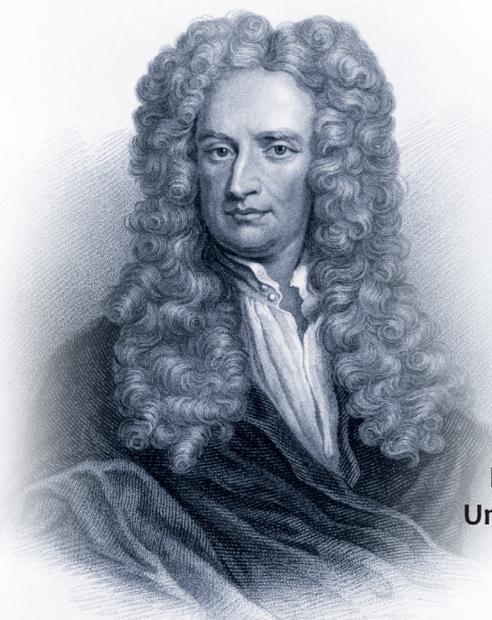




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## PROBLEMS OF REGULATION OF CYBER RISKS AND PRESERVATION OF STABILITY OF THE FINANCIAL SYSTEM

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**Abstract.** The necessity of supervision of cyber risks is explained by the fact that the consequences of their influence can be fatal for individual companies and banks, and can lead to systemic failures in the national economy.

The first line of protection from cyber risks is based on the internal control and audit system, as well as the activities of the risk management service of the commercial bank itself. The role of supervisory authorities is manifested in the development of a “cyber card” of key elements of the financial sector (payment systems, platforms, infrastructure and system institutions), which allows supervisors to gain a general understanding of cyber threats, on the basis of which risk mitigation programs are further developed. Legislatively adopted supervisory requirements should be complemented by rational and consistent monitoring practices, testing mechanisms, and effective reporting and exchange rules. A continuous process is needed to assess the nature and level of acceptable risk, improve the regulatory framework and practice of surveillance of cyber risks.

**Keywords:** cyber risk, financial stability, cybersecurity, cyberattacks, communication channels, business models, outsourcing, digital economy

The development of information technology changes the nature of financial transactions and creates new risks that can constitute a significant menace to the stability of the national economy. Currently, work is underway in all developed countries to counter the negative impact of cyberattacks. According to the forecast estimates, the main trends in the field of cybersecurity business are associated with disinformation; by combining cybercriminals into syndicates and using tools by them, that can automate the process of mass production and distribution of

malicious software, spam and malware distribution programs, etc.; and ecosystem vulnerability issues. Ecosystems are built on the basis of the interdependence of their participants, so the threats that appear in the chains turn friends, partners and customers of the company into a source of danger.

Cyber risks are a sort of danger to the stability of not only national but also global financial systems, as they cause cross-border side effects. Modern financial systems are heavily dependent on information and communication technologies, that is why cyber attacks can damage work and disrupt the provision of critical operations and services, threaten the loss of liquidity and can destabilize the integrity of the financial system.

Basel Committee on Banking Supervision in 2018 published a guide that proposed innovative approaches in identifying potential threats and reducing the negative effects of cyber risks. However, at the national level, the approach to identifying and regulating cyber risks is extremely uneven in individual countries, and the creation of an effective system for monitoring cyber risks requires coordination of the efforts of a large number of systemically important countries.

Currently, cybersecurity, cybersecurity risks and cyber resistance are sometimes used as synonyms in the analysis of financial system stability. The Financial Stability Council defines cybersecurity as “maintaining the confidentiality, integrity and accessibility of information or information systems through a cybernetic environment. In addition, it is necessary to take into account such properties of information as authenticity, accountability, reliability and reliability” [8]. In a broader aspect, “cyber” refers to the environment of an interconnected information structure of the interaction between people, processes, data and information systems. Thus, cybersecurity can be considered as observing information security for a certain period of time, as well as a certain concept of financial management, but with the acceptance of cyber threats.

According to expert estimates of foreign economists, the scale of the problems caused by cyberthreats costs to the companies almost \$ 600 billion annually. [2] In the USA, an average statistical financial company is subjected to cyber attacks 85 times a year, one third of these attacks is a real threat to business, as break through its defense system. The landscape of cyber threats is very dynamic and is changing rapidly; in addition, the nature and methods of threats are changing, because a significant number of cybercriminals now own sophisticated sets of hacker tools. The widespread use of outsourcing by the financial sector creates additional difficulties and increases the level of aggregate risk.

Four main cyber threat scenarios that could harm financial stability can be identified:

1. Attack on payment systems
2. Information leakage and violation of data protection systems
3. Rejection and infrastructure failures
4. Loss of trust and reputation risks.

The problem of safeguarding of cyber security is complicated by the fact that information about cyber attacks is deliberately underestimated, because participants have no incentive to publish data and inform supervisory authorities about such cases, there is no single global system for identifying cyberattacks and standards for their registration.

In 2018, the European Union adopted the Regulation “On Data Protection”, according to which it is necessary to report all incidents to supervisory authorities within 72 hours, for non-compliance with this requirement a fine of up to 20 million euros is set, however, in some supervisory systems, fines are not set because it is assumed that banks themselves are interested in maintaining their financial stability. [1].

Cyber risks in their characteristics have common features with property risks, liability risks, systemic and operational risks. Cyber risks can be aimed at the first goal or an analogue of the goal, they can be insignificant for individual participants, but can cause serious consequences for the system as a whole (shutdown scenario). However, cyber risk may not be related to deliberate attacks. This happens when new hardware or software is introduced, or as a result of natural disasters.

Malicious cyber attacks target three main aspects of information security: confidentiality, integrity, and accessibility. Confidentiality problems arise when customer information is disclosed to third parties, information leakage and violation of the data protection system. Integrity issues are associated with misuse of information systems, as well as fraud. Accessibility issues are related to outages. All three types of cyberattacks have different target effects: malfunctions prevent banks from working, which ultimately leads to loss of income; fraud leads to direct financial losses, the consequences of data system failures require more time to materialize, but also bring reputational consequences, and in some cases lead to higher legal costs. For banks and financial companies, the risk of loss of confidence can be catastrophic, considering their dependence on the degree of customer confidence and the risk of an outflow of customer funds.

For the financial institutions, it is important to assess cyber risks in the system of the probability of a threat and the possibility of attacks, to identify vulnerabilities in their security system.

Information security risk management is based on international standards ISO (2011), which define risk as a combination of consequences and probability of occurrence of events, where probability is a function of the level of threat and ease of using the existing system vulnerabilities.

The level of threats to the financial sector is quite high as a result of cybercrime, hacktivism, and the activities of proxy organizations and other participants of cyber attacks.

The total losses from cyber risks are determined empirically based on the frequency of occurrence of negative events and the distribution of losses depending on the type of risk. Accenture predicts that by 2021, the global cybersecurity services market will increase by 66% to \$ 202 billion. At the same time, the total global damage from cyber attacks can grow by 2021 by 39% to \$ 2.1 billion. [4]

The practice of regulation and supervision of cyber risks is aimed at determining the threat landscape, compiling a map and a cybersecurity network; creation of a legal regulatory system; conducting a supervisory assessment of potential threats; establishing information exchange mechanisms and official reporting standards; providing a system of recovery from possible negative consequences of these risks.

As far as cyber attacks do not know borders, the exchange of information and the development of common reporting standards are important elements in the fight against cyber threats. Data protection requirements should be tightened when creating information exchange platforms and open banking systems (Open API).

Supervisors should collect information on the sources of risk. Information about cyber threats may include technical indicators (such as addresses of malicious Internet protocols, domains, indicators of compromise, etc.); take into account the tactics, methods and procedures of the enemy; possible configurations of security tools; it is also useful to analyze possible threats and already occurred cyber incidents. The purpose of collecting and analyzing information is to help in building of a threat profile for each individual bank and a threat profile for the entire financial sector.

The Financial Stability Council published a “cyber glossary” in November 2018, containing a set of approximately 50 key terms related to cyber security and cyber resilience in the financial sector (Financial Stability Board, 2018). This can help to support an interstate understanding of the relevant terminology of cybersecurity and cyber resistance, laying the foundation for an effective exchange of information between countries.

An effective regulatory and supervisory framework should enable supervisors to significantly increase the resilience of the financial sector to cyber attacks. Regulations should focus more on “what needs to be achieved” and to a lesser extent on “how to achieve this.” For example, rules and regulations should be abstracted from specific technological details and should define the objectives of cybersecurity control, and not describe specific procedures or systems. Although all financial companies regularly face cyber security risks, smaller companies should focus on strengthening cyber hygiene, while the largest and most globally connected firms and banks, as well as settlement and clearing systems, must comply with more stringent regulatory standards.

Cybersecurity rules must be aligned with operational risk management and operational resilience requirements. Operational risk management standards lay the foundation for more specific oversight requirements for cybersecurity. Cybersecurity risks affect the bank management system, their development strategies, and pose an additional threat to banks' equity.

Supervisors should be aware of any significant residual cybersecurity risks of a controlled bank and the extent of their potential impact on the financial system as a whole. As far as risks can develop quickly enough, supervisors should establish requirements so that banks can withstand a critical level of risk, which significantly exceeds their usual acceptable level of risk, and also assess the degree of influence of negative processes on the economic capital of the bank.

Clear indicators should be set, the use of which will help to monitor the potential impact in case of loss of availability, integrity or confidentiality of critical bank information:

1. The level of Internet dependence of information and communication technologies of the bank (ICT);
2. The complexity of the overall landscape of ICT systems;
3. The outdated nature of systemically significant ICTs, etc.

When assessing cybersecurity risks, bank management should also have a clear idea of the nature of potential risks associated with the use of third-party services. In recent years, outsourcing of information and communication technologies has been developing as a result of the desire of banks to reduce costs and increase the efficiency of their activities. As a rule, outsourcing is included in the bank's traditional technological services, such as bank processing, and may also include systems for analyzing a loan portfolio, modeling interest rate risk, or complex bank risk management services.

The Financial Stability Council evaluates the effectiveness of the adopted cyber risk surveillance systems based on the existence of a developed cyber security strategy, rules and guidelines for risk management, effective cyber risk surveillance practices, as well as developed forecasts and regulatory development plans in some countries.

In Russia, the Doctrine of Information Security of the Russian Federation has been developed, which is represented as a system of principles for maintaining the country's information security. [9] The doctrine is aimed at national defense against cyber threats and covers issues of state and public security, economics, science, technology, education and strategic partnership. The main components of the doctrine are:

- A list of major threats to information security;
- Strategic goals and principles of safeguarding of information security;
- Organizational structure of information security.

In September 2019, the Council of Directors of Russian Bank approved the Guidelines for the development of information security in the credit and financial sector for the period 2019-2021. The document defines the key goals and objectives of the development of information security and cyber resistance.

The activities provided for by the Main Areas are designed to implement a set of individual tasks within the framework of federal projects of the national program “Digital Economy of the Russian Federation”. [9]

The main directions correspond to international experience and to the best practices in the field of safeguarding of information security of the financial sector and information security risk management (cyber risk): in developing the Main directions, the experience of the National Institute of Standards and Technology, NIST, Monetary and Credit was used Singapore (Monetary Authority of Singapore, MAS), European Banking Authority (EBA), International Organization of Securities Commissions, IOSCO), Committee on Payments and Market Infrastructures (CPMI), Basel Committee on Banking Supervision (BCBS). [10]

In 2015 The Center for Monitoring and Responding to Computer Attacks in the Credit and Financial Sphere (FinCERT) of the Bank of Russia was established in Russia to consolidate participants in the financial and information security markets in the fight against computer crime. The main objective of FinCERT is the organization of information exchange, which allows you to quickly respond to emerging threats in the field of information security.

Since July 2018, the FinCERT automated incident handling system (ASIC FinCERT) was put into operation. This system allows you to get more information about computer attacks and the spread of malicious software and, thus, to provide a more complete picture of the actions of computer crime in relation to organizations of the financial sector in Russia. In total, FinCERT received information on 687 attacks during the year, including 177 targeted attacks carried out on financial institutions in 2018.

It should be noted that the FinCERT ASOI system made it possible to significantly accelerate the detection and response to cyber attacks in the banking sector. Further development of the subsystem will further reduce the time from the actual implementation of the first attack to an automated response and preventive response to incidents.

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## CONFLICT OF LAWS REGULATION OF MONETARY OBLIGATIONS IN INTERNATIONAL COMMERCIAL CONTRACTS

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**Abstract.** The article reveals the features of the application of the conflict of law method of regulating cross-border legal relations in relation to monetary obligations in international contracts. It is shown that the treaty statute is crucial for the choice of the applicable law in cross-border contractual monetary obligations. The main aspects of the treaty statute are considered: the principle of autonomy of will and special conflict norms, oriented towards the regulation of specific contractual relations. According to the author, the conflict of reference, formulated on the basis of the principle of characteristic performance, directly in the framework of contractual monetary obligations can be interpreted as references to the law of the country of the creditor. At the same time, conflict bindings based on other principles (for example, taking into account the place of creation of the results stipulated by the contract) can be interpreted as references to the law of the debtor's country in a monetary obligation. In the same way, the effect of a treaty statute extends to relations on assignment of creditor rights in a cross-border monetary obligation. Describing the regulatory nature of conflict of laws rules in relation to cross-border monetary obligations, the author indicates that they are applied in combination with the norms of the rule of law to which they refer. In this regard, issues related to the application of foreign law, including peremptory norms of currency legislation, were also touched upon.

**Keywords:** monetary obligations, international commercial turnover, conflict of laws norms, contractual statute, splitting of the contractual statute, currency statute, law of the lender's country, norms of foreign law, assignment of lender's rights, currency regulation.

Monetary obligations in the international commercial turnover are a kind of civil law relations of an international character. Their subjects are the creditor and the debtor incorporated in the legal systems of various states. In such relations, the question of the applicable law inevitably arises. In the absence of applicable unified material standards, this issue is resolved on the basis of the conflict of law regulation method.

Cross-border contractual monetary obligations form part of numerous contractual structures in international trade law. They are associated with such elements of the contractual relationship as the rights and obligations of the parties, the performance of the contract, the consequences of non-performance or improper performance of the contract, termination of the contract. From the point of view of the conflict of laws regulation, these aspects are included in the scope of the treaty statute. Accordingly, the treaty statute is crucial for contractual monetary obligations of a cross-border nature when choosing the applicable law.

The initial principle of a treaty statute is autonomy of the will of the parties (*lex vaountatis*). We are talking about the recognition by the parties of an international commercial agreement of the right to choose the national legal system applicable to their relations. According to the Russian legislation (Article 1210 of the Civil Code of the Russian Federation), the parties to the agreement can choose by agreement between themselves the law that is subject to application to their rights and obligations under this agreement. The agreement of the parties on the choice of the law to be applied should be expressly stated or should definitely follow from the terms of the contract or the totality of the circumstances of the case.

Based on the principle of autonomy of will, the parties to the contract can choose the applicable law both for the contract as a whole and for its individual parts. In the first case, contractual monetary obligations (for example, to pay the price of the goods) will be governed by the law chosen by the parties for the contract as a whole. In the second case (when splitting the contractual statute), it will be the right specially selected by the parties in relation to the contractual monetary obligations, or the right determined on the basis of special conflict bindings.

The splitting of the treaty statute may arise in complex cross-border transactions, including those containing monetary obligations. In particular, these may be transactions on the implementation of large-scale international projects with a plurality of parties and types of private-law relations, as well as with specifically emerging conflicts of law.

According to paragraph 10 of Art. 1211 of the Civil Code of the Russian Federation on agreements containing elements of various agreements, the applicable law for such elements shall be determined separately if this follows from the law, the conditions or the substance of the agreement or the totality of the circumstances of the case. These elements include, for example, financing (loan, credit) relations in an international factoring agreement, independent contractual relations of subjects of cross-border relations for syndicated lending or international trade financing. As the au-

thors of the report on the Rome Convention on the Law Applicable to Contractual Obligations noted, "if the part of the contract to which a separate law is elected is not severable or the choice is not logically compatible with the law governing the rest of the contract, then this choice of law is not recognized by the courts "(1).

A contractual monetary obligation is, as a rule, an attribute of "simple" bilateral paid contractual structures in international commercial turnover. Such a monetary obligation is an insolvent obligation of the debtor and is inextricably linked with the contractual obligations of the creditor. If there is no agreement of the parties on the law to be applied, the international commercial contract applies, according to Clause 1, Art.1211 of the Civil Code of the Russian Federation, the law of the country where, at the time of the conclusion of the contract, the place of residence or the principal place of business of the party carrying out the work, crucial for the content of the contract. As V. Kanashevsky notes, in Russia the approach laid down in Art. 4 of the 1980 Rome Convention on the law applicable to contractual obligations: "there is a general presumption based on the concept of characteristic performance, together with special presumptions for each individual type of contract" (2).

In most types of international commercial agreements, the fulfillment of a monetary obligation to pay a price is not classified as a characteristic performance. In particular, in the contract of international sale, the seller is recognized as the party of characteristic performance and the law of the country where the seller's main place of business is located at the time of conclusion of the contract is applied to the contract. Similarly, the applicable law is defined in international leases (law of the country of the lessor), transportation (law of the country of the carrier), transport forwarding (law of the country of the forwarder) and other agreements: factoring, storage, instructions, commissions, agency services, orders. In all of the above agreements, the performance of obligations is considered to be characteristic performance by the party that receives the payment and is a creditor in a monetary obligation. That is, in such a contractual monetary obligation, the collateral binding *de facto* is the law of the country of the creditor.

The principle of characteristic performance is not always the basis for choosing the applicable law. For example, in cross-border construction contracts and for design and survey work, the law of the country is applied, where the results stipulated by the contract are mainly created. The international commercial concession (franchising) agreement applies the law of the country in the territory of which the user is allowed to use the complex of exclusive rights belonging to the copyright holder, and the cross-border

license agreement applies the law of the country in whose territory the licensee is allowed to use the result of intellectual activity. In monetary obligations under the aforementioned agreements, the law of the country of the debtor is often the de facto applicable law.

A monetary obligation in international commercial circulation is designated and executed in a currency that is foreign to one or both parties to the obligation. The Russian doctrine of private international law did not perceive the independent existence of the so-called currency pegging or pegging to the law of the currency of debt (*lex monetae*), according to which the reference in the contract when determining the amount of debt to the currency of any state means the subordination of the monetary obligation to the law of the country currencies. Lunts L.A. pointed out: "The calculation of the amount of a liability in a foreign currency in itself from the point of view of law is not considered as a foreign element in the composition of this legal relationship." This negates the prerequisite for a "currency statute" (3). According to V.A. Kanashevsky, "an indication of a foreign currency (for example, US dollars) to determine the amount of debt does not mean a reference to the corresponding foreign law (in our example, to US law)" (4). At the same time, the application of the right of a currency country is possible to determine certain characteristics of a debt currency or to justify a legal tender in foreign currency.

The effect of the treaty statute extends to relations by assignment of creditor claim rights in a cross-border monetary obligation. Paragraph 2 of Art. 1216 of the Civil Code of the Russian Federation establishes that the admissibility of the assignment of the claim, the relationship between the new creditor and the debtor, the issue of the proper fulfillment of the obligation by the debtor are determined by the law to be applied to the claim that is the subject of the assignment. Since the creditor's right of claim is part of the content of the monetary obligation, the applicable law will be the law applicable to the monetary obligation. Such a right, depending on the specific type of cross-border agreement (as shown above), may be the law of the country of the creditor or the law of the country of the debtor. For the cross-border assignment under consideration, this will be the right of the original creditor (assignor) or the right of the debtor.

According to the prevailing point of view of the doctrine, conflict of laws norms as a supporting category of private international law act in combination with substantive norms in the process of regulation of cross-border private law relations. As L. Lunts noted, "the conflict of laws rule, together with the material and legal rule to which it refers, forms the present rule of conduct for participants in civil turnover" (5). Anufrieva L.P., considering

theoretical positions regarding the functions of conflict of laws norms, comes to the conclusion about "legal mediation of the international interaction of legal systems as a general function and purpose of conflict of laws norms" (6).

The result of conflict of law regulation may be the appearance in the mechanism of legal regulation of foreign law.

This circumstance was initially interpreted in the legal doctrine as a violation of the principle of absolute sovereignty of the state. However, in private international law, the potential use of foreign law and the real appeal to it in the process of regulating cross-border private law relations is a necessary condition for resolving a conflict situation arising in such relations. Therefore, "the legislator makes valid foreign law within the limits of the operation of its own system of law" (7), but only on the basis and in conjunction with a specific conflict of law norm.

Solving the issue of choosing a competent law and order for the purpose of regulating cross-border relations in an international commercial agreement does not remove the need to take into account peremptory norms of currency legislation. Courts seek to subordinate currency restrictions to the "law of the court" (*lex fori*), regardless of the conflict of reference used to resolve other issues of the contractual monetary obligation. The norms of currency legislation are public in nature and their application does not depend on the will of the relevant subjects of legal relations. So, the parties cannot subordinate the regulation of foreign exchange transactions to foreign law.

The development of international trade has led states to change their tough stance with regard to foreign public law. An example is currency law, the extraterritorial nature of the rules of which was made possible largely thanks to Art. VIII of the Charter of the International Monetary Fund (IMF), according to which foreign exchange contracts contrary to the currency control of a member state are deprived of judicial protection in the territory of any of the IMF member states. Art. VIII of the IMF Charter focuses on the extraterritorial application of foreign currency law, but not the "internal" currency law of a given state. In this connection, we can mention article 13 of the Swiss Law on Private International Law 1987, according to which the application of a provision of foreign law cannot be excluded only because this provision relates to public law.

Thus, the conflict of law refers to peremptory norms of civil law and private international law. The requirements that are imposed on an international commercial agreement by peremptory norms of currency, tax, and customs law are of a fundamentally different nature. At the same time, they also have a significant impact on the implementation of contractual terms, including cross-border monetary obligations.

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## THE CONCEPT AND CONTENT OF CITIZENS' RIGHT TO ACCESS TO JUSTICE IN RUSSIA'S CRIMINAL PROCEEDINGS

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**Abstract.** In the paper, as a result of thorough scientific research, the author formulates the concept of “access to justice”, guided by the fact that the judicial protection of rights and freedoms is a universal, and therefore the most effective mechanism for legal protection of an individual from all developed in world practice.

The conclusions of the study can be used in further scientific research on the issues under consideration.

**Keywords:** court, legal proceedings, justice, criminal procedure, protection of rights, judicial control, participants of the process, judicial protection.

The scientific development of the concept of “access to justice”, the definition of forms and methods for realizing the corresponding right of citizens in the criminal process are not only theoretical, but also practical. In the rule of law, the court is the main guarantor of the rights and freedoms of the individual, including in the field of criminal proceedings, which fully corresponds to its purpose, as enshrined in art. 6 Code of Criminal Procedure of the Russian Federation.

In the specialized literature, several approaches have been developed to define the concept of access to justice, which are mainly confined either to an entity who is in need of actual participation in the trial, or to a problem of a purely material nature associated with the high cost of justice for the poor or observing the terms of the trial, which unjustifiably narrows the content of the investigated legal phenomenon [1, p.12].

Following the semantic interpretation of the studied concept, we propose, when determining the content of the right to access to justice, to start from the original category of “justice”. An analysis of the legislative and doctrinal approaches to the essence of the named legal category suggests that in the modern science of the criminal process

there are three basic interpretations. The first, which can be defined as traditional, interprets justice as the activity of a court in the consideration and resolution of civil and criminal cases [2, p. 57]. The second is legal, stemming from the meaning of the provisions of the Criminal Code of the Russian Federation, where a broader interpretation to the justice is given. Crimes against justice on the patrimonial object relate to crimes against the interests of the state, that is, political. As an object of legal regulation, they cover both the activities of the court and the activities of the bodies for the investigation of crimes and the execution of sentences. In the specialized literature, such an approach is called subject-active, since the legislator uses a similar methodological principle in constructing the corresponding corpus delicti [3, p. 63]. The third interpretation is doctrinal. It seems to us that from the point of view of the science of the criminal process, the definition given by M.S. Strogovich, who understood justice as a state activity carried out by a court, consisting in the fact that the court protects the rights and legitimate interests of citizens, institutions, organizations, officials from any encroachments of the state through proceedings and the resolution of criminal and civil cases in the statutory legal (procedural) forms persons in the behavior of citizens, is staying put [4, p.14]. Subsequently, various authors included additional characteristics in the concept of "justice". All three of these interpretations have their own rational kernel, because they all reflect one side or another of justice as a systemic social phenomenon. The traditional and legal interpretations point to the active side and the subjects of justice, the doctrinal approach focuses on the functions of the judiciary in criminal proceedings, i.e. it determines justice precisely as a type of state activity, which is of the greatest interest.

The doctrinal interpretation of the concept of "justice" allows us to distinguish the following essential features: 1) the implementation of the relevant activities by the court, which in accordance with the Constitution of the Russian Federation is an independent, self-sufficient, main and sole subject of justice, authorized to make final decisions on constitutional, civil, administrative cases and sentences in criminal matters; 2) the regulatory nature of the activities for the administration of justice, as it is regulated by law and is carried out in specific legal, namely procedural forms; 3) the main goal of this type of state activity is the protection of the rights and legitimate interests of citizens and legal entities from unlawful encroachments, the restoration of violated rights.

Subject to the interconnectedness of the concepts of “justice” and “access to justice”, we believe that the latter should be equated with the guaranteed by the state ability of any interested person to freely resort to the procedure of judicial protection of their rights and legitimate interests in both the pre-trial and judicial stages of criminal proceedings. The given interpretation of the studied concept allows including judicial protection in the legal field of the principle of access to justice, which is a universal, and therefore the most effective way to protect violated personal rights and freedoms.

The content of the concept of “access to justice” in the proposed interpretation includes several elements.

Firstly, a *party* with the right to access to justice. As already noted, the fundamental principle of the judiciary is the constitutional consolidation of the very possibility of unhindered appeal to the court of each party of law if its rights are violated or allegedly violated (part 1 of article 46 of the Constitution of the Russian Federation). Consequently, judicial protection extends to an unlimited circle of people, the use of the term “everyone” emphasizes the non-personalization of judicial protection, the absence of any formalized restrictions on the use of this method of protecting subjective law and legal interest.

With regard to criminal proceedings, the party element may be disclosed through the interpretation of Art. 6 of the Code of Criminal Procedure of the Russian Federation, which determines that its purpose is to protect the rights and legitimate interests of persons and organizations who have suffered from crimes - on the one hand, to protect an individual from unlawful and unreasonable accusation, conviction, restriction of her rights and freedoms - on the other. The specified provision of the criminal procedure law is specified in paragraph 1 of the resolution of the Plenum of the Supreme Court of the Russian Federation dated 05.03.2004 No. 1 “On the application by the courts of the norms of the Code of Criminal Procedure of the Russian Federation” [5], which states that when considering criminal cases and making decisions, courts must comply with the established Code of Criminal Procedure of the Russian Federation, the principles of criminal proceedings, which are intended to protect the rights and legitimate interests of victims, as well as protect the individual from unlawful and unreasonable accusations, convictions, restrictions on her rights and freedoms.

An analysis of the procedural status of individual participants in the criminal process suggests that the right to appeal to the court, and, accordingly, the right to access to justice, is not only a victim, suspect, accused,

defendant, convicted, acquitted, but also a private prosecutor (Part 2 of Art. 43 of the Code of Criminal Procedure), a civil plaintiff (part 4 of article 44 of the Code of Criminal Procedure) and his representative (part 3 of article 45 of the Code of Criminal Procedure), a civil defendant (part 2 of article 54 of the Code of Criminal Procedure) and his representative (part 2 Article 55 of the Code of Criminal Procedure of the Russian Federation), witness (part 4 of article 56 of the Code of Criminal Procedure of the Russian Federation), as well as other persons whose rights and legitimate interests were violated in the course of criminal proceedings (for example, the applicant in the case of refusal to accept reports of crime, the person in the room which is conducted the search or seizure, etc.).

Thus, the list of persons with the right of access to justice is not limited only to the participants in the criminal process named in section II of the Code of Criminal Procedure of the Russian Federation, since this can be any interested person who needs judicial protection of the violated right. In this regard, it should be noted that the principle of unhindered access to the court is substantially supplemented by the principle of equality of citizens before the law and the court. Courts do not give preference to any bodies, persons participating in the process, parties on the grounds of their state, social, gender, racial, national, linguistic or political affiliation or depending on their origin, property or official position, as well as on other grounds (part 2 of article 8, part 4 of article 13, part 1 of article 19 of the Constitution of the Russian Federation, part 4 of article 15 of the Code of Criminal Procedure of the Russian Federation).

Secondly, the *subject* of free access to justice, i.e. specific actions (in-action) and decisions of the inquiry officer, investigator, prosecutor and court, which may be appealed in court.

Depending on the stage of criminal proceedings, various actions and decisions may be the subject to judicial appeal.

So, in particular, at the pre-trial stages of the criminal process, the subject of access to justice corresponds with the subject of judicial control. An analysis of the specialized literature made it possible to identify three main approaches to this problem.

The first approach may be called “radical”, because its supporters believe that the right to judicial appeal of actions and decisions of bodies conducting criminal prosecution cannot be limited. The basis of the given position is the broad interpretation of Art. 46 of the Constitution of the Russian Federation, which states that all actions and decisions of public authorities can be appealed to the court [6]. We believe that the given position, despite the apparent attractiveness, does not fully correlate with the purpose

of criminal proceedings and unreasonably expands the scope of judicial review, which will ultimately lead to a decrease in the effectiveness of all pre-trial proceedings. The legislative consolidation of the possibility of judicial appeal of any decision of the preliminary investigation bodies, in our opinion, will lead to the fact that the courts will be drawn into the process of endless inspections, and not only issues related to the appeal of violation or restriction of constitutional rights and freedoms, but also procedural issues whose decision falls within the competence of departmental rather than judicial control.

The second approach is diametrically opposed. Its supporters believe that, in order to avoid unjustified expansion of the limits of judicial review, it is necessary to legislatively fix an exhaustive list of actions and decisions of the prosecution, which can be appealed by interested parties to the court. This "will exclude the possibility of an artificial extension of the investigation period by filing unjustified complaints about any action and decision of an official who is obliged to ensure not only a quick, but also a full investigation of the crime" [7, p.25]. We believe that the supporters of this position do not fully take into account the fact that such legislative regulation of the subject of judicial review may entail a serious restriction of the right to judicial protection, which would contradict the provisions of Art. 18 of the Constitution of the Russian Federation.

The most balanced is the position of those processors who believe that it is objectively necessary to extend the judicial control procedure in pre-trial proceedings only to those actions and decisions that limit the constitutional rights of the individual. Numerous tactical decisions, violations of certain procedural rules, failure to provide procedural rights to participants, if they do not violate constitutional rights and freedoms, do not require immediate court intervention, however, when considering a criminal case, they may become the basis for the evidence collected by the prosecution to be unacceptable [8, p. 42]. This is the position taken by the Supreme Court of the Russian Federation, which indicated in its decision No. 1 dated February 10, 2009 that decisions and actions (inaction) of officials taken at the pre-trial stages of criminal proceedings are subject to judicial appeal if they are capable of causing damage to constitutional rights and freedoms of participants in criminal proceedings or other persons whose rights and legitimate interests are violated or may impede citizens' access to justice (paragraph 2) [9].

At the judicial stages of criminal proceedings, the subject of the appeal is the verdicts, rulings and decisions of the court, issued in the course of consideration and resolution of the criminal case on the merits, as well as its review in higher judicial instances.

In accordance with the International Covenant on Civil and Political Rights of 1966 [10], which obliges the state to provide a person whose rights and freedoms are violated, an effective remedy, even if this violation was committed by persons acting in an official capacity. In this regard, as indicated by the Constitutional Court of the Russian Federation in a number of its decisions [11], that the rights violated by the court cannot be excluded from the scope of judicial protection. The legal position of the Constitutional Court of the Russian Federation, consisting in the statement that the right to judicial protection presupposes the right to protect the rights and legitimate interests not only from the arbitrariness of the legislative and executive authorities, but also from erroneous court decisions, is of fundamental importance.

And, finally, the third element that makes up the content of the principle of free access to justice, in our wording, is the *guarantee* of the implementation of the relevant right by interested parties. The concept of “guarantee” covers the entire set of objective and subjective factors that are aimed at realizing the rights and freedoms of citizens, at eliminating possible causes and obstacles to their incomplete or inappropriate implementation, and protecting the right from violations. Therefore, under the guarantees should be understood the conditions and means that ensure the actual implementation and comprehensive protection of the rights and freedoms of citizens [12, p.683]. In legal science, guarantees of the rights and freedoms of citizens are usually divided into general and legal [13]. The former include economic, organizational and other guarantees, the latter include means enshrined in the law that directly provide for the legitimate implementation, protection and protection of rights.

With regard to the constitutional right to access to justice, a set of guarantees can be presented as follows.

The economic guarantee of access to justice is free of charge. It seems that in practice this guarantee is not fully implemented, since the lawsuit involves a significant amount of expenses from the person who applied for the protection of the violated right.

Firstly, effective protection of rights and freedoms is impossible without the provision of professional legal assistance, and at present lawyer services are quite expensive.

Secondly, the need to pay the state duty in civil matters makes it difficult to go to court.

Thirdly, there is the issue of accessibility of transport services, especially when considering cases in cassation and supervisory instances.

Fourthly, the issue of the burden of paying legal costs is relevant. The listed problems of economic guaranteeing the accessibility of justice are relevant not only in the Russian Federation. In this regard, the Committee of Ministers of the member states of the Council of Europe back in 1981 adopted recommendations of a general nature, "On ways to facilitate access to justice," aimed at minimizing the state fee and paying for the services of lawyers, which also outlines general approaches to sharing the burden of legal costs, acceptance of this burden by the state, etc. [14].

Organizational guarantees are norms that establish the scope and content of management activities carried out by state authorities and local authorities, organizations and officials in order to exercise the constitutional right to access to justice. So, for example, according to Art. 3 of Federal Law of May 27, 2003 No. 58-FL "On the Civil Service System of the Russian Federation" [15], the administrative apparatus is obliged in its activities to proceed from the priority of human and civil rights and freedoms, their direct action, the obligation to recognize them, observe and protection. The most important condition for ensuring the rights of citizens is the effective work of law enforcement agencies, in particular, internal affairs bodies. In accordance with the Federal Law "On the Police" [16], one of the priority tasks of the internal affairs bodies is to protect the rights and freedoms of man and citizen.

A special place in the system of organizational guarantees is taken by guarantees of the effective functioning of the judicial system, i.e. decent material and technical support of the courts, their living conditions, the complete set of the judiciary, the general organization of judicial activity, etc.

Legal guarantees of the right of citizens to access to justice are expressed, first of all, in the norms of federal legislation, which disclose and specify this right and, in particular, establish the procedure for its implementation. So, in particular, the criminal procedure legislation contains a number of guarantees for citizens to exercise their right to access to justice, which, for example, may include: [17]

- 1) an institution for appealing against the actions and decisions of officials conducting criminal proceedings (Chapter 16 of the Code of Criminal Procedure of the Russian Federation), providing not only for the relevant right of a participant in criminal proceedings and other interested parties to file a complaint, but also the obligation of the inquiry officer, investigator, prosecutor and court to clarify the procedure appeal and ensure the possibility of its implementation;

2) the institution of jurisdiction of criminal cases (Articles 31-36 of the Code of Criminal Procedure of the Russian Federation), which provides not only the procedural component of the consideration of a criminal case by an ordinary court, but also a means of realizing the competence component of the constitutional right to access to justice, which implies: the absence of territories for which the competence of the court would extend; convenient location of vessels; the existence of a sufficient number of courts and judges in the state [18, p.246];

3) the institute of procedural terms, by means of which the criminal procedure law regulates rather strict terms for the production of individual procedural actions, the violation of which is the basis for appealing the corresponding action or decision of an official.

In addition, the procedural component of legal guarantees of access to justice is determined by:

- the existence of a criminal procedure;
- the actual participation of a person in a trial to resolve a criminal law dispute;
- ease of understanding of the principles of the structure and functioning of judicial institutions;
- the ability to use qualified legal assistance;
- the presence of a wide range of procedural rights among the participants in the process and a counter obligation of the officials conducting the criminal proceedings to ensure the possibility of their implementation;
- the quality and fairness of the proceedings.

Thus, the analysis of the content of the category “access to justice” in criminal proceedings allows us to understand it as *provided and guaranteed by the state, mandatory for the inquiry officer, investigator, prosecutor and court, the possibility of a participant in criminal proceedings and another person whose rights and legitimate interests are violated, to freely resort to the procedure of their judicial protection.*

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## THE CONTENT OF THE INTELLECTUAL RIGHTS OF THE AUTHOR IN ROMAN-GERMAN AND ANGLO-SAXON LAW

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**Abstract.** The content of intellectual rights in Anglo-Saxon law is examined in accordance with the British legal presumption of authorship and the Romano-German legal system using the example of European and Russian traditions. Initial, primary, derivative rights are allocated. The semantics of authorship categories are highlighted. The importance of the author's natural right in Roman-German law and the right to use the copyright holder in Anglo-Saxon law are emphasized. The mutual influence of legal systems on the legal status of the author of the result of intellectual activity is noted.

**Keywords:** intellectual law, Anglo-Saxon law, Romano-German law, author's right, graphic design

Problems of authorship and its role in law occupy an important place in Russian and foreign legal literature. Discussions reveal authorship ambiguously. L. Bentley, B. Sherman point to foreign experience, defining it more broadly, which allows the authors to recognize those whose contribution to the creation of the work does not meet its definition as creative activity [14. - P. 197]. The personality of the author occupies an exceptional position and is a basic element of most legal constructions and doctrines. The personal status of the author is taken into account when deciding on the admission of a work to protection. In some cases, the labor spent on creating a work of graphic design is a measure of its originality. The duration of copyright for most works is calculated based on the life expectancy of the author. Moral rights in many countries are recognized solely by the author. It is important to note the methods of determining authorship and turn to the legal consequence - to the design of the first copyright holder [14. - P. 180]. This is also provided for in the case of the creation of a work by the work of several persons [2. - P. 9 (1)]. The English word *author* does not have in its exact semantics mean-

ing of “creator of a work of fine art”: the last can only be called an artist (*Artist* English - “painter”). The situation is different with works created using a computer or as a result of organizational activities. L. Bentley and B. Sherman are not inclined to think that typography and computer work can have an author. The creator acts here as a legal and technical structure, a fiction, a pole of securing various rights. Mistakenly, in our opinion, they consider, by definition the author cannot have a work created by a computer, he recognizes as “a person who provided the necessary conditions for creating a work” [2. - P. 9 (4)]. In British law, the author of works embodying the results of organizational activity is the person without whom such a work would never have been created - an *impressionario*, producer.

The countries of the Romano-German legal family always see in the author of any work a person who has made a creative contribution to its creation [11. - P. 320-389]. However, as a result of efforts to harmonize European legislation, this contrast of authorship concepts is gradually softening. According to L. Bentley, B. Sherman, this is largely due to the fact that the harmonization of European copyright is accompanied by the extension of continental authorship paradigms to Anglo-Saxon law. Some objects of British copyright have acquired the qualities of a hybrid substance - between the objects of “authorship” proper and the results of organizational activity. In our opinion, there is a process of mutual influence of the Anglo-Saxon and Romano-German legal systems and practice in the field of intellectual property law, expressed in terms of the content of certain norms of these civil law institutions, the emergence of new intellectual property objects related to graphic design activities [5. - P.63], the formation in this area of a significant amount of actual relations, for example, in remote access and (or) on the Internet and so on [12]. Russian publishers who publish graphic design works separately or as part of a complex (compound) object (work) claim their copyright [13], [5. - P. 63], [3], [4]. Mutual influence is inevitable due to increased international relations in the economy and creativity in recent decades. The fundamental difference between copyright and other types of intellectual property in its automatic occurrence, making it unnecessary to register, perform other formalities. In other branches of intellectual property, the identity of its owner and the nature of the protection sought are ascertained during the registration of the design object. In copyright, the identification of the creator of a work takes place using other methods.

British legal presumption of authorship [2. - P. 104]. provide that in the absence of evidence of another, the person indicated by the author on a copy or original of a work of fine art, as well as computer works, shall be recognized as the author of the work [2. - P. 105]. Continental law, the complex of rights of the author of a work, including graphic design, considers individual subjective powers heterogeneous in nature and includes rights of property and non-property content [8. - P. 224]. Monistic theory considered a single copyright, dualistic theory emphasized in it the fragmentation of its constituent property and non-property rights. The main place in this complex of rights by doctrines has always been assigned to "moral rights". Firstly, they were recognized as a priority in the order of origin of copyrights, and recognition by a person of property rights to use his work was determined by recognition of his copyright. Secondly, in the event of a conflict of interests of authorship with the interests of third parties in case of conflicts of property rights to a tangible medium and property rights to a graphic design work embodied on the medium, the preponderance in favor of the author that happened in court practice was justified by his personal non-property rights.

E.I. Kaminskaya bases this position on the application of natural-law theory to copyright. The rights to his creation are immanent to the author (*Mutatis mutandis*) [8. - P. 225]. The law, not endowing, only confirms the existence of copyright. It would be enough to say that in this case there is recognition of the author of human rights. Copyright is more selective: it is not enough to be a person to use rights. They are recognized in connection with a creative work created by this person. Emerging new practical needs and technical capabilities, changing the balance of power in the eternal conflict of the author with users, in the regulation of relations can change legal guidelines. This is the traditional doctrinal "background" of the problem.

Exploring the position of the author as the holder of the right to a creative result, V. A. Dozortsev considered the grounds for the emergence of rights to it depending on the nature of this result and the functions performed by the participants in its creation. According to the scientist, the right to a tangible result is based on the ownership of the means and conditions of its creation. The living labor of hired labor along with materialized labor is part of these means of production. This principle is fixed fragmentarily only in individual cases, but is not fixed by law, because this goes without saying. For someone whose material and intellectual resource is used to create the result of labor, and the rights to it are fixed. He is assigned to the owners of material resources spent on obtaining the result. Therefore, the

desire to extend the established principle for centuries to the result of creative activity is explicable [6. - P. 280]. We fully agree with this conclusion. Personified by the personality of the author, living work represents creativity as a sphere of exceptional individual activity. Group creative activity generating co-authorship is a type of individual labor, and not collective, as V.A. Dozortsev. Each participant can be clearly individualized. Initial assignment of rights to the author is inherent in creative results. Ownership is important not for the emergence of original rights, but for their transition. Creativity is presented by researchers as the knowledge of a new, previously unknown, and leading to a previously unknown.

According to I.A. Zenin, this subjective category still does not have an acceptable criterion. In practice, this boils down to establishing the fact of the independent creation of RID. Mental activity is recognized as creative, its result is protected by copyright, in the absence of direct copying, "piracy", plagiarism, exclusion from the circle of copyright objects under the law - a kind of presumption of a creative nature, as the mental activity itself, and any of its results [7. - P. 23].

I.V. Svechnikov also considers creative the activity of the human brain, which is capable of creating only ideal images, and not objects of the material world. However, in order to be an object of protection, a work of art must be accessible for human perception, that is, it must exist in some objective form. The objective form of a work has always been and remains one of the indicators of the development of society [10. - P. 31]. Only the new, the result of the creative work of a particular person, is protected. Based on what is already known, creativity is always new. Here, the workforce acts in a different capacity, enshrined in the right of authorship as personal, individual, unique creative work.

V.A. Dozortsev fairly believed that property rights to the results of creativity have a personal, non-proprietary origin and nature. This is the main feature of creative intellectual rights. The combined work of the author and his dependents, creating a creative result, make the right to such work belong only to him. In the case of disunity, when the labor costs of one person, and material resources belong to another, a problem arises. The facts of the sale of his workforce by the author to the employer require special consideration. The worker, also acting as an author, does not sell himself into slavery, but only sells his labor only for specific purposes provided for in the labor contract. The work to create a creative result, which is the basis for recognizing authorship rights and assisting it in the form of personal assistance in achieving RID, its implementation, in providing material resources in intellectual rights, clearly

differs. So, only a personal contribution to the new, created by the creator, is the basis for the emergence of law, but not cooperation or the use of the results of someone else's intellectual labor of an existing, objectified or living [6. - P. 282]

The initial assignment to the author of the right to the result of creativity becomes natural. The origins of law lie in creativity and personality. The origins of the right in the system of copyright holders are the author. The contractual nature of relations, expressed by the dispositiveness of norms, rights from the author pass only by agreement or as part of a succession. Creativity is the basis for the emergence of initial property rights precisely as an element of rights and freedoms. Unlike traditional objects of material production, the results of creativity have fundamentally different reasons for the emergence of rights. This area consists of only one resource of a purely personal nature, which is intelligence. All other factors have a serving, collateral relation to the creation of the result of intellectual activity.

Professor V. A. Dozortsev warned of a confusion of authorship with other property rights, leading to erroneous conclusions. In order to participate in the economic turnover, that is, property rights, there is civil law protection of the results of creative activity [6. - P. 284]. As an institution of civil law, authorship law initially served to individualize a participant in the economic turnover, who contributed to the emergence of his object with his creative activity. It strengthens its significance in civil law by such a function as acting as a benchmark for property rights and the possibility of using the rights of any copyright holder to establish the validity. The commodity principle undergoes some restrictions and organic changes under its influence.

Appearing at the inception of protection on the basis of the feudal system of privileges, when property rights were not based on objective grounds and rights were divorced from the author, from the personality of the creator creating the creative result, the right was arbitrarily determined by the authorities. The system of privileges that has been preserved to this day leaves the principle of disunity of property rights and authorship, concentrating on the former. This system is objectively expressed in the copyright design for the reproduction of a work that focuses on property rights and is isolated from the identity of the author. Copyright corresponds to the patent application filing system. The opposite is the "inventive" system, which recognizes rights and is based on the fact of filing an application by the author or his authorized representative. Both systems retained the conservatism of the original features. As part of a

compromise, according to the Paris Convention, the author is any person who has duly filled out an application in accordance with national law. However, it should be noted that the creator has the right to be named as such in the patent. The system of property law derived from the right of authorship with the gradual development of human rights conquers not only national legislation, but also the world law and order. Russian law firmly and consistently pursues the personal basis for the emergence of intellectual creative rights [6. - P. 285]. The non-transferable and inalienable copyright right, being the initial personal principle in intellectual rights, forms the basis of property rights and gives an essential personal element, limits the effect of the commodity principle. The personal nature of the rights to the results of intellectual activity in absolute as well as in relative - obligatory relations is shown.

It is quite obvious that the activity of, for example, a graphic designer is an art-design process, part of which is always a project. One cannot agree that it is incorrectly perceived as a mechanical, not creative process. A feature of the work of a graphic designer is in his integral authorship.

The division into initial and derivative is not inherent in the right of authorship; it is always original and belongs only to the author. Such a division is characteristic of property rights. This also applies to the inalienable right of authorship, to exclusive property rights that are involved in economic turnover. The remaining persons have derivative rights that did not previously belong to the author and were initially assigned to his assignee. For example, the rights to works created by a graphic designer under an author's contract, the rights to works created during the performance of an employment contract, including a mixed unnamed Civil Code of the Russian Federation. In the literature it is noted that it is necessary to distinguish between primary rights and primary rights that previously did not belong to anyone chronologically, which is seen as a feature of rights to the results of intellectual activity. Primary rights may turn out to be derivative, not initial.

Thus, it is important to distinguish practically the original rights and the primary ones that have arisen. The first subject of the emergence of the right to the result could be the employer, chronologically; the author could never really have the rights to it. Legally, the original right in this case arose for the author-worker, the employer only had a derivative right, albeit primary, since it depends on the rights of the predecessor, which is the main derivative of a derivative right. V.A. Dozortsev noted that in terminology it is necessary to express the difference in chronology and legal content [6.- P. 287].

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**COMPUTER PROGRAMS AS A RESOURCE OF PEDAGOGICAL  
EXPRESS DIAGNOSTICS OF LEARNING OUTCOMES  
OF STUDENTS WITH DISABILITIES**

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**Abstract.** Modern education of children with disabilities requires new approaches to monitoring the results of their education. As promising resources, electronic educational resources of a diagnostic nature can be offered that allow for rapid diagnostics (assessment of learning outcomes by point slices of the basic elements of knowledge).

**Keywords:** children with disabilities, electronic educational resources, computer games, diagnosis of learning outcomes.

Recent years have been marked by significant changes in the system of national education. One of the reasons for these changes was the introduction of primary education standards for students with disabilities, linking together the entire system of domestic education of schoolchildren, regardless of the characteristics of the students. At the moment, the first opportunity has appeared to evaluate the learning outcomes of students with special needs in various groups in the context of the implementation of the above Standards: children are approaching the end of primary education. At the same time, the experience of organizing diagnostic studies, the analytical observation of such events held in educational institutions, leads to the idea that pedagogical diagnostics of an applied nature requires new approaches to their organization. There are several reasons. We will focus only on some of them:

1. The quality of children's activities, the productivity of their performance of diagnostic tasks, largely depend on the quality of the situation, on the conditions in which this activity takes place. The more favorable the situation (the more interesting the assignments and the training mate-

rial, the calmer the pace of work, the more comfortable the workplace, the clearer the instructions, the more visible the workload, etc.), the more effective the student's activity, the more complete the picture of its diagnosis and the more significant the conclusions about possible mechanisms to overcome existing shortcomings.

2. The quality of conclusions will be all the more objective, close to the real state of affairs, the more fully the teacher will complete the tasks of creating a favorable working environment for students, the more attention he will focus on analyzing the process and the result of activities, and not on keeping a protocol and filling out other papers, related to the diagnosis.

The foregoing draws the attention of researchers to the use of electronic educational resources for diagnostic purposes. On the one hand, a modern student is positively inclined towards virtual content. On the other hand, computer programs have wide potential for creating a highly variable functional environment for the formation, training, and testing of knowledge, skills, and the accumulation of experience in the most diverse groups of schoolchildren in terms of educational needs.

As well as training programs, electronic diagnostic materials for children with disabilities are developed not only and not so much on the basis of system studies, but as part of solving applied problems of individual classes, sections, disciplines, taking into account the peculiarities of readiness for working with electronic resources and the specifics of the knowledge system available to specific children. Most often, such diagnostic materials take the form of questionnaires, tests, or games of a competitive nature. They are very individual and, as a rule, have insignificant opportunities for replication of experience. Of course, taking into account the widest variability of the problems of development of children with disabilities, different learning experiences and other individual features of this group of students, this approach is positive and has every right to exist.

Another relevant aspect is the understanding of the situation of monitoring the learning outcomes. The routine nature of this procedure is obvious, taking considerable time and effort of its participants. In addition, children, as a rule, are not interested in such work and are "afraid of control (tests, checks, etc.)", which is why the results are not entirely objective. For children with disabilities, the issue of time and pace of work is particularly relevant. Such students need more time to complete tasks. At the same time, they cannot devote a long time to in-depth tasks, as get tired quickly. The effectiveness of their activities is reduced, the quality of health of the child is deteriorating. The individual pace of work is important for them, the ability to build in their own way an appeal to reference information

and additional help. If we consider observation as the leading monitoring method, then the question arises of organizing the process of recording the results and achieving the required level of objectivity of the data collected and their interpretation. In addition, many students with disabilities have a rather negative attitude to the observation situation and react in every way to this, making the collected results uninformative.

In connection with the foregoing, attention is drawn to the possibility of organizing pedagogical monitoring of game situations. Immersion of a child in the game will help level the negative attitude of children to the diagnostic situation, as well as provide a positive emotional background, on which one can more fully observe the child's abilities and the level of his mastery of certain actions. In addition, the game situation, emotionally "capturing" the child, helps the teacher to see what the child really owns. In the game, the student, as a rule, is focused on the game aspect, leaving the didactic without special attention, which means at the level that the child freely performs. Considering that within the framework of monitoring activities, diagnostic procedures are carried out 2-3 times per school year, it is important that the child treat them positively, and when completing tasks, the effect of training and training on the performance of diagnostic tasks does not occur.

Another important starting point of our study was the awareness of the need to provide for the study of the phenomena of interest to us at a fairly low level of their formation with very little dynamics. Providing such opportunities allows the use of diagnostic materials with children of several age groups (for example, in 1 additional, first and early second grades, when activity assessment in the point system is not performed), with various educational needs (for example, children with mental retardation, mental backwardness (intellectual disabilities, autism spectrum disorders, etc.)), with different levels of academic preparation and development of social skills. Moreover, the selection of those criteria that will help to identify even minor child progress in learning is of great importance.

In the process of the formation and intensification of the educational activities of schoolchildren with disabilities, their development of the academic component and the formation of social competence, it is necessary to especially structure the content of the educational material (clearly identify the main systematizing concepts; form an interconnected set of representations and / or concepts of each subject area; ensure personal and practical significance knowledge and skills; organize the optimal combination of theoretical and practical study specific topic). The same can be said with respect to materials aimed at diagnosing the achieved results:

their consistency, accessibility, and logic are one of the important bases for the success of the development and use of express diagnostics. Its basis is a highly accurate model of the knowledge or action that will be studied, structured taking into account the level of complexity of the elements of concrete knowledge.

The above thoughts became the basis for the development and testing of a computer complex for pedagogical express-diagnostics of the learning results of children with disabilities.

The structure of the diagnostic complex includes 5 series of diagnostic computer games. Each game can be implemented at different levels of difficulty, with materials of a different nature (subject images, symbols and signs, words), using help of a different nature and taking into account different degrees of independence. Thus, the software sets the opportunity to participate in the game for children with a very different level of mastery of the studied knowledge and actions, having different experience working on a particular subject material.

Three modules of the diagnostic complex are substantive in nature. They collected 15 games: five, aimed at studying the features of mastering a child's skills in literacy, five - mastering the score and five - acquaintance with the outside world. In each module, diagnostic games allow you to analyze the state of the basic points. For example, in the "Account" module, the user shows his abilities in the field of correlating numbers (amount) and digit, determining the place of a number in a number series, forming a number, comparing numbers, solving examples.

Two modules, 10 games, are meta-subject in nature, allowing you to monitor the formation of cognitive actions (highlighting the object of study and keeping it in the field of active attention, memorizing, analyzing and synthesizing, classifying and generalizing, abstracting and comparing) and general educational actions (the ability to follow instructions, plan and follow the plan, control activities).

The software product interface provides three main stages of work provided for in monitoring: data entry, data processing and uploading of the generated report. Entering data, the teacher determines those analysis parameters that will interest him in the future, starting with personal data and ending with the specific characteristics of each game. The first is done through a special field. The second is through the settings menu in each game. All the manipulations that the child performs with the virtual game props are collected, analyzed, structured and formed into a report. You can upload a report, both in an individual mode (for one child) and in a group mode (for example, by grade or year of study).

Use of this software product allows you to solve several problems:

- organize express diagnostics in order to determine the reference points of a more detailed study (using the included observation and implementation of diagnostic tasks) of the problems identified in the child;
- the possibility of organizing additional stages of monitoring in intermediate periods, especially in situations of trial education of children, when the decision on the correction of programs of psychological and pedagogical impact must be taken quite quickly;
- the opportunity to concentrate the attention of the teacher on monitoring the quality of the child's participation in the diagnosis, since the fixing of his results and the formation of the report are organized automatically by the software and do not require the attention of the teacher;
- tasks within the framework of expert diagnostics can be given at a very different level of difficulty using different stimulus materials, which allows you to choose the possible level of work for different, even little trained children, as well as take into account their preferred activity and see how the quality of work changes depending on the change of qualities of stimulus material (images, symbols, words);
- during the implementation of the basic stages of monitoring, the variability of tasks can significantly reduce the effect of learning in the course of diagnostics and obtain more objective data;
- children are interested in the game and in electronic products, which ensures a positive attitude, which means that the activity will be carried out as efficiently as possible and the researcher can see the potential possibilities of the subject, shown at the level of his actual development;
- the ability to seek help allows you to analyze the change in the quality of activities occurring in the zone of proximal development.

## MEANING FORMATION FROM TRIALECTIC POSITIONS

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**Abstract.** Continuing the study of semantic regulation, it is proposed to switch from a dual point of view to a trialectic examination of strategies of semantic formation. To do this, a triad is considered: hypoadaptive, hyperactive and pre-adaptive sense-forming strategies. This allows us to establish a more complete picture of the relationship between sense-forming strategies as poles of diverse personality development. Using this, it is possible to identify a personality profile that acts as a multifactor model of potential states of the value-semantic sphere of the experiencing subject.

**Keywords:** semantic formation, triplicity, hyperadaptive strategy, hypoadaptive strategy, pre-adaptive strategy.

The strategy of the formation of meanings reflects a look into the present from the future, aimed at generating new causes as targeted programming of situations for their change and overcoming environmental resistance. In the process of personality formation, the development of strategies for the formation of meanings, on the basis of which the strategy for the formation of vital meanings is actualized, occurs. Senses, like polymodal causal images, form the core of the value-semantic and motivational spheres of the personality that determine its activity at all levels [1]. Then we can give the following definition: a strategy of meaning formation is a way of forming and developing a system of personal meanings organized for them under the influence of motives, needs, goals, experience, subjective relationships for their meaningful and high-quality content, and also reflecting the specifics and dynamics of an individual's actualization of meanings in specific situations of life [3].

Our previous modeling based on bipolar semantic scales seems to be the initial and most simplified description of a personality based on an ensemble of its properties. Such an elementary personological model was built on the basis of dual relationships of personal properties, showing two strategies for organizing the semantic sphere - positive development or personality degradation [2]. However, after such a logically simplest dual description, for a more adequate representation of multidimensional semantic reality, it is necessary to move to the next methodological level. Therefore, the binary logic of the description of strategies for the formation of meaning can be supplemented by a trialectic interpretation. This helps to identify a greater number of semantic nuances and their specific features, manifested in the form of a stable strategy, to show their heterogeneity and, at the same time, their conjugacy, similarity in the logic of behavioral manifestations.

We propose a trialectic approach to the study of the semantic organization of an ensemble of personality traits. The following circumstance, which was revealed in bipolar semantic scales [2], prompted such a ternary approach [2]: sometimes negative personality traits appeared in the scale, although they were semantically close, but at the same time they had a different degree of expression, filling in the form of "deficiency - excess". The intertwined properties can be "untwisted" - from the semantic "pigtail" of one pole two branches can be obtained. Then the third pole appears in the bipolar scale, which becomes the center of the third sense-forming strategy in this construct. The presence of such logically necessary relationships is due to a different measure of manifestation of opposite semantic principles, reflecting their quantitative and qualitative relationship.

The first, hypo-adaptive sense-forming strategy shows the absence or insufficient manifestation of the key personality traits in this semantic dipole. This reflects weak adaptive abilities in interactions in a situation, manifested as a passive device of the type of reactive choice to maintain existing preferences. This is manifested in the form of the absence or fragmentation of a meaningful approach to activity and decision-making. Such a reactive position reflects insufficient work in the inner world for an adequate assessment of what is happening and full integration into the processes of the outer world. This delay shows a lack of personality development - infantilism in the form of maintaining and dominating the set of personality traits inherent in the earlier stages of its development. An infantile person is concentrated only on himself, while as a person he does not develop, and introspection is alien to him. Such people often do not understand others, do not share their views on the world, and practi-

cally do not take their interests into account in their behavior. The main signs of psychological infantilism are: lack of independence and avoidance of problems; lack of life goals and aspirations; unwillingness to develop; inadequate reactions to what is happening; selfishness and irresponsibility; excessive enthusiasm for games, gadgets, shopping; inability to communicate; superficial thinking; sedentary lifestyle [4]. Such features of the worldview form the corresponding personal meanings, which, like causal images, determine a person's life. We propose the following definition: a hypo-adaptive sense-forming strategy is a method of forming causal images based on formal preferences, aimed at passive joining and guided movement in a layer of personal meanings, given by insurmountable circumstances of life without its actual awareness.

The second, hyper-adaptive sense-forming strategy shows an excess of key personality traits, is assimilative, and is aimed at actively adapting a person. In this type of adaptation, the individual expresses the desire to ignore the inevitable changes that come into his life and remain in the comfort zone. To maintain this state of immutability, a person uses all available resources. The key characteristic in this strategy is personality development. This is a process of excessive personalization, when a person tries on other people's roles, masks, which he considers acceptable for himself. There is a loop on one's own person, the main criterion is commensurability with others and personal interest, but not a generally accepted norm, which just breaks. Such self-positioning and the desire to seem, rather than be a person is seen as a desacralization of reality and desocialization of a person as un-learning [5]. Overdevelopment, overexertion and satiety with hyper-adaptability, as a form of social experience, can manifest itself in the supercontrol of both their own and other people's interactions. The state of overdevelopment, as hypertrophy, often leads to an excessive set of material goods and external attributes of success. The presence of a hyper-adaptive strategy shows a reluctance to expand one's experience, and a person in an ever-changing world needs to be tempted by overdevelopment and get rid of the corresponding illusions. The absence of such internal work leads to the formation of corresponding negative causal images that overlap the direction of personal growth and specify the "horizontal" movement - uniform development in self-similar forms. We have formulated the following definition: hyper-adaptive sense-forming strategy is a method of forming causal images based on one's own experience and stereotypical predetermination of goals achieved, aimed at preserving the unchanged content of personal meanings using all available resources and rejecting new opportunities for the development of the semantic sphere.

Between these two adaptive strategies is a neutral state, reflecting the same ratio of polar meanings, translated by key personality traits. This balance is an intermediate position between two ways of forming meanings, in the course of which an equally probable choice is possible.

The third, pre-adaptive strategy of sense formation begins from a neutral point and opens the direction of a paradoxical approach to interaction in situations. As a nonequilibrium third attractor, this shows the direction of the non-obvious, but possible development of the personality with several alternatives. A pre-adaptive strategy shows the presence of such a positive key personality trait that helps to perform additional functions or to successfully interact in the future as in unforeseen conditions of new situations. The accommodative nature of this strategy means the manifestation of personal activity for the variable adaptation of behavioral patterns, which means their anticipatory nature. The ongoing restructuring of the semantic sphere of the individual indicates its self-improvement as spiritual growth.

The two adaptive strategies discussed above proceed from the pre-determination of goals and the norms of situational activity given by the external environment - they reflect the existence of a rigid causal relationship between a person's life relationships and their behavior. To overcome such limitations of adaptability, it is advisable to talk about the supra-situational activity of the subject - pre-adaptability [7]. In this state, existing causal relationships can become less stringent living conditions - there is a variability of development. In the process of improving the personality, the hard reasons for its life, which give rise to the need for unambiguous consequences, are replaced by prerequisites that form the possibility of carrying out one's development. Pre-daptability is one of the main attributes of a person's creative potential. D.A. Leontiev in the study of human behavior offers, in addition to traditional psychology with an emphasis on necessity and determinism (something that cannot be impossible), to identify a "second" psychology that focuses on opportunities and self-determination, which are not generated by strict causal relationships, but *can be*. Moreover, a human trajectory, in addition to a subhuman, low-cost existence, can have a truly human one - an autonomous level of development for orientation of behavior in the space of the possible, which is paradoxical with respect to the everyday determinism of life [6]. A non-linear transition from necessity to a fan of opportunity is a paradoxical act of a synergistic nature that is not justified from the position of lower biological regulators, but is unique and meaningful from the position of higher values.

Since the essence of self-transcendence is the search for the meaning of life as a higher purpose and its implementation, the application of paradoxical logic in ordinary situations is possible when a person knows about higher paths. Finding a destiny is a very big risk, the most difficult job, which may not lead to automatic success. That is why A. Maslow in a late interview said that his thesis that satisfying basic human needs is an unequivocal reason that inevitably and unconditionally generates his personality's transition to self-actualization was not empirically confirmed. He pointed out that after reaching a level where basic needs are not critical for life, one part of people continues to move toward self-actualization, and the other part stops [8]. While a person is searching for himself, he goes over his abilities and cannot feel his viability and maturity - when a person goes into a new one, he is poorly protected in his work - vulnerable in comparison with those who remain in a comfort zone. We propose the following definition: a pre-adaptive sense-forming strategy is a way of creating causal images focused on the recognition of motives and generating relevant goals, aimed at the formation of promising personal meanings and their timely transformation to realize the possibility of spiritual growth under the influence of internal and external circumstances, assessed as surmountable living conditions situations when an individual determines his activity.

The three proposed strategies that determine the direction and qualitative content of the formed meanings implement fundamentally different approaches to interaction in situations. In hypo-adaptive and hyper-adaptive strategies, new information is included in existing schemes and the subsequent schematic action with new objects is based on existing skills. In a pre-adaptive strategy, there is a variable adaptation of behaviors to new situations that require a certain activity, including supra-situational, which means its anticipatory nature. On this basis, it is possible to build a personality profile as a multifactor model of possible states of the value-semantic sphere of the experiencing subject. In terms of behavioral modeling, such a personality profile shows the orientation and qualitative features of semantic regulation - reflects the current strategy for the formation of meanings as polymodal causal images.

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## ROLE COMPETENCE AS A COMPONENT OF THE TEACHER'S PROFESSIONAL AND PERSONAL POTENTIAL

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**Abstract.** The paper analyzes the conceptual field associated with the understanding in psychological and pedagogical research of the teacher's potential and presents his vision of the professional and personal potential. The role competence of the teacher and its role in assessing the professional and personal potential of the teacher in the context of his professionalism are considered.

**Keywords.** Potential, professional and personal potential, role competence of the personality, professionalism of the teacher.

The researches different terms to denote the necessary reserves of the teacher, ensuring the effectiveness of professional activities are used. The phrases "pedagogical potential", "teacher's potential", "professional potential of a teacher", and "personal potential of a teacher" are used quite often in the scientific literature, and the authors, using this term, fill it with different meanings and meanings.

For the first time, the concept of "pedagogical potential" was introduced into science by A.M. Bodnar, considering it as the most accurate indicator of the success of a teacher. The author notes that the pedagogical potential is a special measure that defines the main distinguishing feature of the pedagogical elite. From the author's point of view, the presence of an elite in a professional pedagogical community should create high patterns of behavior for all its members and bear one or another responsibility. An indicator with the help of which you can judge the presence and characteristics of pedagogical potential are some personal qualities of a teacher, namely those that

form the “humanistic syndrome of professionally important qualities” [1, p. 12]. Pedagogical potential is a system, as the elements containing such formations as inclinations and abilities, experience and personal qualities, pedagogical motivation and professional orientation of the teacher’s personality.

The potential of the teacher in our understanding is a complex concept, which is understood as the ability and synthesis of certain personal qualities and properties of a person, ensuring the effectiveness of pedagogical activity and allowing predicting a person’s ability to solve new problems in the face of changes. In this sense, the pedagogical potential is associated with personal (human) potential, as the realization of the personality in the professional sphere. The professional and personal potential of the teacher is manifested in different types of activities, and is directly responsible for the ability of the teacher to carry out effective self-regulation, regardless of the given circumstances. The personal and professional components of the teacher in the process of implementing professional activities, now combine into a single indivisible whole, then separate and in other cases manifest themselves as consecutive chains of one whole. A similar situation is characteristic precisely for pedagogical activity, it allows being simultaneously a mechanism of the teacher’s professional development movement along the path to achieving professional mastery and serves as the basis for successful achievement of tasks in the process of interaction with students. That is, to turn the process of training and education into an educational field in which knowledge is transferred from person to person.

The interest to the topic of potential and its structure is relevant to this day, attracting the attention of many researchers in the context of the problem of teacher professionalism. So, for example, the role component is investigated as specific, as located on the border of the personal and professional. Role behavior is considered as the totality and dynamic combination of personal and social roles, and personality formation is represented as the development of certain roles [10].

The study of the social role and role behavior of personality in Russian psychology is represented by the works of G. M. Andreeva, A. A. Bodalev, L. P. Bueva, P. P. Ermine, A. L. Groyzman, I. S. Kon, R. L. Krichevsky, V. A. Yadov, M. G. Yaroshevsky. In foreign social psychology and psychotherapy, studies of role behavior as a broader personality category were carried out by E. Aronson, E. Byrne, G. Blumer, I. Goffman, M. Kuhn, G. Leitz, R. Linton, M. Lusher, D. Myers, J. Mead, J. Moreno, C. Rudestam, T. Shibusaki and others.

Role competence of an individual includes such elements as role variability, role flexibility, role depth, and the ability to role decentration [9].

Role flexibility reflects the ability to easily switch from one role to another and to take a different role under new conditions, which is an important condition for an individual to adapt to changing conditions of social reality. P.P. Ermine denotes role depth as the possession of the deep structure of the roles and ego-states of a person, the support in role behavior not on the external substructure of the role (projection), but on the deep components (role self-concept, role experience). As the ability to role decentration (complex psychological education, the ability of a person to transform, role empathy, accepting the role of another person, the ability to look at the world from the point of view of his role self-concept) and role reflection (the ability to evaluate one's own role behavior from the point of view vision and perception of other people) [2].

In this context, the professional development of the teacher can be described as the ability of the teacher to development, creativity, flexibility and mobility with the breadth of his role repertoire. A poor non-invariant role structure directly affects the personality of the teacher, restricts behavior and schematizes relationships in the team. The presence of role diversity in a teacher indicates a high level of his professional identity, allows him to be flexible and creative in achieving professional goals.

As, one of the important components of the teacher's professional self-awareness, the researchers directly identify the teacher's idea of his own professional role. The definition of their professional roles metaphorically shows the educators' ideas about their own profession and what they are in this profession. Changing the perception of one's professional role determines other types of personality activity. A limited understanding of their professional role becomes an obstacle to the professional development of the teacher, affects the effectiveness of the activity. L.M. Mitina, in the framework of the theory of professional development, notes that professional self-awareness can be represented as a teacher's awareness of himself, his personal, intellectual and other qualities, deeds and actions, their motives and goals; as a self-esteem of these qualities, awareness of his attitude to the outside world, other people and to himself [7.8].

In L.M. Mitina's concept of professional development determining position is the position of S.L. Rubinstein on two ways of life. She offers a model of adaptive behavior and a model of professional development. With adaptive behavior, the personality consciousness is dominated by the tendency to subject professional activities to external conditions and circumstances. Professional activity is characterized by the use of previously developed algorithms, patterns and stereotypes [6]. Tough professional role-playing behavior impoverishes the learning process itself, leads to professional de-

formations of the teacher, and has a negative impact on the development and health of students. An explicit, detailed consideration of this problem, we can see in L.M. Mitina's concept of professional development of the teacher, where two models of teacher professional work are distinguished: a model of adaptive behavior and a model of professional development [7].

The model of adaptive behavior is characterized by rigid role-playing behavior, lack of creativity and spontaneity, the teacher identifies himself with one role or with a limited set of roles. From the point of view of role competence, adaptive behavior is characterized by role monotony, inflexibility and focus on external expectations, difficulties and inability to accept the role of another person. The uniformity of roles (professional and non-professional) leads to difficulties in changing behavior when the situation changes, quickly leads to the depletion of the psychological health of the teacher. In the model of professional development, teachers have a varied role repertoire that allows them to achieve flexibility in behavior. They have a willingness to accept a different role and the ability to reflect their roles. A high level of development of the integral characteristics of the personality and professional identity, the desire for creativity and self-development are character [6].

I.G. Kolmakova in her work described the characteristics of the teacher's polishing behavior and noted that most teachers are characterized by typically tough professional role-playing behavior, with a minimum number of roles, fixing on one or two roles. Only a small proportion of teachers have an extensive role-playing repertoire; flexibility and variability of behavior [3].

O.V. Kuzmenkova identified and characterized the differences in the perceptions of teachers about their professional roles, depending on the length of service in the profession. The author notes that for a full-fledged existence in the profession, the teacher needs experience that is not limited to one or more professional roles. The author emphasizes the relationship of the professional formation of the teacher with the ordering of the entire range of roles played on the one hand, personally significant, on the other hand demanded by modern society [4].

Thus, we can note that in scientific studies the problem of the influence of role behavior on the educational process and on the personality of its participants is presented in sufficient detail. The relationship between the role component and the teacher's professional identity is highlighted. At the same time, the question of what is the source of the breadth and variability of the role behavior of the teacher remains debatable and opened.

The role component is characterized as a component of the profes-

sional and personal potential of the teacher, as the role competence of the teacher, as an important factor in predicting success in professional activities. A.K. Markova determines the professionalism of the teacher in connection with the integration of various competencies [5]. In our opinion, the presence of role competence as an integral part of professional self-awareness can become an indicator of potential in the individual.

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**FREDERIC WILLIAM MAITLAND'S VIEW ON FEUDALISM AND ITS REFLECTION IN RUSSIAN MEDIEVAL STUDIES OF THE END OF THE XIX-TH – THE BEGINNING OF THE XXI-ST CENTURIES**

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**Abstract.** The article deals with the issues connected with analysis of Frederic William Maitland's view on feudalism and its reflection in Russian medieval studies of the end of the XIX-th – the beginning of the XXI-st centuries. The main points of Maitland's concept of English feudalism are revealed. The author traces the stages of evolution of the assessment of merits of F.W. Maitland in Russian historiography.

**Keywords:** F.W. Maitland, feudalism, concept of feudalism, "centralized feudalism", main features of English feudalism, vassal-fief system, "juristic approach", "critical trend" in British historiography, Russian medieval studies, Russian historical-agrarian school.

Frederic William Maitland (1850–1906), Professor of Law of Cambridge University, the outstanding English historian, lawyer, historian and theorist of law, has made a great contribution to research and study of feudalism in England and continental European countries. He was the pride of the learned Great Britain, and one of the most distinguished legal historians among English, French and German scholars in the XIX – the first half of the XX centuries.

F. W. Maitland was the author of many fundamental works (more than 160 works) [17, c. 22] in the English history, the publisher of the English medieval records, the inspirator of the foundation of "Selden Society" and the scientific historical journal "The English Historical Review". The contemporaries and ancestors of F. W. Maitland highly appreciated his works as classic and himself as a genius historian.

In European and American historical science F. W. Maitland is known as the historian of ideas and institutions such as the idea of law; the idea of "change and continuity"; the idea of non-revolutionary development; the idea of unique development of England; the idea of the self-value of the Medieval

Ages; the idea of release of past from present, present from past, future from present; the idea of English trust; the institution of state; the institution of law; the institution of monarchy; the institution of crown; the institution of parliament; the institution of court; the institution of Secret Council; the institution of King's Council; the institution of trust; the institution of corporation.

A multivalued talented and versatile scholar, F. W. Maitland dedicated his life to the study of English History, mostly its early ages – V-XIII centuries.

In the English Middle Ages F. W. Maitland was interested in key problems: the development of community and manorial relations, the process of formation of cities, constitutional and law history and others. Feudalism he conceived as one of the basic terms of the medieval history, its essence and did much to identify its specific features in England and differences from continental model, especially from French feudalism.

He noted the difficulty of definition of feudalism as phenomenon, which was determined by the attempt to create the universal model and definition of feudalism for all European countries, due to what there appeared complexity in understanding the feudalism in general [7, vol. I, p. 67.]. He spoke about it in his famous Inaugural Lecture, delivered in the Arts School on 13 October, 1888, especially that the concept of feudalism is difficult to apply to the Middle Ages: "...the feudal system was a very early essay in comparative jurisprudence"; "we actually hear nothing about the feudal system in England until it ceases to exist" [6, vol. I, p. 222]. According to F. W. Maitland, the main feature of feudalism was lying in a curious connection of possession/ownership, kinship, relationship between economic and politic. This scientific observation encouraged him to pay attention to the beneficium, which could help to make the problem clear. F. W. Maitland was sure, that the most significant characteristic of feudalism lay in the field of land law, in tenure, but the English law and the prominent English lawyers of the XIII–XVII centuries – H. Bracton, J. Fortescue, E. Coke – says nothing about it, because it was obvious that time. Just this "simplification" of W. Blackstone F. W. Maitland considered the most significant, ironically noted, that feudal system reached its apogee in the middle of the XVIII century – in the works of jurist William Blackstone [7, vol. I, p. 237; 1, p.68].

Among the other characteristic features of feudalism F. W. Maitland maintained the merger of power and property, public and private law. He came to conclusion, that feudalism was not only the system of tenure, but also the system of management and its approval is wrong to reduce only to introduction of military tenure. In comparison with military tenure seigniorial jurisdiction, the court of landlord was more important [5, p. 258; 7, vol. I, p. 68, 230].

The essence of feudalism F. W. Maitland understood as the vassal-fief system with the king ahead, who was the only landowner in England [4, p.143-144]. F.W. Maitland admitted English feudalism developed in the context with other European countries, but from the XII century there appeared distinctions: "If now we speak of the feudal system, it should be with a full understanding that the feudalism of France differs radically from the feudalism of England, that the feudalism of the thirteenth century is very different from that of the eleventh century". F. W. Maitland maintained that of all countries England was the most, or for the matter of that the least, feudalized [4, p. 143]. This paradox he explains within the categories of land law, in the context of which England was "the most feudalized society", because all tenures were feudal, so it was completely "feudalized" after the Norman Conquest [7, vol. I, p. 235]. But from the point of view of political system, public law England was not the feudal country – it was a highly centralized country with a strong power of the king; its "public law did not became feudal" [4, p. 164], because of the Common law, which operated in all spheres of feudal system [7, vol. I, p. 303]. Besides that, English tax system and administration of justice also were never feudalized [4, p. 162-163].

The elements of feudalism existed in England long before the Norman Conquest, in the subsoil of Anglo-Saxon Britain, but the theory, which explained it "came to us from Normandy" [4, p. 148, 151]. So, F. W. Maitland came to conclusion that feudalism developed in England in unusual, irregular shape of "centralized feudalism", but it had common roots with feudalism in the continent.

The results of F.W. Maitland's studies of English medieval history broken down the established stereotypes in European historical science and had a wide resonance. The personality of British historian, his works couldn't help, but attract attention of his Russian contemporary colleagues. The merit of F.W. Maitland on the study of medieval history of England and its institutions were always recognized in Russian historiography, but their valuation, accents were changing during the end of the XIX-th – the beginning the XXI-st centuries.

F.W. Maitland's studies and his scientific school have greatly influences on the development of Russian historical-agrarian school, represented by the names of P.G. Vinogradoff, M.M. Kovalevskij, A.N. Savin, D.M. Petrushevskij, E.A. Kosminskij, V.M. Lavrovskij, S.I. Arhangelskij, V.F. Semyonov, M.A. Barg, K.D. Avdeeva and their pupils.

The greatest Russian historians, the founders of the soviet medieval studies of English history – M.M. Kovalevskij (1851-1916), P.G. Vinogra-

doff (1854-1925), A.N. Savin (1873-1923), D.M. Petrushevskij (1863-1942) – accepted the importance of law aspects in definition of feudalism, did not refused from law-political comprehension of its essence, which was highly spread in European historiography and highly appreciated F.W. Maitland's contribution in that sphere.

P.G. Vinogradoff and A.N. Savin, who knew F.W. Maitland intimately, met him in Britain for many times and were his colleagues, «opened» him for Russian historical science and society. They have made a significant contribution to the study of English medieval history in Russia and Great Britain [9, 15, 16].

Up to the present time all venerable Russian historians, who specialized in English medieval studies, appealed to F.W. Maitland's works and quoted them [11].

In Russian historiography of the soviet period (until the 1980-s), based on Marxist-Leninist methodology, F.W. Maitland's works were known very well, but were almost totally criticized though of their “juristic approach” to the problems of medieval state and society. That's why many of F.W. Maitland's conclusions were considered “erroneous” as belonged to the “bourgeois historiography”, but his introduction of a great amount of new records for scientific use was always appreciated [12, c. 456].

So for a long time F.W. Maitland was a well-known, but less studied historian in Russian historiography until there came the great transformational changes in the country itself and its historical science, which turned to the new methodological positions, based on interdisciplinarity approach and methodological synthesis.

In the end of the XX-th century the historical interest to F.W. Maitland's scientific heritage and so called “critical trend” in British historiography greatly increased (F.W. Maitland, G.B. Adams, J.W. Baldwin, A. Ballard, M. Bateson, N.S.B. Gras, H.L. Gray, G.L. Haskins, F.G. Davenport, D.C. Douglas, E. Jenks, J.E. Jolliffe, H. Cam, A.E. Levett, Ch.H. Mcllwain, W.Sh. McKechnie, N. Neilson, T.F.T. Plucknett, A.F. Pollard, F.M. Powicke, H.G. Richardson, F.M. Stenton, G.O. Sayles, B. Wilkinson) and some special works were published in Russia, dedicated to him and his followers [17].

Today F.W. Maitland's view on feudalism, parliament, borough, manor, villa, seisin etc. are the objects of historical studies of the eminent Russian scholars [13, 14], who accept the importance of “juristic approach” to the studies not only of the English medieval history, but the history on the whole. Russian historians also recognizes the importance and actuality of formalization of special “law trend” in Russian historiography.

We can assume, that “the time for an artistically balanced picture of English medieval law” will come very soon [7, Introduction, vol. I, p. xlviii].

It is obvious, that it is impossible to study the European medial history, feudal relations, neither technically, nor in essence, without the deep study of law questions. Let us remember F.W. Maitland’s words: “Feudalism cannot be explained only by studying of law ideas and forms. But, from the other side, it also cannot be explained without such a study, for almost everything we know of it, we know from the law records” [7, vol. II, p. 226]. There is nothing to be add to that.

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## "NAIVE ART" OF THE NORTH OF RUSSIA

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**Abstract.** The subject of research in the paper is the work of amateur artists of the Komi Republic, who do not have professional training and are not connected by academic rules and canons. Substantive and formal aspects of V. Nechayev's paintings are analyzed, terminology issues are considered. It is concluded that, in response to the social and artistic demands of the time, this art should be assessed as relevant, by the nature of the drawn picture of the world and the used artistic means - as a northern idyll.

**Key words:** naive art, amateur art, mythological, paradise model, idyll.

In this work, the concepts of "amateur" and "naive" art are used. The author of the paper puts the following meaning into them: the concept of "amateur" is used in relation to the educational level of the artist (lack of art education or work in another profession and doing art in his spare time). The practice of amateur creativity shows that in an artistic form it is consciously or unconsciously associated with naive art, as it seeks to give a special picture of the world ("poetic and sublime art worlds in which there is a kind of ideal naive harmony between nature and man" [3, p. 311 -312]). This point of view is the basis of this work. I think that today, works of naive art are becoming the center of artistic practices, attractive to both spectators and professional artists, with a clear and positive outlook on the world, and the return of the archaic of the artistic language.

The period of active development and recognition of naive art in Russia falls on the Soviet era - the 1960s and 70s. At that time, creative studios worked actively, amateur artists took in exhibitions. And even earlier, in the 1920s, the Society of Self-taught Artists was organized, which was engaged in educational work and training for people interested in the profession of an artist. Similar societies existed in the 19th century, but in the post-revolutionary era, the task of developing amateur art acquired the status of a state idea. To support amateur art an extensive network of organizations and public associations were formed, specialties of secondary and higher education were opened, which trained specialists - managers, teachers, etc.

The vast majority of amateur artists, with their origin and often place of residence, were associated with the village, its culture; this determined the permanence of their connections with the folk art.

The North in the history of the formation of naive fine art played a special role, as for a long time it was mainly a rural territory, little captured by the processes of migration of the local population, therefore, the traditional folk culture retained its authority. Artists of urban origin submitted to the influence of folk culture.

What does the creative work of amateur authors of the northern region, which can be attributed to the naive art, represent?

We can judge this by the exhibitions of naive art in the territory of the Komi Republic, which have been held since the end of the last century in regional museums, and since the beginning of this century - on the basis of the National Gallery of the Komi Republic. These are collective and personal exhibitions, including as part of the Golden Dream project for the preservation and development of naive art. The aim of the project is the formation of a fund of naive art, a databank of amateur artists. In 2008, the Golden Dream exhibition was organized, in which works from museum and private funds from Izhemsky, Kortkerosky, Sysolsky, Syktyvdinsky, Ust-Kulomsky regions, the cities of Ukhta and Syktyvkar, as well as the village of Yarensk, Arkhangelsk Region, were presented [1].

The author of the report about the opening of the exhibition, A. Sivkova, reported that all 23 participants of the Golden Dream were self-taught, and most of the names so far were known only to a narrow circle of their relatives. The name of the exhibition "Golden Dream" is associated with one of the basic codes of naive art, reflecting the immersion "in a serene, joyful, blue childhood" [5]. The works of the exhibition give an idea about the motives and images typical for naive art: about the "Garden of Eden", which embodies the northern forest; "Lost paradise", which is most often understood as the irreversible past (childhood, youth); "Earthly paradise" - an expedient, harmonious arrangement of life, including in the field of relations between man and the natural world; motives of walking, communication, the course of everyday life as a ritual action, etc. are frequent.

One of the famous naive artists is Nechaev Valery Alexandrovich. He was born in 1949 in the rural area Storozhevsk of Kortkerosky region. He served in the army, worked in the oil field, as a fireman, fireman. In the announcement of the personal exhibition of V.A. Nechaev "River of Time" (2015), he was called an artist-philosopher, a romantic, whose work is filled with symbols and metaphors, fairy tale [4]. His work is significant in the number of works, diverse in themes, interesting in artistic solutions.

The main images and motives of his work are associated with the house and the forests, which appear as the embodiment of the laws of the universe, understood not rationally materialistically, but mythologically. So, the house in the painting “River of Life” is drawn as the embodied harmony of human and natural, earth-air-water elements, childhood-youth-old age, life-death, instant-eternity. The image “River of Life” is perceived as an endless river of eternal life, giving a person strength and harmony.

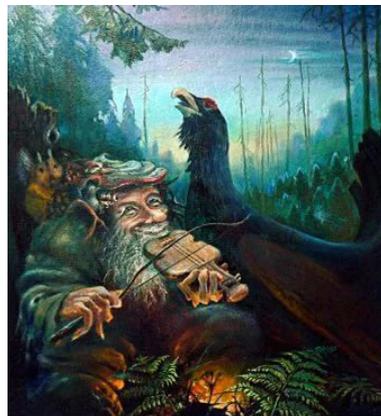
River of Life [2]



Cradle [2]



Taiga song [2]



The forest is inhabited by real and mythological creatures, known by mythological traditions. Those are the goblins and what can be called "forest evil", which lives in the pictures according to the rules of good neighborliness, poetic perception of life, is gifted with curiosity for discoveries and creative talents.

All creatures are equal here in a series of lives; including man does not declare his right to be in charge. A similar image testifies to V. Nechaev's acquaintance with the ideas of Russian philosophy of the late 19th century (for example, VI. Soloviev). The forest is a model of the ideal structure of life related to the concept of paradise. Nechaev's paradise is not lost, it exists in the invisible layers of life, is not touched by technogenic phenomena, we can say that the author creates a poetic version of the universe structure.

This paper discusses the work of one artist, which can be attributed to the naive art, but it has typical features that unite most other artists, so you can draw conclusions of a general nature.

In the modern professional environment, there is a very restrained, sometimes condescending attitude to such phenomena as amateur, naive art. The initial criteria are recognition of creativity as a profession, the availability of special education, as well as formal criteria, such as membership in the Union of Artists, obtaining honorary titles, etc.

However, the formal attributes of a profession are not always a necessary condition for true art, but only its indirect attributes.

The classification of art, based on the separation of professional and non-professional art, does not reflect the current sociocultural situation. Much more productive is the division of art into relevant and irrelevant in the degree of participation of artists in solving major social and artistic problems.

To such a relevant art naive visual art can be attributed, both in the field of content (the participation of artists in solving ethical, aesthetic, moral issues of society, the conscious and active use of the possibilities of self-education and development, etc.), and from the point of view of the formal. Participants in naive art expand their understanding of the systematics of contemporary art, recall the successful artistic practices of the past professional and folk art, and contribute to the development of new approaches to understanding modern processes in the field of fine art.

Naive art has some common substantial and formal features that represent it as a global phenomenon, which does not cancel, however, the presence of national or regional specifics in it.

In the framework of Russian naive art, artists of the North European region have certain characteristics.

For the vast majority of them, the absolute value is the way of life in the countryside, the part of the worldview patriarchal complex that has passed the test of dramatic events and civilization processes of the twentieth century. Also the maintaining of a lively connection with folk culture is important for artists. The geographic and climatic features in which the northern man was formed, and the history of the northern peasantry, devoid of the acuteness of social-class contradictions characteristic of other regions of Russia, formed an idyllic tonality of the artists' work. A significant layer of works of naive art can be defined as a northern idyll, which refers to relations of a family-social nature, and the interaction of man and nature.

The artists are disposed towards a pantheistic worldview, including the theme of lower mythology. Significant life experience, including that of many – military (the vast majority of artists belong to the older generation or have already passed away), formed in them a philosophical outlook on life, the need to create a philosophical subtext of the picture.

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## INFLUENCE OF SUBJECTIVE FACTOR IN CAR DESIGN. PARADOX OF NEW SHAPE

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**Abstract.** The article focuses on the issue of new exterior shapes of car bodies. Dissertation of N.A. Medelets called Car shaping factors (technological aspect), 2013 is The basis of our research. The object of the research is the real cars produced in 10-15 recent years.

**Keywords:** novelty, auto design, shaping, shaping factors, car.

Auto design has significantly changed within recent 50 years. Both: the exterior and interior shapes of the car were transformed. Producing technological and operational aspects of making a project have changed thought the issue of novelty is still relevant.

The novelty of the auto design is one of the factors which determine and influence the successful trade of the brand.

The auto design of cars mostly was not constructively moderated within the last ten years. Basically all stylistic research are determined by a scheme: 4 wheels, a cabin between them and the engine, control and baggage space.

Each auto brand tries its own way to bring novelty to the design. First of all, the age of brand influences it (Fig. 1). The older is the company and the longer it exists in market, the more difficult is to surprise or shock its customers by revolutionary new images as it is connected with the firm style and influences the identification. In this case, the designers choose the traditional way and preserve the brand features. The brands such as: Mercedes, Audi, BMW, Rolls Royce, Bentley very careful and conservative concerning novelty of the design. They change only details of their models.

The young companies which have just appeared in the market choose different way: the image should be unique and different from its analogues as much as it is possible (Fig.2). The new auto companies chose the easiest way as they do not have technical innovative know-how. They just change exterior forms using styling as a main method of shaping. The

method is not quite effective as it includes only the search of new compositional techniques inside of the given constructive scheme which is being used by all manufacturers of cars nowadays.

Thus, it is necessary to take into account the whole selection of car models produced by the competitors. Then the novelty tends to limit and design becomes similar to the competitive analogues. The way to solve the issue is to change or revise the constructive scheme (the complexity increases). It makes it necessary to revise ergonomics, production, technology and operation of the goods as well as the other factors radically (Medelets, 2013)

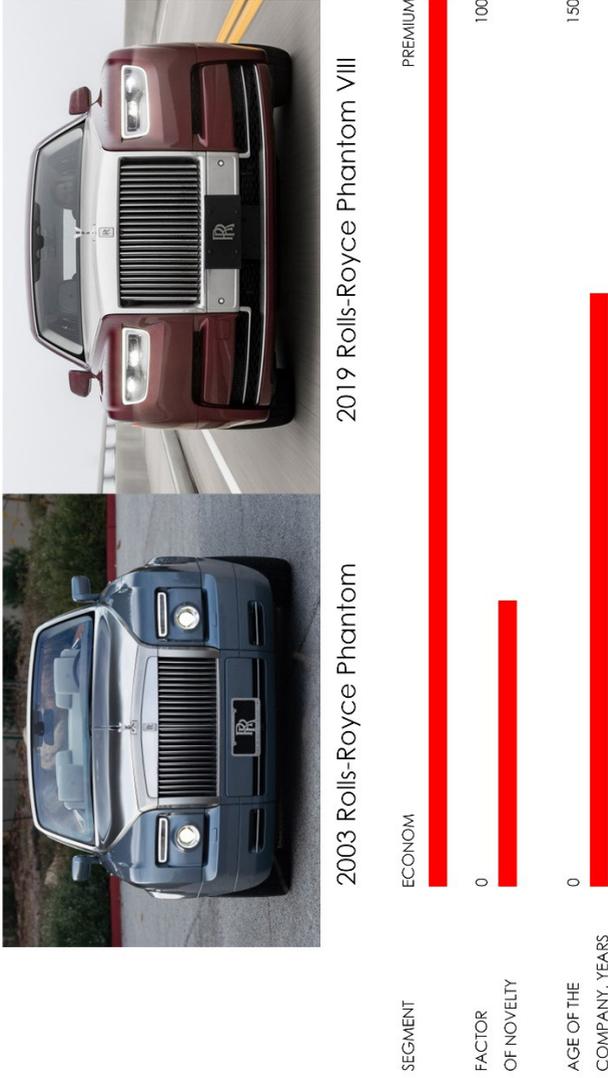
Let us analyze the certain example of the SUV cars. The benchmarking analyse was applied to the models of different brands and they were classified into the groups such as: the cars of traditional shape, expressive shape, sculpture shape, discreet and classic shape, sportive shape; the selection is based on the subjective perception of shape, fashionable trends of auto market and the way the brand place itself. However, the selection is not veritable as there are no certain objective criteria of novelty selection. The author believes that it is the paradox of shape novelty. Thus, the creation of something new, as a rule, is based on personal preferences of those who chose and make decisions (if they like it or not) or the choice may correlate the analogue indicators of the design (if it is similar to the competitive models or not), or there is another way which considers the novelty as the difference, extraordinary features of the compositional decision, but there are less of these examples because there is a risk to make a model which is not respond to the tasted of the customers, it leads to losses.

In other words: a person is able to spot visually the fashionable, old-fashion, sportive and traditional-conservative shapes basing only on his/her aesthetic beliefs. The issue still remains open. Hence, it is necessary to identify the criteria of novelty to assess the shape objectively.

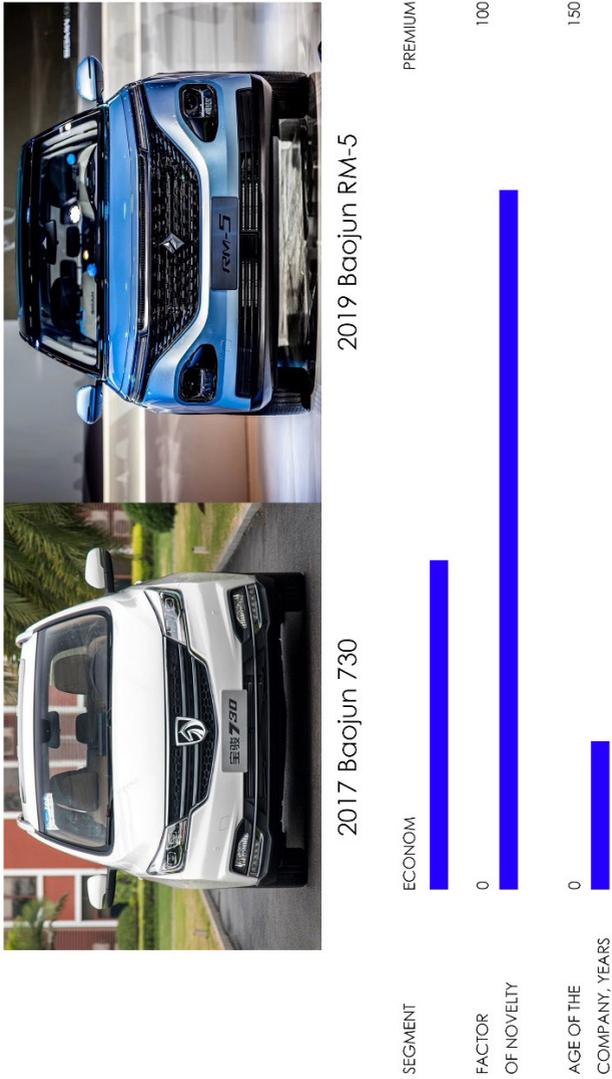
The criteria of novelty: **originality**, which reflects the uniqueness of stylistic decision which is different from traditional one; **innovation** which includes new technologies and materials which improve effectiveness and quality of the car which is needed in the market and is able to respond to the consumer's preferences; **technology** - shows the complexity of the good production.

In this regard, the young brands are more flexible to the innovations than the companies with long history where the shaping is very inert and dependant from style.

Thus, it is necessary to take into consideration the criteria of novelty and factors of shaping, elaborating the car design.



**Fig.1 The example of traditional way and small influence of the novelty on the premium brand design with long history**



**Fig 2. The example of flexible way to the novelty issue of car shaping. The "younger" the brand is, the easier it makes experiments with the shape**

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## RECOMMENDATIONS FOR CHILDREN'S CORRECT FOOD STEREOTYPE FORMATION

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**Abstract.** The article discusses the causes, types and methods of preventing the formation of improper eating behavior.

**Keywords:** eating habits, nutrition, eating behavior, compulsive over-eating, overweight, eating disorders.

**Purpose:** Making recommendations to help prevent the formation of the wrong food stereotype in children

*Habit is habit, and not to be flung out of the window by any man,  
but coaxed downstairs a step at a time  
Mark Twain*

### Relevance

Currently, most people report the presence of the wrong food stereotype, which in most cases leads to the development of noncommunicable diseases. The food stereotype is formed in childhood, so it is very important to instill in children from a young age the basics of proper nutrition.

What is a food stereotype? This is a person's attitude to food and its intake, habitual nutrition in routine and stressful conditions. Eating habits have a direct impact on health, and therefore on the standard of living of a person.

Healthy eating helps prevent noncommunicable diseases and health problems. However, the modern way of life of people, the rapid urbanization of the population, the popularization of fast food have led to a shift in

eating patterns. Now people eat more foods that are high in calories, fats, free sugars and low in vitamins and fiber. The composition of a person's healthy diet is based on the individual characteristics of the body (for example, height, gender, age, level of physical activity) and cultural customs. However, there are generally accepted principles of healthy eating [1], which are summarized below (Figure).

The wrong food stereotype is associated not only with non-observance of the basics of proper nutrition, but also with certain types of eating disorders.

There are three main types of eating disorders: [2,3]

1) **External eating behavior** is manifested by the patient's increased reaction to conditioned food stimuli (covered table, bakery advertisement, food "for company"). With this disorder, a person will eat regardless of how many hours ago the last meal was and if he feels a sense of hunger.

2) **Emotiogenic eating behavior:** with this stereotype, the stimulus for eating is emotional discomfort (fear, resentment, irritation, boredom). There are two forms - compulsive overeating and nocturnal eating syndrome.

Symptoms of compulsive eating behavior according to ICD-11 (code 6B82):

- a) Overeating in a short period of time.
- b) Loss of control over food intake.
- c) Eating food in the absence of a feeling of hunger and with the appearance of unpleasant sensations of an overflow of the stomach.
- d) Food alone due to shame.
- e) Depression and guilt after an episode of gluttony.
- f) The frequency of episodes of gluttony on average twice a week for six months.

Symptoms of the syndrome of nocturnal food:

- a) Low appetite in the morning, the appearance of food can cause disgust.
- b) By evening, the appetite increases, which leads to overeating.
- c) Sleep disorders.
- d) More than 25% of the daily calories consumed in the evening.
- d) Worsening of mood in the evening.

3) **Restrictive eating behavior** is an unsystematic strict diet, followed by bouts of overeating and weight gain. After episodes of disruptions, patients form a feeling of guilt, a decrease in self-esteem, loss of motivation for treatment.

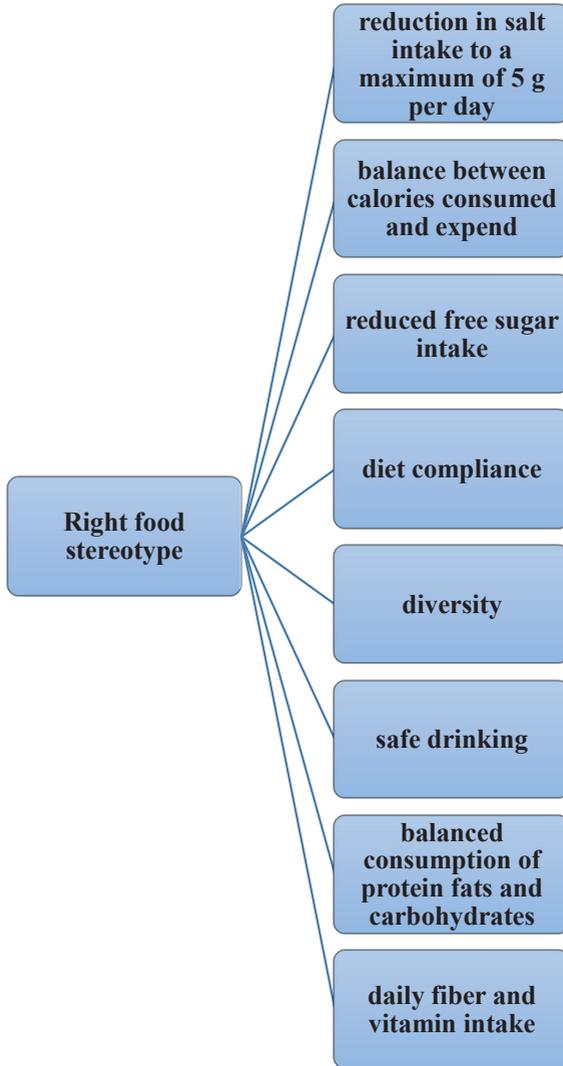


Figure 1

These eating disorders are the basis of diseases such as orthorexia nervosa, anorexia nervosa, bulimia nervosa, compulsive overeating. The latter often leads to overweight.

### **Materials and research methods**

To achieve the goal set, we used documentary, systemic and structurally logical methods, monitoring scientific articles in periodicals. The authors put their own research into the basis of the recommendations made. [4]

### **Results and discussion**

Based on their own research, the authors made recommendations for parents that help prevent the development of the wrong food stereotype (Figure 2).

These recommendations should be a continuation of the basic approaches for the early formation of proper nutritional behavior, which include: ensuring a healthy fetal nutrition in the prenatal period, support for breastfeeding and competent feeding input [5].

### **Conclusion**

The right food stereotype helps to improve the quality of life and reduce the risk of noncommunicable diseases, such as obesity, diabetes, etc. Food habits are laid in childhood, so it is important to observe the following approaches in raising children: do not force-feed the child, do not encourage the child to eat, control the food selection and a child's diet, to show the child the right example. These recommendations should be known to parents, caregivers, and healthcare providers, thus making a significant contribution to preventing the development of eating disorders and the consequences arising from them.

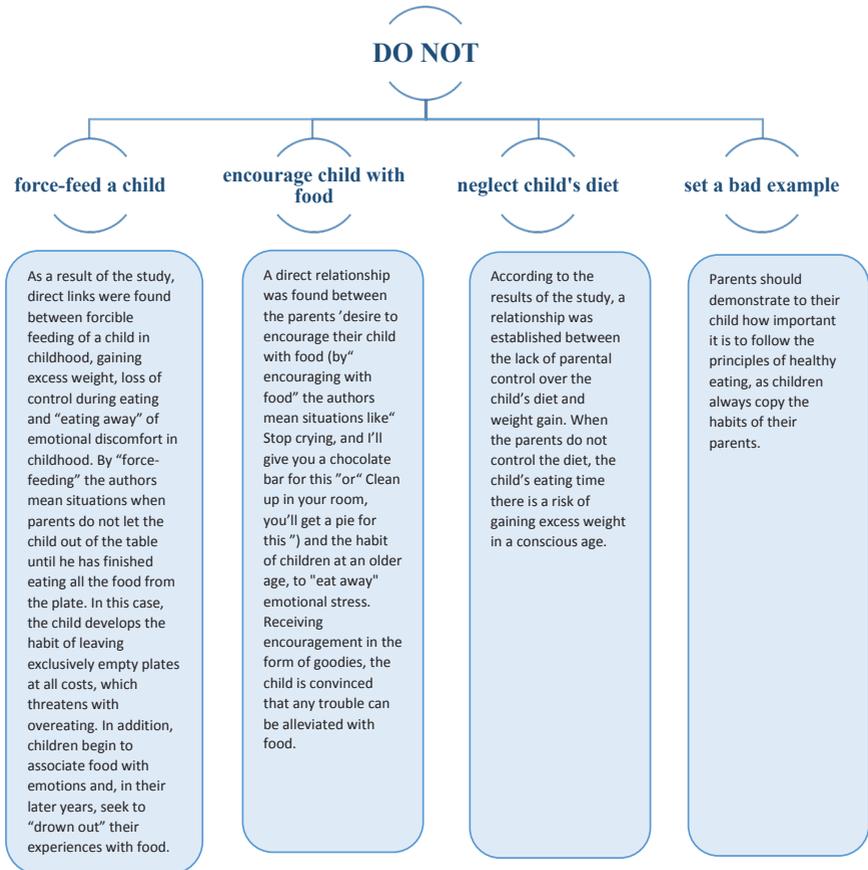


Figure 2

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**MORPHOFUNCTIONAL CHARACTERISTICS OF THE MAST CELL  
POPULATION IN THE LUNGS OF RATS ALTER AN ONCE AND  
REPEATED DEEP IMMERSION HYPOTHERMIA**

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**Annotation.** *The purpose of the work is a comparative analysis of the effect of once and repeated daily deep immersion hypothermia on the morphofunctional activity of lung mast cells (MC) of Wistar rats. The experiment involved 45 rats. Hypothermia was modeled by placing animals in individual cages in water at a temperature of 5 ° C, at an ambient temperature of 7 ° C. The exposure to the cold factor was stopped when the animals reached a deep degree of hypothermia, the criterion of which was a rectal temperature of 20-25 ° C. The material for histological examination was taken immediately after hypothermia and after 2, 7 and 14 days. Immediately after exposure to the cold factor, large MC in the state of granulocytolysis was revealed in the lung tissue of the groups of animals. On the 2nd day of the experiment a single number of MC in the field of view increased by 37.1% with repeated hypothermia compared with a once hypothermia; the MC area increased by 32.2%; the number of degranulating MC increased by 14.4%, and the content of compact forms of MC decreased by 17.9%. On the 7th day with multiple hypothermia, the number of MC in the field of view increased by 32.3%; the number of degranulating MC was 1.9 times greater, and the content of compact MC forms decreased 1.4 times. On the 14th day, the number of MC in the field of view increased 3.1 times; the number of degranulating MC was 1.45 times greater, and the content of compact MC forms decreased by*

1.2 times. Thus, MC are an important element in long-term lung adaptation when they are exposed to repeated deep immersion hypothermia.

**Keywords:** hypothermia, lungs, mast cells, adaptation.

About 3 thousand people are exposed to fatal hypothermia every year in the world [1]. The adverse effects of low temperature to the human organism are possible under various circumstances. First of all, these are natural and climatic factors, especially in the winter season, when the air temperature can reach -40, -50 degrees and below, and, as you know, Russia is the coldest country in the world. V. P. Chashchin (2014) [2] says that the permafrost zone represents up to 70% of the territory of our country. About 7 million people live in the colder regions, which Russian legislation classifies as “the Far North and its equivalent regions”. Therefore, it will be obvious that the Russian Federation has very good reason to consider cold as a national problem. Low temperatures affect humans and many industrial plants.

Hypothermia is classified according to the degree and duration of exposure to the cold factor. According to the degree of exposure to cold, it is distinguished: mild hypothermia, when body temperature is in the range from +35 to +32 ° C; moderate hypothermia, when body temperature varies from +32 to +28 ° C; deep hypothermia when the body temperature is in the range from +25 to +20 ° C and super deep hypothermia when the body temperature is below +20 ° C. The duration of exposure distinguishes between short-term hypothermia, which lasts from several minutes to several hours, and prolonged hypothermia, the exposure time of which is from several hours to several days [3].

The urgent problem is the activation of the human body's adaptation processes under the influence of cold stress. Therefore, the development of adaptogens, the action of which would be aimed at the state of dead-adaptation that occurs during cold exposure, but it is important to study the structural interlacement of the immune system cells and especially mast cells [4], becomes a priority.

MC play an important role in regeneration processes [5, 6], in hypoxic conditions [7], stress [8–10], and they can also stimulate carcinogenesis [11, 12]. According to modern concepts, MC are important in compensatory-adaptive reactions of the human body on the action of damaging extreme factors and hypothermia. Redistribution and migration of MC between organs and tissues under stress and the action of various damaging factors can be considered in the framework of the adaptation syndrome [13]. All this allowed some authors to express the idea that MC are a single independent regulatory system of the body.

MC in the lungs are important. They interact with cellular istromic micro-environment and have direct and inverse relationships with the immune, endocrine nervous system of the body [14]. During granule exocytosis, histamine is released from the MC, which stimulates the secretion of mucus by goblet cells and gland cells of the submucous layer of the trachea and bronchi. Also, MC histamine causes a spasm of smooth muscles of the small bronchi and bronchioles and an increase in the permeability of capillaries of the interalveolar septa. MC activate fibroblasts, macrophages, stimulate the migration of neutrophils and lymphocytes into the lung tissue. But, despite the active study of MC in the respiratory system under physiological and pathological conditions, when exogenous and endogenous extreme factors are exposed to the lung tissue, their morphofunctional activity has not been studied enough.

The purpose of the study was a comparative analysis of the effect of single and multiple daily deep water hypothermia on the activity of lung mast cells of Wistar rats.

**Materials and research methods.** The study was conducted on 45 male Wistar rats with the weight of 200-240 grams. Animals ( $n = 20$ ) were subjected to once and repeated ( $n = 20$ ) daily deep immersion (water) hypothermia (DIH). Hypothermia was modeled as follows: animals that were in individual cages were placed in water at a temperature of  $5^{\circ}\text{C}$  at an ambient temperature of  $7^{\circ}\text{C}$ . The exposure to the cold factor was stopped when the animals reached a deep degree of hypothermia, the criterion of which was a rectal temperature of  $20\text{-}25^{\circ}\text{C}$ . The exposure time of the cold factor averaged  $40 \pm 5$  minutes. Immediately after the cessations of cooling, after 2, 7, and 14 days, the animals were removed from the experiment by decapitation, each group consisted of 5 rats. The control group consisted of 5 rats, which were placed in water at a temperature of  $30^{\circ}\text{C}$  in individual cages, at an ambient temperature of  $22\text{-}25^{\circ}\text{C}$ . The exposure time in the control group corresponded to the exposure time in the experimental group. The use of rats in the experiment was carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used in the Experiment and Directives 86/609 / EEC.

For histological examination, pieces of lung tissue were fixed for 24 hours in a 10% solution of neutral formalin, after which the TISSUE-TEK VIPTM6 machine (Sakkura, Nagano, Japan) was processed, followed by paraffin filling at the TISSUE-TEK TEC 5 paraffin filling station (Sakkura, Nagano, Japan). Slices of 5-7 mcm thick were made on an Accu-Cut SRM rotary microtome (Sakkura, China). The preparations were stained with hematoxylin-eosin in the TISSUE-TEK Prisma auto-tuner (Sakkura, Na-

gano, Japan). MC are detected by the toluidine blue BiOvitrum (St. Petersburg). The preparations were photographed using a LeicaDM 750E200 microscope (Germany) with a LeicaEC3 digital video camera (Germany) at a magnification of x 400. The distribution density of MC was calculated in the VideoTest-Morphology 5.2 program in 5 fields of view with an x400 magnification. The field of view of the microscope was 0.366 mm<sup>2</sup>. It was necessary to determine the index value of mast cells degranulation (the ratio of MC in the state of degranulation to the total number of analyzed cells expressed as a percentage). The morphometric measurements of the MC were carried out by the morphometric program VideoTest-Morphology 5.2. Statistical processing of the obtained data was carried out using the statistical software package Statistica10.0 and statistical analysis software package MSEXEL 2010. For each of the values, the mean (M) and the error of the mean (m) were calculated. The hypothesis of the normality of the probability distribution of the data was checked using the Shapiro-Wilk test. The reliability of the data was evaluated using the parametric criterion of Student t-test. The critical value of the level of statistical significance was 0.05.

**Research results and discussion.** In the lungs of animals of the control study group when staining with toluidine blue MC were visible in the pleura, in the adventitia of the bronchi and vessels. They were small in size and mostly rounded in shape. The distribution density of the MC varied from 1 to 4 and averaged  $2.0 \pm 0.5$  in the field of view with an increase of x 400. The area of the MC was  $82.5 \pm 3.6$  mcm<sup>2</sup>. The compact forms of MC, in which the granules were compact, were  $87 \pm 10.1\%$ ; degranulating forms of MC, when the phenomenon of degranulation was detected, was  $23 \pm 10.1\%$ .

In the lung tissue of experimental animals, immediately after exposure to a single DIH, MC were found predominantly in peribronchial tissue. They were large, rounded or oval in shape and were pale purple in color. The distribution density of the MC ranged from 1 to 6 and averaged  $2.7 \pm 0.8$  in the field of view. The MC area was  $184.5 \pm 14.9$  mcm<sup>2</sup>. It should be noted that a significant part of the identified MC were in a state of devastation as a result of the secretion of granules. The number of degranulating MC was equal to  $75 \pm 17.1\%$ ; there were 25 compact forms of MC-  $25 \pm 17.1\%$ .

With multiple DIH, for a given period of the experiment, the number of MC in the field of view increased to  $2.9 \pm 0.8$ . The MC area increased to  $190.5 \pm 10.9$  mcm<sup>2</sup>. The content of degranulating MC was  $78 \pm 16.1\%$ . The compact forms of MC were  $22 \pm 16.1\%$ . (table. 1.2).

**Table 1.** Quantitative and morphometric parameters of MC of rat lung tissue during once deep water hypothermia

| Mast Cell Parameters               | Experiment Day                   |                         |                           |                           |
|------------------------------------|----------------------------------|-------------------------|---------------------------|---------------------------|
|                                    | Immediately after hypothermia(I) | 2 <sup>nd</sup> day(II) | 7 <sup>th</sup> day (III) | 14 <sup>th</sup> day (IV) |
| The number of MC                   | 2,5±0,8                          | 6,6±0,5                 | 8,0±1,0                   | 4,3±0,3                   |
| The number of compact MC (%)       | 25±17,1                          | 52±8,9                  | 76,7±8,6                  | 70,7±12,2                 |
| The number of degranulating MC (%) | 75±17,1                          | 48±8,9                  | 23,3±8,6                  | 29,3±12,2                 |
| MC area(mcm <sup>2</sup> )         | 184,5±14,9                       | 84,2±3,5                | 107,9±7,3                 | 90,8±6,2                  |

**Note:** for the amount of MC: PI-II, PI-III, PI-IV <0.01. PII-III, PII-IV <0.04. PIII-IV <0.001. For the number of compact MC: PI-II, PI-III, PI-IV <0.001. PII-III <0.01. For amounts of degranulating MC: PI-II, PI-III, PI-IV <0.03. PII-III <0.04. For the MC area: PI-II, PI-III, PI-IV <0.000005. PII-III <0.0004.

**Table 2.** Quantitative and morphometric parameters of lung tissue of rats during repeated deep water hypothermia

| Mast Cell Parameters               | Experiment Day                   |                          |                           |                           |
|------------------------------------|----------------------------------|--------------------------|---------------------------|---------------------------|
|                                    | Immediately after hypothermia(I) | 2 <sup>nd</sup> day (II) | 7 <sup>th</sup> day (III) | 14 <sup>th</sup> day (IV) |
| The number of MC                   | 2,9±0,8                          | 10,5±0,8                 | 10,3±0,6                  | 13,4±1,9                  |
| The number of compact MC (%)       | 22±16,1                          | 42,7±4,2                 | 54,7±2,9                  | 58,5±4,3                  |
| The number of degranulating MC (%) | 78±16,1                          | 56,3±4,2                 | 45,3±2,9                  | 42,5±4,3                  |
| MC area (mcm <sup>2</sup> )        | 190,5±10,9                       | 124,2±7                  | 100,2±3,0                 | 88,0±6,2                  |

**Note:** for the amount of MC: PI-II, PI-III, PI-IV <0.01. For the number of compact MC: PI-II, PI-III, PI-IV <0.001. PII-III <0.01. For amounts of degranulating MC: PI-II, PI-III, PI-IV <0.03. PII-III <0.04. For the MC area: PI-II, PI-III, PI-IV <0.00004. PII-III <0.03. PIII-IV <0.04.

**On the 2nd day** of the posthypothermal period after a once DIH MC groups were located in the walls of thickened interalveolar septa. They were small, had a round or oval shape. The distribution density of the MC varied from 4 to 10 and averaged  $6.6 \pm 0.5$  in the field of view. The MC area on average was —  $84.2 \pm 3.5$  mcm<sup>2</sup>. The number of compact MC was  $52.0 \pm 8.9\%$ , MC in the state of degranulation was  $48.0 \pm 8.9\%$  (Table 1.2).

With repeated DIH, the number of MC in the field of view increased by 37.1%. The area of the MC increased by 32.2%. The content of degranulating MC increased by 14.4%, and the number of compact forms of MC decreased by 17.9%, respectively (Table 1.2).

**On the 7th day** of the posthypothermal period after a once DIH, MC migration to the peribronchial connective tissue was noted, while the number of cells in the capillaries of the interalveolar septa significantly decreased. At this experiment period, the morphometric parameters of the MC were significantly different from the previous period of the experiment: they had larger sizes, more intense coloring and elongated, or irregular, shape. The distribution density of MC ranged from 6 to 12 and averaged  $8.0 \pm 1.0$  in the field of view; their area increased to  $107.9 \pm 7.35 \mu\text{m}^2$ . Compact MC were -  $76.0 \pm 8.6\%$ , degranulating cells was -  $23.3 \pm 8.6\%$ .

With repeated DIH, the number of MC in the field of view increased by 32.3%. The area of the MC did not change significantly. The number of granule MC was 1.9 times greater, and the number of compact forms of MC decreased 1.4 times, respectively (Table 1.2).

**On the 14th day** of the posthypothermal period, MC were located mainly singly or in small groups in the peribronchial tissue. At this time of the experiment, the MC were small in size, round cells prevailed. The distribution density of the MC varied from 3 to 5 and averaged  $4.3 \pm 0.3$  in the field of view, and the cell area was on average  $90.8 \pm 6.2 \mu\text{m}^2$ . The number of compact MC was  $70.7 \pm 13.2\%$ , the number of cells in the state of degranulation was  $29.3 \pm 12.2\%$ .

With repeated DIH, the number of MC in the field of view increased 3.1 times. The area of the MC was not significantly changed. The number of degranulating MC was 1.45 times greater and the number of compact MC decreased 1.2 times, respectively (Table 1.2).

**Discussion.** In a recent study, we studied the morphofunctional activity of MC in the lungs of rats after a once DIH [10]. In the same study, a comparative analysis of the activity of MC was performed during the once and repeated DIH. It was revealed that with the once DIH immediately after exposure to cold stress, the MC system was in a state of exhaustion; most MC were in a state of total degranulation and granulolysis. On the 2nd day after hypothermia, the number of MC increased, the cells were small, and most of them were in the thickened walls of the interalveolar septa, which may indicate the migration of MC into the lung tissue from the bloodstream due to young forms. Migration of MC to the lungs with hypothermia should be considered as part of the adaptation syndrome. Similar data was obtained by other authors. So, O. S. Artashyan (2012) in experiments on rats subjected to immobilization stress revealed a redistribution of MC between organs: an

increase in the content of MC was observed in the adrenal glands, liver, skin, mucous membrane of the stomach and intestines, while their content in the bone marrow and thymus decreased significantly [13]. On the 7th day of the posthypothermic period, MC migrated from the alveoli to the peribronchial connective tissue, and the number of degranulating forms decreased and on the 14th day of the experiment, the content of MC in the state of degranulation was the smallest, and the number of MC was close to normal. With repeated daily DIH at all stages of the experiment in the lung tissue, the number of MC and the number of degranulating forms increased in comparison with the once DIH. On the 2<sup>nd</sup> day, higher MC migration to the lungs was noted, as a result of which peribronchial and perivascular infiltration increased on the 7<sup>th</sup> day, which increased even more on the 14<sup>th</sup> day of the experiment. Thus, the results of the study showed that the morphofunctional activity of MC in the lung tissue of rats depended on the duration of exposure to the cold factor.

The different dynamics of the morphological and functional activity of MC, which we found during once and repeated DIH, in our opinion, was interconnected by compensatory-adaptive reactions. Adaptive reactions are known to be divided into two types: 1) urgent, but unstable and imperfect adaptation and 2) long-term, sustainable adaptation [10]. An urgent adaptive reaction occurs immediately after the onset of exposure to a damaging factor and it is implemented by previously formed biological mechanisms. In this case, the reaction of the body is carried out at the limit of physiological capabilities and the effects of adaptation do not work at full strength. Long-term stable adaptation, as a rule, is formed during prolonged repeated exposure of the damaging factor to the body. As a result, there is a gradual accumulation of certain changes that allow the bodies to acquire new properties and qualities, and turn from unspecialized to adapted. At the same time, the functional reserves of the organs increase, which allows them to tolerate high stress loads.

The results of the study showed that with repeated DIH in rats, a long-term adaptation of the bronchopulmonary apparatus to cold stress was formed. Long-term adaptation in rat lung tissue when exposed to hypothermia, in our opinion, was structurally ensured by an increase in the number of effector MC, as well as an increase in their morphofunctional activity. As you know, hypothermia leads to hypoxia and damage to body tissues. MC express receptors that respond to changes in the partial pressure of oxygen and carbon dioxide; therefore, activation of MC under the influence of a hypoxic factor is a natural process [15].

**Conclusion.** Thus, with repeated daily deep immersion hypothermia in the lung tissue of rats, long-term adaptation phenomena form the structural manifestation of which is an increase in the number of effector MC and an increase in their morphofunctional activity.

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## INFLUENCE OF COOLING MEDIUM ON PLOIDOMETRIC PARAMETERS OF WHITE RAT HEPATOCYTES

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**Annotation.** The research studies the influence of the cooling medium (single immersion hypothermia (water) and single air hypothermia) on the hepatocytes of Wistar rats liver. It is presented that under the influence of deep water hypothermia (rapid cooling rate) immediately after exposure to hypothermia, pronounced hepatocyte alteration was observed, then adaptive compensatory processes were activated on the 7th day with an increase in the number of high-ploid cell pools (up to 13c), and the ploidy of hepatocytes was restored only on the 14 day. Under the influence of moderate air hypothermia (slow rate of cooling), the processes of alterations in the liver proceeded much less intensively (4-5 times lower than in water hypothermia), polyploidization of hepatocytes (the appearance of a pool of 9c-13C) was observed immediately after exposure to hypothermia, and the 2c-4c population was approaching to normal already on day 7. Thus, the cooling medium has a different effect on the ploidometric profile of hepatocytes of experimental animals.

**Keywords:** hypothermia, cooling medium, hepatocytes, ploidy.

The environment temperature is one of the main abiotic factors that influences homeostasis of humans and animals and changes of the thermal regime entails violations of all body systems [11]. At the same time, a significant part of our country population inhabits areas with low ambient

temperature. From 40% to 70% of the Russian territory is the permafrost zone [6], where the air temperature can rapidly decrease and reach 40-50 degrees below zero °C and below, and therefore the cold is our national problem [12,13].

Air cooling (air hypothermia) is characterized by the contact of limited areas of the body surface with the environment. It leads to a longer period of temperature decrease and the formation of local damage. Water cooling (immersion hypothermia) provides full contact with the cooling factor, which is accompanied by a more intense effect of the damaging factor on the body. It leads to a more intense heat transfer and the cooling period takes a minimum time [8].

The restoration of the total cell genome is the general principle of adaptation of damaged mammalian organs. It is achieved either by cell division or by increasing the total genome in the cell, i.e. polyploidy. The liver polyploidy directly reflects the intensity of regenerative processes after injury and correlates with the strength of the damaging factor [10].

There is a small number of works that focus on the tissue and intracellular reorganization of the liver in hypothermia [2,4,5,7,9]. However, there are very few studies of the ploidy characteristics of hepatocyte nuclei under the influence of the cold factor, and we have not found any studies of the effect of hypothermia on liver cells depending on the cooling medium.

**The aim of the research** is to study the ploidy characteristics of Wistar rat hepatocyte nuclei under the influence of hypothermia depending on the cooling medium.

**Materials and methods of research.** 50 white Wistar rats were used for the research purpose. Two hypothermia models were used to study the influence of cooling factor on the animal liver in dependence of cooling medium: single deep water (immersion) and single moderate air. The animals were divided into 3 groups: Group 1 – control group, intact animals on a free diet ( $n = 10$ ); group 2 – animals who underwent deep immersion hypothermia ( $n = 20$ ); group 3 – animals who underwent moderate air hypothermia ( $n = 20$ ).

Single deep immersion hypothermia was simulated by placing animals in individual cells in water with a temperature of 5 °C, at an ambient temperature of 7 °C. the Criterion for termination of the experiment was a rectal temperature decrease to 20-25 °C, the exposure time was  $40 \pm 5$  minutes.

A single moderate air hypothermia was simulated by placing animals in the individual cells into a cooling chamber at an air temperature of -25 °C until a rectal temperature is 30 °C. The exposure time was individual and lasted about  $6 \pm 3$  hours.

The animal from 2,3 groups were removed from the experiment by the decapitation immediately after cooling, then after 2,7 and 14 days (5 animals per 1 time) in accordance with the "Regulations of animal experimentation". Liver samples were fixed in 10% neutral formalin for 24-48 hours, then wired on TISSUE-TEK VIPTM6 (Sakkura, Japan), poured into paraffin Histomix (paraffin filling station TISSUE-TEK TEC 5, Sakkura, Japan). The slices were produced on a rotary microtome Accu-Cut SRM (Sakkura, Japan), stained with hematoxylin and eosin in TISSUE-TEK Prisma (Sakkura, Japan) and enclosed under the film in TISSUE-TEK Film (Sakkura, Japan). The average number of hepatocytes in 5 visual fields was calculated on the medicine stained with hematoxylin and eosin while it was increased in X400 and the alteration index (the ratio of the number of necrotized hepatocytes to the total number of hepatocytes in 5 visual fields).

Cell nuclei sections were stained by Felgen method using cold hydrolysis in 1N HCl solution for 1.5 hours to find the ploidy of rat liver. 25-30 nuclei were tested to find DNA as well as 25 nuclei of small lymphocytes in the same series of slices. The average DNA content in the nucleus of a small lymphocyte was taken as a diploid value (2C). Ploidometry was carried out using Vidiotest-Morphology 5.2. program ("Videotest", Saint-Petersburg, Russia) using modules such as "Standard" and "Ploidy". We were searching for the DNA accumulation index (IADNA) - the average parameter of DNA content in the nuclei of hepatocyte nuclei according to Avtandilov G.G. (2000) [1]. We were building the histograms of cells distribution according to IADNA. The pictures were taken by the Nikon Eclipse E200 microscope (Japan) which has a lens of 1000 x 1.25, light filter - 570 nm and digital video camera VIDICAM (Russia). Lighting conditions of the studied objects were the same during all measurements.

Statistical processing of the material was carried out using Statistica 6.0. package. If the distribution was normal, we used the methods of parametrical statistics (Student's t-distribution). If the measurements did not correlate to the criteria of normal distribution (Shapiro-Wilk criterion  $W = 0.89$ ,  $p < 0.01$ ), we used the methods of non-parametrical statistics: Kolmogorov-Smirnov test or Mann-Whitney U-test. The data were considered reliable at  $p < 0.05$ .

**Research results.** The ploidometric analysis showed that IADNA in the liver cells of the rats control group had special features such as a low value ( $3.5 C \pm 0.1$ ) and that the tetraploid cells prevailed. It corresponds to the literature [3].

**Immediately after** a single water hypothermia was applied to the animals of the second group, the number of hepatocytes in 5 fields of vision increased by 17.8%, the index of alteration increased by 81.25 times, the IADNA in the nuclei of hepatocytes was reduced by 8.6% in comparison to the control group (table). Immediately after a single moderate air hypothermia applied to the animals of the 2 group, the number of hepatocytes in 5 fields of vision decreased by 30.3%, the index of alterations increased 19.25 times, the IADNA in the nuclei of hepatocytes was increased by 2, 3 times compared to the control group (see table.). But comparatively with the 2 group, during this period number of hepatocytes and index of alteration reduced (by 40.8 and 70.3% respectively) and IADNA increased 2.5 times.

**Table.** Morphological and ploidy parameters of hepatocytes in different types of hypothermia

| The parameters of hepatocytes            | The duration of the experiment |                         |                          |                          |                           |
|--|--------------------------------|-------------------------|--------------------------|--------------------------|---------------------------|
|  | Control                        | Right after hypothermia | 2 days after hypothermia | 7 days after hypothermia | 14 days after hypothermia |
| Water hypothermia                        |                                |                         |                          |                          |                           |
| Number of hepatocytes in 5 visual fields | 180.5±5.5                      | 212.6±12.9*             | 174.4±9.3*               | 132.8±3.3*               | 148.7±7.6*                |
| Index of alterations (%)                 | 0.4±0.1                        | 32.5±3.1*               | 38.85±2.2*               | 21.9±1.3*                | 6.6±0.7*                  |
| IADNA (C)                                | 3.5 s±0.1                      | 3.2±0.2*                | 5.7±0.2*                 | 9.3±0.2*                 | 6.6±0.7*                  |
| Air hypothermia                          |                                |                         |                          |                          |                           |
| Number of hepatocytes in 5 visual fields | 180.5±5.5                      | 125.8±4.0*              | 154.6±5.9*               | 174.2±3.3*               | 200.4±5.9*                |
| Index of alterations (%)                 | 0.4±0.1                        | 7.7±1.6                 | 7.2±1.2                  | 4.3±0.4*                 | 1.2±0.2*                  |
| IADNA (C)                                | 3.5 s±0.1                      | 8.05±0.2*               | 5.5±0.1*                 | 4.4±0.1*                 | 3.4±0.1*                  |

**Note.** \*  $p < 0.05$  compared to control group.

**2 days after** hypothermia was applied to the 2 group, the number of hepatocytes in comparison with the control group was reduced by 3.4%, the index of hepatocyte alteration increased 97 times, IADNA in cell nuclei increased 1.6 times, the limits of IADNA oscillations were from 2C to 13C (see table.). In group 3 of the study the dynamics of changes was similar to group 2 after 2 days: in comparison to the control group, the number of hepatocytes reduced by 14.3%, index of alteration increased 18 times, IADNA increased 1.6 times (see table). Comparative analysis applied after 2 days of the experiment to groups 2 and 3 showed that air hypothermia provided a decrease in the number of hepatocytes by 11.3 %, the index of alterations – by 81.5%, IADNA-by 3, 5% in comparison with water hypothermia.

**7 days after** deep hypothermia was applied to group 2 in comparison to the control, the number of hepatocytes in 5 fields of vision was reduced by 26.4%, the index of alterations was increased by 54.75 times, the IADNA in the nuclei increased by 2.7 times (see table.). The dynamics of changes of group 3 was the same as in group 2 in 7 days: in comparison to the control group, the number of hepatocytes reduced by 3.5%, index of alteration increased 10.75 times, IADNA increased by 25.7% (see table). Comparative analysis applied after 7 days of the experiment to groups 2 and 3 showed that air hypothermia provided an increase in the number of hepatocytes by 31.2 %, the index of alterations – by 80.4%, IADNA - by 52.7% in comparison with water hypothermia.

**14 days after** hypothermia was applied to group 2 in comparison to the control, the number of hepatocytes in 5 fields of vision was reduced by 17.6%, the index of alterations was increased by 16.5 times, the IADNA in the nuclei increased by 88.6% (see table.). 14 days after hypothermia was applied to group 3, in comparison to the control group, the number of hepatocytes was increased by 11.0%, the index of alterations was increased 3 times, the index of IADNA in the nuclei decreased by 2.9% (see table.). Comparative analysis applied after 14 days of the experiment to groups 2 and 3 showed that air hypothermia provided an increase in the number of hepatocytes by 34.7 %, the index of alterations – by 81.8%, IADNA - by 48.5% in comparison with water hypothermia.

Analysis of ploidy histograms of hepatocyte nuclei showed that the hepatocytes of the control group were represented by diploid, 2c (20%), triploid, 3c (30%), tetraploid, 4c (46%) and octaploid cells, 8c (4%).

Immediately after hypothermia was applied to the animals of group 2 the distribution of hepatocytes by IADNA was the following: 1c - 3.4%, 2c - 43.8%, 3c - 16.85%, 4c - 21.35%, 5c - 4.5%, 6c - 2.25%, 7c - 6.7% and 8c - 1.15%. The histogram of the IADNA distribution had a shift to the left and a single peak near hepatocytes with ploidy of the nucleus 2c. Immediately after the exposure

of hepatocytes with ploidy from 1c to 4c in the animals of group 3, the number of clones increased from 5c up to 8c (5c - 3.8%, 6c - 14.4%, 7c - 24.4%, 8c - 16.7%) and the closed with IADNA from 9c to 13c emerged (9c - 19.2%, 10c - 14.1%, 11c - 2.6%, 12c - 2.6%, 12c - 2.2). The histogram of the cells distribution by IADNA had a shift to the right and a single peak near 7c region.

2 days after hypothermia was applied to group 2, hepatocytes distribution was as following: 1c - 0%, 2c - 5%, 3c - 12.5%, 4c - 11.25%, 5c - 23.75%, 6c - 15%, 7c - 13.75%, 8c - 7.5%, 9c - 6.25%, 10c - 1.5%, 11c - 2.25%, 12c - 0% and 13c - 1.25%. The histogram of INDNA distribution showed a wide heterogeneity of values, there was a single peak near 5c and a shift to the right. There was 4.1%, 4c - 24.5%, 5c - 24.5%, 6c - 22.4%, 7c - 15.3%, 8c - 6.1%, 9c - 3.1% 2 hepatocytes with nuclei ploidy days after hypothermia was applied to group 3. Analyzing the histogram of the IADNA distribution, it should be noted that hepatocytes with ploidy 3c and 4c have appeared and hepatocytes with 10c – 13c have disappeared. The histogram had a shift to the right and peaks near 4c and 5c.

7 days after the exposure applied to group 2, hepatocytes with ploidy nucleus 1c - 4c disappeared, 5c - 1.4%, 6c - 1.4%, 7c - 6.8%, 8c - 16.4%, 9c - 32.9%, 10c - 27.4%, 11c - 5.5%, 12c - 2.7% and 13c - 5.5%. The histogram of the IADNA distribution was characterized by a shift to the right and had a single peak near 9c. 7 days after exposure in group 3, the number of hepatocytes with core ploidy 3c was 16.25%, 4c - 52.5%, 5c - 13.75%, 6c - 10%, 7c - 6.25%, 8c - 0% and 9c - 1.25%. Histogram analysis showed growth of hepatocyte clones near 3c and 4c and decrease from 5c to 9c. The histogram of the IADNA distribution was characterized by a shift to the left and had a high peak near 4c.

14 days after, the amount of hepatocytes with core ploidy 1c was not observed in group 2, 2c - 6.7%, 3c - 8.3%, 4c - 26.7%, 5c - 23.3%, 6c - 18.3%, 7c - 16.7%, 8c - 0%, 9c - 0%, 10c-13c - 0%. The histogram of the IADNA distribution was characterized by a shift to the right and had a single peak near 4c. After 14 days hepatocytes were distributed as follows in group 3 : 2c - 17.5%, 3c - 30%, 4c - 51.25% and 7c - 1.25%. The histogram of the cells distribution had a shift to the left and a single peak near 4c.

**Conclusion.** Thus, deep water hypothermia had a pronounced damaging effect on the liver of experimental animals, which was expressed, first of all, by an increase in the index of hepatocyte alteration immediately after exposure (81 times) and maintaining high index values up to 14 days; an increase in the number of diploid hepatocytes by 2.2 times and a shift in the histogram of the IADNA distribution to the left. Ploidometric analysis in the posthypothermic period revealed a decrease in the number of 2c

hepatocytes (4 times) on day 2, the disappearance of this pool of cells on day 7 and the appearance of a pool of 2c hepatocytes on day 14 (below the control level by 3 times). IADNA significantly increased on the day 7 (2.7 times), during this period 9c and 10C cells were dominating (histograms had a sharp shift to the right), that may indicate compensatory-adaptive processes in liver tissue. By day 14 of the experiment, IADNA remained 1.9 times higher than control group.

After air hypothermia was used, the index of hepatocyte alteration also increased, but less significantly than in the water regime (19 times versus 81 times relative to the control), gradually decreasing by the end of the observation, but remaining 3 times higher than of the control values. IADNA increased immediately after exposure (2.3 times), normalizing to day 14. Immediately after exposure, hepatocytes 9c and 10c dominated in the liver (the histogram had a sharp shift to the right), which may indicate early adaptation processes. In postgerpeticescoy period – immediately after exposure – ploidy analysis revealed the disappearance of the pool of 2c-4c hepatocytes and the appearance of clones 9c-13c (40% of all hepatocytes); on the day 2 4c hepatocytes emerged (less control by 47%) and the 10c - 13c clone disappeared; on day 7, the growth of 4c hepatocytes clone (above the control by 14%) and the disappearance of 8c and 10c - 13c clones; 14-th day – the emergence of 2c hepatocytes (less control 12.5%) and the growing number of 4c hepatocytes (above the control by 11%).

Thus, the results of the study showed that the cooling medium had a significant impact on the ploidy profile of hepatocytes of experimental animals, and the nature of these changes correlates with the rate of cooling. If the cooling is fast (deep water hypothermia), there was a rapid decrease of genetic material content in the nuclei of hepatocytes immediately after exposure and it increased only in 7 days. If the cooling is slow (moderate air hypothermia) the hepatocyte adaptation and significant increase of IADNA in the nuclei was right after the exposure.

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## THE SIZE OF TUMOR AND HISTOLOGIC STRUCTURE OF PERITUMOROUS ZONE OF RINAL CELL CARCINOMA

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**Annotation.** The authors have studied the peculiarities of histological structure of peritumorous zone (PZ) as well as the biosynthetic and proliferative processes in the tissues near the kidney cancer taking into account the size of tumor. PZ of the tumors which size was  $\geq 4$  cm contained active sclerotic and proliferative processes. Zones of severe sclerosis in PZ had focuses of severe tubular epithelial dysplasia which can not be distinguished from cancer using DNA microspectrophotometry. Also PZ of the tumors of the mentioned size had pathological tumor neoangiogenesis. The high density of vessels in the microcirculation correlated with a high rate of endothelial cell proliferation (according to silvering AgNOR). These changes, which take place in the kidney parenchyma near the tumor which size is  $\geq 4$  cm, should be taken into account making an organ preserving surgery.

**Keywords:** kidney cancer, tumor size, pretumorous zone, angiogenesis.

The research, that focuses on the histological structure of the pretumorous zone (PZ) of a kidney cancer and violation of proliferative and biosynthetic processes it, is relevant because the kidney tumor abound in surgery of organ preserving tactics [6].

The absence of deliberate pathoanatomical researches focusing on kidney cancer PZ makes it possible for some authors to claim that macroscopically "clean" surgical edge is enough to reject urgent histological examination, making kidney resection, which depends on operating surgeon decision due to inordinate amount of false positive and negative results. [9, 12].

It is recognized that one of the leading factors determining the survival of patients with organ-preserving operations of kidney cancer is the size of the tumor. Some authors the survival rate of patients was significantly higher resectioning a kidney tumors of less than 4 cm than at a size of more than 4 cm [11]. However, there is disagreement in determining the maximum tumor size for elective organ-preserving operations. Some studies show that organ-preserving operations of tumors smaller than 4 cm were accompanied by a 27% level of invasion into the peritumorous pseudocapsule [13]. Minervini A. et al. (2009) showed that an increase of tumor size even by 1 cm significantly increased the number of cases when tumor cell growth in the peritumorous pseudocapsule was detected. On the other hand, there is another extreme, when operating surgeons excise the adjacent parenchyma of the kidney at a distance of 3-4 cm [5].

At the same time, there is reason to believe that the histological structure of the PZ and the biological behavior of the tumor are interrelated. Thus, Avdalyan and et al. (2010) according to the detection of CD31 protein in the endothelium and the activity of nucleolar organizers showed that the density of the microcirculatory bed (DMCB) in the PZ influenced the survival of patients with uterine leiomyosarcoma (LMS) more than the DMCB in the tumor itself and DMCB in the PZ was an independent prognostic predictor, relative to the stage and degree of malignancy. Our own studies have shown that DMCB of renal cancer was associated with the detection of distant metastases, and the presence of polyploidy and aneuploidy of renal carcinoma cells led to the proliferation focuses appearance and dysplasia in the epithelium of the tubules of the peritumorous region [7].

**Purpose of research:** to study the features of the histological structure of the PZ as well as the biosynthetic and proliferative processes of its cellular elements depending on the size of the tumor.

**Materials and methods of research.** Surgical material of 42 patients with kidney cancer was studied. The median age was  $57.4 \pm 1.4$  years. There were 25 males (59.5%) and 17 females (40.5%). The tumors were showed according to their histological structure: light cell cancer-36; papillary cancer-5 and spindle cell cancer-1. The size of the tumors varied from 1 to 15 cm and was  $6.8 \pm 0.5$  cm in average.

The material was taken from the center, PZ (PZ was considered to be the directly adjacent to the pseudocapsule tumor tissue, pseudocapsule and tissue located behind the pseudocapsule to the unchanged kidney tissue) and the most distant places from the tumor areas of the unchanged kidney tissue. The tumors were grouped according to the clinical stages (I-IV): 22 (52.4%) observations corresponded to I stage (T1N0M0); 1 (2.4%) observation to II stage (T2N0M0); 8 (19%) - III stage (T1N1M0, T2N1M0, T3N0M0, T3N1M0) and 11 (26.2%) - IV stage (T4N0M0, T4N1M0, T2n2m1, T3n1m1). The degree of malignancy of tumor cells was assessed by Fuhrman S. A. method et al., (1982) [10]. We had 2 (4.8%) tumors of G1 anaplasia degree; 11 (26.2%) tumors of G2 anaplasia; 22 (52.4%) of G3 anaplasia and 7 (16.7%) of G4 anaplasia in our materials.

An integrated approach, namely different methods of research were used to analyze biosynthetic and proliferative processes of PZ elements: histological - staining with hematoxylin and eosin; histochemical - staining on collagen by Van Gieson; elastic fibers - resorcinol - fuchsin by Weigert; silvering of argyrophil fibers by Gomori; neutral glycosaminoglycans (GAG) PAS reaction by McManus; acidic GAG – staining with alcyan blue by Steedman and colloid iron by Hale; DNA by Felgen; on General nucleic acids by Einarson and on the activity of argyrophilic proteins associated with the region of Nucleolar organizers (agnor) by Daskal y et al. [8], in our modification [3,4]. The average number of silver granules (AgNORs) per 1 cell nucleus was calculated. In each case, 25 to 30 cells were examined.

There were two groups of patients, depending on the size of the tumor:

1) tumor size  $\leq$  4 cm;

1) tumor size  $\geq$  4 cm;

Also, in each case, the density of DMCB in 20 randomly selected fields of view was calculated on oil immersion at an increase of  $\times 1000$ .

Morphometric and microspectrophotometric studies were carried out using a computer image analysis system consisting of Leica D2 microscope, Leica EC3 digital camera ("Leica Microsystems AG", Germany), Pentium 4 personal computer and Vidiotest - Morphology 5.2. software. DNA ploidy was performed on histological sections stained according to Felgen. The average DNA content in the nuclei of small lymphocytes was taken as diploid (2c) and used as a standard. 25 to 30 lymphocytes were evaluated in each section to obtain the standard. Then, the index of DNA accumulation (IADNA) was calculated in the studied cells using ploidy units (c). Then the histograms of the clonal cells distribution was built taking into account the amount of genetic material expressed in per cents.

Statistical processing of the material was carried out using Statistica 6.0. package. If the distribution is normal, we used the methods of parametrical statistics (Student's t-distribution). If the measurements does not correlate to the criteria of normal distribution (Shapiro-Wilk criterion  $W = 0.89$ ,  $p < 0.01$ ), we used the methods of non-parametrical statistics: Kolmogorov-Smirnov test or Mann-Whitney U-test. The data were considered reliable at  $p < 0.05$ . The analysis of the dependence between the features was carried out using Pearson's r-test.

**The results of the study and their discussion.** The material was divided into 2 groups. Group I included patients whose tumors were  $\leq 4$  cm (average  $3.5 \pm 0.3$  cm), and group II included patients whose tumors were  $\geq 4$  cm (average  $8.7 \pm 0.5$  cm). Group I consisted of 12 (26.6%) patients, group II - of 30 (71.4%).

PZ of malignant kidney neoplasms had a different histological structure. Its width ranged from 152.5 microns to 2593.2 microns and average width was -  $954.7 \pm 89.5$  microns. The size and morphometric parameters of the cell elements of the PZ depended on the activity of the tumor node size (table.).

**Table.** Morphometric parameters of the PZ elements, depending on the size of the tumor

| PZ parameters  | Tumor size         |                    |
|--|--------------------|--------------------|
|  | $\leq 4$ cm        | $\geq 4$ cm        |
| Width of the pretumorous zone, microns                     | $520.4 \pm 43.2^*$ | $13203 \pm 73.6^*$ |
| The nuclei area of the tubular epithelium, $\mu\text{m}^2$ | $37.9 \pm 2.0^*$   | $54.2 \pm 5.3^*$   |
| The nuclei area of myofibroblasts, $\mu\text{m}^2$         | $32.4 \pm 2.2^*$   | $64.7 \pm 4.2^*$   |
| Density of microcirculation vessels                        | $5.8 \pm 0.6^*$    | $8.6 \pm 0.8^*$    |
| The number of AgNORs in the nuclei of myofibroblasts       | $1.5 \pm 0.2^*$    | $2.8 \pm 0.4^*$    |
| The number of AgNORs in the nuclei of epithelium cannals   | $2.2 \pm 0.2^*$    | $5.15 \pm 0.35^*$  |
| Number of AgNORs in endothelial nuclei                     | $1.7 \pm 0.1^*$    | $3.5 \pm 0.4^*$    |

Note: \* -  $p < 0.05$

Thus, the PZ of I group patient tumor was  $520.4 \pm 43.2$  microns in average. Moderate sclerosis was observed in the PZ. Collagen fibers were painted in pinkish color with areas of yellow, when using Van Gieson staining in such PZ, at the same time collagen fibers were PAS-positive in the McManus reaction to neutral GAG. Acid GAG in connective tissue were not detected, but were determined in the walls of blood vessels. When staining elastic fibers with resorcinol-fuchsin according to Weigert method, a small number of thin convoluted fibers were noted, elastic membranes at the border with the tumor were found only in some areas. Thin "corkscrew-like" argyrophilic fibers were also found in the bundles of collagen fibers.

The density of lymph-plasmocytic infiltration was weak or moderate.

The width of the PZ tumors in patients of group II was  $1320.3 \pm 73.6$  microns in average. Moderate sclerosis was observed in the PZ. When painting by Van Gieson in such PZ, expressed fuchsinophilia of collagen fibers was found, the fibers gave an intense PAS reaction when painting by McManus to neutral GAG. When staining elastic fibers with resorcinol-fuchsin according to Weigert, a large number of thin convoluted fibers of intense lilac color were noted, thick elastic fibers were also noted, which formed membranes at the border between the tumor tissue and the PZ. The argyrophilic fibers were thickened, forming plexuses and membranes at the border of the PZ with the tumor. Acid GAGs were observed in significant amounts of elastic fibers detection areas. The density of lymph-plasmocytic infiltration in the PZ was moderate or high, follicle-like structures were often detected.

The elements of canal kidney apparatus were found in the PZ in various amounts. I group had the round, small, nuclei of epithelial cells, hyperchromia was not found. The area of the cell nucleus was  $38.9 \pm 2.2$  microns<sup>2</sup>. The cells were located on a thin PAS-positive basal membrane. The number of AgNORs in the cores averaged  $2.2 \pm 0.2$  per 1 core.

The renal tubules of the study group had a different structure in the PZ of II group. They were located in dense connective tissue and contained a small number of cellular elements. Such tubules were surrounded by a sharply CHIC-positive basal membrane. When stained with silver nitrate by Homori, the basal membrane looked thickened. The epithelial cells of the tubules had evidence of irregularities: polymorphism and hyperchromia of the nucleus, increase in the nuclear-cytoplasmic ratio, a large number of common NC. The area of the cell nucleus was  $38.9 \pm 2.2$  microns<sup>2</sup>. The number of AgNORs in cell nuclei reached  $5.15 \pm 0.35$  per 1 nucleus. In the areas of such modified tubules it was impossible to differentiate the various departments of the nephron.

When microspectrophotometric study of DNA in the epithelial cells of the tubules of the PZ - group of the study, the DNA content was  $3.9 C \pm 0.2$ , which may indicate hyperplastic and proliferative processes occurring in the epithelium. The histogram of the distribution of cells by the amount of DNA for this group was characterized by peaks at levels 3C and 4C. In II group of patients, an increase in the average DNA content to  $5.5 C \pm 0.2$  was found, indicating severe dysplasia. The increase in the average DNA content in cells was accompanied by an increase in the heterogeneity of populations in the content of genetic material, the phenomena of aneuploidy and polyploidy and the emergence of clones containing 6C and 7C DNA, which indicates an increasing genetic instability of the epithelium. The histogram characterizing the distribution of cell clones in group II was indistinguishable from the histogram of cancer.

Nuclei of cells of myofibroblastic series of PZ I group of patients had an elongated wave-like shape. The core area averaged  $32.4 \pm 2.2 \text{ mm}^2$ . The number of AgNORs was  $1.5 \pm 0.2$  per 1 core. These cells us have been attributed to low activity of the Mature fibroblasts. In group II cells myofibroblastic number had enlarged nuclei. The core area averaged  $32.4 \pm 2.2 \text{ micron}^2$ . The number of AgNORs in cell nuclei reached  $5.15 \pm 0.35$  per 1 nucleus. These cells were represented by actively synthesizing young fibroblasts.

In the study of DMCB in the PZ, the involvement of vessels in pathological tumor neoangiogenesis was established. In most cases, the newly formed vessels did not have a muscular shell, had a tubular or lacunar structure and were formed by a single layer of endothelial cells. In the PZ Group, the DMCB was  $5.8 \pm 0.6$ , in the II GROUP- $8.64 \pm 0.8$ . There was also an increase in the number of AgNORs to  $3.5 \pm 0.4$  in the endothelium of newly formed vessels of the PP GROUP, compared with the group ( $1.7 \pm 0.1$ ). In their own vessels of the kidney, which are also found in a small amount in the PZ of both groups, the phenomena of pronounced elastofibrosis and hyalinosis, with narrowing or obliteration of the lumen, were noted. DMCB in PZ correlated with the presence of regional and distant metastases ( $r = 0.76$ ).

**Conclusion.** Thus, the results of the study showed that the size of the tumor was correlated with the histological structure of renal cancer PZ. In our opinion, the data obtained are not only of theoretical interest, but also of practical importance. Especially interesting to us is the fact that in tumors of size  $\geq 4 \text{ cm}$  on the background of sclerotic processes, the phenomena of intratubular renal neoplasia were noted, which may later become a source of relapse. We believe that in organ-sparing operations, a more thorough revision of the surgical margin of tumors whose size is  $\geq 4 \text{ cm}$  should be carried out. High activity of tumor angiogenesis in the PZ of tumors of size  $\geq 4 \text{ cm}$  should cause alertness with respect to the development of bleeding. A clear tumor pseudocapsule, the presence of which is known to be an indication in organ-sparing surgery, may be due to severe sclerosis, which may make it difficult to isolate the tumor. On the other hand, the presence of a clear and wide capsule (in particular according to the study by instrumental methods) may indirectly indicate a high degree of nuclear gradation of the tumor.

Tumors of size  $\leq 4 \text{ cm}$  in contrast were characterized by a low degree of anaplasia (G1 - G2), and neoangiogenesis in the PZ of such tumors was expressed slightly. Sclerosis, dysplasia and invasion in the PZ of such tumors were not detected by us and the width of the PZ is not large (about 0.5 cm). In our opinion, this should be taken into account when organ-preserving operations and perhaps here it is possible to limit the excision of the kidney adjacent to the tumor parenchyma within the limits not exceeding 0.5-1 cm.

Thus, the study of the histological structure of renal cancer PZ depending on the size of the tumor node may have not only fundamental, but also practical interest.

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## MORPHOFUNCTIONAL CHARACTERISTICS OF NUCLEAR HEPATOCYTES NUCLEUS OF RATS AFTER EXPOSURE TO HYPOTHERMIA

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**Annotation.** *The purpose of the work is to study the morphology of the liver with hypothermia. The experiment involved 20 rats. Hypothermia was modeled by placing animals which were in individual cages into the water at a temperature of 5 °C, at an ambient temperature of 7 °C. The exposure to the cold factor was stopped when the animals reached a deep degree of hypothermia, the criterion of which was a rectal temperature of 20-25 °C. For histological examination, the material was taken immediately after hypothermia. The results of the study showed that after exposure to hypothermia in the liver of rats, the number of mononuclear cells increased by 14%, and the percentage of binuclear liver cells decreased 2.6 times. DNA index in hepatocyte nuclei decreased to  $3.2 \pm 0.2$ . The number of heterochromatin granules in the karyoplasms increased 2.15 times, and the proportion of heterochromatin from the total core area increased 2.9 times. At the same time, heterochromatin formed large aggregates and was localized exclusively along the karyolemma. A morphometric study revealed that the average area of the nuclei decreased 2.3 times, the perimeter decreased 1.5 times, and the diameter decreased 1.5 times. The shape of the nucleus also changed: the indicators of the circle factor and the ellipse factor decreased and amounted to  $0.951 \pm 0.003$  rel. units and  $0.997 \pm 0.0002$ , respectively, while the factor of elongation of the nucleus increased 6.4%. When evaluating the nucleolar organizers, the average number of Ag-NORs decreased 2.8 times. The average area of AgNORs was 2.9 times less.*

**Key words:** *hypothermia, liver, hepatocytes, nucleus.*

The dependence of most vital processes on the temperature of the environment makes temperature effects a critical environmental factor, which can be crucial for human survival. A person often has to meet the influence of low and ultra-low temperatures while working in various industries, as well as because of his living in some climatic zones. In this case, the body stay under conditions of hypothermic exposure can lead to significant metabolic and functional changes.

Under conditions of hypothermia, the liver, as an organ that makes a significant contribution to thermal production, plays a very important role [1-3]. Due to complex biochemical reactions, this organ is able to ensure the body's adaptability to the difficult conditions of existence. The liver provides plastic and energy processes, as well as regulates compensatory-adaptive processes that occur when all exogenous and endogenous adverse processes are exposed. It happens even when these damaging factors do not have a pronounced hepatotropic effect [4]. Therefore, the morphological and functional state of the liver is a reflection not only of the functional state of the organ itself, but also of the reaction of the body as a whole.

Morphological changes in human and animal organs under the influence of exogenous factors have been extensively studied in recent years [5-7]. However, under the action of hypothermia, the histological structure of the liver is studied in a number of works [8, 9] and the obtained data are contradictory. This applies in particular to the characteristics of hepatocyte reactions to the cold factor, the characteristics of the number of binuclear hepatocytes, and the reaction of the nuclei of liver cells in general [10, 11].

Thus, there is little information on the effect of hypothermia on the liver histostructure, and the morphology of the cell nucleus of hepatocytes has not been adequately addressed, and therefore more detailed studies of morphological changes occurring in the nuclei of hepatocytes under the action of the cold factor are necessary.

The purpose of the study is to analyze the dynamics of changes in the state of nuclear cells of Wistar rat liver cells after exposure to a single deep and immersion hypothermia.

**Materials and research methods.** The study was conducted on 15 male Wistar rats in the weight of 200-250 grams. Animals (n = 10) were subjected to a single deep immersion (water) hypothermia. Hypothermia was modeled by placing animals which were in individual cages in water at a temperature of 5 °C at an ambient temperature of 7 °C. The exposure to the cold factor was stopped when the animals reached a deep degree of hypothermia, the criterion of which was a rectal temperature of 20-25 °C. The exposure time

of the cold factor averaged  $40 \pm 5$  minutes. Immediately after the cessation of cooling, the animals were removed from the experiment by decapitation. The control group consisted of 5 rats, each of which was placed in water at a temperature of  $30^\circ\text{C}$ , at an ambient temperature of  $22\text{--}25^\circ\text{C}$ .

For histological examination, pieces of lung tissue were fixed for 24 hours in a 10% solution of neutral formalin, after which the preparations were processed in a TISSUE-TEK VIPTM6 machine (Sakkura, Nagano, Japan), followed by paraffin filling at the TISSUE-TEK TEC 5 paraffin filling station (Sakkura, Nagano, Japan). Accu-Cut SRM rotary microtome (Sakkura, China) made slices which were 5-7  $\mu\text{m}$  thick. The TISSUE-TEK Prisma auto-tuner (Sakkura, Nagano, Japan) stained preparations with hematoxylin-eosin.

The preparations were stained with the Felgen method using 1n cold hydrolysis to determine the ploidy of hepatocyte nuclei HCl for 1 hour 30 minutes. The average DNA content in the nucleus of a small lymphocyte was taken as a diploid value (2c). Fertility measurements were performed in a certified morphometric program which is called VidioTest-Morphology 5.2. (VidioTest, St. Petersburg) using specialized modules Standard and Ploidy. Histograms of the distribution of hepatocytes by the DNA accumulation index (DNA index) in the nucleus were constructed.

To detect heterochromatin, histological sections were stained in a 2% solution of orcein in 45% acetic acid for 30 minutes. Then, the preparations were photographed using a LeicaDM 750E200 microscope (Germany) with a LeicaEC3 digital video camera (Germany) at a magnification of  $\times 1000$ . The average number of granules of heterochromatin per 1 nucleus, their localization and calculated the content of the proportion of heterochromatin from the total area of the cell nucleus. At least 25-30 cell nuclei were studied.

Staining of the nucleolar organizers was carried out according to the two-stage method of Y. Daskal using our modification [12]. Under an oil immersion microscope with an increase of  $\times 1000$ , the number of nucleoli, the area of one nucleolar organizer, and the nucleolar ratio in relative units (rel. units) were calculated.

Statistical processing of the obtained data was carried out using the Statistica 10.0 statistical software package and the statistical analysis package of the MSEXEL 2010 program. For each of the values, the mean (M) and the mean error (m) were calculated. The hypothesis of the normality of the probability distribution of the data was tested using the Shapiro-Wilk test. The reliability of the data was evaluated using the parametric criterion of Student t-test. The critical value of the level of statistical significance was 0.05.

**Research results and discussion. The Control group.** A morphological analysis of the structure of the nuclei of the liver cell nuclei in the control group of animals revealed the following. Most of the cells were mononuclear ( $79 \pm 1.5\%$ ), the percentage of the content of binuclear cells was  $21 \pm 1.5\%$ . In the ploidy analysis of the nuclei, DNK index averaged  $3.9 \pm 0.2$  (Table). The nuclei were represented by six levels of ploidy: cell clones with DNA index 2 were 3.3%, 3 - 30%; 4 - 50%; 5 - 6.7%; 6 - 6.7% and 8 - 3.3%.

**Table.** Morphometric and morphological and functional parameters of hepatocyte nuclei in case of hypothermia in comparison with control ( $M \pm m$ )

| Parameters  | Control      | Hypothermia  | Reliability(p)       |
|---|--------------|--------------|----------------------|
| DNA index (c)   | 3,9±0,2      | 3,2±0,2      |                      |
| Nuclear area (mcm)  | 24,2±1,2     | 10,4±0,5     | <b>p = 0,0000001</b> |
| Nuclear perimeter (mcm)   | 17,6±0,4     | 11,5±0,25    | <b>p = 0,0000001</b> |
| Nuclear diameter (mcm)  | 5,6±0,4      | 3,6±0,1      | <b>p = 0,0000001</b> |
| Circle factor (rel. units)  | 0,969±0,002  | 0,951±0,003  | <b>p = 0,003</b>     |
| Ellipse factor (rel. units)   | 0,999±0,0002 | 0,997±0,0002 | <b>p = 0,0001</b>    |
| Nuclear elongation factor (rel. units)                                      | 1,18±0,02    | 1,26±0,02    | <b>p = 0,03</b>      |
| The number of AgNORs per 1 nucleus  | 3,4±0,2      | 1,2±0,1      | <b>p = 0,0000001</b> |
| The total area of AgNORs per 1 nucleus (mcm <sup>2</sup> )                  | 7,9±0,3      | 2,7±0,2      | <b>p = 0,0000001</b> |
| Area of 1 AgNORs (mcm <sup>2</sup> )  | 2,3±0,1      | 2,1±0,1      | p = 0,2              |
| Nucleus ratio (rel. units)  | 0,11±0,004   | 0,11±0,01    | p = 0,9              |
| The number of mononuclear hepatocytes (%)                                   | 79±1,5       | 91,8±0,8     | <b>p = 0,00007</b>   |
| The number of binuclear hepatocytes (%)                                     | 21±1,5       | 8,2±0,8      | <b>p = 0,00007</b>   |
| The number of heterochromatin granules                                      | 4,7±0,4      | 10,1±1,1     | <b>p = 0,0003</b>    |
| The content of the heterochromatin proportion of the total nuclear area (%) | 12,7±0,5     | 37,2±2,0     | p = 0,0000001        |

**Note:** **Bold text** indicates valid data.

Heterochromatin was contained in the cell nuclei in a moderate amount; its largest blocks were in the perinucleolus zone. A small amount of heterochromatin was localized along the karyolemma. The average number of heterochromatin granules was  $4.7 \pm 0.4$  per 1 nucleus, the content of heterochromatin from the total nuclear area was  $12.7 \pm 0.5\%$  (table).

In a morphometric study, the average nuclear area was  $24.2 \pm 1.2 \mu\text{m}^2$ , the perimeter was  $17.6 \pm 0.4 \text{ mcm}$ , the diameter was  $5.6 \pm 0.4 \text{ mcm}$ , and the circle factor was  $0.969 \pm 0.002 \text{ rel. units}$ , ellipse factor  $0.999 \pm 0.0002 \text{ rel. units}$  and the factor of elongation of the nucleus -  $1.18 \pm 0.02 \text{ rel. units}$

Upon histochemical detection of the nucleolar organizers (AgNOR), the nucleoli were detected against a yellow nucleoplasm in the form of clearly visible black granules. Most AgNORs were localized in the center of the nucleus. The average number of AgNORs was  $3.4 \pm 0.2$  per core. The average total area of AgNORs per nucleus was  $7.9 \pm 0.3 \text{ mcm}^2$ . The average area of 1 AgNORs was  $2.3 \pm 0.1 \text{ mcm}^2$ . The nuclear-nucleolar ratio was  $0.11 \pm 0.005 \text{ rel. units}$

Hypothermia: After exposure to hypothermia, the number of mononuclear cells in the liver of experimental animals increased by 14% ( $91.8 \pm 0.8\%$ ), the percentage of binuclear liver cells decreased 2.6 times ( $8.2 \pm 0.8\%$ ). DNA index in hepatocyte nuclei decreased to  $3.2 \pm 0.2$ . The distribution of clones by DNA index took a completely different form: hepatocytes appeared with ploidy nucleus 1 (3.4%); the number of cells with DNA index 2 increased to 43.8%; the number of hepatocytes with DNA index 3 decreased to 16.85%, with DNA index 4c decreased to 21.35%, 5 to 4.5%, 6 to 2.25% and 8 to 1.15% (table).

The number of transcriptionally inactive heterochromatin granules in the karyoplasts compared to the control group increased 2.15 times and amounted to  $10.1 \pm 1.1$  per 1 nucleus, and the proportion of heterochromatin from the total area of the core increased 2.9 times and amounted to  $37, 2 \pm 2.0\%$  (table), while heterochromatin formed large aggregates and localized exclusively along the karyolemma.

The rat hepatocyte nuclei of the experimental group varied in size. A karyometric study revealed that the average area decreased 2.3 times and amounted to  $10.4 \pm 0.5 \text{ mcm}^2$ , the perimeter decreased 1.5 times and amounted to  $11.5 \pm 0.25 \text{ mcm}$ , the diameter decreased 1, 5 times and was equal to  $3.6 \pm 0.1$  microns. The shape of the nucleus also changed: the indicators of the circle factor and ellipse factor decreased, which amounted to  $0.951 \pm 0.003 \text{ rel. units}$  and  $0.997 \pm 0.0002 \text{ rel. units}$  respectively, and the factor of elongation of the core in this case increased by 6.4% to  $1.26 \pm 0.02 \text{ rel. units}$  (table).

When assessing the activity of the nucleolar organizers, in most cases a marginal arrangement of the nucleoli was noted. The average amount of AgNORs decreased 2.8 times and amounted to  $1.2 \pm 0.1$  per 1 nucleus. The average total area of AgNORs per 1 nucleus was 2.9 times less and amounted to  $2.7 \pm 0.2 \text{ mcm}^2$ . The average area of 1 AgNORs was and the nucleolar ratio was not significantly different from the control group and amounted to  $2.1 \pm 0.1 \text{ mcm}^2$  and  $0.11 \pm 0.01 \text{ rel. units}$  respectively (table).

**Conclusion.** Thus, the influence of the cold factor had a pronounced harmful effect on the nuclei of the liver cells of experimental animals. At the same time, significant morphological changes were noted: a decrease in the number of binuclear hepatocytes; a decrease in the morphometric parameters of the nuclei; an increase in the proportion of heterochromatin in the nucleus; a decrease in DNA index and a decrease in the number of nucleoli and phenomena of segregation of the nucleus-nerves. We consider that the revealed changes are a consequence of metabolic depression of hepatocytes. A decrease in the number of binuclear hepatocytes is associated with inhibition of the regenerative ability of the liver. A response of the genome aimed at maintaining the number of polyploid cells, manifested at the level of binucleolarity, it was distinguished by a lack of intensity: the percentage of binuclear hepatocytes did not reach the control values. As is known, the disorganization of nuclear chromatin on with increasing content of hetero-chromatin reflects inhibition of matrix and synthetic processes in nuclear cells. Also, a change in the structure of the nuclear matrix and chromatin is a result of DNA damage and may be a reflection of the programmed death of hepatocytes, which in our study was confirmed by the presence of karyopiknosis, a decrease in DNA index, an increase in the number of euploid hepatocytes with DNA index 2 with the appearance of hypoploid clones in DNA index 1 it was shown that the size and number of nucleoli in hepatocytes objectively reflect the intensity of ribosomal synthesis and proliferative activity of liver tissue in various pathologies [13-15]. In our study, the effect of hypothermia caused a decrease in the number and segregation of nucleoli, which led to inhibition of the assembly of preribosomal subunits and inactivation of the protein synthesizing function of ribosomes. Lowering the ambient temperature caused a change in the shape of the nucleus, which could occur due to activation of lipid peroxidation, damage to the cell membrane and disruption of ionic homeostasis.

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## PROGNOCTIC MEANING AN EXPRESSION OF THE APOPTOSIS INHIBITOR BCL-2 IN A RENAL CELL CARCINOMA

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**Annotation.** *The work focuses on prognostic meaning of inhibitor bcl-2 apoptosis expression in a renal cell carcinoma. The material for the study was the surgical material of 63 patients with kidney cancer. The median age was  $57.4 \pm 1.4$  years. There were 33 males (52.4 %) and 30 females (47.6%). Correlations between bcl-2, clinical stage ( $r = 0.30$ ;  $p = 0.02$ ), size of tumor node ( $r = 0.29$ ;  $p = 0.02$ ), presence of regional and distant metastases ( $r = 0.35$ ;  $p = 0.005$ ) and histological variant of tumor ( $r = 0.37$ ;  $p = 0.003$ ) were revealed. There was no correlation with sex ( $r = 0.15$ ;  $p = 0.22$ ), age ( $r = 0.16$ ;  $r = 0.22$ ) of patients and tumor gradation according to Furman method ( $r = 0.18$ ;  $p = 0.15$ ). Отсутствие экспрессии bcl-2 в клетках опухоли можно рассматривать в качестве критерия вероятного возникновения метастазов. The correlation of marker expression with the overall survival of patients was found. Low expression of bcl-2 oncoprotein in tumor cells is an unfavorable factor in predicting patient survival.*

**Keywords:** kidney cancer, bcl-2, survival, prognosis.

The study of the prognostic value of apoptosis markers, including the expression of the apoptosis inhibitor bcl-2 in renal cell carcinoma (RCC) has been relevant for several past decades. The efforts of researchers to find relationships between bcl-2 expression, traditional classical prognostic factors and long-term survival results of patients after surgical treatment of RCC have not weakened.

Thus, the relationship between bcl-2 expression and the degree of PCR anaplasia has been studied in a number of studies. Zhang X. et al. (2000) found a relationship between bcl-2 and tumor gradation. According to Gutorov S. L. et al. (2007) in the absence of bcl-2 expression, there was a tendency to increase the degree of tumor anaplasia. Hindermann W. et al. (1997) showed that renal carcinoma of G1 anaplasia degree was characterized by higher bcl-2 values than G2-3 degrees. These authors concluded that the progression of kidney cancer from highly differentiated to low-differentiated was accompanied by a decrease in bcl-2 expression. Other researchers had the same results [5]. At the same time Vasavada S. P. et al. (1998) found no association between bcl-2 expression and tumor gradation.

Few papers focus on the study of the relationship between bcl-2 activity and the clinical stage of the disease. Oudard S. et al. (2002) found a relationship between high bcl-2 activity and low-stage carcinoma. Other researchers had similar results [5]. However, other authors have not found any relationship between bcl-2 expression and clinical stage [12].

Some studies have described the features of bcl-2 expression in different histological variants of RCC. According to these data, bcl-2 expression was correlated with the histological variant of the tumor [13]. Paraf F. et al. (1995) showed that most light cell carcinomas were negative for this marker or contained rare positive cells, and all papillary carcinomas were positive for bcl-2. Other authors found no correlation of the marker with the histological type of tumor [14]. Thus, there was no significant increase in the immunoreactivity of bcl-2 protein in the sarcomatoid components of tumors, compared with other components [7].

There are some researches focus on bcl-2 in primary tumors during metastasis. According to Laurent O. B. et al. (2008) both locally advanced and metastatic CC were not characterized by high levels of bcl-2 protein. N. A. Shustiitsky had the same results (2007). Other authors also found no relationship between bcl-2 expression and the occurrence of metastases [15].

A number of studies have identified a relationship between bcl-2 expression and postoperative survival of patients [5,9], but there are also studies which do not find this relationship[6,14,15].

Thus, despite the abundance of work studying of the prognostic value of the apoptosis inhibitor bcl-2 when a patient has RCC, the data obtained by the authors are contradictory and therefore the value of the expression of this oncoprotein in the prognosis of KC needs further study.

**The aim** of this work was to detect immunohistochemical expression of apoptosis inhibitor bcl-2 in RCC and to search for the relationship of marker expression with the most important clinical and anatomical prognosis factors and postoperative survival of patients.

**Materials and methods of research.** Surgical material of 63 patients with kidney cancer was studied. The median age was  $56.7 \pm 1.3$  years. There were 33 males (52.4 %) and 30 females (47.6%). The tumors were showed according to their histological structure: light cell cancer-39; papillary cancer-15; chromophobic cancer-2; spindle cell (sarcomatoid) cancer-2 and neuroendocrine cancer-4.

The tumors were grouped according to the clinical stages (I-IV): 35 (55.5%) observations corresponded to I stage (T1N0M0); 5 (7.9%) observation to II stage (T2N0M0); 13 (20.6%) - III stage (T1N1M0, T2N1M0, T3N0M0, T3N1M0) and 10 (16%) - IV stage (T4N0M0, T4N1M0, T2n2m1, T3n1m1). The degree of malignancy was assessed by Fuhrman S. A. method et al (1982). The studied material included 17 (27%) tumors of G1 anaplasia degree; 15 (23.8%) tumors of G2 anaplasia degree; 8 (12.7%) of G3 anaplasia degree and 23 (36.5%.) degree G4.

There were 16 metastatic carcinomas, 47 tumors without metastases. The average size of the tumor node was  $7.1 \pm 0.4$  cm.

The material was fixed in 10% neutral buffered formalin for 12-24 hours. Histological medicine was stained with hematoxylin and eosin, collagen by Van Gieson method and acid mucopolysaccharides by colloidal iron by Gale method. Neuroendocrine carcinoma phenotype was detected by immunohistochemical method using monoclonal antibodies to chromogranin A and synaptophysin.

The level of molecular biological marker Bcl-2 expression (clone 124, "DAKO") was determined by immunohistochemical method according to the protocols recommended by the manufacturers. A semi-quantitative method was used to evaluate the immunohistochemical (IHC) staining of bcl-2: 0 points - no staining; + (1 point) - more than 20% of cells with low intensity of cytoplasm staining; ++ (2 points) - moderate cytoplasm staining; +++ (3 points) - more than 20% with intensive cytoplasm staining; ++++ (4 points) - intensive cytoplasm staining more than 80% of cells. In cases where the intensity of staining varied, for example from + (1 point) to ++ (2 points), an average of 1.5 points was obtained.

Data on the patients survival were obtained according to the data of the cancer register and outpatient records.

Statistical processing of the material was carried out using Statistica 6.0. package. If the distribution is normal, we used the methods of parametrical statistics (Student's t-distribution). If the measurements does not correlate to the criteria of normal distribution (Shapiro-Wilk criterion  $W = 0.89$ ,  $p < 0.01$ ), we used the Kolmogorov test, Smirnov or Mann-Whitney U-test. The data were considered reliable at  $p < 0.05$ . The construction of survival curves was carried out using the Kaplan – Meier method, the reliability of differences in indicators was assessed using the log-rank test.

**The results of the study and their discussion.** The result of IHC detection of the apoptosis inhibitor bcl-2 was represented by fine-grained, granular or diffuse brown staining of the cytoplasm of tumor cells. Among all the studied patients, regardless of sex, age, RCC variant, etc., the spread of values of bcl-2 oncoprotein expression was from 0 to 4 points.

In general, the average value of the bcl-2 index in the whole group was  $1.7 \pm 0.2$  points, which, in our opinion, is not a high value. Low levels of apoptosis inhibition were found in 44 tumors (69.8%) and high in 19 (30.2%). If the level of apoptosis inhibition was high, bcl-2 averaged  $3.4 \pm 0.1$  points. If the level of apoptosis inhibition was low, the index was equal to  $0.95 \pm 0.1$  points.

Comparison of bcl-2 expression with classical prognostic clinical and anatomical factors in KC revealed some relationships.

Correlation analysis revealed the connections between bcl-2 and clinical stage ( $r = 0.30$ ;  $p = 0.02$ ), size of tumor node ( $r = 0.29$ ;  $p = 0.02$ ), presence of regional and distant metastases ( $r = 0.35$ ;  $p = 0.005$ ) and histological variant of tumor ( $r = 0.37$ ;  $p = 0.003$ ). There was no correlation with sex ( $r = 0.15$ ;  $p = 0.22$ ), age ( $r = 0.16$ ;  $r = 0.22$ ) of patients and tumor gradation according to Furman method ( $r = 0.18$ ;  $p = 0.15$ ).

Average bcl-2 values of male patients were  $1.7 \pm 0.2$  points, and values of female patients increased to  $2.0 \pm 0.3$  points ( $p = 0.35$ ).

Depending on age, the average bcl-2 expression was:  $1,6 \pm 0,3$  points - for patients aged 40 to 49 years,  $1,45 \pm 0,3$  points - for 50 to 59 years,  $1,7 \pm 0,3$  points - for 60 to 69 years and  $2,8 \pm 0,4$  points for 70 to 79 years old patients. Thus, the highest indicators of the bcl-2 marker index were observed in the age group of patients from 70 to 75 years, and the lowest in the group from 50 to 59 years.

The patients with I clinical stage of the disease had the average bcl-2 expression, namely,  $2.0 \pm 0.2$  points, with stage II -  $2.0 \pm 0.2$  points, with stage III -  $1.2 \pm 0.4$  points and with stage IV -  $1.2 \pm 0.3$  points. Thus, there is a decrease in the expression of oncoprotein as the clinical stage of the pathological process increases.

Depending on the histological type of RCC, the lowest average value of bcl-2 expression was found in light cell ( $1.0 \pm 0.2$  points) and neuroendocrine cancers ( $1.5 \pm 0.6$  points). Chromophobic (2.0 points), fusiform ( $2.5 \pm 0.3$  points) were in the intermediate position. The highest rates of bcl-2 were observed in papillary carcinoma ( $3.1 \pm 0.3$  points) (table. 1) (Fig. 1.).

**Table 1.** The bcl-2 expression depending on the histologic variant of kidney cancer

| <b>Histological variant of RCC</b> | <b>Bcl-2 expression (scores)</b> |
|------------------------------------|----------------------------------|
| Light cell cancer                  | $1.0 \pm 0.2^*$                  |
| Neuroendocrine cancer              | $1.5 \pm 0.6$                    |
| Chromophobic cancer                | 2.0                              |
| Fusiform cell carcinoma            | $2.5 \pm 0.3$                    |
| Papillary cancer                   | $3.1 \pm 0.3^*$                  |

Note: \* -  $p < 0.05$

With an increase in the degree of nuclear atypia by Furman, a tendency to decrease the expression of bcl-2 was found: at GI expression was  $2.1 \pm 0.3$  points, at GII  $2.1 \pm 0.4$  points, at GIII  $1.4 \pm 0.6$  points and at GIV  $1.6 \pm 0.3$  points.

When the size of the tumor node was  $< 7.0$  cm marker expression was  $2.0 \pm 0.2$  points, and with an increase in the size of  $\geq 7.0$  cm- $1.2 \pm 0.2$  points.

In patients without regional and distant metastases, bcl-2 expression was  $2.0 \pm 0.2$  points, and in the presence of metastases it significantly decreased to  $0.9 \pm 0.2$  points ( $p = 0.007$ ) (table. 2) (Fig. 1.).

**Table 2.** Bcl-2 expression depending on the presence of regional and distant metastases

| <b>Distant and regional metastases</b> | <b>Bcl-2 expression (scores)</b> |
|--|----------------------------------|
| Without metastases                     | $2.0 \pm 0.2^*$                  |
| With metastases                        | $0.9 \pm 0.2^*$                  |

Note: \* -  $p < 0.05$

Survival was traced in 32 (50.8%) patients out of 63 patients within 5 years. The Kaplan - Meyer survival analysis, depending on the level of expression of BCL - 2 oncoprotein, showed that when the expression of bcl-2 apoptosis inhibitor was 3 or more points, the cumulative proportion of survivors by day 1800 was 0.92, and when 2 or less points, then no patient lived to 5 years.

Thus, the results of the study showed that PCR, in General, is characterized by low expression of the apoptosis inhibitor bcl-2. Bcl-2 expression has been correlated with a number of important prognostic clinical and anatomical factors and can therefore be used as an additional prognostic factor. The absence of bcl-2 expression in tumor cells can be considered as a criterion for the likely occurrence of tumor metastases. The correlation between the marker expression value and the overall survival of patients was revealed. The low level of the studied oncoprotein is an unfavorable factor in the prediction of 5-year postoperative survival of patients.

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## BIOLOGICAL TREATMENT OF PULP HYPEREMIA ASSOCIATED WITH CANDIDA FUNGI

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**Abstract.** According to epidemiological studies, the incidence of caries in the Earth's population is approaching 100%. Despite the significant successes of dentistry in the prevention and treatment of caries, complicated caries is a widespread pathology of hard tooth tissues. One of the most frequent complications is pulp hyperemia as a result of the introduction of decay products of hard tooth tissues and microorganisms into the pulp along the dentinal tubules. This process is reversible acute, but in the absence of treatment leads to chronic forms of pulpitis and its extraction. Preserving the viability of the tooth pulp is necessary, since the pulp provides nutrition and maintains the normal functioning of all tooth tissues. An alternative to tooth removal is early diagnosis and biological treatment. This study presents the results of microscopy of pulp of teeth in patients with pulp hyperemia, the frequency of detection of *Candida* fungi is established, conservative treatment with direct pulp coating is carried out, methodological methods are developed that allow substantiating the choice of drugs when using the biological method of treating pulp hyperemia, including the need for the use of antifungal drugs in the presence of fungi of the genus *Candida*.

According to the results of the study, it was found that the presence of fungal flora in the inflamed tooth pulp requires complex therapy with the vital method of treating pulp hyperemia using antimycotic drugs.

**Keywords:** pulp hyperemia, tooth pulp microscopy, fungi of the *Candida* genus, biological treatment of pulpitis, antimycotic drugs.

As a result of numerous epidemiological studies, it was found that dental caries is the most common pathology that is diagnosed in almost every person [8]. The modern concept of the etiology of dental caries is based on a combination of tooth surface caries, cariogenic bacteria, fermentable carbohydrates, and poor oral hygiene [10]. In the development of caries, the conditionally pathogenic microflora of the oral cavity and dental plaque, represented by acid-forming bacteria (Str. Mutans, Str. Viridans, Str. Mits, Str. Sungius, Lactobacillus), plays an important role [9]. Due to the production of acids on the surface of the tooth, they diffuse first into the tooth enamel, and then into the dentin. Acids wash out calcium and phosphorus from the hard tissues of the tooth, with a progressive course of caries, the pathological process is complicated by inflammatory changes in the tooth pulp [5, 10].

Pulpitis – is an inflammation of the tooth pulp that develops when infectious agents enter the pulp chamber, primarily cariogenic microflora, which was joined by other microorganisms with a tendency to rapid growth (Str. Agalactiae, Str. Anhaemolyticus, E. coli, fungi of the genus Candida, Streptobacillus, bacteria of the genus Sarcina, etc.) [3,6]. The initial response of the pulp to the action of microbial agents is its hyperemia and is a reversible pulpitis. According to the International Classification of Diseases, code 04.00 is hyperemia of the pulp [5,7].

When establishing a diagnosis of pulp hyperemia, a biological method of treatment is used, which is one of the most progressive methods that allows preserving the viability of the entire pulp. The method is based on the effect of drugs on microorganisms, as the etiological factor of pulpitis, using combined antibacterial and / or antimycotic agents. In order to restore and regenerate tooth pulp for a normal morphofunctional state, most clinicians prefer the use of preparations based on calcium hydroxide or mineral trioxide aggregate, which contribute to the formation of replacement dentin and dentin bridge, in combination with glucocorticoids and antiseptics [1,7,11].

In the absence of therapy for hyperemic pulp, the process progresses, passes into various forms of chronic pulpitis, in which its extraction is the method of treatment. In the future, the depulped tooth becomes brittle, less durable and faster undergoes destruction, the percentage of complications after endodontic treatment is from 35 to 75%, inflammatory changes in the periodontium and the formation of foci of chronic odontogenic infection are diagnosed [2,4].

**Objective:** evaluate the effectiveness of the biological treatment of pulp hyperemia with therapeutic paste for direct pulp coating with the addition of an antifungal component after the detection of Candida fungi.

**Materials and methods.** The object of the study were patients in the amount of 56 people aged 18 to 30 years who came to the clinic. All patients were treated within the first days after the onset of pain symptoms. 27 patients complained of rare aching pains (up to 15 minutes), soreness and discomfort in the tooth while eating solid food, pain from cold. The presence of a deep carious cavity was objectively established, and the diagnosis of pulp hyperemia was confirmed by the results of diagnostic preparation and electroodontometry. The remaining 29 patients went to the clinic with the aim of treating deep caries, however, in the process of preparing hard tooth tissues, the pulp chamber was opened. Of the total number of 56 patients, 2 groups were formed by random selection: 27 people (including 14 with a randomly opened pulp chamber as a result of necrectomy of carious dentin) made up the control group in which the causative tooth was treated with a conservative method using the direct pulp coating technique. The second (main) group consisted of 29 people (including 15 with a randomly opened pulp chamber as a result of necrectomy of carious dentin). For the patients of the main group, the treatment of pulpitis with the biological method of direct coating of the pulp was carried out using the antifungal component Fluconazole. All patients received physiotherapeutic treatment with the Svetozar laser therapy apparatus 5 procedures for 2 minutes every other day. Evaluation of treatment results was carried out after 24 hours, 3, 7, 14, 30 days 3 and 6 months.

After dissection of a deep carious cavity, tissue samples from the dentinal-pulpal border and directly of the tooth pulp were received from all patients. Under a light microscope, a bacterioscopic study was performed to detect a colony of *Candida* fungi. We studied native preparations stained by Gram, Romanovsky-Giemsa and 1% solution of methylene blue.

### **Results and discussion.**

The results of bacterioscopic smear examination in 91% (51 of 56) patients were found to be the fungi of the genus *Candida albicans* (from 15 to 30 in the field of view), including young forms. Biological treatment of patients of the main and control groups was carried out in stages in 2 visits. On the first visit after the cofferdam was placed under local anesthesia, an opening of the tooth cavity, necrectomy of infected dentin, exposure of a small portion of the pulp and formation of the cavity, and control of bleeding by applying aminocaproic acid were performed. After taking the pulp smears, an antiseptic treatment of the cavity with antiseptic solutions was carried out, a paste based on mineral trioxide aggregate for direct pulp coating - ProRoot (Dentsply) was applied to the exposed part of the pulp chamber, Vitrebond insulating gaskets (3M ESPE) and temporary sealing material Clip (Voco). In the main group, granules of the antimycotic drug Fluconazole 0.03 g per

0.2 g of MTA cement were added to the treatment pad. After 14 days, a temporary seal was removed and a permanent seal made of composite material Filtek Z250 (3M ESPE) was installed. The results of the effectiveness of the treatment were carried out after 24 hours, 3, 7, 14, 30 days, 3 and 6 months.

During a percussion study of teeth in the main group, a reaction from the periodontal side was detected in 2 patients (6.9%) - 24 hours after treatment. On the 3rd day in the study group in 3 patients (10.3%), on the 7th knock, sharp pain was also diagnosed, which led to the use of extirpation methods of treatment. On the 14th day, percussion of teeth in all patients was negative (Figure 1).

In the control group, on the first day, the reaction from the periodontium was noted in 5 patients (18.5%), in 7 patients (25.9%) on the 3rd day. By the 7th, 14th, 30th days, respectively, positive percussion was detected in 7 (25.9%), 5 (18.5%), 3 (11.1%) patients. In contrast to the group using paste with an antifungal drug in the control group for 3 months, a periodontal reaction was noted in 2 (7.4%) patients. As a result, 15 patients underwent endodontic treatment. After 6 months, percussion was negative in all patients (Figure 1).

The x-ray of the teeth in the group where the paste was treated with the addition of granules of the antifungal drug does not show periapical changes; on the contrary, the formation of the "dentin bridge" between the pulp chamber and the bottom of the carious cavity is followed in 1 month of observation in 6 patients (20.7%), in 17 patients (58.6%) by the 3rd month of observation, in 3 (10.3%) patients by the 6th month, which confirms the positive dynamics in the treatment of patients in the main study group (Figure 2).

The dynamics of the formation of the dentin bridge is different in the control group, so on the 30th day in 3 patients (11.1%), by 3 months in 7 patients (25.9%), and by 6 months in 2 patients (7, four%). It should be noted that in this group, 5 patients (18.5%) showed changes in periapical tissues.

Thus, the most effective treatment was the biological method with the application of material based on mineral trioxide aggregate with the addition of an antifungal component (86.2%), which confirms the effect of the drug Fluconazole on the healing of inflammation. In the control group, biological treatment was less successful (44.4%) and in 15 cases out of 27 (55.6%), it was ineffective, which led to the development of complications and the use of extirpation methods of treatment. The presence of Candida fungi complicated the inflammatory process in the tooth pulp, which led to the development of the inflammatory process in the tooth pulp tissues. The effectiveness of the treatment is presented in table 1.

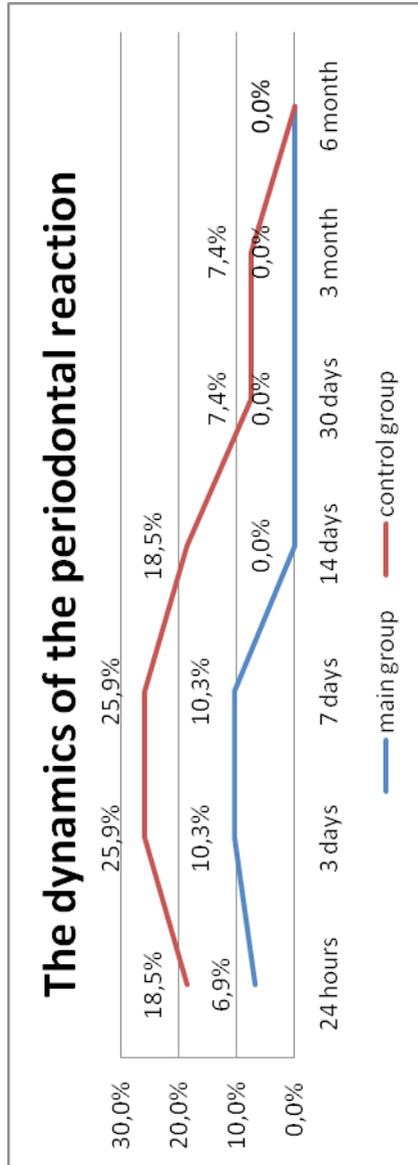


Figure 1. Dynamics of periodontal reaction to irritation



**Figure 2. Dentin “bridge” in a patient of the main group for 3 month of observation**

**Table 1.  
The effectiveness of treatment in patients  
of the main and control groups**

| Research group | Total observations | Effective treatment | Ineffective treatment |
|----------------|--------------------|---------------------|-----------------------|
| Control Group  | 27 (100%)          | 12 (44.4%)          | 15 (55.6%)            |
| Main Group     | 29 (100%)          | 25 (86.2%)          | 3 (10.3%)             |
| TOTAL          | 56 (100%)          | 37 (66.1%)          | 18 (33.9%)            |

Thus, with a correctly selected diagnostic and treatment complex for treating reversible pulpitis (pulp hyperemia) with the biological method, one can judge about the high positive effect of the treatment, which allows you to save the tooth as a full-fledged organ. Preservation of a living full pulp is very important for the tooth and the body as a whole because of the protective, trophic and plastic functions. In the case of pulp death, problems of acute and chronic odontogenic infection and sensitization of the body arise

**Conclusion.** If fungal flora is detected in the carious cavity, the treatment of teeth with pulp hyperemia should include (extempore) antifungal preparations, for example, Fluconazole 0.03 g per 0.2 g of mineral trioxide aggregate in the treatment paste.

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## THE IMPORTANCE OF EARLY DIAGNOSIS OF SUBCLINICAL VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS, COMPLICATED BY DIABETIC NEUROPATHY

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**Abstract.** In this study, an assessment of the levels of holotranscobalamin and homocysteine was used to diagnose subclinical vitamin B12 deficiency in patients with type 2 diabetes mellitus with diabetic polyneuropathy, since they are considered to be more sensitive to the biochemical deficiency of vitamin B12 than the level of vitamin B12 itself in the blood. The effect of vitamin B12, holotranscobalamin and homocysteine levels on the severity of the clinical manifestations of diabetic polyneuropathy according to the TSS and NIS LL scales was also studied.

**Keywords:** subclinical deficiency of cyanocobalamin, hyperhomocysteinemia, diabetic neuropathy, type 2 diabetes mellitus, holotranscobalamin.

Diabetic neuropathy (DN), which according to many researchers is considered the most common complication of diabetes, is one of the main causes of the development of diabetic foot syndrome. The increase in disability and treatment costs for patients with diabetes mellitus is due to an increase in the number of non-traumatic amputations of the lower extremities against the background of diabetic foot syndrome [1]. According to modern concepts, the main role in the pathogenesis of DN is played by hyperglycemia and a high level of glycated hemoglobin (HbA1c) [2]. However, the correction of the above factors does not always lead to a regression of the manifestation of DN. Therefore, the search for the missing links in pathogenesis remains an extremely urgent task. Such a missing link that adversely affects the course of DN can be a biochemical deficiency of vitamin B12 (cyanocobalamin), which, without clinical manifestation, can cause neurological disorders in patients with type 2 diabetes mellitus (T2DM). This is due to the fact that even at the stage of the biochemical deficiency of vitamin B12,

significant changes occur in the metabolism of certain amino acids and fatty acids. As a result, methylmalonate, homocysteine, tumor necrosis factor, toxic to the nervous system, which cause fatty degeneration of neurons and demyelination of nerve fibers, accumulate in the body [3].

The occurrence of vitamin B12 deficiency in patients with T2DM type is explained by the action of the sugar-lowering drug metformin, which disrupts the absorption of glucose through the intestinal wall and intestinal microflora, leading to malabsorption of vitamin B12. Since metformin is a first-line drug of the T2DM type and is preferably combined with other sugar-lowering drugs, the severity of vitamin B12 deficiency in patients receiving metformin becomes clear [3].

In 2017, the American Diabetes Association (ADA) has already proposed that metformin be taken periodically to measure the level of vitamin B12 in the blood, especially in patients with anemia or peripheral neuropathy, explaining that taking metformin can lead to a biochemical deficiency of vitamin B12 [4]. However, determining the level of cyanocobalamin as the main guideline for the diagnosis of vitamin B12-deficient conditions is not advisable, since there is no international consensus document regarding the methods of diagnosis and treatment. In addition, the sensitivity of the method for studying cyanocobalamin is far from 100% and, due to specificity, not all laboratories have the ability to perform it [5].

Therefore, in some cases, for the timely diagnosis of vitamin B12-deficient conditions, it is justified to use more sensitive methods to detect functional or biochemical deficiency of vitamin B12. These tests include the determination of the plasma level of homocysteine (HC) and methyl malonate, since their concentration is more sensitive to the biochemical deficiency of vitamin B12 and increases earlier than the level of vitamin B12 decreases. But determining the level of methyl malonate using gas chromatography / mass spectrometry, being an expensive method, does not have wide application in clinical practice [5].

Some researchers recommend using the level of holotranscobalamin (HT) in the blood to assess the level of vitamin B12-deficient states. HT (a complex of vitamin B12 with transcobalamin) is the only digestible form of vitamin B12 for the body and accounts for only 10-30% of the vitamin B12 circulating in the blood. When a negative balance of vitamin B12 occurs, the concentration of HT in the blood serum decreases first, since the remaining 70-90% of vitamin B12 is biologically inert and has a longer half-life than HT. That is why, in a number of publications, it is concluded that HT is a better indicator of vitamin B12 levels than the total concentration of B12 in the blood [5].

Thus, stating the absence of a "gold standard" for diagnosing vitamin B12 deficiency and analyzing the above, it becomes clear that determining

the level of cyanocobalamin in the blood is uninformative for assessing sub-clinical vitamin B12 deficiency in patients with T2DM type taking metformin. Therefore, the search for more informative markers for the timely diagnosis of vitamin B12 deficiency remains an urgent task.

The aim of our study is to evaluate the clinical significance of early diagnosis and the possibility of using blood levels of HC and HT as markers of subclinical vitamin B12 deficiency in patients with type T2DM complicated by diabetic neuropathy.

### Materials and methods

The study involved 40 patients, 23 women and 17 men, aged  $59.95 \pm 6.35$  years, with a diagnosis of T2DM type more than 3 years old, with distal sensorimotor diabetic polyneuropathy on a tablet or combination (oral hypoglycemic drugs + insulin and/or glucagon-like peptide receptor agonists of the 1st type) therapy with sugar-lowering drugs. Of these, 34 (85%) patients took metformin at a dose of ~ 1500-2000 mg per day as monotherapy or in combination with other sugar-lowering drugs or with insulin.

Inclusion criteria:

1. An established diagnosis of T2DM type with distal sensorimotor diabetic polyneuropathy.

2. Age from 50 to 70 years.

3. The level of glycated hemoglobin (HvA1c) from 6.5% to 9%.

4. The level of vitamin B12 within the reference values (191 - 663 pg/ml).

5. The ability and desire of the patient to follow the research protocol.

Exclusion Criteria:

1. Type 1 diabetes.

2. Severe pathology of the cardiovascular system

3. The presence of acute complications of diabetes

4. Taking drugs and substances within 3 weeks before the start of the study, as well as diseases and the presence of conditions that can lead to impaired metabolism of vitamin B12 and HC.

5. The presence of a diagnosed vitamin B12-deficient condition in history.

6. Clinically significant manifestations of intercurrent disease.

7. Pregnancy, lactation.

**The research methods** included a general clinical examination (examination, medical history, clinical and biochemical blood tests, urinalysis, blood pressure measurements, ECG), carbohydrate metabolism assessment (by determining the level of glycated hemoglobin (HbA1c) and fasting and postprandial venous glucose), determination of the level of vitamin B12 (reference values 191-663 pg/ml), HT (reference values 25.1-165.0 pmol/l) and HC (reference values 5.0 - 15.0  $\mu$ mol/l) in the blood. To assess

the functional state of the peripheral nervous system, the Total Symptoms Score (TSS) scale was used. A physical neurological examination was also performed to evaluate neuropathic disorders of the lower extremities on the Neuropathy Impairment Score in the Lower Limbs - NIS LL.

**Statistical processing**

Statistical processing of the obtained data was carried out using the programs Microsoft Excel 2010, STATISTICA (version 13.3).

The results of statistical analysis are presented in the form of arithmetic means and their standard deviation ( $M \pm SD$ ), as well as the median and intra-quartile range (Me; IQR). Comparison of quantitative traits between the two groups was carried out using Student's t-test, and for data with a distribution distinguishable from normal, the Mann-Whitney U-test. The differences were considered significant at a significance level of  $p < 0.05$ . To assess the relationship between the characteristics in the two groups, the Spearman correlation coefficient ( $r_s$ ) was used ( $r_s \leq \pm 0.3$  - weak connection,  $\pm 0.3 < r_s < \pm 0.7$  - medium connection,  $r_s \geq \pm 0.7$  - strong connection). The statistical significance of the obtained coefficient was evaluated using Student's t-test. The differences were considered significant at a significance level of  $p < 0.05$ .

**Research results**

The general clinical characteristics of patients with T2DM type included in the study are presented in Table 1. It should be noted that a decrease in HT levels below the reference values was not observed in this group of patients, which makes it impossible to use HT as a diagnostic marker of vitamin B12 deficiency in this study.

**Table 1.**

| Indicators  | M      | SD     | Me     | IQR   |
|---|--------|--------|--------|-------|
| Age, years  | 59,95  | 6,4    | 60     | 9     |
| Duration of type 2 diabetes, years                | 9,8    | 6,47   | 8      | 10,5  |
| Weight, kg  | 95,95  | 23,45  | 97,5   | 21    |
| BMI, $kg/m^2$                                     | 33,95  | 6,84   | 33,23  | 9,35  |
| HbA <sub>1c</sub> , %                             | 7,86   | 1,25   | 7,8    | 1,76  |
| Blood glucose before meals, mmol/l                | 6,39   | 1,02   | 6,4    | 1,2   |
| Blood glucose after a meal, mmol/l                | 9,3    | 2,73   | 8,3    | 3,7   |
| The level of vitamin B12 in the blood, PG/ml      | 455,98 | 154,16 | 477,35 | 283,5 |
| The level of HT in the blood, pmol/l              | 103,1  | 37,52  | 107,55 | 62,46 |
| The level of HC in the blood, $\mu mol/l$         | 14,25  | 7,98   | 12,2   | 5,35  |
| The level of HDL cholesterol in the blood, mmol/l | 1,64   | 0,8    | 1,3    | 0,91  |
| The level of LDL cholesterol in the blood, mmol/l | 2,94   | 1,1    | 2,93   | 1,2   |
| TSS score   | 7,5    | 3,6    | 7      | 5,9   |
| NIS LL score                                      | 12,7   | 5,6    | 12     | 8     |

**Assessing the relationship between HC, HT, and vitamin B12 levels in the blood**

A correlation analysis of the data of the studied patients showed that between the levels of vitamin B12 and HT there is a strong positive correlation ( $r_s = 0.99$ ) ( $p < 0.05$ ). A negative correlation ( $r_s = - 0.5$ ) ( $p < 0.05$ ) of average strength is observed between the levels of HC and vitamin B12. Also, the HC level has a negative correlation of average strength with the level of HT ( $r_s = - 0.53$ ) ( $p < 0.05$ ).

The study in 10 patients, 5 women and 5 men, revealed an increase in the level of HC in the blood from the norm (more than  $15.0 \mu\text{mol/L}$ ), despite the fact that in patients the levels of vitamin B12 and HT in the blood were in the range of reference values. Considering the obtained data, it was decided to divide the patients into 2 groups based on the level of HC in the blood: with an increased level of HC in the blood from reference values and with a normal value of HC in the blood.

Since the level of HC in the blood also depends on the amount of animal protein consumed (meat, milk), coffee and alcohol, as well as the number of cigarettes smoked, patient diaries were studied to identify other causes that affect the level of HC in the blood. As a result, no significant differences were revealed, and according to these signs, the groups were comparable. When studying the schemes of hypoglycemic therapy, it was found that the proportion of patients taking metformin is 15% higher in the group with hyperhomocysteinemia compared with the group with normal HC in the blood.

**Assessment of the level of vitamin B12 and HT in the blood in the group with hyperhomocysteinemia**

In this study, the average values of serum levels of HT and vitamin B12 in the group with hyperhomocysteinemia were significantly lower compared to the group with normal values of HC in the blood ( $p < 0.05$ ). (table 2).

**Table 2. Comparison of general clinical characteristics in two groups**

| Indicators                         | 1st group n = 10 (HTC) |           | 2nd group n = 30 (HCC) |          | -    |
|------------------------------------|------------------------|-----------|------------------------|----------|------|
|                                    | M±SD                   | Me;IQR    | M±SD                   | Me;IQR   |      |
| Average value                      | M±SD                   | Me;IQR    | M±SD                   | Me;IQR   | p    |
| Age, years                         | 62,1±6,23              | 62;10     | 59,2±6,3               | 60;9     | 0,3  |
| Duration of type 2 diabetes, years | 10,5±6,7               | 8,5;13    | 9,6±6,5                | 8;11     | 0,7  |
| Weight, kg                         | 93,37±17,32            | 98,5;13,3 | 96,8±25,3              | 95,5;31  | 0,86 |
| BMI, kg\m <sup>2</sup>             | 33,38±7,6              | 31,3;8,1  | 34,1±6,7               | 34,4;9,7 | 0,6  |
| HbA <sub>1c</sub> , %              | 7,7±1,1                | 8;2,3     | 7,9±1,3                | 7,8;1,7  | 0,9  |

|   |             |           |            |             |        |
|---|-------------|-----------|------------|-------------|--------|
| Blood glucose before meals, mmol/l                | 6,2±1,2     | 6,1;1,6   | 6,46±0,97  | 6,45;1,1    | 0,5    |
| Blood glucose after a meal, mmol/l                | 9,6±2,98    | 8,5;4,74  | 9,2±2,7    | 8,2;4       | 0,6    |
| The level of vitamin B12 in the blood, PG/ml      | 346,1±134,7 | 295;85,53 | 493±144,1  | 508,5;254,1 | 0,0067 |
| The level of HT in the blood, pmol/l              | 74,99±32,3  | 65,6;18,9 | 112,5±34,7 | 112,7;55,6  | 0,0054 |
| The level of HDL cholesterol in the blood, mmol/l | 2,1±1,2     | 1,6;2,1   | 1,5±0,6    | 1,3;0,92    | 0,23   |
| The level of HDL cholesterol in the blood, mmol/l | 3,5±1,2     | 3,4;0,2   | 2,7±0,9    | 2,7;1,2     | 0,023  |

In the group with hyperhomocysteinemia, a strong negative correlation is observed between the levels of HC and vitamin B12 ( $r_s = - 0.73$ ) ( $p < 0.05$ ). Such a strong negative correlation is also observed between the levels of HC and HT ( $r_s = - 0.78$ ) ( $p < 0.05$ ). The results obtained indicate that in the range of vitamin B12 levels 295; 85.53 pg/ml and HT 65.6; 18.9 pmol/l, there is a violation of HC metabolism in the studied patients. According to the main indicators, the groups are comparable, since there were no significant differences between the two groups ( $p > 0.05$ ).

**Assessing the relationship of vitamin B12, HT, and HC levels with the severity of diabetic polyneuropathy**

At the beginning of the study, patients were evaluated for the manifestation of neuropathic symptoms according to the TSS scale and neuropathic disorders or neuropathic deficiency of the lower extremities according to the NIS LL scale. Correlation analysis showed that there is a negative correlation between the levels of vitamin B12, HT and TSS and NIS LL scores (Tab. 3), as well as a positive correlation between the HC level and TSS and NIS LL scores (Tab. 3)

**Table.3 Correlation analysis**

| Indicators        | TSS score     | NIS LL score  | p       |
|-------------------|---------------|---------------|---------|
| Vitamin B12 Level | $r_s = -0,42$ | $r_s = -0,3$  | $<0,05$ |
| HT level          | $r_s = -0,43$ | $r_s = -0,31$ | $<0,05$ |
| HC level          | $r_s = 0,61$  | $r_s = 0,43$  | $<0,05$ |

In the group with hyperhomocysteinemia, the mean scores of TSS (12.23;1.6 vs 5.08; 3.6) and NIS LL (20.1;8 vs 10.1;4) were statistically significantly higher than in the group with physiological indicators of HC in the blood ( $p < 0.05$ ). In addition, in the group with hyperhomocysteinemia, a positive correlation was observed between the level of HC and TSS ( $r_s = 0.84$ ) and NIS LL ( $r_s = 0.95$ ) ( $p < 0.05$ ).

### Conclusions

The results of this study indicate that in this category of patients, taking metformin adversely affects the level of cyanocobalamin in the blood. A decrease in the levels of vitamin B12 and HT, and as a result, an increase in the level of HC, leads to more pronounced clinical manifestations of diabetic polyneuropathy, which further requires the development of a concept for the treatment of subclinical vitamin B12 deficiency in this category of patients. Determining the concentration of HC in the blood can be recommended as a marker in the early diagnosis of subclinical vitamin B12 deficiency in patients with type 2 diabetes mellitus complicated by diabetic polyneuropathy.

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## DETERMINING CONTENT OF CARDIAC STEROIDS IN RAW MATERIAL USING SPECTROPHOTOMETRY

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**Abstract.** A spectrophotometric method for the quantitative determination of cardiosteroids was developed based on their reaction with picric acid to form an orange complex with a characteristic absorption maximum at 490 nm. The error in determining the content of the amount of cardiosteroids in terms of convallotoxin does not exceed 5%. The methodology was tested on the medicinal plant material of Adonis grass and lily of the valley leaves and the drug "Adonis Brom" in tablets. It was found that Adonis grass and lily of the valley leaves contained 0.16 and 0.26 mg%, respectively, and Adonis-bromine tablets 0.51% with a norm of 0.56%.

**Keywords:** cardiosteroids, convallotoxin, spectrophotometry, analytical technique, lily of the valley leaves, adonis grass, corglycard, strophanthinidin

Chronic heart failure (CHF) is a disease with a complex of characteristic symptoms associated with inadequate perfusion of organs and tissues. The root cause is a violation of the functioning of the heart is due to damage to the myocardium, as well as an imbalance of vasoconstrictor and vasodilating neurohumoral systems. Chronic heart failure, resulting from many pathologies of the cardiovascular system, is a very common disease (up to 2% of the general population, reaching 10% for people over 70 [2]).

The leading place in CHF drug therapy belongs to the group of cardiotonic drugs that enhance myocardial contractions - cardiac glycosides, which have three main pharmacological effects - positive inotropic, negative chronotropic and neuromodulatory. and their use reduces mortality [3].

Today in the pharmacy assortment of Russia there are cardiotonic preparations containing in their composition cardiosteroids of the subgroup of strophanthus (corglycard, strophanthin K, adonis bromo) as their main active ingredient.

Cardiac glycosides are derivatives of steroid compounds formed from a common biogenetic precursor of triterpene nature – squalene, or as they are more correctly called "cardiosteroids". Cardiosteroids differ from other steroid compounds by the presence of an unsaturated lactone ring at the 17th position, and it is this chemical structure that determines the specific pharmacological action of these compounds. The only sources of obtaining cardiac glycosides are medicinal plants, such as digitalis, strophanthus Combe, May lily of the valley, Adonis spring and some others.

All herbal medicines used must be effective and safe, which can be achieved exclusively with the use of benign medicinal plant materials (MPM). To assess the benign quality of MPM, it is necessary to control the content of cardiosteroids in it. According to the State Pharmacopoeia of Russia [1], the benignity of LRS containing cardiosteroids is controlled by its standardization. The standardization of MPM of this type is carried out by a biological method, which is based on the ability of cardiosteroids in a toxic dose to cause heart failure of animals in systole. The biological standardization method allows you to establish only the strength of the action of SG, but does not allow to determine the quantitative content of the active pharmacologically active substance. In addition, the method is quite time-consuming, has a large test error (up to 25%) and high cost, as well as its implementation is associated with certain moral and ethical problems.

In this regard, it seems relevant to develop a methodology for determining the content of cardiosteroids in MPM.

**Materials and methods:** Korglikard and Strofantin K (injection solutions) were used as objects of study at the stage of development of the method, and at the stage of testing the operability of the method, adonis spring grass and May lily of the valley leaves. The choice of objects was due to the fact that the aglycon of cardiac glycosides (cymarine) Adonis vernalis as well as May lily of the valley is convallotoxin, which is part of the Korgligard preparation and the chemically related strophanthinid from Strofantin K. Adonis spring grass was collected in the Novosibirsk region, and May lily of the valley leaves in the Yaroslavl region in 2018 in the flowering phase. The collected raw materials were brought to an air-dry state and crushed. To test the operability of the methodology, an industrially produced medicinal product - tablets "Adonis-bromine" and an injection drug "Korglikard" were used.

The photometric method was based on the specific reaction of cardiosteroids in an alkaline environment with polynitro compounds - the Ballier reaction. Under these conditions, cardiosteroids form, as a result of interaction with picric acid, orange-colored reaction products having a characteristic absorption spectrum at 490 nm.

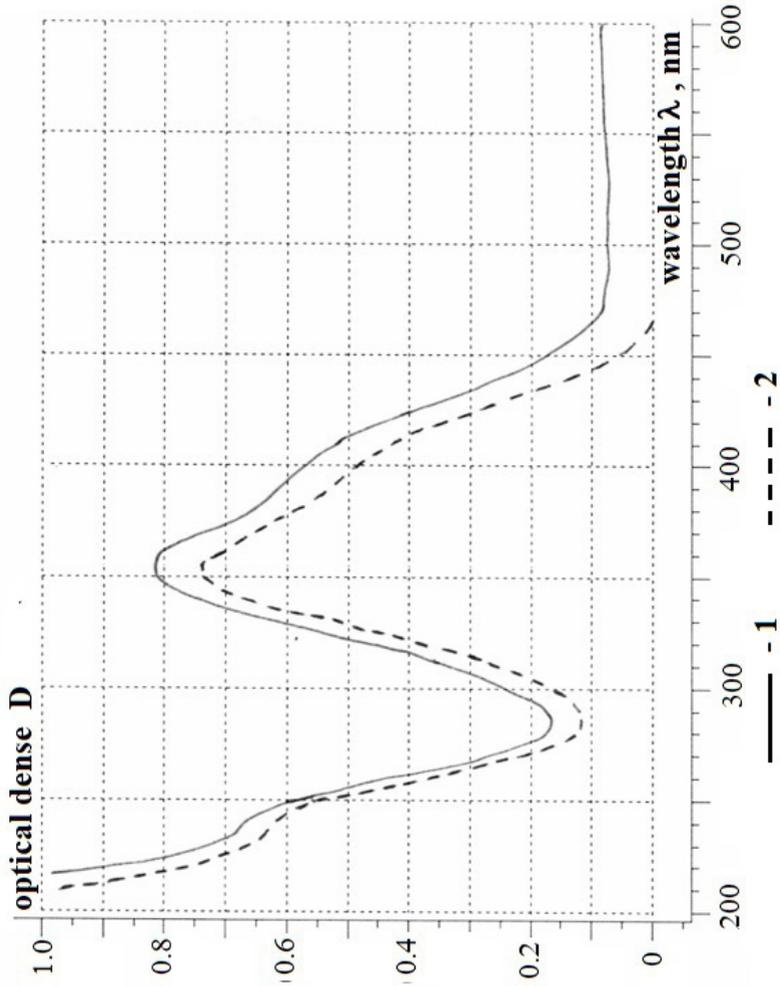


Fig. 1 UV spectrum of picric acid at various pH  
1- pH= 2      2 - pH =12

For the preparation of working solutions of corglycard and strophanthin: 10 ml of purified water was added to 0.5 ml of the drug. The Adonis Bromine tablet was dissolved in 10 ml of purified water. Next, 2.5 ml of a 5% sodium hydroxide solution and 1.25 ml (25 drops) of a 1% picric acid solution were added to 2.5 ml of each of the working solutions.

To prepare a comparison solution: 2.5 ml of 5% sodium hydroxide solution and 1.25 ml (25 drops) of 1% picric acid solution were added to 2.5 ml of purified water.

Differential UV spectra in the range of 200-600 nm were recorded from the obtained solutions using an SF-56 spectrophotometer. To exclude the effect of absorption of picric acid itself, spectra of a 1% picric acid solution with different pH values were simultaneously taken (a change in pH from 2 to 12 was achieved by adding 10%  $\text{NH}_4\text{OH}$  or 2%  $\text{HCl}$ ).

To prepare galenic extraction, the crushed MPM was poured with ethanol in the ratio of raw materials: extractant - 1:25 and placed for 30 min in a boiling water bath. After cooling and filtering, 2.5 ml of alkali solution and 25 drops of picric acid solution were added to 2.5 ml of the obtained filtrate.

To test the efficiency of the method, a control sample was prepared - a solution of corglycard with a fixed content of 0.001 mg of convallotoxin was quantitatively added to the total extract from lily of the valley

**Results and discussion:** An analysis of the spectra of pure picric acid in Fig. 1 at various pH showed the presence of a characteristic absorption maximum at  $\lambda = 350$  nm, the position of which did not depend on the pH of the solution (Fig. 1).

The absorption spectra of the studied solutions of both strophanthin and corglycard (Fig. 2) practically coincided and showed the presence of a maximum absorption at  $\lambda = 490 \pm 3$  nm. Thus, it can be stated with a high degree of probability that the spectrum of cardiosteroids is determined by aglycon, because and corglycard and strophanthin have closely related aglycones.

An analysis of the spectra of the chromogenic complexes of picric acid with the total extraction of adonis and lily of the valley (Fig. 3, curves 1 and 3) shows their proximity and the presence of a maximum absorption at 490 nm.

Thus, the spectral characteristics of cardiosteroids having structurally similar aglycones are determined to coincide, which makes it possible to determine the quantitative content of the sum of cardiosteroids in plant material in terms of convallotoxin.

Quantitative determination of the content of the sum of cardiosteroids in terms of convallotoxin was made according to the obtained optical density values and the extinction value of convallotoxin determined by the working sample of corglycard.

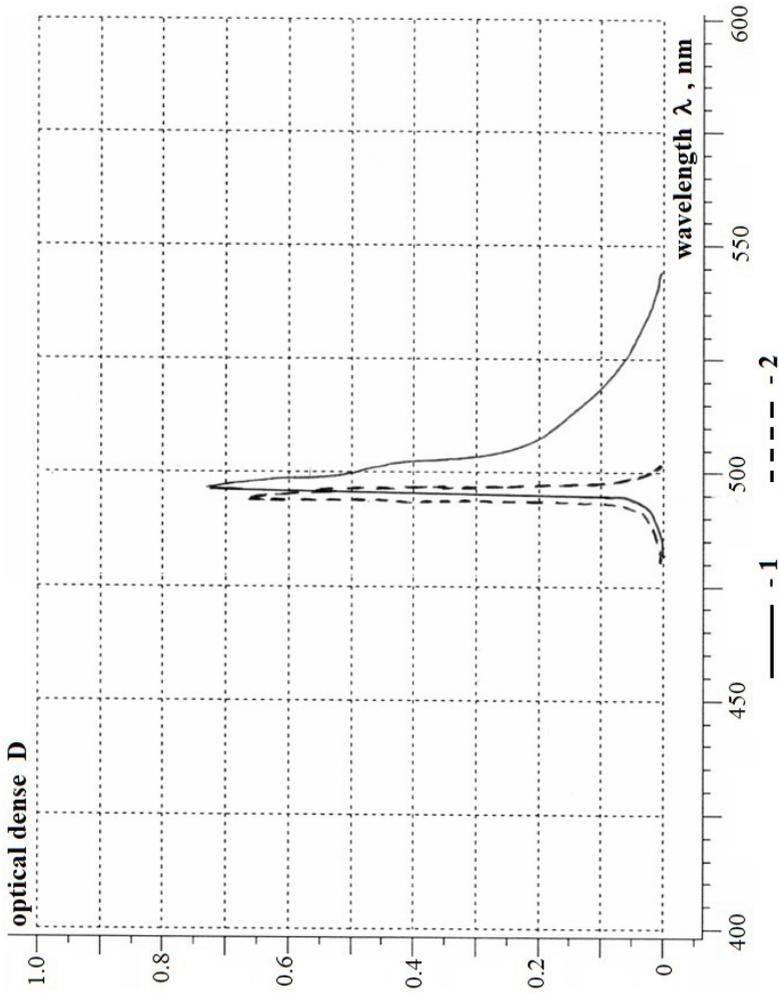


Fig. 2. UV spectrum of the chromogenic complex of standard samples:  
1 - corglycard picric acid 2 - strophanthin-picric acid

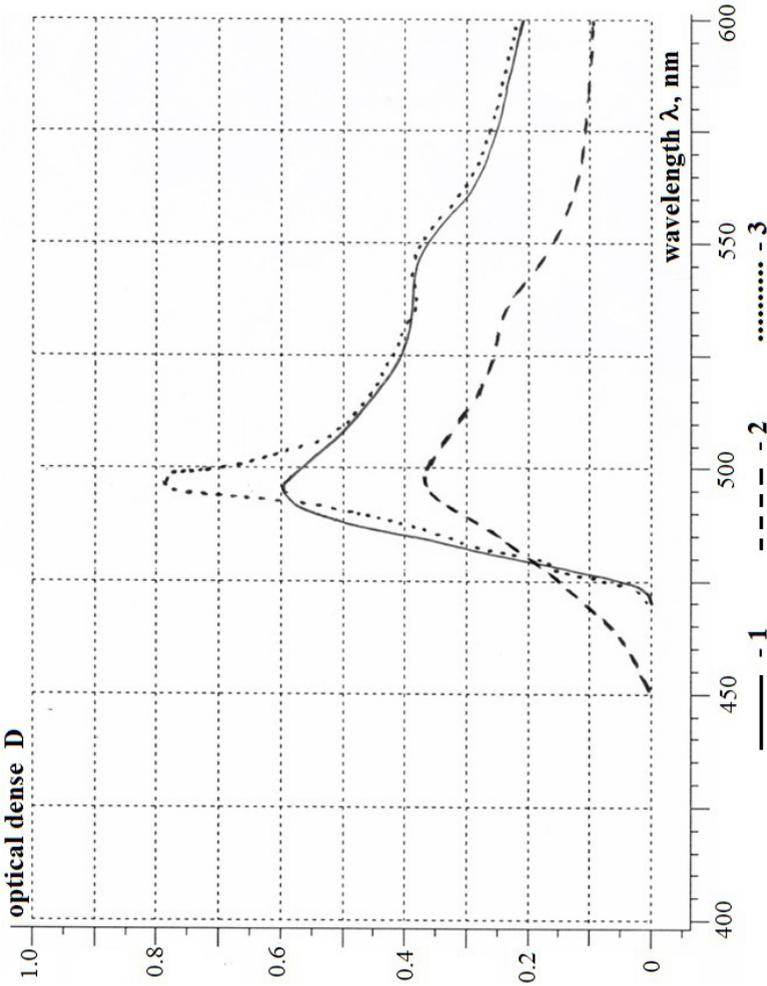


Fig. 3 UV spectrum of the studied solutions 1 – lily of the valley extract , 2 – adonis herb extract  
3 – control sample with the addition of convalotoxin

As a result, it was found that the content of cardiosteroids in adonis herb was  $0.16 \pm 0.004$  mg%, and for lily of the valley  $0.26 \pm 0.008$  mg% (data averaged over 10 samples). For adonis bromine tablets, a value of  $0.51 \pm 0.06\%$  was obtained with a norm of 0.56%.

The optical density of the control sample was used to calculate the amount of added convalotoxin which amounted to  $0.00097 \pm 0.00007$  mg (data for 12 samples) and thus the measurement error did not exceed 5%.

### Conclusion

As a result of the studies, a method for the quantitative determination of the content of cardiosteroids using the photometry method was developed, based on the ability of the chromogenic complex formed by cardiosteroids with picric acid to produce a reproducible analytical signal in the form of an absorption maximum at  $493 \pm 3$  nm. Convalotoxin determination error did not exceed 5%

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## THE ROLE OF *CANDIDA ALBICANS* IN THE DIGESTIVE TRACT IN CANDIDIASIS OF GEESE

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**Abstract.** In a number of farms of the Republic of Bashkortostan we have registered goose candidiasis. They manifested a violation of the natural microbiocenosis in all departments of the digestive tract of birds. A special role was played by *Candida albicans*. Moreover, candidiasis cause enormous economic damage to goose breeding. To date, there are no effective methods for the prevention and treatment of avian candidiasis [1, 2, 3, 4]. The article presents data on the dynamics of *Candida albicans* in scrapings from goiter, muscle and glandular stomach, small and large intestines from 7 days to 90 days of age of birds. Comparative methods for the treatment of goose candidiasis showed the high efficiency of complex enzyme-probiotic propolisotherapy. It helped restore the content of *Candida albicans* to their physiologically acceptable values in the gastrointestinal tract of geese.

**Keywords:** geese, candidiasis, *Candida albicans*, goiter, muscular and glandular stomach, thin and thick intestine, mycobiotic, lyticase, probiotic, propolis.

**Materials and research methods.** The work was carried out in the conditions of goose-breeding farms of the republics of Tatarstan and Bashkortostan on birds of the Linda breed, from 7 days to 90 days of age. Microbiological studies were carried out in the bacteriological departments of district and republican laboratories, the microbiology laboratory of the Department of Microbiology and Immunology of the Russian State Agrarian University. *Candida albicans* was isolated on Saburo media, meat peptone glucose agar. Material for research was taken before the start of the

experiment - background (7-days), and then on 14, 30, 60 and 90 days from the start of the drug administration. Birds, according to the principle of analogues, were divided into 7 groups. The first group was the control - healthy birds, 2 - 7 infected with candidomycosis. No treatment manipulations were performed with the birds of group 2. Goose of group 3 was subjected to traditional antibiotic therapy with nystatin, group 4 - enzyme therapy with lithase, group 5 - enzyme therapy with probiotic therapy with lactobifid, group 6 - enzyme therapy with propolis therapy, group 7 - complex enzyme therapy with probiotic and propolisotherapy.

**Research results and discussion.** In the goiter content of geese of the control group, a low content of *Candida albicans* was found at all periods of the experiment. This is due to the fact that it is very difficult to create conditions in the farms in which goose candidiasis of geese was created without *Candida albicans* in the environment. However, in this case, not all birds exhibit pronounced candidiasis. On the 7th day of the experiment, the level in the goiter of birds of the 1st group was 1.44 lg COE/g. This figure slightly increased in terms of research (up to 30 days of experiment), exceeding the initial indicator by 1.38 times, with a subsequent decrease. By the 90th day of the experiment, the content of *Candida albicans* in the goiter of group 1 geese was 1.28 times higher than the initial value.

In materials from scraping and goiter contents of sick geese of group 2, *Candida albicans* was secreted in large numbers. On the 7th day from the beginning of the otitis, the level of *Candida albicans* in the goiter of group 2 geese not subjected to therapeutic manipulations exceeded the control figure by 3.29 times. The reproduction of *Candida albicans* in the goiter of geese of group 2, according to the duration of the experiment, actively progressed. On the 14th, 30th, 60th and 90th days from the start of the experiment, the content of *Candida albicans* in the goiter of group 2 birds exceeded its level in birds of the control group by 5.07; 5.12; 7.0; 8.59 times.

Traditional antimycotic therapy using nystatin (group 3) contributed to a moderate inhibition of the activity of *Candida albicans* in goiter, compared with its content in birds of group 2. Indicators of geese of group 3, in terms of *Candida albicans* in goiter, were lower than in birds of group 2 on the 7th, 14th, 30th, 60th and 90th days of the experiment — 1.13; 1.19; 1.64; 2.08 and times. However, nystatin therapy was not sufficient to restore the balance of *Candida albicans* in goose goiter in the form of a decrease in its level to physiologically acceptable values. The content of *Candida albicans* in the goiter of birds of group 3 significantly exceeded the indicators of birds of the 1st control group: on days 7, 14, 30, 60 and 90 — at 2.92; 4.26; 3.26; 3.87 and 4.13 times.

A significant decrease in the goiter of geese *Candida albicans* was recorded against the background of enzyme therapy with the use of a lithicase preparation (group 4). The level of *Candida albicans* in the goiter of birds of this group decreased, compared with the data for groups 2 and 3, for these experimental periods, respectively, in 1.13 and 1.07; 1.32 and 1.11 times; 2.09 and 1.27 times; 2.86 and 1.63 times; 3.56 and 1.71 times. However, enzyme therapy alone was also not enough to restore mycological activity of the organ against candida, because the indicators of birds of the 4th group continued to exceed the control parameters of geese of the 1st group by 7, 14, 30, 60, and 90 days — 2.7; 3.83; 2.55; 2.36 and 2.41 times.

The use of lithicase in combination with a probiotic (group 5) and lithicase in combination with propolis (group 6) had a more favorable effect on reducing the level of *Candida albicans* in goiter. Under the influence of probiotic and propolis, the activity of lithicase increased against candida. The maximum effect with respect to suppressing the propagation activity of *Candida albicans* was exerted by the complex use of lyticase with probiotic and propolis (group 7). The level of *Candida albicans* in the goiter of geese of group 7 decreased, compared to its value in birds of group 2, on days 7, 14, 30, 60 and 90 — at 1.58; 1.89; 5.37; 9.21 and 11.9 times. At the same time, by the 30th day of the experiment their level decreased to the indices of birds of the 1st control group, and by 60 and 90 days it was lower than in the control by 1.36 and 1.39 times.

Ambiguous indicators of the content of *Candida albicans* were recorded in the muscle and glandular regions of the geese stomach. The level of *Candida albicans* in the muscle stomach of geese 1 of the control group was not high. At the beginning of the study (7 days from the start of the experiment), it amounted to 1.96 lg COE/g. In the subsequent periods of the experiment, it was noted, with an increase and formation of the immune mechanisms of birds, a decrease in the number of fungi of the genus *Candida albicans* in the muscle stomach of geese: on days 14, 30, 60 and 90 — 1.1; 1.35; 1.44 and 1.53 times.

The content of *Candida albicans* fungi in the muscle stomach of group 2 geese increased according to the duration of the study. On the 7th day of the experiment, their level was 1.86 times higher than in birds of the 1st control group. In the following periods (on days 14, 30, 60 and 90), the activation of *Candida albicans* in the muscle stomach of birds of group 2 continued, and they exceeded the parameters of birds in the control group by 2.69; 5.25; 6.57 and 7.24 times.

Different methods of therapy, to varying degrees of activity of the manifestation, contributed to inhibition of reproduction in the muscular stomach of geese *Candida albicans*. So, in the muscle stomach of birds of group 3, the level of *Candida albicans* decreased, compared with its value in birds of group 2 on the 7th, 14th, 30th, 60th and 90th days of the experiment at 1.1; 1.16; 2.15; 2.69 and 3.05 times. But the indices of birds of the 3rd group were significantly higher compared with the data of geese of the 1 control group and exceeded them by these periods of the experiment by 1.67; 2.31; 2.48; 2.44 and 2.37 times. A significant decrease in the level of *Candida albicans*, compared with their content in the muscle stomach of birds of group 2, was recorded against the background of the use of lyticase for the treatment of the enzyme preparation (group 4). Here, the described indicator decreased, compared with its number in the muscle stomach of birds of group 2 on the 7th, 14th, 30th, 60th and 90th days of the experiment, at 1.21; 1.31; 2.5; 3.19 and 3.52 times. At the same time, the indicators of the 4th geese group were much closer, but still exceeded the data for the 1st control group, respectively 1.53; 2.05; 2.13; 2.06 and 2.05 times.

But the use of probiotic (group 5) and especially propolis (group 6) against the background of lithicase, significantly suppressed the growth of *Candida albicans* in the muscular stomach of geese. The content of *Candida albicans* in the muscle stomach of group 6 geese (lithicase + propolis) decreased compared to their indices in birds of group 2 at 7, 14, 30, 60 and 90 days — by 1.38; 2.18; 4.19; 5.51; 6.53 times. At the same time, the level of *Candida albicans* in the muscle stomach of group 6 geese significantly approached the indicators of birds in the control group.

The most favorable effect on the process of reducing the activity of *Candida albicans* and creating conditions that significantly inhibit their growth and reproduction in the muscular stomach of geese was exerted by the complex use of lithicase with probiotic and propolis in the 7th experimental group. Over the entire study period, the content of *Candida albicans* in the muscle stomach of geese of group 7 was lower, not only in comparison with indicators of birds of all experimental groups, but also of 1 control group, corresponding to its physiological value.

In the glandular stomach of geese of the 1st control group, microorganisms from the genus *Candida albicans* tended to increase on the 14th and 30th days from the start of the experiment, compared with its level on the 7th day of the study. On the 60th and 90th days of the experiment, a moderate decrease in the content of *Candida albicans* was noted.

The level of *Candida albicans* in the glandular stomach of geese of group 2 already by 7 days of the experiment exceeded the indicator of birds of the 1st control group by 1.64 times. This trend has progressed during the experiments. On the 14th, 30th, 60th and 90th days from the beginning of the experiments, the level of *Candida albicans* in the glandular stomach of geese of group 2 was higher compared to its value in birds of the 1st control group at 2.57; 3.87; 5.10; 8.12 times.

Against the background of treatment of birds with antimycotics (group 3), a slight not remarkable improvement was noted in comparison with the data for group 2. The content of *Candida albicans* in the glandular stomach of geese of group 3 was lower at all stages of the experiment, compared with their value in birds of group 2. On days 7, 14, 30, 60 and 90, this difference was 1.17; 1.23; 1.94; 2.64 and 3.82 times. Nonetheless, the microbiocenosis did not recover and the level of *Candida albicans* in the glandular stomach of group 3 geese, for these study periods, continued to exceed their content in the control 2.26; 2.04; 2.0; 1.93 and 2.12 times.

Remarkable rearrangements in the microbiocenosis of the glandular stomach of geese were recorded under the influence of the lyticase enzyme (group 4). They also manifested themselves in a remarkable inhibition of candida activity. The most striking differences were with the indicators of birds of the 2nd group. The level of *Candida albicans* in the glandular stomach of geese of group 4 decreased, compared with their value in birds of group 2, on the 7th, 14th, 30th, 60th and 90th days of the experiment, at 1.46; 2.0; 4.92; 7.02 and 10.7 times.

The content of *Candida albicans* in the glandular stomach of birds of groups 5 and 6 also continued to decrease, compared with their value in birds of the previous groups. However, the severity and intensity of this process in these groups was not active, compared with their value in geese of group 4. Propolis and probiotic in combination with an enzyme preparation (groups 5 and 6) contributed to an even more pronounced suppression of the growth and reproduction of *Candida albicans* in the glandular stomach of geese.

The most effective result of treatment of candidiasis and restoration of the level of *Candida albicans* to physiologically acceptable values in the glandular stomach of geese was recorded against the background of complex enzyme-probiotic-propolisotherapy (group 7). Here, the level of *Candida albicans* was lower, compared with the data for groups 1 and 2, by 7, 14, 30, 60, and 90 days of the experiment — 1.3 and 7.85 times, 1.49 and 3.83 times, at 2.0 and 7.75; 2.23 and 11.4; 2.2 and 17.8 times.

By the end of the experiments (90 days), the level of *Candida albicans* in the glandular stomach of geese of group 7 was lower than in birds of group 3 - by 4.67 times and only slightly lower than their performance in geese of groups 4, 5 and 6 - by 1.67 ; 1.49 and 1.21 times.

Similar to the dynamics of *Candida albicans* in the stomach, a change in the dynamics of candida in the intestines of birds was observed (table , figure ).

In the small intestine segment, geese of the 1 control group *Candida albicans* was secreted at all stages of the experiment, but in a small amount - from 1.72 to 2.14 log COE/g. The background content of *Candida albicans* in the small intestine of sick birds of groups 2-7 was increased.

On the 7th day from the beginning of the experiments, the level of *Candida albicans* in the small intestine of geese of group 2 was higher compared to the control index by 4.4 times. The activation process of *Candida albicans* in the small intestine of geese of group 2 intensively progressed during the experiments. At 14, 30, 60, 90 days from the start of the experiments, the level of *Candida albicans* here exceeded the control value of 4.89; 5.9; 7.43 and 10.2 times.

The level of *Candida albicans* in the small intestine of the geese of group 3 from the 7th day from the start of studies against the background of antimycotic therapy decreased compared to its content in birds of the 2nd group: by 7, 14, 30, 60 and 90 days - by 1.2; 1.23; 1.47; 1.48 and 1.63 times, which shows the lack of effectiveness of the treatment method. This is also confirmed by the fact that the indicators of geese of the 3rd group, for these periods of the experiment, significantly exceeded the data of birds of the 1st control group: 3.98; 3.66; 4.0; 5.0 and 6.27 times.

A significant decrease in the level of *Candida albicans* in the small intestine segment of the geese was observed against the background of lithium enzyme therapy. On 7, 14, 30, 60 and 90 days from the start of administration of this preparation, the indices of candida content in the small intestine of geese of group 4 were lower, compared to their value in birds of group 2, at 1.89; 2.55; 4.02; 5.13 and 6.57 times. According to this, the level of *Candida albicans* in the small intestine of geese of group 4 continued to slightly exceed the control numbers of geese of group 1 for these study periods — 2.32; 1.91; 1.46; 1.44 and 1.55 times. In this regard, the therapy was carried out for goose with candidiasis by lithiasis with a probiotic (group 5) and lithiasis with propolis (group 6). In the small intestine of geese of groups 5 and 6, a further decrease in the content of *Candida albicans* was observed. But more significant successes in this work were established against the background of complex therapy with lithase with

probiotic and propolis - group 7. The content of *Candida albicans* in the small intestine of geese of group 7, over the entire duration of the experiment, continued to decrease towards their physiological values. On the 14th, 30th, 60th and 90th days from the start of the experiment, the level of *Candida albicans* in the small intestine of the geese of group 7 was lower compared with the data of birds of groups 1 and 2 in 1.11 and 5.45; at 1.46 and 8.61; at 1.78 and 13.2; 2.03 and 20.7 times.

Similar to the dynamics of changes in the content of *Candida albicans* in the small intestine with goose candidiasis, its dynamics also changed in the large intestine.

The level of *Candida albicans* in the small intestine of geese of the 1 control group ranged from 2.62 to 3.36 log COE/g. This indicator was slightly higher compared to the acceptable physiological level of candida in the large intestine of geese. This is due to its constant presence in the environment and with insufficiently active immune status of geese in those farms and farms in which we conducted research.

Indicators of *Candida albicans* in the large intestine of sick geese of 2-7 experimental groups at the beginning of the experiment were higher than the control figures. On the 7th day from the start of the experiment, their value in the intestines of geese of group 2, which were not subjected to medical manipulations, exceeded the control figure by 3.49 times. For this period, the level of *Candida albicans* in the large intestine of the geese of groups 3-7 has already decreased, compared to its value in geese of the 2nd group, at 1.25; 2.02; 3.2; 3.47 and 4.24 times, which emphasizes the need for treatment of birds against the background of developing candidiasis.

By this period of research, the level of *Candida albicans*, compared with its value in the colon of birds of groups 3 and 4, still remained elevated, exceeding the rate of geese of the 1 control group by 1.7; 1.09. The data of birds of groups 6 and 7 corresponded to the geese of the control group. This trend persisted throughout the entire experiment.

In the 3, 4, 5, 6, and 7 experimental groups, a further decrease in the level of *Candida albicans* in the large intestine was recorded, compared with the data of birds of the 2nd group. On the 14th day of the experiment, the content of *Candida albicans* in the large intestine of the birds of these groups decreased, compared to its level in birds of the 2nd group, by 1.37; 3.02; 3.32; 3.73 and 4.26 times. On the 30th day from the beginning of the experiments, this difference was with the data for group 2, towards the decrease in the content of *Candida albicans*, for groups 3, 4, 5, 6, 7 — by 1.51; 4.22; 4.47; 4.9 and 6.33 times; for 60 days - at 1.61; 6.39; 6.13; 6.86 and 9.28 times; for 90 days, at 2.29; 7.08; 7.8; 10.1 and 12.7 times.

**Conclusion.** Candidomycoses of the digestive tract of geese are characterized by pronounced activation and reproduction in the goiter, muscle and glandular sections of the stomach, sections of small and large intestines of micro fungi from the genus *Candida albicans*. This requires the adoption of mandatory measures for the prevention and therapy of this pathology. Conducting only traditional therapy with candidacotics is not effective enough for the destruction and removal of candida from the digestive tract of geese. The developed new enzyme preparation, lythicase, has a significant antimycotic effect against *Candida albicans*. The best results for the complete restoration of *Candida albicans* level were obtained using lithicase with a probiotic or with propolis (groups 5 and 6) and, especially, their complex use (lithicase + probiotic + propolis) - group 7.

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## THE IMPORTANCE OF THE NORMOFFLORA OF THE DIGESTIVE TRACT IN CANDIDIASIS OF GEESSE

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**Abstract.** In recent years, candidiasis has caused great damage to goose breeding in the republics of Tatarstan and Bashkortostan. Until now, they have not been given any significance. In this regard, we conducted research to find effective methods for the prevention and treatment of goose candidiasis [1, 2, 3]. The article presents data on the dynamics of lactobacilli and bifidobacteria and in scrapings from goiter, muscle and glandular stomach, thin and thick intestines from 7 days to 90 days of age birds. It has been established that complex therapy with the new enzyme drug lithase in combination with the use of probiotic and propolis helps to restore the balance of normoflora in the gastrointestinal tract of geese to their physiological values.

**Keywords:** geese, candidiasis, *Lactobacillus spp.*, *Bifidobacterium spp.*, goiter, muscle and glandular stomach, thin and thick intestines, mycobiotic, lyticase, probiotic, propolis.

**Materials and research methods.** The work was carried out in the conditions of goose-breeding farms of the republics of Tatarstan and Bashkortostan on birds of the Linda breed, from 7 days. up to 90 days age. Microbiological studies were carried out in the bacteriological departments of district and republican laboratories, the microbiology laboratory of the Department of Microbiology and Immunology of the Russian State Agrarian University. Isolation of *Bifidobacterium spp.* was carried out on Blaurock medium, *Lactobacillus spp.* - on the medium of IFAs. Material for research was taken before the start of the experiment - background (7 daily), and then on 14, 30, 60 and 90 days. from the beginning of giving

drugs. Birds, according to the principle of analogues, were divided into 7 groups. The first group was the control - healthy birds, 2 - 7 infected with candidomycosis. No treatment manipulations were performed with the birds of group 2. Goose of group 3 was subjected to traditional antibiotic therapy with nystatin, group 4 - enzyme therapy with lithase, group 5 - enzyme therapy with probiotic therapy with lactobifid, group 6 - enzyme therapy with propolis therapy, group 7 - complex enzyme therapy with probiotic and propolisotherapy.

**Research results.** The background value indicator of *Lactobacillus spp.* in goiter of healthy geese of the 1st control group, as well as its background level in birds of 2–7 experimental groups, ranged from 4.12 to 4.88 lg CFU/g. On the 14th day from the beginning of the experiments, the indicator of birds of the 1st control group increased by 1.53 times compared to the background value. The content of lactobacilli in the goiter of group 2 birds was 1.8 times lower than in the control by this period of the experiment. At the same time, data on 3-7 groups that underwent different methods of therapy exceeded the level of *Lactobacillus spp.* in goiter of geese of the 2nd group: by the 3rd group by 1.18 times, by the 4th, 5th, 6th and 7th groups - by 1.57; 1.92; 1.82; 1.75 and 2.01 times. On 30, 60 and 90 days from the start of the experiments, the contents of *Lactobacillus spp.* in the goiter of geese of the 2nd group, which were not subjected to medical manipulations, decreased by 6.63 compared with the data of birds of the 1st control group; 7.26 and 4.24 times. Indicators of birds of 3 - 7 experimental groups, on the contrary, tended to increase. This process had a different degree of severity and manifestation, depending on the adaptogens used for therapy. By day 30 of the experiment, the level of *Lactobacillus spp.* in the goiter of geese of the 3rd, 4th, 5th, 6th and 7th groups it was higher in comparison with its value in birds of the 2nd group, at 4.23; 7.03; 7.04; 6.47 and 8.3 times. The maximum amount of *Lactobacillus spp.* 3 - 7 experimental groups was secreted in the goiter of geese for 60 days of the experiment. By this research period, the value of this indicator for geese of the 3rd, 4th, 5th, 6th and 7th groups was higher, in comparison with the data of birds of the 2nd group, at 4.72; 7.94; 8.29; 7.66 and 9.45 times. By the 90th day of the experiment, the level of *Lactobacillus spp.* in the goiter of the surviving birds, 2 groups increased 1.59 times compared with the previous study period (60 days). But the data of birds of the 3rd, 4th, 5th, 6th and 7th groups, by the end of the experiment (90 days), were higher than the indicator of birds of the 2nd group, 2.81; 5.0; 5.03; 4.84 and 5.25 times.

In the muscular section of the geese's stomach, the background level of lactobacilli was secreted at level from 2.94 to 3.56 lg CFU/g. In infected and not subjected to therapeutic manipulations birds of group 2, the content of *Lactobacillus spp.* dynamically decreased and inferior to the indicators of birds of the 1st control group on the 14th, 30th, 60th, 90th days of the experiment at 2.77; 6.25; 11.56 and 20.5 times. Level of *Lactobacillus spp.* in the muscular stomach of geese 3, 4, 5, 6 and 7 groups dynamically increased during the experiment. It was higher compared to the data of geese of the 2nd group on the 14th day of the experiment at 1.69; 2.39; 2.8; 2.46 and 3.32 times, for 30 days - 4.13; 6.4; 7.45; 6.37 and 8.55 times; at 60 days - at 7.78; 13.2; 14.4; 12.9 and 16.7 times; for 90 days - at 13.6; 27.0; 29.8; 26.9 and 30.7 times.

Background value of *Lactobacillus spp.* in the glandular stomach of geese of the control and experimental groups ranged from 4.0 to 4.6 lg CFU/g. The content of *Lactobacillus spp.* in the glandular stomach of sick geese of groups 2, 3, 4, 6 by the 14th day of the experiment was lower than in the control, 5 groups corresponded to the control level, and 7 groups exceeded the rate of birds of the 1 control group 1.17 times. The content of *Lactobacillus spp.* in the glandular stomach of geese 3, 4, 5, 6 and 7 of the experimental groups exceeded the data for birds of the 2nd group on the 14th day of the experiment, at 1.47; 1.94; 2.17; 1.93 and 2.54 times. This trend continued during the experiment. At 30 days from the start of the experiments, the level of *Lactobacillus spp.* in the glandular stomach of geese of the 3rd, 4th, 5th, 6th and 7th groups was higher than in birds of the 2nd group, 2.76; 3.06; 3.26; 2.94 and 5.11 times, for 60 days - 7.75; 10.65; 11.06; 10.5 and 13.0 times, for 90 days - 13.0; 19.8; 19.13; 19.4 and 21.5 times.

Violation of microbiocenosis against the background of goose candidiasis was also observed from the side of the small and large intestines. By the beginning of the experiment, the level of *Lactobacillus spp.* in the small intestine of geese of groups 2–7 was lower than in the control by 1.05–1.15 times. In the subsequent periods of the experiment, the content of lactobacilli in the small intestine of geese of group 2 intensively decreased and was inferior to the indicators of geese of the 1 control group on the 14th day of the experiment at 1.65; at 30 days - at 2.89; at 60 days, 3.64 times; and at 90 days, 3.79 times. Level of *Lactobacillus spp.* in the intestines of birds 3, 4, 5, 6 and 7 of the experimental groups tended to recover and increase. By the 14th day of research, this indicator for 3–7 groups exceeded its value in the intestines of geese of the 2nd group in 1.24; 1.49; 1.6; 1.46 and 1.8 times. Activation of lactobacilli in the small intestine of

geese of groups 3–7 increased during the experiment and by 30 days their level was higher, compared to the data of birds of the 2nd group, at 2.08; 2.47; 2.76; 2.32 and 3.42 times. The maximum content of *Lactobacillus spp.* in the small intestine of geese of 3-7 groups was recorded at 60 days of the experiment. It exceeded the data of geese of the 2nd group, not subjected to therapeutic measures in 2.67; 3.29; 3.59; 2.9 and 4.25 times. By the 90th day of the experiment, a slight decrease in the content of lactobacilli in the small intestine of geese was noted in all groups. However, the data of birds of 3-7 experimental groups continued to exceed the level of *Lactobacillus spp.* in the intestines of birds 2 groups in 2.32; 3.77; 4.3; 3.63 and 4.82 times.

Similar to the dynamics of *Lactobacillus spp.* in the small intestine, their content in the large intestine of the geese changed. The level of *Lactobacillus spp.* in the large intestine of geese were generally lower than in the small intestine. The indicator of geese of group 2 decreased during the experiment and by the 14th, 30th, 60th and 90th days of the experiment was lower than its value in birds of the 1st control group at 2.28; 3.54; 9.53; 11.6 times. A significant increase in the level of *Lactobacillus spp.* was recorded in the large intestine section of geese of 3–7 experimental groups from 14 days of testing. By 14 days, their level exceeded the data of birds of the 2nd group in 3-7 groups at 1.86; 2.44; 2.79; 2.41 and 3.1 times; by 30 days - at 2.87; 3.78; 4.35; 3.69 and 5.52 times, by 60 days - 5.74; 9.9; 11.16; 9.04 and 13.34 times, by 90 days - by 5.43; 12.0; 14.0; 12.0 and 17.2 times.

Candidamycosis with damage to the digestive tract of geese leads to a marked inhibition of reproduction in the goiter, muscle and glandular sections of the stomach, small and large intestines of *Lactobacillus spp.* Treatment with the traditional method using antibiotic therapy using nystatin inhibits the process of reducing the level of lactobacilli, but does not restore the level of *Lactobacillus spp.* to the control value. Positive effect on the recovery and increase in the level of *Lactobacillus spp.* in the digestive tract of geese, enzyme therapy with the use of lithicase, as well as lithicase with a probiotic and lithicase with propolis, are provided. Significant activation of *Lactobacillus spp.* in the gastrointestinal tract of geese, complex enzyme therapy with lithiasis is provided against the background of probiotic and propolisotherapy.

Similar to the dynamics of lactobacilli with geese candidiasis, the dynamics of bifidobacteria changed in the gastrointestinal tract. The content of *Bifidobacterium spp.* in the goiter of geese of the 1st group, during the experiment period, it increased upwards from 7 days to 90 days of the experiment 2.12 times. The value of this indicator in goiter of birds of the

2nd group, birds with candidiasis, on the contrary, dynamically decreased during the experiment, and by the end of the study it was 2.34 times lower than the initial value. Moreover, already at the beginning of the experiments - 7 days, this indicator was 1.52 times lower than in the control, and by the end of the experiments (90 days) it was 7.56 times lower than the data of geese of the 1 control group.

*Bifidobacterium spp.* level in goiter of birds 3 increased compared with the data of geese of group 2 subjected to antimycotic therapy. It was higher in comparison with its level in group 2 by the 90th day of the experiment by 3.78 times. However, the content of *Bifidobacterium spp.* in goiter of birds of group 3 did not reach the indicator of birds of 1 control group. And by the end of the experiments, it was 2.0 times lower than the control figure.

Enzyme therapy of geese with lithase has a more positive effect on the activation of *Bifidobacterium spp.* in the goiter of geese 4 groups. Here, the indicator of the level of bifidobacteria dynamically and significantly increased during the experiment and by the end of the study (90 days) exceeded their parameters in geese 1, 2, 3 groups of 1.35; 10.23; 2.7 times.

A higher content of bifidobacteria was released from goiter of group 5 geese, which were subjected to probiotic therapy against the background of enzyme therapy with lithase. Content data of *Bifidobacterium spp.* in goiter of birds of the 5th group on 7, 14, 30, 60 and 90 days from the beginning of the experiment were higher, compared with their value in birds subjected only to enzyme therapy, respectively, at 1.09; 1.31; 1.65; 1.29 and 1.05 times. Moreover, the content of bifidobacteria in goiter of group 5 geese by the end of the experiment was 1.42 times higher in comparison with their level in birds of the control group 1, 10.7 times in sick and untreated birds of group 2, and birds subjected to traditional antimycotic therapy (Group 3) - 2.85 times.

The use of complex enzyme therapy and propolisotherapy (group 6) for the treatment of infected with candidiasis geese (group 6) also contributed to an increase in the activity of *Bifidobacterium spp.* in goiter of birds with candidiasis. These birds of group 6 almost corresponded to their values in geese of group 5 and only slightly inferior to them. By the end of the experiment, they amounted to 9.1 lgCOU/g in group 6 (9.38 lgCOU/g in group 5).

Significant activation of *Bifidobacterium spp.* in goiter goose was recorded in birds of group 7, in which the birds were subjected to complex enzyme-probiotic propolis therapy. In the goiter of geese of group 7, the level of bifidobacteria by the end of the experiment exceeded their level in geese of 1, 2, 3, 4, 5, and 6 groups, at 1.94; 14.7; 3.89; 1.44; 1.36 and 1.4 times.

Candidamycosis inhibited the growth and reproduction of *Bifidobacterium spp.* in the muscular and glandular stomach of geese. In the muscle stomach of geese of the 1 control group *Bifidobacterium spp.* tended to a dynamic moderate increase in the duration of the experiment. By the end of the experiment (90 days), they exceeded the initial indicator (7 days) by 2.17 times.

*Bifidobacterium spp.* level. in the muscle stomach of birds of group 2, infected and not subjected to medical manipulations, intensively decreased during the experiment, and by the end of the experiment it was 16.3 times lower than in birds of the 1st control group.

The content of *Bifidobacterium spp.* in the muscle stomach of geese of group 3 by the end of the experiment increased slightly, compared with its initial value in the group, by 1.4 times, compared with the data of birds of group 2 for this period of the experiment - by 9.0 times, but inferior to the control birds 1.81 times.

A more pronounced increase in *Bifidobacterium spp.* in the muscle stomach of geese of 4 group were recorded, where by the end of the experiment their level was higher, in comparison with the data of birds of groups 1, 2 and 3, at 1.05; 17.0; 1.89 times.

Significant activation of *Bifidobacterium spp.* was recorded in the muscle stomach of group 5 geese. Here, in all periods of studies, the content of bifidobacteria exceeded the data for the above groups, and by the end of the experiment the level of *Bifidobacterium spp.* was higher, in comparison with indicators of birds of 1, 2, 3, 4 groups, at 1.72; 28.0; 3.12 and 1.65 times.

The dynamics of *Bifidobacterium spp.* changed in a similar way. in the muscle stomach of geese of group 6. The maximum value is the level of *Bifidobacterium spp.* was reached by geese of group 7 in the muscle stomach, where by the end of the experiment their content exceeded the data of geese 1, 2, 3, 4, 5 and 6 of the group, in 2.28; 37.2; 4.14; 2.19; 1.33 and 1.29 times.

The content of bifidobacteria in the glandular stomach of geese in a quantitative ratio was lower than in the muscle stomach. However, the dynamics of the content of *Bifidobacterium spp.* in the glandular section of the stomach of geese were typical with its dynamics in the muscular section.

In healthy geese of group 1, the content of *Bifidobacterium spp.* in the glandular stomach, during the experiment, changed upward. By the end of the experiment, their value increased, compared with the initial level, 2.1 times.

In group 2 geese, the content of *Bifidobacterium spp.* in the glandular stomach, there was a tendency to a pronounced decrease and by the end of the experiment (90 days) their level was 4.07 times lower than the initial value.

Although treatment of geese with candidiasis with antimycotics (group 3), suspended a further active decrease in the activity of *Bifidobacterium spp.*, It was not sufficiently effective. Here, the level of bifidobacteria in the glandular stomach of geese did not even reach their indicator in the control group, losing to it by 1.49 times by the 90th day of the experiment. In this case, *Bifidobacterium spp.* in the glandular stomach of geese of group 3 were higher than in birds of group 2 by 8.93 times.

Lithium enzyme therapy (group 4) contributed to a more significant activation in the glandular stomach of geese of *Bifidobacterium spp.*, the content of which by the end of the experiment exceeded their indices in geese of groups 1, 2 and 3, by 1.35; 18.07; 2.02 times.

Favorable effect on the growth and reproduction of *Bifidobacterium spp.* in the glandular stomach, was reinforced by complex enzyme-probiotic therapy of goose candidiasis. The data of geese of group 5 were higher, compared with their level, in all periods of the experiment, for all previous groups. By the end of the experiment, they exceeded the data for groups 1, 2, 3, and 4, by 2.38; 31.8; 3.57 times.

*Bifidobacterium spp.* level in the glandular stomach of geese of group 6 (complex enzyme-propolis therapy) did not have any special differences compared with the data of birds of group 5, while significantly exceeding the indices of groups 1, 2, 3 and 4 by 2.37; 31.6; 3.54 and 1.75 times.

The most beneficial effect on activation in the glandular stomach of geese of *Bifidobacterium spp.* was provided by complex enzyme therapy with lithase against the background of probiotic and propolisotherapy (group 7). In all periods of the experiment, the content of *Bifidobacterium spp.* in the glandular stomach of geese of group 7 was higher than their values for all previous groups. By the end of the experiment, they exceeded the data for 1, 2, 3, 4, 5, and 6 groups, at 2.89; 38.8; 4.42; 213; 1.21 and 1.22 times.

The content of *Bifidobacterium spp.* in the small intestine section of geese of the 1 control group during the experiment dynamically increased, exceeding the initial indicator 7 days after the start of the study on 14, 30, 60 and 90 days at 1.17; 1.45; 1.93 and 2.24 times.

In the small intestine of geese of group 2, on the contrary, a significant dynamic decrease in the level of *Bifidobacterium spp.* was recorded. On the 7th, 14th, 30th, 60th and 90th days of the experiment, the content of *Bifidobacterium spp.* in the small intestine of the geese of group 2, it was lower compared to its level in the control group, 1.6; 2.09; 3.02; 5.31 and 7.86 times.

Level indicators of *Bifidobacterium spp.* in the small intestine section of geese, group 3 slightly increased compared to the data of birds of group 2 and by 7, 14, 30, 60 and 90 days of the experiment exceeded their indices of 1.33; 1.8; 2.26; 3.41 and 4.4 times, but they continued to be significantly inferior, for these periods of research, to the control figures of birds of the 1st group: 1.2; 1.16; 1.34; 1.56 and 1.78 times.

Remarkable changes in the content of geese *Bifidobacterium spp.* In the small intestine. were recorded in birds of 4 groups, against the background of enzyme therapy with lithase. Here the level of bifidobacteria was higher than in birds of the 2nd group, on days 7, 14, 30, 60 and 90 of the experiment, at 1.84; 2.89; 3.64; 5.18 and 7.2 times. Moreover, the geese of the 4th group significantly approached the control level, and on the 14th and 30th days of the experiment exceeded it.

Higher levels of *Bifidobacterium spp.* in the small intestine of geese reached 5 and 6 groups. The indices of birds of these groups were even significantly higher compared with their data in group 4. The maximum level of *Bifidobacterium spp.* reached in the small intestine of geese of group 7. The indices of geese of group 7 exceeded the data of birds of groups 1 and 2 on the 7th day of the experiment 2.04 and 3.28 times, on the 14th day - 2.19 and 4.58 times, on the 30th day - 2.2 and 6, 67 times, for 60 days - 1.74 and 9.21 times, for 90 days - 1.58 and 12.4 times.

Similar to the dynamics of *Bifidobacterium spp.* In the small intestine of geese, the dynamics of bifidobacteria in the large intestine of birds changed. In the large intestine of the geese, an active decrease in the activity of bifidoflora in birds of the 2nd group was recorded. On the 7th, 14th, 30th, 60th and 90th days from the beginning of the experiments, their level was lower than in the control, at 1.55; 1.89; 3.1; 5.35 and 9.39 times. In the large intestine of the birds of the 4th group, a moderate increase in the level of *Bifidobacterium spp.* Was observed, compared with the data for the 2nd group. Active propagation of *Bifidobacterium spp.* recorded in the minesweeper of geese of the 4th group. It was enhanced against the background of enzyme therapy with probiotic and propolis (groups 5 and 6). The maximum increase in the level of *Bifidobacterium spp.* observed in the large intestine of geese of group 7. Indicators of geese of group 7 were higher than their level in birds of groups 1 and 2 on the 7th day of the experiment 2.26 and 3.51 times, on the 14th day - 2.26 and 4.28 times, on the 30th day - 2.4 and 7.47 times, for 60 days - 1.7 and 9.11 times, for 90 days - 1.62 and 15.2 times.

**Conclusion.** Candidiasis causes an imbalance of lactobacilli and bifidobacteria in the digestive tract of geese. The most favorable effect on the restoration of growth and reproduction of lactobacilli and bifidobacteria is provided by complex therapy with the enzyme drug lithase in the presence of probiotic and propolisotherapy.

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