

Designing a Histological Analyzer for Diagnosing Pathomorphological Changes in Tissues as an Example of Chlamydial Infection

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Abstract: - The article is devoted to the development of a device to study tissue destruction caused by damage to the histo-hematic barriers of the body, under the influence of chlamydial infection. Cell pathology refers to changes in its components and ultrastructures with causal relationships. Chlamydiae is a spectrum of diseases that, because of their polymorphism, cannot be united by a specific symptom complex, and sometimes affect all systems and organs. Due to the lack of organotropy and host specificity of the different representatives of chlamydiae, the clinic of chlamydiae is extremely diverse. The pathological process in chlamydial infections may localize in many organs, thus causing pathomorphologic changes in various body structures. The complex of adequate and modern methods of investigation makes it possible to evaluate the changes occurring in the macroorganism at the cellular and ultrastructural level. Emerging dystrophic, dyscirculatory, inflammatory processes in general, while not specific for chlamydia, are complemented by signs pathognomonic for this infection (presence of chlamydial antigens in cells in immunohistochemical method of study, detection of chlamydial structures in cells in electron microscopy). Currently, automation and robotization of research are penetrating all areas of medicine and veterinary medicine, including histological analysis. Currently, in the preparation of histological preparation, the technological process is automated in a fragmented way. The development of a histology robot will help to solve the problem of the shortage of highly qualified histology lab technicians and pathologists and reduce the burden on medical personnel in general. Processes of automation and modeling of technological flows and resources in the preparation of histological images and acceptance of the diagnosis in medicine and veterinary medicine is an urgent tasks. In order to identify pathological processes at the cellular level, as well as to reduce the error in the performance of histological manipulations, approaches to the design of a histological robot were developed. The model of the express analyzer structurally consists of two modules: a histological image preparation module and a pathology recognition module. Laboratory experiments were carried out to identify indicators of pathologies. Software for programmed OMRON controllers has been developed. Analysis of the simulation of the circuit operation showed positive results. The probability of pathology recognition was 0.8-0.9.

Key-Words: - chlamydia, PLC Omron, ladder diagram, pattern recognition, neural networks

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1 Introduction

Numerous studies, [1], [2], [3], [4], have been devoted to epidemiological and microbiological infections caused by Chlamydia. The biological properties of chlamydiae are closely related to obligate intracellular parasitism. Chlamydiae are prokaryotes, but their reproduction is closely dependent on the host cell. Their unique cycle of development determines their independent position in the world of microorganisms, [5], [6]. According to modern concepts, chlamydiae are small (0.25–1.5 μm in diameter) gram-negative microorganisms that occupy an intermediate position between bacteria and viruses. Originally, chlamydiae were classified as viruses because of their ability to multiply in the host cell cytoplasm and persist for a long time intracellularly. Currently, it is believed that chlamydiae are more similar to bacteria, being similar to them due to the presence of a bacterial envelope (containing muramic acid), DNA and RNA content, maintenance of morphological essence throughout the life cycle, division of vegetative forms, enzymatic activity, sensitivity to several antibiotics (tetracyclines, macrolides, quinolones), [7], and the presence of a common genus-specific antigen. All these facts made it possible to classify them as bacteria and assign them to the family Chlamydiaceae, [8]. Chlamydia refers to such diseases in which the permeability of the histo-hematic barriers is violated, leading to degenerative changes in the cellular structures of the body and, accordingly, to the development of the symptom complex characteristic of this disease, [9]. Chlamydia disrupts the barrier functions of the endothelium, which forms a semi-permeable barrier between the contents of blood vessels and the surrounding tissues. As a result of this process, some of the endotheliocytes slough off into the lumen of the vessels and are destroyed, which contributes to the generalization of infection throughout the body, [10], [11]. At the same time, we are talking about identifying general patterns of cell tissue damage. These may include reception of pathogenic information by the cell and response to damage, disturbances in cell membrane permeability and intracellular fluid circulation; cell metabolism disorders, cell necrosis, cellular dysplasia and metaplasia, hypertrophy and atrophy, pathology of cell movement, its nucleus and genetic apparatus.

Currently, there are semi-automatic devices that can automate some stages of histological specimen preparation, which prolongs the process of making a diagnosis of the disease and, accordingly, taking measures for treatment. The device under development will consist of two modules: a module

for the preparation of histological specimens, including the necessary procedures for preparing a slice, fixing the biomaterial, and processing with reagents, and a module for recognizing morpho-structural changes in tissues as an example of pathologies initiated by chlamydial infection.

2 Problem Formulation

Scientific works on automation of research in histology are mainly devoted to pattern recognition, [12], [13], [14], [15]. The development of automated instruments has been greatly developed for liquid media. The field of automation of studies for solid media for the study of morpho-structural changes in tissues has received much less attention. Some design fragments on research automation for the food industry have been developed, [16], [17]. Technological equipment for individual stages of histological slice preparation and processing, [18], [19], [20], is being developed. No histological analyzer that performs a full cycle of biomaterial preparation and diagnoses morpho-structural changes in tissues has been developed.

3 Materials and Methods

The following equipment was used for the histological study: technical and analytical scales, pH-meter, microtomes (sled, rotary, freezing), cryostat or cryokite, water bath, table for melting paraffin sections, set of automatic pipettes, thermostat, refrigerator, microscope, wiring machine.

Material for the study was fixed in 10% formalin. The next day we cut out the slices, and then we wired them in alcohol of increasing strength. For histological studies, the material was fixed in a 4% formaldehyde solution, and the tissues were embedded in paraffin.

Histological sections were stained with hematoxylin and eosin; hematoxylin stains the cell nucleus membrane and chromatin in blue-violet tones. Eosin stains the cytoplasm and some structures (fibers) in pink-red-orange tones.

Slices up to 5 microns thick were made from prepared blocks on a sledge microtome. The obtained preparations were studied using a Zeiss microscope (Axioskop40) at an eyepiece magnification of x10, with lenses x4, and x10.

The approaches of systems analysis theory, circuit and signal theory, and finite state machines were used in this work. The Ladder Diagram was constructed and simulated using CX-One Software.

4 Designing the Histological Image Preparation Module

4.1 Development of the Device Flowchart

The tasks currently performed by pathological anatomy place it in a special position among medical problems: on the one hand, it is a theory of histological analysis, which, revealing the material substrate of disease, serves clinical practice; on the other hand, it is clinical morphology for establishing a diagnosis. The study of the structural basis of disease occurs at different levels: systemic, tissue, cellular, and molecular. The study at the tissue and cellular level is carried out with the help of microscopic methods of examination. Making micro preparations of good quality is impossible without understanding the principles underlying the method of staining and professional mastery of the techniques of histological techniques. The last decades are marked by rapid growth in the number of new laboratory methods and the introduction of immunohistochemical methods. The use of digital technologies for image registration and archiving creates prerequisites for creating new standards of quality of images of micro samples. In pathology departments, clinical morphology is performed by pathologists, the quality of whose work directly depends on the skills of the middle level of the department - histology laboratory assistants.

Having analyzed the methods of histological study, [16], [21], [22], we made a flow chart of the device under design. Structurally, the device analyzer is planned to be divided into two modules: the histological image preparation module and the tissue pathology recognition module.

The histological image preparation module describes mechanical and chemical-biological processes, which are reflected in the following procedures: 1.1 – loading of biomaterial; 1.2 – excision (excision) of biomaterial; 1.3 – fixation of material in fixative liquid to stop biochemical processes; 1.4 – technological break; 1.5 – washing (fixative removal); 1.6 – dehydration in alcohol of ascending concentration; 1.7 – sealing (pouring into paraffin); 1.8 – preparation of histological sections; 1.9 – staining and conclusion of sections.

The –issue pathology diagnosis recognition module (2) includes a light and/or electron microscope. Pathology diagnosis recognition uses software based on the neural network construction

technique and the pathology indicator technique. The technological map of the designed device is shown in Figure 1.

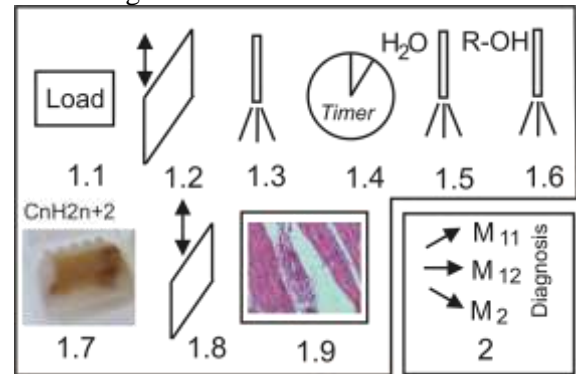


Fig. 1: Technological map of the device:

Histological image preparation module:

- 1.1 – loading of biomaterial, 1.2 – excision,
- 1.3 – material fixation, 1.4 – technological break;
- 1.5 – washing, 1.6 – dehydration, 1.7 – compaction (CnH₂n+2), 1.8 – microtome, 1.9 – staining and imaging slices;
- 2 – Pathology diagnosis recognition module (M₁₁ – indicator method;

M₁₂ – sequential automaton; M₂ – neural networks).

4.2 Designing the Histological Imaging Module

4.2.1 Development of a Fabric Sample Loading/Unloading Module

The tissue sample loading/unloading module is designed to load the biomaterial to be examined for chlamydial infections. The material should be taken as early as possible after death or, if possible, from a living subject to preserve the structure of the test cells as best as possible. During sampling, the slice should not be more than 5 mm thick to allow the fixative solution to penetrate the full depth of the tissue. The Equation (1) of the container operation is written in the form:

$$\begin{cases} Y_{1on} = (Load \vee Y_{1on}) \cdot \overline{Open} \cdot \overline{Close} \\ Y_{1off} = (UnLoad \vee Y_{1off}) \cdot \overline{Open} \cdot \overline{Close}, \\ Y_{1off} = set(Q1) \end{cases} \quad (1)$$

where *Load* – button to load a tissue sample; *Open*, *Close* – end sensors; *Q1* – flag to load biomaterial.

4.2.2 Development of the Pre-Cutting Fabric Module

The module is designed to cut the required amount of tissue sample from the incoming biomaterial. The cutting mechanism performs a reciprocating motion. Let's describe the module's work with a logical equation (2):

$$\begin{cases} Y2on = Q1 \cdot (Cut \vee Y2on) \cdot \overline{Top \cdot Bottom} \\ Y2off = (Cutoff \vee Y2off) \cdot \overline{Top \cdot Bottom}, \\ Y2of = set(Q2) \end{cases} \quad (2)$$

where *Cut* – cutting operation; *Top*, *Bottom* – upper and lower end sensors; *Q2* – operation completion flag.

4.2.3 Development of the Module Fixing Material

The module is intended for the fixation of material in fixing liquid to stop biochemical processes (in practice different fixers are used: simple ones containing one component (formalin, alcohol, acetone) and complex ones containing two or more components (Carnois liquid: absolute alcohol, chloroform, glacial acetic acid; Zenker liquid: potassium dioxide, sodium sulfate, bicarbonate, formalin). The operation of the module consists in feeding the reagent by means of a nozzle:

$$\begin{cases} Y3 = Q2 \cdot (LD3 \vee Y3) \cdot \overline{Timer3} \\ Y3 = set(Q3), \end{cases} \quad (3)$$

where *LD3* is the activation of the material fixation module; *Q3* – operation completion flag.

4.2.4 Development of the Technological Break Module

The technological break is necessary for the final fixation of the material and is 24 to 48 hours, [21], [22]. The criterion for sufficient fixation is the uniform compaction of the object and its identical appearance both from the surface and in the control section. In the pieces not fully fixed on the control sections, red or pink focal points can be seen. Some tissues take on a brown color after formalin fixation, which depends on the transition of oxyhemoglobin to methemoglobin. The technological break is described by equation (4):

$$\begin{cases} Y4 = \overline{Timer4} \\ Y4 = set(Q4). \end{cases} \quad (4)$$

4.2.5 Flushing Module

The flushing module is designed to remove the fixative or its precipitates. Depending on the used fixative, either flowing water or alcohol is used. The operation of the flushing module is described by equation (5)

$$\begin{cases} Y5 = Q4 \cdot (LD5 \vee Y5) \cdot \overline{Timer5} \\ Y5 = set(Q5). \end{cases} \quad (5)$$

4.2.6 Designing the Dewatering Module

The work of the module will consist of dehydration of the sample with alcohols of increasing strength. The module operation will be described by a system of equations (6)

$$\begin{cases} Y61 = Q5 \cdot (LD61 \vee Y61) \cdot \overline{Timer61} \\ Y61 = set(Q61), \\ Y62 = Q61 \cdot (LD62 \vee Y62) \cdot \overline{Timer62} \\ Y62 = set(Q62). \end{cases} \quad (6)$$

4.2.7 Development of a Sealing Module

Paraffin acts as a sealing medium. Paraffin is preheated to the melting temperature (56°C) and transitions to the liquid phase

$$Y7 = Q62 \cdot (LD7 \vee Y7) \cdot \overline{Timer7} \cdot RT, \quad (7)$$

where *RT* – is the temperature relay.

4.2.8 Development of a Module for Preparing Histological Sections

A Microtome or Laser can be used to obtain histological sections of 5 μm thickness. This procedure produces the final slice of the biomaterial for the examination of abnormalities.

$$\begin{cases} Y8on = (Cut \vee Y8on) \cdot \overline{Top \cdot Bottom} \\ Y8off = (Cutoff \vee Y8off) \cdot \overline{Top \cdot Bottom} \\ Y8of = set(Q8). \end{cases} \quad (8)$$

4.2.9 Staining and Section Conclusion Module

Histological sections were stained with hematoxylin and eosin; hematoxylin stains the cell nucleus membrane and chromatin in blue-violet tones. Eosin stains cytoplasm and some structures (fibers) in pink-red-orange tones. Figure 2, Figure 3, Figure 4, and Figure 5 showcase some of the cell abnormalities studied experimentally in chlamydia infection and cancer, [14].

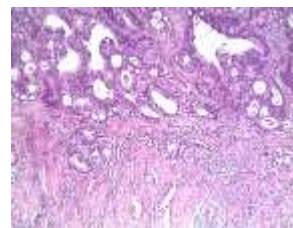


Fig. 2: Atypical cells in cancer. X 200

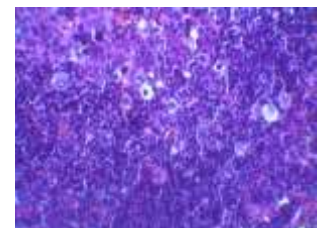


Fig. 3: Karyopycnosis. X 400



Fig. 4: Hydropic

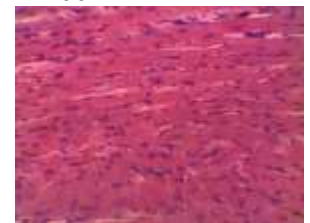


Fig. 5: Cardiomyocyte

dystrophy. X 400

dystrophy. X 400

4.3 Designing the Recognizer Module

The development of automated devices for rapid diagnosis of diseases in veterinary and medicine is currently given much attention. One of the directions in medical instrumentation is the development of techniques for automated disease diagnosis. In this regard, one of the research tasks was to automate the diagnosis (determination) of pathologies in histological analysis. The topology of the pathology of morphostructural changes in cells can have a tree-like structure, which makes it relevant to develop a methodology and hardware-software implementation of tools for determining the pathology of the disease. When designing the recognizer module, methods based on the construction of a neural network, [15], and the method of pathology indicators using a light microscope were previously investigated. Electron microscopy and sequential automaton synthesis technique can be used to study cell nucleus pathology in more depth, [23].

The method of pathology indicators consists of the establishment of patterns and the synthesis of logical equations. The development of this module can be found in [14]. The scheme of the method of pathology indicators and instrument panel of histology lab technicians are shown in Figure 6 and Figure 7.

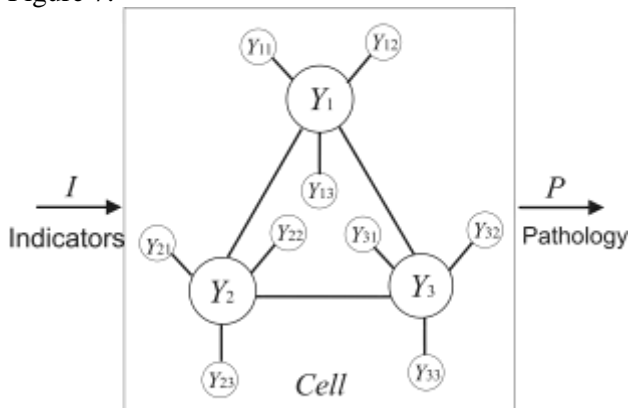


Fig. 6: Scheme of the pathology indicator method



Fig. 7: Histology lab technician's instrument panel with an example of recognition of pathology indicators

A fragment of the truth table implementing the methodology of pathology indicators is shown in Table 1.

Table 1. Fragment of the truth table

N	Pathology	
1.1	Cell wall pathology	Fenestration
1.2		Edema
1.3		Decay
1.4		Plasma impregnation
2.1	Pathology of the cytoplasm	Plosmorexis
2.2		Plasmolysis
2.3		Inclusion
3.1	Lysosome pathology	Swelling of lysosomes
3.2		Lysosome breakdown
4.1	Ribosome pathology	Ribosome swelling
4.2		Ribosome breakdown
5.1	Pathology of mitochondria	The collapse of the cristae
5.2		Homogenization of the internal structure
5.3		Decay of the organoid
6.1	Core pathology	Karyopyknosis
6.2		Karyorrhexis
6.3		Karyolysis

The implementation of the ladder diagram according to Table 1 is shown in Figure 8.



Fig. 8: Ladder diagram simulation implementing the pathology indicator method

For a more in-depth analysis of the cause-and-effect relationships of pathological processes, we can consider the sub-tree of pathologies presented in Figure 9, Figure 10 and Figure 11.

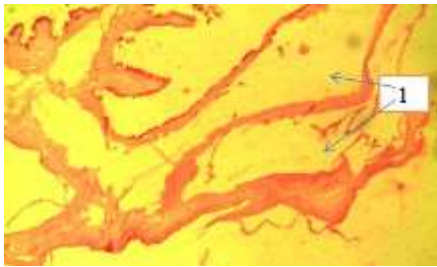


Fig. 9: Phase 1. Inflammatory process causing placental sheath edema (1). Van Gieson staining. x 100

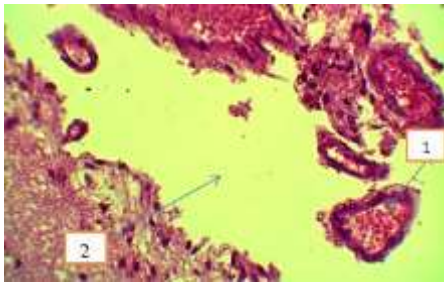


Fig. 10: Phase 2. The process of exudation causing full-thickness veins (1) of the soft dura mater of the fetal cortex and detachment of the soft dura mater (tissue separation) (2). Hematoxylin and eosin staining. x 400



Fig. 11: Phase 3. Alteration process causing necrobiosis of pear-shaped neurocytes in the cerebellum. Nissl staining. x 100

The method of synthesizing a sequential automaton is to identify the cause-and-effect patterns that form the tree (Figure 12).

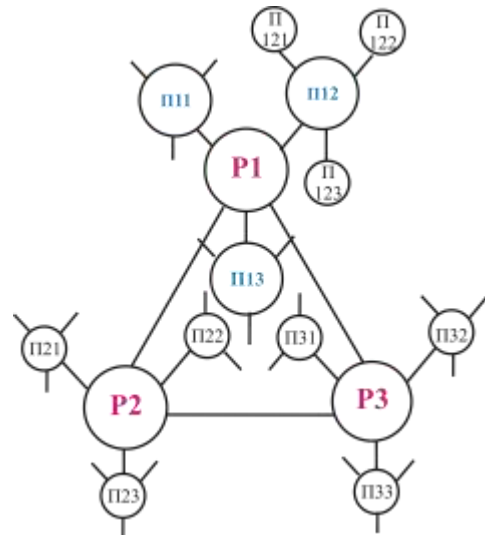


Fig. 12: Method for synthesizing a sequential automaton

The method of synthesis of the sequential automaton consists of the construction of the primary table of states and transitions and further synthesis of the logical equations (Figure 13), [24].

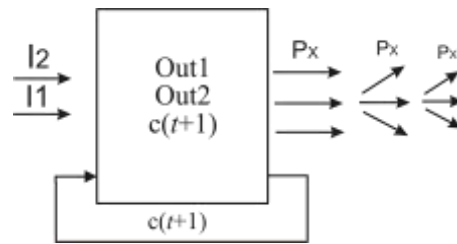


Fig. 13: Generalized structure of automatic pathology indicator-recognizer

The first branch of pathologies can be coded as follows (Table 2).

Table 2. Coding of the first branch level indicators

N	I ₂ I ₁	Process indicator name	Indicator
0	0 0	<i>Infectious specific</i>	P ₀
1	0 1	<i>Infectious nonspecific</i>	P ₁
2	1 0	<i>Non-Infectious</i>	P ₂
3	1 1	<i>Reserve</i>	

The second branch of the first branch P₁ will also be coded in the same way (Table 3).

Table 3. Coding of the indicators of the second sublevel of the P₁ branch

N	I ₂ I ₁	Process indicator name	Indicator
0	0 0	<i>Irreversible adhesion to endothelium</i>	n ₀₀
1	0 1	<i>Reversible adhesion</i>	n ₀₁
2	1 0	<i>Hypertrophy</i>	n ₀₂
3	1 1	<i>Exudation</i>	n ₀₃

The coding of the indicators of the third sublevel of the "Infectious Specific / Exudation" branch is shown in Table 4.

Table 4. Coding of the indicators of the third sublevel of the "Infectious Specific / Exudation" branch

N	I ₂ I ₁	Process indicator name	Indicator
0	0 0	<i>Lymphostasis</i>	<i>n030</i>
1	0 1	<i>Sclerosis</i>	<i>n031</i>
2	1 0	<i>Alteration</i>	<i>n032</i>
3	1 1	<i>Desquamation</i>	<i>n033</i>

The other branches of the pathology tree (Figure 12) can be coded using the same technique. Let us consider the problem of recognizing indicators for the pathology "Infective Specific / Exudation / Alteration", which corresponds to the branch coding - (P₀)/ n03/ n032, then this branch will represent a sequential set: 032.

Further, using the method of synthesis of a sequential automaton, [24], the logical equations for this branch of pathologies were synthesized:

$$\begin{cases} c(t+1) = u_2 \vee u_1 \vee c \\ Out1 = \overline{cu_1} \vee \overline{cu_2} \\ Out2 = \overline{cu_1}u_2 \end{cases}, \quad (9)$$

where *c* – trigger (Figure 13).

Similarly, we can obtain logical equations for the other branches of the pathology tree.

The neural network method is currently widely used for the development of pattern recognition software, [25], [26]. The application of the neural network method to recognize the diagnosis of pathologies using the example of the rat soft dura mater can be seen in [27] (Figure 14 and Figure 15).

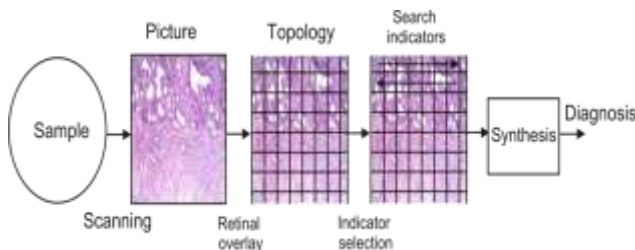


Fig. 14: Neural network method

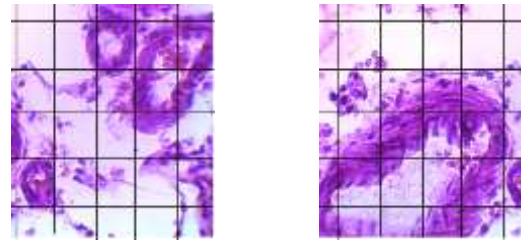
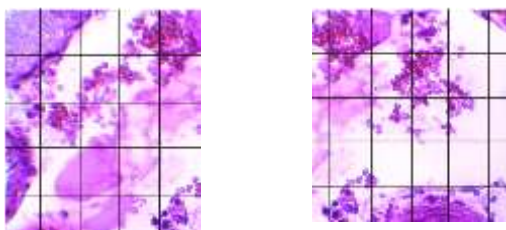


Fig. 15: Examples of training samples

The probability of pathology recognition was 0.8–0.9.

5 Conclusion

Currently, no fully automated histological analyzer exists. This article develops a design of an express analyzer covering all stages from the loading of the examined biomaterial to the issuance of a diagnosis on the recognition of pathologies caused by chlamydial infection. We obtained logical equations implemented in the combinational scheme of the device. Structurally, the express analyzer consists of two blocks: a histological image preparation block and a histological image analyzer block. The image preparation block contains 9 processes including necessary procedures of histological image formation. The recognizer block includes recognition programs based on neural networks and methods based on the definition of pathology indicators. Simulation modeling was performed to determine the indicators of the types of pathologies, which are represented in the form of a tree structure. The developed method of determining indicators of diseases is proposed to be used when designing an automated histological analyzer. The developed software-diagnostic complexes will allow the revealing of infectious pathologies at early stages that will promote the maintenance of a stable epidemiological situation. Designing and manufacturing the histological express analyzer will help solve the problem of the shortage of highly qualified personnel in the field of preparation and diagnosis of histological images.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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