical manifestations.

Many conditionally pathogenic as new discovered microorganisms are characterized with intracellular localization of the pathogens. Such infections can cause widely spread pathological disorders and they are more difficult with their diagnosis and treatment.

An immune system is one of the major targets of the affection of the environment negative factors according to the modern conception. There are six basic factors:

Human demographics and behavior. The important factors in changing human demographics include increases in the number of susceptible persons, the use of day care and immigration. A number of factors cause a rise in number of susceptible persons and the greater the population percentage that is susceptible to the infectious diseases, the greater is the potential for the disease transmission. In many countries in the developed world the number of seniors is growing. Since aging is associated with an increased susceptibility to the infectious diseases, the potential for the disease transmission is also increasing in these countries. In the USA, the percentage of the population over 65 years was about 4 % in 1900 and will reach almost 25 % in 2040. Certain underlying diseases also place more patients at risk for various infectious diseases, and these have also increased. For example, the reported incidence of diabetes mellitus in the USA increased from 0.5 % of the nation's population in 1935 to over 3 % in 1995. It is estimated that there are actually 16 million persons with diabetes in the USA, so the true incidence of this disease may be greater than 5 % of the population. The rates for many malignancies are also increasing, and these patients have increased susceptibility to infectious diseases from the disease process, during chemotherapy and, in some cases, lifelong even after the cure. Some of the most highly susceptible patients are those receiving immunosuppressive therapy following organ transplantation. Almost 20,000 organ transplants were performed in the USA in 1995. Worldwide the greatest factor increasing susceptibility may be the spread of HIV, which has led to millions of persons at increased risk for a variety of infectious diseases.

Such social changes as the increased use of day care also affect the emergence of infectious diseases. The increasing frequency of both parents working outside home or of single parent families led to a greater use of day care. The combination of susceptible children, inadequate hygiene, frequent infections, and frequent antimicrobial use is the perfect setting for the emergence of antimicrobial resistance. Thus, it is no surprise that day care attendance has been an important factor associated with the emergence of penicillin-resistant *Streptococcus pneumoniae*. A recent study demonstrated a 4-fold greater relative risk for colonization with a high-level penicillin-resistant *Streptococcus pnenmoniae* among children attending day care.

The increase of immigration and changing the patterns of immigration also contribute to the emergence of the infectious diseases. Between 1984 and 1992,

0.5-1.5 million immigrants and refugees were admitted to the USA each year. In contrast to the previous waves of immigration many of these individuals came from the parts of the world where certain infections such as tuberculosis are common. This is an important factor in the resurgence of tuberculosis in the USA as the percentage of patients who were foreign-born increased from 22 % in 1986 to 37 % in 1996.

A variety of human behaviors also influence the emergence of the infectious diseases. The impact of the sexual revolution on the frequency of gonorrhoea, syphilis, and HIV is evident. Perhaps less evident is the impact of other changes such as changes in eating habits. There are changes in the types of food that people eat, how this food is prepared, and where the food is prepared. This can result in the new exposures to unfamiliar food or the dependency upon others to handle and prepare food safely. All these factors have contributed to the emergence of some of the newer food borne diseases. Another important factor influencing the emergence of resistance has been the unnecessary use of antimicrobial agents. In 1992 over 110 million courses of antimicrobial drugs were prescribed to outpatients in the USA. Since three-quarters of these drugs are prescribed for upper respiratory infections that are often caused by viruses, over half of these 110 million courses may be unnecessary.

Technology and industry. The impact of technology and industry falls into three general areas. These include new technologies and products, changes in food production processing and preservation, and changes in industrial demographics. New technologies and products may have unexpected disease implications such as the association of air conditioning and whirlpool spase with Legionnaires disease, or new tampons with toxic shock syndrome, or the fast-food hamburger with *E. coli* O157:H7.

The second area, the changes in how food is produced, processed, and preserved has also been important. For example, in the last 50 years many of the new agricultural production strategies involve intensive rearing of young animals under environmental conditions that are conducive to the transmission of the infectious diseases. These production strategies often depend upon increased antimicrobial use. Thus, only substituting young animals for children, the situation is similar to the day care setting and has resulted in an increase in antimicrobial resistance for organisms that are transmitted through the food chain from animals to humans. Between 1979 and 1989, the frequency of drug resistance in human *Salmonella* isolates almost doubled from 17 % to 31 %. Today the resistance in humans is the result of antimicrobial use in animals. The many changes in food processing and preservation are also influencing disease emergence. The recent emphasis on "natural" foods has led to use of fewer preservatives or secondary barriers to prevent spoilage. Thus, some foods are protected only by refrigeration. This has resulted in increasing problems with organisms that grow in the cold, such as *Listeria* or *Yersinia*. The lack of secondary barriers also

increases the risk of food handling errors leading to diseases such as botulism. In the last 10 years, several outbreaks of botulism have occurred when "keep refrigerated" foods were not kept refrigerated.

The third change, that of industrial demographics, is characterized by consolidations of industry, larger market size, and wider geographic distribution for a variety of food products. Although these changes have the potential for greater quality control and better safety, when something goes wrong, it can really go wrong. Thus, in 1994, an ice cream product produced by a single company in Minnesota led to thousands of cases of salmonellosis in over 41 states.

Economic development and land use. Changes in economic development and land use are often cited in discussions of emerging viral diseases. Encroachment on rain forests, for instance, may lead to exposure to new agents such as Ebola or Marburg viruses. However, such changes are also influencing the emergence of other infectious diseases. For example, population growth and spread lead to environmental change and pollution. The inadequacies of hygiene and sanitation that exist in many of the "mega cities" in the developing world are potential ticking time bombs for the emergence of infectious diseases. Other types of development and land use practices are contributing to specific problems. Conservation activities, such as those directed toward deer populations, have contributed to the emergence of Lyme disease. Coastal agriculture expansion is leading to blooms of toxic microorganisms, while coastal population growth is leading to human faecal contamination of shellfish beds and transmission of a variety of viral and bacterial pathogens.

International travel and commerce. Advances in technology have had a rapid impact on international travel and commerce. A person or a food can be almost anywhere in the world in 24-48 hours. This facility in travel and commerce has increased the potential for the introduction of emerging pathogens to new geographic areas by infected travellers, by contaminated food, or even by transporting vehicles.

Microbial adaptation and change. As humankind is instituting a number of changes, the microbes themselves are changing. This is leading to the evolution of new pathogens, the development of new virulence factors, the development of antimicrobial resistance, and tolerance to adverse environmental conditions. A good example of this microbial change has been the emergence of *E. coli* 0157:H7, which probably evolved from an entero-pathogenic *E. coli* that acquired Shigella genes. As a food borne pathogen, it combines the worst of *Shigella* and *Salmonella*. Like *Shigella*, this organism has a low infectious dose, requiring only a few organisms to cause disease. This leads to subsequent person-to-person transmission once the organism is introduced into a community and also poses a high risk for cross-contamination in the kitchen. This organism is more similar to *Salmonella* in its tolerance to adverse environmental conditions. Thus, it has been associated with outbreaks that were caused by foods with pH 4.0, conditions that are usually inhibitory to most bacterial pathogens.

The breakdown of public health measures. The breakdown of public health measures has been the result of a series of often unrelated factors. Earlier successes in the war against infectious diseases led to complacency. Thus, coupled with limited resources and competing priorities in public health, often led to the transfer of resources from infectious diseases to other areas or to newly emerging infections.

The impact of the breakdown of public health measures can easily be seen during wars, population movements, and natural disasters. One such example has been the emergence of epidemic shigellosis in Africa. Since 1979, massive epidemics of shigellosis caused by *Shigella dysenteriae* type 1 have occurred in cities, rural areas, and refugee camps in Central and Southern Africa. The epidemics have affected all age groups, often with case-fatality ratios greater than 10 %. In 1991 alone, the disease caused 60,000 deaths in Burundi and at least 200,000 deaths in the rest of Africa. In contrast to *Shigella* species, which are more common in parts of the developed world, this organism is essentially resistant to all available oral antimicrobial drugs. Some of the newer fluoroquinolones are the last remaining effective oral agents.

Now even in developed countries approximately for 40 % of adult population tap different imunopathologic states that explains atypical and lingering How even of classic infectious diseases, more often development of mixed-infection, superinfection, continuous, microbe carrying.

The diagnostic of the infectious disease should be as early as possible. Such haste is connected not only with the necessity of assignina the conforming treatment but also with the demand of carring out urgent preventive actions, especially, if the disease has arisen in the collective. The diagnosis is grounded on the combination of symptoms characteristic for this or that infectious process. As in case with other diseases, the symptoms should be collected beginning with the complains of a sick person, anamnestic information of the development of illness symptoms, the nature of the epidemiological situation. Objective data should be taking during the physical examination of the patient, and then at auscultation, percussion and laboratory investigations.

At the identification of the infectious diseases as well as other diseases, anamnesis is of great importance. It is necessary to point out one of the most important peculiarities of the anamnestic data in infectious diseases, it is epidemiological anamnesis. The epidemiological anamnesis should be extremely careful and full. When the patient himself cannot give the necessary data (grave condition, age), the information should be obtained from relatives or the people around him.

Collecting the epidemiological anamnesis is as difficult as obtaining the disease anamnesis, and the skill of its collecting needs to be developed just as the skill of objective examining, the more so as collecting the correct anamnesis is considered to be more difficult to learn than the procedure of the objective

examination. At the inept approach to the patient and frivolous attitude to the epidemiological anamnesis obtaining, the doctor cannot get the necessary information. Sometimes it is difficult to take the correct anamnesis because in case of the disease with a long incubative period the patient and his relatives can forget some data, which are of the diagnostical and epidemiological value.

The following points are the most important for the epidemiological anamnesis:

1. Way of living and living conditions of the patient. It is necessary to explicitly find out whether the ambient situation could have promoted the intrusion of an infectious agent. If during the last three weeks before the onset of the disease the patient lived at the place of spreading of the infectious diseases, the patient can have developed a similar disease. The information about the cases of this or that infection in the patient's house confirms this idea even more. The use of unboiled water, milk, dirty fruit, pot herb, meat and fish products of poor quality can be a source of intestinal infection. The wounds, bruises, splinters are characteristic features of erypsipelas, tetanus, septic diseases.

2. The patient's occupation. Thus the workers of cattle-breeding farms can more often get sick with brucellosis, the agricultural workers – with leptospirosis, hemorrhagic fever, tick epidemic typhus, the workers of rice fields are subject to the infection of ankylostomidosis and strongyloidosis.

3. The previous diseases and preventive vaccinations. This information is necessary as the previous diseases in a number of cases is evident against the disease which is suspected at this moment. However, it is always necessary to take into consideration that there is not a single infectious disease, which would not repeat, though in rare cases. Such diseases as flu, malaria, shigellosis, diphtheria, erypsipelas are the most recurring. And vice versa measles, epidemic typhus results in a strong and continuous immunity which guarantees from the recurrence of the diseases. Vaccination in anamnesis does not eliminate a possibility of the disease caused by the same infection, but there are often distorted, atypical forms of the disease, the so-called deleted forms in case of vaccination. Having taken the epidemiological anamnesis one starts to inquire about the main complaints and symptoms, paying attention to every detail in the sequence of their development.

The temperature rise is one of the earliest symptoms which gives ground to think of an infection when there are still no other clinical manifestations of the illness. The temperature which rises in the morning or in the evening up to 37 °C usually is not considered normal. However, it is necessary to take into consideration the individual peculiarities of the patient, as for some patients the normal temperature limits are 37.0-37.3 °C, and on the contrary for a number of patients the normal temperature does not rise above 36.2-36.3 °C and a slightest rise even on some tenths of a degree already is evidence of abnormal temperature.

The temperature rise can be fast (acute), when the patient clearly marks even the hour of the onset of the disease (ornithosis, leptospirosis, etc.). In case

of the fast temperature rise, as a rule, the patient marks the chills of different grade − from slight chills up to severe chills (malaria). The temperature may rise gradually in other diseases (typhoid, paratyphoids).

According to the grade of the fever there are distinguished the following conditions: a subfebrile condition (37.0-37.9 °C), a moderate fever (38.0-39.9 °C), a high fever (40.0-40.9 °C) and hyperpyrexia (41 °C and higher). Taking into consideration the pathogenesis of the fever, the subfebrile condition should also be considered as a fever.

The nature of the temperature curve. In some infectious diseases the temperature curve is so characteristic that it determines the diagnosis (malaria, typhoid fever). It is accepted to determine several types of a temperature curve, which are of a diagnostic value.

The constant fever (*febris continua*) is characterized by the permanently high body temperature often up to 39 °C and higher, the daily temperature fluctuations are less than 1°C and observed in typhoid-paratyphoid diseases, Q- fever, epidemic typhus, etc.

The remittent fever (*f. remittens*) is distinguished by daily fluctuations of the body temperature from more than 1°C but not more than 2 °C (ornithosis, etc.).

The intermittent fever (*f. intermittens*) is manifested by the correct change of the high or very high and normal temperature with daily fluctuations of 3-4 °C (malaria, etc.).

The relapsing fever (*f. recurrens*) is characterized by the correct change of the high-fever and fever-free periods that last several days (typhoid fever, etc.).

The undulating or undulant fever (*f. undulans*) is distinguished by a gradual increase of the temperature up to the high points and then its gradual decrease to the subfebrile and sometimes normal temperature; in 2-3 weeks the cycle is repeated (visceral leishmaniasis, brucellosis, lymphogranulomatosis).

The hectic (exhausting) fever (*f. hectica*) − a prolonged fever with considerable daily fluctuations (3-5°C) with the decrease to the normal or subnormal temperature (sepsis, generalized virus infection, etc.).

The irregular (atypical) fever (*f. irregularis*) is characterized by large daily amplitude, a various degree of a temperature increase, an indeterminate duration. It stands closer to the hectic fever, but does not have a regular rythm (sepsis, etc.).

The distorted (inverted) fever (*f. inversa*) is distinguished by a higher morning temperature than the evening one.

Besides these generally accepted types we consider expedient to mention two more: an acute undulating fever and a relapsing one.

The acute undulating fever (*f. undulans acuta*) in contrast to the undulate one is characterized by relatively short waves (3-5 days) and by the absence of remissions between the waves; the usual temperature curve represents a series of damped waves, i.e. each subsequent wave is less expressed (in the altitude

and duration) than the previous one (typhoid, ornithosis, mononucleosis, etc.): when the subsequent wave is caused by adding of a complication, the revertive interrelations are observed, i.e. the second wave is more expressed, than the first one (epidemic paratitis, flu, etc.).

The relapsing fever (*f. recidiva*) in contrast to the recurrent fever (the regular alternating of the fever waves and apyrexy) is characterized by a relapse (usually one) of the fever which develops in different terms (from 2 days to one month and more) after the termination of the first temperature wave (typhoid, ornithosis, etc.). The relapses develop in some of the patients (10-20 %). In this connection if the relapse has an important diagnostic value, the absence of it does not eliminate a possibility of the mentioned above diseases at all.

Each infectious disease can have different variants of a temperature curve, among which some are more frequent, they are typical for this or that nosological form. Sometimes they even allow to diagnose the disease quite accurately (tetrian fever, etc.).

The duration of a feveris is an important value for the differential diagnosis. A number of diseases are characterized by a short-term fever (herpangina, acute shigellosis, etc.). And if, for example, the fever lasts more than 5 days, it already allows to eliminate such frequently encountered diseases, as flu and other acute respiratory virus diseases, angina (certainly, if there are no complications).

On the contrary, the long-term fever (more than a month) is observed rather seldom and only in some infectious diseases which lend to the lingering or chronic flow (brucellosis, toxoplasmosis, visceral leishmaniasis, tuberculosis). Thus the grade and characteristic of a temperature curve and the duration of a fever allow to differentiate certain groups of infectious diseases, among which the differential diagnosis is based on other parameters.

For the differential diagnosis the interval between the onset of a fever and the appearance of organic lesions is particularly important. In some infectious diseases this period is less than 24 hours (herpetic infection, scarlatina, rubella, meningococcemia), in others it lasts from 1 up to 3 days (measles, shigellosis), and, at last, in a number of diseases it lasts more than 3 days (typhoid fever, virus hepatitis).

The nature and level of the infectious diseases rate also matters. For example, any feverishness during the epidemic of flu suggests a possibility of flu. The indication to the contact with the people sick with measles, scarlatina, water-pox, rubella and other droplet infections is important. These data are compared to the terms of an incubation period. Other epidemiological data (the stay on the territory which is endemic on malaria, and other diseases) also matters.

For the differential diagnosis the change of a temperature curve under the influence of etiotropic medications is important. Delagilum stops malarial attacks, in endemic typhus the temperature quickly becomes normal after the reception of tetracyclines and others. There are a number of peculiarities of the fever

syndrome, which one can use for the differential diagnosis. The differential diagnosis of a fever needs to be done to distinguish it from the body temperature rising of another nature (thermal shock, hyperthyroidism).

The second component which is not less important for the diagnosis and differential diagnosis of the infectious diseases is a rash on the skin −exanthema. It is because the rashes are a symptom of many infectious diseases, besides, they are well visible, quite often catch one's eye even at the first examination of the patient.

There are exanthemas, characteristic of this or that infectious disease and they are an obligatory component of a clinical symptomatology of this or that infectious disease.

The expressiveness and nature of exanthemas can be miscellaneous and are not always observed in other infectious diseases. Due to this factor their presence or absence in different infectious diseases essentially differs.

The exanthemas in infectious diseases are rather diverse. They differ in nature of different elements of an eruption, localization, terms of appearance, stages of a rash, the dynamics of development of separate elements, etc. All these features are taken into consideration while making a differential diagnosis. In the diagnostics process the legible definition of separate elements of an eruption and unified comprehension of the terms are very important. Dermatologists and infectionists do not always define some elements of an eruption in the same way. The following nomenclature is generally accepted in infectious diseases.

Roseola − is a small spot (diameter 2-5 mm) of pink, red or purple-red color, more often with a spherical form. It is formed as a result of a local vasodilatation of a papillary layer of skin. The roseola disappears when pressing the eruption area with a transparent glass-spreading rod or when stretching a skin and comes up again after the stopping of pressure (stretching) that is the main distinctive feature of it.

The so-called punctate rash is close to roseola. It consists of a set of shallow (in a diameter of about 1 mm) elements of the red color. At stretching the skin these elements, as well as roseolas, disappear. Each element rises a little above the level of the skin that stipulates a special "velvety" of the skin at the eruption area.

The macule (macula) represents an element of the eruption similar to the roseola, but larger (5-20 mm), it does not stick above the level of the skin, its color is the same as roseola's. The development of the spot, as well as in case of roseola, is based on vasodilatation. The form of maculae can be oval, spherical or more often small or with festoon edges. Unlike the dermatologists the infectionists distinguish - spot eruption, in which the elements of an eruption vary in diameter from 5 up to 10 mm, and "large-spot eruption" with the elements' diameter of 11-20 mm. This distinction has a differential − diagnostic value. For example, in a patient with rubella there is a small-spot eruption, and in a patients with measles − a large-spot one.

Papule (papula) − a superficial formation without a cavity, rising above the level of the skin. It has a mild or dense consistence, the reverse development ends without the formation of a scar. There are inflammatory and noninflammatory

papules. In the infectious diseases only inflammatory ones occur. They are caused by the proliferation of epidermis and infiltrate development in the papillary layer of derma with vasodilatation and limited edema. Papulas have the same color as roseola and macula. There are papulas of a different size (1-20 mm). Small papulas (1-1.5 mm) are called milliar ones, the larger (2-3 mm) papulars – lenticularis ones. The confluence of separate papules results in the formation of the eruptions elements called plaque.

Erythema – is vast fields of the bloodshot skin which are red, purple-red or magenta. The erythema is formed as a result of large maculae joining. Therefore the erythema has festoon blurry edges. Inside arythmetic fields there can be separate fields of the skin with normal coloring. There is no expressed inflammatory process.

Unlike the infectionists the dermatologists consider that the term "erythema" means inflammatory fields with a diameter from 2 cm up to several dosen centimeters (active erythema), and also cyanosis conditioned by the venous congestion (passive erythema).

Tubercle (tuberculum) — a formation without cavities which arise as a result of the development of an inflammatory infiltrate of granulematous constitution in derma. The hillock differs from a papule, it lies deep in the derma and the infiltrate is determined at the palpation. The hillocks have legible borders and a tendency to grouping. As against papules at further development the hillock can narcotize, forming ulcers and leaving a scar. The hillocks develop in dermal and visceral leishmaniasis, deep mycosis.

Node (nodus) — a limited dense formation with a diameter from 1 up to 5 cm and more that has a spherical or oval form and is situated in the deep layers of derma and hypodermic fat. More often they develop as a result of the inflammatory process.

In some cases they disappear without any traces (nodal erythema), in chronic illnesses they ulcerate and heal leaving a scar.

Wheal (urtica) – an element of an acute inflammatory nature that has no cavity. There develops an acute restricted edema of the skin papillary layer. It develops owing to the trichangiectasia of the papillary layer of derma, the increase of their penetrability and the outcome of protein-free exudation through a vascular wall, which then compresses the vessels. As a result dense formations of different size and form suddenly develop on the surface of the skin and rise above its level. The cyanolic porcelain-white coloring in the center and the pink-red one on the peripherals are typical. An itch and a burning sensation of the skin appear with the development of a blister. The blisters develop in a serum disease, medicinal allergy and sometimes in some infectious diseases (leptospirosis, virus hepatitis).

Vesicle (vesicula) — a small cavity formation containing serouse, less often serouse-hemorrhagic fluid. The blister develops directly in the false skin, under the keratinous layer, in middle or on border with derma. It rises above the level of the skin as a half-round element with a diameter from 1.5 up to 5 mm. Hereinafter a blister can dry out, forming a semidiaphanous yellowish or brown

crust. If a blister is opened (damaged), soaking superficial pink or red erosion develops on its place.

Herpetic eruption (herpes) — a bunch of small closely set bubbles on the erythematic inflammatory base (herpetic infection, surrounding deprive).

Pustule (pustula) is also a blister but its contents is cloudy (purulent) because of a clump of a big amount of leucocytes.

Blister (bulla) — a cavity formation with a dimension of more than 5 mm (up to 10 cm and more). The borders of a vesica are legible, the outline is round or oval. The vesica rises above the level of the skin. It is usually unicameral and rolls off after a puncture. The cover of a vesica can be tight and flabby. The contents is serouse or serouse-hemorrhagic.

The vesicles can be situated on the background of the inflamed skin (a violent form of erysipelas, anthrax, multiform exudative erythema, Stivens − Johnson's syndrome).

Hemorrhages (hemorrhage) − an extravasation into the skin of different kinds and dimensions. They develop as a result of the erythrocytes yield from veins to the ambient connecting tissue of derma or hypodermic fatty tissue. It can be a result of the damage (breakage) of the vessel or heightened permeability and fragility of a vascular wall.

According to the value and form hemorrhages are divided into the following elements: petechias (petechiae) − dotted hemorrhages on the background of the normal skin (primary petechias) or on the background of roseolas (secondary petechias); purpura (purpura), in which the dimensions of the elements oscillate from 2 up to 5 mm (the dermatologists consider purpura to be hemorrhages with a diameter up to 2 cm): ecchymomas (ecchymosis) — hemorrhages of the irregular-shaped form with a diameter of more than 5 mm.

Ecchymoses (sugillationes) − hemorrhages on places of injections that are not the sort of an exanthema but have a diagnostic value as a parameter of a heightened fragility of vessels, that is often observed in the development of a hemorrhagic syndrome.

The hemorrhagic elements of the eruption are observed in many infectious diseases and have a great value both for the differential diagnostics and for the evaluation of the illness severity.

All the reviewed above exanthemas belong to the primary morphological elements of the eruption. However, the secondary morphological elements of the eruption also have a diagnostic value. The dyschromias of the skin, flake, peel, anabrosis. ulcers, seams belong to them.

Erosion (erosio) − a defect of the epidermis which develops after opening of the cavity primary elements (vesicles, pustules, vesica). The bottom of the erosion is covered with epidermis or partially with the papillar layer of the derma. By the size and form the erosion corresponds to the primary element. After healing the erosion do not leave any stable changes of the skin.

Ulcer (ulcus) − a deep defect of the skin which affects the epidermis. derma,

and sometimes underlying tissues. The ulcers develop as a result of the disintegration of the primary infiltrating elements in the deep parts of the derma − pimples, clusters, and the opening of the deep pustules. The form and the edges of the ulcer are of great importance for differential diagnostics. The edges of the ulcer can be undermined, vertical saucer-shaped, callous, mild, etc. The ulcer always heals leaving a cicatrix. The ulcers develop both in the infectious diseases (dermal leishmaniasis, anthrax, tularemia) and in the illnesses related with the competence of other specialists (lues, tuberculosis, trophic ulcers, neoplasm).

Skin dischromia (dyschromia cutis) − a disorder of the pigmentation, which develops on the place of the resolved morphological elements of the dermal eruption. The expressiveness and duration of the hyperpegmentation are various. As a rule, pigmentary spots are brown. Sometimes they are sharply distinguished, for example, after measles maculepapulas eruption, especially in case of its hemorrhagic impregnation. Sometimes it is only a hardly noticeable brown blot (for example, on the place of typoid roseola), which disappears fast and does not leave any traces.

Scale (squama) is a loosened tearing away ceel of the corneous layer, which lost its connection with the underlying epidermis. Depending on the size of the flakes there is micro- and macrolaminar pityriasis.

Small-laminar, branny pityriasis (desquamatio pityriasiformis) is observed in measles, branny lichen. The smallest flakes get detached and the skin looks as though it is powered with flour.

Macrolaminar pityriasis (desquamatio lamallosa) is characterized with a larger dimension of the flakes, and they can get detached from the skin by the whole layers. The similar pityriasis is characteristic of scarlatina, pseudo-tuberculosis, toxidermias. The pityriasis develops in the period of convalescence from the infectious diseases and what is important for differential diagnostic − in the late period of illnesses or during reconvalescence.

Crust (crusta) − a product of thickening and desiccation of different kinds of other elements exudates of the eruption (pustules, vesicles, anabroses, ulcers). There are serouse crusts (semidiaphanous or grayish), purulent (yellow or green-yellow) and hemorrhagic (brown or dark red). The size of the crusts corresponds to the size of the preceding element.

Cicatrix (cicatrix) − coarse-fibroid growth of the connecting tissue, which substitutes deep defects of the skin.

The listed above elements of exanthema are basic and can be observed in infectious diseases, the differential diagnostics is based on their exposure. In case of the eruption it is necessary to identify the type of separate elements and, besides, to specify other peculiarities of exanthema.

The very important signs are the terms of the eruption development.

The localization of the eruption elements and the place of the greatest concentration of exanthema are of a diagnostic value. In some cases the sequence of the rush development is of the diagnostic value. The duration of the eruption elements existence is also important. Repeated rashes and the inclination for

joining the elements of the eruption can be of a diagnostics value.

Enanthema — the rashes on the mucous — can be observed less often in infectious diseases and is less important for the differential diagnostics. However, in a number of illnesses the changes of the mucous are rather informative at their identification at the initial stage. The lesions of the oral cavity and eyes conjunctiva are of the greatest practical value.

The most essential characteristic symptoms of the infectious diseases are the hyperadenosises, icterus, catarrh of respiratory tract, diarrhea, meningeal symptoms.

Hyperadenosis is the result of the frequent involvement of the lymphatic system in the infectious process. The degree of their affection can essentially differ from a moderate enlargement to the development of a bubo with a diameter of 3-5 cm. The ability to detect the changes of the lymph nodes is of great importance in the differential diagnostics. This symptom is especially important now when HIV-infection is widely spreading in all the areas. At the same time the physicians quite often do not pay proper attention to the state of the lymph nodes and do not always correctly carry out the examination for the differential diagnostics.

The improvement of the infectious diseases diagnostics is closely connected with the development of microbiologic, gene-diagnostic. immunological methods of investigation. The latest methodological achievements allow not only to essentially raise the level of etiological confirmation of the diagnosis, but also to present the detailed characteristic of the microbe behavior in the organism. In particular, it is not possible to judge about the quantity of microbial bodies in different substrates of the organism, to determine the availability and concentration of antigens, toxins and even separate molecules of the microorganism. The gene-diagnostics opens rather comprehensive possibilities, however, the biosensory (including immunosensory) methods of investigation, which are already being worked out in a number of the countries, are next in turn.

But a great number of the laboratory investigations that are available for a doctor are not always important for the diagnosis and are sometimes overestimated and distract the attention from the clinical diagnostics. The clinical examination of the patient is of a primary importance and the laboratory and instrumental methods are supplementary. Every laboratory test should be evaluated according to its specific features, sensibility and informativity, it is necessary to determine the indications and terms of the investigations in different nosologic forms and to state their comparative diagnostic value.

The treatment of infectious diseases is more complicated task in comparison with therapy of other palhologic conditions as besides the correction of the disorders in the function of the organs and systems, it has a complicated task — to eliminate and suppress the infectious agent.

In the historical aspect only from the 17th century when the improvement of the agricultural production resulted in a better nutrition, it had an immediate effect on the outcome of some infectious diseases. At the beginning of the 19lh century

the improvement of the sanitary-hygienic control over food and water resulted in the decrease of many infectious diseases transmission. Later the knowledge of the specific etiology of the infectious diseases promoted the creation of the scientific base for their prevention and treatment. In the 20th century when the methods of immunization were widely used and especially when the antibiotics appeared the morbidity and mortality from infectious diseases were considerably reduced. The children's mortality was sharply reduced. The lifetime in the developed countries increased from 47 years on the average till 70 years.

Despite the increasing role of the microbial factor under different pathologic conditions, the practice of treating patients in polyclinics and somatic hospitals has not changed essentially. The treatment of the patients is mainly based on trial-and-error assigning the coolest or the most available antibiotic, as there are no real possibilities and the doctors striving to study the development of the infectious process in dynamics. At its best a single-pass serological or microbiologic research revealing the infectious agent is used as a sufficient argument for the statement of the clinical diagnosis and assigning the therapy. Therefore it is not surprising that there is no noticeable progress in outcomes of treatment, and there is an increase of negative consequences such as the medical disease, immunodefence disorders, development of dysbacteriosis, appearance of polyrefractory microorganisms.

Due to the technological achievements a large number of antibacterial and antiviral drugs have been made. The availability of drugs considerably dilates therapeutic capabilities, but also demands a scientifically reasonable differentiated approach.

The semi-centennial experience of the antibiotic therapy in the infectious disease treatment has not justified the initial hopes. After a considerable increase of the treatment efficiency of bacterial infections in the 50-60s, despite the appearance of a broad spectrum of new antibiotics, the multiple increase of uptaken doses, there have been no adequate progress in the results of treatment, but the number of cases of the drugs intolerance and therapy complications have increased.

The indispensable condition of the therapy efficiency is the differentiated approach to drugs in dependence on the way they act, capability to the intracellular infiltration, bacteriostatic or bactericidal influence.

Control questions:

1. The origin of infectious diseases.
2. The main features of infectious diseases.
3. The basic types of interrelations between micro- and macroorganism.
4. Human demographics and behavior.
5. Microboial adaptation and changes.
6. The rate of pulic health measures.
7. The nature of temperature curve.
8. The exantemas in infectious diseases.
9. Another essential characteristics of infectious diseases.

THE PRINCIPLES OF THE DIAGNOSTICS, TREATMENT AND PREVENTION OF INFECTIOUS DISEASES

The principles of the infectious diseases diagnostics

In present time the diagnostics of the infectious diseases preserves the traditional characteristics. The methods of the distinction of the diseases are improved. The looking for new more effective methods are performed. The necessity of further elaboration of the methods of diagnostics of infectious diseases is connected with change of pathomorphology and clinic of infections.

The tendency to increase of number of asymptomatic, atypical, lindering forms of infectious diseases occurs. The frequency of mixed infections of bacterial and bacterial-viral etiology increases. These features are connected with change of all the factors, which participate in development of infectious disease (microorganism, macroorganism and conditions of environment). The courses of this transformation are the increase of common specific reactivity of the organism, massive vaccination and revaccination of the population, wide inculcation into practice of antibiotics and other chemical drugs, increasing nonspecific allergization of the organism.

The early, exact and maximally concretive diagnostics is the basis for effective therapy, prevention of complications and infavorable outcomes of the disease. The early diagnostics of the infectious diseases is basis of antiepidemic and prophylactic measures.

The diagnostics of infectious diseases is based on comprehensive and systemic examination of the patient, including anamnesis, epidemiological anamnesis, physical examination of the organs and systems, analysis of the results of laboratory and instrumental examination of the patient.

Anamnesis of the disease (Anamnesis morbi)

The physician must take the history actively and carefully. It is necessary to indicate features of the onset of the disease (an acute or gradual), presence of the fever, chill, degree of increase of the temperature, it's oscillations, duration, the character of the stool, localization and intensity of the pains (headache, abdominal pains, pains in the muscles and joints), violations of the sleep and other. The epidemiological amamnesis permits to receive data about place, circumstances and conditions of infection, and also about possible ways of the transmission of the agent. The data about contact of patient with other patients with same infection, about personal contact with animals (for example, professional), about stay in endemic or epizootic focus have especial value.

The data about food of the patient, wounds after bites of the insects, traumas, operations, hemotransfusions have an important value too. Informations about transferred infections in last time, about prophylactic vaccination, use of immunoglobulines, glucocorticoides, antibacterial drugs are exceptionally important.

Clinical examination

There is the definite order of the clinical examination of the patients. At first, it is necessary to evaluate the common state of the patient (preservation or violation of the consciousness, excitement or brake action, adequacy of the behavior).

Due to examination of the skin it is necessary to mark pale skin or hyperemia, jaundice, humid or dry skin, and presence or absence of the rash. In presence of the rash it's localization, spread, and character (roseola, pethechias, papules or vesicula) are marked.

Then conjunctives, mucous membrane of the mouth's cavity are examinated. Due to some infectious diseases (diphtheria, scarlet fever, and infectious mononucleosis) the changes of the mucous membrane of the throat and tonsils are developed. In these cases the degree of hyperemia and edema of mucous membrane, presence of coats, it's localization, color and spread are marked.

In some infectious diseases the enlarged lymphatic nodes are observed. It may be enlarged of separate lymphatic nodes (tularemia) and multiple lymphatic nodes (brucellosis, infectious mononucleosis, HIV-infection). It is necessary to mark size of the lymphatic nodes, consistence, tenderness, motility.

There is the definite order of objective examination of the internal organs (cardiovascular system, respiratory system, gastrointestinal tract, blood system, immune system, urinary system, nervous system).

The rule evaluation of haemogramma has great meaning in diagnostics of infectious diseases. The tests of haemogramma, connecting with clinics of the disease help in diagnostics of many infectious diseases (infectious mononucleosis, typhoid fever, viral hepatitis, HIV-infection and others). In leptospirosis, haemorrhagic fever with renal syndrome the analysis of urine may help too.

In infectious pathology the largest part of common symptoms are nonspecific. The high temperature, chill, vomiting, violation of the sleep, decrease of the appetite, weakness are observed almost due to all infectious diseases. These symptoms have not decisive meaning in diagnostics. Because, the pathognomonic symptoms have great value. These symptoms are specific symptoms only for one nosologic form.

The classic examples are Filatov-Koplik's spots in measles, crampic cough with reprises in whooping cough, opistotonus in tetanus, haemorrhagic star-like rash in meningoccemia, vesicular rash along turm of nerves in herpes Zoster, hydrophobia in rabies and other.

Besides common (nonspecific) and pathognomonic symptoms, there is a great group of signs with intermediate position. These signs are typical as for many

infectious diseases as for noninfectious diseases. So, enlarged liver may be in case of typhoid fever, epidemic typhus fever, malaria, acute or chronical viral hepatitis, sepsis, diseases of the blood, cirrhosis of the liver, acute and chronical heart's insufficiency. In typhoid fever, visceral leishmaniasis, diseases of the blood, sepsis enlarged spleen are observed. There is no enlarged liver and spleen in grippe. The different abdominal pains, diarrhea, cramps are symptoms from this group too.

In diagnostics the important moment is revelation of syndrome. Syndrome is combination of the signs, caused by united pathogenesis (intoxication, haemorrhagic, meningeal, colitis, hepatolienal, and syndrome of gastroenteritis, jaundice, cholesthasis and other). The different syndromes have nonidentical meaning. So, syndrome of intoxication occurs due to all infectious diseases. Intoxicative syndrome plays the great role in evaluation of the severity of the course and prognosis of the disease.

In present time near 1,500 syndromes and more than 5,000 diseases are known. The identical syndrome may be due to different diseases. For example, meningeal syndrome is observed in subarachnoidal hemorrhage, serous and purulent meningitis, meningismis. Hemorrhagic syndrome occurs in viral hepatitis, leprospirosis, and meningococcal infection, hemorrhagic fevers, in diseases of the blood and other. The nosological form is characterized by few constant and typical syndromes. For example, colitis syndrome and syndrome of intoxication are observed in shigellosis. Symtomocomplex is combination of syndromes and symptoms, which typical for absolute majority cases of nosological form. Symptomocomplex has high specific, but it may be different in different periods of the disease. For example, there is combination of syndromes of intoxication, dyspeptic and other syndrome in prejaundiced period of viral hepatitis. Syndrome of jaundice, hepatolienal syndrome and sometimes syndrome of cholesthasis are observed in period of jaundice.

Laboratory methods

The different laboratory methods are used in diagnostics of infectious diseases (bacteriological, virological, parasitological, immunofluorescennt and others). The purpose of these methods is to establish etiology of the disease.

The bacteriological method includes sowing of the material on the nutritive mediums, isolation of the clean culture of the agent, it's identification.

The blood, urine, stool, cerebrospinal fluid may be material for the bacteriological investigation. For example, in typhoid fever the bacteriological method is used for isolation of agent from the blood, urine, stool (hemoculture, coproculture, urineculture). In meningococcal infection the blood and cerebrospinal fluid are the material for investigation. Besides that, smears from the pharynx and nose are investigated for isolation of the agent. Bacteriological method is used in diagnostics of cholera, shigellosis, salmonellosis, diphtheria and other diseases.

Parasitological investigation is based on microscopy of the thick drop and blood's smears (malaria), smears of the blood and bone marrow (leishmaniasis),

smears of the blood and gland puncture (trypanosomomiasis), stool (amoebiasis and balantidiasis).

The virological method is more complicated. In virological diagnostics the culture of the tissues and hen's embryo are used.

The bacteriological and virological methods may be complete, accelerated and expressive. For example, expressive method is immunofluorescense method (Cooms's method). The method is based on specific fluorescence of the antigen-antibody complex. The primarily material is processed by specific fluorescent serum. The antigen-antibody reaction is basis of the serological methods of laboratory diagnostics of infectious diseases. The serological reactions are used for antibodies revelation in the blood serum of the patients. The investigations are performed with well-known antigens.

Reaction of agglutination, passive (indirect) hemagglutination, precipitation, and complement fixation have greatest spread.

In the last years immunofermentive method is used in specific diagnostics of parasitaric and viral infections. The new method of serological diagnostics is definition of belonging of antibodies to definite classes of immunoglobulines (IgM, IgG, IgA and other). This method helps to identificate primary infectious disease from repeated disease and infectious disease from artificial immunization.

In diagnostics some infectious diseases skin's test with allergen is used. The examples are positive intraskin reaction to tularine (tularemia), brucelline, Burne's test (brucellosis) and others.

The laboratory-instrumental methods of nonspecific character occupy the considerable place in the diagnostics of infectious disease (biochemical, endoscopic, hystological, ultrsoundic).

The principles and methods of the infectious diseases treatment.

The treatment of the infectious patients should be complex, etiotropic and pathogenetic, and also individually depending on the state of the patient, on severity and period of the disease. In complex therapy of infectious diseases different remedies, directing to decrease of activity of the agent and neutralization its toxins, increase protective powers of the organism are used.

The remedies of specific action are used with purpose to increase protective powers of the organism. There are remedies, regulating immunogenesis (immuno-stimulating therapy) and remedies of nonspecific action (vitamins, preparations of the blood, preparations of pyrimidine — methyluracil, pentoxil).

In treatment of infectious diseases pathogenetic therapy is widely used. Pathogenetic therapy is directed to correct the violation of homeostasis (correction of water-electrolytic, protein balance, acid-alkaline state; liver, kidney, respiratory and cardiovascular failure and to decrease allergic manifestations).

In treatment of infectious diseases it is necessary to mention the form and period of the disease, severity of the course and features of the organism (age, reactivity, accompanied diseases and other).

Some infectious diseases have declination to prolonged course and relapses. For these patients it is necessary to use special principles of the therapy (immuno-modulating therapy, interferones and other).

Chemotherapy of infectious diseases

The brilliant success in fighting of severe infectious diseases in many cases is connected with application of antibiotics.

In medical practice near 500 antibiotics are used. However, the application of antibiotics is accompanied by negative consequences: increase of antibiotic's resistant agents, depression of immunocompetentive system function, development of nonspecific sensibilization, increasing of endogenic infections mixed infections and superinfections.

The selection of antibiotic depends on the type of the agent. It is known, that the remedies of the penicillin group have high efficiency for gram-positive (streptococci, staphylococci, pneumococci) and gram-negative cocci (gonococci, meningococci, and also for agent of Siberian ulcer, leptospirosis. Cephalosporins have wide spectrum of the activity. They are effective such for gram-positive, as for gram-negative microorganisms.

The remedies of streptomycin group are more effective for gram-negative microorganism (plague, tularemia, and tuberculosis). Chloramphenicol is effective for many gram-negative and gram-positive bacteriums, rickettsias, spirochetas. Tetracyclines have wide spectrum of activity. They depress the growth of the majority of gram-positive and gram-negative bacterium's, rickettsias.

Aminoglycosides (monomicin, kanamycin and gentamicin) render the activity to majority of gram-positive and gram-negative microorganisms. This antibiotics are effective for resistant microorganisms to penicillin, chloramphenicol, tetracycline.

At the last decades the remedies of the new generation came into displacement of natural antibiotics: half-synthetic penicillins (ampicillin, oxacillin, amoxicillin); aminoglycosides (amikacin, tobramycin), tetracycline (doxycycline), rifampicins (rifampicin, rifadin). These antibiotics are characterized by acid-resistant, ferment-resistant wide spectrum of the activity.

Besides antibiotics, there are other kinds of medications that have influence on the agent of the disease. Derivates of nitrofuran (furazolidone, furodonine and furacillin) have a high antimicrobial activity. They are effective for many gramnegative and gram-positive bacteria − resistant to antibiotics and sulfonamides, and also for some protozoa (trychomonades, lamblia).

Sulfonamides don't lose their value. However, recently the decrease of their therapeutic action is observed connecting with appearance of the resistant forms of the microorganisms.

However, different complications may be due to treatment of infectious diseases by chemoremedies. There are 3 types of the complications in chemotherapy of infectious diseases: allergic, endotoxic and dysbacteriosis.

Allergic reactions are observed more frequently. They are manifested by capillartoxicosis, catarrhic change of mucous membranes, dermatitis edema. Sometimes, anaphylactic shock arises. The development of allergic reaction doesn't depend from the dose and duration of application of the drug.

Endotoxic reactions arise, as a rule, after injection of the large shock doses of antibiotics. These reactions depend on intensive disintegration of the microorganisms with liberation of endotoxin.

In development of dysbacteriosis autoinfection arises due to reproduction of the microorganisms naturally living in it, for example some kind of gram-negative microorganisms and fungi from the *Candida* species.

Recently, antiviral remedies, interferon or inductors of endogenic interferon are used in the treatment of infectious diseases.

Serotherapy of infectious diseases

In treatment of some infectious diseases homological and heterological immune serums and immune gammaglobulines are used. Serums and gammaglobulines are used for treatment and for prophylaxis of the infectious diseases.

There are antibacterial and antitoxical serums. Antitoxical serums contain specific antibodies to toxins – antitoxins. The mechanism of the action of these serums is neutralization of toxins, producing by the agent. Antitoxical serums are serums against diphtheria, botulism, and tetanus.

The effect of the serum depends on the dose and date of its injection. The result will be better if the serum will be injected early because serum inactivates only toxins, circulating free in the blood. The duration of the toxin circulation in blood is 1-3 days, and then toxins connect with cells and tissues.

In treatment of some infectious diseases immune gammaglobulines are used, obtained from the blood serum of the donors (homological). These remedies have high concentration of antibodies. The balastic substances are absent in these gammaglobulines. Iinjection of the gammaglobulines is not accompanied by side reactions.

At the present time immunoglobulines are used in treatment of grippe, tick encephalitis, staphylococcous infection, anthrax and other diseases. Due to application of heterogeneous serum may be anaphylactic shock and serum's disease. The development of shock occurs immediately after injection of the serum. It is necessary to inject serum by divided doses for prevention of development of shock. The serum's disease develops in 5-12 days after injection of the serum. The clinical manifestations are fever, edema of mucous membranes, lymphadenitis, spotted-papular rash. The duration of the disease is 6-12 days. The prognosis is usually favorable. Sometimes the injection of the serum is accompanied by reaction only in the place of the injection. Hyperemia and edema without fever occur.

Pathogenetic therapy

The pathogenetic therapy is based on study of important characteristics of homeostasis and its violations in infectious diseases. In pathogenetic therapy it

is necessary to allow for tests of acid-alkaline state, water-electrolytic balance, reological properties of the blood, and also disorder of microcirculation in the organs and tissues. The basic methods of pathogenetic therapy are desintoxication, rehydration, dehydration, and correction of the other violations of homeostasis.

In treatment of infectious diseases desintoxicative therapy is prescribed more frequently. Crystalloid solutions (Ringer's solution, threesalt, quartasalt acesalt and other) and colloid solutions (neohemodesis, polyglucin, reopolyglucin, albumin) are widely used.

The value of the pathogenetic therapy may be shown in the pattern of the infectious-toxic shock treatment.

The number of pathogenetic factors is known in the development of infectious-toxic shock. There are disorganization of blood circulation, violation of the microcirculation in the organs and tissues. Disorder of blood supply is accompanied by aggravation of provision of oxygen to cells, and also by difficulty in liberation of toxic products of metabolism from the cells.

Capillary system plays an important role in the development of shock. In shock damage of liver, functional insufficiency of kidney are observed.

Maintenance of homeostasis is ensured by dynamic balance of biologically active substances and their inhibitors (histamine, acetilcholine, catecholamines, proteolitic ferments, kallikreine-kinine system, cyclic nucleoproteins and prostaglandin's ensure maintenance of homeostasis.

In shock one of the more early reaction of the organism on damage is hyperfermentemia. Its biological meaning is concluded in supply of the organism with energy and destruction of damaging factors. Analysis of condition and level of ferments allows to consider pathogenetic based conclusion of proteolitic ferment's inhibitors in the therapy of shock.

One of the most important disorders of homeostasis is DIC-syndrome (synonyms – thrombohemorrhagic syndrome, coagulopathy of consumption, disseminated intravascular coagulopathies). The basis of this syndrome is diffusive coagulation of blood in small vessels, development of blockade of microcirculation in the organs (lungs, kidneys, liver and other), and deep disorders of the functions of these organs. Serious hypoxia and acidosis develop, leading unrarely to death. The formation of clots on the level of capillaries is connected with surplus quantity of thrombin. Transformation of fibrinogen into fibrin happens very quickly.

In the development of DIC-syndrome 3 clinical stages are differentiated:

- First stage is hypercoagulation of blood and formation of friable microthrombs and development of blockade of microcirculation in organs;

- Second stage is hypocoagulation. This stage is characterized by deep exhaustion of factors of coagulation. The clinical manifestations of the second stage are profuse bleedings;

- Third stage is outcome and residual appearances of DIC-syndrome.

Infectious-toxic shock may be caused by viruses, rickettsia, fungi, gram-positive microorganisms (pneumococcus, streptococcus, staphylococcus) and gram-negative microorganisms (meningococcus). The most frequent reasons of infectious-toxic shock are infections of urinary tract (especially, in elderly age and in weakened patients), infections of respiratory tract due to bacterial pneumonia (especially, in condition of tracheotomy), complications of septic childbirth, septic abortions, peritonitis of different origin, pancreonecrosis, sepsis of any origin. In infectious clinics reasons of infectious-toxic shock are usually meningococcal infection, typhoid fever, salmonellosis, diphtheria, leptospirosis and other diseases. Besides hypotonia, toxinemia plays great role in clinic of infectious-toxic shock. Toxinemia leads to damage of liver, kidneys and heart. The compulsory development of DIC-syndrome is another important manifestation of infectious-toxic shock.

The basis of treatment of infectious-toxic shock is complex of measures, including application of antibiotics and directed on improvement of blood circulation therapy. The duration of infectious-toxic shock is very serious, with high mortality (50 % of the patient die during the first 48 hours of the disease). That's why it is necessary to prescribe intensive therapy immediately. Broad spectrum antibiotics are prescribed. Steroid hormones have important value in the treatment of infectious-toxic shock. Hormones decrease general reaction of the organism on toxin, positively impact on hemodynamics. Treatment by glucocorticoids is conducted during 3-4 days, because depression of adrenocortical function does not arise.

Infusion therapy should be started with injection of crystalloid solutions: quartasalt, Ringer's solution, glucose-polarizing admixture (5 % solution of glucose with calcium chloride in dose 20-100 mg of 10 % solution per one liter of glucose). Besides salt solutions, synthetic colloid solutions are used (neoheamodes, polyglucin, reopolyglucin in dose 0.4-0.8 L) with purpose of desintoxication and liquidation of hemodynamic disorders.

The basic principles of treatment of DIC-syndrome are heparinotherapy and transfusion of fresh frozen plasma. It is necessary to inject to patients 2,500-500 units of heparin in isotonic solution of sodium chloride, solution of native or fresh frozen plasma. In this case fresh frozen plasma is donator of plasminogen and antithrombin. Content of antithrombin in fresh frozen plasma is up to 200-250 % from norm. Daily dose of heparin is 10,000-15,000. Simultaneously reopolyglucin is transfused as desagregant. Inhibitors of proteolitic ferments are injected also (75,000-100,000 units trasilol or adequate dose of contrical).

Pathogenetic therapy is the basic principle of the treatment of hypovolemic shock. Hypovolemic shock (on the base of dehydration) is more frequently observed at cholera. Cholera is characterized by loss of fluid with stool and vomiting, which reaches in very small period. The loss of fluid may exceed up to 2 times the body mass of the patient. Hypersecretory processes are the main mechanism of diarrhea origin. They develop as a result of the exotoxin action –

cholerogen on ferment adenylcyclase and accumulation of cyclic 3,5-adenosine-monophosphotase, leading to increase secretion of electrolytes and water. Deficit of potassium arises; reaching sometimes one third of it's content in the organism. Thickening of the blood, hypovolemia, hemodynamic insufficiency, metabolic acidosis, hypoxia and renal failure develop in consequence. The impetuous development of the disease already at the first 8-12 hours leads to dehydration, reaching 10 % from body's mass and more. The clinical manifestations of dehydration are pinched face, deeply sunken in the orbits, cold clammy skin. The skin is shriveled. The turgor of the skin decrease ("washwoman's hands"). A voice becomes hoarse. The general cyanosis, prolonged tonic muscles cramps are observed. The temperature is subnormal (34.5 °C). There is no pulse. The arterial pressure is not determined. Anuria and hypovolemic shock develop.

The treatment of hypovolemic shock is conducted immediately. Treatment consists from 2 stages: primary rehydration for compensation loss of fluid and correction of continued fluid loss. Preliminarily heated solution up to 36-38 °C is injected in stream with speed 70-120 mL in minute (up to 5-7 liters during 1.5-2 hours).

It is necessary to restore as a volume of circulating blood as a volume of extracellular liquid, because rehydration must be intensive. In hypovolemic shock it is necessary to use special salt solution: Phillips's solution № 1 (threesault), Phillips's solution № 2 (desault), quartasault, acesault and other. Ionic composition of these solutions is similar to composition of the patient's fluid loss.

It is prohibited to prescribe the remedies with high molecular weight (polyglucin, reopolyglucin). These remedies restore a volume of circulating blood, but they don't liquidate dehydration of the organs and tissues. It is prohibited to inject heart's glycosides. The heart's glycosides increase shortenic ability of myocard, but the heart is empty. The exhaustion of myocard develops as a result. It may be death from heart's stop. It is prohibited to inject pressory amines (adrenaline, noradrenaline). These remedies increase arterial pressure and cause change of microcirculation. The kidneys may perish as a result. So, the treatment of cholera patients is concluded into injection of adequate quantity of fluid relatively to losses.

Dehydration may develop due to other infections (shigellosis, salmonellosis, toxical food-borne infections). However, in salmonellosis, shigellosis, toxical food-borne infections there is combination of the signs of damage of gastrointestinal tract (gastritis, gastroenteritis, or gastroenterocolitis), signs of general intoxication and dehydration. In this diseases pathogenetic therapy is performed in 2 directions, in dependence of predominated clinical manifestations (desintoxication and rehydration).

In meningitis and meningoencephalitis pathogenetic therapy is directed to elimination of the brain edema (dehydrative therapy) and intoxication. In case of generalized form of meningococcal infection pathogenetic therapy is performed

simultaneously with etiotropic therapy. Its basis is intoxication treatment. Simultaneously dehydrative therapy is performed (lasix, mannitol).

In severe cases of meningococcal infection glucocorticoides are prescribed. Dose depends on dynamics of the basic symptoms and presence of complications. Usually, hydrocortisone in dose 3-7 mg/kg/day, prednisolon in dose 1-2 mg/kg/day are prescribed.

Development of Waterhause-Fridrichsen's syndrome is possible at fulminant form of meningococcal infection, connected with hemorrhage into adrenal glands. In such cases the therapy is directed to the struggle with adrenal glands insufficiency (replacing therapy). The large doses of corticosteroid are prescribed.

Pathogenetic therapy is widely used in treatment of the patients with viral hepatitis. Due to investigations of the last years it was shown that activation of the processes of peroxide oxygenation of lipids plays the essential rose in the pathogenesis of viral hepatitis and leads to alteration of structure and functions of hepatocytes, thrombocytes and other cells membranes. Besides that, there is correlation between activation of peroxide oxygenation of lipids and duration of intoxication. Its worths to underline that simultaneously with activation of POL (peroxide oxygenation of lipids) the considerable depression of antioxydantic activity of the blood serum is marked.

The definition of the factors of intensification of the processes of peroxide oxygenation of lipids in the patients with viral hepatitis B became the basis for application of the remedies with antioxydantic mechanism of the action in complex therapy.

The degree of immunity development in considerable measure determines the possibility of formation of prolonged and chronic forms of the disease. Owing this the great quantity of works were performed last years on study of cell's immunity and its role in pathogenesis of acute viral hepatitis B according to the form, degree of gravity and period of the disease.

It was established that in patients with cyclic forms of acute viral hepatitis during of the process of the disease the secondary immune deficiency develops, with tendency to restoration of functions of immunocompetentive cells during period of reconvalescence. Decreased quantity of T-helpers and T-suppressors is observed. The subpopulation of T-suppressors was changed more than subpopulation of T-helpers. The correlation of tests of T-system of immunity and gravity of the disease course is marked. In patients with prolonged duration of acute hepatitis the strong decreasing of T-helpers is observed.

The determination of the considerable role of immune mechanisms in pathogenesis of viral hepatitis is pathogenic basis for application of immuno-correcting therapy.

The application of preparations of thymoid gland – thymalin, tactivin, synthetic peptide of thymus-thymogen may be used for to improvement of cell's interactions, disappearance of dysbalance in correlation of T-helpers and T-suppressors.

The data about molecular mechanisms of damage of hepatocytes's membranes were received last years. Because the remedies with stabilizative action to hepatocyte's membrane are used (carsil, legalon and other hepatoprotectors) in complex therapy of acute viral hepatitis.

Pathogenetic therapy of acute viral hepatitis, directing to the struggle with intoxication, regulation of water-electrolyte balance, regulation kallekrein- kininic system, elimination of hemorrhagic syndrome is used in practice widely.

However, the application of different schemes of pathogenetic therapy with use modern desintoxicative methods, doesn't always conduct to favorable course and outcomes of acute viral hepatitis, it doesn't prevent development of complications (acute hepatic encephalopathy), formation of prolonged course and relapses.

For this reason the looking for chemotherapeutic remedies, preventing from replication of virus in hepatocytes is an actual question. The remedies with antiviral action were received last years: arabinozid-nucleotid A, amphotherycin B, virazol, aplizarin and other. However, the antiviral remedies application in treatment of viral hepatitis doesn't always are effective clinically, doesn't give complete elimination of viral antigens. Because, the application of these remedies is limited in clinical practice.

The application of interferon and remedies, stimulating its produce is perspective direction owing this. Interferones are low molecular proteins depressing viruses reproduction. Leucocytaric and fibroblastic interferones may be produced practically by all cells. Immune gamma-interferon is produced by gamma-interferon immunocompetentive cells during immune response.

Interferon is the most important factor of nonspecific resistance. However, interferon has influence to differentiation and activation of effectoric cells of immune system. The activation of monocytes (macrophages) increases generation of peroxide radicals, increased phagocytes activity are observed under influence of interferon. Thus, at the present time interferon is used not only as antiviral remedy, but also as important regulator of interaction between cells.

It is established that there is decreased produce of interferon in patients with viral hepatitis B, especially in patient with severe duration of the disease. In fulminate course of acute viral hepatitis B interferon is no revealed in the serum of blood.

In accordance with opinion of many investigators, virus of hepatitis B is week inductor of interferon. The firm insufficiency of produce of interferon is one from decisive factors of crossing infectious process into chronic form. The application of interferon in infectious diseases may be possible in two directions: injection of ready-made interferon (exogenic interferon) and stimulation of synthesis of own interferon (endogenic interferon).

The decreased production of interferon in patients, decreased ability of virus hepatitis B (VHB) to induce interferon output, and also low cytotoxicity of natural killers are pathogenetic basis for interferontherapy application in patients with hepatitis B and C.

The considerable effeciency of leucocytic interferon is marked in patients with medium and severe course of acute viral hepatitis B. The positive influence of interferon on clinical manifestations dynamics, decreasing of intoxication and improvement of biochemistric tests were observed.

The stimulation of endogenic interferon producing by organism is the most perspective direction. At the present time some hundreds inductors of interferon are known. The basic criteria of interferon inductors effeciency are their interferon-inducing and antiviral action. Some remedies are more effective in viral infections (larifan, ridostin, camedon, amixin, cycloferon and other).

Intensive therapy and reanimation

Many infectious diseases have declination to serious duration and complications development. It may happen at fulminant course of some infectious diseases (meningococcal infection, viral hepatitis B and other). The gravity of course depends on degree of violation of water – electrolyte balance, acid-alkaline state, blood coagulative system and other criterions of the patient state. The methods of intensive therapy and reanimation are inculcated in clinical practice last years. These methods are directed to restoration of vitalitive important functions of the organism altered due to acute violations. Intensive therapy is performed in the special department under control of express clinical laboratory investigations. Efficiency of this therapy is determined by intensive observation of the patient. The observation after a patient is performed continuously and through short intervals of the time with fixation of physiological parameters (registration of pulse, breath, arterial pressure, data of electrocardiogram, electroencephalography and other tests of the patient state).

The methods of intensive therapy are pharmacotherapy, artificial pulmonary ventilation, hyperbolic oxygenation, artificial hypothermia, oxygenation, hypothermic, different methods of extracorporal hemodialysis (hemosorbtion, perfusion of liver, abdominal hemodialysis, dialysis with help of artificial kidney apparatus and other).

Intensive therapy of infectious diseases includes antibacterial serums, immunoglobulines, and different chemotherapeutic remedies. Intensive therapy is used for treatment of the patients with meningococcal infection, malaria, typhoid fever, salmonellosis, cholera, leptospirosis and other infectious diseases.

Prophylaxis of infectious diseases

At the last decades certain successes were achieved in fighting with infectious diseases, massive epidemics of most dangerous infectious diseases (epidemic typhus fever, plaque, smallpox, tick-borne relapsing fever and other). The struggle is realized successfully with diphtheria, poliomyelitis, measles, and many zoonozic infections. Undoubt success is achieved in malaria control. However, the deliverance of humanity from malaria requires time, considerable efforts and great expenses. More than billion cases of infectious diseases of gastrointestinal and respiratory tract are registered in the world every year. For example, grippe

is registered in some years in 10-15 % of population only of the countries of Europe and America. More than 75 millions of the people become ill by other acute viral diseases of the respiratory tract. Pandemic of grippe acquires character of the calamity and causes enormous economic detriment to all the countries. Every years multiple cases of streptococcous and staphylococcous infections, cholera, helminthiases, viral hepatitis, meningococcal infection and diseases caused by conditional pathogenic flora are registered in the world.

Thus, prophylaxis of infectious diseases is actual question. The measures of prophylaxis of infectious diseases may be conditionally divided on 2 groups: general and special measures. The general measures are state measures, directed on increase of material favorable condition, improvement of medical service, and conditions of work and rest of the population, sanitary-technique, hydrotechnic measures and also international measures in attitude to quarantine infections.

It is known about 3 links for development of epidemic process: the source of infection, ways of the transmission and susceptibility of the organism. The absence or rupture either of this links leads to cessation of epidemic process.

There are 3 groups of prophylactic measures:

1. The measures directing on the source of infection, its elimination.

2. The measures, directing on the mechanism of the transmission of infection. Their purpose is rupture of the ways of transmission of infection.

3. The measures directing on increasing of unsusceptibility of population to infection.

Prophylactic measures, directing on the source of infection play an important role. It is known that when antroponozic infection the source of infection is a sick man or carrier of the agent. The source of infection is sick animal at zoonotic infections. Prophylactic measures of this group are diagnostic, isolative, medical and regimen-limitary measures. In some infectious diseases hospitalization into infectious hospital is obligatory (especially dangerous infections, typhoid fever, epidemic typhus, diphtheria, meningococcal disease). In case of other diseases isolation may be at home if epidemiological and clinical contraindications are absent (shigellosis, escherihiosis, measles and others).

An important prophylactic measure is active revealing of carriers and their sanation. Revealing of carriers is performed in focuses of infection, among reconvalescents, and also among persons of food establishments, water pipe stations, and children's establishments. It is necessary to perform their bacteriological examination and treatment.

Isolation of persons, contacting with patient is necessary in case of especially dangerous infections (plague, cholera). The duration of isolation depends on maximal incubation period: in plague – 6 days, in cholera – 5 days. This measure is named observation. Observation is one of the quarantine measures. The word "quarantine" was originated from Italian word "*quarantine*" (*quaranta gieri* – 40 days). At this historic period duration of incubation period was not known.

Because isolation of patients with plague and some other infectious diseases was 40 days.

The measures about sanitary guard of borders have an important meaning. In 1969 on Universal Public Health Assembly "International medical-sanitary rules" have been accepted. Infections, having international meaning are divided on 2 groups:

Diseases, which are submitted to these rules (plague, cholera, yellow fever).

Diseases for international surveillance (epidemic typhoid fever, tick-borne relapsing fever, grippe, poliomyelitis and malaria).

All countries-members of World Health Organization should report about all cases of this diseases, and also perform proper antiepidemic measures. In zoonozic infections prophylactic measures have one's own features. If the source of infection are domestic animals, than it is necessary to perform sanitary-veterinary measures about their health. If the source of infection are mice and rats it is necessary to perform deratization.

In prophylaxis of infectious diseases an important measure is influence on mechanism of transmission of infection. Transmission of the agent from sick man to healthy man is realized with help of different factors (water, food, air, dust, soil and other). Prophylactic measures, directing on the second link of epidemic process are divided on 3 groups: sanitary-hygienic, disinfection and disinsection. The basic factors of transmission of the agent are food, water, rarely-flies, dirty hands in case of intestinal infections with fecal-oral mechanism of transmission of infection (typhoid fever, cholera, shigellosis). In prophylaxis of these infectious diseases general sanitary and hygienic measures have the most important value.

Prophylactic measure, directed on the ways of transmission is disinfection, which is performed in the focuses of infectious diseases, public place (railroad station, transport, and public toilets).

At infections of the respiratory tract (measles, rubella, diphtheria, scarlet fever, meningococcal infection, grippe) preventive measures are sanation of air, application of respirators. Disinfection is performed only due to scarlet fever and diphtheria, because the agents of the majority infections of respiratory tract are nonresistant in environment.

At transismissive infections the method of disinsection has the great meaning, directed on distruction of insects.

The measures, directed on the third link of epidemic process are increasing of general nonspecific resistance of the organism and also specific prophylaxis. Specific prophylaxis is directed on creation of artificial immunity (active or passive) against infectious diseases.

Specific prophylaxis is performed with help of vaccines, anatoxins serums, gammaglobulines. Vaccines and anatoxins create active immunity, serums and gammaglobulines – passive immunity. Vaccines are divided on living and killed vaccines.

Microorganisms with weakening of virulence are used for preparation of vaccines. In 1798 Edward Jenner proposed vaccine against smallpox, containing agent of cowpox. This agent has a little virulence for humans. Jenner called his new method of preventing smallpox "vaccination", from the Latin word "*vacca*", that is "a cow". In 1885 Paster proposed vaccine against rabies from weakening vaccine strain. Living vaccines are used for prophylaxis such infectious diseases, as tularemia, poliomyelitis, yellow fever, measles and other. These vaccines create tense and prolonged immunity (3-5-8 years).

Killed vaccines are divided on corpuscular and molecular (chemical). Killed vaccines are used for prophylaxis of intestinal infections. Efficiency of killed vaccines is less, than living vaccines. The duration of immunity is from 6 months till 12 months.

Anatoxins are also used for creation of artificial active immunity. Anatoxins have no toxic properties, but they preserve antigenic and immunogenic properties. At the present time anatoxins are used for prophylaxis of diphtheria, tetanus, botulism.

Artificial active immunity appears after injection of vaccine through few weeks. Artificial passive immunity develops more quickly. It is caused by injection of blood serum with ready antibodies (immune serums and immunoglobulines). There are preparations used for prophylaxis of tetanus, measles, tick-encephalitis and other infectious diseases.

Control questions:

1. Basic principles of anamnesis collection.
2. Principles of clinical examinations of infectious patients.
3. Value of additional methods of diagnostics.
4. The principles and methods of the infectious diseases treatment.
5. What are the remedies of specific action used for the treatment of the infectious diseases?
6. Basic principles of infectious diseases prophylaxis.
7. Groups of prophylactic measures and their characteristics.

TYPHOID FEVER AND PARATYPHOID

Typhoid fever, paratyphoid A and B are acute illnesses from the group of intestinal infections. They are characterized by cyclic course, bacteremia, intoxication, rash on the skin, lesions of the lymphatic apparatus of the small intestine. Besides that, typhoid fever is characterized by high fever of different duration, development of so-called status typhosus, hepatosplenomegaly, lesions of organs of the gastrointestinal tract, relapses and various complications.

Historic reference

Typhoid fever is well known for a long time as an illness of mankind.

The causative agent of typhoid fever was described by Ebert in 1880. Pure culture of the agent was isolated by Gafki in 1884.

Typhoid fever was one of the most widespread and serious infectious disease in 19th century and in the beginning of 20th century in all countries of the world, especially in the large towns due to groupment of the people. Building of waterpipe and canalization allowed to decrease morbidity in the large towns. But almost every calamity (hunger, earthquake) and wars were accompanied by outbreaks of typhoid fever.

Now, the morbidity is sporadic in European countries. However, high level of morbidity occurs in some countries due to features of climate, ecological conditions and social factors (Mexico, India, Afghanistan, countries of Northern Africa and other).

Etiology

The causative agent of typhoid is *Salmonella typhi* of *Enterobacteriacea* family, genus *Salmonella*, serological group D.

Salmonella are not-spore-forming rods and motile by peretrichous flagella. Like other enterobacteria, *Salmonella* have somatic (O) antigens which are lipopolysaccharide components of the cell wall and flagellar (H) antigens, which are proteins. There are approximately 60 O-antigens, which are designated by numbers at letters. The Kauffmann-White scheme categorizes *Salmonella* on the basis of somatic antigens, each group having a major determinant which is a strongly reaching somatic antigens and one or more major somatic antigen. *Salmonella typhi* also has a capsular or virulence (Vi) antigen composed of a homopolymer of N-acetyl galactosaminuronic acid. The presence of Vi-antigen on the cell surface may block agglutination by anti-O serum.

Salmonella can be differentiated from other *Enterobacteriaceae* on basis of certain biochemical reactions, including fermentation. Most *Salmonella* ferment

glucose and mannose to produce acid and gas but do not ferment lactose or sucrose; *S.typhi* does not produce gas. Thus, *Salmonella* typhi has some antigenic and biochemical features. That is why typhoid fever is isolated from the other diseases, caused by *Salmonella*. *Salmonella* organisms grow on the media with addition of bile. The resistance of agent of typhoid fever and paratyphoid in the environment is very high. They endure low temperatures very well. The agents of typhoid fever and paratyphoid diseases survive from 1-2 till 25-30 days, in food products.

Epidemiology

Typhoid fever is anthroponosis. The source of infection is sick man or bacteriocarrier. The patients with typhoid fever discharge the agent with stool, urine, rarely − with saliva and milk. The discharge of the agent is observed at the end of incubation period, during all disease, and sometimes in the period of reconvalescence. In some cases the discharge continues till three months (acute carriers) or more than three months (chronic carriers). Chronic carriers may be from six months till some years.

The mechanism of the infection transmission is fecal-oral. The factors of transmission may be water, milk, various food-stuffs and contaminated feces of the patient or bacterial carriers. Flies can play the supplementary role.

Susceptibility to agent of typhoid fever and paratyphoid diseases is rather high, however clinical manifestation can be of different grade. The care rate of typhoid fever and paratyphoid diseases depends on seasonal prevalence. It increases in summer-autumn period, due to consumption of a huge amount of flies, quite often from unknown sources, unwashed fruit and vegetables. The strong immunity develops after disease.

Pathogenesis

The next phases are distinguished in the pathogenesis of typhoid fever:
1. Penetration of the causative agent into the organism.
2. Development of lymphadenitis and lymphangitis.
3. Bacteremia.
4. Intoxication.
5. Parenchymatous diffusion.
6. Discharge of the agent from the organism (excretory phase).
7. Allergic reaction, mainly of lymphoid tissue of the small intestinum.
8. Formation of immunity.

The first phase is penetration of the agent into the macroorganism. However, penetration does not always lead to the development of the pathological process. It depends on the quantity of the agent and the state of barrier functions (It is stomach in this case). The further path of *Salmonella typhi* is lymphatic apparatus of intestine.

The second phase is lymphadenitis, lymphangitis. *Salmonellae* achieve the small intestine and actively penetrate into solitary follicules, Peyer's patches. There is the reproduction of the agents and formation of the focus of infection. Microorganisms penetrate to regional lymphatic nodes (mesenterial) along the lymphatic patches. There is the other focus of infection. In the lymphatic apparatus, the typical morphological alterations with proliferation of tissue and formation the large typhoid cells develop.

Bacteria achieve the definite quantity and enter into the blood circulation through the thoracic duct. It is the next phase of pathogenesis — bacteremia. In clinic bacteremia means the end of incubation period and beginning of the clinical manifestations. The blood has bactericidal properties. It leads to the death of the part of microbes. Intoxicative syndrome develops. Intoxication is the fourth phase of pathogenesis. The action of endotoxins causes changes of the state of the central nervous system, adynamia, fever, headaches, violations of dream, appetite.

The fifth phase of a pathogenesis is parenchymatous diffusion of microbes. By the flow of the blood *Salmonella* of typhoid fever and paratyphoid also are delivered over the organism, enter into all organs. Microbes are fixated especially in liver, spleen, bone marrow, skin. Secondary focuses are formed (typhoid granulomas), from which bacteria likewise from the primary focuses (lymphatic apparatus of the intestine) enter into the blood, supporting bacteremia. The settling of microbes in the reticuloendothelial system and their destruction in the structures of reticuloendothelial system causes the cleaning of the organism from infection.

The sixth phase of pathogenesis is discharge of the agent from the organism. The agents enter into the intestine from the liver through the bile ducts. They are excreted into the external environment with feces of the patient. The part of the agents repeatedly penetrates from the small intestine into lymphatic apparatus of the intestine and cause sensibilization to microbes. The expressive changes of lymphoid tissue develop due to repeated implantation of *Salmonella typhi* with development of morphological changes from cerebral-like swelling to necrosis and formation of ulcers.

This process is considered as the seventh phase of pathogenesis — allergic response of lymphoid tissue of the small intestine. Eighth phase of pathogenesis is formation of immunity and restoration of the physiological equilibrium.

Anatomic pathology

Sequential changes in tissue in the ileocecal area of the intestinal tract occur during typhoid fever and have been classified into four phases:
1. Hyperplasia.
2. Necrosis and sloughing.
3. Ulceration.
4. Healing.

During the first week of clinical symptoms, hyperplastic changes occur in Peyer's patches in the ileum and in the lymphoid follicles in the cecum, causing

there tissue to project into the bowel lumen. The hyperplasia regresses after 7-10 days or undergoes necrosis with sloughing of overlying mucosa leading to the formation of characteristic ulcers that parallel the long axis of the ileum. Small punctuate lesions develop in the cecum. Ulcers usually heal completely with little residual scarring, but they may be the sites of hemorrhage or may penetrate to the serosa and lead to bowel perforation.

Clinical manifestations

Typhoid fever and paratyphoid are characterized by cyclic course. There are such periods during course of the infectious process: incubation, initial, period of climax, early reconvalescence and outcomes.

The incubation period of typhoid fever is usually 10-14 days but it may be from 7 to 21 days. The incubation period is influenced by the number of organisms ingested. The duration of incubation period also depends on virulence of microorganism and state of macroorganism.

Manifestations of enterocolitis occasionally occur within hours after the ingestion of food or drink contaminated with *S.typhi* if the dose of organisms is large. In these instances symptoms of nausea, vomiting and diarrhea usually resolve completely before the onset of symptoms of typhoid fever.

The onset of typhoid fever is insidious in contrast to sepsis produced by most other gram-negative organisms. The initial manifestations are nonspecific and consist of fever, malaise, anorexia, headache and myalgias. Remittent fever is prominent with gradually increasing evening temperature elevations from less than 38 °C to values in the range of 40 °C by the end of the first week of illness.

The disease turns into the next stage (climax of the disease) at the end of the first week. The appearance of the patients is very typical in this period. The skin is pale. Patient is apathethic. Intoxication is increased. Temperature is constant and most typical syndrome of typhoid fever and paratyphoid. At first the temperature was described by Wunderlich in 19th century. Temperature curve riminds trapezium. The phase of increase of the temperature is near one week. The phase of climax is near two weeks. The phase of decrease of the temperature is near one week. Temperature curve of Wunderlich occurs rarely. Temperature curve has wave-like character more frequently (temperature curve of Botkin).

Chills and diaphoreses are seen in about one-third of the patient even in the absence of antimicrobial therapy. Either constipation or diarrhea may occur. Respiratory symptoms, including cough and sore throat may be prominent. Neuropsychiatries manifestations, including confusion, dizziness, seizures, or acute psychotic behavior, may be predominant in an occasional case. Status typhosus is observed in serious course of the disease.

In present time patient with typhoid fever usually appears acutely ill. Fever is usually prominent, and in many instances the pulse is slow relative to the temperature.

In typhoid fever symptoms of violation of cardiovascular system are constant and expressive. The basis of hemodynamic disorder is violation of the tonus of the vessels, damage of heart muscle due to intoxication. Myocardiodystrophy develops as a result. In typhoid fever relative bradycardia is the clinical feature of cardiovascular disorders. The muffed heart sounds, systolic murmur at the heart apex, hypotension are marked inrarely. Relative bradycardia develops due to endotoxin action of the agent on X pair of cerebrospinal nerves.

Rose spots, 2-4 mm erythematous, maculopapular lesions that blanch on pressure, appear on the upper abdomen or on the lateral surface of the body. Roseolas are few (5-15) in number (Fig. 1). The lesions are transient and resolve in hours to days. Rose spots are observed on the 7-10 day of the disease near in half of patients. Sometimes they dissapears, sometimes exist longer than fever.

Cervical lymphoadenopathy may be present. Examination of the chest may reveal moist rales. The abdomen is tender, especially in the lower quadrants-Abdominal distention is common, and peristalsis is often hypoactive. The sensation of displacing air − and fluid-filled loops of bowel on palpating of the abdomen is considered to be characteristic. In percussion short sound is marked in ileocaecal area due to enlarged mesenteric lymphatic nodes. Hepatomegaly is noted in about 40-50 % of the patient, and a soft, tender spleen can be palpated in about 40-60 %. In about 10 % of the patients, changes in consciousness are present and manifest as lethargy, delirium, or coma.

Without antimicrobial therapy, the disease pursues a prolonged course with slow resolution of signs and symptoms 3-4 weeks after onset if there are no complications. Sustained fever is common during the second and third weeks of disease. Fever decreases slowly by lysis, unlike the resolution by crisis seen in the preantibiotic era in many cases of pneumococcal pneumonia. Headache, confusion, respiratory symptoms, and abdominal pain and distention gradually resolve, and the pulse more characteristically reflects degree of fever acute manifestations subsiding. Profound weight loss invariably occurs in untreated patient. Many of the complications of typhoid fever occur during the period of resolution in the third or fourth week after onset.

Complications

Complications of typhoid fever can be classified as secondary to toxemia (myocarditis, hyperpyrexia, hepatic and bone marrow damage), secondary to local gastrointestinal lesions (haemorrhage and perforation), secondary to prolonged severe illness (suppurative parotitis decubiti, and pneumonia), secondary to growth and persistence of typhoid fever bacilli (relapse, localized infection − meningitis, endocarditis, osteomyelitis or arthritis) and secondary to therapy (bone marrow suppression, hypersensitive reactions and toxic shock).

In the preantimicrobial era, 12-16 % of the patients with typhoid fever died, frequently from complications in the third or fourth week of the disease. Fatalities still occur occasionally, probably in less than one percent of the patients receiving

appropriate antimicrobial and pathogenetic therapy. However, in certain specific geographic areas of Indonesia, India, and Nigeria, fatality rations of 9-32 % have been reported last 10-15 years. It is likely that these results are consequent to suboptimal health and medical care rather that an increase in the clinical severity of typhoid fever.

The complications attributed to "toxemia" might be considered as manifestations of severe disease. Toxic myocarditis occur in severely ill patients, frequently children, and is manifested by tachycardia, weak pulse, muffled heart sounds, and hypotension. The electrocardiogram shows low voltage and T-wave flattening or inversion. Atrial or ventricular arrhythmia may occur.

Major intestinal hemorrhage is usually a late complication that occur during the second or third week of illness. In the preantimicrobial era, gross intestinal hemorrhage occurred in about 5-7 % of the patient with typhoid fever. The incidence of hemorrhage requiring transfusions has been reduced to 1 or 2 percent, due to chloramphenicol use. There is an important sign of the massive intestinal hemorrhage symptom of "scissors". Suddenly the temperature is decreased up to normal or subnormal. But tachycardia is observed. The arterial pressure is reduced. Intestinal perforation usually occurs during third week of illness. Perforation occurs in the terminal ileum where the number of lymphoid aggregates is the largest and ulcerations most frequent. In general, perforation has reported in recent years in one percent or less of cases as compared with 2-5 % in several series collected in the preantibiotic era.

Relapse, a recurrence of the manifestation of typhoid fever after initial clinical response, occur in about 8-12 % of the patient who have not received antimicrobial therapy. The relapse rate was found to be doubled in patients receiving chloramphenicol therapy for 2 weeks. Ampicillin probably does not affect the rate of relapse.

Localization of infection, which may lead to abscess formation, can occur in almost any organ or tissue. Although bacteremia can be assumed to develop in all patient with typhoid fever, localized infections such as meningitis, endocarditis, osteomyelitis, or thyroiditis occur in less then one percent.

The chronic carrier state is detained as documented excretion of *S. typhi* in stool or urine for a year or more. The chronic carrier state usually follows typhoid fever but as many as one − third of the chronic carriers give no history consistent with this illness. Underlying biliary or urinary tract diseases, especially with stone formation, increase the probability of the chronic enteric or urinary carrier state in patients with typhoid fever. One to 3 % of the patients with typhoid fever become chronic enteric carriers; however, the incidence is higher in older patients (at the sixth decade) and in women.

Clinical features of paratyphoid

Epidemiology, pathogens, morphology and clinics of paratyphoid A and B, have, in principal, mutual signs with typhoid fever. However, paratyphoids have some clinical features.

In paratyphoid A incubation period is shorter than in typhoid fever. It's duration is 8-10 days. The onset of the disease is an acute. Sometimes, the onset of the disease is accompanied by cough, catarrh. Facial hyperemia, blood injection of the sclera's vessels, herpes on the lips are observed during examination. The temperature is wave-like or remittent. The fever is accompanied by chills and than by diaphoreses. In paratyphoid A the rash appears in more early periods than in typhoid fever. The rash is polymorphic. Roseolas, petechias and measles-like rash may be observed. The intoxication is temperate. There is no status typhosus. There is normal quantity of leukocytes in peripheral blood. But leukocytosis and lymphocytosis may occur too.

In majority of the patients the disease has a moderate course. But the severe forms may be observed too, with complications (intestinal hemorrhage, intestinal perforation and other). The relapses are frequently observed in case of paratyphoid A.

Paratyphoid B incubation period is 5-10 days. The onset of the disease is acute, with expressive chill, myalgia and diaphoreses. At the initial period of the disease the intoxication may be combined with symptoms of acute gastroenteritis. The temperature is not prolonged. Status typhosus is absent in majority of the patients. The symptoms of intoxication disappeares very quickly. The rash is polymorphic, plenty. It appears at the earlier period. In some cases the course of paratyphoid B may be severe with septic manifestations (purulent meningitis, meningoencephalitis, septicopyemia). In peripheral blood leukocytosis and neutrophylosis are observed.

Diagnosis

Definitive diagnosis of typhoid fever and paratyphoid is made on the basis of pathogen isolation from the patient's blood. Isolation of the organism from stool, especially in endemic areas, does constitute strong presumptive evidence of typhoid fever in the patient with a typical clinical course. Serologic studies may be helpful, but in many cases of typhoid fever there is no increase in titer of agglutinins during the course of infection, and other illnesses, especially infections with other gram − negative bacilli, may cause nonspecific elevations of agglutinins because of cross − reaching antigens. In untreated disease only about 50 % of the patient have a fourfold or greater increase in titer of agglutinins (Widal's test) against typhoid fever O-antigen at any time during the course of disease. Antimicrobial therapy may also impede immunologic response. Immunization with typhoid fever vaccine may produce an impressive increase in titer of anti-O-agglutinins and nonspecific changes in titer may occur during the course of many febrile illnesses. Agglutinins against H-antigen, irrespective of change of titer, are not of value in diagnosis. A number of other serodiagnostic methods, e.g., detection of IgM antibody to *S.typhi* lipopolysaccharide antigen by an enzymelinked immunosorbent assay (ELISA), are being studied and seen promising, but none is ready for routine diagnostic use.

The majority of isolates of *S.typhi* from blood are obtained as a result of the first blood culture, but a second or third culture should be collected in suspected cases, as these culture significantly improve the percentage of positives. Stool cultures become positive in about one − third to two − thirds of the patients during the second through fourth week of illness.

Differential diagnosis

The differential diagnosis of typhoid fever requires consideration of many disease processes characterized by fever and abdominal complaints. Early in the disease the predominance of fever and upper respiratory tract symptoms may suggest influenza or other viral infections. Cough and fever suggest acute bronchitis and, when coupled with rales, raise the question of bacterial pneumonia. Headache, confusion, and fever may prompt consideration of bacterial or aseptic meningitis or meningoencephalitis. Delirium, catatonia, or coma may suggest a diagnosis of psychosis or other neuropsychiatries illness. The abdominal findings may lead to a consideration of acute appendicitis, acute cholecystitis, or intestinal infarction. Bacillary, amebic or ischemic colitis may enter the differential diagnosis if blood diarrhea occurs. As fever continues over a period of weeks, other possibilities might include brucellosis, yersinosis, lymphoma, inflammatory bowel disease, bacterial endocarditis, miliary tuberculosis, malaria, sepsis, epidemic typhus and many other diseases.

Treatment

Antibacterial therapy is indicated to all patients. The basic preparation is levomycetin (chloramfenicole) in tablets 0.5. It is administered per os (PO) in dose of 0.5 gm (4 times per day) for half an hour before meal till the 10th day of body temperature stabilization, a daily dose is reduced usually till 1.5 on the last 4-5 days of treatment. At severe course of illness it is possible to increase a daily dose gradually, on first days levomycetin should be taken up to 3 gm but not more. If using of the levomycetin (PO) is impossible (a nausea, vomiting, a pain in epigastric area) levomycetin succinate in bottles should be prescribed − 0.5 intramuscularly (IM) daily dose 3-4 gm or in suppositoriums, and in serious cases intravenous or endolymphatic 0.5-1 (2 times in days) application.

When there is no effect after using of levomycetin during next 5 days and there are contraindications, that is effective to prescribe ampicillin till the 10th day of normal body temperature. Alternative remedies are bactrim, azitromicin (sumamed) and fluoroquinolones derivates ciprofloxacin and ofloxacin, which are effective in case of tolerance to levomycetin. Also cefalosporines of III generation: cefoxim or ceftriaxone may be used.

To prevent relapses and formation of chronic bacteriocarrier the antibiotic therapy is desirable for carrying out in a complex with Vi-antigen, stimulating creation of specific immunity. Preparation of typhoid bacteria is injected on 400

mg threefold under a skin with 7 days interval or twice the same dose, or 800 mg with 10 days interval.

Plentiful drinking, sorbents (SKN, Vesта), sillard P, enterodes are prescribed as desintoxication agents at mild disease course. Solution of glucose intravenously (IV) with solution of ascorbic acid, qurtasault, acesault, lactasault, a solution of donor albumin are injected at moderate disease course. If process has severe course, reopolyglycin is injected both with polyionic colloid solutions at increasing of intoxication for 7 days, prednisolonum 30-60 mg and more per day parenterally during 5-7 days. Oxybarotherapy, plasmaferesis are indicated. Inhibitors of proteolytic enzymes − contrical, gordoxe, trasylole should be prescribed.

Obligatory components of complex therapy are bed regime and diet № 2. For stimulation of nonspecific organism resistance and reparative process methyluracil, pentoxil, thimalin are indicated

During antibiotic therapy the intestinal dysbacteriosis may develop. Nistatin or levorin, one of bacterial remedies bificol, bifidumbacterin, lactobacterin are indicated in such cases. If allergical reactions have appeared, calcii gluconate, dimedrol, diprazin, tavegil, gismanal, zestra, loratidin, alegra, telfast are indicated.

A strict confinement to bed (position of the patient on back), cold on stomach region, forbiding of feeding for 10-12 hours are necessary in case of intestinal bleeding. Ascorbic acid in tablets, Vicasole, calcy chlorid, hypertonic solution of sodii chloride 5-10 mL (IV), an aminocapronicy acid, etamsylat, adroxone, gelatinole, infusions of the donor blood, saline solutions are indicated in such case.

The immediate surgical operation is indicated in case of intestinal wall perforation. In case of infectional-toxic shock, dofamin, high doses of prednisolone, reopolyglycin, quartasault or lactasault in a vein (a single dose 0.05-0.15 gm, in serious cases up to 0.4 gm) in isotonic solution of sodii chloridum, contrical are indicated.

Treatment of chronic bacteriocarrier is not developed. It is possible to achieve the time termination of allocation salmonelas by realization of 10-day's course of treatment by ampicillin in a daily dose of 2 gm in combination with immunostimalatores and di- or a monovalent vaccine in a combination with cleared Vi-antigen.

Prophylaxis

Control of *Salmonella typhi* infection transmitted from person to person depends on high standards of personal hygiene, maintenance of a supply of uncontaminated water, proper sewage dispose and identification, treatment, and follow-up of chronic carriers. Hand washing is of paramount importance in controlling person to person spread although hands of convalescent carriers are often contaminated after defecation detectable *Salmonella* are easily removed by washing the hands with soap and water.

Typhoid fever vaccine, a saline suspension of aceton or heat/phenol killed *S.typhi* enhances the resistance of human beings to infection with *S.typhi* under experimental and natural conditions. Vaccine efficacy ranges from 51 to 67 %.

There is also renewed interest in testing the capsular polysaccharide of *S.typhi* (Vi-antigen) as a parenteral typhoid fever vaccine.

Typhoid fever vaccine should be considered for persons with intimate continuing exposure to a documented typhoid fever carrier and for persons traveling to areas where there is a recognized appreciable risk to exposure to typhoid fever.

Control questions:

1. Epidemiology of typhoid fever and paratyphoid.
2. Phases of typhoid fever pathogenesis.
3. Clinic of initial period of typhoid fever.
4. Clinical manifestations of acute phase.
5. Clinical manifestations of paratyphoid fever.
6. Clinical classification of typhoid fever.
7. Specific and nonspecific complications.
8. Clinic of the intestinal bleeding and its medical treatment.
9. Clinic of bowel perforation, tactician of doctor.
10. Changes in the clinical blood test due to typhoid fever.
11. Differential diagnosis of typhoid fever.
12. Laboratory diagnosis of typhoid fever.
13. Blood collection for hemoculture.
14. Collection of material for copro- and urine culture.
15. Antibacterial therapy of typhoid fever.
16. Pathogenetic therapy of typhoid fever and paratyphoid.
18. Antiepidemic measures in the place of typhoid fever outbreak.
19. Prophylaxis of typhoid fever.

BRUCELLOSIS

Brucellosis is disease of domestic and wild animals that is transmittable to humans (zoonosis). The array of nonspecific signs and symptoms of brucellosis led Simpson to remark "No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations".

Historic reference

In 1859 Marston reported the first accurate description of brucellosis as a distinct entity. Marston, an assistant surgeon in the Royal Artillery, detailed his personal experience with "Mediterranian gastric remittent fever" while stationed in Malta during Crimean War. The causative agent remained unknown until 1886, when Bruce isolated *Micrococcus* (later *Brucella*) *melitensis* from the spleen of a fatal case of Malta fever. Zammit, a physician working with the Mediterranean Fever Commission (1904-1907) made observations that ultimately identified goats as the reservoir of brucellosis in Malta. Restrictions on the consumption of unpasteurized goats milk led to a dramatic decline in the incidence of brucellosis among military personnel. Meanwhile in 1895, the Danish veterinarian Bernard Bang identified *Bacillus* (later *Brucella*) *abortus* as the cause of contagious abortions in cattle. The relationship between the agents of Malta fever and Bang's disease was not recognized until the 1920s from the work of American bacteriologist Alice Evans, who recommended renaming the genus *Brucella* to honor Bruce. In 1914 Traum isolated *B. suis* from aborting swine, and in 1966 Carmichael identified *B. canis* as the cause of contagious abortions in Beagle dogs. *B. ovis* (1953) and *B. neotomae* (1957) were isolated from sheep and wood rats, respectively, but neither is pathogenic for humans. In 1897, Wright first applied the serum agglutination test to the diagnosis of brucellosis; this test remains the standard against which other serologic methods are compared.

Etiology

Brucellae are small, gram-negative coccobacilli that are nonmotile and do not form spores. They grow aerobically, although *B. abortus* and *B. ovis* may require supplement for primary isolation. Nutritional requirements are relatively simple. Any high-quality peptone-based media enriched with blood or serum can be used; however, initial isolation may require prolonged (2-30 days) incubation. *Brucella* strains are always catalase-positive, but oxidase and urease activities and the production of H_2S are variable. Traditionally, the major nomen species of *Brucella* have been differentiated by selective inhibition of growth on media containing dyes, such as thionin and basic fuchsin. A series of brucella-phages can also be used for typing smooth and nonsmooth brucellae.

Although six nomen species of *Brucella* are recognized, the results of DNA-DNA hybridization studies indicate that the genus comprises a single species (*B. melitensis*) with multiple biovars. Nevertheless, the nomen species designations are retained for taxonomic purposes and to avoid confusion. Phylogenetically, *Brucella* spp. appear to have a common origin with free-living, soil-dwelling organisms. Based on 16S rRNA sequences, *Brucella* spp. are classified in the a-2 group of the a-proteobacteria together with *Agrohacterium tumefaciens* and *Bartonelta (Rochalimaea) henselae*.

Chromosomal exchange among the brucellae by transformation, conjugation, or transduction is unknown, and no plasmids or temperate bacteriophages have been found. Studies using restriction endonuclease techniques indicate that *B. melitensis* contains two independent chromosomes. In addition, the genes for structural proteins, and functional enzymes have been cloned from *B. abortus*.

The major cell wall antigen of the brucellae is endotoxic lipo-polysaccharide (LPS), the structure of which accounts for serologic cross-reactions among smooth strains and with other gram-negative bacteria. The A and M antigens first described by Wilson and Miles have been characterized; the A chain consists of a homopolymer of l,2-linked-4-formamido-4,6-dideoxy-manno-pyranose residues, whereas the M chain is identical except that every fifth glycose residue is linked through the 1,3- rather than the 1,2-carbon atoms. Other outer membrane proteins resemble the OmpF and OmpA of *Escherichia coli*.

Epidemiology

Brucellosis is a zoonosis and virtually all infections derive directly or indirectly from animal exposure. The disease exists worldwide especially in the Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and in parts of Mexico and Central and South America. *Brucella abortus* is found principally in cattle, but other species such as buffalo, camels, and yaks can be of local importance. *Brucella melitensis* occurs primarily in goats and sheep, although camels appear to be an important source in some countries. *Brucella suis* biovars 1-3 occur in domestic and feral swines and can cause abattoir-associated infections. *Brucella suis* biovar 4 is confined to reindeer and caribou or their predators in the tundra regions of subarctic. *Brucella canis is* found primarily in kennel-raised dogs; it is the least common cause of human brucellosis. In animals, brucellosis is a chronic infection that persists for the life of the animal. Localization of brucellae within the female and male reproductive organs accounts for the major clinical manifestations: abortion and sterility. Brucellae are shed in large numbers in milk, urine, and products of pregnancy from infected animals. The disease is transmitted to humans by direct contact with infected animals, their carcasses, or via ingestion of unpasteurized milk or milk products. Occupations associated with an increased risk of brucellosis include animal husbandry, veterinary medicine, abattoir work, meat inspection, and laboratory science. The ingestion of

contaminated dairy products such as fresh goat's milk cheese is the source most likely to involve the general population. Meat products are rarely a source of brucellosis because they are not usually eaten raw and the numbers of organisms in muscle tissue are low. Unusual food "delicacies" such as blood and bone marrow have also been implicated in the transmission of brucellosis. Human-to-human transmission of brucellosis is extremely rare. Reports of sexual transmission are circumstantial, but the potential exists because brucellae have been isolated from human spermatozoa. Accidental self-inoculation with live *Brucella* vaccines is a risk for infection among ranchers and veterinarians.

Brucellosis in children is not rare as once thought, especially in areas where *B. melitensis* is enzootic. The manifestations of brucellosis are similar in neonates, children, and adults. It is not uncommon to observe outbreaks of the disease within families especially when a common food source is involved.

The role of wildlife in the epidemiology of brucellosis remains controversial. Wild hares in Europe are a reservoir for *B. suis* biovar 2 and can sporadically transmit the disease to domestic and feral swines.

Pathogenesis

Brucella usually gain entry to the body through abrasious in the skin in the course of handling infected animals or their carcasses. Accidental inoculation of the conjunctival the eyes is another route of infection that is especially common to veterinarians using live *Brucella* vaccines. Infect the respiratory tract is a special risk for abattoir work engaged in the slaughter of infected animals. *Brucella melitensis* is generally transmitted via ingestion of unpasteurizel products and appears to be more resistant than *B. abortus* to inactivation by gastric juices. Antacids and other drugs that decrease gastric acidity have been implicated in brucellosis transmitted by the oral route. The incubation time from exposure to the onset of symptoms is generally 2-3 weeks, although this may vary according to the inoculum size and perhaps the route of inoculation. Subclinical infection is suggested by the finding of antibodies to *Brucella* in individuals lacking symptoms or signs of disease.

Spink compared brucellosis to typhoid fever, with bacteria entering the lymphatics and replicating in regional lymph nodes. Hematogenous dissemination is then followed by localization of bacteria in organs rich in elements of the reticuloendothelia system (RES), including the liver, spleen, lymph nodes, bone marrow, and kidneys. Normal human serum has bactericidal activity against some *Brucella* spp. and is able to opsonize organisms for phagocytosis by polymorphonuclear (PMN) leukocytes. Strains of *B. melitensis* are generally more resistant to bacteriolysis, which may help explain the greater virulence of this species.

The brucellae are facultative intracellular pathogens that have the ability to survive and even multiply within the phagocytic cells of the host. The mechanisms by which the brucellae evade intracellular killing by PMN leukocytes is incompletely

understood; however, properties of the bacterial surface appear to enable it to escape detection. Factors believed to contribute to the intracellular survival of brucellae include the production of adenine and 5-guanosine monophosphate, which suppress the loperoxidase-H_2O_2-halide system of neutrophils, substances that inhibit phagosome-lysosome fusion in macrophages, and enzymes, such as superoxide dismutase, that defend against oxidative destruction. Brucellae are also ingested by macrophages of the RES, in which they initially survive and multiply. Growth of the pathogen in the spleen appears to be important for the induction of cell-mediated immunity, and bacterial cell wall endotoxin is a potent spleen mitogen.

The major virulence factor of the brucellae is smooth LPS. Nonsmooth strains usually have reduced virulence and are more susceptible to killing by normal serum from a variety of potential host species. Naturally nonsmooth species (*B. canis* and *B. ovis*) have a greatly restricted host range and a limited capacity to infect other species. Growth of *B. abortus* in placental tissues of cattle is stimulated by the presence of erythritol, which may explain the localization of brucellae in the genital tract of ungulates. Differences in host responses to various *Brucella spp.* is suggested by experimental animal studies in which *B.abortus* induces granulomas, whereas *B. melitensis* and *B. suis* produce tissue abscesses.

Anatomic pathology

The main factors of pathomorphologic disorders are allergic reactions, which occur in places of brucella localization, and cause considerable focal changes. The most vulnerable are connective tissue, vessels, neurologic and lymphatic systems. Brucellosis granulomas form in acute period, gradually they are exposed to fibrous transition or sclerosis, though some granulomas can even suppurate. Such morphologic changes causes stable functional lesions of affected organs.

Clinical manifestations

The onset of symptoms of brucellosis is acute in approximately one-half of cases and insidious in the remainder. They usually begin from 2 to 8 weeks after inoculation. Symptoms are nonspecific (fever, sweats, malaise, anorexia, headache) and patients are sometimes misdiagnosed as suffering from "the flu". An "undulant" fever pattern is observed if go untreated for long periods of time. Some patients complain of malodorous sweat and a peculiar taste in their mouth. Depression is common, and often in excess of the severity symptoms. In comparison to the myriad of somatic complaints, physical abnormalities may be few. Mild lymphadenopathy occurs in 10-20 % and splenomegaly in 20-30 % of cases. Hepatomegaly is reported in 20-60 %, but may vary with the species of brucellae or the presence of concomitant parasitic and protozoal infections in some populations.

Brucellosis is a systemic infection that can involve many organs and tissues. When patients present with manifestations involving a specific organ, some authors refer to this as "focal" or localized disease. However, there is little compelling

evidence to suggest that such complications necessarily represent a distinct subset of patients. Nevertheless, when the infection involves the central nervous system or cardiovascular structures, such cases are difficult to treat and the outcome can be affected.

With appropriate treatment most patients recover within weeks to months, although a minority will experience a more delayed recovery. Since it is necessary to treat for prolonged periods of time, relapses are not uncommon, especially if therapy is discontinued prematurely. Relapse is not due to antibiotic resistance, since strains of brucellae isolated during relapse have been shown to have antimicrobial sensitivity patterns identical to the original infecting organism.

Since the onset of symptoms of brucellosis can be insidious, it is often difficult to distinguish acute from chronic forms of the disease. Spink defined chronic brucellosis as symptoms persisting for more than 12 months after the diagnosis was made. Most patients with chronic brucellosis have persisting foci of infection, such as suppurative lesions in bones, liver, or spleen. Some patients who have had brucellosis will continue to complain of nonspecific symptoms, such as fatigue, malaise, and depression, in the absence of objective evidence of infection. Although low levels of brucella antibodies may be present in their serum, they lack the elevated titers of IgG antibodies seen in chronic or relapsing brucellosis. Symptoms in such patients resemble the "chronic fatigue syndrome" and most likely represent a preexisting psychoneurosis.

Veterinarians using *B. abortus* strain 19 vaccine for immunizing cattle are at risk of accidental self-inoculation by needle stick or conjunctival splash. Although the vaccine has attenuated virulence for animals, it is capable of producing brucellosis in man. Inoculation of strain 19 into individuals with preexisting brucella antibodies generally causes localized inflammation at the injection site and transient fever and chills. This response is self-limited, lasting 24-48 hours, and is thought to represent hypersensitivity to brucella antigens. In contrast, individuals without preexisting antibodies are at risk of developing brucellosis if the inoculum of vaccine is sufficient.

Gastrointestinal tract. Brucellosis, like typhoid fever, is an enteric fever in which systemic symptoms generally predominate over complaints localized to the gastrointestinal tract. Nevertheless, when sought, alimentary tract complaints are elicited in up to 70 % of patients. These include anorexia, abdominal pain, vomiting, diarrhea, or constipation. Hyperemia of the intestinal mucosa with inflammation of Peyer's patches has been reported. Inflammation of the ileum has been documented radiographically and histologically in patients presenting with colitis caused by *B. melitensis*.

Because it is the largest organ of the RES, the liver is probably always involved in brucellosis; however, liver function tests are usually only slightly elevated. The spectrum of pathologic findings in brucella hepatitis is varied. Infection with *B. abortus* is characterized by granulomatous hepatitis

indistinguishable from sarcoidosis. The range of hepatic lesions caused by *B. melitensis* includes small aggregates of mononuclear cells within portal triads and larger aggregates extending into the parenchyma resembling viral hepatitis. Occasionally one finds collections of mononuclear cells including histiocytes forming loose granulomas. *Brucella suis* can cause suppurative abscesses involving the liver and spleen. Hepatic lesions resolve with anti-microbial therapy and, in the absence of other toxins, cirrhosis does not occur. Brucellosis is also a rare cause of cholecystitis, pancreatitis, and spontaneous bacterial peritonitis.

Skeletal. Osteoarticular manifestations of brucellosis are reported in 20-60 % of patients. The spectrum of bone and joint lesions includes arthritis, spondylitis, osteomyelitis, tenosynovitis, and bursitis. Sacroiliitis is the most commonly reported complication. Peripheral joints most often involved are hips, knees, and ankles. *Brucella* are a rare cause of sterno-clavicular arthritis. Spondylitis is more common in elderly patients, and may result in paraspinal abscesses.

Radiographic abnormalities are late findings, whereas bone scans may detect inflammation early in the disease. Bone scan may be useful to differentiate hip from sacroiliac involvement. In cases of spondylitis, the earliest radiographic findings are straightening of the spine and disk space narrowing, followed by epiphysitis as the main sign of bone destruction. Computed tomography may reveal early signs of joint destruction and is especially useful to detect paraspinal abscess formation.

Analysis of synovial fluid from peripheral joint effusions reveals a predominance of mononuclear cells, and brucellae are isolated in about 50 % of cases. A reactive spondyloarthropathy has been described in some patients with brucellosis that is believed to be caused by circulating immune complexes; however, no association with a specific human leukocyte antigen (HLA) phenotype has been found.

Neurologic. Neurologic manifestations of brucellosis include meningitis, encephalitis, meningovascular complications, parenchymatous dysfunctions, peripheral neuropathy/radiculopathy, and psychosis. Rare cases of intracerebral and epidural abscesses have also been reported. Central nervous system involvement occurs in less than 5 % of patients and usually presents as acute or chronic meningitis. Meningitis can be the presenting manifestation or it can occur late in the course of brucellosis. There is little to distinguish it from other causes of meningitis except that nuchal rigidity occurs in less than one-half of cases. Cerebrospinal fluid (CSF) analysis reveals a lymphocytic pleocytosis, elevated protein content, and low to normal glucose level. Cultures of CSF are positive in less than one-half of cases, but the diagnosis is made by finding specific antibodies in the CSF.

Cardiovascular. Endocarditis occurs in less than 2 % of cases, but it accounts for the majority of brucellosis-related deaths. Before effective antimicrobial therapy, and surgery to replace infected heart valves, brucella endocarditis was nearly always fatal. The aortic valve is involved more often than the mitral valve, and aneurysms of the Valsalva sinus are especially common. Mycotic aneurysms of

the ventricles, brain, aorta, and other arteries have been reported. Rapid techniques to recover brucellae from blood, combined with echocardiography, have improved our ability to make a diagnosis. Although some cases have been treated successfully with antibiotics alone, combined medical and surgical treatment is usually required. Other cardiovascular complications include myocarditis and pericarditis.

Pulmonary. Respiratory symptoms are reported in up to 25 % of patients with brucellosis, after inhalation of contaminated aerosols or via bacteremic spread to the lungs. Respiratory involvement in brucellosis ranges from flulike symptoms with a normal radiograph, to bronchitis, bronchopneumonia, solitary or multiple nodules, lung abscesses, miliary lesions, hilar lymphadenopathy, and pleural effusions. Rarely are brucelle identified in stains or cultures of expectorated sputum.

Genitourinary. Although brucellae can be recovered from the urine of patients with brucellosis, genitourinary complications are rare. In men, unilateral epididymo-orchitis is the usual manifestation. Interstitial nephritis, exudative glomerulonephritis, and IgA nephropathy have also been reported. Pyelonephritis and abscess are rare complications and may resemble renal tuberculosis.

The principal manifestation of brucellosis in animals is abortion, and the presence of erythritol in placental tissues of susceptible animals is believed to play a role in the localizatiol of brucellae in the genital tract. Although brucellosis can cause abortion in women, there is little evidence that the incident higher than with other bacteremic infections.

Hematologic. The hematologic manifestations of brucellosis are variable, including anemia, leukopenia, or thrombocytopenia. Pancytopenia is rare, but may be associated with evidence of bone marrow erythrophagocytosis.

Cutaneous. Cutaneous manifestations of brucellosis have been reporte about 5 % of cases. Many transient, nonspecific lesions are described, including erythema nodosum, papules, rashes and ulcers. Petechiae, purpura, and cutaneous vasculitis have also been reported.

Diagnosis

Because the symptoms of brucellosis are nonspecific, it is imperative that the clinician obtain a detailed history, including occupation, exposure to animals, travel to enzootic areas, and ingestion of high-risk foods (unpasteurized dairy products). Somatic complaints (weakness, fatigue, malaise, anorexia, body aches, mental inattention, and depression) predominate over objective physical findings (fever, malodorous sweats, lymphadenopathy, and hepatosplenomegaly).

Routine laboratory tests, such as the white blood cell (WBC) count may not suggest an infectious process. The WBC count is usually normal or depressed, rarely exceeding 10,000 cells/mm^3. Anemia, leukopenia, and thrombocytopenia are common. The erythrocyte sedimentation rate (ESR) is variable and of little diagnostic value. The diagnosis of brucellosis is made with certainty when brucellae are recovered from blood, bone marrow, or other tissues. The rate of isolation

from blood varies from 15 to 70 % depending on the methods and the duration of incubation. Because brucellae are facultative intracellular pathogens, cultures of bone marrow may have a higher yield than blood. The Castaneda biphasic technique is said to improve the yield while avoiding the need for I subcultures. Most clinical laboratories now employ rapid isolation methods (Bactec, DuPont Isolator, etc.), which are satisfactory for isolating brucellae from blood when they are maintained for a sufficient time (=30 days). The isolation time for *Brucellae* may be reduced by lysis-concentration techniques and other systems capable of detecting low concentrations of bacteria. Although preliminary studies with the polymerase chain reaction (PCR) using rRNA sequences show promise, further studies are needed to determine its role as a rapid diagnostic test for brucellosis. Once a microorganism is isolated, many clinical laboratories employ rapid identification systems based on the pattern of biochemical reactions. Biochemical profiles for *Brucella* are not included in all corn-Rial computerized data bases and brucellae have been identified as *Moraxella*.

In the absence of bacteriologic confirmation, serologic tests are used to make a presumptive diagnosis. Although a number of techniques have been developed to measure *Brucella* antibodies, the serum agglutination test (SAT) is the simplest and most widely used. The SAT measures the total quantity of agglutinating antibodies. Treatment of the serum with agents that reduce disulfide bonds (2-mercaptoethanol or dithiothreitol) permits the differentiation of immunoglobulin classes, since they destroy the agglutinability of IgM but do not alter IgG. No single titer of *Brucella* antibodies is always "diagnostic"; however, most cases of active infection will have titers 1:160 or greater, with IgG antibodies being present. A decline in IgG antibodies over time is prognostic of a good response to therapy, whereas a second rise in Ig G presages bacteriologic relapse. The antigen used in the SAT is prepared from *B. abortus* 1119, which reacts with other smooth brucellae (*B. melitensis* and *B. suis*). Since *B. canis* is a rough species lacking smooth O-polysaccharide, it is necessary to use antigen prepared from *B. canis or B. ovis* for serodiagnosis of canine brucellosis.

The use of standardized reagents and procedures in the performance and interpretation of *Brucella* serologic tests cannot overemphasized. Although enzyme-linked immunosorbent assay (ELISA) is reportedly more sensitive than the SAT, the lack of a standardized antigen makes it difficult to compare results from different laboratories. Reliable *Brucella* antigens for the SAT are commercially available; however, the antigen used in the "febrile agglutinins" screening test is insensitive unreliable for diagnosing brucellosis. False-negative reactions can occur if serum is not diluted beyond 1:320 owing to a prozone, and false positive reactions can occur with serum containing antibodies to the organisms of cholera, tularemia, and yersiniosis. In very rare instances, false-negative reactions result from the presence of serum-blocking substances. When so-called "blocking antibodies" are suspected, they can be detected using other serologic techniques, such as the Coombs test or a blocking antibody assay.

Differential diagnosis

Polyorganic lesions and multiple clinical manifestations complicate diagnostics of brucellosis, especially on early stages (acute brucellosis). Acute beginning, triad of clinical signs (chill, fever, sweat), hepatosplenomegaly require differentiation with malaria, the same manifestations can be caused by sepsis. Continuous fever, hepatosplenomegaly, bradycardia, leucopenia also are characteristic signs of abdominal typhus. Diferential diagnosis with generalized form of tularemia, Q-fever, infectious mononucleosis, rheumatism, lymphogranulematosis also should be considered. Anyway, the final confirmation of diagnosis is possible only after obtaining of results of laboratory methods of diagnostics.

Treatment

Treatment is carried out according to clinical period and gravity of disease course. At acute brucellosis, relapses of subacute and chronic forms the antibiotics are used, mainly: tetracyclin, aminoglygoside, tienamicines, levomycetin, rifampicin, which often are administered in combination for better effect. For example: streptomycin, gentamicin or kanamycin are used in combination with tetracyclin, doxycycline or rifampicin. The course of the combined antibiotic therapy lasts for 10 – 20 days and more. Then during 10 days inject levomycetin 0.5-1 (IM) or (IV) twice per day, levomycetin 0.5 4 times per day or tienam 0.5-0.75 every 12 hours in a muscle. One of schemes of treatment provides using of medicines of prolonged action – doxycycline 0.2 per day or 0.1 every 12 hours (PO) during 20 days, and then 0.1 daily during 10 days.

Antibiotics must be injected during all feverish period and during 10 – 12 days after normalization of body temperature. They act selectively only on the brucellas, freely circulating in blood and lymph. Taking into account, that brucellas are localized intracellularly, and also in connection with probability of relapses, through 7-10 days antibiotic therapy will be repeated by preparation which was not prescribed yet, during 10-12 days.

Preparation of a choice may be bactrim (trimetoprim sulfamethaxazol) which component "trimethoprim" influences on intracellularly posed brucellas. One of the approved circuits provides indication of bactrim (2 tablets per day during 20 days then carry out 10-day course of treatment by tetracyclinum). The best results are received at a combination of biseptole with rifampicin.

Antibacterial therapy is expedient for combining with an antibrucella immunoglobulin in ampoules on 1.5 mL by two or three courses with an interval of 20 days. Each course consists of 3 (IM) injections of immunoglobulin 2-4-6 ml, 2-3 days.

The basic method of treatment of chronic brucellosis, which manifests with focal disorders, is the vaccinotherapy. It consists of the medical polyvalent brucellous inactivated vaccine. Two courses of accine intravenous injection are most effective. Instead of a medical vaccine it is possible to use a brucellin.

Among nonspecific medicines prescibe butadion, acetylsalicylic acid, ibufrofen, indomethacin, mefenemic acid.

In an exudative-proliferative stage of inflammation indicate rheopyrinum, in proliferative-sclerotic ortophen (voltaren). Glucocorticoids are indicated at disorders of central and perepheric nervous system, at myocarditis, orchitis and at other expressed focal changes. Prednisolone is indicated in dose 20-30 mg per day during 2-3 weeks. Among antihistaminics use dimedrole, suprastin, tavegil etc. In complex treatment prescribe an acid ascorbic, vitamin preparations of group B, rutin.

At calming infectious process, chronic and residual brucellosis – methyluracil, natry nucleinic, prodigiosan, polybiolin, polyoxydony immuno-and biostimulators timogen or T- activin are indicated. For a resorption of proliferation of a connecting tissue and acceleration of neogenesis use lydasa, ronidas, gumisole, rumalone, an extract of aloe. A pharmacotherapy is widely combined with physiotherapeutic methods.

Prophylaxis

Prevention of brucellosis in men depends on the control or eradication of the disease in domestic animals. In addition, calfhood immunization using *B. abortus* strain 19 vaccine and routine pasteurization of milk have resulted in a dramatic decline in the incidence of human brucellosis. The use *of B. melitensis* strain Rev-1 vaccine in countries where caprine brucellosis is enzootic has resulted in a decrease in human brucellosis due to this species. Although no effective vaccine exists for *B. suis,* improved swine husbandry practices have lowered the incidence of porcine brucellosis. In the past, live-attenuated brucella vaccines were used for human immunization in some countries; however, they were restricted to high-risk personnel in areas of high endemicity. No vaccine is coursely available for human use. Laboratory-acquired brucellosis can be prevented by adherence to biosafety level 3 precautions.

Control questions:

1. Etiology of brucellosis.
2. Epidemiology of brucellosis.
3. Pathogenesis of brucellosis.
4. Anatomic pathology of disease.
5. Main clinical symptoms and signs of brucellosis.
6. Laboratory methods of brucellosis diagnostics.
7. Criteria of brucellosis diagnosis.
8. Differential diagnosis of brucellosis.
9. Treatment of brucellosis.
10. Prevention of brucellosis.

SHIGELLOSIS

Shigellosis is general infectious disease of human, caused by bacterium of genus *Shigella*.

Shigellosis is characterized by principal damage of mucous membrane of distal section of the large intestine. The disease is accompanied by symptoms of general intoxication, abdominal spastic pain, frequent watery stool with admixture of mucus and blood, and tenesmus.

Historic reference

The term "*dysenteria*" was used by Hippocrates to indicate a condition characterized by frequent passage of stool containing blood and mucus accompanied by straining and painful defecation.

In 1898 Shiga conclusively demonstrated that a bacterium was present in the stools of many patients with shigellosis and that agglutinins could be demonstrated in the serum of the infected patient. Two years later, Flexner found a similar but serological different organism in stool of other patients with shigellosis acquired in Philippines.

Etiology

The agents of shigellosis are regarded to genus *Shigella*, family *Enterobacteriacea*. There are approximately 50 serotypes of *Shigella*.

According to modern international classification genus of *Shigella* is divided into four groups: group A (*S. dysentery*), group B (*S. flexneri*), group C (*S. bojdii*), group D (*S. sonnei*). Each group is divided into serologic types and subtypes.

All *Shigellas* are similar morphologically. They are small gram-negative rods, nonmotile and nonencapsulated. Shigellas are facultative anaerobias. They grow well on the simple nutritive mediums. Shigella contain thermostable somatic O-antigen, including group and standard antigens.

Depending on character of toxinoformation *Shigella* are divided into two groups. Shigella Grigoriev-Shiga's belongs to the first group. They produce strong exotoxin, having protein's origin, and also endotoxin. All other types of *Shigella* (Flexneri, Sonnei) are treated to the second group, they produce only endotoxin. Endotoxin consists of proteins and lipopolysaccharide. Protein part of endotoxin and exotoxin have expressive neurotropic action. Endotoxins has enterotropic action.

Epidemiology

The sources of infection are ill patients, persons in period of reconvalescence and bacteriocarries. The patients with acute shigellosis are especially dangerous.

The patients with acute shigellosis discharge the agent during all period of the disease, especially during period of expressive colitic syndrome. The persons with obliterated, light forms of the disease are dangerous too. These persons don't address for medical help and don't receive treatment. Because, these "atypical" cases of acute shigellosis have predominant epidemiological meaning. The patients with chronic shigellosis are dangerous for other persons, especially in the period of aggravation.

The mechanism and factors of the transmission of the infection. The mechanism of the transmission of the infection is fecal-oral. The transmission of the infection is realized through contaminated food-stuffs and water. Infection of food-stuffs, water, different objects happens due to direct contamination by infected excrements, through dirty hands and also with participation of flies. The factors of transmission have leading meaning in epidemiology of shigellosis. Depending on factors of transmission there are the next ways of contamination - contact, alimentary and water. Now, the alimentary way has more important meaning. Contamination over food-staffs may be through contaminated vegetables and berries with insufficient processing before use. Food-stuffs, prepared for use have the most important meaning in transmission of the infection (milk, milk products, especially, sour cream, meat stuffing and other meat products, bread, soft drinks, fruits, vegetables).

The susceptibility of human is high. It doesn't depend on sex or age. Shigellosis occurs as in infants as in seniors. However, the morbidity of adult population is lower than children of early age.

Shigellosis is characterized by seasonal spread as the other intestinal infections. It is registered more frequently in summer and autumn.

Pathogenesis

Pathogenesis of shigellosis is complicated. It is studied insufficiently. In some cases the agents perish in the upper section of the gastrointestinal tract under the influence of acidic conditions. In other cases *Shigella* may pass through intestine, and it is excreted into environment without reply of the macroorganism.

Diverse theories of pathogenesis of shigellosis were pulled out in different years. The next theories are known:

1. Bacteriemic theory. Reproduction of the agent in the blood is the basis of pathogenesis of shigellosis according to this theory.

2. Toxico-infections Shiga's-Brauer's theory. Many positions of this theory don't lose one's own meaning in modern ideas about pathogenesis of shigellosis.

3. Allergic theory. According to this theory, shigellosis is general allergic infection disease.

4. Nervous-reflexious theory. According to this theory the damage of nervous system has leading meaning in pathogenesis of shigellosis.

5. Theory of intracellular parasitism. According this theory, all features of the shigellosis course are connected with parasitism of *Shigella* in the epithelium of mucous membrane of distal section of the large intestine.

In was established by investigations of the last years that secondary immune insufficiency plays considerable role in pathogenesis of shigellosis. At present time it is known that development and course of the different forms of shigellosis is connected with some factors. There are functional state of the organism; interaction of the human's organism, agent and environment; biological properties of the agent (toxigenecity, invasiveness, fermentic activity and other).

Bacteremia of short duration may be observed in decreased resistance, in entering of the large doses of the agent. However, bacteremia hasn't essential meaning in pathogenesis of shigellosis. Bacteremia is marked only in one third of the patients with Grigoriev's-Shiga's shigellosis.

Toxins, which are absorbed from the intestine, play an important role in pathogenesis of shigellosis. At first, toxins influence directly on the mucous membrane of the intestine and substances, disposing under mucous membrane (nervous endings, vessels, receptors). Second, toxins are absorbed and influence to different sections of central nervous system. Involvement of small intestine in pathological process from the first days of the disease is explained by toxinemia (violation of its motile, absorbing and digestive functions). The evidence of toxinemia is delivery of endotoxin into patient's blood serum from the first days of the disease and its delivery into urine.

Exotoxin of Shigella Grigoriev's-Shiga's and protein part of endotoxin possesses significant neurotoxic action. Neurotoxins influence on the central nervous system and peripheral gangiums of vegetative nervous system. It is manifested by severe intoxicative syndrome and violation of all types of the balance of substances.

Lipopolysaccharide part of endotoxin damages principally mucous membrane of distal section of large intestine, and in a less degree, other sections of gastrointestinal tract. It possesses cytotoxic action and causes activation of adenylcyclase.

Activation of adenylatecyclase leads to accumulation of cyclic 3,5-adenosine-monophosphates, increased secretion of electrolytes and water. The violation of water – electrolytes balance is observed in gastrointeritic variants of acute shigellosis course. It is necessary to allow for degree of dehydration of the organism. Dehydration of II-III degree develops in severe course of gastroenterocolitic and gastroenteritic variant of acute shigellosis. In severe (hypertoxic) form it may be development of hypovolemic shock and acute renal insufficiency.

Shigella toxins cause sensibilization of the mucous membrane of the intestine, render damaging action on it with development of inflammatory changes and erosions formation and ulcers in severe course of the disease.

Toxin stimulates discharge of biological active substances (histamine, serotonine, kinines, prostaglandines) into blood, causes violation of microcirculation of the blood in the intestine's wall, increases intensity of inflammatory process and disorders of functions of the intestine (motorics, absorbtion, secretion).

The violation of innervation of the intestine, microcirculation, electrolytic balance and inflammatory changes of mucous membrane are manifested clinically

by sharp spastic pains in the stomach. Spasms of separate sections of the intestine lead to excretion of scanty stool ("fractional stool"). Spastic shortening of the muscles of sigmoid and rectum cause fecal urgency and tenesmus.

Allergic factor plays definite role in pathogenesis of shigellosis. Pathological process develops in large intestine after preliminary sensibility. However, it was shown experimentally, that shigellosis is not typical allergic disease.

However, intracellular parasitism was not confirmed due to biopsy of mucous membrane of the intestine in the patients with shigellosis. It is not expected, that phenomenon of intracellular parasitism plays certain role in shigellosis too.

In shigellosis, the invasion of *Shigellas* into epithelial cells is observed in large intestine, principally in rectum. It is caused by comparatively prolonged accumulation of intestinal content, toxins and bacteriums in the large intestine. They create favorable conditions for invasion of the agent into epitheliocytes. It is promoted by intestinal dysbacteriosis too. Intestinal dysbacteriosis develops inrarely under influence of antibioticotherapy. This therapy causes destruction of considerable part of symbiotic flora.

The disease may have prolonged or chronic course due to addition of supplementary factors of chronic process. The cases of formation of chronic shigellosis develops due to unfavorable premorbid state, delay of macroorganism functions replacement, decreased activity of immune system.

The recovery of the patients is prolonged in presence of damages at any portions of gastrointestinal tract (defects of masticatory apparatus, anomalies of intestinal tube, gastritis, ulcerous disease, appendicitis, pancreatitis, hepatitis, cholecystitis); presence of supplementary diseases (tuberculosis, brucellosis, malaria, helminthiases); state of endocrine system, dysbalance of vitamins. The factors, promoting to prolonged and chronic course of the disease, are late hospitalization of the patients, incorrect treatment, violation of alimentary regime after discharge of the patients from the hospital.

Immunity. In shigellosis postinfectious specific immunity is shaped and typed-specific.The investigations of humoral immunity revealed dependence of the level of blood serum immunoglobulins of the patients with shigellosis from gravity of the disease, kind of the agent, and also, from treatment. Antibodies play essential role in execution of functions of phagocytes. However, presence of antibodies can not be used for rendering of diagnosis and for estimate of complete sanation of the organism from the pathogen. In shigellosis humoral factors of immunity preserve the meaning only during one year.

Immunological examination reveales depression of the tests T-system of immunity with different course of acute shigellosis, which is more expressive in the patients with severe, moderate and lingering course of the disease.

Decrease of the tests T-system of immunity is appearance of short duration. It was mentioned a considerable decrease of functional activity and quantity of T-lymphocytes in the patients with lingering course of shigellosis and in chronic form of the disease.

Investigations of subpopulations of T- and B-lymphocytes were an important stage for deciphering of violation of immune system in shigellosis. These data allow to establish the most important links of pathogenetic process. Corrections of these links may be the most perspective.

Detailed analysis of subpopulations of immune system had proved the presence of secondary immune deficiency in shigellosis. So, decrease of T-supressors is observed in case of moderate and severe course of acute shigellosis. In chronic form of the disease the activity of T-supressors increases, but the level of T-helpers decreases.

However, the factors of cell immunity must be estimated according to humoral and especially, local immunity. It is possible, that absence of the local immune reaction is a risk factor of lingering, chronic forms of the disease development and also for postdysenteric colites.

The local immune response of lymphoid tissue of intestine is promoted by antibodies − forming cells of mucous membrane-produced antibodies of classes IgA, IgG, IgM. The class of IgA has the leading role in the protection of the organism.

Thus, the secondary immune deficiency in patients with different forms of shigellosis is connected in general with violation of regulative and effectoric links of immune system. The causes of secondary immune deficiency development is inhibitory influence of antigenic-toxic complexes of the agent at immune system in infectious diseases.

It is known, that endotoxinemia is one of the mechanisms of pathogenesis of shigellosis. Toxins of the agent render depressive influence on hemopoesis, phagocytosis and cause the disorder of microcirculation. Correlation is marked between degree of intoxication, level of depression of cell immunity and natural resistance of the organism.

The study of different cells populations, their metabolic activity allow to determine their role in different forms of shigellosis. These investigations give a possibility of application of basic regulation of cell's functions with use immunocorrecting therapy for preventation of the formation of lingering, chronic forms of the disease and postdysenteric colites.

Anatomic pathology

In shigellosis pathomorphologic changes are revealed, generally, in distal portion of the large intestine (sigmoid, rectum). There are 4 stages of inflammatory changes:

1. Acute catarrhic inflammation.
2. Fibrinous necrotic.
3. Ulcerous and folliclic-ulcerous.
4. Stage of formation of scars.

At present time fibrinous-necrotic and ulcerous damages occur rarely. Catarrhic inflammatory process is observed more frequently. It is confirmed by data of pathologoanatomic investigations due to biopsy of rectum. Catarrhic inflammation is characterized by edema, hyperemia of mucous membrane and

submucous layer of rectum. Small hemorrhages and erosions are observed in the mucous membrane in the part of the patients. In rectoscopy mucous or mucous-hemorrhagic exudation is revealed on the surface of mucous membrane and in the intestine.

In microscopical investigation disorders of vessels are marked: increased permeability, local hemorrhages. Edema of strome and basal membrane leads to dystrophic changes of epithelium, in severe cases – to formation of ulcers and erosions. Hyperproduction of mucus is typical.

Fibrinous-necrotic changes are manifested by dirty, gray and dense coats on mucous of the intestine. The membranes consist of necrotic tissue, leukocytes and fibrin. Necrosis may achieve submucous and muscleous and fated submucous layer. Purulent damages and necrosis lead to formation of ulcers. In shigellosis ulcers are superficial with dense borders.

The regeneration of epithelium begins on the 2-3 day of the disease in acute phase of catarrhic inflammation. However, complete anatomical recovery may be on 4-5 month after discharge the patient from the hospital even in mild course of shigellosis. Regeneration comes slowly in the destructive changes in the intestine, and disorders of vessels are preserved for a long time. Regeneration is combined frequently with focuses of inflammatory changes. In chronic shigellosis the morphological changes are characterized by multiple forms and flabby duration of inflammatory process.

Clinical manifestations

There are the next clinical variants of acute shigellosis:
1. Colitic variant.
2. Gastroenterocolitic variant.
3. Gastroenteric variant.

Depending on gravity of the course of the disease there are mild, moderate and severe course of shigellosis, and also carriers.

Colitic symptomocomplex is typical for shigellosis. Incubation period lasts from 2 till 5 days, rarely – 7 days.

Mild course. Onset of the disease is acute. The temperate pains appears in the lower part of the stomach, principally, in the left iliac area. These pains precede act of the defecation. Tenesmus are observed in some patients. Stool is from 3-5 till 10 times a day. It contains mucus, sometimes – blood. Temperature is normal or subfebrile. Catarrhic inflammation of mucous membrane is observed at rectorhomanoscopy, sometimes erosions and hemorrhages.

Moderate course. Onset of the disease is acute or with short prodromal period. It is characterized by weakness, malaise, discomfort in the stomach. Then, spasmatic pain appears in the lower part of the stomach, tenesmus. At first, stool has fecal character. Then, mucus and blood appear in stool. Stool loses fecal character and has appearance of "rectal spit" (excretion of scanty stool –

"fractional stool"), with mucus and blood. Stool is accompanied by fecal urgency and tenesmus. Stool is from 10-15 times a day.

In patients with medium serious course of acute shigellosis temperature increases up to 38-39 °C for 2-3 days. Subfebrile temperature is possible. The patients complain of weakness, headache. It may be collapse, dizziness. The skin is pale. Hypotonia, relative tachycardia are observed. Tenderness and condensation of sigmoid are revealed. In the peripheral blood leukocytosis and temperate neutrophylosis are observed. In coprocystoscopy erythrocytes (more then 30-40 in the field of vision) are revealed. In rectorhomanoscopy diffusive catarrhic inflammation, local changes (hemorrhages, erosions ulcers) are revealed. In patients with moderate course of acute shigellosis functional and morphological restoration may be prolonged − till 2-3 months.

Severe course. Onset of the disease is acute. Temperature is increased up to 39 °C and higher. The patients complain of headache, harsh weakness, nausea, something vomiting. Strong abdominal spasmodic pains, frequent stool with smaller volume "without account", with mucus and blood are marked.

There are hypotonia, harsh tachycardia, breathlessness, skin cyanosis. Harsh tenderness at the left iliac area, especially in the area of sigmoid are marked during palpation of the stomach. It is possible pasesis of intestine. There are expressive leukocytosis neutrophylosis with shift to the left. ESR is accelerated.

During microscopical examination of stool erythrocytes are marked through the field of the vision. In rectorhomanoscopy infusive catarrhic or fibrinous inflammation, presence of the local changes (erosions, ulcers) are marked. The functional and morphological restoration of intestine is longer than 3-4 months in patients after colitic variant of acute shigellosis.

Gastroenterocolitic variant of shigellosis. The principal feature of this variant of the acute shigellosis course is acute impetuous onset of the disease after short incubation period (6-8 hours). More frequent way of the transmission of the infection is alimentary. The factors of transmission are milk, milk products and other.

Intoxicative syndrome and symptoms of gastroenteritis are observed in the initial period. The manifestations of enterocolitis predominate in the period of climax.

There are mild, moderate and severe course of gastroenterocolitic variant of acute shigellosis. During estimate of the disease course gravity it is necessary to allow for not only degree of intoxication and damage of gastrointestinal tract, but also degree of dehydration, because repeated vomiting and plentiful diarrhea are observed. It may lead to dehydration of I-II-III degree.

Gastroenteritic variant of shigellosis. The principal feature of this variant of the acute shigellosis course is predominance of clinical symptoms of gastroenteritis and presence of certain degree dehydration symptoms. Nowedays, besides clinically distinct sings of the disease, lingering and obliterated course of shigellosis is observed. Obliterated course is characterized by insignificant clinical manifestations. The great ratio of the patients do not apply to physician. Careful

bacteriological examination of the patient with different gastrointestinal disorders of unknown etiology has large meaning for correct diagnostics. In these patients catarrhic inflammatory changes of mucous membrane of distal portion of rectum is revealed in the majority of cases during rectorhomanoscopy (Fig. 2).

Clinical recovery comes through 2-3 weeks in the majority of the patients with uncomplicated course of all variants of acute shigellosis. Complete functional and morphological restoration of gastrointestinal tract happens in 1-2 months and later. Relapses may arise in some part of the patients. The factors, promoting to relapses of the disease are the violation of diet, alcohol use, incorrect therapeutic tactics. The disease may have lingering course. Insufficient reactivity of the organism, sharp decrease of cell immunity in acute period of the disease promote to lingering course of shigellosis.

Lingering course of shigellosis. Shigellosis is estimated as lingering, if clinical manifestations of the disease are observed over 3-4 weeks. Declination to lingering course of the disease depends on gravity of the course of shigellosis in acute period. Colitic variant of severe course of acute shigellosis has prolonged course more frequently than moderate variant. The period of functional and morphological restoration of the intestine is over 3 months. In some patients lingering course is manifested only by persistent bacterioexcretion. Bacterioexcretion is combined with prolonged inflammatory process in rectum.

Bacterioexcretion. Dysfunction of intestine is absent at the period of examination and preceded 3 months in presence of bacterioexcretion (subclinical bacterioexcretion) or excretion of Shigella after clinical recovery (reconvalescent excretion) in this form of infectious process.

Diagnosis

The principal methods of diagnostics of shigellosis are bacteriological and serological methods of investigation.

Excretion of coproculture of *Shigella* is more reliable method of confirmation of diagnosis of shigellosis. It is necessary to take the material for bacteriological investigation before beginning of the treatment.

Diagnosis may be confirmed by serological methods. Reaction of indirect agglutination with standard erythrocytic diagnosticum is used more widely. Diagnostic titer is 1:200 with increase of titer in 7-10 days.

Differential diagnosis

Differential diagnosis is performed with the following diseases – salmonellosis, toxic food-borne infections, rotaviral gastroenteritis, amebiasis, balantidiasis, intestinal shistosomiasis, trichocephaliasis, enterobiasis, cancer of large intestine, appendicitis, ileus, hemorrhoids, diverticulitis, ischemic colitis, Crohn's disease, non-specific ulcer colitis, secondary colitis in patients with severe therapeutic pathology, radiation affections and poisonings with different chemical and biologic substances.

Treatment

The complex of treatment is indicated, which depends on features of disease. In the first days the diet № 4, and diet № 2 (till clinical convalescence) are indicated.

At mild course of shigellosis etiotropic agents are not applied, at disease of average degree of gravity use basically preparations of nitrofuranes: furazolidon, nifuroxasid 0.1 gm 4 times per day. Use derivatives of 8-oxyquinoline – enteroseptol, intestopan, among other groups of preparations – intetrix, nalidix acid, ftalazol. At ambulatory treatment of shigellosis with moderate stage of gravity sulfanilamid preparations of prolonged action are indicated – phthazin, sulfadimethoxin.

In case of severe shigellosis course use antibiotics - ampicillin or a polymyxin; when there is no effect – ciprofloxacin or ofloxacin in combination with gentamicin or cefazolin are prescribed. Duration of course of etiotropic treatment at moderate course of shigellosis is 2 - 3 days, at severe case it lasts not longer than 4 - 5 days.

A solution of regidron, in severe cases quartasault, lactosault are applying per os with the purpose of desintoxication and rehydratation. For the adsorption of bacterial toxins and metabolites from the intestine lumen and for their subsequent removing from the organism enterodes, coal microspherical sorbents, sillard P, smecta are used. Rectal pollination with sillard P in a dose 6 gm (1 - 3 procedures) is effective. There are proved methyluracil, pentoxyl, thymalin as natural factors of nonspecific protection of the organism and stimulators of regeneration. Calcy gluconate, dimedrol, suprastin, tavegil are indicated as pathogenetic treatment.

According to parameters of coprocytogram use mono or polycomponental fermental preparations. At presence of plenty of fat drops in feces pancreatin, pancitrat, pancurmen, and at detection of a cellulose, amyl, muscular fibers - pansinorm, festal, mezym-forte, abomin, vobensim are applied.

There are indicated widely vitamins preparations, these are ascorbic acid, nicotinic acid, thiamin chlorid, riboflavin, pyridoxine hydrochloride, calcy pangamat, folic acid, rutin. It is better to use per os the balanced vitamin complexes - dekamevit, glutamevit.

Collibacterin, bifidumbacterin, bificol, lactobacterin, bactisubtil, linex, hilac forte, α- bacterin, enterole-250 are indicated for elimination of intestinal dysbacteriosis and restoration of the normal biocenosis. Course of treatment is 2 weeks and longer.

Collectings of herbs and fruits of a bilberry, mint peppery, knot-herb ordinary, camomiles medicinal, herbs of a yarrow, centaury are helpful ordinary. Collecting with the shepherd's bag ordinary, grasses of St.-Johns wort are effective at hemocolitis. Fermentative and putrefactive processes reduces at lingering colitis, that is why collecting of grass of a sage-brush, a horsetail field, grasses of a yarrow ordinary, roots of snakeweed are applied.

Broths and juices of herbs, oil of dog rose for microclysters after a cleansing enema, 0.5 % solution of a colloid silver as medical clysters, insufflations of oxygen are used locally for stimulation of reparative processes in the mucosa of colon.

Prophylaxis

Prophylaxis of shigellosis includes complex of measures, directed to revelate the source of the infection, interrupt the ways of the transmission, increase of the organism resistance. Keeping the rules of personal hygiene and rules of food's cooking plays the principal role in prophylaxis of the disease. Sanitary education of population has an important meaning in shigellosis prophylaxis too.

Control questions:

1. Etiology of shigellosis.
2. Epidemiology of shigellosis.
3. Pathogenesis of shigellosis.
4. Anatomic pathology of disease.
5. Main clinical symptoms and signs of shigellosis.
6. Variants of shigellosis infection.
7. Laboratory methods of shigellosis diagnosis.
8. Criteria of shigellosis diagnosis.
9. Differential diagnostics of shigellosis.
10. Treatment of shigellosis.
11. Prophylaxis of shigellosis.

SALMONELLOSIS

Sallmonellae are widely dispersed in nature, being found in the gastrointestinal tracts of domesticated and wild mammals, reptiles, birds, and insects.

May present clinically as a gastroenteritis, enteric fever, a bacteremic syndrome, or focal disease. An asymptomatic carrier state may also occur.

Historic reference

The term "*salmonellosis*" unites a large group of diseases, caused by multiply serotypes of bacteria from genus *Salmonellae* (more than 2,000).

Sallmonellae are named for the pathologist Salmon who first isolated *S. choleraesuis* from porcine intestine. The antigenic classification or serotyping of *Salmonella* used today is the result of study of antibody interactions with bacterial surface antigens by Kauffman and White in the 1920s to 1940s. Ames and coworkers in 1973 reported the development of the test that uses *S. typhimurium* auxotrophic mutants to test the mutagenic activity of chemical compounds.

Salmonellosis is disease of animals and humans. It is characterized by essential damage of gastrointestinal tract, and more rarely by typhus-like or septicopyemic duration.

Etiology

Salmonella are non-spore-forming gram negative rods of the family *Enterobacteriaceae*. *Salmonella* are motile by peritrichous flagella. Salmonella strains demonstrate sufficient differences in biochemical reactions, antigenic structure, host adaptations, and geographical distribution to be grouped into 10 distinct subgroups, which have been variously designated in proposed taxonomic schemes. Virtually all strains isolated in clinical laboratories and implicated in disease in humans (more than 700 serotypes).

Like other enterobacteria, salmonella has somatic O-antigens, which are lipopolysaccharide components of the cell wall, and flagella H-antigens, which are proteins. There may be detached some serological groups on the basic of the differences in structure of O-antigens. *Salmonella* preserve viability in external environment for a long time: in water — 11-120 days, in the sea water — 15-27 days, in soil — 1-9 months, in sausage products — 60-130 days, in the eggs, vegetables and fruits till 2,5 months. The optimal temperature for reproduction is 35-37 °C. There are serological groups A, B, C, D, E and other.

Salmonella can be differentiated from other *Enterobacteriaceae* on the basis of certain biochemical reactions, including fermentation reactions with specific sugars.

Salmonella organisms grow readily on simple media in aerobic or anaerobic conditions. Cultures of specimens that are normally sterile, such as blood, joint

fluid, or cerebrospinal fluid, can be done on ordinary media such as blood agar. Excretions or secretions, such as feces or sputum, which have high concentrations of other microorganisms, are usually grown on selective or differential media, such as bismuth sulfate agar or desoxychlorate agar, which contains inhibitors of growth of non-pathogenic organisms of the normal flora.

Epidemiology

Animals suffering from primary or secondary salmonellosis, water swimming birds and also human-sick or carries are the main sources of infection in salmonellosis. Mechanism of transmission of infection is fecal-oral. The factors of the transmission of the infection are food-stuffs of animal origin and other products which are polluted by excretions of animals and humans. The promotive factors are violation of the preservation and preparing of the food and also sanitary.

The diseases occur as separate sporadic cases and as outbreaks. Susceptibility of human depends from the premorbidal state of the macroorganism and from the quantity and variety (serotypes) of *Salmonella*.

Salmonella are primarily pathogens of lower animals. The reservoir of infection in animals constitutes the principal source of nontyphoidal *Salmonella* organisms that infect man, although infection may be transmitted from person to person, Salmonella have been isolated from almost all animals species, including poultry (chickens, turkeys and ducks), cows, pigs, pets (turtles, cats, dogs, mice, guinea pigs and hamsters), other birds (doves, pigeons, parrots, starlings, sparrows), sheep, seals, donkeys, lizards and snakes.

The most accurate information on sources of human salmonellosis is derived from studies of outbreaks. Poultry (chickens, turkeys, ducks) and poultry products (primarily eggs) are the most important sources of human infection and are estimated to be responsible for about one-half of the common − vehicle epidemic. Salmonella in feces of infected hens may contaminate the surface of egg shells or penetrate into the interior of the egg through hairline cracks. In hens with ovarian infection, organism may gain access to the yolk. Meat, especially beef and pork, are quite often implicated, accounting for about 13 % of the outbreaks, and dairy products, including raw and powdered milk account for about 4 % of the epidemics.

Cross-infection with spread by person to person is responsible for virtually all the outbreaks in neonatal nerseries and in pediatric wards and is important in many outbreaks among hospitalized adults.

The stage is set for cross-infection when *Salmonella* are introduced into the hospital by admission, or for example, a patient with acute enterocolitis or as asymptomatic carrier with other medical problem or by the introduction of a contaminated common- course vehicle. Hospital personnel then may carry infection on hands or clothing from patient to patient; in some cases fomites (dust, delivery room, furniture), may be implicated in transmission. Hospital personnel who are excreting *Salmonella* in stools may also occasionally transmit infection to patient.

Pathogenesis

The development of disease after ingestion of *Salmonella* is influenced by the number and virulence of the organisms and by multiple host factors.

A large number of *Salmonella* must be swallowed in most instances to produce disease in healthy human being. However, in the event of infection with unusually virulent organisms or in patients with reduced resistance, symptomatic infection may result from extremely small inocula. Ingested organisms pass from the mouth to the stomach. In the stomach *Salmonella* are exposed to gastric acid and low pH, which reduce the number of viable organisms. Most *Salmonella* are perished rapidly at 2.0 pH, which is readily achieved in the normal stomach. Viable bacilli that survive then pass into the small intestine, where the organisms may be further reduced in number or eliminated entirely. The antimicrobial activity observed in the small bowel is related at least in part to the normal microbial flora of the intestine, which elaborate short-chain fatty acids and perhaps other substances capable of killing or inhibiting growth of *Salmonella*. Studies in animals have shown that the increased susceptibility to Salmonella infection produced by administration of antibiotics rapidly reverts to normal with reestablishment of the normal intestinal flora.

Salmonella that survive the antibacterial mechanisms in the stomach and upper small bowel may multiply in the small intestine. Multiplication of *Salmonella* in the intestinal tract may be asymptomatic, associated only with transient excretion of organism in stools, or symptomatic, associated with clinical manifestations of either enterocolitis (acute gastroenteritis) enteric fever or bacteremia.

Blood stream invasion, which occurs with variable frequency, may lead to localization of infection and suppuration at almost any site.

Local factors in the stomach and upper intestinal tract are important determinants of the disease. Factors that neutralize the low pH of the stomach or decrease the time the pathogen is exposed to stomach acid diminish local bactericidal action and increase the probability that an infections inoculums will reach the small intestine. The importance of gastric acidity as a defense mechanism is emphasized by the increased incidence of severe *Salmonella* enterocolitis in persons with achlorhydria, prior gastroectomy, gastroenterostomy, or vagotomy, conditions that reduce acidity or cause faster gastric emptying time.

The oral administration of buffering compounds also increases susceptibility to intestinal infection. It has been suggested that ingestion of organisms in food allows for longer exposure to gastric acid, thereby necessitating the presence of a relatively larger inoculums to produce disease, whereas water or other liquids, which have a fast gastric transit time, may be less heavily contaminated and still cause disease.

The small intestine provides other protective mechanisms through motility and normal flora. Alteration of the intestinal flora by antibiotics markedly reduces the size of the inoculums required to produce *Salmonella* infection in animals and humans and prolongs the convalescent carrier state. Prior antimicrobial

therapy also enhances the possibility of infection with antibiotic − resistant *Salmonella* strains.

Age is an important determinant of disease produced by *Salmonella*. *Salmonella* enterocolitis occurs with highest incidence in children less than 5 years old; newborns and infants less one year of age are especially susceptible. The influence of age on incidence may reflect immaturity of humoral and cellular immune mechanisms, diminished antibacterial action of the normal intestinal flora, a high frequently of fecal − oral contamination, or other factors. In some instances, increasing resistance with age is related to immunity consequent to previous exposure to the organism, even though disease has not been produced.

Patient with impaired cellular and humoral immune mechanisms are at increased risk for development of salmonellosis. Impairments of host defenses caused by malnutrition, malignancy, infection with human immunodeficiency virus or therapeutic measures such as corticosteroid or immunosuppressive therapy also predispose to infection and disease.

Salmonella causing enterocolitis are thought to produce diarrhea by a true infection with mucosal invasion and possibly by elaboration of an enterotoxin that acts on upper intestinal transport. *Salmonella* invasion of intestinal mucosa may lead to local production of inflammatory exudates of mediators that stimulate electrolyte secretion and smooth muscle contraction.

There are two types of toxins: exotoxins and endotoxins. Exotoxins are the toxic products of bacteria which are actively secreted into environment. Endotoxins are toxic substances which are liberated only during the lysis of microbial cells. The principal factor responsible for development of this disease is endotoxical complex of *Salmonella*, but we should remember that these bacteria produce even exotoxins. Exotoxins and endotoxins have toxical properties.

In salmonellosis the development of infectious process has next stages:
1. Colonization (setting) of pathogenic organism in the place of the inculcation.
2. Invasion and reproduction.
3. Death of the pathogenic bacteria and endotoxins liberation.

Infectious process may stop at the stage of colonization due to unknown reasons. Invasion may be limited by nearest tissues. In majority cases it leads to development of gastrointestinal forms of salmonellosis. For development of the first stage of pathogenesis of salmonellosis the factors violating structural and functional state of gastrointestinal tract play important role (dysbacteriosis, hypovitaminosis and other). These conditions may promote to development of the disease even due to small quantity of bacteria in food-stuffs.

In salmonellosis the principal pathologoanatomical changes develop in the place of inculcation of the agent in the small intestine. Data about changes of small intestine in gastrointestinal forms of salmonellosis may be received only as a result of its biopsy. But biopsy is not used in practice. Investigation of material during biopsy testifies dystrophical changes of epithelium, infiltration of epithelium of mucous membrane by macrophages. Increased quantity of interepithelial leukocytes, polymorphonuclear leukocytes and macrophages is marked.

Anatomic pathology

Principal changes develop in lamina propria of mucous membrane of small intestine in salmonellosis. These changes are accompanied by hyperemia, hemorrhages, edema and intensification of cell infiltration. At the same time the changes of the different parts of gastrointestinal tract develop. There is an acute inflammatory process, dystrophic changes of epithelium, edema, hyperemia and cell infiltration in stomach. There are dystrophy, erosions, hyperemia, edema in mucous of large intestine. Changes in all parts of gastrointestinal tract are transient. They are exposed to reverse development in clinical recovery of the patients.

In half of the patients with salmonellosis nonsharp violations of liver are marked. These changes are considered as compensatory mechanism.

In connection with sufficient efficiency of modern methods of treatment the fatal outcomes are rare. Dystrophic changes of parenchymatous organs were revealed in autopsy of deceaseds from gastrointestinal forms of salmonellosis. These changes were direct cause of death. Inrarely, edema of the lungs and brain, hyperplasia of spleen and mesenteric lymph nodes may develop.

Clinical manifestations

In connection with considerable variability of clinical duration of salmonellosis there are multitude classifications of this disease. The next classification is more comfortable for practice use:
1) Localized (gastrointestinal) forms of salmonellosis:
    a) Gastritic variant;
    b) Gastroenteritic variant;
    c) Gastroenterocolitic variant.
2) Generalized forms:
    a) Typhus-like form;
    b) Septic form (septicopyemia).
3) Carrier state:
    a) Acute carriers;
    b) Chronic carriers;
    c) Transitory carriers.

Clinical symptoms of salmonellosis are studied sufficiently completely. Gastrointestinal forms of salmonellosis are observed in most of cases of the disease. According data of different authors they occur from 79 to 85 %.

Incubation period is from 4-6 hours up to some days. Onset of the disease is an acute. Prodromal period is not typical or very short. Weakness, malaise, and slight chill characterize it. Then temperature increases to subfebrile in moderate and severe forms accordingly.

After ingestion of contaminated food or water, illness begins in many patients with nausea and vomiting; these symptoms usually resolve within a few hours. Myalgia and headache are common. The cardinal manifestation is diarrhea, which may vary from a few loose stools to fulminate diarrhea. In most cases, stools are loose, of moderate volume, and without blood, swamp-like (Fig. 3). In exceptional

cases, the stools may be watery and of great volume ("cholera-like"), or, in other instances, of small volume and associated with tenesmus and gross blood ("shigellosis-like"). Temperature elevations to 38-39 °C are common, as are chills; both appear in the majority of patients in whom definitive diagnosis is established. Abdominal cramps occur in about two-thirds of the patient and are often localized to the periumbilical region or lower abdominal quadrants. Bowel sounds are increased and abdominal tenderness is present. At microscopic examination, stool show a moderate number of polymorphonuclear leukocytes and, occasionally, red blood cells. Cross blood is unusual but may be seen in severe cases. Peripheral leukocyte count is usually normal, although neuthrophilia with a shift to younger forms may be present.

The duration of fever is less than 2 days in the majority of cases. Diarrhea usually persists less than 7 days, although, rarely, gastrointestinal symptoms may last for several weeks. Prolonged fever and diarrhea suggest a complication or a different diagnosis.

Localization of pain in the right lower quadrant of the abdomen in patients with enterocolitis may lead to a diagnosis of acute appendicitis. At surgery, such patients may have normal appendices or occasionally acute appendicitis rarely with perforation.

Clinic of salmonellosis is characterized by symptoms of damage of cardiovascular system. The basis of these violations is water-electrolytes loss and change of reological properties of the blood.

Changes in organs of respiratory systems are not typical for uncomplicated cases of gastrointestinal forms. But sometimes breathlessness may be observed.

Toxicosis takes place when localized forms of salmonellosis. It is manifested by headache, pain in the muscles, mild ataxia, asymetric reflexes. Development of toxic encephalitis is possible.

Electrolyte and water depletion may be severe during illness, leading to hypovolemic shock. The disease is more severe in children, in seniors, and in patient with achlorhydria, gastroectomy, gastroenterostomy, sickle cell anemia, or other conditions that impair resistance to infection. The frequency of transient bacteremia is less than 5 % in adults. It is increased in children and in persons with severe preceded diseases. Bacteremia has been shown to occur in 8-16 % of infants and children of 3 years age or younger who are hospitalized with *Salmonella* enterocolitis. *Salmonella* intestinal infections has tendency to be prolonged in children, who continue to excrete agent in stool for a longer time than adults after subsidence of clinical manifestation of infection.

Salmonella enterocolitis may develop in hospitalized patients. The illness may be a nosocomial infection or it may result of activation of pre-existing asymptomic intestinal infection by antimicrobial therapy, of surgical diseases of abdomen or from other causes.

In one-two third of children over 5 years and adults positive cultures are observed during second or third week from the onset of the disease. In this time majority of the patients have no symptoms of the disease.

Salmonella can produce an illness characterized by fever and sustained bacteremia without manifestations of enterocolitis. This syndrome may be caused by any *Salmonella* serotypes. The clinical syndrome of salmonella bacteremia is characterized by a hectic febrile course lasting for days or weeks. The organism is isolated from blood, but stool cultures are often negative. More than 70 % of cases of generalized forms of salmonellosis begin as gastrointestinal form with dyspeptic manifestations. Then, in typhus like variant after subsidence of dyspeptic manifestations the disease acquires signs of typhus infection. The second febrile wave-like or incorrect type continues in most cases during 10-14 days. The principal symptoms of the period of climax of the disease are weakness, adynamia, severe headache, sleeplessness, pains of muscles and joints.

Typical typhus state is not characteristic for this variant of salmonellosis. In majority of the patients enlarged liver and spleen, distantion of abdomen are observed.

Approximately, in 25 % of the patients scanty rose sports are observed. Rash appears on 4-10 day, sometimes later. In peripheral blood leukocytosis is observed only in early period of the disease. Then leukopenia is marked, but with neutrophilosis. Sometimes typhus like variant may be without appearances of gastroenteritis. The principal symptoms of beginning period in that cases are fever, chill, headache, weakness. In the period of climax adynamia, pale skin, injections of scleras are observed.

There are single rose spots on the skin of abdomen and chest. In this variant of generalized form of salmonellosis relapses may observed, and rarely, complications, which are typical for typhus fever. Typhus like variant may be with temperate manifestations of intoxication and dyspeptic appearances, with short duration fever. There is marked catarrh, hyperemia of pharynx, laryngotra-cheobronchitis in these patients rarely.

Septic variant (septicopyemia) is sepsis of *Salmonella* etiology. The development of sepsis is evoked by sharp decrease of the immuneprotective strengths of the organism of the patient. This variant of generalized of Salmonellosis is characterized by acyclic development of the disease, prolonged fever, chills, sweating, hepatosplenomegaly, sometimes development of jaundice, plural purulent metastases in different organs and tissues.

Usually, the disease begins from manifestations of gastroenteritis. Then typical septicopyemia develops with hectic fever. The signs of influence of intoxication on central nervous system are marked from the first days of the disease. They are manifested by irritation, violations of sleep, motive trouble, sometimes delirium. The skin is pale. Rash may appear on the skin (petechias or large hemorrhages).

The secondary purulent focuses may be in any organs and tissues. Localization of infection may be in thyroid, brain membranes, bones, heart, lungs, kidneys, adrenals, pancreas, spleen, liver, pericardium and soft tissues.

Complications

Meningitis is a rare complication of *Salmonella* infection and occur almost exclusively in infants, particularly neonates. Even epidemics of meningitis have

been reported during outbreaks of *Salmonella* infection in hospital nurseries. Clinical manifestations are the same as those of any bacterial meningitis in this age group. The clinical course is usually long and marked by relapse. Acute neurologic complications are common and include subdural empyema, cerebral abscesses, and ventriculitis. Acute or chronic hydrocephalus may occur. Mortality is high, despite appropriate antimicrobial therapy.

Pleuropulmonary disease. Pneumonia or empyema, the predominant types of serious respiratory diseases, occur usually in elderly patients or in patients with underlying diseases such as diabetes mellitus, malignancy, cardiovascular disease, or pulmonary disease. Mortality is high.

Arterial infection. *Salmonella* infection may be with localization in major vessels, including the thoracic and abdominal aortas, coronary arteries, peripheral arteries. Atherosclerotic intrarenal aortic aneurysms are by far the most common vascular sites of localization. The risk of endothelial infection is high in persons over the age of 50 years who have *Salmonella* bacteremia.

The mechanism of arterial infection is through to be direct implantation at a site of endothelial injury in the bacteremia patient on to extension from an adjacent inflammatory lesion, such as vertebral osteomyelitis. Mortality is high.

Osteomyelitis and arthritis. Osteomyelitis can develop in normal bone but especially likely to occur in patient with sickle – cell hemoglobinopathies, systemic lupus erythematosus, immunosuppressive therapy, bone surgery or trauma. *Salmonella*, not *Staphylococcus*, is the most common cause of osteomyelitis in patients with sickle-cell anemia.

Salmonella may cause a metastatic supportive arthritis. Pyogenic arthritis is much less frequent than reactive arthritis.

Splenic abscess and hepatic abscess. Splenic abscess is a rare complication of *Salmonella* infection. Localization occurs after bacteremia in posttraumatic subcapsular hematomas or splenic cysts. The clinical manifestation is one of left upper quadrant tenderness, fever and leukocytosis.

Salmonella liver abscesses may occur. Usually, the patients have pre- existing liver disease including amebic abscesses, ecchinococcal cysts, and hematomas. Association with biliary tract disease exists in occasional cases.

Urogenital tract. *Salmonella* in stools of carriers or persons with acute illness may gain access to the urinary tract to produce cystitis or pyelonephritis. Localization of *Salmonella* blood form with abscess formation in kidneys, testicles, or ovaries is also occasionally reported.

Bacteriocarrier of *Salmonella* is developed after disease. There are acute, chronic and transitory carriers. Acute and chronic carriers are divided depending on duration of excretion of *Salmonella*. Acute carrier has the duration of excretion of *Salmonella* from 15 days till 3 months after clinical recovery. The persons, excreting *Salmonella* over a year, are chronic carriers. The conditions of development of transitory carrier are insignificant dose of the agent and its avirulence.

Complications and outcomes of salmonellosis, as and multiple clinical forms are exposed to wide oscillations. Even gastrointestinal forms of salmonellosis with favorable duration are not finished clinical recovery.

Generalized form of salmonellosis, as rule, is accompanied by complications. Exceeding expression of symptoms of salmonellosis frequently leads to collapse (1.5-6 % of the cases). Collapse may develop at the first day of the disease on the altitude of clinical manifestations before dehydration. Endotoxinemia plays leading role in development of collapse. It is a manifestation of infectious-toxic shock.

Besides expressive hypodynamic disorders acute renal insufficiency, edema of brain, edema of lungs and hemorrhagic syndromes develop. The development of dysbacteriosis is connected with large doses of antibiotics use at any clinical forms of salmonellosis. Dysbacteriosis may be compensated or latent.

Outcomes of salmonellosis depend on premorbidal state, age, clinical forms, timely diagnostics and treatment.

Diagnosis

Diagnostics of salmonellosis is performed on the basis of epidemiological, clinical and laboratory data. Bacteriological and serological methods are used for confirmation of salmonellosis. The main materials for bacteriological investigation are vomiting masses, water after irrigation of stomach, stool, blood, urine.

Serological investigations are used. These are reaction of agglutination (RA) (7-8th day of the disease) and indirect hemagglutination (RIHA). RIHA is more sensitive. It gives positive results on the 5th day of the disease. Diagnostical titer is 1:200. Serological investigation should be done in dynamics of the disease.

Differential diagnosis

Differential diagnosis of salmonellosis is performed with other intestinal diseases – shigellosis, toxic food-borne infections, esherichiasis, cholera; with surgical diseases – appendicitis, pancreatitis, cholecyctitis, thrombosis of mesenterial vessels; gynecological pathology and with therapeutic pathology (myocardial infarction, chronic gastritis aggravation, enterocolitis, ulcerous disease), with acute gastroenteritis of viral origin (enteroviral, rotaviral etiology), poisoning by organic and inorganic poisons, poisoning by mushrooms.

Generalized form of salmonellosis is necessary to differentiate from sepsis of different etiology, pneumonia, malaria, acute pyelonephritis, tuberculosis.

Treatment

The volume of medical actions depends on the clinical form and a stage of gravity of disease. At gastrointestinal form immediately wash out stomach and intestine with boiled water (isotonic solution of sodii chloridum is the best) then give sorbents per os and give a warm drink. For restoration of hydro-electrolityc balance and normalization of circulatory disorders there should be indicated per os glucosole or rehydroni. Infusion therapy is indicated at expressed dehydration

— threesault, quartasault, lactasault. At severe stage of dehydratation one of the specified solutions is infused in vein with rate 80-120 mL/min, 5-10 L of solution is necessary on course of treatment. If hypotension and toxicosis are marked prednisolon and hidrocortizon, polyglucin, reopoliglycin are infused in vein. Pathogenetically 5 % solution of glucose is indicated with desintoxication purpose and restoration of power balance, a solution of sodium hydrocarbonat for acidosis correction, heparin for improvement of reologic properties of blood, preparations of antiallergic action — calcii chloridi, dimedrol, tavegil, indomethacin are prescribed in case of diarrhea (for inhibition of prostaglandines synthesis), calcium gluconate. Antibiotics at gastrointestinal form of salmonellosis are not used.

However at syndrome of hemocolitis and lingering diarrhea furazolidon is indicated in combination with fermental preparations — festal, panzynorm, pancreatin, mezym-forte, pancitrat, vobensim. The broths of herbs has anti-inflammatory, disinfectant and astringent properties, and also properties raising organism reactivity. They are vitamin preparations, pentoxyl, methyluracil, thymalin, enterol-250 also indicated. bificol, colibacterin, bifidumbacterin, linex is used at intestinal dysbacteriosis.

At generalized form simultaneously with pathogenetic therapy there are indicated antibiotics — levomycetin, ampicillin, monomycin, gentamycini sulfas, cefazolin (kefzol), cefotaxim (claforan). At the septic form of disease antibiotics are better to infuse parenteraly. For sanitation of chronic carriers of salmonelas the specified antibiotics use in average therapeutic doses in combination with preparations stimulating nonspecific and immunological reactivity (pentoxyl, methyluracil, splenin, thymalin, T- activin).

Prophylaxis

The measures of prophylaxis are veterinary-surveillance upon animals and production of meat and dairy industry, laboratory control of food stuffs.

It is necessary to reveal carriers on milk farms, in foods, children's and medical establishments. The maintenance of the rules of personal hygiene and rules of food's cooking plays an important role in prophylaxis of salmonellosis.

Control questions:
1. Etiology, epidemiology and incidence of salmonellosis.
2. Pathogenesis of salmonellosis.
3. Anatomic pathology of disease.
4. Main clinical symptoms and signs of salmonellosis.
5. Complications and outcomes of salmonellosis.
6. Laboratory methods of salmonellosis diagnosis.
7. Criteria of diagnosis.
8. Differential diagnosis of salmonellosis.
9. Treatment of salmonellosis.
10. Prophylaxis of salmonellosis.

CHOLERA

Cholera is an acute anthroponosic infectious disease with fecal-oral mechanism of transmission. Cholera is characterized by dehydration due to loss of the fluid with watery diarrhoea and vomiting. Cholera is concerned to the group of the diseases, which are submitted to "International medical-sanitary rules".

Historic reference

Illness and death due to dehydrating diarrhea and vomiting can be recognized in the writings of Hippocrates and Galen. The heartland of cholera is India, the Ganges river's delta. From there it has spred from time to time to many other countries.

There were 7 pandemic of cholera in the world. Fives pandemics of appalling magnitude have occurred during the 19th century, spreading from India through Asia Minor, Egypt and Russia.

In 1816 cholera broke out with unusual severity and high mortality in the area of the Ganges river's delta. Over the next 8 years it spread over much of Asia and the Middle East, but did not invade Europe.

The great pandemic is of importance as being the first to invade Europe. It started in India in 1828 and advancing slowly reached Iran in 1829, extending thence by way of Astrakhan to Russia, Sweden, Northern Europe and England. By 1832 it has spread over the whole Europe. In the same year 1832, it reached Canada and thence extended to Fort Dearborn, where it infected the soldiers who subsequently carried the disease down the Mississippi valley.

Cholera was also introduced into New York and Boston and spread from there to south and west, so that by 1836 cholera was present in most parts of the United States, not disappearing until 1838. It disappeared in Europe in 1839.

The next European outbreak, or third pandemic, lasted from 1844 to 1864 and was traced from India by the way of land and sea, that by land following the caravan route by way of Iran and Russia and that by sea from Indian pilgrims going to Mecca. This pandemic reached the United States in 1848.

The fourth great pandemic invaded Europe by the usual routes and continued from 1865 to 1875. In 1865 it was carried by sea from Bombay to Arabia and Mecca and was then spread by the returning pilgrims throughout Egypt, Syria, and the Southern European ports to the East coast of Africa.

The fifth pandemic (1883-1896) began in India, reaching Egypt and Europe. It was during this epidemic, in 1883 that Koch working in Egypt discovered the cause of cholera, vibrio comma (*Spirillum cholera*). However, as the epidemic in Alexandria soon subsided, he proceeded to India where, after a study of 42 cases of cholera and 28 autopsies, he gave confirmatory evidence of the etiology of the disease.

A very serious outbreak of cholera originated in 1891 in pilgrims from the delta of the Ganges attending a religious festival. It was spread of cholera by returning pilgrims and reached Europe in 1892. Almost a million deaths occurred in Russia. It was during this epidemic that cholera appeared with great virulence in Hamburg. In that city within 2 months there were nearly 17,000 cases and over 8,000 deaths. This outbreak gave opportunity for those careful studies as to the transmission of the disease to be later referred to.

It is usual to recognize a sixth pandemic (1900-1926) which began in Aravia and spread over India, China and Philippines. This pandemic continued to cause great mortality in Europe and from 1908 to 1910, there were reported some 71,000 cases and 26,000 deaths in Russia.

The seventh pandemic began in 1961. It is caused by a vibrio cholera El-Tor.

In 1905 Gotschlich isolated six peculiar strains of vibrio cholera from the dead bodies of returned Mecca pilgrims at the quarantine camp of El Tor. These strains, which produced hemolysins, came from typical cases of cholera and agglutinated in the classical typing serum. However, not until 1961 when the "El Tor" biotype produced an epidemic of major proportions in the Philippines was there general agreement that hemolytic vibrio cholera could be responsible for severe epidemic human disease.

Etiology

There are two forms of the vibrio cholera: classical biotype, which was discovered by Koch in 1883 and El Tor biotype.

The vibrion is short. It is gram-negative and curved organism which, from its shape, is often called the comma bacillus. Typically it is small, comma-shaped rod. It frequently occurs in S-shapes, owing to the attachment of a pair of organisms at their ends, and especially in the old and virulent cultures long treads showing a somewhat spiral appearance may be seen. The vibrio cholera is strictly aerobic and grows readily upon ordinary culture media. There are no spores and capsules.

Vibrio cholera has two antigens – flagellar H-antigen and somatic O-antigen.

The somatic O- antigens do distinguish *V. cholera* Ogawa, Inaba and Hikojima, which are responsible for epidemics.

V. cholera has 3 fractions of toxin. Cholerogen-exotoxin plays the most important role in the development of dehydration. Cholerogen consists of two types of toxin: cholerogen A and cholerogen B. Cholerogen A consists of peptide A1 and peptide A2. Peptide A1 penetrates through the cells membrane. Then it manifests the specific toxication. Peptide A2 connects peptide A1 with peptide B. Peptide B is untoxic, it connects the whole molecule of toxin with cell receptors. *V. cholera* survives in low temperature. The boiling kills V. cholera during one minute. It survives in sea water (till 60 days).

Vibrio cholera is present in the intestine and in the rice water-like stool during acute stage of infection.

Epidemiology

Cholera is anthroponosic intestinal disease with tendency to pandemic spread. Reservoir and source of infection is infected man. Discharge of vibrions is realized with excrement.

The sources of infection may be sick man with typical or obliterated form of cholera, reconvalescent after cholera and clinically healthy vibrio-carriers.

The patients with clinical picture of cholera are the most intensive source of agents. They discharge till 10-20 liters of fluid with watery diarrhea during first 4-5 days of the disease with great content of vibrions (10^6-10^9 vibrions in 1 mL).

The source of infection may be reconvalescents-vibriocarriers. They discharge vibrions into environment in average during 2-4 weeks.

Healthy (transitory) carriers can discharge the agent periodically during some month. The mechanism of transmission of the infection is fecal-oral. It is realized by water, alimentary and contact ways. The leading way of the transmission of the agents of cholera is water. This way may lead to epidemic distribution of cholera. Infection may happen due to use of infected water and also after use this water for wash of vegetables, fruits or bathing.

Food has also been implicated in some epidemics. The cases of cholera were described due to infected milk use, boiled rice and other food-stuffs.

It is established that inhabitants of different water reservoirs (fish, crayfishes, mollusks, frogs and other hydrobionts) are able to accumulate and preserve vibrio El-Tor for a long time. They are temporary reservoir of infection and may be factors of transmission of the agents.

The susceptibility to cholera is general and high. In endemic areas morbidity is observed more frequently in children and elderly persons.

Pathogenesis

Cholera is cyclic infection with essential fermental systems damage of the enterocytes. Vibrions cholera enter the organism through the mouth with water or food. Some part of vibrions perishes under influence of acid medium of the stomach. Another part of vibrions enters small intestine. Intestine reproduction and destruction of vibrions is accompanied with discharge of large amount of endo- and exotoxic substances. There is no inflammatory reactions.

Cholera is characterized by dehydration due to loss of fluid and salts with watery stool and vomiting. Hypersecretory processes play the leading role in the mechanism of the diarrhea origin. These processes are promoted by activation of ferment adenylcyclase in the epithelial cells of the intestine under action of exotoxin-cholerogen and accumulation of cyclic 3,5-adenosinemonophosphates, leading to increase of secretion of electrolytes and water. In cholera the loss of fluid with stool and vomiting reaches such a great volume in a short period, practically not met during diarrhea of other etiology. The general volume may exceed in some cases up to 2 times the body's mass of the patient. The loss of

electrolytes plays essential role in pathophysiology of cholera. So, loss of potassium may reach one third its content in the organism. It is manifested by disorder of function of myocardium, damage of kidneys and also paresis of the intestine. In cholera dehydration is isotonic. Fluid contains 135 mmole/L Na, 18 mmole/L K, 48 mmole/L HCO_3 and 100 mmole/L Cl (or 5g NaCl, 4g $NaHCO_3$ and 1g KCl in 1 liter of defecations. An acute extracellular isotonic dehydration develops in the patients with cholera. It is accompanied with decreasing of the volume of circulated blood and hemoconcentration, leading to hemodynamic disorders and violation of tissue metabolism. Hypovolemia, metabolic acidosis, hypoxia, thrombo-hemorrhagic syndrome and acute renal failure develops.

Anatomic pathology

In cholera basic tragedy happens in a zone of the jejunal capillaries. Liquid get into the intestine from them through the epithelium cells. A venous return is diminished and as a result of that the heart's return diminishes too. Blood pressure decreases. The organism reacts with a tachycardia on that (there is no cholera without tachycardia).

The other compulsory sign is decreased diuresis. It is explained by increase of the water resorbtion by the renal canaliculi. If the loss continues venous flow diminishes acutely. Tachycardia can not compensate it already and blood pressure decreases.

The organism includes a pressory mechanisms to preserve functions of the vital important organs (heart, brain, kidneys). A capillary spasm begins. It improves for some time blood supply of the heart and brain. Blood pressure is equated but venous return decreases more. As a result of it oxygen transport to the organs and tissues and metabolic products transport are violated. pH balance of the organism changes to acidosis. The organism reacts on acidosis. It includes a new compensatory mechanism. It is dyspnea. Respiratory alkalosis develops, but it can not cause neutral pH balance due to violation of microcirculations.

A pressory mechanism is proper for kidneys too. The kidneys capillaries are spasmated. Tissue acidosis develops. Resorbtion of water and products of metabolism is altered. That excludes the kidney as organ regulating homeostasis. Renal filtration stops entirely under the decrease of blood pressure less than 80 mm. The kidney is sensitive for hypoxia. Hypoxia causes dystrophic changes in the epithelium of the sinous canals.

These changes are reversible in case of moderate hypoxia (a renovation period is not shorter than a week). But if the patient did not get from the hypovolemic shock a necrosis of the sinous canals comes (death from anuria — "shock kidney"). In case of prolonged loss of water all compensatory mechanisms become unable to keep blood pressure. An original decompensation comes. It coincides with the loss of the liquid equal to 8-12 % of the body's weight. Then the unreversable changes become and therapy is uneffective. The volume of loss shouldn't be more than 10 %.

In accordance with WHO classification the patients with cholera may be divided on three groups:

1. The first degree of dehydration. There are the patients which have loss of fluid volume equaled to 5 % of body weight.

2. The second degree of dehydration. There are the patients which have loss of fluid volume equal to 6-9 % of body weight.

3. The third degree of dehydration. The patients which have loss of fluid volume over 10 % of body weight. That dehydration is dangerous for life if the reanimation measures are not entertained.

According to classification of V. I. Pocrovsky patients can be divided in four groups:

1. The first degree of dehydration with loss of fluid 1-3 % of body weight.

2. The second degree of dehydration with loss of fluid 4-6 % of body weight.

3. The third degree of dehydration with loss of fluid 7-9 % of body weight.

4. The fourth degree of dehydration with loss of fluid more then 10 % of body weight.

It's worth to underline that the clinical manifestation of the third degree of dehydration (by the WHO classification) or the fourth degree (by classification of V. I. Pocrovsky) is hypovolemic shock.

Clinical manifestations

Clinical manifestations of cholera, caused by classic vibrion and vibrion El-Tor are similar.

Incubation period is from several hours till 5 days (in average 48 hours). Cholera may be present in typical and untypical forms. In typical course the next forms of the disease are differented in accordance with the degree of dehydration: mild, moderate and severe form. In untypical course obliterated, fulminant forms may be present.

The onset of the disease is an acute, as a rule. In case of mild course of cholera the gradual development occurs in the part of the patients. The prodromal period may be 1-1.5 days. The patients mark weariness, ailing, headache, sometimes subfebrile temperature, heartbeating, sweet.

A diarrhoea is the first clinical manifestation of cholera. It appears suddenly, without the pain, often at night or in the morning. Diarrhoea is accompanied by gurgation in the stomach. After 1-2 defecation stool has typical shape. It is cloudy, white, fluid, without smell and "rice water-like".

The mild course (dehydration of the first degree). The loss of fluid is till 3 % of body weight. In majority patients stool may be till 10 time per day, scanty. In one-third of the patients vomiting may occur 1-2 times. Thirst, light dizziness, weakness trouble the patients. Their state is satisfactory. Skin is humid, usual color. The mucous of the mouth is dry. There is no hypothermia. Subfebrile temperature may be in the part of the patients. There are no changes

of the pulse and arterial pressure. An insignificant painfulment occurs due to palpation of the stomach. The changes of the blood are not typical. There is no blood condensation, changes of it's pH and electrolytes balance.

After proper therapy a vomiting, dizziness, weakness disappear on the first day. The stool become normal on the 2-3 day of the treatment.

Middle-severe course (dehydration of the second degree). The loss of fluid is 4-6 %. There is considerable weakness, dizziness, thirst in patients. A quantity of the defecation is from 10 till 20 times in a day. The stool is liquid, plentiful. Dehydration appears already after 3-5 defecation at the half of the patients. A vomiting is annexed early, and it is rice-water-like. The skin is pale. The moderate cyanosis of lips and extremities may be in the part of the patients. There is horse whishpering voice. Turgor of the skin decreases. The feature of this degree of dehydration is appearance of the cramps without tonic tension. The pulse is frequent up to 100 per minute. The arterial pressure is decreases till 100 mm. There may be olyguria.

There are no changes of the red blood. Erythrocyte sedimentation rate (ESR) is lightly accelerated. Leukocytosis, neutrophylosis with the shift of the formula to the left, lymphopenia, monocytopenia and uneosinophilia occur in the part of the patients. Hematocrit is 51-54 L/L. The relative density of the plasma is 1026-1029. The change of electrolytes is insignificant. Hypokalemia and hypochlorinemia are more expressed. Hypotension disappears usually through 20-30 minutes from the onset of rehydration. Turgor is restored through 3-4 hours. The skin becomes pink. A vomiting continues till a day. Rarely a vomiting is observed on the second day. The stool becomes facesic through 1-3 days, and it becomes normal to 4-5 day. The general loss of the fluid is 5-7 liters in this patients.

Severe course (dehydration of the third degree) occurs more rarely, approximately in 10 % of the patients. The loss of fluid is 7-9 % of body weight. The detachment this degree of dehydration is connected with necessity of prevention of development extremly severe course. There are no secondary changes of the important system of the organism due to this degree of dehydration. Because, it may be possible rapid compensation of dehydration and restoration of electrolytes. The third degree is characterized by more intensive clinical manifestations of dehydration and unfirm compensation.

The disease develops impetuously. The stool is watery, abundant from the first hours of the disease. Sometimes the patient cannot count a quantity of defecations. In patients sharp weakness, adynamia, severe thirst, cramps of the muscles are observed. The state of the patients is serious and very serious.

A cyanosis of lips and extremities is observed. The skin is cold and shriveled. The turgor decreases. The face is pinched, eyes are deeply sunken in the orbits. In a third of the patients a symptom of "black eyeglasses" is observed. The mucous of the mouth cavity is dry. The lips are dry too. Tongue is dry and covered. A voice becomes hoarse. The cramps are often of long duration, with

tonic character. Cramps are accompanied with pain. The cramps of the trunk muscles and diaphragm are not observed. The temperature is 35.7-35.5 °C. The pulse is 120-130 per minute, weak. The arterial pressure is low 80/50 mm Hg. Sometimes the breathlessness occurs. Renal failure is manifested with olyguria, in 25 % of patient – with anuria. There are erythrocytosis, leucocytosis, neutrophylosis with the shift of the formula to the left, lymphopenia, uneosinophilia. The concentration of hemoglobin increases. Protein and leukocytes are observed in urine. Hematocrit is 55-65 L/L in these patients. The relative density of plasma is 1030-1035. There is considerable change of electrolytes. Hypokalemia, hypochlorinemia are expressive.

Extremly severe course (dehydration of the forth degree) or decompensated dehydration. It occurs more rarely than the other clinical variants. The loss of fluid is 10 % of body weight and more. In this case the organism cannot compensate the indigence of water-electrolytes balance and function of the significant organs. It leads to hypovolemic shock. The relapsing vomiting is observed. Decompensated dehydration may develop through 6-8 hours and even at the first 2-3 hours. The state of the patients is serious and very serious. In the last hours diarrhoea and vomiting may be absent. It is connected with paresis of the stomach and intestine muscles, with hypokalemia and metabolic acidosis. At the same time there are expressive symptoms of dehydration: cold clammy skin, intensive total cyanosis.

The color of the hand's clusters, nouse, aural areas, lips and eyelids is violet or black. The face is pinched, eyes deeply sunken in orbits. There is impression of the suffering and entreaty about help on the face (facies cholerica).

The skin is shriveled. The turgor of the skin is decreased ("washwoman's hands"). A voice becomes hoarse. The temperature is 34.5 °C. The generalized tonic muscles cramps are observed, including muscles of the abdomen and back. The agonizing hiccup may be due to clonic spasm of diaphragm. There is no pulse. The arterial pressure is not determined. The breathing is frequent and superficial. There is anuria. The condensation of the blood is observed. In peripheral blood the concentration of hemoglobin increases. Expressive leucocytosis, neutrophylosis, lymphopenia, uneosinophilia occur. Hematocrit is higher than 66 L/L. The relative density of the plasma is 1036 and more. The alterations of electrolytes are very expressive: hypokalemia, hypochlorinemia. Hyponatremia is expressed in a smaller degree. Dehydration has isotonic character. The deficit bicarbonium (more than 10mmol/L) leads to decompensated metabolic acidosis and respiratory alkalosis.

Untreated patients die. The cause of the death is an acute heart's failure (at the first three days of the disease) or renal failure (up to 14-16 day).

Complications

The next complications may develop in patient with cholera: pneumonia, sometimes abscesses, phlegmon. The number of complications are connected

with intensive therapy: pyrogenic reactions, phlebitis, thrombophlebitis, hyperkalemia and other.

Diagnosis

The bacteriological research of material from the patient or corpse is the principal method of laboratory diagnostics. The purpose of bacteriological method is detachment of choleraўs agent and itўs identification.

The correct collection of the material has a great meaning for bacteriological research as the delivery of material to the laboratory. A quantity of the material is 0.1-0.2 gm, because the enormous quantity of the agent is contained at stool. It is necessary to take a bigger quantity of the agent from the patient with light form or carriers. The sowing is done to the dense or liquid nutritive mediums near patient's bed. If there is no possibility delivering of the material to the laboratory, quickly, it is necessary adding of conservant, because vibrio cholera begins to perish already at the first 1-2 hours in usual conditions. An alkaline peptonic water is used for the sowing. The material for the sowing is necessary to take till beginning of the treatment. The preliminary answer may be through 12 hours, the final − through 24 hours.

The serological methods may be also used for diagnostics of cholera. There are methods of discovering antibodies to vibrio cholera in blood, the methods of detaching antigens of vibrio cholera at stool and other materials. At the last years luminescent-serological method is used. The result may be received through 1.5-2 hours.

Differential diagnosis

Differential diagnostics of cholera is performed with toxical food-borne infections, esherichiosis, rotaviral gastroenteritis. In some untypical cases of cholera, especially in obliterated course of the disease it is necessary to perform differentiation of gastrointestinal form of salmonellosis, gastroenterocolitic variant of acute shigellosis, poisoning with mashrooms, organic and inorganic chemical remedies.

Treatment

Patients needs immediate hospitalization in choleric department. They require emergency treatment which should be started at the pre-admission stage. It's necessary to prescribe pathogenetic preparations with the purpose of compensation of liquid and electrolytes loss, and corrections of metabolic changes. Isotonic polyionic solutions − threesault, acesault, lactasault, quartasault, hlosault are indicated. Quartasault is more effective.

Quantity of liquid, which should be infused for initial rehydratation (during 1-2 hours), should correspond to stage of the organism dehydratation. At III and IV stages of dehydratation it makes accordingly 7-9-10 % of body weight and more. Polyionic solutions infuse in vein initially-stream introduction, then volumetric rate 70-120 mL/minute. To infuse liquid with such rate, it is necessary to use simultaneously two and more systems for transfusion. Stream introduction

of liquid is replaced by dropwise infusion after normalization of pulse, restoration the arterial blood pressure and normalization of body temperature, hemoconcentration and acidosis.

The next infusions of polyionic solutions is determined by rate of proceeding loss of water and salts. The compensatory rehydratation is provided during several days in severe cases. For definition of its volume it is necessary every 2 hours to determine quantity of excrements and vomitive masses to investigate clinical (a pulse rate, the arterial pressure, body temperature) and every 4 − 6 hours laboratory (relative density of blood plasma, haematocrite number, concentration of electrolytes in blood plasma and erythrocytes, pH, concentration of standard Sodii hydrogenii) parameters.

For prevention of side reactions of polyionic solutions should be preliminary warmed up to 38 − 40 °C, at the first hours of treatment infuse prednisolon 0.5 gm/kg per day. At infusion there is plenty of solution threesault the metabolic alkalosis and hyperkalemia can be developed. In these cases infusion therapy is continued with solution desault.

It cases of not compensated hypokalemia it is necessary to infuse preparations of potassium in addition. At a pernicious vomiting, cramps, anaphylactoid reaction dimedrol or suprastin with promedol should be used. As at patients with severe course of cholera the clotting develops, cordiamin, coffein or epinephrin of hydrochlorid is contrindicated.

In case of I-II stages dehydration (liquid loss up to 6 % of body weight) and more severe dehydration is managed by intravenous injection of saline solutions, at absence of vomiting recommend to apply peroral indication of glucosani in tablets or rehydroni in packages 18.9 gm: dissolve the content of 1 package in 1 L of boiled water and drink small portions.

Water-salt therapy should be over after appearance of excrements of normal character and at prevalence of quantity of urine over quantity of excrements in the last 6-12 hours.

Panangin or asparcam during 1 month are indicated during early reconvalescence.

Antibiotics are the additional remedies. They accelerate clinical convalescence and prevent the further allocation of choleric vibrioes. A remedy of a choice is ciprofloxacin: 0.25-0.5 gm 2 times per day, in serious cases enlarge up to 0.75-2 times per day during 5-7 days or erythromicin, or laevomycetin. Tetracyclin and doxycyclin are effective. However, for the last years the majority of choleric vibrio culture, allocated on territory of Ukraine, appeared not to be sensitive to this antibiotic. For sanitation of vibrio carriers use the same antibiotics during 3-5 days.

Complications of rehydration. It may be pyrogenic reaction to solutions, hypokalemia, hyperkalemia.

Hypokalemia is observed more than 25 % of the patients with III degree of dehydration. The clinical manifestations are: distention of the stomach, pain in the stomach (hypokalemitic ileus).

The next formula may be used for correction of potassium:

$$1.44 \times P \times (5 - X) = \text{ mL of 1 \% KCl,}$$

where $1.44 -$ coefficient,

   $P -$ weight of the patient,

   $X -$ contant of potassium in patient's serum.

   $5 -$ normal content of potassium in blood serum.

Hyperkalemia develops in 15 % of the patients. The clinical manifestations are: red face and upper part of the body, cardialgia, typical changes of ECG, bradycardia. In this case it is necessary to inject Phillips solution №2. Phillip's solution № 1 is injected again after signs of hyperkalemia elimination.

Etiotropic therapy is performed with antibiotics. Antibiotics cause shortening of diarrhoea duration and give possibility to decrease a quantity of fluid for injection.

Doxicycline is prescribed in dose 0.1 mg through 12 hours at the first day, than 0.3-0.5 mg through 6 hours during 3 days. Tetracycline is used for teratment of the patients with cholera in dose 0.3-0.5 mg through 6 hours during 5 days. It is possible to use chloramphenicol in 0.5 mg dose through 6 hours during 5 days.

Prophylaxis

The measures of prophylaxis depend on epidemic situation in the country. The information of world health organisation about cases of cholera in different countries has an important meaning.

The incidence of disease can be diminished by sanitary-hygienic measures, sanitary disposal of human feces, purification and protection of water supplies, pasteurization of milk and milk products, strict sanitary supervision of preparation and serring of flood exclusion of persons with diarrhea from handling food, organization of the work about diseases of gastrointestinal tract and their examination on cholera.

Specific prophylaxis of cholera is performed by corpuscular vaccine and cholerogen-anatoxin.

Parenterally inoculated killed complete cell vaccine has been available for years, this vaccine stimulates high titers of serum vibriocidal antibodies, but it does not induce antibodies to toxin. Protection by vaccine has been induced for approximately 1 years, with vaccine efficacy approximately 70 %. Local gastrointestinal tract immunity against the organism and against the toxin should provide a better, less reactogenic immunogen using recombinant DNA technology an "attenuated" *V. cholerae* organism that lacks the genes for production of the A and B subunits of toxin was created. A plasmid containing the subunit gene was then constructed and inserted. Thus a candidate live V. cholera vaccine containing all the cell-was antigens necessary for adherence and the capacity to produce only the subunit of toxin has been engineered.

Control questions:

1. Definition of cholera.
2. Etiology of cholera.
3. Classification of clinical forms of disease.
4. Clinical symptoms and signs of cholera.
5. Differential diagnosis with toxic food-borne diseases, esherihiosis, salmonellosis, shigelosis, poisoning by salts of heavy metals.
6. Classic bacteriologic cholera diagnosis, methods of express-diagnosis.
7. Dehydration during cholera (dehydration primary, compensatory).
8. Etiotropic therapy and medical supervision after contacts with cholera patient.
9. Preventive measures in spot of cholera outbreak: quarantine measures, observation, disinfection measures, immediate prophylaxis of cholera, specific prophylaxis and terms of discharge from the hospital.

BOTULISM. TOXIC FOOD-BORNE DISEASES. CAMPYLOBACTERIOSIS

BOTULISM

Botulism is a life-threatening infectious disease, produced by neurotoxins elaborated by *Clostridium botulinum*. Botulism is characterized with intoxication of the organism with the principal damage of the central and vegetative nervous system.

Historic reference

Because early accounts of botulism frequently incriminated sausages, the name of the disease was derided from the Latin word for sausage – "*botulus*". Outbreaks of "sausage poisoning" were common in Germany during the nineteenth century, and Justinius Kerner, poet and physician, published several monographs on the subject. For a time, botulism was known as "Kerner's disease". Investigating an outbreaks in 1895, the Belgian bacteriologits Van Ermengem performed classic experiments in which he isolated the causative anaerobic spore-forming bacillus from the incriminated ham and demonstrated that both the ham and a toxin produced by the organism could induce a paralytic illness in cats.

Etiology

Clostridium botulinum is a gram-positive, anaerobic and forming spores bacillus. Eight immunologically distinct toxin types have been described (types A, B, C, D, E, F, G. Types A, B and E most commonly cause disease in man; types F and G have only rarely caused human illness. Types C and D are associated with animal botulism, especially in cattle, ducks and chickens.

One of the peculiarities of the agent is mobility. It is connected with presence of flagellars. The spores of *C.botulinum* are heat resistant; they can withstand 100 °C for hours. Fortunately, the toxins are rather heat labile; boiling for 10 minutes or heating at 80°C for 30 minutes destroy them.

All serotypes of *Clostridium botulinum* produce neurotoxin. Neurotoxin is protein, it consists of 19 aminoacids. Neurotoxin of *Clostridium botulinum* is one of the most strong natural poisons.

Epidemiology

Botulism is saprozoonosis. The spores of *C.botulinum* are ubiquitous in soil; the distribution of type A and B spores is worldwide. The principal reservoirs of the agent of botulism are grass feeding animals, and rarely fish, mollusks and crayfishes which absorbing the spores of *C.botulinum* with water and food.

The human is infected by botulism due to use of the contaminated food by spores. The greatest part of the cases of botulism is connected with use home-canned food, for example mushrooms, vegetables, fish, meat and other.

The disease occurs under three circumstances: 1) botulism food poisoning results from eating food that contains preformed toxin; 2) wound botulism occurs when toxin is produced by *C.botulinum* organisms contaminating traumatic wounds; 3) infant botulism is due to toxin production by *C.botulinum* within the gastrointestinal tract of infants.

Pathogenesis

The vegetative forms of the agent and botulotoxin enter into the human organism due to use contaminated food-stuffs. The action of the toxin is intensified in the stomach under influence of proteolytic enzymes. The people are more sensitive to serotypes of toxin A, B, E.

The toxin are absorbed primarily from the stomach and small bowel. The digestive enzymes do not destroy the toxin molecules. The toxins interfere with neurotransmission at peripheral cholinergic synapses by binding tightly to the presynaptic membrane and presenting the release of the neurotransmitter acetylcholine. Adrenergic fibers are spared. The effect of botulinus toxin on cholinergic pathways in the central nervous system remains in dispute. The motoneurones of spinal cord and oblong brain have special sensitiveness to botulism. The bulbaric and paralytic syndromes develop as a result.

Hypoxia plays the leading role in the pathogenesis of botulism. The development of progressive respiratory insufficiency is connected with depression of the activity of the large motoneurones, innerving the respiratory muscles.

Anatomic pathology

The pathologoanalomic alterations in botulism have nonspecific character. They are connected with deep hypoxia. There are hyperemia of the internal organs, edema of the cerebrum, small hemorrhages into mucous membrane of the gastrointestinal tract.

Clinical manifestations

The incubation period ranges from 2-12 hours till 10 days (in average 6-24 hours). There are the next leading syndromes in botulism: paralytic, gastrointestinal and intoxicative syndromes. The onset of the disease is, as a rule, an acute. In patients pain in the epigastric area, nausea, vomiting, diarrhea occur. The vomiting and diarrhea are not prolonged. The temperature is normal or subfebrile. The rapid fatigue, progressive muscle's weakness are marked. The symptoms of the defeat of the muscles, of cranial nerves and paralytic violations of innervation of the internal organs develop through 3-4 hours after the onset of the disease. These violations are characterized by symmetrical defeat.

The first typical signs of botulism are usually dryness in the mouth (Fig. 4) and ophthalmoplegic symptoms. The patients complain of vision disorders, "net" or "fog" in front of the eyes. The patients cannot read, because the paresis of the accommodation and diplopia develop. Medriasis (Fig. 5), decreased reaction on the light, the limitation of the eyes motion, sometimes full inmotility, ptosis (Fig. 6), squint, horizontal nystagmus are observed.

The violations of the swallow and speech are early observed. These violations is connected with damage of IX and XII nucleuses of cranial nerves pairs. In patients dysphonia, dysarthria, nose shade of the voice are marked. The paresis of the throat muscles develops. In the patients dysphagia appears as a result. The liquid is poured out through the nose.

Botulism is accompanied with functional disorders of cardiovascular system. The widening of the heart's borders and muffed heart sounds are observed.

The violations of the functions of the gastrointestinal tract are accompanied with dryness of the mucous membranes of the mouth, thirst, distention of the abdomen, retention of stool, and intestine paresis.

The large motoneurones of the neck's and chest's portions of the spinal cord are involved into the process. This process leads to development of paresis and paralysis of the muscles. The patient may breathe with difficulty. The patient must accept special position. The cough's reflex disappears. The disorder and break of breath is one of the leading causes of the death at botulism.

In terminal period the appearances of myoneuralgia are observed: myasthenia and adynamia. The muscles have like-dough consistence. The recovery comes slowly, during 1-1.5 months.

In peripheral blood moderate leukocytosis, neutrophylosis are marked with shift of the formula to the left. In botulism the prognosis is always serious. When adequate therapy is not applied the lethal outcomes compose near 25 %.

Diagnosis

The diagnosis is made on the basis of clinical manifestations of the disease, epidemiological data and results of the laboratory researches. The toxin and the agent may be revealed in the materials, collected from the patient (blood, vomitory masses, water after irrigation of the stomach, stool) and also at the suspicious food-stuffs. The reaction of neutralization may be used for revelation of toxin.

Differential diagnosis

Botulism may be confused with the Guillant-Barre syndrome, poliomyelitis, stroke, myastenia gravis, tick paralysis, and poisoning due to curare or belladonna alkaloids.

Treatment

The first aid (independently of term, that pasted from the beginning of disease) consists of careful lavage of stomach and intestine with 2-5 % solution of a Sodii carbonate. It is necessary to remember, that at muscles paralysis of

pharynx, larynx and tongue, the probe may penetrate into a trachea, therefore before lavaging it is necessary to be convinced that the probe is in stomach. After lavaging prescribe enterosorbent-SKN, enterodes, sillard P.

Medical antibotulism serums are injected at first hours of the disease. Before determination of species of the infection inject mixture of serums types A and E 10,000 IU and type B on 5,000 IU. After definition of specie of infection monovalent serum is used. In serious cases during 1st day 4 − 6 medical doses of serum are prescribed, 2 of them − intravenous by drops in isotonic solution of Sodii chloride or 5 % solution of glucose. Before injection of serum intracutaneous test is made. Serum is injected according the method of fractional deallergization depending on degree of disease gravity during 2 − 4 days. Etiotropic agent is specific treatment with homological plasma 250 mL, 1-2 times per day.

Nonspecific desintoxication therapy consists of injection of glucose solution, polyionic solutions (lactasault, threesault, quartasault) and simultaneously diuretics − furosemid (lasix).

For suppression of infection in a digestive tract ampicillin, oxacillin, levomycetin or tetracyclin are indicated. A course of antibiotic therapy lasts for 5-7 days.

In serious cases and for prophylaxy of serum disease prednisolone on 40 mg per day or its analogues is indicated. At disorders of respiration of the patient he is required to hospitalize to reanimation departament and transfer on controlled artificial respiration immediately.

At failure of cardiovascular system there are prescribed cordiamin, sulfocamphocain, cardiac glicosides, at disorders of nervous system − vitamin preparations of group B, cocarboxylase, riboxin. At allergic reactions, development of a serum disease there are used prednisolone, antihistaminics − suprastin and also calcy gluconate, phencarole, terfenadin.

Prophylaxis

The observance of the sanitary and hygienic rules at processing, transportion, keeping and preparing of the food-stuffs experts possibility of accumulation of botulotoxin. It is necessary to perform the strict control under sterilization and keeping preserved food-stuffs.

The explanation to the people of the rules of the procurement and preservation of food-stuffs in home conditions has important value especially such food-stuffs as meat, mushrooms, vegetables.

TOXIC FOOD-BORNE INFECTIONS

Toxic food-borne infections are acute transitory diseases, caused by conditionally pathogenic bacteria. These bacteria are capable to produce exotoxin (in food-stuffs). The disease is accompanied with symptoms of the damage of the upper parts of the gastrointestinal tract (gastritis, gastroenteritis) and by violation of the water-electrolyte balance.

Etiology

Many types of the conditionally pathogenic bacteria may be agents of the toxic food-borne infections and produce exotoxin out of the human organism on the different food-stuffs. Enterotoxins (thermoliable and thermostable) increase the secretion of the fluids and salts into the stomach and intestine. Cytotoxins damage the membranes of the epithelial cells and violate the protein synthetic processes. The agents, producing enterotoxins are *Clostridium perfringeus, Proteus vulgaris, Proteus mirabilis, Bacillus cereus*. These enterotoxins are also formed by agents from the families of *Klebsiella, Enterobacter, Citrobacter, Serrafia, Pseudomonas, Aeromonas, Edwarsiella*. The majority of these enterotoxins are thermoliable.

Epidemiology

Pathogenic organisms of the toxic food infections are widely spread in the nature. They may be everywhere: in the fecal matters of human and animals; in the soil; in the water; in air and on the different subjects. The way of the spread of the infection is alimentary. The factors of the transmission of the disease are solid products (sausages, eggs, meat and fish canned food) and liquid products (soup, milk, juices, compotes, jellies, lemonade, beer, cocktails). They are the nutritive mediums for bacteria.

The susceptibility to this group of diseases is very high, sometimes till 90-100 %. The typical sign of the toxic food-borne infections is not only group but explosive character of illness due to all participants of the outbreak become ill during a short period (over a few hours). The toxic food-borne infections are registered during the whole year, but especially in summer.

Pathogenesis

In toxic food infections exotoxin is contained in food, besides bacteria. Due to this the incubation period is very short. Time of the of clinical manifestations development after influence of toxins to the mucous membrane is from 30 minutes till 2-6 hours.

Pathogenesis and clinical manifestations of the disease depend on the type and dose of exotoxin, and also from other toxical substances of microbial origin, containing in the food-stuff. Enterotoxins (thermoliable and thermostable) are connected with the epithelial cells of stomach and intestine and act to the fermental system of the epitheliocytes, but don't cause morphological changes in these organs. Enterotoxin activates ferments adenylcyclase and guanylcyclase, increasing formation of the biological active substances (cyclic adenosinemonophosphates and cyclic guanidinmonophosphates) in the cells of the mucous membranes. All these changes lead to the increase rate of secretion of water and salts into the stomach and intestine and to the development of diarrhea and vomiting.

Anatomic pathology

Cytotoxins damage the membranes of the epithelial cells and violates synthetic processes. It may increase the permeability of the intestinal wall for different

types of the toxical substances, and for oneself microorganisms, development of intoxication and violation of microcirculation and localized inflammatory alterations of the intestinal mucous membrane.

Clinical manifestations

The clinical manifestations of the toxic food-borne infections caused by only enterotoxins are less severe. In the majority of the cases of the disease there is no fever and just considerable inflammatory changes of the mucous membrane of the stomach and intestine.

The course of the disease become more severe due to accumulation of enterotoxin and cytotoxin in the food-stuffs. The high fever and considerable change of the mucous membrane of the gastrointestinal tract are observed.

In toxic food-borne infections there is combination of the signs of the damage of the gastrointestinal tract (gastritis, gastroenteritis or gastroenterocolitis) and signs of the general intoxication and dehydration. The incubation period is from 30 minutes to 24 hours (generally 2-6 hours). The beginning of the disease is an acute. At first the nausea occurs. Frequently the replated, agonizing and unrestrained vomiting occurs. Almost at the same time with vomiting the diarrhea starts. Stool is watery from 1 to 10-15 times a day. In considerable part of patients the disease is not accompanied by severe pain in the stomach and increase of the body temperature of the body. However the disease may be with spasmatic pains in the stomach, with the raise of the body temperature up to 38-39 °C. The raise of the body temperature takes place at the early hours of the disease and through 12-24 hours the temperature is reduced to normal.

During objective examination of the patients the pale skin, sometimes cyanosis, cold extremities are observed. The tongue is coated. Stomach is soft and painful in the epigastrium during palpation. The cardiovascular system also suffers. There is bradycardia (during hyperthermia – tachycardia). The arterial pressure decrease. In some cases collapse of short duration develops. Due to repeated vomiting and plenty diarrhea the signs of dehydration develop. It may be possible of the appearance of the muscle's cramps of extremities, decrease of the diuresis and reduced turgor of the skin. The liver and pancreas are not expanded. In hemogram leukocytosis, neutrophylosis and temperate accelerate ESR are noted.

The duration of the disease in majority of the cases is 1-3 days. The toxical food infection may be accompanied by severe complications. Hypovolemic shock and an acute heart insufficiency, connecting with violations of electrolytic balance (hypokalemia) are observed.

Diagnosis

The diagnosis of the toxic food-borne infections is made according the results of the clinical symptoms estimation, epidemiological and laboratory data. The typical signs are the impetuous development of the disease after short incubation period, presence of symptoms of gastritis, gastroenteritis or gastroenterocolitis in combination with intoxication, dehydration, disposition to the vascular dystonia.

It is necessary to consider the simultaneous disease of the group of the persons, use one itself food-stuff, the features of this product, sanitary-hygienic state of commercive institutions, public nutrition when taking epidemiologic data. It is necessary to reveal the sick men or bacteriocarries among personnel of these institutions, because they may be a source of infection of the food.

Materials for bacterial examination are suspicious food products, vomitory masses, water after irrigation of the stomach, stool of the patient. Serological methods does not have independent meaning in the diagnostics.

Differential diagnosis

Differential diagnosis of toxical food infection is performed with acute intestinal infections (cholera, acute shigellosis, gastrointestinal form of yersiniosis, rotoviral gastroenteritis, campylobacteriosis, dyspeptic variants of preicteric period of viral hepatitis and others), with surgical diseases (acute appendicitis, cholecystopancreatitis, thrombosis of mysentrical vessels, perforation of ulcers in the stomach and duodenum), with gynecological diseases (ectopic pregnancy, toxicosis of the pregnancy), with therapeutic diseases (myocardial infarction, hypertension crisis), with neurological diseases (acute failure of cranial blood circulation, subarachnoidal hemorrhage), with urological diseases (pyelonephritis, acute renal failure). During the diagnostics it is necessary to consider the food poisoning, poisoning by mushrooms, salts of hard metals.

Treatment

It is necessary to wash out a stomach and intestine to release them from microbes and toxins as soon as possible. For a lavage it is better to use isotonic solution of sodium chloridum, boiled water or 1-2 % solution of sodium hydrocarbonate. Then give inside the activated microspherical coal (SKN brand). Alternative preparations are sillard P, smecta, enterodes and other enterosorbents. Their early indication promotes the fastest improvement of health state, preserves intoxication, development of the serious form of bacterial endotoxicosis. In case of development of infection-toxic shock we should immediately infuse in blood colloid and cristaloid solutions: polyglucin, reopoliglycin, donor albumin, threeisault, acesault, quartasault, and also glucocorticoides.

Etiotropic treatment is indicated only at serious forms with development of colitic syndrome: furazolidon or enteroseptol. Antibiotics are indicated in case of development of sepsis – levomycetin, gentamicin, ampicillin, ofloxacin (or tarivid).

Prophylaxis

Prophylaxis of the toxical food infection is concluded in prevention of infection of the food-stuff, of the reproduction of the microorganisms in the food. It is necessary to keep the food-stuffs and prepared food at the temperature from 2 till 4 ℃.

The mechanization and automatization of the food objects, the elaboration of the new methods of the preserving and storage of the food-stuff, the freezing at low temperature are conductive to the successful prophylaxis of the toxical food infection.

CAMPYLOBACTERIOSIS

Campylobacteriosis refers to the group of the infections caused by gram-negative bacteria of the genus *Campylobacter*. Among the most common bacterial infections of humans in all parts of the world, campylobacters cause, both diarrhoeal and systemic illnesses and are highly associated with gastritis and peptic ulcer disease. *Campylobacter* is derived from the Greek "*campylo*", meaning curved, and "*bacter*", meaning rod, so named to distinguish this genus from identically appearing vibrios.

Etiology

Campylobacters are motile, non-spore-forming, comma-shaped gram-negative rods. Originally isolated from aborted sheep fetuses in 1909, these and similar organisms were called *Vibrio fetus*. There are now 14 recognized species within the genus.

Three types of illnesses are associated with *Campylobacter* species-enteric, extraintestinal, and gastric. For each of these illnesses one *Campylobacter* species predominates while other species are less commonly present. The prototype for enteric infectionis *C. jejuni*, for extraintestinal infection it is *C. fetus*, and for gastric infection it is *C. pylori*.

The campylobacters can be distinguished from other microorganisms oh the basis of several standard criteria and can be distinguished from one another on the basis of biochemical testing. Similar to other bacteria whose ecologic niche is the gastrointestinal tract of mammals, the serotypic diversity of *C. jejuni* is enormous. More than 90 different serotypes based on somatic O-antigens and 50 different serotypes based on heat-labile (capsular and flagellar) antigens have been identified.

Epidemiology

Campylobacteriosis is a worldwide zoonosis. Campylobacters are commonly found as commensals of the gastrointestinal tract of wild or domesticated cattle, sheep, swine, goats, dogs, cats, rodents. Primary *Campylobacter* infections of animals often occur early in life and may produce morbidity or mortality, but in most infected animals a lifelong carrier state with specific immunity develops. The vast reservoir in animals is probably the ultimate source for most enteric *Campylobacter* infections of humans.

Direct contact with infected animals may result in transmission. Household pets, especially young dogs and cats with diarrhea, have been implicated as vectors for campylobacteriosis. Since healthy dogs, cats, rodents, and birds may excrete campylobacters.

As with other enteric pathogens, fecal-oral person-to-person transmission of *C. jejuni* has been reported. Those in contact with the excreta of infected persons who are not toilet trained (such as infants) are themselves at risk for infection. Perinatal transmission, from a mother who was not necessarily symptomatic may be due to exposure in utero, during passage through the birth canal, or during the first days of life.

Campylobacter jejuni infections occur year-round, but with a sharp peak то summer and early fall. Campylobacter fetus infections show the same seasonal variation, but the peak is less marked.

Campylobacter jejuni and other campylobacters are important causes of the acute diarrheal illnesses suffered by travelers visiting developing areas.

Pathogenesis

Not all *Campylobacter* infections produce illness. Although all factors responsible for this phenomenon are not known, two of the most important appear to be the dose of organisms reaching the small intestine and the specific immunity of the host to the pathogen ingested. Among exposed persons who become ill, the incubation period varies from 1 to 7 days, a characteristic that is probably inversely related to the dose ingested.

Anatomic pathology

Campylobacter jejuni multiplies in human bile, a characteristic that aids colonization of the bile-rich upper small intestine early in infection. The sites of tissue injury include the jejunum, ileum, and colon, with similar pathologic features in each. Inspection of affected tissues may reveal a diffuse, bloody, edematous, and exudative enteritis, but pathologic examinations are generally performed on patients with the most severe cases. Microscopic examination of rectal biopsy specimens has shown a nonspecific colitis with an inflammatory infiltrate of neutrophils, mononuclear cells, and eosinophills in the lamina propria; degeneration; atrophy; loss of mucus; crypt abscesses in the epithelial glands; and ulceration of the mucosal epithelium. Campylobacter outer membranes contain lipopolysaccharides with typical endotoxic activity. Extracellular toxins with cytotoxic activities have been found, and classic enterotoxins have been demonstrated, although generally at low concentrations. Infected persons do not develop neutralizing antibodies to these toxins.

Clinical manifestations

The clinical manifestations of infections due to all of the *Campylobacter* species that cause enteric illnesses appear identical, *C. jejuni* may be regarded as the prototype. Acute enteritis is the most common presentation of *C. jejuni* infection. Symptoms may last from 1 day to 1 week or longer. Often there is a prodrome with fever, headache, myalgia, and malaise 12-24 hours before the onset of intestinal symptoms. The most common symptoms are diarrhea, malaise, fever, and abdominal pain. Diarrhea may vary from loose stools to massive watery stools or grossly bloody stools. *Campylobacter* enteritis is frequently self-limiting, with a gradual improvement in symptoms over several days; however, illnesses lasting longer than 1 week occur in about 10-20 % of patients seeking medical attention, and relapses may be seen in another 5-10 % of untreated patients.

Infection may also be manifested as an acute colitis, with symptoms of fever, abdominal cramps, and bloody diarrhea persisting for 1 week or longer. Fever may be low grade or consist of daily peaks above 40 °C. Initially, stools may be

watery, but as the illness progresses it may become frankly bloody; tenesmus is a common symptom. Because of the propensity of *Campylobacter* infection for young adults and this presenting clinical picture, it may be readily confused with ulcerative colitis or Crohn's disease.

Occasionally, acute abdominal pain may be the major or only symptom of infection. Although any quadrant of the abdomen may be affected, it has been right lower quadrant pain that has elicited the most attention. As with *Yersinia enterocolitica* and *Salmonella enteritidis*, *C. jejuni* may cause pseudoappendicitis. In most cases, the removed appendix has shown minimal or no inflammation. Enlarged mesenteric nodes (mesentericadenitis) and terminal ileitis also may be responsible for the symptoms.

Fever also may be the sole manifestation of *C. jejuni* infection. Temperature elevation may be so severe and persistent that typhoid fever is the initial diagnosis until *C. jejuni* is isolated from stools. Febrile convulsions in young children before the onset of the enteric phase of illness also may occur.

Campylobacter fetus infection. In contrast to *C. jejuni, C. fetus* less frequently causes diarrheal illness. *Campylobacter fetus* infection may cause intermittent diarrhea or nonspecific abdominal pain without localizing signs. The diarrheal illness may be manifested exactly like *C. jejuni* infection. Clinical manifestations are similar, and sequel are uncommon. *Campylobacter fetus* also may cause a prolonged relapsing illness characterized by fever, chills, and myalgias, without a source of the infection being demonstrated. Occasionally, secondary seeding to an organ will occur and lead to a more complicated infection and sometimes to a fulminant fatal course.

Campylobacter fetus infections appear to have a tropism for vascular sites; vascular necrosis occurs in patients with endocarditis and pericarditis. Thrombophlebitis may be associated with *C. fetus* bacteremia, but whether it is the primary event or a secondary manifestation of the infection is uncertain. Infections during pregnancy primarily have been manifested by upper respiratory symptoms, pneumonitis, fever, and bacteremia. Central nervous system (CNS) infections with *C. fetus* occur in neonates and adults. The prognosis is poor for premature infants. Infection is manifested as a meningoencephalitis with a cerebrospinal fluid polymorphonuclear pleocytosis; subdural effusion may complicate, infection.

Campylobacter fetus has been shown to cause a variety of other types of localized infections, including septic arthritis, spontaneous bacterial peritonitis, salpingitis, lung abscess, empyema, cellulitis, urinary tract infection, vertebral osteomyelitis and cholecystitis.

Diagnosis

A clinical diagnosis of enteric campylobacteriosis may be made by demonstration of the organisms in direct microscopy of feces or isolation of the organisms. The use of serologic methods for diagnosis is at present a research only.

Differential diagnosis

Campylobacteriosis could take dysentery-like course, in this case it should be differentiated with shigellosis, salmonellosis, esherichiosis, intestinal yersiniosis, intestinal invagination. The main common signs of all these diseases are abdominal ache, hemocolitis, intoxication. For correct diagnostics the characteristic clinical signs of campylobacteriosis and corresponding laboratory findings should be considered.

Treatment

Fluid and electrolyte replacement are the cornerstones for treating diarrheal illnesses. Patients with *Campylobacter* infections who are badly dehydrated should undergo rapid volume expansion using intravenous solutions of electrolytes in water. For those with less severe depletion, oral rehydration using glucose and electrolyte solutions.

C. jejuni is susceptible to a wide variety of antimicrobial agents, including erythromycin, the tetracyclines, aminoglycosides, chloramphenicol, nitrofurans.

C. fetus infections requires parenteral therapy, and erythromycin is not always effective. When isolates are susceptible, ampicillin treatment has been associated with good results. Patients with other serious infections also should be treated with parenteral gentamicin or other aminoglycosides, ampicillin, or chloramphenicol for at least 2 weeks.

Prophylaxis

Antimicrobial prophylaxis is effective, but because of increasing drug resistence and the possibilities of side effects, are recommending to avoid antimicrobial prophylaxis and, instead, use care in their consumption of contaminated food and water.

Control questions:

1. Etiology of botulism.
2. Epidemiology and pathogenesis of botulism.
3. Basic clinical manifestations of botulism.
4. Principles of botulism treatment.
5. Prophylaxis of botulism.
6. Etiology of toxic food-borne infections.
7. Sources and ways of transmission of infection.
8. Clinical features of toxic food-borne infections.
9. Differential diagnosis of toxic food-borne infections.
10. Laboratory methods of diagnosis and their estimation.
11. Prophylaxis of toxic food-borne infections.
12. Infectious agents of campylobacterioses.
13. Epidemiology of campylobacterioses.
14. Clinical manifestations of campylobacterioses.
15. Principles of campylobacterioses treatment.
16. Prophylaxis of campylobacterioses.

PSEUDOTUBERCULOSIS

Pseudotuberculosis is an acute infectious disease characterized by the polymorphism of the clinical manifestations, affection of the alimentary tract, locomotor system, liver and other organs, general intoxication, exanthema and frequently prolonged course with relapses.

Historic reference

The French scientists L. Malasser and W. Vignal first reported on the pseudotuberculosis microbe. In 1883 they isolated it from the organs of a guinea pig infected with the suspension of the caseous regenerated lymph node of the child who had died from "tuberculosis" meningitis.

In 1885 C. Eberth introduced the term "pseudotuberculosis" when he observed spontaneous epizootic in the rabbits, it was accompanied by an abrupt emaciation of the animals. At the post-mortem examination of the dead animals the anatomic pathological changes of the timer organs looked like the tuberculosis ones, but it was impossible to discover the tuberculosis pathogen, and the morphological characteristics of the isolated pathogen were identical to the microbe.

In 1889 A.Pfeiffer studied the characteristics of this microbe in detail and gave it the name "*Bacterium pseudotuberculosis rodentium*", he connected the isolation of this pathogen with a certain clinical picture in animals.

Etiology

The pseudotuberculosis microbe is a polymorph bacillus, which does not form spores and often has an ovoid form. It is Gram-negative, well painted by all aniline dyes. The question of a capsule in the pseudotuberculosis bacteria is still under discussion. The pseudotuberculosis bacteria grows at a temperature of 4-30 °C are actively mobile, have flagellum, whose length is 3-5 times bigger than the length of the body of the bacterial cell. At a temperature higher than 30 °C the flagellum atrophy and the mobility of the bacteria ceases. The pseudotuberculosis microbe is a facultative anaerobe, it is quite undemanding to the nutrition, and that is why it grows well on the common dense nutrient media, it can grow on the media without peptone. This characteristic of the pathogen was used to distinguish the pseudotuberculosis bacteria from the plague pathogen.

The bacteria contain H-antigen and O-antigen, which determine their variability. The H-antigen is thermolabile and is destroyed at boiling, it is synthesized at a temperature of 2-30 °C best of all.

Different biologically active substances, which are necessary to initiate and develop an infectious process, are produced in the process of the yersinia pathogen

vital activity. Besides this it is established that the yersiniosis pathogen strains of different pathogenicity circulate in the human population.

Epidemiology

Before the 60s of the 19th century the epidemiology of the human yersiniosis was almost unstudied. It is explained by the fact that the disease appeared in the form of sporadic cases. In such situations it was often impossible to discover the pathogen, find the disease source, discover the mechanism of its spreading. The situation changed when the Far East scarlatiniform fever mainly manifested by massive epidemic outbreaks was brought to light in the Far East.

Yersiniosis mainly embraces the urban population as in the cities there are more opportunities for the development of big outbreaks among the contingents of people united by public feeding. On the other hand, a more active revealing and better diagnostics of the disease as compared with the rural area is of a certain importance. Children fall ill the most often as compared with the other age groups of the population. The epidemic outbreaks are quite often observed in the organized collectives, especially, the preschool ones. First of all such outbreaks depend on the conditions of the fruit and vegetables storage as well as the condition of feeding the population.

Animals are a reservoir of the infection under the natural conditions. The pseudotuberculosis microbe was isolated from the organs and excrement of many kinds of the mammals, birds, reptiles, fish and arthropoda. Such a diverse and spontaneous infection of many kinds of animals by the pseudotuberculosis microbe gives a ground to think that none of them are a specific biological host of this pathogen and it testifies that in case its ubicvator spreading in nature all kinds of animals get involved in the general process of the microbe circulation and serve as a short-term or prolonged reservoir of the pathogen depending on the species susceptibility to it.

Rodents are the most frequent reservoir of the pseudotuberculosis microbe. It is explained by the fact that on the one hand, rodents are distinguished by a high susceptibility and sensitivity to the pseudotuberculosis microbe and on the other hand, they are considerably widespread on the Earth and the speed of their replication is high.

The infection of humans can occur at a direct contact with domestic and wild animals, birds while skinning them and processing the carcasses. A possible mechanism of the infection of humans is using the food and water contaminated by the discharge of rodents and birds – carriers of the pseudotuberculosis microbe. Besides this there is a number of convincing investigations confirming that soil is a reservoir of the pseudotuberculosis pathogens. The authors think that the pseudotuberculosis microbe cannot exist in the soil for a long time without reproduction as it cannot form spores. It has saprophytic and parasitic characteristics and correspondingly has two natural biospheres of existing – the

warm-blooded animals and environment. The pseudotuberculosis pathogen was isolated during the bacteriologic investigation of the soil from the fields where vegetables and edible roots, as well as wash-outs from them (beet-roots, carrots, cabbages, onions, potatoes).

The epidemiological examination of many outbreaks of the disease made it possible to ascertain that among all the food staffs vegetables, edible roots, dry food, some dry products, which are eaten without any thermal processing, are of the most importance in the pathogen transmission. The importance of vegetables and edible roots as a factor of the pathogen transmission was proved by the isolation of the pseudotuberculosis microbe from them during the outbreaks, the microbes were identical by their serologic variant to the cultures isolated from the sick people who had eaten that food. Such outbreaks most often occur when dishes from fresh cabbage are used as food at the public feeding places.

Besides vegetables and edible roots, the second important factor in the pseudotuberculosis pathogen transmission is dairy products. Such dairy products as cottage cheese, sour cream are the most important. It is necessary to note that the pasteurization of milk (at a temperature of 65 °C for 30 minutes) does not destroy the pathogen.

Water can also be a factor of the pseudotuberculosis microbe transmission under the favorable conditions.

Pathogenesis

The pathogens mainly penetrate the human organism through the mouth with the infected food and water. A further movement of the microbes to the esophagus and then stomach characterizes this phase. The acid medium of the stomach contents ruins most pathogenic microbes of the intestinal group perhaps including the pseudotuberculosis pathogen. Having overcome the stomach barrier, the pathogen gets into the intestines and an enteral phase develops, it is characterized by the penetration of the microbe into the mucous membrane of the intestines, then it goes to the regional mesenteric lymph nodes along the lymph paths. Here they reproduce and accumulate, later overcoming the lymphatic barrier the bacteria penetrate the blood and cause the reciprocal reaction of the organism to the toxic substances, which get into the blood vessels during the destruction and life of bacteria.

In rare cases an airborne way of infection, even marking out a pulmonary form of this infection. The pseudotuberculosis microbe possesses pneumotropism with the development of pneumonia and even lung abscess. As the clinical picture of pneumonia develops in later terms of the disease in experimental pseudotuberculosis, the lungs may be only an entrance gate for the development of the generalized process. Taking into account all the mentioned above facts, there is a ground to suppose that irrespective of the entrance gate pseudotuberculosis immediately takes a course of a generalized infection.

The pathological process can stop at any of its phases. The pathogen of the disease can be blocked by the secretory immunoglobulins even on the mucous membranes of the intestines and respiratory tracts. While overcoming this barrier yersinia pseudotuberculosis penetrate the regional lymph nodes. Different macrophagal elements, immunoglobulins and immunocompetement cells take defensive measures.

The clinical process has periods of remissions and acute conditions. The recovery occurs after any phase. Thus, in human pseudotuberculosis there are two expressed pathogenic stages: 1) the pathogen penetration, primary and regional focal manifestations of the disease; 2) bacteriemia, hematogenic drift and septicemia, which develops, as a rule, after the first period, though sometimes it is not expressed distinctly.

The hematogenic dissemination of the pseudotuberculosis pathogen results in the development of the phase of the secondary focal changes in the organs and tissues. As a rule, this stage is accompanied by an expressed organism allergization.

The following phase of the pseudotuberculosis pathogenesis development is the phase of the specific immunity increase, which is followed by the release of the organism from the pathogen and recovery. Cultivating a strong antimicrobic immunity completes the disease. The possibility of the development of the disease chronic form is very rare.

Anatomic pathology

The pathoanatomists have found small necrotic or abscess-like grayish-white nodes in the enlarged liver and spleen, as well as in the lungs. Many researchers call these abscesses necrotic granulomas. Such granulomas with the central necrosis are considered to be a characteristic symptom of pseudotuberculosis. Besides this, there is swelling and necrosis of the lymph nodes follicles of the intestines and mesentery, hyperemia of the peritoneum covering them, edema and infiltration of the distal part of the iliac and proximal part of the large intestine, catarrhal-desquamative and ulceric enteritis (ileitis), congestion plethora, brain edema, dystrophy of the parenchymatous organs and hemorrhages in them. In some cases there is a picture of catarrhal, phlegmonous and gangrenous appendicitis.

Clinical manifestations

The diversity of the pseudotuberculosis clinical manifestations, the involvement of different organs and systems in the pathologic process are the basis for the suggestions of numerous classifications of this disease. The least cumbersome classification, though it does not lack drawbacks, is the classification by N.U. Zalmower, which is based on the syndrome principle with the following clinical forms:

1. A scarlatiniform characterized by the general intoxication symptoms, fine-dot rash, fever.

2. An arthralgic form resulting in the joints affection, it takes a course of arthralgia, less often − arthritis.

3. An abdominal form with the primary affection of different parts of the alimentary tract, sometimes in the initial period.

4. A generalized form with the affection of different organs and systems when it is impossible to pick out any main syndrome.

5. An icteric form, in which the affection of the liver with a jaundice syndrome is the primary symptom.

The clinical manifestations of pseudotuberculosis are characterized by a great polymorphism with the prevalence of the general intoxication, which makes an early diagnostics extremely difficult. As well as other acute diseases pseudotuberculosis has a certain cyclic recurrence. The development of the cycle's periods with a certain time limitation, which is accompanied by different morphologic, immunologic and clinical changes, results in a characteristic picture of the disease. There are following periods in pseudotuberculosis: an initial period, a high point, a period of acute courses and relapses, convalescence.

Evaluating the descriptions of the clinic given in the literature and observing the patients, it is necessary to note that in each certain case these periods can be manifested in different ways depending on the reactivity of the macroorganism, virulence of the pathogen, the time when the treatment began, the quantity of the daily and course doses of the medications and other factors. All the periods of the disease can be observed in the typical cases in half the patients (especially, in case of the pathogenic therapy and short courses of some antibiotics). In other cases some of them cannot be observed or they can be slightly manifested. There can be only some symptoms of the initial period without a temperature rise in the deleted forms of the disease.

Judging by the epidemiological history, the incubation period in this infection most often lasts 7-10 days with the fluctuations from 3 to 18 days. In this period the disease does not usually have any clinical manifestations, the people consider themselves to be practically healthy and continue working.

The initial period is the time when the first symptoms of the disease develop till the highest possible development of the clinical picture with the symptoms of the local affection.

In most patients the disease has an acute course with a rapid temperature rise, which is accompanied by chills. The prodromal phenomena in the form of malaise, slight chills, the development of uncertain pains in the abdomen, which developed 1-2 days before the onset of the disease, were described only in some cases.

This period is clinically characterized by expressed polymorphism and absence of specific symptoms typical of only this disease. The temperature rise is accompanied by a headache of different intensity with its primary location in the forehead and temple areas, pain in the muscles, joints, waist, general asthenia, weakness and lack of appetite. In a number of cases the sick people complain of

the pain in the throat at swallowing. In some cases patients complain of pain in the stomach, diarrhea 2-3 times a day, nausea and single or recourse vomiting. There is brief fainting in some patients in the first hours of the disease together with general asthenia. An early toxicosis resulting in a lethal outcome can develop in rare cases, especially, in children during 2-4 days.

While examining the patients it is possible to observe hyperemia of face and neck, some puffiness of the face, hyperemia of the conjunctiva and an injection of the sclera vessels, there is a pale nose-lip triangle in some patients. There is often herpetic rash on the lips and the nose wings, expressed hyperemia of the throat, which is of different intensity, less often − an enanthema on the soft palate, angina. During the first days of the disease the tongue has a grayish-white patch, which begins to clear and becomes raspberry with expressed papilla on the third day.

There are symptoms of acute catarrh of the upper respiratory tract such as a running nose, cough, pains in the throat at swallowing in most patients in the initial period of the disease. Similar symptoms of the disease sometimes result in diagnosing catarrh of the upper respiratory tract and difficulties in deciphering the outbreak.

Such diversity of symptoms testifies about the involvement of different organs and systems in the pathological process even on the first days of pseudotuberculosis infection, which is often the reason for a false diagnostics in this period. The most part of such patients are treated at home, the smaller part is sent to a hospital with the diagnoses: acute respiratory disease, polyarthritis, gastroenteritis, catarrhal angina, scarlatina and others. These diagnoses often remain the final ones as a doctor examines a patient for a second time only in the period of convalescence and does not pay attention to some important symptoms of the disease (rash, "raspberry" tongue, pain in the ileocecal area, etc.)

Rash is one of the most striking symptoms of this period. It develops on the 1-4th day of the disease, sometimes on the 5-6th day. According to its character it is often fine-spotted on the hyperemic background or normal skin. During the first outbreak of the disease in some patients it is fine-spotted, and in combination with angina, the enlargement of the submandibular lymph nodes, "raspberry" tongue, the development of peeling typical of scarlatina in the later period gave a ground to first diagnose "scarlatina" in all patients. Later during the development of other pseudotuberculosis outbreaks and the exposure of the sporadic cases of this disease it was found out that the rash can be spotty (looking like German measles and measles) and confluent erythematous. The spreading of the rash can be different, if it is spread all over the body, it is mainly located on the symmetrical parts. The rash is not often found on the face and neck. There is often hyperemia and swelling of the skin on the hands and feet − the symptoms of "gloves" and "socks". The petechial-hemorrhagic elements are mainly localized in the natural folds of the skin and on each side of the chest. The development of hemorrhages in the form of stripes and changes on the side surfaces of the shoulders and in the area of the armpit line. There are endothelial

symptoms of plait, pinch with hemorrhages in the patients with a severe form. The development of rash can be accompanied by the deterioration of the patients' condition, pulse acceleration, hypotonia and even a collapse condition.

There is scaly laminar peeling on the skin of the chest, abdomen, lobes of the ear and then on the dorsal surface of the hands, feet, palms during the 2-3rd week of the disease. The duration of the initial period is 1-5 days.

The highest point of the pseudotuberculosis infection is manifested by the maximum development of fever and other symptoms of intoxication and expressed signs of the local affection. The highest point of the disease, especially, the first days are characterized by considerable intoxication, which is manifested by the affection of the central nervous system – general asthenia, hypotonia, dizziness, intense headache, tactile hyperesthesia, photophobia, vomiting, insomnia, increased excitability or suppression. In a severe course there are manifestations of meningoencephalitis with the symptoms characteristic of it: a headache, nausea, vomiting, drowsiness, suppression, consciousness disorders, signs of irritation of the meninges and the substance of the brain. There are such meningeal symptoms as rigidity of the neck muscles, Kernig and Brudzinsky symptoms, in the cerebrospinal liquid the cytosis is more than 400 cells, the increased protein contents. Besides the mentioned symptoms there are characteristic disorders of the vegetative nervous system function. In some patients the affection of the nervous system is similar to the intercostal and nape neuralgia or lumbosacral radiculitis.

The changes of the locomotor system are observed almost in all patients. There is often arthralgia, sometimes with very intense pain in the sacrum, waist, joints and less often – acute polyarthritis, which is characterized by swelling of the tissues around the joints with skin hyperemia. The radiocarpal, interphalangeal, knee and ankle joints are most often affected in pseudotuberculosis, less often – shoulder and hip joints. Acute polyarthritis is often confused with the attacks of acute rheumatism in case of the poor knowledge of the pseudotuberculosis clinic. The pain syndrome depends on the severity of the disease and can be weak or strong, hindering free movement. The joints are swollen, painful, hot.

Most patients complain of myalgia in the acute period of the disease. It prevails in the muscles of the neck, abdomen, and extremities. In some cases myalgia of the abdomen muscles is sharply expressed, which simulates "acute abdomen". In such cases it is necessary to pay attention even to slight manifestations of other symptoms of the disease.

The submaxillary, neck and axillary lymph nodes can be enlarged in the acute period of the disease. They are slightly painful, elastic, not united with one another and the surrounding tissue.

The changes of the cardiovascular system at the highest point of the disease are manifested by hypotonia, dullness of the heart sounds, and in some patients there is a systolic murmur at the apex and extrasystole. In spite of the fact that in a considerable number of patients the subjective symptoms of the heart affection (pain, heartbeat, arrhythmia, and others) are extremely rare, the

electrocardiograms show changes, some of them are considerable. The decrease of P and T waves voltage is the most frequent of them, less often − the deformation as a result of the toxic-infectious influences on the cardiac muscle. There were sometimes symptoms of its diffusive affection.

The respiratory organs also get involved in the pathological process in pseudotuberculosis. Pain in the throat, hyperemia of the fauces mucous membrane, spotted enanthema on the mucous membrane of the soft palate, rhinitis, cough, dry rale in the lungs testify of their affection. There is dulling of the percussion sound over the pulmonary fields and moist rale in the limited areas in some patients who suffer a severe course of the disease. The x-ray investigations usually demonstrate the intensification of the bronchial-vascular picture, the opacity of the roots, less often − infiltration of the lung tissue.

In a mild case of the disease the affection of the alimentary tract is manifested by complaints of a poor appetite, nausea, less often − vomiting diarrhea. The stool is fluid or watery 3-5 times a day with admixture of mucous. The pain at the abdomen is observed in a half of the patients and is often revealed only at palpation. The tongue is furred, it becomes raspberry when it gets cleaned.

The changes of the alimentary tract are strongly expressed and prevail over the rest ones in a more severe course. In this case a pseudotuberculosis abdominal form is diagnosed. It is characterized with a pain in the epigastric area of the abdomen, umbilical or right iliac area, less often -in the right hypochondrium and left iliac area. The abdominal syndrome is clinically revealed primarily in the form of the symptoms of mesenteric lymphadenitis, terminal ileitis, acute appendicitis. Mesenteric adenitis of the pseudotuberculosis etiology without any other manifestations is quite often observed in the countries of Western Europe. The affection of the mesentery lymph nodes can occur in different periods of the infectious process, more often in the initial period and at the high point of the disease. In this case there is pain in the right iliac and paraumbilical area, the palpation demonstrates an enlarged, painful and "grumbling" cecum and mesenteric lymph nodes. Such patients come to hospital with various diagnoses: "acute appendicitis", "acute cholecystitis". These patients can come to both infectious and surgical hospitals, and only the carefully collected history of the disease and the clinical investigation data allow to diagnose pseudotuberculosis.

The intensity of pain in the ileocecal area can be different. In some patients that is revealed only at palpation, in others there are constant aches, in some patients they are so intense that the patients groan and take a forced position with their knees pulled to the abdomen. The patients cannot remain in the same position for a long time. The pain subsides and ceases troubling the patients on the 2-3th day from the time of their appearance. However, in 3-4 days they recommence and become more intense.

The local manifestations of mesadenitis are usually accompanied by general symptoms. They are temperature increase, sometimes up to 39 °C, chills, which intensify with the development of pain in the abdomen, diarrhea − 2-3 stools a

day without admixture of mucous or blood, nausea, and vomiting in almost half of the patients. Besides the patients complain of headaches, pains in the joints of the upper and lower extremities, body muscles, general asthenia, sore throat.

The skin of the face, neck, chest is often hyperemic in the patients with mesenteric lymphadenitis. In certain cases there is fine-spotted rash, which rise above the skin in the area of the chest, abdomen, groin folds, axillary region, forearms and thighs, the rash gets pale at pressing.

There is muscles tension and other symptoms of the peritoneum irritation, which are very similar to the picture of the "acute abdomen" in case of a severe course of the disease. However, in contrast to acute appendicitis in the mesadenitis patients the pain in the abdomen do not increase when the abdominal press is strained. This new symptom was observed in all the cases of pseudotuberculosis mesadenitis.

The clinic of acute appendicitis in pseudotuberculosis has its peculiarities connected with the fact that besides the affection of the vermicular process the patients have the manifestations of the main disease. As a rule, the patients, in whom the appendicular syndrome develops during treatment in the infectious hospitals or who arrived with the diagnosis "pseudotuberculosis" and have an expressed appendicular syndrome are not operated on, and the disease has a favorable outcome after the conservatory treatment. It is natural that such patients should be carefully observed by both an infectious doctor and a surgeon in order not to miss authentic appendicitis, whose pathogen can be pseudotuberculosis along with other microbes. It is known that the pseudotuberculosis microbe is isolated in about 7 % cases during the bacteriological investigation of the processes ablated during the appendectomy. The surgical aspects of pseudotuberculosis are of a great practical interest and need to be thoroughly studied.

Regional ileitis in the abdominal form of pseudotuberculosis is more often observed in the relapse and remission period of the disease. In this case the pains in the abdomen develop on the background of the seeming convalescence, they are accompanied by a recurring rise of the body temperature up to 38-39 °C and chills. The pain is usually moderate, it is of attack-like character. In 2-3 days from pain development it becomes less intensive, in some cases it ceases troubling a patient. However, on the 3-4th day they increase and become very intense.

In some patients pseudotuberculosis begins with the symptoms of regional ileitis. In such cases the pseudotuberculosis symptoms are poorly expressed. This results in the diagnostic mistakes. In case of regional ileitis the pain in the stomach is often accompanied by nausea. In half of the patients there is vomiting, sometimes repeated. The affection of the terminal part of the ileum can be accompanied by watery stool up to 3 times a day without an admixture of mucous and blood. The abdomen is sometimes bloated. The right iliac area is the most painful, there is also muscle tension of the front wall of the abdomen. The similarity of the clinical picture of regional ileitis to that of acute appendicitis is a characteristic feature. In many cases it is extremely difficult to diagnose the case before a surgery.

The patients with the pseudotuberculosis abdominal form often have gastroenteritis. Its development can be observed in all periods of the disease. Gastroenteritis usually has a rapid development. The disease starts with pain in the abdomen, nausea, vomiting, it is usually accompanied by the abdomen inflation, watery or pasty stool up to 2-3 times a day, general asthenia, chills, headache and other pseudotuberculosis manifestations. Sometimes gastroenteritis takes a chronic course. In these cases patients complain of the periodic pain in the abdomen, which disturb them, general asthenia, headache, general malaise. The stool in such patients is unstable. There is an expressed asthenia right after the meals. The pains in the abdomen can resemble attacks and do not have a distinct localization. The symptoms of the general intoxication are often expressed.

The affection of the alimentary system is not only limited by the pathologic changes of the gastrointestinal tract. The liver affection of any degree is often observed in almost half of the patients, actually it is acute parenchymatous hepatitis, its expressiveness depends on the severity of the disease. The affection of the liver is manifested by the enlargement of its size, icteric color of the skin and scleras, the bilirubin increase in the blood, it sometimes resembles the clinic of viral hepatitis.

The thorough comparison of the clinical symptoms with the biochemical investigations shows the involvement of the pancreatic gland in the pathologic process. The patients complain of pain in the abdomen, which resembles attacks and is localized in the epigastric area, in the right and left hypochondrium. In some cases it irradiates in waist or back. The patients complain of nausea, vomiting and general asthenia. There can be watery stool. The amylase level of blood and urine as well as the lipase activity in blood can confirm the diagnosis. Some authors pay much attention to elastase. In 1986 V. A. Ivanis noted that the elastase level depended on the severity of the disease and its indexes normalized in the period of convalescence.

The generalized form of the disease is characterized by the combination of a high temperature, exanthema, and severe intoxication with all the main syndromes of the disease: terminal ileitis, parenchymatous hepatitis, acute polyarthritis, meningeal symptoms and a long relapsing character.

Diagnosis

There are no reliable diagnostic tests on pseudotuberculosis among the nonspecific laboratory signs. In particular the blood clinical analysis is not informative. The changes of the morphological blood contents do not take place in all the patients and are of a moderate character.

The specific laboratory diagnostics of pseudotuberculosis is very important in its diagnosing. It is of primary importance in the mild and unexpressed forms of the disease, especially, occurring in the form of separate sporadic cases.

The main material for the bacteriologic investigation is excrement and in lesser degree − washouts from the fauces, urine and the appendicular processes, which are ablated during the surgery. The pseudotuberculosis patients excrete

bacteria with mucous from the fauces, excrement, urine. The duration of their excreting with mucous and urine is not long. The pseudotuberculosis pathogen is found in excrement during all the disease and in the period of relapses. In separate cases it can be excreted with excrement for about 75 days.

The serologic investigations began to be done after the discovery of the Far East scarlatiniform fever. In the beginning the agglutination reaction with alive cultures as an antigen was used, later a reaction of indirect hemagglutination as well as the reaction of the bacterial lysis, method of fluorescent antibodies and others. In spite of the fact that the pseudotuberculosis diagnostics is improving every year, it does not satisfy the practical doctors so far. The percentage of the bacteriologic confirmation of the diagnosis remains low, and the reaction of indirect agglutination, which is used everywhere, is not enough sensitive and specific. The reaction of coagglutination and immune ferment analysis, which make it possible to discover both the antigen and antibodies to it during the first 3-5 days from the disease onset, is considered to be promising.

Differential diagnosis

The variety of pseudotuberculosis clinical manifestations often causes big amount of diagnostic errors. Thus, acute beginning, intoxication, headache, cough, face reddening can be considered as influenza. Fever, intoxication hepatomegaly, lymphadenopathy, sore throat make us think about infectious mononucleosis. In case of catarrhal manifestations, intoxication, characteristic skin eruption measles and rubella should be excluded. The list of diseases to be considered in process of pseudotuberculosis differential diagnostics could be continued. So such main disease characteristics should be taken into account in order to make correct diagnosis: period of disease, its recurrence, polyorganic disorders due to pseudotuberculosis, correct interpretation of laboratory findings. Sometimes only results of bacteriologic research can verify the diagnosis.

Treatment

It is impossible to agree with the recommendations of some author about the possibility of treating the pseudotuberculosis patients at home. In spite of some positive results the possibility of sudden acute forms development and relapses obliges to treat the patients only in hospital and to follow thoroughly the regimen and an according nursing.

The patients do not need a special diet. The nutrition is typical of the patients with an acute fever. The food should be easily assimilating and high-calorie, containing a sufficient amount of vitamins. A daily food allowance should contain 3,200-3,500 kcal. The patients with the predominant liver affection, are prescribed diet № 5 containing a sufficient amount of carbohydrates and a limitation of fat, especially, refractory.

The treatment depends on the clinical form, the period and gravity of disease. Among etiotropic agents there are used levomycetin, metacyclin, tetracyclin,

streptomycin, gentamicin, ampicillin in moderate therapeutic doses during not less than 7 days and more. At severe course of disease, the septic form the best results can be gained if simultaneously use 2-3 antibiotics and one of them infuse into vein: course of treatment prolongs up to 10-14 days, and through 6-7 days it is replaced by preparations with the account of antibioticosensitivity of allocated yersinias. Cefazolin (kefzol), cefotaxim (claforan) are effective as alternative preparation may be bactrim (biseptol). Less effective are nitrofuranes and sulfanilamid preparations.

With the purpose of desintoxication and rehydratation of the organism 5 % solution of a glucose, a seralbum, reopolyglycin, threesault, quartasault are indicated. Widely there are used vitamins, antihistamine preparations and agents stimulating regenerative processes – diprazin, suprastin, tavegil, methyluracil (methacil), pentoxyl, apylac, natrii nucleinic, thymalin etc. At gastroenterocolitic form enterosorbents (activated microspherical coals, sillard P, enterosgel, smecta), replaceable fermental therapy (festal, pancreatin, pancurmen, pancitrat), diet № 4 are indicated. Colibacterin, bificol and other biological preparations are indicated in case of development of dysbacteriosis. At acute tonsillitis gargles should be indicated. Development of arthritis, myocarditis, Reiter syndrome is the indication to use indomethacin, ibufrofen, diclofenac-natrii (ortophen) and other not steroid preparations.

All the patients are prescribed vitamin therapy in the form of complex B, vitamins A, C, PP and others.

The therapeutic tactics should be strictly individual in case of every patient who is to be constantly looked after. Only an individual approach and a complex of the treatment measures can bring invariable success and allow to achieve good results.

Prophylaxis

In spite of the achieved success in the pseudotuberculosis study, the problems of the specific prophylaxis have not been worked out so far.

A complex of nonspecific measures directed at the source and transmission factors is widely used in the medicine to prevent the pseudotuberculosis spreading.

Control questions:
1. Etiology, epidemiology, and incidence of pseudotuberculosis.
2. Pathogenesis of pseudotuberculosis.
3. Anatomic pathology of disease.
4. Main clinical symptoms and signs of pseudotuberculosis.
5. Laboratory methods of pseudotuberculosis diagnostics.
6. Criteria of diagnosis.
7. Differential diagnosis of pseudotuberculosis.
8. Treatment of pseudotuberculosis.
9. Prophylaxis of pseudotuberculosis.

LEPTOSPIROSIS

Leptospirosis is an acute generalized infectious disease, characterized by extensive vasculitis, caused by spirochetes of the genus *Leptospira*. It is primarily disease of wild and domestic mammals; humans are infected only through direct or indirect contact with animals.

Historic reference

A. Weil (1886) was the first who described leptospirosis as an independent disease, four cases with a high temperature, jaundice, hemorrhages and the renal affection.

R. Virchout (1865) considered the described disease as a kind of typhoid fever and called it "typhus biliosus" differentiating it from "katarrhalischen icterus".

In 1888 in the book "Infectious Jaundice" S.P.Botkin's disciple N.K.Vasiliev informed about twelve cases of a similar disease but did not paid much attention to the character of the temperature, the expressiveness of jaundice, the time when hemorrhages and the renal affection appear, he comes to the conclusion that the new disease is different from typhoid fever and catarrhal jaundice.

For a long time leptospirosis was divided into icteric and non-icteric forms. The first description of non-icteric leptospirosis was given by W.A.Bashenin in 1928, he suggested naming me disease "water fever".

Leptospirosis is registered in many countries.

Etiology

The leptospirosis pathogen belongs to the genus of *Leptospira nogychi* and can be divided into 2 kinds – parasitic and saprophytic. There are hundreds of serotypes in each kind. The body of the leptospira consists of a long axis thread which is covered with a cytoplasmatic spiral that has a three-layer membrane. The average length of leptospiras is 10-14 mkm, the number of cons – 10-12. There are no spores or capsules. Leptospiras have energetic and complex movements. This explains their high invasive ability. Leptospiras do not get well painted with common aniline dyes. Some special liquid media containing animal (rabbit) serum are used to cultivate leptospiras. Leptospiras are unstable in the environment but are adapted to living in water.

The leptospira life time in water oscilates within wide limits – from several days to many months depending on pH, the salty composition and the microflora of the reservoirs.

It has been discovered that leptospiras have hemolysin and also lipases that can have a cytotoxic influence on the organs and tissues which are rich with lipids. There is endotoxin in the leptospira cells.

The modem classification of leptospiras is based on their antigenic structure. There have been discovered 200 serovars united in 25 serological groups.

There are two active serologic complexes among the antigens of leptospiras each of them has a complex set of components. One of them is situated on the cell surface and determines its typospecific qualities, the other − in the depth of the microbe and characterizes genospecific peculiarities of leptospiras.

The vital capacity of leptospiras in the environment depends on many factors. There is a considerable discrepancy in the whimsicality of leptospiras (the necessary conditions of their survival are high humidity, warmth, pH of the water and soil 7.0-7.4, the limited amount of salt). In the water of the rivers, pools, lakes and marshes leptospiras remain viable for 5-10 days but in the sea water they die in several hours. Leptospiras remain viable in the damp soil up to 270 days, in dry soil − not more than 3 days. Leptospiras can easily endure low temperatures and remain viable during prolonged freezing, however, they quickly die when warmed, dried if exposed to salt or acid.

Epidemiology

Leptospirosis is a zoonotic infection. The source of the infection is animals wild, domestic and game animals (pigs, cattle, foxes, white foxes, nutrias and others). They form anthropurgias foci.

The small mammals who live in the forests, near the reservoirs (volemice) play the main role in maintenance the leptospirosis foci. Their infection takes a form of a symptomless chronic process in the kidneys. Leptospiras multiply in the tubules of the kidneys and go out with urine.

The natural foci are situated in low lying areas. They are marshes, flood-lands, water-meadows, the marsh-ridden parts of the rivers and irrigation system, overgrown with bushes and abundant grassy vegetation. The infection of people in the natural foci is of a seasonal character (June-September), it usually occurs during the agricultural work (mowing the meadows, collecting hay, growing rice, flax, hemp and other abundantly irrigated crops, felling and during hunting, fishing, gathering mushrooms, drinking water and washing with water from the contaminated shallow reservoirs). The morbidity in the natural foci has a sporadic or group character. The development of natural resources, unorganized rest result in the immediate contact of people with nature and create an opportunity for infecting people with leptospiras. The natural foci are the source of infection for the domestic animals.

In recent years the gray rat has been playing a more important part in the epidemiology of leptospirosis, its infectedness has been proved in many countries of the world. For a long time leptospirosis was considered a disease of big cities, mainly ports. However, in the present situation the intensive processes of urbanization, creation of large cattle-breeding complexes, growing rice and other elements of the economic activity of man gave changed the ecology of the gray

rat, so the anthropurgias foci of leptospirosis can be both in the rural areas and in the cities.

The foci which appear in the cattle-breeding industries as a result of bringing animals that are leptospira-carriers or infecting the cattle, pigs m the natural foci in the pastures, watering-places play the most important part in the epidemiology of the disease. The agricultural animals often have leptospirosis in the obliterated, symptomless form. That is why the sick animals are not isolated in time, they excrete leptospiras into the environment and infect water, forage, pastures, soil.

In many big cities, especially ports, there is a high rate of leptospirosis among the gray rats. This is the reason for the citizens to fall ill with leptospirosis if due to their occupation they contact sinanthropos rodents or the things contaminated by them.

The clinical symptoms of leptospirosis among dogs had been described before the pathogen was discovered and the term "*leptospirosis*" appeared. In 1898 in Stuttgart there was described a disease of dogs which had the following symptoms: hemorrhagic gastroenteritis, ulcerative stomatitis, renal affection (Stuttgart disease).

The infection is mainly transmitted from animals to humans by water. The contact way is considerably less important. The transmission of the infection through food is rare. Humans can be infected while swimming in the reservoirs, drinking water from them or using it for economic needs, during different kinds of the agricultural work in the marsh-ridden places, when fishing. There have been described some cases of leptospirosis infection among the personal of the slaughter-houses, meat-packaging plants.

The leptospirosis incidence increases in June-September. In other months some sporadic cases are registered, which are not connected with the infection in the open reservoirs.

Leptospirosis can be considered as professional disease. The people who are involved in the agricultural work in the marsh-ridden places fall ill more often, they include cattle-breeders, the personal of meat-packaging plants, miners, dockers, plumbers.

There have been some cases when people fell ill after being bitten by a coypu rat, as well as the personal of the laboratories, who work with leptospiras. The susceptibility of people to leptospirosis is high. A typospecific immunity remains for a longtime after having the disease.

Pathogenesis

The pathogenesis of leptospirosis is characterized by changing several phases. The first phase includes the pathogen penetration and a short-time primary leptospiremia. The leptospiras penetrate the human organism through the skin of the mucous membranes, travel along the lymph tracts, penetrate the blood and then various organs − the liver, kidneys, adrenal glands, spleen, lungs and others. This phase lasts 7-20 days, it corresponds to the incubate period.

The second phase includes secondary leptospiremia, it coincides with the beginning of the clinical manifestations of the disease, the generalization of the process. The leptospiras penetrate the organs and tissues with the blood flow again, fix on the cell surface (especially, in the kidneys, liver, adrenal glands), can overcome the hametoencephalic barrier. The leptospiras do not cause a destruction and they do not parasites intracutaneously. They stick to the cell surface, can stay in the inter-cell space.

The third phase is a phase of toxinemia that is accompanied by an expressed fever. The most important pathogenic factor of this phase is capillary toxicosis. The rupture of the capillary endothelium results in the diapedesious hemorrhages into various organs and tissues. It is clinically manifested as a hemorrhagic syndrome. Thrombocytopenia plays a part in the origin of the hemorrhagic syndrome, it is connected with the influence of the leptospira lipase on the phospholipids of thrombocytes membranes and their gluing together with the formation of the primary thrombocytous congestion. The vessels of the liver, kidneys, adrenal glands get affected most of all, there may develop Waterhause – Fridrichsen syndrome. The degenerative and partially necrotic changes of the liver parenchyma as well as hemolysis oferythrocytes under the affection of hemolysins are the cause of jaundice which has a mixed character.

The influence of leptospiras and their metabolites on the cellular wall results in the affection of the adrenal gland epithelium, all the cortical and subcortical layer of the kidney that results in the uropoiesis affection. There is a possibility of the development of renal insufficiency.

The fifth phase includes the formation of the sterile immunity. The tense humoral immunity is combined with the expressed local organic and cellular immunity. Then a stable recovery comes.

Anatomic pathology

Leptospirosis is characterized by the affection of the capillary endothelium of a various organs and tissues. The walls of the vessels are fragile, their permeability is increased, this is accompanied with numerous hemorrhages in the kidneys, liver, lungs, endocardium and pericardium, mucous membrane of the gastroenteral tract. The liver is enlarged, plethoric and with smooth surface.

The histological investigation shows an edema of the interstitial tissue, dystrophy of the hepatic cells without an expressed cytoptesis of hepatocytes, biliary thromboses in the central zone of the lobules.

The most considerable changes can be found in the kidneys. The kidneys are considerably enlarged, there are such typical symptoms as a stroma edema, numerous hemorrhages, a sharply expressed granular degeneration of the convoluted tubules epithelium up to necrosis. The kidney affection in leptospirosis can be considered as nephrosonephritis.

There are hemorrhages in the adrenal glands, sometimes considerable. The muscle affection is also characteristic of leptospirosis, especially the affection of

musculus gastrocnemius and musculus thoracic. There are hemorrhages of various sizes; an uneven swelling of the fibers, degenerative changes in the synapses of the muscular fiber and nerve, sometimes coagulation necrosis which causes myalgia.

Dystrophy and lipid dystrophy develops in the heart muscle, sometimes there is interstitial myocarditis. There are hemorrhages in the lungs as well as in other organs. There is often an edema of the meninx vasculosas.

Clinical manifestations

The course of leptospirosis can be mild, middle-moderate and severe. The severity of the course depends on the microbe virulence, the dose of infection, the reactivity of the microorganism.

The main criteria of the severity are follows: the degree of toxicity, the expressiveness of the affection of the liver, kidneys, central nervous system, heart, adrenal glands, hemorrhagic manifestations.

There are cycles in the leptospirosis course. There is and incubate period, the beginning, height and convalescence.

The incubate period lasts 2-20 days (more often 7-10 days). The disease has an acute onset. The patient can indicate not only to the date but even the hour of the disease onset. The fever usually has a remitting or constant character, it lasts 5-9 days then it falls down in the form of accelerated lysis. There can be another wave (a relapse).

From the first hours the patients complain of intense headaches, pain in the muscles, especially, musculus gastrocnemius, the muscles of the scalp, neck, back and abdomen. In 1888 W. P. Vasiliev wrote that there is no such an intensive myalgia in the musculus gastrocnemius in case of any other disease. The abdomen pain can be so intense that there is a suggestion about an acute surgical pathology.

The symptoms of toxicity increase. The patients are flaccid, adynamic. The patients has a characteristic appearance — the face is edemic, hyperemic, the vessels of the scleras are injected.

There is often herpetic rash on the lips. In some patients (in 30 % cases) a polymorphic symmetric rash which stays for several days appears on the third — fifth day of the disease.

In some cases there is an enlargement and painfulness of the peripheral lymph nodes. The liver gets enlarged early, on the second-third day of the disease. Jaundice develops in the moderate severe — course as well as in the severe course. The liver has a dense consistence, it is painful at palpation. In a half of the patients the spleen gets enlarged.

There are considerable changes in the cardiovascular system: dull heart sounds, sometime relative bradycardia, arrhythmia, extrasystole. In case of an expressed toxicity the arterial pressure sharply decreases (up to collapse) as a result of a decrease of the precapilary arteries.

The initial period of leptospirosis is characterized by the peculiar changes in the central nervous system, in some patients there are such symptoms as

disorders of the consciousness and even unconsciousness, cramps besides an expressed persistent headache, insomnia, delirium. In 10-40 % cases there are meningeal symptoms: rigidity of the occipital muscles, Kernig's sign, Brudzinsky's sign that are distinctly manifested on the fifth-eighth day of the disease. In such patients the spinal puncture confirms the diagnosis of serous leptospirous meningitis – cerebrospinal fluid flows out under an increased pressure, it is transparent. The microscopia of the cerebrospinal fluid shows leptospiras, during the regular one outside the dark field of vision – moderate lymphocytic pleocytosis. The amount of protein is increased. Leptospirous meningitis usually has a nonmalignant character, it usually lasts 8-10 days.

At the end of the first week, and sometimes earlier. Jaundice develops in some patients (12-20 %). The intensity of jaundice and its duration depends on the severity of the disease and can last several weeks (1-4). A moderate skin itching is quite possible. The urine is dark, the color of the excrements is not changed.

With the development of jaundice the condition of the patients usually worsens. The most severe manifestations of leptospirosis appear at the end of the first week – at the beginning of the second week of the disease.

The hemorrhagic syndrome appears on the seventh-tenth day: petechial eruption on skin, hemorrhages under the conjunctive, hemorrhages in the nose, gums, stomach, intestine, uterus. The hemorrhages can be repeated, massive and result in anemia. Many clinicians have observed that the expressiveness of the hemorrhagic syndrome corresponds the severity of leptospirosis and has a certain prognostic significance (Fig. 7). The degree of the kidneys affection is even more significant while evaluating the severity of leptospirosis, the kidneys are always affected to some degree in leptospirosis.

From the first days of the disease there can be oliguria, moderate proteinuria, in the urine there are fresh erythrocytes, leukocytes as well as hyaline casts and the cells of the renal epithelium. The symptom of the kidneys affection become the most expressed from the seventh-tenth day of the disease. Oliguria can be followed by anuria, an acute renal insufficiency may develop, m spite of the development of an acute renal insufficiency, there is usually no edema and arterial hypertonia in leptospirosis. Sometimes an acute renal insufficiency develops very early, on the fourth day of the disease. It is an acute renal insufficiency resulting in uremia that is a frequent cause of the lethal outcome of the disease. If the therapy is timely and adequate, the kidneys affection in leptospirosis can be cured. Oliguria is followed by polyuria, and function of the kidneys gets gradually normalized.

The second week corresponds to the height of the disease. At this time jaundice becomes the most intensive, the hemorrhagic and meningeal syndromes increase or appear for the first time. The changes in the cardiovascular system increase: the pulse is rapid and weak, a systolic murmur is sounded in the apex cordis, there can be extrasystolia. The electrocardiogram shows diffusive changes of the myocardium.

At this period of the disease the infiltrates connected with the hemorrhagic foci are sometimes formed in lungs, this is accompanied by the sanguinolent sputum secretion.

By the end of the second week the condition of the patients improves. The headache and myalgia reduce, the jaundice intensity gradually decreases, a great amount of urine begins to excrete. The patients feel weak for a long period. The duration of the disease averages to 3-4 weeks. Some patients (20-60 %) may have relapses. In 5-7 days after the feverish period the temperature rises again, headaches and myalgia appear. The relapses and acute forms are not so severe as the first phase, as a rule. The temperature does not usually rises very high, the fever does not last more than 2-3 days. Some patients have 3-4 acute forms of relapses.

In leptospirosis the hemogram is characterized by the progressive anemia, a low reticulocytes number. In the patients with a hemorrhagic syndrome there is expressed thrombocytopenia, an increased period of the blood coagulability. Leukocytosis is a characteristic feature. The number of leukocytes increases up to $12\text{-}25 \times 10^5$ in 1 mkL. In the differential blood count there is neutrophilia with a shift to the left, expressed lymphopenia. The ESR reaches 40-60 mm/h.

The bilirubin amount in blood increases in case of the icteric form. The level of prothrombin may moderately decrease. The activity of transaminases is either normal or slightly increased on the tenth-fifteenth day of the disease.

The asthenovegetative syndrome is a characteristic feature of the convalescence period. Anemia and proteinuria remain for a long time.

Some patients have eye affections – uveitis, iritis, iridocyclitis that develop in 2 weeks and in several months after the onset of the disease. There can be other complications in the acute period – massive hemorrhages, an acute renal and hepatic insufficiency, uremia, myocarditis, an acute cardiovascular insufficiency.

Complications

The most common complications of leptospirosis, which are characteristic for its severe course are infectious-toxic shock, renal-hepatic failure, massive internal bleeding, DIC-syndrome, acute heart failure.

Diagnosis

It is quite difficult to diagnose leptospirosis, especially during the first days of the disease. The bacteriological method is of a little practical importance because leptospiras grow badly and slowly on the artificial media. The correctly taken epidemiological history plays the most important part in diagnosing leptospirosis. It is necessary to take into account the patient's occupation, his contact with agricultural animals, work in the meadows, swimming in the rivers and ponds, the existence of rodents in the surroundings. The epidemiological history not only determines the direction of diagnosis but gives an opportunity to control the environment. The following peculiarities of the clinical symptoms

are taken into consideration: jaundice, accompanied by fever, myalgia, hematuria, hemorrhages. The diagnosis based on the clinical-epidemiological investigation, is confirmed by the laboratory data.

The materials used for diagnosing leptospirosis are blood, urine, cerebro-spinal fluid.

The following methods of the laboratory diagnosis are used:

1. Bacteriological, bacterioscopic.
2. Serologic.
3. Biologic.

The bacteriologic investigation includes the primary microscopia of the initial material and its inoculation of media for acquiring the leptospira clean culture. The patient's blood serum, cerebrospinal fluid or urine are centrifuged. The fall out is investigated with microscope in a dark floor. Leptospiras are found as thin sinous mobile threads that look grayish-whitish on the dark background. That is necessary to note that the presence of leptospiras in blood is undoubtedly indicative of leptospirosis, but the negative result does not allow us to exclude the disease. The initial material inoculation of the water-serum medium consists of the native rabbit serum. The inoculation is incubated for 30 days at a temperature of 28-30 °C, the inoculation is examined on the dark floor of the microscope every 5-7 days.

The serologic investigations are done in the dynamics of the disease including the convalescence period. The reaction of the microscopic agglutination and lysis, as well as the complement fixation reaction are used to find antibodies in the serum of the sick people.

The reaction of the microscopic agglutination and lysis are done by a drop method with various serums of the patient's blood and with those leptospira serotypes which can be found hi this area. The results of the reaction are taken into account with the help of a microscope with a dark floor. In the positive case there are phenomena of sticking together, the leptospira agglomeration in form of small "spiders" and different degrees of their lysis. The titer is considered to be diagnostic when the serum is diluted 1:50-1:100.

The specific antibodies are discovered in the patient's serum at the end of the first − the beginning of the second week of the disease. The antibodies can remain in patients for several years, that is why the investigation of the twin serums are of a great diagnostic importance.

Leptospiras appear in liquor later than in the blood, that is why its investigation (microscopia and inoculation of the same media as the blood) are done when there are symptoms of meningitis. Urine can be investigated from the first day to 3 months from the disease onset.

The guinea-pigs that are very sensitive to *L. icterochaemorrahaigae* are used as a model for the biological test. The animals are infected by injecting the infected material (blood, urine, cerebrospinal fluid taken sterile from the sick

person) intraperitoneally, intracutaneously, intravenously, through the scarified skm and mucous membranes. The material is taken at the time when the bacteriological and bacterioscopic investigations are done. The animals die if there are leptospiras in the initial material.

Differential diagnosis

However, in some cases there are diagnostic difficulties because of the polymorphism of the clinical picture, separate symptoms of which make it difficult to diagnose a disease (jaundice, fever, abdomen pain, myalgia, meningeal syndrome).

First of all it is required to differentiate the disease from flue, typhoid fever, hemorrhagic fever with a renal syndrome (HFRS), virus hepatitis, meningitis.

In case of flue the headache has a distinct location (in the superciliary arch area), there is no hepatosplenomegaly, jaundice. There are expressed catarrhal symptoms. The hemogram shows leukopenia, neutropenia, the ESR is usually normal. The fever last from 2-3 to 5 days.

If there are such symptoms as an acute onset of the disease, a high temperature, intense headaches, the appearance of the patients, the liver and spleen enlargement, it is necessary to differentiate leptospirosis from typhoid fever. However, the following symptoms are characteristic of the initial period of typhoid fever: Kiari-Avtsin's sign, Govorov-Godelie's sign, Rozenberg's sign, and early increase of the spleen. There appears massive roseole-petechial eruption on the side surfaces of the breast, abdomen, extension surface of the extremities.

In HFRS there are no pains in the musculus gastrocnemius, there are such characteristic symptoms as loin pains, Pasternatsky's positive sign, petechial eruption located in the area of the shoulders and armpits. There is prolonged hypoisosthenuria, and in the urine fall out there are waxy casts, degenerative cells of the renal epithelium besides erythrocytes, hyaline casts. There is no jaundice and meningeal syndrome. The hemogram shows leukopenia at the increased ESR at the onset of the disease.

Virus hepatitis has a gradual onset, without chills, the temperature rises at the pre-icteric period. Muscle pains, scleritis, conjunctivitis are not characteristic of it. There are no meningeal and renal syndromes. The activity of transaminases is considerably increased. The hemogram shows leukopenia, low ESR.

If it is necessary to differentiate leptospirous meningitis form serous meningitis of another etiology, it is necessary to take into account the epidemiological history, pain in the musclus gastrocnemius; the development of the meningeal syndrome in 4-6 days after the disease onset, the simultaneous affection of the liver, kidneys; hemorrhagic syndrome.

Treatment

The most effective etiotropic agent is combination of antibiotics and antileptospirosis immunoglobulin if they are indicated in an initial stage when leptospires are in blood. Benzylpenicillin, tetracyclin, erythromicin and streptomycin

are indicated more often. The daily dose of benzylpenicillin can be changed from 3 to 12 millions units, however, the dose 6 – 8 millions units is more often indicated per day (in a muscle). It dosage depends on gravity of the disease course. The maximal dose of a preparation is indicated at development of meningitis. Ampicillin, oxacillin, ampiox are effective semisynthetic penicillins. Benzylpenicillin or semisyntetic analogue can be combined with streptomycin, tetracyclin is indicated 0.2-0.3 gm 4 times per day, it less often, than penicillins, causes reaction such as Yarish-Gersgeimer, however strengthens a permeability of vascular wall and promotes development of a hemorrhagic syndrome. It is contrindicated at the icteric form of leptospirosis fever and development of renal failure. Treatment with antibiotics is carried out during all feverish period and 2-3 days of normal temperature. In case of occurrence of relapse a new course of an antibiotic therapy must be indicated.

Clinical observations of last years has testified the inefficiency heterogeneous antileptospirosis immunoglobulin, oppression of immune system by it. The allogenic donor immunoglobulin which is effective in the first 3-5 days of disease are applied in medical practice, has no side-effects. The preparation prevents development of acute renal failure.

With the purpose of desintoxication and improvements of microcirculation in a vein there are infused solution of glucose, reopolyglucin, rheogluman, threesaultl, quartasault, and ascorbic acid. Good desintoxication effect is produced by the preparations that neutralize ammonia: rnithine, ornicetil, glutargin. At severe intoxication prednisolon and its analogues are indicated. The initial dose of prednisolon is 60-120 mg and more, it is used for short course, quickly reducing dose in process of clinical improvement. Enterosorbtion with using of granulated coal SKN, sillard P, enterosgel, polyphepan can be effective. At the icteric form there should be prescribed diets № 5, 5A, and at pathology of kidneys – a diet № 7.

At the development of the disseminated intravascular coagulation (DIC) carry out a complex of medical actions according to hematological research. At I stage (hypercoagulation) infuse in a vein heparin 2,500 units 4 times per day, reopolyglycin, dipiridamol (curantyl), pentoxyfilin (trental) contricali in bottles, ascorbic acid 5 % solution in ampoules 1 mL: 5-10 mL 2 times per day. At II stages heparin can be infused under the control of blood clotting time, other preparations (reopolyglycin, curantyl, trental) – in the same doses, as at I stage of syndrome. At III stage of DIC infusing of heparin is not indicated. At hypocoagulation there is indicated native plasma or cryoprecipitat of plasma, trombocite mass. At hypofibrinolisis there are given acid aminocapronic, contrical, gordox, at secondary hyperfibrinolysis – synthetic antifibrinolitics, inhibitors of proteases – streptokinase, fibrinolysin are indicated.

At the bleeding with a tamponade cold, and infuse calcii chloridum, vicasol, aminocapronic acid are used. Infusions of a blood plasma, a red cells mass, albumin are indicated at bleeding. If hepatonephric insufficiency develops simultaneously plasma transfusion of blood with infusion of erythrocytar and

trombocytar mass 2-3 times, and are used instead of albuminous preparations, a mixture of amino acids, for example alveosin-neo is recommended.

In occurrence of acute renal insufficiency (oliguria, hypoisosthenuria) there should be repeated lavages of stomach and an intestine 2-4 % solution of sodium hydrocarbonate, intravenous infusion of 40 % of glucose solution, euphyllin, mannit. At later infuse furosemid (lasix). At development of metabolic acidosis indicate natrii hydrocarbonas and Tris-buffer. If medicamental therapy is not effective and oliguria stage lasts more than 3-4 days, there is a necessity in plasmaferesis or plasmasorbtion or extracorporal dialysis by means of artificial kidney.

Prophylaxis

The deratization and sanitation veterinary measures are the essential part of the prevention. Deratization is for decreasing of the activity of the natural foci (wild rodents control) and the sanitation of the anthropurgias foci (the sinanthropos rodents control).

One of the directions of leptospirosis prevention is the actions which break the transmission of the disease by water in the natural foci (mechanization of agricultural work, the supplying of workers with water-proof clothes, a ban to swim in the infected reservoirs and to use unboiled water). Vaccination is recommended for the people who permanently stay in the natural foci. The people who belong to a group of high risk infection (cattle-breeders, veterinary doctors, the meat packing plant personal, night-men, deratizators) should be vaccinated with inactivated vaccine.

Control questions:

1. Definition of leptospirosis.
2. Mechanism of leptospirosis contamination.
3. Who can more likely get ill with leptospirosis?
4. What organs are damaged during leptospirosis infection?
5. Clinical manifestations and data of objective and laboratory examinationin in initial period, height of illness and in the period of reconvalestation.
6. Differential diagnosis of leptospirosis with influenza, viral hepatitis, rash and abdominal typhus, sepsis.
7. Complications of leptospirosis.
8. Principles of medical treatment of leptospirosis.
9. Leptospirosis prevention.

HERPETIC DISEASES

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) infections are among the most common maladies affecting humans. Often they are annoying and troublesome, occasionally they are life-threatening.

Historic reference

The term "herpes" is derived from the Greek word meaning "to creep", and clinical descriptions of herpes labialis go back to the time of Hippocrates. Astruc, physician to the king of France, is credited with the first description of genital herpes in 1736. Between 1910 and 1920, the infectious nature of herpes lesions was demonstrated by producing corneal lesions in rabbits with material derived from herpes keratitis and labialis. As techniques for isolating and characterizing the virus became more simplified and serologic procedures were developed, our understanding of the HSV clinical spectrum has greatly expanded. Studies during the past two decades have brought insights into the molecular biology of HSV. the mechanisms of HSV latency and recurrence, and the first successful approaches to therapy for certain types of HSV infections.

Etiology

Herpes simplex virus (*herpesvirus hominis*) shares many properties with other members of the herpesvirus groups, which in humans includes varicella-zoster, cytomegalovirus, Epstein-Barr virus, and human herpesviruses type 6 and 7. The members of this group have an internal core containing double-stranded DNA, an icosahedral capsid with 162 hollow capsomeres, and a lipid-containing laminated membrane or envelope. The overall diameters of enveloped herpesviruses are 150-200 nm. Replication occurs primarily within the cell nucleus and is completed by the addition of protein envelopes as the virus passes through the nuclear membrane. Complete virus replication is associated with lysis of the productive cell. All members of the human herpesvirus group can also establish latent states within certain types of cells they infect, although the physical nature of the viruses during periods of latency is unclear.

The development of monoclonal antibody and restriction enzyme technologies have permitted an even finer definition of variations among individual HSV isolates. It is now clear that HSV-1 and HSV-2 share certain glycoprotein antigens (gB) and differ with respect to others (gG). Serologic differentiation between HSV-1 and HSV-2 infections can be readily made by detection of type-specific IgG antibodies.

Epidemiology

Herpes simplex viruses have a worldwide distribution. There are no known animal vectors for HSV, and although experimental animals can easily be infected, humans appear to be the only natural reservoir. Direct contact, with transmission through infected secretions, is the principal mode of spread. HSV-1 is transmitted primarily by contact with oral secretions and HSV-2 by contact with genital secretions. Transmission can occur both from overtly infected persons or from asymptomatic excretors, although virus titers are higher in persons with active lesions and thus transmissability may be greater. Approximately 15 % of the adults may be excreting HSV-1 or HSV-2 at any given time depending on the population studied. For example, because shedding of HSV-2 is related to sexual activity, prostitutes may have unusually high rates of excretion.

The risk of heterosexual acquisition of HSV is greater in women than men, and previous HSV-1 infection reduces the risk of subsequent HSV-2 infection.

Pathogenesis

On entry into skin sites HSV replicates locally in parabasal and intermediate epithelial cells, which results in the lysis of infected cells and the instigation of a local inflammatory response. This series of events results in the characteristic lesion of superficial HSV infection, that is, a thin-walled vesicle on an inflammatory base. Multinucleated cells are formed with ballooning degeneration, marked edema, and characteristic Cowdry type A intranuclear inclusions. Such lesions are indistinguishable from those caused by *Varicella-zoster virus*. Lymphatics and regional lymph nodes draining the site of primary infection become involved. Further virus replication may result in viremia and visceral dissemination, depending on the immune competence of the host. In murine models the maturity of macrophages at the site of local infection helps determine whether virus remains localized or disseminates. Subsequently, other host defense mechanisms, for example, the production of interferons, natural killer cells, protective antibodies, and sensitized killer lymphocytes, are elicited to prevent the spread of infection.

Clinical manifestations

Primary HSV-1 infection is frequently asymptomatic but may present as gingivostomatitis and pharyngitis most commonly in children under the age of 5 years but occasionally in older persons. Incubation periods range from 2 to 12 days and are followed by fever and sore throat with pharyngeal edema and erythema. Shortly after its onset, small vesicles develop on the pharyngeal and oral mucosa: these rapidly ulcerate and increase in number, often involving the soft palate, buccal mucosa. tongue, and floor of the mouth. Gums are tender and bleed easily and lesions may extend to the lips and cheeks. Fever and toxicity may persist for many days, and the patient complains of severe mouth pain. Breath is fetid, and cervical adenopathy is present. In children, dehydration may result from poor intake, drooling,

and fever. In college-aged persons, primary HSV infection often presents as a posterior pharyngitis or tonsilitis. Included in the age-related differential diagnosis are streptococcal or diphtheritic pharyngitis, herpangina. aphthous stomatitis, Stevens-Johnson's syndrome, Vincent's infection and infectious mononucleosis.

Herpes simplex virus infections of the eye are usually caused by HSV-1. Primary infections may be manifested by a unilateral follicular conjunctivitis with regional adenopathy and/or blepharitis with vesicles on the lid margin. Photophobia, chemosis, excessive tearing, and edema of the eyelids may be present. Some patients develop dendritic figures or coarse, punctate, epithelial opacities. If disease is limited to the conjunctiva, healing takes place within 2-3 weeks. However, if systemic symptoms and signs of stromal involvement are present, the healing phase may be delayed. Spontaneous healing of the conjunctiva and cornea is usually complete.

Primary genital infection is most common in adolescents and in young adults and is usually (in 70-95 % of the cases) caused by HSV-2. Incubation periods are 2-7 days. In men, vesicular lesions on an erythematous base usually appear on the glans penis or the penile shaft. In the female, lesions may involve the vulva, perineum, buttocks, cervix, and vagina and are frequently accompanied by a vaginal discharge). Extra-genital lesions occur during the course of primary infection in 10-20 % of patients. Primary infection in both sexes may be associated with fever, malaise, anorexia, and tender bilateral inguinal adenopathy. Although vesicular lesions may persist for several days in men, in women they rapidly ulcerate and become covered by a grayish-white exudate. Such lesions may be exquisitely tender, and urethral involvement may result in dysuria or urinary retention. Herpetic sacral radiculomyelitis accompanying genital infection may also lead to urinary retention, neuralgias, and obstipation; in such patients a loss of anal tone, diminished bulbocavernosus reflex, and cystometrographic evidence of lower motor neuron dysfunction can sometimes be demonstrated. Lesions of primary genital herpes may persist for several weeks before healing is complete. Previous HSV-1 infection may reduce the severity and duration of a first episode of genital herpes caused by HSV-2. In the diagnosis of genital herpes. other sexually transmitted infections such as chancroid or syphilis, erosions secondary to excoriation, genital manifestations of Behcet syndrome or erythema multiforme, and local candidiasis must all be distinguished.

Although primary infections are usually in perioral (Fig. 8), ocular or genital areas, any skin site may be initially involved. Primary HSV skin infections may be extensive and mimic herpes zoster, although a dermatomal distribution is not usually maintained and the pain is less severe.

Primary perianal and anal HSV-2 infection is becoming increasingly well recognized, both in women and in male homosexuals. Pain is the primary symptom, with itching, tenesmus, and discharge also noted. Systemic complaints of fever, chills, malaise, headache, difficulty in urinating, and sacral paresthesias may be present. On examination, vesicles and ulcerations may be seen in perianal and sometimes in

anal areas. They may become confluent and result in a grayish ulcerating cryptitis surrounded by a red edematous mucosa. Bilateral inguinal adenopathy is common. The course is generally self-limited unless bacterial infection supervenes, with healing occurring in 1-3 weeks. However, in the setting of the acquired immunodeficiency syndrome (AIDS), herpes proctitis as well as other cutaneous manifestations of HSV infection may be prolonged and progressive.

Recourse herpes labialis is frequently heralded by prodromal symptoms (pain, burning, tingling, or itching) generally lasting for less than 6 hours but occasionally as long as 24-48 hours. Vesicles appear most commonly at the vermillion border of the outer lip and are associated with considerable pain. The lower lip is more frequently involved, although individual patients may have stereotyped lesions at similar sites during each recurrence. The lesion area is usually less than 100 mm^3, and lesions progress from the vesicle to the ulcer/crust stage within 48 hours. Pain is most severe within the first 24 hours after the appearance of lesions. Healing is generally complete within 8-10 days. Rarely, recurrences may occur in the mouth or on the nose, chin or cheek. Systemic complaints do not usually accompany recourse herpes labialis, although local adenopathy may occur.

Ocular infection may recur as keratitis, blepharitis or kerato-conjunctivitis. Recourse keratitis is usually unilateral but is rarely (in 2-6 % of the cases) bilateral. Two main types of keratitis may develop: dendritic ulceration or stromal involvement. Branching dendritic ulcers that strain with fluorescein are virtually diagnostic and are often accompanied by a loss in corneal sensation. Visual acuity may be decreased because the ulcers frequently involve the pupillary portion of the cornea. They may be accompanied by minimal anterior opacification or deep stroma involvement. Occasionally, extensive ameboid corneal ulcers may evolve, particularly if topical steroids have been applied. Superficial keratitis usually heals, but recourse infection may lead to deep stromal involvement and uveitis, which may in part be mediated by hypersensitivity reactions to viral or altered cellular antigens. A gradual diminution in visual acuity takes place, and individual attacks may last for several months with the formation of dense scars, corneal thinning, and neovascularization. Permanent visual loss may result, and rarely, rupture of the eyeball develops.

Recourse genital lesions in both sexes are generally associated with less severe systemic symptoms and less extensive local involvement than are primary attacks. A prodrome of tenderness, itching, burning or tingling is often noted for several hours before a recurrence. Lesions in women are most often noted on the labia minora, labia majora, and perineum and less commonly on the mons pubis or buttocks. Lesions in men are most often found on the glans or penile shaft. In women recurrences tend to be more severe. Healing generally occurs in 6-10 days. Virus shedding diminishes more slowly in women and can occur between recurrences in both sexes. Occasionally, genital recurrences are associated with headache and even with aseptic meningitis. Urethral stricture and labial fusion have also been reported after recourse genital infections.

Recourse HSV-1 or HSV-2 infections may develop on extremities; occasionally such lesions are associated with severe local neuralgia. Local edema and lymphangitis may also occur during recurrences on extremities.

Relationship to other diseases

Erythema multiforme. Allergic cutaneous and mucous membrane disorders may accompany or follow acute HSV infections. Up to 75 % of all cases of erythema multiforme are regularly preceded by an attack of herpes simplex. Both HSV-1 and HSV-2 may be involved, and the cutaneous manifestations range from mild to severe (Stevens-Johnson syndrome) and may be recourse. Inactivated HSV antigens injected intra-dermally into persons subject to erythema multiforme have induced such attacks, and HSV antigen has been identified in skin biopsy specimens from affected lesions.

Cancer. Although HSV has been suspected as a cause of cervical and other cancers on the basis of both epidemiologic and laboratory studies, many recent studies do not support its etiologic role in human cancers.

Idiopathic neurologic syndromes. Herpes simplex virus infections have been implicated as possible factors involved in the pathogenesis of various neurologic disorders of unknown etiology, including idiopathic facial paralysis (Bell's palsy), multiple sclerosis, atypical pain syndromes, ascending myelitis, trigeminal neuralgia, Mollaret's meningitis, and temporal lobe epilepsy. The associations are based on the known predilection of HSV for nerve tissue, on serologic or nucleic acid studies, and on the occasional observations of temporal relationships between attacks of herpes labialis or genitalis and attacks of the neurologic syndrome.

Complications

Herpes simplex encephalitis is a rare complication of herpetic infection and yet is one of the most common acute sporadic viral diseases of the brain. Although little is known about the pathogenesis of HSV-1 encephalitis in humans, the virus is believed to spread by neural routes into the brain during either primary or recourse infection. Temporal lobes are the principal target areas of the virus, and a necrotizing hemorrhagic encephalitis results.

Herpes simplex encephalitis occurs at all ages in both sexes, and in all seasons. The clinical course may begin suddenly or after a brief influenzalike prodrome. Headache, fever, behavioral disorders, speech difficulties, and focal seizures are prominent features; olfactory hallucinations may be present. Cerebrospinal fluid examination is variable but frequently shows a moderate pleocytosis with mononuclear and polymorphonuclear leukocytes: protein levels are slightly elevated, and glucose is generally normal. Infectious virus is rarely present in cerebrospinal fluid during encephalitis, and brain biopsy with appropriate histologic and cultural techniques is coursely the most reliable way to make the diagnosis. Although various antibody and antigen assays may provide adjunctive information. they are not sensitive enough to provide a sufficiently early diagnosis.

Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid has been reported by certain research laboratories. Herpes simplex virus encephalitis must be distinguished from other forms of viral encephalitis, tuberculous and fungal meningitis, brain abscesses, cerebrovascular accidents, and brain tumors.

The course in untreated patients is usually one of rapid deterioration over several days that progresses to coma and death. Mortality in untreated biopsy-proven cases is 60-80 %, and fewer than 10 % of the patients are left without significant neurologic sequelae.

Diagnosis

Although experimental animals and embryonated eggs are susceptible to infection with HSV strains, tissue cultures have largely replaced these hosts for diagnostic purposes. Primary human embryonic kidney, rabbit kidney, and human amnion cells readily support the replication of HSV. Continuous cell strains or cell lines of human diploid origin and certain continuous monkey kidney cell lines also support HSV replication, but to a lesser extent. Cytopathic effects usually appear rapidly, within 24-48 hours if the virus inoculum is high. Cells become rounded and clump, with rapid progression of cytopathic effects throughout the cell monolayer. Ballooning degeneration and the formation of multinucleated syncytial giant cells may be observed, particularly with HSV-2 isolates. Vesicles contain their highest titers of virus within the first 24-48 hours, and specimens should be collected early and promptly inoculated into tissue cultures. If a delay is unavoidable, specimens can be stored in appropriate carrying medium at 4-9 °C for a few hours. but for longer period they should be stored at -70 °C. Typing of isolates can be accomplished by using a variety of serologic techniques including immunohistochemistry or microneutralization. When tissue specimens such as neural ganglia are being studied for the presence of virus, tissue explantation or cell cocultivation techniques have proved useful in facilitating virus isolation.

The recent development of monoclonal antibodies to individual herpes virus antigens should allow for the more precise identification and typing of HSV isolates. HSV-1 and HSV-2 have both type-specific and cross-reactive antigens that are useful for both grouping and type discrimination. Moreover, the cloning of herpes DNA fragments in recombinant bacteria may permit the production of probes to identify herpes genomes in the absence of infectious virus.

For a rapid diagnosis of skin or mucous membrane lesions, scrapings from suspect lesions may be smeared, fixed with ethanol or methanol and stained with Giemsa or Wright preparation. The presence of multinucleated giant cells indicates infection with HSV or varicella-zoster virus. When using cytologic techniques, e.g. the Papanicolaou cervicovaginal stain or the Paragon multiple stain, intranuclear inclusions may also be seen. Alternatively, such material can be examined for herpes antigens by immunohistochemical techniques or by in situ DNA hybridization.

Serologic techniques may be helpful in diagnosing primary HSV infections but are rarely of value in recourse infections. A variety of assays have been used including neutralization, complement fixation, passive hemagglutination, indirect immunofluorescence, radioimmunoassay, enzyme immunoassays, complement-mediated cytolysis, and antibody-dependent cellular cytolysis. During primary infections, a fourfold or greater rise in titer is observed between acute and convalescent sera. In recourse infections such rises may or may not be observed. Many licensed enzyme immunoassays appear to give inaccurate information concerning HSV-infecting subtypes.

Measurement of IgM HSV antibodies in infants may be helpful in the diagnosis of neonatal infection. Such antibodies usually appear within the first 4 weeks of life in infected infants and persist for many months. Measurement of IgM antibodies in older persons has not proved useful in separating primary from recourse infections.

Approaches to detect specific HSV antigens, antibodies, or DNA in cerebrospinal fluid are under development. Such techniques may circumvent the need for invasive procedures such as brain biopsy to make the diagnosis of herpes encephalitis.

Differential diagnosis

HSV causes various pathologies, which clinical manifestations can differ a lot. Sometimes only complicated laboratory research helps to verify diagnosis of HSV infection. The most common sign of HSV infection is vesicular eruption, so differential diagnostics is necessary with diseases, which can be accompanied by the same eruptive lesions. They are chicken-pox, VZV-infection, enterovirus herpangina, Hand-Fuss-Mund Krankheit (HFMK), erysipelas, anthrax.

Treatment

A number of nucleoside derivatives interfere with the synthesis of HSV DNA. Some of these (trifluorothymidine, vidarabine) are useful in and licensed for the topical treatment of herpes keratitis. Vidarabine and acyclovir are also useful for systemic HSV infections. None of these agents affects latent virus.

In the immunocompromised host, acyclovir is useful as both treatment and suppression of recourse mucocutaneous HSV lesions. For the treatment of acute episodes, virus shedding, local symptoms (pain), and time to healing can be reduced by intravenous or oral regimens (400 mg five times per day). Acyclovir is also useful in the prevention of herpetic recurrences in immunocompromised hosts including transplant recipients, leukemics undergoing induction chemotherapy, and patients with AIDS. Regimens of 200-400 mg from two to five times per day have been satisfactory in preventing recurrences among seropositive patients.

Parenteral acyclovir is indicated for disseminated or central nervous system HSV infections. In patients with biopsy-proven HSV encephalitis, acyclovir was compared with vidarabine and found to be superior in reducing mortality. Doses of 10 mg/kg every 8 hours for 14-21 days are recommended. In newborns with

disseminated HSV infections, acyclovir and vidarabine appear equivalent but because of ease of administration, acyclovir is recommended.

Acyclovir has little acute toxicity. Drug-related neurotoxicity (disorientation, hallucinations, tremors, ataxia, seizures) has been described rarely, and reversible renal dysfunction may occur, particularly following a rapid bolus infusion.

Prophylaxis

Experimental vaccines against HSV have shown promise in animal models, and some are undergoing human trials. Limited trials in humans, however, have been unsuccessful, and it is unlikely that a human HSV vaccine will be generally available in the near future.

The prevention of neonatal disease in the offspring of mothers with genital infection presents special problems.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus (VZV) causes two distinct clinical diseases. Varicella, or more commonly chickenpox, is the primary infection and results from exposure of a susceptible individual to the virus. Chickenpox is ubiquitous and extremely contagious, but for the most part, it is a benign illness characterized by a generalized exanthematous rash. It occurs seasonally and in epidemics. Recurrence of infection results in the more localized phenomenon known as herpes zoster, often referred to as shingles, a common infection among the elderly.

Historic reference

Shingles has been recognized since ancient times as a unique clinical entity because of the dermatomal vesicular rash; however, chickenpox was often confused with smallpox. In 1875, Steiner successfully transmitted VZV by inoculation of the vesicular fluid from an individual suffering from chickenpox to volunteers. The infectious nature of VZV was further defined by von Bokay who observed chickenpox in individuals who had close contact with others suffering from herpes zoster. He correctly described the mean incubation period for the development of chickenpox in susceptible patients as well as the average range in days. Kundratitz in 1925 showed that the inoculation of vesicular fluid from patients with herpes zoster into susceptible individuals resulted in chickenpox. Similar observations were reported by Brunsgaard and others, and in 1943 Garland suggested that herpes zoster was the consequence of the reactivation of latent VZV.

Since early in the twentieth century, similarities in the histopathologic findings of skin lesions and in epidemiologic and immunologic studies indicated that varicella and herpes zoster were caused by the same agent. Tyzzer described the histopathology of skin lesions resulting from VZV infections and noted the development of intranuclear inclusions and multinucleated giant cells. The histopathologic descriptions were amplified by Lipschutz in 1921 for herpes zoster.

Etiology

Isolation of VZV in 1958 permitted a definition of the biology of this virus. Viral isolates from patients with chickenpox and herpes zoster demonstrated similar changes in tissue culture, specifically the appearance of eosinophilic intranuclear inclusions and multinucleated giant cells. These findings are virtually identical to those encountered with clinically available biopsy material. Taken together, these data provided a universal acceptance that both diseases were caused by VZV. By 1958, Weller and colleagues had been able to establish that there were no differences between the viral agents isolated from patients with these two clinical entities from either a biologic or immunologic standpoint.

Varicella-zoster virus is a member of the *Herpesviridae* family and shares structural characteristics with other members of the family. The virus has icosahedral symmetry containing centrally located double-stranded DNA with a surrounding envelope. The size of the virus is approximately 150-200 nm and has a lipid-containing envelope with glycoprotein spikes. The organization of the viral genome is similar to other herpesviruses.

Varicella-zoster virus is highly cell associated and spreads from cell to cell by direct contact. Virus can be isolated in a variety of continuous and discontinuous cell culture systems of human and simian origin. Approximately 8-10 hours after infection, virus-specific immunofluorescence can be detected in the cells immediately adjacent to the initial focus of infection. This parallels the microscopic observation of the radial spread of cytopathology.

Epidemiology

The epidemiology of herpes zoster is somewhat different. *Varicella-zoster virus* characteristically becomes latent after primary infection. It is presumed that VZV establishes latency within the dorsal root ganglia. Reactivation leads to herpes zoster, a sporadic disease. Histopathologic examination of the nerve root after infection with VZV demonstrates characteristics indicative of VZV infection. In those individuals who die after recent herpes zoster infection, an examination of the dorsal root ganglia reveals satellitosis lymphocytic infiltration in the nerve root, and degeneration of the ganglia cells. Intranuclear inclusions can be found within the ganglia cells. Although it is possible to demonstrate the presence of VZV by electron microscopy, it has not been possible to isolate this virus in cultures usually from explants of dorsal root ganglia, as has been done after herpes simplex virus infection. The biologic mechanism by which VZV establishes latency remains a mystery at this time.

Herpes zoster is a disease that occurs at all ages, but it will afflict about 20 % or more of the population overall, mainly among the elderly. Herpes zoster, known also as shingles, occurs in individuals who are seropositive for VZV or more specifically, in individuals who have had prior chickenpox. Herpes zoster has occurred within the first 2 years of life in children born in women who have had chickenpox during pregnancy. These particular cases likely reflect in utero chickenpox with reactivation early in life.

Pathogenesis

The pathogenesis of VZV infection that results in chickenpox reflects the natural history of the disease. Chickenpox occurs in susceptible individuals who are exposed to virus after intimate contact. The appearance of a diffuse vesicular rash has been well studied from a pathologic standpoint. Histopathologic findings in human VZV infection, whether chickenpox or herpes zoster, are virtually identical. The vesicles involve the corium and dermis. As viral replication progresses, the epithelial cells undergo degenerative changes characterized by ballooning, with the subsequent appearance of multinucleated giant cells and prominent eosinophilic intranuclear inclusions. Under unusual circumstances, necrosis and hemorrhage may appear in the upper portion of the dermis. As the vesicle evolves, the collected fluid becomes cloudy as a consequence of the appearance of polymorphonuclear leukocytes, degenerated cells, and fibrin. Ultimately, the vesicles either rupture and release infectious fluid or gradually become reabsorbed.

Transmission is likely by the respiratory route, followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and, ultimately, viremia. The occurrence of viremia in patients with chickenpox is supported by the diffuse and scattered nature of the skin lesions and can be verified in selected cases by the recovery of virus from the blood. As noted, the mechanism of the reactivation of VZV that results in herpes zoster is unknown.

Clinical manifestations

Herpes zoster, or shingles, is characterized by a unilateral vesicular eruption with a dermatomal distribution. Thoracic and lumbar dermatomes are most commonly involved (Fig. 9). Herpes zoster may involve the eyelids when the first or second branch of the fifth cranial nerves is affected, but keratitis heralds a sight-threatening condition, herpes zoster ophthalmicus. Although lesions on the tip of the nose are said to presage corneal lesions, absence of such skin lesions does not guarantee corneal sparing. Keratitis may be followed by severe iridocyclitis, secondary glaucoma, or neuroparalytic keratitis. Ophthalmologic consultation should be requested for any patient with suspected herpes zoster ophthalmicus. Generally, the onset of disease is heralded by pain within the dermatome that precedes the lesions by 48-72 hours. Early in the disease course erythematous, macropapular lesions will appear that rapidly evolve into a vesicular rash. Vesicles may coalesce to form bullous lesions. In the normal host these lesions continue to form over a period of 3-5 days, with the total duration of disease being 10-15 days. However, it may take as long as 1 month before the skin returns to normal.

Unusual cutaneous manifestations of herpes zoster, in addition to herpes zoster ophthalmicus, include the involvement of the maxillary or mandibular branch of the trigeminal nerve, which results in intraoral involvement with lesions on the pallet, tonsillar fossa, floor of the mouth, and tongue. When the geniculate ganglion is involved, the Ramsay-Hunt syndrome may occur, with pain and vesicles in the external auditory meatus, loss of taste in the anterior two-thirds of the tongue.

No known factors are responsible for the precipitation of the events of herpes zoster. If herpes zoster occurs in children, the course is generally benign and not associated with progressive pain or discomfort. In adults, systemic manifestations are mainly those associated with pain, as noted below.

The most significant clinical manifestations of herpes zoster are the associated acute neuritis and, later, post-herpetic neuralgia. Post-herpetic neuralgia, although uncommon in young individuals. may occur in as many as 25-50 % of patients over the age of 50 years. It is estimated that as many as 50 % of individuals over 50 years of age will have debilitating pain that persists for over 1 month. Post-herpetic neuralgia may cause constant pain in the involved dermatome or consist of intermittent stabbing pain. Pain may be worse at night or on expose to temperature changes. At its worst, the neuralgia can be incapacitating.

Extracutaneous sites of involvement include the central nervous system as manifested by meningoencephalitis or encephalitis. The clinical manifestations are similar to that of other viral infections of the central nervous system. However, a rare manifestation of central nervous system involvement by herpes zoster is granulomatous cerebral angiitis which usually follows zoster ophthalmicus. It should be noted that involvement of the central nervous system in cutaneous herpes zoster probably is more common than is recognized clinically. Frequently, patients who undergo cerebrospinal fluid examination for other reasons during episodes of shingles are found to have evidence of pleocytosis without elevated cerebrospinal fluid protein levels. These patients are without signs of meningeal irritation and frequently complain of headaches.

Classically, VZV infection involves dorsal root ganglia. Motor paralysis can occur as a consequence of the involvement of the anterior horn cells in a manner similar to that encountered with polio. Patients with involvement of the anterior horn cells are particularly likely to have excruciating pain. Other neuro-muscular disorders associated with herpes zoster include Guillain-Barre syndrome, transverse myelitis, and myositis.

Herpes zoster in the immunocompromised host is more severe than in the normal individual. Lesion formation continues for up to 2 weeks, and scabbing may not take place until 3-4 weeks into the disease course. Patients with lymphoproliferative malignancies are at risk for cutaneous dissemination and visceral involvement, including varicella pneumonitis, hepatitis, and meningoencephalitis. However, even in the immunocompromised patient disseminated herpes zoster is rarely fatal.

In recent years, herpes zoster has been recognized as a frequent infection in individuals with human immunodeficiency virus (HIV) infection, occurring in 8-11 percent of patients. Although the occurrence of cutaneous dissemination is infrequent, complications such as VZV retinitis, acute retinal necrosis, and chronic, progressive encephalitis have been reported.

Chronic herpes zoster may also occur in the immunocompromised host particularly those individuals with a diagnosis of HIV infection. Individuals have

sustained new lesion formation with an absence of healing of the existing lesions. These syndromes can be particularly debilitating and, interestingly, have been associated with the isolation of VZV isolates resistant to acyclovir.

Diagnosis

The diagnosis of shingles is usually made by history and physical examination. The recent development of monoclonal antibodies to individual herpes virus antigens should allow for the more precise identification and typing of HSV isolates.

Differential diagnosis

Differential diagnosis of varicella and herpes zoster is less confusing than it was 20-30 years ago. Smallpox or disseminated vaccinia was confused with varicella because of the similar appearance of the cutaneous lesions. With the worldwide eradication of smallpox and the discontinuation of vaccination, these disease entities no longer confound the clinical diagnosis. For the most part the characteristic skin rash with lesions in all stages of development provides the basis for the clinical diagnosis of infection. The localization and distribution of a vesicular rash makes the diagnosis of herpes zoster highly likely; however, other viral exanthems can occasionally be confused with this disease.

Impetigo and varicella can also be confused clinically. Impetigo is usually caused by group A (β-hemolytic) streptococci and often follows an abrasion of the skin or inoculation of bacteria at the site of the skin break, and can lead to small vesicles in the surrounding area. Systemic signs of disease may be present if progressive cellulitis or secondary bacteremia develops. Unroofing these lesions and careful Gram staining of the scraping of the base of the lesion should reveal gram-positive cocci in chains, which are streptococci presumably, or gram-positive cocci in clusters, which are staphylococci presumably, another cause of vesicular skin lesions. Treatment for these latter infections is distinctly different from that of chickenpox and requires administration of an appropriate antibacterial remedies.

In a smaller number of cases, disseminated vesicular lesions can be caused by herpes simplex virus. In these cases, disseminated herpes simplex virus infection is usually a consequence of an underlying skin disease such as atopic dermatitis or eczema. In this situation, an unequivocal diagnosis can only be confirmed by isolation of the virus in tissue culture.

More recently, it has been recognized that disseminated enteroviral infections, particulary those caused by group A coxsackieviruses, can cause widespread distal vesicular lesions. These rashes are more commonly morbilliform in nature with a hemorrhagic component rather than vesicular or vesiculopustular appearance. Generally these infections occur during the enterovirus season in late summer and early fall and are associated with lesions of the oropharynx, palms, and soles. This latter finding is most helpful in distinguishing enteroviral disease from chickenpox.

Treatment

Acyclovir is approved for the treatment of herpes zoster in the normal host. Adolescents and adults can receive up to 800 mg 5 times a day. Oral therapy of herpes zoster in the normal host accelerates cutaneous healing and reduces acute neuritis. The effect of therapy on post-herpetic neuralgia is marginal at best. Properly designed and controlled clinical trials have not supported the utility of corticosteroids as an adjunct to antiviral therapy.

Corticosteroid therapy alone has been suggested to be useful for decreasing both acute neuritis and the frequency of post-herpetic neuralgia: however, these data are controversial. In the immunocompromised host or with the appearance of visceral complications such as varicella pneumonitis in the normal host, the use of either intravenous acyclovir or vidarabine is of value. Vidarabine has been extensively studied for the treatment of herpes zoster in the immunocompromised hosts. Although efficacy is apparent, it has been replaced by acyclovir.

The management of acute neuritis and/or post-herpetic neuralgia can be particularly problematic. It requires the judicious use of analgesics ranging from non-narcotic to narcotic derivatives and may include the deployment of such drugs as amitriptyline hydrochloride and fluphenazine hydrochloride.

Prophylaxis

Disease can be prevented by administering zoster immune globulin (ZIG), derived from the sera of patients recovering from herpes zoster, or varicella zoster immune globulin (VZIG) prepared from pooled plasma containing high titers of specific antibody. Such preparations should be given within 96 hours after exposure to be effective.

Control questions:
1. Etiology, epidemiology and incidence of herpes simplex virus infections.
2. Pathogenesis of herpes simplex virus (HSV) infections.
3. Main clinical symptoms and signs of primary HSV infections.
4. Clinical manifestations of recourse HSV infections.
5. Complications of HSV infections.
6. Etiology of Varicella-zoster virus (VZV) infections.
7. Pathogenesis of VZV infections.
8. Clinical manifestations of VZV infections.
9. Complications of VZV infections.
10. Laboratory methods of herpetic diseases diagnosis.
11. Differential diagnosis of herpetic infections.
12. Treatment of herpetic infections.
13. Herpetic diseases prophylaxis.

ERYSIPELAS. ERYSIPELOID

ERYSIPELAS

Erysipelas is an acute inflamation of the skin, with marked involvement of cutaneus lymphatic vessels.

Etiology

Erysipelas is almost always caused by group A streptococci (sometimes by group C or G). Group B streptococci cause erysipelas of newborn children.

Epidemiology

Erysipelas is common disease of infants, children of early age, and old people. Formerly, the face was often involved, and antecedent streptococcal respiratory tract infection preceded cutaneous involvement in about one-third of patients, even though streptococci might not be found on culture when skin lesions became evident.

Pathogenesis

Most interest is focused on streptococcal pyrogenic exotoxins (SPEs). In edition to mediating the scarlatinal rush, SPE exibit a variety of adverse biologic effects, including the multiorgan damage and lethal shock. There is an amino acid homology of 50 % and immunologic reactivity between SPE A and staphylococcal enterotoxins B and C. SPE of group A streptococcus is a superantigen and it is a potent inducer of tumor necrosis factor.

The antistreptolysin O response after cutaneous streptococcal infection is weak. There is experimental evidence to suggest that this may be due to local inactivation of streptolysin O by skin lipids. The immune response to antiDNase B is brisk, and antihyaluronidase reactivity is also a useful test in the serodiagnosis of erysipelas.

Clinical manifestations

Now the localization of erysipelas has changed: 70-80 % of the lesions are on the lower extremities and 5-20 % are on the face. Entry gates are commonly skin ulcers, local trauma or abrasions, psoriatic or eczematous lesions, fungal infections; in the neonate, erysipelas may develop from infection of the umbilical stump. Predisposing factors include venous stasis, paraparesis, diabetes mellitus, and alcohol addiction. Patients with the nephrotic syndrome are particularly susceptible. Erysipelas tends to occur in areas of preexisting lymphatic obstruction or edema (e.g. after radical mastectomy). Also, because erysipelas itself produces

lymphatic obstruction, it tends to recur in an area of earlier infection. Over a 3-year period, the recurrence rate is about 30 %, predominantly in individuals with venous insufficiency or lymphedema.

Streptococcal bacteremia occurs in about 5 % of patients with erysipelas; group A, C, or G streptococci can be isolated on throat culture from about 20 % of cases.

Erysipelas is a painful lesion with a bright red, edematous, indurated ("peau d'orange") appearance and an advancing, raised border that is sharply demarcated from the adjacent normal skin. Fever is a feature. A common form of erysipelas involves the bridge of the nose and the cheeks (Fig. 10). Uncomplicated erysipelas remains confined primarily to the lymphatics and the dermis. Occasionally, the infection extends more deeply, producing cellulitis, subcutaneous abscess, and necrotizing fasciitis.

Leukocytosis is common sign of erysipelas. Group A streptococci usually cannot be cultured from the surface of the skin lesion, and only rarely they can be isolated from tissue fluid aspirated from the advancing edge of the lesion. In cases of erysipelas complicating infected ulcers, group A streptococci have been isolated from the ulcerated area in 30 % of patients.

Complications

Bacteremic spread of the streptococci may result in a variety of metastatic foci of infection, for example, suppurative arthritis, endocarditis, meningitis or brain abscess, osteomyelitis, liver abscess, and so forth. The local complications are abscess and streptococcal cellulitis, skin necrosis and ulcers, thrombophlebitis, otitis and others. Suppurative lymphadenitis may also occur.

Diagnosis

Diagnosis is usually easy due to characteristic manifestatioms of erysipelas. It is difficult to isolate culture of erysipelas infectious agent from the lesion, but it may occasionally be cultured from the blood.

Differential diagnosis

The diagnosis is made on the basis of characteristic manifestatioms of the lesion and the clinical setting. Early herpes zoster involving the second division of the fifth cranial nerve may resemble unilateral facial erysipelas but can be distinguished by the pain and hyperesthesia preceding the skin lesions. Occasionally contact dermatitis or giant urticaria may look like erysipelas but can be distinguished by the absence of fever and the presence of pruritus. Lesions closely resembling erysipelas, but apparently not due to streptococcal infection, may occur recurrently in patients with familial Mediterranean fever. Diffuse inflammatory carcinoma of the breast may mimic a low-grade erysipelas. Erythema chronicum migrans, the cutaneous lesion of Lyme disease, resembles

erysipelas but is not painful and progresses much more slowly, and the associated fever is less marked. An erysipelas-like skin lesion has occurred in several patients with hypogammaglobulinemia and *Campylobacter jejuni* bacteremia.

Treatment

Treatment is carried out according to the clinical form and gravity of disease. Antibiotics of penicillinic lines are effective. In case of initial and repeated erysipelas benzylpenicillin has to be given during 7-10 days. At serious course, complications, rapid local inflammatory changes, enlarge daily dose of preparation up to 8 − 12 million units. Among semisynthetic penicillines, ampicillin, oxacillin, amoxacillin (bactox, ospamox) are considered effective. At serious course of disease, development of a sepsis one have to use a combination of two antibiotics, for example ampicillin and gentamicin. For treatment of frequently relapsing erysipelas one should apply ampicillin, ampiox, amoxyclav, oletetrin, lincomicin, cefaloridin, cefazolin (kefzol), cefotaxim (claforan), at intolerance of antibiotics − furazolidon, bactrim. Course of treatment is 8 -10 days. If the residual phenomena of disease are keeping, after 7 − 10 days one should indicate repeated course of treatment by other antibiotic. Indicate fluoroquinolones − ofloxacin, ciprofloxacin (ciprobai, ciprobid) etc.

Patients with the mild form of erysipelas can be treated ambulatory, using bactrim, furazolidon, furagin, chingamin (delagil) in average therapeutic doses during 10 days.

At presence of expressed infiltration and pain syndrome indicate non steroid anti-inflammatory preparations − indomethacin, mefanamic acid, paracetamol. Indication of immunostimulators is proved − prodigiosan, sodii nucleinat, splenin, methyluracil. The best results is reached in case of the combination of 2 − 3 imunostimulatores. Course of treatment is 10 days.

The patients with frequently relapsing erysipelas and the phenomena of lymphostasis should administer, besides antibiotic therapy, prednisolon in tablets 0.005 gm − 20-30 mg per day with a gradual dose decline or its analogue.

It is expedient to apply preparations which reduce a permeability of capillaries − rutin in tablets 0.02 gm, ascorutin in tablets, an ascorbic acid in tablets 0.05 gm, calcii gluconat in tablets 0.5 gm, vitamin preparations of B group, retinoli acetat and also desensitizing agents − dimedrol in tablets 0.05 gm, suprastin in tablets 0.025 gm, tavegil in tablets 0.001 gm, diazolin in tablets 0.05 gm.

The patients with serious form of erysipelas and expressed intoxication are given reopoliglycin, 5 % solution of glucose with addition of corglykon, cocarboxylase, ascorbic acid, diuretic preparations − furosemid, etacrin acid, spironolacton (veroshpiron) are also indicated.

At bullous form large bubbles should be cut off and use bandage with solution of aethacridin, 0.02 % solution of furacilin or ectericid with chlorophylypt, juice of calanhoe − fifty-fifty with 0.5 % solution of novocain.

If purulent-septic process appeares, phlegmon is formed, applications with 30 % a solution of dimexidum with the dissolved antibiotic in a single dose 5000 units of heparinum in every 12 hours during 4-5 days are locally applied. The same antibiotics are infused parenterally. Unguental bandages at local purulent processes are contrindicated.

Local treatment is combined with indication of physiotherapeutic procedures: in acute period ultra violet radiation and photoradiotherapy, during reconvalescence period — inductothermy, electroforesis of potassii iodidi, calcii chloridi, lydasi; ozocerit or parafin, radon baths.

After transferred initial, repeated and seldom relapsing erysipelas at presence of the residual phenomena give bicillin-5 (in bottles 1,500,000 units): in muscle in every 4 weeks during 3-4 months. The patients with often and repeated relapses are treated. Bicillin-5 is infused monthly during 2-3 years. Necessity of repeated injections with bicillin-5, it is expedient for checking with the help of thermal imager researches. Paralelly with bicilinoprofilaxis stimulators of immune system — methyluracil, prodigiosan, natrii nucleinici, fortifying treatment — polyvitamines, eleuterococ extract, tinctura araliae, pantocrin etc are indicated. The sanitation of chronic streptococcal infection, mycosis is indicated.

Prophylaxis

Adherense to good regimens of personal hygiene, with special attention to frequent scrubbing with soap and water, is the most effective preventive measure currently available. The in time treatment of streptococcal pharyngitis is of much importance.

ERYSIPELOID

Erysipeloid is an acute, but slowly ewolwing, skin infection.

Historic reference

First isolated from mice by Robert Koch in 1878 and from swine by Louis Pasteur in 1882, it was established as the etiologic agent of swine erysipelas in 1886 by Loeffler and as a human pathogen in 1909 when Rosenbach isolated it from a patient with localized cutaneous lesions. Rosenbach coined the term "erysipeloid" to avoid confusion with "erysipelas", a superficial cellulitis with prominent lymphatic involvement that is almost always caused by group A streptococci.

Etiology

Erysipelothrix rhusiopathiae is a straight or slightly curved aerobic or facultatively anaerobic bacillary organism; it is 0.2-0.4 mm diameter and 0.8-2.5 mm in length. It is gram-positive but may appear gram-negative because it "decolorize" readily. Organisms may be arranged singly, in short chains, in pairs in a "V" configuration or grouped randomly. Nonbranching filaments that can

be greater than 60 mm in length are sometimes seen. There is a dual colonial and microscopic appearance that varies with the medium, pH and temperature of incubation. After growing for 24 hours at 37 °C, colonies are small and transparent with a smooth glistening surface.

Erysipelothrix rhusiopathiae is sometimes confused with other gram-positive bacilli, in particular with *Listeria monocytogenes, Actinomyces (Corynebacterium) pyogenes*, and *Arcanobacterium (Corynebacterium) haemolyticum,* but these three species are β-hemolytic on blood agar and do not produce hydrogen sulfide in the butt on TSI agar slants. Furthermore, *L. monocytogenes* is catalase-positive and motile.

Epidemiology

Erysipelothrix rhusiopathiae is found worldwide. It has been reported as a commensal or a pathogen in a wide variety vertebrate and invertebrate species, but the major reservoir believed to be domestic swine. It does not appear to cause disease in fish but can persist for long periods of time in the mucoid exterior slime of these animals. It may live long enough in soil to cause infection weeks or months after initial contamination. The greatest commercial impact of *E. rhusiopathiae* infection is due to disease in swine, but infection of turkeys, ducks, and sheep is also important. The organism is communicable from animals to human by direct cutaneous contact. The risk of human infection with *Erysipelothrix* is related to the opportunity for exposure to the organism, and hence, most human cases are related to occupational exposure. Although infection with *Erysipelothrix* has been associated with a wide variety of occupations, those at greatest risk include, fisherman, fish handlers, butchers, slaughterhouse workers, veterinarians, and housewives. Infection is especially common among individuals who handle fish. "Whale finger" is erysipeloid seen in those who sustain cuts to their fingers and hands while engaged in whaling. Human-to-human transmission of infection has not been mentioned.

Pathogenesis

Abrasions or puncture wounds of the skin probably serve as the portal of entry of *E. rhusiopathiae* in most cases of infection in humans and in other animals. *Erysipelothrix rhusiopathiae* produces a neuraminidase and a hyaluronidase. The activity of these enzymes may correlate with virulence. The neuraminidase may have a role in the pathogenesis of arteritis and thrombocytopenia in an experimental rat model of *Erysipelothrix* infection. The rhomboidal skin lesions seen in swine are the result of thrombotic vasculitis of end arterioles.

Clinical manifestations

Three clinical categories of human disease have described: (1) erysipeloid, a localized skin lesion, (2) a diffuse cutaneous eruption with systemic symptoms, and (3) bacteremia, which is often associated with endocarditis.

The localized cutaneous form or "erysipeloid of Rosenbach", a subacute cellulitis, is the most common type of infection seen in humans. It is a cellulitis. Because the organism is acquired through contact with infected animals, fish, or their products, with organisms gaining entrance via cuts or abrasions on the skin, most lesions are on the fingers. Following an incubation period of 2-7 days, pain (which is often severe and described as burning, itching or throbbing) and swelling of the involved digit or part of the hand develop. The lesion is well-defined, slightly raised, and violaceous in color. As it spreads peripherally, the central area fades. Vesiculation may occur. Regional lymphadenopathy and lymphangitis occur in approximately one-third of cases. There may be arthritis of an adjacent joint. Systemic symptoms are uncommon. Part of patients have low-grade fever and arthralgias. Erysipeloid can be distinguished clinically from staphylococcal or streptococcal cellulitis by the absence of suppuration, the lack of pitting edema, the violaceous color, and the disproportionate pain. Because pathogens are located only in deeper layers of the skin in cases of erysipeloid, aspirates or biopsy specimens should be of the entire thickness of the dermis and from the periphery of the lesion to maximize the chance of recovery of the organism. Erysipeloid usually resolves without treatment within 3 or 4 weeks.

The diffuse cutaneous form, which is rare, occurs when the violaceous cutaneous lesion progresses proximally from the site of inoculation or appears at remote areas. Lesions may appear urticarial with the rhomboid pattern characteristic of swine erysipelas. Fever and arthralgias are common. Blood cultures are negative. The course is more protracted than in the localized form and recurrence is common.

Systemic infection with *E. rhusiopathiae* is unusual. In approximately 60 % of patients, *E. rhusiopathiae* endocarditis developed on previously normal heart valves. In patients with bacteremia and/ or endocarditis, routine blood culture techniques are adequate for recovery of the organism.

Complications

Complications of *Erysipelothrix* endocarditis include congestive heart failure, myocardial abscess, aortic valve perforation, meningitis, and glomerulonephritis.

Bacteremia without endocarditis has been reported with increasing frequency. It has occurred primarily in immunocompromised hosts. Brain abscess, osteomyelitis, and chronic arthritis have also been reported.

Diagnosis

Definitive diagnosis of infection with *Erysipelothrix* requires isolation of the organism from a biopsy specimen or blood. There are no reliable serologic tests for the diagnosis of infection in humans.

Differential diagnosis

Erysipeloid must be differentiated from erysipelas, arm of hand herpes zoster, contact dermatitis and angioneurotic edema.

Treatment

Susceptibility data for *E. rhusiopathiae* are limited. Most strains are highly susceptible to penicillins, cephalosporins, clindamycin, imipenem, and ciprofloxacin. Penicillin and imipenem are the most active agents in vitro. Susceptibility to chloramphenicol, erythromycin, and tetracycline is variable. Most strains are resistant to vancomycin, sulfonamides, trimethoprim-sulfamethoxazole, novobiocin, teicoplanin, and aminoglycosides. Resistance to vancomycin is important because this agent is often used empirically to treat bacteremia due to gram-positive organisms. Use of fluoroquinolones may be considered in *Erysipelothrix* infections when b-lactams are contraindicated. In cases of endocarditis, the duration of intravenous antibiotic therapy should be 4-6 weeks, although shorter courses (2 weeks of intravenous therapy followed by 2-4 weeks of oral therapy) have been successful. Although erysipeloid usually resolves spontaneously, healing is hastened by antibiotic therapy.

Prophylaxis

Prevention of infection for those in high-risk occupations depends on the use of protective attire such as gloves. Unprotected direct contact with animal body tissues and secretions should be avoided. There are live attenuated vaccines available for veterinary use. Use of vaccination along with other measures such as improved waste disposal has helped to control swine erysipelas.

Control questions:

1. Etiology, epidemiology and incidence of erysipelas and erysipelotrix.
2. Pathogenesis of erysipelas and erysipelotrix.
3. Clinical manifestations of erysipelas and erysipelotrix.
4. Laboratory methods of diagnosis.
5. Criteria of diagnosis.
6. Differential diagnosis of erysipelas and erysipelotrix.
7. Treatment of erysipelas and erysipelotrix.
8. Prophylaxis of erysipelas and erysipelotrix.

ANTHRAX

Bacillus anthracis is a gram-positive spore-forming bacillus that can cause acute infection in both animals and humans. It is primarily a disease of herbivores, which acquire infection after coming into contact with soil-borne spores. In its spore form it can persist in nature for prolonged periods, possibly years. The distribution of anthrax is worldwide.

The disease occurs primarily in three forms: cutaneous, respiratory and gastrointestinal. The incidence of anthrax has decreased in developed countries but it remains a considerable health problem in developing countries.

Historic reference

The earliest known description of anthrax is found in the book of Genesis: the fifth plague (1491 BC), which appears to have been anthrax, was described as killing the Egyptians cattle. There are descriptions of anthrax involving both animals and humans in the early literature of Hindus, Greeks, and Romans. In the 17th century, a pandemic referred to as "the black bane" swept through Europe, causing many human and animal deaths. Later the disease in humans was described as "the malignant pustule".

Several distinguished microbiologists in the 19th century characterized the pathology of the disease and attempted to develop a vaccine because of serious problems with anthrax in the livestock industry. Pasteur developed and field tested in sheep his attenuated spore vaccine in 1881. In 1939, Sterne reported his development of an animal vaccine that is a spore suspension of an avirulent, noncapsulated live strain. This is the animal vaccine currently recommended for use.

Occupational anthrax occurred 18th century in industrial European countries such as England and Germany. Early in this century, in the United States, it occurred in individuals who handled materials that had been woven from contaminated animal fibers.

From the beginning of this century the annual number of cases reported in developed countries has steadily decreased. This decrease is the result of the use of a cell-free anthrax vaccine in humans who are in high-risk industrial groups, decreased use of imported potentially contaminated animal products, improved hygiene in industry, and improved animal husbandry.

Etiology

Pus or tissue from patients suspected to have anthrax should be stained by both Gram stain, to reveal gram-positive bacilli, and polychrome methylene blue, to show the polypeptide capsule. Bacilli are usually abundant in the specimen and easy to culture on standard blood or nutrient agar. In heavily contaminated

specimens such as stool it may be necessary to use selective agar or deconta-mination methods that rely on the resistance of the anthrax spores to heat or ethanol. The colonies are gray-white to white and nonhemolytic. Identification of the isolate depends on biochemical tests, presence of a capsule, lack of motility, catalase positivity, lysis by bacteriophage, penicillin susceptibility, and aerobic endospore production. Commercially available test strips and fluorescent antibody staining can be used to aid identification.

Epidemiology

Anthrax is usually a disease of herbivores and only incidentally infects humans who come into contact with infected animals or their products. Because anthrax remains a problem in developing countries, animal products imported from these areas continue to pose a risk.

Human cases may occur in an industrial or in an agricultural environment. Industrial cases result from contact with anthrax spores that contaminate raw materials that are used in manufacturing processes. In the United States, occasional epidemics occurred in industrial settings, probably related to the processing of batches of highly contaminated imported animal fibers, particularly goat hair. These epidemics were primarily of cutaneous anthrax.

One epidemic was recently reported in Switzerland. Within less than 3 years, 25 workers in one textile factory contracted the disease; 24 cases had cutaneous and one inhalation anthrax. The infection was imported in goat hair from Pakistan. The rarity of the illness contributed to a general lack of experience and therefore hindered recognition of the clinical symptoms. In addition, repeated attempts failed to identify the pathogenic agent conclusively.

Human cases of anthrax in an agricultural environment result from direct contact with animals that are sick or have died from anthrax.

In Africa there have been multiple epidemics of human disease associated with epizootics of anthrax in cattle. The largest reported agricultural outbreak occurred in Zimbabwe, with more than 10,000 cases reported between 1979 and 1985. Endemic cases continue to occur in the involved area. The majority of patients had cutaneous infections located primarily on the exposed parts of the body; some gastrointestinal cases were also reported. Domestic cattle deaths were noted. A similar large outbreak of human and animal anthrax occurred in Chad, mainly in the Department of Chari Baguirmi, from September to December 1988, infecting more than 50 % of donkeys and horses. There were 716 human cases reported, with 88 deaths.

In African wildlife, which cannot easily be vaccinated and in which the other aspects of control are not relevant, the disease remains a major cause of uncontrolled mortality in herbivores.

Organisms can also be transmitted by a common vehicle such as food (meat), although this is more rare. Large outbreaks have been reported in Thailand and Russia. This last outbreak of human anthrax occurred in north central Russia in 1979, in which the government health authorities of the former U.S.S.R. reported

that the source of infection was contaminated meat. Officially there were 96 cases: 79 of gastrointestinal anthrax and 17 of cutaneous anthrax. However, there is novel evidence concerning the real nature of this anthrax outbreak. Intelligence authorities in the United States had initially reported hundreds of fatalities, including military personnel, and had suspected that an explosion at a secret germ warfare facility in Sverdlovsk had sent deadly anthrax spores airborne. The United States has repeated this allegation, but it never formally accused the former U.S.S.R. of violating the germ warfare treaty or substantiated its charge. The hospital records of the patients affected by this outbreak including the autopsy reports have been unavailable.

Recently two Russian pathologists published hidden secret information describing the necropsy of 42 cases, which consistently revealed pathologic lesions diagnostic of inhalation anthrax. Main features include hemorrhagic necrosis of the thoracic lymph nodes in the lymphatic drainage of the lungs and hemorrhagic mediastinitis. This information underscores the potential use of *B. anthracis* in biological warfare.

Pathogenesis

The virulence of *B. anthracis* is determined by the presence of three components: edema toxin, lethal toxin, and capsular material. To exert their effect within cells, both edema and lethal toxin require participation of a common transport protein called protective antigen. The capsule material contains poly-D-glutamic acid, which helps protect the bacillus from ingestion by phagocytes. Production of the toxic factors is regulated by one plasmid and that of the capsular material by a second plasmid.

The effects of anthrax toxin components on human neutrophils have been studied in detail. Phagocytosis of opsonized and radiation killed *B. anthracis* was not affected by the individual anthrax toxin components. However, a combination of lethal toxin and edema toxin inhibited bacterial phagocytosis and blocked the oxidative burst of polymorphonuclear neutrophils. The two-toxin combination also increased intracellular cyclic AMP levels. These studies suggest that two of the protein components of anthrax toxin increase host susceptibility to infection by suppressing polymorphonuclear neutrophil function and impairing host resistance.

Experiments performed in animals suggest that spores deposited beneath the skin or in the respiratory or intestinal mucosa germinate and the resulting vegetative forms multiply and produce a toxin. The local lesion results from the action of the toxin on the surrounding tissue, which causes tissue necrosis. The toxin or organisms or both may disseminate by the vascular system, causing systemic symptoms and signs of toxicity or bacteremia. Organisms are also often picked up by the lymphatic system, resulting in lymphangitis and lymphadenopathy.

Anatomic pathology

The most significant findings at autopsy are those seen in patients who have died of inhalation anthrax. The classic finding is that of hemorrhagic mediastinitis

with enlarged, hemorrhagic lymphadenitis. There may be inflammation of the pleura and some pleural effusion. Some patients may have hemorrhagic meningitis, and hemorrhages may be seen in the gastrointestinal tract.

In deaths due to gastrointestinal anthrax there is typically hemorrhagic enteritis, with congestion, thickening, and edema of the intestinal walls. Mucosal ulcers with necrosis may be seen in the terminal ileum and cecum. The regional lymph nodes are enlarged, edematous, and hemorrhagic with some necrosis. There may be acute splenitis. Peritonitis with ascitic fluid is often present.

Clinical manifestations

Approximately 95 % of anthrax cases in developed counties are cutaneous and 5 % are respiratory: confirmed epidemic cases of gastrointestinal anthrax have often been reported in "Third World" countries.

Cutaneous anthrax. The clinical presentation of cutaneous anthrax is so characteristic that the diagnosis is not often missed by physicians familiar with the disease. Most of the cases occur in exposed skin areas mostly on the arms and hands followed by the face and neck. The infection begins as a pruritic papule that resembles an insect bite. The papule enlarges and within 1 or 2 days develops into an ulcer surrounded by vesicles. The lesion is usually 1-3 cm in diameter and usually remains round and regular. A characteristic black necrotic central eschar develops later with associated edema. The lesion is most often painless and may first be noticed because of pruritus. After 1-2 weeks the lesion dries, and the eschar begins to loosen and shortly thereafter separates, revealing a permanent scar. There may be regional lymphangitis and lymphadenopathy and some systemic symptoms such as fever, malaise, and headache. Antibiotic therapy does not appear to change the natural progression of the lesion itself: however, it will decrease or inhibit development of edema and systemic symptoms. Differential diagnosis include conditions due to potential contact with infected animals such as plague and tularemia.

Respiratory anthrax. Respiratory anthrax shows a biphasic clinical pattern with a benign initial phase followed by an acute, severe second phase that is almost always fatal. The initial phase begins as a nonspecific illness consisting of malaise, fatigue, myalgia, mild fever, nonproductive cough, and, occasionally, a sensation of precordial oppression.

The illness may cause disorder of upper respiratory tract such as a cold or influenza. After 2-4 days, the patient may show signs of improvement. However, there is then the sudden onset of severe respiratory distress characterized by severe hypoxia and dyspnea. In several cases, subcutaneous edema of the chest and neck has been described. The pulse, respiratory rate and temperature become elevated. Physical examination reveals moist, crepitant rales over the lungs and possibly evidence of pleural effusion. Radiographic examination of the chest may reveal widening of the mediastinum and pleural effusion. Patients soon become hypotensive and septicemia and meningitis may develop. Death occurs in most

persons with inhalation anthrax within 24 hours after the onset of the acute phase. Inhalation anthrax is very difficult to diagnose early.

Gastrointestinal anthrax. The incubation period of gastrointestinal anthrax is commonly 3-7 days. There are two clinical presentations following ingestion of *B. antracis* - contaminated food: abdominal and oropharyngeal.

The symptoms of abdominal anthrax are initially nonspecific and include nausea, vomiting, anorexia, and fever. Lesions are frequently described in the cecum and adjacent areas of the bowel. Some reports have described lesions in the large bowel, and rarely in the duodenum. With progression of the disease abdominal pain, hematemesis. and bloody diarrhea develop. With further progression toxemia develops, with shock, cyanosis, and death. The time from onset of symptoms to death has most frequently varied from 2 to 5 days.

In the oropharyngeal form edema and tissue necrosis occur in the cervical area. There are several reports describing the development of an inflammatory lesion resembling a cutaneous lesion in the oral cavity involving the posterior wall, the hard palate, or the tonsils. The main clinical features are sore throat, dysphagia, fever, regional lymphadenopathy in the neck and toxemia. Most of these patients die with toxemia and sepsis.

Meningitis. Meningitis, seen in less than 5 % of anthrax cases, may be a complication of any of the three forms of primary anthrax infection.

Diagnosis

Of importance in considering a diagnosis of anthrax is a source of exposure to the infectious agent. Only rarely cases have occurred for which the source of infection could not be identified. Cutaneous anthrax should be suspected when an individual describes a painless, pruritic papule, sometimes surrounded by vesicles usually on an exposed part of the body. For the detection of anthrax bacillus, sterile swabs should be soaked in the fluid of the vesicles, vesicular fluid should reveal *B. anthracis* organisms microscopically and on culture. Anthrax bacilli are easily seen on Gram stain smears and cultures from vesicular fluid.

An enzyme-lined immunosorbent assay (EL1SA) has been developed that measures antibodies to the lethal and edema toxins. The diagnosis may be confirmed serologically by demonstrating a fourfold change in liter in acute- and convalescent-phase serum specimens collected 4 weeks apart or by a single titer of greater than 1:32. Although extensive serologic studies have not been conducted, antibody liters in some surveys of exposed individuals suggest some degree of previous subclinical infection.

Differential diagnosis

Includes staphylococcal disease, plague and tularemia. The initial symptoms of inhalation anthrax are nonspecific and resemble those of an upper respiratory tract infection. Characteristically, with the sudden development of the acute phase there is severe respiratory distress, and radiographic examination of the chest should reveal widening of the mediastinum, a typical occurrence with inhalation anthrax.

In gastrointestinal anthrax, the patient presents with signs and symptoms of gastroenteritis. Organisms may be demonstrable in vomitus and feces from the infected individual. The differential diagnosis includes diseases that cause moderately severe gastroenteritis, such as shigellosis and *Yersinia gastroenteritis*. In the cervical form, the signs and symptoms might suggest severe pharyngitis, such as is sometimes seen with streptococcal infections.

In anthrax meningitis and in septicemia there should be a primary site of infection. Cerebrospinal fluid (CSF) and blood contain *B. anthracis*.

Treatment

The basic agents are antibiotics and antianthrax immunoglobulin. Among the antibiotics ciprofloxacin or ofloxacin are preparations of choice. At generalized infection ciprofloxacin is used 0.4 or 0.5 gm twice a day. Course of treatment is 5-10 days. Benzylpenicillini natrium sodium salt 500,000-1 million units is effective, 6-8 times per day. At the generalized form of disease enlarge a daily dose of preparation up to 12-24 million units. It is possible to use semipenicillines – ampicillin or oxacillin. Course of treatment not less than 7-8 days. Alternative preparations can be tetracyclin, levomycetin, streptomycin, gentamicin.

The best results are reached with the combined therapy of antibiotics and antimalignant anthrax immunoglobulin. Last infuse in muscle in a dose from 20 up to 100 mL. Depend on clinical form and degree of gravity of disease. Preliminary make intracutaneous test on sensitivity of organism to horse protein. It is necessary in 1-2 days infuse immunoglobulin repeatedly before clinical improvement. The course dose reaches sometimes 400 mL.

At serious current of disease use infusions of 5 % solution of glucose, reopoliglycin, poliionic solutions, furosemid (lasix), glucocorticoides, oxygenotherapy.

Prophylaxis

Early in this century, as an example of health preventive intervention, a formaldehyde disinfecting station was built by the British government in Liverpool. All "dangerous" imported wool and goat hair were first washed in formaldehyde baths, which successfully reduced contamination of the animal fibers with *B. anthracis*.

The resistance of the spore form of *B. anthracis* to physical and chemical agents is reflected in the persistence of the organism in the inanimate environment. Organisms have been demonstrated to persist for years in factories in which the environment became contaminated during the processing of contaminated imported materials of animal origin. Accordingly, they may serve as the source of infection for people who work in the area. Special efforts are required to decontaminate this environment; one method is to use paraformaldehyde vapor, which is successful in killing *B. anthracis* spores. In the laboratory, surfaces may be decontaminated with either 5 % hypochlorite or 5 % phenol (carbolic acid); instruments and other equipment may be autoclaved.

Employees should be educated about the disease and the recommendations for working in a contaminated environment and for reducing the risk of developing

the disease. Medical consultation services should be available to the employees. Adequate cleanup facilities and clothes-changing areas should be available so that workers do not wear contaminated clothes home.

It should be noted that the risk of industrial infection has been reduced significantly as the use of imported animal products decreased because of changing business conditions, the increased use of synthetic materials, and the use of human vaccine.

Gastrointestinal anthrax can be prevented by forbidding the sale for consumption of meat from sick animals or animals that have died from disease. Depending on the circumstances, it may be important to alert individuals who may come in contact with contaminated meat about the disease and about the need to cook all meats thoroughly. Prophylactic penicillin may be used if contaminated food has been ingested.

Animals that graze in areas known as anthrax districts should be vaccinated annually with the animal vaccine. All animals suspected of dying from anthrax should be examined microbiologically: blood or tissue smears can be examined microscopically, and cultures can be set up from these same materials. Necropsies with spillage of contaminated blood with resultant sporulation of organisms should be avoided. All animals that have died with a confirmed diagnosis of anthrax should be thoroughly burned and the remaining bones and other materials buried deeply.

Control of the disease in humans ultimately depends on control of the disease in animals. Effective animal vaccines are available, and all cases should be reported to state veterinary authorities.

Both an attenuated live vaccine and a killed vaccine have been developed. However, the only human vaccine in current use is the killed vaccine derived from a component of the exotoxin. This vaccine was field tested in employees of four different textile mills in the United States, and an effectiveness of 92.5 % was demonstrated. This vaccine should be used for all employees who may be exposed to contaminated materials or environment. Additionally, anyone who comes into a mill processing *B.antracis* - contaminated materials should also be vaccinated. Currently, the vaccine is given parenterally with three doses at 2-week intervals followed by three booster inoculations at 6-month intervals and the annual booster inoculations. Veterinarians and other persons who, because of their occupation, have potential contact with anthrax should also be immunized with the human anthrax vaccine.

Control questions:

1. Etiology, epidemiology and incidence of anthrax.
2. Pathogenesis of anthrax.
3. Anatomic pathology of disease.
4. Clinical manifestations of anthrax.
5. Laboratory methods of anthrax diagnosis.
6. Criteria of diagnosis.
7. Differential diagnosis of anthrax.
8. Treatment of anthrax.
9. Prophylaxis of anthrax.

VIRAL HEPATITES

The problem of the viral hepatites remains most actual, as these diseases according to their spread step down only to acute respiratory and acute intestinal infections. Viral hepatites is most frequent cause of chronic hepatitis and liver cirrhosis. In some patients viral hepatites may have lethal outcomes.

The problem of the viral hepatitis is present under fixed attention of many scientists of the whole world. At present time definite successes in study of etiology, epidemiology, clinic, diagnostics of this polyetiological viral disease have been possessed.

Etiology

At present time further viruses, causing viral hepatitis are known: virus of hepatitis A (VHA), virus of hepatitis B (VHB), virus of hepatitis E (VHE), virus of hepatitis D (VHD), associated with VHB, virus of hepatitis C (VHC), virus of hepatitis G, and recently new types of probable causative agents of hepatitis were discovered − Sen and TT viruses, the role of virus of hepatitis F is under discussion. Search of new viruses, causing viral hepatitis continues. In literature one may come across different names of disease, caused by these viruses: infection hepatitis, epidemic hepatitis, serum hepatitis, syringe hepatitis. Uniting all these terminis − Botkin's disease. Indicated diseases caused by different viruses, possess many in general, however highly essential clinical, epidemiological, biochemical and immunological peculiarities that have been revealed. These peculiarities demand conduction of differential diagnosis between them. As a result of the above said, group of experts of WHO recommend to differentiate further variants of viral hepatitis: viral hepatitis A (VHA); viral hepatitis B (VHB); viral hepatitis E (VHE); viral hepatitis C (VHC); viral hepatitis D (VHD), viral hepatitis G (VHG).

Virus of hepatitis A (VHA). Agent was first discovered in 1973 by Feinstone. This is RNA-containing virus. Complete viral bodies as well as empty parts (capsules) with size of 27-30 nm can be noticed under electronic microscope. On their surfaces capsomeres are seen. Nucleopeptide of VHA does not possess surface projections and covering. Core structure is not revealed in the virion. Virus contains 4 peptides (VP1-4), participating in reactions of immune precipitation. It is assumed that VP1 and VP3 are located pertly on the surface and VP2 and VP4 are present inside the virion. However, up till date, there is not authentic informations about their meaning in relation to antiqenicity and immunogenicity.

VHA is stable during pH 3.0-9.0, sensitive to formaldehyde, may remain preserved for a period of few months or even years during temperature + 4 °C, for weeks − during room temperature. Complete inactivation of virus takes

place during 85 ^{0}C in a period of 5 minutes. VHA is resistant to chlorine, in comparison with other viruses of this group and may enter through barriers of water cleaning stations. Complete inactivation of virus steps on during concentration of chlorine 2.0 − 2.5 mg/L with exposition for a period of 15 minutes, of lime chloride − 10 mg/L during 15 minutes.

Virus of hepatitis A may reproduce in number of human and monkey cellular cultures, from where viral antigen is obtained. It is necessary to remark, that successful adaptation of VHA towards culture of cells is very much necessary for study of biological properties, for obtaining of source of reagents for diagnostics (antigen, antiserum), as well as for construction of vaccines (live, killed).

Virus of hepatitis B (VHB). VHB in natural condition is revealed in sick people and carriers, in forest marmots, in carth squirrels, in Peiking ducks. This DNA-containing virus is pathogenic for human and few types of primates − chimpanzee, gorillas. VHB causes acute and persistent infection, primarily damages liver.

Virus consists of nucleus and covering. Further antigenic structure of VHB is differentiated: HBsAg − surface, HBcAg − internal (core), HBeAg − reflects infectiouness of virus.

Towards these antigens in organism of patients antibodies are produced: anti-HBs, anti-HBc, anti-HBe.

Presence of HBsAg in human organism testifies the presence of acute and latent proceeding infection. It is assumed, that prolonged conservation of HbsAg in serum of the blood in sick man may testify transfer of the process into chronic form. HBsAg is revealed in majority of patients in incubation stage. HBcAg is practically not determined in blood and fixed in directly by DNA-polymerize reactions, falling positive in acute period of disease, as well as after many months and years in carriers. Soon after discovery of HBsAg in blood of patients anti-HBc appear. Most often they are observed in carriers of infection. In early stages of disease HBeAg is revealed, which is then replaced by anti-HBe. Very important diagnostic information may be obtained by using methods of determination of DNA HBV. For this purpose molecular hybridization of nucleic acids and polymerize chain reaction (PCR) is used. Genospecific viral DNA is observed in serum of blood, in bioptates of liver, in lymphocytes of peripheral blood. Mentioned method enables to discover very small quantities of viral DNA in investigated samples, which moderately increases reliability of diagnosis.

Virus of hepatitis C (VHC). Virion of virus of hepatitis C consists of nucleus and lipid external membrane. Genome is represented by single chain RNA. VHC is heavily resistant in environment, and particularly in biological fluids such as preparations of blood, sperm and others. It is sensitive to chloroform, to other desinfective solutions and high temperatures (100 °C and more).

Antigenic structure of VHC is less studied. It is established, that antibodies (Ig of M and G class) are produced to virus in the organism of the patient. Their discovery in blood serum of patient testifies presence of acute or chronic disease.

Antibodies may stick to definite level during 6-9 months, and thereafter their titers in serum decrease upto complete disappearance.

Virus of hepatitis D (VHD). VHD represents itself as defective virus particle of size 30 − 35 nm, contains internal antigen (HDAg), made up of small circular RNA and surface covering, which is HBsAg VHB. It is considered that reproduction of virus is possible only during presence of HBsAg in organism of patient, therefore hepatitis D proceeds always as a coinfection or superinfection, joining to VHB.

Human's organism replies to VHD infection by production of antibodies of IgM class, which are used in diagnostics of the disease.

Virus of hepatitis E (VHE). Virus of hepatitis E has been isolated from feces of patients with jaundice. Spherical particles similar to virus were able to discover due to the method of immune electronic microscopy. Material for investigation was collected from volunteers, infected by material from patients with jaundice with assumed diagnosis of viral hepatitis E. It is supposed, that VHE may be caused by few strains of virus of different antigens.

At present time a test-system, giving the possibility of discovering antigens of virus in fecal matter has been elaborated. Serums of reconvalescenes are used for that.

Epidemiology

Viral hepatitis A is an antroponosis. The source of disease is sick person in prejaundice period and during 15-20 days of climax period of the disease and virus carrier. Primary localization of virus is gastrointestinal tract. Mechanism of transmission is fecal-oral. Virus is excreted from the organism of sick person with feces. Specific factors of hepatitis A virus transmission are water and blood. Character of water infection depends upon conditions of water supply and its relation with fecal contamination. Intermediate factors of transmission are flies, transferring virus with feces on products of nutrition, dishes.

Susceptibility to the disease is high. Mainly children and adults under 30 year fall ill.

The source of hepatitis B virus in nature is ill person with acute or chronic form, healthy carrier. Natural way of transfer is sexual. Infection may be transferred even during kisses through traumatized mucous, through milk of mother, through placenta from ill mother to fetus (vertical path of transmission). Parenteral way of the transmission includes blood and its preparations transfusion, injections, manipulations, operative interventions.

Susceptibility to the disease is high. Most often drug addicts, homosexuals, prostitutes, medical personnel (surgeons, obstetrician-gynecologists, workers of hemodialysis departments, manipulative nurses, doctors-infectionists) fall ill with hepatitis B.

Epidemiology of viral hepatitis D has been studied insufficiently. It is assumed, that source of infection is sick person, basic path of transmission is parenteral.

Persons suffering from VHB or HBsAg—carriers are more susceptible.

Epidemiology of viral hepatitis E is identical to epidemiology of VHA, and hepatitis C — to hepatitis B.

Pathogenesis

Pathogenesis of viral hepatitis is still not studied completely due to big difficulties, caused by absence of accessible experimental model of the disease. At the base of existing notions about pathogenesis of acute viral hepatitis lay clinical observations, life time investigations of liver tissue and comparative study of viral hepatitis in animals.

Entrance of the agent of the disease into the organism of patient takes place perorally (VHA, VHE), by sexual way (VHB, VHC), parenterally (VHB, VHC, VHD and not excluded for VHA and VHE), vertically (not excluded for all viral hepatitis).

The agent approaches regional lymphatic glands, where its massive reproduction takes place — the second phase of pathogenetic process. The agent causes damage of cells and their death. Organism replies on this negative influence by immune reaction of reticular tissue of the lymphatic glands, executing "barrier" function. This corresponds to period of incubation. On this level infections process may stop. In insufficiency of "barrier" function the phase of generalization of infection (primary virusemia) begins.

Virus continues to enter from lymphatic glands into blood in a large quantities. Clinically this phase is manifested by signs of intoxication and beginning of the damage of liver. In this phase viruses of hepatitis are connected with thrombocytes. Due to composition of their phospholipid membrane they violate, metabolism of arachidonic acid is intensified, that leads to increase in their adhesive and aggregate activeness. Viruses of hepatitis also render action on cells of endothelium of small vessels, cause destruction of the structure of their biomembrane. As a result of such influence, highly active endoperoxides are formed from arachidonic acid (compulsory component of phospholipids of membrane), rendering powerful influence on adhesion and aggregation of thrombocytes, erythrocytes. Such influence of viruses of hepatitis on the blood cells and endothelium of vessels already in the phase of virusemia renders essential influence on coagulative and anticoagulative system of the blood causes disseminated intravascular coagulopathy. The first stage of DIC-syndrome develops. Degree of these disorders depends on massivity of virusemia and determines the disease course.

The phase of virusemia is confirmed by determination of HBsAg in the blood of the patient. Besides virusemia parenchymatous diffusion also happens. Viruses of hepatitis penetrates into the liver cells. Reproduction of virus is realized in hepatocytes. Virus also revealed in erythrocytes, thrombocytes, in the cells of pancreas, reticuloendothelial system. The inculcation of virus into hepatocytes leads to disorder of intracellular metabolic process, especially in

membranes of hepatocytes. The lesion of membranes accelerates destruction of hepatocytes.

The mechanism of the damage of hepatocytes, other cells of the organs and systems is studied insufficiently. Syndrome of cytolisis also plays the leading role in pathogenesis of viral hepatitis B. However, virus of hepatitis B doesn't possess the direct cytopathogenic action.

F.Dubleu, A. Bluger consider that immune reactions, connected with T-cells, have the leading meaning in the pathogenesis of syndrome of cytolisis. The penetration of virus into hepatocytes and reproduction in hepatocytes leads to accumulation of viruses in surface membrane. Circulation of antigens in the blood causes sensibilization of T-lymphocytes. The activation of T-lymphocytes leads to distinction and depression of the agent and to differention of subpopulation of T-lymphocytes. Effect of T-killer causes cytolisis of hepatocytes. Autoimmune reactions intensify cytolitic syndrome and necrosis of liver.

Pathogenesis of viral hepatitis B is explained from viral-immunogenetic position, because it is known that power of immune response is genetically determinated. Immune reaction may be strong (in fulminate form of hepatitis), flabby and adequate. Only adequate immune reaction promotes cyclic course and favorable outcomes of the disease.

The scientific achievements of the last years opened new points of view to pathogenesis and therapy of different forms of viral hepatitis. The study of metabolic processes on the level of cell allowed to open new aggressive components, which have negative influence on its structure and functions.

The surplus activity of the processes of free radical oxygenation renders destructive influence on cells membranes. As a result free radicals are accumulated in the cells. The process of lipids oxygenation is intensified (peroxide oxygenation of lipids – POL). It is known that lipids are the basic structural component of the cells. Antioxydant system of the organism is defending mechanism, supporting free radical oxygenation of the physiological level. Due to research of the last years it was shown that activation of the processes of peroxide oxygenation of lipids plays the essential role in the pathogenesis of viral hepatitis and leads to alteration of structure and functions of membrane of hepatocytes, thrombocytes and other cells. It's worth to underline that simultaneously with activation of POL the considerable depression of antioxydantic activity of the blood serum is marked.

In case of extremely high activity of POL exhaustion of AOS takes place, which leads to disorder of activity of cellular ferments, particullary of glucolysis, glucohenolysis and to rupture of phoshorilation. As a result, cell loses energetic potential. It leads to destruction of cell. Along with this permeability of membrane of hepatocyte and its internal structural components are disturbed. Corrosion of hepatocyte takes place, its synthetic, disintoxicative and other function are lost. Disturbance of permeability of lysosomal membranes causes exit proteolytic ferment into cytoplasm, which complete the death of hepatocyte.

At the last years data about molecular mechanism of the damage of hepatocytes membranes were received. It is known that interferones cause depression of reproduction of viruses.

Leukocytaric and fibroblastic interferones may be produced practically by all cells. Immune gamma-interferon is produced by gamma-interferon immunocompetentive cells during immune response.

Interferon may influence on complex of defensive reaction (phagocytosis, inflammation, antigen expression). Interferon is the most important factor of nonspecific resistance. However, interferon has influence on differentiation and activation of effector cells of immune system. The activation of monocytes (macrophages), increased generation of peroxide radicals, increased phagocytes activity are observed under influence of interferon. Thus, at the present time interferon is considered not only as antiviral remedy, but also as important regulator of interaction between cells. Due to investigations of the last time it was established that antiviral effect of interferon is not connected with direct interaction with viruses. Antiviral effect is connected with change of metabolic processes in the cells.

It is established that there is decreased produce of interferon in the patients with viral hepatitis B, especially in patient with severe course of the disease. In fulminate course of acute viral hepatitis B interferon is not revealed in the blood serum.

Anatomic pathology

Morphological changes in liver take place in all tissual components — parenchyma, connective tissue, reticuloendothelium, in lesser degree in bile pathway, diffuse damage of the organs occurs. Degree of damage fluctuates from insignificant dystrophic and single necrotic changes of epithelial tissue of lobules of liver during mild forms till massive and submassive necroses of liver parenchyma. Three variants of acute form of the disease are differentiated: acute cyclic, cholestatic and massive necrosis of liver.

During acute cyclic form diffuse damage of epithelial and mesenchymial elements is observed. Decompensation of beam structure with orderly placement of hepatocytes with their considerable polymorphism is noted.

Along with the dystrophic changes, expressed processes of regeneration with figures of mitosis and abundance of double nuclear cells are determined. Characteristics are presence of scattered necrosis hepatocyties in all lobules. Changes of mesenchymial elements inside the lobules are expressed in proliferation of Kupffer's cells with their change into macrophages. Cytoplasm of these cells are basophilic, contains bile pigment. Capillaries in the center of lobules are dilated. Proliferation of lymphohistocytary elements with admixtures of plasmatic cells eosinophills and neutrophils are marked in the portal tract. Along with this, reticular hyperplasia of spleen and portal lymphatic vessels is observed. Clinical manifestations of the disease correspond to the severity of destructive changes in parenchyma of liver.

During cholestatic variant of viral hepatitis majority of morphological changes are observed in intrahepatic bile passages with picture of cholangitis and pericholangitis.

Clinical manifestations

Clinical picture of all viral hepatites is very much similar and differs in percent relation by severity of the course of the disease and its outcomes. Viral hepatitis A and E are characterized by cyclic benign course with complete reconvalescence. In hepatitis B, C and D medium serious and serious course, lingering and chronic forms of disease and lethal consequences are inrarely observed.

Depending upon the expressiveness of clinical manifestations of the disease and degree of functional disorders of liver, established by biochemical tests, light, medium serious, serious and malignant (fulminate) forms of viral hepatitis are differentiated. All atypical cases of the disease (non-jaundice, obliterated, subclinical) are concerned to mild forms, because as clinical manifestations and functional changes are weakly expressed in such patients.

During evaluation of severity of the disease, expressiveness of intoxication and jaundice is taken into attention along with enlargement of sizes of liver and spleen, loss in weight, level of bilirubin in blood serum.

High intoxication, polyarthralgia, expressed dyspeptic symptomocomplex are typical for fulminate and serious forms of viral hepatitis. Prolonged intensive jaundice, hypotonia, bradycardia, changing into tachycardia, slackness, subfebrile temperature, decrease in diuresis, testifies about serious or even malignant course of viral hepatitis with indefinite prognosis.

Laboratory tests are used for evaluation of severity of disease: tests of concentration of general bilirubin in blood serum of patients, the prothrombin index.

Viral hepatitis have principally cyclic course. Incubation period is different. In hepatitis A it is in average 15-30 days, during viral hepatitis B 30-180 days. The disease begins with signs of general intoxication – so called pre-jaundice period. There are the next variants of prejaundice period:

1) Dyspeptic variant – patients complain of appetite absence, nausea, sometimes vomiting. Temperature is subfebrile. Duration of period is 3-7 days.

2) Astenovegetative variant – patients complain of weakness, headache, malaise, decrease of appetite. Body temperature is subfebrile or 37-38 °C;

3) Influenza-like variant – patients complain of headache, weakness; muscular pain, decrease of appetite. Body temperature is 37.5-39 °C, and in separate cases 39-40 °C. Duration of 2nd and 3rd variant of prejudice period is of 5-7 days;

4) Polyarthralgic variant – it is observed mainly during hepatitis B and C. Patients complain of pain in joints, sometimes muscular pain, weakness, decrease of appetite. During this, subfebrile temperature is in majority of the patients. Duration of this period is 7-14 days;

5) Mixed type – all above mentioned signs of intoxication in various degree of manifestation.

The next period of the disease is climax period. The state of the majority of the patient becomes better. The temperature is normalized, urine becomes dark, colorness stool. Scleras are icteric, jaundice grows gradually (Fig. 11). The further course of the disease depends on degree of liver damage by the virus, which determines

the severity of the disease. During light course of viral hepatitis jaundice grows in a period of 3-5 days. It is present on one level during one week. Disappearance of jaundice is observed on 15-16 day. Urine becomes more light at the end of the first-second week of the jaundice period, it is of yellow or orange color.

During medium serious and serious course of the disease yellowish coloring of scleras and skin is more intensive, jaundice period is prolonged (20-45 days). In majority of the patients the signs of cardiovascular system disorder are observed. There are hypotonia, bradycardia, muffed hearts sounds. In 80-90 % of the patients liver is enlarged, its surface is smooth, borders are curved, moderately painful. In 30-40 % of patients spleen is palpated. During serious course of viral hepatitis in some patients meteorism of abdomen, caused by disorders of digestion (signs of damage of pancreas, secretory glands of stomach and disorders of biocenosis of gastro-intestinal tract) is observed. In some patients skin itch is observed – the so called cholestatic variant of the course of the disease.

Different changes are observed in central nervous system. Already during mild course of viral hepatitis adynamia, slackness, disorders of sleep may be present.

In serious cases clear cerebral disorders caused by considerable dystrophic changes in the liver, endogenic intoxication and increase of the activity of the processes of POL are observed.

In the period of reconvalescence reverse development of symptomatic of disease, normalization of biochemical indices is marked.

Outcomes of the disease. Viral hepatitis most often ends with complete reconvalescence. In some patients may be cholecystitis, cholangitis, pancreatitis, dyskinesia of bile excreting pathways after an acute hepatitis. In 5-10 % of patients lingering course with periodical aggravations, caused by prolonged persistence of virus is observed. In such cases chronic hepatitis develops. This variant of the course of the disease is typical for viral hepatitis B and C; chronic hepatitis may end up by liver cirrhosis.

Complications

The most threatening outcome of viral hepatitis is acute or subacute massive nercosis of liver, during which picture of acute or subacute hepatic encephalopathy is observed. An acute hepatic encephalopathy (AHE) is typical for acute hepatites.

The term "acute hepatic encephalopathy" denotes unconscious condition of the patient with violation of reflex activity, convulsions, disorder of life vital functions as a result of deep brake of action of cerebral cortex with its spread on to subcortex and below laying parts of central nervous system. This sharp brake action of nervous-psychic activity is characterized by disorder of movements, sensibility, reflexes and by absence of reactions on different irritators.

Hepatic coma is an endogenic coma, caused by endogenic intoxication as a result of loss of function and breakdown of liver.

There are the next stage of AHE – precoma I, precoma II and properly coma.

Precoma I is characterized by non constant disorder of consciousness, unsuitability of mood, depression, lowered capability towards orientation, tremors, inversion of sleep. Patients are irritated, sometimes − euphoric. They are troubled by paroxysms of depression, doom, presentiment of death. Fainting, short time unconsciousness, giddiness, hiccup, nausea, vomiting may be observed. Jaundice grows. Bradycardia is changed by tachycardia. Tendon reflexes are raised. Such condition prolongs from few hours to 1-2 days with moving into second stage.

In the second stage of precoma consciousness is more hampered, losses in memory is a characteristic feature, alternated with attacks of tachymotor and sensory exciment till delirium. During awakening orientation in time, space and action is absent. Tendon reflexes are high. Jaundice raises sharply. Muffed heart sounds, tachycardia, hypotonia are revealed.

Rhythm of respiration is disturbed. Liver begins to decrease in size. Hepatic insufficiency is inrarely accompanied with hemorrhagic syndrome due to development DIC-syndrome. In $1/3$ of patients nasal hemorrhages, gastrointestinal hemorrhages, uterine bleeding and hemorrhages of other localization are observed. Diuresis decreases. Abdomen is inflated, peristaltic of intestine is decreased. Such condition continues for 12 hours − 2 days.

During the third stage − properly coma − complete loss of consciousness and disappearance of reflexes is marked. Pathological reflexes may be too. Rigidity of muscles of extremities, hyperkineses, convulsive syndrome, and thereafter complete areflexia are observed. Expressed tachycardia, hypotonia, disorder of rhythm of respiration are revealed. Diuresis decreased considerably till anuria. The death of the patients is through 6-24 hours. The patients perish from massive hemorrhages or in development of severe metabolic acidosis.

Diagnosis

Preliminary diagnosis of viral hepatitis is based on epidemiological anamnesis, finding of the development of the disease, clinical picture with account of peculiarities of the ways of the transmission, duration of incubation period, presence of prejaundice period, presence of typical subjective and objective signs with account of the patients age.

Diagnosis is confirmed by routine and specific laboratory tests. In routine blood test of the patients with viral hepatitis lymphocytosis is observed with moderately expressed course and in serious course of the disease − anemia and leucopenia. ESR is slightly decreased. In urine urobilin and bile pigments are observed. During climax period, particularly during medium serious and serious forms, there are no stercobilin in stool.

 Increased content of general bilirubin, primarily on account of its direct fraction is observed in blood serum during all jaundice period. Ratio of direct and indirect fraction composes 3:1. In all patients already in pre-jaundice period of the disease, during all jaundice period and in the period of early reconvalescence increased activity of ALT, AST is observed, testifying about the presence of cytolytic processes in liver.

Specific antigens (HBsAg) and antibodies to antigens of all known at present time viruses of hepatitis are revealed in the blood of patients with help of these methods. Discovery of antibodies of class of IgM testifies about acute disease. Discovery of other classes of immunoglobulins antibodies testifies about lingering or chronic course of viral hepatitis or about earlier infectious process or about disease in the past.

Differential diagnosis

Differential diagnosis of viral hepatites is necessary to perform with diseases like leptospirosis, yersiniosis, mononucleosis, malaria, mechanic and hemolytic jaundice, toxic hepatoses.

Leptospirosis is characterized by acute beginning of the disease, often with chill, continuation of fever during of climax of the disease and jaundice, pain in muscles, especially in calfs, hemorrhagic syndrome. In blood leucocytosis with neuthrophillosis and shift in the formula to the left, accelerated ESR are observed. Activity of ALT and AST is moderately raised or normal relation of direct and indirect bilirubin 1:1. In blood serum concentration of urea and residual nitrogen increases. Stool is colored. In urine erythrocytes, leukocytes, like wax cylinders are marked in large quantity. Diuresis decreased till anuria.

In generalized forms of yersiniosis jaundice may be also observed, however it is accompanied by fever, metastatic focuses in other organs and tissues, leucocytosis with nuetrophilosis, accelerated ESR, aggravations and relapses. Diagnosis is confirmed by serological methods with specific yersiniotic antigen.

In malaria there are clear alternation of attacks fever with chills, replaced by heat and sweat and periods of apyrexia. Often painful, increased in size spleen is marked. In blood hemolytic anemia, in fat drop blood and smear different forms of malarial plasmodia are reveled. In blood serum indirect fraction of bilirubin predominates.

In mechanic jaundice stones in gall bladder and bile passages, enlargement of head of pancreas and other signs are revealed with help of ultrasound investigation. In majority of the patients moderate increase of activity of ALT, AST, leukocytosis, accelerated ESR are marked. Hemolitic jaundice is characterized by anemia, accelerated ESR, increase of indirect fraction of bilirubin. Stercobilin is always present in stool.

Differential diagnosis of viral hepatites with hepatoses is complicated and demands from doctor thoughtful and painstaking work. During this essential significance possesses correctly taken anamnesis.

Treatment

Treatment is used in complex and depends on the clinical form and gravity of disease course. At mild course of a viral hepatitis in the acute period it is possible to prescribe only semi-bed regime, diet № 5, polyvitamines and desensitizing preparations: calcium gluconate, diazolin, diprazin or tavegil. In

case of meteorism, feeling of gravity in epigastrium area after the meal, unstable feces — festal, pancurmen, allochol, cholenzym are indicated.

At medioserious and serious current of the acute form of hepatitis a bed regime is provided together with the specific treatment. Desintoxication therapy consists of plentiful drink; 5 % solution of glucose, saline solutions, ringer's solution, threesault, quartasault, 20 % solution of sorbit (sorbitoli), donor Albumin (given in vein), one of enterosorbents — SKN, carbaphosfer, carbosilan, sillard P, enterosgel, polyphepan. The quantity of drunk liquid should be balanced with daily urine. Polarizing admixture: 3.7 gm potassium of Sody chlorid and 12 units of insulin on 1 liter of 5 % solution of glucose is recommended. The preparations improving metabolism in hepatocytes are indicated: ascorbinic acid, thiamin chlorid, pyridoxine hydrochloride, cocarboxylase, potassy orotat, riboxin, cytochrom C, lipamid, calcii pangamat. Last two preparations are indicated mainly in case of accompanying hepatoses with fatty infiltration of liver (alcoholism, diabetes, thyrotoxicosis, obesity). For acidosis decreasing 2 % solution of sodium of a hydrocarbonate 25-50 mL per os 3-4 times per day or on 150-200 mL intravenously should be infused.

Among etiotropic agents human recombinative α-2-interferon has moderate medical effect at acute virus hepatitis — reaferone, intron A, Realdironi or analogue laferone in powder, in amp. 1,000, 000 IU: from 1st to 5-10th day of the icteric period. Next days their efficiency falls. At acute hepatitis B laferon is infused 1,000, 000 IU 2 times per day during 5-6 days, then 1,000,000 IU 1 time per day during 5 days. If medical effect is insufficient, there should be continued infusing 1 million UN 2 times per week during 2 weeks. It is worthy to use leicinferone as the basic component which is the admixture of natural 6-interferons of donor leucocytes, the factor of necrosis of tumours and interleikin-1. However many clinicians challenge expediency of indication of interferon for treatment of hepatitis in acute period. More physiologic is the stimulation of endogenic interferonogenesis with the help of such inductores, as mefanam acid, prodigiosan, pyrogenal, nifluril, cycloferon.

At threat of hepatonecrosis — glucocorticoids 150-200 mg are prescribed. The dose of prednisolon per day must be reduced after the patient gets out of extremely serious condition. The volume of infusion solutions is enlarged up to 30-50 mL/kg per day. Ornithin (ornicetyl) promotes a linkage and removing out of organism nitrous bonds and improves a metabolism.

A lactulose reduces an adsorption of ammonia from intestine in blood, especially in combination with neomycin. With the aim of oppression of processes of an autolysis there should be used inhibitors of proteolytic enzymes contrical or gordox each 8 hours (I V) intravenous dropping, at improvement of a condition synthetic inhibitors. At retention of liquid in organism it is required to use spironolacton (veroshpiron), kaliumsaving diuretics, or saluretics — furosemid, etacrinic acid. Psychomotor exaltation is stopped by sodii hydroxybutyrate in combination with sibazon (seduxen), haloperidol. At increasing of hepatic failure antilymphocytic gamaglobulin is used during 1-5 days with the control of quantity

of lymphocytes in a periphery blood, apparatus methods of patients blood clearing, hyperbaric oxygenation.

At cholestatic form of a virus hepatitis the are effective preparations which form complexes inside intestine with cholic acids which can not be soaked up, cholestiramin and bilignin. Fenobarbital is used which is the inductor of synthesis of glucouroniltransferas. This enzym is necessary for conjugation of bilirubin with glucuronic acid, and stimulating its egestion with bile. Fenobarbital is indicated with combination of cyanocobalamin. Simultaneously for intensifying secretion of bile nospan and cholenzym are indicated. After the termination of an acholia duodenal tubages 5-10 % solution of magnesy sulfat (1/4 - 1/2 glasses), sorbit or xilit (20 gm on 100 mL of hot water) 1 hour before breakfast are applied.

Bioflavonoids – convaflavin, carsili, legalone, silibor, quercetin are indicated in case of the alonged reconvalescence. At hyperaminotransferasaemia – aevit or tocopherol acetas, thymalin, T-activin, dipiridamol (curantyl), isoprinosin (has also antiviral property) – give positive effects. Saparal, methyluracil (methacil), natry nucleinic, thymalin in a combination with dipiridamol, hofitol are also used.

Cholagogue agents – broths of flowers of immortele, hips, thyme, mints peppery in dose of 1 dining spoon of a herb or a mixture to 1 glass of water are indicated for convalescents. Fenobarbital with cyanocobalamin are applied during 10 days in case of hyperbilirubinemia with prevalence of untied fraction of pigment; preparations of choice can be cordiamin or sibazone (seduxen) which also stimulate glucoruniltransferase of hepatocytes. At hyperbilirubinemia mainly at the expence of connected fraction stimulate a bile secretion using oxygen cocktails with cholagogue herbs and honey. Vitohepat or cobamamid stimulate neogenesis and hemopoes, accelerate regenerative processes in liver, course of treatment lasts 15-20 days. At asthenia and hypoproteinemia, and also for elimination of catabolitic influences of glucocorticoids which were used at the acute period, anabolic hormones: such as methandrostenolon (nerobol), phenobolin (nerobolil) or retabolil are indicated. For elimination of the asthenic phenomena, there are used novopasit, tinctura of valeriana root (20 gm: 200 mL), herbs of neetle, thyme, bromidums, and in rather serious cases – chlozepid (elenium), sibazon (seduxen), relanium, barbiturates.

At the dyspeptic phenomena caused by oppression of secretory function of digestion organs, also allochol, liobily, cholenzym, festal, panzynorm forte, pancurmen, pancreatin, pancitratit, vobensym are widely used.

At posthepatitic hepatomegalias without signs of cytolisis it is reasonable to prescribe lydase – promoting a resorption of a fibrous tissue, 10 injections every two days. It can be infused only after exclusion of inflammatory process in hepatobiliar ways (control duodenal intubation is necessary).

Chemotherapeutic preparations are indicated in case of the bacterial cholecystitis. At mild course of disease it is possible to use only a fortnight course of nicodin, in case of serious disorders antibiotics or nitrofurans preparations are indicated.

It is possible to define sensitivity of microorganisms, isolated from the bile, to antibiotics. For such definition mediums are used, which content bile of the patient as it influences on essentially activity of antibiotics. Use ampicillin, carbenicilin dinatry salt, erythromicin, cefazolin, furazolidone, furagin, at *Candida* infection sody salt of levorin. Chemiopreparations are prescribed in average therapeutic doses during 7-8 days.

Specific therapy of chronic virus hepatitises is carried out by preparations of α-interferon (intron A, roferon, realdiron, reaferon, laferon). They are effective in case of low replicative activity of the virus determined in blood virus DNA (HBeAg) at a hepatitis B and virus RNA at hepatitis C. The additional indication is high activity of serum alanineaminotransferase. One of the specified preparations inject (IM) or subcuteneous 3-5 million IU per day 3 times per week during 6 months. Treatment should be stopped, if positive results were not observed after 3 months. The positive effect is observed at 40-50 % of patients with hepatit B and at 20-30 % of patients with hepatit C. At chronic hepatit D less than 10 % of patients are released from viruses even if treatment lasts 1 year. In some cases the success of immunotherapy of virus hepatites may be increased if preliminary short course of glucocorticoids treatment (about 6 weeks) is prescribed. Combined usage of interferon and thymalin, essentiale, lamivudin, chenodesoxycholyc acids has been proved.

The side-effects of α-interferon are noticed at half of patients right after injection, among them are headache, fever, myalgia, arthralgia, general weakness. They can be prevented by means of analgetics. Among the remote side-effects are: nausea, diarrhea, depression, irritability, leuco- and thrombocytopenia. Decreasing of a dose of preparation allows to weak these disorders. There are serious complications (sepsis, psychosis, autoimmune diseases), that demand an immediate cancellation of interferonotherapy.

At chronic hepatitis B in a phase of replication peroral preparation lamivudin (zeffix) is prescribed. It provides the same level of seroconversion, as standard course of treatment by interferon.

At chronic hepatitis with low replicative activity of a virus preference is given to pathogenetic agents improving metabolic and reparative processes in liver, such as: silibor, carsil, liv-52, hepatofalk, planta, hepabenne, antral, tocopherol acetat etc.

Prophylaxis

If the patient is hospitalized, he should be placed in a private room with separate toilet facilities. The major reason for such isolation is to prevent the spread of type A hepatitis. Even with lax precautions, such spread is very rare; most patients with type A hepatitis are no longer excreting virus once they have become symptomatic. Nevertheless, there are exceptions, and isolation is prudent. Secretions and blood products should be handled with care gowns, masks, and

gloves are not necessary, but a prominent sign reading "needle and blood precautions" is appropriate. Labeling of blood specimens from a patient with hepatitis, is a common practice. It should be stressed, however, that all blood from any patient should be handled as if potentially infectious.

If the patient with viral hepatitis is at home, the patient should be advised about care in personal hygiene − careful hand washing. Attention also should be paid to blood and blood products and the handling of cuts and lacerations.

Recommendations regarding the prevention of acute hepatitis are governed by the type of viral hepatitis that is being considered. In the case of acute type A hepatitis, all family members, and close personal contacts should receive immune serum globulin (ISG) at a dosage of 2-5 mL in as soon as possible after exposure. Office, factory, and school contacts do not need to be treated. Immune serum globulin can be given for up to 4 weeks after exposure, but it probably is only effective if given within 7-14 days.

In the case of acute type B hepatitis, prophylaxis only needs to be provided for "regular" sexual contacts. The best form of protection is argued Hepatitis B immune globulin (HBIG) at a dosage of 5 mL in as soon as possible and again 1 month later has been the conventional recommendation in this situation. However, the efficacy of HBIG in preventing the sexual spread of acute type B hepatitis has not been well proved. In addition, there is now evidence that postexposure immunization with HBV vaccine, can attenuate or prevent acute type B hepatitis. Vaccine should be given as soon as possible and then 1 month and 6 months later.

Control questions:

1. Etiologic classification of viral hepatitis.
2. Epidemiology of viral hepatitis.
3. Clinical forms of viral hepatitis.
4. Syndromes of pre-icteric period of viral hepatitis.
5. Basic criteria of viral hepatitis diagnosis.
6. Clinical manifestations of hepatitis.
7. Laboratory findings due to hepatitis.
8. Criteria of diagnosis of anicteric forms of viral hepatitis.
9. Clinic-laboratory signs of fulminative form of viral hepatitis.
10. Basic manifestations of chronic persistent hepatitis.
11. Basic manifestations of chronic active hepatitis.
12. Complications of viral hepatitis.
13. Consequences of viral hepatitis.
14. Differential diagnosis of viral hepatitis in a different periods of disease.
15. Medical treatment of patients depending on patient's weight.
16. Prophylaxis of viral hepatitis.
17. Preventive measures in the spot of hepatitis outbreak.

INFLUENZA

Influenza is an acute infectious disease which occurs in epidemics and is caused by a virus, it is characterized by an abrupt onset and such manifestations as general intoxication and affection of the respiratory tract mucosa.

Together with the diseases of the cardiovascular system and tumors, influenza takes the leading position in the human pathology. Influenza and other acute respiratory diseases constitute about 75 % of all infectious diseases, and 85 − 90 % in epidemics, thus resulting in great social and economic damage. Thus, in Ukraine in 1968-1972 in the epidemic period the economic damage equaled 112 millions roubles (about $120 million according to the exchange rate in those years). During the epidemic outbreak it equaled 420 million roubles. The main thing is that besides relatively mild cases of the disease, there are severe cases resulting in disability and sometimes death when children or old people contract a disease. According to the USA statistics influenza takes the tenth position concerning fatal outcomes.

Historic reference

The first pandemic which spread from Asia to Europe and America was registered in 1580. There have been 23 great epidemics and pandemics since that time. During the pandemic of 1780-1782 the modern term "flu" or "influenza" appeared (from the French word "*gripper*" meaning catch, envelope, from the Latin "*influere*" and Italian − "*influenza*" meaning penetrate, invade, instill).

In the manuscripts of the 14 − 15th centuries eight epidemics are mentioned, their names are "mass epidemic", "fatal infection", "catarrhal fever", "infectious fever", "quick catarrh" etc. Even the names show the essence of the disease. In spite of it, the authenticity of the information is not absolute.

It is impossible to determine the regularity of epidemics in the past. In some cases they were of local character affecting the population of few countries. In other cases influenza spread pandemically and affected the population of several continents.

Etiology

During the influenza pandemic of 1918-1919 filter-passing virus was more often considered to be influenza pathogen. This notion was confirmed by the classical experiments carried out by P. Zeiter who infected himself with washing off taken from the nasopharynx of an influenza patient and bacteriologically filtered.

In 1933 English scientists W. Smith, K. Andrews, P. Loudlow isolated influenza virus from a sick person, starting a new stage in the scientific study of the

influenza etiological structure. In 1940 T. Frensis and T. Magil isolated a virus which was quite different from the ones isolated earlier. It was suggested to name the first virus – influenza type A virus, and the virus isolated by T. Frensis – type B. In 1947 R. Tailor isolated and described a new type of influenza virus which was later named type C.

The influenza pathogen belongs to the group of orthomyxoviruses. Virions have a ball form and a diameter of 100-120 nm, they have a core of a tightly turned spiral of ribonucleic acid in the case of protein molecules.

On the external capsule there are glycoproteids in the form of a fence of pins: hemagglutinins (HA) and neuraminidase (NA) causing the development of a specific immunity after the disease.

The influenza virus quickly dies at drying, high temperature, it is resistant to low temperatures, extremely sensitive to ultraviolet rays and many disinfectants.

A characteristic feature of influenza type A virus is the changeability of its antigenic structure, changing under the influence of the population immunology.

Influenza B virus has a more stable antigenic structure and doesn't change so often. It has one neuraminidose but different hemagglutinins.

The most stable in relation to antigens is virus C. It causes only sporadic diseases and small outbreaks. It is spread mostly in Ukraine, Moldova and other southern regions.

Epidemiology

Influenza remains the most spread mass disease nowadays, which does not recognize any borders and affects great masses of the population (up to 50 % and more) at short periods of time. The influenza contagious character was noticed even in 1735 by Gexgame during the epidemic in Scotland, he called the disease "epidemicus".

A sick person is the only source of the disease. The epidemiological role of virus carriers has not been studied well. The virus quickly multiplies in the epithelial tissue of the respiratory tract mucous membrane of a sick person and in 24-48 hours there is an aerosol cloud with a great concentration of influenza virus around a patient at sneezing and coughing. As the immunity of a specific type forms very quickly, the virus disappears from the organism of a sick person on the fifth day of the disease.

Influenza infection is spread with the help of small particle aerosol dispersion. The mechanism of virus spreading is based on the condition that the virus is in the air for a long time, it has an ability to keep its infectious force under unfavorable conditions of the environment and the ability of virus particles to move with air at long distances and penetrate different parts of respiratory tracts infecting a person.

The influenza virus of full value can live and be infectious in the air for 2-3 hours. It can live for 1-2 days on the furniture and other surfaces. The ultraviolet

rays, humidity decrease and temperature increase and other factors shorten the virus life time. The virus lives within the limits of 1-3 meters. The speed of influenza spreading depends on the speed of people moving on the territory. The considerable increase of transportation, the movement of great numbers of people within separate countries, between countries and continents ensures a constant possibility of the virus spreading at considerable distances and the ability to infect people in any part of the globe.

There are small local epidemics and pandemics. The epidemics last 10-14 weeks.

The majority of people are naturally susceptible to influenza. The sick rate depends on many factors. First of all, on the level of the population specific immunity and on the circulation of the influenza virus serotypes.

The number of the influenza cases among adults has considerably decreased during the last years, as for the children aged 7-14 the number of influenza cases is growing slowly but steadily.

The influenza B sick rate tends to grow in all the age groups.

Pathogenesis

After penetrating the respiratory tracts, the virus sticks to the epithelial cells which have receptors − things of the lipid and carbohydratic nature. When the virus fixes on the cell surface receptors some complex enzymatic processes begin to occur, they ensure its penetration a cell in which it reproduces. This complex multistage process results in the cell death, and new virions born in the cells occupy new areas of the mucous membranes. The virus multiplication cycle lasts 7-10 hours. Every virion which penetrated a cell gives birth to 1,000 virions and there will be 10^{27} of them in a day. That's why the influenza incubation period is so short.

If there were no obstacles for reproduction, the entire tissue of the respiratory tract would be affected in 1-2 days and it would result in a lethal outcome. It happens in rare cases − "quick influenza" develops and a patient dies in 2 days. But it doesn't usually happen so, because a cell, in which virus reproduces, produces and secretes interferon. This interferon gets into the neighboring cells and after that they are not defenseless against the virus invasion. Interferon prevents virus protein from synthesis. The further development of virus infection depends on the struggle of these two forces − virus genome and cell interferon: either it stops at the very beginning or the disease lasts a short time and a patient gets well or the infection spreads in the lungs and fatal pneumonia develops.

The cells affected by a virus are rejected and the products of their decomposition are absorbed, causing a general feverish disease. At the same time in the submucous membrane there develop inflammatory processes with distinctive circulatory disorders, that clinically manifests by hemorrhage syndrome.

When the process spreads in the lung tissue, in severe cases with the development of influenza pneumonia, there are signs of general edema with scattered or confluent foci of hemorrhage.

Under these conditions the influenza virus easily penetrates the blood and virusemia develops. However, virusemia at influenza doesn't last long, as the virus quickly dies under the influence of nonspecific immunity factors – interferon, complement, properdin, β-lysines, β-inhibitors, histones, leukins, etc.

It is quite possible that the affection of the visceral organs at influenza is connected with virusemia. However, the great majority of authors doubt the specificity of such affections, as there are no specific receptors in all the other organs, and they think that in the pathogenesis of affections the leading role doesn't belong to the cytopathogenic phenomena, it belongs to the organism reaction to toxic products or other substances, which appear at the influenza virus reproduction process.

Besides, it is a fact that even in the mild cases of the disease there are signs of the organism hemopoietic and immune system considerable depression. The number of leukocytes in blood decreases and their functions are suppressed. Macrophages become less active. Due to it bacteria and viruses become more active and the accompanying diseases take an acute form. So influenza infection is mostly a combined virus-bacterial or virus-virus infection.

In conclusion it is necessary to note that interferon production is very important for the disease outcome in the struggle between viruses and the organism protective forces. Antibodies of class IgM appear only at the end of the first week of the disease when the organism wins the first main battle, and antibodies of class IgG in two weeks.

Anatomic pathology

There are three main groups of pathoanatomic changes at influenza: the first one – primary changes, caused by the virus itself; the second ones – secondary changes, caused by influenza virus in combination with cocci and bacterial flora; the third ones – late changes in patients who had influenza and died of complications or worsening of other diseases.

The most important morphological signs of the first group are dystrophic changes of the respiratory epithelium and lungs with distinctive disorders of microcirculation; sharp plethora, edema and pericellular infiltration of submucous membrane and thickening of basal membrane.

The interalveolar septum of lung tissue are considerably thickened due to plethora and edema with leukocytic-lymphoid infiltration. The walls of small vessels and capillaries are thickened, in some vessels there are fibrous and leukocyte thromboses. The cells of alveolar epithelium became partially hyperplastic, in some places – died, there is a small microphagic exudate in the alveoli lumens.

In the second group there remain signs of pure influenza infection, but more or less they are prevailed by the purulent affections of the respiratory system and serious blood circulation disorders in the lungs. Pyo-hemorrhagic and pyo-

necrotic tracheitis with a destruction of epithelium is developed in trachea. The lung tissue is low-pneumatic, the surface of the incision is motley, with alternation of large dark-red and gray foci. During microscopy massive foci of pyo-hemorrhagic pneumonia are found.

In the third group there are different kinds of pneumonia with various inflammatory exudate: purulent, pyo-hemorrhagic and abscess, plethora, edema and in some places hemorrhages into parenchymal organs, and also changes, which are characteristic of the accompanying chronic diseases.

Clinical manifestations

The incubation period at influenza is short – from several hours to 2-3 days. Its duration depends on the dose and toxic characteristics of the virus. The incubation period is short if the dose is big and the virulence is considerable. Thus, its duration has a prognostic meaning for a doctor.

There have been different opinions about the preliminary symptoms of the disease. It should be admitted that there is a prodromal period, which is characterized by elevated temperature for a short period of time (2-3 hours), slight malaise, chilliness, myalgias. These symptoms don't last long and are usually ignored by both a patient and a doctor. The disease begins to develop on the next day. In some patients the disease develops so fast that a practically healthy person becomes seriously ill in several minutes or hours.

The first symptoms are chilliness (always clear or poor manifested), high temperature, headaches, dizziness, a syncope condition, fever, malaise, pain in different parts of the body i.e. the symptoms of general intoxication. The headache is located in the forehead, temples and over the brows, it can be of different intensity. There is an early distinctive symptom – pain in the eye pupils especially intense at the eye movement or pressing, hyperemia of conjunctivas and sometimes scleras. Dizziness and syncope conditions are characteristic of teenagers and old people. The fever which is one of the main symptoms of influenza does not last long – 1-4 days (in 86 % patients). The "two-humped" character of the temperature is connected with the condition when the chronic infection takes an acute form or a secondary flora joins. Such symptoms as unconsciousness, delirium, convulsions and meningeal manifestations are characteristic of children at intense toxicosis.

Such symptoms as malaise, pain in the limbs and muscles, bones or in the whole body appear during the first hours of the disease and disappear when fever and other signs of toxicosis decrease. Adynamia, malaise can be considerable and are manifested from the first day of the disease. The skin on the face is hyperemic during the first 2-3 days, in severe cases they become pale with cyanotic shade. It is often a bad prognostic sign. Sweating is a characteristic feature. Intoxication is a characteristic feature of influenza, its degree and frequency vary in case of different microbes. In different epidemics there is hemorrhage syndrome, in 10-20 % cases, its symptoms are nasal bleeding, sometimes recipro-

cal, hemorrhage in the fauces, metrorrhagia, short hemoptysis and gum bleeding sickness. Cough appears during the first days of the disease, dry, excruciating, heart-rending which is accompanied by the feeling of tickling, scratching behind the breast bone. Almost all the patients have a catarrhal syndrome which has such symptoms as rhinitis, pharyngitis, tracheitis. There are often such combined affections of the mucous membrane as rhinopharyngitis, laryngotracheitis, tracheobronchitis, etc. They usually appear in the first days of the disease. Such symptoms as herpetic rash is quite frequent, but appears on the 3rd-4th day. Photophobia and lacrimation are finite rare.

There are no specific changes on the skin. Different kinds of rash which were described result from other reasons (taking drugs, accompanying diseases). As it has been mentioned before, quite often there is herpetic rash, theoretically there is a possibility of petechiae, hemorrhages, if we take into consideration the affection of vessels and their hyperpermeability. There can be random rash.

A natural manifestation of the influenza infection is the affection of the respiratory organs, as different pathological processes take place in them, they are located on a certain level, but sometimes affect the entire area. The affection of the upper respiratory tracts is accompanied with hyperemia and swelling of mucous membrane, sometimes with slight hemorrhages. There is nasal obstruction, rough breathing, and discharge of different nature and consistence: mucous, mucopurulent and sttaguinolent — in severe cases. During rhinoscopy swelling and hyperemia of mucous membrane can be seen, especially at the middle turbinate bone. At the same time accessory nasal sinus can be affected (maxillary sinusitis, frontal sinusitis, eustachitis with the development of otitis) with different nature of affection — from catarrhal to purulent.

During fauces examination the hyperemia of tonsils, uvula palatina and posterior wall of the throat could be found. Sometimes there are granules with vascular injection and hemorrhages on the soft palate. The development of influenza laryngitis and false croup is extremely dangerous, especially in children. Patients become pale, cyanosis develops, they often breathe with the help of additional musculature, the voice remains. Lethal outcomes are not rare, because not only larynx is affected, but trachea and bronchi as well, they are full with croupous superposition. The swelling of the mucous membrane of trachea and bronchi results in their permeability and leads to the deterioration of lung ventilation. Depending on the severity of the disease the degree of manifestations is different — from the hidden forms, which can be found with the help of pharmacological tests (aerosolic injection of eusporinum) to the severe forms accompanied with dyspnea and cyanosis.

Complications

The most common and dangerous complication of influenza is pneumonia. It is necessary to mention, that even during the first days of the disease there are roentgenologic strengthening of the vessel picture in the inferiomedial parts, that

looks like indistinct infiltrate, and hurried breathing, shortening of the percussion sound and appearance of so called "conductive" rhonchi, resemble pneumonia. But they often disappear without any traces in 2 − 3 days. It may not be pneumonia, but some circulatory disorders. Not everything is clear in the problem of pneumonia origin. After the detection of pathogen it was considered that during the first three days pneumonia is of virus etiology, on the 3-5 day − virus-bacterial, later − bacterial etiology. There is a picture of the so called "big motley lung" on the section. Hemorrhage pneumonia foci of different sizes can be seen along the whole length, they are small and large and separated by some parts of unaffected tissue. The foci of festering appear quite early. The rough beginning with severe toxicosis, catarrhal syndrome, significant and diverse changes in the lungs, are characteristic of influenza infection, which is complicated with pneumonia.

Diverse changes in the cardiovascular system have been described. The vascular system is usually affected, and sometimes considerably, it is probably connected with a toxic action of influenza virus on capillary vessels. Dilation of capillaries, turbid background, sometimes formation of the arterial aneurysms, are seen at the capillaroscopy. Arterial and venous pressure decreases, especially in case of pneumonia, the speed of blood flow slows down. The pulse corresponds the fever very often, there is sometimes tachycardia, especially at the beginning of the disease, in some cases there is bradycardia. The heart sounds are muffled, heart borders are widened, slight systolic murmur and sometimes extrasystoles appear. All these manifestations disappear when the general condition of the patient becomes better. There is elongation of the PQ interval, decreasing and notching, and sometimes inversion of the wave T at different abductions on the ECG. These disorders are interpreted as toxic and dystrophic. They are unstable and disappear in 1-2 weeks. The myocarditis described at influenza is disputed by other authors. More severe and diverse disorders are found in patients with chronic affections of the cardiovascular system (coronary atherosclerosis, rheumatic heart diseases, etc.). These disorders are not pathognomonic for influenza, and arise because of the aggravation of the main disease under the influence of influenza infection.

There are various affections of the nervous system during the influenza infection. The functional disorders of the vegetative nervous system are distinctively manifested. We have already got acquainted with such symptoms as sweating, changes of the pulse rate, dizziness etc. However, all these changes quickly disappear. At the same time serious affections of the central and peripheral nervous systems are observed, they are manifested as meningitis, meningoencephalitis, radiculitis, neuritis, etc. The rate of these complications is different in different epidemic outbreak. The pathogenesis of these diseases is still a difficult question. Side by side with the theories of the toxic and parainfectious factors in their development, it is possible, that the virus invasion plays a significant role.

The complications in the digestive system are less frequent, and there are evidently no specific disorders, although fur, dryness in the mouth, decreased

appetite, and heaviness in the epigastrium are observed. These symptoms are characteristic not only of influenza, but of any disease with fever. And now such forms of influenza as gastrointestinal, intestinal and abdominal which were the results of diagnostic mistakes are mentioned in conversations but not in literature.

The changes in the urinary tracts are manifested as pyelitis, pyelocystitis and sometimes nephritis, which result from metabolic-dystrophic manifestations of fever and bacterial superinfection.

The described affections of the endocrine system (adrenal gland, thyroid and pancreas glands) are very rare and it is not possible to completely exclude the influence of influenza virus in these cases.

Diagnosis

Besides careful clinical and epidemiological findings, modern methods of lab diagnostics are used for influenza diagnosis and differential diagnosis of other diseases.

Diagnosis does not seem to be difficult during epidemic outbreaks. However, at the same time besides influenza there 30-60 % patients with the respiratory tracts affection syndrome are registered, they are not of the influenza etiology, and clinical diagnosis is even more difficult during a non-epidemic period. As we see, influenza doesn't have specific symptoms which are characteristic of it only, but there are 3 strongly pronounced symptoms: abrupt onset with chilliness, general intoxication and the affection of the upper respiratory tracts. But they also accompany other acute respiratory diseases, and that is why there are many cases when patients with the diagnosis "influenza" are taken to hospital, but they have different other infectious and non-infectious diseases. That is why it is always important first of all to take into account the epidemic situation in the region.

A short incubation period is characteristic of influenza that is why the contacts with sick people, especially in the foci 1-3 days before the disease should be taken into account. If it is possible it is advisable to make up a general conception of the disease clinical picture in the people the patient contacted.

A careful and detailed physical examination of the patients, analysis and a comparative evaluation of the revealed changes with the consideration of the time past from the disease onset is also of great importance. It is important to remember that the preceding therapy can have a considerable influence on the natural disease course, sometimes changing or allaying some symptoms, and in other cases, on the contrary, resulting in the development of the new symptoms which are not typical of influenza. These can be various manifestations of the medication disease: skin rash, lymphoadenopathy, the toxic affection of the liver, hemogenic system, development of asthmatic syndrome, etc. Only a careful analysis of all the clinical symptoms can reveal the main syndromes, the peculiar mosaic of which is characteristic of one or another nosological form.

There is not any typical temperature curve. A relatively short febrile temperature reaction (5-6 days) with a quick rise and maximum values during

the first 2-3 days and shortened lysis should be considered to be more or less typical if the fever lasts longer than this period, it is always necessary to think of a possibility of another disease or joining of a complication. The usage of antibiotics, analgetics, sulfanilamides and glucocorticoides can considerably change a natural course of the temperature curve.

The changes in the hemogram are manifested as leukopenia or normocytosis. If there are no complications and accompanying diseases, there is absence or decrease of the eosinophils, neutropenia and relative lymphocytosis in the hemogram at influenza (the percentage of lymphocytes increases whereas their absolute number is the same). ESR is normal or insignificantly increased. The connection of the bacterial complications is accompanied with leukocytosis and neutrophilia. It is important to take into account the absolute number of elements of white blood in the dynamic of the disease.

The infection of the chicken embryos is universal method of the primary isolation and cultivation of influenza virus. This method is more accessible and sensitive than the infection of the laboratory animals. It is performed by insertion of the virus containing material in the amniotic or allantoic cavities and causes the infection of organs and tissues of the chicken embryo with the following accumulation of the influenza viruses in the embryos liquid. The presence of the influenza virus in the allantoic or amniotic liquid is stated by the hemagglutination reaction (HAR). The simultaneous erythrocytes of the chicken an guinea pig testifies in favor of the viruses A and B presence, various the agglutination of only chicken erythrocytes suggests the presence of virus type C. In case of the erythrocyte agglutination absence it is necessary to make 2-3 additional passages by the way of embryos infection with the mixture of allantoic and amniotic liquid from the previous passage. In case of the negative results of HAR after the passages the investigation of the material is finished.

The methods of the influenza virus isolation in the tissue culture are preliminary and demand the following pathogen cultivation on the chicken embryo. The trypsineted cultures from the kidneys of monkeys and human foetus are the most suitable for the influenza virus isolation.

The serological diagnostics of influenza ensures an accurate determination of etiology by the way of revealing the quantitative growth of specific antibodies in blood while the disease dynamics. The serological diagnostics is especially important in case of the atypical or symptomless course of the influenza infection. In such cases the discovery of antiinfluenza antibodies in the blood of the examined people in the dynamics of the increasing concentration independently of virusological investigation is the only truthful of the influenza virus participation in the development of the disease and its cooperation with the human organism. Among the methods of influenza serological diagnostic the reaction of hemagglutination inhibition (RHAI) and the reaction of complement banding (CB) is the most widely spread.

The immunefluorescent method is recommended by WHO as one of the reliable means of quick deciphering of the etiology of acute respiratory diseases. The sorting of patients with acute respiratory diseases is done on the bases of the immunofluorescent method data, it is especially important for the prevention of the cross infection of children of an early age. Being widely used this method is an important and reliable means of control of the etiological structure of the acute respiratory diseases in different periods according to the epidemic situation. The essence of the immunefluorescent method is in specific reaction of antigen-antibody which reveal the presence of viral antigens in the cells by the way of joining antibodies to them, the antibodies are connected with the fluorescent mark, which lights in the ultraviolet rays.

Differential diagnosis

An intoxication syndrome is the main in influenza, and various symptoms of the syndrome can be expressed in different ways and occur in different combinations. A headache and general malaise are the most frequent. But they are typical of many other diseases, mainly the infectious ones, and do not have a diagnostic value. In influenza there is no skin rash except a herpetic one. In acute meningitis of different etiology there is a complete or incomplete meningeal syndrome and typical changes of the spinal liquor. It is not meningitis but meningism that is typical of the severe hypertoxic form of influenza. Meningism is characterized with incomplete meningeal syndrome, liquor hypertension without any inflammatory changes in the spinal liquor, the spinal puncture solves the diagnostic problem in these cases.

The development of brain edema is accompanied by sopor, coma, convulsions, olygopnoe and bradycardia. These condition should be distinguished from coma and convulsion syndrome of another nature. A general malaise, dizziness, fainting, asthenisation, do not have a diagnostic value, but in combination with a headache and retroorbital pain as well as with catarrhal symptoms might help diagnose influenza. Nasal bleeding is the most frequent manifestation of the hemorrhagic syndrome in influenza, but it also occur in other diseases and can help in diagnostics only in combination with other characteristic symptoms. The appearance of the blood admixture in sputum is almost always a bad symptom. Acute hemorrhagic toxic edema of the lungs is one of the variants of hypertoxic influenza, its clinical symptoms are asphyxia, cyanosis, bubbling breathing and liquid pink foamy sputum. It must be distinguished from poisoning connected with breathing in vapors of poisonous substances, acute left ventricular heart insufficiency. Taking into account the epidemic situation, high temperature, intoxication and tracheitis can help diagnose influenza.

The appearance of sputum containing blood (pus and blood) in influenza, which is complicated by pneumonia, often testifies about the latter's staphylococcus nature. The pleura is often involved in the pathological process, severe respiratory

and cardiovascular insufficiency develops. Hemorrhagic pneumonia and influenza should be distinguished from the croup pneumonia. In croup pneumonia there are no symptoms of the upper respiratory tract affection which are characteristic of influenza, the disease has a sudden onset with pain in the side and sudden temperature rise, there is "liver" dullness over the affected lobe and bronchial breathing with the following development of moist rale, the sputum is rusty though there can be admixture of crimson blood in it.

The fever and vomiting, which are observed in influenza may be diagnosed as alimentary toxic infection of salmonelesis or another etiology. But in influenza there are other symptoms of intoxication which are considerably expressed, they are combined with the nose stuffing, tickle in the throat, pain behind the sternum and dry cough. Sometimes even in influenza there are pains in the upper part of abdomen stipulated by mialgia. Diarrhea often occurs in this disease. That is why in case of moderate toxicosis, vomiting, pain in the abdomen and frequent watery stool with an admixture of slime and blood it is necessary to think of some acute alimentary disease, but not influenza.

The development of symptoms of the upper respiratory tract in influenza makes one distinguish this disease from other acute respiratory diseases caused by adenoviruses respiratory-syncytial viruses, paragrippal viruses, rhinoviruses, reoviruses, coronaviruses, ECHO-viruses, Koksaky viruses, mycoplasma pneumonia.

The catarrhal syndrome in influenza develops later and is less expressed than intoxication. Tracheitis, to be more exact laryngotracheitis is the main syndrome in influenza. Scattered dry rale together with hard breathing develop when the inflammatory process spreads along the bronchial tree. The symptoms of laryngotracheitis stay even in case of the development of pneumonia or other complications, this helps to suspect influenza as the main disease. Rhinitis and pharyngitis in influenza do not always occur and have peculiarities in the form of dryness and stagnant hyperemia of the nose and throat mucous membranes, absence of scanty discharge from the nose, spontaneous nasal bleeding.

Adenoviral infection is characterized by a more prolonged incubation period (7-14 days). The fact that there are simultaneous cases with various clinical picture in the foci of adenoviral infection is a characteristic feature; the clinical picture: acute rhinitis, rhinopharyngitis, pharyngoconjunctivitis, covering conjunctivitis, exhantema, hepatolienal syndrome, etc. A less acute than in influenza onset, moderate intoxication in spite of the high and sometimes prolonged temperature reaction is typical of the adenoviral infection. However the syndrome of intoxication is less important as compared with the expressed catarrhal changes on the part of upper respiratory tract and conjunctiva, which are of exudative character. The pathological process sort of "crawls over" from one zone to another, and the involvement of each new are of the respiratory tract is accompanied with a temperature rise which results in the two or three top character of the temperature curve. Together with this or some time later peculiar tonsillitis may develop together with exudative

pharyngitis which manifests itself with edema and bright hyperemia of the back wall of the throat, on which one can see hypertrophic lymph follicles. If the disease starts with rhinitis (it can be limited by it), the discharge from the nose can be abundant, serouse. Laryngitis and tracheitis in contrast to influenza are not characteristic of adenoviral infection.

If the adenoviral infection is complicated by pneumonia, in adults it has approximately the same course as a moderate severe affection of the lungs in influenza and can be cured by usual antibacterial therapy. The adenoviral infection itself preserves its main clinical features, which allow to distinguish it from influenza. In case of the combination of influenza and adenoviral infection the disease has the symptoms characteristic of both nosological forms.

The respiratory-syncytial infection (RS) in adults is usually a sporadic disease, which equally effects all the age groups. In contrast to influenza the disease does not often have acute onset. The intoxication syndrome is expressed moderately or slightly. The temperature is subfebrile or moderately febrile. The changes of the upper parts of the respiratory tract are slightly expressed. The symptoms of acute bronchitis which are often accompanied with bronchial spastic component (continuous cough that is dry or has some scanty sputum, scattered dry rale and rare medium bubbling moist rale, prolonged inhaling, difficult exhalation, swelling of the lungs and others) dominate. The liver gets involved more often in the respiratory-syncytial viral infection in adults than in other acute respiratory diseases. At the high point of the disease it is enlarged and sensitive at pulpation, the Orthner symptom becomes positive (pain at beating on the costal arc).

Paragrippal diseases in adults like RS-infection have a more gradual onset the intoxication is slight or moderate as well as the temperature reaction, which in fact lasts longer than in influenza. Rhinitis and pharyngitis are moderately expressed, laryngitis is considered to be typical. There is no syndrome of false croup in adults as compared with children.

The rhinoviral infection occurs only in adults. The disease is characterized with subfebrile or normal temperature, slight intoxication symptoms or their complete absence and expressed exudative inflammation of the nose mucous membrane with abundant rhinorea, which is the main clinical symptom.

The coronaviral infection is also not severe disease, which is difficult to distinguish from a rhinoviral one and which affects not only adults but also children, and besides rhinitis the patients may have slight pharyngitis and even bronchitis.

ECHO- and Koksaky viruses can cause the diseases with affection of the upper respiratory tract. But the involvement of the brain meninx and spinal radices in the pathological process is more characteristic of the enteroviral infection.

Mycoplasma pneumonia can cause a respiratory disease in adults. It has a gradual onset and has a course with both low and febrile temperature, relatively slight symptoms of intoxication, slight affection of the upper parts of the respiratory tract, prolonged and persistent bronchitis.

The disease named "*legionaries*" disease is given to a new disease, which appeared in 1976 in the USA, its bacteriological nature was proved later. Now it is determined that this disease is widely spread in all the countries. The most cases are registered in the warm season. The elderly men suffering from different chronic diseases or alcoholics, who use immunedepressors and smoke a lot fall ill more frequently. The disease takes a course of severe progressive abscedic pneumonia with parapneumonic pleuritis and affection of the parenchimal organs.

Ornitosis and Q-fever are diseases which must be no often differentiated from influenza complicated with pneumonia. Both diseases are not accompanied with affection of the upper respiratory tract but have an expressed intoxication and prolonged fever hepatolienal syndrome and atypical affection of the lungs. Well gathered epidemiological anamnesis (contact with birds or their discharge in ornitosis, contact with different animals, usage of raw milk and other dairy products, usage of cotton brought from endemic regions, helps to diagnose the disease.

It is necessary to say in conclusion that the differential diagnostics of influenza and its complications in spite of the seeming simplicity is actually quite difficult. The basis of diagnostics and differential diagnostics should be a careful analysis of clinical epidemiological data which can allow either to suspect influenza or doubt this diagnosis. The most simple clinical investigation of blood, urine and spinal liquor help in the diagnostics. The serological, bacteriological and immunefluorescent methods of investigation are of primary importance.

The virusological methods of diagnostics are used to isolate and identify the influenza virus. As a rule these methods are used to find out the nature of the outbreaks but not the sporadic cases of the disease because they are very laborious and less sensitive as compared with the serologic methods.

Treatment

Among antiviral agents which are indicated at influenza type A, remantadin is recommended in such doses: at 1st day 0.1 gm 3 times per day, at 2nd and 3-rd day 0.1 gm 2 times, at 4th 0.1 gm after meal.

The positive effect at influenza of type A and B is at using adampromin. synthetic preparation ribamidil (ribavirin) has positive influence on viruses of grippe of types A and B which is indicated at a daily dose 0.3-0.6 gm during 5 days, however in clinical conditions rather inconsistent data are received. Perspective combined indication of ribavirin with remantadin or adampromin as medical aerosols is represented, adampromin influences on viruses of an influenza A and B. similar antiviral property have midantan, deitiforin, arbidole.

As agent of a choice can be a human leukocytic interferon: 3-5 drops in each nasal meatus through 1-2 hours not less than 5 times per day during 2-3 days or as aerosole with the same frequency. Treatment of virus rhinitis includes: unguent of oxolini, grease mucosa of nose 2-3 times per day 3-4 days. The preparation is indicated at herpetic superinfection, however its efficiency is low.

The specified antiviral agents should be applied in the first days of disease, later they are not effective.

To decrease a body temperature, and to reduce a headache and muscular pain analgin, ascofen, upsarin with vitamin C, eferalgan, paracetamol are indicated. As a preparation of a choice you can use non narcotic analgetic Amison, rendering analgetic, anti-inflammatory, antipyretic and interferonogenic action. The fever is the major adaptive and protective reaction of organism, induces synthesis of an endogenic interferon. Antipyretic preparations are indicated only at a hyperpyrexia and expressed cerebral and cardiovascular disorders in adegnote dose to lower a body temperature on 1-1.5 °C.

As the stimulation of endogenic interferon formation amixin is applied 0.125-0.25 gm per day for 2 days, then 0.125 gm in 48 hours for one week or in the first 2-3 days; mefanam acid 0.5 gm 2 times per day is prescribed. For patients polyvitamines, ascorutin are indicated. At excruciating tussis indicate codein phosphat, codterpin, tablets against tussis, at labored nasal respiration — halazolin, farmasolin or naphthyzin, efedrin hydrochloride, pinosol, at exaltation and disorders of sleeping — mixture of behterev, fenobarbitalum for the night.

In serious cases of influenza and the weakened patient, with indicated specified agents, infuse antiinfluenza donor immunoglobulin 3 mL (IM) unitary, sometimes repeatedly in 6-12 hours.

Reopolyglucin, solution of albumin, isotonic solution of Sodium chloride, 5 % a solution of glucose (IV) should be infused to treat severe toxicosis. For prevention of hypertension in a pulmonary blood circle, it is necessary to infuse not more than 500-800 mL of liquids slowly and simultaneously to use diuretic preparations — furosemid, diacarb, etacrinic acid. Appoint corglykon, sulfocamphocain, euphyllin, inhalations of oxygen or carbogen.

Patients with especially serious (hypertoxic) form of influenza should be treated in departament of intensive treatment. Antiinfluenza gamma-globulin or a serum polyglobulin is prescribed in dose of 3-6 mL in 4-6 hours (in muscle or even in vein). Infuse (IV) admixture of the following structure: blood plasma — 150-200 mL, solution of glucose 40 % 20 ml, mesaton 1 % or noradrenalin 0.2 % 1 ml, strophanthin 0.05 % or corglykon 0.06 % 0.5 1 ml, furosemid (lasix) 40-80 mg; hydrocortizon 250-400 mg, euphyllin 2.4 % 1 ml, ascorbic acid solution 5 % 5-10 ml, calcii chlorid solution 10 % 10 ml, polyglobulin — 3 mL. At disorders of cardiac activity — corglykon or strophanthin are used. At increase of hypoxia and fluid of lungs that should be prescribed to inhale oxygen-alcohol mixture on extremity impose venous garrots, apply diuretic preparations.

In case of development of acute edema and brain swelling in a vein infuse mannit (mannitole), furosemid (lasix), preparations of a potassium, glucocorticoids.

Widely use tinctura of the herbs, with sudorific, anti-inflammatory, soothing, spasmolytic, expectorative and antimicrobial properties.

The collecting № 1 consists of root of Altea medicinal (2 parts), buds of birch white (1 part), flowers of elder black (1 part), rhizome with roots of inula

(1 part), grass of St.-John's wort (7 parts), berries and leaves of raspberry ordinary (2 parts), leaves of mint peppery (2 parts), buds of pine ordinary (2 parts), grass of a sage medicinal (2 parts), leaves of eucaliptus (2 parts);

The collecting № 2 consists of root sweetflag (1 part), buds of a birch white (2 parts), herbs of Origana ordinary (3 parts), a root of Valeriana medicinal (1 part), a herb of St.-John's wort (3 parts), leaves of Viburn ordinary (2 parts), a seed of flax sowing (2 parts), a herb of a yarrow ordinary (2 parts), fetuses of fennel garden (2 parts). It is necessary to fill 4 or 6 dining spoons of the collecting in a thermos (0.7-1 L) to fill up to top with abrupt boiled water, to sustain 3-4 houres and to drink all within day in 3-4 receptions. Course of treatment by such shock doses lasts 3-5 days. The next days use usual doses making 2-3 dining spoons of an admixture 0.5 L of boiled water. Among other medicinal herbs for preparation tinctures it is possible to use leaves of fragarias wood, tussilagoes farfara, flowers of camomily calendulaes, an elder black, lindens. For inhalations use broths of leaves of sage, eucalyptus, grasses of thyme, pine buds, buds and young branches currants, birches, raspberries, a root of willow-leaf inula, better acidified- then rinse a mouth, a throat and wash out a nose. Revaitl garlick pearls is indicated to rise immunity. The heating of a thorax with the help of Sinapismuses, mustard wrappings or pepper emplastry is prescribed. The same agents put to a plantar surface of the feet and shins.

Antibiotics at an influenza are indicated in following cases: 1) at serious course of disease (the hypertoxical form with encephalitis if disease begins with a pneumonia); 2) to children of the first 2 years of the life, the pregnant, to weaken patients, to persons of elderly and senile age; 3) at bacterial complications; 4) at accompanying chronic diseases of inflammatory character which may become aggravated at influenza. In other cases antibiotics are contrindicated, as they strengthen allergization of organism and enlarge frequency of various complications.

Treatment of bacterial complications is necessary to start, before getting results of bacterial inoculation and definitions of sensitivity on antibiotics of the allocated microflora. At the pneumonia indicate benzylpenicillin or one of semisynthetic penicillins. At a hypersensibility of organism to these preparations one can use erythromicin, oleandomycin or doxycyclin. At ambulatory treatment also frequently are indicated one of the combined preparations – oletetrin, tetraolen, and at more serious current of pneumonia – vancomycin, tienam and antiinfluenza gamma-globulin or polyglobulin. The expressed effect is spotted at a combination of preparations of tetracyclines or cefalosporines with semisynthetic penicillins and gentamicin, infused parenterally. At unsuccessful treatment after 5 – 7 days choose antibiotic in view of sensitivity of microflora of sputum. Alternative preparations may be a fusidin-natrii, bactrim, nitroxolin.

At serious bacterial complications of influenza apply macrolides of II-III generations: sumamed, claritromicin, cefalosporines of III-IV generations – cefotaxim, cefoperason, cedex, cefpirom, combinations of cefalosporines and penicillins with

inhibitors of β-lactamazes (clavulanic acid, sulbactam, tasobactam) and aminoglicosides. Preparations of a choice may be ftorhinolones – ofloxacin, ciprofloxacin, pefloxacin and others, which have high antibacterial activity and wide spectrum of action, including influence on polyresistant Gram-negative and Gram-positive bacteries.

Use antitussive (glaucini hydrochloride, libexin, tusuprex), expectorating (terpin hydrate, natrii benzoic, broth of a herb of termopsis, a root of althaea), mucolytic (acetylcystein, bronchoclar, bromhexin, ambroxole, lasolvan, fluditec) agents, physical methods of treatment.

Prophylaxis

Vaccines that include the prevalent strains of influenza viruses effectively reduce the incidence of infection among vaccinees for 1 or 2 years after vaccination. Vaccines is prepared as inactivated whole virus or as subunits of the virus, either semi-purified viral hemagglutinin or disrupted virion components. Both types of vaccine are equally protective. Under development are attenuated live vaccines given intranasally. They have the advantage of eliciting specific secretory antibody at the portal of virus entry.

Vaccination is especially important for the aged and for patients with cardiac, pulmonary or other chronic diseases. Pregnant women whose 3rd trimester occurs during the winter months should be vaccinated also. With the presently available purified vaccines, local or constitutional reactions are uncommon or minor, except sometimes in children.

Amantadine 100 mg orally can be used prophylactically against influenza A. During influenza A epidemics, it should be given to family members and other close contact of patients and to persons at high risk of increased morbidity from influenza. During administration of amantadine, persons at high risk of infection who have not been vaccinated previously should receive vaccine, then amantadine may be discontinued in 3 wk. If vaccine cannot be given, amantadine must be continued for the duration of the epidemic, usually 6 or 8 weeks.

At the time of epidemic also can be used another chemical remedies (oxolinum, tebrophenum) and interferon preparations.

Control questions:

1. Etiology, epidemiology and incidence of influenza.
2. Pathogenesis of influenza.
3. Anatomic pathology of disease.
4. Main clinical symptoms and signs of influenza.
5. Complications of influenza infection.
6. Laboratory methods of influenza diagnosis: the serological, bacteriological and immunefluorescent.
7. Criteria of diagnosis.
8. Differential diagnosis of influenza.
9. Treatment of bacterial complications of influenza.
10. Treatment of influenza.
11. Prophylaxis of influenza.

ACUTE RESPIRATORY VIRAL DISEASES

PARAGRIPPAL INFECTION

Paragrippe is an acute viral disease, accompanied with moderate intoxication and affection of the respiratory tract with the predomination of laryngitis.

The problem is urgent because the paragrippal infections constitute an essential part of the acute respiratory diseases with a viral etiology. The age structure of the sickness rate indicates that a considerable percentage of cases is primarily registered among children and a lower percentage among the adults. Such complications as the development of laryngitis with croup and pneumonia in some cases are dangerous for a patient's life. In spite of the achieved success in studying this infection, the problems of the disease pathogenesis and especially, prophylaxis cannot be considerably investigated.

Historic reference

In 1952 in the Japanese city of Senday N.Kuroga isolated the hemagglutinin virus from the lungs of a newborn child who had died from pneumonia and named it "Senday" virus. In 1954 in the USA R.Chanock isolated the CA virus (croup associated) from a patient with croup. In 1958 the same researcher isolated two more viruses which adsorbed erythrocytes on the infected cells and named them hemadsorption viruses (HA-1 and HA-2). All the three isolated viruses had similarities with the influenza virus, that is why they were called paragrippal in 1959. In 1960 K.Johnson and his co-authors isolated another similar virus and named it M-25.

Etiology

Nowadays paragrippal viruses are divided into four antigen types. The antigenic differences are based on the structural peculiarities of the superficial nucleocapsid antigens. The viral genome consists of the single-lane RNA. These viruses quickly die in the environment. They endure freezing well. The ultraviolet rays are destructive to them.

Epidemiology

The paragrippal viruses of the human are widely spread pathogens of the acute respiratory diseases, including the tropics. They circulate both among adults and children. The etiologic meaning of the paragrippal infection in the pathology of the respiratory tract reaches its maximum value in children under 3 years of age and progressively decreases in senior children.

The human society is a reservoir of the infection, there is always a certain number of patients who keep or spread the infection. The infection is airborne. A sick person most intensively secretes the pathogen during the first 2-3 days of the disease. In case of a lingering course the secretion is prolonged. The duration of a patient's secretion of the virus into the environment lasts from 3 to 10 days. The symptomless carriage is extremely rare. The infection occurs during the direct contact. The virus spreads with big aerosol particles or slime drops and it retains infection on the objects around the patient for a long time, however, the oral infection is not of considerable importance. The disease occurs in the form of sporadic cases and local outbursts. Epidemics have not been described. All age groups are susceptible to the disease. The disease is registered all the year round.

Pathogenesis

All the four virus types are pathogenic for humans. The pathomorphologic data are very limited as the disease usually ends with full healing.

The entering gate and the main reproduction place of the viruses is the cylindrical epithelium of the upper respiratory tract. The inflammatory process in them is characterized by a slow development. The viruses have a special tropism to the mucous membrane of the pharynx and cause its edema and swelling. There is hyperplasia of the epithelium, its nuclei become bigger and lighter. During the acute stage on the 4-5th day there is an expressed leukocyte infiltration of the epithelium with small foci of degeneration.

Anatomic pathology

One of the most characteristic symptoms of paragrippe is a peculiar growing of the epithelium mostly in the medium and small bronchus. Along with the abundant pillow like growth of the bronchus epithelium, there is some smaller papillary growth. In most patients with paragrippe there is a greatly expressed peribronchial lymphoid infiltration. As a rule, pneumonia has a small-foci character and is observed in the spots of the expressed cells proliferation with follicle nuclei. Pneumonia in paragrippe, in contrast to influenza and its combinations, has a purulent nature, as well as bronchitis.

The affection of the nervous system in paragrippe does not occur very often but it is not something extraordinary. Serous meningitis, meningoencephalitis, polyneuritis and neuritis of the facial nerve have been described in children.

Clinical manifestations

The duration of the incubation period lasts from several hours to 7 days and depends on the virus type. Thus in type 1 it is more prolonged – up to 5-6 days and in type 3 it is shorter – 1-3 days. In the typical cases the disease develops gradually, the temperature rises up to the subfebrile and only in 3-4 days reaches 39 °C.

During the first days in adults the intoxication is not well expressed and it reveals in a slight indisposition, often without a fever, dryness and burning in the

nasopharynx, hoarse voice, stuffed nose, running nose and sometimes catarrhal conjunctivitis. In the little children along with the mild forms there are more often moderate and severe forms with the affection of the respiratory tract revealed in the form of bronchitis or pneumonia. In the paragrippal infections the severity of the course and the diffusion of the process considerably depends on the age and the premorbid condition of the patients. The disease takes the most severe course in newborn babies and in children during the first months of life.

During the following days in many patients the inflammatory process gets down the respiratory tract. Pharyngitis is often observed, it is manifested by hyperemia of the pharynx mucous membrane and painful swallowing. Most authors consider laryngitis with slightly expressed stenosis to be the most typical manifestation of the paragrippal infection.

In the mild courses of the disease the symptoms of laryngitis are manifested by a sore throat dry rough cough, burning in the trachea without clinical symptoms of bronchitis. The voice becomes hoarse. The fever is within the limits of 37.5-38 °C. The outcome is favorable in case of the timely treatment. However, the manifestations of laryngitis may intensively increase and stenosis of the pharynx develops. Stenosis is clinically manifested by a labored loud breathing with a more or less expressed retraction of the pliable areas of the thorax and epigastrium. Croup is often the main and only manifestation of the disease. As a manifestation of the main disease, croup develops during the first 1-2 days with the temperature increase up to 38.5-39 °C and a rough barking cough. Only in case of the croup viral nature, there is hyperemia of the mucous membrane of the larynx, especially in the infraglottica area edema and plethora. The mucous membrane is covered with blurred mucous. The course of the viral nature croup without joining the bacterial flora is usually favorable.

As a rule, the severe forms of croup are observed in case of the mixed viral-bacterial infection, when descending obturating stenotic laryngobronchitis develops. In the pathogenesis of stenotic laryngotracheobronchitis it is not the constriction of the glottis caused by the inflammatory changes in the infraglottica area that is of main importance, but the obstruction of the lower respiratory tract because of the fibrinous-necrotic process caused by joining the secondary bacterial flora. The croup course in such cases is undulating with a long lasting high temperature, expressed shortness of breath. Viscous sputum forms dry crusts, which result in the bronchi occlusion and lead to frequent and severe bronchospasm as well as atelectasis. The lethal outcomes are observed as the result of the development of the diffusive process in the respiratory tract.

The bronchitis joining is usually observed on the 4-5th day of the disease, in such cases one can hear dry rale over the lungs. Paragrippal pneumonia often develops in the viral affection of the lower respiratory tract. They have an acute development accompanied by a high temperature, expressed cyanosis, shortness of breath and absence of distinct changes in the percussion sound, scanty

auscultation data. They usually take a non-malignant course. The joining of the secondary bacterial flora considerably worsens the course of the disease: the intoxication intensifies, the shortness of breath and cyanosis become more expressed, the cough with sputum discharge becomes more frequent. The percussion reveals the shorting of the percussion sound, a lot of moist rale can be heard at the same areas.

Complications

Paragrippe can be complicated by tonsilitis, sinusitis, otitis, eustachiitis and can cause the worsening of thc chronic unspecitic diseases of the lungs. Along with the affection of the respiratory tract there are some changes of the nervous system in many paragrippal patients, even in case of the mild course of the disease. They are mainly some slightly expressed symptoms of the functional malaise, headache, dizziness, aches all over the body etc. However, during the clinical examination serouse meningitis with the posterior nuchae muscles rigidity and symptoms of Kernig and Brudzinsky was diagnosed in some patients. The cerebrospinal fluid flew out under the increased pressure, lymphocyte pleocytosis oscillated in a wide range from 70 to 850 and higher in that case. The paragrippal virus type 3 was most often found in the fluid. The normalization of the cerebrospinal fluid and fading of the meningeal symptoms were not always parallel with the catarrhal changes in the mucous membrane of the respiratory tract.

The reinfection with the paragrippal viruses, especially type 3, was registered several times in adults and in children. The frequency of the reinfection remains still unknown, it is possible that many patients are reinfected more than once. The results of the observation in the series of the consequent outbursts of the type 3 infection showed that 17 % of the children infected during the first outburst were reinfected during the following outbursts, although the interval between the outbursts did not exceed 9 months. The disease develops more rarely in case of the reinfection and its course is much easier as compared with that of the primary infection.

Diagnosis

The laboratory confirmation of the disease etiology is an important stage in the examination of the patient. The main method used under the conditions of the practical laboratories is an immunofluorescent test that is used for the discovery of virus antigens in the epithelial cells of the upper respiratory tract. This method provides a fast deciphering of the disease etiology.

Among the other express methods of diagnosis of the respiratory diseases an immunoferment test on the solid phase has become widely spread, it is used for the serological diagnostics. The radioimmunoassay and chain polymerize reaction are also used.

Another direction in the serological diagnostics is the investigation of single serum samples, it is aimed at the determination of IgM because it constitutes the

basis of the primary immune response. A test of immunosorbent hemadsorption has been devised for this purpose. The laboratory diagnostics of the paragrippal infection based on the isolation of viruses in the sensitive cell cultures has not lost its importance.

Differential diagnosis

During the first days of the disease the clinical diagnosis is often difficult, as some symptoms are similar to influenza. In such cases it is important to thoroughly study the onset of the disease. Influenza is characterized by a sudden onset and temperature increase up to 38 °C and higher and always more or less expressed chill, and the catarrhal component absence. In paragrippe the temperature increases gradually and there is a cough with sputum discharge from the first days. Croup in paragrippe is often clinically manifested by the symptoms of acute laryngitis, which is sometimes limited by the affection of the infraglottica area of the larynx only, and the severity of the patient's condition depends on the severity of stenosis, the intoxication manifestations are less expressed. In influenza, especially, in the severe cases, there are symptoms of laryngotracheobronchitis and the severity depends on the intoxication degree.

Treatment

In mild and moderate cases bed regimen is recommended till the temperature decreases. The dairy and vegetable diet, abundant drink (tea, cranberry juice, alkali mineral water) are prescribed. Both adults and children are prescribed symptomatic treatment (syrup, paracetamol, mucaltinum, inf. althaeae – to delute sputum, pertussin, broncholytin, bromhexin – in case of the increased cough reflex and others).

In severe cases the following medicines are prescribed: immunoglobulin (hyperimmune and normal), monoclone antibodies, interferon, ribamidil, bonaphtonum, alpisarinum. The antibacterial medicines are prescribed in case of complications with the bacterial flora. The hot foot baths, steam inhalations, corticosteroids are the most effective in larynx stenosis.

Prophylaxis

The specific prophylaxis of the paragrippal infection has not been worked out so far. The non-specific prophylaxis is similar to the one in other acute respiratory virus diseases.

RESPIRATORY-SYNCYTIAL INFECTION

The respiratory-syncytial virus causes an acute respiratory disease in which the lower parts of the respiratory tract are mainly affected with the development of bronchitis, bronchiolitis and pneumonia. The urgency of the problem is also due to the fact that the virus attacks the most sensitive age contingent – children under the age of one year old.

Historic reference

The respiratory-syncytial virus was first isolated in 1956 by J.A.Morris and his co-authors from the respiratory tract of a chimpanzee and a laboratory worker who had been in contact with it. The increase of complementbound and neutralizing antibodies was observed in the blood of the chimpanzee and the man after the recovery. A year later R.Chanock and his co-authors reported on the isolation of the virus from the children with the affection of the lower parts of the respiratory tract. After this there were a number of reports on the role of the above mentioned virus in the respiratory diseases in children and adults. The viruses isolated from the humans and chimpanzees turned out to be identical. The pathogen received its name as a result of the peculiar cytopathogenic effect in the cells of the sensitive tissue cultures, it causes the formation of the syncytial areas.

Etiology

The RS virus has all the main characteristics of microviruses. Its peculiarity is in the absence of hemagglutination hemadsorption and its inability to reproduce in the chicken embryos. The antigenic structure of the virus is stable. The virus is very sensitive to freezing, that is why it is recommended to immediately use it for infection. The inoculum (nasal secrete) should be taken from the patients as soon as possible when the clinical symptoms develop.

Epidemiology

The RS virus is a pathogenic microorganism of the respiratory tract, it is airborne. It is highly contagious for the population of all age groups. The degree of contagiousness is especially high under the conditions of the nosocomial infection. However, it is still unclear which age groups of the population are considered to be the reservoir and source of the infection at the periods of annual seasonal increases of morbidity and between the epidemic periods. The especially urgent problem of the healthy virus carriage without any clinical symptoms for the RS virus still remains unsolved.

In the areas of the moderate climate the autumn-winter-spring seasonably is considered to be finally ascertained, and the increase of the RS infection morbidity is never observed in the summer, whereas in the tropical countries they can be observed in the hot season as well. Not only children, but also adults are highly susceptible to the RS infection in spite of the fact that in the majority of adults it is usually reinfection. The transmission of the RS virus from man to man is fast and effective.

In the experimental study of the RS virus transmission mechanisms, the observations of the volunteers show that the infection occurs mainly through the nose less frequently through the eyes. The study of the nosocomial outbreaks of the RS infection confirmed the mentioned facts and determined that the per oral infection does not play a considerable role in spreading the RS infection.

The social-economic conditions noticeably influence the beginning and development of the RS infection epidemic outbreaks. There is a distinct correlation between the degree of overcrowding and the frequency of the virus isolation.

Pathogenesis

The mucous membrane of the respiratory tract is an entrance gate for the RS virus. The beginning of the virus replication occurs in the epithelial cells of the nose and nasopharynx causing the local inflammation which sometimes leads to the obstruction of the nasal paths and Eustachian tube. The process spreads to the trachea, bronchus, bronchioles and the lungs parenchyma in the majority cases in the children of an early age and in fewer cases in the people of other age groups.

Anatomic pathology

On the basis of the known tacts it is possible to come to the conclusion that a severe affection of the bronchioles is typical of the RS infection. The considerable proliferation of the epithelium with a big amount of mitosis figures and impurities of the cytoplasm are observed in them. The multcellular offshoots appear in them in the process of proliferation, they resemble symplasts in their form. The symplasts jut out into the bronchioles opening like buds. Sometimes they desquamate and partially obstruct the bronchus or fill the alveoli. There is a round-cell infiltration and thickening of the intra-alveolar partitions around the affected bronchus.

The virus is isolated in the nasal discharge a day before the disease onset and during the first 7-9 days of the disease. There is virusemia in the experimental infection.

Clinical manifestations

The incubation period lasts 4-5 days with the fluctuations from two to seven days. The characteristic features of the initial period are a moderate affection of the upper parts of the respiratory tract with the slightly expressed catarrhal symptoms in the form of a labored nasal breathing, infrequent dry cough, scanty nasal discharge. The hyperemia of the throat, airfoils, back wall of the throat is expressed insignificantly. There is no temperature reaction or the temperature is subfebrile with a shivering, moderate headache and myalgia. In case of the mild form of the infection the symptoms disappear during 3-7 days and the recovery comes. However, during the first days or on the following days the lower parts of the respiratory tract very often get involved in the process, especially, in the children of an early age. In several hours a child's skin becomes cyanotic, an asthmatic dyspnea develops up to 60 a minute with a prolonged whistling expiration accompanied by pulling the compliant areas of the thorax. A number of dry and mixed moist rales suddenly appear in the lungs, the rale can be heard at a distance. The areas of a percussion sound shortening alternate the areas with a box shade. An asthmatic syndrome is one of the typical symptoms of the

RS infection. The reverse development occurs very quickly – in 3-7 days, it indicates the affection of the bronchial tubes only.

In the development of pneumonia the temperature rises up to 39-40 °C and remains for a long time. The condition of the patient considerably worsens and the reverse development of the process goes very slowly – up to 2-3 weeks. In such patient's blood analysis there is leukocytosis, neuthrophylia and increase of ESR.

The adults usually develop a mild form of the disease without fever and it is limited by the upper part of the respiratory tract only. The infection and the development of the disease occur irrespective of the presence of the high titers of the virus neutralizing antibodies in the serum. The ability of the RS virus to avoid the organism resistance mechanisms of the host and to cause the disease during reinfection is still a matter of meditation.

Complications

The acute complications of RS infection in infants include apnea, respiratory failure, and rarely secondary bacterial infection. The long term complications are pulmonary function abnormalities.

Diagnosis

The methods of the laboratory diagnosis are the same as in case of paragrippe.

Differential diagnosis

A great similarity of the RS infection to other ARVI complicates the diagnosis based on the clinical picture only. It is possible to clinically diagnose the disease for certain in the children under one year old if there is bronchiolitis and pneumonia with an asthmatic component on the background of the subfebrile temperature because the RS virus causes the affection of the lower parts of the respiratory tract in most patients. It is necessary to take into account the prevalence of the bronchitis symptoms over the symptoms of the upper parts of the respiratory tract affection accompanied by a slightly expressed intoxication. The laboratory diagnostics methods are of major importance.

Treatment

Good supportive care is of the utmost importance in the management of severely ill infants. Alleviation of the hypoxemia and monitoring of the infant's respiratory status and blood gas levels are essential in the management. Because the hypoxemia is related to an unequal ratio of ventilation to perfusion, most infants respond to relatively low concentrations of inspired oxygen of about 40 %. Corticosteroids in controlled studies have failed to show benefit in the clinical course of infants with bronchiolitis or in their pulmonary function during the acute or convalescent stages. The use of bronchodilators in bronchiolitis and other forms of RSV lower respiratory tract disease has been controversial, and studies evaluating their use have given conflicting results.

Ribavirin, a synthetic nucleoside that is a broad-spectrum antiviral agent, is the only currently approved specific treatment for RSV lower respiratory tract disease in hospitalized infants. The drug is administered as a small-particle aerosol into a tent, oxyhood, mask, or ventilator for a period of 12-20 hours each day, usually for 2-5 days, depending on the time to improvement. Shorter and intermittent periods of treatment may be as beneficial. Ribavirin also inhibits the RSV-specific IgE response in the nasal secretions, which has been associated with the development of wheezing and hypoxemia. Aerosolized ribavirin appears to be well tolerated, and toxicity has not been reported in controlled studies. Aerosol administration for 8-20 hours gives drug levels in secretions that are hundreds of times greater than the median inhibitory concentration for RSV, but relatively little is systemi-cally absorbed, and blood levels are low.

Prophylaxis

Prevention over treatment is the preferable but as of yet unattained goal for control of RSV infection. The very young age at which RSV first attacks and at which it has its greatest impact makes prophylactic intervention problematic. Breast-feeding appears to offer the infant some protection against RSV lower respiratory tract infection. Prevention of infection through interruption of transmission of the virus is probably impossible at home. However, on hospital wards attempts to prevent spread of the virus are warranted. RSV may be spread by close contact and by direct inoculation of droplets of the secretions from an infected person. In addition, however, RSV possibly may be spread indirectly from hands that touch infectious secretions that contaminate surfaces in the environment. Hence, careful handwashing by all personnel is of particular importance. The use of eye-nose goggles has been shown to diminish appreciably the nosocomial infection rate, presumably by decreasing self-inoculation of the virus into the eyes and nose.

ADENOVIRAL INFECTION

Adenoviral infection is a disease developing mainly in children and having the symptoms of the mucus affection of the respiratory tract, eyes, intestines as well as lymphoid tissue.

Historic reference

The pathogens of the adenoviral diseases were first isolated in 1953 by W. Rowe and his staff from the tissues of the surgically extracted glands and adenoids. The belonging of the isolated viruses to the respiratory infection pathogens was established in 1954 when M.R. Hilleman and J.H. Werner discovered the increase of the neutralizing complement binding to them antibodies in the blood serum. In April of 1954 F. Neva and J.F. Enders isolated a similar virus from the excrement of a two-year-old child who had a fever accompanied by conjunctivitis,

pharyngitis and the increase of the neck and groin lymph nodes. A year later R. J. Huebner and W.P .Rowe reported on the isolation of more than 100 cultures of viruses from the nasopharynx, conjunctiva and excrement of the patients who had different forms of the acute febrile diseases of the respiratory tract.

In 1956 the commission at the International committee of the nomenclatures that studied viruses named the isolated viruses "Adenoviruses" as they had first been isolated from the adenoids and the diseases caused by them got the name "adenoviral diseases".

In 1962 J.Trentin and his co-author R.Huebner together with their co-authors made some experiments on the newbom hamsters that showed that the adenoviruses were oncologically active.

Etiology

The adenoviruses constitute a family of *Adenoviridae* including two clans: *Mastadenovirus* (M) (mammal) of more than 90 kinds and *Aviadenovirus* (A) (birds) − 18 kinds. The gene of the adenoviruses is a lineal double spiral DNA. They are thermolabile, get destroyed at 56 °C in 30 minutes, stable to pH 5-9. They can be preserved in the frozen form. They can be lyophilized without losing the infectious titer.

Epidemiology

The adenoviral diseases are registered everywhere all the year round, more often in the cold seasons. The natural reservoir of the adenoviruses for humans is a human. The infection is spread by both the people with the clinically expressed disease and virus carriers. The adenoviruses are excreted from the respiratory tract till the 25th day of the disease, and from excrement for two months. Though the main way of the infection transmission is an airborne one, an alimentary way cannot be excluded. In the period of the epidemic spread the adenoviruses can also be isolated from the sewage. The diseases can be observed both in the form of the epidemic outbreaks and sporadic cases. The epidemic process during the outbreaks develops slowly. At first the single cases of the disease and then a more rapid growth. Taking into account the meaning of the separate serotypes in the pathology and the peculiarities of the epidemic process the adenoviruses are divided into epidemic, latent and a group which role in the pathology is unclear. The adenoviruses of the latent group also cause acute diseases but in this case there is a less intensive coverage of people at outbreaks, a higher per cent of the latent infection and a mild course are observed.

Pathogenesis

The adenoviruses usually affect different organs and tissues: the respiratory tract, eyes, lymphoid tissues, intestines and urinary bladder.

The upper parts of the respiratory tract and conjunctivas are the most frequent entrance gates. The virus penetrates the lower parts from the upper part through the bronchial paths and causes atypical pneumonia in adults and children. The virus intensively reproduced in the parenchyma of the lungs and in the cells of the upper respiratory tract. Virusemia is one of the stages of the adenoviral infection. Because of virusemia the virus can penetrate not only the lower respiratory tract but also other organs and tissues by a hematogenic way. In the diseases connected with the adenoviruses of the academic type, virusemia is observed in the acute period from the 1st to the 8th day. In the latent type cases the period of virusemia lasts up to 2-3 weeks.

Anatomic pathology

The viruses are supposed to affect the endothelium of the vessels and thus cause the exudative type of affection, inclination towards the prolapse of fibrin, necrotic changes in the mucus membrane (exudative pharyngitis, tonsillitis, conjunctivitis).

Irrespective of the fact that an adenoviral disease has only respiratory or respiratory and intestines symptoms the reproduction of the adenoviruses is observed in the small intestine for longer periods of time (10 days and longer) than in the respiratory tract.

An association of the adenoviruses with the immune deficiency conditions has been described. They were isolated from the urine and excrements of the AIDS patients as well as from the urine of the patients who were ill with other immune deficiency illnesses.

Not only have the latent viruses a disposition for lymphadenopathy, but also a group of the epidemic ones. Lymphadenopathy has such symptoms as the increase of the tonsils, periphery lymph nodes, liver, spleen, tracheobronchial, bronchopulmonal and mesenteric nodes.

Clinical manifestations

The disease caused by the adenoviruses is characterized by the polymorphism of the clinical manifestations, that do not develop simultaneously. There are symptoms of the affection of the respiratory tract, eyes, intestines mucous membrane, the disease is accompanied by a prolonged fever and a moderately expressed intoxication. The incubation period lasts 5-7 days with the fluctuations from 4 to 12 days. The adenoviral infection is mainly characterized by a gradual development of the disease with the accumulation of the clinical symptoms, the replacement of some symptoms by others and the prevalence of the local symptoms over the general ones. Besides, an acute onset of the disease is also possible. As a rule the expressed catarrhal symptoms with a labored nasal breathing come to the foreground. The intoxication is expressed by flabbiness, adynamia, the appetite worsening, moderate and inconstant headaches, sometimes vomiting. The rise of

the temperature is usually gradual, in the beginning 37.2 °C, on the following days − 38 °C and sometimes higher. The duration of the fever is 5-7 days less often − up to 12 days.

The acute respiratory disease is the most frequent clinical manifestation. There are usually no pathognomonic symptoms. In the beginning its diagnostics is considerably difficult, especially, in the first cases because they do not practically differ from catarrh caused by different other pathogens. The onset can be acute or gradual. Already on the first day there is a labored nasal breathing, and on the second-third day an abundant serous or serous-mucous discharge. There develops hyperemia of the nasopharynx mucous membrane, edema of the uvula, hyperplasia of the lymphoid tissue, especially, on the back wall of the throat. There is sometimes a vesicular rash on the mucous membrane of the mouth cavity. The submandibular lymph nodes and the ones on the back of the neck are enlarged. The cough is usually dry, it becomes rough, barking when laryngitis develops. Sometimes the voice becomes hoarse, but there is no aphonia. In contrast to influenza croup develops in the first hours of the disease. The physical manifestations in the lungs are absent or they are poorly expressed.

Acute pharyngitis. It is usually in the cold season of the year that the disease is observed, the general condition often remains satisfactory. The main complaint is pain in the throat at swallowing. Moderate hyperemia of the airfoils, back wall of the throat with hyperplasia of the lyinphoid tissue can be noticed during the throat examination. The mucous membrane of the throat, airfoils, uvula, tonsils is loosened, edematic. On the surface of the tonsils there is a thin whitish patch in the form of dots which covers the tonsils. The exudate often spreads beyond the borders of the airfoils to the soft palate, back wall of the throat. The patches disappear during 5-6 days, but the edema of the mucous membranes of the throat and rhinitis usually remain longer. At the same time the peripheral lymph nodes are often enlarged. The cough is frequent, but not constant, it is moist, rarely dry.

Pharyngoconjunctival fever is the most typical clinical variant of the adenoviral infection. The term "pharyngoconjunctival fever" (PCF) was proposed by J.A. Bell and his co-authors (1965) while describing an outburst in the children's summer camp. They also most fully described the clinical form characterized by the triad: fever, pharyngitis with the enlargement of the lymph nodes and conjunctivitis. As a rule, the disease starts with the increase of the temperature, which often increases up to 39-40 °C and remains for 2-10 days (5-6 days on the average). There is a lytic temperature decrease. The main complaints of the patients are redness and uncomfortable sensation in the eyes, watery eyes, affection of the throat, headache. Somnolence and malaise often develop at the end of the feverish condition. Nausea, vomiting, diarrhea and nasal bleeding are observed very rarely. The bone-muscle aches and weakness are often observed in adults. During the throat examination the hyperemia of the back wall of the throat and lymphatic nodes is observed. The submaxillary lymph nodes are often

enlarged even if there is no pain in the throat. The disease is accompanied by the one-side nonpurulent follicular conjunctivitis, which remains from several days to three weeks and is manifested by the injection of the eye and eyelid vessels. The enlargement of the parotid lymph nodes is sometimes observed. There is no photophobia and pain in the eyes. The iris of the eye and cornea are usually not involved in the process. The exudate is almost always serous. The clinical symptoms (fever, pharyngitis and conjunctivitis) are manifested in different combinations. The pharyngoconjunctival fever in the form of sporadic cases or outbursts is registered in different countries.

Eye affection. The intensely expressed inflammation of the conjunctiva with bright hyperemia and scarce discharge is a peculiarity of adenoviral conjunctivitis. The inflamed mucous membrane of the conjunctiva looks like a "conflagration without a fire". Unlike in conjunctivitis of another etiology only the lower eyelid is usually affected. In the beginning the inflammatory process in the eye develops only on one side and only later the second eye gets involved in the process, but the changes in it are less expressed. There are such forms of the eye affection as catarrhal follicular membranous conjunctivitis and keratoconjunctivitis. The last ones usually develop in adults; a long recurring course is typical of them.

In case of the catarrhal form hyperemia tissue infiltration, edema of the eyelids and conjunctiva are observed. The edema and the infiltration of the tissues usually disappear in 2-5 days, but the hyperemia of the conjunctiva remains up to three weeks, sometimes − up to a month.

In case of the follicular form of conjunctivitis along with conjunctiva infiltration and edema of the eyelids there is abundant eruption of the large follicles on the conjunctiva. There is no discharge or it is scarce. One third of the patients have a hemorrhage into the sclera of the eyeball. The hemorrhage dissolves slowly, during 7-9 days and then during 3-4 days a vessels netting "sclera injection" can be observed. Sometimes the hemorrhages are so large that the eye looks like a rabbit's one.

In case of membranous conjunctivitis the tissue infiltration, eyelid edema are much more expressed (often a patient cannot even open the eye) than in catarrhal or follicular forms, and the edema of the eyelids is soft in contrast to the diphtheritic one. The hemorrhages into the conjunctiva and sclera of the eye are more massive. The gray dense films appear on the 4-6th day of the disease. The bleeding surface remains after their removal. The discharge is scanty, very often there is sanioserous discharge. Parents say that "the child cries with bloody tears".

In case of keratoconjunctivitis the disease has an acute onset and is manifested by hyperemia and the conjunctiva edema. On the 2-3rd day together with the eyelid edema, redness of the eyeball conjunctiva, lachrymal muscle and semilunar fold, the hemorrhages appear on the eyelid conjunctiva and the hypodermic fold. In some cases the films appear on the eyelid conjunctiva. The abundant eruption on the eyelid conjunctiva and transitional folds of the superficial follicles is very typical. The

discharge is usually scanty. The enlargement and tenderness of the parotid and sometimes submandibular lymph nodes are important diagnostic symptoms.

The typical changes in the cornea appear on the 7-14th day of the disease. Their appearance often coincides with the disappearing of the inflammatory processes in the conjunctiva. On the cornea, usually in the center, in the pupil zone, there are delicate subepithelial round infiltrates, which do not tend to ulceration. The disease is sometimes accompanied by the temperature increase. Quite often the patients complain of a headache and general malaise. A patient considers the dimness of the cornea to be a foreign body, photophobia and vision disorder. In half of the patients only one eye is affected, but in some time (7-10 days) the second eye can get involved in the process. The disease lasts from 8-10 days to 6-7 weeks. The foci of dimness on the cornea dissolve slowly, during 3 months. In some cases the dimness remains for a long time and causes the vision worsening.

Pneumonia. Among different forms of the adenoviral diseases pneumonia causes the greatest alarm, especially, in the children of the young age. Clinically the symptoms of the pneumonia in case of the adenoviral infection are expressed quite distinctly. The disease has an acute onset with the temperature increase up to 38-39 °C, the temperature curve is usually irregular, with oscillations, quite often the fever period has a lingering character up to 20 days and longer. The temperature reaction is not expressed or absent in the children of the first months. Pneumonia is accompanied by the expressed catarrhal manifeslations in the upper respiratory tract. The fauces mucous membrane is hyperemic, edematic, the tonsils are enlarged and in some cases they are covered with whitish fur. The nasal discharge is abundant. The discharge is mucous or mucopurulent. The cough is painful, often excruciating, dry or with the discharge of the mucopurulent sputum. During the first days of the disease the physical changes in the lungs may not be found, they usually develop later. From the 3-4th day of the disease along with the shortening of the resonance with the tympanic inflection there is a big amount of dry and mixed moist rale. The rale can disappear, and then come back again. Sometimes an asthmatic component joins these manifestations. The massive affection of the lung tissues is revealed during the X-ray examination. The inflammatory foci flow together. They dissolve slowly. A tendency to relapses, exacerbation and a slow reparation of the inflammatory process in the lungs are characteristic of adenoviral pneumonia. A severe course of pneumonia with an unfavorable outcome is usually observed in the children of the early age, and in other patients who are weakened by previous diseases or accompanied diseases. Pleuritis and abscesses can complicate pneumonia, but it occurs comparatively rarely.

Complications

The changes of some inner organs and systems, which are typical of the adenoviral disease (lymphadenopathy, hepatosplenic syndrome, changes in the cardiovascular, nervous system, hematological changes) are more expressed in

case of pneumonia and occur more often comparing with the uncomplicated course of the disease. Encephalitis and meningoencephalitis cases occur sporadically. Adenoviruses have been implicated as a cause of pericarditis, chronic interstitial fibrosis, congenital anomalies.

Diagnosis

The clinical diagnostics of the RS infection is based on the primary affection of the lower parts of the respiratory tract, quite often with an asthmatic component and respiratory insufficiency. The changes in the upper parts are less expressed.

The confirmation of the diagnosis is based on the laboratory investigations. The collection of the material and the investigation methods are the same as in case of other viral infections of the respirators tract.

Differential diagnosis

The problems in the differential diagnostics of the diseases which form this group are due to the fact that different viruses can cause similar clinical syndromes and first of all the syndrome of the acute disease of the respiratory tract.

The differential diagnostics is possible only in case of the typical course of the disease during the clinical recognition of the nosologic forms taking into consideration the peculiarities of the location of the pathological process, the degree of the toxicosis, the presence and expressiveness of the catarrhal manifestations as well as changes in other organs and systems.

Times, in contrast to influenza in the adenoviral diseases the local limited outbreaks are registered, the incubation period in the infected patients is longer, the catarrhal manifestations with an abundant discharge are considerably expressed, there are typical changes in the fauces, the lymph nodes, liver and spleen are enlarged, relapses occur later.

In contrast to paragrippe the onset of the adenoviral diseases is often acute. the exudative component is more expressed, there is lymphoadenopathy one-side conjunctivitis.

Treatment

Treatment will carry out in view of gravity of current and the clinical form of disease. Localy there are used the etiotropic preparation desoxyribonucleasa which is instilated into conjunctival bag and nasal courses as the solution. Apply also a solution of oxolin, oxolin unguent, or florenal for pawning edges of blepharons and for greasing mucosa of nose. As agent of a choice use solution of human interferon as inhalations, dispersion or drops in a nose through every 1-2 hours during 2-3 days. Efficiency of treatment above correlates than earlier it is begun. Among inductores of interferon and imunomodulatores there are indicated amixin, amizin, cycloferon, proteflazid, erbisol. At serious forms of disease human placental or serumal immunoglobulin (3-6 mL unitary) is used, at absence of effect it is given repeatedly in 6-8 houres or on next day. 5 % glucose solution with

ascorbic acid is infused according to the indications. Reopolyglucin, sault solutions, humidified oxygen are used through a nasal catheter.

There are recommended a hot drinks of tinctura of raspberries, lime color, flowers of a black elder, tea with lemon, sudorific collectings. For inhalations there should be used warm broths of leaves of eucalypt, sage, pine buds, grasses of thyme, buds of a birch (separately or in admixture), for a gargle of pharynx and an oral cavity there are given broths of flowers chamomiles, calendula, grasses of a yarrow, sage. There are indicated also sinapismuses on thorax and soles.

In case of rhinitis we instill into nose vasoconstrictive preparations,such as: naphthyzin, ephedrin hydrochloride, pharmasolin. For cupping of inflammatory process apply into nasopharynx faringosept or falimint. The other remedies recommended are pectusin or terpin hydrate, ascorutin, calci of gluconate, methyluracil, and also diazolinum, suprastin, tavegil, gismanal, zestra, loratidin, alegra, telfast.

In case of bacterial complications antibiotics and others chemotherapeutic agents are indicated in view of kind of the originator and its medicinal sensitivity. benzylpenicillin sodic salt, ampicillin sodium salt, carbapenicilin dinatri salt, ampiox, erythromycin, oleandomycin phosphas or doxycyclin hydrochloride, cefalosporines (cefazolin, cefotaxim, ceftriaxon) are used.

Prophylaxis

Because of the ubiquity and severity of adenovirus respiratory disease in certain populations, vaccines were developed to prevent the disease. Although these live and inactivated virus vaccines were reasonably effective, the findings that adenoviruses were oncogenic and could combine with simiar virus 40 to produce an even more oncogenic hybrid virus curtailed the use of parenteral vaccines. Vaccines have also been produced by using capsid components free of DNA. These vaccines have been effective in volunteer studies but are not currently available for general administration.

Oral vaccines have been developed for use in military recruits. These vaccines contain live adenovirus types 4 and 7 in an enteric-coated capsule. These viruses are not attenuated, but advantage is taken of the fact that inoculation of these adenoviruses into the gastrointestinal tract does not result in illness, in contrast to inoculation into the respiratory tract. Their efficacy and safety have been well established in the past 10 years, and the problem of acute respiratory disease in recruits has been markedly diminished.

RHINOVIRAL INFECTION

Rhinoviral infection is an acute viral disease of the upper respiratory tract, which is accompanied by the symptoms of the nose and nasopharynx mucous membrane affection.

Historic reference

The infectious nature of contagious rhinitis (common cold) was proved in 1914 by W.Kruse and confirmed in 1916 by G.Foster. After that, especially after 1952, the virus agents were repeatedly isolated but their etiological role remained unproved and only in 1960 in Solsbery D.Tyrell proposed a new virus cultivation method and isolated a whole group of them during 1961 and 1962 and proved their etiological role. They were named rhinoviruses after the proposal of C.Andrewes. In 1963 rhinoviruses were included into the family of picornaviruses.

Etiology

The rhinoviruses of the human include 114 serotypes which cause an acute respiratory disease without an expressed intoxication. The virus genome is represented by non-fragmentary filament of the RNA. The viruses inactivate at a temperature of 56 °C quickly in 10 minutes. They die at drying in the air in several minutes.

Epidemiology

The rhinoviruses are widely spread and affect all the age groups of people all the year round. The human viruses develop only in humans, no sensitive laboratory animals have been found, sometimes it is possible to infect a chimpanzee. The strains, which are cultivated on the human's cells, were named H-strains, and the ones on the monkey cells − M-strains. The virus replication takes place in the epithelial cells of the nose and they are excreted with the nasal discharge during 2 weeks. The virus is airborne. The transmission from the hands of an infected person to the hands of the susceptible ones is possible, and then an auto-infection of the nose or conjunctiva occurs.

Pathogenesis

The disease development mechanism has been studied on the volunteers and on the organic cultures. The possibility of the disease development was shown during the experiments on the volunteers when the virus was dropped into the nose or rubbed in the mucous membrane of the nose or eye, whereas rubbing into the back wall of the throat or insertion through the mouth did not cause the disease. The virus was found in the nasal discharge in 24 hours or maximum in 3-4 days. The rhinoviruses can join other pathogens of the lower respiratory tract worsening the course of them. The virus-bacterial associations are discovered quite often.

Clinical manifestations

The incubation period lasts 2-3 days. The disease starts with sneezing. feeling of dryness, tickling in the throat, pain in the throat and slight cough. From the first hours of the disease the leading symptom is rhinitis with abundant serouse discharge,

which is of a watery character in the beginning, then it becomes slimy and thickly mucopurulent. On average rhinitis lasts 6-7 days but it can be prolonged up to 14 days. During this period the patients complain of a feeling of heaviness and nagging pain in the sinuses. The skin at the nose entrance gets macerated, the herpetic eruption develops on the lips. The mucous membrane of the front part and back wall of the throat becomes moderately hyperemic, slightly edematic. The small granularity develops in the area of the soft palate. The sclera vessels are usually injected, the conjunctiva is hyperemic, and the eyes may be watery.

The symptoms of intoxication are not typical of the rhinoviral infection. The general condition is slightly affected. The patients mention a slight malaise, headache in the forehead area. The body temperature remains normal or slightly increased during 1-2 days. The picture of the peripheral blood does not change.

Complications

The joining of the bacterial flora causes the complications: sinusitis, otitis, bronchitis, and pneumonia.

Diagnosis

The rhinoviral infection is clinically diagnosed in case of the expressed rhinitis with abundant rhinorrhea and pharyngitis, which develop during the first hours of the disease without any intoxication symptoms. The confirmation of the diagnosis is based on the laboratory investigations. The material collection and the methods of the investigation are similar to the ones in other viral infections of the respiratory tract.

Differential diagnosis

The problems in the differential diagnostics of the diseases which form this group are due to the fact that different viruses can cause similar clinical syndromes and first of all the syndrome of the acute disease of the respiratory tract.

The differential diagnostics is possible only in case of the typical course of the disease during the clinical recognition of the nosologic forms taking into consideration the peculiarities of the location of the pathological process, the degree of the toxicosis, the presence and expressiveness of the catarrhal manifestations as well as changes in other organs and systems.

Someimes, in contrast to influenza in the adenoviral diseases the local limited outbreaks are registered, the incubation period in the infected patients is longer, the catarrhal manifestations with an abundant discharge are considerably expressed, there are typical changes in the fauces, the lymph nodes, liver and spleen are enlarged, relapses occur later.

In contrast to paragrippe the onset of the adenoviral diseases is often acute. the exudative component is more expressed, there is lymphoadenopathy one-side conjunctivitis.

Treatment

Only symptomatic treatment is available for rhinovirus colds at present. Penicillin and other antibiotics have no place in therapy, since they neither ameliorate the viral illness nor reduce the frequency of bacterial complications.

Rest, hydration, nasal decongestants, saline gargles, and cough suppressants remain the mainstay of treatment. Constitutional symptoms are not usually prominent with rhinovirus infection, but will respond to aspirin and acetaminophen when present. Nasal decongestants may be used on a regular basis during the acute stage of illness. The regular application of a petrolatum-based ointment helps prevent painful maceration of the nares. Patients with secondary bacterial sinusitis or otitis media require appropriate antimicrobial therapy.

Prophylaxis

No effective vaccine is available.

Control questions:

1. Etiology and epidemiology of acute respiratory viral diseases.
2. Pathogenesis of acute respiratory viral diseases.
3. Clinical manifestations of parainfluenza, adenoviral infections, other acute respiratory viral diseases.
4. Complications of parainfluenza, adenoviral infections, other respiratory viral infection.
5. Laboratory methods of diagnosis: the serological, bacteriological and immunefluorescent.
6. Criteria of diagnosis.
7. Differential diagnosis of acute respiratory viral diseases.
8. Treatment of acute respiratory viral diseases.
9. Preventive measures in spot of disease outbreak.

MYCOPLASMA PNEUMONIAE INFECTION

Mycoplasma pneumoniae infection is an acute respiratory disease characterized by the polymorphism of the clinical manifestations, frequent lung affection.

Historic reference

In 1944 M. D. Eaton and his co-authors isolated a filtrating agent form the patients with pneumonia, it caused pneumonia in cotton rats and could be neutralized with the serum of the recovered patients. The pathogen was called Eaton factor after the name of the author. It was considered to be a virus till 1962. when in 1962 R. Chanock and his co-authors proved that Eaton factor belonged to *Mycoplasmiaceae* and in 1963 this factor was named *Mycoplasma pneumoniae* after the proposal of the same authors.

Etiology

The mycoplasma is noted for extreme polymorphism because of the absence of the cell wall. Their cell consists of three morphological elements: an elementary membrane, ribosome and nucleoid, which is represented by DNA − like filaments. The problem of the mycoplasma pneumonia replication is still open.

Mycoplasma can be destroyed by the ultrasound, alternating freezing and defrosting in the distilled water, warming up at a temperature of 40 °C and higher. There is a considerable amount of liquid, solid and semisolid mediums, which can be used for mycoplasma cultivation. The temperature optimum is 37 °C. The appearance of the colony on the agar medium is very typical: the center or the whole colony is situated below the surface of the agar.

Epidemiology

The characteristic peculiarities of the epidemiology of the mycoplasma pneumoniae infection are that it is airborne, and that it is spread widely and everywhere. It usually causes local outbreaks in the organized groups of children and adults and a whole spectrum of diseases develops from the latent infection and the diseases of the upper parts of the respiratory tract to bronchopneumonia which is sometimes accompanied by pleuritis. The ability of the infected organism to spread the infection for a long time is proved, as the pathogen remains for a long time in the respiratory tract of the patients even in case of the clinically effective antibiotic therapy. Mycoplasma pneumoniae infection is registered all the year round, the distinct seasonally has not been ascertained.

Pathogenesis

The study of the mycoplasma pneumoniae infection pathogenesis was mainly done under the conditions of the experimental modeling in the experiments on the volunteers. The intranasal infection showed the possibility of the development of the pathological changes, which are characteristic of the natural infection, and the formation of the specific antibodies. Pneumonia, laryngitis, an acute respiratory disease, accompanied with fever developed in the volunteers on the 5-13th day after the infection.

Anatomic pathology

The peculiarity of the experimental mycoplasma pneumoniae infection is the development of the moderate inflammatory reaction in the lung tissue and appearance of the growing productive-infiltrative reaction with the formation of the peribronchial, perivascular and interstitial lymphoid-monocyte infiltration. Which is an evidence of the specific immunomorphologic rebuilding in the lungs.

Clinical manifestations

Mycoplasma pneumoniae infection is distinguished by the polymorphism of the clinical manifestations. Mainly causing the diseases of the respiratory organs mycoplasma can cause the affection of other organs or systems. Most often mycoplasma pneumoniae infection causes pneumonia. However, it plays an important role in the affection of the upper respiratory tract, which takes a course of an acute respiratory disease. In case of an acute respiratory disease, after the incubation period of 3-11 days. there is often a gradual onset with the temperature increase up to the subfebrilc values, the development of indisposition, malaise, aches in the body headaches. In one-two days the temperature increases, the symptoms of intoxication get worse, especially, the headache, in some patients there are symptoms of meningism with meningeal signs. Along with it an acute onset of the disease is also possible, when the temperature reaches 39-40 °C during the first hours. The fever period lasts 4-6 days but hyperthermia not more than 2-3 days. In some cases after the temperature decrease there is a monotonous subfebrile condition during 10-12 days. There are symptoms of the upper respiratory tract affection from the first days of the disease. The most frequent of them are the dryness and tickle in the throat, stuffed nose and cough.

There is a bright hyperemia in the throat, especially, on the back wall and an enlargement of the follicles. Pharyngitis is usually accompanied by rhinitis. All the patients complain of the labored nasal breathing. It is caused by an edema of the nose mucous membrane, but there is not any expressed rhinorrhea. One of the main symptoms is a dry cough. In most patients it is excruciating, sometimes it reminds the attacks of the whooping-cough, causes vomiting, pain in the chest and in the abdomen. It remains for 6-10 days but it can last longer. Quite often the symptoms of bronchitis join the mentioned symptoms. The breathing becomes hard, dry rale appear. There are no other physical changes.

The disorder of the cardiovascular system is not characteristic of this form of mycoplasma pneumoniae infection. The pulse corresponds with the temperature. The picture of the peripheral blood is characterized by the normal amount of leukocytes, often lymphocytosis, ESR is normal or slightly increased.

Mycoplasma pneumonia. The incubation period is longer than that in an acute respiratory disease and lasts from 7 to 28 days. In the majority of the adults the disease develops gradually with the symptoms of an acute respiratory disease: malaise, moderate headache, stuffed nose, dry cough. The chill appears in 3-4 days and the temperature increases up to 39-40 °C. The fever lasts not more than 10-12 days. The acute development of the process is also possible, when the temperature reaches the high points on the first days.

In contrast to bacterial pneumonia there is no severe intoxication. Nausea, vomiting, sleep disorders are very rare. Much more often the patients complain of joint, muscles aches, especially, in the waist. The cough is the permanent symptom, which develops on the first day of the disease and lasts 10-15 days and sometimes longer. In the beginning it is usually dry, exhausting, but by the end of the 2nd week it starts to be productive, but the sputum is discharged with difficulty and in a small amount. On the first days of the disease the symptoms of pneumonia are not observed. The pain in the chest develops in half of the patients on the 5-7 day. As for the physical changes in the lungs, they are either scanty or absent, though, the inflammatory changes are observed during the x-ray examination. In this case shortness of breath, cyanosis are not typical symptoms of the pulmonary (respiratory) insufficiency. However, the changes of the ventilation function of the lungs and the disorder of the bronchial permeability are observed during the spirographic examination.

The x-ray picture of mycoplasma pneumonia is variable. The process can take the segmental focal or interstitial pneumonia course. The infiltrates are most often found in the lower lobe where they capture 1-2 segments. The lobe affections are rare. The foci may not be homogeneous, without distinct borders. Atelectasis and pleural exudate may be the manifestations of the inflammatory process. However, neither of the mentioned manifestations can be a diagnostic symptom.

The cardiovascular system is not considerably affected. The changes in the function of the alimentary tract are not ascertained. The increase of the lymphocytes is characteristic of the peripheral blood.

Complications

Of all the extrapulmonary manifestations of *M. pneumoniae* cardiac abnormalities are the most commonly reported. The signs of heart involvement are arrhythmia, congestive failure, chest pain, ECG abnormalities. Among neurologic complications aseptic meningitis, meningoencephalitis, brain stem dysfunction have been reported.

Diagnosis

An acute respiratory disease caused by the *Mycoplasma pneumoniae* does not have any specific symptoms, that is why its clinical diagnosis is very difficult. In spite of some peculiarities of the course mycoplasma pneumonia does not have any pathognomonic symptoms, that is why the results of the x-ray and laboratory investigations are conclusive in the diagnosis.

The laboratory diagnosis is based on the method of neutralization of the growth suppression, reaction of the indirect hemagglutination and detection of the mycoplasma pneumoniae infection antigen in the cells of the washouts from the throat with the immunofluorescent method. The skill test with mycoplasma pneumonia allergen can be used starting from the second week.

Differential diagnosis

Diferential diagnosis is complicated. Because the mycoplasma pneumoniae infection does not have any specific symptoms, it should be based both on the data of clinical examination, and on the data of laboratory methods of diagnosis.

Treatment

Tetracycline and erythromycin are the most effective etiotropic treatment. In case of the sole affection of the upper respiratory tract parts the antibiotic treatment is pointless, the symptomatic medications are enough.

In case of severe pneumonia with a tendency to a long course, when enteral and parenteral antibiotic usage is not effective, it is recommended to use them in the form of the ultrasound aerosol with the proteoclastic enzymes. The prognosis is usually favorable, but it can be serious in case of the severe complications, especially, in children.

Prophylaxis

The vaccines did induce specific antibody responses, but protection against infection was limited to more than 50 % of vaccine recipients. Live vaccines using attenuated wild-type and temperatyre sensitive mutant mycoplasma have proven no more effective.

Control questions:

1. Etiology and epidemiology of mycoplasma pneumoniae infection.
2. Pathogenesis of mycoplasma pneumonia.
3. Clinical manifestations of mycoplasma pneumonia.
4. Complications of mycoplasma pneumonia
5. Laboratory methods of diagnosis.
6. Criteria of diagnosis.
7. Differential diagnosis of mycoplasma pneumonia.
8. Treatment of mycoplasma pneumonia.
9. Preventive measures in spot of disease outbreak.

MENINGOCOCCAL INFECTION

Meningococcal infection is an acute infectious disease of the human, caused by meningococcous *Neisseria meningitidis*. The mechanism of the transmission of the infection is air-drop. The disease is characterized by damage of mucous membrane of nasopharynx (nasopharingitis), generalization of the process in form of specific septicemia (meningococcemia) and inflammation of the soft cerebral membranes (meningitis).

Historic reference

Epidemic cerebrospinal meningitis (one of the most clinically expressive forms of the disease) was known else in profound antiquity. The description of outbreaks of this infection is contained in reports of Areteus (III century), Egynsky (VII century).

Epidemic cerebrospinal meningococcal meningitis was first described by Vieusseaux in 1805. Subsequent reports throughout the nineteenth century confirm its episodic epidemic nature with a propensity for affecting young children and military recruits assembled in stationary barrack situations. In 1887, Weichselbaum isolated the meningococcus from the cerebrospinal fluid, and the etiologic relationship between this organisms and epidemic meningitis was firmly established.

Kiefer in 1896 and Albrecht and Ghon in 1901 found that healthy persons could become carriers of the meningococcus. Serotypes of the meningococcus were first recognized by Dopter in 1909. This laid the basis for serum therapy in the treatment of meningococcal infection. The agent was isolated from the blood by V. Osler in 1899. It had an important meaning, because many problems of pathogenesis of the disease were explained. It was evidence that meningitis is not single manifestation of the disease.

In 1937, sulfonamide therapy radically altered the outcomes of meningococcal infection. With the advent of antibiotic agents, treatment of meningococcal infection became more effective, and mortality declined. With the subsequent world wide emergence of resistant strains and with the absence of effective chemoprophylaxis, renewed interest in immunoprevention has occurred and has led to the development of safe and effective vaccines against the groups A, C, Y and W-135 meningococcal group.

Meningococcal infection occurs on the all continents. It is serious problem for public health. It is registered in 170 countries of the world.

Etiology

The causative agent is *Neisseria meningitidis*. It is small gramm-negative diplococcus, aerobic, catalise and oxidase-positive, not-motile and possess a

polysaccharide capsule, which is the main antigen and determines the serotype of the species. Meningococcus may be seen inside and outside of neutrophills. The main serogroups of pathogenic organisms are A, B, C, D, W_{135}, X, Y, Z and L. The bacterial membrane is a lipopolysaccaride.

The pathogenic properties of meningococcus are known insufficiently, because meningococcal infection is anthroponosis. The factors of pathogenic action of meningococcus are biological properties, promoting its attachment on the mucous membrane of nasopharynx, depression symbiotic microflora, penetration through mucous barriers, toxic properties and other.

One of such properties is specific attachment or adhesion of meningococcous to the cells of epithelium of respiratory tract. Adhesion is phenomenon, promoting to colonization of meningococcus on the mucus. Physical factors (adsorption of microbes on the surface of the cell) and fermentative processes have the meaning in the appearance of adhesion.

Meningococci are very exacting to composition of nutritive mediums. Its reproduction may be only in presence of human's protein or animal's protein. Due to destruction of the microbe's cell endotoxin is delivered (of lipopoly-saccharide origin). Exotoxin is not produced. The agent of meningococcal infection is characterized by low resistance in the environment. Meningococci perish during temperature 50 °C during 5 minutes, during temperature 100 °C — during 30 seconds. Meningococci have a little resistance to low temperature.

Epidemiology

Meningococcal infection is typical anthroponosis. The sourses of infection are healthy carriers of meningococcus, the patients with meningococcal nasopharingitis and the patients with generalized forms of the disease.

The patients with generalized form are more dangerous. It is proved that they are dangerous for surrounding persons in 6 times than healthy carriers. However, the main sources of the infection are carriers, because 1,200-1,800 (according other data — 50,000) carriers have occasion to one patients with generalized form of the disease.

Thus, the patients with generalized form of the disease are the source of infection for 1-3 % of infected persons, the patients with meningococcal nasopharingitis — for 10-30 %, carriers are the sources of infection for 70-80 % from general number of infected.

The level of healthy carriers promotes the level of morbidity in certain region. So, carriers may compose 3-12 %. It is temperate sporadic morbidity. Carriers may achieve 20 %. This situation is marked as unsatisfactory. The outbreaks are observed. Carriers may achieve 30-40 %. In this case epidemic of meningococcal infection arises.

The mechanism of transmission of the infection is air-drop. The infection is realized during cough, sneezing. In this the narrow contact and sufficient exposition

are necessary. It is proved by A.A. Favorova (1976) that the infection is realized on the distance less 0.5 meter.

The wide distribution of meningococcal infection is promoted some causes in the countries of equatorial Africa. The main causes are connected with social factors (unsatisfactory sanitary-hygienic conditions of the life of the majority part of the population, high density of the population and other).

In meningococcal infection one of an important characteristic of epidemic process is periodical rise and fall of the morbidity. The duration of the period with high morbidity is different. It may be 5-10 years and more. Then the period of the fall of the morbidity becomes. It is continued from 5 till 20 years.

In meningococcal infection epidemic process is characterized by seasonal spread. It is manifested especially during epidemics. The morbidity may compose 60-70 % from year's morbidity during seasonal rise. The onset of the seasonal rise is in January in the countries with temperate clinimate. It achieves of maximum in March – April.

The estimate of the age morbidity of meningococcal infection testifies about that 70-80 % of the cases of the diseases have occasion to children. Children of the age 1-5 years compose 50 %. Meningococcal infection is marked rarely at the first three month of the life.

The persons of the young age (15-30 years) compose the majority among adult patients. It is explained by social factors and features of the life young people (service in the army study in the educational establishments, living in the hostel). These factors explain predomination of men in the structure of the morbidity.

The age of carriers of meningococcal infection is different from the age of the patient. The larger part of carriers is reveled among adults. The portion of the children is small. The morbidity is higher in the towns then rural locality.

The considerable outbreaks of the diseases were described in the educational establishments of the closed type and especially among military (as at peaceful time such as during war).

Pathogenesis

In meningococcal infection entrance gates are mucous membrane of nasopharynx. It is place of primary localization of the agent. Further meningococci may persist in epithelium of nasopharynx in majority of the cases. It is manifested by asymptomatic healthy carriers. In some cases meningococci may cause inflammation of mucous membrane of upper respiratory tract. It leads to development of nasopharingitis.

The localization of meningococcus on mucous membrane of nasopharynx leads to development of inflammation in 10-15 % of the cases.

The stages of inculcation on the mucous membrane of nasopharynx and penetration of meningococcus into the blood precede to entrance of endotoxin into the blood and cerebrospinal fluid. These stages are realized with help of

factors of permeability. It promotes of the resistance of the meningococcus to phagocytosis and action antibodies.

Meningococci are able to break local barriers with help of factors of spread (hyaluronidase). Capsule protects meningococci from phagocytosis. Hematogenous way is the principal way of the spread of the agent in the organism (bacteremia, toxinemia). Only the agent with high virulence and invasive strains may penetrate through hematoencephalitic barrier. The strains of serogroup A are high invasivicity.

Meningococci penetrate into the blood after break of protective barriers of mucous membrane of upper respiratory tract. There is hematogenous dissemination (meningococcemia). It is accompanied by massive destruction of the agents with liberation of endotoxin. Meningococcemia and toxinemia lead to damage of endothelium of the vessels. Hemorrhages are observed in mucous membrane, skin and parenchymatous organs. It may be septic course of meningococcemia with formation of the secondary metastatic focuses in the endocardium, joints, internal mediums of the eyes.

In most of the cases penetration of meningococci in the cerebrospinal fluid and the soft cerebral covering is fought about by hematogenous ways through the hematoencephalic barrier. Sometimes meningococci may penetrate into the skull through perineural, perilymphatic and the perivascular way of the olfactory tract, through the enthoid bone.

Thus the meningococci enter into subarachnoid space, multiply and course serous-purulent and purulent inflammation of the soft cerebral coverings. The inflammatory process is localized on the surface of the large craniocerebral hemispheres, and rarely, on the basis, but sometimes it may spread in the covering of the spinal cord. During severe duration of the inflammatory process the cranium is covered by purulent mather (so-cold "purulent cap"). It may lead to involvement of the brain's matter into inflammatory process and meningoencephalitis.

The process may engulf the rootlets of VII, VIII, V, VI, III and XII pairs of cranial nerves.

Pathogenic properties of the agent, state of macroorganism, state of immune system, functional state of hematoencephalitic barrier have the meaning in the appearance of meningitis of any etiology.

Endothelium of capillaries, basal membrane, "vascular pedicles" of glyocytes and basic substance of mucopolysaccharide origin are the morphologic basis of hematoencephalic barrier. Hematoencephalic barrier regulates metabolic processes between blood and cerebrospinal fluid. It realizes protective function from the alien agents and products of disorder of metabolism. The most alterations are observed in reticular formation of the middle brain.

In purulent meningitis some pathogenic moments are promoted by rows of paradoxical appearances in hematoencephalic barrier and membranes of the brain. In physiological conditions hematoencephalic barrier and brain's membranes create closed space, preventing brain's tissue from influence of environment. In

this case secretion and resorbtion of cerebrospinal fluid are proportional. In meningitis closed space leads to increased intracranial pressure due to hypersecretion of cerebrospinal fluid and to edema of the brain. The degree of swelling-edema of the brain is decisive factor in the outcome of the disease.

The next stages may single out in pathogenesis of purulent meningitis:

1. Penetration of the agent through hematoencephalic barrier, irritation of receptors of soft cerebral membrane of the brain and systems, forming cerebrospinal fluid.

2. Hypersecretion of cerebrospinal fluid.

3. Disorder of circulation of the blood in the vessels of the brain and brain's membranes, delay of resorbtion of cerebrospinal fluid.

4. Swelling-edema of the brain hyperirritation of the brain's membranes and radices of cerebrospinal nerves.

Besides that, intoxication has essential meaning in pathogenesis of purulent meningitis. Vascular plexuses and ependime of ventricles are damaged more frequently. Then the agent enters into subarachnoid space and brain's membranes with the spinal fluid flow.

In some cases, especially in increated patients the process may turn into ependima of the ventricles. As a result it may be occlusion of the foramina Lushka, Magendie, the Sylvius aqueduct. It leads to development to hydrocephaly.

In the pathogenesis of meningococcal infection toxic and allergic components play an important role. Thus, in fulminate forms of meningococcal infection infectious-toxic shock develops due to massive destruction of meningococcus and liberaton of considerable quantity of endotoxin. In infectious-toxic shock the development of thrombosis, hemorrhages, necrosis in different organs are observed even in the adrenal glands (Waterhause − Fridrechsen syndrome).

The severe complication may develop as a result of expressive toxicosis. It is cerebral hypertension, leading frequently to lethal outcome, cerebral coma. This state develops due to syndrome of swelling of the brain with simultaneous violation of outflow of cerebrospinal fluid and its hyperproduction. The increased volume of the brain leads to pressure of brain matter, its removement and wedging of medulla oblongata into large occipital foramen, pressure of oblongate brain, paralysis of breath and cessation of cardiovascular activity.

Anatomic pathology

In meningococcal infection pathologoanatomical changes depend on form and duration of the disease.

Nasopharingitis is characterized by hyperemia of the pharyngeal walls, edema of the epithelial cells, regional infiltration, hyperplasion and hyperthrophy of lymphoid follicles. Signs of catarrhic inflammation are found in trachea and bronchi.

Cases of fulminate meningococcal infection is characterized by blood vessels disorders and severe impairments of blood circulation. The main target are the

microcirculation vessels. The vascular lumen turns narrow, thrombs are found. Thrombs are usually found in small veins. Hemorrhages into skin, subcutaneous tissue, lungs, myocardium, subendocardial hemorrhages, hemorrhages into renal parenchyma, adrenals, brain and subarachnoidal space are typical.

Meningococcous meningitis is characterized by serous or purulent inflammation of pia mater.

Clinical manifestations

The incubation period is 1-10 days, more frequently 5-7 days.
Classification of the clinical forms of meningococcal infection:
I. Primarily localized forms:
   a) meningococcal carrier state;
   b) acute nasopharyngitis;
   c) pneumonia.
II. Gematogenously generalized forms:
   a) meningococcemia: typical acute meningococcal sepsis, chronic;
   b) meningitis, meningoencephalitis;
   c) mixed forms (meningococcemia + meningitis, meningoencephalitis);
   d) rare forms (endocarditis, arthritis, iridocyclitis).
In meningococcal carriers the clinical manifestations are absent.

Meningococcal nasopharingitis. The most common complains of the patients are headache, mainly in the frontal-parietal region, sore throat, dry cough, stuffed nose, fatigue, weakness, loss of appetite, sleep disorders. In most of the patients body temperature rises upto subfebrile and lasts for not more than 3-7 days, sometimes 5-7 days. The skin is pale, conjunctival vessels and sclera are injected. There are hyperemia and edema of the mucous membrane of the nose. In many patients the posterior wall of the pharynx seem to be covered by mucous or mucous – purulent exudation.

Inflammatory changes in the nasopharynx can be noticed after 5-7 days, hyperplasion of lymphoid follicles lasts longer (till 14-16 days). In the peripheral blood temperate leukocytosis with neutrophylosis and shift of leukocyte formula to the left, increase in ERS may be revealed. Nasopharyngitis precedes to development of generalized forms of the disease.

Meningitis. It may start after meningococcal nasopharyngitis, but sometimes primary symptoms of the disease arise suddenly. In meningitis three symptoms are revealed constantly: fever, headache and vomiting. Temperature increases quickly with chill and may reach 40-41° during few hours. Intermittent, remittent, constant, double waved types of the temperature occur in meningitis. The patients suffer from severe headache, having diffuse or pulsatory character. Headache is very intensive at night. It increases due to change of body position, sharp sounds, bright light. Vomiting arises without precedent nausea. There is no connection with food and relief after vomiting. It is rule abundant, like "fountain", repeated. Sometimes, vomiting arises on the peak of headache.

In meningitis hyperthermia, hyperkynesia, photophobia, hyperalgesia, hyperosmia are noticed. These symptoms are revealed more frequently in children. The severe convulsions arise in the many patients at the first hours of the disease (clonic, tonic or mixed types). In small children meningococcal meningitis may start with convulsions.

The disorders of consciousness occupy the great place in clinical picture (from sopor till coma). The loss of consciousness develops after psychomotoric excitement. The loss of consciousness at the first hours of the disease is unfavorable sign.

During objective examination meningeal symptoms stand at the first place. It is described near 30 meningeal signs. A few meningeal signs are used in practice: rigidity of occipital muscles, Kernig's symptom, Brudzinsky's symptom (upper, middle and lower). The estimate of state of fontanelle is very important in infants. There are three symptoms of meningitis in infant: swelling, tension and absence of fontanelles pulsation.

There is no accordance between expression of meningeal syndrome and severity of the disease. The expression of different symptoms is no similar at the same patient. The patient has compulsory pose during serious cases. He lays on side with deflection of the head backwards. The legs are curved in knee-joint and pelvic-femoral joint. The legs are pulled to abdomen. Asymmetry and increased tendinous, periostal and dermal reflexes are observed in the patients. These reflexes may be decreased during expressive intoxication. Pathological reflexes may be revealed (such as Babinski's, Hordon's, Rossolimo's reflexes, foot's clones), and also symptoms of damage cranial nervous (more frequently III, VI, VII, VIII pairs).

The multiple symptoms of the lesion of the other organs and systems are connected with intoxication. There is tachycardia at the first hours of the disease. Then it may be bradycardia. Arrhythmia, tachypnoea (30-40 per minute) are possible. The tongue is covered by dirty brownish coat. It is dry. Abdomen is pulled inside. There is tension of abdomen muscles.

The external appearance of the patients is very typical. There is hyperemia of the face and neck. Sclera's vessels are injected.

In hemogram high leukocytosis, neuthrophylosis with shift of formula to the left, increased ERS are observed. Small proteinuria, microhematuria, cylinderuria are marked in urine.

Fulminate course of meningitis with syndrome of brain's swelling and edema is the most unfavorable variant. There is hypertoxicosis during this form and high percentage of mortality. The main symptoms are consequence of inclination of the brain into foramen magnum and strangulation of medulla oblongata by tonsils of cerebellum. Immitant symptoms from cardiovascular and respiratory systems develop quickly. Bradycardia appears. Then it is changed by tachycardia. Arterial pressure may fall catastrophically, but it increases more frequently till high level. Tachypnoea arises (till 40-60 per min) with help of axillary muscles. The disorders

of breath lead to its sudden interruption. These symptoms develop in hyperthermia, clonic cramps and loss of consciousness. Cyanosis of the skin, hyperemia of the face are marked. Pyramidal signs, sometimes symptoms of damage of cranial nerves, decreased corneal reflexes contraction of pupils and its decreased reaction on light are determined. Death occurs due to respiratory failure at the first hours of the disease, rarely on 2-3 day or on 5-7 day.

Meningitis with syndrome of cerebral hypotension. It is rare variant of the course of meningococcal meningitis. It is observed principally in children. The disease develops impetuously, with sharp toxicosis and exicosis. Stupor develops quickly. Cramps are possible. Meningeal signs are not expressive, because, the diagnostics is difficult. Intracranial pressure rapidly falls. In this case the volume of the fluid in the brain's ventricles decreases. Ventricular collapse develops. In infant the large fontanelle is depressed. In adults and children supporting moments in diagnostics are clinical signs of dehydration and hypotension of cerebrospinal fluid, which flows out by rare drops. The fall of intracranial pressure may lead to development of severe complication − subdural hematoma.

Meningitis with syndrome of ependimatitis (ventriculitis). Now it is rare form of meningitis. This form develops during late or insufficient treatment of the patients. Especial severity of the disease is connected with spread of inflammation on ventricles membranes (ependime) and involvement of brain's substance in to pathological process.

The principal clinical symptoms are total and expressive muscular rigidity. The patients accept the particular pose. The disorder of psychic, sleeping, tonic and clonic cramps are observed. The body temperature is normal or subfebrile during general severe state of the patient. Vomiting is constant symptom. Hydrocephalia and cachexia develop due to prolonged course and (or) noneffective therapy of ependimatitis.

Meningoencephalitis. It is rare form of meningococcal infection. In this case the symptoms of encephalitis predominate, but meningeal syndrome is weakly expressed. Meningococcal encephalitis is characterized by rapid onset and impetuous cramps, pareses and paralyses. Prognosis is unfavorable. The mortality is high and recovery is incomplete even in modern conditions.

Meningococcemia (meningococcal sepsis). The disease is more impetuous, with symptoms of toxicosis and development of secondary metastatic foci. The onset of the disease is an acute. Body temperature may increase upto 39-41 °C and lasts for 2-3 days. It may be continous, intermittent, hectic, wave-like. It is possible the course of the disease without fever. There is no accordance between degree of increasing of the temperature and severity of the course of the disease.

The other symptoms of intoxication arise simultaneously with fever: headache, decreased appetite or its absence, general weakness, pains in the muscles of the back and limbs. Thirst, dryness in the mouth, pale skin or cyanosis, tachycardia and sometimes dysphnoea are marked. The arterial pressure increases in the

beginning of the disease. Then it decreases. It may be decreased quantity of urine. Diarrhea may be in some patients. It is more typical for children.

Exanthema is more clear, constant and diagnostically valuable sign of meningococcemia (Fig. 12). Dermal rashes appear through 5-15 hours, sometimes on the second day from the onset of the disease. In meningococcal infection rash may be different over character, size of rash's elements and localization. Hemorrhagic rash is more typical (petechias, ecchymosis and purpura).

The elements of the rash have incorrect ("star-like") form, dense, coming out over the level of the skin. Hemorrhagic rash is combined inrarely with roseolous and papulous rash.

The severe development of the rash depends on the character, size and depth of its elements. The deep and extensive hemorrhages may be necrosed. Then it may be formation of deep ulcers. Sometimes deep necrosis is observed on the limbs and also, necrosis of the ear, nose and fingers of the hands and legs. During biopsy meningococci are revealed. Exanthema is leucocytaric-fibrinous thrombosis, contained the agent of meningococcal infection. Thus, in meningococcal infection rash is the secondary metastatic foci of the infection.

Joints occupy the second place over localization of metastases of the agent. At the last years arthrites and polyarthrites are marked rarely (in 5 % of the patient during sporadic morbidity and in 8-13 % of the patient during epidemic outbreaks). The small joints are damaged more frequently. Arthritis is accompanied by painful motions, hyperemia and edema of the skin over joints.

Arthrites appear later then rash (the end of the first week – the beginning of the second week of the disease).

Secondary metastatic foci of the infection may appear rarely in the vascular membrane of the eye, in myocardium, endocardium, lungs and pleura. Similar foci arise very rarely in kidneys, liver, urinary tract, bone marrow.

In the peripheral blood high leukocytosis ($20-40 \times 10^9$ and more), neuthrophillosis with shift of the formula to the left aneosinophyllia, increased ESR are observed. Thrombocytopenia develops inrarely.

There are alterations in urine as during syndrome of "infectious-toxic kidneys". Proteinuria, microhematuria, cylinderuria are marked.

Meningococcal sepsis is combined with meningitis in majority cases. In 4-10 % of the patients meningococcemia may be without damage of the soft cerebral covering. Frequency of meningococcal sepsis is usually higher in the period of epidemic.

Fulminate meningococcemia (acutest meningococcal sepsis, Waterhause-Friedrichsen syndrome). It is the most severe, unfavorable form of meningococcal infection. Its base is infectious-toxic shock. Fulminate sepsis is characterized by acute sudden beginning and impetuous course. Temperature of body rises up to 40-41 °C. It is accompanied by chill. However, hypothermia may be observed through some hours. Hemorrhagic plentiful rash appears at the first hours of the

disease with tendency to confluence and formation large hemorrhages, necroses. A purple-cyanotic spots arise on the skin ("livors mortalis"). The skin is pale, but with a total cyanosis. Patients are anxious and excited. The cramps are observed frequently, especially in children. The recurrent blood vomiting arise inrarely. Also, a diarrhea of blood character may be too. Gradually, a prostration becomes more excessive and it results in a loss of the consciousness.

Heart activity decreases catastrophically. Anuria develops (shock's kidney). Hepatolienalic syndrome is revealed frequently. Meningeal syndrome is inconstant.

In the peripheral blood hyperleukocytosis (till 60 x 10^9/L), neutrophylosis, sharp shift leukocytaric formula to the left, thrombocytopenia, increased ESR (50-70 mm/h) are reveled. The sharp disorders of hemostasis are marked – metabolic acidosis, coagulopathy of consumption, decrease of fibrinolitic activity of the blood and other.

Mixed forms (meningococcemia + meningitis). These forms occur in 25-50 % cases of generalized meningococcal infection. In the last years there is tendency of increase frequency of mixed forms in general structure of the disease, especially in periods of epidemic outbreaks. It is characterized by combination of symptoms of meningococcal sepsis and damage of cerebral membranes.

Chronic meningococcemia. This form of meningococcal infection is rare. The duration of the disease is from some weeks till some years. One case was described with duration of meningococcemia during 25 years. Fever is usually intermittent. The disease is accompanied by polymorphic exudative erythema. The temperature may be normal during period of the remission. Rash becomes pale. It may disappear. The patient's state is improved. In chronic meningococcemia arthritis and polyarthritis are possible. Splenomegaly is revealed inrarely.

In the peripheral blood leukocytosis, neuthrophylosis, increased ESR are marked. There is temperate proteinuria in urine. Endocarditis (pancarditis) were described in chronic meningococcemia. It is possible the development of meningitis after some weeks or month from the onset of the disease.

Rare forms of meningococcal infection (arthritis, polyarthritis, pneumonia, iridocyclitis). These forms are consequence of meningococcemia. Prognosis is favorable in opportune and sufficient therapy.

Complications

Meningococcal arthritis occurs primarily in adults. The overall incidence, as a complication of bacteremia, is about 2 to 10 %. There are two forms of meningococcal arthritis. The first is seen within the first few days of treatment and is characterized by severe arthralgias and few objective signs of joint inflammation. The second, more common form appears to be a hypersensitivity phenomenon. It is usually noted three to seven days after the recognition of meningococcemia, often at a time when the patient appears to be improving from the meningitis or sepsis. The knee, wrist, elbow, and ankle joints are most commonly involved.

Pericarditis, as a complication of meningococcal disease, occurs in 3 to 5 % of cases. It generally occurs in a patient with meningococcemia but has been reported as an isolated event without septicemia or meningitis.

Pericarditis is presumed to be a late complication of meningococcal disease, since clinical symptoms such as fever, dyspnea, or substernal chest pain (or even cardiac tamponade) usually do not appear until the fourth to the seventh day of illness.

Myocarditis was noted at autopsy in 78 % of patients with fatal meningococcal disease. Myocarditis was noted most often in adults, and was more severe than in children.

Numerous other complications include cranial nerve palsies, radiculitis, hemiplegia, seizure disorders, ophthalmic complications, associated herpetic lesions (developing on four or five day of disease), hydrocephalus and arachnoiditis. Orchitis, epididymitis and salpingitis are rare complications.

Diagnosis

The diagnosis of all forms of meningococcal infection is based on the complex of epidemiological and clinical data. The final diagnosis is established with help of the laboratory examination. Separate methods have different diagnostical significance in various clinical forms of meningococcal infections. The diagnosis of meningococcal carrier is possible only by use of bacteriological method. The material for analysis is the mucus from proximal portions of upper respiratory tract. In diagnostics of meningococcal nasopharyngitis epidemiological and bacteriological methods occupy the main place. Clinical differention of meningococcal nasopharyngitis from nasopharyngitis of the other genesis is not possible or very difficult.

In recognition of generalized forms, anamnestic and clinical methods of diagnostics have real diagnostic significance, mainly in case of combination of meningococcemia and meningitis. The examination of cerebrospinal fluid (CSF) has great meaning in diagnostics of meningitis. In lumbar punction cerebrospinal fluid flows out under high pressure and by frequent drops. The cerebrospinal fluid may flow out by rare drops only due to increased viscosity of purulent exudation or partial blockade of liquor's ways. Cerebrospinal fluid is opalescent at the initial stages of the disease. Then it is turbid, purulent, sometimes with greenish shade. Pleocytosis achieves up $10\text{-}30 \times 10^3$ in 1 mcL. Neuthrophils leukocytes predominate in cytogram. Neuthrophilous compose 60-100 % of all cells. In microscopy neuthrophils cover intirely all fields of vision, inrarely. Quantity of protein of cerebrospinal fluid increases (till 0.66-3.0 gm/L). There is positive Nonne-Appelt's reaction. The reaction of Pandy composed (+++). Concentration of glucose and chlorides are usually decreased.

In generalized forms the final diagnosis is confirmed by bacteriological method. In diagnostics immunological methods are used too. Reactions of hemagglutination, latex agglutination are more sensitive.

Differential diagnosis

In meningococcemia the presence of rash requires of differential diagnostics with measles, scarlet fever, rubella, diseases of the blood (thrombocytopenic purpura, Werlgoff's disease, hemorrhagic vasculitis − Sheinlein-Henoch's disease). Sometimes it is necessary to exclude epidemic typhus, grippe, hemorrhagic fevers.

It is necessary to differentiate meningococcal meningitis with extensive group of the diseases:

1. Infectious and noninfectious diseases with meningeal syndrome but without organic damage of central nervous system (meningismus). Meningismus may be in grippe, acute shigellosis, uremia, lobar pneumonia, toxical food-borne infectious, typhoid fever, epidemic typhus, infectious mononucleosis, pielitis, middle otitis.

2. Diseases with organic damage of central nervous system, but without meningitis (brain abscess, tetanus, subarachnoid hemorrhage).

3. Meningitis of other etiology. In purulent meningitides etiological factors may be pneumococci, staphylococci, streptococci, *Bacterium coli*, salmonella, fungi, *Haemophilus influenzae.* In purulent meningitis of nonmeningococcal etiology it is necessary to reveal primary purulent focus (pneumonia, purulent processes on the skin, otitis, sinusitis, osteomyelitis).

Treatment

The therapeutic tactics depends on the clinical forms, severity of the course of the disease, presence of complications, premorbid state. In serious and middle serious course of nasopharyngitis antibacterial remedies are used. Peroral antibiotics oxacillin, ampyox, chloramphenicol, erythromycin are used.

The duration of therapy is 3-5 days and more. Sulfonamides of prolonged action are used in usual dosages. In mild course of nasopharyngitis the prescription of antibiotics and sulfonamides is not obligatory.

In therapy of generalized forms of meningococcal infection the central place is occuped by antibiotics, in which benzylpenicillin stands at the first place. Benzylpenicillin is used in dosage of 200,000-300,000 IU/kg/day. In serious form of meningococcal infection daily dosage may be increased to 500,000 IU/kg/day. Such doses are recommended particularly in meningococcal meningo-encephalitis. In presence of ependimatitis or in signs of consolidation of the puss the dose of penicillin increases to 800,000 IU/kg/day.

In similar circumstances it is necessary to inject sodium salt of penicillin intravenously in dose 2 to 12 million IU per day. Potassium salt of penicillin is not injected intravenously, because it is possible the development of hyperkalemia. Intramuscular dose of penicillin is preserved.

Endolumbar injection of penicillin is not used practically last years. Daily dose is injected to the patient every 3 hours. In some cases interval between injections may be increased up to 4 hours. The duration of the therapy by penicillin is decided individually depending on clinical and laboratory data. The duration of penicicllin therapy is usually 5-8 days.

Recently increase of meningococcus resistant strains is marked (till 5-35 %). Besides that, in some cases the injection of massive doses of penicillin leads to unfavorable consequences and complications (endotoxic shock, hyperkalemia due to using of potassium salt of penicillin, necroses in the places of injections and other). Also, the patients occur with allergy to penicillin and severe reactions in anamnesis. In such cases it is necessary to perform etiotropic therapy with use of other antibiotics. In meningococcal infection semisynthetic penicillins are very effective. These remedies are more dependable and preferable for "start-therapy" of the patients with purulent meningitis till etiological diagnosis determination. In meningococcal infection ampicillin is the best medicine, which is prescribed in dosage 200-300 mg/kg/day intramuscularly every 4 hours.

In the most serious cases the part of ampicillin is given intravenously. Daily dose is increased to 400 mg/kg/day. Oxacillin is used in dose not less than 300 mg/kg/day every 3 hours. Metycyllin is prescribed in dose − 200-300 mg/kg every 4 hours. In meningococcal infection chloramphenicol is highly effective. It is the medicine of the choice in fulminate meningococcemia. It is shown, that endotoxic reactions arise more rarely during treatment of the patients by chloramphenicol than during therapy by penicillin. In cases of meningo-encephalitis chloramphenicol is not prescribed due to its toxic effects on neurons of brain. Chloramphenicol is used in dose 50-100 mg/kg 3-4 times a day. In fulminate meningococcemia it is given intravenously every 4 hours till stabilization of arterial pressure. Then chloramphenicol is injected intramuscularly. The duration of the treatment of the patients by this antibiotic is 6-10 days.

There are satisfactory results of the treatment of meningococcal infection by remedies from the group of tetracycline. Tetracycline is injected in dose 25 mg/kg intramuscularly and intravenously in the cases of resistant agents to the other antibiotics.

Pathogenetic therapy has exceptional significance in therapeutic measures. It is performed simultaneously with etiotropic therapy. The basis of pathogenetic therapy is the struggle with toxicosis. Salt solutions, macromolecular colloid solutions, plasma, albumin are used. Generally 50-40 mL of fluid is injected on 1 kg of body's mass per day in adults under the control of diuresis. Prophylaxis of hyperhydratation of the brain is performed simultaneously. Diuretics (lasix, uregit) are injected. In serious cases glucocorticosteroids are prescribed. Full doses is determined individually. It depends on dynamics of the main symptoms and presence of complications. Generally hydrocortisone is used in dose of 3-7 mg/kg/day, prednisolone − 1-2 mg/kg/day. Oxygen therapy has great significance in the treatment of the patients.

The therapy of fulminate meningococcemia is concluded in the struggle with shock. Adrenaline and adrenomimetics are not used due to possibility of capillary spasm, increased hypoxia of the brain and kidneys and development of acute renal failure. The early hemodialysis is recommended in the case of acute renal failure due to toxicosis.

The basis of the therapy of infectious-toxic shock is complex of measures, including application of antibiotics, improvement of blood circulation. The course of infectious-toxic shock is very serious, with high mortality (50 % of the patient die during the first 48 hours of the disease). Because, it is necessary to prescribe intensive therapy immediately. Antibiotics of wide spectrum of action are prescribed. Steroid hormones have important meaning in the treatment of infectious-toxic shock. Hormones decrease general reaction of the organism on toxin, positively impact on hemodynamics. Treatment by glucocorticoids is conducted during 3-4 days.

Prophylaxis

Prophylactic measures, directed against the sources of meningococcal infection include early revelation of the patients, sanation of meningococcal carriers, isolation and treatment of the patients. Medical observation is provided in the focuses of the infection about contact persons during 10 days.

The measures, directed on the rupture of the mechanism of the transmission of the infection, consist of performance of sanitary and hygienic measures and disinfection. It is necessary to liquidate the congestion, especially in the closed establishments (children's establishments, barracks's and other). The humid cleaning with using of chlorcontaining disinfectants, frequent ventilation, ultra-violet radiation are performed at the lodgings.

 The measures, directional on receptive contingents, include increase nonspecific resistance of the people (tempering, timely treatment of the diseases of respiratory tract, tonsils) and formation of specific protection from meningococcal infection. Active immunization is more perspective with help of meningococcal vaccines. There are several vaccines, for example, polysaccharide vaccines A and C.

Vaccine from meningococcus of the group B was also obtained. However, the group B capsular polysaccharide is not sufficiency immunogenic to produce a reliable antibody response in humans to be effective, several solutions to this problem are being studied, including the chemical alterations of the capsular B antigen to make it more immunogenic and the search for other cell wall antigens that are capable of eliciting bactericidal antibodies against B meningococci with a minimum of serious side effects. New vaccines against meningococcus are under development.

Control questions:
1. Mechanism of contamination by meningococcous.
2. Localization of infectious agent, meningococcous transmition.
3. The generalized forms of disease, their clinical manifestations.
4. Laboratory diagnosis of meningococcal infection.
5. Differential diagnosis of meningococcous meningitis.
6. Principle of medical treatment of meningococcous infection.
7. Principles of steroid therapy in case of Waterhouse-Friderichsen's syndrome.
8. Criteria of patients discharge from hospital.
9. Duration of supervision and rehabilitation of patiens in polyclinic.
10. Preventive measures in the spot of disease outbreak.

DIPHTHERIA

Diphtheria is an acute infectious disease caused by Leffler bacilli, transmitted mainly in an air-drop way and characterized by the symptoms of general intoxication, local inflammation of the mucous membranes mainly with the formation of fibrinogenous fur and typical complications on the part of the nervous system, cardiovascular system and excretory system.

Historic reference

Diphtheria belongs to the most ancient epidemic diseases of mankind. Homer and Hippocrates mentioned this disease. Artemey Kapadokes gives the extremely detailed descriptions of diphtheria under the title of the Egyptian Syrian ulcer about 19 centuries ago. The records of diphtheria were found in the Middle Ages.

The first writer who gave the classic description of diphtheria and mainly its pathologic anatomy basics was Bretonno; he also proposed the term "diphterit" from the Greek word "diphtera" (membrane). Bretonno's student Truss elaborated the doctrine about the specific nature of diphtheria as an infectious disease, he was the first who proposed the word "diphtheria" for the title of the disease, instead of Bretonno's anatomical term "diphterit". Klebs and Leffler, who received clean diphtheria bacilli on blood serum, discovered diphtheria pathogen in 1883-1884. Ru and Yersen received diphtheria toxin and studied its qualities in 1888-1900; Bering and Ru made the discovery of antitoxin in the form of antidiphtheria serum in 1894. The idea of active immunization against diphtheria belongs to Bering.

Klebs discovered the diphtheria pathogen *Corynebacterium diphtherias* in the sections of diphtheria membranes in 1883. In 1884 Leffler extracted it in clean culture and infected a number of animals, among which Guinea pigs turned out to be responsive to the infection.

Etiology

The distinctive quality of the diphtheria microbes is their polymorphism. Gram-positive coloring and the typical location of rods in the form of "bristling fingers" or V-figures. The diphtheria microbes are immobile, they don't produce spores, and do not have capsules or flagellums. They are usually situated one by one, however, in the diphtheric membranes and clean cultures they are often found in the form of assemblage resembling a constitution of felt.

On the Lefler medium the diphtheria microbes yield the best growth (colonies) during 16-20 hours; the growth can be observed even in 6-8-10 hours after sowing.

All aniline paints can tincture diphtheria microbes. They are well tinctured by Neisser's method. The diphtheria pathogens located in membranes do not die

at a temperature of 98 °C within one hour. The clean culture can survive at a temperature of 60 °C only within several minutes. However, at low temperatures, absence of light and moisture the diphtheria microbe is not destroyed for a long time (even below 0 °C); it can tolerate even freezing and thawing. At the same time straight sunlight kills it comparatively fast.

The main biological quality of the diphtheria microbe is its capacity to produce toxin (exotoxin) that causes the pathogenicity of this microbe.

Epidemiology

The source of diphtheria is a person in whom it is manifested in various clinical forms − from serious toxic forms up to the deleted ones and healthy bacteria-carrying. There are infrequent reports on people being infected with diphtheria from animals.

The duration of the microbe vegetation in the organism and the terms of purification mostly stipulate the epidemic danger of the bacteria-carrier as a source of infection; In practice it is difficult to determine the true duration of bacteria discharge because of the absence of precise information about its beginning.

The most epidemically dangerous are the bacteria-carriers who discharge microbes for a long time (up to 1 month and longer), it is more often observed in patients with chronic diseases of the upper respiratory tracts particularly with tonsillitis.

It is known that the diphtheria infection is transmitted in an airdrop way, which is inherent for the majority of respiratory infections. Nevertheless it is necessary to briefly mention some aspects of the transmission mechanism, particularly the pathogen survival rate in the environment. Various enviromental factors can influence the transmission of the diphtheria infection, however, they play a small role and more often have casuistic nature. The leading role in the epidemiology of diphtheria belongs to the drop mechanism of the transmission.

The periodicity and seasonal prevalence of the case rate are characteristic of diphtheria as an infection with a dropping mechanism of transmission. These epidemiological peculiarities were more considerably expressed during the pre-vaccinating time when the periodic growth of the sickness rate was observed every 10 years.

The autumn-winter seasonably is characteristic of diphtheria. In the 20s − 50s the specific prophylactic agents of diphtheria were introduced into the practice of public health services of many countries, it resulted in the considerable decrease of the sickness rate. The diphtheria sickness rate decreased considerably fast in the USA, Canada and most countries of Europe.

Diphtheria used to be one of the major causes of children's mortality a century ago. Even in the 1920s the incidence in the USA and Canada was approximately 150 cases per 100,000 people, but decreased to 10/100,000 in the 1940s. The introduction of immunization resulted in the decrease of the

yearly number of notified cases to single figures in most Western countries, in the USA a total of 1,288 cases were reported during 1971-1981, compared to, only 40 cases in 1980-1993. In England and Wales, there were 800,000 notifications of diphtheria during 1920-1934 with 50,000 deaths. The number of cases decreased from over 40,000 in 1940 to 37 in 1957, and during the period of 1970-1994 only 124 cases were identified. In some countries, including Finland and Sweden, decades passed without any cases after the implementation of diphtheria vaccinations in the 1950s. Reduction in the number of diphtheria cases has also taken place m the developing world, but the cutaneous forms of the *C. diphtheriae* infection especially still remain endemic in several tropical countries.

The factors leading to the start of diphtheria epidemics are poorly understood. The last major epidemic in Europe, before the current one, occurred in the 1940s. In 1943 the annual incidences per 100,000 population were as high as 212 in Germany, 760 in Norway and 622 in the Netherlands. It has been estimated that in 1943 there were 1 million cases and 50,000 deaths due to diphtheria in Europe. Limited epidemics have thereafter been reported both in developing (including China, Tajikistan, Ecuador, Jordan, Lesotho, Sudan, Yemen and Algeria) and industrialized (USA, Sweden, Germany) countries. These epidemics have all been local and relatively small; numbers of cases have varied from a few to a few hundred. The carriage rate of *C. diphtheria* even, in the proximity of the patients, has been low, and no significant spread of the infection has occurred in the general population. Since 1990, a massive epidemic has prevailed in Eastern Europe, mostly in the Russian Federation, Ukraine and their neighboring countries. A smaller epidemic occurred previously in 1983-1985, when the annual number of cases in the Soviet Union exceeded 1,400 − being less than 200 in preceding years. After a few-years of low incidence, rates per 100,000 population started to increase from 0.5 in 1990 to 10.2 in 1993, 26.9 in 1994 and 24.2 in 1995. Especially in large cities, the rates were high (St. Petersburg, 52.5/100,000 and Moscow, 47.1/100,000). In some areas the incidence rate even exceeded 100/100,000. Over 63,000 cases were reported from Russia in 1990-1994. Thereafter, the epidemic started to decline and, in 1996, the incidence was only 9.2/100,000.

Another country suffering badly from the epidemic is Ukraine. The annual number of diphtheria cases remained below 100 until the end of 1980s, but increased rapidly thereafter. The incidence rates increased from 0.1/100,000 in-1989 to 5.7 both in 1993 and in 1994. The total number of cases in Ukraine between 1990 and 1994 was estimated at nearly 9,000. Reflections of the epidemic can also be seen in other countries close to Russia and Ukraine, although the numbers are smaller. In 1994, Belarus reported 230 cases (incidence 2.5/100,000), Estonia 7 (0.4), Latvia 250 (9.6), Lithuania 31 (0.3), and Moldova 372 cases (8.6/100,000). Case fatality rates in this epidemic ranged from 3 % to 21 % in different countries.

Features that might be important in understanding the dynamics of the epidemic and its prevention have been studied. The most important is the high

percentage of adults, 60-77 % of cases. This is, in contrast with the experience from the prevaccination period, when the corresponding figure used to be below 30 %. Certain groups at increased risk were suggested: medical staff, teachers, vendors, transport employees, food handlers, and military personnel.

No significant spread occurred outside the countries of the former Soviet Union. The European Union countries reported only a few cases of diphtheria during the period of this epidemic. In 1990-1996, there were 27 cases in Germany, 33 in the UK, 3 in Belgium, 10 in Finland, 3 in Greece, 4 in Italy, 2 in the Netherlands and 3 in Portugal. 23 of the 85 cases in EU countries could be linked epidemiologically to Eastern Europe. None of the other EU countries reported cases in this period.

Pathogenesis

The diphtheria infection develops only in case of the parenteral entering of poison into the organism.

Implanting in the organism through covering tissues the diphtheria pathogens form local foci of histic damage. More often it happens on the mucous membranes of the stomatopharynx, nasal-courses where the microbes utilize slime as a medium, less often the foci develop on the skin and even less often on the mucous membranes of an eye and vulva-vaginal area. Alongside with classic exotoxin, which is a true lethal factor, the diphtheria microbes in the zone of inoculation produce numerous solvable local-acting factors (hyaluronidase and neuraminidase) damaging the cells and facilitating the diffusion of bacteria and toxins in the tissues.

That is why the damage of almost all tissues is observed in the inoculation zone including the mucous membranes, skin, muscles, and nervous fulcrums. Hyperemia, retardation of the blood flowand sharp rising of the permeability of hysto-hematic barriers promote the formation of exudate which is rich in protein and fibrinous membranes in the damaged tissue area.

At the intranevral injection the diphtheria toxin causes the primary lesion of oligodendrocytes (Shvann cells) and myelin with the subsequent development of the sectional demyelination in area of inoculation.

The local cytopathogenic effect of the toxin is determined by the rate of the poison entering the tissues, by the toxin-aggregating capacity of the cells and the availability of the microbial spreading factors (neuraminidase, hyaluronidase). If poison enters slowly, there appear conditions for the manifestation of its local cytotoxic action in the area of inoculation, but if the toxin concentration in this area increases rapidly, then in a short time the "threshold" dose is accumulated, and in case of its exceeding the poison is reabsorbed in the circulation system and already has a predominantly systemic pathogenic effect.

In the blood the toxin contacts with globulins, and at a greater saturation with albumines. The poison forms complexes with hemolysins and hemagglutinins.

The process of the poison fixation in tissues is not accompanied by any disorders of proteins, carbohydrates and fat metabolism. After the completion of

the latent stage and the development of the characteristic symptoms of toxic diphtheria the patients have only a mild increase of the sugar content in the blood without changing the tolerance to galactose and levulose.

There is noticeable weakening of phosphorylation processes in toxic diphtheria. The changes of oxidative phosphorylation in mitochondrions are not the result of the toxin direct pathogenic action, but the indirect one through the neurohumoral part including the sympaticoadrenal system.

The results of research of the metabolism violations in toxic diphtheria of the humans and animals are the evidence of the absence of specific changes of carbohydrates, proteins and fat metabolism in dynamics of the disease up to the fatal outcome. The nature of these violations is similar to the damages caused by any pathogenic matter with general toxic properties.

Anatomic pathology

Fibrinous inflammation is the pathomorphologic manifestation of the macro- and microorganism interaction in diphtheria. The form of this inflammation directly relates to the constitution of the affected mucous membrane. If the process develops on the mucous membrane covered with the single-layer cylindrical epithelium (for example in the respiratory tracts), croupous inflammation develops; the cover that develops includes a necrotic epithelial layer. The cover is not firmly connected with the underlying tissue and can be easily separated from it. If the process develops on the mucous membranes covered with a multilayer flat epithelium (lumen of fauces, pharynx), it is not only the epithelial layer that necropsies, but partially the joint tissue basis of the mucous membrane (tunica propria mucosae). A thick fibrinous cover develops, it can be hardly removed from the underlying tissues. It is diphtheria inflammation.

The regional lymph nodes get involved in the process: they are enlarged owing to the expressed plethora, edema and the proliferation of the cell-like predominantly reticuloendothelial elements. Local necroses develop in them. In the toxic form of diphtheria develops the edema of the fauces mucous membrane, pharynx, and also the edema of cervical fat in the immediate proximity of the affected regional lymph nodes. In the basis of this edema there is a serous inflammation in the form of numerous cell-like infiltrates.

The diphtheria intoxication is characterized by the affection of the nervous system (mainly the peripheral nerves of the sympathetic ganglions), cardio-vascular system, paranephroses and nephroses.

The changes of the peripheral nerves are manifested by multiple toxic parenchymatous neuritis, in diphtheric polyneuritis the process can spread on the intraganglion fibers of intervertebral nodes and their cranial homologues.

The cardiovascular system is considerably affected in the diphtheria intoxication. The vessels affection is mainly manifested in their paretic dilatation with the symptoms of stagnation which can transform into stasis. The deep

degenerative changes are observed on the part of myocardium. The changes of myocardium in the hearts of children who died on the 3-5-th day of the third degree toxic diphtheria or hemorrhagic diphtheria were manifested only in expressed plethora, an edema of the intermuscular tissue with frequent hemorrhages: the fibrinous degeneration of the vessels walls was constantly observed.

The typical picture of diphtheria myocarditis (hyperemia, hemorrhage, the cell-like infiltration) was observed in children who died during the 2-3rd week of the disease. As a rule, the conductive system of the heart is also affected. The simultaneous affection of the cardiac muscle, nervous system (sympathetic system), which enervates the vessels and stipulates their tone, the violation of the paranephros function results in cardiovascular weakness, which is so characteristic of the serious forms of diphtheria. Depending on these lesion combinations, the phenomena of either cardiac or vascular weakness can dominate. The degenerative processes in epithelia of canaliculi develop in the kidneys, it looks like nephrosis.

Clinical manifestations

The incubation period, as in the other forms of diphtheria, lasts from 3 to 10 days. The disease has either an acute, sudden, or step-by-step oncoming with hardly noticeable symptoms, in the first case the temperature immediately rises up to 38-39 °C, there is a headache, malaise. In the second case a child develops poor appetite, flaccidity, slight temperature rise (37.5-38 °C) during several days. Quite often even senior children do not complain of a sore throat or the pain is insignificant, and if the doctor is not in the habit of examining a throat in each patient with a fever, diphtheria in such cases is not revealed by the parents and the doctor as well. If the patient is examined during the first day of the disease it is possible to notice a slight pulse acceleration, which correlates with the temperature; the cervical glands are usually slightly enlarged on one side, painful at pressing. The tongue is furred, the tonsils are swollen either both or mostly, one of them, turn red, but the erythema is strictly localized and does not spread on the uvula and soft palate as in scarlatina. It is possible to discover fur on the reddened tonsil, during the first hours of the disease it looks like a mild combustion of the mucous membrane or a heavy-bodied web grid; it is possible even to remove it by a cotton plug but a new one appears on its place extremely fast, and it cannot be removed any more. By the end of the first day or by the beginning of the second day the fur gets a characteristic diphtheria cover properties: it is dirty-gray or yellowish, rather thick, rises above the mucous membrane surface, it cannot be removed without bleeding; plenty of fibrin and diphtheria bacilli can be discovered under the microscope in it. The manifestations of the general intoxication remain insignificant: a headache, malaise, poor appetite. The borders of the heart are normal and the tones are clean. The pulse is accelerated; the blood pressure is in the normal range or slightly heightened. The liver and spleen are not changed; the urine does not contain protein. There is moderate leukocytosis (10,000-12,000) and neuthrophylia

in the blood. The following course of the disease can be diverse. Nowadays, when the serum treatment is widely applied, the natural course of diphtheria can be observed very seldom. Therefore, it is necessary to distinguish the diphtheria course during serum treatment and without it.

If serum is injected, sometimes within the first day there is no essential change in the patient's condition: the temperature remains elevated, the general condition is also abnormal, fur can even increase. But as a rule, there is a sharp improvement in 24 hours: the temperature critically drops, sometimes down to normal, the child becomes vigorous and cheerful, the appetite improves, the cervical glands-get smaller, the fur changes its appearance: it becomes more porous, it looks as if it is uplifted above the mucous membrane, there is a girdle of sharply expressed erythema on the edges, the diffusion of the fur, is intercepted. Within the following day and night the considerable part of the fur disappears, in 2-3 days the fauces completely refine, and the child recovers. If serum is injected in time, the consequences of the intoxication (paralyses, heart weakness) don't usually develop.

There are also cases when the temperature drops on the 3-5th day and the fur also disappears rather fast without any serum treatment. But such cases are an exception. In most cases the disease progresses, the fur covers both tonsils, it can spread to the uvula and aerofoil; the cervical glands are enlarged, painful, but there is no edema of the cervical cellular tissue and fauces. There are sometimes traces of protein in urine. The temperature is of the remittent (febris remittens) or improper type and lasts during 7-12 days. The fur disappears slowly without any ulcerations or detects of the mucous membrane. The disease ends on the 7-15th day; the isolated paralyses (paralysis of the soft palate) and unexpressed cardiac disorders are sometimes observed.

In the eases when the disease is not treated with serum, it is impossible to be sure in the complete recovery of the patient even if the process stops and the fur disappears. The fur sometimes appears again and can spread to the nasopharynx and nasal cavity or the process goes downwards to the larynx.

Diphtheria of the fauces and diphtheria of the nose.

The transfer of the process from the tonsils to the nasal cavity is implemented either directly or skipping the soft palate and pharynx, the process affects the nasopharynx and rear parts of the nose. Such transfer is usually observed not earlier than on the 3-5th day of the disease and is accompanied by a new temperature rise and deterioration of the general condition, and there are characteristic symptoms indicating the affection of the nasopharynxes and nasal cavity. The voice becomes nasal, the mouth is open, the tongue is dry and coated with peels, a slimy at first and then sanious discharge comes out of the nose, and frets the skin 'around the nostrils and on the lips. An abundant purulent discharge can also be seen on the rear wall of the pharynx. Not only the submandibular lymphatic glands, but also the lymphatic glands situated around m. sterno-cleido-mastoideus swell up a little on-the neck. If the process has gone far and has

affected the forefronts of the nose, it is possible to see the covers without any instruments having cleared the nose entrance from purulent discharge and peels. The spreading of diphtheria on the nose worsens the prediction, as sometimes an edema of the cervical cellular and the symptoms of general intoxication accompany it, i.e. the widespread diphtheria changes into toxic one. In other cases the process can proceed to the nasal sinuses and middle ear. Clinically this transfer can remain unnoticed or corresponding symptoms may appear (edema of blepharous and the back of the nose, discharge form the ears). Whether this transfer is caused by the diphtheria infection itself or a mixed infection plays some role (streptococcus, pneumococcus), — it is not always possible to find out (the information on primary diphtheria of the nose can be found below).

Diphtheria of the fauces and diphtheria of the mouth.

If the process spreads to the oral cavity, dirty-gray densely sitting covers develop on the palate (Fig. 13), on the mucous membrane of the lips and cheeks, and also on the tongue. The bacteriological research discovers Leffler's bacilli in the covers.

The clinical symptoms: abundant salivation, smell from the mouth, painful mastication and swallowing, large swelling of submandibular glands. The covers disappear slowly leaving the ulcers that do not heal for a long time.

The diphtheric affection of the larynx and respiratory tracts is known under the name of a croup.

Croup (true, diphtheric) can be secondary, if it develops after the affection of the fauces or the nose, and primary — at the primary localization of the diphtheria process in the larynx.

The course of croup can be divided into three stages.

1. A croup cough stage. The first symptom indicating the starting affection of the larynxes is sharp loud cough, which becomes rasping, barking very soon. Senior children complain of the sense of smart and pressure in the larynx; the palpation of the larynx appears to be painful. At the same time the voice becomes hoarse, unclean, and then completely silent (aphonia). At the examination with a laryngeal mirror it is often possible to see an edema and hyperemia of the epiglottis, and often there are no covers at this stage. This period lasts 1-2-3 days and develops into a second stage.

2. A stenosis stage. The respiration becomes labored, unclean; at each inspiration the sawing or whistling sound is audible. This sound is weak at the beginning and audible only during exaltation and the child's cry, then it becomes sharp, constant and is audible from the distance. Another symptom is the larynx narrowing — retraction of compliant, weaker places of the thoraces. As the insufficient amount of air enters the lungs through the narrowed glottis, the intrapulmonic pressure becomes lower than the atmospheric one and under its influence- the compliant places of the thoraces — the supraclavicular and bulbar-fossas; intercostal spaces, anticardium — are more or less sharply retracted at

each inhalation. At first a child is quiet, satisfactorily manages the air deficiency. Then the oxygen deficiency develops – the child becomes restless, rushes in bed, jumps up, grasps the handles of the bed, wants to be held in his mother's arms, showers his head to the back. The auxiliary muscles start to work – intercostal, mm. sterno-cleido-mastoidei, mm. scaleni. The sterno-clavicular muscle appears to be noticeably tight at the palpation during an inhalation. When the child is in such a condition, injecting the serum and providing the adequate treatment (an operation and other treatment measures; (see treatment of croup below) can save him. If the disease has its natural course, the condition improves and the stenosis easies in the extremely infrequent cases when the cover disappears; in most cases the disease reaches its last stage.

3. An asphyxia stage. In the struggle with stenosis the child exhausts, the respiratory muscles get tired. The child becomes calm, sleepy, he inditfferently lies in bed. The respiration is accelerated, but it is superficial, the retractions are already not so visible. The lips, tip of the nose and nails become blue, the face turns pale, sweat quite often appears on the forehead. The extremities are cold, the pulse is very rapid, thready, sometimes paradoxical (abasement of the pulse wave during the inhalation). From time to time there are attacks of acute dyspnea – the child jumps up, rushes because of air-deficiency, the eyes express fright, the face becomes cyanotic; sometimes such attacks result in the immediate death; in other cases the child dies after a more or less continuous agony with the symptoms of exhaustion of respiratory and circulation centers.

Toxic diphtheria.

The typical form sometimes develops on the 3-5th day of the disease from the localized form when the process affects the nasopharynx and oral cavity, more often it develops as it is from the very beginning. In this case the disease has an acute oncoming, which is more rapid than in localized diphtheria. The temperature immediately rises up to 39-40 °C, there is a headache, repeated vomiting, sometimes abdominal pains. Senior children complain of a pain at swallowing. The pulse is rapid: 140-160 beats per minute, the face is pale, there is malaise, sleeplessness, sometimes exaltation. The submandibular glands are enlarged, painful; it is possible to see a quaggy pasty edema of the cellular under the low jaw angle, usually on one side; sometimes an edema develops only on the second day.

At the mouth examination you can see that the tongue is dry and furry, the fauces are dark-red and hydropic; there is usually dirty-gray fur on one tonsil, it cannot be removed by a cotton plug. This fur affects the entire tonsil, passes to the uvula, sometimes to the soft palate extremely fast, within several hours. On the second or third day the disease is in full swing, and it is not difficult to clinically diagnose toxic diphtheria. The temperature remains high: 39-40 °C. The face is pale, pathy. There is sanious fluid discharge from the nose, it frets the skin. The mouth is open, the lips are dry and cracked; the smell can sometimes be sensed even from the distance. The respiration is hoarse, the voice is muffled, with a strong nasal tone. The

glands are enlarged even more, but it is more difficult to palpate them because the edema of the fat cellular takes a considerable part of the neck (Fig. 13). The glands are not so tight because of the edema of the cellular, as compared with scarlatina. Thick, dirty-gray covers are not only on the tonsils and uvula, but also on the mild and firm palate; the edema of the whole fauces is considerably expressed; the uvula is especially edemic and enlarged; it is squeezed and strangulated by the enlarged tonsils, sometimes it is twisted backwards, so that the back wall of the pharynx is not visible. As a result of such swelling of the fauces the respiration becomes labored, stenotic (stenosis of the pharynx). The swallowing is extremely painful, and the feeding of the patient becomes difficult. Simultaneously with worsening of the local process the phenomena of the general intoxication also increase: the pulse is rapid and weak, the heart sounds are dummy, the blood pressure is low; there is protein in urine, sometimes cylinders; general malaise is considerably expressed. There is considerable leukocytosis in the blood (up to 15-20 thousands) and neutrophilia.

Complications

The most frequent diphtheria complication for adults is myocarditis. The affection of the heart is especially typical for the toxic forms of the disease.

The severe form of myocarditis develops only in the patients with toxic diphtheria (except subtoxic) at overdue (after the 5th day of the disease) specific treatment and is always accompanied by complications on the side of the kidneys and nervous system.

The complications caused by the affection of the nervous system are observed less frequently. In the mild forms of diphtheria (localized, wide-spread) the adults develop only the soft palate paresis − mononeuritis, which has an easy short-term course (no more than 10-14 days), characterized by a snuffling voice and chokes while eating liquid food. In more than 1/3 cases toxic diphtheria is complicated by polyneuritis in various combinations and polyradiculoneuritis. Among the cranial nerves the IX, X, III, VII, XII pairs are affected more often, it results in paresis or paralyses of the soft palate, pharynx, tongue, accommodation paresis and mimicry affection.

The severe forms of polyradiculoneuritis develop only in patients with concomitant alcoholism, they are characterized by deep wide-spread paralyses of the extremities, body, neck, respiratory muscles in combination with the affection of the cranial nerves, resulting not only in the long-lived disorders of the working capacity, but also in lethal outcomes, even in subtoxic diphtheria.

One or two-sided focal pneumonia quite often develops at the early stage of the disease in toxic diphtheria.

Diagnosis

The modern microbiologic diagnosis of diphtheria is based on the clean culture isolation and identification of the pathogen by the cultural-morphological, biochemical and toxicogenic properties. Thus, it is necessary to strictly observe

a number of conditions. The slime from the stomatopharynx and nose as well as the secret from other areas of the pathological process localization are collected by separate wads before eating or after it but not earlier than in 2 hours, and also before gargling and other kinds of treatment (drops, ointments, wads).

Taking the material for research correctly is of great importance. In the stomatopharynx slime is taken from the tonsils, palatal aerofoils, uvula and trailing wall of the pharynx by rotary movements of a wad obligatory with the help of a glass spreading rod, not touching the mucous membrane of the cheeks and tongue. If there is fur of fibrinous nature, the material should be taken both from the affected tissues and the healthy tissues adjacent to them. A small part of the removed coat, which is carefully ground between glasses, or a smear taken by a separate wad are sent to the laboratory for the direct bacterioscopic investigation. The scooping of the material from the nose should be done after the careful preliminary purification of it from the slime by a dry cotton plug or after blowing the nose.

Though the streamlining of some stages of the bacteriological research accelerates the terms of carrying out an analysis to some extent, they all remain rather prolonged and do not guarantee the early diagnostics of diphtheria.

Serological, immune-chemical and the immunological methods play a more and more relevant role in the diagnostics and epidemiological evaluation of the disease. On their basis are designed the accelerated methods of discovering diphtheria toxin in clean and blended cultures in case of growing them in liquid mediums and other substrates.

The serological tests are applied to study collective immunodeficiency. RDGA is the most accessible, simple and quite informative.

Differential diagnosis

The diagnosis of diphtheria of any localization is quite difficult, as it is similar to many diseases of the infectious and non-infectious origin. The number of diagnostic mistakes increased in the period of diphtheria elimination, at a sporadic case rate, as the vigilance towards this infection vanished. The mistakes are the most frequent in diagnosing diphtheria of the stomatopharynx — the most widely spread form of the disease.

The localized form of diphtheria of the stomatopharynx is the most difficult for the clinical diagnostics. The disease should be suspected if there is dense and nitidous fur situated on the domed surface of the tonsils, their swelling, which corresponds to the area of the fur, limited hyperemia of the mucous membrane in the form of a thin rim with a cyanotic shade. The diffuse bright hyperemia, which affects all the departments of the stomatopharynx, is not characteristic of localized diphtheria. The absence of the tonsils edema in case of vast fur on them testities against diphtheria. While observing the patients it is possible to notice other symptoms, which help to diagnose the case. So, such symptoms as a short-living (1-3 days) fever, the absence of pain at swallowing in 2-3 days with the remaining fur are characteristic of localized diphtheria of the stomatopharynx.

It is necessary to remember that in the patients suffering from chronic tonsillitis the symptoms of diphtheria may be distorted. In such patients the fever remains long, the fur is situated in the hypertrophied tonsils lacunas, and the hyperemia of the mucous membrane is of a diffuse nature. If there are no convincing symptoms of angina in the patient who is in the diphtheria focus, it is necessary to diagnose diphtheria even if there is no bacteriological confirmation of the diagnosis.

In comparison with other diseases, localized diphtheria of the stomatopharynxes should be differentiated from follicular and lacunar angina of the streptococcal and staphylococcal etiology more frequently. The considerable intoxication (malaise, weakness, joint aches, headache) is characteristic of these diseases even if there is slight fur on the tonsils. The fur that is located on the lacunas and has a quaggy, viscid consistence, yellow or virescent color is different too. The fur is localized or solid, usually dull and can be easily removed by a glass spreading rod. The hyperemia of the mucous membrane is more often bright and diffuse. The appearance of the patient is also different: palenesses characteristic of diphtheria, but feverish blush, shine in the eyes, brightness and dryness of the lips are characteristic of angina.

Ulcerus-necrotic angina of Simanovsky-Vincent's is quite often taken for diphtheria and vice versa. The peculiarity of this angina is the absence or minor expressiveness of intoxication. The temperature is subfebrile or normal, the pain at swallowing is slight. As a rule, the process is one-sided. On the tonsil develops the ulceration in the shape of a crater, coated by clotted fur of the virescent color. The areas of necrosis can also be found on the palatal airfoil, uvula or soft palate.

The angina form of tularemia looks like diphtheria by the form of the fur on the tonsils, but it differs by a rather late development (on the 3-5th day), absence of an edema of the tonsil, the ulcer-necrotic-nature of a lesion (the fur not only rises above the level of the healthy tissue, but is also located below it), a considerable increase of the regional lymph nodes that continue enlarging after the disappearance of tonsillitis.

Necrotic angina in scarlatina can be considered to be diphtheria owing to the vastness of the lesion areas and dense fur cohesion with die tonsils surface. However, in this case the affected areas of the tonsils do not rise above the level of the healthy tissue, the edema of the mucous membrane is insignificant, the hyperemia is extremely bright and at the same time has a distinct border. It is also necessary to take into consideration the patient's appearance: bright hyperemia of the cheeks and paleness of the nosolabial triangle. The development of the small-dot rash in the typical places for scarlatina solves the problem of the diagnosis.

Widespread diphtheria of the stomatopharynx is diagnosed easier than localized one: the spreading of the fur from the tonsils on the adjacent parts of the stomatopharynx − palatal aerofoils, uvula − indicates that the process is not ordinary. The edema of the mucous membrane testifies in favor of diphtheria. While diagnosing widespread diphtheria, it is necessary to be convinced of the absence of the hypodermic cellular edema of the neck not to fail to diagnose toxic diphtheria.

Toxic diphtheria of the stomatopharynx is characterized by in especially bright clinical picture, nevertheless, the greatest number of mistakes is made in both children and adults in this case. Apparently, the main cause of it lies in the fact that toxic diphtheria is a comparatively rare disease and the doctor lacks personal observations, which could help him to diagnose the disease. The main symptoms of the early period of toxic diphtheria are edema of the neck — hypodermic, cellular, edema of the stomatopharynx mucous membrane and widespread fur on it.

Contagious mononucleosis should sometimes be differentiated from toxic diphtheria. The resemblance is explained by the fur on the tonsils that has irregular depth irregular consistence of the neck hypodermic cellular above the enlarged lymph nodes. In contrast to toxic diphtheria contagious mononucleosis develops step-by-step, the quaggy fur on the tonsils occurs not earlier than on the 3-4th day, it can be rather easily removed by a glass spreading rod and is triturated. A long-lived fever, polyadenitis with primary enlargement of the posterior neck lymph nodes, hepatolienal set of symptoms and characteristic pattern of the peripheral blood, in which one the uninuclear cells dominates, — testify in favor of contagious mononucleosis.

Treatment

Hospitalization of patients is obligatory. In case of a toxic diphtheria patients transport only laying. The severe confinement bed regime is necessary during 20-25 days, then at absence of complications the patient allow to sit and gradually dilate impellent regime. At mild forms (localized diphtheria of pharynx, diphtheria of nose) duration of confinement bed regime is reduced up to 5-7 days. In the acute period of disease fluid and semifluid nutrition is necessary. Treatment may be specific and pathogenic.

Specific treatment will carry out by high purified horse hyper immune serum. For prevention of anaphylactic reactions infuse serum by Bezredko method. First of all 0.1 mL diluted 1 : 100 of serum infuse intracutaneous of forearm. If after 20-30 min on a place of injection there are not changes or the papule in diameter is not more than 0.9 cm, — reaction is negative, and infuse 1 mL of undiluted serum sub dermal, and at absence of reaction — after 30 min all prescript dose in muscle.

At toxic diphtheria II-III stage and the hyper toxic form a serotherapy is carried out necessarily, under protection of hormonal preparations, and sometimes — narcosis. In case of positive intradermal assay or at presence of anaphylactic reactions further subdermal infusion of serum only behind unconditional indications. Serum in dilution 1: 100 is infused in a sub dermal fat of brachium in doses 0.5, 2, 5 mL consecutive with intervals 20 min. At absence of reaction to previous dose infuse 0.1 mL of undiluted serum subcutaneously. If reaction is not present, through 30 min infuse all prescribed dose subcutaneously. In unusual cases serum is infused under narcosis.

Antitoxic serum neutralizes only a toxin, which circulates in a blood, and does not influence on fixed in tissues. Therefore specific treatment may be carried out as soon as possible (optimum in 1 − 3 rd day of disease).

The form of diphtheria determines doses of serum for the first introduction and course of treatment.

At late (after 2nd day of disease) beginning of treatment of patients with the widespread or toxic form the first dose of serum should be increased. The form of disease also determines frequency rate of infusion of serum. In case of localized diphtheria of a throat, nose, rare localization of process and early serotherapy is possible to be limited by disposable infusion of serum. If diphtheria of throat is widespread, infuse serum during 2-3 days (at the toxic form − through every 12 hours). The first dose makes $1/3 − 1/2$ course; in first two days patient may receive $3/4$ of course doses.

Serum dose depends on toxicosis stage, process spread and lesions localization; it fluctuates in limits of 5 through 500,000 units,

Usually the course of serotherapy lasts no more than 3-4 days. Indications for stopping of serotherapy are disappearance or decreasing of spot, edema of pharynx and hypodermic fat of the neck, at croup − complete disappearance or decrease of stenotic respiration. At suspicion on toxic diphtheria serum should be infused immediately; at localized form − it's possible waiting for results of bacterioscopy, otolaryngology examination etc., but under condition of constant surveillance in hospital; on diphtheritic croup − infusion of serum is obligatory if this diagnosis is not refused after carrying out of intensive cure during 1-1.5 hours.

In order to intensify action of serum, infusion of 25 % solution of magnesium sulfates intramuscularly once a day right after beginning of serotherapy is recommended.

Pathogenetic treatment is directed on desintoxication, restoration of hemodynamic and elimination of adrenal gland insufficiency. Desintoxication therapy provides intravenous infusion of 10 % solution of glucose with insulin, albuminous preparations and colloid solutions in the ratio 1:1. A liquid is infused at the rate of 20-30 mL/kg of mass. Diuretic agents, are indicated under the control of arterial pressure and diuresis.

For improvement of tissue metabolisms cocarboxylase, acidum ascorbinicum, a nicotinic acid, ATP are indicated. The nicotinic acid decreases also an influence of diphtheritic toxin, and ascorbic − stimulates imunogenesis and function of cortex of the adrenal glands.

Prednisolonu m (2-3 mg/kg) or hidrocortizonum (5-10 mg/kg per day) are prescribed to the patient with widespread and toxic forms of diphtheria with the purpose of replaceable, anti-inflammatory and hyposensibilisative treatment for 5-6 days. In the first 2-3 days glucocorticoides are infused in vein, then per os. In case of hypertoxic and hemoragic forms the daily dose of prednisolonum is enlarged up to 5-20 mg/kg according to stage of shock.

At toxic form of diphteria, since the first day there is indicated 0,1 % solution of strychninum of sodium nitritum (0.5-1.5 mL subcutaneously) during 2-3 weeks and more. Strychninum stimulates tone of the central nervous system, stimulates respiratory and vasomotor centers, tones up sceletal muscles and a myocardium, stimulates oxidant-recreated processes in myocardium. Use of cordiaminum, corazolum raise a tone of organs of circulation. At cases of DIC for desagrigation, except reopolyglucini, indicate antihistamines, vasodilators, trentalum, ksantinol. For reception of anticoagulative effect infuse heparin (150-400 U/kg per day). Inhibitors of proteases are recommended.

Antibacterial therapy is prescribed with the purpose to eliminate *Corynebacteria diphtheria* and secondary flora. It is expedient to apply benzylpenicilini, tetracyclinums, cefalosporines, erythromicini.

Treatment of patients with diphtheria of larynx. Patogenic treatment is indicated: sibazonum (seduxenum). Oxygen therapy is provided. In case of a stenosis of larynx without respiratory failure the good effect gives a warm soda drink, sinapismuses. Hyposensibilisative preparations (dimedrolum, pipolfeni, tavegili) are used to decrease the edema of mucous, locally antiedema and anti-inflammative therapy in aerosols (inhalations) is prescribed.

Complex treatment provides also indication of glucocorticosteroides, in particular prednisolonum (2-3 mg/kg per day), which, except for anti-inflammatory action, assist decrease of edema of larynx, reduce a permeability of wall of capillaries and exudation. Half of daily dose is infused intravenous or in muscle, the rest is given per os. After prescriptions desintoxicative therapy will carry out. Antibiotics of wide spectrum action are prescribed. If conservative treatment is not effective, operative measures are used.

Triad of signs is the indication to initial intubation (tracheostoma):

a) Paradoxical pulse (inspiratory asystolia of Raufus); b) sign of Baie: continuous contraction of sternocleidomastoideus muscles during inspiration; c) proof cianosis of labiums and face. In case of a localized croup – long nasotracheal intubation, at a wide-spread descending croup tracheostomy with the following drainage of trachea and bronchuses are indicated.

Treatment of complications. At myocarditis optimum duration of the bed period regime is near 3-4 weeks. There are indicated strychninum (a long course); solution of glucose with cocarboxylase, acidum ascorbinicum, ATP, calcium pangamatis, agents which influence on tissue metabolism (a methandrostenolone, a potassium orotatis). At serious and medium myocarditis prednisolonum per os and parenteraly (in a daily dose 40-60 mg) is recommended. Introduction of cardiac glicosodes is supposed only at manifests of heart insufficiency without disorders of contraction. Anticoagulants of indirect action are prescribed for prophylaxis of tromboembolitic complications (dicumarinum, neodicoumarin, pelentanum).

The patient with diphtheric polyneuritis should be treated with strychninum, vitamins of group B, glucocorticosteroides. In the recreating period an oxazili

inside during 15-20 days, massage, medical gymnastics (cautiously), diathermy, galvanization, quartz are prescribed.

In case of respiratory muscles disorders antibiotics of wide spectrum of action are used in the maximal doses for prophylaxis of pneumonia. Patient can be transfer on apparatus respiration in conditions of departament of reanimation after indications. Proceeding from action of diphtheritic toxin as inhibitor of acetylcholinesterase, proserini at neurologic complications is indicated after fading acute displays of disease.

Treatment of toxygenic corinebacterias diphtherias carriers. At repeated allocation of bacteria − antibiotics of tetracycline lines, rifampicini are recommended. After a seven-days course usually there comes sanitation. The basic attention should be payed to chronic disease of nasopharynx. Treatment begins with fortifying (methyluracilum, pentoxylum, aloe, vitamins) and hyposensibilisative agents with physiotherapy (ultraviolet radiation, ultrasound).

Duration of hospitalisation is determined by gravity of diphtheria and character of complications. If complications are not present, patients with the localized form may be discharged from the hospital at 12 − 14th day of disease, with spread form at − 20 − 25th (bed regime − 14 days). Patients with subtoxic and toxic forms should be on bed regime 25-30 days; they may be discharged at 30 − 40th day of disease. In case of a toxic II − III degree diphtheria and serious course of disease the regime lasts 4-6 weeks and more. The obligatory condition for patient's leaving the hospital with any form of a diphtheria is negative result of two control inoculations received with an interval of 2 days.

Prophylaxis

The major manifestations of diphtheria can be prevented in individual patients by immunization with formalin-inactivated toxin. Therefore, documentation of inadequate levels of antitoxin in large proportion of the adult population in North America and Western Europe has caused great concern that a toxigenic strain introduced into these populations could cause a major outbreak of disease. Serum antitoxin levels can be measured by toxin neutralization tests in rabbit skin, in Vero cell culture, or by hemagglutination, with roughly equivalent results. Concentrations of 0.1 − 0.01 (international units) generally are thought to confer protection. For example, data from a recent outbreak showed that 90 % of clinical cases had antitoxin levels below 0.01 IU/mL, whereas 92 % of asymptomatic carriers had liters above 0.1 IU/mL. Following immunization, antitoxin levels decline slowly over time so that as many as 50 % of individuals over age 60 have serum liters below 0.01 lU/mL. For this reason, booster doses of toxoid should be administered at 10-year intervals, to maintain antitoxin levels in the protective range.

Recommendations from the Immunization Practices Advisory Committee in 1991 are as follows.

For children from 6 weeks to 7 years of age: three 0.5-mL intramuscular injections of (DPT) vaccine should be given at 4-8-week intervals, beginning at 6-8 weeks of age, followed by a fourth dose 6-12 months after the third.

For persons of 7 years or more: 0.5 mL Td (toxoid—adult) is given twice at a 4-8-week interval, with a third dose 6-12 months later. Because the pertussis component of DPT is responsible for most of its side effects, and the risk of pertussis is much less after age 6, that component of the vaccine is omitted. Moreover, because subjects over age 7 have a higher incidence of local and systemic reactions to the concentration of diphtheria toxoid in pediatric DPT vaccine (7-25 limit flocculation [Lf] units) and because a lower dose of toxoid has been shown to induce protective levels of antitoxin, the Td formulation of vaccine contains a maximum concentration of 2 Lf units of diphtheria toxoid. If the recommended sequence of primary immunizations is interrupted, normal levels of immunity can be achieved simply by administering the remaining doses without need to restart the series.

Booster immunizations: children who have completed their primary immunization before age 4 should receive a booster dose of DPT at the time of school entry. Persons above 7 years of age should receive booster immunization with Td at 10-year intervals. As a help to memory, this should be done at decade or mid-decade intervals (e.g., ages 15, 25, 35, etc., or 20, 30, 40, etc.). Travelers to areas where diphtheria is still endemic should be particularly careful to be sure their immunization is current. Although the recommended booster dose of 1.5-2.0 Lf units will increase antitoxin levels to above 0.01 IU in 90-100 % of previously immunized individuals, some authorities have recommended using 5 Lf units, because antitoxin levels remain above 0.01 lU/mL for a longer period than with 2 Lf units.

Patients should receive toxoid immunization in the convalescent stage of their disease because clinical infection does not always induce adequate levels of antitoxin. Close contacts whose immunization status is incomplete or unclear should promptly receive a dose of toxoid appropriate for their age, and complete the proper series of immunizations. In addition, they should receive prophylactic treatment with erythromycin or penicillin, pending the results of pretreatment cultures. Given these preventive measures, the prophylactic use of antitoxin is considered unwarranted.

Control questions:

1. Source of infection and mechanism of diphtheria transmission.
2. Pathogenesis of disease and pathomorphologic changes.
3. Classification of clinical forms of diphtheria.
4. Clinical features of certain disease forms.
5. Clinic of the urgent states at diphtheria.
6. Complication of diphtheria.
7. Laboratory diagnosis of diphtheria.
8. Differential diagnosis of diphtheria.
9. Specific, etiotropic, pathogenetic and symptomatic treatment of patients with diphtheria.
10. Medical aid in case of croup, hypertoxic forms of diphtheria.
11. Principles of discharge of patient from hospital.
12. Prophylaxis and preventive measures in spot of infection outbreak.

RICKETTSIOSIS

Rickettsioses are group of acute infectious diseases caused by especial organisms − *Rickettsia* and transmitted by insects.

Rickettsioses of human are divided into five groups.

1. Typhus group − epidemic typhus (Louse-Borne typhus), Brill-Zinsser disease and the endemic typhus (Murine typhus).

2. Spotted fever group − Rocky Mountain spotted fever, Boutonneuse (Marseilles fever), North-Asian tick-borne typhus, Queensland tick typhus, rickettsialpox.

3. Tsutsugamushi group − scrub typhus.

4. Q-fever group.

5. The group of the paroxysmal rickettsioses − trench fever (volynian fever).

EPIDEMIC TYPHUS FEVER

Synonyms − jail fever, ship fever, putrid fever, petechial fever, typhus exanthematicus.

Epidemic typhus fever is an acute infections disease caused by *Rickettsia prowazekii*. Epidemic typhus fever is characterized by development of generalized thrombovasculitis, meningoencephalitis, severe common intoxication, by appearance of rash, enlargened liver and spleen. It is transmitted by the lice, *Pediculus humanus*.

Historic reference

Epidemic typhus fever has been one of the great epidemic diseases of the world. Its history belongs to the dark pages of the world's story, at times when war, famine and misery of every kind are present.

The disease was first described with sufficient accuracy by Fracastoro, in the 16th century, to enable us distinctly to differentiate it from plaque; the stuporous states of the two disease having previously caused them to be confounded.

Epidemics of typhus have very frequently been associated with war. In fact, severe epidemics have occurred during practically every great war in Europe with the exception of the Franco-Prussion war in 1870. In the World War, the epidemic which raged in Serbia in 1915 was one of the most severe which has occurred in modern times. It was characterized not only by its high virulence and high mortality. During the epidemia the number of new fever cases entering the military hospitals alone, reached as high as 2,500 per day, and the number of reported cases among the civilian population was approximately three times was this number. The mortality during the epidemic varied during the epidemic at

different periods in different localities between 30 and 60 %, and in complicated cases sometimes reached 70 %. Over 150,000 deaths occurred within 6 months, before the epidemic could be suppressed. An astonishing 30 million cases occurred in Russia and Eastern Europe during 1918-1922, with an estimated 3 million deaths. During World War II, typhus struck heavily in concentration camps in Eastern Europe and in North Africa.

In the present time this disease may be occurs in Africa (Burundi, Ethiopia), in the Central America (Mexico, Peru).

Etiology

The etiologic agent is *Rickettsia prowazekii*, an obligate intracellular bacterium that is closely related antigenically to the agent that causes murine typhus (*Rickettsia typhi*). The organism is cocobacillary but has inconstant morphologic characteristics. Reproduction is by binary fission and diplobacilli are produced that are frequently seen in tissue sections. Special staining (Giemsa) provides good visualization of the organisms in the cytoplasm of cells.

Epidemiology

The source of infection is a sick man. Epidemic typhus (Louse-Borne typhus) is transmitted from person to person by the body louse (*Pediculus humanus corporis*). The louse feeds on an infected, rickettsemic person. The organism in the louse infects its alimentary tract and results in large numbers of organisms in its feces within about 4-5 days. Close personal or clothing contact is usually required to transmit lice to others. When the louse takes a blood meal, it defecates. The irritation causes the host to scratch the site, thereby contaminating the bite wound with louse feces. Human infection might also occur by mucous membrane inoculation with contaminated louse feces.

Human conditions that foster the proliferation of lice are especially common during winter and during war or natural disasters – where clothing is not changed, crowding occurs, and bathing is very infrequent.

In epidemic the susceptibility is high for all age groups.

Pathogenesis

After local proliferation at the site of the louse bite, the organism spreads hematogenously. *Rickettsia prowazekii*, as with most rickettsia, produces a vasculitis by infecting the endothelial cells of capillaries, small arteries, and veins. The process results in fibrin and platelet deposition and then occlusion of the vessel. Perivascular infiltration with lymphocytes, plasma cells, histiocytes, and polymorphonuclear leukocytes occurs with or without frank necrosis of the vessel. The angiitis is most marked in the skin, heart, central nervous system, skeletal muscle, and kidneys.

The mechanism of the development of epidemic typhus may be represented by the next phases:

1. Penetration of *Rickettsia prowazekii* into organism and reproduction in the endothelial cells of the vessels.

2. Destruction of endothelial cells and penetration of rickettsia into the blood – rickettsiemia, toxinemia.

3. Functional violations of the vessels in all organs and tissues – vasodilatation, slowdown of the stream of the blood.

4. Destructive and proliferative alterations of the capillaries with formation specific granulemas (nodules).

5. Formation of immunity.

Anatomic pathology

Small hemorrhages in the conjunctivae are frequent. The heart usually shows slight gross changes. Microscopically the blood vessels show similar lesions to those observed in the skin, and sometimes there is considerable infiltration with mononuclear and polymorphonuclear cells. Thrombi are rarely found in the larger blood vessels.

The blood is usually dark colored and liver and kidneys show cloudy swelling. The spleen is somewhat enlarged during the early stages of the disease but tends to be normal in size later on. It is often very soft and then may rupture from being handled at autopsy. Microscopically, engorgement with blood, with extensive phagocytosis of red blood corpuscles and diminution of lymphoid elements, is commonly present.

The lesion in the brain, particularly in the basal ganglia, medulla and cortex of the cerebrum, and more rarely in the white matter and cerebellum, correspond in size to miliary tubercles and are secondary to lesions of the small blood vessels and capillaries, as in the skin. They first consist of a collection of large cells of vascular and perivascular origin, endothelium, and monosytes, with necrosis resulting from occlusion of the vessels.

Clinical manifestations

Epidemic typhus is cyclic infectious disease. There are the next periods in the course of the disease: incubation period (it's duration is from 6 till 25 days). Initial period till appearance of the rash (it's duration is 4-5 days), period of climax – from appearance of rash till normalization of the temperature (it's duration is from 4-5 days till 8-10 days) and period of reconvalescence (it's duration is 2-3 weeks).

After an incubation period an abrupt onset with intense headache chills, fever and myalgia is characteristic. There is no eschar. The fever worsens quickly and becomes unremitting and the patient is soon prostrated by the illness. Giddiness, backache, anorexia, nausea are observed in the patients. The appearance of the patient is typical. The face is edemaous, flushed. Eyes are brilliant with injected sclera ("rabbit's eyes"). Enanthema (small hemorrhages) on the basis of uvula is marked on the second-third day of the disease (symptom

of Rosenberg). The petechial rash may be revealed on transitive folds of conjunctiva from the third-forth day (symptom of Kjary-Aucyne). The early sign is tremor of the tongue, it's declining to the side (symptom Govorov-Godeljae) due to bulbaric disorders. Splenomegaly is marked on the 3-4 day of the disease in the majority of the patients.

Climax period is characterized by development of all clinical manifestations of the disease. The temperature is definite high level (febris remittans). Temperature decreases frequently on the 3-4, 8-9 and 12-13 day of the disease and than the temperature increases again. Climax period is accompanied with intoxication and damage of central nervous system.

The appearance of the rash is an important sign of climax period. A rash begins in the axillary folds and upper part of the trunk on about the fifth day of illness and spread centrifugally. Initially, the rash consists of nonconfluent, pink macules that fade on pressure, may be rose- and petechial like. Within several days, the rash becomes maculopapular, darker, petechial and confluent and involves the entire body, palms and soles but never the face. Disappear with decreasing of temperature.

Circulatory system. Very outspoken is cardiac weakness due to myocardial degeneration. The heart sounds are very weak and the pulse feeble, rapid and irregular. The blood pressure often is very low, especially the diastolic, and may remain so throughout the disease. Bradycardia may be marked during convalescence.

Respiratory system. Cough may appear in the first days, but usually is first troublesome about the time of the eruption. By the end of a week, the cough becomes loose and rales of various types may be noted.

Alimentary tract. Constipation is usually noted. Very marked is the tendency of the mouth and tongue to become dry and sordes to collect on the teeth. It is often difficult to get the patient to protrude his tongue when told to do so. In the patients with epidemic typhus splenomegaly and hepatomegaly (from one second week) are marked.

Nervous system. Clouding of the consciousness may be as marked in this disease. Dull aching frontal headache is common and is an early predominating symptom. It frequently diminishes before the eruption appears. A dull stuporous state soon comes on. Delirium is marked in some cases. There are often the faces and mental state of alcoholic intoxication. There may be meningitis, meningoencephalitis.

In epidemic typhus fever it may be leucocytosis, neutrophylosis, monocytosis in the blood. ESR is accelerated.

Variants of the disease course.

There are mild, medium serious and serious course of the epidemic typhus fever. During the light course of the disease the occurrences of intoxication are expressed insignificantly. The temperature increases till 38 °C. The consciousness

is no changed. The rash predominates as roseoles. The liver and spleen increases in a third of patients. The duration of fever is till 9 days. The mild course is observed in 10-20 % patients.

The medium serious course of the disease occurs more frequently (60-65 % of patients). The temperature increases till 38-39 °C. The duration of the fever is 12-14 days. The signs of the intoxication are expressed temperate.

During the serious course of the epidemic typhus fever expressive intoxication, hypotonia, tachycardia (till 140 beats per minute) are observed. The tones of the heart are muffled. There is acrocyanosis. The dyspnea occurs, it may be violation of the rhythm of the breathing. The cramps of the muscles, the violation of the swallowing are marked. The temperature increases up to 40-41 °C. The rash is petechial, it may be hemorrhage. The serious course occurs in 10-15 % patients. The serious and very serious course of the disease takes place in elderly people.

Complications

Bronchitis, pneumonia, otitis media, parotitis, nephritis, tromboses of various vessels, both abdominal and peripheral may occur.

Diagnosis

In the proper setting of cold weather, infrequent bathing and changing clothes, crowded conditions, and the presence of lice, the clinical symptomatology described before is compelling evidence for the presence of louse-borne typhus. The progression of rash serves to distinguish the disease from Rocky Mountain spotted fever (RMSF), which progresses centripetally, beginning on the wrists and ankles. Diagnosis requires a high index of suspicion because of the great variability in presenting symptoms. It is important to examine the axillary folds repeatedly for evidence of rash. During the colder months of November throq March, if RMSF is suspected from the clinical picture, tt should be a clue in considering the diagnosis of epidenj typhus. The Weil-Felix reaction is the same as in murine typhus; special serologic methods are used to differentiate louse-borne typhus from murine typhus. The polymerase chain reaction may provide an full alternative to serodiagnosis or rickettsia cultivation.

The methods of the laboratory diagnostic are serological: indirect hemagglutination, indirect immunofluorescence, complement fixation.

Differential diagnosis

Nonrickettsial infections at some time during the course, may mimic louse-borne typhus include meningococcemia, measles, typhoid fever, bacterial meningitis, secondary syphilis, leptospirosis, relapsing fever, infectious mononucleosis, and rubella.

During the period of onset of the diseasethe differential diagnosis is performed with grippe, pneumonia, meningitis, hemorrhagic fevers. During the period of the

climax the differential diagnosis is performed with typhoid fever, ornithosis, drug disease, leptospirosis, infectious mononucleosis, trichinellosis.

Treatment

Preparations of tetracyclines – tetracyclin, metacyclin, doxycyclin are most effective.

Laevomycetin, erythromicin has less expressed action. At serious course of disease infuse antibiotics in vein or in muscle. Course of treatment carry out during all period of fever and 2 days of normal body temperature.

With desintoxication purpose in vein infuse solution of glucose, solution of Ringer-loc, donor albumin, reopoliglyc, polyvitamin, ascorutin. At psychomotor exaltation and deliriums – aminasin, fenobarbital, sodium hydroxybutyrat, sibazon (seduxen); for rising a tone of cardiovascular system and disorders of circulation – cordiamin, coffein-sodii benzoat, sulfocamphocain, ephedrini hydrochlorid, corglykon or strophanthin are indicated. At rising of intracranial pressure and the phenomena of meningism dehydration with due to furosemid (lasix), mannit is administered, sinapismuses or pepper emplastrum on nape and thorax, gastrocnemius muscle, feet, simultaneously intensive desintoxicative therapy and correction of hydro-electrolytic structure of a blood are also effective. At serious and very serious current of typhus use glucocorticoid preparations, anticoagulants (heparin or derivatives of dicumarin).

Prophylaxis

Control of the human body louse and the conditions that foster its proliferation is the mainstay in preveting louse-borne typhus.

Typhus vaccine is prepared from formaldehyde-inactivated *Rickettsia prowazekii* grown in embryonated eggs. Typhus vaccination is suggested for special risk group.

BRILL-ZINSSER DISEASE

Brill-Zinsser disease occurs as a recrudescence of previous infection with *Rickettsia prowazekii*. It is endogenic relapse of epidemic typhus. Brill-Zinsser disease is characterized by sporadic morbidity in absence of louse.

In Brill-Zinsser disease the pathogenesis and morbid anatomy are similar to epidemic typhus, however the process is less expressive, because the concentration of *Rickettsia prowazekii* is similar in the blood. The course of Brill-Zinsser disease is more mild than epidemic typhus, but the patients have all typical symptoms of the disease.

Initial period (it's duration is 3-4 days) is accompanied by temperate intoxication. Headache, disorder of sleep, increase of the temperature up to 38-39 °C are marked. Enanthema is observed rarely (in 20 % of the cases). The duration period is usually 5-7 days. It is characterised by temperate hyperthermia (38-39 °C) of remittent or rarely constant type.

The signs of the damage of the central nervous system are expressed temperately. Meningeal signs are revealed rarely.

A rash is observed in 60-80 % of the patients. The signs of the damage of the cardiovascular system are marked frequently. Enlarged liver and spleen are revealed inconstantly.

In Brill-Zinsser disease the complications develop rarely. It may be pneumonia, thrombosis, thrombophlebitis.

The treatment is similar to epidemic typhus.

The differentiation of primary louse-borne typhus is made by showing that the antibody produced is IgM (primary louse-borne) or IgG (Brill-Zinsser disease).

ENDEMIC TYPHUS (MURINE TYPHUS)

Murine typhus is widely distributed throughout many parts of the world. It has been encountered in the southeastern United States, South America, Syria, Greece, Africa, China and the Philippines.

Historic reference

Epidemic typhus fever was identified with epidemic typhus fever and other rickettsioses for a long time. It was described as independent disease by T.Hone (1922). The agent of the disease was isolated by M.H. Neil (1917). H. Mooser (1922) discovered rickettsia-like inclusions in the mesothelial cells of quinea-pigs infected by patient's blood. In Baltimore, Dyer, Rumreich, Badler (1931) isolated rickettsiae from the brain of rats and from rat fleas. In the same year H. Mooser, M.R. Castanedia, H. Zinsser isolated rickettsial from the brain of rats during epidemic in Mexico.

Etiology

The etiologic agent of murine typhus is *Rickettsia mooseri*, an obligate intracellular organism that shares common soluble antigens with *Rickettsia prowazekii*. The organism is less pleomorphic than *R. prowazekii* is; mostly coccobacillary form can be seen in cytoplasm on infected cells when using Giemsa stain.

Epidemiology

Murine typhus is zoonotic rickettsiosis. The disease occurs in those people whose occupation or living conditions brings them into close contact with rats and therefore the ectoparasites of these rodents. The rat flea *Xenopsylla cheopis* is the primary vector that causes human infection. Illness in human is a peripheral occurrence to the natural transmission of the organism in rodents.

Worldwide outbreaks and sporadic disease occur where conditions favor the proliferation of rats and where inadequate ectoparasite control exists.

In the rat, the disease is nonfatal. It is transmitted rat to rat by the tat flea and possibly by the rat louse. In the flea, the organism multiplies in the cells of

the digestive tract without harm to the insect. *Rickettsia mooseri* is now thought to be transmitted transovarially in the flea.

When the flea takes a blood meal, it defecates. Its feces is heavily contaminated with organisms and produces infection in humans by soiling the bite wound. Infection may also occur by mucous membrane (conjunctivae or nasal mucosa) contamination with flea feces or by aerosol in laboratory personnel.

Pathogenesis

It is similar to epidemic typhus fever, but the pathologic process is less intensive. The destructive and thrombotic changes in the vessels and knotty changes in the brain are less expressed. The intoxication is temperate. There is an allergic factor of the disease. Its manifestations are the papular rash, damage of the joints of the hands and legs.

Anatomic pathology

The discription of murine typhus are pure because disease is rarely fatal. Necropsy showed intestinal pneumonia, alveolar hemorrhages, cerebral petechial, interstitial myocarditis, nephritis, splenomegaly. *R. mooseri* was demonstrated in the lungs, brain, kidney, liver, and heart. The histopathologic features that are described show the fatal illness to be quite similar to louse − borne typhus.

Rickettsia mooseri produces vasculitis by infecting the endothelial cells of capillaries, small arteries and veins. The process results in fibrin and platelet deposition and then occlusion of the vessel. Perivascular infiltration with lymphocytes, plasma cells, histiocytes and polymorphonuclear leukocytes occurs with or without frank necrosis of the vessels. The angiitis is most marked in the skin, heart, central nervous system, skeletal muscle and kidneys. If local thrombosis is extensive, gangrene of skin and / or distal portions of the extremities occurs.

Clinical manifestations

After an incubation period of 1-2 weeks, the disease begins abruptly without prodromal signs and manifests like epidemic typhus fever. Frequently, a nonproductive cough occurs early in the course. Although the illness is infrequently prostrating, patients are nonetheless unable to work because of headache and myalgia.

Rash occurs in 60-80 % of the patients, and it first becomes evident on the third to fifth day of illness. The rash is initially macular and occurs on the upper thorax and abdomen, and it remains central in distribution. This distribution is quite distinct from the primarily peripheral (ankles, wrists and face) distribution of spotted fever. Later, the rash of murine typhus becomes maculopapular and remains for 4-8 days. The rash may vary greatly in duration and intensity, and it may be quite evanescent.

In the untreated adult, temperature between 38.9 °C and 40 °C usually lasts 12-16 days. With antirickettsial antimicrobial therapy, the temperature defervesces in 2-3 days. In either situation, convalescence is rapid. The disease is very mild

in young children. The disorders of the cardiovascular system are expressed temperatly. Usually the pulse corresponds to the temperature. It may be bradycardia. There is a tendency to hypotonia. The tones of the heats are muffled. Sometimes it may be a systolic murmur on the apex of the heart. It is manifestation of the infectious myocarditis. The changes in the lungs are observed rarely. It may be pneumonia or bronchitis. The liver is increased in 30-50 % of cases, the spleen is increased in 50 % of patients. The disorders of the central nervous system are less expressed than in epidemic typhus fever. The meningeal signs are absent. There are no typical changes of the blood. In the serious course it may be leukocytosis.

Complications

The complications occur rarely. It may be thrombophlebitis, pneumonia, otitis. The manifestation of the infectious myocarditis may also be present.

Diagnosis

The methods of diagnostics of the murine typhus are serological (complement fixation tests can be used for diagnosis).

In diagnostics of endemic typhus it is necessary to allow for similarity its some forms of the course with epidemic typhus (serious forms), Brill-Zinsser disease (medium serious and light forms) and other rickettsioses (Marseilles fever, Rocky Mountain spotted fever). In these cases gomologic diagnosticums are used. In abcence of differences biological tests is used for revealation of Nale-Mooser's scrotal phenomenon in males of white rats or quinea-pigs on 1-4 day after infecting by patient's blood.

Differential diagnosis

The differential diagnosis of murine typhus is quite complicated because of its usually nonspecific presentation. Aside from the rickettsioses and ehrlichiosis, alternative diagnoses that may need to be considered include meningococcemia, measles, typhoid fever, bacterial and viral meningitis, secondary syphilis, leptospirosis, toxic shock syndrome, and Kawasaki disease.

Treatment

The preferred therapy for *R. typhi* infection is tetracycline, doxycycline or chloramphenicol. Recent clinical trials of fluoroquinolones in the treatment of spotted fever group rickettsioses have been performed in Europe; the results of these trials and individual case reports suggest that such drugs including ciprofloxacin, ofloxacin, and pefloxacin may be effective alternatives. Whether such results may be extrapolated for broad treatment of *R. typhi* infection awaits additional studies. The current recommendation for tetracycline is 25-50 mg/kg/day in four divided oral doses, and for doxycycline, 100 mg is recommended. Chloramphenicol is effective when used at 50-75 mg/kg/day in

four divided oral doses. In severely ill patients, intravenous therapy may be required, and doxycycline or chloramphenicol is preferable for patients in renal failure. Corticosteroids are occasionally used for severe CNS disease, but no controlled study to evaluate efficacy has been performed. Infected pregnant patients must be evaluated individually and either chloramphenicol (early trimester) or doxycycline (late trimester) may be used if necessary. Single dose therapy is not advocated since relapse may occur, and antimicrobial therapy should be continued until 2-3 days after defervescence. After initiation of therapy, patients become afebrile at a median interval of 3 days.

Prophylaxis

The measures for prophylaxis of murine typhus are systemic extermination of rats and mousses, prevention of bringing rodents into ports by ship, guarding food-stuff from infecting by urine of rodents.

The patients with murine typhus are not dangerous for surrounding people. The hospitalization is not obligatory.

The extermination of the sources of the infection (rodents and their ectoparasites) is performed by means of deratization and disisection. Killed vaccine from rickettsia Mooser is used in case of wide spread of the infection.

Mortality is very uncommon in murine typhus. Recovery is complete.

MARSEILLES FEVER

This disease has been designated by many geographic names: Marseilles fever, Mediterranean spotted fever, Kenya tick typhus, South African tick bite fever, Israel tick typhus and Indian tick typhus.

Historic reference

Marseilles fever was first described by Connor and Bruch in 1910 in Tunis. Subsequently different French and Italian observers reported the existence of a disease in the Mediterranean regions, in Marseilles and among other districts in southern France, as well as in Italy, Portugal, Spain, Greece and Rumania. The disease was said to resemble the mild typhus reported by Brill but small black spots of linear appearance resembling insect bites were often reported. There was no history of lice infestation.

Etiology

The etiologic agent is *Rickettsia conori*. *R. conori* is a typical spotted fever group rickettsia, having more than 90 % DNA homology with *Rickettsii*. There are also cross-reactive protein, lypopolysacharide antigens and cross-protection antigens, shared among *R. conori, R. sibirica* and *R. rickettsii. R. conori* is an obligate intracellular and intranucleus agent. It has both toxical and hemolytic activity.

Epidemiology

Marseilles fever is transmitted by the common dog tick, *Rhipicephalus sanquineus*.

V.Durand has shown that the dog constitutes the reservoir of the *R. conori*. Dogs have been shown to be susceptible to inoculation and their blood has been proved to be infective both for man and monkeys. *R. conori* is maintained transovarially in ticks and is transmitted to humans by tick bite. Cases occur mainly in warm months with the peak incidence in July, August, and September in many Mediterranean locations.

Pathogenesis

Pathogenesis is similar to rickettsioses of the group of epidemic typhus fever, but the changes of the vessels is less expressed. The primary affect ("black spot"), regional lymphadenopathy and allergic manifestations are typical. The primary affect is local inflammation of the skin on the place of the reproduction of rickettsial with necrosis in the center. The black crust appears on the 5-8 day till rising of the temperature.

Anatomic pathology

Dermal and epidermal necrosis and perivascular edema are the consequences of endothelial injury by *R. conori*. Necrosis of fatal cases reveal disseminated vascular infection and injury by *R. conori* including meningoencephalitis and vascular lesions in kidneys, lungs, gastrointestinal tract, liver, pancreas, heart, spleen, and skin.

Clinical manifestations

The primary affect ("black spot") is an early sign of the disease. The crust usually falls on 4-5 day of the normal temperature. The localization of the primary affect is the strips of the skin covering by clothes. It is revealed by difficulty, because the bite of the tick is painless. After the incubation period of 7 days, fever, myalgia, and headache characterize the onset of the disease. On the 2-4 day of the disease the rash appears on the abdomen and then by the chest and alone all the body, including palms and soles. The rash is maculopapular. There is no itch. The changes from the side of the internal organs are such as other rickettsioses. Often the spleen is enlarged, the liver is enlarged rarely. The meningeal syndrome is not typical. The leukopenia, lymphocytosis, the raising ESR is temperate.

Complications

The complications occur rarely. It may be thrombophlebitis, pneumonia.

Diagnosis

The methods of the laboratory diagnostics are serological (complement fixation and indirect hemagglutination, with antigen from *Rickettsia conori*).

Differential diagnosis

The differential diagnosis need to be considered with other rickettsioses because Marseilles fever has usually nonspecific manifestations. Alternative diagnoses that may include meningococcemia, measles, typhoid fever, bacterial and viral meningitis, secondary syphilis, leptospirosis etc.

Treatment

The treatment is similar to the other rickettsioses.

Prophylaxis

In endemic areas prophylaxis includes obligatory registration of the dogs every year, the processing of the dogs and the places of the tick.

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever belongs to the large group of spotted fevers – tick and mite-borne zoonotic infections.

Historic reference

Rocky Mountain spotted fever (RMSF) was first described in Idaho in the late nineteenth century. Ricketts established the infectious nature of the illness and demonstrated the role of the tick as the vector in western Montana in 1906.

Etiology

The etiologic agent, *Rickettsia rickettsii*, belongs to the spotted fever group of rickettsia, which are genetically related but differ from one another in their surface antigenic proteins.

Spotted fever group rickettsial are obligate intracellular bacteria that reside in the cytosol and less often in the nucleus of their host cells. The rickettsiae are small, the cell wall has the ultrastructural appearance of a gram-negative bacterium and contains lipopolysaccharide.

Among the protein antigens of *Rickettsia rickettsii*, two surface proteins contain heat labile epitopes that seem critical to immunity. Some epitopes of these proteins are species specific, and others are spared among the members of the group.

The lipopolysaccharide of spotted fever group rickettsiae contains highly immunogenic antigens that are strongly cross-reactive among all members of the group.

Epidemiology

The usual method of transmission in nature is through the bite of the tick. The tick is both the vector and the main reservoir. *Dermaceptor* variables, the American dog tick, is the prevalent vector in the eastern United States; *D. andersoni*, the Rocky Mountain wood tick in the western States; *Rhipicephalus sanguineous* – in Mexico.

Rickettsia rickettsii is transmitted trans-stadially and transovarially in ticks, thus maintaining the agent in nature. Of three tick stages, larva, nymph, and adult, only the adult *Dermaceptor* ticks feed on humans.

The tick transmits the disease to humans during feeding. The bite is painless and frequently unnoticed. After the attached tick has fed for 6-10 hours, rickettsia are released from the salivary glands. An even longer period may be required for reactivation of rickettsial virulence in unfed ticks. Human may also be infected by exposure to infective tick hemolymph during the remove of tick from humans or domestic animals, especially when the tick is crushed between the fingers. Most cases of Rocky Mountain spotted fever are diagnosed during late spring and summer.

Pathogenesis

Rickettsiae introduced into the skin apparently spread via lymphatic and small blood vessels to the systemic and pulmonary circulation where they attach to and enter their target cells, the vascular endothelium, to establish numerous disseminated foci of infection. After entry by induced phagocytosis, the rickettsiae escape from the phagosome into the cytoplasm and less frequently the nucleus. Rickettsiae proliferate intracellulary by binary fission and are released than the infected cells via long thin cell projections. The presence of large quantities of rickettsiae in damaged cells supports the concept of direct cell injury. The major pathophysiologic effect of endothelial cell injury is increased vascular permeability, which in turn results in edema, hypovolemia, hypotension and hypoalbuminemia. High quantities of rickettsiae infecting the pulmonary microcirculation increase the vascular permeability and cause noncardiogenic pulmonary edema.

Anatomic pathology

Vascular injury and the subsequent host mononuclear leukocytic response correspond to the distribution of rickettsiae and include interstitial pneumonia, interstitial myocarditis, perivascular glial nodules of the central nervous system, and similar vascular lesions in the rash, gastrointestinal tract, pancreas, liver, skeletal muscles, and kidneys. Severe vascular injury may lead to hemorrhage.

Clinical manifestations

The incubation period ranges from 2 to 14 days, with a medium of 7 days. Rocky Mountain spotted fever is one of the most serious rickettsioses. There is no primary affect. The disease usually begins with fever, myalgia, and headache. Gastrointestinal involvement with nausea, vomiting, abdominal pain, diarrhea, and abdominal tenderness occurs in substantial portions of patients and may suggest gastroenteritis or an acute surgical abdomen.

The rash, the major diagnostic sign, appears in a small fraction of patients on the first day of the disease, usually appearing 3-5 days after the onset of fever. The rash typically begins around the wrists and ankles but may start on the trunk or be diffuse at the onset. Skin necrosis or gangrene develops in 4 %

of cases as a result of rickettsial damage to the microcirculation. Gangrene involves the digits or limbs and occasionally requires amputation.

Headache is usually quite severe. Focal neurologic deficits, transient deafness, meningismus, and photophobia may suggest meningitis or meningoencephalitis.

Renal failure is an important problem in severe Rocky Mountain spotted fever. Prerenal azotemia related to hypovolemia responds to intravenous hydration; however, acute tubular necrosis may require hemodialysis. Pulmonary involvement is suggested by cough and radiological changes including alveolar infiltrates, interstitial pneumonia and pleural effusion. The liver and spleen are increased. The changes of the central nervous system are typically: the severe diffuse headache, sleeplessness, exiting, delirium and hallucinations, paralysis, decreasing of the hearing and vision, psychical changes, neurosis. This changes may be maintained for a long time (till month and more), but than they disappear without consequences. The duration of the acute period of the disease is 2-3 weeks. The recovery comes slowly, sometime during some months.

There are ambulatory, aborted, typical and malignant (fulminate) forms of the disease. The fulminate form is characterized by severe toxicosis and lethal result during 3-4 days. This form of Rocky Mountain spotted fever was described in the literature as Brazilian typhus fever.

Complications

At present time the complications are observed rarely. It may be hemorrhages, phlebitis, neuritis, myocarditis.

Diagnosis

Serology, the usual method for confirmation of the diagnosis, is retrospective, serum antibodies becoming detectable during convalescence. Four methods for the detection of antibodies to specific rickettsial antigens are indirect hemagglutination, indirect immunofluorescence, latex agglutination and complement fixation. The biological methods may be used (the infection by blood of the patient of guinea-pigs and following detachment of the agent).

Differential diagnosis

The differential diagnosis at the first consultation includes typhoid fever, measles, rubella, respiratory tract infection, gastroenteritis, acute surgical abdomen, viral meningoencephalitis, meningococcemia, leptospirosis, thrombotic thrombocytopenic purpura, infectious mononucleosis and other rickettsial diseases.

Treatment

The methods of the treatment are similar to epidemic typhus fever. Since the introduction of chloramphenicol and the tetracycline, including doxycycline, the lethality of the disease decreased dramatically to 3-7 %.

Prophylaxis

There are two ways of the prophylaxis: the struggle with ticks and vaccination of persons in the endemic areas (formalized Cox vaccine).

SCRUB TYPHUS (TSUTSUGAMUSHI FEVER)

Scrub typhus is an acute, febrile illness of humans that is caused by *Rickettsia tsutsugamushi (R. orientalis),* it is transmitted to human by the bite of larval – stage thrombiculid mites.

Historic reference

At the first the disease was described in Japan in 1810 year by Huchimoto which called this disease "tick's disease". Scrub fever occurs over a wide area of Earsten Asia, and the Western Pacific region, from Korea to Australia, and from Japan to India (the areas of the mountains) and Pakistan.

Etiology

Rickettsia orientalis is an obligate intracellular bacterium that grows free in the cytoplasm of infected cells, that has no vacuolar membrane. The organism can best be seen in tissue by using the Giemsa stain. It is rather unusual among rickettsiae because of its large number of serotypes.

Epidemiology

Scrub typhus is a zoonotic infection. The principal reservoir of the infection is thrombiculid mites. The supplementary reservoir is rodents. In endemic areas the infection of the man is happened in the places with scrubs and forests, where the trombiculid mites live. The larval chigger the agent of the disease with blood and transmittes it transovarially to the new generations of the chiggers. So, only the new generation of the chiggers may transfer the agent to the human and animals next year. The disease is registered frequently in July-August.

Pathogenesis

The links of the pathogenesis may be represented in the next form:

1. Inculcation of *Rickettsiae* into human organism (after the site of the trombiculid mite). In the laboratory conditions it may be penetration of the agent through the mucous membranes of the eyes and by the aerogenic way.

2. Parasitation of the *Rickettsiae* at the endothelial cells of the vessels with forming of the first affect regional lymphadenopathy.

3. Penetration of the *Rickettsiae* into the circulative system, development at the endothelial cells of the vessels and forming of the granulomas.

4. Rickettsiaemia with forming of the generalized polyadenitis.

5. Intoxication.

6. Diffusive entering of the agent into parenchimatous organs and tissues.

7. The development of the inflammatory changes in the mucous cavities (pericardial, pleuritic, abdominal) and appearance of the exudation.

8. Development of the reactive allergic reactions.

9. Immunological reactions.

Anatomic pathology

The morbid anatomy of scrub typhus have a large similarity with the morbid anatomy of endemic typhus. The primary affect and regional lymphadenopathy are typical.

Clinical manifestation

The period of the incubation is from 5 to 21 day (often 7-11 day). The onset is usually sudden and is characterized by fever, severe headache, and myalgia. There is usually tender lymphoadenopathy in the region of the bite wound or eschar. Temperature usually rises quickly in the first several days of disease to 40-40.5 °C. Early in the course of illness, the pulse is relatively slow. Other symptoms at this time may include ocular pain, conjunctival injection, nonproductive cough, and apathy. After about 5 days of illness, rash occurs on the body and spreads to the extremities; it begins as a macular rash and may become papular. It is sometimes evanescent. At this time, there is generalized lymphoadenopathy and splenomegaly.

In untreated patients, fever subsides after an illness of about 2 weeks. Specific antirickettsial therapy shortens the illness considerably and reduces mortality to essentially nil. Mortality rates have ranged in untreated patients.

Complications

In a small proportion of patients, tremors, delirium, nervousness, slurred speech, deafness, or nuchal rigidity may develop in the second week of illness. Cerebrospinal fluid from such patients is either normal.

Diagnosis

The methods of the laboratory diagnostic are serological. Because of the susceptibility of white mice to *R. orientalis*, intraperitoneal injection of patient's blood can be used diagnostically.

Differential diagnosis

The differential diagnosis includes typhoid fever, brucellosis, leptospirosis, infectious mononucleosis and flavivirus infection such as dengue fever.

Treatment

Tetracycline or chloramphenicol are both effective in treating scrub typhus; fever dissipates in less than 24 hours in most patients.

Evidence is accumulating that shows single − dose doxycycline therapy to be effective in treating scrub typhus and in preventing relapse (200 mg orally weekly).

Prophylaxis

Individuals who travel to endemic areas should wear protective clothes and use insect repellants to avoid chigger bites.

An effective vaccine for humans has not been developed.

Q − FEVER

Q-fever is zoonotic infection. It occurs worldwide. Q-fever has acute, subacute and chronic course. It is characterized by polymorphic clinical manifestations.

Historic reference

Derrick, a medical officer of health in Australia in 1935 investigated a febrile illness that affected 20 of 800 employs of Brisbane meat works. He coined the term "Q (or query) fever". Burnet and Freeman showed that the organism isolated from the blood and urine of these patients was a rickettsia. At about the same time Davis and Cox isolated a microorganism from ticks (*Dermaceptor andersoni*). Later Dyer showed that *R. burnetii* (Burnet and Freeman's organism) was the same as *R. diaporica* (Cox's organism) − it is now known as *Coxiella burneti*. Q-fever has been reported from at least 51 countries on five continents.

Etiology

Coxiella burneti, the etiologic agent of Q fever, is a highly pleomorphic coccobacillus with a gram-negative cell wall. Large and small cell variants exist, and spore stage has been described. *Coxiella burneti* has ability passing through bacterial filters. They may transform into L-forms by action of antibiotics. *Coxiella burneti* is steady in the external environment. They don't perish in pasteurization of the milk. They perish only in boiling during 10 minutes. *Coxiella burneti* may preserve in the dry cultures and secretions during some years.

Epidemiology

The principal reservoir of the agent is the wild animals and domestic animal (92 species), the wild and domestic birds (72 species), ticks (73 species). In animals the agent detaches into external environment with fecal matter. The infection happens by the aerosol rate or in eating of the corpses of the animals. The agricultural animals have the principal epidemiological meaning (cows, sheep, horses, pigs, camels and other). The infection of the human happens by the aerosol rate, alimentary, contactive or transitive rate.

The most common animals reservoirs for this zoonosis are cattle, sheep and goats. These domestic ungulates, when infected, shed the agent in urine, feces, milk and especially in birth products. The placenta of infected sheep contains up to 109 organisms per gram of tissue. *Coxiella burneti* has also been isolated from human milk, and human placentas.

Pathogenesis

There are the next links of the pathogenesis:

1. Inoculation of the agent into the organism through the damaged mucous membranes and skin.

2. Lymphagenic spreading of the agent into the circulative system.

3. Primary rickettsiaemia.

4. Dissemination of the rickettsia into the parenchimatous organs of the reticuloendothelial system.

5. Reproduction and development of the rickettsiae in the histiocytes and macrophages.

6. Secondary rickettsiaemia and toxinemia with dissemination in new focuses of reticuloendothelial system.

7. Development of the allergic manifestations.

8. Formation of the immunity and convalescence.

Anatomic pathology

Q-fever is of high quality reticuloendotheliosis without development of panvasculitis. It's anatomic pathology is similar with others rickettsioses. The typical "doughnut granulomas" is seen on liver biopsy. This is a granulomas with a dense fibrin ring surrounded by a central lipid vacuole. *C. burnetii* has been isolated from the liver of patients with Q-fever hepatitis, but the organism has not been visualized within the hepatic parenchyma.

Clinical manifestation

An incubation period is from 2 till 30 days (in aberage – 20 days). The disease begins acuity. The severe headache, weakness, fever, chills, fatigue, myalgia are observed in the patients. The clinical manifestations are polymorphs. The prolongation of the fever is different (from 2 till 2-4 weeks). It may be recurrences of the fever through 4-8 days of the normal temperature. It may be the rash on the 6-8 days of the disease without clear localization (rose-spot, papular, petechial).

There are several clinical syndromes as a result of *C. burnetii* infection:

1. A self-limited febrile illness (2-14 days).

2. Pneumonia.

3. Endocarditis.

4. Hepatitis.

5. Osteomyelitis.

6. Q-fever in the immunocompromised host.

7. Q-fever in infancy.

8. Neurologic manifestation – encephalitis, aseptic meningitis, toxic confusional states, dementia, extrapyramidal disease, manic psychosis.

Self-limited febrile illness – this is probably the most common form of Q-fever. In many areas 11-12 % of individuals have antibodies to *C. burnetii* – most do not recall pneumonia or other severe illness. It is likely that the age at

which infection occurs and the dose of the agent determine whether or not Q-fever is a mild self-limited febrile illness. There is also a suggestion that some infections may be totally asymptomatic.

Pneumonia. There are three presentations of this form of Q-fever: atypical pneumonia, rapidly progressive pneumonia, and pneumonia as an incidental finding in a patient with a febrile illness.

Endocarditis – is the prime manifestation of "chronic" Q-fever. Q fever endocarditis is rare in children. The manifestations are the same as those in adults.

Hepatitis. There are three kinds of Q-fever hepatitis:

1. An infectious hepatitis-like picture.

2. As an incidental finding in a patient with acute Q-fever pneumonia.

3. Fever of unknown origin with characteristic granulomas on liver biopsy.

Neurologic manifestations, vertebral osteomyelitis and infection in the immunocompromised host are uncommon manifestations of Q-fever.

In the peripheral blood the leucopenia, lymphocytosis, monocytosis occur, an accelerated ESR.

Complications

The complications includes hemorrhages, phlebitis, neuritis, myocarditis, vertebral osteomyelitis, bone marrow necrosis, hemolytic anemia.

Diagnosis

In diagnostics the serological methods may be used (reaction of agglutination and compliment fixation) and also the skin-allergic test with allergen (antigen from the killed *Coxiella burneti*). The materials for recovering of the agent are blood, urine, cerebrospinal fluid, mammary milk, sputum. In diagnostics of Q-fever the biological test may be used on guinea-pigs and white mice.

Differential diagnosis

Differential diagnosis of Q-fever is performed with grippe, epidemic typhus, typhoid fever and paratyphoid, brucellosis, ornithosis, acute pneumonia, sepsis.

Treatment

The most effective etiotropic remedy is antibiotics of the group of tetracycline. Tetracycline is prescribed on 2 gm a day till 7-10 day of the normal temperature. The prescription anti-inflammatory and antihistamine remedies is indicated in connection with allergic reorganization of the organism, especially in prolonged and chronic forms of the disease with serious duration.

Prophylaxis

Prophylaxis includes complex veterinary, antiepidemiological and sanitary-hygienic measures. The specific prophylaxis is carried out using killed or living vaccine. In Q-fever endemic areas persons, working with animals, must be vaccinated.

Control questions:

1. Classification of rickettsioses.
2. Etiology, epidemiology and incidence of epidemic typhus fever.
3. Main clinical symptoms and signs of epidemic typhus fever.
4. Pathogenesis and morbid anatomy of epidemic typhus fever.
5. Clinical manifestations of disease.
6. The variants of the course of the disease.
7. Complications of epidemic typhus fever infection.
8. Laboratory diagnosis of epidemic typhus fever.
9. Treatment of epidemic typhus fever.
10. Etiology and epidemiology of Brill-Zinsser disease and other rickettsioses.
11. Main clinical symptoms and signs of Brill-Zinsser disease and other rickettsioses.
12. Clinical manifestations of Brill-Zinsser diseases.
13. Laboratory diagnosis of Brill-Zinsser disease and other rickettsioses.
14. Treatment of rickettsioses.
15. Preventive measures against rickettsioses.

VIRAL ENCEPHALITIS

Viral encephalitis and myeloencephalitis are group of acute infectious diseases. These diseases are accompanied by fever and lesion of the brain and/or spinal cord. The title "encephalomyelitis" descended from Greek word "encephalon" – brain, "myelon" – spinal cord. There are 2 groups of encephalites the primary encephalites and the secondary encephalites.

The primary encephalites are independent diseases, for example: Tick encephalitis and Japanese encephalitis.

The secondary encephalitis is syndrome of some other disease, for example: encephalitis due to measles, smallpox, herpetic infection.

Viral transmissive encephalites and myeloencephalites are diseases from group of arboviral infections. Arboviral diseases are characterized by endemic and seasonal spread, transmissive way of the transmission. All arboviral encephalites are zoonotic infections.

Arboviral encephalitis are accompanied by general toxic syndrome, high temperature and mainly by damage of the central nervous system.

The agents of this group of the diseases are arboviruses, i.e. "arthropod-borne viruses". The general characteristics of arboviruses is ability to parasite in the organism of animals and arthropods.

Arboviruses are typical parasites of the birds, rodents, mammals, reptiles. *Arboviruses* evoke latently persistent or subclinical infection in the organism of birds and animals. Human is included to ecological chain accidentally, and as rule he is not a source of the infection, except for some arboviral fevers, which having declination to epidemic spread (Denge fever, yellow fever, flebothomic fever and other). The group of *Arboviruses* is detached on the basis of their general ecology. The live cycle of viruses consists of the next stages:

1. Reproduction in the organism of vertebral hosts.

2. Crossing to attaching insects and reproduction in the organism of anthropoids.

3. Transmission by bite to new vertebrate hosts. The vertebrate hosts become the source of infection due to accumulation of virus in the blood.

The transfer of *Arboviruses* by anthropoids (gnats, ticks, mosquitoes) is not mechanical process. Virus, entering the insect's organism with blood is reproduced and accumulated in the cells of the salivatory glands. It enters the wound with saliva due to bite. The condition of the infection is concentration of virus in the saliva. The infection of anthropoids is also possible in sufficiently high quantity of virus in the blood of vertebrate hosts. Arboviral infection doesn't harm anthropoids. Virus is preserved in the organism of anthropoids during all life.

In infected ticks virus is transmitted transovarially. The forming posterity becomes carrier of virus, it may be able to transmit infection to the vertebrate hosts.

The tropical countries are regarded as historical heartland of arboviruses. At the present time these countries are areas of the most spread of arboviral infections. The variety of species of insects, the considerable density of the population of vertebrate hosts and anthropoids and high temperature of air promote spread of arboviral infections.

The important factor of the activity and epidemic manifestations of the focuses of arboviral infections is activity of human and violations of ecological balance. For example, Japanese encephalitis is registered in all regions of rise fields and conditions of pigs. The irrigated rise fields are the places of replication of vectors of agents; *Culex* mosquitoes and infected pigs are the reservoir of infection.

All arboviral infections are natural focal diseases. There are the next groups of arboviral diseases:

I. Arboviral encephalites and encephalomyelites.

II. Arboviral systemic feverish diseases.

The next diseases are concerned to the first group:

1. *Venezuelan equine encephalitis* is widespread in the northern, southern and central areas of America. The birds, rodents, monkeys, mammals are the reservoir of virus. Amount domestic animals-sheeps, goats and horses may be the source of infection. The mosquito is a factor of transmission. The lethal rate is 6-9 % of cases in adult and 35 % in children.

2. *Eastern equine encephalitis* is widespread in the almost whole American continent. The sources of infection are the horses and some kinds of the birds. The diseases is transmitted by mosquitoes. The lethal rate is 70-75 %.

3. *Western equine encephalitis* is widespread in the some regions of American continent. The reservoir of infection is some kinds of the birds, snakes, frogs and horses. The disease is transmitted by mosquitoes. Lethal rate is 15 %.

4. *Sant-Louis encephalitis*. It is widespread in the countries of American continent and on the islands of Caribbean basin. The reservoirs of infection are pigeons, sparrows, chickens and cattle. The factors of transmission are mosquitoes and ticks. The lethal rate is 15-20 %.

5. *Ilheus encephalitis* is registered in some areas of the South and Central America. The reservoir of infection has not been determined. The factor of transmission is mosquitoes. There is no facts about lethal outcomes. Australian X-disease (Murray Valley encephalitis). The disease is observed in Australia. The reservoir in nature is wild birds. It is possible that mammals are the reservoir of infection too. The lethality is 50 − 70 %.

6. *Kyansanur forest disease*. This encephalitis occurs in New Guinea, in India. The reservoirs of infection are monkeys, palm squirrels, forest rats. The factors of transmission are ticks. The lethal rate is 5 − 10 %.

7. *Scotland encephalitis (Scotland sheep's encephalitis)*. The disease is widespread mainly in Scotland, rarely in Northern England. The reservoir of

infection in nature is sheep. The factor of transmission is ticks. In human the course of the disease is light. There are no lethal outcomes.

Japanese encephalitis and tick encephalitis are widespread and more studied forms of arboviral infections.

JAPANESE ENCEPHALITIS

Synonyms: mosquito, autumn encephalitis.

Japanese encephalitis is an acute viral transmissive, seasonal zoonotic infection. The disease is characterized by development of serious meningoencephalitis, expressive general toxic syndrome, high temperature. The disease is accompanied by high percent of invalidity and firm residual manifestations.

Historic reference

The clinical manifestations of Japanese encephalitis was described more than 100 years ago. However, this disease was considered as epidemic cerebrospinal meningitis. Japanese encephalitis was recognized as independent disease in 1924 year.

Etiology

In 1933 Gayashi proved the viral etiology of the disease in Japan. In 1940 Shubladze and Smorodincev described virus in the Soviet Union. According to its characteristics virus is similar to virus of Sant-Louis encephalitis and West Nile-encephalitis. The agent of Japanese encephalitis is virus from genus *Flavivirus*, family *Togaviridae*, ecological group *Arboviruses*.

Flaviviridae are small (40 nm in diameter) enveloped viruses with single-stranded, positive-sense RNA genomes. Virions form on the endoplasmic reticulum of infected cells are released by exocytosis or cell lysis. Flaviviruses are readily inactivated by heat (56 °C, 10 minutes) detergents, ultraviolet irradiation, trypsin digestion, formaldehyde and chlorine and phenolic disinfectants.

The virus is replicated in a variety of vertabrate and arthropod cells in culture with or without producing of cytopathic effects; extensive serologic relatedness, due to shared group-specific antigens links members of the family; crossing is most extensive by hemagglutination inhibition, intermediate by complement fixation and least by neutralization tests.

Outbreaks of this disease has been registered in Japan, Russia, China, Korea, Vietnam, Philippines, India, Indonesia, Taiwan, Australia and on the coast of the Eastern Africa.

Epidemiology

According to its epidemic characteristics, grassland, sea, coastal and forest forms of natural focuses are differentiated. The reservoir of infection is mammals and birds. During the epidemic outbreaks the patient may be the source of

infection and also the domestic animals (horses, cows, pigs). These sources lead to formation of rural and urban focuses. The factor of transmission is mosquitoes of family *Culex*. The disease is registered in August – October.

Pathogenesis

After bite of mosquito, arboviruses enter the blood stream. The agents enter with blood stream the central nervous system. The agents multiply and cause the edema of the soft cerebral coverings and cerebral matter, edema and hyperemia of the cerebral vessels. The small hemorrhages are observed in the covering and in the region of the ophthalmic gyrus, striapallidaric system, where the formation of mildnessial focuses is possible. After reproduction in considerable quantity in the nervous system virus enters the blood again and affects the vessels and internal organs. There are venous overflow, hemorrhages, degenerative changes in the vessels and parenchymal organs with serous-hemorrhagic edema of the liver, kidneys, myocardium, and formed pneumonic focuses in the lungs.

Anatomic pathology

The most severe morphologic changes take place in the brain and spinal cord: differentiated serous-hemorrhagic inflammation of the covering and of the matter of the cranial and spinal cord. Perivascular infiltrations and granular infiltrations around vessels, nervous cells and zones of necrosis are observed. The most expressive changes occur in ophtalmic gyrus, substancia nigra, red matter, olivia, cerebellum.

Clinical manifestations

The next periods of the disease are differented: incubation period, initial, climax period and reconvalescence. Incubation period is from 5 till 21 days, in average – 8-14 days.

The duration of initial period is 3-4 days. The onset of the disease is acute with increase of the temperature till 40-41°C. The temperature is accompanied by chill and severe headache, especially in the area of forehead. At the same time the severe pain in loin, stomach, extremities, nausea, vomiting are observed. There are hyperemia of the face, sclera, upper part of the chest, increased sweat. The pulse rate is accelerated till 120-140/min. The arterial pressure increases. The pain of muscles is frequently marked. Rigidity of occipital muscles, increase of muscle's tonus and increase of tendon reflexes are observed. In severe course of the disease death of the patient may occur.

Climax period is characterized by progressive symptoms of the local brain damage. Meningeal syndrome increases. The depression of consciousness till coma is marked. Psychial disorders appear frequently: delirium, hallucinations.

Muscular tonus of pyramidal and extrapyramidal character increases. Muscular hypertension spread on masticatory and occipital muscles. In case of severe damage of pyramidal system spastic hemipareses, monopareses and paralyses may arise.

In severe course of the disease clonic and tonic cramps develop. In some patients stereotonia is marked – frequent repetition of identical motions.

During examination of the blood neuthrophilic leukocytosis with shift of the formula to the left is observed, ESR accelerates. During cerebrospinal puncture, liquor is transparent. The mild lymphocytic pleucytosis is observed. The pressure of cerebrospinal liquor increases.

The duration of the period of reconvalescence is 4-7 weeks. The temperature is usually normal or subfebrile. Some signs of the organic damage of the brain are preserved (hemiparesis, disorder of the motions coordination, muscular, weakness, psychical violations). The late complications occur (pneumonia, pyelonephritis).

Complications

The most common complication is syndrome of brain edema. It may be also pneumonia. In the case of the recovery the residual manifestations such as firm paralyses of the limbs are observed. Sometimes psychical changes occur with considerable decrease of intellect till to idiotia.

Japanese encephalitis is severe disease with lethal rate from 25 % till 80 %. Death becomes more frequent during the first 7 days in state of coma, bulbaric manifestations and cramps.

Diagnosis

The diagnosis is based on the epidemiological data, season, typical clinical signs. Diagnosis is confirmed by isolation of virus from the blood and cerebrospinal fluid at the first days of the disease. The serological methods of diagnostics may be used from the second week of the disease (complement fixation, indirect hemagglutination, reaction of neutralization of virus).

Differential diagnosis

The differential diagnosis is performed with tick encephalitis, serous meningitis and encephalites of the other etiology.

Treatment

Specific treatment is performed with use of hyperimmune horse's serum and gammaglobulins. Pathogenetic therapy includes desintoxicative therapy, diuretics, hyperbaric oxygenation. During of the period of the recovery the massage, physiotherapy are indicated. Dibasol, prozerin, galantamin are also prescribed.

Prophylaxis

Specific prophylaxis in the endemic regions is performed by means of killed vaccine. It is necessary to vaccinate both people and domestic animals in focuses of infection. During epidemic outbreaks passive immunization of the people is performed with specific gammaglobulin. The methods of prophylaxis are use of repellents and the defense from the mosquitoes.

TICK ENCEPHALITIS

Synonyms: spring-summer, Far East tick encephalomyelitis. Tick encephalitis is typical seasonal natural-focal transmissive infection, cuused by *Flavivirus* species in ecological group *Arboviruses*.

Historic reference

As a new nozologic form tick encephalitis was discovered in 1937 in the Far East by Chumakov, Chubladze and other during special expedition. The leader of this expedition was famous scientist L.A. Zilber. During a short period agent and the factor of transmission of the disease were discovered. The epidemiological features of tick encephalitis, clinical manifestations, pathomorphology were studied, also methods of specific prophylaxis and treatment were elaborated. The original course of the disease as two-wave-like type (milk fever) was described by Smorodincev and Chumakov in 1951-1954. In this case the agent of the disease was isolated from goat and cow milk.

Etiology

The agent of tick encephalitis belongs to *Flavivirus* species in ecological group of *Arboviruses*. This is RNA-virus, covered by a protein membrane. In connection with the peculiarities in antigenic structures viruses are divided on west and east types, causing various nozogeographical forms of tick encephalitis.

Virus is very well cultivated at the hen's embryos and also on the different cell's cultures. The white mices, monkeys, goat, sheep and horses may be used as laboratory models for study of infection. Virus is unfirm to high temperature and different physical and chemical agents.

Epidemiology

Tick encephalitis is typical seasonal natural-focal transmissive infection. The basic reservoir and carrier of *Arbovirus* is ixodes ticks of varies types. The tick becomes infected through 6-7 days after sucking of blood from infected organism (different types of mammals, squirrels, moles, porcupines, rats, field mousses and also a man). The viruses are in the lymphatic system of the tick. Then they spread and concentrate in the sexual organs and salivary glands. Viruses are preserved during all life of the tick (till 4 years). The tick transfers viruses transovarially to the next generations of the ticks.

The infection of the ticks is supported with help of many forest mammals. There is an alimentary way of the transmission of infection in tick encephalitis due to use of unboiled goat or cow milk.

There are 3 types of focuses of the disease: natural focuses, transitional focuses with changes of biocenosis in certain territory, antropurgic. Tick encephalitis is registered in antropurgic focuses in 70 % of all cases. The morbidity has seasonal character (May-June). The focuses of tick encephalitis are known in Central Europe, Scandinavia, Russia.

Pathogenesis

Penetration gate is mainly the skin, but the intestinal mucous membrane may be also a place of the entrance. Virus enters the lymphatic nodes, internal organs and central nervous system. Viruses multiply in the cells of the central nervous system. The virus causes the degeneration of the cells, multiplies in the mesenchymal cells and supports the inflammation. The inflammatory process is concentrated mainly in the gray matter of the brain and spinal cord, especially in the motile neurones of the brain and cervical part of the spinal cord. The middle brain, thalamus, hypothalamus and cerebellum are also involved into the process.

Anatomic pathology

Edema of the cerebral membranes and the brain matter is marked and also the dilatation and hyperemia of the vessels of the various calibres, hemorrhages occur. The extensive proliferation of the glial cells, necrobiosis of the frontal corns of the cervical part of the spinal cord, reticular formation and nucleus of cranial nerves are also observed. Hemorrhages are observed in mucous membranes of the stomach, intestine, extensive hyperemia of the internal organs occur.

Clinical manifestations

Incubation period is 10-14 days, but it may be from 3 till 60 days. The onset of the disease is acute, with high temperature till 40.0 − 41.0 °C. The disease is accompanied by chill, severe headache, pains in the loin, region pains in the eyeballs. In some cases short prodromal period occurs: weakness, fatigue, headache, sleeplessness, sometimes psychic violations. The next phases are differented in the course of the disease: initial phase with predominance of general toxic syndrome; the phase of neurological disorders with different variants of the central nervous system lesion; the phase of outcomes (recovery or residual manifestations − pareses, paralyses).

There are 5 principal forms of the disease:
1. Feverish form.
2. Meningeal form.
3. Meningoencephalitic form.
4. Meningoencephalomyelytic form.
5. Polyradiculoneuritic form.

It's worth to underline that the severe paralytic forms of tick encephalitis occur more frequently due to eastern variant of the course (Far East, Siberia). In accordance with gravity of the course of the disease the next types of tick encephalitis are differented:

1. Mild form with fever during 3-5 days, signs of the serious meningitis and recovery during 3-5 weeks.

2. Middle serious form with meningeal symptoms and recovery during 1.5-2 month.

3. Serious forms with high lethal rate, lingering course, uncomplete recovery with pareses and paralyses.

The fulminate forms are known too. The fulminate forms may be finished by death of the patient during the first day of the disease.

In usual course of tick encephalitis the signs of the damage of the central nervous system are noted from the first days or sometimes from the first hours (pareses, paralyses of the limbs, cramps, disorders of the cerebral nerves.

The violation of the consciousness is observed. It is possible delirium, soporotic state, coma. There is hyperemia of the face, neck and chest, conjunctivitis. The decreased arterial pressure, bradycardia, muffed heart tones are marked. In serious course of the disease myocardiodystrophy develops. It may be development of acute heart failure. Frequently, the disorders of the respiratory center are revealed. It may lead to respiratory failure. It is possible the development of edema of lungs on the background of disorder of myocardium.

In alimentary infection the disorders of intestine is noted. It is accompanied by meteorism, constipations, hepatolienalic syndrome. In the peripheral blood expressive neurotrophilic leukocytosis with the shift of the formula to the left, increased ESR are observed.

Feverish form of tick encephalitis is characterized by the rapid course with development of general toxic syndrome.

Meningeal form is characterized by development of general toxic syndrome and signs of serous meningitis. The severe headache, fever, vomiting are noted. The meningeal signs are revealed: rigidity of occipital muscles, Brudsyndky's symptoms, Kernig's symptom. In some cases the cramps and loss of conciousness may observed. In cerebrospinal puncture the increased pressure of liquor is noted. During testing cerebrospinal liquor the lymphocytic pleocytosis, increased of containment of protein, sugar and chlorides are determined.

Meningoencephalitic form is accompanied by diffusive or local disorder of the brain. In diffusive disorder the manifestations of brain's coma come out on the first plan. The gravity of the state increases due to progressing of edema of brain: from light soporosic state till deep coma. In state near coma the hallucinations may be observed and also delirium, psychomotoric excitement. Cramps of skeletal muscles are marked. During local damage of the nervous system the neurological symptoms are determined in zone of the damage of the substance of central nervous system. Thus in damage of the white substance of the cerebral brain spastic paralysis and pareses of the extremities may arise depending on localization of the pathological process and damages of the cranial nerves and also disorder of the speech. Frequently, hyperkinesises and attacks of the cramps are observed.

Besides that the signs of the violations of innervation of the eyes (diplopia, ptosis, squint) and damages of the nucleuses of the cranial nerves may observed depending on localization of viral damages of the brain.

Bulbaric symptoms (dysphonia, dysarthria, dysphagia) arise due to damage of the basis of the brain. In increase of bulbaric signs lethal outcomes may be due to disorder of the breath and asphyxia.

Meningoencephalopolyomyelitic form of the disease is characterized by general toxic, meningeal syndromes and sings of diffusive encephalitis, local encephalitis and damage of grey matter of spinal cord. Due to this flabby pareses develop from 3 – 4 days of the disease, especially of the muscles of the neck, upper extremities and shoulder belt. Rarely the intercostal muscles and diaphragm are damaged. Subsequently the atrophy of the muscles of the neck, shoulder belt and hands develop. The head turns down towards the chest. The volume of the movements of the upper extremities is limited harshly, till full loss of the functions. In rare cases, the damages of the lower extremities may occur too, with violation of the function of the pelvic organs.

Polyradicyloneurotic form of tick encephalitis is manifested by general toxic, meningeal symptoms and signs of the damage of the radices and peripheral nerves.

Two-wave meningoencephalitis (two-wave milk fever) is registered in European focuses of tick encephalitis. This form is characterized by development of two phases of the temperature reaction. The duration of every wave is 2-15 days with interval 1-2 weeks. The first wave of the temperature is accompanied by predominance of general toxic syndrome. The second wave is characterized by development of meningeal signs with frequent positive dynamics and complete recovery without residual appearances.

Complications

The most common complications are asymmetric lower motor neuron paralyses and others neuropsychiatric residua.

Diagnosis

The diagnosis of tick encephalitis is based on the epidemiological and laboratory data.

The specific diagnosis is concluded in detachment of the virus from the blood and cerebrospinal liquor in the early periods of the disease (4-7 day). The different cultures are used for this purpose – chicken's embryo, kidney's epithelium and other. Besides that, the biological method of the of infection by material from the sick infant white mouses is used. The identification of the viruses may be performed also with help of the method of the fluorescence antibodies. The diagnosis may be confirmed serologically by method of pair serums with help of the complement fixation reaction, indirect hemagglutination and neutralization.

Differential diagnosis

The differential diagnosis of tick encephalitis is performed with meningites and encephalites of other etiology (meningococcal infection, tuberculosis, viral diseases), with polyomyelitis, vascular damages of the brain, with coma of different

genesis (uremic coma, diabetic coma), tumors of the central nervous system, abscess of the brain. It's worth to underline the leading role of the epidemiological anamnesis.

Treatment

The specific treatment of tick encephalitis is performed with help antiencephalitic donor's gammaglobulin, which is injected in a dose of 5-10 mL intramuscularly during 3 days. The course of the treatment is necessary to repeat in case of severe form of encephalitis.

The pathogenetic therapy plays the great role. The remedies for desintoxication, dehydration, sedative remedies and hyperbarric oxygenation are used. In severe cases the artifical ventilation of the lungs is necessary.

Prophylaxis

The prophylaxis of tick encephalitis is performed in the area of the disease. The active specific prophylaxis is performed by epidemic indications over 1 month till appearance and activity of the ticks. The living or killed attenuative vaccines are used. The vaccine is injected subcutaneosly in a dose of 1.0 mL three times with interval of 3-4 months. The revaccination is performed one time every year (1.0 mL of vaccine, subcutaneously). Besides that the measures of the individual prevention are used – special clothes, repellents.

Control questions:

1. Classification of viral encephalitises.
2. Etiology and epidemiology of Japanese encephalitis.
3. Pathogenesis of Japanese encephalitis.
4. Anatomic pathology of disease.
5. Main clinical symptoms and signs of Japanese encephalitis.
6. Complications of encephalitis.
7. The methods of diagnosis of Japanese encephalitis.
8. Differential diagnosis of Japanese encephalitis.
9. Treatment of Japanese encephalitis.
10. Etiology and epidemiology of tick encephalitis.
11. Pathogenesis of tick encephalitis.
12. Main clinical symptoms and signs of tick encephalitis.
13. Complications of tick infection.
14. The methods of diagnosis of tick encephalitis.
15. Differential diagnosis of tick encephalitis.
16. Treatment of tick encephalitis.
17. Preventive measures against encephalitises.

RABIES

An acute infectious disease of mammals, especially carnivores, characterized by central nervous system wrilation followed by paralysis and death.

Historic reference

Rabies in dogs and the importance of saliva in its transmission may have been recognized in Pharaonic times and in China at least seven centuries BC. But it now seems doubtful whether much-quoted passages from the Babylonian pre-Mosaic Eshnunna code (around 2300 BC) and those attributed to Democritus (500-400 BC) referred specifically to rabies. Aristotle (322 BC) described rabies in animals but seems to deny that humans could be infected or could die from the disease. Celsus in "De medicina" (1st century) described hydrophobia in afflicted humans and recognized that the disease was spread by saliva, although his use of the Latin word "*virus*" did not imply a specifically infective origin. He discussed local treatment for the wound, including cupping, suction and cauterization, and the immersion of the patient in sea water. Other persistent myths that arose at that time were the idea that surgical excision of a dog's "tongue worm" (frenulum linguae) would protect it from rabies (as pointless and malicious an operation as that for "tongue tie" in children) and the belief that rabies could be generated spontaneously in dogs. In the sixteenth century, Fracastoro strengthened the concept of rabies as a contagious disease. A scientific or experimental approach to rabies was delayed until 1793, when John Hunter published his very important paper "Observations and heads of enquiry on canine madness". Hunter suggested that the transmission of rabies should be studied by inoculating saliva from rabid animals and humans into dogs and that attempts should be made to inactivate the "poison" in the saliva. These ideas may have inspired the experiments by Zinke (1804) and Magendie and Breschet (1813). Zinke used a paintbrush to introduce saliva from rabid dogs into incisions made in the skin of dogs, cats, rabbits, and chickens, which duly developed signs of rabies. In the same year Magendie and Breschet infected dogs with saliva from human patients with hydrophobia.

Galtier (1879) was responsible for an important technical advance. He found that rabbits could be infected with rabies and were far more convenient experimental animals than dogs. Pasteur adopted the use of rabbits in his studies of rabies beginning in 1880. He was the first to recognize that the major site of infection was the CNS. "Street virus" from a naturally infected dog was passaged through a series of rabbits to produce "fixed virus" with a consistent minimum incubation period of 6 or 7 days. Attenuation of the fixed virus was achieved by desiccation of rabbit

spinal cord for up to 14 days. Pasteur was able to protect dogs from challenge by immunizing them with the desiccated material, and in 1885 he used his vaccine for the first time in Joseph Meister, a boy severely bitten by a rabid dog. In 1891 passive immunization, using whole blood from vaccinated dogs and humans, was studied by Babes and Cerchez. Negri (1903) described his diagnostic inclusion body, which allowed the laboratory diagnosis of rabies. The introduction of the more specific and sensitive immunofluorescence method by Goldwasser and Kissling in 1958 has now largely replaced the Seller's stain for Negri bodies. The nature of the infective agent was further elucidated by Remlinger (1903), who showed that it would pass through a Berkefeld filter. It was not until 1936 that the size of the virus was established by reliable ultrafiltration studies (Galloway and Elford), and it was first seen as a bullet-shaped particle by electron microscopy in 1962 (Almeida and colleagues).

Improvements in Pasteur's vaccine were achieved by Semple and Fermi, who killed the virus rather than attenuated it, and by Fuenzalida and Palacios, who developed a suckling mouse brain vaccine which carried a lower risk of neuroparalytic complications.

Successful growth of rabies virus in tissue culture was achieved by Kissling in 1958, leading to the development of human diploid cell strain vaccine by Wiktor and his colleagues in 1964 and of other safe and highly potent tissue culture vaccines. The use of passive immunization with equine hyperimmune serum has been vindicated by the famous natural experiment following an attack by a rabid wolf on 29 people in Iran in 1954.

Etiology

The *Rhabdoviruses* (Greek "rhabdos" – rod) are a group of about 140 RNA viruses of plants, arthropods, fish, reptiles, birds, and mammals. Rabies and its five related viruses constitute the genus *Lyssavirus*. The rabies virion is approximately 180 x 80 nm.

Rabies virus is rapidly inactivated by heat: at 56 °C the half-life is less than 1 minute and, experimentally, the titer decreased by 10^5 infectious doses within 15 minutes. At 37 °C the half-life is prolonged to several hours in moist conditions.

Repeated intracerebral passage in animals of "street virus" from naturally infected animals results in a "fixed virus" of uniformly shortened incubation period and reduced pathogenicity which is used in vaccine production.

Epidemiology

Rabies is enzootic in mammal populations in most countries. Rabies-free countries include the British Isles, Norway, Sweden, Iceland, Mediterranean and Atlantic islands, Australia, New Guinea, Borneo, New Zealand, Malaysia, Singapore, Japan, Taiwan, and Antarctica. Rabies is spread among animals by bites, ingestion of infected prey, inhalation of aerosols

Important reservoirs of sylvatic rabies include skunks, foxes, raccoons, and insectivorous bats in North America, foxes in the Arctic, mongooses in Granada

and Puerto Rico, vampire bats in Trinidad, Mexico, Central and South America; wolves, jackals, and small carnivores in Africa and Asia; foxes, wolves, raccoon dogs, insectivorous bats in Europe. Rodents are unlikely to be important. Transmission is mainly by species such as foxes and bats in Europe and foxes, skunks, raccoons, and bats in North America. A separate strain of rabies virus may be peculiar to each mammalian host species.

Domestic dogs, and to a much lesser extent cats, are the main reservoir of urban rabies, which is responsible for more than 90 % of human cases worldwide..

Bat rabies was discovered in the Ukraine in 1964 when a rabid animal was found in Kiev, and two girls have died of bat-transmitted rabies, one in 1977 in Voroshilovograd and the other in 1985 in Belgorod.

The true global incidence of human rabies has been obscured by underreporting. Recently, a figure of 50,000 human deaths per year in India alone was suggested. Other countries reporting a high incidence of human rabies include Pakistan, Bangladesh, Sri Lanka, Philippines, Thailand, Indonesia, Brazil, Colombia, El Salvador, Peru, Ecuador, Mexico and China.

Intact skin is an adequate barrier to the infection, but broken skin and intact mucosa can admit the virus. Human infections usually result from inoculation of virus-laden saliva through the skin by the bite of a rabid dog or other mammal. Scratches, abrasions, and other wounds can be contaminated with infected saliva. The following are very unusual routes of human infection:

1. *Inhalation*. This has been reported in caves densely populated with insectivorous bats, which can create an aerosol of rabies virus from infected nasal secretions and possibly urine. In the United States there have been two laboratory accidents involving the inhalation of fixed virus during vaccine preparation.

2. *Vaccine-induced rabies (rage de laboratoire)*. In the worst incident, 18 people developed paralytic rabies in Fortaleza, Brazil, in 1960. The incubation period was 4 to 13 days after inoculation of a vaccine in which the virus had not been inactivated.

3. *Comeal transplant grafts*. Seven cases have been reported in France, the United States, Thailand, Morocco, and India in which infected comeae were transplanted from donors who had died of unsuspected rabies. Six of the recipients developed rabies and died.

4. *Transplacental infection*. This has been observed in animals but until recently had not been reported in humans, whereas a number of women who developed rabies encephalitis in late pregnancy were delivered of healthy babies. Transmission of rabies by breast milk is well documented in animals and has been suspected in at least one human case.

Animals can be infected through the gastrointestinal tract (per os and per rectum). In the previrologic era, there were claims that eating infected meat and sexual intercourse could transmit rabies to humans, but these routes remain unproven.

Pathogenesis

In experimental animals, injected rabies virus replicates locally in striated muscle but is soon detectable at neuromuscular junctions and neuromuscular and neurotendinal spindles. Direct invasion of nerve cells may also occur without prior infection of muscle. Various possible cell surface receptors for attachment of the rabies virus have been suggested, such as phosphatidylserine, carbohydrates, phospholipids, and sialylated gangliosides. At neuromuscular junctions and in the CNS, the postsynaptic nicotinic acetylcholine receptor is an important attachment site for the virus. Binding at these sites is competitive with cholinergic ligands, including the snake venom neurotoxin, alphabungarotoxin, which shows sequence homology with rabies virus glycoprotein.

Once inside peripheral nerves, the virus is carried centripetally by the flow of axoplasm to the dorsal root ganglia where there is further replication, explaining perhaps the characteristic prodromal symptom of paresthesia at the site of the inoculation. Spread along peripheral nerves can be blocked experimentally by local anesthetics, metabolic inhibitors, and section of the nerves. Spread is rapid through the spinal cord and brain, and there is massive viral replication on membranes of neurons and glial cells and direct transmission of virus from neuron to neuron via the synapses. Virus also exists free and spreads within extracellular spaces such as the CSF. In the early stages of the encephalomyelitis, there is selective infection of certain neuronal populations. Finally, there is a phase of passive centrifugal spread of virus from the nervous system in the axoplasm of many efferent nerves, including those of the autonomic nervous system. Virus has been found in many tissues including skeletal and cardiac muscle, intestine, kidney, liver, pancreas, and brown fat. Extraneural viral replication has been observed in salivary glands, brown fat, and cornea. Virus is shed from salivary and lacrimal glands, taste buds, respiratory tract, and rarely in urine and milk. Viremia has rarely been detected in animals and is not thought to be involved in pathogenesis or spread.

Anatomic pathology

Rabies is an acute nonsuppurative meningoencephalomyelitis. By the time the patient dies, ganglion cell degeneration, perineural and perivascular mononuclear cell infiltration, neuronophagia, and glial nodules may be widespread throughout the brain, spinal cord, and peripheral nerves. However, considering the clinical severity, changes are often surprisingly mild. Inflammatory changes are most marked in the midbrain and medulla in furious rabies and in the spinal cord in paralytic rabies. The diagnostic intracytoplasmic inclusion bodies (Negri bodies) contain viral ribonucleoprotein and probably fragments of cellular organelles such as ribosomes, giving the essential internal structure. They are found in up to 80 % of human cases and are most numerous in the pyramidal cells of Ammon's horn in the hippocampus, in cerebellar Purkinje cells, and in

the medulla and ganglia. Apart from these inclusion bodies there are no histologic features that distinguish rabies from poliomyelitis or other forms of viral encephalitis. The brain stem, limbic system, and hypothalamus appear to be most severely affected. A spongiform encephalopathy has been demonstrated in skunks and foxes. It probably represents an immunologic effect of infection. Extraneural changes include focal degeneration of salivary and lacrimal glands, pancreas, adrenal medulla, and lymph nodes. An interstitial myocarditis with round cell infiltration has been described. This may be associated with cardiac arrhythmias. The brain of a fatal human case of Mokola virus encephalitis showed perivascular cuffing with lymphocytes and lymphoblastoid cells. Neurons contain large numbers of homogeneous cytoplasmic inclusion bodies, which were quite different in size and appearance from Negri bodies.

Clinical manifestation

The incubation period is between 20 and 90 days and more than two-thirds of cases, with an extreme range of 4 days to more than 20 years. In some animals, latent infections can be reactivated by corticosteroids and stress, providing a possible explanation for the rare authentic reports of very long incubation periods in humans. Facial and severe multiple bites, transmission by corneal transplant, and accidental inoculation of live virus (rage de laboratoire) are associated with relatively short incubation periods. A few days of prodromal symptoms may precede the development of definite signs of rabies encephalomyelitis. These may consist of fever, changes of mood, and nonspecific "flulike" symptoms, but in more than one-third of cases itching, neuritic pain, or paresthesia at the site of the healed bite wound suggests impending rabies. The existence of two distinct clinical patterns of rabies, furious (agitated) and paralytic ("dumb", "rage mue" or "rage muette"), depends on whether the brain or spinal cord is predominantly infected and may reflect differences in the infecting strain of rabies virus or in the host's immune response.

Furious rabies, the more common presentation in humans except those infected by vampire bats, is characterized by hydrophobia, aerophobia, and episodic generalized arousal interspersed with lucid intervals of normal cerebration. Hydrophobia is a reflex series of forceful jerky inspiratory muscle spasms provoked by attempts to drink water and associated with an inexplicable terror. A draft of air on the skin produces a similar reflex response, "aerophobia".

Initially, the spasms affect the diaphragm, sternomastoideus, and other accessory muscles of inspiration, but a generalized extension response may be produced ending in opisthotonos and generalized convulsions with cardiac or respiratory arrest. Without supportive care, about one-third of patients with furious rabies die during a hydrophobic spasm in the first few days of their illness. There is hyperesthesia and periods of generalized excitation during which the patient becomes hallucinated, wild, and sometimes aggressive. These grotesque symptoms are explained by a selective

encephalitis involving the brain stem and limbic system. In rabies, unlike most other encephalitides, patients may remain intermittently conscious and rational. Hypersalivation, lacri-mation, sweating, and fluctuating blood pressure and body temperature result from disturbances of hypothalamic or autonomic nervous system function. Conventional neurologic examination may fail to disclose any abnormality unless a hydrophobic spasm is observed. Physical findings include meningism, cranial nerve and upper motor neuron lesions, muscle fasciculation, and involuntary movements. Increased libido, priapism, and frequent spontaneous orgasms may be the presenting symptom in some patients, suggesting involvement of the amygdaloid nuclei. Furious rabies naturally progresses to coma and death within a week, but some patients have been kept alive for several months in intensive care units.

Paralytic rabies is apparently much less common than the furious form in humans but is frequently undiagnosed. The paralytic form of rabies was also seen in patients with postvaccinal rabies. It seems more likely to develop in patients who have received antirabies vaccine. After the prodromal symptoms (see above), paralysis, fasciculation, pain, and paresthesia start in the bitten limb and ascend symmetrically or asymmetrically. There is progression to paraplegia with sphincter involvement, quadriparesis, and finally paralysis of bulbar and respiratory muscles. Hydrophobia is usually absent. Patients with paralytic rabies may survive for several weeks even without intensive care.

Complications

A large number of complications have been documented in rabies, most occur during the coma phase. Neurologic complications reported in addition to those previously noted include increases in intracranial pressure that may occur during the late neurologic or coma phases; hypothalamic involvement producing inappropriate secretion of antidiuretic hormone and/or diabetes insipidus, and autonomic dysfunction leading to hypertension, hypotension, cardiac arrhythmias, or hypothermia. Seizures are common, may be generalized or focal, and may be accompanied by cardiac arrhythmias, cardiac arrest, or respiratory dysfunction. Respiratory complications occur in all cases. Hyperventilation and respiratory alkalosis appear to be common during the prodrome and early neurologic phase, whereas hypoventilation and respiratory depression develop routinely during the acute neurologic phase. Progressive hypoxia, which is not corrected by increasing the inspired oxygen concentration, and decreased pulmonary compliance also develop later. Cardiac supraventricular arrhythmias are common, and severe bradycardia and cardiac arrest may occur in association with hypoxia. Histologic evidence of myocarditis has been reported. The hypotension that accompanies these problems aggravates preexisting hypoxia, and death follows.

Diagnosis

In the mammal responsible of the bite, rabies can be confirmed within a few hours by immunofluorescence of acetone-fixed brain or spinal cord impression

smears, a technique that has replaced the classic Seller's stain for Negri bodies which is notoriously difficult to interpret. A simple ELISA test can be used if fluorescence microscopy is not available, and a sensitive avidin-biotin peroxidase method has recently been developed for use with formalin-fixed histologic sections.

Rapid examination of CNS tissue in animals suspected of being rabid is now preferred to observing them in captivity for 10 days. In patients, rabies can be confirmed during life by immunofluorescence of skin, and brain biopsies, but the corneal impression smear technique is falsely negative too often to be useful. Early in the illness, rabies virus can be isolated from saliva, brain, CSF, and even spun urine but not blood. Virus isolation in neuroblastoma cell cultures can produce a result in 2 to 4 days instead of the 2 to 3 weeks required for the traditional intracerebral inoculation of mice. In patients who have not been vaccinated or given rabies immune globulin, rabies antibody in serum and especially in the CSF is diagnostic of rabies encephalitis. Rabies-neutralizing antibody leaks across the blood-CSF barrier in patients with postvaccinal encephalomyelitis, but a very high titer suggests a diagnosis of rabies. The only reliable method for distinguishing rabies from postvaccinal encephalomyelitis during life is by the immunofluorescence of skin biopsies. In rabies, lymphocyte pleocytosis rarely exceeds a few hundred cells per microliter. A neutrophil leukocytosis is commonly found in the blood.

Differential diagnosis

The spasms of pharyngeal tetanus may resemble hydrophobia, and this disease can also complicate an animal bite. Severe tetanus is distinguished by its shorter incubation period, the presence of trismus, the persistence of muscular rigidity between spasms, the absence of pleocytosis, and a better prognosis. The rare encephalopathy complicating serum sickness and anaphylactic reactions to Hymenoptera venoms are said to resemble rabies encephalitis. Rabies phobia is an hysterical response to the fear of rabies. It differs from true rabies in its shorter incubation period, often a few hours after the bite, by the emphasis on aggressive and dramatic symptoms, and by its excellent prognosis. Few hysterics could accurately simulate a hydrophobic spasm.

Paralytic rabies should be considered in patients with rapidly ascending flaccid paralysis, suspected Guillain-Barre syndrome, and transverse myelitis. In tropical developing countries that are still dependent on Semple-type and suckling mouse brain rabies vaccines, the most important differential diagnosis is postvaccinal encephalomyelitis. This usually develops within 2 weeks of the first dose of vaccine but has no clinical or laboratory features that reliably distinguish it from rabies while the patient is still alive, except for the absence of demonstrable rabies antigen in skin biopsies (see below). In poliomyelitis there are no sensory abnormalities. Herpes simiae (B virus) encephalomyelitis, which is transmitted by monkey bites, has a shorter incubation period than rabies (3 to 4 days).

Vesicles may be found in the monkey's mouth and at the site of the bite. The diagnosis can be confirmed virologically and the patient treated with acyclovir.

Treatment

Human rabies remains virtually incurable. Intensive care offers the only hope of prolonging life and, perhaps in a very few cases of paralytic rabies or infection with attenuated virus, of survival. Problems arising during intensive care include a variety of respiratory complications such as aspiration pneumonia, pneumothorax, and respiratory arrest, cardiac arrhythmias, hypertension, pulmonary edema and effects of myocarditis including congestive cardiac failure, generalized convulsions, cerebral edema, inappropriate secretion of antidiuretic hormone or diabetes insipidus, polyneuropathy, hyper- and hypothermia, and hematemesis associated with ulceration or tears in the mucosa of the upper gastrointestinal tract. Heavy sedation and analgesia should be given to relieve the agonizing symptoms. Immunosuppressant agents, including corticosleroids, rabies hyperimmune serum (which may have accelerated death), antiviral agents such as ribavirin, and alpha-interferon have not proved useful. Studies of intrathecal live attenuated vaccines in animals suggest the possibility of applying the treatment in human cases.

Prophylaxis

In rabies endemic areas, those at high risk of exposure to rabid animals should be given pre-exposure vaccination. These include veterinarians, health care personnel, laboratory workers, and dog catchers. In areas where animal rabies is highly prevalent, especially among domestic dogs, there may even be a case for including rabies vaccine in the expanded programs of immunization for children. In nonendemic areas those who come into contact with imported mammals in quarantine, who work with rabies virus in laboratories, or who intend to travel to rabies endemic areas should be vaccinated. Travelers at particular risk of exposure to rabies are zoologists and other field workers, foresters, cave explorers, and those whose work involves walking and cycling in urban and rural areas of India, Southeast Asia, and Latin America. Only tissue culture vaccines are safe enough to use for pre-exposure prophylaxis.

Postexposure prophylaxis. Cleaning the wound as soon as possible after a bite or other contact with a rabid animal is essential first aid and is particularly effective for superficial wounds. The wound should be scrubbed with soap or detergent and generously rinsed under a running tap for at least 5 minutes. Foreign material and dead tissue should be removed under anesthesia. The wound should be irrigated with a viricidal agent such as soap solution, povidone iodine, 0.1 % aqueous iodine, or 40 to 70 % alcohol. Quaternary ammonium compounds, hydrogen peroxide, and mercurochrome are not recommended. Suturing may inoculate virus deeper into the tissues and so should be avoided or delayed when possible. The risk of other viral, bacterial, fungal, and protozoal infections must be considered after bites by animals and humans.

Control questions:

1. Etiology, epidemiology and incidence of rabies.
2. Pathogenesis of rabies.
3. Anatomic pathology of disease.
4. Immunology response to rabies encephalomyelitis.
5. Response to vaccination.
6. Main clinical symptoms and signs of human rabies encephalomyelitis.
7. Laboratory methods of rabies diagnosis.
8. Differential diagnosis of rabies.
9. Treatment of human rabies encephalomyelitis.
10. Prevention and control of rabies.
11. Pre- and postexposure prophylaxis.

TETANUS

Tetanus is a disease of the nervous system characterized by persistent tonic spasm, with violent brief exacerbations. The spasm almost always commences in the muscles of the neck and jaw, causing closure of the jaws (trismus, lockjaw) and involves the muscles of trunk more than those of the limbs. It is always acute in onset, and a very large proportion of those affected die.

Historic reference

Tetanus was well known to the ancients, descriptions by Egyptian and Greek physicians survive to the present. They recognized the frequent relationship between injuries and the subsequent development of fatal spasms. Cowers provided the quintessential description of tetanus in 1888. Nicolaier isolated a strychnine-like toxin from anaerobic soil bacteria in 1884, 6 years later. Behring and Kitasato described active immunization with tetanus toxoid. This latter discovery should have reduced tetanus to a historical curiosity, but we still fail to fulfill this promise.

Etiology

Clostridium tetani is an obligate anaerobic bacillus that is gram-positive in fresh cultures but that may have variable staining in older cultures or tissue samples. During growth, the bacilli possess abundant flagellae and are sluggishly motile. Two toxins, tetanospasmin (commonly called tetanus toxin) and tetanolysin, are produced during this phase. Tetanospasmin is encoded on a plasmid, which is present in all toxigenic strains. Tetanolysin is of uncertain importance in the pathogenesis of tetanus. Mature organisms lose their flagellae and develop a terminal spore, coming to resemble a squash racquet. The spores are extremely stable in the environment, retaining the ability to germinate and cause disease indefinitely. They withstand exposure to ethanol, phenol, or formalin, but can be rendered noninfectious by iodine, glutaraldehyde hydrogen peroxide, or autoclaving at 121 °C and 103 kPa for 15 minutes. Growth in culture is optimal at 37 °C under strictly anaerobic conditions, but culture results are of no diagnostic value. Antibiotic sensitivity is discussed below.

Epidemiology

The global incidence of tetanus is thought to be about one million cases annually or about 18 per 100,000 population. In developing countries, mortality rates are as high as 28 per 100,000.

Up to one-third of neonatal tetanus cases are in children born to mothers of a previously afflicted child, highlighting failure to immunize as a major cause of tetanus. Immunization programs clearly decrease neonatal tetanus deaths.

Acute injuries account for about 70 % of cases, evenly divided between punctures and lacerations. Other identifiable conditions are noted in 23 %, leaving about 7 % of cases without an apparent source. Other studies cite rates of cryptogenic tetanus as high as 23 %.

Pathogenesis

Tetanospasmin is synthesized as a single chain. The nature of the receptor to which tetanospasmin binds, previously thought to be a ganglioside, remains debated. The toxin enters the nervous system primarily via the presynaptic terminals of lower motor neurons, where it can produce local failure of neuromuscular transmission. Tetanospasmin appears to act by selective cleavage of a protein component of synaptic vesicles, synaptobrevin II. It then exploits the retrograde axonal transport system, and is carried to the cell bodies of these neurons in the brain stem and spinal cord, where it expresses its major pathogenic action.

Once the toxin enters the central nervous system, it diffuses to the terminals of inhibitory cells, including both local glycinergic interneurons and descending neurons from the brain stem. By preventing transmitter release from these cells, tetanospasmin leaves the motor neurons without inhibition. This produces muscular rigidity by raising the resting firing rate of motor neurons, and also generates spasms by failing to limit reflex responses to afferent stimuli. Excitatory transmitter release in the spinal cord can also be impaired, but the toxin appears to have greater affinity for the inhibitory systems. The autonomic nervous system is affected as well: this is predominantly manifested as a hypersympathetic state induced by failure to inhibit adrenal release of catecholamines.

Toxin binding appears to be an irreversible event. At the neuromuscular junction recovery depends on sprouting a new axon terminal: this is probably the case at other affected synapses as well.

Anatomic pathology

Due to spasmatic syndrome bone fractures, especially compressive spinal cord fracture, ruptures of muscles and tendines occur. Microscopy of sceletal muscles shows basophylic muscular fibres with signs of their degeneration and necrosis.

Clinical manifestations

Tetanus is classically divided into four clinical types: generalized, localized, cephalic, and neonatal. These are valuable diagnostic and prognostic distinctions, but reflect host factors and the site of inoculation rather than differences in toxin action. Terms describing the initial stages of tetanus include the incubation period (time from inoculation to the first symptom) and the period of onset (time from the first symptom to the generalized spasm). The shorter these periods, the worse the prognosis. Various rating scales are available. Certain portals of entry (compound fractures) are associated with poorer prognoses. Tetanus may be particularly severe in narcotic addicts, for unknown reasons.

Generalized tetanus is the most commonly recognized form, and often begins with trismus ("lockjaw", masseter rigidity) and a risus sardonicus (increased tone in the orbicularis oris). Abdominal rigidity may also be present. The generalized spasm resembles decorticate posturing, and consists of opisthotonic posturing with flexion of the arms and extension of the legs. The patient does not lose consciousness, and experiences severe pain during each spasm, which are often triggered by sensory stimuli. During the spasm, the upper airway can be obstructed, or the diaphragm may participate in the general muscular contraction. Either of these compromise respiration, and even the first such spasm may be fatal. In the modern era of intensive care, however, the respiratory problems are easily managed, and autonomic dysfunction, usually occurring after several days of symptoms, has emerged as the leading cause of death.

The illness can progress for about 2 weeks, reflecting the time required to complete the transport of toxin, which is already intra-axonal when antitoxin treatment is given. The severity of illness may be decreased by partial immunity. Recovery takes an additional month, and is complete unless complications supervene. Lower motor neuron dysfunction may not be apparent until spasms remit, and recovery from this deficit in neuromuscular transmission may take additional weeks. Recurrent tetanus may occur if the patient does not receive active immunization, because the amount of toxin produced is inadequate to induce immunity.

Localized tetanus involves rigidity of the muscles associated with the site of spore inoculation. This may be mild and persistent and often resolves spontaneously. Lower motor neuron dysfunction (weakness and diminished muscle tone) is often present in the most involved muscle. This chronic form of the disease probably reflects partial immunity to tetanospasmin. However, localized tetanus is more commonly a prodrome of generalized tetanus, which occurs when enough toxin gains access to the central nervous system.

Cephalic tetanus is a special form of localized disease affecting the cranial nerve musculature. Although earlier reports linked cephalic tetanus to a poor prognosis, more recent studies have revealed many milder cases. A lower motor neuron lesion, frequently producing facial nerve weakness, is often apparent. Extraocular muscle involvement is occasionally noted.

Neonatal tetanus follows infection of the umbilical stump, most commonly due to a failure of aseptic technique where mothers are inadequately immunized. Cultural practices may also contribute. The condition usually presents with generalized weakness and failure to nurse; rigidity and spasms occur later. The mortality rate exceeds 90 %, and developmental delays are common among survivors. Poor prognostic factors include age less than 10 days, symptoms for fewer than 5 days before presentation to hospital, and the presence of risus sardonicus or fever.

Complications

Thre are early and late complications of tetanus. Early complications are pneumonia, muscules ruptures, fractures of bones due to great muscle tension. The most common late complication is muscle contractures.

Diagnosis

Tetanus is diagnosed by clinical observation, and has a limited differential diagnosis. Laboratory testing cannot confirm or exclude the condition, and is primarily useful for excluding intoxications that may mimic tetanus. Electromyographic studies are occasionally useful in questionable cases. Such testing becomes more important when no portal of entry is apparent. Antitetanus antibodies are undetectable in most tetanus patients, but many reports document the disease in patients with antibody levels above the commonly cited "protective" concentration of 0.01 IU/L. Rare patients apparently develop antibodies that are not protective.

Attempts to culture *C. tetani* from wounds are not useful in diagnosis, because (1) even carefully performed anaerobic cultures are frequently negative; (2) a positive culture does not indicate whether the organism contains the toxin-producing plasmid; and (3) a positive culture may be present without disease in patients with adequate immunity.

Differential diagnosis

Strychnine poisoning, in which glycine is antagonized, is the only condition that truly mimics tetanus; toxicologic studies of serum and urine should be performed when tetanus is suspected, and tetanus should be considered even if strychnine poisoning appears likely. Because the initial treatment of tetanus and strychnine intoxication are similar, therapy is instituted before the assay results are available. Dystonic reactions to neuroleptic drugs or other central dopamine antagonists may be confused with the neck stiffness of tetanus, but the posture of patients with dystonic reactions almost always involves lateral head turning, which is rare in tetanus. Treatment with anticholinergic agents (benztropine or diphenhydramine) is rapidly effective against dystonic reactions. Dental infections may produce trismus, and should be sought, but do not cause the other manifestations of tetanus.

Treatment

The patient with tetanus requires simultaneous attention to several concerns. Attention to the airway and to ventilation is paramount at the time of presentation, but the other aspects of care, especially passive immunization, must be pursued as soon as the respiratory system is secure.

Tetanic spasms sometimes demand that the airway be secured before other lines of therapy are possible. An orotracheal tube can be passed under sedation and neuromuscular junction blockade; a feeding tube should be placed at the same time. Because the endotracheal tube may stimulate spasms, an early tracheostomy may be beneficial.

Benzodiazepines have emerged as the mainstay of symptomatic therapy for tetanus. These drugs are GABA agonists, and thereby indirectly antagonize the

effect of the toxin. They do not restore glycinergic inhibition. The patient should be kept free of spasms, and may benefit from the amnestic effects of the drugs as well. Diazepam has been studied most intensively, but lorazepam or midazolam appear equally effective. Tetanus patients have unusually high tolerance for the sedating effect of these agents, and commonly remain alert at doses normally expected to produce anesthesia.

The intravenous formulations of both diazepam and lorazepam contain propylene glycol; at the doses required to control generalized tetanus, this vehicle may produce lactic acidosis. Nasogastric delivery of these agents is often possible, but some tetanus patients develop gastrointestinal motility disorders and do not absorb drugs well. Intravenous midazolam (5-15 mg/h or more) is effective and does not contain propylene glycol, but must be given as a continuous infusion because of its brief half-life. Propofol infusion is also effective, but is currently very expensive, and the amount necessary to control symptoms may exceed the patient's tolerance of the lipid vehicle. When the symptoms of tetanus subside, these agents must be tapered over at least 2 weeks to prevent withdrawal. Intrathecal baclofen is also effective in controlling tetanus, but has no clear advantage over benzodiazepines. Neuroleptic agents and barbiturates, previously used for tetanus, are inferior for this indication and should not be used.

Rare patients cannot be adequately controlled with benzodiazepines alone; neuromuscular junction blockade is then indicated, with the caveat that sedation is still required for psychological reasons. All of the available drugs have side effects, including the potential for prolonged effect after the drug is discontinued. Vecuronium (by continuous infusion) or pancuronium (by intermittent injection) are adequate choices. These agents should be stopped at least once daily to assess the patient's progress, and to observe for possible complications.

Most tetanus patients will still have the portal of entry apparent when they present. If the wound itself requires surgical attention. This may be performed after spasms are controlled. However, the course of tetanus is not affected by wound debridement.

Passive immunization with human tetanus immunoglobulin (HTIG) shortens the course of tetanus and may lessen its severity. A dose of 500 units appears as effective as larger doses. There is no apparent advantage to intrathecal HTIG administration. Intrathecal HTIG has also been shown ineffective in neonatal tetanus. Pooled intravenous immunoglobulin has been proposed as an alternative to HTIG. Active immunization must also be initiated.

The role of antimicrobial therapy in tetanus remains debated. The in vitro susceptibilities of *C. tetani* include metronidazole, penicillins, cephalosporins, imipenem, macrolides, and tetracycline. A study comparing oral metronidazole to intramuscular penicillin showed better survival, shorter hospitalization, and less progression of disease in the metronidazole group. This may reflect a true advantage of metronidazole over penicillin, but it more likely corresponds to a

negative effect of penicillin, a known GABA antagonist. Topical antibiotic application to the umbilical stump appears to reduce the risk of neonatal tetanus.

Autonomic dysfunction generally reflects excessive catechol-amine release, and may respond to combined α- and β-adrenergic blockade with intravenous labetalol. Beta blockade alone is rarely employed, because the resulting unopposed alpha effect may produce severe hypertension. If beta blockade is chosen, the short-acting agent esmolol should be employed. Other approaches to hypertension include morphine infusion, magnesium sulfate infusion, and epidural blockade of the renal nerves. Hypotension is less common, but if present may require norepinephrine infusion. Myocardial dysfunction is also common, and may represent a further reflection of catecholamine excess.

Nutritional support should be started as soon as the patient is stable. The volume of enteral feeding needed to meet the exceptionally high caloric and protein requirements of these patients may exceed the capacity of the gastrointestinal system.

The mortality rate in mild and moderate tetanus is presently about 6 %; for severe tetanus, it may reach as high as 60 %, even in expert centers. Among adults, age has very little effect on mortality, with octogenarians and nonagenarians faring as well as middle-aged patients. Tetanus survivors often have serious psychological problems related to the disease and its treatment that persist after recovery, and that may require psychotherapy.

Prophylaxis

Tetanus is preventable in almost all patients, leading to its description as the "inexcusable disease". A series of 3 monthly intramuscular injections of alum-adsorbed tetanus toxoid provides almost complete immunity for at least 5 years. Patients less than 7 years of age should receive combined diphtheria-tetanus-pertussis vaccine and other patients combined diphtheria-tetanus vaccine. Routine booster injections are indicated every 10 years; more frequent administration may increase the risk of a reaction. Some patients with humoral immune deficiencies may not respond adequately to toxoid injection: such patients should receive passive immunization for tetanus-prone injuries regardless of the period since the last booster. Most young patients with human immunodeficiency virus (HIV) infection appear to retain antitetanus antibody production if their primary immunization series was completed prior to acquiring HIV. Vitamin A deficiency interferes with the response to tetanus toxoid. A recent report documented tetanus in babies of women immunized with toxoid later shown to be devoid of potency; this disconcerting report underscores the need for quality control in toxoid production.

Although any wound may be inoculated with tetanus spores. Some types of injury are more frequently associated with tetanus and are therefore deemed tetanus-prone. These include wounds that are contaminated with dirt, saliva or

feces; puncture wounds, including unsterile injections, missile injuries, burns, frostbite, avulsions and crush injuries. Patients with these wounds who have not received adequate active immunization in the past 5 years, or in whom immunodeficiency is suspected should receive passive immunization with HTIG (250-500 IU intramuscularly) in addition to active immunization.

Mild reactions to tetanus toxoid (local tenderness, edema, low-grade fever) are common. More severe reactions are rare, some are actually due to hypersensitivity to the preservative thiomersal.

Control questions:
1. Etiology, epidemiology and incidence of tetanus.
2. Pathogenesis of tetanus.
3. Anatomic pathology of disease.
4. Main clinical symptoms and signs of tetanus.
5. Laboratory diagnosis of tetanus.
6. Criteria of tetanus diagnosis.
7. Differential diagnosis of tetanus.
8. Treatment of tetanus.
9. Preventive measures against tetanus.

MALARIA

Malaria (from the colloquial Italian "mala" – bad, and "aria" – air) is an infection characterized by certain febrile disturbances caused by protozoan parasites of the class *Sporozoa* and of the family *Plasmodiidae*. Man is the intermediate host of these parasites, which undergo an asexual stage of development in the red corpuscles. The parasite undergoes a sexual phase of development in the *Anopheles* mosquito, which is hence the definitive host. Man acquires infection from the bite of such an infected mosquito. Clinically, malaria is characterized by periodic attacks of fever, associated with anemia and enlargement of the spleen, and if untreated, with cachexia and a deposit of black pigment in the various organs. The malady is amenable to treatment with quinine and several other synthetic compounds inimical to the life of the parasite.

Historic reference

Malaria was formerly supposed to be due to poisonous emanations from damp ground, hence the term "malaria", introduced into English literature about 1829. Hippocrates in his book on epidemics, noted the existence of periodic fevers, divided them into quotidian, tertian, quartan, and subtertian, and referred to the enlarged spleen. Celsus recognized 2 types of tertian fever, one benign and similar to quartan fever, the other in which the attack is of longer duration and far more severe in character, the fever occupying 36 of the 48 hours and not entirely subsiding in the remissions, but being only mitigated.

Columella, about 116 B.C., suggested that the virus of malaria emanated from marshes and associated the disease with insects originating in them which attacked man in swarms. Also in the time of Caesar, views were expressed by Varro that swamp air might be the cause of malaria and furthermore that animals, so small that the eye could not follow them, might transmit diseases by way of the mouth or nose. In view of our present knowledge, it is remarkable that Lancisi in 1718, should have associated marshes with the development of gnats, which insects he thought could not only introduce with their proboscides the putrefying organic matter of such swamps, but animalcules as well.

Etiology

The year 1880 was a most important one in the history of malaria, when Laveran first recognized the parasites of malaria while carrying on investigations as to the origin of the "pigmented bodies" and pigmented leukocytes. He observed not only spherical pigmented bodies, but also crescents, and in particular the flagellation of the male gamete, which demonstrated to him that these were living

organisms. He proposed the name *Oscillaria malarias* on account of the movements of the flagellate body, but this had to be dropped as not valid, the generic name *Oscillaria* having been previously applied to another organism.

In 1894 Manson formulated the hypothesis of the mosquito transmission of malaria. He based this upon facts he observed in tracing the life-history of filaria and upon the fact that in malaria the flagellation of the male gametocyte does not take place for several minutes after the removal of the blood from the peripheral circulation. He also suggested that larvae might feed upon infected mosquitoes dying upon the water and thus acquire the disease.

Ross for 2 years caused mosquitoes to feed upon the blood of malarial patients which contained crescents, but as he used insects of the genera *Culex* and *Aedes* no development of the parasites in the tissues of the mosquitoes occurred, in 1897 he used eight dappled-wing mosquitoes (*Anopheles stephens*) and in 2 of these, upon dissection, he noted the development of the pigmentary bodies to be different from anything he had observed in hundreds of dissections of other mosquitoes.

In 1886 Metschnikov, from observation of sporulating parasites in the brain capillaries at the autopsy of a malarial case, considered them to be coccidial in nature.

Four parasites, all of this genus, may give rise to malaria in man, the names of the species are *Plasmodium vivax* which produces benign tertian malaria, *Plasmodium malarias* — quartan malaria, *Plasmodium ovale* — another tertian parasite and *Plasmodium falciparum,* which causes malignant tertian malaria. Each of these species shows the following characters which are possessed by the genus, as it affects man.

One speaks of an "asexual cycle" of development of the parasite in man and a "sexual cycle" of development in the mosquito.

Trophozoite. The growing form of the parasite in the blood of man; it includes the ring and all stages onwards, except the fully grown gametocyte and the schizont.

Schizont. A form which is in process of dividing asexually; it is called "immature" when division has just begun and "mature" when division is complete, and the parasitized cell is just about to rupture.

Schizogony. A process of asexual reproduction by which the nucleus and cytoplasm divide into many subsidiary parts simultaneously, each part being a merozoite. The process occurs in the liver cells and red blood corpuscles of man.

Sporogony. A process or cycle of sexual reproduction, which results in the formation of sporozoites; in the mosquito.

Gametocyte. The stage of the parasite containing the gamete. The origin of these forms is not definitely known; they are probably derived from merozoites produced by schizogony in the blood stream.

Gametes. The male gamete or spermatozoon, and the female gamete or ovum before fertilization has taken place.

Zygote. The fertilized ovum.

Ookinete. A zygote capable of moving.

Oocyst. An ookinete which has settled down, become rounded and covered with a membranous cyst wall.

Hemocoele. This is the body cavity functioning as the blood vascular system in insects.

The species of parasites causing malaria in man differ from each other in morphology, but the general course of their life-history is similar. All of the parasites have an asexual and a sexual cycle of development. The first known as the endogenous cycle, is passed in man and the process of reproduction during this cycle is called schizogony. The second or sexual, known as the exogenous cycle, is passed in some species of mosquito and the process of reproduction during this cycle being called sporogony.

P. vivax

Asexual forms.

Small trophozoites. The ring or signet-ring form. The rings of *P. vivax,* the benign tertian parasite, are stout, large rings, which measure about one-third the diameter of the red cell.

Large trophozoites. The term large "growing" forms is applied to all forms of malaria parasite, which have grown beyond the ring but have not yet reached a stage when they can be classified as schizonts on one hand, or full-grown gametocytes on the other.

The large trophozoites of *P. vivax* are very irregular in shape, and of delicate structure; many pseudopodial processes are seen because the parasites were in active amoeboid movement at the moment the film was made, and have died, and been fixed, in various postures. These are evidence of the capacity for active though restricted amoeboid movement, which the name "vivax" implies. The vacuolic area, which is present at the ring stage and is characteristic of it, is no longer seen. Another change has occurred; the parasite, in addition to growing large has, in the process of its metabolism, produced fine grains of brown pigment or hematin, and these are contained in its body. They are probably derived from the hemoglobin of the infected red cell.

Schizonts. The mature schizont of the species is a body which is itself as large as a normal red cell, so that the parasitized corpuscle becomes distended and larger than the normal. The nucleus of the parasite has, at this stage, divided into numerous fragments, each enclosed in a portion of cytoplasm, thus forming daughter parasites or merozoites. In mature schizonts of *P. vivax* there are about sixteen merozoites. The pigment of the parent, at this stage, is collected in a clump and there is a portion of cytoplasm, enclosing this pigment which has not been used up in the process of merozoite formation, this is residual material.

Sexual forms.

Gametocytes. The full-grown gametocyte of *P. vivax* is rounded. It occupies most of the enlarged infected red cell, and is the same size as a normal red cell to

spite of this, it shows no sign of segmentation; the nucleus is still single and the cytoplasm undivided. The males and females are distinguished from each other by the characters given below under *P. falciparum,* but the pigment remains scattered and the diagnosis is less easy. The gametocytes of *P. vivax* are commonly found in the peripheral blood about the end of the first week of parasitemia.

P. malariae

Asexual forms.

Small trophozoites. The rings of *P. malariae,* the quartan parasite, are large, stout rings which measure about one-third the diameter of the red cell.

Large trophozoites. The large trophozoites of this species are not of the flimsy amoeboid structure seen in *P. vivax,* but are much more solid-looking. They very frequently assume a characteristic "band" form lying across the diameter of the red cell. The band may be narrow or wide, and may have the edges almost parallel, and well defined. The pigment present is much coarser and blacker than in *P. vivax*.

Schizonts. The mature schizont of this species, although it also nearly fills the cell, is considerably smaller than that of *P. vivax* since the infected red cell never enlarges, as with P. *vivax*. In *P. malariae,* moreover, the nucleus and cytoplasm have segmented into only about eight merozoites. At this stage, the pigment is collected into a dense black clump, around which, in some cases, the merozoites are arranged in a rosette-like regular manner.

Sexual forms.

Gametocytes. The full-grown gametocyte is rounded and occupies most of the infected red cell, which, however, is not enlarged. The nucleus and cytoplasm are undivided, and the coarse black pigment is scattered through it. Males and females can be distinguished as below, but not easily. The gametocytes of *P. malariae* appear irregularly and late in the infection.

P. ovale

This parasite morphologically has some characters of *P. vivax* and others of *P. malariae*.

Asexual forms.

Small trophozoites. The rings are stout and large, occupying about one-third of the red cell.

Large trophozoites. The large trophozoites of this species are solid-looking, not amoeboid, and there are occasional band forms.

Schizonts. The mature schizonts of this species give rise to about twelve merozoites.

Sexual forms.

Gametocytes. These are indistinguishable from those of *P. malariae* except for the stippled decolourised red cell. They appear early in the infection.

P. falciparum

Asexual forms.

Small trophozoites. The ring of *P. falciparum,* the parasite of malignant tertian malaria, is usually very delicate-looking and small, measuring only about one-fifth the diameter of the red cell. In *P. falciparum* again, the ring has frequently two nuclear dots of chromatin, which may either be placed close together on one side of the ring, or lie separate from each other, even on opposite sides of the ring. Further, in this parasite more commonly than in the other species, the nucleus of the ring may appear in the vacuolic white area. These delicate rings of *P. falciparum* may be seen on the margin of the red cell as if attached to the exterior of the corpuscle (marginal or accole forms), or may be drawn out in the process of spreading the film in a linear manner, with the nucleus elongated (bacillary forms). In this species, often more than one ring may occur in a red corpuscle; this condition of double or multiple infection of the cell is more frequent in malignant than in any of the other infections. But besides these very small rings, it is not unusual to find, in *P. falciparum* infections, rings of such a size and bulk that they cannot be distinguished from those of *vivax, malariae* or *ovale*. If therefore only one or two large stout rings are found in a preparation, it will be quite impossible to determine the species.

Large trophozoites. As we show in dealing with pathogenicity this parasite leaves the peripheral circulation as soon as it has passed the large ring stage, and completes its growth in the blood vessels of the internal organs. Consequently large trophozoites of this species are not found in the peripheral blood unless the patient is moribund.

Schizonts. This stage of the asexual cycle of *P. falciparum* remains in the internal organs and is not seen in the peripheral blood, except in moribund cases. The mature schizont contains about twenty-four merozoites.

Sexual forms.

Gametocytes. The full-grown gametocyte or mature sexual form in this species has a characteristic shape, like that of a curved sausage, and is usually referred to as a crescent. This, together with the peculiarities in the life history of this species referred to above, by which multiplication during the asexual cycle takes place in the internal organs, has been accepted as a generic distinction by some authors; they therefore call the malignant tertian parasite *Laverania falcipara* instead of *P. falciparum*. The crescents can be distinguished as regards sex in the stained preparations. The male or, as it is called, the microgametocyte, has pale blue cytoplasm, with the blackish-brown pigment of the parasite distributed through it and a more diffuse arrangement of the large nucleus. The female or macrogametocyte has dark blue cytoplasm, with the pigment collected together, around the compact small nucleus. The red cells in which they lie are frequently only faintly visible, as a pale-staining convex line which extends across the concavity of the crescent. These forms do not appear in the blood simultaneously

with the rings, at the commencement of the infection, but are seen usually about ten days later. In the tropics they are often so scanty that they cannot be found.

Epidemiology

Conditions which favour the presence and breeding of anopheles mosquitoes tend to the increase of malaria, and vice versa, whatever favors access of those insects and the parasites they contain, also favours the acquisition of malaria.

In subtropical regions subtertian malaria is a primary infection in summer and early autumn, hence the popular term – "cestioo-autumnal fever". This peculiarity can be explained to some extent by the higher atmospheric temperature required for its development in the mosquito. Hence, though benign and subtertian forms are frequently associated, and the latter can be acquired at any time in the tropics, it is only in the summer and early autumn that subtertian can be acquired in more temperate zones. When the temperature falls below 15 °C development of the oocyst in the mosquito is arrested, but when once the sporozoites have entered the salivary glands, they are capable of infecting man, even during the winter season.

Malaria incidence is usually endemic, but hyperendemicity is a distinct form, demanding for its production such an intensity of transmission that a high degree of tolerance to the effects of reinfection is induced in those who experience its effects over a number of years, especially as a result of repeated infections in early childhood.

Pathogenesis

Life history of the parasite comprises two cycles or phases of development:

a) schizogony in the tissues of man, which is succeeded by schizogony occurring in the blood stream of man; these form the asexual cycle of the parasite;

b) sporogony, the sexual cycle, which occurs in the body of an anopheline mosquito.

Schizogony. When the sporozoite is introduced into man's skin by the bite of an anopheline mosquito it passes into the blood stream from which it rapidly disappears to enter a parenchyma cell of the liver. Here a process of growth and multiplication occurs, known as preerythrocytic schizogony, which results in the development of a large schizont, containing thousands of tiny merozoites. The mature schizont ruptures about the seventh to the ninth day liberating the merozoites which enter the circulation and invade red blood corpuscles. This starts the phase of erythrocytic schizogony which, however, may not become demonstrable by the examination of blood films until one or two days later.

Erythrocytic schizogony occurs in the circulation and extends from the newly liberated merozoite which is ready to infect a fresh cell, to the rupture of the mature schizont with its contained daughter merozoites. This cycle occupies a period of forty-eight hours in *PP. vivax, ovale, falciparum* and seventy-two in *P. malariae,* for its completion. The merozoites attack fresh cells, and in them

develop into rings, after which the parasites grow through the large trophozoite stage, attain full size, and then proceed to reproduce by division. As soon as this has commenced, when there is evidence that the nucleus has divided and the cytoplasm begun to segment, the term "immature schizont" is applied. Later, when the parasite has reached the stage at which it is fully segmented, and when the merozoites are just about to be liberated by the disruption of the red cells, it is called a "mature schizont". The distended cell ruptures, and the merozoites are thus liberated into the plasma. The residual material is at the same time set free, and, with its contained pigment, is quickly ingested by fixed endothelial cells of the blood vessels, or by wandering phagocytes, usually large mononuclears. Such pigmented leukocytes may be found in stained films if the blood is examined soon after the schizonts have ruptured. The liberated merozoite contains no pigment, immediately enters a fresh red cell and starts the cycle again. As a result of repetition of the erythrocytic cycle and progressive invasion of fresh cells, the infected person in the course of ten days or so develops fever; the period of incubation may, however, be shorter or much longer than this.

There is strong indirect evidence to suggest that in the case of *P. vivax, P. ovale* and *P. malariae* the tissue phase of the parasite does not end with the rupture of the pre-erythrocytic schizont and the invasion of the circulation by its merozoites. It is believed that a cycle, known as exoerythrocytic schizogony, continues in the tissues, some of the liberated merozoites invading fresh liver cells and again proceeding to schizogony. According to this hypothesis, even when parasites are absent from the blood, schizogony is continuing repeatedly in the tissues, persisting often for years. On occasions merozoites are discharged into the circulation where they infect red blood corpuscles and thus recommence erythrocytic schizogony, causing parasitaemia. No such evidence exists in the case of *P. falciparum,* and it is thought that when the preerythrocytic schizonts of this species have discharged their merozoites into the blood stream the cycle of the parasite in the tissues ends.

Sporogony. The sexual or sporogony cycle occurs almost entirely in the anopheline mosquito. In this method of reproduction there are, however, as we saw, preliminary, and also terminal, stages in the blood. Certain merozoites, instead of repeating the asexual cycle, become gametocytes, of which some are male and some are female. These are found in the peripheral blood. If they are taken up by the mosquito in biting, further development very quickly occurs, the remains of the infected red cell being discarded during the process. The asexual parasites ingested with the blood by the mosquito are destroyed in the gut; it is only the gametocytes which survive, and are able to infect the insect. In the case of P. *falciparum,* as we saw, the gametocytes are crescent-shaped, and the first step in the development is that they assume a rounded form like those of *P. vivax* and P. *malariae*. The next step is, that in the male, or microgametocyte, the pigment is suddenly observed to be in violent commotion and soon several filaments are extruded

each of which contains a granule of the nuclear chromatin. These are extremely active, and it is they which caused the rapid movements of the pigment granules. They detach themselves and swim away; these are the male gametes or the microgametes, which correspond to spermatozoa. The female or macrogametocyte has meanwhile undergone a nuclear reduction process by which it is transformed into the female gamete or macrogamete. This is an unfertilized ovum, and it attracts the active microgametes, one of which penetrates and fertilizes it. After this, the ovum or zygote, as it is now called, is capable of slow movements and hence is known as an "ookinete". This passes between the cells lining the insect's gut, till it reaches the outer limiting membrane. It then ceases to move, becomes round and proceeds to grow, the membrane acting as a cyst wall. This stationary growing ookinete with its covering is called the oocyst. Since the zygote is simply the female malaria parasite after fertilization by the filamentous male gamete, there is still some pigment in it, and this can be detected inside the oocyst. The nucleus of the zygote divides repeatedly, and finally there are produced, inside the oocyst, thousands of minute thread-like structures called sporozoites. When the oocyst becomes mature it ruptures, and the contained sporozoites are set free in the insect's haemocoele, the circulation of which carries them to all parts of the mosquito's body.

Some of them invade the cells of the salivary glands, pass through them and reach the lumen, which communicates with the salivary ducts. The mosquito is now infective. When next it bites man, the salivary fluid containing the sporozoites passes into the skin wound. A mosquito may acquire and be able to transmit a double infection. It is possible for a single infective mosquito to transmit malaria to several people in succession, and at considerable intervals. The supply of sporozoites in the salivary ducts is replenished by a further passage of those in the hemocoele, through the gland cells, into the lumen.

The *sporozoite* is a narrow, slightly curved organism, it tapers at both ends, has an elongated central nucleus and is devoid of pigment. It is capable of slight undulatory movement As already noted, when it is inoculated into man it is carried in the blood stream to the cells of the liver, which it enters; there it rounds up, starts to grow, and so commences the asexual cycle in man.

The sexual cycle in the mosquito requires about eight to eighteen days for completion, depending on conditions such as moisture and temperature. In the case of *P. malariae* the sexual cycle in the mosquito is commonly as long as four weeks.

The asexual cycle can be started in a person otherwise than by the bite of an infective mosquito, for example, by inoculating blood which contains asexual forms, into a fresh subject. If it happens that the only forms present in the infected person's blood are gametocytes, such as the crescents of malignant tertian malaria, no infection will result, as these can only infect the mosquito, and do not infect man.

The first part of the cycle of sporogony described above, may be watched under the microscope, in ordinary fresh films of the blood containing fully developed gametocytes. The process can readily be followed on the slide, up to the exflagellation of the male gametocyte.

Alterations in the infected red corpuscles in malaria infections.

P. vivax. In the peripheral blood, infected corpuscles may be found containing any stage of parasite; as the organism grows, after the ring form, the red cell enlarges and, at the same time, becomes pale. If the preparation is heavily stained there may be seen on the infected corpuscle a very fine red stippling called Schufmer's dots; these are more plentiful, much smaller, and more constant than are the Maurer's spots in *P. falciparum.*

P. malariae. The infected red cell is not enlarged, nor does it show constant colour changes; neither Schufmer's dots nor Maurer's spots are present, though dots (Ziemann's) are occasionally seen.

P. ovale. The red cell containing the parasite is frequently of oval shape with irregular margin. It is pale, but seldom notably enlarged and Schufmer's dots are present.

P. falciparum. The only forms of this parasite which are commonly found in peripheral blood are rings, or crescents, or both. The infected red cell is not enlarged by the presence of the rings, but its circular outline is altered when it contains a crescent There is no change in the color of the red cells such as the fairly constant pallor — often obscured by Schufmer's dots — of those infected with *P. vivax,* but a few blotchy marks of relatively large size, called Maurer's spots, may be seen.

The pigment of the parasite are the dots on the infected corpuscles. It should be remarked that the malaria pigment hematin, is in the body of the parasite, and that this derives it probably from the red cell. Since it only arises as a result of growth and metabolism, it is natural that the young ring form should have none, and that the pigment should increase in proportion as the trophozoite grows at the expense of the red cell.

The conditions known as Maurer's and Schufmer's dots, are due to an altered staining reaction on the part of the cytoplasm of the red cells themselves. They are in the red cell, and not in the parasite, and are not pigment.

In addition to the changes in the red cell enumerated above, which depend on the particular species present, there is also, in infection by any malaria parasite, a varying degree of anemia. This may be very slight or extreme and there may, therefore, be seen in the uninfected red corpuscles some or all of the changes which have been mentioned under anemia.

Anatomic pathology

The pathology of malaria is based really upon subtertian infections (*P. falciparum*). Most of the lesions in the internal organs are due to infection of red

blood corpuscles with consequent disturbance of the oxygen supply to the tissues. The vascular flow within the organs is disturbed by vascular collapse, obstruction of the smaller vessels by auto-agglutination, thrombosis, infarctions and similar effects brought about by the clumping together of parasitised cells. All these factors slow down the circulation and cause "ludging" (Knisely) which is thought to be mainly due to the production of a fibrin-like substance. Cardiac and vascular failure may ensue. In addition there are explosive discharges of protein from the liberated merozoites and the disintegration of disrupted red cells, defunct parasites and extrusion of pigment. The spleen, when grossly enlarged, used to be popularly known as the "ague cake". Although it is apt to fluctuate in size it is most certainly always swollen during an acute attack. On section the surface is dark, at times almost black, dark-red, purple or chocolate color from congestion and melanin pigmentation. In severe subtertian infections, the parenchyma may be so softened as to be almost diffluent and so swollen that the capsule is tightly stretched. When the pulp is washed, the malpighian bodies stand out as gray particles.

In chronic cases perisplenitis develops from stretching or tearing of the capsule, so that rupture may occur spontaneously or as the result of violence. On microscopic examination the organ contains a large number of macrophage cells, the special cells of Billroth, fibrinous cords, and sinus-lining littoral cells. In the chronic stage there is replacement by fibrous tissue. The malpighian bodies shrink while the pigment becomes scattered. All erythrocytic stages of the parasites can be detected in the red cells (*P. vivax* or *P. falciparum*) as well as the merozoites set free in the pulp. Numerically they are more numerous than in any other organ.

Malaria pigment is readily recognized free within the tissue spaces and enclosed within the reticulo-endothelium, and especially in the mononuclear cells. In acute cases the reticulo-endothelial system becomes blocked with pigment and in the later stages this is also replaced by fibrous tissue. Areas of thrombosis and hemorrhagic necrosis also occur.

The liver is usually congested, enlarged, pigmented, and olive-brown in color, especially in the left lobe which receives the splenic blood. Glisson's capsule which surrounds the portal system is thickened and stretched. In chronic malaria there is fibrosis and round-cell infiltration which originates, it is thought, from the cryptozoic or tissue stages of the parasites. In infancy and early childhood, the enlargement, is mainly due to sinusoidal dilatation; in later years, the congestion is mainly confined to the center of the lobule, and so the appearance resembles that, of the "nutmeg" liver of heart failure. The slaty gray color frequently encountered is due to deposits of pigment. Parasitized erythrocytes and melanin (hemozoin) pigment are found within Kupffer cells.

It is probable that the slight periportal fibrosis which is commonly encountered in African livers has a dual pathology because, in addition to malaria, there is malnutrition which is responsible for diffuse, piecemeal necrosis of the hepatic

cells. Parasites, in all erythrocytic stages, are found in the sinusoids and in the parasitized erythrocytes. The parenchyma, cells do not usually take up malaria pigment, but contain granules of hemosiderin. Lysis of the red cells leads to obstruction and over-distension of the bile canaliculi which become obstructed by bile pigment. The parenchyma cells show all stage of degeneration, and in severe *P. falciparum* infections there is widespread focal necrosis surrounding the central vein. Small hemorrhagic areas may also be present.

Malaria pigment is now termed hemozoin, and is a compound of hematin which contains non-ionizable iron; hemosiderin also does so but it does not give the Prussian blue reaction with potassium ferrocyanide, unless first acted upon by nitric acid and hydrogen peroxide. In the kidneys, it is to be noted that albuminuria is common in malaria and may adumbrate serious renal damage, and this is specially true in subtertian and quartan infections. Sometimes there is azotemia with hyperpiesia and cardiac hypertrophy. In severe cases the lumen of the tubules becomes filled with granular casts and the cells show fatty changes resembling parenchymatous degeneration. Signs of glomerulonephritis are also sometimes present. In quartan nephrosis Surbek (1931) occasionally found the enlarged, pale, white kidneys typical of degenerative parenchymatous nephrosis.

The changes in the heart in subtertian malaria are edema due to cardiovascular failure. In the bone marrow the yellow and adipose tissues are very vascular. The red marrow is of a chocolate brown, especially at the periphery and this is due to deposits of pigment. Phagocytosis is evident with hemozoin, macrophages and parasitized cells in large numbers. In chronic cases the reticulo-endothelium is hypertrophied. In the marrow itself there is a normoblastic response. Occasionally megaloblasts may be seen and reticulocytes are increased in the peripheral blood.

In the pancreas there is often focal necrosis, affecting the nutrient vessels of the Islets of Langerhans. Rarely the pancreas is hemorrhagic. The suprarenals are attacked in subtertian malaria, resulting in partial or complete loss of lipoids in the cortex, with congestion and blockage of vessels with malaria parasites; this is probably responsible for algid symptoms in subterian malaria. In the placenta the maternal sinuses are packed with parasites interfering with the nutrition of the fetus, which may become infected at birth, possibly through the umbilical cord, or through a tear in the placenta. In the intestinal tract achlorhydria is common in the I acute stages. The blood capillaries are loaded with parasites and degeneration of the mucosa is encountered which may give rise to dysenteric symptoms in life.

The brain usually bears a leaden hue due to deposition of hemozoin and the presence of parasitized cells in the capillaries. The gray matter is smoky gray while the white matter is speckled with punctiform hemorrhages (cerebral purpura). The smaller capillaries become completely blocked with parasitized cells and the plugging is most common at the bifurcation of the blood vessels.

Malarial granulomata are focal degenerations in the brain substance, the result of former hemorrhages. Granuloma is sometimes an inappropriate term, for these lesions somewhat resemble tubercles and are formed by an agglomeration of glial cells around a focus of degeneration.

In massive infection the capillaries are blocked and thrombosed. As Maegraith has pointed out, thrombosis takes place. There are numerous small hemorrhages with "granulomata" in the subcortical zones. Clinically this is associated with malarial coma. Generalized toxemia is characterized by fits and convulsions. There are small and scattered hemorrhages. Embolism produces punctiform hemorrhages, especially in the corpus callosum.

Clinical manifestations

An attack of malaria may either be a primary attack or a relapse. A primary attack normally develops after an incubation period of 10-14 days; by direct blood inoculation it is about 11 days. In insect transmitted subtertian malaria, where the number of infecting bites is high, the incubation period tends to be shorter and may only be five days. In naturally transmitted benign tertian malaria, especially in Europe, there may be latent period of several months before symptoms appear; the latent period usually covers the winter months. *P. ovale* may also show very long latent periods (Trager and Most, 1963). This is known as latent malaria. The latent period preceding the primary attack is known as incubation latency; a period or periods following upon the primary attack are know as infection latency. In subtertian malaria there is no latency in the same sense as in benign tertian. The type of temperature curve, whether intermittent or remittent, is less significant than formerly considered to be the case. Thus primary benign tertian infections may produce a remittent temperature curve before assuming the classical intermittent character. Two or more generations of tertian parasites, maturing in the blood at different times, will produce quotidian fever and two or more generations of quartan will give a fever on two successive days — *quartana duplex* — or conversely on three successive days, a quotidian fever — *quartana triplex*.

Relapses are defined as recurrences of malarious symptoms and the reappearance of malaria parasites in the peripheral blood, following recovery from the initial attack. Therefore relapses must be distinguished from reinfections.

Recrudescences of malaria are defined as relapses of the patient at the time he is removed from the endemic area. Relapses often follow the cessation of suppressive treatment, exposure to cold, exertion, parturition, or surgical operations.

The characteristic ague is divided into three stages : (1) cold stage, (2) hot stage and (3) sweating stage. One or even all these stages may be absent on occasions, especially when the infection is of long standing, whilst in subtertian fever many symptoms are so bizarre that they may be most misleading, so as to enforce the conviction that in many respects it is quite a different disease.

Herpes on lips and nose (fever sores), often extensive, frequently follow the rigors and are an accompaniment of all forms of malaria. Similar eruptions have been noted on the ears.

Premonitory stage. For several days before the actual attack the patient may be conscious of headache, lassitude, a desire to stretch or yawn, aching in the bones, anorexia, sometimes vomiting.

Cold stage. This usually lasts one to two hours, and is the rigor, or "ague". The feeling of cold is intense and universal. The teeth chatter, the patient shivers from head to foot and wraps himself up in any garment he can lay his hands upon. Vomiting may be most distressing. The features are pinched, the fingers shrivelled and the skin blue like "goose-skin" (cutis anserina). The feeling of cold is purely subjective, because the temperature is rapidly rising. Children usually have convulsive fits.

Hot stage. The hot stage may last from three to four hours. The shivering abates and gives place to, or alternates with, sensations of great heat. The clothes are thrown off. The face is flushed; pulse full, bounding and usually dicrotic; headache intense; vomiting usual; respiration hurried; skin dry and burning; the temperature rising to 40 °C, sometimes 41.1 °C, rarely higher.

Sweating stage. This usually lasts from two to four hours. The patient breaks out into profuse perspiration with sweat literally running off him in streams, saturating clothes and bedding. With sweating the fever rapidly declines. Headache, thirst and distress give place to a feeling of relief and tranquillity. When it has ceased the patient may feel exhausted, but quite well and able to go about. The body temperature is now subnormal and remains so until the approach of the next paroxysm, one or two days later. The total duration of the fever cycle may be from six to ten hours.

Urine and feces in ague. During the cold stage the urine is abundant and limpid, and micturition frequent; during the hot sweating stages it is scanty, cloudy, sometimes albuminous. Urea excretion is increased during the rigor and hot stages, and so is that of the chlorides and sulphates. Phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. Augmentation in urea excretion commences several hours before the attack, attains its maximum towards the end of the rigor, and decreases during the terminal stages, though still above the normal figure.

A fleeting glycosuria has also been observed from time to time. The urine usually contains urobilinogen and urobilin in excess during the attack, but they decline with the temperature and form a valuable diagnostic sign, especially in subtertian malaria. The corresponding pigment in the feces (hydrobilirubin) is increased twenty times the normal amount whilst parasites persist in the blood.

The spleen during ague. The spleen is enlarged and painful during the rigor, but in early infections is not always palpable, a feature which became specially noticeable in the second World War in India, Birma, and New Guinea, in benign as well as in subtertian infections. At first, the enlargement recedes during remission, but later, when relapses and reinfections occur, it becomes permanent as in the "ague cake". In primary infections the spleen is soft and spongy and

therefore difficult to palpate, but in subsequent relapses it becomes harder and more fibrous. Spontaneous rupture of the spleen has been reported more frequently in *P. vivax* infections them with other species. Usually it is the result of violence, but Bearn (1961) has shown that in an adherent spleen it may be due to extensive subcapsular hematoma. Successful splenectomy does not necessarily extirpate the malarial infection.

Period of the day at which ague commences. Quite a large proportion of agues "come off" between midnight and noon or in the early afternoon. This time factor may constitute an important point in diagnosis, especially as pyrexial attacks somewhat simulating malarial agues may be caused by liver abscess, tuberculosis, *Escherichia coli* infections of the urinary tract and septic conditions, in all of which febrile recurrences are apt to take place during the afternoons or evenings.

Course of benign tertian and quartan fevers. Benign tertian ague usually lasts ten hours or less and may be taken as the type of a malarial attack. In some cases the rise of fever is rapid and high, and the temperature may reach 40.6 ° to 41.1 °C within an hour or so; on the other hand, in some cases none of the clinical phenomena are present and the temperature does not rise above 37.2°-37.8 °C. Benign tertian, unless complicated, is not usually fatal; but the persistent and relapsing character makes it a tiresome disease and, if prolonged, it may produce severe anemia and debility. It may also produce thrombocytopenia.

Certainly many strains of *P. vivax* seem to exist which differ in their virulence; some are mild, as in Holland; sometimes the fever is trivial and isolated attacks, without recurrence, are common enough. Various strains of *P. vivax* have been found to possess distinctive characters and vary in the number and frequency of the relapses they produce.

The presence of a rigor appears to be an index of severity. The mean maximum temperature for the paroxysms is 40.1 °C. As a general rule, the duration of a simple benign tertian infection before the parasites die out from the peripheral blood is nine months to one year after leaving the endemic area, but exceptions to this rule occur, as clinical relapses, with parasites in the blood, have been recorded as long as three years after the original infection. As it is seldom fatal, the pathology is not so well known as that of subtertian malaria, but it resembles it in a minor degree.

The fever in quartan malaria is generally smart while it lasts, and is well defined in its various stages, but it does not produce much systemic disturbance or cachexia or rigors. It has often been remarked that, whilst individual attacks of this infection are amenable to quinine and atebrin, the disease is more persistent than tertian or subtertian, so that attacks are apt to occur from time to time over a period of many years and may persist as long as 12-21. It is becoming increasingly realized that sometimes quartan parasites may be present in the blood without evoking any special symptoms. Parasites are usually scarce in the peripheral blood. They are more resistant to antimalarial drugs in the sense that they persist in the bloodstream for a week or more while the patient is taking the drug.

Quartan periodicity is the hall-mark of quartan malaria and is hardly ever found in any other disease. Double quartan and triple quartan fevers may be observed. In the latter the temperature course becomes quotidian. Occasionally, quartan fevers are encountered without splenomegaly and apparently when parasites can be found in the blood only after prolonged search: sometimes not at all, so that their true nature can be ascertained solely by the action of chloroquine by injection.

Relapses in quartan malaria may be of two forms: those occurring after a short interval are due to exacerbation of a low-grade parasitemia, but those in the longer interval of several months to release of exoerythrocyte parasites from the liver into the bloodstream.

Quartan malaria nephrosis. Although kidney changes are associated with subtertian malaria, nephrosis is commonest in countries where the quartan parasite predominates.

According to Giglioli both sexes are susceptible, and especially children, in whom quartan malaria is most common, but in adults males predominate. He regarded albuminuria in a febrile attack as an indication of parenchymatous nephritis; Goldie, on the other hand, took a less serious view and considered the pathological picture as one of nephrosis and due to the production of malarial toxin's over a long period.

Additional evidence of the association of the quartan parasite with nephrosis comes from Bruce-Chwatt and others in Nigeria and Giglioli in Guiana who have shown that this serious complication in children has disappeared since the success of DDT suppression campaigns.

Course of ovale tertian malaria. This type closely resembles benign tertian and the attack may be ushered in by an initial remittent phase; but, generally speaking, the attacks are sudden, short and mild, and not accompanied by any grave degree of anemia, whilst the rigors are more apt to take place; during the evenings. Rheumatic-like pains in various parts of the body, especially the lumbar region, are characteristic, and sometimes pain referred to the appendix may suggest appendicitis. There is usually no excess of urobilinogen in the urine. Occasionally severe infections are encountered, with rigors, a temperature of 40.6 °C, irregular tertian periodicity and persistent headache. It may evince considerable latency. Recurrences have never been observed. Peaks of fever are not usually as high as in benign tertian.

Course of subtertian or malignant malaria. There are probably many strains of *P. falciparum* differing from one another in virulence as James has shown with his Sardinian strain. Herpes labialis is commoner with this form.

In distinguishing subtertian malaria the rigor stage is relatively less marked, or may be absent entirely. The primary attack begins with a sense of chilliness. The hot and sweating stages are more prolonged and liable to be followed by an adynamic condition, together with vomiting, intestinal irritation, bone pains, anorexia, headache and supra-orbital neuralgia and a degree of moderate sweating. After apparent recovery from fever there is a tendency to recrudescence at shorter

intervals than in benign tertian. Subtertian fevers are accompanied by rapid hemolysis toxemia and succeeded by marked cachexia. The underlying pathology is due to the sporulation of parasites in the internal capillaries so that, at any time during the course, and especially in primary infections, symptoms of the gravest character may appear. The tendency for successive paroxysms to overlap, or to become subintrant, is marked. When intermissions are distinct the crisis is what is called "a double crisis". Thus, when the fever has attained its apparent fastigium, there is a drop of one or more degrees of temperature – a false crisis – followed by a fresh rise which is then succeeded by a true crisis. This peculiar phenomenon has been attributed to the presence of two generations of parasites in the blood, one of which matures somewhat later than the other; it occurs ordinarily in one other tropical fever: kala-azar. Such an infection may therefore produce a quotidian typhoid-like temperature chart. Even at this stage the temperature may not exceed 39.4 °C – 40 °C. The liver is usually enlarged and tender, especially in the region of the gall-bladder which itself is generally swollen and turgid with bile, as the result of extensive hemolysis. These phenomena may give rise to the impression of gallbladder disease.

Though this fever may be justly regarded as dangerous to life, yet it is singular that subtertian parasites may exist in the blood for months without seriously interfering with health. Sometimes attention is drawn in other directions - to edema of legs, diarrhea, dyspepsia or some other apparently small complaint, quite unconnected with malaria - and these may appear in men returning from West Africa in whom the first symptoms of ill-health may be noted after several weeks' residence in a temperate climate.

Manson said "What one sees in the peripheral circulation is only a reflection of the drama which is occurring in the internal circulation".

Bilious remittent. One type of subtertian fever – bilious remittent – has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhea, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish yellow or saffron tint of skin and scalars – a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified hemoglobin (serum bilirubin) free in the blood or deposited in the skin and sclerotics. Sometimes cases are seen with intense icterus, high serum bilirubin and jaundiced sclera, without splenomegaly, but with large numbers of parasites in the peripheral blood. This type may be readily mistaken for various forms of obstructive jaundice.

Pernicious attacks. The French neatly designate these acces pernicieux. They characterize subtertian infections, and may supervene in apparently mild cases and carry off the patient with horrifying suddenness – as suddenly as an attack of malignant cholera. Pernicious attacks are apt to develop in drug addicts. They are classifiable into: (1) *septiccemic* (or toxemic) type, accounting for about 30 %, with numerous parasites in the blood, death taking place from

cardiac failure; (2) *cerebral,* accounting for some 55 %, ending usually in coma, in which, compared with other forms, parasites are usually very scanty in the peripheral blood; (3) *algid,* with subnormal temperatures and a clinical syndrome resembling that of shock, accounting for some 14 %, and finally (4) *renal,* with edema and nephritic signs which amount to about 1 % of the total. Field found that the case mortality rates rose significantly when the patient, before treatment, showed 100,000 parasites per mm^3 of blood.

Cerebral forms.

In the course of what seems to be an ordinary malarial attack the body-temperature, instead of stopping at 40 °C or 40.5 °C, may continue to rise and, passing 41 °C, rapidly mount to 42 °C (or even, rarely, to 42.5 °C). The blood shows hyperinfection with *P. falciparum* and more than 5 % of erythrocytes are infected and most contain about two parasites in each corpuscle. The patient, after a brief state of maniacal or, perhaps, muttering delirium, becomes rapidly unconscious. The pupils are dilated and the corneal reflex absent. The fundi are usually normal. The skin is hot and burning. The legs are usually spastic. Fever sores (*herpes labialis*) are often observed around the lips and mouth. There is an almost distinctive facies. The pulse is rapid and dicrotic, and there may be generalized muscular twitchings. Splenic pain may be present. At first there is a disorientation with motor aphasia. Incontinence is usually a dangerous sign. Changes in behavior, such as insolence or insubordination, may often be encountered in the early stages, excitement, mania and coma then follow.

Coma. Sometimes the patient, without hyperpyrexia (the temperature perhaps not rising above, or even up to 40 °C), may lapse into coma. The coma may pass away with a crisis of sweating; on the other hand, an asthenic condition may set in and death supervene. There is often a paralytic squint, extensor plantar response and Cheyne-Stokes respiration. When subcortical hemorrhages are present, death usually ensues. There is a marked increase of pressure in the cerebrospinal fluid, with increase of lymphocytes up to 400, as well as of albumin and globulin. Occasionally, granules of malarial pigment may be found. It is important to note that parasites may be very scanty in the peripheral blood and not infrequently they may be absent altogether. The coma may persist for as long as 46 hours and then recovery ensue with quinine injections (or chloroquine).

Other cerebral manifestations are cerebral depression, excitation, cerebellar ataxia (Sawyer-Brown variety), behavior changes and character alterations, meningismus closely simulating meningitis. Rarely a focal spine lesion may cause paraplegia.

Algid forms.

The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface of the body or, in other words, by peripheral vascular failure. These symptoms usually co-exist with elevated axillary and rectal temperature. Flooding of the peripheral blood

with vast numbers of parasites in all stages of development − gametocytes as well as schizonts − is sometimes found. The prognosis is usually bad, but rarely this may be seen in an attack of average severity. It indicates a continuous fever of at least two weeks, or a relapse of short duration.

There are some misleading clinical forms of subtertian malaria which are important, for instance the gastric, choleraic, dysenteric, hemorrhagic, and edematous forms. The last with generalized anasarca were prevalent in war refugees from Givece (1945) and in the great Ceylon epidemic of 1934. Acute hemolitic anaemia, resembling pernicious anemia, may be a prominent of subtertian malarial cachexia. More rarely seen are the edematous forms with anasarca and ascites and also with nephritic signs with blood cells and albumin in the urine.

Complications

Complications of plasmodial infection are:

Plasmodium falciparum − cerebral malaria, including seizures and coma, acute renal failure, severe anemia, pulmonary edema, tropical splenomegaly (chronic). *Plasmodium vivax* − late splenic rupture (2-3 months after the initial infection). *Plasmodium malariae* − immune complex glomerulonephritis based on parasite antigen and host immuno-globulin (IgG).

Diagnosis

The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections; in the subtertian, however, fever may be most irregular, or there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity, but in early, and it may be very severe, cases it may not be sensibly enlarged at all, and therefore fails entirely as a clinical guide; usually, however, in the absence of splenic enlargement, splenic pain is present during the attack. Moreover, the patient may be suffering from some totally different disease, and the palpable spleen may be the result of a long-standing malaria infection, quite unconnected with the attack in question.

To the clinician accustomed to many cases, the general appearance of malaria patients, the bright glistening eye, set in rather a dusky orbit, contrasted with the pale and ochreous complexion, combine to create an almost diagnostic appearance. Amber colored urine due to excessive urobilinuria, especially in subtertian malaria, and even in the absence of parasites in the peripheral blood, may be suggestive.

Sudden fever in a previously healthy person who has recently arrived from a malarious country usually turns out to be malaria. The patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for, occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the conditions, may run a very severe course; this is especially the

case with recent arrivals from the west coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite lying dormant in the blood-stream perhaps as long as eight months; in the benign form a year or more. It should be borne in mind that, in the case of *P. vivax, P. malarias* and P. *ovale* all "prophylactic" drugs are in reality only suppressive. A possible diagnosis of malaria should therefore not be discounted on the grounds that drugs were continued for the advised 14 days after return to a non-malarious country.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. Tertian and quartan periodicity usually occur only in malarial disease, but have been seen in meningococcal septicaemia.

Differential diagnosis

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical.

The following are often mistaken for malarial fever cerebro-spinal meningitis, fever of urinary origin (sometimes renal calculus), the fever attending the passage of gall-stones, or inflammation of the gall-bladder, that associated with pyelitis and surgical kidney; perirenal abscess; amoebic hepatitis and amoebic abscess of liver; lymphangitis, particularly that form associated with elephantiasis and other filarial diseases; undulant fever, relapsing fever, trypanosomiasis, kala-azar, "short-term fevers" of which dengue and sandfly fever are the most typical; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anemia, with splenic leucocythemia, with visceral syphilis, with pulmonary carcinoma, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions.

Treatment

At cupping of fever attacks at any kind of a malaria there are used preparations with shizotropic action: chingamin (delagil, hlorohin, nivachin, resochin, trochin), and also quinine sulfas, quinine dichlorid, hydroxyhlorin (plaquenil), chloridin (pyrimethamin, tindurin), sulfanilamid preparations, meflohin, tetracyclin, doxycyclin. These preparations are active against bloody shizontes. The greatest action has chingamin. Concerning tissue forms of plasmodiums the most active is primachin.

At acute disorders of disease there is used chingamin diphosfat during 3 days more often: in 1 day 1.5 gm (at once 1 gm and in 6 hours the others 0.5 gm), in 2nd and 3rd day − unitary 0.5 gm. The serious form of a tropical malaria demands prolongation of treatment course by chingamin 2 days 0.5 gm 1 time a day. If plasmodiums are refractory to chingamin, indicate quinine dichlorid 2 mL

50 % of solution 2 times in 6 − 8 hours or in a vein very slowly 1 mL in 20 mL 40 % solution of glucose, and then two injections under skin 1 mL 50 % of solution, chloridin in combination with sulfanilamides preparations of prolonged action or the combined preparation fansidar, which contains 0.5 gm of sulfadoxin and 0.025 gm of chloridin: 3 tablets unitary. Fansidar may be given also for prophylaxis of relapse of tropical malaria.

The mentioned preparations provide complete convalescence at tropical malaria. In case of tetrian fever and oval malaria primachin is indicated which have action upon tissue shizontes and prevent appearance of recedives. Similar activity have also tetracyclin. Primachin is indicated simultaneously with chingamin or right after terminations of treatment by it.

Treatment of specific complications is carried out in the urgent order. At development of malarial coma a solution of quinine dihydrochlorid is used. The next days indicate the preparations per os. Simultaneously desintoxication therapy with reopolyglycin, polyglucin, albumin, rheogluman, polyionic solutions is performed. The total quantity of infused liquid should not exceed 1500 mL. There may be infused up to 150 mg of prednisolon in vein. Among other agents diprazin, suprastin, furosemid are indicated.

At hemohlobinurine fever treatment starts with an immediate cancellation of quinine, primachin, sulfanilamide preparations which might cause this complication. cordiamin, corglykon or strophanthin, phenylephin hydrochlorid, prednisolon, and also reopolyglycin, quartasol or another polyionic solutions should be infused. In case of development of serious anemia the blood of the same group, blood plasma may be transfused.

Individual chemioprofilaxis is carried out for the persons leaving in the endemic regions. For this purpose chingamin 0.5 gm once a week is applied, and in hyperendemic regions − 2 times per one week. Preparation is indicated during 5 days before arrival, all period of stay and during 8 weeks after departure. Among local population chemioprofilaxis begin 1-2 weeks before occurrence of mosquitoes. Occurrence of the tropical malaria is caused by drug resistant plasmodiums, prevent by reception of fansidar once a week. To the persons who have arrived from endemic center of a tetrian fever, seasonal prophylaxis of relapses by primachin in tablets 0.027 gm per day during 2 weeks is carried out.

Severe malaria.

Drug resistance has narrowed the therapeutic options in severe malaria. Chloroquine should no longer be used for severe malaria outside the few areas where sensitivity is retained. For nearly all the tropical world, the choice now lies between quinine (or quinidine) and either artemether or artesunate. The artemisinin derivatives are more rapidly parasiticidal than quinine, and safer in severe malaria (they do not cause hypoglycaemia), but to date large randomised trials have largely involved artemether which is relatively slowly absorbed particularly in severe malaria. These have not shown significant benefit in terms

of mortality for artemether. Although there has been some evidence of a decline in the efficacy of quinine in severe malaria in southeast Asia, these recent large randomised comparative trials with artemether have provided reassuring evidence that the mortality with quinine treatment is not rising significantly.

The prevention of resistance. Resistance develops most rapidly when a population of parasites encounters sub-therapeutic concentrations of antimalarial drug. These act as a selective pressure filtering out the more resistant parasites within the infecting population. Selection is most efficient when single point mutations confer high level resistance. The mutations which confer reduced drug susceptibility within an infecting parasite population are thought to occur independently of drug pressure. Drugs with long terminal elimination phases, such as mefloquine, are particularly vulnerable because sub-therapeutic concentrations may occur for weeks or months after a single therapeutic dose. Selection for resistance in microorganisms is greatest at "intermediate" levels of drug activity (generally between 20 % and 80 % of maximum effect). Although chloroquine has the longest of all the elimination phases (terminal half-life 1-2 months), the blood concentrations during the terminal phase are very low and may lie below the "sensitive" part of the concentration effect relationship where selective pressure is greatest.

The pharmacological characteristics which predispose a drug to the development of resistance are weak intrinsic activity with a "flat" dose-response or concentration effect relationship, single or double point genetic mutations which confer marked reductions in susceptibility, and a long terminal elimination phase during which blood concentrations fall slowly down the concentration effect curve for the infecting population of parasites.

Initially at low levels of resistance selection occurs only from newly acquired infections, but, as resistance worsens, some of the primary infections are able to survive the initial therapeutic onslaught and to recrudesce subsequently. These are by definition the most resistant parasites, and they are preferentially transmitted because gametocyte carriage is more likely during the recrudescent infection. The chances of a resistant mutant parasite surviving can be reduced considerably if a second drug, with an independent locus of antimalarial action, is added. Escape would now require two simultaneous but independent mutational events. Mutations are rare events and the chance that two independent mutations would occur in the same parasite is the product of their individual mutation frequencies. This rationale for combination chemotherapy in malaria was applied originally to mefloquine/sulphadoxine/pyrimethamine but it did not work because of the pharmacokinetic mismatch between the three compounds, and because where it was introduced in Thailand in 1984, *P. falciparum* was already highly resistant to both pyrimethamine and sulphadoxine. Combinations of artemisinin derivatives with slower acting and more slowly eliminated antimalarials are particularly effective because of the considerable biomass reduction achieved by artemisinin

compounds with a treatment course as short as 3 days (circa 10^8 - fold reduction in parasite numbers). This ensures that there are relatively few parasites (maximum 10^5) remaining for the second, weaker drug to eliminate. Furthermore, these parasites are exposed to maximum concentration of the second drug. The artemisinin derivative is also "protected" by the second drug. This would argue for combining an artemisinin derivative with all slowly acting antimalarial drugs.

Prophylaxis

Because of increasing drug resistance, alternative measures such as reducing vector-human contact are progressively more (rather than less) important. Insecticide-impregnated bed nets (with permethrin or deltamethrin) markedly reduce intradomi-ciliary vector populations, and should offer significant protection against the risk of malaria. Alternatively, insect repellents such as diethyltoluamide (DEET) may also reduce the risk of transmission and infection.

Because malaria does not produce immunity, there is no model of effective immunity to plasmodial infection, and no guarantee that numeral or cellular immune responses to specific antigens will protect against either infection or disease. In fact, one of the major unsolved questions is whether different mechanisms may be responsible for protection from infection vs. disease.

Control questions:

1. Source of malaria infection and mechanisms of transmission.
2. Types of malaria infectious agents.
3. Cycles of plasmodium malariae development.
4. Tissue shizogony, its duration during different forms of malaria.
5. Red blood cell's shizogony, its features at different forms of malaria.
6. Technique of preparation of "thick drop" method.
7. Pathogenesis of malarial attacks.
8. Types of temperature curves at different forms of malaria.
9. Clinical manifestations of malaria.
10. Outcomes of malaria.
11. Parasitosis and its epidemic value.
12. Differential diagnosis of malaria with leptospirosis and viral hepatitis.
13. Complications of malaria.
14. Medical treatment of malaria.
15. Prophylaxis of malaria.

PLAGUE

Plague is an acute infectious disease caused by *Yersinia pestis* with severe intoxication, fever, affection of lymphatic system and lungs. It belongs to the group of the extremely dangerous infections (quarantines).

Historic reference

Many researchers of the history of medicine relate the plague epidemics to the most ancient times of the human history. The information about mass mortality, mentioned as a punishment of Jehova for the people's sins is the main argument for such conclusions. Now it is hard to say if they were really plague epidemics or other infectious diseases. In the historic times a mass disease, described by Fukidid (430-426 BC), was considered to be a plague epidemic, now it is looked a as a typhus epidemic. The old foreign researchers of plague consider an epidemic described in the book of Moses and in the books of Judges and Prophets as a plague epidemic. At the times of the exodus of the Jews from Egypt (about 1320 BC) people of Palestine came back to the God of Israel carrying 5 golden images of tumours (bubos) and 5 images of mice − showing the connection of the human disease with rodents.

Later there were many indications showing that the plague in Egypt existed from the ancient times. However the first doubtless information about plague in Egypt was found at Ruth from Efese at the time of emperor Troyan (98-117 AD) in which the outbreaks of bubonic plague with high mortality in Livia, Egypt and Syria were described, that epidemic took place at those times and earlier starting from the end of 3rd century DC. Apparently, the word "plague" comes from the ancient Arabic word "jumma" which means "bean".

During the last 2000 years, *Y. pestis* has caused social and economic devastation on a scale unmatched by other infectious diseases or by armed conflicts. It is generally considered that there have been three world pandemics of plague and credible estimates indicate that together these resulted in 200 million deaths. During these pandemics, the disease occurred in both the bubonic and pneumonic forms. The first of these, the Justinian plague, occurred during the period AD 542 to AD 750. This pandemic is thought to have originated in Central Africa and then spread throughout the Mediterranean basin. The second pandemic started on the Eurasian border in the mid-14th century. It is this pandemic which resulted in 25 million deaths in Europe and which is often referred to as the "black death". This pandemic lasted for several centuries, culminating in the Great Plague of London in 1665. The third pandemic started in China in the mid-19th century, spread East and West, in 87 ports, in almost all continents.

Eight epidemic breakouts of plague have been registered in Odessa. The biggest epidemic took place in 1812, when about 3,000 people fell ill and more than 2,000 people died. All the dead people were buried behind the first Christian cemetery, where there is still a hill called a plague hill or just "chumka". The last epidemic of plague in Odessa took place in 1910, when 141 persons fell ill and 43 of them died.

Professor V.Stefansky – the first head of the chair of infectious diseases in Odessa medical institute was one of the pioneers of using serum for the treatment of sick people.

Current incidence of plague

World Health Organization (WHO) figures indicate that there is still a public health problem from plague, especially in Africa, Asia and South America and plague, cholera and yellow fever are the only internationally quarantinable infectious disease. As a class 1 notifiable disease, all suspected cases must be reported, and investigated by public health authorities and confirmed cases must be reported to the WHO in Geneva, Switzerland. During the period 1967-1993, the average worldwide incidence of plague was 1,666 cases. Although the incidence trend was downwards until 1981, there has been an apparent increase in the incidence of disease over the last decade, possibly because of more efficient diagnosis and reporting of cases. Even today, many cases of plague are not diagnosed and it is likely that the true incidence of disease is several times the WHO figures.

The Indian outbreak of plague in 1994. Despite the high incidence of plague in India during the first half of this century, the number of cases had declined since 1950, and the last recorded case occurred in 1966. However, between August and October 1994 two outbreaks of suspected plague occurred. One of bubonic plague in the Beed District of Maharashtra State, and the other of pneumonic plague in the city of Surat in Gujarat State. The Surat epidemic caused panic throughout India, resulting in a mass exodus of up to half a million people from the city, and attracted international media attention.

At the peak of the epidemic, over 6,300 suspected cases were recorded. However, official figures released later indicated that only 876 presumptive cases of plague were identified (by serological testing for antibodies to *Y. pestis*) and there were 54 fatalities. The cases were confined to six states in central and western India; none of the suspected cases in other states, such as Bihar, Punjab, Rajasthan and West Bengal, had positive serological markers for presumptive plague.

During the outbreaks, one of the major problems was the failure to collect systematically clinical samples for analysis. Routine tests to confirm a diagnosis of plague were not carried out and pure isolates of *Y. pestis* were not cultured from blood, sputum or autopsy samples. As a result, the exact nature of the outbreaks in Maharashtra and Surat has provoked controversy and alternative causative agents have been proposed. To address concerns, a team of experts

from the WHO visited India in October 1994. Although the WHO team was unable to isolate *Y. pestis* from clinical samples, it established that there was clinical, epidemiological and serological evidence of an outbreak of plague.

In response to the crisis, the Indian government constituted a Technical Advisor Committee (TAC) in 1994 "to elucidate the factors responsible for the current outbreak of plague and its spread". In clinical and environmental studies coordinated by the TAC, pure *Y. pestis* was isolated from the sputum of 11 pneumonic plague cases in Surat, and the tissues of 6 rodents trapped in Beed and 1 rodent trapped in Surat. The biochemical, genetic and immunologic similarity of the Surat and Beed isolates suggested that they arose from the same *Y. pestis* strain and, for the first time, provided evidence that the outbreaks were linked.

The TAC also conducted studies to identify the events leading up to the epidemics. In the Beed District of the Maharashtra State, the seeds of the outbreak were laid in October 1993 when the residents of Mamla village abandoned their homes in fear of tremors associated with a major earthquake in the neighboring districts of Latur and Osmanabad. Large quantities of grain remained in the homes, which provided a source of food for domestic rats leading to a population explosion and a rodent epizootic of plague. The initial source of human infection was the wild rodent population located in habitats surrounding the village. During August 1994, a heavy flea nuisance and "rat fall" was reported in the village and. shortly afterwards, the first cases of bubonic plague occurred.

The origin of the pneumonic plague outbreak in Surat is less well understood. Monsoon flooding occurred in the city in the first week of September 1994 causing people to leave their homes. Although such disruptions to the local ecological balance are known to contribute to plague outbreaks, there is no evidence that this occurred in Surat. The index case locality of the pneumonic plague outbreak was traced to Laxminagar colony in the north of the city and, although the origin of the disease remains obscure, the most likely scenario is that an individual with pneumonic plague who travelled from the Beed district to Surat was the source of the epidemic.

Etiology

Yersinia pestis (Bacillus pestis), the etiological agent of plague was first described by A. Yersen in 1894 in Hong-Hong, the International committee of systematization of bacteria (1982) referred it to *Yersinia* genus together with bacillus pseudotuberculosis and yersiniosis.

In its characteristic form this organism is a short, oval bacillus with rounded ends. In the tissues a typical capsule may be observed; in cultures grown at 37 °C material can be demonstrated by means of India ink preparations, but it no well-defined.

The organism is Gram-negative, and when stained with a weak stain (e.g. methylene blue) shows characteristic bipolar staining which is an important feature in identification.

In culture the plague bacillus is less typical. Longer forms are frequent and polar staining is less obvious. Pleomorphism is marked especially in old cultures, and involution or degeneration forms are particularly noticeable. These are markedlly enlarged, stain faintly and include globular, pear-shaped, elongated or irregular forms. In fact the microscopic picture of an old culture often suggested that of a yeast or mould. Involution in culture can be hastened by the presence of 3 % sodium chloride and this has sometimes been utilized in identifying the organism.

In fluid culture the bacilli tend to be arranged in chains. The organism is non-motile and non-sporing.

Epidemiology

Rodents are natural reservoir for plague infection. Yersen was the first to notice the connection between a rats plague epizootic and a human epidemic. Bacillus pestis carriage was proved for black and gray rats and for such steppe rodents as gophers, marmots, sandworts, small mousekind rodents and others. There are almost 300 species and subspecies of basic sources and keepers of plague infection. Besides, during an epizootic among rodents, there can be found other mammals contaminated with plague − polecats, shrews, foxes, monkeys (makaky genus), domestic cats, one- and two-humped camels. Epizootics among rodents are kept by different species of fleas − carriers of plague infection.

It is now known that plague is not communicable from animal to animal by simple contact, but is readily communicated by fleas, which bite man, dogs and other animals. These act as passive intermediaries and carriers of the bacillus. *Y. pestis* multiplies in the stomach of the flea, retaining its virulence for over twenty days and is then passed out in the feces, so that the flea serves not only as a carrier, but also as a multiplier of the germs.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer fleas from a plague-infected to a healthy animal, or to place the latter in a room in which plague rats had died recently and had been subsequently removed. The fleas that have left the body of the dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected, if the precaution is taken to surround the cage with "tangle foot", so as to keep off the fleas.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and esophagus, which become blocked with blood-clot containing a pure culture of *Y. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection. At the same time bacilli are passed in the feces and may infect through any existing abrasion. They further observed that the "blocked" fleas died very

rapidly, apparently of thirst, if placed in a warm, dry atmosphere. There is apparently little difference between wild rodent and domestic rat fleas in the readiness of infection. The life-span of the infected flea is comparatively short, about 3-2 days.

In temperate climates fleas are most numerous during the warmer weather, hence, summer and autumn are the bubonic plague seasons. In warm climates bubonic plague is most likely to become epidemic when temperature ranges between 10 °C and 30 °C − temperatures favorable to the multiplication and activity of the flea. Temperatures over 30 °C are unfavorable, especially if the atmosphere is dry. The flea, then, communicates plague either by its fouled mandibles, by regurgitation, in the act of sucking, or by provoking scratching and consequent inoculation of the bacilli deposited in its feces.

In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. It requires ideal tropical conditions for propagation. The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months, should the temperature of the air be low.

Apart from the very serious danger arising froin vermin infected with chronic plague, which may hang about a house, the house itself does not retain the infection for any length of time. The Plague Commission has shown that floors of cow-dung contaminated with *Y. pestis* do not remain infective for more than forty-eight hours and that floors of "chunam" cease to be so in twenty-four hours.

Evidence of rat-mortality is not always conspicuous, even when the epizootic is severe. Dead rats may not be found in the open, but many may be discovered if search is made in the right places. Black rats which live in the roofs of tropical houses usually fall down on to the floor when stricken with plague.

Other means of infection. Human infection, however, is not always transmitted by fleas. In a small percentage of the bubonic cases, infection occurs from exposure of abraided surfaces of the skin to the plague bacillus. Instances of such infection have occurred in barefooted individuals with small wounds of the feet from walking on floors or stepping on material infected with plague bacilli, or through abrasions on the hands of those who have performed autopsies on or handled the bodies of those who have died of plague, or who have shot and skinned rodents infected with plague.

Infection in primary human septicemic plague is usually acquired through the mucous membranes, particularly of the mouth and throat and the conjunctivae. Particles of infected sputum which have been accidentally coughed into the eye have produced human septicemic plague. Animals such as monkeys may be given primary septicemic plague by instilling a few drops of a culture of *Bacillus pestis* in the eye, or by rubbing a small amount of the culture on the mucous membranes of the gums without producing visible erosions. Infection of the mucous membranes of the mouth may occur also in man through the hands conveying infection, as might occur in individuals who have shot or skinned infected rodents.

There has been an outbreak of septicemic plague reported in Ceylon in which there was an absence of plague in rats. The infection was possibly transferred directly through human fleas or bedbugs.

In epidemics of primary pneumonic plague, infection does not occur as in bubonic plague through the agency of heavily infected fleas, or through the skin. but directly from man to man airborne through droplets of infected sputum expelled by coughing, as was conclusively shown by Teague and the writer in the Manchiirian epidemic. In no other infectious disease have such enormous numbers of uniformly highly virulent microorganisms been demonstrated in the droplets of sputum coughed up by patients with primary epidemic plague pneumonia.

It is a matter of experience that the transference of plague from place to place generally occurs from infected rats or infected fleas which have been transported by ships, though sometimes by rail and other conveyances. A case of bubonic plague in a ward with other patients would not be a source of danger, provided there was freedom from fleas and that no plague patient developed a secondary pneumonia. It is very doubtful as to human infection ever taking place by way of the alimentary canal, although there is some evidence that rarely the tonsil may be primarily involved. Monkeys are very susceptible to plague, but no epizootics among them have been recorded.

Pathogenesis

When flea ingests blood meal from bacteremic animal infected with *Y. pestis,* the coagulase of the organism causes the blood to clot in the foregut, leading to blockage of the flea's swallowing. *Yersinia pestis* multiplies in the clotted blood. During attempts to ingest a blood meal, a blocked flea may regurgitate thousands of organisms into a patient's skin. The inoculated bacteria migrate by cutaneous lymphatics to the regional lymph nodes. The flea-borne bacilli possess a small amount of envelope antigen (fraction 1) and are readily phagocytized by the host's polymorphonuclear leukocytes and mononuclear phagocytes. *Yersinia pestis* resists destruction within mononuclear phagocytes and may multiply intracellularly with elaboration of envelope antigen. If lysis of the mononuclear cell occurs, the bacilli released are relatively resistant to further phagocytosis. The involved lymph nodes show polymorphonuclear leukocytes, destruction of normal architecture, hemorrhagic necrosis, and dense concentrations of extracellular plague bacilli. Transient bacteremia is common in bubonic plague, and in the absence of specific therapy, purulent, necrotic, and hemorrhagic lesions may develop in many organs. Hypotension, oliguria, altered mental status, and subclinical disseminated intravascular coagulation (DIC) may be noted and are attributable to endotoxinemia.

Anatomic pathology

The chief points noted in a plague autopsy are:

1) The marked involvement of the lymphatic system as shown by intense congestion and hemorrhagic edema of the lymphatic glands. Not only are the

glands involved tributary to the site of inoculation, thus forming the primary bubo, but there is secondarily more or less inflammatory change in many of the lymphatic glands of body. There is also a marked periglandular edema, with hemorrhagic extravasations of the connective tissue surrounding the primary bubo, this mass being made up of a group of glands matted together by this periglandular exudate.

2) The marked destructive effect of the toxin of the plague bacillus, upon .the endothelial cell lining of blood vessels as well as of lymphatic ones. This causes the extensive blood extravasations so characteristic of plague as shown by petechial spots, not only of the skin, but of the serous and mucous membranes as well throughout the body.

There is a general congestion of all organs of the body. The meninges of the brain are deeply congested and there may be hemorrhagic extravasations in the brain substance itself. However meningitis has been reported only in a few cases. The spleen is generally markedly congested and enlarged to 2 or 3 times its normal size. There may be hemorrhagic extravasations throughout the spleen pulp. The bacilli are chiefly scattered throughout the venous sinuses. There is also active congestion of the liver. The kidneys are intensely congested, hemorrhages beneath the capsule are usual, and we often find hyaline fibrin thrombi in the tufts of the Malpighian bodies as was emphasized particularly by Herzog in Manila. The plague toxin has a marked effect on the cardiac muscle so that we usually find dilatation of the right side of the heart with fatty degeneration of the muscle fibers. In a study of the pathology of primary pneumonic plague. Strong noted pericardial and pleural ecchymoses with fibrinous pleurisy over the affected lung areas. The process was at first lobular, but later might involve the entire lobe. There was marked congestion of the bronchial mucosa with involvement of the bronchial glands. The larynx and trachea are also intensely congested. Microscopically there is a distension of the alveoli and bronchial passages with a hemorrhagic exudate. There is practically no fibrin in the alveolar exudate. The process seems to extend by continuity along the bronchi and bronchioles. Plague bacilli pack the exudate found in the bronchi and bronchioles. In a report on the autopsy findings of septicemic plague in Ceylon in cases where plague bacilli were demonstrated in smears and cultures from spleen and blood, Castellani noted especially meningeal congestion and some splenic enlargement.

Clinical manifestations

Incubation period. The incubation period of human plague varies usually from 2 to 10 days, but is generally from 3 to 4 days. In primary pneumonic plague it may not be over 2 or 3 days.

Symptoms and course of bubonic plague. In bubonic plague premonitory symptoms are not usually observed, though occasionally there may be 1 or 2 days of malaise and headache. The onset, except in mild cases, is usually abrupt, with fever commonly accompanied by a moderate rigor or repeated shivering.

The temperature rises rapidly to 39.4 °C or 40 °C, sometimes even reaching 41.7 °C. The pulse becomes rapid and the respirations increased. There is headache which is usually severe and mental dullness, and this condition is generally followed by mental anxiety or excitement. The patient may become maniacal. The skin is hot and dry, the face bloated, the eyes injected, and the hearing dulled. The tongue is usually swollen and coated with a creamy fur, or later with a brown or black layer. The symptoms usually complained of within the first 24 hours are very severe headache and backache. Burning in the throat or stomach, and nausea and vomiting may occur. Constipation is present as a rule. The pulse is either very small and thread-like or full and bounding. At times there may be acute delirium; at others, lethargy and coma. In children, convulsions usually occur. The urine is scanty and generally does not contain more than a trace of albumin and no casts. Later in the disease the albumin may increase somewhat, The high febrile stage lasts from 2 to 5 days or longer. The decline in temperature may be sudden or gradual. Cases that do well usually show a gradual fall of temperature, and after 14 days the temperature may be subnormal. Buboes, inflammatory enlargements of the lymph glands are sometimes the first sign to attract attention by their pain. They more often make their appearance from the second to the fifth day after the onset of the fever. The temperature frequently shows a decline when they appear. The affected gland is often hard and painful to the touch. In fatal cases, it may retain these characteristics; in others it suppurates. The average size of the bubo is from a walnut to an egg. Buboes appear in 75 % of the cases. In the cases in which buboes are present, they occur in the inguinal glands in approximately 65-70 %, in the axillary − 15-20 %, and the cervical − 5-10 %. Carbuncles appear in about 2 %, in which there are reddened indurated patches of skin, which subsequently necrose. The spleen is frequently moderately enlarged, but often cannot be palpated. Hemorrhages from the stomach and intestine are not uncommon, and when the disease is complicated with the pneumonic form they may occur from the lung. Epistaxis is also not infrequent. The blood usually shows a leucocytosis of forty thousand or more the increase being in the polymorphonuclear leucocytes. The plague organism can be isolated front the blood in about forty-five per cent of the bubonic cases.

The attack of high fever lasts generally three to five days or longer, but the patient may die earlier. If however, he lives for five days there is greater chance of recovery. If the bubo suppurates recovery may be delayed from two or three weeks to a month.

Symptoms and course of pneumonic plague. The onset of the disease is usually somewhat abrupt; prodromal symptoms are rare. The disease usually begins with chilly sensations, but a distinct rigor is unusual. Epistaxis is also rare. There is headache, loss of appetite, an increase in the pulse rate, and fever. Within from twenty-four to thirty-six hour after the onset, the temperature usually has reached 39.4 °C or 40 °C, and the pulse 110 to 130 or more beats

per minute. Cough and dyspnoe appear within twenty-four hours after the onset of the first symptoms. The cough is usually not painful. The expectoration is at first scanty, but soon becomes more abundant. The sputum at first consists of mucus which shortly becomes blood-tinged. Later the sputum becomes much thinner and of a bright red color; it then contains enormous numbers of plague bacilli in almost pure culture. The typical rusty sputum of croupous pneumonia was not observed. The conjunctiva become injected, and the tongue coated with either a white or brownish layer. The expression is usually anxious, and the face frequently assumes a dusky hue. Labial herpes is very uncommon. The patients sometimes complain of pain in the chest, but usually this is not severe. Apart from the disturbances due to the dyspnoe and their anxiety for their condition, they usually appear to suffer but little and usually do not complain of pain. In the later stages of the disease, the respirations become greatly increased and the dyspnoe usually very marked, the patients frequently gasping for air for several hours before death. Cyanosis is then common.

The signs of cardiac involvement are always marked in the advanced cases, the pulse becoming gradually more rapid, feeble, and running; finally it can not be felt.

Symptoms and course of septicemia plague. Septicemic plague occur during the course of bubonic plague, always occurs in pneumonic plague, and may occur as a form of primary infection. When primary septicemic plague results, the infection has usually occurred through the mucous membrane of the mouth and throat, death resulting from septicemia before macroscopic lesions are visible in the lymphatic glands or lungs. Nevertheless, at autopsy, at least some of the lymphatics are usually found to be enlarged, congested, and even hemorrhagic, and in a few instances early buboes may develop shortly before death.

In this form, the nervous and cerebral symptoms often develop with great rapidity and intensity, and the course of the disease is very rapid, the bacilli appearing in the blood almost at the onset of severe symptoms. The attack usually begins with trembling and rigors, intense headache, vomiting, and high fever. The countenance usually depicts intense anxiety. Extreme nervous prostration, restlessness, rapid shallow respirations, and delirium are common symptoms. In some cases the cardiac symptoms are the most prominent. The patients soon pass into a comatose condition and die sometimes within 24 hours of the onset of the attack, but sometimes not until the third day. Cases of primary septicemic plague are always fatal. Hemorrhages from the intestine sometimes occur in this form of plague as well as in bubonic plague. There is no distinct evidence that such cases are of primary intestinal origin. Hemorrhages from the nose and kidneys are also not uncommon.

The plague bacillus produces a powerful endotoxin which often causes a dilatation of the arteries, lowering of the blood pressure, and alterations in the functional activity of the heart, as well as degenerative changes in the heart muscle. It also acts particularly upon the endothelial cells of the blood vessels and lymphatics,

the inflammatory reaction frequently causing circulatory obstruction. One of the most characteristic features of the pathology of plague is the tendency to produce general dilatation and engorgement of the vessels, with cutaneous, subserous, submucous. parenchymatous, and interstitial hemorrhages. In patients who have died of plague, the most common of the latter are in the epicardium, the pleura, peritoneal surfaces, the stomach and intestines, and the mucosa of the stomach and small intestine. Sometimes extensive hemorrhages are found in the peritoneal, mediastinal or pleura cavities. In the kidneys there are frequently subcapsular and renal hemorrhages, and blood extravasation into the pelves of the kidneys and ureters, as well as in the bladder and generative organs.

Sometimes there are considerable extravasations of blood into the substance of the brain. In bubonic plague, numerous hemorrhages are almost always present in the bubo. The tissues are characterized by vascular dilatation and engorgement. followed by edematous infiltration, the effect of the toxin being evident on the vessel walls. The endothelial cells become swollen, proliferated, and degenerated. Later hyaline degeneration of the walls may occur.

During the clinical course of the disease, hemorrhages are frequent. The bleeding may take place from the nose, mouth, lungs, stomach, or kidney, and sometimes from the uterus and bladder. These hemorrhages generally occur in severe cases of the disease. On examining the skin small punctiform hemorrhages from about 1 to 2 millimeters in diameter are sometimes observed scattered over the skin in greater or less profusion. The petechie may occur on the face, neck, chest, abdomen or extremities. Sometimes larger patches of ecchymosis, in the neighborhood of 1 centimeter in diameter are observed in the skin. Larger cutaneous effusions of blood are rarely seen, except at autopsy. The purpuric hemorrhages in bubonic plague usually do not appear before the third day of the disease. However, in septicemic plague they may be seen earlier.

At autopsy, the right side of the heart and the great veins are usually distended with fluid or only partially coagulated blood. During the disease, the patient frequently experiences a feeling of oppression over the precardial region. The heart sounds at first are clear, and the second pulmonic sound may be accentuated, but as the disease progresses they become feebler, or embryocardiac, in character and die first sound may be no longer heard. Sometimes heart failure may occur without any other sign of collapse. It may occur following exertion. such as sitting up, but it sometimes takes place while the patient is lying in bed. In primary septicemic plague, the course of which is very rapid, the cardiac symptoms are frequently the most prominent ones. In pneumonic plague, the limits of dullness of the heart are sometimes increased to the right of the sternum. At onset, the second pulmonic may be accentuated, but it soon becomes indistinct. As the disease progresses, gallop rhythm may occur. Death takes place usually from cardiac paralysis and exhaustion.

The pulse in bubonic plague varies greatly. More commonly, at the onset of the disease it is full and bounding, 100 to 120 per minute, becoming later still

more rapid, 120 to 140 per minute, small, thready, irregular, and often dicrotic. However, in some cases it is small and thread-like, and very rapid from the onset of symptoms. In cases likely to prove fatal, the pulse becomes so rapid and thready that it is impossible to count it. In such cases, however, the larger arteries can often be observed to pulsate forcibly. In mild cases of plague, the pulse may only show slight acceleration.

The temperature curve in plague is often very irregular and not characteristic. In the severe cases, the initial rise is usually rapid and may be anywhere from 39.4 °C to 41.1 °C. The temperature may reach its highest point on the evening of the first day of fever, but usually the height of the curve is not readied till the close of the second or third day. From the third to the firth day, there is usually a remission of several degrees. Later the temperature may again rise, and in fatal cases it may reach 41.7 °C before death. A sudden fall of temperature during the height of the disease, with a collapsed condition, sometimes occurs and usually also indicates a fatal issue. In more favorable cases, after the secondary rise the temperature often falls slowly and gradually, with more marked remissions each morning, until the normal or even subnormal point is reached. The course of the fever often lasts in uncomplicated cases from 6 to 12 days. Suppuration of the buboes, however, may cause great irregularity of temperature, and the occurrence of complications may considerably prolong the period of fever. As a rule, the higher and more continuous the temperature, the severer the other symptoms. In mild cases of bubonic plague, the temperature may fall to normal as early as the second or third day, and it may not reach over 37.7 °C during the attack. In primary septicemic plague, the temperature usually rises suddenly and remains high until death supervenes. Occasionally, however, if the patient lives from forty-eight to seventy-two hours after the onset, the temperature may fall suddenly, reaching normal or becoming subnormal just before the fatal outcome. In primary pneumonic plague the onset of the temperature is rapid and reaches the maximum point usually within twenty-four to thirty-six hours. In this form of the disease the temperature also often declines to below normal before death.

Early in the disease there is no reduction in the number of red blood corpuscles or in the percentage of the hemoglobin. In fact, both Rogers and Castellani have observed that the red cells and hemoglobin are not infrequently increased above normal. In the late stages of bubonic plague, particularly in the cases with complications, a moderate secondary anemia may occur. A leucocytosis is almost invariable in bubonic plague except in the mildest cases, during the first three days of the disease. Usually the count is in the neighborhood of from twenty to twenty-five thousand. In about 5 % of the cases it may be higher, the leucocytes occasionally numbering forty thousand or even more. A differential count will show that the polymorphonuclear leucocytes are found to be increased and the large mononuclear cells usually diminished. In some of the very rapidly fatal septicemic and primary pneumonic cases in which collapse and death appear

early, there may be no leucocytosis. In such cases plague bacilli may sometimes be present in the blood in such numbers that a simple microscopical examination of a hardened and stained specimen suffices for their detection. The plague bacillus can be cultivated from the blood in the primary septicemic and primary pneumonic cases, as well as in about one-half of the bubonic cases of plague. The plague bacilli after they appear in the blood in bubonic plague increase up to the time of death and they can always be cultivated from the blood at autopsy. Over 90 % of the cases of bubonic plague in which the bacilli appear in the blood terminate fatally.

Buboes or inflammatory swellings of the lymphatic glands, which develop in about three-fourths of the cases of plague, may become noticeable any time from the onset of the attack to the fifth day. More often they develop within forty-eight hours of the onset of the fever. Usually they increase rapidly in size.

At first a single gland may be felt enlarged, but more commonly several adjacent glands are involved. Sometimes groups of glands become successively infected, in which case there is always more or less periglandular infiltration. Thus a bubo in the inguinal region not infrequently extends into the iliac region affecting the lymphatic glands of the abdominal cavity, and forming secondary buboes which can sometimes be felt as a mass through the abdominal wall. This condition has been mistaken for an appendicular abscess. The buboes vary greatly in size, more commonly they are about the size of a walnut, but they may be as large as an egg or even an orange. They are usually single, but in about 10-12 % of the cases they may be multiple and form on both sides of the body. As has been emphasized, the buboes form in the inguinal region in from about 60-70 %, one or more of the inguinal or femoral glands being involved. In about fifteen to twenty per cent they occur in the axillary region where the bubo often occludes the axillary space and obliterates the outline of the margin of the pectoralis major. In this region there is usually extensive inflammatory exudation which extends over the side of the chest and sometimes upwards to the shoulders and even to the side of the neck. Such cases frequently result fatally, and cases with axillary buboes often become septicemic early in the disease. In about five to ten per cent of the cases the bubo forms under the jaw or at its angle; more rarely elsewhere in the neck or in the tonsils. In these situations there is often much edema and exudation especially in the vicinity of the bubo and the patient may die from suffocation, the trachea and glottis first becoming very edematous. In some instances in which the buboes have occurred in the tonsils, cases have been mistaken for diphtheria and even scarlet fever. More rarely buboes form in the epitrochlear region or popliteal space, the mammary gland, testicle, or in isolated glands in other parts of the body.

Generally the plague bubo at the onset is hard to the touch and very painful. Often at the time of onset of the bubo, pain in it is the symptom of all others of the disease most complained of. In rare instances, however, the pain may not be marked. Usually if the bubo is in the groin the pain is sufficient so that the

patient lies in bed with the thigh flexed and the leg drawn up to relieve any pressure on the inflamed glands while if the bubo is in me axillary region the affected arm is held away from the side. The bubo may terminate by resolution, suppuration, or induration.

If the bubo suppurates, the gland becomes at first more swollen and the overlying skin gradually more inflamed and tense during the first week. Later the gland begins to soften and necrosis then occurs more quickly. Frequently the whole center of the gland breaks down into an abscess cavity and perforation then occurs, revealing a cavity with dark scarlet or bright red walls. Later the walls become reddish yellow in appearance and emit whitish-yellow pus. On microscopical examination of the pus normal and degenerating plague bacilli are found and many polymorphonuclear leucocytes and degenerating endothelial cells. The bacilli are often seen engulfed in phagocytic cells. In the later stages the buboes often become secondarily infected with other microorganisms, particularly the pus cocci. Rarely the bubo does not perforate for several weeks. Sometimes its suppuration is accompanied by much sloughing of the skin in the vicinity when fairly large ulcers result with indurated infiltrated margins. In some instances the lesions may heal in from a week to ten days, but with larger buboes sometimes complete cicatrization does not occur for a month or two. In many other cases the bubo terminates by resolution. The tenderness, and periglandular infiltration then gradually decrease, the overlying and adjacent skin becomes softer, and the glands may eventually return almost to their normal size with but moderate induration about them. In other instances an enlarged cicatricial node remains at the site of the bubo.

Cellulo-cutaneous plague. The occurrence of petechiae and of larger ecchymoses in the skin have already been referred to. Plague carbuncles have also been reported. They occur most commonly on the buttocks or back, sometimes on the flanks or abdomen, the shoulders or posterior surface of the legs and arms. They generally make their appearance in the later stages of the disease and usually originate about ecchymotic patches. Subsequently a vesicle is formed, which soon ruptures and reveals a well circumscribed patch which may measure 1 centimeter or more in diameter. The base of the lesion is usually moist and either brownish red or bluish in color, while the margins are indurated and infiltrated. The necrosis in some instances becomes deeper, and large indolent ulcers are formed. Sometimes there is considerable edema about the ulcers, and plague bacilli may be found in the edematous fluid which exudes. However in indolent ulcers, degenerating plague bacilli and pus cocci are often found, and not infrequently other bacilli. In a small proportion of bubonic plague cases, what probably constitutes the primary lesion may be observed. This consists usually of a small vesicle or papule which may become pustular, and which is situated on the skin drained by the inflamed lymphatics in the region of the bubo. It perhaps sometimes indicates the original point of the infected flea bite.

Microscopical examination of the contents of these lesions frequently shows large numbers of plague bacilli.

In severe cases of bubonic plague, oppression of the chest is often complained of. As the disease progresses, the breathing becomes labored and the respirations increase in frequency, sometimes numbering from 30 to 60 per minute. Cough is frequently present. The sputum may be viscid at first, but often becomes purulent and sometimes blood-stained. Auscultation and percussion frequently reveal signs of congestion and edema at the bases of the lungs. Bronchitis is also not uncommon. Pneumonia occurs in plague, first as primary plague pneumonia in which the alveoli and sputum contain plague bacilli in enormous numbers. This form has already been thoroughly discussed elsewhere in this article. Secondary bronchial pneumonia also due to the plague bacillus may result metastatically and emboli and abscesses may be formed in the lungs. In addition, pneumonia in bubonic plague may occur as a result of infection with *Diplococcus pneumonias,* and in some of these lesions both the diplococcus and the plague bacillus may be encountered. In the metastatic form of pneumonia, it is frequently very difficult to recognize the condition clinically. Occasional crepitant rale may be heard over small areas. In such cases the rapid decline in the general condition of the patient may suggest the condition. However, if the lesions are sufficiently extensive in the lungs, plague bacilli may sometimes be found in the sputum.

The kidneys are usually markedly affected in plague. Congestion and parenchyniatous degeneration are almost always present. Extensive hemorrhages may occur in the pelves of the kidneys, ureters, or bladder. Microscopically, profound cloudy swelling of the epithelium of the uriniferous tubules, with the presence of granular or hyaline material in the latter, is almost always present in fatal cases. A very characteristic change in the kidneys in plague sometimes observed is the presence of hyaline fibrin thrombosis of the glomerular capillaries. A lesion which was first emphasized in Manila by Herzog (1909). These lesions explain in a general way the urinary disturbances which may be observed clinically. The urine is usually diminished in quantity, of a high color, sometimes smoky, and of high specific gravity. It usually contains a moderate amount of albumin, but albumin is not always present in the less severe cases. The urea, uric acid, and chlorides are often decreased. Microscopically, epithehal cells, pus cells, and sometimes red blood corpuscles and even plague bacilli may be observed. The plague bacillus does not usually occur in kidney tissue in particularly large numbers, and it is probable that only when this organism is present in considerable numbers in the capsular space of the glomeruli, or where there has occurred hemorrhage in the urinary system, will the plague bacillus be found in the urine. In grave cases of plague, hematuria is not uncommon, and suppression or retention of urine occasionally occurs. Severe uterine hemorrhages may develop, and in pregnant women abortion always occurs, which is usually fatal to both mother and child.

The mucous membranes of the mouth and throat are more or less hyperemic and occasional hemorrhagic patches are present. The tonsils may be swollen and hyperemic and in instances in which infection has occurred through the mucous membrane of the mouth or throat, a bubo may form in the tonsil and edema of the glottis may occur. In these instances, as well as in pneumonic plague, the sputum contains the plague bacillus. Apart from the hemorrhages which may occur in the mucous membrane of the stomach or intestine, the other lesions of the alimentary tract are not of special clinical significance. Vomiting, preceded by nausea, is a common early symptom of plague; sometimes the vomiting persists and then the vomits is likely to contain blood. Constipation is usual in plague, but diarrhea sometimes occurs, and in some cases the stools are dysenteric in character and contain much blood. During the epidemic of primary pneumonic plague in Manchuria several cases of primary intestinal plague were reported in which bloody diarrhea appeared to be the most prominent symptom. However, none of these cases was studied at necropsy and it appears that no definite evidence of the occurrence of primary intestinal infection during the epidemic was produced. In the few instances in which plague bacilli were reported in the feces, infection had evidently occurred secondarily from the blood. Albrecht and Ghon, in the report of the Austrian Commission, have mentioned the only suggestive case of primary intestinal plague occurring during a bubonic epidemic of plague, and even in this case the evidence of such infection is not conclusive. However, it seems established that primary intestinal plague has been produced in rats by feeding large quantities of virulent plague bacilli. In many instances during the Manchurian epidemic, the patients with pneumonic plague must have swallowed enormous numbers of plague bacilli in the saliva and sputum. Nevertheless, in none of the necropsies performed during the epidemic were evidences of primary intestinal infection present, nor was serious involvement of the intestine encountered. This fact certainly speaks strongly against the existence of primary intestinal plague in man, and would seem to show that even if the intestines are sometimes secondarily involved, this condition in human beings must be very rare. It has not been possible to isolate the plague bacillus from the feces in cases of bubonic plague, probably sometimes largely on account of its association with so many other microorganisms, though it seems very probable that in those cases in which the plague bacillus is present in the blood during life, and extensive intestinal hemorrhage has occurred, that it may be present in the bloody evacuations also.

Pathological anatomical conditions in the nervous system are unusual. Meningitis occurs only occasionally, as does hemorrhage of any degree in the brain substance. A few punctate hemorrhages may be more commonly observed at autopsy in the meninges, mesencephalon, and medulla oblongata. The nervous symptoms, which are often marked, are largely dependent upon the toxaemia and congestion, and hence are functional.

Complications

One of the feared complications of bubonic plague is secondary pneumonia, which in addition to high mortality is highly contagious by airborne transmission. Plague meningitis is a rarer complication and typically ocurrs more then 1 week following inadequately treated bubonic plague.

Diagnosis

The materials for the bacteriological diagnostics are taken from the inflamed lymphatic node or bubo with the help of the sterile syringe. After the skin, which is over it, is cleansed, the node is fixed by the left hand and the needle attached to the syringe is slicked into it. It is better to take the punctate from the peripheral dense part of the bubo. With the slight movement of the needle several times up and down in the node the aspiration is made. The received liquid is poured into a small test-tube and when with all the required precautions it is to be send to the special laboratory, where one drop is used for the inoculation into of ligue agar, and another one for the smears, and the rest is injected under the skin of the guinea-pig.

For the bacteriological examination the blood is taken from the vein cubitas at the amount of five to ten milliliters. The smears are prepared immediacy near the patients bed, one or two milliliters of the received blood are mixed with the melted agar, 5 mL are poured into the small bottle with a hundred milliliters of the bouillon, which is used for further examinations in the laboratory. The residual 1-2 milliliters are injected under the skin of the guinea-pigs.

The sputum is gathered into the broad-mouth jar with the ground in taps. At the pneumonic form of the plague the sputum is to be examined by the direct microscopy and by the inoculation on the medium for the isolation of the pure culture. Usually the pneumonic form of the plague contains a big amount of plague bacillus, but sometimes at the bubonic form, which is complicated with the pneumonic plague, a small amount of bacillus is discharged or there are no bacillus at all. In such cases when the pathogen is not detected at microscopy the inoculation on the medium for the isolation of the pure culture and infection of the animals are used.

All the glassware is warped up into the serviettes wetted with disinfecting solution, placed into a box and sent to the laboratory.

Differential diagnosis

Mild or moderately severe cases of bubonic plague with adenitis may be confused sometimes with climatic bubo, venereal bubo, febrile adenitis, filarial infection, or certain other diseases. Since the bacteriological examination is a simple procedure and gives reliable information, the final diagnosis should always depend upon it and in bubonic plague the bacillus should be sought for in the bubo or swollen lymphatics and in the blood.

The bacteriological diagnosis is the only certain one for excluding pneumonic infection due to microorganisms other than *Bacillus pestis*, but from the general condition of the patient, in connection with the absence of marked physical signs in the lungs, the diagnosis of pneumonic plague infection is often particularly suggested. Labial herpes has not been observed in primary pneumonic plague. The presence of numerous coarse, piping or sibilant bronchial rales in the lungs is an argument against pneumonic plague infection. The sputum in pneumonic plague is not purulent as it frequently is in catarrhal bronchitis or in bronchial pneumonia, and it is not so tenacious and has not the rusty appearance of the sputum so often seen in croupous pneumonia. The cough is usually not so painful as in croupous pneumonia. The duration of the disease is usually less than two days, though many cases do not have longer than sixteen hours after the onset of symptoms. Cases sometimes survive for three and, more rarely, for four days, but not ever one week without antibiotic treatment. Nowadays the early use of the large doses of antibiotics results in recovery.

Treatment

Patients, which suffer from plague necessarily, hospitalize in appropriate hospitals where they are transported by ambulance.

Treatment should be started already on place of revealing of the patient. Early prescription of antibiotics (during the beginning of disease), as a rule, salvages the life. Efficiency of antibioticoterapy in later terms is considerably lowest.

From etiotropic agents the most effective is streptomycinum. At the bubonic form immediately 1 gm of preparation is infused into muscle, and then in hospital is indicated 0.5-1.0 gm 3 times per day during one week. At a pulmonary and septic plague a dose of streptomycinum is enlarged to 5-6 gm. Antibiotics of tetracyclines (oxytetracycline, chlortetracycline), 0.25-1.0 gm 4-6 times are recommended. From other antibiotics it is possible to indicate monomicin, morphocyclin, ampicilini. After clinical indications it will be carried out pathogenic and symptomatic treatments.

After normalization of a body temperature and reception of negative datas of bacteriological researching from nasopharynx, sputum, punctate of bubones, patients are discharged from the hospital after 4-6 week.

Prophylaxis

Dispensary observation during 3 months is necessary for reconvalescense with obligatory bacteriological researching from mucosa of pharynx and sputum.

It is necessary to protect people from expansion of plague diseases. This work is carried out by workers of sanitation center, ambulatory-polyclinic network and antiplague establishments. Plague is the quarantine disease, so the international medico-sanitary rules (WHO, 1969) are distributed on it.

Workers of the general medical network observe health of the population with the purpose of early revealing the patients on plague. Each medical worker

should know the basic signs of disease, the rules of personal prophylaxis, be able to carry out initial antiepidemic actions.

At presence of epizootia among rats and diseases of camels vaccination of the population by local services under the control of antiplague establishment will be carried out. As active immunization living plague vaccine is used (dose for epicutaneous indication for children under 7 years is 1 billion, 7-10 years − 2 billion, adults 3 billion of microbes bodies, at a hypodermic immunization 1/10 of epicutaneous doses). Immunity is kept during 6 months, then, if necessary, revaccination is performed in one year.

At occurrence of a plague among the population the antiepidemic actions are carried out which are directed on localization and liquidation of epidemic pesthole. They include: revealing of patients and their hospitalization in special hospitals in isolation wards with severe antiepidemic regime; and establishment of territorial quarantine: revealing and isolation of all persons which was in contact with patients, they must be isolated for 6 days and undergo emergency prophylaxis with antibiotics − streptomycinum 0.5 gm 2 times per day in muscle or tetracyclinum − 0.5 gm 3 times a day per os, during 6 days; revealing the patients with fever and their hospitalization in special departaments; final disinfection, and also disinfestation and deratization on territory of settlement and around it. Invaluable things are liable to destruction. The personnel should be work in antiplague costumes. Persons who need to leave zone of quarantine, will undergo medical observation.

Control questions:

1. Infectious agent of plague and its properties.
2. Epidemiology of plague.
3. Pathogenesis and pathomorphologic changes.
4. Classification of clinical forms of plague.
5. Clinical features of the mainly localized forms of plague.
6. Clinic-epidemiological features of outer disseminated forms of plague.
7. Description of inner disseminated forms of plague.
8. Diagnosis of plague.
9. Differential diagnosis of plague.
10. Principles of medical treatment of patients with plague.
11. Prophilaxis measures against plague.

TULAREMIA

Tularemia is an acute infectious disease of a septicemic character that is manifested by intoxication, fever and the affection of the lymph nodes; it belongs to the zoonosis group with natural foci.

Historic reference

In 1910 the american bacteriologist named Mc Coy who studied plague in the shot of ground squirrels in California discovered in them anatomic pathologic changes similar to plague, but the plague pathogen was not isolated. In 1911 having used a special dense medium cultivated by himself Mc Coy together with Chapin isolated the pathogen of this disease from ground squirrels in the clean medium. After the name of the district Tulare, the word "tule" means "large cane" in aztec, the pathogen was named "*Bacterium tularense*" in 1912. During the work Chapin had a feverish disease for 28 days, it was not accompanied by an enlargement of the lymph nodes, after the recovery he discovered complement bound antigens and agglutinins to *B. tularense* in his own blood serum.

In 1912 Vail observed a patient with conjunctivitis and an enlargement of the regional lymph nodes. Wherry and Lamb isolated the *B. tularense* culture from an eye of the pathologic material taken from this patient for the first time in the medical practice. Some time later they reported on the isolation of the same microbe from two hares that had been found dead. In 1919 and 1920 having examined seven patients (one of them died on the 28th day of his disease) Francis isolated the *B. tularense* from the blood and pus taken from them. In 1921 this gave him a ground to suggest the name "tularemia" for the disease, it became part of the international nomenclature.

Etiology

The tularemia bacteria have very small dimensions, they have an ability to pass the bacterial filter of Zeits. In case of cultivation on the small coccus, and in the animals organs it can be more often found in the form of coccobacteria. In the cultures on the nutrient medium tularemia bacteria are polymorphic, it is especially expressed in the American variety. The microbe is immobile, it does not make spores, it has a small capsule. It is characteristic of the bacteria to produce mucous in the cultures, it can be easily detected during the preparation of smears on the glass. The tularemia bacteria can be tinctured with all kinds of stains, which are usually used in the laboratory practice. The tularemia bacteria are preserved in water as well as in other objects of the environment comparatively long under the condition of a low temperature and increased humidity. The microbe is not very sensitive to low

temperatures, it survives in the frost of 30 °C; it can be preserved in the frozen meat up to 93 days. The tularemia bacteria are not stable to the temperature increase. The higher the temperature is the quicker the microbes die. Thus, the pathogen remains in the animal skins at a temperature of 8-12 °C for more than a month, and at a temperature of 32-33 °C − only during a week. The microbe dies at a temperature of 60 °C in 20 minutes, and boiling kills them momentarily. The tularemia bacteria die under the influence of the sun rays in 20-30 minutes, their vital capacity remains in the diffused light up to 3 days. The tularemia bacteria are not stable to common disinfectants and are destroyed by an ultrasound.

Epidemiology

Tularemia is epidemically defined as zoonosis which has natural foci mainly supported by wild rodents and blood sucking insects. The adherence of the people who live in the rural areas to this disease is one of the main peculiarities of the tularemia epidemiology, it is connected with the natural foci of this infection and the absence of the conditions for spreading among the home rodents in the big cities. The cases of the people infection in the cities are infrequent and connected with bringing infected food or animals from the rural areas. More often the city-dwellers get infected when they go to the country where there are natural foci.

The main sources of the tularemia infection for humans are rodents, especially, common field voles, water-rats, house mice, sometimes muskrats and hamsters as well as hares. The infection of humans occurs either as a result of the contact with sick or dead rodents and hares or the bites of the infected blood-sucking arthropoda or due to water, food, straw and other substrata contaminated by the discharge of the animals sick with tularemia. A typical feather of the tularemia microbe is its ability to penetrate the organism of the humans and animals through small scratches on the skin, unaffected mucous membranes of the eye, throat, pharynx, the respiratory tract, and in case of a considerable dose the infection may penetrate through the unaffected skin. One of the typical epidemiological peculiarities of tularemia is almost 100 % susceptibility of the humans to it irrespective of age and also the fact that the sick people are not contagious for the healthy ones.

The mentioned above peculiarities of the tularemia infection, e. i. a great adaptation of the pathogen in nature, its possible ability to be transmitted by the animals or different objects of the environment (water, food etc) and a high susceptibility of the human to this infection resulted in the tularemia outbreaks, which involved great numbers of people under certain conditions. The tularemia outbreaks often reminded the epidemics of grippe or malaria in their character, and earlier they were diagnosed like this. Many materials on the tularemia epidemiology confirm this.

The concrete ways (mechanisms) of the tularemia infection of the humans are the following: contagious, alimentary, aspirational, transmissional. The infection

often occurs by means of a contact with sick animals, a contact with the objects contaminated by them (hay, straw, corn, etc), swimming in the reservoirs. The diseases belonging to this group are mainly typical of hunters-producers and in some cases of the members of their families who helped them to skin the shot animals. Besides this, there have been described some sporadic cases and even separate outbreaks occurring as a result of hunting hares. Not only did the hunters fell ill, but also the housewives who were infected while cutting carcasses.

The aspirational way of infection often occurred during the belated agricultural work while inhaling the dust rising into the air from the infected straw, corn and other substrates during their machinery or manual processing, cleaning, transportation, etc. In some cases the infection was accompanied by a contagious way.

The alimentary way of infection occurs while using the water and food containing the tularemia pathogen. The water way of the microbe transmission is due to the fact that it is considerably stable in water, especially, at a low temperature. The reservoir infection is due to the sick with the infection water rats that live on their banks. The infection of the humans usually occurs in the summer, the morbidity increase is connected with hay mowing and other field work during which the population widely uses the water from the open reservoirs for drinking and washing.

The disease of the alimentary type is often connected with house mice penetrating the human's house or food stores, warehouses and other facilities and contaminating the food with their discharge. Bread, milk, cookies, crackers can be among such kinds of food.

The transmission outbreaks depend on the infection transmission by mosquitoes and gadflies, less often – by ixodes ticks. The insects are infected while sucking the blood of the sick animals but there are indications that the gadflies can be infected by the carcasses of the water rats as well as the water infected with tularemia. The infection of the humans at the transmission outbreaks occurs exclusively in the warm season and, as a rule, not far from the reservoirs, on the flood lands, during hay mowing and haymaking.

Pathogenesis

The tularemia pathogen can be brought into the human organism by different ways: through the skin, mucous membrane of the eye, respiratory tract, the gastroenteric tract and by a combined way. The localization of the infection gate undoubtedly influence the tularemia clinical manifestations. But it would be a mistake to consider this fact to be the only one and a decisive one. The ways of the human infection combined with immunobiologic reactions of the microorganism and the pathologic peculiarities of the pathogen determine the development of one or another clinical form of tularemia, one or another clinical course of the disease.

The tularemia pathogen is not known to have ability for an independent movement. That is why it is clear that from the entrance gate where its primary

adaptation may take place, the following movement of the infect can be only in the direction of the liquid substrate. As a rule, it actually takes place with the lymph flow and very seldom with the blood flow. The tularemia pathogen often gets into blood some time later, this causes bacteremia and may result in the generalized process. Hence in the pathogenesis of the tularemia infection in the humans the phase of the lymphatic mole precedes the pathogen penetration into blood. It is by the phases of the lymphatic mole and corresponding reactions of the microorganism that the formation and presence of the tularemia local clinical manifestations, that are so important for the diagnostics, are determined. Among such clinically expressed symptoms tularemia lymphadenitis, which is more often called a bubo, is sure to take the first place. Pathogenically a sum of the reactive local changes in response to the influence of the tularemia bacteria is the basis for the development of such buboes. They remain in the lymph node during the lymph filtration and due to phagocytosis. The tularemia bacilli brought with the lymph flow reproduce in the lymph node and partly dying influence the node and the surrounding tissues by the secreted endotoxins, it results in adenitis and later periadenitis, e. i. the tularemia bubo development. Pathogenically the buboes can be divided into primary and secondary. The primary ones are often connected with the location of the entrance gate and are divided into the buboes of the first, second degree, etc. In contrast to the primary tularemia buboes the secondary ones do not have a territorial connection with the localization of the infection gate. Pathogenically they develop as a result of the hematogenic metastases. According to the terms of the development they are delayed and less expressed clinically. The secondary buboes do not usually produce any puriform softening. It is clear that it is not only the reproduction of the tularemia microbes that takes place in the foci of their concentration, but also their death with the excretion of endotoxins, which stipulate the symptoms of the general intoxication. Thus every clinical form of tularemia has the symptoms of the general intoxication though the intensity and character of the local changes are different and retain their diagnostic value. Hence, the general intoxication of the patient's organism with specific endotoxins is the basis of the general manifestations of the disease.

The tularemia pathogen penetrates the organism through the mucous membranes of the eyes, respiratory tract, gastroenteric tract and the localization of the entrance gate influences the development one or another clinical form of tularemia. However theoretically the ways of the tularemia pathogen movement remain the same − the lymphatic and then the hematogenic one. The bacteremia breaks of the tularemia bacilli followed by metastases in the lungs, liver, spleen, marrow is the basis of the specific pathomorphologic changes and the development of the multiple foci, which is the basis for the possible development of the tularemia process as a septic one. In some patients such metastases stipulate the presence of such specific complications of the secondary character as. for example, secondary tularemia pneumonia, tularemia meningitis, etc. In the most

severe cases with the increasing symptoms of intoxication the lethal outcomes are possible (severe secondary tularemia sepsis).

The mentioned subsequent phases of the tularemia pathogenesis cannot be considered to be obligatory in each separate case of the disease. On the contrary, the infectious process can be stopped at the first stages, it is of the practical importance for solving the problems of the rational treatment. Bacteremia is not a constant phenomenon and in some cases the localization of the tularemia infection can be limited by a lymph node, because the lymphatic barrier cannot be always broken.

Anatomic pathology

The anatomic pathologic changes in human tularemia have not been studied very well partly because of the low mortality. The formation of the tularemia granulomas in the form of whitish or whitish-yellow nodes is very typical. The granulomas are characterized by a zonal structure: there are epithelioid cells in the center, then – lymphoid plasmatic and neutrophilic erythrocytes then fibroblasts and often eosinophils. The central necrotic disintegration is crumb-like, acidophilic with a great number of chromatin clods in the fresher granulomas. The granulomas gradually enrich themselves with fibroblasts, argyrophil and collagenic fibrae that result in the granulomas scarring. There are no capillaries in the granulomas and they desolate soon. There are focal hemorrhages on the periphery of the granulomas. The granulomas in tularemia are similar to those in tuberculosis.

On the spot of the primary affect on the skin develops a papule, which quickly suppurates and ulcerates. The bottom of the ulcer, which is often brown, is a dry necrosis. The healing occurs by replacing the defect with cicatrizing connective tissue. The confluent areas of necrosis and granulomas occur in the regional lymph nodes. These nodes usually suppurate and open through the skin. Periadenitis often develops. Hyperplasia of the lymphoid tissue and reticuloendothelium is first observed in the nodes through a microscope, then the granulomas and the areas of necrosis, which are followed by suppuration. In the secondary (not regional) lymph nodes there are less expressed necrotic and granulomatous changes, which are not accompanied by suppuration. In the generalized form the spleen increases 2-3 times, in the chronic forms – insignificantly. The pulp is cherry-red and can be scraped off.

There is multiple small foci of necrosis in the tissue of the organ. The hystologic changes are identical to those in the secondary buboes.

In abdominal tularemia a granulation inflammatory process with focal necrosis and possible ulceration of the mucous membrane develops in the stomach and intestines. There are granules and necrosis foci in the perigastrial and mesenteric lymph nodes. There is stagnant plethora, dull swelling and adiposity of parenchyma in the liver. The necrotic and granulematous foci are not so widely spread as in the spleen. There is parenchymatous and fatty degeneration of the

convoluted tubules epithelium in the kidneys. There are frequent lymphoid infiltrates in stroma. The granulomas and necrotic changes are not constant.

Catarrhal laryngotracheobronchitis often develops in the primary pulmonic forms. The inflammatory changes of the lungs are macrofocal and can be similar to croupous pneumonia but tularemia pneumonia develops as serous or serous-fibrinous with a conversion to necrotic one. The abscess formation is usually observed. Pneumonia is usually complicated by serous-fibrinous or purulent pleuritis, later by similar pericarditis. There are changes typical of tularemia (necrosis, granulomas, suppuration) in the peribronchial and mediastinal lymph nodes.

In the anginous-glandular form one tonsil is affected. The process can only be limited by plethora and hyperplasia. However, more often focal necrosis develops in the beginning, then it is followed by extended necrosis and ulceration with purulent melting or diphtheritic patches. The transformation of the submaxillary, superior cervical lymph nodes into buboes occurs simultaneously.

The eye disease can be in the form of the primary eye-glandular form and in the form of the secondary affections. At first there develop papules mainly in the lower eyelid mucous membrane, they suppurate and ulcerate with the discharge of purulent exudate. The eyelids are sharply swollen. The cornea is not often affected. The buboes typical of tularemia are localized in the parotid lymph nodes but the superior cervical lymph nodes also be affected.

Clinical manifestations

The incubation period in tularemia often lasts from 3 to 7 days. The cases of the incubation period in humans within the limits of the first 24 hours are practically very rare exceptions, and the cases of the incubation period exceeding two weeks are very doubtful.

There are three periods in the clinical course of the disease: 1) primary, 2) high point of the disease, 3) period of convalescence. It is extremely important to pay special attention to the first period for the sake of both clinical and epidemiological diagnostics.

The onset is always acute without prodromal phenomena, which are accompanied by chills or expressed shivering and abrupt temperature increase up to 39 °C and higher. Most patients name not only the day but also the hour of the disease onset without any difficulties. The patients complain of a headache, malaise, various muscle aches, which are often in the sural and waist areas. Besides this there is dizziness and appetite worsening, which develops into complete anorexia. The sleeping disorders as well as increased sweating, especially at night, are quite typical. In more severe cases there is vomiting, nose bleeding and later there can develop the conscious darkening and delirium. The headaches are the most persistent and prolonged. The hyperemia of the face and sometimes of the fauces is objectively observed. On the part of the upper respiratory tract there are usually no catarrhal symptoms, rhinitis and sneezing are very rare. Conjunctivitis and watery eyes are the most clearly expressed in the primary eye affection.

As the primary period of tularemia does not have any pathognomonic symptoms, the epidemiological anamnesis, which should be distinctly reliable and exhaustive, is of great importance. The total duration of the primary period is 2-3 days. Later the clinical symptoms of the disease develop in different ways depending on the development of tularemia in one or another clinical form.

The forms of tularemia which are distinguished according to the clinic-pathogenic and epidemiological data are as follows. The bubonic, ulcer-bubonic, eye-bubonic forms develop when the infection penetrates through the skin and eye mucous membrane. In the anginous-bubonic and abdominal forms the infection penetrates through the mouth. In the pulmonic (bronchial and pneumonic variants) the infection penetrates through the respiratory tract. Besides there is a generalized or primary septic form (it is observed in any way of infection, especially, in weakened people).

The bubonic form of tularemia is characterized by the development of the inflammatory process in the regional lymphatic node (Fig. 14). A bubo (lymphadenitis) is an obligatory and fundamental symptom of the disease here. There are primary and secondary buboes. The primary buboes develop in a lymphogenous way and are connected with the area of the pathogen penetration. The secondary buboes develop as a result of the hematogenic spreading and are not connected with the localization of the entrance gate. The size of the tularemia buboes varies from the size of a small nut to a chicken egg and larger. It is usually not a separate regional node that gets involved in the process, but several nodes in a particular area. The buboes are dense, slightly painful, there is no expressed periadenitis. There can be several main variants of the tularemia bubo outcome: complete dissolving, suppuration, ulceration with the following scarring and sclerotization. If there is no suppuration, the reverse development or dissolving is slow and undulating with changing of improvement and an acute condition. The process lasts up to 2 and more months. The softening of the bubo begins in 2-3 weeks from the disease onset, but sometimes even later. The suppurating softening develops approximately in half of the cases. At first there is no distinct reaction on the part of the surrounding cellular and skin but soon there develops swelling and skin reddening gradually increasing in intensity and extensity and, finally, there is a breakage with buboes draining. The puss of the tularemia buboes is thick, white, without any smell, it looks like cream or sour cream. There are often primary inflammatory changes at the area of the infection entrance gate in case of a cutaneous way of infection. These changes of the primary character are the basis for diagnosing the cutaneous-bubonic or ulcer-bubonic forms. A cutaneous ulcer develops during the first days of the patient's feverish condition. The inflammatory process often affects all the skin depth but sometimes is limited by the superficial layers in the form of erosion. At first a spot develops, it often remains unnoticed, then it quickly turns into a papule. A vesicle soon develops on the top of the papule, it first has transparent serous and then serous-

purulent contents. The vesicle bursts, out and turns into an ulcer. The form of the ulcer is round or oval with a size of a dime. The redness and swelling on the ulcer circumference are insignificant. The redness quickly loses its brightness, and the ulcer becomes pink and later it has a cyanotic-reddish tint. The ulcer discharge is serous-purulent, purulent and very seldom it is of a sanies character. The tenderness at touching is insignificant, that is why the patients cannot often name the time of its development. The ulcer course is dull with a slow healing during 15-45 days.

Many authors describe the allergic eruption in the form of roseola, petechia, papules, erytematous-papuleous eruption, etc. In case of tularemia, more often in the second period of the disease, it has a diverse localization, sometimes symmetrical. There is usually peeling, sometimes scaly and less often macrolaminar after the disappearance of such eruption.

The bubonic form of tularemia with the primary affection on the part of the sight organ – eye-bubonic form develops if the pathogen penetrates the eye mucous membrane. In this case there is expressed conjunctivitis, sometimes the presence of papules and ulcers besides regional (parotid, front cervical, submaxillary) lymphadenitis on the part of an eye. The eyelids are swollen and dense, the patients complain of their tenderness at moving, the amount of the mucopurulent discharge is moderate. On the eyelid mucous membrane there are inflammatory small foci in the form of the cone, they are yellowish and have a whitish top with the size of a pin's head. There is a considerable number of separate groups of yellow dots on the lower eyelid on the background of a big number of scattered formations, a smaller number of them is observed on the upper eyelid.

There are inflammatory small foci with a bunch of the superficial widened vessels on the sclera conjunctivas, the foci are almost always located near the limbus. No changes on the part of the cornea or other refracting media of the eye have been found. In a number of cases the eye-bubonic form is accompanied by dacryocystitis. The lachrymal sack phlegmons have been described. Almost all the patients have an affection of the parotid and submaxillary lymph nodes, in some patients their increase is observed on the 3-10th day of the disease. The clinical course of the eye tularemia affection is within the limits of 20 days to 3 months. The eye affection may be secondary, in this case the eye changes as well as the eyelid skin ones take a course similar to that of metastatic granulomatosis and is observed in different clinical forms of tularemia.

The anginous-bubonic form of tularemia is first accompanied by the development of angina with characteristic local changes on the part of the tonsils: hyperemia, hyperplasia, grayish-whitish patch, which is often on one side. There are local pains and swallowing difficulties. The degree and quality of the local affections in the anginous-bubonic form as well as the dynamics of the process are diverse. According to the clinical peculiarities there are three types of tularemia angina: catarrhal patch-diphtheritic and infiltrative-ulcerative.

There is hyperemia of the fauces, pain at swallowing, high temperature, enlargement of the cervical lymph nodes – the formation of buboes in the catarrhal variant of tularemia angina. The fauces hyperemia remains up to 8-10 days, the buboes – up to 1 month and longer. A white patch firmly sticking to the mucous membrane develops on the tonsils and airfoils in the second form. There is hyperemia with a cyanotic tint in the circumference of the grayish-greenish covers. The covers usually remain for a long time and begin to tear away only two weeks later. A massive, quite dense infiltrate, which has no inclination to abscess forming and which goes up till the hard palate, develops from the very beginning in case of infiltrative-ulcer variety. Its reverse development lasts 2-3 weeks and in some cases ulcers develop in the area of the infiltrate.

Expressed catarrhal pharyngitis, cyanosis of the mucous membrane with a crimson tint that looks like venous congestion are observed in all cases. The congestion phenomena in the fauces remain for a long time, even after the end of the ulcerative-necrotic processes. The insignificant subjective feelings during a severe ulcerative-necrotic destructive process in the fauces are typical of tularemia angina. In some cases the enlargement and tenderness of the cervical lymph nodes coincide with the changes in the throat, sometimes buboes are formed only by the moment of the angina disappearance. A bubo remains for 2-8 months, less often shorter. Tularemia angina is characterized by a strict localization in most cases the changes are limited by one tonsil irrespective of the severity of the changes.

The abdominal form of tularemia has not been studied well so far, so it is supposed to occur more often than it is diagnosed. Severe pains in the stomach are typical of the abdominal form. The process is characterized by a deep localization of the affected, mainly mesenteric lymph nodes, in contrary to other variants of the bubonic form with the peripheral buboes localization. This variant cannot be united with the generalized form as in this case the affection of the lymph nodes of a certain (abdominal) area prevails. Epidemiologically it is most often observed at the outbreaks, which are characterized by the massive doses of infection that penetrate through the throat (water outbreaks).

The disease is manifested by a general feverish condition with a high temperature, chills, in some patients – sickness and vomiting, less often – delirium. The spasm-like pains in the abdomen of different duration and intensity, meteorism, and sometimes constipation are also typical. In some patients the abdomen pains can be so intense that resemble the picture of the "acute abdomen" and can result in the surgery. The clinical phenomena in the abdominal variant of the bubonic form depend on the inflammatory changes (hyperemia, swelling, etc.) in the mesenteric nodes that causes the irritation of the peritoneum followed by acute pains, sickness, vomiting, etc. The cases of the tularemia abdominal form, which are accompanied by suppuration of the mesenteric lymph nodes and peritonitis, have been described. There are cases, which where diagnosed posthumous.

The difficulties of the clinical diagnosing of the tularemia abdominal form are connected with the peculiarities of the clinical manifestations, and perhaps a relatively bad knowledge of the doctors.

In case of the distinct data of the anginous-bubonic form, in which the infection occurs through the mouth, the possibility of the affection of the intestines and the mesenteric lymph nodes, especially, in the people who suffer from deferred acidity or achylia, can't be excluded. That is why it is necessary to thoroughly investigate the abdomen even if there are certain symptoms of the anginous-bubonic form.

The pulmonary (thoracal) form of tularemia occurs in case of the aspiration way of infection and is characterized by the development of the primary inflammatory process in the lungs. Epidemiologically this pneumonia is connected with certain conditions of infection. Thus, during threshing when the stacks are infected with the discharge of the mouse-like rodents, the infection is airborne and several people fall ill. The airborne infection in the laboratories is less frequent, with separate cases.

In case of the primary pulmonary form the inflammatory process develops in the lungs from the very beginning. There can be two main variants in this case: bronchial, when the process occupies only the large respiratory tracts, and bronchial pneumonic when the deeper parts are affected − bronchioles, alveoles. The clinical picture is diverse and depends on the localization of the intensity process and the combination of the inflammatory changes. Only tracheitis, bronchitis and their combinations are possible, this confirms their aspirational way of infection. Hence in some cases the pulmonary tissue does not get involved in the pathological process. But the process is localized in the chest and spreads on the mediastinal lymph nodes, that is why these forms of tularemia are named thoracal.

The bronchial pneumonic variant, or tularemia pneumonia, is characterized by a dull and exhausting course, it lasts up to a month, less often 2 months and longer. Anatomically these are small foci, which have a tendency to confluence and cause lobar pneumonia.

Besides the dry rale (as in the first variant) it is possible to auscultatorily hear the moist and often crepitant fine bubbling rale. In some patients they remain for a long time and are heard even in the period of convalescence. During the X-ray examination besides the darkening of the pulmonary tissue it is possible to notice the inflammatory phenomena in the lymph nodes of the mediastinum and the lungs roots, they are limited only by one area confirming in this way the local manifestations of the disease.

Pneumonia has a severe course but it does not have a cyclic course. it has a tendency to relapses and the formation of different specific complications: bronchiectasia, abscesses, the lungs gangrene, dry and moist pleuritis. Necrosis in the affected parts of the lung can result in the cavity formation − tularemia caverns. Sometimes the changes in the lung tissue have a dull prolonged character with clinically expressed intoxication. The patient with tularemia pneumonia is not contagious for the surrounding people.

It is necessary to distinguish this primary tularemia form from the secondary one, which can join any other clinical form as a complication. It develops in a

metastatic way later and deteriorates the course of the disease. The terms of the end of such pneumonia are quite various – from 2 weeks to 2 months and longer.

In case of the generalized form of tularemia the fundamental sign is the development of the general symptoms of the disease without previous local symptoms, which are absent in the future, as a rule. It is the only form of tularemia, which does not have a primary and a regional reaction. Clinically the generalized form is distinguished by more severe manifestations of intoxication, sometimes even fainting and delirium.

The headaches are intense and persistent, adynamia and muscle aches are very expressed. The fever lasts about 3 and more weeks, and the temperature curve is often oscillatory. A rash similar to exudative polymorph erythema often develops during the second half of the disease. The rash on the upper and lower extremities is usually symmetric, pink-red, later has a crimson-coppery tint and at the end it has a cyanotic shimmer in the form of the tularemia "gloves", "gaiters", "socks". The rash remains for 8-12 days, there is peeling and prolonged pigmentation after the rash disappears.

In the generalized form of tularemia the capacity to work is recovered especially slow, the relapses are not excluded.

Diagnosis

There are several methods of the tularemia pathogen isolation in the laboratory. These are direct bacterioscopia, bacteriology with the microbes identification and a biological method. However the immunologic methods are more often used to diagnose the disease in people than the bacteriological ones. It depends on the fact that the tularemia pathogen belongs to the first group of microorganisms, that is why its isolation and identification can be done only in the specially equipped laboratories of the departments for the especially dangerous infections.

The agglutination reaction is the most popular method of the serologic diagnostics. The reaction is considered positive when serum is diluted 1:100 and higher and becomes positive from the second week of the disease.

The compliment binding reaction (CBR), hemagglutination reaction, precipitation reaction and others can also be used.

An intracutaneous allergic reaction on the injection of allergen -tularin, 1 mL of which contains 100 million microbic bodies killed by heating at a temperature of 70 °C during an hour, is highly specific. The test is quite specific (it is necessary to take into account the possibility of inoculative or anamnestic reaction) and usually allows to diagnose the disease from the fifth day after its onset.

Differential diagnosis

The tularemia diagnosis in case of the sporadic morbidity is difficult because of the polymorphism of the clinical symptoms and various localization of the process. The diagnostic mistakes are often made at the initial period. First of all

it is necessary to take into account the epidemiological data for the clinical diagnostics: patient's occupation, rural living conditions, a rapid reproduction and intensive death of rodents. Plague should be put in the first place because tularemia is still known under the name "plague-like disease".

Commonplace lymphadenitis of the strepto- and staphylococci etiology is characterized by an intense tenderness, early suppuration, frequent lymphangitis and local edemas. There are often inflammatory processes at the area of the infection entrance gate.

Tuberculosis lymphadenitis is distinguished by a gradual development of the disease, subfebrile temperature, density and absence of tenderness. They are often located in the form of a chain, characterized by a comparatively rare change of the skin over it and are considerably smaller than in tularemia.

The anginous-bubo form of tularemia can imitate different forms of angina, mainly Symanovsky-Vincent angina and diphtheria of the fauces.

The distinguishing of the eye-bubonic form of tularemia from adenoviral conjunctivitis and eye diphtheria is based on the serous-allergic reactions and bacteriologic investigation for diphtheria.

The differential diagnosis of tularemia from pneumonia of a different etiology is the most difficult.

In the generalized and the abdominal form there is sometimes a typhus-like condition of the patients that gives one a ground to suppose typhoid fever and spotted fever.

Treatment

The patients are treated in the infectious hospital. Antibiotics are the main in complex therapy. Streptomycin is the most effective: 0.5 gm 2 times per day in a muscle. At pulmonary and generalized forms daily dose of streptomycin enlarges till 2 gm. Course of treatment lasts all period of fever and the next 5 days with normal body temperature. Streptomycini sulfas has bactericidal effect, after its introduction Yarish-Hercscheimer reaction may be observed. Therefore in serious cases antibiotic therapy is combined with prednisolon or its analogues.

Tetracyclin, doxycyclin, levomycetin, kanamycin, gentamicin, rendering bacteriostatic action are less effective. At pulmonary and generalized forms daily dose of the specified antibiotics is enlarged in 1.5 times. Preparations of tetracyclin are expedient for combining with aminoglycosides.

At lingering course and relapses of tularemia combined treatment is provided with antibiotics and inactivated vaccine which infuse parenteraly in a single dose 1.5 — 15 million microbic bodies with interval 5 — 6 days. Course of treatment consists of 6 — 12 infusions.

As desintoxication therapy it is expedient to use reopoliglycin, standard saline solutions with glucose. Vitamin preparations are widely used as desensitizing agents. At pyesis of buboes they should be opened and a bandage with unguenti of streptomicin should be used.

At anginous-bubonic form of tularemia the inhalation of chlorophilyptus are recomended. At procces of eyes 20-30 % a solution of sulfacyl-natrii is indicated.

The treatment is complex, the antibacterial therapy plays the main role in it. Streptomycin, tetracycline, chloromycetin are the most effective medicines. A day's dose of streptomycin 1-2 gm, tetracycline − 1.5-2 gm, chloromycetin − 2 gm. At the highest point of the disease detoxication therapy is prescribed (intravenous injection of the salt solutions, haemodesum, polyglucinum, 5 % solution of glucose, ascorbic acid). The detoxication therapy is done by taking enterodesum and other preparations of this group. Calcium gluconate, diphenylhydramine, pipolphen, diazolinum are used to decrease the allergic manifestations.

In case of relapses and acute forms it is necessary to prescribe antibiotics courses, but it is necessary to remember about dysbacteriosis.

Compresses, ointment bandages and wanning treatment are used at the area of buboes at the stage of dissolving. If the buboes suppurate, they are widely opened and treated as a purulent wound together with treating the main disease. In case of the timely and valuable treatment the prognosis is usually favorable. The lethality is up to 0.5 % and occurs in the complicated pulmonary and abdominal forms of tularemia. The ability to work is recovered slowly.

Prophylaxis

The prophylaxis includes the control over the natural foci, the interruption of the mechanism of the disease transmission, as well as the vaccination of the population in the epidemic foci. The planning and the fulfillment of this work in the tularemia foci are done by the sanitary-antiepidemic service with the participation of the medical workers of the medical institutions who perform the rounds in the houses and the vaccination of the population.

Control questions:

1. Tularemia etiology.
2. Epidemiology of tularemia.
3. Pathogenesis and pathomorphology of tularemia.
4. Classification of clinical forms of tularemia.
5. Clinical manifestations of different tularemia forms.
6. Laboratory diagnosis of tularemia.
7. Differential diagnosis of tularemia.
8. Treatment of patients with tularemia.
9. Preventive measures against tularemia.

AQUIRED IMMUNODEFICIENCY SYNDROME

(AIDS/HIV INFECTION)

Secondary immunodeficiency syndrom is caused by a virus and characterized by severe immune deficiency resulting in opportunistic infections, malignancies, and neurologic lesion in individuals without prior history of immulogic abnormality.

Historic reference

In June 1981 the "Morbidity and Mortality Weekly Report" carried a report of five deaths due to overwhelming *Pneumocystis carinii* pneumonia in Los Angeles, California. *P. carinii* has been recognized for many years as a human opportunist infection, infrequently causing life threatening pneumonia in patients with naturally occurring or iatrogenic immunosuppression. Since the development of immunosuppressive regimens for overcoming transplantation rejection, pneumocystis has been seen in patients with compromised cellular immunity. All of the five patients reported had been homosexual men with no prior illness or history of congenital immunodeficiency, and none had taken know immunosupresive drugs. In December 1981 three reports in the "New England Journal of Medicine" described the medical presentation and laboratory characterisation of a further 20 homosexual men who had died of unexplained immunodeficiency. In every case previously healthy young men (mean 35 years) had developed overwhelming opportunist infections associated with profound cellular immunodeficiency, or Kaposi's sarcoma, a tumor previously associated with immunosupresion. All the patients had an absolute decrease in the number and proportion of CD-4 T-lymphocytes, and a specific loss of T-cells immunity. The syndrome was initially termed "gay-related immune deficiency" (GRID), but by the end of 1982, cases of this acquired immunodeficiency had been reported in intravenous drug users, female sexual partner of index cases, children of affected women and in heterosexual men and women from Haiti resident in the US. As this disease was clearly not linked exclusively to homosexuality, the term acquired immunodeficiency syndrome (AIDS) was adopted.

The disease was described in homosexual men and intravenous drug users through Europe, South Africa and Australia by the end 1982. Subsequently in 1984 it was reported that heterosexual cases of AIDS were occurring in large numbers in West, Central and Eastern Africa, involving minimally the countries of Zaire, Uganda and Ruanda. The global distribution of cases and the occurrence suggested strongly that the infections agent was responsible for epidemic and, as blood-born transmission was common, it was most likely to be a virus. Two distinct patterns of transmission were observed: pattern 1 was that the blood-

born agent which was transmitted in a similar manner to the hepatitis B virus and was prevalent in homosexual men, intravenous drug users, their sexual partners and recipients throughout the western world, and had turned the US cases into a pandemic over a very short period. Pattern 2 transmission was more similar to a classical sexually transmitted disease, and approximately equal number of male and female cases were found; pattern 2 transmission predominated in the developing world, in particular in sub-Sahar Africa.

From early 1982 onwards, efforts to identify the causative agent intensified and in may 1983 group from the institute Pasteur in Paris, reported about the isolation and propagation of a T-lymphotropic retrovirus, lymphoadenopathy associated virus, LAV from the lymph node of a patients with persistent lymphoadenopathy, a syndrome know to be assotiated with, and preceding the development of AIDS.

This virus had been fully characterized by 1984 and formally termed the human immunodeficiency virus type 1 (HIV-1) in 1986. Serological assays for antibodies to HIV-1 were widely commercially available by 1985 allowing large-scale sero-epidemiology and screening to be undertaken. Examination of stored sera revealed that HIV-1 had been introduced into homosexual men in the US during 1978, and had not existed in the US priori to that time. Subsequently, a serological variant HIV-2 was identified in West Africa. HIV-2 leads to persistent lifelong infection, and is also associated with the clinical development of AIDS, many years after infections. However, there are reproducible data which show that the likelihood of AIDS developing after HIV-2 infection are lower at 10 years post infection than with HIV-1, and that HIV-2 is generally less pathogenic, and less transmissible, than HIV-1. These epidemiological observation are matched by an apparent lower HIV-2 viral load in peripheral blood than seen in the corresponding time from infection in HIV 1 infected subject, the full-lenght sequencing of HIV-1 and HIV-2 isolates revealed that these viruses were lentiviruses of the retrovirus family, and that all isolated shared a common tropism for T-lymphocytes, through the use of the CD 4 receptor. The emergence of a new infections agent in a human population can have only a limited range of explanation; either the infection was previously in an isolated human population from which it had been exported though some societal change, or else it might have been a zoonosis newly exposed to human transmission. A third line of explanation, that of an extraterrestrial or even a man-made origin, has been popular with conspiracy theorists, but will not be furthers discussed. The natural history of HIV-1 infection is marked by the long period of time between infection and disease.

Etiology

The cause is a retrovirus that has been termed the human T-lymphotrophic virus Type III (HTLV-III), lymphadenopathy-associated virus (LAV), and the AIDS-

associated retrovirus (ARV) by different laboratories. More recently, it has also been referred to as the human immunodeficiency virus (HIV), the term that will be used here.

Retroviruses are very small viruses composed of a single strong of RNA, the intermediate nucleic acid in the production of proteins. Normally, the flow genetic information starts with a piece of DNA, which makes a piece of RNA, which in turn codes for, protein. Everything flows in that direction.

Retroviruses contain an enzyme called reverse transcriptase that can convert viral RNA in the cytoplasm into DNA, which may replicate from extrachromosomal sites or move into the cell nucleus where it becomes part of the host cell DNA. These integrated viral genes are duplicated with normal cellular genes, and all progeny of the originally infected cell will contain the viral genes. Expression of the viral genes for some retroviruses may be oncogenic, converting the cell into a cancer, or may have other pathologic effects which may alter normal cell function or produce cell death. Retroviruses have been known to cause malignant and nonmalignant diseases, and the same virus may cause different diseases in different animals; e.g., bovine leukemia virus causes a B cell lymphoma in cows, a T cell lymphoma in sheep, and an immunodeficiency disorder similar to AIDS in rabbits.

There are 3 groups of retroviruses that affect humans, and all have a remarkable affinity for lymphocytes, particularly for T4 lymphocytes. HIV preferentially infects the major subset of T-cells, defined phenotypically as T4 and functionally as "inducer/helper" cells, which are then depleted, resulting in a reduced ratio of T4 helper (Th) to T8 suppressor (Ts) cells. However, the virus also is capable of infecting some nonlymphoid cells, such as macrophages and nervous tissue cells, and presumably remains present for life.

Epidemiology

The major transmission routes of human immunodifficiency virus are sexual contact, parenteral exposure to blood and blood products and perinatal transmission. Early in the AIDS epidemic, epidemiological studies establish that receptive rectal intercourse was the predominant mode of HIV-1 acquisition by homosexual man. Other practices that could traumatize the rectal mucosa appeared to increase further the infection risk for the receptive partner. Insertive rectal sex could also place a men at risk for HIV-1 infection, although the insertive partner would be at lower risk than the receptive partner.

On a world-wide basis sex between man and women apparently is the most common mode of acquiring HIV-1 infection heterosexual transmission accounts for the vast majority of cases. In other country where AIDS cases attributed to heterosexual transmission, although still a small percentage of the total number of reported cases comprise the most rapidly growing category. Therefore an understanding of the rate at which HIV-1 is transmitted between heterosexual couples and of the factors that may impede or enhance heterosexual transmission is important in slowing the worldwide HIV-1 epidemic.

In the country, where HIV-1 infection is more common in men than women, studies of female-to-male transmission of HIV-1 infection are both fewer and smaller than studies of male-to-female transmission. Available date suggest female-to-male transmission may be less efficient than male-to-female transmission.

Overall these American and European studies suggest that heterosuxual transmission from HIV-infected persons to their regular sex partner is relatively inefficient, especially female-to-male transmission. Furthermore, the risk of heterosexual transmission is not related simply to the number of episodes of sex with HIV-infected person because some people have remained uninfected after hundreds of such contacts whereas others have become infected after a single episode of intercourse.

Infectivity may be higher during early infection before the development of antibodies to HIV-1, also genital ulcer diseases and inflammation of the genital tract lead to increased susceptibility to HIV infection.

Perinatal or vertical transmission. Mother-to-infant transmission of HIV apparently is relatively efficient; without treatment approximately one in the four infants born to seropositive mothers is infected. With one rapid spread of infection to women of reproductive age perinatal transmission is now a major consequence of HIV epidemic. The precise rate of perinatal transmission in a given setting has been difficult to define because of problems in the infant and the difficulties in maintaining long-term follow-up. Uninfected children born to seropositive mothers may retain passively aquired maternal antibody for 6 to 18 months.

The timing mechanisms, and risk factors for perinatal transmission might occur and guiding the development of effective interventions. These factors include maternal stage of disease maternal antibody response to infection, viral titer, variations in viral genotype and phenotype, and obstetric factors such as preterm birth, mode of delivery, and maternal or placental coinfection. Perinatal HIV transmission can occur both in utero or at birth. Several lines of evidence support the occurrence of human placenta tissue express CD4 receptors and are suseptible to HIV infection. Virus has been isolated from amniotic fluid and has been identified in fetal abortus tissue by culture, PCR and in situ hybridization. However, other investigators have not found HIV in fetal tissue and it is difficult to exclude contamination of these tissues by maternal blood. Clinically, the fact that subsets of infected infants have detectable virus at birth immunologic abnormalities in the neonatal period and rapid progression to AIDS in the first four months of life suggest in the utero transmission. The proportion of infants actually infected in utero and the time during gestation when this is most likely to occur, however, are not known.

Intraportum transmission, analogous to the vertical transmission of hepatitis B, likely occurs through direct contact with maternal blood secretions as the infant is delivered through the birth canal. HIV has been isolated from cervical secretions. Also the virus might be able to pass directly through maternal-fetal

transfusions, particularly during placental separation at birth. The fact that many infected children are born without detectable virus or immunologic abnormalities supports the likelihood that delivery represents a high risk for HIV transmission. Interestingly there has not been strong evidence that that delivery by caesarean section is protective. However, a recent report based on an international twin registry suggests that being the first of two twins delivered and vaginal delivery are risk factors for infection in twin births. This hypothesis and its relevance for singleton births warrant further study. Although it has not been shown that intrapartum fetal scalp monitoring facilitates transmission, avoiding invasive of the fetus whenever possible, seem prudent.

Postpartum perinatal transmission of HIV through breast-feeding has been reported. Free virus has been found in the cellfree fraction of breast milk and might directly penetrate the infant's gastrointestinal mucosa. However, data from several cohort studies suggest that the additional risk of postpartum transmission is low in pregnant mother already infected with HIV. These finding may result from low viral titers in breast milk of previously infected women, concomitant IgA antibody or some other factor.

Extensive laboratory research and epidemiological studies indicate that HIV is not transmitted by shaking hands, hugging, kissing, contacting bodily secretion such as sweat, mucus (as in sneezing or coughing) or salive. Nor is HIV transmitted by food, swimming at a pools, drinking at a water fountain and also bloodsucking mosquitoes or other arthropods.

Pathogenesis

Following infection across a genital surface, involving infection of CD-4 bearing cells in the mucosa or submucosa, the virus presumably migrates to a regional lymph node, where viral replications occurs. A number of rounds of viral replication than occur within the bounds of the regional lymph node as no detectable virus or immune respons occurs for up to 42 days post infection. When the quantity of infected cells exceeds a threshold, viremia occurs, and the symptoms of an acute non-specific viral illness with tende adenopathy, sore troath, diffuse macular rush, arthralgia and fever. Following the acute viremia, when up to 10^7 viral particles/mL plasma can be found, a primary immune response develops with antibodies to viral proteins and a cytotoxic T-cells response, which limit viral replication and clear viral particles from the plasma. The reduction the viral load in plasma is not matched by a clearance of provirus in peripheral blood mononuclear cells, and cellular viremia continues in the face persistent and sustained cellular and humoral immune response for the duration of the infection. Even while plasma viral load is suppressed by the immune response, CD-4 T-lymphocyte number foll in linear manner over time. The most plausible explanation for the pathogenesis of AIDS over time is the sustained less CD-4 cells by ongoing HIV viral replication in nature peripheral blood T-cells

and by a slight failure of production of match peripheral destruction of HIV CD-4 cells. However, recent controversy over the pathogenic mechanisms and homestasis of T-cells has revealed that simple viral cytopathic effect on CD-4 cells may be overly simplistic model.

During the course of HIV infection, CD-4 cells continue to decline in peripheral blood and plasma viral load slowly rises. Over a definite period CD-4 cells number declines from 800 to 200 mL; at this level, the probability of the cellular immune system containing latent or environmental infections such as *P. carinii* falls and clinical opportunist infection becomes increasingly possible. As the viral l retrovirus load rises. HIV isolates with altered co-receptor usage appear which can use the CXCR-4 chemocine receptor rather than CCR-5; these isolates are more cytopathic in vitro, and may lead to wider tissue distribution of HIV in later disease, AIDS is therefore, the clinical condition of an immune system which is sufficiently compromised by HIV infection that there is an inability to protect against the growth of low grade pathogenes or viral indeced tumors.

The fact that this virus, after infection of the host, besides destroyed strong immune system also can spread to many body tissues. The ultimate outcode of the infection depends on the host's immune reaction to the virus either through suppression of HIV replicationor through killing of the infected cell. In some individuals an active immune system has prevented development of the disease for years. The factors important in maintaining this immune response are not yet know and merit close attention. The immune deficiency produced by HIV infection makes patients suseptible to infection by a variety of organisms, including viryses, bacteria, fungi and parasites that are of low pathogenecity in the normal individual and of variable prevalence in different part of the world. In some individuals the immune system appears to make enhancing antibodies to HIV and this phenomenon occurs particularly with progression of disease. It is related to change to antibodies made and in some cases to modifications in the virus so that is more sensitive to enhancing antibodies. Moreover, the immune system can hyperreact, with production of antibodies that might also hasten the development of disease. Clearly changes in the virus and the immune response of the host play important roles in the ultimate steps leading to AIDS.

Anatomic pathology

Forty to sixty percent of AIDS patients develop neurologic dysfunction and up to 90 % have neuropathologic changes at autopsy. HIV itself can cause brain disease manifested as meningoencephalitis, mild cognitive dysfunction, or frank dementia. It is felt that the pathogenesis of this neurologic damage is related to the presence of infected tissue macrophages that may release viral proteins or cytokines that result in brain dysfunction, inflammation, and tissue destruction. In this regard, studies of brain tissue from AIDS patients have shown that the predominant cell type infected with HIV is the monocyte/macrophages (M/M).

Infected M/M may release factors resulting in reactive glial cell growth, and, because glial cells have been shown to be infectable with HIV in vitro, infected brain M/M may provide a source of infectious HIV to these glial cells. The HIV envelope protein can inhibit neuronal growth in vitro; this may be due to competition between neuroleukin and gpl20 for binding to the neuroleukin receptor, because there is partial sequence homology between these two proteins. It is possible, but not yet demonstrated, that infected M/M in the brain may release large quantities of gpl20 resulting in the inhibition of neuronal growth.

A wide variety of hematologic abnormalities occur in HIV-infected individuals including pancytopenia and myelodysplasia. Although the etiology of these multiple abnormalities has not been completely delineated, it has been shown that the CD34+ bone marrow myeloid progenitor cell can be infected with HIV in vitro with the resultant production of large amounts of predominantly intracellular virus and minimal cytopathic effects. More recently, CD34+ cells isolated from the bone marrow of some infected individuals have been shown to be infected with HIV. Whether these precursor cells produce large amounts of virus in the bone marrow in vivo and the potential contribution of these cells to the hematologic abnormalities observed are currently unknown. Infected macrophages within the bone marrow have been reported to produce factors, presumably cytokines, which appear to suppress hema-topoiesis through their effects on the CD34 + precursor cell. Whether bone marrow macrophages are an important reservoir of HIV has not been definitively determined.

Finally, cells of the monocytic lineage that populate other organs are susceptible to infection with HIV and may contribute to pathogenesis of disease at these sites. Specifically, lung alveolar macrophages, Kopffer cells of the liver, and peritoneal macrophages are infectable in vitro with HIV, and alveolar macrophages from HIV-infected individuals are clearly infected in vivo. It is currently unknown whether these cells contribute to tissue-specific disease, such as the diffuse pulmonary fibrosis that occurs frequently in pediatric AIDS patients

Clinical manifestations

The time from exposure to HIV until the onset of the acute clinical illness is typically 2 to 4 weeks, although longer incubation period have been reported. The clinical illness is acute in onset and lasts from 1 to 2 weeks. It can be associated with an appreciable degree of morbidity and patient may require hospitalization. The main clinical features of primary HIV infection reflected both the lymphocytopatic and neurologic tropism of HIV. Patients report fever, lethargy, fatigue, headaches, retro-orbital pain, sore throat, muscular pain, occasional diarrhea, maculopustular rash and the onset of swollen lymph nodes (swollen glands). Meningoencephalitis may also occur. Lethargy and malaise are frequent, often severe and may persist for several months after resolution of the other clinical manifestations of primary HIV infection. Lymphoadenopathy (Fig. 15) develops

in approximately 70 % of persons, generally in the second week of the illness and usually concomitant with the development of peripheral lymphocytosis, reflects the fact that HIV has activated B-lymphocytes to become plasma cells and secrete HIV antibodies.

The lymphoadenopathy may be generalized, but the occipital, axillary and cervical nodes are most commonly involved. The lymph node enlargement persist after the acute illness bat tend to decrease with time. Splenomegaly has also been reported. The mechanism for this splenomegaly is not apparent; it may be related to increased clearance of virally infected lymphocytes. The most frequently reported dermatologic evidence of primary. HIV infection is an erythematous, nonpruritic maculopapular rash. This rash is generally simmetric, with lesions 5 to 10 mm in diameter, and affects the face or trunk, but it can also affect the extremities including the palms and soles, or can be generalized. Other skin lesions noted during primary HIV infection include a roseola-like rash, diffuse urticaria, vesicular, pustular exanthema and enanthema, desquamation of the palms and soles and alopecia. Mucocutaneous ulceration is a distinctive feature of primary HIV infection. Ulcer have been reported on the buceal mucosa, gingiva, or palate, esophagus, anus, and penis. They are generally round or oval and sharply demarcated, with surrounding mucosa that appears normal. The tongue of patient showing the characteristic symptoms of thrush. Note the milk-white flakes of *C. albicans* on the tongue surface. An unexplained incident of thrush is often considered an early sign that HIV infection is present. Patients also experience weight loss of as much as 10 % of baseline body weight or more. Constant low-grade fever at about 37.3-37.8 °C and diarrhea extending over several weeks. In addition, the fatigue may be so overwhelming that patients cannot lift their heads from the pillow on waking in the morning. One of the most troublesome aspects is the night sweats. Individuals perspire so heavily at night that the bed linens and nightwear become drenched with sweat. Saturation can be extensive enough to require linen changes, and sleep is fitful at best. Few other microbial diseases are accompanied by such heavy sweating.

The isolation of HIV from cerebrospinal fluid (CSF) during primary HIV infection indicates that infection of the central nervous system (CNS) occurs soon after exposure. Elevated neopterin and β_2-microglobulin levels have also been found in CSF during primary HIV infection both in individuals with and without clinical meningitis, suggesting that the cellular immune system in the CNS may be activated during this stage even without the development of overt neurologic symptoms or signs. The most common neurologic symptoms are headaches, retro-orbital pain (particularly during eye movement) and photophobia. Several cases of aseptic meningoencephalitis during primary HIV infection have been reported.

Prolonged infection with HIV is often completely asymptomatic; however, a minority of patients complain of nonspecific constitutional symptoms in the month or years after primary infection. Patients commonly complain of being

easily fatigued and report the need to reduce their normal activities somewhat. In patients with more advanced HIV disease and severe de pletion of CD4 cells, constitutional disease may primarily reflect immunosupression or may herald the onset of opportunistic infections or malignancies. Patients with progressive constitutional symptoms should be evaluated carefully for opportunistic pathogens. A history of respiratory, neurologic, gastrointestinal and dermatological symptoms should be elicited and a thorough physical examination completed.

In the late stages of HIV infection when immune defenses have been severely compromised and systemic complications have begun to accumulate, the nervous system becomes highly susceptible to a wide array of disorders involving all levels of the neuraxis, including meninges, brain, spinal cord, peripheral nerve, and muscle.

Several disorders may involve the leptomeninges in patients with advanced HIV disease, with symptomatology ranging from mild headache to severe disability with hydrocephalus and cranial nerve palsies. Among the true meningitides a syndrome of aseptic meningitis, presumably relating to direct HIV infection of the meninges, can occur acutely in the setting of seroconversion as described above, but it is more common in patients with advanced HIV infection. The cerebrospinal fluid (CSF) shows mild mononuclear pleocytosis, usually with normal or mildly depressed glucose and slightly elevated protein levels. The presumption that this conditions is due to direct HIV infection of the meninges related to two observations: the virus can be isolated from the CSF, and no other cause has been identified.

The most important meningeal infection in HIV infected patients is caused by seemingly uncommon in HIV infected patients. Meningeal involvement by syphilis in HIV infected individuals may take form of acute meningitis or meningovascular syphilis.

Systemic lymphoma complicating HIV infection may secondarily to the central nervous system involving the meninges, clinical manifestation may be cryptic but usually include cranial nerve palsies, head aches, or increased intracranial pressure.

From an early stage it become clear that the nervous system was frequently involved in HIV infected patients. Among the severe and life-threatening infections experienced by those with immune deficiency were brain abscesses due to toxoplasmsis. As other neurologic manifestations emerged without signs of recognizable opportunistic infection it became clear that HIV was probably directly neurotropic as well as lymphotropic.

Toxoplasma gondii is an obligate intracellular parasite for which the primary host is the cat. Humans may acquire it from the cat by the fecal-oral route in man primary infection is usually asymptomatic unless congenitally acquired. The organism forms cysts in all tissues which persist for life and are the source of recrudescent infection in the compromised host. Infection in the brain is usually multifocal as old encysted parasites become actively pathogenic again. The clinical

presentation may be focal or diffuse but is a cerebrovascular accident, but is more usually progressive aver a few days or a week or two.

Peripheral neuropathies of several types can complicate the various stages of HIV infection. Early in the course of HIV infection a Guillain-Barre type of neuropathy may be seen. The clinical picture is the same as the familiar acute inflammatory or postinfectious neuropathy, with weakness of limb and facial muscles, minor sensory symptoms and loss of tendon reflexes. The weakness tends to be both proximal and distal. There may be backache and limb pains. There is evidence that the axonal neuropathy in the late stages of the disease correlated with the presence of dementia. Its ethnology is unknown, but it has been suggested that it may be a direct effect of HIV.

The most prevalent opportunistic disease among persons with HIV in late stage is *Pneumocystis carinii* pneumonia. Chagas initially in 1906 considered *P. carinii* with trypanosome. Subsequently it was reclassifiedby the Delanoes as parasite. Recently, however, studies of ribosomal RNA of *P. carinii* have shown that phylogenetically the organism is most closely related to the *Ascomycetes* (yeasts): thus *P. carinii* should probably be considered a fungus rather than a parasite. This reclassification has little clinical relevance but may suggest new therapeutic approaches and culture techniques. *P. carinii* is thought to have a life cycle consisting of three stages: cyst, whish are spherical or crescent-shaped form 5 to 8 mm in diameter; sporozoites or intracystic bodies, found only within the cyst; and tropozoites, found outside the cyst and believed intermediate between the sporozoite and the cyst. The Giemsa stain is taken up by both the intracystic sporozoites and extracystic tropozoites; cyst are not pozitively stained and cannot be seen except as negative images within the matrix of a clump of tropozoites. Infection with *P. carinii* is common early in the life and dose not generally results in symptomatic disease in immunocompetent hosts. Until the occurrence of the epidemic of infection with the HIV *P. carinii* pneumonia was an uncommon, sporadic disorders that occurred primary in patient with leukemia or other recognized causes of impairment of host defences and in patients who were given immunosuppressive therapy. Several studies in the United States have shown that circulating antibodies to *P. carinii* develop in most children by age 2 to 3 years, leading to the conclusion that asymtomatic infection with *P. carinii* is nearly universal at least in the areas where these studies were conducted. Patients with P. carinii pneumonia usually have had non-specific symptoms such as fever, fatigue, and weight loss for weeks to months before developing respiratory symptoms and often have other HIV-related disorders that indicate severe immunosupression. The most common presenting symptoms of *P. carinii* pneumonia are fever, non-productive cough, and progressive shortness of breath. In patient with *P. carinii* pneumonia chest radiographs most often show diffuse interstitial infiltration involving all portions of the lungs. Several variations may be seen. The infiltration may be heterogenously distributed throughout the lung, or it may be miliary in appearance.

Diffuse or local air-space consolidation may also be noted. In patients who are being given aerosol pentamidine prophylaxis, focal upper lole infiltration are relatively common. Cystic changes or pneumatoceles may occur, especially during the healing process, and cavitation withing pre-existing nodular lesions has been described. Probably as a result of the cystic or cavitary processes, spontaneous pneumothorax may occur. Pleural effusion and intrathoracic adenopathy are very uncommon with *P. carinii* pneumonia.

Since the beginning of the HIV epidemic an increasing association of *Mycobacterium tuberculosis* infection with HIV infection has been noted. Between 1978 and 1985 the yearly rate of tuberculosis more than doubled at one New York City hospital. Although the pathogenesis of most HIV associated tuberculosis appears to involve reactivation of latent *M. tuberculosis* infection, the clinical presentation is generally typical of reactivation tuberculosis only for those patients whose immune function is still relatively intact, whereas that of patients with HIV is much more typical of progressive primary tuberculosis. Only one-third to one halt of HIV-associated tuberculosis is confined to the lungs. The most frequent radiographic manifestations of pulmonary tuberculosis in patients with HIV are (1) hilar or mediastinal adenopathy or both and (2) localized infiltrates limited to the middle or lower lung fields. Pulmonary cavitation is rarely seen. The classic radiographic picture of apical infiltrates in the absence of hilar or mediastinal adenopathy has been reported in less than 10 % of HIV-associated cases. One half to two thirds of HIV-related tuberculosis involves extrapulmonary sites (with or withoutpulmonary involvement). Peripheral lymph nodes and bone marrow are the extrapulmonary biopsies but rarely in pulmonary biopsies. Other extrapulmonary sites that have revealed *M. tuberculosis* include urine, blood, bone, joint, cerebrospinal fluid, liver, spleen, skin, gastrointestinal mucosa and ascites fluid. Two extrapulmonary tuberculosis syndromes described in HIV patients are of particular interest: *M. tuberculosis* bacteremia and central nervous system mass lesions. On the other hand, tuberculosis in patients with otherwise asymptomatic HIV infection usually is clinically similar to tuberculosis in immunocompetent hosts.

The association of disseminated *Mycobacterium avium* complex (MAC) infection with HIV was recognized early in the HIV epidemic. Disseminated MAC infection has been reported only rarely in patients without HIV. Disseminated MAC infection occurs exclusively in patients with very advanced HIV disease essentially only in patients with CD4 lymphocyte counts<100/mL. MAC is a ubiquitous soil and water saprophyte. The source of MAC invasion in HIV patients may be gastrointestinal or respiratory. The presence of large clusters of mycobacterium within macrophagas of the small bowell lamina propria suggests the bowel wight be the portal of entry. However, respiratory isolation of the MAC also frequently precedes disseminated infection, suggesting MAC infection may begin in the lungs as well. Since most HIV patients with disseminated MAC

infection have other concomitant infections or neaplasms and since MAC appears to cause little histopathologic evidence of inflammatory response or tissue destruction, the relationship between constitutional symptoms, organ dysfunction, and MAC infection has been uncertain.

Four clinical syndromes often overlapping, have been associated with disseminated MAC infection.

- Systemic symptoms. Fever, malaise, weight loss often associated with anemia, neutropenia.

- Gastrointestinal symptoms.

- Chronic diarrhoea and abdominal pain (MAC infection of colon often observed at autopsy).

- Chronic malabsorbtion (histopatologic changes in small intestine similar to those with Whipple's disease often observed at autopsy).

- Extrabiliary obstructive jaundice secondary to periportal lymphadenopathy.

Cryptococcus neaformans and tuberculosis are the major opportunistic infection complicating the HIV epidemic world-wide. Although other pathogens may dominate on individual continents or in specific regions, no other major pathogen poses as great a global threat to those immunocompromised by HIV infection. The high mortality and morbidity rates associated with cryptococcal infection and the toxicity of traditional therapy have sparred intense interest in new treatment alternatives. A better understanding of the natural history of HIV-mediated immunodepression has seen the emergence of debate about the use and advisability of fungal prophylactic. This organism a common resident of the lung, is often inhaled from the air. It grows actively in the droppings of pigeons and enters the air in wind borne particles. The fungus is generally noninfectious, but in patients with HIV it multiplies in the lungs, spreads to the blood and localized on the brain and its coverings. The clinical presentation of cryptococcal disease in HIV patient is often subtle and nonspecific. A prolonged febrile prodrome, indistinguishable from that accompanying other opportunistic infections is common. Frequently no localizing signs or symptoms are present to guide the physician toward the diagnosis of cryptococcal disease. Although the portal of entry for *C. neoformans* is the lung. Pulmonary cryptococcosis is usually clinically. Most cases of pulmonary cryptococcal infection are discovered serendipitously, not because of organ specific signs or symptoms. Occasionally, however, pulmonary symptoms dominate the clinical presentation and progression to respiratory failure and death are not unknown. However, among those HIV-infected patients with cryptococcal disease and without CNS involvement, fully two thirds had cough and shortness of breath. In contrast only 18 % of those patients with culture-proven CNS disease had respiratory symptoms. These numbers add weight to the argument that all patients with CNS involvement have or have had antecedent pulmonary infection. Blood-borne spread to any organ, but the organism has a predilection for the CNS. It causes a granulomatous

meningitis with or without clinically evident pulmonary or disseminated infection. In addition, there may be small cysts in the cerebral cortex. The clinical presentation is usually with headache, fever, and constitutional upset; neck stiffness, photophobia and focal neurologic signs are present.

Skin disease is an extremely common complication of HIV infection, affecting up to 90 % of persons. Some of the skin conditions also are commonly seen in uninfected persons (e.g. seborrheic dermatitis) but are of increased severity in the HIV infected person. Other skin diseases are relatively unique to HIV infection (Kaposi's sarcoma). The average HIV infected patient has at least two and often more different skin conditions simultaneously. It is useful to classify the cutaneous disorder seen with HIV disease as either infectious disorder, hypersensitivity disorders and drug reactions, or neoplasms.

Oral lesions have been recognized as prominent features of HIV infection since the beginning of the epidemic. Some of these changes are reflections of reduced immune function manifested as oral opportunistic conditions, which are often the earliest clinical features of HIV infection. Some, in the presence of known HIV infection are highly predictive of the ultimate development of the full syndrome, whereas others represent the oral features of AIDS itself. The particular susceptibility of the mouth to HIV disease is a reflection of a wider phenomenon. Oral opportunistic infections occur in a variety of conditions in which the teeming and varied microflora of the mouth take advantage of local and systemic immunologic and metabolic imbalances.

They include oral infections in patients with primary immunodeficiency, leukemia, and diabetes, and those resulting from radiation therapy, cancer chemotherapy and bone marrow supression. In the prospective cohorts of HIV infected homosexual and bisexual men hairy leukoplakia is the most common oral lesion, and pseudomembranous candidiasis is next most common.

Kaposi's sarcoma (KS) in patients with AIDS produces oral lesions in many cases. The lesions occur as red or purple macules, papules, or nodules. Occasionally the lesions are the same color as the adjoining normal mucosa. Although frequently asymptomatic, pain may occur because of traumatic ulcerisation with inflammation and infection. Bulky lessions may be visible or may interfere with speech and mastication. Diagnosis involves biopsy. Lesions at the gingival margin frequently become inflamed and painful because of plaque accumulation.

From the very outset of the HIV epidemic, cliniciane everywhere noted a high prevalence of the gastrointestinal (GI) signs and symptoms. Some of these manifestation such as weight loss, dysphagia, anorexia, and diarrhoea are almost universally among patients with HIV. Early and complete invasive and noninvasive evulation of these patients should be undertaken with particular attention to treatable non-HIV-associated biliary tract disease. Hepatic parenchymal disease likewise is common in patient with HIV infection.

Cramping paraumbilical abdominal pain, weight loss (Fig. 16) and large-volume diarhea are common in patient with HIV disease. The majority of HIV

patients with these complaints has specific small bowel infection. Certainly routine colonic bacterial pathogens such us *Salmonella, Shigella and Campylobacter*, which may be persistent and mimic chronic inflammatory bowel disease, should be excluded by the adequate culture techniques. Likewise, routine and atypical parasitic infestation including that caused by *Giardia lamblia, E. histolytica, Criptosporidium* and *I. belli* must be excluded. Colonic diarrhea usually is associated with frequent small volume stools, left lower quadrant or suprapubic cramping, rectal urgency (tenesmus), and proctalgia and dyskenesia (painful defecation). On occasion a small amount of bright red blood may be noted. Once again, in the majority of these patient with diarrhea of colonic origin, specific bacterial and parasitic pathogens can and should be easily isolated by careful analysis of the stool. In addition some patient may have classic herpetic perianal ulceration which can be diagnosed by specific viral culture of swabs taken directly from the perianal area. CMV proctocolitis has been described as having sigmoidoscopic features suggestive of focal ishemic colitis that is submucosal hemorrhages and discrete shallow ulceration of distal colonic mucosa. Once again, obtaining specific biopsy specimens for histology and viral culture is indicated. Even in the absence of focal or diffuse colonic mucosal changes, biopsy specimens should be taken for histologic evaluation to look for the occasional patient with *Cryptosporidium* whose stools have been negative for this organism.

On occasion, patients with HIV may suddenly develop ascites. Since some HIV-infected patient may have underlying cirrhosis (caused by either alcohol consumption or viral hepatitis), a sizeable percentage of them will have transudative ascites related to their chronic liver disease. Careful evaluation of the ascites fluid, including performing cytology, and acid-fast stains should be done early to exclude patients with malignancy and tuberculosis peritonitis.

Malignancies as a complication of immunodeficiency have been well described in the literature, being recognized long before the advent of the HIV epidemic. The incidence of both Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) are marked by increased in immunosuppressed allograft recipients. It is therefore not suprising that patients with HIV infection, who also have proformed defects in cell-mediated immunity also develop these two malignancies. KS once a rarely reported malignancy is the most common neoplasm affecting HIV-infected individuals (Fig. 17, 18). It is seen primarily in homosexual men and has only rarely been reported in intravenous drug users or other risk groups. The pathogenesis of KS and HIV-infected patients remain uncertain. The natural history of KS associated with HIV infection more closely resembles that observed in immunosuppressed allograft patients. The disease tends to progress with time and is associated with the appearance of larger and more numerous cutaneous lesions. However, the course of the disease is unpredictable. A patient may have relatively few lesions that remain stable over time. New cutaneous lesions may not appear for many months but may be followed by a sudden and rapid increase

in disease activity. Visceral involvement with KS is extremely common and can involve almost any visceral site. Careful endoscopic examination will reveal gastrointestinal sites of disease in most patient. Athough KS is usually not a direct cause of death in HIV-infected, the morbidity associated with more advanced disease with more advanced disease can be significant.

Cutaneous lesions may become painful and if large cutaneous surfaces are involved can restrict movement. Lymphatic obstruction is common and can result in severe edema, most commonly involving the extremities or the face. Visceral spread of KS is rarely symptomatic, particularly when it involves the gastrointestinal tract. Careful examination of the skin and oral cavity at each clinic visit is the key to early diagnosis. Once lesions are identified, histologic confirmation should be obtained.

The non Hodgkin's lymphomas are a heterogenous group of malignancies. Their biologic behavior ranges from indolent requiring no therapy, to aggressive malignancies with few long-term survivors. In the most commonly used classification system for the NHL, these malignancies are divided into three major categories: low grade, intermediate grade, and high grade, according to pathologic characteristics of involved lymph nodes and morphologic criteria of the lymphoma cells.

The first cases of NHL in homosexual men were reported in 1982 and increasing numbers of cases have been reported since that time. The finding of an intermediate or high-grade B-cell NHL in an HIV-infected individual constitutes an AIDS diagnosis as defined by the Centers for disease control. Advanced extranodal disease is commonly found at presentation, and median survival times have been short.

Infection with the HIV is associated with a wide spectrum of hematologic abnormalities. These abnormalities are found in all stages of HIV disease and involve the bone marrow, cellular elements of the peripheral blood and coagulation pathways. The cause of these abnormalities is multifactorial. A direct suppressive effect of HIV infection, ineffective hematopoiesis, infiltrative disease of the bone marrow, nutritional deficiencies, peripheral consumption secondary to splenomegaly or immune dysregulation, and drug effect all contribute to the variety of hematologic findings in these patients. Many of these abnormalities are clinically significant, whereas others are more of academic interest.

Peripheral cytopenias are common in HIV-infected individuals and are due to either decreased production in the bone marrow or accelerated destruction in the peripheral circulation. In general the cytopenias increase in frequency as HIV-disease progresses. Anemia is the most common hematologic abnormality noted in patients with HIV disease. The largest HIV infection affects the lymphocyte, neutrophil and macrophage monocyte cell lines. Despite the hyperhammahlobulinemia noted in these patients, they suffer complications from both defective cellular immunity and dysregulated humoral immunity. The hallmark of HIV infection is progressive depletion of the CD-4 lymphocytes. This decrement

presumably occurs through direct viral invasion of these cells. Early in HIV infection an initial increase in the CD-4 population occurs before a decline in the number of CD-4 cells is noted. Granulocytopenia independent of drug use is noted in approximately 50 % of patients with HIV. Drug-induced neuthropenia is in the HIV-infected individual. Medication used to treat infection such as *P. carinii* pneumonia, toxoplasmosis and cytomegalovirus retinitis or colitis cause neuthropenia. Similarly, ridovudine is implicated as a cause of neuthropenia, often necessitating dose reduction or cessation of teraphy. As for the complication of neuthropenia, most documented infection involve gram-negative organisms. The most common platelet abnormality found in HIV-infected patients is thrombocytopenia have only minor submucosal bleeding. characterized by petechiae, echymoses and occasional epistaxis. Rare patients have gastrointestinal blood loss. Laboratory findings reveal that patients generally have isolated thrombocytopenia, which usually is not accompanied by anemia and leukopenia. Patients with HIV infection, including those being treated with antibodies for an AIDS-opportunistic infection and those being treated with cytotoxic chemotherapeutic agents for HIV-related malignancies, may also develop thrombocytopenia secondary to a therapeutic intervention. In these patients severe thrombocytopenia should be managed as it is in the non-HIV-infected individual. Medications causing thrombocytopenia should be discontinued and platelet transfusion should be administered when indicated.

Diagnosis

The first test developed to detected HIV infection was isolation of the virus through tissue culture. Unfortunately although sensitive for viral isolation the tissue culture procedure is expensive, time consuming and labor intensive. As a result soon after the initial discovery of HIV several tests were developed using protein products of the newly discovered virus to detect antibodies produced by the infected host. The two antibodi tests used most commonly are the enzyme-linked immunosorbent assay (ELISA) and the western blot. In addition to being less expensive, faster and easier to perform than viral culture, the ELISA and the Western blot test do not require working with like virus and therefore are safer. Over the best some years several novel techniques have been developed. The radioimmunoprecipitation assay (RIPA) is a more time consuming, and labor intensive test the Western blot, yet it provides much finer resolution of the high-molecular-weight envelope proteins than the western blot test. The RIPA is considered more sensitive and specific than the Western blot test, however, the time, expense, and need for active cell lines and radioactive materials make the RIPA a poor choice for routine testing in commercial laboratories. Rather its use is best reserved for difficult-to-diagnose cases. Like the RIPA the indirect immunofluorescence assay (IFA) requires preparation of HIV antigens that are expressed on infected cells and are stained subsequently. Infected cells are

placed on the glass slides in a fixed monolayer and are incubated with patient serum. Anti-HIV antibodies present within the serum bind to antigens expressed on the surface of cells, and these bound antibodies are then detected with anti-human antibody that has been labeled with fluorescein isothiocyanate an ultraviolet-activated dye compound. after appropriate processing, the slide is viewed under a fluorescent microscope and the number of cells the intensity of staining and the staining pattern are assessed. Polymerase chain reaction (PCR) technique, introduced in the late 1980s, represent a major advance in the diagnosis of many disorders, including HIV infection. This powerful technique can amplify DNA existing in very small quantities through a series of binary replicative cycles. The PCR procedure can also be applied to RNA.

The pool of human lymphocytes possesses specific glycoproteins of their surface that play an important role in the cells activity and function CD-4 positive lymphocytes are the primary target of HIV infection, and the CD-4 receptor is the primary binding site of HIV. Throughout the course of chronic HIV infection the number of CD-4 lymphocytes is depleted and the loss of these cells is associated with development of the characteristic opportunistic infection and malignancies of AIDS. Thus the measurement of CD-4 positive lymphocytes is one of the most impotent determinates for clinically staging the disease status of HIV infected patients. In uninfected controls normal values for the CD-4/CD-8 ratio are 2.0 to 1.0. Normal values for CD-4 counts are generally 500 to 1,000 cells/mL^3 in adults.

Differential diagnosis

The differential diagnosis of the acute retroviral syndrome includes a number of other illnesses: infectious mononucleosis; other viral infections such as influenza, measles, rubella, and herpes simplex; and secondary syphilis. Evaluation of patients presenting with an illness consistent with acute retroviral infection should include a careful history to elicit risks for HIV infection, laboratory tests to rule out mononucleosis and syphilis, HIV antibody and antigen tests, and complete blood counts and differential. Sequential HIV antibody tests may need to be performed over several months to confirm the diagnosis.

The differential diagnosis of persistent generalized lymphadenopathy (PGL) includes HIV infection and a wide variety of other processes that are associated with generalized lymphadenopathy: sarcoid, secondary syphilis, and Hodgkin's disease, for example. In patients with HIV infection, lymphadenopathy may also be caused by mycobacterial infections, KS, and lymphoma. In patients with clinical findings suggesting opportunistic disease, needle aspiration of lymph nodes may help establish a specific diagnosis. Examination of aspirates with cytologic, acid-fast, and Gram stains is valuable in identifying infection or malignancy. If a specific diagnosis is not determined after staining and culture of node aspirates, then lymph node biopsy is indicated. Aspiration of lymph nodes in patients with PGL usually reveals

benign cells. Biopsy specimens show follicular hyperplasia, with the normal architecture distorted by greatly expanded germinal centers composed of B lymphocytes. It is now known that active viral replication is occurring in these follicular cells and dendritic cells, although the patient may appear well clinically.Most patients with PGL require no invasive evaluation and can be managed expectantly for the occurrence of other AIDS-related manifestations.

A limited differential diagnosis of isolated thrombocytopenia in an HIV-infected person includes drug-induced thrombocytopenia, particularly in heroin addicts and alcoholics, consumptive thrombocytopenia, or splenic sequestration. Some patients with thrombocytopenia may also present with leukopenia or anemia. The presence of constitutional symptoms and pancytopenia suggests an opportunistic infection, particularly disseminated mycobacterial or fungal infection, or a lymphoma.

Treatment

Basic therapy consists of indication of antiviral agents. There are used preparations, that inhibit the return transcriptasa of the virus: azydotymidin (AzT), didanosin (ddi), zalcytobyn (ddc), stavodin (d4T), lamivudin, abacavir (ABC), nevirapapin (NVP).

Till now monotherapy AZT (retrovir, zidovudin) was used. The preparations are prescribed 0.2 gm 3 times per day constantly or courses, duration is not less than 3 months. Treatment will be carried out under the control of the general blood analysis with 2 times per one month during the first 2 months and subsequently once per month. In a stage of preAIDS (secondary diseases) AZT is necessary to indicate till disappearance of a clinical symptomatology. If the clinical picture is not better zidovudin is indicated only for that patient in which blood concentration are less than 500 cells in 1 mkL. With such treatment it is possible to prolong patients life, the number of resistant viruses to a preparation however is marked. So, monotherapy AZT is recommended only for prophylaxis of infection of fetus from mother.

Among new means with other mechanism of action a specific inhibitor of proteases krixivan is used, which is effective concerning resistant to AZT populations of a virus 0.8 gm every 8 hour. Preparations of a choice may be rotonavir, nelfinavir, sacvinar-SGC, amprenavir.

Recently it is proved, that efficiency of treatment essentially can be increased using a combination of two or three antiviral preparations. Therefore monotherapy was changed for polytherapy. The most frequently combination of two inhibitors of virus return transcriptasa (stavudin + didanosin, stavudin + lamivudin, zidovudin+didanosin, zidovudin + lamivudin, zidovudin+abacavir) and one inhibitor of a protease is used. At patients with high risk of disease progress (viraemia over 1 million copies/mL), and also in urgent cases the two inhibitors of proteases and 1-2 inhibitors of virus return transcriptasa are used.

Efficiency of specific treatment is controlled by monitoring with following criteria: 1) level HIV RNA in plasma; 2) quantity of T-lymphocytes CD4; 3) a clinical condition of the patient; 4) morphology and biochemistry of a blood (for detection of undersirable effects of an organism). Level HIV RNA in plasma is researched after 4-8 and 12-16 weeks from the beginning of treatment and subsequently each 3-4 months. The major condition of successful antiretrovirus therapy is its usage during all life of the patient, however it is interfered by a high toxicity of preparations and the complications connected with them. Complete treatment of patients with AIDS remains an unsolved problem. Last combination is considered the most effective, but also it does not cure patients with AIDS.

It is not less important preventive treatment of secondary diseases at AIDS. Against pneumocystic pneumonias the basic agent is bactrim. For initial prophylaxis of this disease bactrim is indicated 1 tablet during 3 days each week. At occurrence of pneumonia daily reception of preparation is prescribed. In case of an intolerance of bactrim it is possible to indicate dapsone or primachin in a combination with clindamicin. At presence of herpetic infections indicate acyclovir.

Against criptococus and other funguses amphotericinum is used, against bacteria – the appropriate antibiotic. At Kaposi's sarcoma freezing of eruption elements by liquid nitrogen, irradiation, chemotherapy is indicated. The immunotherapy of AIDS is at developing stage.

Prophylaxis

Most infections occur as a result of repeated and close contact with a carrier of HIV, specifically mucous membrane contact with blood or body fluids of the carrier. Sexual relationships are the major source of such contacts, and people must be educated to modify sexual practices, to avoid sexual encounters with persons in high-risk groups, reduce the number and frequency of sexual contacts, avoid high-risk practices (e.g., anal intercourse), and use protective devices such as condoms. Consistent use of condoms should reduce transmission of HIV by preventing exposure to semen and infected lymphocytes. Whether symptomatic or not, persons who know they carry the HIV virus should be counseled to avoid sexual contacts in which body fluids may be exchanged with uninfected persons.

Since HIV may be transmitted in utero or during or after birth, women carriers and those in high-risk groups should be counseled, and testing for antibody to HIV should be offered to women in high-risk groups. Women known to be HIV-positive should be advised to defer pregnancy.

Parenteral drug users need to be educated and counseled with regard to the risk of sharing needles with other drug users.

Testing for antibody to HIV should be offered on a confidential basis to anyone requesting it, but only in conjunction with pre- and post-test counseling by someone familiar with its significance. Confidentiality is necessary because

the patient's job, insurability, and social life can be jeopardized. Counseling is necessary because test results require sophisticated analysis; patients need to be well informed before the tests are performed, and the results must be fully explained afterward.

HIV carriers and persons belonging to a high-risk group (even if their HIV antibody test results are negative) should not donate their blood (or organs for transplantation), and should inform medical and dental professionals of their status. The latter should wear gloves when examining all patients if contact with mucous membranes may occur, and body fluids and tissue samples should be handled in the same manner as those from patients with hepatitis B.

Accidental needle sticks of health care personnel are remarkably common and special emphasis must be placed on teaching all health care students and professionals how to avoid these potentially very dangerous accidents. While the risk of HIV transmission appears to be much less than that of hepatitis B transmission, the potential consequences are much worse.

Surfaces contaminated by blood or other body fluids should be cleaned and disinfected; HIV is readily inactivated by heat and commonly used disinfecting agents, including peroxide, alcohols, phenolics, and hypochlorite. Although AIDS patients are not particularly contagious to other hospital personnel or patients, their body fluids and blood should be handled with extreme care, following the same procedures used with patients who carry hepatitis B virus.

Control questions:

1. Infectious agent of AIDS, its biological properties.
2. Epidemiology of AIDS, contingents of the promoted risk of AIDS infection.
3. Mechanisms and ways of contamination.
4. Pathogenesis of AIDS.
5. Basic periods of AIDS development, their clinical symptoms.
6. Manifestation of AIDS in children.
7. Epidemiological and clinical criteria of diagnosis.
8. Laboratory diagnosis.
9. Principles of medical treatment.
10. Prophylaxis of AIDS.

SEPSIS

The term "sepsis" has been used for a clinical situation in which there is evidence of infection plus a systemic response as manifested by an elevated temperature, tachycardia, increased respiration, leukocytosis or an impaired peripheral leukocyte response, and/or the presence of immature band forms of peripheral circulation.

Sepsis has essential differences from the other infectious diseases:

1. Sepsis is polyetiological disease. The agents of sepsis may be different microorganisms – aerobia and anaerobia.

2. There is no united entrance gates.

3. There is no cyclicy of the course.

4. There is no immunity development in sepsis.

Etiology

The most frequent etiologic factor of sepsis are auto- or external microflora. These agents are staphylococci, streptococci, colibacilli and other so called conditionally pathogenic microorganisms. Rarely, a reason of the sepsis may be obligate parasites. Septic agent may be the blue pus bacilli, gonococci, meningococci, *Bacillus anthracis, Salmonella,* fungi and other. But, at last time staphylococcus is found more often than others, so it should be on the first place by significance. According to international classification 3 types of staphylococci are detached: *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus*. *Staphylococcus aureus* plays the most important role in the pathology of human.

Epidemiology

Staphylococcous infection is widely spread among hospitalized persons. Intrahospital distribution is typical feature of epidemiology of staphylococcous infection.

Intrahospital infections are characterized by large quantity of the sources of infection, multiply ways and factors of transmission of the agent multiply persons with increased risk of the infection. The sources intrahospital infection are patients with different forms of staphylococcous purulent infection, carriers of staphylococcus. Carriers of staphylococcus from medical personnel play an important role in the conditions of the hospital.

The ways and factors of transmission of staphylococcous infections are different: respiratory-drug, contact and alimentary. Transmission of the agent may be realized by alimentary way. For example, it is possibly infection of infants in maternity

hospital by solutions for drink and milk, using for supplementary nourishment. Staphylococcous infection have sporadic character in observance of sanitary-antiepidemic regime. Epidemic outbreaks of intrahospital staphylococcous infections may be in violation of regime.

Staphylococcous infection develops as rule in persons with decreased nonspecific resistance, with different infectious diseases (especially of viral etiology), after chronic diseases, in persons after massive doses of immunodepressors, antibiotics, hormones, X-ray therapy.

Pathogenesis

The factors of risk, promoting the penetration of normal germs of skin and mucous membranes into internal mediums of the macroorganism system, may be different causes injuries, inflammations, trophic disorders, aggression of different microflora, congenital anomalies. The following distribution of microbes in macroorganism may go by different ways − via blood, lymph and direct methastasing. The intermediate localization of the process appears. It may be phlegmona, abscess or other destructive processes. The process is sepsis, when it has generalized character with damage liver, spleen, lungs, kidneys, vessels and other organs and systems.

The agents of sepsis, penetrating into tissues, causes an inflammatory process. In some cases the process develops impetuously. The purulent inflammatory focus arises on the place of the penetration with reproduction of microbes (primary focus). But in other cases inflammatory manifestations are less expressive and rapidly disappear, but agent penetrates inside tissues by lymphatic and blood ways and causes inflammatory focus in distant place. This inflammatory focus may lead to development of sepsis, in corresponding change of reactivity and resistance of the organism.

Portal of infection may be in any organ and tissue. The primary focus is in tissues with large quantity of lymphatic and blood vessels more frequently. For example, in wound sepsis the skin is a portal more frequently. In urosepsis and gynecological sepsis mucous membranes are portal. Prolonged course of sepsis is marked in patients with localization septic and primary foci in bones, muscles, urogenital system. In some cases, there are no visual foci, except the primary septic focus. These forms are called septicemia. But in other cases, metastatic secondary purulent foci are formed. These forms are named pyemia. But, also there is possible a transitional form − septicopyemia.

The distribution of infection is realized from the primary focus via blood and lymphatic ways. The distribution of the agents is realized by veins too, with formation of thrombosis and thrombophlebitis. Microbes and their toxins may penetrate to lymphatic vessels and cause lymphangites and lymphadenites. Metastases may be as an infiltrations, phlegmons, abscesses. Purulent infiltrates may appear in intestine too. In the serous cavities they are characterized by purulent exudations (arthritis, pleurisy, peritonitis, pericarditis).

The localization of metastases in the lungs is on the first place, kidneys are on the second place, then — other organs.

Allergic component has an important role in pathogenesis of the septic process. Primary and secondary septic foci transfer into a source of sensibilisation of human organism.

In sepsis the violations of metabolism, acid-alkaline balance, deep changes of balance of proteins and vitamins are observed. Anemia develops due to damage of bone marrow.

DIC–syndrome plays an important role in the development of septic state and complications. In some cases of sepsis DIC–syndrome comes out on the first plan and cause fatal outcome in considerable degree.

DIC–syndrome is "proteolytic explosion" with activation and following exhaustion of coagulation, fibrinolytic, kallekrein-kinine systems and system of complement.

In sepsis dysbalance of immune system has the pathogenetic meaning. Immune deficiency is manifested by decrease of quantity of T-helpers, reduce of activity natural killers and phagocytic activity of granulocytes. These changes lead to development of generalized infectious inflammatory process.

Anatomic pathology

In sepsis pathologoanatomy alterations are very various. Petechial rash is marked on the skin. Hemorrhages are observed in organs and tissues, especially on mucous membranes. The alteration of myocardium are marked from turbid swelling till excessive lipid dystrophy. Erosions are revealed in endocardium. Thrombosis of veins are often observed. Spleen is enlarged. There is a turbid swelling or lipid infiltration in liver. Lymphatic nodes are increased. There are a plural hemorrhages in kidneys. Also, they are marked in the gastrointestinal tract. Hemorrhages are observed in the suprarenal glands. There is edema in the lungs. Sometimes there are foci of bronchopneumonia. The infarction foci are not rare. There are edema and hyperemia of brain matter. In sepsis with metastases (pyemia) purulent process are observed in brain (purulent meningoencephalitis), lungs (like abscessing infarctions), kidneys, thyroid gland. Besides that, purulent pleurisies, peritonitis, pericarditis, phlegmons are observed in different places.

Classification

I. According to spreading of the disease:
1. Purulent-resorptive fever is characterized by presence of purulent foci, wave-like course, general intoxication.
2. Septicemia is characterized by severe general state, hectic temperature, severe disorders of central nervous system and cardiovascular system.
3. Septicopyemia. This is combination of septicemia and presence of secondary purulent foci in different organs.
4. Chronic sepsis. There is purulent foci in anamnesis during this form. The diseases is accompanied by prolonged wave-like fever, presence of period of remission and relapses, periodical formation of purulent foci.

II. According to prolongation of course the next form of the diseases are differed:
  1. Fulminant sepsis (24-48 hours).
  2. Acute sepsis (from 5-7 days till some weeks).
  3. Subacute sepsis (3-4 months).
  4. Chronic sepsis (from some month till one year and more).
III. According to date of process appearance the next variants are differed:
  1. Early sepsis (till 3 months from appearance of the primary focus).
  2. Late sepsis (later than 3 months).
IV. According to character of microorganism sepsis is differed on:
  1. Sepsis, caused by gram-positive flora. It leads, inrarely, to development of septicopyemia.
  2. Sepsis, caused by gram-negative flora. Infectious-toxic shock may be in such cases.

Clinical manifestations

There is no specific incubation in septic patients. In some cases, septic process develops through weeks and months after localized focus (abscess), but in other cases sepsis may be on its background.

Complains of these patients are different as a clinical manifestations — weakness, headache, pain in joints, chill with following sweats or chilling, dry mucous membrane of the mouth, poor appetite, sometimes — diarrhea.

Fever is frequently of hectic character in patients with sepsis. Different variants of the temperature may be — remittent and intermittent types, sometimes, the temperature is higher in the morning (the reversal type). The temperature may be not high in weak, cachectic patients and elders, but it doesn't report about mild course of sepsis.

Patient's skin is pale, moist, even icteric in severe cases. Different rashes are observed. Rash of hemorrhagic type is marked more frequently, sometimes — pustules, ulcers, erythema. Eruption may be on skin of trunk, limbs and face.

Mucous membranes of lips, oral cavity are dry and may have erosions, ulcers, fissures, bleeding sickness. Often, there are hemorrhages on conjunctiva.

Pulse is frequent. Arterial pressure decreases. Heart is enlarged. There are a systolic murmur above cardiac apex, tachycardia and "pendulous" rhythm during auscultation the alterations of myocardium are revealed during cardiogram. The type of these alteration is diffuse or diffuse-focal. Sometimes, the signs of damage of endocardium and large peripheral vessels are revealed (arteritises, phlebitises).

The alterations of respiratory tract are revealed frequently in the patients with sepsis: dyspnoe, bronchitis and pneumonia. Pneumonia has tendency to formation of abscesses. Inrarely, serous, purulent, hemorrhagic and mixed pleurisy arises in the patients.

There is a dry coated tongue in these patients. Appetite is poor. Sometimes, vomiting arises. Spleen is frequently enlarged, soft consistence. Liver also is

enlarged and painful during palpation. The abscesses may arise inside abdominal cavity.

Septic patient, often, have a disorders of kidneys and urinary track. Sometimes toxic nephrites, purulent paranephrites arise. The alterations of uterus, perimetrium may be in women. The primary location of inflammatory process is marked inrarely in urogenital organs. It may give generalization of the process.

Osseous-muscular system is involved to pathologic process too. There are reports about the serous and purulent mono- and polyarthritis, foci of osteal destruction, degeneration of born marrow, myocytes. Also, the osteal tissue may be site of the primary foci (osteomyelitis).

Different manifestations may be from nervous system, such as meningismus, purulent meningitis, cerebral and spinal hemorrhages, hemorrhages into the vegetative ganglions.

The signs of anemia are revealed in the blood: decreased erythrocytes quantity and hemoglobin. Also, there are signs of the anisocytosis, poikilocytosis, thrombocytopenia. Neutrophilic leukocytosis with shift to myelocytes, increased ESR are marked; leukopenia may be in cachestic patients with fulminate forms of sepsis.

Biochemical changes of the blood are expressive in the patient with sepsis. Increased content of bilirubin and increased activity of transaminases are marked.

In sepsis the proteins of serum blood are sharply changed. A quantity of albumines decreases and globulines increased. The changes of concentration of IgA, IgG, IgM depend upon gravity of the course and outcomes of sepsis.

Fulminate sepsis is a rare form, the example, meningococcal sepsis. It has several synonyms. There are – fulminate meningococcemia, acutest meningococcal sepsis, Waterhouse-Friedrichen syndrome. It is the most severe, unfavorable form of meningococcal infection. Its base is infectious-toxic shock. Fulminate sepsis is characterized by acute sudden beginning and impetuous course. Temperature of body rises up to 40-41°C. It is accompanied by a chill. However, hypothermia may be through some hours. Hemorrhagic plenty rash appears at the first hours of the disease with tendency to confluence and formation large hemorrhages, necroses. A purple-cyanotic spots arise on the skin ("cadaveric spots"). The skin is pale, but with a total cyanosis. Moist, covered with a clammy sweat. Patients are anxious and excited. The cramps are observed frequently, especially in children. The recurrent bloody vomiting arises inrarely. Also, a bloody diarrhea may be too. Gradually, a prostration becomes expressive and it results in a lose of the consciousness.

Acute sepsis is the most frequent form of sepsis. Staphylococcus sepsis is occurred more frequently. It is accompanied by considerable fatal outcomes. In majority of the cases the onset of disease is an acute with chill and increase of the temperature. Fever may be of different character: constant, intermittent, remittent and irregular. Sometimes sepsis may be with subfebrile temperature.

Anemia increases in majority of the patient, the skin is pale. Sometimes skin has jaudiwish shade due to haemolysis or toxic hepatitis.

The rash is petechial. Rash is localized on the skin of the chest, forearms, hands, upper extremities, on the mucous membrane of the mouth, conjunctiva and all gastrointestinal tract. Hemorrhages on the mucous membrane of gastrointestinal tract may evoke bloody vomiting and diarrhea. The sizes of hemorrhages are different — from small points till large hemorrhages. An appearance of hemorrhagic rash is explained by present of hemorrhagic vasculitis. Rash may be purulent or erythematosus character due to infectious-allergic dermatitis. The damage of joints is observed in 25-30 % of the causes. The large joints are damaged more frequently, but small joints may be damaged too. The joints are edematous. There is hyperemia of the skin over joints. The motions are painful.

In sepsis symptoms, connecting with damage of different organs and systems are always expressed. They appear as a result of expressive intoxication, or as primary or secondary purulent inflammatory process. The symptoms, connecting with damage of cardiovascular system is revealed more frequently. Staphylococcous sepsis may be without damage of endocardium. In this case the clinical symptoms are evoked by distrophic changes of myocardium. Tachycardia, decreased arterial pressure, cardial pain of indefinite character, enlargement of the borders of the heart, muffled heart sounds are observed. The damage of the vessels may be manifested in form of phlebitis, development of thromoembolism and also embolism of small vessels of the skin and internal organs, in violation of coronaric circulation.

Oxygenic insufficiency and damage of respiratory center leads to breathlessness. In some patient bronchitis, pneumonia, abscesses and pleurisy are observed. Hemorrhagic pleurisy is more typical for staphylococcus sepsis.

In staphylococcous sepsis the typical sign is increased liver. The severe septic hepatitis may be observed with development of jaundice and violation of all functions of liver and also cholangitis, abscesses. Enlarged spleen (septic mesenchymic spleenitis) is frequent symptom. Spleen is soft in an acute period, and it is difficulty to define spleen in pulpation. However, enlarged spleen is clearly defined in percussion. During prolonged course of sepsis spleen becomes dense. The damage of kidneys has essential meaning in clinic of sepsis. In acute process the local nephrite of microbial embolic origin develops, diffusive nephritis develops later.

The symptoms of damage of nervous system are the principal clinical manifestations in the patient with sepsis. In acute sepsis consciousness is preserved even in high temperature. In this period severe headache, sweat, violation of the sleep and dizziness are usual complaints of the patients. In severe cases depression, irritation, sometimes excitement are observed in the patients. Due to edema of the brain meningeal syndrome may be too. It is possible development of secondary purulent meningitis. The appearance of meningitis is characterized by intensification of headache, addition of vomiting, development of meningeal symptoms.

Meningoencephalitis, arachnoiditis and abscess may develop. The course of acute sepsis is from 2 weeks till 3 months.

Thus, clinic of acute sepsis is characterized by severe course, expressive symptoms of intoxication and symptoms of damage of separate organs. Frequent manifestation of acute sepsis is development of bacterial endocarditis and purulent inflammatory focuses in different organs (phlebitis, abscesses, pneumonia, pleurisy, pancreatitis, cholangitis, osteomyelitis, otitis, cystitis, violations of brain's blood circulation, hemorrhage into retina of the eye and other.

Subacute sepsis. The course of this sepsis is 3-4 month. It is differented from acute sepsis by lesser intensity of symptoms. Metastases appear more rarely than in acute sepsis. The prognosis is better in this form. This form of sepsis arises in case of heart damage by rheumatic process.

Chronic sepsis is characterized by prolonged course (till one year and more).

This form is accompanied with remissions and aggravations with a severe morphologic alterations. Chronic sepsis has a wound origin, for example, the septic process in inflammatory of the billiary tract and portal vein. In some cases, billiary tract is secondary infected due to of any general cyclic infectious disease. In other cases, billiary tract may be as septic focus.

Outcomes of the disease depends on the premorbid condition, opportunity, of the therapy and its effectiveness. Prognosis of a sepsis is frequently unfavourible, especially for an infants and elder patients.

Diagnosis

Bacteriologic investigations is an important diagnostic test in sepsis. The results of the bacteriologic investigations never must be account without a data of case history, clinical features and other laboratory tests. The bacteriologic results are not always positive in septic patients. The negative results are especially frequent in sowing of the blood.

In sepsis the excretion of the agent and estimation of received results are inrarely complicated problem. It is because in sepsis the circulation of agent in the blood is not constant. A quantity of the agent in the blood vary and may be insignificant. The treatment by antibiotics has a large influence on bacteremia.

Differential diagnosis

It is necessary to perform a differentiation with various diseases accompanied by prolonged fever, rigors, sweating, various eruptions.

Typhoid and paratyphoid fever remind sepsis by fever, pale skin, increased liver and spleen. But they are different from septic process by cyclic course, not so severe anemia and rarity of the hemorrhagic eruptions. Isolation of the agent of typhoid and paratyphoid fever, result of IHA-test (indirect hemagglutination reaction) help in decision of the problem.

In some cases, tuberculosis, especially its milliary forms in young patients, is difficult for diagnostics. During this, fever, sometimes of hectic type, dyspnoe,

sweating may be as in sepsis. It is necessary to study carefully the epidemiological data, repeated radiological investigation and sowings of the blood.

Also, the hectic fever, sweating may be in acute period of brucellosis. In brucellosis there are mild violations of the general state of the patients. There is no hemorrhagic syndrome. During the second stage there are signs of the locomotor system affection. At the early stages of brucellosis, positive result of Wright's reaction are marked. Positive intracutaneous allergic test is observed some later.

Sepsis should be differentiated with a pneumonia, because pneumonia may be a result of sepsis. The following systematic observation and the metastatic foci in joints, endocardium and brain maters are usually helpful for decision of this problem.

In epidemic typhus there are typical clinical symptoms. They are Jarry-Auvcyne's symptom, Govorov-Godelyae 's symptom, Rosenberg's symptom, early enlargement of spleen. Typical eruption appears on the 4-5 day of the disease. Serologic methods are very useful, especially for the final diagnosis.

Tropical malaria, also is accompanied by a prolonged fever and hepato-splenomegaly. The typical features of the fever in tropical malaria are prolonged paroxysms (to 24-36 hours and over), poorly expressed apyrexia periods. Rigor and sweating are less excessive, that is caused by some fluctuation of temperature. These attacks are accompanied with severe headache, low back pain, nausea and sometimes vomiting. Abdominal pain and watery stool appear inrarely. The information of the patients about location in focus of malaria, departure to tropical countries have an important epidemiological meaning. Microscopic blood examination (blood smear and voluminous drop) are needful and reliable laboratory methods to diagnostics of malaria.

Four diseases are problems for differential diagnostics: tuberculosis, colla-genoses (lupus erythematosus and so called "non-differentiated" collagenoses or diffuse diseases of connective tissue), malignant neoplasm (especially hepatomas and hypernephromas, also as a lymphogranulomatosis and leukemia).

At the last time it is necessary to allow for increased rate of fungal infections in diagnostics of sepsis. They are mainly candidoses of the bronchopulmonal, intestine, urogenital and osseous systems. Fungi of genus *Candida albicans* have the most meaning among fungal damages. Fungi *Candida albicans* are revealed in the normal flora of the oral cavity, intestine.

It is necessary to perform differential diagnosis of sepsis with intestine yersiniosis. This disease may have prolonged (more than 3 months), relapsing course. In prolonged yersiniosis alteration of periods of relapses and remissions is observed. The period of relapse is characterized by prolonged fever, reactive polyarthritis, myocarditis, prolonged gastroenteritis, hepatolienal syndrome, erythema.

The repeated sowings are produced on special mediums for determination of the agent's origin: blood, sugar, billiary broth. It is recommended to take the blood in a quantity 15-20 mL on 80-100 mL of the medium. The agent may be revealed from hemorrhagic elements, sputum, urine, content of abscess and other materials.

Treatment

Therapy of sepsis should include at least two obligatory components − suppression of the pathogen and restoration of immunity.

Basis of sepsis therapy is oppression and liquidation of the pathogen. The means of syndromes treatment which restore immunity and all others if there is a necessity should not be ignored, but all of them can not cure the patient with sepsis without appropriate ethiotropic therapy.

Antibiotic therapy of sepsis may be successful, if:

1) It is carried out according to the agent definition and its antibiotic sensivity;

2) It will be carried out by bactericidal drugs. Bacteriostatic drugs are used only additionally;

3) It is applied at early septicemia (at this stage of illness recovery is achieved in 100 % with one antibiotic without all other means of treatment);

4) Dozes of antibiotics are maximum high, and β-lactamic antibiotics (penicillines, cephalosporines) are used in megadozes;

5) Empirical antibiotic therapy (if the agent is unknown) is carried out on the basis of the clinical supposition about a nature of the agent (empirical antibiotic therapy is should not be carried out by random);

6) Combination of antibiotics is carried out by a rule: bactericidal drugs with the various mechanism of action;

7) Usage of more than two preparations in one combination is not expedient, as with increase of number of drugs harmful actions grow faster, than therapeutic effect;

8) It is not necessary to start antibiotic therapy from reserve antibiotics (carbopenems, cephalosporines of 4th generation).

If treatment is successful, antibiotic therapy is cancelled last, after liquidation of all infection foci, but not earlier 5th day of a normal body temperature. Sepsis is a general clinical medical problem. Comprehension of sepsis should become the common medical property because such patients are in all medical establishments without exception.

Among various combinations of antibiotics the greatest recognition has received combination of cephalosporines of 3rd generation (ceftriaxoni, cefotaximi, ceftazidimi) with aminoglicosides (gentamicini, amikacinum). All these combinations are effective enough at patients with sepsis without a neutropenia. Appreciable interest to ceftriaxoni is caused by duration of its period of semiconclusion, that allows to apply preparation once per day. Other preparations have shorter period of semiconclusion and demand repeated injection during a day. At sepsis caused by *Pseudomonas aeruginoza*, high efficiency of combination of penicillines with antipyocyanic activity (ticarcilini, clavulanati, aztreonami) and aminoglicosides is marked.

At sepsis caused by Gram-positive flora (meticilini-resistant *Staphylococcus aureus*, coagulasenegative staphylococcuses, enterococcus), using of vancomycinum, rifampicinum is effective.

Carbapenemes (tienamicines) – special group of β-lactames antibiotics (imipenicemi, tienami, meropenemi, biapenemi), the infections created for empirical therapy with serious current, including leukopenia. Very wide spectrum of action, high bactericides, that is not accompanied by superfluous remission of endotoxins at destruction of bacteria, allow to use with success carbapenemes as monotherapy at the most severe infections, including sepsis.

After isolation and identification of the pathogen, definition of antibioticogram the choice of effective antibacterial therapy is considerably facilitated. In such cases monotherapy is frequently used. Nevertheless, the question of indication of monotherapy or a combination of antibacterial preparations remains debatable and, apparently, should be discussed in each concrete case. Determining arguments, probably, will be estimation of gravity of infectious process and condition of reactivity of organism, danger of occurrence of hospital infections in connection with invasive methods of diagnostics and treatment, transplantation of extraneous bodies. Nevertheless, at Gram-negative infections, in opinion of many scientists, the combined therapy is more expedient.

Antibiotics, as a rule, do not suppress immunity. It is proved, that lincosamides and macrolides have immunomodulative properties and are capable to stimulate the certain parts of the immune responce.

Duration of antibiotic therapy is determined by course of inflammatory process. As a rule, preparations cancel at proof normalization of temperature (absence of signs of generalized process), absence of the clinical and laboratory data on presence of the localized center of an infection or joining of nosocomial infections. At average therapy lasts 2-3 weeks. At revealing clinical efficiency of empirical or purposeful therapy by antibiotics change of a combination or separate preparation is inexpedient during all period of treatment.

The immunotherapy should be directed on blocking of effects of endotoxin and citocines. Application of pentoxifilini is perspective, which has protictive influence on lungs, systemic hemodynamics, improves microcirculation and oxygenation of tissues, stabilizes electrolytic balance, preventing occurrence of hyponatremia.

Citoprotective antioxidantes (vitamin E, acetylcysteinum) oppress activity of free radicals and may improve the forecast at sepsis. Hyperproduction of free radicals which are metabolites of an arachidonic acid is lowered also by ibuprofenum.

In 70th years efficiency of polyclonal antibodies to *E. coli* and *Salmonella* which at septic shock caused by Gram-negative bacteria's, reduce a lethality almost on 50 % was proved. Now polymyxin B or neutrophile bactericidal penetrating protein is used.

Efficiency of application for prophylaxis of the systemic responce on inflammation of vactination of patients by derivative of endotoxin – mono-phosphorolipides A is now studied. Monoclonal antibodies to interleucines,

phospholipase, to adhesive molecules and contact factors are received and pass clinical approbation of antibody to lipid A and endotoxin. It is possible, that in future by identification of mediators it will be possible to create "cocktail" from antibodies which block receptors and enable to stop progresive process at the systemic inflammatory answer.

Interferons − native and genoengineering preparations which concern mainly to IFN (roferoni A, introni A, realdironi, laferoni) − natural ways of imunocorection and protection against infections, with success are applied at present of acute and chronic infectious diseases.

Combined using of carbapenemes, roncoleucines or interferons is advanced achievement of modern therapy of septic diseases.

At serious course of a sepsis stabilization of hemodynamics has crucial importance. First of all it is necessary to restore volume of circulating blood. For this purpose cristaloides and colloid solutions are infused in ratio 2-4:1 under the control of hemodynamics parameters, including the central venous pressure.

The proof hypotension, even after fast restoration of blood volume circulation, may be connected with disorders of regulation of vascular tone. Application of inotropic preparations − dopaminum, dobutaminum, dobutrexi in this case is expedient. The clinical effect from dopaminum will increase the cardiac emission (β-adrenergic effect), rising of peripheric vessels tone (α-adrenergetic effect), improvement of circulation in parenchymatous bodies, first of all in kidneys (dopamineergetic effect). Using of α-adrenomimetics (epinephrine) may be necessary only in case of inefficiency of high doses of dopaminum.

Respiratory support is necessary for significant amount of patients with sepsis, however application of different methods of artificial ventilation of lungs is limited to cases of disease with development of acute respiratory insufficiency. In a combination of inotropic therapy ventilating support promotes decrease of work of muscles, improvement of oxygenation of blood and function of systemic circulation.

In support of appropriate level of metabolic and immune processes the important value has a feed of patients. The early high-caloric enteronutrition with the enlarged contents of fibers and amino acids (arginine, ornithine) reduces frequency of complications and duration of treatment. It is necessary to use enteral alimentary admixtures (enpites), balanced under the contents of fibers, adepses and carbohydrates.

It is expedient to use solutions of amino acids for parenteral feeding (alvesini, aminosoli-600, aminosoli-800, aminosoli KE, infesoli 40 etc), dextrosum, lipide emulsions (intralipid).

DIC demands correction only in stage of decompensation.

Prophylaxis

It is necessary to perform opportune treatment of primary foci. The measures, directing on increase of resistance of the organism have an important meaning. These measures are rational diet, regime of work and rest, physical training.

Staphylococci are more frequent etiological factor of sepsis, because prophylaxis of intrahospital staphylococcous infection is necessary. The early revealing and prohibition of work of medical personnel with purulent inflammatory diseases (sore throat, pyodermia) and opportune hospitalization of the patients with staphylococcal infection in special departments or wards. It is necessary the revealing of prolonged bacteriocarriers of hospital strains of staphylococcuses and its sanation for patients with immunodeficiency and operating-room.

The maintenance of sanitary-hygienic regime has leading meaning in the hospitals of different profile.

It is necessary to use remedies, increasing nonspecific resistance of the organism of the patients in the groups of risk (infants, patients with immuno-deficiency and others).

Control questions:

1. Essential differences of sepsis from others diseases.
2. Etiology and epidemiology of sepsis.
3. Classification of sepsis.
4. Sepsis pathogenesis and pathologic anatomy.
5. Clinical manifestations of sepsis.
6. Sepsis diagnosis.
7. Differential diagnosis of sepsis.
8. Treatment of sepsis.
9. Sepsis preventive measures.

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Fig. 1. **Roseoles ("rose spots") in patient with typhoid fever.**
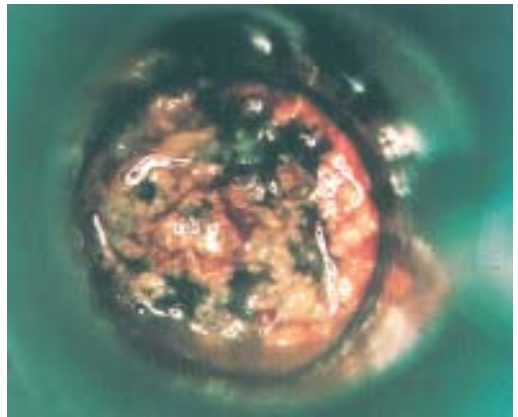

Fig. 2. **Rectoronanoscopic picture of shigellosis.**
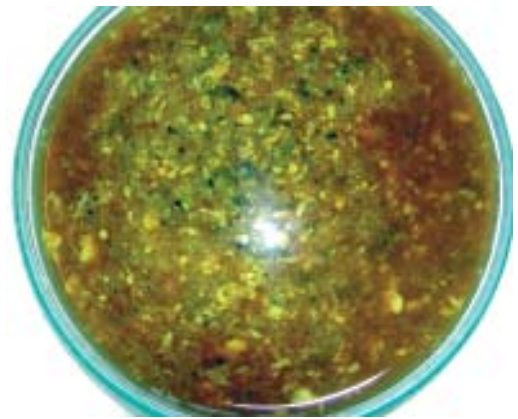

Fig. 3. **Faeces of patient with salmonellosis.**

Fig. 4. **Dryness in the mouth in patient with botulism.**

Fig. 5. **Squint, midriasis and anizocory in patient with botulism.**

Fig. 6. **Ptosis in patient with botulism.**

Fig. 7. **Hemorrhagia in injection's places in patient with leptospirosis.**

Fig. 8. **Herpes simplex. Severe case of recurrent disease.**

Fig. 9. **Herpes zoster.**

Fig. 10. **Erysipelas. A typical rash on the leg.**

Fig. 11. **Jaundice in patient with viral hepatitis.**

Fig. 12. **Meningococcemia.**
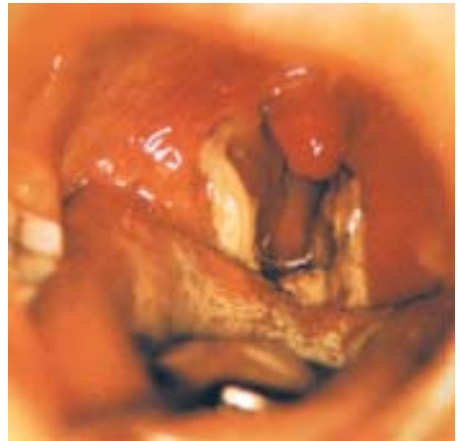
Fig. 13. **Diphtheria. Gross swelling and congestion of the pharyngeal and tonsillar area.**

Fig. 14. **Tularemia lymphadenitis.**

Fig. 15. **Limphadenopathy with AIDS.**

Fig. 16. **Weight loss in patient with AIDS.**

Fig. 17. **Elements of Kaposi's sarcoma.**

Fig. 18. **Suppuration and ulceration of
Kaposi's sarcoma elements.**