Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

LEPROSY

Methodological recommendations
for the preparation of applicants of higher medical education
of the 4th year in the discipline **“**Dermatology, venereology”

Electronic resource

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Leprosy : methodological recommendations for the preparation of applicants of higher
L 56 medical education of the 4th year in the discipline "Dermatology, venereology" [Electronic resource] / compilers T. I. Lyadova, O. V. Volobuyeva, D. M. Dorosh. – Kharkiv : V. N. Karazin KhNU, 2023. – (PDF 25 p.)

The methodological recommendations were developed by the team of teachers of the Department of infectious diseases and clinical immunology of V. N. Karazin Kharkiv national university of the School of medicine. An indicative map of the applicants work for higher medical education is provided, with clear, consistent and detailed recommendations for preparation at each stage of the practical training. The list of basic theoretical questions and practical skills, structure and content of topics, test modules for the initial and final level of knowledge control are given, the basic and additional literature is specified, there are references to the electronic resources of department's educational materials in the annexes

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CONTENTS

ESTIMATED MAP OF WORK FOR HIGHER MEDICAL EDUCATION APPLICANTS FOR PRACTICAL CLASSES PREPARATION

	PREPARATORY phase:
1.	To know the **interdisciplinary integration** of practical classes topics with acquired theoretical knowledge and practical skills in basic disciplines (medical biology, medical and biological physics, Latin language, human anatomy, normal and pathological physiology, biological and bioorganic chemistry, pathological anatomy, microbiology, virology and immunology, pharmacology, philosophy etc.). Acknowledge the terminology (including Latin transcription).
2.	**Motivational characteristic** and **substantiation of the topic** of the practical lesson **on behalf of the formation of clinical thinking**, in particular for the further development of skills in knowledge application in diagnosing of the main symptoms and syndromes and the possibilities of modern laboratory and instrumental methods of internal organs examination in the process of further study and future professional work.
3.	To give better insights into the types of student's educational activity, information provided on the reference stands of the department: thematic calendar plans of lectures, practical classes and extra-curriculum independent work of the 4th year higher medical education applicants corresponding to the curriculum of the model and working program of the discipline «Dermatology, venereology».
4.	Utilization of the basic and additional **educational and methodical literature:** ● **textbooks and tutorials** (printed and electronic versions), which are listed in these guidance after the theoretical section; ● **educational and methodological materials of the department** (methodical recommendations for independent preparation for practical classes for the 4th year higher medical education applicants in the discipline «Dermatology, venereology» and methodological recommendations for independent student's work); ● attendance of **lectures** (on-site supply of the educational process using multi-media presentations during lectures) - according to the thematiccalendar plan. Usage of **printed publications** for classes preparation, they can be obtained from the library and / or **electronic versions of it** available on the official site of the V. N. Karazin KhNU http://www.univer.kharkov.ua/en/departments (navigation for sections: ... /Faculties / Departments / Infectious diseases and clinical immunology) - ref. Annex 1;

	and in the open interactive database of the electronic archive of the Repository of the V. N. Karazin KhNU resources http://ekhnuir.univer.kharkov.ua (navigation: Faculty of Medicine / Educational editions, Medical Faculty) - ref. Annex 2. It is advisable to note the main issues in the form of notes
MAIN phase: Practical classes duration is 4 academic hours, they are held at the **clinical base** — Municipal non-profit enterprise «State Dermatovenerologic Dispensary №1» of Kharkiv municipal council. (Kharkiv, Tsilinogradskaya Street, 50) – see Annex 3. **ATTENTION!** Its forbidden to attend department classes without a medical uniform, replaceable shoes, medical cap, mask, shoe covers, stethofonendoscope.	
1.	To achieve the educational goal of practical classes and mastering the theoretical part of the subject, it is necessary to **LEARN** and **ASKNOWLEDGE** the answers to **the main theoretical questions** of the lesson's topic (ref. to the list of the main theoretical questions) that will be checked by the lecturer through an oral and / or written survey (correction, refinement, additional answers) on the main phase of practical classes conduction.
2.	**TO BE ABLE TO** solve with explanations of theoretical, multiple choice (for control of the initial and final level of knowledge), situational tasks proposed for the mastering of the topic.
3.	**TO MASTER PRACTICAL SKILLS on the topic** ● Take active part in the teacher's demonstration of the methodology of patient's examination, and to assign practical skills near the patient's bed under the supervision of a teacher. To perform the patient's examination, interpret the received laboratory and instrumental investigations data, be able to use tools needed. ● Make syndromic diagnosis. To perform a differential diagnosis, to analyze the principles of the treatment, to give prescriptions for essential medicines prescribed.
4.	**EXECUTE** obligatory tasks foreseen for independent student work
FINAL phase:	
1.	On the basis of theoretical knowledge and practical skills mastering on the topic to form clinical thinking and syndromic diagnosis making skills for further study in the medical profession.

Purpose and main tasks of the work on the topic of the practical lesson

LEPROSY. CLINICAL COURSE, DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, CONFIRMATION OF DIAGNOSIS AND TREATMENT

Increase the level of knowledge on the etiology, pathogenesis, classification, clinical features and diagnosis of patients with allergodermatoses: the main clinical and instrumental methods of examination, to teach students of higher medical education in the 4th year of training modern tactics of management of patients with skin pathology.

MAIN QUESTIONS

As a result of studying the 4th year higher medical education applicants

must KNOW (the main theoretical questions):

1. etiology of leprosy;
2. pathogenic characteristics of leprosy;
3. features of classification and clinical manifestations of leprosy;
4. principles of treatment;
5. prevention of leprosy.

must BE ABLE (basic practical skills on the topic of the practical lesson):

1. properly collect patient history on leprosy;
2. make a diagnosis on clinical grounds;
3. run diagnostic (skin) tests to confirm the diagnosis;
4. make a differential diagnosis;
5. assign individual pathogenetic treatment.

Tests to control the INITIAL LEVEL OF KNOWLEDGE

1. Average duration of treatment of multibacillary leprosy?
   A. 1 year
   B. 2 year
   C. 3 year
   D. Life long

2. The most effective drug against M.leprae is ?
   A. Dapsone
   B. Rifampicin
   C. Clofazimine
   D. Prothionamide

3. Multidrug therapy is given for?
    A. Syphilis
    B. Leprosy
    C. Herpetiformis
    D. Icthyosis vulgaris

4. All lesions are seen in leprosy except?
    A. Erythematous macule
    B. Hypopigmented patch
    C. Vesicles
    D. Flat and raised patches

5. Which pathogen causes leprosy?
    A. *Mycobacterium tuberculosis*
    B. *Mycobacterium leprae*
    C. *Mycobacterium bovis*
    D. *Mycobacterium africanum*

6. Which is other name of leprosy?
    A. Lella's disease
    B. Giems's disease
    C. Hensen's disease

7. Lepromin test help in?
    A. In the diagnosis of leprosy
    B. In prognosis and classification of leprosy
    C. In prognosis

8. The first sensation to be lost in leprosy is?
    A. Temperature
    B. Pain
    C. Both at the same time
    D. None

9. In leprosy nerves commonly involved are?
    A. High ulnar, low median
    B. High median, low ulnar
    C. Triple nerve palsy
    D. High radial, low median

10. Skin biopsy in leprosy is characterised by?
    A. Periappendegial bacilli
    B. Periappendegeal lymphocytosis
    C. Perivascular lymphocytosis

D. All of the above

Standards of answers: 1–A, 2–B, 3–B, 4-C, 5–B, 6–C, 7–B, 8–A, 9–A, 10–D.

STRUCTURE AND CONTENT OF THE TOPIC

Leprosy is also referred to as Hansen disease. It is a chronic granulomatous infection generally caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, both of which primarily affects the skin and peripheral nerves.

"Mycobacterium leprae complex" comprises *M. leprae and M. lepromatosis*. Though both mycobacteria are classified as different species because of there DNA sequences, they both are obligate intracellular organisms and have many similar features causing the same clinical disease.

Leprosy is of great concern in the medical community. This disease is not highly contagious, contrary to belief, and treatment is readily available for this ailment. Through awareness and early medical intervention, significant reduction causing disability in the eyes, hands, and feet is possible. Relapses tend to be rare, but any damage caused by neuropathy is irreversible and may require lifelong care.

Etiology. *M. leprae* is gram-positive, acid-fast bacilli of *Mycobacterium leprae* complex, which is comprised of *M. leprae* and *M. lepromatosis*. The former of these two multiply slowly compared to the latter, with an estimated 12 to 13 day generation time. This obligate intracellular organism cannot be cultured with artificial media and contains less than half of functional TB's genes.

Lab tests show that *M. leprae* optimally grow at approximately 27 to 33 C. This reinforces the initial theory for *M. leprae*'s predisposition to spread more efficiently at cooler regions of the body. This includes the skin, nerves close to the surface of the skin and membranes in the upper respiratory tract. This strain also grows strongly within the nine-banded armadillos, which naturally has a core temperature of 34 C and is mostly found in south-central United States. Aside from armadillos, the chimpanzee, mangabey monkeys, and cynomolgus macaque also have harbored *M. leprae.*

The genomes for *M. leprae* and *M. lepromatosis* have been determined and show that the genetic makeup for both strains contains a large number of pseudogenes. Also, there are several missing genes to be used as key enzymes for metabolic pathways. The excess number of pseudogenes have allowed mycobacteria to develop itself strongly within the classification as an obligate intracellular organism.

De novo sequencing of *M. lepromatosis* has shown differing nucleotide polymorphisms. This has allowed scientists to develop a hypothesis that *M. leprae* and *M. lepromatosis* diverged from a common ancestor more than 13 million years ago.

Epidemiology. In 2000, the World Health Organization (WHO) identified leprosy as completely eradicated. Ultimately, infection elimination was defined as the overall reduction in prevalence to less than 1 case per 10,000 people. In the span

from 1985 to 2011, the recorded cases fell from 5.4 million to approximately 219000. By 2011, the prevalence rate in terms of 10,000 people, dropped from approximately 21.1 to 0.37, excluding Europe.

Leprosy is typically found in developing countries, with its prevalence being variable. Approximately 16 countries reported about 1000 new cases in 2009. Most cases were shown to be in India, Indonesia, Brazil, Nigeria, and Bangladesh. Data obtained for leprosy shows that not all cases are reported. When efforts were made to go door to door in Bangladesh, there was a near fivefold increase in cases compared to self-reported findings only.

Within the United States, 75 percent of cases were shown to be from immigrants. For U.S. born citizens who contracted leprosy, international exposure was the contributing factor in a number of cases. If not from another individual, exposure by infected armadillos was also shown to be a possibility. Also, when looking at gender specificity, leprosy is seen more in males with an approximate 3 to 2 ratio. In 2009, multibacillary cases were shown to be 61 percent of the new patients, while it spanned from 33 to 94 percent globally.

Pathophysiology. Leprosy transmission is not completely understood, but it is believed to spread through respiratory means. Untreated individuals with lepromatous infections usually contain many bacilli. The general mode of dissemination, once within the body, starts at the upper respiratory tract. Reports indicate that host infection can potentially occur through broken skin as well.

M. leprae's affinity for peripheral nerve cells, preferentially attacking Schwann cells (SCs), causes nerve demyelination and loss of axonal conductance, which presents clinically as numbness.

The primary mechanism for spreading *M. leprae* and environmental conditions harboring the microorganism is still being scrutinized. *M. leprae* has shown resilience and viability after ingestion by amoebae. It has also been seen to maintain viability for as long as eight months continuously completely. Ticks have also been seen to contribute to transmission by transfer of the organism to their eggs. With the modern-day technological advances in molecular identification, additional studies can be done to identify reservoirs and vectors to assess viability. It is important to note that many people do not contract the disease after initial exposure. The disease's growth and development depend on many factors, including immune function and genetic predisposition.

Th1 immune response is strong and is associated with lower bacterial counts and limited disease, whereas Th2 response is weak and results in higher bacterial counts and more severe disease.

Risk Factors. Factors attributing to the contraction of leprosy include:

- ***Close Contact:*** Direct contact with a patient with leprosy considerably increases the chances of obtaining the disease compared to the rest of the population.
- ***Armadillo Exposure:*** Within the southern US, the *M. leprae* strain is native in the nine-banded armadillo. Though not completely understood how the bacteria is transmitted from armadillos to humans, molecular typing procedures have proven the animal to human transfer.

- ***Age:*** Older members of society are more prone to risk in the acquisition of leprosy. Some studies show a bimodal relationship with age. Elevated risk showed between 5 to 15 and continued risk after 30.
- ***Genetic Influences:*** As previously mentioned, genetics plays a role in the immunologic response. Innate immunity is attributed to genetic factors, specifically through the PARK2/PACRG gene. A study including more than 1000 patients with recent diagnoses of leprosy combined with 21,000 contacts showed that genetic relations were important. These relations confirmed genetics as a relevant risk factor, regardless of the distance in contact.
- ***Immunosuppression:*** Following the suppression of the immune system, there is an increased chance of acquiring this infection. Leprosy development typically occurs after solid organ transplantation, chemotherapy, HIV infection, or after administering agents for rheumatologic symptoms.
- **Histopathology.** The histopathological manifestations of leprosy are diverse and depend on the cellular immune response to the M.leprae complex.

Tuberculoid leprosy (TT) and borderline tuberculoid (BT): characterized by infiltration of dermis and subcutaneous fat with well-defined epithelioid non-caseating granulomas and few or absent acid-fast bacilli (AFB).

Lepromatous leprosy (LL) and borderline leprosy (BL): Consists of macrophages with a vacuolar cytoplasm, plasma cells, lymphocytes, and numerous acid-fast bacilli (AFB).

History and Physical. Leprosy is a disease with myriad different presentations, largely due to the broad immune response towards the *M. leprae* strain.

Ridley-Jopling classification system covers the entire depth of the clinical feature. From an intense immune response with a small number of tuberculoid organisms to a minor response with an elevated number of multibacillary cells. Overall, this classification is applied using a cutaneous, biopsy, and neurologic outcomes from the body. This gives medical professionals a reasonable estimate of the immune response to be produced. The previously mentioned findings are also related to the acid-fast bacilli that exist in the dermis.

This includes:

- Tuberculoid (TT)
- Borderline tuberculoid (BT)
- Mid-borderline (BB)
- Borderline lepromatous (BL)
- Lepromatous (LL)
- Indeterminate (I)]

There are varying degrees of severity in the presentation of this disease. In cases where there is a significantly elevated cell-mediated immune response along with delayed hypersensitivity presentation consists of well-demarcated lesions with central hypopigmentation and hypoesthesia. Mentioned specifically as a polar tuberculoid, this inflamed granulomatous growth is also coupled with uncommon acid-fast bacilli within the tissues as well.

In individuals with no observed resistance to the *M. leprae* strain are shown to have several ill-marked, raised lesions throughout the body. This type of infection, with a considerable affliction of disease, is labeled as polar lepromatous. It is important to note that these persons have no record of immunosuppression; however, they are not able to build immunity to *M. leprae*.

Initial presentation of lesions is shown as broad-based perineural invaders where acid-fast bacilli are potentially determined. Without developed establishment criteria, it is then further labeled as indeterminate. These cases usually present in children with spontaneous healing. This classification is recommended to only be utilized when biopsy results show confirmed leprosy; however, not progressive enough to lock in the severity on the spectrum. Indeterminate cases are recommended to be confirmed through lab or visual means before labeling as such.

WHO Classification. Another classification profile was developed for cases where minimal clinical or lab support would be available. This system is based on the number of lesions present. In situations where five or fewer skin lesions are present without any bacilli evident on skin smears, it would be considered as paucibacillary (PB) leprosy. Where if only a single lesion is seen, it is labeled as a single lesion PB. Six or more lesions with a positive skin smear test are considered as multibacillary (MB) leprosy.

Additional physical features evident when considering leprosy includes symptoms such as:

- Reddish skin patches with sensory loss
- Paresthesias with associated numbness in extremities
- Painless burns in extremities
- Lumps or swelling on the earlobes
- Enlarged sensitized peripheral nerves

Findings found after significant development include weakness with claw fingers, facial paralysis, lack of eyebrows and eyelashes, or perforated nasal septum. Generally, the severity of the manifestations relies on the level of nerve immersion, the classification type, and any active immune responses.

Skin lesions that are commonly seen in leprosy can be categorized in the following subsections:

- ***Tuberculoid leprosy (TT)***
    - This presents with large hypopigmented or erythematous lesions with clear demarcation and raised margins. Plaque presentation was shown to be scaly.
- ***Borderline tuberculoid (BT***)
    - BT is defined as macules with a “target” appearance in lesions. In this specific disease, the number of lesions is higher than TT and usually shows on one side of the body. When referencing the previously mentioned WHO classification, these types of lesions are considered “paucibacillary.”
- ***Mid-borderline (BB)***

- Referenced as “multibacillary,” this disease most closely emulates BT leprosy or border-lepromatous with its appearance of “punched out” lesions. Note, the central areas are mostly anesthetic.

- ***Borderline lepromatous leprosy (BL)***
  - Lesions, in this case, include erythematous macules, nodules, or papules that show no distinct pattern of appearance on the body. Though normal patches of skin can be found, the delineation of the lesions is not clear and spread out. Larger sized lesions are shown to have a disproportionate distribution.
- ***Lepromatous leprosy (LL)***
  - Significantly progressed cases present with body hair loss along with nodular enlargement of earlobes. Mucosal invasion can resemble stuffiness, similar to the common cold. A perforated septum or collapse could occur unless treatment is readily sought after. Also, asymptomatic presentation is possible with sporadic bacteremia during this disease. M.leprae, in this case, progresses with focal lesions in several organs. Some situations show organisms to be present in the liver or marrow after biopsies have been requested. Involvement with testicles and larynx is also possible.
- ***Indeterminate disease***
  - Shows as a hypopigmented or erythematous macule with little to no sensation. Bacilli are not usually found in this biopsy. If the lesion shows not to be fully developed, it should develop into another type within the leprosy spectrum.

Neuropathy. Nerve association is evident early in the progression of leprosy, measured through the general decrease of sensation in lesions. Lowering injury to peripheral nerves is a top goal, and proper investigation of these nerves is paramount to proper evaluation. The onset of neuropathy is coupled to loss of sensory perception, but in some cases, pain arises as well later on in the path of the disease.

In individuals with tuberculoid disease, depending on the nerves located around the areas of the skin lesion, potential sensory and motor loss could occur. In cases involving lepromatous disease, the damage is more generalized. The involvement of nerve trunks of the body includes ulnar/median nerves, the peroneal nerve, posterior tibial nerve, facial nerve, and the great auricular nerve.

Subclinical neuropathy seems to be increasingly involved than originally anticipated. Testing has shown that using sensitive methods, including monofilaments, depicts that impairment of nerves occurs a lot earlier in lepromatous disease as compared to tuberculoid disease. Usual tests included sensory nerve conduction and heat perception. The results from these tests usually became abnormal approximately 3 or more months before identification with monofilaments. In the final presentation of nerve injury for this disease, a common theme is segmental demyelination. Though ill-understood, general methods to study the pathogenesis of this disease prove to be difficult. Biopsy of tissues impacted by this disease cannot be completed due to the major involvement of peripheral nerve trunks involved.

Ophthalmic Injury. Diminishing innervation of nerves associated with the muscles in the eyelids and signal to the cornea could potentially lead to lagophthalmos, corneal abrasion and ulceration, and drying. Full ocular assessment is important to comprehensive examinations.

Immunologic Reactions. These types of reactions are systemic responses that could occur before the start of treatment, during treatment, or even a significant time after the treatment has been completed. There are two different types of leprosy reactions, T1R (Type 1 reversal reaction) and T2R, also known as erythema nodosum leprosum (ENL). Patients with borderline disease involve T1R, while lepromatous disease usually involves T2R. Both of these reactions require further investigation, specifically the mechanisms of response and the overall factors needed for them to proceed.

In all reaction types, fatigue, malaise, and fever are possible with other presentations, including neuritis, arthritis as well as nasopharyngeal symptoms. The nerve injury consequent from the immune reactions can lead to paralysis and deformity. An important note is to realize that drugs do not cause these reactions, and the treatment originally specified should progress. The following is a review of the previously mentioned reactions:

Type 1 Reaction (T1R). Typically comes up in BT, BB, or BL cases. Presentation includes:

- Red, swollen areas with existing lesions associated with nerve trunk or face
- Erythema of skin lesions present
- Inflammation due to reactions leading to deformity and paralysis
- Edema
- Ulceration of lesions on the skin
- Weakness or loss of nerve function

Without treatment, the pathway for T1R lasts approximately a couple of months. Further studies have shown that this reaction appears to arise from the free development of cell immunity as well as hindered hypersensitivity to *M. leprae* antigens. Biopsies could show edema, the elevated number of multinucleated cells, and granulomatous presentation. In these cases, the general initial event to start the progression is not completely understood. As a result, it becomes very difficult to predict patients possibly contracting this situation. There should be no change in regimen to lower the chances of reactions.

Type 2 Reaction (T2R, ENL).

- Presented in individuals with BL and LL
- The scale has been developed to further support physicians in further understanding the specific case.

Type 2 reactions usually present as sudden onset of painful nodules, which could be either superficial or deep within the dermis. Pustule formation is possible with the excessive discharge of pus. The exudate is shown to contain polymorphs and acid-fast bacilli. Lesions are primarily located on the surfaces of limbs and face with the typical life of a small number of days.

A specific condition, labeled as the *Lucio phenomenon*, is considerably rare that could present in cases with Type 2 reaction and manifests with the onset of necrotizing vasculopathy in individuals with ignored lepromatous leprosy.

Known risk factors related to T2R incorporate puberty, pregnancy, and lactation. The overall mechanisms involving this type 2 reaction are not completely understood. Researchers and clinicians see this immune response as pertaining to complexes, but data does not support this claim. Increased amounts of TNF-alpha coupled with other cytokines have been seen, but it still not understood how they impact the overall process. It has been seen that T and B cells are modified during ENL, and lesions also contain neutrophils as well.

Evaluation. Development of laboratory techniques revolved around histopathological analysis using skin biopsies and PCR. A commonality when evaluating for leprosy using laboratory tests was as follows: elevated leukocyte, decreased hemoglobin, low hematocrit, increased liver function tests, and presence of elevated serum C-reactive protein.

Skin Biopsy. Looking at the severity of the lesions and the infiltration of the nerves, a complete biopsy, including subcutaneous tissues, is recommended for the most dynamic and active margin of the lesion. Hematoxylin and eosin sectioning is used to show the dramatic variation in the spectrum mentioned earlier.

In type 2 reactions, the polymorphonuclear leukocytes are characteristic, while in lesions called Lucio's phenomena, demonstration of fibrin thrombi is evident. There are currently studies underway to further define histologic criteria for type 1 reactions. An important note in evaluating the mycobacterial cultures is to ensure that cutaneous infections, such as *M. tuberculosis* and non-tuberculin mycobacteria, are ruled out from interfering with potential evaluation.

Polymerase Chain Reaction. The lab technique PCR is readily used for detecting *M. leprae* and *M. lepromatosis* DNA in tissue. PCR is more applicable when used as a detector rather than an identifier. In current studies, biopsy PCRs had a sensitivity of more than 90 percent and specificity of 100 percent. In cases with tuberculoid disease, results showed a sensitivity of 34 percent and specificity of 80 percent.

In devising of skin tests, proteins, and peptides remaining in the sample are removed so that only *M. leprae* remained. Another test, mentioned as the "lepromin test," uses injected and calibrated autoclaved *M. leprae* into the skin with an evaluation after 3 to 4 weeks. A positive result from this technique indicates the possibility for the development of a granuloma following exposure to the strain, but it does signify exposure to leprosy in question. In a highly endemic area, it was seen that 70 percent of controls had positive results, while only 15% to 50% confirmed leprosy patients had a positive response.

Serologic Test. In serology studies, the specified *M. leprae* phenolic glycolipid-1 (PGL-1) is referenced but not commonplace within the United States clinical practice procedure as it is not very sensitive in the absence of clinical and histological evidence. Individuals diagnosed with the lepromatous disease tend to have an elevated polyclonal immune response to the *M. leprae* phenolic glycolipid-

1 (PGL-1) and many false-positive results. The tuberculoid disease does not typically incite the production of antibodies to PGL1, so this means of testing becomes void for this specific set of patients. In summary, PGL1 has not been demonstrated as confirmatory or even semi-predictive of infection development. Serologic studies continue to understand better and improve existing methods.

Treatment / Management. General treatment of leprosy usually involves multiple drug therapy (MDT) to ensure no microbial resistance. The MDT treatment is effective against *M. leprae* and quickly gets the patient to a non-infectious state. Using MDT also decreases the chances of drug resistance Medications used include dapsone, rifampin, and for the lepromatous disease, clofazimine is preferred. Combined, these drugs prove to be the most efficient. Traditional leprosy therapy works well in battling both *M. leprae* and *M. lepromatosis.*

Historically, the initial antimicrobial agent used for the treatment of leprosy was promine, a sulfone. This sulfate's efficacy was further proved with dapsone, its related compound. However, after some time of monotherapy, resistance towards this drug was demonstrated by the strain.

In 1982, the World Health Organization published a recommendation to use dapsone and rifampin for tuberculoid leprosy and in combination with clofazimine for managing the lepromatous disease.

The effectiveness of the agents has been clinically proven alongside mouse trials. There have been no controlled trials at this point comparing the different drug combinations. Without an accurate endpoint and a very long observation period for the identification of relapse, devising trials is difficult.

Selecting a Regimen. Treatment is as follows:

- Tuberculoid disease: dapsone (100 mg daily) with rifampicin (600 mg daily) for 12 months
- Lepromatous disease: dapsone, rifampicin, and clofazimine (50 mg daily) for 24 months

The treatment approach presented by the United States National Hansen's Disease Program (NHDP) is usually the general consensus. There has been advocacy for daily rather than monthly doses of rifampin coupled with longer treatment times. The recommended treatment timeline by WHO in 1982 was 0.5 to 1 year for tuberculoid disease (TT/BT) and 2 years for lepromatous disease (BB/BL/LL).

2018 WHO guidelines now advise for uniform MDT with the recommendations for treatment from 1998 still maintained. This entails administering three drugs: rifampin, dapsone, and clofazimine, to individuals despite the classified type. The variance from prior regimens is the added daily clofazimine for the paucibacillary disease. There is no change in multibacillary cases. Using the uniform MDT treatment decreases the chances of undertreatment of individuals with multibacillary disease misclassified as paucibacillary.

Other potential drugs that could be used include minocycline, ofloxacin, moxifloxacin, levofloxacin, and clarithromycin. There is still work that needs to be done to demonstrate the overall effectiveness of these drugs. A study combining rifampin (600 mg), minocycline (100 mg), and ofloxacin (400 mg) showed less

improvement compared to normal paucibacillary treatment regimen after 18 months. Other studies showed a single-month trial of rifampin and ofloxacin was not enough for treating lepromatous (MB) disease.

Clinical Response and Follow Up. Once therapy has begun, the general erythema and hardening of the lesions should dissipate after some months. However, it may be a few years for lesions involving cutaneous features to fully clear. All cases vary, depending on the general number of lesions and severity of the infection.

Bacilli killed by the treatment are removed from tissues at a decreased rate, lasting for a couple of years. There is no general therapeutic endpoint for the treatment due to there being no way to culture *M. leprae* and *M. lepromatosis*. Also, just having bacilli present in tissues cannot give us a definitive understanding of whether treatment is effective or not. There has been no established correlation between treatment and removal of dead bacilli from bodily tissues.

Studies have shown that *M. leprae* is killed at an elevated rate once in contact with rifampin and other drugs. As of late, clinicians have seen satisfactory results with MDT, with a minimal number of relapses, after employing NHDP and WHO procedures. These results are cases having one to two years of treatment. Accordingly, by observing the procedures outlined for MDT, bacilli eradication, and complete resolution of lesions are very likely.

Treatment of Immunologic Reactions. Immune reactions are inflammatory responses that generally ensure before treatment, during, or even months to years after completion of the regimen. Fatigue and fever could occur with other presentations, including arthritis, neuritis, and nasopharyngeal symptoms. With inflammation comes the potential for nerve injury leading to paralysis and deformity.

Type 1 reaction (T1R). Mild cases without symptoms such as ulceration or neuritis could be carefully approached with assistive care. Severe situations with neuritis may need immediate clinical intervention with corticosteroids to minimize irreversible nerve damage. Prednisone, approximately 40 to 60 mg/day, is recommended with a progressive decrease as the situation is managed. Cases, where individuals have severe reactions, may need additional corticosteroid treatment for some time because of excessive nerve problems. It has been shown that elevated doses and extended time frames have more of a benefit in subsiding pain and inflammation as compared to smaller and shorter doses of corticosteroids. Prophylaxis with corticosteroids does not seem to have any considerable result in reducing type 1 reactions. In patients with diabetes, methotrexate can be substituted for a steroid regimen.

Secondary treatment options for type 1 reactions include cyclosporine, useful for patients non-responsive in corticosteroid treatment. This drug has shown to help with nerve impairment and lesions in selected cases; however, toxicity was also seen.

Type 2 reaction (T2R). Mild reactions can be cared for through carefully planned clinician management. In severe type 2 reaction cases, immediate treatment with corticosteroids is administered to prevent nerve damage. Prednisone, approximately 40 to 60 mg/day, is given until the case is under control. It is

recommended to gradually decrease the dosage, over at least a two-week window, after control is achieved. If extended therapy is necessary, adjusting doses to an alternate day schedule could lower the overall side effects of the steroids.

Clofazimine is valuable in chronic cases with minimal effect for acute type 2 reactions. Increasing doses of approximately 300 mg daily for one month with a gradual decrease to 100 mg/day in one year. Clofazimine may have a role in protection against some reactions since it's the reduction in usage after MDT gained popularity. Clofazimine prescription in the US requires an investigational drug request to the FDA.

Thalidomide is considered an extremely viable option to treat type 2 reactions, but it could affect women capable of childbearing. The efficiency of thalidomide in treatment is the primary reason as to why it has not been outlawed. The initial dose of 300 to 400 mg daily controls the reaction in the body within 48 hours. After treatment has begun, the dose should be lowered to maintenance concentration around 100 mg daily, every couple of months. In attempts to control ENL (erythema nodosum leprosum), thalidomide treatment can proceed for a number of years. Neuropathy advancement should indicate immediately stopping treatment.

Alternative Agents. Cytokines are not readily used for leprosy treatment, but there is some data discussing the effect of using these agents. Inhibition of TNF-alpha has been seen to help in several cases of type 2 reactions. Unknowingly, administering these agents for people with advanced arthritis could be a risk for leprosy development in some patients.

Research of lepromatous leprosy through intralesional injection of interferon or interleukin-2 has shown signs of promise. But an inadvertent increase in the percentage of type 2 reaction development has been seen with the administration of this treatment.

Differential Diagnosis. Confirmatory indication of leprosy is when the patient is unable to perceive any sensory stimulus in the lesion, ranging from light touch to pin-prick. The establishment of the diagnosis is usually done through a skin biopsy. Differential includes the following:

- **Granuloma annulare**
  - The presentation is as an asymptomatic, erythematous, and scale-less plaque with marginal papules. The border is generally rope-like with a clearing in the center. General sites of manifestation include wrists, hands, feet, and ankles.
- **Fungal infection**
  - The fungal infection starts as a scaling, rounded, and erythematous patch with a radial distribution with a clearing. The border is raised and erythematous as well. Confirmatory diagnosis is through potassium hydroxide preparation.
- **Annular psoriasis**
  - This annular lesion is not very common with psoriasis but occasionally occurs. The diagnosis for this is also associated with the detection of

increasingly frequent symptoms of psoriasis, such as classic plaques/nail disease. A biopsy is needed for confirmation.

- **Systemic lupus erythematosus**
  - Presentation of lupus with cutaneous lesions can be localized (butterfly rash) or generalized. Additional erythematous macular eruption after exposed skin to outside sunlight also occurs.
- **Keloid**
  - Keloids are dermal lesions with a raised appearance around the wound site. There can be an extension beyond the boundaries of the initial wound with progression to areas next to the primary site.
- **Mycosis fungoides**
  - There is a non-uniform cutaneous presentation with the inclusion of patches, tumors, erythroderma, and alopecia. Confirmation of the diagnosis is through a skin biopsy.
- **Neurofibromatosis**
  - Cutaneous appearance involves café-au-lait macules, axillary and inguinal freckles. There is also evidence of neurofibromas. Establishing this case is primarily based on clinical characteristics.
- **Cutaneous leishmaniasis**
  - Lesions under this category generally occur on exposed areas of skin. Local cases start as pink papules that grow and develop to nodules. Following nodule formation comes the onset of ulceration with no pain and localized hardening.

In type 1 reactions, the diagnosis is usually completed just using clinical evaluation. Typical lab exams are not readily available for aid in diagnosis. High serum levels of chemokine CXCL10 have been shown to be related to type 1 reactions. CXCL10 should not be considered as an indicator for T1R. CXCL10 is not shown to be present in high concentrations in advance of the reaction; hence there is low confidence in its predictive ability.

Prognosis. Prognosis of leprosy depends on multiple factors, which include: stage of disease at diagnosis, early initiation of treatment, patient's access to treatment, and compliance with therapy.

With the start of multidrug therapy (MDT) in a timely manner after the initial onset, leprosy is generally seen as a curable disease. The treatment with MDT can prevent extensive deformity and neurological disability. By correctly adhering to the specified therapy, the extent of neurologic impairment can be restricted. But there have been cases that show there is partial to no recovery from any muscle weakness or loss of sensation sustained before the start of therapy. Relapse (reappearance of disease after completion of treatment) is minimal after MDT is applied, and fatalities are uncommon as well.

Complications. In individuals with leprosy, there remains a chance for the development of abscesses on nerves. Mostly seen on the ulnar nerve, this type of complication requires immediate surgical intervention to prevent irreversible sequelae. Nerve related complications also involve the eyes causing cranial nerve

palsies coupled with corneal insensitivity and lagophthalmos. This could lead to trauma, infection as well as corneal ulcerations and opacities. Blindness in third-world countries is correlated with the number of positive leprosy cases. Neuropathy in the extremities is also a complication associated with leprosy, causing insensitivity to fine touch, pain, and heat receptors and consequently leading to loss of distal digits. In cases involving patients with leprosy, the loss of distal sensitivity is possible, although this process is not fully understood and could be some ill-understood osteolytic process. In inflamed immunological reactions, chances of morbidity are high. Erythema nodosum leprosum (ENL) is usually presented with painful erythematous papules that resolve within a week. This type of papule occurs in nearly 50% of individuals closer to the LL type of leprosy.

Apart from the damage caused to skin and peripheral nerves mostly, it also involves reticuloendothelial, endocrine, and hemopoietic systems along with muscles, bones, and eyes.

Test to control the FINAL LEVEL OF KNOWLEDGE

1. An 8-year old boy from Bihar presents with a 6 month history of an ill defined hypopigmented slightly atrophic macule on the face. What is the most likely diagnosis?
   A. Ptyriasis alba
   B. Indeterminate leprosy
   C. Morphacea
   D. Calcium deficiency

2. The following drug is not used for the treatment of type II lepra reaction (ENL)?
   A. Chloroquine
   B. Thalidomide
   C. Cyclosporine
   D. Corticosteroids

3. The main cytokine involved in ENL (Erythema Nodosum Leprosum) reaction is?
   A. Il-2
   B. Ifn-Gamma
   C. Tnf-Alpha
   D. Mcsf

4. The following test is not used for diagnosis of leprosy?
   A. Lepromin test
   B. Slit skin smear

C. Fnac
D. Skin biopsy

5. A 27 year old patient was diagnosed to have borderline leprosy and started on Multibacillary multi-drug therapy. Six weeks later, he developed pain in the nerves and redness and swelling of the skin lesions. The management of his illness should include all of the following except?
A. Stop anti-leprosy drugs
B. Systemic corticosteroids
C. Rest to the limbs affected
D. Analgesics

6. Antileprotic drug also used in lepra reaction is?
A. Rifampicin
B. Dapsone
C. Ciprofloxacin
D. Clofazimine

7. Best method of treatment of ulnar nerve abscess in case of leprosy is?
A. High doses of steroid
B. Incision and drainage
C. Thalidomide
D. High dose of clofazimine

8. Inverted saucer shaped lesion is found in?
A. Lepromatous leprosy
B. Tuberculoid leprosy
C. Borderline leprosy
D. Indeterminate leprosy

9. Lepromin test is positive in which leprosy?
A. Lepromatous
B. Indeterminate
C. Histoid
D. Tuberculoid

10. A 16 year old student reported for the evaluation of multiple hypopigmented macules on the trunk and limbs. All of the following tests are useful in making a diagnosis of leprosy except?
A. Sensation testing
B. Lepromin test
C. Slit smears
D. Skin biopsy

Standards of answers: 1- B, 2 – C, 3 – C, 4 –A, 5 – A, 6 – D, 7 – B, 8 – C, 9 – D, 10 – B.

SELF-WORK
of the 4th year higher medical education applicants
on the topic of the practical lesson

1. To provide curation of patients with a detailed history taking and complaints.
2. To give interpretation to the obtained laboratory methods of research.
3. To give interpretation to the obtained instrumental research methods.
4. Set a preliminary diagnosis during the patient's curation.

Recommended literature

Basic:

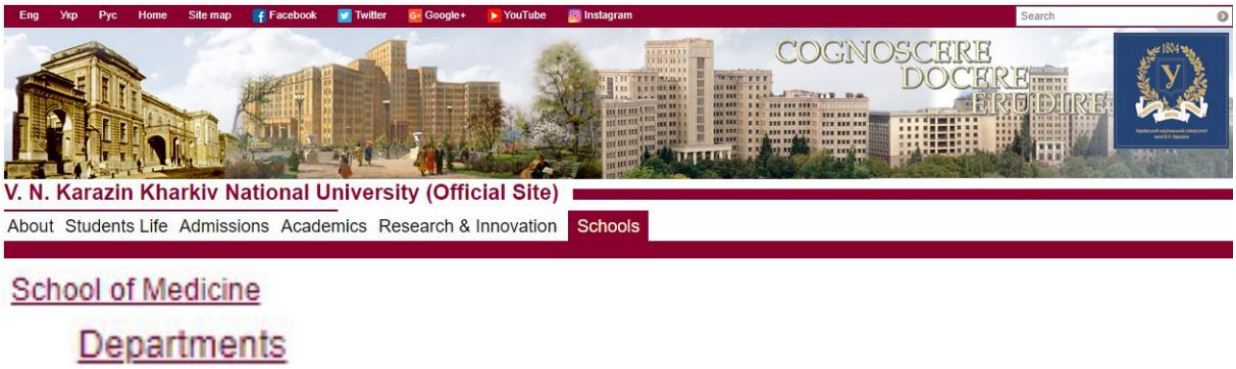
1. Arndt H.A. Manual of dermatologic therapeutics / H.A. Arndt, J.T.S. Hsu. – 7-th ed. –2007. – Lippincott Williams&Wilkins. – 363 p.
2. Gross G. Sexually transmitted infections and sexually transmitted diseases / G. Gross, S. Tyring. – Springler. – 2011. – 943 p.
3. Hemps W. Dermatopathology / W. Hemps, M. Hantschke. Springler. – 2008. – 300 p.
4. Holmes K. Sexually transmitted diseases / K. Holmes, P. Sparling, W. Stamm. –4 ed. – McGraw-Hill. – 2007. – 2192 p.
5. Hywel W. Evidence-based dermatology / Hywel W. ; William Hywel BMJ Publishing Group. – 2003. – 758 p.
6. Kerdel F.A. Dermatologic therapeutics: a pocket guide.-McGraw-Hill /F.A. Kerdel, P. Romanelly, J.T. Trent – 2005. – 419 p.
7. Handbook of dermatology: a practical manual / M.W. Mann, D.R. Berk, D.L. Popkin, S.J. Bayliss. –Bkackwell, 2009. – 300 p.
8. Wolff K. Fitzpatrick's Color atlas and synopsis of clinical dermatology / K. Wolff, R.A. Jonson. – Mc Graw-Hill, 2009. – 1114 p.

Additional:

1. Fry L. An atlas of psoriasis / L. Fry. – 2 ed. – Taylor&Francis. – 2005. – 99 p.
2. Harrison's Manual of medicine / D.L. Kasper, E. Braunwald, A.S. Fauci et al. – McGraw-Hill. – 2005. – 1087 p.
3. Lima H. Psoriasis: types, causes and medication. InTech.-2013.-189p.
4. Nossatenko V. Educational diagnostic guide into oncologic dermatology / V. Nossatenko, N. Gutzu, A. Nossatenko. – Kharkov, 2005. – 127 p.

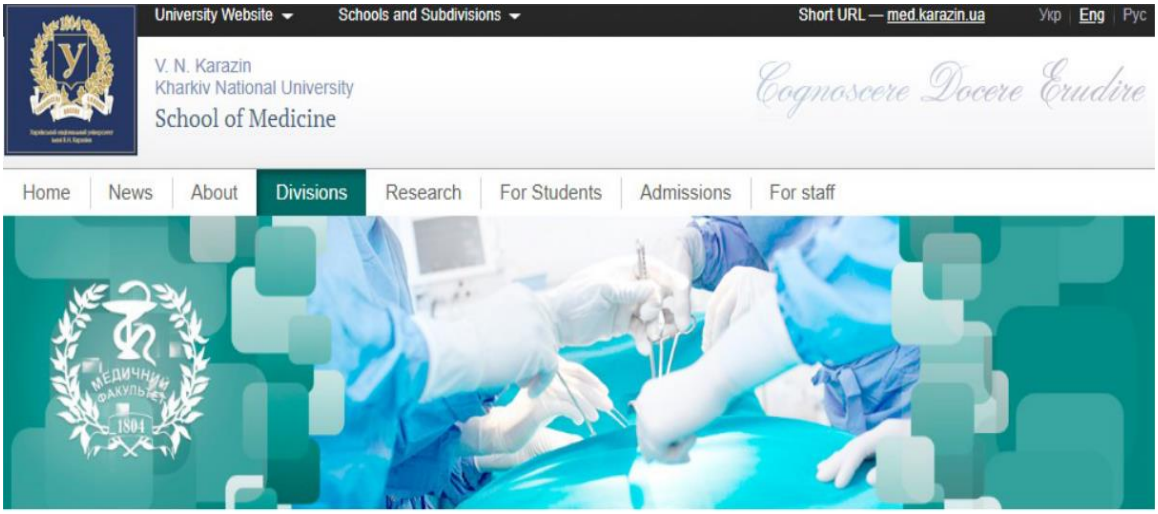
Annex 1

Official site: http://www.univer.kharkov.ua/en/departments



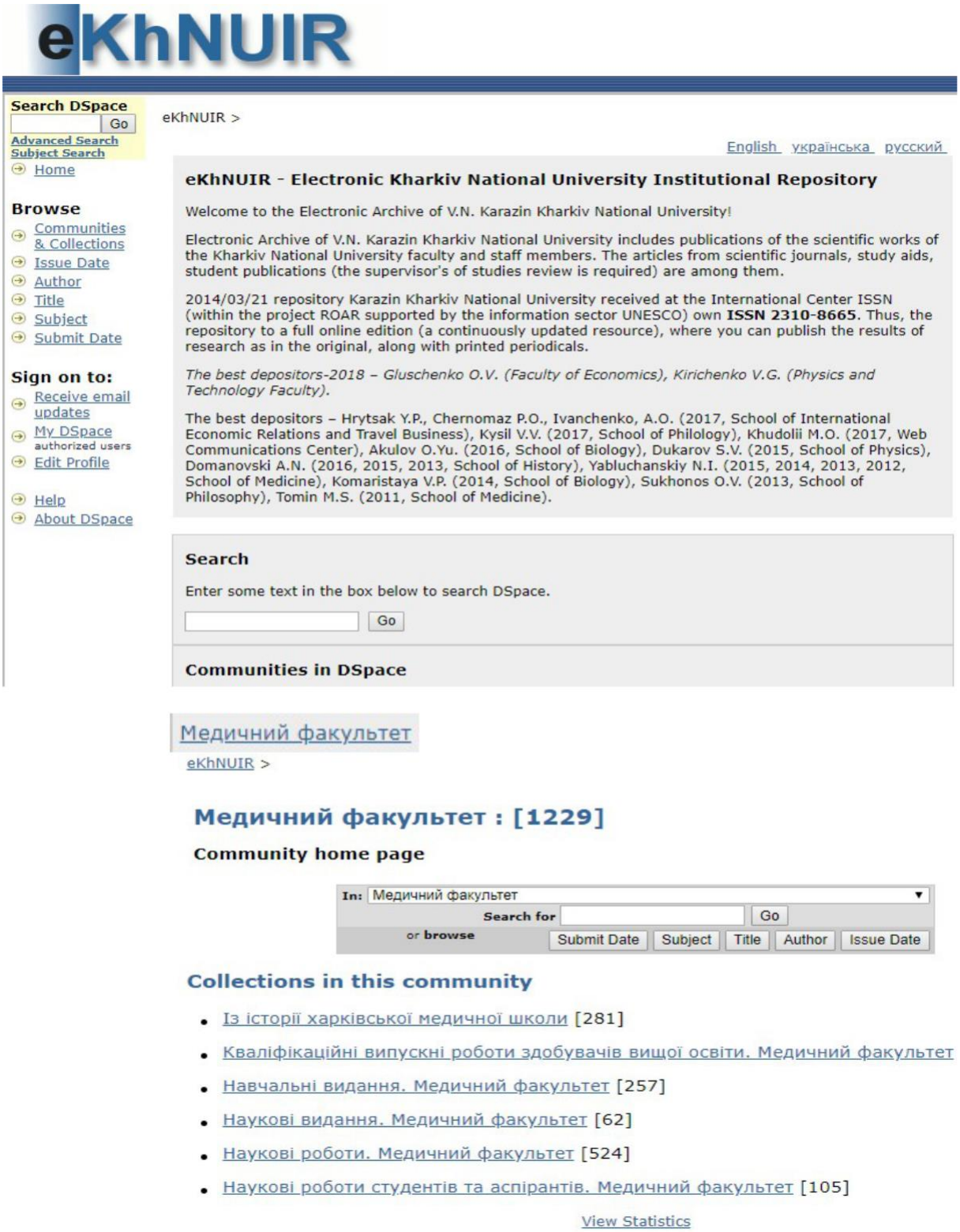
Department of infectious diseases and clinical immunology of V. N. Karazin University

http://medicine.karazin.ua/en/departments/kafedra-zagalnoi-ta-klinichnoi-imunologii-ta-alergologii



Electronic Kharkiv National University Institutional Repository

http://ekhnuir.univer.kharkov.ua/



Annex 3

Department of infectious diseases and clinical immunology of the V. N. Karazin Kharkiv national university.

News, announcements, useful information for students

How to get there? The clinical base of the department is located at: st. Tsilinogradskaya, 50. You can get to this place just from the city center, using the bus 245e (the bus takes passengers just near the metro "Derzhprom"), you need to get to the stop "Tsilinogradskaya", and then walk about 500 meters. You are in place! Or use the subway to the stop "Alexeyevskaya".

Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

Лядова Тетяна Іванівна
Волобуєва Ольга Вікторівна
Дорош Діана Миколаївна

ЛЕПРА

Методичні рекомендації
для самостійної підготовки до практичних занять
здобувачів вищої медичної освіти 4-го року навчання з дисципліни
«Дерматологія, венерологія»

(Англ. мовою)

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