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## CLINICAL EVALUATION OF FUNCTIONAL STATE OF IMMUNE SYSTEM PARTICULAR COMPONENTS IN PATIENTS WITH OPIUM ADDICTION

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### ABSTRACT

In this study, a comprehensive research of the phagocytic activity of neutrophils in patients with heroin addiction was carried out. It was found that heroin addiction is accompanied by pronounced changes in the cellular-humoral defense system of the body. Opiate substances have a mainly suppressive effect on immunocompetent cells. The disorganization of the immune systems, which are closely interconnected with the central nervous system, leads to disruption of cellular and humoral homeostasis and aggravates the process of drug addiction. One of the existing hypotheses of the cause of this process is the theory of a decrease in the function of immunocytes under the damaging effect of heroin on the human body.

**Research objective:** The aim of this study is to determine the phagocytic activity of neutrophils in patients with heroin addiction.

**Materials and methods.** The total number of patients was 57 (43 men and 14 women), whose age varied from 23 to 34 years.

**Results.** Analysis of the anamnestic data of drug addicts revealed a tendency to infectious diseases, while chronic infections were predominant – sinusitis. At the end of pharmacotherapy, patients of the 1st group noted an improvement in their condition, a decrease in the symptoms of pathological craving for alcohol, and returned to their familiar social environment.

**Conclusion.** Summary: Based on a comprehensive study of the phagocytic activity of neutrophils in patients with heroin addiction, it was found that heroin addiction is accompanied by pronounced changes in the cellular-humoral defense system of the body.

**Keywords:** opium addiction, heroin, phagocytic activity, immune system.

## INTRODUCTION

Currently, there is a large amount of information showing the immunological failure of patients with opium addiction, which leads to an increase in research on the impact of chronic drug intoxication on immunity [1,2]. A complex effect of various systems on the immune components of the body was revealed, that determines protection of a human's body [3,4,5]. Numerous studies have shown that neutrophilic white blood cells are a significant component of the immune system [6,7]. The protective effect here is determined by the phagocytosis system - the most reliable system in terms of protection against the effects of foreign influences [8, 9]. It was proven that regulation provided by cerebral structures play a great role in functional state of neutrophils [10, 11]. That lead to understanding that white blood cells are under influence secretory effects of cerebral structures, which determines their activity [12, 13]. Thus, activity of mutual relations is regulated and functional state of the human body can be determined [14, 15].

As noted, phagocytosis serves as a specific function of various types of neutrophils that take part in the metabolism of individual processes of regulation and defense of the body from exposure to harmful agents [6]. It should be noted that not all steps of phagocytosis have been studied thoroughly, this makes particularly urgent the study of modern research methods and new approaches in the study of individual steps of the chronic drug intoxication pathogenesis [3, 5].

**The aim of this study** is to determine the phagocytic activity of neutrophils in patients with heroin addiction.

## MATERIALS AND METHODS

There are close to none scientific studies on the individual components of nonspecific immune resistance in drug addicts. Considering the foregoing, 57 patients were the object of the

study on immunological characteristics for determination of immunological links in the pathogenesis of patients with opium addiction. The average age in 33 patients was from 23 to 27 years, 12 patients - from 28 to 34 years, 10 patients - from 35 to 40 years, 2 patients - from 40 to 43; 43 of them were male, 14 were female patients. 6 patients had determined inclination to addictive disorders. Regarding social status, 7 patients were students, 21 patients were engaged in casual earnings, 29 patients did not exercise their initial occupation. 12 patients were involved in criminal activities (drug trafficking). 27 patients were raised in complete families with a low cultural level. 30 patients were brought up in an incomplete family without a father or in a relatives' family. All patients used heroin (the main drug) intravenously.

It is important to note that due to heroin deficiency all patients used marijuana 2-3 days a month, and 2-3 days a month they used pregabalin, baclofen, codeine containing drugs and diphenhydramine. All patients were divided into 2 groups according to the duration of their use of opium drugs. The duration of chronic drug intoxication in 1st group was up to 5 years (31 patients). In the 2nd group duration of chronic drug intoxication was from 5 to 10 years and over (26 patients).

In the clinical picture of the disease, all patients had a developed withdrawal syndrome with all its inherent components. Patients with heroin addiction were examined: during the period of withdrawal syndrome, immediately after discharge from the hospital; in a state of a post-abstinence syndrome. The control group included 30 healthy people of both genders. The age of healthy people averaged  $37.5 \pm 1.7$  years. The identification of the relative and an absolute number of lymphocytes in peripheral blood was carried out by conventional methods. The level of  $CD^{4+}$  and  $CD^{8+}$  lymphocytes was determined using monoclonal antibodies by the method of indirect membrane immunofluorescence.

## RESULTS AND DISCUSSION

Statistical processing of research results was performed on a computer, graphic processing of materials using the Excel 2013 application package. For mathematical data processing, the CSS3.1 "Computer Biometrics" package was used. The text, tables, and figures show the average values of the studied indicators and the mean square error.

The significance of differences in the indicators between the compared samples was determined using the i-Student parametric criterion. Differences in the compared groups were considered significant at a significance level of 95% ( $P < 0.05$ ). Particular attention to study the characteristics of the immune system of patients with GB was determined by the history of life and disease of patients with GB. Attention is also paid to the presence of criticism of his illness and the level of intensity of the desire to abandon the drug. It was obligatory to work with close

relatives, given the falsehood of patients with heroin addiction, the inconsistency of evidence necessarily collected objective data. Of great importance was the clarification of the beginning of the terms of chronic drug intoxication, the number of dosages, the presence or absence of additional drugs, tolerance, the number of intravenous infusions per day. The composition and components of the withdrawal syndrome, the intensity of its links, were carefully studied.

Analysis of the anamnestic data of drug addicts revealed a tendency to infectious diseases, while chronic infections were predominant - sinusitis (9 patients) and other ENT diseases (5 patients), bronchitis, (4 patients) pneumonia (3 patients).

In addition, the majority of examined patients at the time of registration for the dispensary complained of frequent (up to 4-5 times a year) colds, mainly acute respiratory viral infections. In modern concepts of the immunopathogenesis of opium addiction, an important role is given to a decrease under the influence of drugs of the functional activity of CD<sup>4+</sup> lymphocytes, as well as the activation of CD<sup>8+</sup> lymphocytes.

**Table 1.**

**Clinical features of patients with opiate addiction with different duration of the disease.**

Factors	1st group (n=31)		2nd group (n=26)		$\chi^2$	P
	abs.	%	abs.	%		
Positive treatment attitude	27	87,1	15	57,7	6,31	<0,05
Understanding of the disease	16	51,6	9	34,6	1,66	>0,05
Physical status without severe pathology	24	77,4	7	26,9	14,53	0,001
Did not violate public order	30	96,8	8	30,8	27,72	0,000
Complete family	24	77,4	5	19,2	19,16	0,001
Presence of drug monitoring at home	23	74,2	8	30,8	10,75	0,001
Ability to stop contact with drug addicts	21	67,7	11	42,3	3,71	>0,05

However, until now there is no common understanding of the pathogenetic mechanisms of the development of these changes, which is largely due to a lack of data characterizing the immunotropic effects of exogenous opiates. There is practically no information about the effect of heroin on the nonspecific immunological reactivity of the body - the main link in the occurrence of immune disorders. The latter depends, in particular, on the duration of chronic

drug intoxication. However, it must be emphasized that at this time, studies on the state of the immune system in conditions of chronic drug intoxication are mainly experimental and clinical data and studies are practically absent. Given the significant predisposition of patients with opium addiction to various exogenous harmfulnesses (infections, viruses), naturally, the hypothesis of significant immunological disorders is assumed, since there is a fairly large number of publications confirming the increased sensitization of patients with opium addiction as a result of chronic drug intoxication to infection.

Analysis of the currently available data suggests that the abuse of opium drugs leads to an intense inhibitory effect on the main immunity links of patients with opium addiction. Therefore, studies aimed at detecting pathological changes as a result of chronic narcotic intoxication in patients with opiate addiction in various periods of the disease are of particular relevance. Initially, the assessment of the studied parameters in patients with opium addiction in the period of withdrawal was carried out. As shown in Table 2, in the withdrawal syndrome of the disease, certain changes occurred in quantitative indicators.

**Table 2.**

**Quantitative indicators of the content of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes in the blood of patients in the period of withdrawal syndrome**

	Control group	1st group	2nd group
CD4 <sup>+</sup>	47,4 ±0,6)	38,4±0,6***	31,4± 0,6***
CD8 <sup>+</sup>	22,7±0,6	31,9±0,9 ***	66,2±0,4 ***

Note: \* - Differences relative to control group data are significant (\*\*\*) - P<0,001).

The information obtained in the withdrawal period of the disease revealed pathological disorders in these indicators. It should be noted that the more pronounced, in comparison with the control, the nature of these changes was registered in the 2nd group than in the 1st. In particular, it was found that with a shorter duration of the disease, a significant decrease in the number of CD4<sup>+</sup> lymphocytes (38.4±0.6 compared with the control group - 47.4±0.6) and an increase in qualities of CD8<sup>+</sup> lymphocytes (31.9±0.9 compared with the control group 22.7±0.6) in peripheral blood (p<0.05). Similar patterns were revealed in the 2nd group, however, these changes were less pronounced than in the 1st group, concerning CD4 +, and more pronounced with CD8<sup>+</sup> (66.2±0.4 compared with the control group - 22.7±0.8).

Somewhat different patterns were identified when determining the studied parameters in the examined patients at the end of the therapy. The results obtained in this regard are shown in Table 2. The analysis of the data in Table 2 indicates that the therapeutic measures carried out in

the 1st group led to almost complete normalization of the quantitative indicators of blood CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes.

Concerning a similar category of patients of the 2nd group, although they contributed to a certain increase in the blood level of CD4<sup>+</sup> lymphocytes and a decrease in the blood level of CD8<sup>+</sup> cells, they did not lead to their normalization to control values.

Moreover, the values of these elements in patients of the 2nd group in the post-abstinence period had a statistical difference from the similar data of healthy people in the control group. It follows from this that pharmacotherapeutic interventions aimed at correcting the symptoms of acute withdrawal syndrome have a mixed effect on the components of the immune system in patients of both groups. If in patients of the first group it was possible to achieve almost complete leveling of the revealed changes, then in patients of the 2nd group a similar effect could not be achieved.

**Table 3.**

**The level of CD4<sup>+</sup> and CD8<sup>+</sup> components in a result of therapy**

	Control group	1st group	2nd group
CD4 <sup>+</sup>	47,4 ±0,6)	43,3±0,1***	30,3±0,2***
CD8 <sup>+</sup>	22,7±0,6	22,6±0,2	65,3±0,6***

Note: \* - Differences relative to control group data are significant (\*\*\*-P<0,001).

At the end of pharmacotherapy, patients of the 1st group noted an improvement in their condition, a decrease in the symptoms of pathological craving for alcohol, and returned to their familiar social environment. At the same time, positive therapeutic dynamics were observed in patients; an almost complete reduction in psychopathological manifestations occurred, symptoms of pathological attraction to heroin decreased, a distinct decrease in the residual manifestations of the disease (neurosis-like disorders, asthenic manifestations, autonomic dysfunction) was recorded. After 2-3 weeks in the examined patients in remission, we conducted another study aimed at assessing the quantitative parameters of immunocompetent cells in them, the results of which are shown in Table 4.

**Table 4.**

**Quantitative parameters of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes of peripheral blood of patients with heroin addiction during remission.**

	Control group	1st group	2nd group
CD4 <sup>+</sup>	47,4 ±0,6	45,3±0,8	37,5±0,5***
CD8 <sup>+</sup>	22,7±0,6	22,5±0,1	36,7±1,4***

Note: \* - Differences relative to control group data are significant (\*\*\* - P<0,001).

As follows from the data presented, during the period of remission, restoration processes continued to occur with the studied parameters in patients of the 2nd group. It should be noted that the leveling of differences concerning the control in terms of the quantitative characteristics of CD4<sup>+</sup> lymphocytes occurred more intensively than in the quantitative characteristics of CD8<sup>+</sup> lymphocytes. The latter, although they were decreasing, however, continued to reliably exceed the control level (P <0.05). As for the results obtained during the examination during the period of remission in patients with heroin addiction of the first group, the studied parameters were at the level of control values.

The cells that take an active part in the implementation of the basic functions of the immune system, as well as occupy key positions in non-specific immunological resistance, include dendritic cells, neutrophils, and other components of the cellular elements of the immune system. With the functioning of the immune system, neutrophils are important. A significant part of our research is devoted to these components in terms of assessing their condition in patients who abuse opium. The absorption function of neutrophils has also been the subject of our research. Neutrophils with this function are called activated. We determined the number of such components in the blood of patients with opium addiction (the proportion of activated neutrophils).

**Table 5.**

**The state of proportion of activated neutrophils of peripheral blood in patients with opium addiction with different duration of the disease.**

	The proportion of activated neutrophils in the withdrawal period	The proportion of activated neutrophils after treatment	The proportion of activated neutrophils in remission
1st group	34,8±3,2%	38,5±3,8%	39,8±3,6%
2nd group	25,7±2,3%**	29,8±2,8%*	30,7±3,3%*
Control group	41,0±3,9%	41±3,9%	41±3,9%

Note: \* - Differences relative to control group data are significant (\*\*\*) - P<0,001).

The data in the table indicate that the most intense decrease in the proportion of activated neutrophils in patients with heroin addiction was recorded in the withdrawal period, in patients of the second group with a long history of the disease (over 5 years). The indices of phagocytic cells were the smallest and amounted to 26.3±1.4%. These indices were statistically lower than those in healthy individuals of the control group. Our further studies found that these figures, bypassing the symptoms of acute withdrawal symptoms and in the post-withdrawal period, tended to increase, but did not reach the parameters of the control group. In patients of the first group with a duration of chronic drug intoxication of up to 5 years, similar violations were also

found. The correlation between the timing of drug use and the level of the proportion of activated neutrophils was revealed. Similar changes were found by us concerning the number of phagocytes. The fraction of lymphocytes in the peripheral blood was estimated by the magnitude of the phagocytic number, while the fraction of activated neutrophils and phagocytic number also correlate with each other.

**Table 6.**

**The state of the phagocytic number in the blood of patients with opiate addiction with different duration of the disease.**

	In the withdrawal period	After the withdrawal period	In the period of abstinence
1st group	7,7±0,65	8,9±0,55	8,0±0,72
2nd group	6,7±0,45	7,5±0,55	7,8±0,77
Control group	8,4±0,67	8,4±0,67	8,4±0,67

Thus, it was revealed that in patients with opiate addiction during various periods of the disease there are changes and from the side of immunocompetent cells with CD4<sup>+</sup> and CD8<sup>+</sup> phenotypes, in particular, their number changes. Moreover, with an exacerbation of the disease, a decrease in the number of CD4<sup>+</sup> lymphocytes in the peripheral blood of patients and an increase in the number of CD8<sup>+</sup> lymphocytes occur. In the remission of heroin addiction, the revealed differences in comparison with the control level are gradually approaching the control indicators, and in the first group, this happens more intensively than in the second, in which, even during prolonged abstinence from the drug, indicators did not reach normal levels.

We also studied the state of the humoral mechanisms of the immune system of patients with heroin addiction. At present, it is well known that the metabolism of phagocytizing neutrophils is determined by the presence in their composition of a certain amount of chemically active substances of an antibacterial nature. A significant role in the antibacterial effect is played by the degree of activity of these components in the process of phagocytosis and other effects of oxidative metabolism. In this process, the duration of chronic use of opium drugs is important.

Myeloperoxidase enzyme plays an important role in the degree of phagocytosis activity. All components involved in phagocytosis can act not only inside the cell but also released into the surrounding tissues, as well as blood, thus constituting, together with other active components (complement, lysozyme, 3-lysines, lymphokines, monokines, and others), the humoral component of the immune system. Given the foregoing, it is relevant to assess in chronic opium intoxication this stage of the bactericidal process. At this stage of the study of the phagocytosis process, the determination of serum concentrations of myeloperoxidase, a key

enzyme of oxygen-dependent phagocytic metabolism, is important. The results of studies in this direction showed that in the acute period of the disease, the concentration of this enzyme in the blood serum of the examined patients was significantly lower than the control indicators.

**Table 7.**

**The level of myeloperoxidase in patients with opium addiction at different stages of the disease.**

	In the withdrawal period	After the withdrawal period	In the period of abstinence
1st group (n=31)	219,7±10,75**	228,4±12,45	238,8±20,56
2nd group (n=26)	208,7±9,73***	215,7±7,19***	225,7±4,53***
Control group	252,5±3,19		

Note: \* - Differences relative to control group data are significant (\*\*\*) -  $P < 0,001$ .

As can be seen from the table, the use of heroin leads to a decrease in the level of serum myeloperoxidase in the examined patients at all stages of the disease. Depending on the duration of drug administration, the magnitude of myeloperoxidase was recorded significantly at a lower level than in the control group ( $P < 0.001$ ).

The insufficiency of phagocytic systems in patients with opium addiction is clinically manifested in the form of infectious and inflammatory processes in the internal organs. The above information determines the relevance of a comprehensive study of acquired defects of phagocytosis, determines the feasibility of creating new methods for studying the functional activity of neutrophils and developing methods for their pathogenetic prevention.

## CONCLUSION

Based on a comprehensive study of the phagocytic activity of neutrophils in patients with heroin addiction, it was found that heroin addiction is accompanied by pronounced changes in the cellular-humoral defense system of the body. Narcotic substances of opium nature have a mainly suppressive effect on immunocompetent cells. A comprehensive study of the functional activity of neutrophils expands the possibilities of the pathogenetic interpretation of the clinical manifestations of drug addiction and helps to develop additional methods for the correction of ongoing therapeutic measures. The disorganization of immune systems, which are closely interconnected with the central nervous system, leads to disruption of cellular and humoral homeostasis and exacerbate the process of drug addiction. The exact reasons for such changes are not fully investigated. One of the assumptions can be that a decrease in the function of immunocytes under the influence of heroin may be due to the damaging effect of heroin.

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